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The Nervous System

PART
XXV

Chapter 630

Neurologic Evaluation

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HISTORY

A detailed history is the cornerstone of neurologic assessment. Although parents may be the primary informants, most children older than 3-4 years can contribute to their history and should be questioned. The history should begin with the chief complaint and its significance in the context of normal development (see Chapters 21-28). The latter step is critical because a 13-month-old who cannot walk may be normal, whereas a 4-year-old who cannot walk might have a serious neurologic condition.

Next, the history of the present illness should provide a chronological outline of the patient's symptoms, with attention paid to location, quality, intensity, duration, associated features, and alleviating or exacerbating factors. It is essential to perform a review of systems because abnormalities of the central nervous system (CNS) often manifest with vague, nonfocal symptoms that may be misattributed to other organ systems (e.g., vomiting, constipation, urinary incontinence). A detailed history might suggest that vomiting is a result of increased intracranial pressure (ICP) rather than gastritis or that constipation and urinary incontinence are caused by a spinal cord tumor rather than behavioral stool withholding. In addition, a systemic illness may produce CNS manifestations, as do lupus erythematosus (seizures, psychosis, demyelination), mitochondrial disorders (developmental delay, strokes, hypotonia), or celiac disease (headaches, seizures, peripheral neuropathy).

After obtaining the chief complaint and history of the present illness, the physician should obtain a complete birth history, particularly if a congenital or perinatal disorder is suspected. The birth history should begin with a review of the pregnancy, including specific questions about common complications, such as pregnancy-induced hypertension, preeclampsia, gestational diabetes, vaginal bleeding, infections, and falls. It is important to quantify any cigarette, alcohol, or drug (prescription, herbal, illicit) use. Inquiring about fetal movement might provide clues to an underlying diagnosis, because decreased or absent fetal activity can be associated with chromosomal anomalies and CNS or neuromuscular disorders. Finally, any abnormal ultrasound or amniocentesis results should be noted.

The mother's labor history should address the gestational age at birth and mode of delivery (spontaneous vaginal, vacuum- or forceps-assisted, cesarean section) and should comment on the presence or absence of fetal distress. If delivery was by cesarean section, it is essential to record the indication for surgery.

The birthweight, length, and head circumference provide useful information about the duration of a given problem, as well as insights into the uterine environment. Parents can usually provide a reliable history of their child's postnatal course; however, if the patient was resuscitated or had a complicated hospital stay, it is often helpful to obtain the hospital records. The physician should inquire about the infant's general well-being, feeding and sleeping patterns, activity level, and the nature of the infant's cry. If the infant had jaundice, it is important to determine both the degree of jaundice and how it was managed. Features of neurologic dysfunction at full term include inability to breathe spontaneously; poor, uncoordinated suck; or the need for an inordinate amount of time to feed or a requirement for gavage feeding. Again,

it is important to consider the developmental context because all of these issues would be expected in premature infants, particularly those with a very low birthweight. Double-checking the newborn screening results may provide a clue to abnormal neurologic manifestations in an infant.

A major component of the neurologic history is the **developmental assessment** (see Chapters 21-28). Careful evaluation of a child's social, cognitive, language, fine motor skills, and gross motor skills is required to distinguish normal development from either an isolated or a global (i.e., in two or more domains) developmental delay. A static abnormality in development from birth suggests a congenital, intrauterine, or perinatal cause, but a loss of skills (**regression**) over time strongly suggests an underlying degenerative disease of the CNS, such as an inborn error of metabolism or genetic disorder. The ability of parents to recall the precise timing of their child's developmental milestones is extremely variable. It is often helpful to request old photographs of the child or to review the baby book, where the milestones may have been dutifully recorded. In general, parents are aware when their child has a developmental problem, and the physician should show appropriate concern. [Table 630.1](#) outlines the upper limits of normal for attaining specific developmental milestones. [Chapter 28](#) includes a comprehensive review of developmental screening tests and their interpretation.

Next, the family history must be reviewed. Most parents are cooperative in securing medical information about family members, particularly if it might have relevance for their child. The history should document the age and history of neurologic disease, including developmental delay, epilepsy, migraine, stroke, and inherited disorders, for all first- and second-degree relatives. It is important to inquire directly about miscarriages or fetal deaths and to document the sex of the relevant embryo or fetus, as well as the gestational age at the time of demise. When available, the results of postmortem examinations should be obtained, because they can have a direct bearing on the patient's condition. The parents should be questioned about their ethnic backgrounds because some genetic disorders occur more commonly within specific populations (e.g., Tay-Sachs disease in the Ashkenazi Jewish population). They should also be asked if there is any chance that they could be related to each other, because the incidence of metabolic and degenerative disorders of the CNS is increased significantly in children of *consanguineous* marriages.

The social history should detail the child's current living environment and the child's relationship with other family members. It is important to inquire about recent stressors, such as divorce, remarriage, birth of a sibling, or death of a loved one, because they can affect the child's behavior. If the child is in daycare or school, one should document the child's academic and social performance, paying particular attention to any abrupt changes. Academic performance can be assessed by asking about the child's latest report card, and peer relationships can be evaluated by having the child name his or her best friends. Any child who is unable to name at least two or three playmates might have abnormal social development. In some cases, discussions with the daycare worker or teacher provide useful ancillary data.

NEUROLOGIC EXAMINATION

The neurologic examination begins during the interview. Indirect observation of the child's appearance and movements can yield valuable information about the presence of an underlying disorder. For instance, it may be obvious that the child has dysmorphic facies, an unusual posture, or an abnormality of motor function manifested by a hemiparesis or gait disturbance. The child's behavior while playing and interacting with his or her parents may also be telling. A normal child usually plays independently early in the visit but then engages in the interview process. A child with attention-deficit/hyperactivity disorder

Table 630.1 Screening Scheme for Developmental Delay: Upper Range

AGE (MO)	GROSS MOTOR	FINE MOTOR	SOCIAL SKILLS	LANGUAGE
3	Supports weight on forearms	Opens hands spontaneously	Smiles appropriately	Coos, laughs
6	Sits momentarily	Transfers objects	Shows likes and dislikes	Babbles
9	Pulls to stand	Pincer grasp	Plays pat-a-cake, peek-a-boo	Imitates sounds
12	Walks with one hand held	Releases an object on command	Comes when called	One to two meaningful words
18	Walks upstairs with assistance	Feeds self from a spoon	Mimics actions of others	At least six words
24	Runs	Builds a tower of six blocks	Plays with others	Two- to three-word sentences

might display impulsive behavior in the examining room, and a child with neurologic impairment might exhibit complete lack of awareness of the environment. Finally, note should be made of any unusual odors about the patient, because some metabolic disorders produce characteristic scents (e.g., the musty smell of phenylketonuria or the sweaty feet smell of isovaleric acidemia; see [Chapter 104](#)). If such an odor is present, it is important to determine whether it is persistent or transient, occurring only with illnesses.

The examination should be conducted in a nonthreatening, child-friendly setting. The child should be allowed to sit where the child is most comfortable, whether it be on a parent's lap or on the floor of the examination room. The physician should approach the child slowly, reserving any invasive, painful, or discomforting tests for the end of the examination (e.g., measurement of head circumference, gag reflex). In the end, the more that the examination seems like a game, the more the child will cooperate. Because the neurologic examination of an infant requires a somewhat modified approach from that of an older child, these two groups are considered separately (see Chapters 21-23 and 115 vs Chapters 24-27).

Mental State

Age aside, the neurologic examination should include an assessment of the patient's mental state in terms of both the level of arousal and the interaction with the environment. Premature infants born at <28 weeks of gestation do not have consistent periods of alertness, whereas slightly older infants arouse from sleep with gentle physical stimulation. Sleep-wake patterns are well developed at term. Because the level of alertness of a neonate depends on many factors, including the time of the last feeding, room temperature, and gestational age, serial examinations are critical when evaluating for changes in neurologic function. An older child's mental state can be assessed by watching the child play. Having the child tell a story, draw a picture, or complete a puzzle can also be helpful in assessing cognitive function. Memory can be evaluated informally as patients recount their personal information, as well as more formally by asking them to register and recall three objects or perform a digit span.

Head

Correct measurement of the **head circumference** is important. It should be performed at every visit for patients younger than 3 years and should be recorded on a suitable head growth chart. To measure, a nondistensible plastic measuring tape is placed over the mid-forehead and extended circumferentially to include the most prominent portion of the occiput. If the patient's head circumference is abnormal, it is important to document the head circumferences of the parents and siblings. Errors in the measurement of a newborn skull are common because of scalp edema, overriding sutures, and the presence of cephalohematomas. The average rate of head growth in a healthy premature infant is 0.5 cm in the first 2 weeks, 0.75 cm in the third week, and 1.0 cm in the fourth week and every week thereafter until the fortieth week of development. The head circumference of an average term infant measures 34-35 cm at birth, 44 cm at 6 months, and 47 cm at 1 year of age (see Chapters 21 and 22).

If the brain is not growing, the skull will not grow; therefore a small head frequently reflects a small brain, or **microcephaly**. Microcephaly



Fig. 630.1 Congenital hydrocephalus. Note the enlarged cranium and prominent scalp veins.

may develop in utero or postnatally and may, for example, be related to intrauterine infection or drug exposure or to perinatal or postnatal injury. Conversely, a large head may be associated with a large brain, or **macrocephaly**, which is most commonly familial but may be from a disturbance of growth (Sotos syndrome), neurocutaneous disorder (e.g., neurofibromatosis), chromosomal defect (e.g., Klinefelter syndrome), or lysosomal storage disorder. Alternatively, the head size may be increased secondary to hydrocephalus ([Fig. 630.1](#)) or chronic subdural hemorrhages. In the latter case, the skull tends to assume a square or boxlike shape, because the long-standing presence of fluid in the subdural space causes enlargement of the middle fossa.

The shape of the head should be documented carefully. Plagiocephaly, or flattening of the skull, can be seen in normal infants but may be particularly prominent in hypotonic or weak infants, who are less mobile. A variety of abnormal head shapes can be seen when cranial sutures fuse prematurely, as in the various forms of inherited **craniosynostosis** (see [Chapter 631.10](#)).

An infant has two **fontanels** at birth: a diamond-shaped anterior fontanel at the junction of the frontal and parietal bones that is open at birth, and a triangular posterior fontanel at the junction of the parietal and occipital bones that can admit the tip of a finger or may be closed at birth. If the posterior fontanel is open at birth, it should close over the ensuing 6-8 weeks; its persistence suggests underlying hydrocephalus or congenital hypothyroidism. The anterior fontanel varies greatly in size, but it usually measures approximately 2 × 2 cm. The average time of closure is 18 months, but the fontanel can close normally as early as 9 months. A very small or absent anterior fontanel at birth might indicate craniosynostosis or microcephaly, whereas a very large fontanel can signify a variety of problems. The fontanel is normally slightly depressed and pulsatile and is best evaluated by holding the infant upright while the infant is asleep or feeding. A bulging fontanel is a potential indicator of increased ICP, but vigorous crying can cause a protuberant fontanel in a normal infant.

Inspection of the head should include observation of the venous pattern, because increased ICP and thrombosis of the superior sagittal sinus can produce marked venous distention. Dysmorphic facial features can indicate a neurodevelopmental aberration. Likewise, cutaneous abnormalities, such as cutis aplasia or abnormal hair whorls, can suggest an underlying brain malformation or genetic disorder.

Palpation of a newborn's skull characteristically reveals **molding** of the skull accompanied by **overriding sutures**—a result of the pressures exerted on the skull during its descent through the pelvis. Marked overriding of the sutures beyond the early neonatal period is cause for alarm, because it suggests an underlying brain abnormality. Palpation additionally might reveal bony bridges between sutures (**craniosynostosis**), cranial defects, or, in premature infants, softening of the parietal bones (**craniotabes**).

Auscultation of the skull is an important adjunct to the neurologic examination. **Cranial bruits** may be noted over the anterior fontanel, temporal region, or orbits and are best heard using the diaphragm of the stethoscope. Soft symmetric bruits may be discovered in normal children younger than 4 years of age or in association with a febrile illness. Demonstration of a loud or localized bruit is usually significant and warrants further investigation because it may be associated with severe anemia, increased ICP, or arteriovenous malformations of the middle cerebral artery or vein of Galen. It is important to exclude murmurs arising from the heart or great vessels, because they may be transmitted to the cranium.

Cranial Nerves

Olfactory Nerve (Cranial Nerve I)

Anosmia, or loss of smell, most commonly occurs as a transient abnormality in association with an upper respiratory tract infection or allergies. Permanent causes of anosmia include head trauma with damage to the ethmoid bone or shearing of the olfactory nerve fibers as they cross the cribriform plate, tumors of the frontal lobe, intranasal drug use, and exposure to toxins (acrylates, methacrylates, cadmium). Occasionally, a child who recovers from purulent meningitis or develops hydrocephalus has a diminished sense of smell. Rarely, anosmia is congenital, in which case it can occur as an isolated deficit or as part of **Kallmann syndrome**, a familial disorder characterized by hypogonadotropic hypogonadism and congenital anosmia. Although not

a routine component of the examination, smell can be tested reliably as early as the 32nd week of gestation by presenting a stimulus and observing for an alerting response or withdrawal, or both. Care should be taken to use appropriate stimuli, such as coffee or peppermint, as opposed to strongly aromatic substances (e.g., ammonia inhalants) that stimulate the trigeminal nerve. Each nostril should be tested individually by pinching shut the opposite side.

Optic Nerve (Cranial Nerve II; see also Part XXVII)

Assessment of the optic disc and retina (see Chapters 659, 670, and 671) is a critical component of the neurologic examination. Although the retina is best visualized by dilating the pupil, most physicians do not have ready access to mydriatic agents at the bedside; therefore it may be necessary to consult an ophthalmologist in some cases. Mydriatics should not be administered to patients whose pupillary responses are being followed as a marker for impending cerebral herniation or to patients with glaucoma or cataracts. When mydriatics are used, both eyes should be dilated, because unilateral papillary fixation and dilation can cause confusion and worry in later examiners unaware of the pharmacologic intervention. Examination of an infant's retina may be facilitated by providing a nipple or soother and by turning the head to one side. The physician gently strokes the patient to maintain arousal while examining the closer eye. An older child should be placed in the parent's lap and should be distracted by bright objects or toys. The color of the optic nerve is salmon-pink in a child but may be gray-white in a newborn, particularly if the newborn has fair coloring. This normal finding can cause confusion and can lead to the improper diagnosis of optic atrophy.

Disc edema refers to swelling of the optic disc, and **papilledema** specifically refers to swelling that is secondary to increased ICP. Papilledema rarely occurs in infancy because the skull sutures can separate to accommodate the expanding brain. In older children, papilledema may be graded according to the Frisen scale (Fig. 630.2). Disc edema must be differentiated from **papillitis**, or inflammation of the optic nerve.

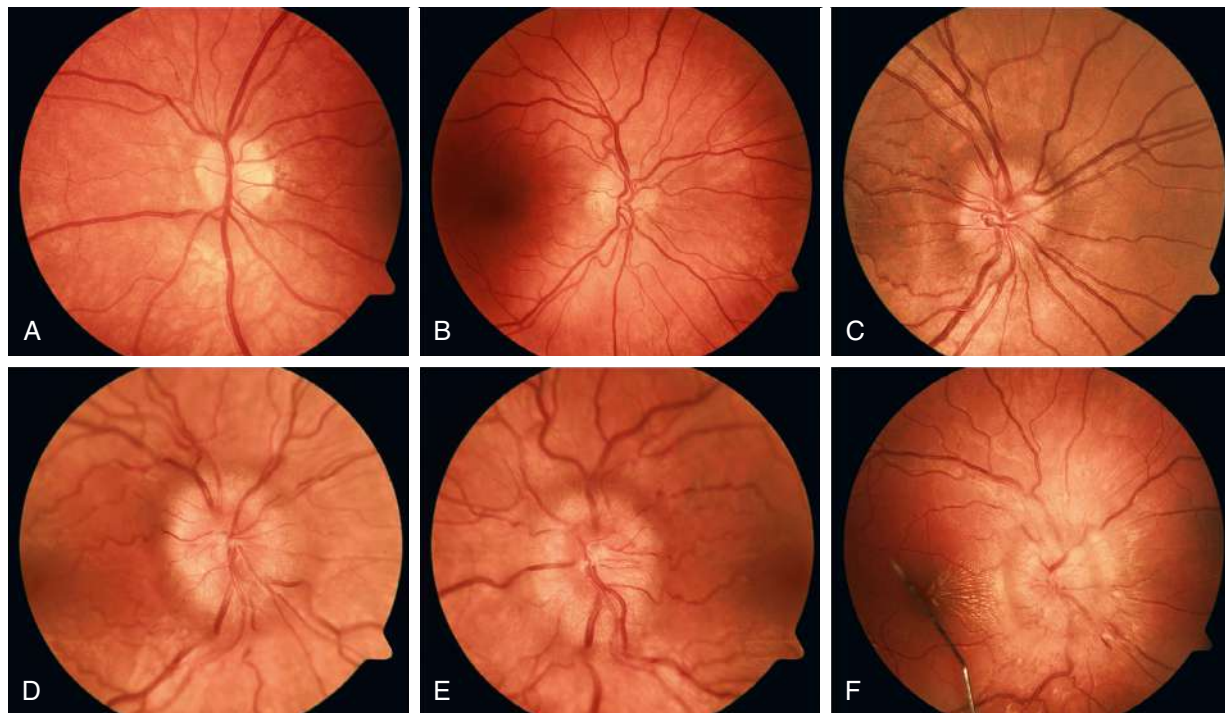


Fig. 630.2 Stages of papilledema (Frisen scale). A, Stage 0: Normal optic disc. B, Stage 1: Very early papilledema with obscuration of the nasal border of the disc only, without elevation of the disc borders. C, Stage 2: Early papilledema showing obscuration of all borders, elevation of the nasal border, and a complete peripapillary halo. D, Stage 3: Moderate papilledema with elevation of all borders, increased diameter of the optic nerve head, obscuration of vessels at the disc margin, and a peripapillary halo with finger-like extensions. E, Stage 4: Marked papilledema characterized by elevation of the entire nerve head and total obscuration of a segment of a major blood vessel on the disc. F, Stage 5: Severe papilledema with obscuration of all vessels and obliteration of the optic cup. Note also the nerve fiber layer hemorrhages and macular exudate. (A-C courtesy Dr. Deborah Friedman; D-F courtesy Flaum Eye Institute, University of Rochester.)

Both conditions manifest with enlargement of the blind spot, but visual acuity and color vision tend to be spared in early papilledema in contrast to what occurs in optic neuritis.

Retinal hemorrhages occur in 30–40% of all full-term newborn infants. The hemorrhages are more common after vaginal delivery than after cesarean section and are not associated with birth injury or with neurologic complications. They disappear spontaneously by 1–2 weeks of age. The presence of retinal hemorrhages beyond the early neonatal period should raise a concern for nonaccidental trauma.

Vision

A full description of the age-appropriate evaluation of vision can be found in [Chapter 659](#). Evaluation of vision in the premature infant presents unique challenges. At 28 weeks of corrected gestational age, a premature infant blinks in response to a bright light, and at 32 weeks, the infant maintains eye closure until the light source is removed. The pupil reacts to light by 29–32 weeks of corrected gestational age; however, the pupillary response is often difficult to evaluate, because premature infants resist eye opening and have poorly pigmented irises. A normal 37-week infant turns the head and eyes toward a soft light, and a term infant is able to fix on and follow a target, such as the examiner's face.

Oculomotor (Cranial Nerve III), Trochlear (Cranial Nerve IV), and Abducens (Cranial Nerve VI) Nerves

The globe is moved by six extraocular muscles, which are innervated by the oculomotor, trochlear, and abducens nerves. These muscles and nerves can be assessed by having the patient follow an interesting toy or the examiner's finger in the six cardinal directions of gaze. The physician observes the range and nature (conjugate vs dysconjugate, smooth vs choppy or saccadic) of the eye movements, particularly noting the presence and direction of any abnormal eye movements. Premature infants older than 25 weeks of gestational age and comatose patients can be evaluated using the oculocephalic (doll's eye) maneuver, in which the patient's head is quickly rotated to evoke reflex eye movements. If the brainstem is intact, rotating the patient's head to the right causes the eyes to move to the left and vice versa. Similarly, rapid flexion and extension of the head elicits vertical eye movement.

Dysconjugate gaze can result from extraocular muscle weakness; cranial nerve (CN) III, IV, or VI palsies; or brainstem lesions that disrupt the medial longitudinal fasciculus. Infants who are younger than 2 months can have a slightly dysconjugate gaze at rest, with one eye horizontally displaced from the other by 1 or 2 mm (**strabismus**). Vertical displacement of the eyes requires investigation because it can indicate trochlear nerve (CN IV) palsy or **skew deviation** (supranuclear ocular malalignment that is often associated with lesions of the posterior fossa). Strabismus is discussed further in [Chapter 663](#).

The oculomotor nerve innervates the superior, inferior, and medial recti, as well as the inferior oblique and levator palpebrae superioris muscles. Complete paralysis of the oculomotor nerve causes ptosis, dilation of the pupil, displacement of the eye outward and downward, and impairment of adduction and elevation. The trochlear nerve supplies the superior oblique muscle, which depresses and internally rotates the globe during activities such as reading and walking down stairs. Patients with an isolated paralysis of the trochlear nerve often have a compensatory head tilt away from the affected side, which helps to alleviate their diplopia. The abducens nerve innervates the lateral rectus muscle; its paralysis causes medial deviation of the eye with an inability to abduct beyond the midline. Patients with increased ICP often respond positively when questioned about double vision (**diplopia**) and exhibit incomplete abduction of the eyes on lateral gaze as a result of partial palsies of nerve VI. This false-localizing sign occurs because CN VI has a long intracranial course, making it particularly susceptible to being stretched. **Internuclear ophthalmoplegia**, caused by a lesion in the medial longitudinal fasciculus of the brainstem which functionally serves the conjugate gaze by connecting CN VI on one side to CN III on the other, results in paralysis of the medial rectus function in the adducting eye and nystagmus in the abducting eye.

When there is a subtle eye movement abnormality, the **red glass test** may be helpful in localizing the lesion. To perform this test, a red glass

is placed over one of the patient's eyes and the patient is instructed to follow a white light in all directions of gaze. The child sees one red/white light in the direction of normal muscle function but notes a separation of the red and white images that is greatest in the plane of action of the affected muscle.

In addition to gaze palsies, the examiner might encounter a variety of adventitious movements. **Nystagmus** is an involuntary, rapid movement of the eye that may be subclassified as being **pendular**, in which the two phases have equal amplitude and velocity, or **jerk**, in which there is a fast and a slow phase. Jerk nystagmus can be further characterized by the direction of its fast phase, which may be left-, right-, up-, or downbeating; rotatory; or mixed. Many patients have a few beats of nystagmus with extreme lateral gaze (**end-gaze nystagmus**), which is of no consequence. Pathologic horizontal nystagmus is most often congenital, drug-induced (e.g., alcohol, anticonvulsants), or a result of vestibular system dysfunction. By contrast, vertical nystagmus is often associated with structural abnormalities of the brainstem and cerebellum. **Ocular bobbing** is characterized by a downward jerk followed by a slow drift back to primary position and is associated with pontine lesions. **Opsoclonus** describes involuntary, chaotic, conjugate oscillations of the eyes, which are often seen in the setting of neuroblastoma or viral infection.

Trigeminal Nerve (Cranial Nerve V)

The three divisions of the trigeminal nerve—ophthalmic, maxillary, and mandibular—convey information about facial protopathic (pain, temperature) and epicritic (vibration, proprioception) sensation. Each modality should be tested and compared with the contralateral side. In patients who are uncooperative or comatose, the integrity of the trigeminal nerve can be assessed by the corneal reflex, elicited by touching the cornea with a small pledget of cotton and observing for symmetric eye closure, and nasal tickle, obtained by stimulating the nasal passage with a cotton swab and observing for symmetric grimace. An absent reflex may be because of a sensory defect (trigeminal nerve) or a motor deficit (facial nerve). The motor division of the trigeminal nerve can be tested by examining the masseter, pterygoid, and temporalis muscles during mastication and by evaluation of the jaw jerk.

Facial Nerve (Cranial Nerve VII)

The facial nerve is a predominantly motor nerve that innervates the muscles of facial expression—the buccinator, platysma, stapedius, and stylohyoid muscles—and the posterior belly of the digastric muscle. It also has a separate division, called the *chorda tympani*, that contains sensory, special sensory (taste), and parasympathetic fibers. Because the portion of the facial nucleus that innervates the upper face receives bilateral cortical input, lesions of the motor cortex or corticobulbar tract have little effect on upper face strength. Rather, such lesions manifest with flattening of the contralateral nasolabial fold or drooping of the corner of the mouth. Conversely, lower motor neuron or facial nerve lesions tend to involve upper and lower facial muscles equally. Facial strength can be evaluated by observing the patient's spontaneous movements and by asking the patient to mimic a series of facial movements (e.g., smiling, raising the eyebrows, inflating the cheeks). A facial nerve palsy may be congenital; idiopathic (**Bell palsy**); or secondary to trauma, demyelination (Guillain-Barré syndrome), infection (Lyme disease, herpes simplex virus, HIV), granulomatous disease, neoplasm, or meningeal inflammation or infiltration. Facial nerve lesions that are proximal to the junction with the *chorda tympani* will result in an inability to taste substances with the anterior two thirds of the tongue. If necessary, taste can be tested by placing a solution of saline or glucose on one side of the extended tongue. Normal children can identify the test substance in <10 seconds. Other findings that may be associated with facial nerve palsy include hyperacusis, resulting from stapedius muscle involvement, and impaired hearing.

Vestibulocochlear Nerve (Cranial Nerve VIII)

The vestibulocochlear nerve has two components within a single trunk: the vestibular nerve, which innervates the semicircular canals of the inner ear and is involved with equilibrium, coordination, and

orientation in space, and the cochlear nerve, which innervates the cochlea and carries auditory sensory information.

Dysfunction of the vestibular system results in **vertigo**, the sensation of environmental motion. On examination, patients with vestibular nerve dysfunction typically have nystagmus, in which the fast component is directed away from the affected nerve. With their arms outstretched and eyes closed, their limbs tend to drift toward the injured side. Likewise, if they march in place, they slowly pivot toward the lesion (**Fukuda stepping test**). On Romberg and tandem gait testing, they tend to fall toward the abnormal ear. Vestibular function can be further evaluated with **caloric testing**. Before testing, the tympanic membrane should be visualized to ensure that it is intact and unobstructed. In an obtunded or comatose patient, 30–50 mL of ice water is then delivered by syringe into the external auditory canal with the patient's head elevated 30 degrees. If the brainstem is intact, the eyes deviate toward the irrigated side. A much smaller quantity of ice water (2 mL) is used in awake, alert patients to avoid inducing nausea. In normal subjects, introduction of ice water produces eye deviation toward the stimulated labyrinth followed by nystagmus, with the fast component away from the stimulated labyrinth.

Because hearing is integral to normal language development, the physician should inquire directly about hearing problems. The parents' concern is often a reliable indicator of hearing impairment and warrants a formal audiologic assessment with either audiometry or brainstem auditory evoked potential testing (see [Chapter 677](#)). Even in the absence of parents' concern, formal testing is recommended in all newborns with the goal for all infants to be tested within the first month of life. Children at risk for hearing problems include those with a family history of early-life or syndromic deafness or a personal history of prematurity, severe asphyxia, exposure to ototoxic drugs, hyperbilirubinemia, congenital anomalies of the head or neck, bacterial meningitis, and congenital TORCH (toxoplasmosis, other infections, rubella, cytomegalovirus, herpes simplex virus) infections. For all other infants and children, a simple bedside assessment of hearing is usually sufficient. Newborns might have subtle responses to auditory stimuli, such as changes in breathing, cessation of movement, or opening of the eyes and/or mouth. If the same stimulus is presented repeatedly, normal neonates cease to respond, a phenomenon known as *habituation*. By 3–4 months of age, infants begin to orient to the source of sound. Hearing-impaired toddlers are visually alert and appropriately responsive to physical stimuli but might have more frequent temper tantrums and abnormal speech and language development.

Glossopharyngeal Nerve (Cranial Nerve IX)

The glossopharyngeal nerve conveys motor fibers to the stylopharyngeus muscle; general sensory fibers from the posterior third of the tongue, pharynx, tonsil, internal surface of the tympanic membrane, and skin of the external ear; special sensory (taste) fibers from the posterior third of the tongue; parasympathetic fibers to the parotid gland; and general visceral sensory fibers from the carotid bodies. The nerve is tested by stimulating one side of the lateral oropharynx or soft palate with a tongue blade and observing for symmetric elevation of the palate (**gag reflex**). An isolated lesion of CN IX is rare because it runs in close proximity to CN X. Potential causes of injury and/or dysfunction include birth trauma, ischemia, mass lesions, motor neuron disease, retropharyngeal abscess, and Guillain-Barré syndrome.

Vagus Nerve (Cranial Nerve X)

The vagus nerve has 10 terminal branches: meningeal, auricular, pharyngeal, carotid body, superior laryngeal, recurrent laryngeal, cardiac, pulmonary, esophageal, and gastrointestinal. The pharyngeal, superior laryngeal, and recurrent laryngeal branches contain motor fibers that innervate all of the muscles of the pharynx and larynx, with the exception of the stylopharyngeus (CN IX) and tensor veli palatini (CN V) muscles. Thus unilateral injury of the vagus nerve results in weakness of the ipsilateral soft palate and a hoarse voice; bilateral lesions can produce respiratory distress as a result of vocal cord paralysis, as well as nasal regurgitation of fluids, pooling of secretions, and an immobile, low-lying soft palate. Isolated lesions to the vagus nerve may be a

complication of thoracotomies or may be seen in neonates with type II Chiari malformations. If such a lesion is suspected, it is important to visualize the vocal cords. In addition to motor information, the vagus nerve carries somatic afferents from the pharynx, larynx, ear canal, external surface of the tympanic membrane, and meninges of the posterior fossa; visceral afferents; taste fibers from the posterior pharynx; and preganglionic parasympathetics.

Accessory Nerve (Cranial Nerve XI)

The accessory nerve innervates the sternocleidomastoid (SCM) and trapezius muscles. The left SCM acts to turn the head to the right side and vice versa; acting together, the SCMs flex the neck. The trapezius acts to elevate the shoulder. Lesions to the accessory nerve result in atrophy and paralysis of the ipsilateral SCM and trapezius muscles, with resultant depression of the shoulder. Because several cervical muscles are involved in head rotation, unilateral SCM paresis might not be evident unless the patient is asked to rotate the head against resistance. Skull base fractures or lesions, motor neuron disease, myotonic dystrophy, and myasthenia gravis commonly produce atrophy and weakness of these muscles; congenital torticollis is associated with SCM hypertrophy.

Hypoglossal Nerve (Cranial Nerve XII)

The hypoglossal nerve innervates the tongue. Examination of the tongue includes assessment of its bulk and strength, as well as observation for adventitious movements. Malfunction of the hypoglossal nucleus or nerve produces atrophy, weakness, and fasciculations of the tongue. If the injury is unilateral, the tongue deviates toward the side of the injury; if it is bilateral, tongue protrusion is not possible, and the patient can have difficulty swallowing (**dysphagia**). Werdnig-Hoffmann disease (infantile spinal muscular atrophy, or spinal muscular atrophy type 1) and congenital anomalies in the region of the foramen magnum are the principal causes of hypoglossal nerve dysfunction.

Motor Examination

The motor examination includes assessment of muscle bulk, tone, and strength, as well as observation for involuntary movements that might indicate central or peripheral nervous system pathology.

Bulk

Decreased muscle bulk (**atrophy**) may be secondary to disuse or to diseases of the lower motor neuron, nerve root, peripheral nerve, or muscle. In most cases, neurogenic atrophy is more severe than myogenic atrophy. Increased muscle bulk (**hypertrophy**) is usually physiologic (e.g., body builders). **Pseudohypertrophy** refers to muscle tissue that has been replaced by fat and connective tissue, giving it a bulky appearance with a paradoxical reduction in strength, as in Duchenne muscular dystrophy.

Tone

Muscle tone, which is generated by an unconscious, continuous, partial contraction of muscle, creates resistance to passive movement of a joint. Tone varies greatly based on a patient's age and state. At 28 weeks of gestation, all four extremities are extended and there is little resistance to passive movement. Flexor tone is visible in the lower extremities at 32 weeks and is palpable in the upper extremities at 36 weeks. A normal term infant's posture is characterized by flexion of all four extremities.

There are three key tests for assessing postural tone in neonates: the traction response, vertical suspension, and horizontal suspension ([Fig. 630.3](#); see Chapters 115 and 122). To evaluate the **traction response**, the physician grasps the infant's hands and gently pulls the infant to a sitting position. Normally, the infant's head lags slightly behind the infant's body and then falls forward upon reaching the sitting position. To test **vertical suspension**, the physician holds the infant by the axillae without gripping the thorax. The infant should remain suspended with the infant's lower extremities held in flexion; a hypotonic infant will slip through the physician's hands. With **horizontal suspension**, the physician holds the infant prone by placing a hand under the



Fig. 630.3 Normal tone in a full-term neonate. A, Flexed resting posture. B, Traction response. C, Vertical suspension. D, Horizontal suspension.

infant's abdomen. The head should rise and the limbs should flex, but a hypotonic infant will drape over the physician's hand, forming a U shape. Assessing tone in the extremities is accomplished by observing the infant's resting position and passively manipulating the infant's limbs. When the upper extremity of a normal term infant is pulled gently across the chest, the elbow does not quite reach the mid-sternum (**scarf sign**), whereas the elbow of a hypotonic infant extends beyond the midline with ease. Measurement of the **popliteal angle** is a useful method for documenting tone in the lower extremities. The examiner flexes the hip and extends the knee. Normal term infants allow extension of the knee to approximately 80 degrees. Similarly, tone can be evaluated by flexing the hip and knee to 90 degrees and then internally rotating the leg, in which case the heel should not pass the umbilicus.

Abnormalities of tone include spasticity, rigidity, and hypotonia. **Spasticity** is characterized by an initial resistance to passive movement, followed by a sudden release, referred to as the **clasp-knife** phenomenon. Because spasticity results from upper motor neuron dysfunction, it disproportionately affects the upper-extremity flexors and lower-extremity extensors and tends to occur in conjunction with disuse atrophy, hyperactive deep tendon reflexes, and extensor plantar reflexes (**Babinski sign**). In infants, spasticity of the lower extremities results in scissoring of the legs upon vertical suspension. Older children can present with prolonged commando crawling or toe-walking. **Rigidity**, seen with lesions of the basal ganglia, is characterized by resistance to passive movement that is equal in the flexors and extensors regardless of the velocity of movement (**lead pipe**). Patients with either spasticity or rigidity might exhibit **opisthotonos**, defined as severe hyperextension of the spine caused by hypertonia of the paraspinal muscles (**Fig. 630.4**), although similar posturing can be seen in patients with Sandifer syndrome (gastroesophageal reflux or hiatal hernia associated with torsional dystonia). **Hypotonia** refers to abnormally diminished tone and is the most common abnormality of tone in neurologically compromised neonates. A hypotonic infant is floppy and often assumes a frog-leg posture at rest. Hypotonia can reflect pathology of the cerebral hemispheres, cerebellum, spinal cord, anterior horn cell, peripheral nerve, neuromuscular junction, or muscle.

Strength

Older children are usually able to cooperate with formal strength testing, in which case muscle power is graded on a scale of 0-5 as follows: 0 = no contraction; 1 = flicker or trace of contraction; 2 = active movement with gravity eliminated; 3 = active movement against gravity; 4 = active movement against gravity and resistance; and 5 = normal power. An examination of muscle power should include all muscle groups, including the neck flexors and extensors and the muscles of respiration. It is important not only to assess individual muscle groups but also to determine the pattern of weakness (i.e., proximal vs distal; segmental vs regional). Testing for **pronator drift** can be helpful in localizing the lesion in a patient with weakness. This test is accomplished by having the patient extend his or her arms away from the body with the palms facing upward and the eyes closed. *Together, pronation and downward drift of an arm indicate a lesion of the contralateral corticospinal tract.*

Because infants and young children are not able to participate in formal strength testing, they are best assessed with functional measures. Proximal and distal strength of the upper extremities can be tested by



Fig. 630.4 Opisthotonos in a brain-injured infant.

having the child reach overhead for a toy and by watching the child manipulate small objects. In infants younger than 2 months, the physician can also take advantage of the palmar grasp reflex in assessing distal power and the Moro reflex in assessing proximal power. Infants with decreased strength in the lower extremities tend to have diminished spontaneous activity in their legs and are unable to support their body weight when held upright. Older children may have difficulty climbing or descending steps, jumping, or hopping. They might also use their hands to climb up their legs when asked to rise from a prone position, a maneuver called **Gowers sign** (**Fig. 630.5**).

Involuntary Movements

Patients with lower motor neuron or peripheral nervous system lesions might have **fasciculations**, which are small, involuntary muscle contractions that result from the spontaneous discharge of a single motor unit and create the illusion of a bag of worms under the skin. Because most infants have abundant body fat, muscle fasciculations are best observed in the tongue in this age-group.

Most other involuntary movements, including tics, dystonia, chorea, and athetosis, stem from disorders of the basal ganglia. Tremor seems to be an exception, as it is thought to be mediated by cerebellothalamic-cortical pathways. Further detail on the individual movement disorders is provided in Chapter 637.

Sensory Examination

The sensory examination is difficult to perform on an infant or uncooperative child and has a relatively low yield in terms of the information that it provides. A gross assessment of sensory function can be achieved by distracting the patient with an interesting toy and then touching the patient with a cotton swab in different locations. Normal infants and children indicate an awareness of the stimulus by crying, withdrawing the extremity, or pausing briefly; however, with repeated testing, they lose interest in the stimulus and begin to ignore the examiner. It is therefore critical that any areas of concern are tested efficiently and, if necessary, reexamined at an appropriate time.

Fortunately, isolated disorders of the sensory system are less common in the very young pediatric population than in the adult population, so



Fig. 630.5 A-D, Gowers sign in a child with hip girdle weakness because of Duchenne muscular dystrophy. When asked to rise from a prone position, the patient uses his hands to walk up his legs to compensate for proximal lower extremity weakness.

Table 630.2 Timing of Selected Primitive Reflexes			
REFLEX	ONSET	FULLY DEVELOPED	DURATION
Palmar grasp	28wk gestation	32wk gestation	2-3mo postnatal
Rooting	32wk gestation	36wk gestation	4-6mo postnatal
Moro	28-32wk gestation	37wk gestation	5-6mo postnatal
Tonic neck	35wk gestation	1mo postnatal	6-7mo postnatal
Parachute	7-8mo postnatal	10-11mo postnatal	Remains throughout life

detailed sensory testing is rarely warranted. Furthermore, most patients who are old enough to voice a sensory complaint are also old enough to cooperate with formal testing of light touch, pain, temperature, vibration, proprioception, and cortical sensation (e.g., stereognosis, two-point discrimination, extinction to double simultaneous stimulation). A notable exception is when the physician suspects a spinal cord lesion in an infant or young child and needs to identify a sensory level. In such situations, observation might suggest a difference in color, temperature, or perspiration, with the skin cool and dry below the level of injury. Lightly touching the skin above the level can evoke a squirming movement or physical withdrawal. Other signs of spinal cord injury include decreased anal sphincter tone and strength and absence of the superficial abdominal, anal wink, and cremasteric reflexes.

Reflexes

Deep Tendon Reflexes and the Plantar Response

Deep tendon reflexes are readily elicited in most infants and children. In infants, it is important to position the head in the midline when assessing reflexes, because turning the head to one side can alter reflex tone. Reflexes are graded from 0 (absent) to 4+ (markedly hyperactive), with 2+ being normal. Reflexes that are 1+ or 3+ can be normal as long as they are symmetric. Sustained clonus is always pathologic, but infants younger than 3 months old can have 5-10 beats of clonus, and older children can have 1-2 beats of clonus, provided that it is symmetric.

The ankle jerk is hardest to elicit, but it can usually be obtained by passively dorsiflexing the foot and then tapping on either the Achilles tendon or the ball of the foot. The knee jerk is evoked by tapping the patellar tendon. If this reflex is exaggerated, extension of the knee may be accompanied by contraction of the contralateral adductors (**crossed**

adductor response). Hypoactive reflexes generally reflect lower motor neuron or cerebellar dysfunction, whereas hyperactive reflexes are consistent with upper motor neuron disease, although acute upper motor neuron injury can result in hypoactive or absent deep tendon reflexes. The plantar response is obtained by stimulation of the lateral aspect of the sole of the foot, beginning at the heel and extending to the base of the toes. The **Babinski sign**, indicating an upper motor neuron lesion, is characterized by extension of the great toe and fanning of the remaining toes. Too vigorous stimulation may produce withdrawal, which may be misinterpreted as a Babinski sign. Plantar responses have limited diagnostic utility in neonates because they are mediated by several competing reflexes and can be either flexor or extensor, depending on how the foot is positioned. Asymmetry of the reflexes or plantar response is a useful lateralizing sign in infants and children.

Primitive Reflexes

Primitive reflexes appear and disappear at specific times during development (Table 630.2), and their absence or persistence beyond those times signifies CNS dysfunction. Although many primitive reflexes have been described, the Moro, grasp, tonic neck, and parachute reflexes are the most clinically relevant. The **Moro reflex** is elicited by supporting the infant in a semierect position and then allowing the infant's head to fall backward onto the examiner's hand. A normal response consists of symmetric extension and abduction of the fingers and upper extremities, followed by flexion of the upper extremities and an audible cry. An asymmetric response can signify a fractured clavicle, brachial plexus injury, or hemiparesis. Absence of the Moro reflex in a term newborn is ominous, suggesting significant dysfunction of the CNS. The **grasp response** is elicited by placing a finger in the open palm of each hand; by 37 weeks of gestation, the reflex is strong enough that the examiner

can lift the infant from the bed with gentle traction. The **tonic neck reflex** is produced by manually rotating the infant's head to one side and observing for the characteristic fencing posture (extension of the arm on the side to which the face is rotated and flexion of the contralateral arm). An obligatory tonic neck response, in which the infant becomes stuck in the fencing posture, is always abnormal and implies a CNS disorder. The **parachute reflex**, which occurs in slightly older infants, can be evoked by holding the infant's trunk and then suddenly lowering the infant as if he or she were falling. The arms will spontaneously extend to break the infant's fall, making this reflex a prerequisite to walking (Fig. 630.6).

Coordination

Ataxia refers to a disturbance in the smooth performance of voluntary motor acts and is usually the result of cerebellar dysfunction. Lesions to the cerebellar vermis result in unsteadiness while sitting or standing (**truncal ataxia**). Affected patients might have a wide-based gait or may be unable to perform tandem gait testing. Lesions of the cerebellar hemispheres cause appendicular ataxia, which may be apparent as the patient reaches for objects and performs finger-to-nose and heel-to-shin movements. Other features of cerebellar dysfunction include errors in judging distance (**dysmetria**), inability to inhibit a muscular action (**rebound**), impaired performance of rapid alternating movements (**dysdiadochokinesia**), intention tremor, nystagmus, scanning dysarthria, hypotonia, and decreased deep tendon reflexes. Acute ataxia suggests an infectious or postinfectious, endocrinologic, toxic, traumatic, vascular, or psychogenic process, and chronic symptoms suggest a metabolic, neoplastic, or degenerative process.

Station and Gait

Observation of a child's station and gait is an important aspect of the neurologic examination. Normal children can stand with their feet close together without swaying; however, children who are unsteady may sway or even fall. On gait testing, the heels should strike either side of an imaginary line, but children with poor balance tend to walk with their legs farther apart to create a more stable base. Tandem gait testing forces patients to have a narrow base, which highlights subtle balance difficulties.

There are a variety of abnormal gaits, many of which are associated with a specific underlying etiology. Patients with a **spastic gait** appear stiff-legged like a soldier. They may walk on tiptoe as a result of tightness or contractures of the Achilles tendons, and their legs may scissor as they walk. A **hemiparetic gait** is associated with spasticity and circumduction of the leg, as well as decreased arm swing on the affected side. **Cerebellar ataxia** results in a wide-based, reeling gait like that of a drunk person, whereas **sensory ataxia** results in a wide-based **step-page gait**, in which the patient lifts the legs up higher than usual in the

swing phase and then slaps the foot down. A **myopathic**, or waddling, **gait** is associated with hip girdle weakness. Affected children often develop a compensatory lordosis and have other signs of proximal muscle weakness, such as difficulty climbing stairs. During gait testing, the examiner might also note hypotonia or weakness of the lower extremities; extrapyramidal movements, such as dystonia or chorea; or orthopedic deformities, such as pelvic tilt, genu recurvatum, varus or valgus deformities of the knee, pes cavus (high arches) or pes planus (flat feet), and scoliosis.

GENERAL EXAMINATION

Examination of other organ systems is essential because myriad systemic diseases affect the nervous system. Dysmorphic features can indicate a genetic syndrome (see Chapter 95). Heart murmurs may be associated with rheumatic fever (Sydenham chorea), cardiac rhabdomyoma (tuberous sclerosis), cyanotic heart disease (cerebral abscess or thrombosis), and endocarditis (cerebral vascular occlusion). Hepatosplenomegaly can suggest an inborn error of metabolism, storage disease, HIV infection, or malignancy. Cutaneous lesions may be a feature of a neurocutaneous syndrome (see Chapter 636).

SPECIAL DIAGNOSTIC PROCEDURES

Lumbar Puncture and Cerebrospinal Fluid Examination

Examination of the cerebrospinal fluid (CSF) and measurement of the pressure it creates in the subarachnoid space is essential in confirming the diagnosis of meningitis, encephalitis (autoimmune, infectious), and idiopathic intracranial hypertension (previously referred to as *pseudotumor cerebri*), and it is often helpful in assessing subarachnoid hemorrhage; demyelinating, degenerative, and collagen vascular diseases; and intracranial neoplasms. Having an experienced assistant who can position, restrain, and comfort the patient is critical to the success of the procedure.

The patient should be situated in a lateral decubitus or seated position with the neck and legs flexed to enlarge the intervertebral spaces. As a rule, sick neonates should be maintained in a seated position to prevent problems with ventilation and perfusion. Regardless of the position chosen, it is important to make sure that the patient's shoulders and hips are straight to prevent rotating the spine.

Once the patient is situated, the physician identifies the appropriate interspace by drawing an imaginary line from the iliac crest downward perpendicular to the vertebral column. In adults, lumbar punctures are usually performed in the L3-L4 or L4-L5 interspaces. Next, the physician dons a mask, gown, and sterile gloves. The skin is thoroughly prepared with a cleansing agent, and sterile drapes are applied. The skin and underlying tissues are anesthetized by injecting a local anesthetic (e.g., 1% lidocaine) at the time of the procedure or by applying a eutectic mixture of lidocaine and prilocaine (EMLA) to the skin 30 minutes before the procedure. A 22-gauge, 1.5- to 3.0-inch, sharp, beveled spinal needle with a properly fitting stylet is introduced in the midsagittal plane and directed slightly cephalad. The physician should pause frequently, remove the stylet, and assess for CSF flow. Although a pop can occur as the needle penetrates the dura, it is more common to experience a subtle change in resistance.

Once CSF has been detected, a manometer and three-way stopcock can be attached to the spinal needle to obtain an opening pressure. If the patient was seated as the spinal needle was introduced, the patient should be moved carefully to a **lateral decubitus position** with the head and legs extended before the manometer is attached. In children between 1 and 18 years of age, the reference range parameter for abnormally elevated opening pressure, determined as the 90th percentile for all patients in the reference population, is 28 cm of water. The threshold for an abnormally reduced pressure in the 10th percentile is 11.5 cm of water. The most common cause of an elevated opening pressure is an agitated patient. Sedation and a high body mass index can also increase the opening pressure (see Chapter 645).

Contraindications to performing a lumbar puncture include suspected mass lesion of the brain, especially in the posterior fossa or

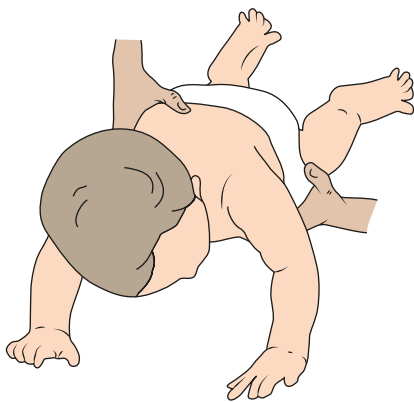


Fig. 630.6 Infant in the parachute reflex position. This primitive reflex develops later in infancy (around 6 mo), and its absence can signal delayed walking. It is elicited by holding the infant face down and rapidly lowering the infant, causing the infant to extend out the arms.

above the tentorium and causing shift of the midline; suspected mass lesion of the spinal cord; symptoms and signs of impending cerebral herniation in a child with probable meningitis; critical illness (on rare occasions); skin infection at the site of the lumbar puncture; and thrombocytopenia with a platelet count of $<20 \times 10^9/L$. If optic disc edema or focal findings suggest a mass lesion, a rapid CT scan of the head should be obtained before proceeding with lumbar puncture to prevent uncal or cerebellar herniation as the CSF is removed. In the absence of these findings, routine head imaging is not warranted. The physician should also be alert to clinical signs of impending herniation, including alterations in the respiratory pattern (e.g., hyperventilation, Cheyne-Stokes respirations, ataxic respirations, respiratory arrest), abnormalities of pupil size and reactivity, loss of brainstem reflexes, and decorticate or decerebrate posturing. If any of these signs are present or the child is so ill that the lumbar puncture might induce cardiorespiratory arrest, blood cultures should be drawn and supportive care, including antibiotics, should be initiated. Once the patient has stabilized, it may be possible to perform a lumbar puncture safely.

Normal CSF contains up to $5/mm^3$ white blood cells, and a newborn can have as many as $15/mm^3$. Polymorphonuclear cells are always abnormal in a child, but $1\text{--}2/mm^3$ may be present in a normal neonate. An elevated polymorphonuclear count suggests bacterial meningitis or the early phase of aseptic meningitis (see Chapter 643). CSF lymphocytosis can be seen in aseptic, tuberculous, or fungal meningitis; demyelinating diseases; brain or spinal cord tumor; immunologic disorders, including collagen vascular diseases; and chemical irritation (after myelogram, intrathecal methotrexate).

Normal CSF contains no red blood cells; thus their presence indicates a traumatic tap or a subarachnoid hemorrhage. Progressive clearing of the blood between the first and last samples indicates a traumatic tap. Bloody CSF should be centrifuged immediately. A clear supernatant is consistent with a bloody tap, whereas **xanthochromia** (yellow color that results from the degradation of hemoglobin) suggests a subarachnoid hemorrhage. Xanthochromia may be absent in bleeds <12 hours old, particularly when laboratories rely on visual inspection rather than spectroscopy. Xanthochromia can also occur in the setting of hyperbilirubinemia, carotenemia, and markedly elevated CSF protein.

The normal CSF protein is $10\text{--}40$ mg/dL in a child and as high as 120 mg/dL in a neonate. The CSF protein falls to the normal childhood range by 3 months of age. The CSF protein may be elevated in many processes, including infectious, immunologic, vascular, and degenerative diseases; blockage of CSF flow; as well as tumors of the brain (primary CNS tumors, systemic tumors metastatic to the CNS, infiltrative acute lymphoblastic leukemia) and spinal cord. With a traumatic tap, the CSF protein is increased by approximately 1 mg/dL for every $1,000$ red blood cells/ mm^3 . Elevation of CSF immunoglobulin G, which normally represents approximately 10% of the total protein, is observed in subacute sclerosing panencephalitis, in postinfectious encephalomyelitis, and in some cases of multiple sclerosis. If the diagnosis of multiple sclerosis is suspected, the CSF should be tested for the presence of oligoclonal bands.

The CSF glucose content is approximately 60% of the blood glucose in a healthy child. To prevent a spuriously elevated blood:CSF glucose ratio in a case of suspected meningitis, it is advisable to collect the blood glucose before the lumbar puncture when the child is relatively calm. Hypoglycorrhachia is found in association with diffuse meningeal disease, particularly bacterial and tubercular meningitis. Widespread neoplastic involvement of the meninges, subarachnoid hemorrhage, disorders involving the glucose transporter protein type 1 (e.g., GLUT1 deficiency), fungal meningitis, and, occasionally, aseptic meningitis can produce low CSF glucose as well.

A Gram stain of the CSF is essential if there is a suspicion for bacterial meningitis; an acid-fast stain and India ink preparation can be used to assess for tuberculous and fungal meningitis, respectively. CSF is then plated on different culture media depending on the suspected pathogen. When indicated by the clinical presentation, it can also be helpful to assess for the presence of specific antigens or

polymerase chain reaction studies (e.g., *Neisseria meningitidis*, *Haemophilus influenzae* type b, or *Streptococcus pneumoniae*) or to obtain antibody or polymerase chain reaction studies (e.g., herpes simplex virus 1 and 2, West Nile virus, Zika, enteroviruses). In noninfectious cases, levels of CSF metabolites, such as lactate, amino acids, and autoimmune encephalitis panel, can provide clues to the underlying metabolic disease.

Neuroradiologic Procedures

Skull x-rays have limited diagnostic utility. They can demonstrate fractures, bony defects, intracranial calcifications, or indirect evidence of increased ICP. Acutely increased ICP causes separation of the sutures, whereas chronically increased ICP is associated with erosion of the posterior clinoid processes, enlargement of the sella turcica, and increased convolutional markings.

Cranial ultrasonography is the imaging method of choice for detecting intracranial hemorrhage, periventricular leukomalacia, and hydrocephalus in infants younger than 6 months with patent anterior fontanels. Ultrasound is less sensitive than either cranial CT scanning or MRI for detecting hypoxic-ischemic injury, but the use of color Doppler or power Doppler sonography, both of which show changes in regional cerebral blood flow velocity, improve its sensitivity. In general, ultrasound is not a useful technique in older children, although it can be helpful intraoperatively when placing shunts, locating small tumors, and performing needle biopsies.

Cranial CT is a valuable diagnostic tool in the evaluation of many neurologic emergencies and in some nonemergent conditions. It is a noninvasive, rapid procedure that can usually be performed without sedation. CT scans use conventional x-ray techniques, meaning that they produce ionizing radiation. Because children younger than 10 years of age are several times more sensitive to radiation than adults, it is important to consider whether imaging is actually indicated and, if it is, whether an ultrasound or MRI might be the more appropriate study. In the emergency setting, a noncontrast CT scan can demonstrate skull fractures, pneumocephalus, intracranial hemorrhages, hydrocephalus, and impending herniation. If the noncontrast scan reveals an abnormality and an MRI cannot be performed in a timely fashion, nonionic contrast should be used to highlight areas of breakdown in the blood-brain barrier (e.g., abscesses, tumors) and/or collections of abnormal blood vessels (e.g., arteriovenous malformations). CT is less useful for diagnosing acute infarcts in children because radiographic changes might not be apparent for up to 24 hours. Some subtle signs of early (<24 hours) infarction include sulcal effacement, blurring of the gray-white junction, and the hyperdense middle cerebral artery sign (increased attenuation in the middle cerebral artery that is often associated with thrombosis). In the routine setting, CT imaging can be used to demonstrate intracranial calcifications or, with the addition of three-dimensional reformatting, to evaluate patients with craniofacial abnormalities or craniosynostosis. Although other pathologic processes may be visible on CT scan, *MR is generally preferred because it provides a more detailed view of the anatomy without exposing the patient to ionizing radiation* (Table 630.3).

Cranial CT angiography is a useful tool for visualizing vascular structures and is accomplished by administering a tight bolus of iodinated contrast through a large-bore intravenous catheter and then acquiring CT images as the contrast passes through the arteries.

Brain MRI is a noninvasive procedure that is well suited for detecting a variety of abnormalities, including those of the posterior fossa and spinal cord. MR scans are highly susceptible to patient motion artifact; consequently, many children younger than age 8 years require sedation to ensure an adequate study. The need for sedation has decreased in some centers as MRI technology improves and allows for faster performance of studies and as visual distraction techniques are better designed to be used by a child while in the MRI scanner. Because the American Academy of Pediatrics recommends that infants be kept nothing by mouth (NPO) for 4 hours or longer and older children for 6 hours or longer before deep sedation, it is often difficult to obtain an MRI on an infant or young child in the acute

Table 630.3 Preferred Imaging Procedures in Neurologic Diseases

ISCHEMIC INFARCTION OR TRANSIENT ISCHEMIC ATTACK CT/CTA (head and neck) ± CT perfusion for patients who are unstable or are potential candidates for tissue plasminogen activator or other acute interventions Otherwise, MRI/MRA (head and neck) with and without gadolinium and with diffusion-weighted images If the examination findings localize to the anterior circulation, carotid ultrasound should be performed rather than neck CTA or MRA Obtain an MRV if the infarct does not follow an arterial distribution CT or MRI can detect infarcts more than 24 hours old, although MRI is generally preferred to avoid exposure to ionizing radiation INTRAPARENCHYMAL HEMORRHAGE CT if <24 hr; MRI if >24 hr MRI and MRA to assess for underlying vascular malformation, tumor, and so on Catheter angiography if MRA is nondiagnostic ARTERIOVENOUS MALFORMATION CT for acute hemorrhage; MRI and MRA with and without gadolinium as early as possible Catheter angiography if noninvasive imaging is nondiagnostic CEREBRAL ANEURYSM CT without contrast for acute subarachnoid hemorrhage MRA or CTA to identify the aneurysm Catheter angiography may be necessary in some cases TCD to detect vasospasm HYPOXIC-ISCHEMIC BRAIN INJURY Ultrasound in infants If ultrasound is negative or there is a discrepancy between the clinical course and the sonogram, obtain an MRI In older children, CT if unstable; otherwise, MRI MRS can show a lactate peak even in the absence of structural abnormalities and can be useful for prognostication purposes METABOLIC DISORDERS MRI, particularly T2-weighted and FLAIR images Diffusion-weighted images may be useful in distinguishing acute and chronic changes MRS, SPECT, and PET may be useful in certain disorders HYDROCEPHALUS Ultrasound (in infants), CT with and without contrast, or MR with and without gadolinium for diagnosis of communicating hydrocephalus MR with and without gadolinium for diagnosis of noncommunicating hydrocephalus Ultrasound (in infants) or CT to follow ventricular size in response to treatment	HEADACHE CT with and without contrast or MRI with and without gadolinium if a structural disorder is suspected (MRI is preferred in nonemergent situations because it does not involve ionizing radiation and provides a better view of the parenchyma) HEAD TRAUMA CT without contrast initially MRI after initial assessment and treatment if clinically indicated; diffusion tensor imaging and/or diffusion kurtosis sequences may be useful to detect subtle white matter abnormalities EPILEPSY MRI with and without gadolinium; thin slices through the mesial temporal lobes may be helpful if a temporal focus is suspected PET Interictal SPECT BRAIN TUMOR MRI with and without gadolinium MRS PET MULTIPLE SCLEROSIS MRI with and without gadolinium Obtain sagittal FLAIR images MENINGITIS OR ENCEPHALITIS CT without and with contrast before lumbar puncture if there are signs of increased ICP on examination MRI with and without gadolinium after initial assessment and treatment for patients with complicated meningitis or encephalitis BRAIN ABSCESS MRI with and without gadolinium Diffusion-weighted images and MRS can help to differentiate abscess from necrotic tumor If the patient is unstable, CT with and without contrast followed by MRI with and without contrast when feasible MOVEMENT DISORDERS MRI with and without gadolinium PET DaTscan (SPECT scan using ioflupane iodine-123 as the contrast agent for detecting dopamine transporters in suspected parkinsonian syndromes)
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CTA, computed tomographic angiography; FLAIR, fluid-attenuated inversion recovery; ICP, intracranial pressure; MRA, magnetic resonance angiography; MRS, magnetic resonance spectroscopy; MRV, magnetic resonance venography; PET, positron emission tomography; SPECT, single-photon emission computed tomography; TCD, transcranial Doppler ultrasonography.

setting. MRI can be used to evaluate for congenital or acquired brain lesions, migrational defects, dysmyelination or demyelination, post-traumatic gliosis, neoplasms, cerebral edema, and acute stroke (see Table 630.3). Paramagnetic MR contrast agents (e.g., gadolinium-diethylenetriaminepentaacetic acid [DTPA]) are efficacious in identifying areas of disruption in the blood-brain barrier, such as those occurring in primary and metastatic brain tumors, meningitis, cerebritis, abscesses, and active demyelination. **MR angiography** and **MR venography** provide detailed images of major intracranial vasculature structures and assist in the diagnosis of conditions such as stroke, vascular malformations, and cerebral venous sinus thrombosis. MR angiography is the procedure of choice for infants and young children because of the lack of ionizing radiation and contrast; however, CT angiography may be preferable in older children because it is faster and can eliminate the need for sedation; it is particularly useful for looking at blood vessels in the neck, where there is less interference from bone artifact than in the skull-encased brain.

Functional MRI is a noninvasive technique used to map neuronal activity during specific cognitive states and/or sensorimotor functions. Data are usually based on blood oxygenation, although they can also be based on local cerebral blood volume or flow. Functional MRI is useful for presurgical localization of critical brain functions and has several advantages over other functional imaging techniques. Specifically, functional MRI produces high-resolution images without exposure to ionizing radiation or contrast, and it allows coregistration of functional and structural images.

Proton MR spectroscopy (MRS) is a molecular imaging technique in which the unique neurochemical profile of a preselected brain region is displayed in the form of a spectrum. Many metabolites can be detected, the most common of which are *N*-acetylaspartate, creatine and phosphocreatine, choline, myoinositol, and lactate. Changes in the spectral pattern of a given area can yield clues to the underlying pathology, making MRS useful in the diagnosis of inborn errors of metabolism, as well as the preoperative and posttherapeutic

assessment of intracranial tumors. MRS can also detect areas of cortical dysplasia in patients with epilepsy because these patients have low *N*-acetylaspartate:creatine ratios. Finally, MRS may be useful in detecting hypoxic-ischemic injury in newborns in the first day of life because the lactate peak enlarges and the *N*-acetylaspartate peak diminishes before MRI sequences become abnormal.

Catheter angiography is the gold standard for diagnosing vascular disorders of the CNS, such as arteriovenous malformations, aneurysms, arterial occlusions, and vasculitis. A four-vessel study is accomplished by introducing a catheter into the femoral artery and then injecting contrast media into each of the internal carotid and vertebral arteries. Because catheter angiography is invasive and requires general anesthesia, it is typically reserved for treatment planning of endovascular or open procedures and for cases in which noninvasive imaging results are not diagnostic.

Positron emission tomography (PET) provides unique information on brain metabolism and perfusion by measuring blood flow, oxygen uptake, and/or glucose consumption. PET is an expensive technique that is most often used in the context of epilepsy surgery programs. **Single-photon emission CT** using ^{99m}Tc hexamethylpropyleneamine oxime is a sensitive and inexpensive technique to study regional cerebral blood flow. Single-photon emission CT is particularly useful in assessing for vasculitis, herpes encephalitis, dysplastic cortex, and recurrent brain tumors. PET-MRI is only available in a few pediatric centers in the United States; it provides better resolution and tissue definition than single-photon emission CT. This emerging clinical modality is of particular use in epilepsy surgery evaluation and neuro-oncology.

Electroencephalography

An electroencephalogram (EEG) provides a continuous recording of electrical activity between reference electrodes placed on the scalp. Although the genesis of the electrical activity is not certain, it likely originates from postsynaptic potentials in the dendrites of cortical neurons. Even with amplification of the electrical activity, not all potentials are recorded because there is a buffering effect of the scalp, muscles, bone, vessels, and subarachnoid fluid. EEG waves are classified according to their frequency as delta (1-3 Hz), theta (4-7 Hz), alpha (8-12 Hz), and beta (13-20 Hz). These waves are altered by many factors, including age, level of alertness, eye closure, drugs, and disease states.

The normal waking EEG is characterized by the posterior dominant rhythm—a sinusoidal, 8- to 12-Hz rhythm that is most prominent over the occipital region in a state of relaxed wakefulness with the eyes closed. This rhythm first becomes apparent at 3-4 months of age, and most children have achieved the adult frequency of 8-12 Hz by age 8 years.

Normal sleep is divided into three stages of non-rapid eye movement sleep—designated N1, N2, and N3—and rapid eye movement sleep. N1 corresponds to drowsiness, and N3 represents deep, restorative, slow-wave sleep. Rapid eye movement sleep is rarely captured during a routine EEG but may be seen on an overnight recording. The American Electroencephalography Society Guideline and Technical Standards states that “sleep recordings should be obtained whenever possible”; however, it appears that sleep deprivation—not sleep during the EEG—is what increases the yield of the study, particularly in children with one or more clinically diagnosed seizures and in children older than 3 years of age.

EEG abnormalities can be divided into two general categories: epileptiform discharges and slowing. Epileptiform discharges are paroxysmal spikes or sharp waves, often followed by slow waves, which interrupt the background activity. They may be focal, multifocal, or generalized. Focal discharges are often associated with cerebral dysgenesis or irritative lesions, such as cysts, slow-growing tumors, or glial scar tissue; generalized discharges typically occur in children with structurally normal brains. Generalized discharges can occur as an

epilepsy trait in children who have never had a seizure and, by themselves, are not an indication for treatment. Epileptiform activity may be enhanced by activation procedures, including hyperventilation and photic stimulation.

As with epileptiform discharges, slowing can be either focal or diffuse. Focal slowing should raise a concern for an underlying functional or structural abnormality, such as an infarct, hematoma, or tumor. Diffuse slowing is the hallmark of encephalopathy and is usually secondary to a widespread disease process or toxic-metabolic insult.

Long-term video EEG monitoring provides a precise characterization of seizure types, which allows specific medical or surgical management. It facilitates more accurate differentiation of epileptic seizures from paroxysmal events that mimic epilepsy, including recurrent psychogenic seizure-like attacks. Long-term EEG monitoring can also be useful during medication adjustments.

Evoked Potentials

An evoked potential is an electrical signal recorded from the CNS after the presentation of a specific visual, auditory, or sensory stimulus. Stimulation of the visual system by a flash or patterned stimulus, such as a black-and-white checkerboard, produces **visual evoked potentials (VEPs)**, which are recorded over the occiput and averaged in a computer. Abnormal VEPs can result from lesions to the visual pathway anywhere from the retina to the visual cortex. Many demyelinating disorders and neurodegenerative diseases, such as Tay-Sachs, Krabbe, or Pelizaeus-Merzbacher disease, or neuronal ceroid lipofuscinoses show characteristic VEP abnormalities. Flash VEPs can also be helpful in evaluating infants who have sustained an anoxic injury; however, detection of an evoked potential does not necessarily mean that the infant will have functional vision.

Brainstem auditory evoked responses (BAERs) provide an objective measure of hearing and are particularly useful in neonates and in children who have failed, or are uncooperative with, audiometric testing. BAERs are abnormal in many neurodegenerative diseases of childhood and are an important tool in evaluating patients with suspected tumors of the cerebellopontine angle. BAERs can be helpful in assessing brainstem function in comatose patients because the waveforms are unaffected by drugs or by the level of consciousness; however, they are not accurate in predicting neurologic recovery and outcome.

Somatosensory evoked potentials (SSEPs) are obtained by stimulating a peripheral nerve (peroneal, median) and then recording the electrical response over the cervical region and contralateral parietal somatosensory cortex. SSEPs determine the functional integrity of the dorsal column-medial lemniscal system and are useful in monitoring spinal cord function during operative procedures for scoliosis, aortic coarctation, and myelomeningocele repair. SSEPs are abnormal in many neurodegenerative disorders and are the most accurate evoked potential in the assessment of neurologic outcome after a severe CNS insult.

Specific and General Genetic and Metabolic Testing

Children with intellectual disability or developmental delay are often evaluated with metabolic and/or genetic testing. Newborn screening study results should be rechecked before new studies are done. Specific accompanying features of the child's history and physical examination may point to a particular disorder or group of disorders, allowing for specific genetic or metabolic testing or for chromosomal studies to be fruitful. Whole exome sequencing is often used in situations in which these studies are negative or there are no distinguishing features of the child's history or physical examination that point to a particular subgroup of diagnoses.

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Chapter 631

Congenital Anomalies of the Central Nervous System

Sara K. Trowbridge, Edward Yang, and Christopher J. Yuskaitis

631.1 Neural Tube Defects

Sara K. Trowbridge, Edward Yang, and Christopher J. Yuskaitis

Neural tube defects (NTDs) account for the largest proportion of congenital anomalies of the CNS and result from failure of the neural tube to close properly during development. The etiology of NTDs appears to be multifactorial and remains incompletely understood. There is evidence for various environmental risk factors, including hyperthermia, teratogens (e.g., valproic acid, dolutegravir), maternal malnutrition, suboptimal folate levels, and maternal obesity or diabetes. Genetic determinants also play a role; studies have revealed relatively few monogenic causes and suggest a polygenic mode of inheritance. Genes associated with NTDs are also linked to known environmental risk factors (maternal obesity/diabetes and folate metabolism). NTDs vary widely in type and severity, depending on when and how the developmental process is disrupted.

The human nervous system originates from the primitive ectoderm, which, along with the endoderm and mesoderm, form the three primary germ layers (Fig. 631.1). During primary neurulation (3–4 weeks postgestation), the dorsal neural ectoderm differentiates into the neural plate. The neural plate then begins to invaginate as the edges fold upward, forming the neural tube, the structure that will ultimately give rise to the brain and spinal cord. Initial closure of the neural tube is accomplished in the area corresponding to the future junction of the spinal cord and medulla and moves rapidly both caudally and rostrally. As the neural tube is closing, a conglomerate of cells from the dorsal tube differentiates into the neural crest, which forms the peripheral nervous system, leptomeninges, and Schwann cells. The surrounding mesoderm gives rise to the dura and vertebrae. Defects in primary neurulation lead to open NTDs, in which neural tissue is exposed. Failure of the neural tube to close allows excretion of fetal substances (e.g., α -fetoprotein [AFP], acetylcholinesterase) into the amniotic fluid. *Fetal ultrasonography has a higher sensitivity to detect NTDs and has largely replaced prenatal screening of maternal serum for AFP in the 16th to 18th wk of gestation; both can be used to identify pregnancies at risk for fetuses with NTDs in utero.* The type of open NTD depends on the location of the defect. Anterior NTDs affect the brain (anencephaly, encephalocele), whereas posterior lesions affect the spinal cord (myelomeningocele).

Secondary neurulation occurs after completion of primary neurulation during weeks 5–6 of gestation and refers to the formation of the caudal neural tube. Defects in secondary neurulation are thought to underlie closed NTDs (occult spinal dysraphism), in which the neural tissue is covered by skin and not exposed. Relative to the severity of open NTDs, closed NTDs usually present with relatively mild, if any, neurologic deficits.

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631.2 Myelomeningocele

Sara K. Trowbridge, Edward Yang, and Christopher J. Yuskaitis

Myelomeningocele is the most common NTD and results from incomplete closure of the posterior neural tube, leading to protrusion of neural tissue through a defect in the vertebra. This is also known as an *open* NTD because the neural tissue is exposed to the environment.

ETIOLOGY

The etiology of myelomeningocele remains incompletely understood, but as with all neural tube closure defects, a genetic predisposition exists. The risk of recurrence after one affected child is 3–4% and increases to 10% with two prior affected children. Both epidemiologic evidence and the familial aggregation studies indicate polygenic risk factors contribute to the etiology of NTDs.

Nutritional and environmental factors have a role in the etiology of myelomeningocele as well. In particular, folate is intricately involved in the prevention and etiology of NTDs. Folate coenzymes are involved in DNA synthesis, purine synthesis, and amino acid interconversion—specifically, the conversion of homocysteine to methionine. Pathogenic variants in the genes encoding the enzymes involved in homocysteine metabolism may play a role in the pathogenesis of meningomyelocele. These enzymes include 5,10-methylenetetrahydrofolate reductase (encoded by *MTHFR*), cystathionine β -synthase, and methionine synthase. An association between a thermolabile variant of *MTHFR* and mothers of children with NTDs might account for up to 15% of preventable NTDs.

PREVENTION

See also Chapter 67.6.

Maternal periconceptional use of folic acid supplementation reduces the incidence of NTDs in pregnancies at risk by at least 50%. The US Public Health Service recommends that all women of childbearing age who can become pregnant take 0.4–0.8 mg of folic acid daily. To be effective, folic acid supplementation should be initiated before conception and continued until at least the 12th week of gestation, when neurulation is complete. If a pregnancy is planned in high-risk women (previously affected child), supplementation should be started with 4 mg of folic acid daily, beginning 1 month before the time of the planned conception.

The modern diet provides about half the daily requirement of folic acid. To increase folic acid intake, fortification of flour, pasta, rice, and cornmeal with 0.15 mg folic acid per 100 g was mandated in the United States and Canada in 1998. Although this decreased the incidence of NTDs, the added folic acid is insufficient to maximize the prevention of preventable NTDs, and it is believed that many women may still have suboptimal folate levels, estimated as a red blood cell folate level less than 900–1,000 nmol/L. Therefore informative educational programs and folic acid vitamin supplementation remain essential for women planning a pregnancy and possibly for all women of childbearing age. In addition, certain drugs, including drugs that antagonize folic acid, such as trimethoprim and some anticonvulsants (valproic acid, carbamazepine, phenytoin, phenobarbital, and primidone), increase the risk of myelomeningocele. The anticonvulsant valproic acid causes NTDs in approximately 1–2% of pregnancies when administered during pregnancy, prompting some epilepsy clinicians to recommend that all female patients of childbearing potential who take anticonvulsant medications also receive folic acid supplements.

Diagnosis is usually made prenatally by fetal ultrasonography (see Chapter 117.7). Measurement of maternal serum AFP is an alternative screening test, although it has been shown to have a lower sensitivity than second-trimester ultrasonography. Early diagnosis allows time for prenatal counseling, further testing, and early treatment options, including fetal surgery. When a prenatal diagnosis is made, it is helpful to look for other associated anomalies. Genetic testing, particularly

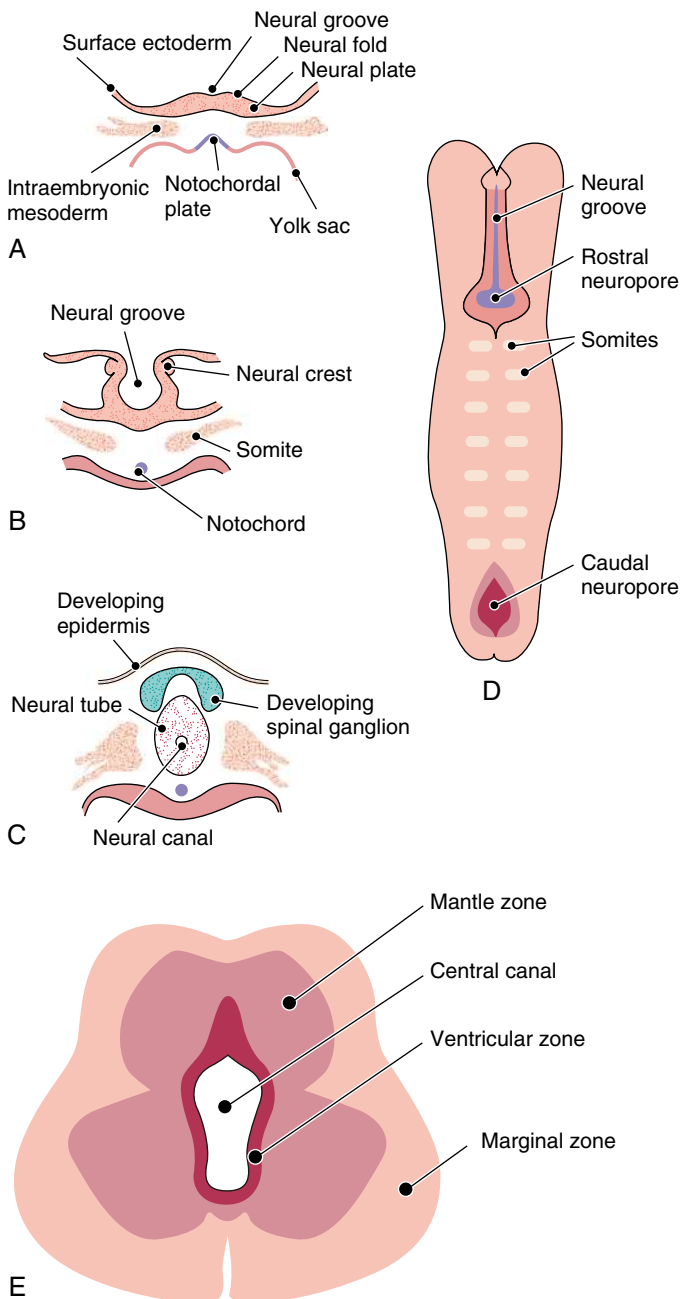


Fig. 631.1 Diagrammatic illustration of the developing nervous system. **A**, Transverse sections of the neural plate during the third wk. **B**, Formation of the neural groove and the neural crest. **C**, The neural tube is developed. **D**, Longitudinal drawing showing the initial closure of the neural tube in the central region. **E**, Cross-sectional drawing of the embryonic neural tube (primitive spinal cord).

chromosomal microarray, can be considered because chromosomal abnormalities are found at higher rates in fetuses with NTDs, particularly in the setting of other associated anomalies. Current cell-free fetal DNA prenatal tests only detect trisomies and sex aneuploidies as screening tests and are not diagnostic and do not detect NTDs.

CLINICAL MANIFESTATIONS

Neurologic deficits are hypothesized to be caused in part by neurodegeneration of the exposed area of the spinal cord secondary to contact with amniotic fluid in utero. The extent and degree of the neurologic deficit depend largely on the location of the myelomeningocele and any associated intracranial abnormalities.

Although a myelomeningocele may be located anywhere along the neuraxis, the lumbosacral region accounts for ~75% of the cases. The majority of patients with myelomeningocele have bowel and bladder incontinence. Ambulation and motor control over the lower extremities depend greatly on the level of the lesion. Generally, patients with a lesion in the low sacral region are ambulatory, in contrast to patients with lesions above L2, who are usually nonambulatory; those with intermediate lesions may walk with assistive devices (crutches, braces). Cervical myelomeningoceles are rare and differ in their anatomy from other myelomeningoceles because the spinal cord structure is usually close to normal and the neural tissue itself is covered by skin (i.e., a closed NTD). Therefore patients with these lesions generally have a more favorable prognosis, although they can have bowel/bladder dysfunction.

On exam, the myelomeningocele is generally readily apparent as a saclike cystic structure covered by a thin layer of partially epithelialized tissue or an exposed flat neural placode without overlying tissues (Fig. 631.2C). When a cyst or membrane is present, remnants of neural tissue are visible beneath the membrane, which occasionally ruptures and leaks CSF.

Examination of the infant generally shows a flaccid paralysis of the lower extremities, an absence of deep tendon reflexes, a lack of response to touch and pain, and a high incidence of lower-extremity deformities (clubfeet, ankle and/or knee contractures, and subluxation of the hips). Some children have constant urinary dribbling and a relaxed anal sphincter. Other children do not leak urine and in fact have a high-pressure bladder and sphincter dyssynergy. Myelomeningocele above the midlumbar region tends to produce lower motor neuron signs because of abnormalities and disruption of the conus medullaris and higher spinal cord structures.

Most children with a myelomeningocele also have displacement of the cerebellum and brainstem down through the foramen magnum, which is termed a **Chiari II malformation** (see Fig. 631.2A). Because this malformation can lead to obstruction of CSF outflow, hydrocephalus is a common complication, particularly if surgical repair is not pursued early. Therefore there should be a low threshold for consideration of hydrocephalus, which can present with classic signs of increased intracranial pressure (ICP), including a bulging anterior fontanel, dilated scalp veins, setting-sun appearance of the eyes, irritability, and vomiting in association with an increased head circumference. Older children may also have headache, emesis, and lethargy. Additionally, approximately 15% of infants with hydrocephalus and Chiari II malformation develop symptoms of hindbrain (brainstem) dysfunction, including difficulty feeding, choking, stridor, apnea, vocal cord paralysis, pooling of secretions, and spasticity of the upper extremities, which, if untreated, can lead to death. This **Chiari crisis** is caused by downward herniation of the medulla and cerebellar tonsils through the foramen magnum, as well as endogenous malformations in the cerebellum and brainstem.

Other CNS anomalies are associated with myelomeningocele, including cortical dysplasias, polymicrogyria, callosal abnormalities, and cerebellar abnormalities. Long-term complications include tethered cord, usually secondary to scar tissue at the surgical repair site, and hydromyelia, which is CSF buildup in the central canal of the spinal cord caused by worsening hydrocephalus.

TREATMENT (SEE ALSO CHAPTER 754)

Management and supervision of a child and family with a myelomeningocele require a multidisciplinary team approach, including surgeons, other physicians, and therapists, with one individual (often a pediatrician) acting as the advocate and coordinator of the treatment program.

Surgery to close the lesion is usually performed prenatally or within the first 72 hours of life (see Chapters 117 and 118). After repair of a myelomeningocele (especially postnatal repair), most infants require a shunting procedure for hydrocephalus. If symptoms or signs of hindbrain dysfunction appear, early surgical decompression of the posterior fossa is indicated. Clubfeet can require taping or casting. The

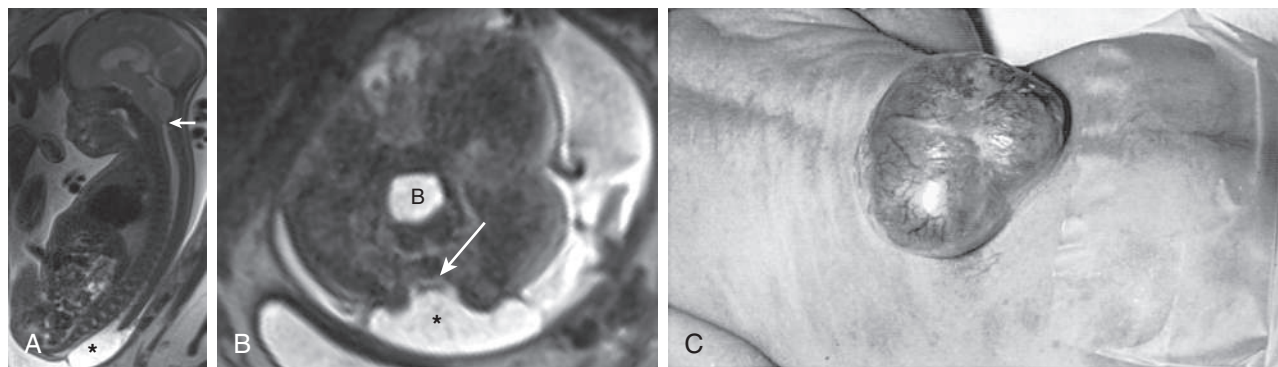


Fig. 631.2 Typical MRI imaging and physical exam findings of a lumbosacral myelomeningocele. **A**, Single-shot sagittal T2-weighted image of a fetus at 28 wk gestation demonstrates a lumbosacral spinal defect with protruding myelomeningocele sac (asterisk) and herniation of the brainstem/cerebellum into the upper spinal canal, a Chiari II malformation (arrow). **B**, Single-shot axial T2-weighted images of the same fetus at the level of the myelomeningocele demonstrates a neural placode (arrow) at the base of the myelomeningocele sac (asterisk). Urinary bladder marked with B. **C**, A lumbar myelomeningocele is covered by a thin layer of skin.

Management of Myelomeningocele Study (MoMS) has demonstrated the success of in utero surgical closure (see Chapters 117.7 and 118) with a lower incidence of hindbrain abnormalities and hydrocephalus (fewer shunts). Long-term follow-up of prenatal treatment into the school-age years demonstrates improved motor outcomes, although there are no differences in cognitive functioning. This suggests that some deficits may be progressive in utero and that prenatal closure might prevent the development of further loss of function.

Careful evaluation and reassessment of the genitourinary system is an important component of management. Teaching the parents and, ultimately, the patient, to regularly catheterize a neurogenic bladder is a crucial step in maintaining a low residual volume and bladder pressure that prevents urinary tract infections and reflux, which can lead to pyelonephritis, hydronephrosis, and bladder damage. *Latex-free catheters and gloves must be used to prevent development of latex allergy.* Periodic urine cultures and assessment of renal function, including serum electrolytes and creatinine as well as renal scans, vesiculourethrograms, renal ultrasonograms, and cystometrograms, are obtained according to the risk status and progress of the patient and the results of the physical examination. This approach to urinary tract management has greatly reduced the need for urologic diversionary procedures and has decreased the morbidity and mortality associated with progressive renal disease in these patients. Some children can become continent with bladder augmentation at a later age.

Incontinence of fecal matter is common and distressing to patients and families; occasionally, fecal impaction and/or megacolon may develop. Many children can be bowel-trained with a regimen of timed enemas or suppositories that allows evacuation at a predetermined time once or twice a day. Special attention to low anorectal tone and enema administration and retention is often required. Appendicostomy for antegrade enemas may also be helpful.

Functional ambulation may be possible, depending on the level of the lesion and on intact function of the iliopsoas muscles (see Chapter 754). Most children with a sacral or lumbosacral lesion obtain functional ambulation; approximately half the children with higher defects ambulate with the use of braces, other orthotic devices, and canes. Ambulation is often more difficult as adolescence approaches and when body mass increases. *Deterioration of ambulatory function, particularly during earlier years, should prompt referral for evaluation of tethered spinal cord, shunt malfunction, hydromyelia, and other neurosurgical issues.*

PROGNOSIS

For a child who is born with a myelomeningocele and who is treated aggressively, the mortality rate is 10–15%, and most deaths occur before age 4 years, often the result of hydrocephalus, infections, and cardiac/respiratory complications. However, life-threatening complications

occur at all ages, and renal dysfunction is one of the most important determinants of mortality. At least 70% of individuals (nonsyndromic, no associated anomalies) have no intellectual disability, but learning problems and seizure disorders are more common than in the general population. Previous episodes of meningitis (shunt infections) or ventriculitis may adversely affect intellectual and cognitive function. Because myelomeningocele is a chronic disabling condition, periodic and consistent multidisciplinary follow-up is required for life.

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631.3 Occult Spinal Dysraphism

Sara K. Trowbridge, Edward Yang, and
Christopher J. Yuskaitis

Occult spinal dysraphisms, often called *spina bifida occulta*, are a closed NTD that consist of a midline defect of the vertebral bodies without protrusion of the spinal cord or meninges. The most common type only affects the vertebra, which are often asymptomatic and lack neurologic signs. Other clinically more significant forms of closed spinal cord malformations can be associated with developmental abnormalities of the spinal cord, including syringomyelia, diastematomyelia, lipoma, fatty filum, dermal sinus, and/or a tethered cord. In most of these cases, there are overlying cutaneous manifestations such as a hemangioma, discoloration of the skin, pit, lump, dermal sinus, or hairy patch (Figs. 631.3 and 631.4). A spine x-ray in simple spina bifida occulta shows a defect in closure of the posterior vertebral arches and laminae, typically involving L5 and S1; there is no abnormality of the meninges, spinal cord, or nerve roots. However, a spine x-ray in cases with spinal cord involvement might show bone defects or may be normal. *All cases of occult spinal dysraphism are best investigated with MRI (Fig. 631.5 and see Fig. 631.4).* Initial screening in the neonate may include ultrasonography, but MRI is more accurate at any age.

A **meningocele** is formed when the meninges herniate through a defect in the posterior vertebral arches or the anterior sacrum. The spinal cord is usually normal and assumes a normal position in the spinal canal; therefore neurologic outcome is often normal. However, there may be tethering of the cord, syringomyelia, or diastematomyelia, so careful neurologic examination and follow-up are necessary. Orthopedic and urologic examination should also be considered. In asymptomatic children with normal neurologic findings and full-thickness skin covering the meningocele, surgery may be delayed. Given the high rate of association between meningocele and tethered cord syndrome, exploration of the spinal canal is necessary to potentially release the associated tethered cord.

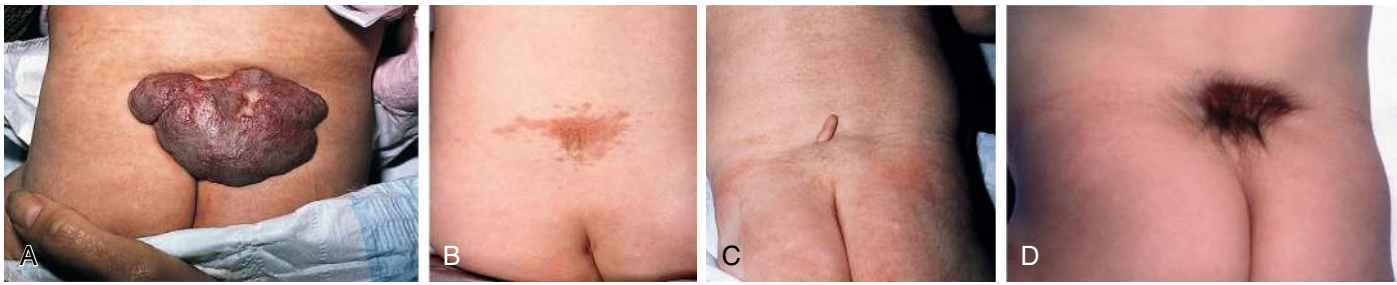


Fig. 631.3 Clinical aspects of congenital median lumbosacral cutaneous lesions. A, Midline sacral hemangioma in a patient with an occult lipomyelomeningocele. B, Capillary malformation with a subtle patch of hypertrichosis in a patient with a dermal sinus. C, Human tail with underlying lipoma in an infant with lipomyelomeningocele. D, Midline area of hypertrichosis (faun tail) overlying a patch of hyperpigmentation. (A–C from Kos L, Drolet BA. Developmental abnormalities. In: Eichenfield LF, Frieden IJ, Esterly NB, eds. *Neonatal Dermatology*, 2nd ed. Philadelphia: WB Saunders; 2008; D from Tay VS, Kornberg A, Cook M. Spine and spinal cord: developmental disorders. In: Schapira AH, ed. *Neurology and Clinical Neuroscience*. Philadelphia: Mosby; 2007, Fig. 38–11C.)

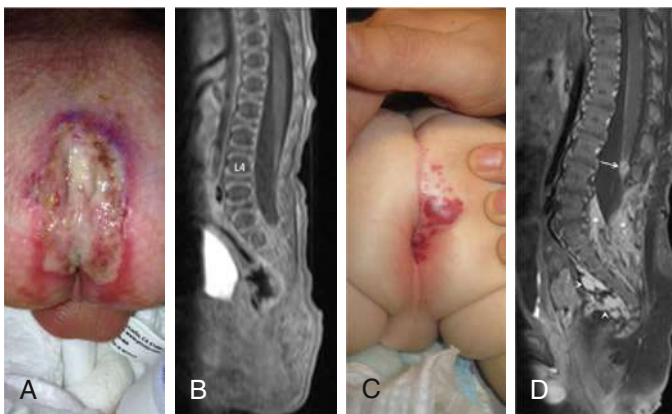


Fig. 631.4 A, Lumbosacral ulcerative plaque with surrounding red vascular rim was noted on initial examination. B, Midline sagittal contrast-enhanced, T1-weighted, fat-saturated image of the lumbosacral spine at presentation reveals low-lying conus at the L4 vertebral level suggestive of tethered cord. C, Recurrence of lumbosacral hemangioma after discontinuation of oral propranolol. D, Midline sagittal contrast-enhanced, T1-weighted, fat-saturated image of the lumbosacral spine at 6 mo of age shows new nodular enhancing lesion at the lower end of the conus (arrow) compatible with intrathecal hemangioma. In addition, there is a large hemangioma in the epidural space in the sacral spinal canal (asterisks) with presacral extension (arrowheads). (From Yu J, Maheshwari M, Foy AB, et al. Neonatal lumbosacral ulceration masking lumbosacral and intraspinal hemangiomas associated with occult spinal dysraphism. *J Pediatr*. 2016;175:211–215.)

A **congenital dermal sinus** is a tract between the skin and the spinal cord, sometimes indicated at the skin surface by protruding hairs, a hairy patch, or a vascular nevus. Dermal sinuses occur in the midline at the sites where meningoceles or encephaloceles can occur: the lumbosacral region or occiput, respectively, and occasionally in the cervical or thoracic area. Dermal sinus tracts can pass through the dura, acting as a conduit for the spread of infection. Recurrent meningitis of occult origin should prompt careful examination for a small sinus tract in the posterior midline region, including the back of the head. Lumbosacral sinuses are usually *above* the gluteal fold and are *directed* cephalad. Tethered spinal cord syndrome may also be an associated problem.

Diastematomyelia is when the spinal cord is split, or bifid, and commonly has bony abnormalities that require surgical intervention along with untethering of the spinal cord.

An approach to imaging of the spine in patients with cutaneous lesions is noted in [Table 631.1](#).

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631.4 Encephalocele

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Two major forms of dysraphism affect the skull, resulting in protrusion of tissue through a bony midline defect, called **cranium bifidum**. A cranial **meningocele** consists of a CSF-filled meningeal sac only. Cranial **encephalocele** contains the sac plus cerebral cortex, cerebellum, or portions of the brainstem ([Fig. 631.6](#)). These abnormalities are one tenth as common as neural tube closure defects involving the spine. Microscopic examination of the neural tissue within an encephalocele often reveals abnormalities, but not always, which has led to speculation that the primary problem is not abnormal neurulation, but rather abnormal mesodermal development leading to skull anomalies. The cranial defect occurs most commonly in the occipital region at or below theinion. However, in certain parts of the world, frontal or nasofrontal encephaloceles (transethmoidal, sphenothmoidal, sphenomaxillary, sphenoorbital, transsphenoidal) are more common. Some frontal lesions are associated with a cleft lip and palate.

Cranial encephalocele is often part of a larger syndrome. One of the more commonly associated genetic syndromes is **Meckel-Gruber syndrome**, a rare autosomal recessive condition caused by pathogenic variants in multiple genes involved in cilia function. This syndrome is characterized by an occipital encephalocele, cleft lip or palate, microcephaly, microphthalmia, abnormal genitalia, polycystic kidneys, and polydactyly. Other associated syndromes include muscular dystrophy–dystroglycanopathy type A1 (Walker-Warburg syndrome, due to pathogenic variants in *POMT*) and Knobloch syndrome (due to pathogenic variants in *COL18A*).

Determination of maternal serum AFP levels and ultrasound measurement of the biparietal diameter, as well as identification of the encephalocele itself, can diagnose encephaloceles in utero. Fetal MRI can help define the extent of associated CNS anomalies and the degree of brain herniated into the encephalocele.

Infants with a cranial encephalocele are at increased risk for developing hydrocephalus because of **aqueductal stenosis**, **Chiari malformation**, or **Dandy-Walker syndrome**. Examination might show a small sac with a pedunculated stalk or a large cystlike structure that can exceed the size of the cranium. The lesion may be completely covered with skin, but areas of denuded lesion can occur and require urgent surgical management. Transillumination of the sac can indicate the presence of neural tissue. A plain x-ray of the skull and cervical spine is indicated to define the anatomy of the cranium and vertebrae. Ultrasonography is most helpful in determining the contents of the sac. MRI or CT further helps define the spectrum of the lesion. Children with a cranial meningocele generally have a good prognosis, whereas patients with an encephalocele are at risk for vision problems, microcephaly, intellectual disability, and seizures. Generally, children with neural

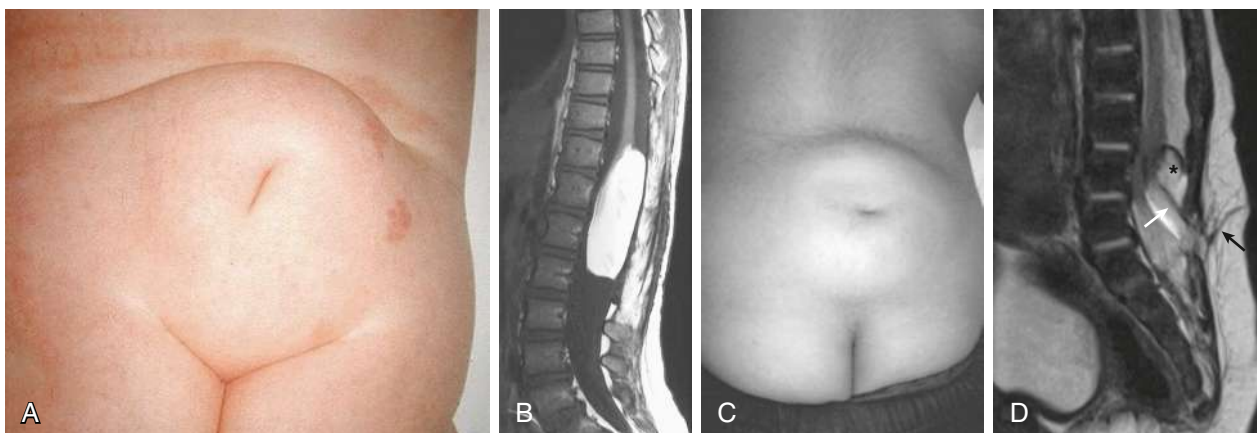


Fig. 631.5 Clinical features and imaging findings associated with occult spinal dysraphism. **A**, Lumbosacral lipoma. The subcutaneous lipoma is in continuity with the spinal cord via a defect in the underlying muscles, bone, and dura. **B**, Sagittal T1-weighted image shows a huge intradural lipoma merging with the conus medullaris superiorly. **C**, Lipoma and central dermal sinus. **D**, A sagittal T2-weighted MRI of the lumbar spine demonstrates a dermal sinus (black arrow) looping underneath the lowest lamina before ascending to the low-lying conus medullaris, which it tethers. The intradural portion of the sinus tract (white arrow) is encircled by intradural lipoma (asterisk). (A from Thompson DNP. *Spinal dysraphic anomalies: classification, presentation and management*. *Paed Child Health*. 2014;24:431–438, Fig. 4; B from Rossi A, Biancheri R, Cama A, et al. *Imaging in spine and spinal cord malformations*. *Eur J Radiol*. 2004;50[2]:177–200, Fig. 9a; C, From Jaiswal AK, Garg A, Mahapatra AK. *Spinal ossifying lipoma*. *J Clin Neurosci*. 2005;12:714–717, Fig. 1.)

Table 631.1 Cutaneous Lesions Associated with Occult Spinal Dysraphism

IMAGING INDICATED

Subcutaneous mass or lipoma
Hairy patch
Dermal sinus or cyst
Atypical dimples (deep, >5 mm, >25 mm from anal verge)
Vascular lesion (e.g., hemangioma or telangiectasia)
Skin appendages or polypoid lesions (e.g., skin tags, tail-like appendages)
Scarlike lesions (aplasia cutis)

IMAGING UNCERTAIN

Hyperpigmented patches
Deviation of the gluteal fold

IMAGING NOT REQUIRED

Simple dimples (<5 mm, <25 mm from anal verge)
Coccygeal pits

From Williams H. Spinal sinuses, dimples, pits and patches: what lies beneath? *Arch Dis Child Educ Pract Ed*. 2006;91:ep75–80.

tissue within the sac and associated hydrocephalus have the least favorable prognosis.

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631.5 Anencephaly

Sara K. Trowbridge, Edward Yang, and Christopher J. Yuskaitis

An anencephalic infant presents with a large defect of the calvarium, meninges, and scalp associated with a rudimentary brain. Anencephaly is a result of failure of closure of the rostral neuropore, the opening of the anterior neural tube. The opened neural tube leads to failure of the development of the skull vault. The embryologic precursor stages of anencephaly start with acrania (absence of the skull), followed by exencephaly (cerebral tissue protruding without an overlying skull), and ultimately the cerebral tissue degenerates because of prolonged exposure to the amniotic fluid.

In anencephaly, the cerebral hemispheres and cerebellum are usually absent, and only a residue of the brainstem can be identified

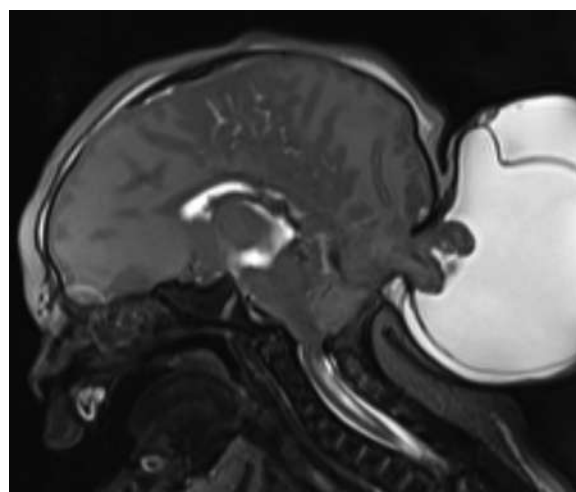


Fig. 631.6 Occipital encephalocele. Sagittal T2-weighted MRI of a newborn with prenatally diagnosed cephalocele demonstrates encephalomalacic brain protruding through an occipital skull defect with entrapped CSF in the cephalocele sac representing a mixture of subarachnoid (deep) and subdural (superficial) fluid. Note that the intracranial subarachnoid spaces (e.g., basal cistern) are contracted because of the large extracranial CSF reservoir.

(Fig. 631.7). The pituitary gland is hypoplastic, and the spinal cord pyramidal tracts are missing because of the absence of the cerebral cortex. Additional anomalies, including folding of the ears, cleft palate, and congenital heart defects, occur in 10–20% of cases. Most anencephalic infants are stillborn or die within several days of birth.

The incidence of anencephaly in the United States has been decreasing since the 1990s and approximates 0.2–0.3 in 1,000 live births; this varies across the world. As with myelomeningoceles, the recurrence risk is approximately 4% and increases to 10% if a couple has had two previously affected pregnancies. Environmental factors in addition to genetics are implicated as a cause of anencephaly, including low socioeconomic status, nutritional and vitamin deficiencies, as well as certain exposures. It is very likely that several noxious stimuli interact on a genetically susceptible host to produce anencephaly. Approximately 50% of cases of anencephaly have associated polyhydramnios. Couples who have had an anencephalic infant should have successive

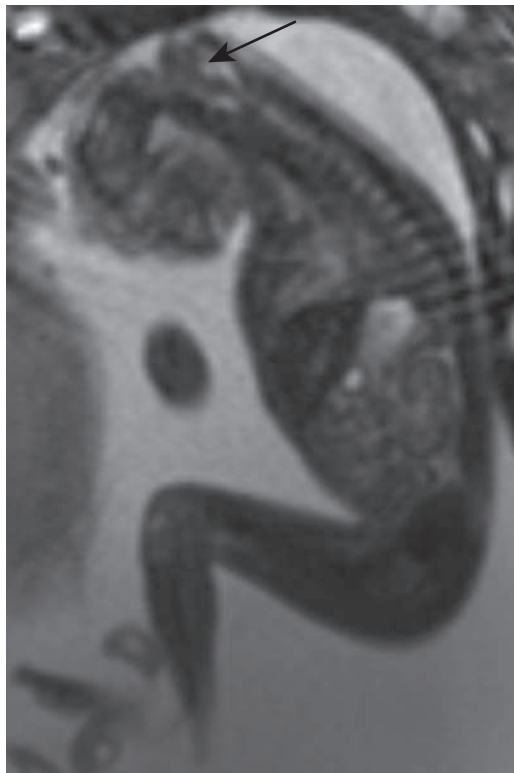


Fig. 631.7 Anencephaly. On this sagittal MR image of an 18-wk-gestational-age fetus, there is abrupt truncation of the neuraxis above the brainstem (arrow), no cerebral tissue, and an open skull defect exposed to amniotic fluid consistent with anencephaly.

pregnancies monitored, including with amniocentesis, determination of AFP levels, and ultrasound examination, between the 14th and 16th weeks of gestation. Prenatal folic acid supplementation decreases the risk of this condition.

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631.6 Malformations of Cortical Development

Sara K. Trowbridge, Edward Yang, and Christopher J. Yuskaitis

Disorders of neuronal proliferation, migration, and organization can cause a spectrum of abnormalities of CNS structure and/or function. Often these present with developmental delays/intellectual disability and/or epilepsy; less severe cases may be detected as incidental findings on a brain MRI.

The major period for neuronal proliferation in the developing human brain occurs between 8 and 15 weeks of gestation. Neural progenitor cells and radial glial cells (which generate both neurons and glial cells) proliferate in the ventricular and subventricular zones. The radial glial cells then play a critical role in the control of neuronal migration, as they form the radial glial fiber system that guides cortical projection neurons to their proper sites. Migrating neurons attach to the radial glial fiber and disembark at predetermined sites to form the precisely designed six-layered cerebral cortex by 28 weeks of gestation. Another important mechanism is the tangential migration of progenitor neurons destined to become cortical interneurons. The severity and the extent of a disorder of neuronal proliferation, migration, and/or organization depend on numerous factors, including the timing of a particular insult and a host of environmental and genetic contributors.

Disorders of neuronal proliferation generally present with abnormal brain size (microcephaly, megalencephaly). Disorders of neuronal

migration and organization may also present with associated abnormalities in brain size, but this is not always present. *These disorders often present clinically with either seizures and/or developmental delays and are best diagnosed by identification of the specific cortical malformation by brain MRI.* Although many brain malformations can be apparent from early in life (even on fetal MRI), some more subtle malformations (e.g., focal cortical dysplasias) may not be clearly visible until myelination is largely completed (around 2 years of age). *Genetic testing is indicated given the increasing number of identifiable genetic causes of brain malformations (Table 631.2).* Somatic variants have been found to cause some disorders of migration/organization. Somatic variants are genetic changes that occur after conception and do not affect the germ cells. Mosaicism from somatic variants is often not detected by standard clinical genetic testing.

MICROCEPHALY

Microcephaly is defined as a head circumference that measures more than 2-3 standard deviations (SD) below the mean for age and sex. Microcephaly may be subdivided into two main groups: primary (genetic) microcephaly, thought to be caused by defects in neuronal proliferation, and secondary (nongenetic) microcephaly, generally associated with destructive events after initial neuronal proliferation (e.g., hypoxic-ischemic injury, infection). A precise diagnosis is important for genetic counseling and for prediction of future pregnancies.

ETIOLOGY

Primary microcephaly refers to a group of conditions that follow a mendelian pattern of inheritance or are associated with a specific genetic syndrome and is generally thought to be secondary to a disruption in neuronal proliferation. Affected infants are usually identified prenatally or at birth because of a small head circumference. **Microcephaly vera** refers to a group of autosomal recessive disorders characterized by isolated microcephaly, with 16 genetic loci implicated to date. Many of the causative genes at those loci have been identified, including several involved in normal mitosis (e.g., *CDK5RAP2*, *ASPM*, *CENPF*). The genetic causes of microcephaly also include autosomal dominant and X-linked recessive disorders, as well as a series of chromosomal syndromes (Table 631.3); some of these are associated with other malformations of cortical development. **Secondary microcephaly** can result from a number of noxious agents that affect early neurodevelopment; these include irradiation, maternal alcohol or cocaine use, maternal hyperphenylalaninemia, and infections (rubella, cytomegalovirus, HIV, Zika virus).

Acquired microcephaly, which develops postnatally, can be seen as a result of parenchymal injury (e.g., hypoxic ischemic injury), as well as various genetic conditions, including Rett, Seckel, and Angelman syndromes and developmental epileptic encephalopathy syndromes.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

A thorough family history should be taken, seeking additional cases of microcephaly or disorders affecting the nervous system. It is important to measure a patient's head circumference at birth to diagnose microcephaly as early as possible. A very small head circumference implies a process that began early in embryonic or fetal development. An insult to the brain that occurs later in life, particularly beyond the age of 2 years, is less likely to produce severe microcephaly. Serial head circumference measurements are more meaningful than a single measurement, particularly when the measurement is borderline or if the microcephaly is progressive. The head circumference of each parent and any siblings should be recorded. The timing and progression of microcephaly, along with familial measurements, may help narrow the differential diagnosis.

Laboratory investigation of a microcephalic child is determined by the history and physical examination. If the cause of the microcephaly is unknown, the mother's serum phenylalanine level should be determined. High phenylalanine serum levels in an asymptomatic mother can produce marked brain damage in an otherwise normal nonphenylketonuric infant. Newborn screening in the United States will detect most of these cases. *Array comparative genomic hybridization*

Table 631.2 Malformations of Cortical Development

CLASSIFICATION	CLINICAL FINDING	GENETIC/METABOLIC ETIOLOGY
Disorders primarily of neuronal proliferation	Microcephaly	Primary microcephaly (MCPH 1-18)*: <i>MCPH1</i> , <i>WDR62</i> , <i>CDK5RAP2</i> , <i>CASC5</i> , <i>ASPM</i> , <i>CENPJ</i> , <i>STIL</i> , <i>CEP135</i> , <i>CEP152</i> , <i>ZNFX35</i> , <i>PHC1</i> , <i>CDK6</i> , <i>CENPE</i> , <i>SASS6</i> , <i>MFSD2A</i> , <i>ANKLE2</i> , <i>CIT</i> , <i>WDFY3</i>
		Syndromic microcephaly
		Acquired microcephaly
	Macrocephaly†	Metabolic:
		• Organic acid disorders (e.g., glutaric aciduria – <i>GCDH</i>)
		• Lysosomal storage disorders (e.g., Tay-Sachs disease – <i>HEXA</i>)
		• Leukoencephalopathies (e.g., Alexander disease – <i>GFAP</i>)
Disorders primarily of neuronal migration	Lissencephaly-pachygyria spectrum	Somatic overgrowth: <i>NSD1</i> , <i>GPC3</i> , <i>GPC4</i> , <i>FMR1</i> , <i>EZH2</i> , <i>PTEN</i>
		Neurocutaneous: <i>NF1</i> , <i>NF2</i> , <i>TSC1</i> , <i>TSC2</i>
		More than 300 listed conditions in OMIM
		Isolated: <i>PAFAH1B1</i> (<i>LIS1</i>)
		Miller-Dieker syndrome: 17p13.3 deletion (<i>PAFAH1B1</i> , <i>YWHAE</i>)
		Subcortical band heterotopia: <i>DCX</i> (female)
	Neuronal heterotopias	X-linked: <i>DCX</i> (male), <i>ARX</i>
		Tubulinopathies: <i>TUBA1A</i> , <i>TUBB2A</i> , <i>TUBB2B</i>
		Cobblestone: <i>POMT1</i> , <i>POMT2</i> , <i>POMGNT1</i> , <i>FKTN</i> , <i>FKRP</i> , <i>LARGE</i>
		More than 50 listed conditions in OMIM (e.g., <i>RELN</i> , <i>VLDLR</i>)
Disorders primarily of neuronal organization	Polymicrogyria	Over 200 listed conditions in OMIM (also see Table 631.4)
	Schizencephaly	In utero injury/infection
Mixed disorders	Hemimegalencephaly	For most cases, unclear genetic etiology; few cases associated with <i>COL4A1</i> , <i>SHH</i> , <i>SIX3</i>
	Focal cortical dysplasia	<i>AKT1</i> , <i>AKT3</i> , <i>DEPDC5</i> , <i>MTOR</i> , <i>PIK3CA</i> , <i>PIK3R2</i> , <i>PTEN</i> , <i>TSC1</i> , <i>TSC2</i>
		<i>DEPDC5</i> , <i>MTOR</i> , <i>NPRL2</i> , <i>NPRL3</i> , <i>PIK3CA</i> , <i>TSC1</i> , <i>TSC2</i>

*See Jayaraman D, Bae BI, Walsh CA. The genetics of primary microcephaly. *Annu Rev Genomics Hum Genet.* 2018;19:177–200 for comprehensive review.

†See Winden KD, Yuskaitis CJ, Poduri A. Megalencephaly and macrocephaly. *Semin Neurol.* 2015;35(3):277–287 for comprehensive review.

(chromosome microarray) study and/or karyotype is obtained if a chromosomal syndrome is suspected or if the child has abnormal facies, short stature, or any additional congenital anomalies. Whole exome sequencing or gene panel testing should also be considered, as pathogenic genetic variants can also cause primary microcephaly and syndromic microcephaly. MRI is useful in identifying any associated structural abnormalities of the brain, such as lissencephaly, pachygyria, and polymicrogyria. CT scanning is useful to detect intracerebral calcification. Additional studies include a fasting plasma and urine amino acid and organic acid analysis; serum ammonia determination; toxoplasmosis, rubella, cytomegalovirus, and herpes simplex (TORCH) titers; HIV testing of the mother and child; and a urine sample for the culture of cytomegalovirus. Zika virus–specific testing is also indicated when the infant is born in a high-risk environment or if a parent has a history of travel to endemic areas.

MACROCEPHALY AND MEGALENCEPHALY

Megalencephaly is an anatomic disorder of brain growth defined as a brain weight:volume ratio of more than the 98th percentile for age (or ≥ 2 SD above the mean) that is usually accompanied by macrocephaly (an occipitofrontal circumference >98 th percentile). Macrocephaly can also be secondary to enlarged skull bones, hydrocephalus/ventriculomegaly, and enlarged extraaxial spaces.

Megalencephaly can be categorized as anatomic or metabolic. Although metabolic diseases can present with microcephaly as well, there are certain syndromes (e.g., Alexander disease, Canavan disease,

megalencephalic leukoencephalopathy with subcortical cysts) that classically present with macrocephaly and should be considered in the differential diagnosis.

The most common cause of anatomic megalencephaly is **benign familial macrocephaly**. This condition is easily diagnosed by a careful family history and measurement of the parents' head circumferences (occipitofrontal circumferences). Other common megalencephaly-associated macrocephaly syndromes include syndromes with prenatal and/or postnatal somatic overgrowth, such as Sotos (*NSD1*), Simpson-Golabi-Behmel (*GPC3* and *GPC4*), fragile X (*FMR1*), Weaver (*EZH2*), and macrocephaly–cutis marmorata telangiectatica congenita syndromes. Multiple somatic overgrowth syndromes are associated with macrocephaly and pathogenic variants in *PTEN*, including Bannayan-Ruvalcaba-Riley, Cowden, and Proteus-like syndromes. *PTEN* has also been commonly implicated in patients with autism spectrum disorder and macrocephaly.

Additionally, many of the neurocutaneous syndromes, including neurofibromatosis (*NF1* and *NF2*), Sturge-Weber syndrome, and tuberous sclerosis, can present with macrocephaly. Tuberous sclerosis results from pathogenic variants in *TSC1* or *TSC2*, encoding the proteins hamartin and tuberin, which act in the mammalian target of rapamycin (mTOR) signaling pathway, a pathway known to be critical to regulating cell growth and proliferation. Indeed, variants in many genes in the mTOR signaling pathway have emerged as important causes of cortical malformations (Fig. 631.8) (see Hemimegalencephaly and Focal Cortical Dysplasia).

Table 631.3 Causes of Microcephaly	
PRIMARY MICROCEPHALY	
Isolated microcephaly	Microcephaly vera (autosomal recessive microcephaly) Autosomal dominant microcephaly X-linked microcephaly
Syndromic microcephaly	Chromosomal abnormalities • Trisomy 13 • Trisomy 18 • Trisomy 21
	Chromosomal deletions • 4p deletion (Wolf-Hirschhorn syndrome) • 5p deletion (Cri-du-chat syndrome) • 7q11.23 deletion (Williams syndrome) • 17p13.3 deletion (Miller-Dieker syndrome)
	Over 1000 other syndromes listed in OMIM, including: • Feingold syndrome (<i>MYCN</i>, <i>MIR17HG</i>) • Cornelia de Lange syndrome (<i>NIPBL</i>, <i>SMC1A</i>, <i>SMC3</i>, <i>RAD21</i>, <i>HDAC8</i>) • Smith-Lemli-Opitz syndrome (<i>DHCR7</i>) • Rubinstein-Taybi syndrome (<i>CREBBP</i>, <i>EP300</i>)
ACQUIRED MICROCEPHALY	
Genetic acquired microcephaly	Rett syndrome (<i>MECP2</i>) Angelman syndrome (<i>UBE3A</i>) Developmental epileptic encephalopathies
Intrauterine infection	Toxoplasmosis Cytomegalovirus Rubella Zika virus
Teratogens	Alcohol Hydantoin Radiation
Other exposures/injury	Maternal hyperphenylalaninemia Maternal diabetes mellitus Hypoxic-ischemic injury

Adapted from Abuelo D. Microcephaly syndromes. *Semin Pediatr Neurol.* 2007;14(3):118–127.

HEMIMEGALENCEPAHLY

Hemimegalencephaly, or unilateral macrocephaly, appears to result from a more focal aberrancy in neuronal proliferation during development, which also results in abnormal neuronal migration and organization (see Fig. 631.8). These patients generally present with early-onset refractory epilepsy and developmental delays. Various syndromes are associated with hemimegalencephaly, including epidermal nevus syndrome, Proteus syndrome, and hypomelanosis of Ito. As with other malformations of cortical development (see Macrocephaly and Megalencephaly and Focal Cortical Dysplasias), the mTOR signaling pathway appears to play a critical role in the pathogenesis of hemimegalencephaly, with many cases resulting from variants in genes involved in this pathway, including *AKT1* in Proteus syndrome.

FOCAL CORTICAL DYSPLASIAS

Focal cortical dysplasias consist of abnormal cortical lamination in a discrete area of cortex and are thought to be disorders of neuronal proliferation, migration, and organization. These can be difficult to detect, particularly in younger children with immature myelination. Therefore high-resolution, thin-section MRI can be useful, particularly in patients with refractory epilepsy undergoing consideration for surgery (see Fig. 631.8). Increasingly, germline and somatic pathogenic variants in genes involved in the mTOR pathway (*DEPDC5*, *NPRL2*, *NPRL3*, *AKT3*, others) have been implicated in the pathogenesis of focal cortical dysplasias.

LISSENCEPHALY-PACHYGYRIA

Lissencephaly, or agyria, is a rare disorder that is characterized by the absence of cerebral convolutions and a poorly formed sylvian fissure, giving the appearance of a 3- to 4-month-old fetal brain. The condition is probably a result of faulty neuronal migration during early embryonic life. The cortical layering of a lissencephalic brain is disrupted and results in a two- to four-layered cortex, rather than the usual six-layered one. A unique form of lissencephaly is subcortical band heterotopia, or double-cortex syndrome, in which a thick band of gray matter is located deep to the cortex, which may appear normal. **Pachygyria** is on the milder end of the lissencephaly spectrum, with some gyri present, although these are abnormal and markedly reduced in number.

Infants with lissencephaly-pachygyria present with failure to thrive, progressive microcephaly, marked developmental delay, and

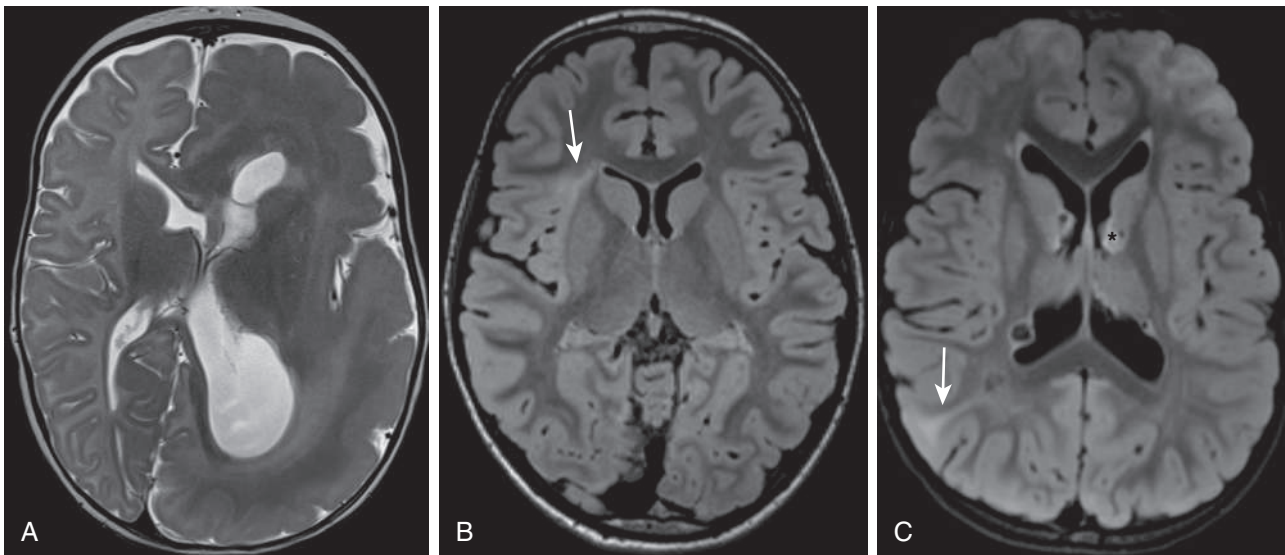


Fig. 631.8 Spectrum of *mTOR*-related cortical malformations on brain MRI. **A**, An axial T2-weighted image of a 4-mo-old female with hemimegalencephaly caused by a somatic *mTOR* variant demonstrates diffuse enlargement of the left hemisphere, cortical thickening, and white matter T2 hypointensity consistent with some combination of accelerated myelination and heterotopic neurons. **B**, Axial FLAIR imaging of a 6-yr-old female with intractable epilepsy demonstrates a transmantle region of signal abnormality (arrow), which fans out as it extends centrifugally from the periventricular white matter to the cortex, a typical appearance of focal cortical dysplasia type IIB. **C**, By comparison, an axial FLAIR image of a 4-yr-old male with tuberous sclerosis demonstrates a multiplicity of transmantle signs consistent with tubers (largest right occipital focus denoted by an arrow) as well as subependymal nodules lining the lateral ventricles and a subependymal giant cell tumor at the left caudothalamic groove (asterisk).

often refractory epilepsy. Various genetic causes of lissencephaly have been identified, including pathogenic variants in *PAFAH1B1* (*LIS1*) on chromosome 17p13.3 (Fig. 631.9); larger deletions at this locus (encompassing the *YWHAE* gene in addition to the *PAFAH1B1* gene) are linked to **Miller-Dieker syndrome**, characterized by lissencephaly and other features, including distinctive facies (a prominent forehead, bitemporal hollowing, anteverted nostrils, a prominent upper lip, and micrognathia), and cardiac and genital anomalies. *DCX* is on the X chromosome, with genetic disruption leading to lissencephaly in males and subcortical band heterotopia in females (see Fig. 631.9). Pathogenic variants in *ARX* are a rarer cause of X-linked lissencephaly in males. The tubulinopathies (related to variants in *TUBA1A*, *TUBB2A*, *TUBB2B*, and others) are another important cause of lissencephaly. Certain disorders (e.g., Walker-Warburg syndrome, Fukuyama congenital muscular dystrophy, and muscle-eye-brain disease) present with a cobblestone lissencephaly, an overmigration disorder, with a bumpy cortical surface composed of groups of heterotopic neurons and altered myelination (see Fig. 631.9).

NEURONAL HETEROTOPIAS

Subtypes of neuronal heterotopias include **periventricular nodular heterotopias**, **subcortical heterotopia** (including band type), and marginal glioneuronal heterotopias. Intractable seizures are a common feature. Several genes have been identified that are a cause of these conditions, including most commonly the X-linked *FLNA* gene, which causes bilateral periventricular nodular heterotopia in affected females (Fig. 631.10).

POLYMICROGYRIA AND SCHIZENCEPHALY

Polymicrogyria is characterized by an augmentation of small convolutions separated by shallow enlarged sulci (Fig. 631.11). Polymicrogyria is commonly seen in the temporal lobes in the perisylvian region. Pathogenic variants in numerous genes have been associated with polymicrogyria, as noted in Table 631.4. Epilepsy, including drug-resistant forms, and oromotor discoordination are common features.

Schizencephaly is the presence of unilateral or bilateral *clefts* within the cerebral hemispheres caused by an abnormality of morphogenesis (see Fig. 631.11). The cleft may be fused or unfused and, if unilateral and large, may be confused with a porencephalic cyst. Not infrequently, the borders of the cleft are surrounded by abnormal brain, particularly polymicrogyria.

When the clefts are bilateral, many patients are severely intellectually challenged, with seizures that are difficult to control and microcephaly with spastic quadriplegia. Some cases of bilateral schizencephaly are associated with **septo-optic dysplasia** and endocrinologic disorders. Unilateral schizencephaly is a common cause of **congenital hemiparesis**. Schizencephaly is associated with fetal cytomegalovirus infection. It can also be secondary to in utero vascular injury, sometimes in the setting of pathogenic variants in *COL4A1*, a gene associated with increased risk of intracranial hemorrhage. Some reports have suggested the involvement of the sonic hedgehog signaling pathway, but most cases remain without a clearly defined genetic etiology.

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631.7 Disorders with Midline Defects

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HOLOPROSENCEPHALY

Holoprosencephaly encompasses a group of developmental disorders that result from defective prosencephalic cleavage. These disorders span a spectrum of severity and are classified into three groups, alobar, semilobar, and lobar, depending on the degree of the cleavage abnormality (Fig. 631.12). **Alobar holoprosencephaly** is the most severe form, with complete fusion of the cerebral hemispheres and deep nuclei and complete absence of the corpus callosum and olfactory bulbs and tracts. **Semilobar holoprosencephaly** presents with fusion of the anterior cerebral hemispheres and absence of the anterior corpus callosum. **Lobar holoprosencephaly**, the least severe form, generally presents with full separation between the cerebral hemispheres, partial or full separation between the deeper nuclei, and full development of the posterior corpus callosum, with some underdevelopment of the anterior corpus callosum. A fourth type, the middle interhemispheric variant, or **syntelencephaly**, involves a segmental area of nonseparation of the posterior frontal and parietal lobes. Facial abnormalities, including cyclopia, synophthalmia, cebocephaly, single nostril, choanal atresia, solitary

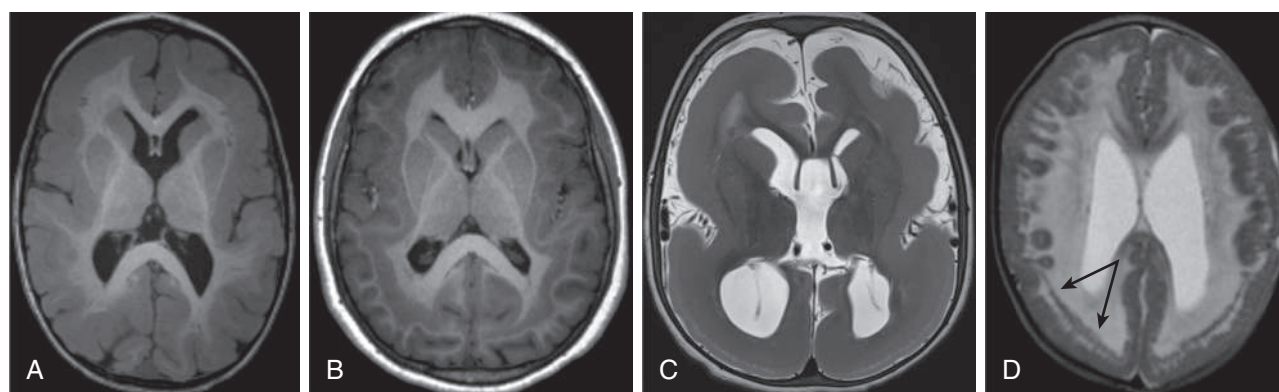


Fig. 631.9 Pachygyria and subcortical band heterotopia spectrum on brain MRI. **A**, An axial T1-weighted image of an 18-mo-old male demonstrates thickening of the cortex and attenuation of gyration, hallmarks of pachygyria. In this patient with a pathogenic *DCX* variant, there is greater severity of the pachygyria anteriorly, which is typically the case for pachygyria caused by mutations in this gene. **B**, By contrast, an axial T1-weighted sequence of a 10-yr-old female demonstrates a normal-thickness cortical ribbon with a subjacent layer of gray matter signal, consistent with subcortical band heterotopia. This patient also has a pathogenic *DCX* variant but has an attenuated phenotype because of X-linked inactivation and mosaic expression of the disease-causing variant. **C**, An axial T2-weighted image of a 4-yr-old female demonstrates marked cortical thickening and severe posterior predominant agyria (lissencephaly), the latter being a classic manifestation of the patient's *LIS1* variant. **D**, An axial T2-weighted image of cobblestone malformation (previously called type II lissencephaly) from a 3-mo-old female with infantile spasms, occipital cephalocele, developmental delay, and elevated creatine kinase levels. Note the centrifugal streaks of gray matter extending to a smooth thickened cortex. Although superficially reminiscent of lissencephaly like that in the prior case, a key distinguishing feature is the nodularity of the gray-white matter interface and the centrifugal islands of gray matter (e.g., arrowed right occipital foci). The islands of gray matter represent migration of neurons through the pial limiting membrane into the subarachnoid space, a typical feature of cobblestone malformation.

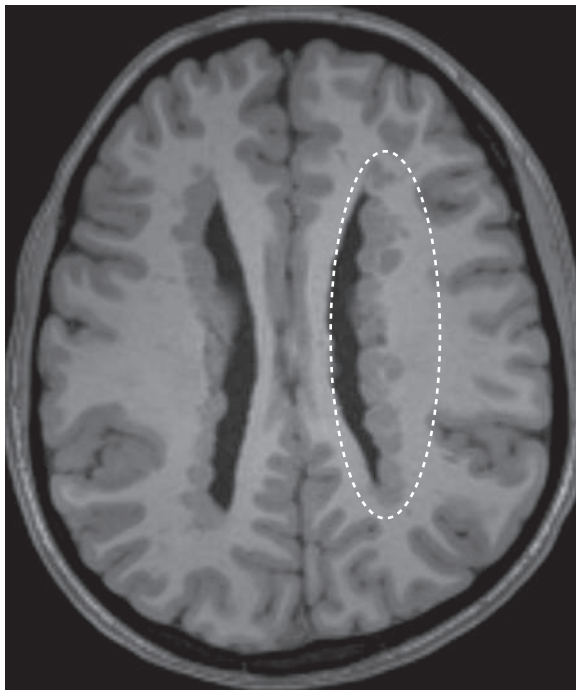


Fig. 631.10 Periventricular nodular heterotopia. An axial T1-weighted brain MR image of a 16-yr-old female with valvular heart disease and joint laxity demonstrates confluent subependymal nodules of gray matter signal consistent with periventricular nodular heterotopia (marked with dashed oval). The patient was ultimately found to have a pathogenic *FLNA* variant.

central incisor tooth, and premaxillary agenesis, are common in severe cases, because the prechordal mesoderm that induces the ventral prosencephalon is also responsible for induction of the median facial structures. Milder facial abnormalities, such as ocular hypotelorism, can be seen in milder forms.

Affected children with the severe alobar type have a high mortality rate within the first year of life, but some can live for years. Mortality and morbidity with milder types are more variable, with neurologic symptoms generally correlating with the severity of the underlying abnormality. In addition to neurologic symptoms, patients with impaired hypothalamic cleavage can also have various endocrinopathies. The incidence of holoprosencephaly is 1 in 10,000 live births. A prenatal diagnosis can be confirmed by ultrasonography after the 10th week of gestation for more severe types, but fetal MRI at later gestational ages gives far greater anatomic, and therefore diagnostic, precision.

Genetic and environmental factors both play a role in the development of holoprosencephaly. Chromosomal abnormalities account for approximately 60% of all cases, of which trisomy 13 is the most common. Other associated chromosomal abnormalities include trisomy 18 and deletions or trisomies of chromosomes 2, 3, 7, and 21. Diagnosis with a chromosomal abnormality in the setting of holoprosencephaly is a negative prognostic factor, with most patients not surviving past the first year of life. Monogenic syndromic causes include CHARGE syndrome (*CHD*), Pallister-Hall (*GLI3*), Rubenstein-Taybi (*CREB-BP*), and Smith-Lemli-Opitz (*DHCR7*) syndromes. Genetic variants, particularly in the sonic hedgehog signaling pathway (*SHH*, *SIX3*), have also been implicated in non-syndromic holoprosencephaly. Environmental factors, particularly maternal diabetes, are risk factors for holoprosencephaly.

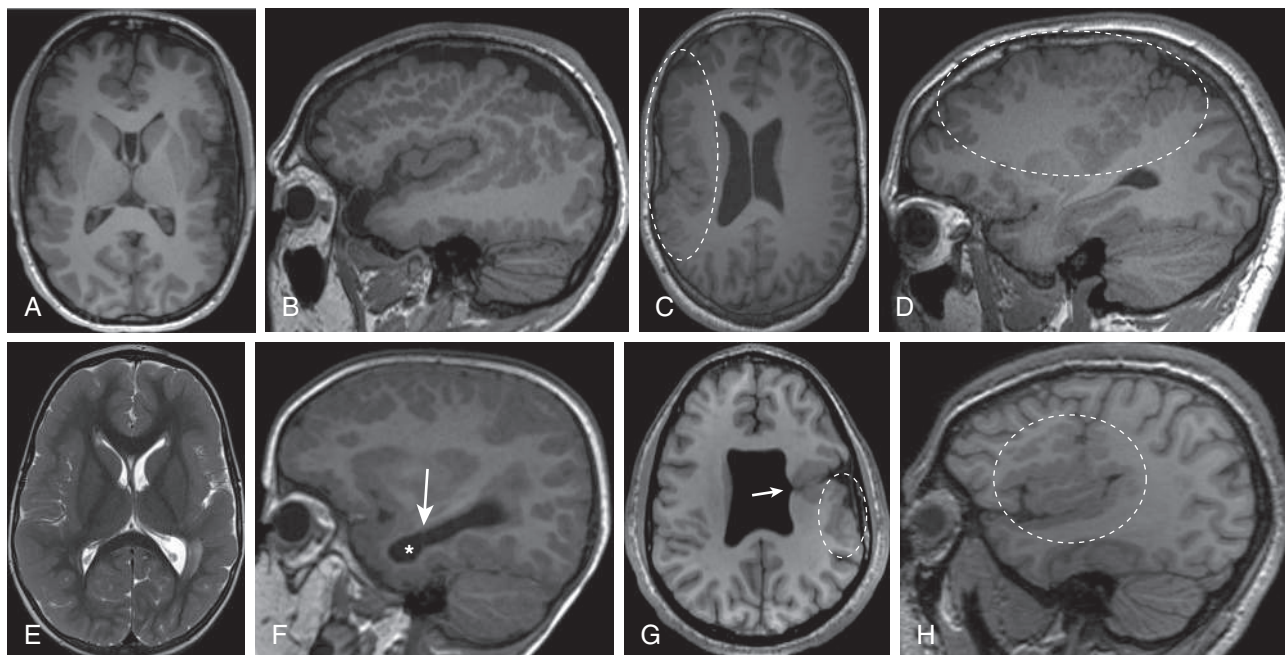


Fig. 631.11 Polymicrogyria spectrum by brain MRI. Axial (A) and sagittal (B) T1-weighted images of a 17-yr-old male with 22q11 deletion syndrome demonstrate diffusely increased gyral frequency and a bumpy surface contour of the cerebral cortex consistent with polymicrogyria, with some sparing of the frontal poles and occipital lobes. Axial (C) and sagittal (D) T1-weighted images of a 23-yr-old male demonstrate a unilateral area of right perisylvian polymicrogyria (dashed ovals) with reduced underlying white matter volume. Axial T2-weighted (E) and sagittal T1-weighted (F) sequences demonstrate diffuse polymicrogyria in a 28-mo-old with hearing loss, developmental delay, and congenital cytomegalovirus (CMV) exposure. Although the calcifications associated with TORCH infections are frequently not evident on MRI, clues to CMV as the etiology for polymicrogyria include microcephaly on clinical evaluation and subependymal cysts, the latter evident in this patient at the classic temporal horn location (asterisk) where it is separated from the remaining ventricular system by a thin membrane (arrow, F). Axial (G) and sagittal (H) T1-weighted images of a 17-yr-old male demonstrate an absent septum pellucidum and an apposed gray matter lined cleft through the left frontal lobe consistent with closed-lip schizencephaly (arrow, G). As is invariably the case in schizencephaly, the schizencephalic cleft is margined by polymicrogyria (ovals, G and H).

Table 631.4 Genes Associated with Polymicrogyria

PATHWAY/ PATHOLOGY	GENE ¹	HEAD SIZE ²			BRAIN FINDINGS	DISORDER NAME	MOI
		MAC	MIC	N/MS			
mTORopathies	AKT3	x			Bilateral perisylvian PMG	MPPH syndrome	AD
	CCND2	x					
	MTOR	x					
	DEPDC5	x			Diffuse, focal, or multifocal PMG (less common than FCD)	Smith-Kingsmore syndrome	AD
	PI4KA			x	Perisylvian PMG		AR
	PIK3CA	x			Bilateral perisylvian PMG	MCAP syndrome	See footnote 4
	PIK3R2	x				MPPH syndrome	AD
	PTEN	x			Diffuse, focal, or multifocal PMG		AD
Tubulinopathies	DYNC1H1		x	x	Frontal or diffuse PMG		AD
	KIF5C			x	Perisylvian PMG		AD
	TUBA1A		x	x	Diffuse, focal, or multifocal PMG; bilateral, asymmetric, perisylvian PMG	Lissencephaly 3	AD
	TUBB		x		PMG		AD
	TUBB2A		x		Bilateral, asymmetric, anterior predominant PMG		AD
	TUBB2B		x	x			
	TUBB3		x	x	Frontoparietal PMG		AD
Cobblestone dysplasia – alpha dystroglycanopathies	FKTN			x	Diffuse (cerebral and cerebellar) PMG		AR
	POMGNT1			x	PMG		AR
	POMT2			x	PMG		AR
Cobblestone dysplasia – other (laminopathies and congenital disorders of glycosylation)	ADGRG1 (GPR56)			x	Bilateral frontoparietal PMG		AR
	COL3A1	x		x	Diffuse cobblestone cortex; PMG A > P		AR
	ATP6V0A2		x	x	Frontoparietal PMG	Autosomal recessive cutis laxa type 2A	AR
	LAMA2			x	Occipital PMG; white-matter signal abnormalities	Muscular dystrophy, congenital merosin-deficient, 1A	AR
	LAMB1	x		x	Porencephaly; cobblestone lissencephaly P > A	Lissencephaly 5	AR
	LAMC3			x	Occipital PMG		AR
	SNAP29		x		Perisylvian or diffuse PMG		AR
	SRD5A3			x	Frontal PMG	SRD5A3-CDG (CDG-Iq)	AR

Continued

Table 631.4 Genes Associated with Polymicrogyria—cont'd

PATHWAY/ PATHOLOGY	GENE ¹	HEAD SIZE ²			BRAIN FINDINGS	DISORDER NAME	MOI
		MAC	MIC	N/MS			
Other	<i>BICD2</i>			x	Perisylvian PMG		AD
	<i>COL18A1</i>			x	Frontal PMG	Knobloch syndrome 1	AR
	<i>DDX3X</i>		x	x	Frontoparietal or diffuse PMG	<i>DDX3X</i> -related neurodevelopmental disorder	XL
	<i>EML1</i>	x			Ribbon-like heterotopia with overlying PMG; ACC		AR
	<i>EOMES(TBR2)</i>		x		Bilateral perisylvian or diffuse PMG		AR
	<i>EZH2</i>	x			Bilateral perisylvian PMG	Weaver syndrome	AD
	<i>FIG4</i>		x	x	Bilateral or temporo-occipital PMG		AR
	<i>GPSM2</i>	x			Parasagittal PMG; ACC	Chudley-McCollough syndrome	AR
	<i>GRIN1</i>		x		Extensive bilateral PMG		AD
	<i>GRIN2B</i>		x	x	Diffuse PMG		AD
	<i>KIFBP (KIAA1279)</i>		x		Diffuse PMG	Goldberg-Shprintzen syndrome	AR
	<i>MAP1B</i>				Perisylvian PMG; PNH		AD
	<i>NDE1</i>		x		Diffuse PMG		AR
	<i>NEDD4L</i>			x	Bilateral perisylvian PMG; PNH		AD
	<i>OCLN</i>		x		Bandlike calcifications with diffuse PMG	Pseudo-TORCH syndrome 1	AR
	<i>OFD1</i>	x			Frontal and parietal PMG	Joubert syndrome (XLR); orofaciodygital syndrome 1 (XLD)	XL
	<i>PAX6</i>		x		Variable temporal PMG		AR
	<i>RAB18</i>		x	x	Diffuse or frontal PMG	<i>RAB18</i> deficiency ³	AR
	<i>RAB3GAP1</i>		x	x			
	<i>RAB3GAP2</i>		x	x			
	<i>RTTN</i>		x		Variable diffuse, asymmetric PMG		AR
	<i>TBC1D20</i>			x	Diffuse or bilateral frontal PMG	<i>RAB18</i> deficiency ³	AR
	<i>TCTN1</i>			x	Frontal PMG	Joubert syndrome	AR
	<i>TMEM216</i>			x	Variable PMG	Meckel-Gruber syndrome, Joubert syndrome	AR
	<i>WDR62</i>		x		± Diffuse or asymmetric PMG		AR
Metabolic disorders	<i>FH</i>		x		Variable PMG	Fumeric aciduria	AR
	<i>PEX</i> genes		x	x	Perisylvian PMG	Zellweger spectrum disorders	AR

¹Genes are in alphabetic order.²Head size:

N/MS = normal/mildly small (i.e., head circumference >3 SD and <97%)

MIC = severe microcephaly (i.e., birth head circumference <3 SD or earliest HC <4 SD)

MAC = macrocephaly (i.e., head circumference >97%)

³*RAB18* deficiency is a spectrum that includes Warburg microsyndrome (at the severe end) and Martsolf syndrome (at the mild end). Additional findings are eye involvement (bilateral congenital cataracts, microphthalmia, and microcornea); severe-to-profound intellectual disability; and hypogonadism.⁴De novo germline pathogenic variants in *PIK3CA* are reported; however, most affected individuals with MCAP reported had somatic mosaicism for pathogenic variants in *PIK3CA*, suggesting that the mutation occurred post fertilization in one cell of the multicellular embryo. <https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/de-novo/>
A, Anterior; ACC, absence of the corpus callosum; AD, autosomal dominant; AR, autosomal recessive; CDG, congenital disorder of glycosylation; FCD, focal cortical dysplasia; MCAP, megalencephaly-capillary malformation-PMG; MOI, mode of inheritance; MPPH, megalencephaly-polymicrogyria-polydactyly-hydrocephalus; P, posterior; PNH, periventricular nodular heterotopia; XL, X-linked; XLD, X-linked dominant; XLR, X-linked recessiveAdapted from Stutterd CA, Dobyns WB, Jansen A, et al. Polymicrogyria overview. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews*. Seattle, WA: University of Washington; 2005.

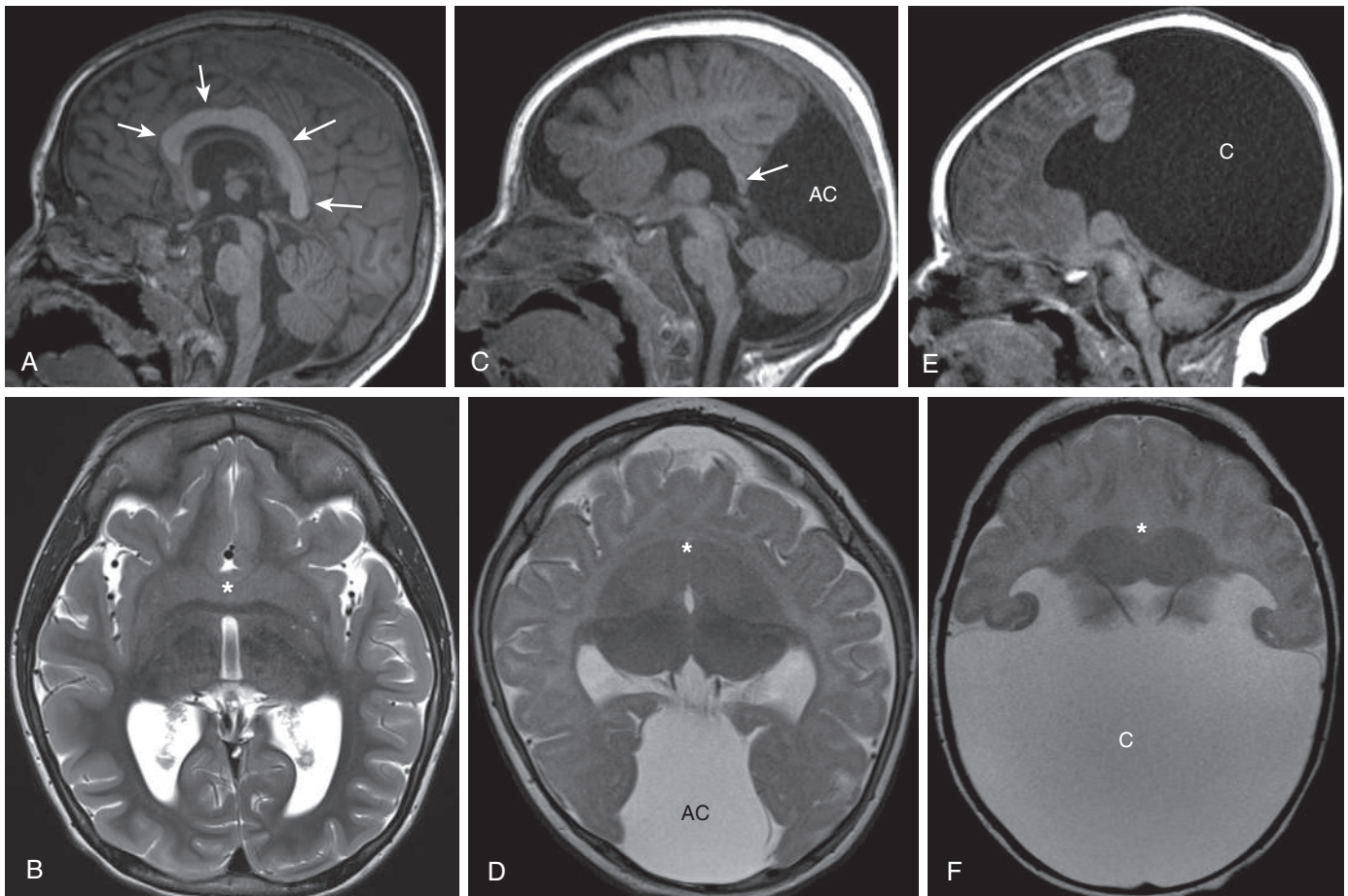


Fig. 631.12 Gradations of severity in holoprosencephaly. Holoprosencephaly results from incomplete cleavage of the cerebral hemispheres early in embryogenesis. As illustrated in these pairs of brain MRI sagittal T1-weighted (A, C, and E) and axial T2-weighted images (B, D, and F), severity ranges from mildly affected patients with lobar holoprosencephaly (A, B), to more severely affected patients with semilobar holoprosencephaly (C, D), to the most severely affected patients with alobar holoprosencephaly (E, F). More mildly affected holoprosencephaly patients have greater separation of the cerebral hemispheres, particularly anteriorly and ventrally (e.g., less deep gray matter structure fusion marked with asterisks in B, D, and F). Milder holoprosencephaly also demonstrates greater formation of the corpus callosum (arrows in A, C) which is absent in alobar holoprosencephaly (E). Unlike alobar holoprosencephaly, which typically demonstrates a monoventricle with or without a dorsal cyst (C in E, F), semilobar and lobar holoprosencephaly demonstrate partial to complete formation of the lateral ventricles (e.g., frontal/temporal horns). The shown case of semilobar holoprosencephaly (C, D) has an arachnoid cyst (AC), but it is not in communication with the ventricular system.

AGENESIS OF THE CORPUS CALLOSUM

Agenesis of the corpus callosum consists of a heterogeneous group of disorders that result from defective midline prosencephalic development. These disorders vary in clinical presentation from patients with severe intellectual deficits and neurologic abnormalities to the asymptomatic and normally intelligent patient (Fig. 631.13). In addition, patients may experience hypothermia or hyperthermia and hyperhidrosis (Shapiro syndrome).

When agenesis of the corpus callosum is an *isolated* phenomenon, the patient may be asymptomatic. When it is accompanied by associated brain anomalies, such as heterotopias, polymicrogyria, and pachygyria (broad, wide gyri), and/or other syndromic or genetic disorders, patients often have significant neurologic abnormalities, including intellectual disability, microcephaly, hemiparesis or diplegia, and seizures.

The anatomic features of agenesis of the corpus callosum are best depicted on MRI and include widely separated frontal horns with an abnormally high position of the third ventricle between the lateral ventricles. MRI precisely outlines the extent of the corpus callosum defect. **Colpocephaly** refers to an abnormal enlargement of the occipital horns of the ventricular system and can be identified as early as the fetal period. It is often associated with agenesis of the corpus callosum, but it can occur in isolation. There are numerous genetic causes of agenesis of the corpus callosum, including chromosomal abnormalities, syndromic genetic disorders, and nonsyndromic monogenic disorders (Table 631.5).

Aicardi syndrome is one syndrome that presents with partial or complete agenesis of the corpus callosum, as well as other brain abnormalities

(e.g., cortical dysplasias, periventricular nodular heterotopias, intracranial cysts) and distinctive chorioretinal lacunae. Patients are almost all female, suggesting that the genetic abnormality is X-linked dominant. Seizures, including infantile spasms, are common and are typically resistant to anticonvulsants. An electroencephalogram shows independent activity recorded from both hemispheres as a result of the absent corpus callosum and often shows hemihypsarrhythmia. All patients have severe intellectual disability and can have abnormal vertebrae that may be fused or only partially developed (hemivertebra).

ABSENCE OF THE SEPTUM PELLUCIDUM

Absence of the septum pellucidum is another developmental midline defect that is almost always associated with other brain anomalies, particularly schizencephaly, although it can also be seen with holoprosencephaly, agenesis of the corpus callosum, and septo-optic dysplasia. It can also result through destruction of the septum pellucidum, secondary to hydrocephalus or ischemic injury. Therefore the clinical presentation of patients with absence of the septum pellucidum largely depends on the etiology, associated brain anomalies, and any underlying chromosomal and/or genetic diagnosis. **Cavum septum pellucidum** refers to the cavity between the two septal leaflets; although this is normal in the fetal brain, the septal leaflets generally fuse during development. A persistent cavum septum pellucidum is generally considered to be a normal variant (Fig. 631.14).

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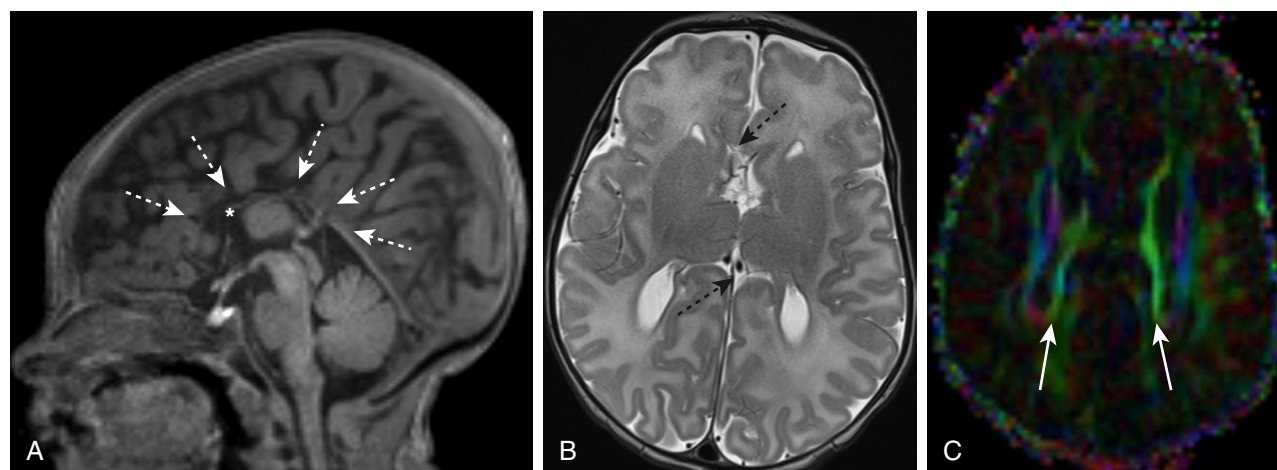


Fig. 631.13 Complete corpus callosum (callosal) agenesis by brain MRI. **A**, Sagittal T1-weighted sequence of a newborn with callosal agenesis demonstrates lack of a normal corpus callosum (*dashed arrows* along expected course) with multiple sulci radiating without interruption from the third ventricle (*asterisk*). **B**, An axial T2-weighted image of this patient demonstrates a parallel rather than curved course of the lateral ventricles (missing callosal genu and rostrum denoted by *dashed arrows*). **C**, Redirection of white matter tracts (Probst bundles) can be directly visualized in callosal agenesis using colored fractional anisotropy maps, where green denotes anteroposterior fiber tracts running parallel to the lateral ventricles rather than crossing the midline.

Table 631.5 Disorders Associated with Agenesis of the Corpus Callosum*

DISORDER	SALIENT FEATURES
WITH IDENTIFIED GENES†	
Andermann syndrome (<i>KCC3</i>)	ACC, progressive neuropathy, and dementia
Donnai-Barrow syndrome (<i>LRP2</i>)	Diaphragmatic hernia, exomphalos, ACC, deafness
Frontonasal dysplasia (<i>ALX1</i>)	ACC, bilateral extreme microphthalmia, bilateral oblique facial cleft
XLAG (<i>ARX</i>)	Lissencephaly, ACC, intractable epilepsy
Microcephaly (<i>TBR2</i>)	ACC, polymicrogyria
Microcephaly with simplified gyral pattern and ACC (<i>WDR62</i>)	ACC, other brain malformations
Mowat-Wilson syndrome (<i>ZFHX1B</i>)	Hirschsprung disease, ACC
Pyridoxine-dependent epilepsy (<i>ALDH7A1</i>)	ACC, seizures, other brain malformations
Pyruvate dehydrogenase deficiency (<i>PDHA1</i> , <i>PDHB</i> , <i>PDHX</i>)	ACC with other brain changes
ACC with fatal lactic acidosis (<i>MRPS16</i>)	Complexes I and IV deficiency, ACC, brain malformations
HSAS/MASA syndromes (<i>L1CAM</i>)	Hydrocephalus, adducted thumbs, ACC, MR
ACC SEEN CONSISTENTLY (NO GENE YET IDENTIFIED)	
Acrocallosal syndrome	ACC, polydactyly, craniofacial changes, MR
Aicardi syndrome	ACC, chorioretinal lacunae, infantile spasms, MR
Chudley-McCullough syndrome	Hearing loss, hydrocephalus, ACC, colpocephaly
FG syndrome	MR, ACC, craniofacial changes, macrocephaly
Genitopatellar syndrome	Absent patellae, urogenital malformations, ACC
Temtamy syndrome	ACC, optic coloboma, craniofacial changes, MR
Toriello-Carey syndrome	ACC, craniofacial changes, cardiac defects, MR
Vici syndrome	ACC, albinism, recurrent infections, MR
ACC SEEN OCCASIONALLY (PARTIAL LIST)‡	
ACC with spastic paraparesis (<i>SPG11</i> , <i>SPG15</i>)	Progressive spasticity and neuropathy, thin corpus callosum
Craniofrontonasal syndrome	Coronal craniosynostosis, facial asymmetry, bifid nose
Fryns syndrome	CDH, pulmonary hypoplasia, craniofacial changes
Marden-Walker syndrome	Blepharophimosis, micrognathia, contractures, ACC
Meckel-Gruber syndrome	Encephalocele, polydactyly, polycystic kidneys

Table 631.5 Disorders Associated with Agenesis of the Corpus Callosum —cont'd

DISORDER	SALIENT FEATURES
Nonketotic hyperglycinemia (<i>GLDC</i> , <i>GCST</i> , <i>GCSH</i>)	ACC, cerebral and cerebellar atrophy, myoclonus, progressive encephalopathy
Microphthalmia with linear skin defects	Microphthalmia, linear skin markings, seizures
Opitz G syndrome	Pharyngeal cleft, craniofacial changes, ACC, MR
Orofaciodigital syndrome	Tongue hamartoma, microretrognathia, clinodactyly
Pyruvate decarboxylase deficiency	Lactic acidosis, seizures, severe MR and spasticity
Rubinstein-Taybi syndrome	Broad thumbs and great toes, MR, microcephaly
Septooptic dysplasia (de Morsier syndrome)	Hypoplasia of septum pellucidum and optic chiasm
Sotos syndrome	Physical overgrowth, MR, craniofacial changes
Warburg micro syndrome	Microcephaly, microphthalmia, microgenitalia, MR
Wolf-Hirschhorn syndrome	Microcephaly, seizures, cardiac defects, 4p–

*Reliable incidence data are unavailable for these very rare syndromes.

[†]Gene symbols in parentheses.

[‡]Many of these also may consistently have a thin dysplastic corpus callosum, such as Sotos syndrome or agenesis of the corpus callosum (ACC) with spastic paraparesis (SPG11). The overlap between ACC and these conditions is still under investigation. Other gene symbols are omitted from this section.

4p–, Deletion of the terminal region of the short arm of chromosome 4, defines the genotype for Wolf-Hirschhorn patients; ACC, agenesis of the corpus callosum; ARX, Aristaless-related homeobox gene; CDH, congenital diaphragmatic hernia; HSAS/MASA, X-linked hydrocephalus/mental retardation, aphasia, shuffling gait, and adducted thumbs; KCC3, KCl co-transporter 3; L1CAM, L1 cell adhesion molecule; MR, mental retardation; MRPS16, mitochondrial ribosomal protein S16; SPG11, spastic paraplegia 11; XLAG, X-linked lissencephaly with absent corpus callosum and ambiguous genitalia; ZFX1B, zinc finger homeobox 1b.

From Sherr EH, Hahn JS. Disorders of forebrain development. In: Swaiman KF, Ashwal S, Ferriero DM, Schor NF, eds. *Swaiman's Pediatric Neurology*, 5th ed. Philadelphia: WB Saunders; 2012: Table 23-2.

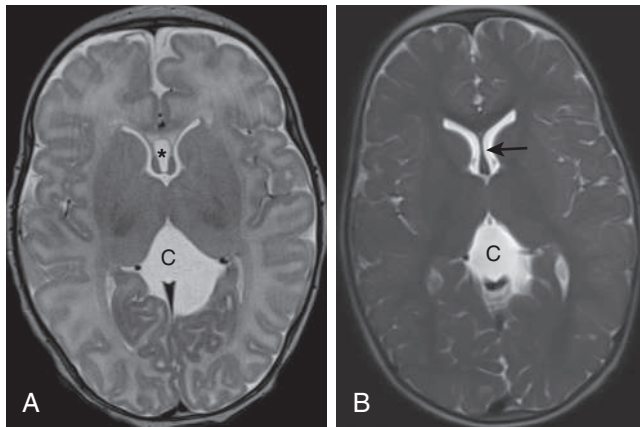


Fig. 631.14 Age-expected evolution of the septum pellucidum. Throughout fetal life, the septum pellucidum exists as paired leaflets enclosing a midline CSF space. This configuration is known as a *cavum septum pellucidum* and undergoes fusion into a single membrane during the first months of postnatal life. **A**, A brain MRI axial T2-weighted image of a 42-day-old female followed for a cistern of the velum interpositum cyst (C) demonstrates normal separation of the septal leaflets with an intervening CSF pocket, the *cavum septum pellucidum* (asterisk). **B**, An axial single-shot T2-weighted brain MR image at 13 mo in the same patient demonstrates expected fusion of the leaflets into a single membrane (arrow).

631.8 Dysgenesis of the Cranial Nerves and the Posterior Fossa

Sara K. Trowbridge, Edward Yang, and Christopher J. Yuskaitis

The classification of disorders of development of the cranial nerve, brainstem, and cerebellum remains anatomic, but future classification systems will likely be based on the molecular biology of brain development based on the genes involved and the roles they play in orchestrating brain architecture.

CONGENITAL CRANIAL DYSINNERVATION DISORDERS

Congenital cranial dysinnervation disorders (CCDDs) are congenital nonprogressive disorders that affect the cranial nerves, primarily presenting with abnormal eye and/or facial movements. These disorders include Möbius syndrome, Duane syndrome, and congenital fibrosis of the external ocular muscles (CFEOM). Increasingly, genetic causes for these disorders have been identified.

Möbius syndrome is generally characterized by bilateral facial weakness (seventh cranial nerve) and sixth nerve palsies (limited eye abduction). Injury or abnormal development at any level (i.e., cranial nerve nuclei, roots, nerves, or muscles) can lead to Möbius syndrome, but most patients have pathology at the level of the cranial nerve nuclei. The genetics of Möbius syndrome remain incompletely understood. Genetic linkage mapped inheritance to chromosome 13q12.2-q13, with identification of *de novo* pathogenic variants in *PLXND1* and *REV3L* in some patients. Environmental factors may also play a role. Affected infants present in the newborn period with facial weakness, causing feeding difficulties owing to a poor suck. Möbius syndrome can also be associated with other congenital anomalies, including talipes equinovarus (clubfoot), arthrogryposis, and syndactyly. Over 30% of patients with Möbius syndrome are reported to have autism spectrum disorder and/or intellectual disability.

Duane retraction syndrome is characterized by congenital limitation of horizontal globe movement and globe retraction and palpebral fissure narrowing on attempted adduction. This is caused by underdevelopment or absence of the abducens nuclei and nerves, as well as aberrant innervation of the lateral rectus muscle by the oculomotor nerve. Duane syndrome often occurs in families with an autosomal dominant pattern of inheritance, with three genes (*CHN1*, *MAFB*, and *SALL4*) identified thus far as well as associations with chromosome 8q13, 20q12, and 2q21.1.

Congenital fibrosis of the extraocular muscles (CFEOM) is characterized by severe restriction of eye movements and ptosis from abnormal oculomotor and trochlear nerve development and/or from abnormalities of extraocular muscle innervation. The most common form is caused by pathogenic autosomal dominant variants in *KIF21A*, which encodes a kinesin motor protein. Variants in *KIF21A* therefore lead to abnormal axonal transport. Other autosomal dominant causes

of CFEOM include pathogenic variants in the tubulin genes *TUBA1A*, *TUBB2B*, and *TUBB3*. Malformations of cortical development can also be associated with these and other tubulinopathy genes. Autosomal recessive forms of CFEOM are associated with variants in *PHOX2A* and *COL25A1*.

BRAINSTEM AND CEREBELLAR DISORDERS

Disorders of the posterior fossa structures include abnormalities not only of the brainstem and cerebellum but also of the CSF spaces.

Chiari malformation, the most common malformation of the posterior fossa and hindbrain, consists of downward displacement of the cerebellum and sometimes the brainstem through the foramen magnum. Often, there is an associated developmental abnormality of the bones of the skull base leading to a small posterior fossa. Chiari malformations are divided into three groups (type I, II, and III). In **Chiari type I**, the cerebellar tonsils are downwardly displaced (Fig. 631.15). Chiari type I malformations can be asymptomatic. When symptoms develop, they often do not do so until late childhood. Symptoms include headaches that are worse with straining and other Valsalva maneuvers that increase ICP. Symptoms of brainstem compression such as diplopia, oropharyngeal dysfunction, spasticity, tinnitus, sleep apnea, and

vertigo can also occur. Type I malformations are not associated with hydrocephalus. Syringomyelia of the spinal cord, especially in the cervical region, should be looked for on MRI imaging. This can result in neck pain, urinary frequency, and progressive lower extremity spasticity. Although the pathogenesis is unknown, a prevailing theory suggests that obstruction of the caudal portion of the fourth ventricle during fetal development is responsible. Chiari type I malformations may be associated with Ehlers-Danlos syndrome.

With **Chiari type II**, the inferior cerebellar vermis, cerebellar tonsils, and medulla are displaced through the foramen magnum. Most patients with myelomeningocele have a Chiari type II malformation (also see Neural Tube Defects). **Chiari type III**, the rarest form, also consists of downward displacement of the medulla, as well as a high cervical or occipital encephalocele. Chiari type II is usually identified early in life because of the association with myelomeningocele and, as with Chiari type I, can cause symptoms from brainstem compression. Complications for all the Chiari malformations include obstructive hydrocephalus and/or syringomyelia. Patients with Chiari type III are more severely affected, with high mortality and neurologic morbidity.

Dandy-Walker malformation consists of cystic dilation of the fourth ventricle, hypoplasia or agenesis of the cerebellar vermis, and an enlarged posterior fossa with elevation of the lateral venous sinuses and the tentorium (Fig. 631.16). Various associated brain malformations can also be seen, including agenesis of the corpus callosum and malformations secondary to abnormal neuronal migration. Most patients will develop hydrocephalus in infancy, and variable degrees of neurologic impairment are usually present. The etiology of Dandy-Walker malformation is heterogeneous and includes chromosomal abnormalities, single gene disorders, and exposure to teratogens. It is important to distinguish Dandy-Walker malformation from other causes of posterior fossa CSF collections (see Fig. 631.16). These include the **Blake pouch cyst**, a benign variant that consists of enlargement of the fourth ventricle, caused by persistence of the developmental Blake pouch structure. Isolated **mega cisterna magna**, another benign normal variant, refers to an enlarged cisterna magna with otherwise normal cerebellar architecture and size. Finally, posterior fossa **arachnoid cysts** can lead to hydrocephalus caused by obstruction of CSF flow but often remain asymptomatic.

Joubert syndrome and related disorders are a group of autosomal recessive disorders in which there is cerebellar vermis hypoplasia and the pontomesencephalic **molar tooth sign** (a deepening of the interpeduncular fossa with thick and straight superior cerebellar peduncles) (Fig. 631.17). It is associated with hypotonia, ataxia, characteristic breathing abnormalities including episodic apnea and hyperpnea (which improves with age), global developmental delay, nystagmus, strabismus, ptosis, and oculomotor apraxia. Joubert syndrome is

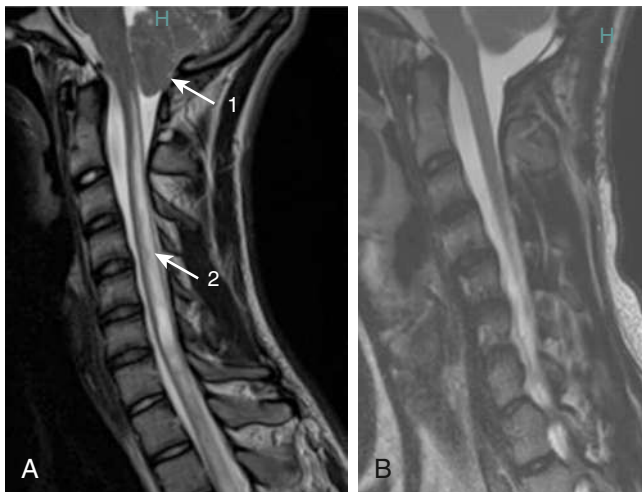


Fig. 631.15 A, A 16-yr-old male with Chiari malformation type 1 (arrow 1) and syringomyelia (arrow 2). B, Postoperative MRI reveals decompression of the Chiari malformation and resolution of the syrinx. (From Albert GW. Chiari malformation in children. *Pediatr Clin N Am*. 2021;68:783–792, Fig. 1, p. 786.)

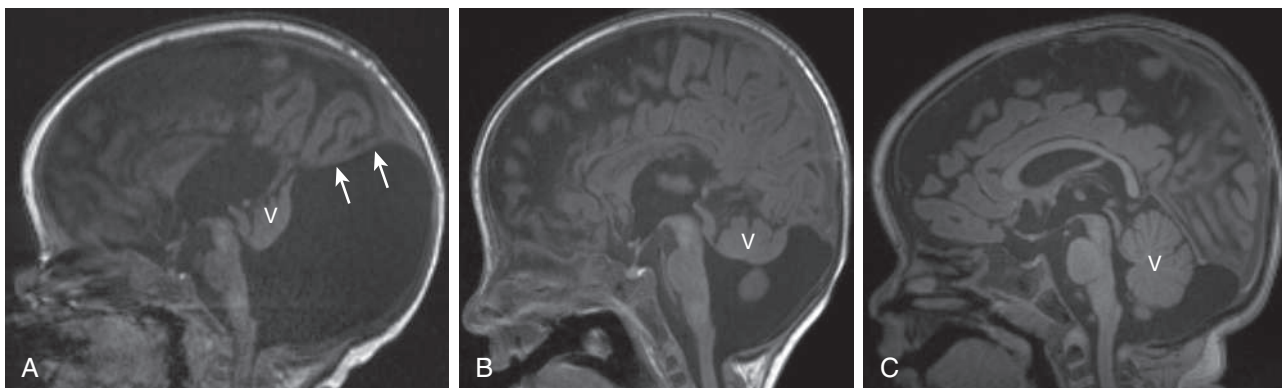


Fig. 631.16 Dandy-Walker spectrum posterior fossa abnormalities. Abnormal fenestration of embryologic outlets of the fourth ventricle and associated hypoplasia of the vermis (V in A–C) result in so-called Dandy-Walker spectrum. As illustrated by these sagittal T1-weighted brain MRI sequences, the most severe end of the spectrum consists of the classic Dandy-Walker malformation (A) where there is severe vermian hypoplasia and a remodeling of an enlarged posterior fossa CSF space (e.g., elevation of the tentorium and torcula above the confluence of the lambdoid sutures, arrows). At the least severe end of the spectrum, the vermis is fully formed but there is a prominent retrocerebellar and cisterna magna CSF space without expansion of the posterior fossa: a mega cisterna magna (C). In between these extremes, one may encounter vermian hypoplasia and posterior fossa CSF space prominence without overt expansion of the posterior fossa (e.g., vermian hypoplasia with rotation in B).

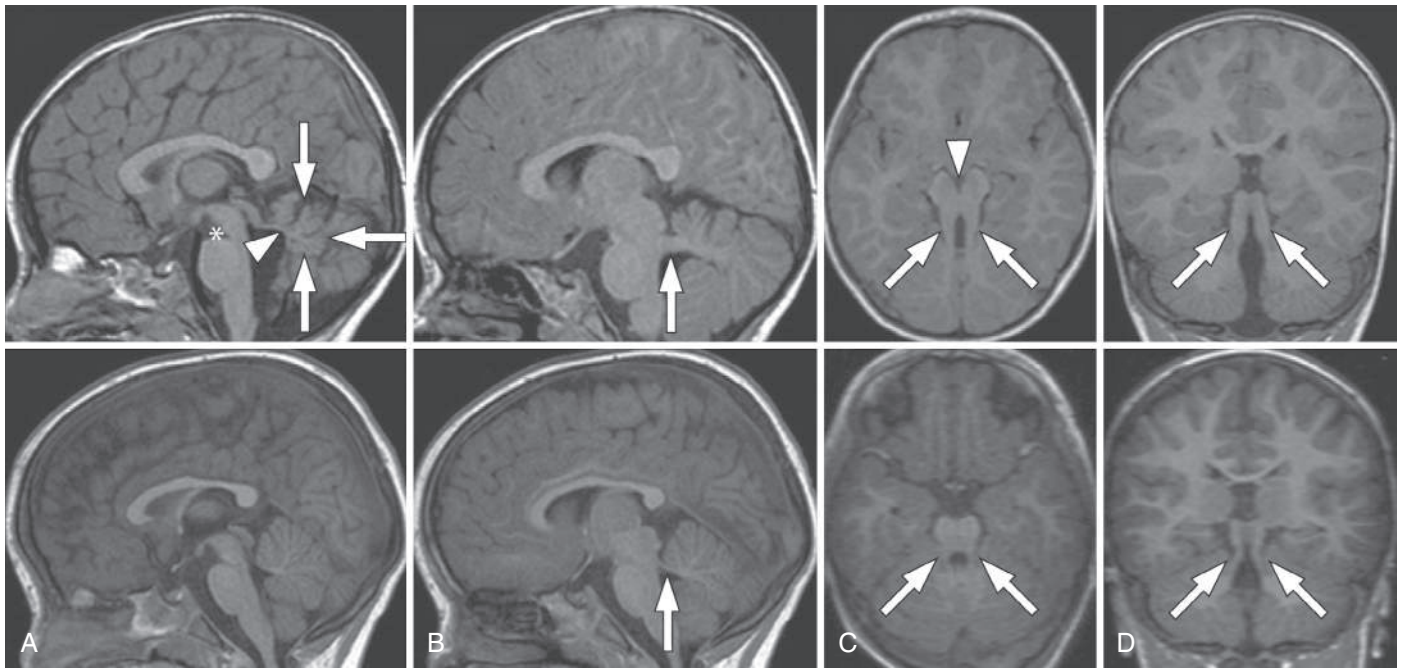


Fig. 631.17 Neuroimaging findings in a 2-yr-old child with pure Joubert syndrome (upper panels) compared with a healthy control (lower panels). A, Parasagittal T1-weighted image shows the thickened, elongated, and horizontally oriented superior cerebellar peduncles (white arrow). B, Mid-sagittal T1-weighted image demonstrates a moderate hypoplasia and dysplasia of the cerebellar vermis (white arrows) with secondary distortion and enlargement of the fourth ventricle, with rostral shifting of the fastigium (white arrowhead). A deepened interpeduncular fossa is also noted. C, Axial T1-weighted image at the level of the pontomesencephalic junction shows the molar tooth sign with a deepened interpeduncular fossa (white arrowhead) and elongated, thickened, and horizontally oriented superior cerebellar peduncles (white arrows). Additionally, the cerebellar vermis appears to be hypoplastic and its remnants dysplastic. D, Coronal T1-weighted image reveals the thickened superior cerebellar peduncles (white arrows). (From Romani M, Micalizzi A, Valente EM. Joubert syndrome: congenital cerebellar ataxia with the molar tooth. *Lancet Neurol.* 2013;12:894–905, Fig. 1.)

considered a ciliopathy, as many of the 35 genes implicated encode for proteins important in cilia function (e.g., *AH11*, *CC2D2A*, *CEP290*). There can also be associated systemic features, including progressive retinal dysplasia (Leber congenital amaurosis), coloboma, congenital heart disease, microcystic kidney disease, liver fibrosis, polydactyly, tongue protrusion, and soft tissue tumors of the tongue (Fig. 631.18).

Rhombencephalosynapsis consists of an absent or small vermis associated with a nonseparation or fusion of the deep midline cerebellar structures. Ventriculomegaly or hydrocephalus is often seen. There is a variable clinical presentation from normal function to cognitive and language impairments, epilepsy, and spasticity.

The **pontocerebellar hypoplasias** (PCHs) are a group of autosomal recessive disorders characterized by impairment of cerebellar and pontine development. Ten types have been defined to date, with increasing identification of underlying genetic causes (e.g., *TSEN2*, *TSEN34*, *RARS2*). Patients tend to be severely affected, with hypotonia, feeding difficulties, developmental delay, breathing difficulties, and seizures. Other disorders can also present with some PCH, most commonly including Walker-Warburg syndrome, muscle-eye-brain disease, congenital disorders of glycosylation type 1A, and mitochondrial cytopathies.

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631.9 Hydrocephalus

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Hydrocephalus is not a specific disease; it represents a diverse group of conditions that result from impaired circulation and/or absorption of CSF or, in rare circumstances, from increased production of CSF by a choroid plexus papilloma (Tables 631.6 and 631.7).

PHYSIOLOGY

The CSF is formed primarily in the ventricular system by the choroid plexus, which is situated in the lateral, third, and fourth ventricles. Although most CSF is produced in the lateral ventricles, approximately 25% originate from extrachoroidal sources, including the capillary endothelium within the brain parenchyma. There is active neurogenic control of CSF formation because adrenergic and cholinergic nerves innervate the choroid plexus. Stimulation of the adrenergic system diminishes CSF production, whereas excitation of the cholinergic nerves may double the normal CSF production rate. In a normal child, approximately 20 mL/hr of CSF is produced. The total volume of CSF approximates 50 mL in an infant and 150 mL in an adult. Most of the CSF is extraventricular. The choroid plexus forms CSF in several stages; through a series of intricate steps, a plasma ultrafiltrate is ultimately processed into a secretion, the CSF.

CSF flow results from the pressure gradient that exists between the ventricular system and venous channels. Intraventricular pressure may be as high as 180 mmH₂O in the normal state, whereas the pressure in the superior sagittal sinus is in the range of 90 mmH₂O. Normally, CSF flows from the lateral ventricles through the foramina of Monro into the third ventricle. It then traverses the narrow aqueduct of Sylvius, which is approximately 3 mm long and 2 mm in diameter in a child, to enter the fourth ventricle. The CSF exits the fourth ventricle through the paired lateral foramina of Luschka and the midline foramen of Magendie into the cisterns at the base of the brain. Hydrocephalus resulting from obstruction within the ventricular system is called *obstructive* or *noncommunicating hydrocephalus*. The CSF then circulates from the basal cisterns posteriorly through the cistern system and over the convexities of the cerebral hemispheres. CSF is absorbed primarily by the arachnoid villi through tight junctions of their endothelium by the pressure forces that were noted earlier. CSF is absorbed to a much lesser

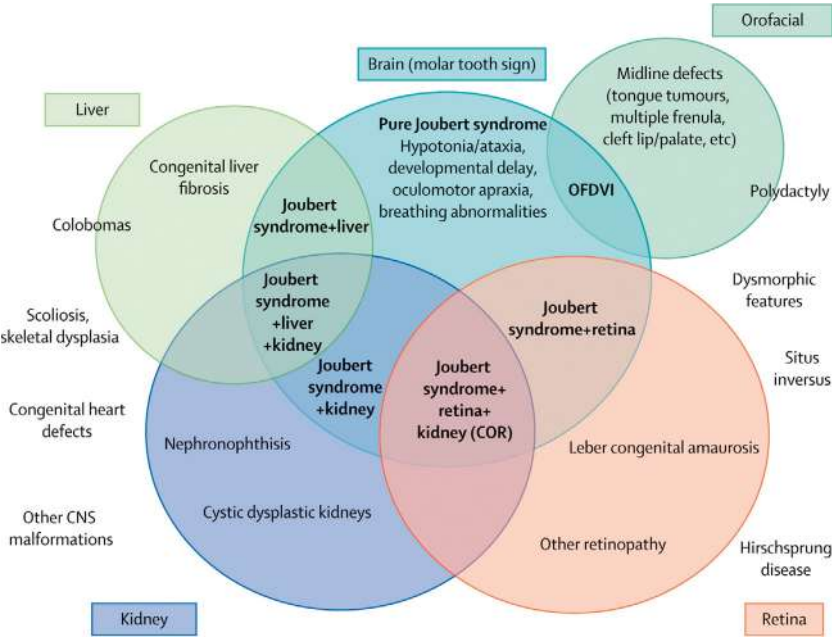


Fig. 631.18 Spectrum of organ involvement in Joubert syndrome and classification in clinical subgroups (*in bold*). Chorioretinal colobomas are more frequently found in the subgroup of Joubert syndrome with liver involvement but can be present also in other subgroups. Similarly, polydactyly (especially if preaxial or mesoaxial) is invariably present in the orofaciodigital type VI subgroup, but postaxial polydactyly is frequently observed also in association with other Joubert syndrome phenotypes. Other clinical features outside the circles occur more rarely, without a specific association to a clinical subgroup. CNS, Central nervous system; COR, cerebello-oculorenal; OFDVI, orofaciodigital type VI syndrome. (From Romani M, Micalizzi A, Valente EM. Joubert syndrome: congenital cerebellar ataxia with the molar tooth. *Lancet Neurol.* 2013;12:894–905, Fig. 3.)

Table 631.6 Causes of Pediatric Hydrocephalus		
CAUSE		PROPOSED MECHANISM
ACQUIRED HYDROCEPHALUS		
Inflammatory		
Subarachnoid hemorrhage or infection	Arachnoid scar	Dysfunctional subarachnoid space
Intraventricular hemorrhage or infection	Ependymal scar	Ventricular obstruction
Neoplasm		
Parenchymal brain tumor	Mass effect	Ventricular obstruction
Spinal cord tumor	Altered CSF composition	Dysfunctional subarachnoid space
Disseminated tumor	Tumors with meningeal infiltration (e.g., primitive neuroectodermal tumor)	Dysfunctional subarachnoid space
Choroid plexus tumor	Altered CSF composition	Dysfunctional subarachnoid space
Choroid plexus tumor	Mass effect	Ventricular obstruction
Choroid plexus tumor or hyperplasia	Altered choroid plexus function	CSF overproduction or hyperdynamic intraventricular pulsations
Vascular		
Vascular malformation	Ventricular obstruction (e.g., vein of Galen malformation); venous hypertension (e.g., arteriovenous malformation)	Ventricular obstruction; decreased venous compliance or decreased CSF absorption
Disordered cerebral venous function	Extrinsic venous obstruction (e.g., skeletal dysplasias); intrinsic venous obstruction (e.g., venous sinus thrombosis); idiopathic venous dysfunction (e.g., congenital idiopathic hydrocephalus)	Decreased venous compliance or decreased CSF absorption
CONGENITAL OR DEVELOPMENTAL HYDROCEPHALUS		
Congenital aqueduct stenosis	Third ventricle outlet obstruction	Ventricular obstruction
Neural tube defects (e.g., myelomeningocele and Chiari II malformation)	Third or fourth ventricle outlet obstruction; altered venous compliance; arachnoid or ependymal scar	Variable
Posterior fossa malformations	Fourth ventricle outlet obstruction (e.g., Dandy-Walker complex); Chiari I malformation	Ventricular obstruction
Developmental cysts	Mass effect	Ventricular obstruction
Congenital foramen of Monro atresia	Lateral ventricle outlet obstruction	Ventricular obstruction

From Kahle KT, Kulkarni AV, Limbick DD Jr, et al. Hydrocephalus in children. *Lancet.* 2016;387:788–798, Table 1.

extent by the lymphatic channels directed to the paranasal sinuses, along nerve root sleeves, and by the choroid plexus itself. Hydrocephalus resulting from obliteration of the subarachnoid cisterns or malfunction of the arachnoid villi is called *nonobstructive* or *communicating hydrocephalus*.

Table 631.7 Genetic Abnormalities Associated with Pediatric Hydrocephalus

	PUTATIVE GENETIC LINK
X-linked hydrocephalus with aqueduct stenosis (307000)	<i>L1CAM</i>
Nonsyndromic autosomal recessive hydrocephalus (HYC; 236600 [HYC1]; 615219 [HYC2])	<i>CCDC88C</i> ; <i>MPDZ</i>
Fried-type syndromic mental retardation (304340)	<i>AP1S2</i>
Walker-Warburg syndrome (multiple subtypes)	<i>POMT1</i> , <i>POMT2</i> , <i>POMGNT1</i> , and others
Neural tube defects (folate-sensitive [601634] and insensitive [182940] forms)	Multiple susceptibility genes involved in planar-cell polarity (e.g., <i>FUZ</i> , <i>VANGL1/2</i> , <i>CCL2</i> , and others); folate-sensitive neural tube defects associated with genes in folate synthesis pathway (<i>MTR</i> , <i>MTRR</i> , <i>MTHFR</i> , <i>MTHFD</i>)
Primary ciliary dyskinesias and other ciliopathies (including the many heterogeneous subtypes of Meckel-Gruber syndrome and Joubert syndrome)	Multiple genes involved in cilia structure, function, and regulation (e.g., <i>CC2D2A</i> , <i>TMEM67</i> , <i>MKS1</i> , and others)
RAS-opathies (e.g., neurofibromatosis type 1, Noonan syndrome, Costello syndrome, cardiofaciocutaneous syndrome)	<i>NF1</i> ; Ras-Raf-MEK-ERK pathway genes) e.g., <i>KRAS</i> , <i>BRAF</i> , <i>PTPN11</i> , and others)
VACTERL-H (association of vertebral, anal, cardiac, tracheoesophageal, renal, and limb anomalies plus hydrocephalus; 276950)	<i>PTEN</i>
X-linked VACTERL-H (300515)	<i>FANCB</i>

Numbers given are Online Mendelian Inheritance in Man (OMIM) identifiers. From Kahle KT, Kulkarni AV, Limbick DD Jr, et al. Hydrocephalus in children. *Lancet*. 2016;387:788–798, Table 2.

PATHOPHYSIOLOGY AND ETIOLOGY

Obstructive or noncommunicating hydrocephalus develops most commonly in children because of an abnormality of the aqueduct of Sylvius or a lesion in the fourth ventricle. Aqueductal stenosis results from an abnormally narrow aqueduct of Sylvius that is often associated with branching or forking (Fig. 631.19). In a small percentage of cases, aqueductal stenosis is inherited as a sex-linked recessive trait. These patients occasionally have minor neural tube closure defects, including spina bifida occulta. Rarely, aqueductal stenosis is associated with neurofibromatosis. Aqueductal gliosis can also give rise to hydrocephalus. As a result of neonatal meningitis or a subarachnoid hemorrhage in a premature infant, the ependymal lining of the aqueduct is interrupted, and a brisk glial response results in complete obstruction. Intrauterine viral infections can also produce aqueductal stenosis followed by hydrocephalus. A vein of Galen malformation can expand and, because of its midline position, obstruct the flow of CSF. Lesions or malformations of the posterior fossa are prominent causes of hydrocephalus, including posterior fossa brain tumors, Chiari malformation, and Dandy-Walker syndrome, as previously discussed.

Nonobstructive or communicating hydrocephalus most commonly follows a subarachnoid hemorrhage, which is usually a result of intraventricular hemorrhage in a premature infant. Blood in the subarachnoid spaces can disrupt CSF flow through the cisterns or damage the arachnoid villi resulting in obstruction of CSF flow. Pneumococcal and tuberculous meningitis have a propensity to produce a thick, tenacious exudate that obstructs the basal cisterns, and intrauterine infections can also destroy the CSF pathways. Leukemic infiltrates can seed the subarachnoid space and produce communicating hydrocephalus. Tumors or arteriovenous malformations in the spinal cord or cauda equina are uncommon etiologies of communicating hydrocephalus.

CLINICAL MANIFESTATIONS

The clinical presentation of hydrocephalus is variable and depends on many factors, including the age at onset, the nature of the lesion causing the obstruction, and the duration and rate of increase of the ICP. In an infant, an accelerated rate of enlargement of the head is the most prominent sign. In addition, the anterior fontanel is wide open and bulging, and scalp veins can be dilated. The forehead is broad, and the eyes might deviate downward (i.e., setting-sun eye sign) because of impingement of the dilated suprapineal recess on the brainstem tectum. Long-tract signs, including brisk tendon reflexes, spasticity, clonus (particularly in the lower extremities), and Babinski sign, are common because of stretching and disruption of the corticospinal fibers originating from the leg region of the motor cortex. In an older child, the cranial sutures are less accommodating, so that the signs of hydrocephalus may be subtler. Irritability, lethargy, poor appetite, and vomiting are common to both age-groups, and headache is a prominent symptom in older patients. A gradual

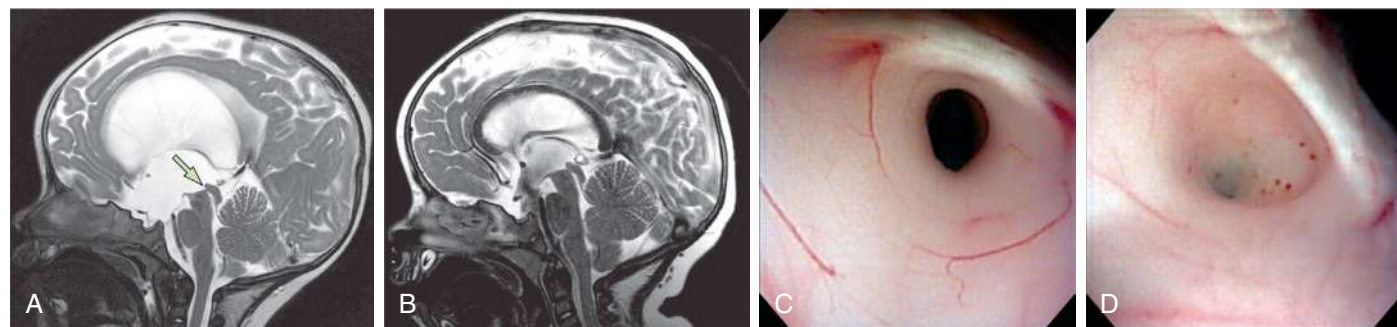


Fig. 631.19 Aqueeduct stenosis. A, Sagittal brain T2-weighted MRI of infant with hydrocephalus secondary to congenital aqueduct stenosis. Arrow indicates point of obstruction. B, Same patient after endoscopic third ventriculostomy; note dark flow void indicating flow across endoscopic third ventriculostomy. C, Endoscopic view of healthy patent aqueduct. D, Endoscopic view of obstructed aqueduct in aqueduct stenosis; note posterior commissure at dorsal margin of the aqueduct ostium in both A and B. (From Kahle KT, Kulkarni AV, Limbick Jr DD, et al. Hydrocephalus in children. *Lancet*. 2016;387:788–798, Fig. 1.)

change in personality and deterioration in academic productivity suggest a slowly progressive form of hydrocephalus. Percussion of the skull might produce a cracked pot sound or Macewen sign, indicating separation of the sutures. Serial head circumference measurements, with special attention to the velocity of growth, are important measurements when identifying hydrocephalus and tracking resolution. A foreshortened occiput suggests Chiari malformation, and a prominent occiput suggests Dandy-Walker malformation. Papilledema, abducens nerve palsies, and pyramidal tract signs, which are most evident in the lower extremities, are apparent in many cases.

Type II Chiari malformations can manifest with progressive hydrocephalus. Approximately 10% of type II malformations produce symptoms during infancy, consisting of stridor, weak cry, and apnea, which may be relieved by shunting or by decompression of the posterior fossa. A more indolent form consists of abnormalities of gait, spasticity, and increasing incoordination (including the arms and hands) during childhood. Plain skull radiographs show a small posterior fossa and a widened cervical canal. CT scanning with contrast and MRI display the cerebellar tonsils protruding downward into the cervical canal and the hindbrain abnormalities. The anomaly is treated by surgical decompression, but asymptomatic or mildly symptomatic patients may be managed conservatively.

Approximately 90% of patients with Dandy-Walker malformation have hydrocephalus, and a significant number of children have associated anomalies, including agenesis of the posterior cerebellar vermis and corpus callosum. Infants present with a rapid increase in head size and a prominent occiput. Most children have evidence of long-tract signs, cerebellar ataxia, and delayed motor and cognitive milestones, probably because of the associated structural anomalies. Dandy-Walker malformation is managed by shunting the cystic cavity (and on occasion the ventricles as well) in the presence of hydrocephalus.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Investigation of a child with hydrocephalus begins with the history. Familial cases suggest X-linked or autosomal hydrocephalus secondary to aqueduct stenosis. A history of prematurity with intracranial hemorrhage, meningitis, or mumps encephalitis is important to ascertain. Multiple café-au-lait spots and other clinical features of neurofibromatosis point to aqueductal stenosis as the cause of hydrocephalus.

Examination includes careful inspection, palpation, and auscultation of the skull and spine. The occipitofrontal head circumference is recorded and compared with previous measurements. The size and configuration of the anterior fontanel are noted, and the back is inspected for abnormal midline skin lesions, including tufts of hair, lipoma, or angioma, that might suggest spinal dysraphism. The presence of a prominent forehead or abnormalities in the shape of the occiput can suggest the pathogenesis of the hydrocephalus. A cranial bruit is audible in association with many cases of vein of Galen arteriovenous malformation (Fig. 631.20). Transillumination of the skull is positive with massive dilation of the ventricular system or in Dandy-Walker syndrome. A fundoscopic exam is mandatory because the finding of chorioretinitis suggests an intrauterine infection, such as toxoplasmosis, as a cause of the hydrocephalus. Papilledema is observed in older children but is rarely present in infants because the cranial sutures separate in the setting of the increased pressure.

An ultrasound is a quick and easy study to perform on infants with an open fontanelle to identify and monitor the trajectory of hydrocephalus. Brain MRI has the capability to perform specific sequences to evaluate CSF flow dynamics as well as evaluating for etiology and additional abnormalities that may be present. In many centers, CT scans are often limited to evaluating for acute symptomatic hydrocephalus and skull abnormalities to avoid radiation exposure. Although rarely used, plain skull films can show separation of the sutures, erosion of the posterior clinoids in an older child, and an increase in convolutional

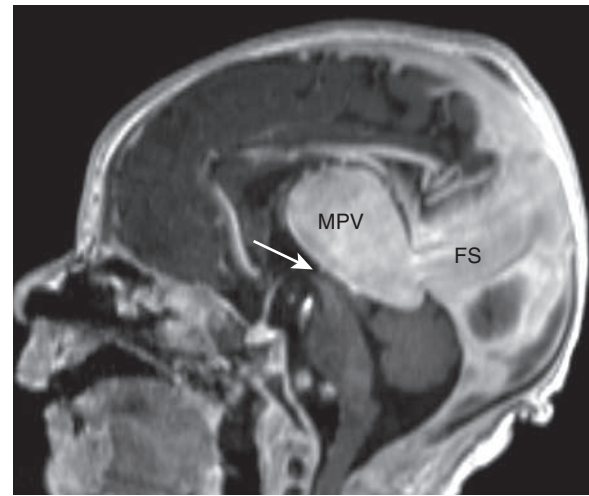


Fig. 631.20 Vein of Galen malformation. A vein of Galen malformation is an arteriovenous fistula between intracranial arteries and the embryologic median prosencephalic vein. As seen in this postcontrast sagittal T1-weighted brain MR image of a newborn with a prenatally diagnosed vein of Galen malformation, this vascular malformation is characterized by marked distension of the median prosencephalic vein (MPV) and distension of downstream dural sinuses, commonly through a persistent embryologic falcine sinus (FS). The ensuing high-velocity arteriovenous shunting can cause venous hypertension, communicating hydrocephalus, and high-output cardiac failure. Although large median prosencephalic veins can compress the cerebral aqueduct (arrow), the primary treatment modality is still endovascular intervention (embolization) rather than CSF diversion.

markings (beaten-silver appearance) on the inside of the skull with long-standing increased ICP.

Rapid head growth raises suspicion of hydrocephalus; however, other etiologies must be considered. Accelerated skull growth from a thickened cranium can result from chronic anemia, rickets, osteogenesis imperfecta, and epiphyseal dysplasia. Chronic subdural collections can produce bilateral parietal bone prominence. Benign external hydrocephalus is often associated with macrocephaly with notable increase in volume of the subarachnoid spaces on brain imaging. No intervention is required for this self-limited hydrocephalus, which is hypothesized to be the result of a delayed maturation of the arachnoid villi. Various metabolic and degenerative disorders of the CNS produce megalencephaly as a result of abnormal storage of substances within the brain parenchyma. These disorders include lysosomal diseases (Tay-Sachs disease, gangliosidosis, and the mucopolysaccharidoses), the aminoacidurias (maple syrup urine disease), and the leukodystrophies (metachromatic leukodystrophy, Alexander disease, Canavan disease). In addition, cerebral gigantism (Sotos syndrome), other overgrowth syndromes, and neurofibromatosis are characterized by increased brain mass. Familial megalencephaly is inherited as an autosomal dominant trait and is characterized by delayed motor milestones and hypotonia but normal or near-normal intelligence. Measurement of the parents' head circumferences is necessary to establish the diagnosis.

Ventriculomegaly can exist without increased ICP (normal-pressure hydrocephaly) or in patients with loss of white or gray matter secondary to prior injury (cerebral atrophy with ventricular dilation ex vacuo). It can be difficult to distinguish between ventriculomegaly and true hydrocephalus by static neuroimaging alone unless CSF flow assessment is included in the MRI. Additional clinical information (e.g., clinical context, fundoscopic exam, lumbar puncture with pressure measurements) may also be required. This is an important clinical distinction to make, as the management of ventriculomegaly secondary to hydrocephalus is quite different from the management of ventriculomegaly secondary to brain volume loss.

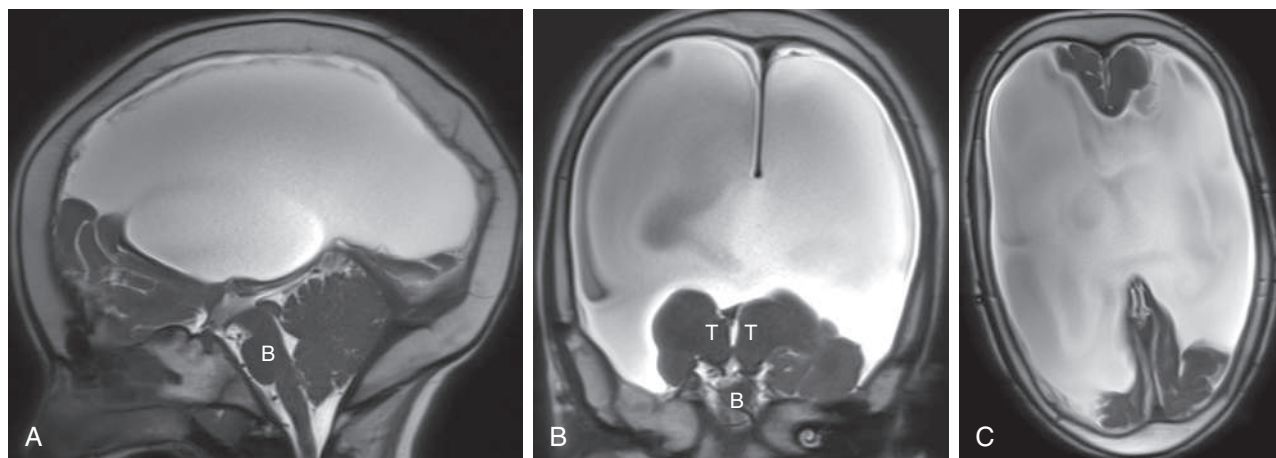


Fig. 631.21 Hydranencephaly. Brain MRI sagittal (A), coronal (B), and axial (C) single-shot T2-weighted images of a 13-yr-old female with severe neurologic impairment demonstrates lysis of the cerebral hemispheres apart from small remnants of the frontal/occipital poles and left temporal pole. There is preservation of the thalami (T) and brainstem (B). This congenital lysis of the cerebrum is dubbed *hydranencephaly* and believed to reflect anterior circulation vascular insufficiency in utero.

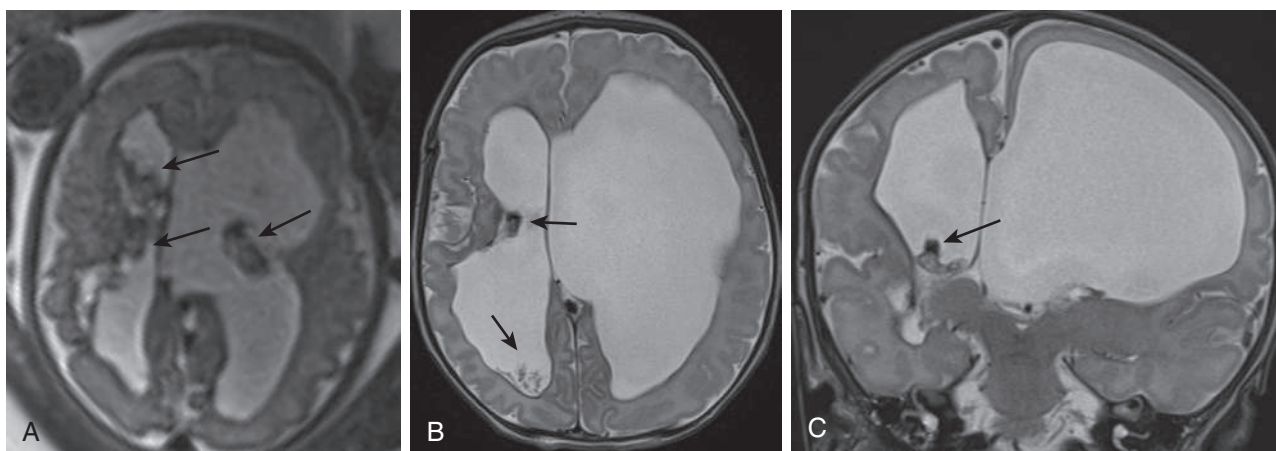


Fig. 631.22 Porencephaly from in utero encephaloclastic/hemorrhagic injury. High-grade in utero germinal matrix hemorrhage results in venous infarction and hemorrhagic injury to the brain parenchyma. As a result, there is focal lysis and thinning of the brain parenchyma, resulting in a hemispheric cavity in communication with the ventricular system called *porencephaly*. A, Axial single-shot brain MR T2-weighted imaging of a fetus at 32 wk demonstrates severe ventriculomegaly with a clot in the ventricular system (arrows) and hemosiderin-stained (hypointense) tissue lysis in the surrounding cerebral hemispheres. Axial (B) and coronal (C) T2-weighted imaging of the same patient during the first day of life better depicts the areas of hemosiderin staining and parenchymal thinning/lysis as well as residual clot in the ventricular system (arrows).

HYDRANENCEPHALY

Hydranencephaly may be confused with hydrocephalus. The cerebral hemispheres are absent or represented by membranous sacs with remnants of frontal, temporal, or occipital cortex dispersed over the membrane. The midbrain and brainstem are relatively intact (Fig. 631.21). The cause of hydranencephaly is unknown, but bilateral occlusion of the internal carotid arteries during early fetal development would explain most of the pathologic abnormalities. Affected infants can have a normal circumference at birth that grows at an excessive rate postnatally because of excessive CSF production and absorption. Transillumination shows an absence of the cerebral hemispheres. The child is irritable, feeds poorly, develops seizures and spastic quadriplegia, and has little or no cognitive development. A ventriculoperitoneal shunt prevents massive enlargement of the cranium.

PORENCEPHALY

Porencephaly is the presence of cysts or cavities within the brain that result from developmental defects or acquired lesions, including

infarction of tissue. True porencephalic cysts are most commonly located in the region of the sylvian fissure and typically communicate with the subarachnoid space or the ventricular system, or both. They represent developmental abnormalities of cell migration and are often associated with other malformations of the brain, including microcephaly, abnormal patterns of adjacent gyri, and encephalocele. Affected infants tend to have many problems, including intellectual disability, spastic hemiparesis or quadriplegia, optic atrophy, and seizures.

Several risk factors for porencephalic cyst formation have been identified, including hemorrhagic venous infarctions, various thrombophilias such as protein C deficiency and factor V Leiden variants, perinatal alloimmune thrombocytopenia, von Willebrand disease, maternal warfarin use, maternal cocaine use, congenital infections, trauma such as amniocentesis, and maternal abdominal trauma. Pathogenic variants in the *COL4A1* and *COL4A2* genes have been described in cases of familial porencephaly (Fig. 631.22).

TREATMENT

Therapy for hydrocephalus depends on the cause. Medical management, including the use of acetazolamide and furosemide, can provide temporary relief by reducing the rate of CSF production, but long-term results have been disappointing. Most cases of hydrocephalus require extracranial shunts, particularly a ventriculoperitoneal shunt. Endoscopic third ventriculostomy is a viable approach, and criteria have been developed for its use, but the procedure might need to be repeated to be effective. Endoscopic fenestration of the floor of the third ventricle with drainage into the subarachnoid space (pre-pontine cistern) is attempted in patients over 6 months of age with noncommunicating hydrocephalus. It often requires cauterization of the choroid plexus as an additional procedure (see Fig. 631.19). Ventricular shunting may be avoided with this approach. The major complications of shunting are occlusion (characterized by headache, papilledema, emesis, and mental status changes) and bacterial infection (fever, headache, meningismus), usually caused by *Staphylococcus epidermidis*. With meticulous preparation, the shunt infection rate can be reduced to <5%. The results of intrauterine surgical management of fetal hydrocephalus have been poor (possibly because of the high rate of associated cerebral malformations in addition to the hydrocephalus) except for some promise in cases of hydrocephalus associated with fetal meningomyelocele.

PROGNOSIS

The prognosis depends on the cause of the dilated ventricles and not on the size of the cortical mantle at the time of operative intervention, except in cases in which the cortical mantle has been severely compressed and stretched. Children with hydrocephalus are at increased risk for various developmental disabilities. The mean intelligence quotient is reduced compared with the general population, particularly for performance tasks as compared with verbal abilities. Many children have abnormalities in memory function. Vision problems are common, including strabismus, visuospatial abnormalities, visual field defects, and optic atrophy with decreased acuity secondary to increased ICP. The visual evoked potential latencies are delayed and take some time to recover after correction of the hydrocephalus. Accelerated pubertal development in patients with shunted hydrocephalus or myelomeningocele is relatively common, possibly because of increased gonadotropin secretion in response to increased ICP. It is imperative that children with hydrocephalus receive long-term follow-up in a multidisciplinary setting.

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631.10 Craniosynostosis

Irene M.J. Mathijssen

See also Chapter 101.4.

Craniosynostosis is defined as premature closure of the cranial sutures and is classified as primary or secondary. It is associated with varying types of abnormal skull shape (see Fig. 101.5). Primary craniosynostosis refers to closure of one or more sutures owing to abnormalities of skull development, whereas secondary craniosynostosis results from failure of brain growth and expansion (e.g., microcephaly or after insertion of a ventriculoperitoneal shunt), specific medication during pregnancy (e.g., valproate), or metabolic disorders. The incidence of primary craniosynostosis approximates 1 in 2,000 live births. The cause is unknown in the majority of children; however, genetic syndromes account for 10–20% of cases (see Table 101.5). The distinction between craniosynostosis and deformational forces is important in occipital and frontal plagiocephaly to allow successful intervention to be offered in the form of physical therapy for torticollis and other positional asymmetries that lead to plagiocephaly.

Table 631.8 Commonly Used Clinical Genetic Classifications of Craniosynostoses

DISORDER	CAUSE
ISOLATED CRANIOSYNOSTOSIS	
Unicoronal synostosis	Unknown, consider <i>TWIST1</i> , <i>FGFR1</i> , <i>FGFR2</i> , <i>FGFR3</i> , <i>TCF12</i> , <i>IL11RA</i> , <i>ERF</i> pathogenic variants
Metopic and sagittal synostosis	<i>SMAD6</i>
SYNDROMIC CRANIOSYNOSTOSIS	
Antley-Bixler syndrome	<i>FGFR2</i> , <i>POR</i>
Apert syndrome	Usually one of two pathogenic variants in <i>FGFR2</i>
Beare-Stevenson syndrome	<i>FGFR2</i>
Baller-Gerold syndrome	<i>RECQL4</i>
Carpenter syndrome	<i>RAB23</i> in most; <i>MEGF8</i> in some
Craniofrontonasal syndrome	<i>EFNB1</i>
Crouzon syndrome (and Pfeiffer syndrome)	Numerous different pathogenic variants at <i>FGFR2</i> ; rarely <i>FGFR1</i>
Crouzon acanthosis nigricans syndrome	Ala391Glu pathogenic variants in <i>FGFR3</i>
Muenke syndrome	Pro250Arg pathogenic variants in <i>FGFR3</i>
Saethre-Chotzen syndrome	Pathogenic variants or deletion in <i>TWIST1</i>
TCF-12 related craniosynostosis	Pathogenic variants or deletion of <i>TCF12</i>
IL11RA-related craniosynostosis	<i>IL11RA</i>
ERF-related craniosynostosis	<i>ERF</i>
Shprintzen-Goldberg syndrome	Pathogenic variants in <i>FBN1</i> or <i>SKI</i>

DEVELOPMENT AND ETIOLOGY

The bones of the cranium are well developed by the fifth month of gestation (frontal, parietal, temporal, and occipital) and are separated by sutures and fontanels. The brain grows rapidly in the first several years of life and is normally not impeded because of equivalent growth along the suture lines. The cause of craniosynostosis is largely unknown. Genetic factors have been identified for some isolated and for many syndromic causes of craniosynostosis (Table 631.8; see Table 101.5).

CLINICAL MANIFESTATIONS AND TREATMENT

Most cases of craniosynostosis are evident at birth and are characterized by a progressive skull deformity that is a direct result of premature suture fusion. Fusion of metopic and sagittal suture reveals a palpable prominent bony ridge, and fusion of the suture may be confirmed by plain skull roentgenograms, ultrasound, 3D-CT scan, or black bone MRI (Table 631.9).

Scaphocephaly is the result of premature closure of the sagittal suture and produces a long and narrow skull, the most common form of craniosynostosis. Scaphocephaly is associated with a prominent occiput, a broad forehead, and a triangular-shaped anterior fontanel. The condition is sporadic, is more common in males, and can cause difficulties during labor because of cephalopelvic disproportion resulting from a head circumference of ≥ 2 SD. Scaphocephaly is associated with increased ICP in about 10% of patients

Table 631.9 Epidemiology and Clinical Characteristics of the Common Craniosynostoses

TYPE	EPIDEMIOLOGY	SKULL DEFORMITY	CLINICAL PRESENTATION
Sagittal	Most common CSO affecting a single suture, 80% male	Dolichocephaly or scaphocephaly (boat-shaped)	Frontal bossing, prominent occiput, palpable keel ridge; OFC increased and reduced biparietal diameter
Coronal	More common in girls Associated with various syndromes	Unilateral: plagiocephaly Bilateral: brachycephaly	Unilateral: flattened forehead and elevated orbit on affected side, nose deviation; higher supraorbital margin Bilateral: broad, flattened forehead.
Lambdoid	Rare	Unilateral: Lambdoid/occipital plagiocephaly Bilateral: pachycephaly	Unilateral: flattening of ipsilateral occiput, bulging of ipsilateral forehead, ipsilateral ear and mastoid is inferiorly displaced, curvature in face Bilateral: brachycephaly with bilateral inferiorly displaced ears and mastoids
Metopic	SMAD 6 mutation; genetic overlap with developmental delay disorders	Trigonocephaly	Pointed forehead and midline ridge, hypotelorism
Multiple	Often syndromic	Depending on which sutures are involved	

CSO, Craniosynostosis; OFC, occipital–frontal circumference.

at the age of 12 months if left untreated and thus requires surgical treatment.

Trigonocephaly is the next most common form of craniosynostosis, caused by premature fusion of the metopic suture. These children have a keel-shaped forehead and hypotelorism and are at risk for associated cognitive impairment, behavioral problems and visual disturbances. The phenotype also includes milder presentations, which are usually self-limiting over time. Metopic ridging occurs with closure of the suture around the time of birth and is a physiologic process. The risk on increased ICP is limited, even in the more severe presentation.

Frontal plagiocephaly is characterized by unilateral flattening of the forehead, elevation of the orbit and eyebrow, and a caudal displacement of the ear on the corresponding side, with contralateral bossing of the forehead. The condition is more common in females and is the result of premature fusion of one of the coronal sutures. These children can present with raised ICP in up to 16% at 1 year of age and have a high risk of visual disturbances. Therefore skull surgery is indicated in addition to close monitoring by the optometrist. Unicoronal synostosis can be a presentation of a syndrome, and genetic analysis is always indicated (see Table 101.5).

Occipital plagiocephaly is most often a result of positioning during infancy and is more common in an immobile child or a child with a disability, but fusion of the lambdoid suture can cause unilateral occipital flattening and caudal displacement of the ipsilateral ear and mastoid and of the contralateral parietal bone. Surgery is indicated to prevent the development of distinct asymmetry of the face.

GENETIC DISORDERS

The most prevalent genetic disorders associated with craniosynostosis include Crouzon, Apert, Saethre-Chotzen, and Muenke syndromes.

Crouzon syndrome (including Pfeiffer syndrome) is characterized by premature craniosynostosis and is inherited as an autosomal dominant trait. The shape of the head depends on the timing and order of suture fusion but often is a compressed back-to-front diameter or **brachycephaly** resulting from bilateral closure of the coronal sutures. Pansynostosis is also common, in which all sutures close and the skull shape appears to be normal initially. The orbits

are underdeveloped, and ocular proptosis is prominent. Hypoplasia of the maxilla and orbital hypertelorism are typical facial features. Crouzon syndrome can be associated with the skin condition acanthosis nigricans.

Apert syndrome has many features in common with Crouzon syndrome. Apert syndrome is usually a sporadic condition and linked to increased paternal age, although autosomal dominant inheritance can occur. It is associated with premature fusion of multiple sutures, especially the two coronal sutures. Apert syndrome is characterized by symmetric complex syndactyly of the hands and feet. Severe acne often develops during puberty, and most patients have a developmental delay.

Saethre-Chotzen syndrome is characterized by unicoronal or bicoronal synostosis. The condition is inherited as an autosomal dominant trait. It is associated with ptosis of one or both eyelids, short fingers, and soft tissue syndactyly of the second and third fingers and/or toes.

Muenke syndrome is the most prevalent of the genetic syndromes and usually presents with bicoronal synostosis. It is associated with sensorineural hearing loss and behavioral issues.

Pathogenic variants of the fibroblast growth factor receptor (FGFR) gene family have been shown to be associated with specific types of craniosynostosis. Crouzon syndrome is mainly caused by variants in *FGFR2* and incidentally of *FGFR1* and *FGFR3*. Apert syndrome is mainly caused by two specific types of *FGFR2* variants. Saethre-Chotzen syndrome results from variants or deletions in *TWIST1*, and Muenke syndrome is solely caused by the Pro250Arg variant in *FGFR3*.

Each of the genetic syndromes poses a risk of additional anomalies, including hydrocephalus, increased ICP, optic atrophy, respiratory problems secondary to upper airway anomalies, and disorders of speech and hearing. Vault expansion is mandatory for management of increased ICP, treatment to reduce the respiratory difficulties such as midface advancement, and a multidisciplinary craniofacial team is essential for the long-term follow-up of affected children until adulthood. Craniosynostosis may be surgically corrected with good outcomes and relatively low morbidity and mortality, especially for nonsyndromic infants.

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Chapter 632

Deformational Plagiocephaly

Megan L. Dietze-Fiedler and John A. Girotto

Deformational plagiocephaly (DP), also known as positional plagiocephaly, is the development of cranial flattening and asymmetry in the infant as a result of extrinsic molding forces placed on the skull, such as consistently sleeping on the same area of the head. Since the suggestion was made to place sleeping infants on their backs for the prevention of sudden infant death syndrome, the incidence of DP has risen dramatically, up to 46.6% and peaking between 7 weeks and 4 months of age.

EPIDEMIOLOGY AND ETIOLOGY

Risk Factors

Infants cannot reposition their heads in the first few postnatal weeks and are unable to hold their heads up until about 4 months of age. It is for this reason that DP is most severe around 4 months of age. It is also during this time that an infant's head circumference increases rapidly: about 2 cm/month in the first 3 months, 1 cm/month from 4 to 6 months of age, and 0.5 cm/month after 6 months of age. By ~6 months of age, infants have developed head control, and this ability to actively reposition their head allows for the gradual improvement of the cranial shape because of pressure offloading and continued brain growth.

Congenital torticollis, positional preference when sleeping, and lower levels of activity are especially prominent in patients with DP. Table 632.1 lists other risk factors. Many of these risk factors cannot be prevented, but sleeping supine with the head always turned to the same side is associated with DP independent of the other factors, and this factor can be prevented. There may be an association between developmental delay and DP. Although not causal, studies have identified significant differences in gross motor development (e.g., sitting up, crawling, and rolling back to side) between babies with and without DP. Family demographics, such as lower maternal education, primiparity, more prenatal education, and siblings with cranial asymmetries, may also be associated with the development of DP. The increased prevalence of DP in infants of mothers receiving more prenatal education is considered related to the emphasis placed on sudden infant death syndrome and the Back to Sleep campaign.

Causes

Prenatal causes of DP include uterine compression and intrauterine constraint, such as occurs with oligohydramnios or multifetus

pregnancy. Postnatal causes of DP include infant sleeping position and congenital muscular torticollis.

Muscular torticollis is a condition that is present in as many as one in six newborns and causes continuous tightening of muscles in the neck, preventing passive rotation (see Chapter 721.1). It is thought that this condition precedes the development of cranial deformity. However, head position preference may result from cervical asymmetry that leads to torticollis and later flattening of a side of the skull from acquired positional preference. Muscular and positional issues lead to nonsynostotic plagiocephaly rather than the opposite. Given that DP results from more time spent on one side of the head and that torticollis (and other neck muscle imbalances) are likely to lead to this disproportional partitioning of time, they are most likely causes, not effects, of DP.

Sleeping position plays a major role in the incidence of DP. When an infant continuously sleeps with the same part of the skull resting on a flat surface, a continuous force is placed in this area. During this time of rapid skull development, the growth is inhibited at the area where it rests on a hard surface, causing a flat spot. Because of this inhibition, growth is increased in opposite directions, causing a deformation that can be distinguished from other types of plagiocephaly.

EXAMINATION AND DIFFERENTIATING BETWEEN DEFORMATIONAL PLAGIOCEPHALY AND CRANIOSYNOSTOSIS

An abnormal head shape in an infant is distressing for parents. DP is a clinical diagnosis. Management also requires accurate counseling about its cause and treatment. It is especially important to be able to rule out **craniosynostosis** as a primary cause for cranial asymmetry in infants because management of this condition is quite different from that of DP and requires immediate referral to a craniofacial surgeon for evaluation (see Chapter 631.10). Craniosynostosis occurs in approximately 1 in 2,000 live births and results in plagiocephaly as a consequence of the early closure of skull sutures. Craniosynostosis must be distinguished from DP because the management is different. Lambdoidal craniosynostosis, although extremely rare (1 in 300,000 live births), presents with features most similar to those of DP. It can be distinguished from DP by a variety of historical and physical findings. Bilateral coronal synostosis also presents similarly to posterior DP.

History and Physical Examination

Tables 632.2 and 632.3 outline the key components of the history and physical examination.

Observation of cranial shape and ear displacement are the first steps. It is critical to observe the child anteriorly, laterally, and from a vertex view. When cranial shape is viewed from above, DP typically looks like a **parallelogram**, and the ear on the same side of the flat or bald spot is **displaced anteriorly**. In lambdoidal craniosynostosis, the head has a trapezoid shape and the ear on the same side as the flat spot is posteriorly displaced (Fig. 632.1). It is important to note that the ear position, though more likely to be anterior in DP and posterior in lambdoidal craniosynostosis, may present anteriorly in both conditions.

Palpation will help to differentiate these two conditions. Craniosynostosis presents with palpable ridges along the suture, whereas DP does not. Additionally, patients with craniosynostosis will not have mobile calvarial bones. This can be tested by applying gentle pressure on two adjacent skull bones separated by a suspected synostotic suture. If the plates do not move relative to each other, then the suspicion for craniosynostosis is raised.

Verifying neck muscle tone and range of motion is a key part of the examination because it helps in evaluating motor development and in diagnosing congenital torticollis. Resistance to passive motion raises the concern for torticollis. Decreased tone should prompt further evaluation of motor development. Infants do not gain the muscle control to turn or lift their heads until approximately 4 months of age, and delays in motor development could increase the infant's risk of DP at later

Table 632.1 Factors that Increase the Risk for Deformational Plagiocephaly

- Male
- First-born child
- Prematurity
- Multiple pregnancy (twins, triplets)
- Limited passive neck rotation at birth (e.g., congenital torticollis)
- Developmental delay
- Sleep position is supine at birth and at 6 wk
- Bottle feeding only
- Tummy time <3 times/day
- Lower activity level, slower milestone achievement
- Sleeping with head to same side, positional preference

Table 632.2 Important Factors to Evaluate in the History and Physical Examination of the Patient with Plagiocephaly

	DEFORMATIONAL	SYNOSTOTIC
Birth history	Intrauterine compression First-born child	Typically no complications
Head shape at birth	Typically normal	Can be irregular
Age at which shape irregularity first noticed	Usually in first few months of life	Can be at birth
How patient prefers to sleep	Same side, same position Same even during naps	Variable
Bald spot	Yes	No
Motor development for age	If age is atypical for deformational plagiocephaly, motor development is typically slow for age Torticollis present History of limited activity or mobility	Varies depending on presence of concomitant syndrome
Tummy time	Decreased	Suggested time
Signs or symptoms of increasing intracranial pressure	No	Possible

Table 632.3 Key Differences Between Synostotic (Craniosynostosis) and Deformational Plagiocephaly

	DEFORMATIONAL PLAGIOCEPHALY	CRANIOSYNOSTOSIS
Causes	External forces applied to the skull Prenatal: uterine compression, intrauterine constrained Postnatal: congenital torticollis, sleeping position	Premature fusion of one or more cranial sutures
Common types	Lateral Posterior	Bilateral coronal Sagittal Metopic
Common distinguishing features	Normal round head shape at birth Parallelogram shape to head Ipsilateral ear anteriorly displaced No palpable bony ridges or open fontanelles	Can have abnormal head shape at birth Trapezoid shape to head Ipsilateral ear posteriorly displaced Palpable bony ridges
Management	Repositioning Physical therapy Helmet in some cases	Surgery Helmet in some cases

Adapted from Niel LS, Brunner MD, Kamat D. The infant with a misshapen head. *Clin Pediatr (Phila)*. 2007;46:292–298, Tables 1 and 2.

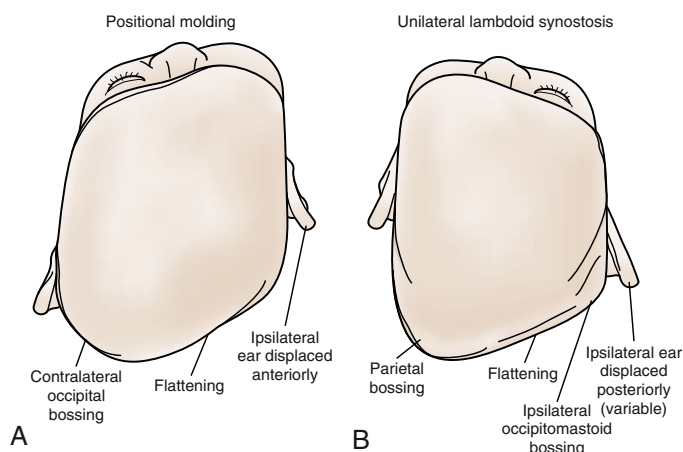


Fig. 632.1 Differentiating physical findings between deformational plagiocephaly and craniosynostosis. Vertex views. **A**, Right-sided deformational plagiocephaly exhibiting a parallelogram head shape. **B**, Right-sided lambdoid craniosynostosis exhibiting a trapezoid-like head shape. (From Lin AY, Losee JE. *Pediatric plastic surgery*. In: Zitelli BJ, McIntire SC, Norwalk AJ, eds. *Zitelli and Davis' Atlas of Pediatric Physical Diagnosis*, 6th ed. Philadelphia: Elsevier; 2012: Fig. 22-5.)

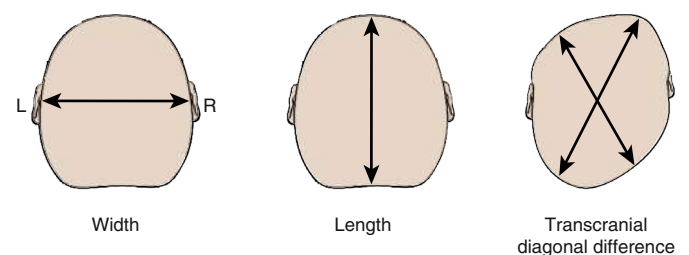


Fig. 632.2 Cranial measurements. (Modified from Looman WS, Flannery AB. *Evidence-based care of the child with deformational plagiocephaly, part I: assessment and diagnosis*. *J Pediatr Health Care*. 2012;26:242–250, Table 1.)

ages than those at which it usually occurs. Decreased range of motion can also be seen in cervical spine abnormalities, although this is rare. Early recognition of these conditions is critical in treatment, management, and outcome.

Accurate and consistent measurements will help to distinguish etiologies and manage infants presenting with an abnormally shaped skull. Along with the usual head circumference measurements, the clinician should also measure cranial width, length, and transcranial diagonal diameter (Fig. 632.2), which is best performed with calipers. These

Table 632.4 Diagnostic Guide for Determining Type and Severity of Lateral and Posterior Deformational Plagiocephaly

LATERAL DEFORMATIONAL PLAGIOCEPHALY		POSTERIOR DEFORMATIONAL PLAGIOCEPHALY (BRACHYCEPHALY)			
DETERMINING TYPE BASED ON CLINICAL FINDINGS					
Occiput (vertex view)	Ipsilateral occipital flattening; contralateral occipital bossing	Uniform occipital flattening			
Ear position (vertex view)	Ipsilateral ear may be anteriorly displaced	Normal			
Face, forehead (anterior, lateral, and vertex views)	May be normal; more severe cases may present with the following: mandibular asymmetry, ipsilateral frontal bossing, contralateral forehead flattening, ipsilateral cheek anteriorly displaced	Temporal bossing, increase in vertical height in severe cases			
Other	Torticollis, head position preference	Large size, history of limited activity or limited mobility			
DETERMINING SEVERITY					
Mild	TDD 3-10mm	Type I	Flattening restricted to back of the skull	CI: 0.82-0.9	Central posterior deformity (ping-pong ball depression)
Moderate	TDD 10-12 mm	Type II	Malposition of ear	CI: 0.9-1.0	Central posterior deformity and widening of posterior skull
		Type III	Forehead deformity		
Severe	TDD > 12 mm	Type IV	Malar deformity	CI: >1.0	Vertical head, head growth, or temporal bossing
		Type V	Vertical or temporal skull growth		

CI, Cephalic index (cranial index); TDD, transcranial diagonal diameter difference.

measurements allow the clinician to diagnose, determine severity, and monitor the plagiocephaly:

- **Cranial length:** Distance from the most prominent point between the eyebrows to the most prominent point of the occiput.
- **Width:** Maximum transverse diameter, horizontal.
- **Cephalic index** (cranial index): Ratio of the cranial width to the cranial length.
- **Occipital-frontal transcranial diameter:** Find the points on either side of the head where the deformation is the worst (two on the right, two on the left), then measure the diagonal distances between these points.
- **Transdiagonal difference** (transcranial diagonal difference): The difference between two transcranial diagonal diameters.
- **Cranial vault asymmetry:** Ratio of oblique measurements. This is difficult to implement because different physicians and authors propose varying points to use for these measurements.

One technology for the evaluation of the severity and improvement over time of DP is the three-dimensional photographic system. Advantages of this system include an easy and comfortable ability to image in an unbiased manner. Similarly, the use of laser scanners for the prefabrication scans for helmets is frequently employed by orthotists.

After observations and measurements, the clinician can determine the type and severity of the DP (Table 632.4 and Fig. 632.3). For lateral DP, bossing of the occiput occurs opposite the flattened deformity and the ear on the same side as the flat area can be anteriorly displaced. This type of DP is typically associated with infants who have torticollis or a head position preference to one side. Transdiagonal diameter is typically abnormal in this type of plagiocephaly, and this measurement is the gold standard for determining severity.

In posterior DP, the occiput is uniformly flattened, temporal bossing can occur, and the ears are normal. It is usually associated with large head size and a history of limited activity or mobility. The cephalic index is increased with posterior DP.

Time and accurate exam records can help in management. If deformation is worsening when DP typically begins to demonstrate improving head shape, craniosynostosis should be suspected.

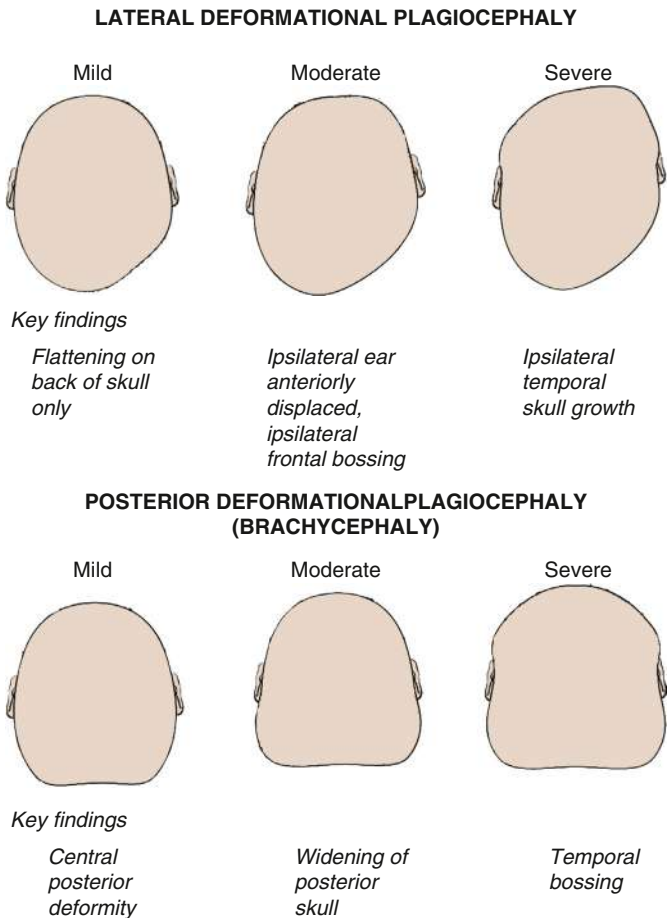


Fig. 632.3 Types of deformational plagiocephaly. (From Looman WS, Flannery AB. Evidence-based care of the child with deformational plagiocephaly, part I: assessment and diagnosis. J Pediatr Health Care. 2012;26:242–250, Fig. 1.)

TREATMENT

Prevention

The sleep position should be monitored and varied. Alternating the infant's head to face the head and foot of the crib on alternate nights will allow the infant to sleep facing into the room without always lying on the same side of the head. Consistently alternating the sleeping position early on allows the infant to have equal time on both sides of the occiput, and the infant will become used to this pattern. Infants who have an obvious positional preference for a particular side will take more time and make more effort to purposefully reposition themselves counter to their preference. Parents must be counseled in the benefit of this strategy in preventing bald spots or flat spots that can progress to cranial deformity.

Tummy time is the term used to describe the infant's awake time spent lying on the stomach. The suggested amount of tummy time is 10-15 minutes at least 3 times a day. Reassure parents that sleep is the only time during which the prone position should be avoided, and educate the parents as to the benefits for the infant of awake prone positioning to help progression of motor development.

Treatment Options

Cranial asymmetry from DP does not usually spontaneously improve, nor do the more severe manifestations of facial and ear asymmetry disappear. Once a flat spot develops, it is unlikely that the infant will be able to overcome the pull to lie on the same spot in time to allow for reversal of the asymmetry.

Watch-and-wait management is not recommended in infants with DP. Evidence suggests that, at a minimum, repositioning and physiotherapy (RPPT) should be initiated as soon as asymmetry is observed.

RPPT includes the counseling and teaching of parents about positional changes and tummy time for their child, as well as the referral to physical therapy in the case of congenital torticollis. RPPT is the optimal treatment choice for patients younger than 4 months of age who have mild or moderately severe DP. The earliest types of behavioral modifications can be as simple as increasing tummy time or repositioning the infant's crib such that everything interesting in the room is on the side opposite the DP.

Molding therapy (helmet therapy) is the use of an orthotic helmet to promote the resolution of cranial asymmetry while the infant's head is still rapidly growing. Orthotic helmets do not actively mold the skull; rather, they protect the areas that are flat and allow the child to grow into the flat spot. Helmet therapy achieves correction 3 times faster and better than repositioning alone. This therapy is still debated because of its expense, time requirements, coverage, and side effects (irritation, rashes, and pressure sores). Combined treatment with helmet therapy and RPPT is the most beneficial management of infants older than 4 months with severe DP or with worsening of mild or moderate DP trialed on RPPT. Infants with severe DP should be considered for helmet therapy at any age.

Studies suggest helmet therapy should be started for significant DP between 4 and 8 months and continued for 7-8 months. Parents should be counseled on the commitment involved in this treatment because helmets need to be worn up to 23 hours per day. Noncompliance has been documented in 80% of study patient populations in as little as 4 months.

Risk factors are associated with failure of RRPT and helmet therapy. Table 632.5 provides a list of these risk factors by treatment modality. These are important to consider when prescribing treatment regimens

Table 632.5

Risk Factors for Failure of Conservative and Helmet Therapy in the Treatment of Deformational Plagiocephaly

CONSERVATIVE THERAPY	HELMET THERAPY
Poor compliance	Advanced age*
Advanced age*	Poor compliance
Presence of torticollis	
Presence of developmental delay	
Increases severity of cranial deformity at time of therapy (via cranial ratio and diagonal difference)	

*Advanced age is defined as older than 6 mo.

to families in order to give the patient the best chance at a successful outcome.

Patients with **craniosynostosis** require surgery. Sometimes, a molding helmet can be used as an adjunctive therapy after surgery but never as monotherapy.

OUTCOMES

Outcomes may be better when helmet therapy is started before 6 months of age; infants starting therapy later than that do not achieve the same degree of normal head measurements as those whose helmet therapy is started before 6 months of age. Significant improvements in asymmetry are usually obvious at 4-11 weeks after starting helmet therapy. An 8-year single-center review analyzing 4,378 patients found complete correction in 77.1% of patients undergoing conservative (RRPT) therapy and 94.4% of patients treated with helmet therapy.

Studies in patients with a median follow-up age of 9 years found that 75% of cases had what both parents and patients considered to be a normal head appearance. Nine percent of patients and 4% of parents noted residual asymmetry that they considered significant. Though some literature hints at more satisfaction and less anxiety in parents of helmeted children, there is evidence to suggest that the treatment modality and outcome make no difference regarding parents' long-term satisfaction.

There is a small but growing body of literature that suggests conservative therapy (RPPT) may be as effective as helmet therapy for correcting certain cases of DP. Generalization of these findings to larger populations is not currently possible.

Cognitive and academic outcomes may be different depending on the side of deformity. Poorer academic performance and greater speech abnormalities were found in patients with left-sided deformities than in those with right-sided deformities. This manifested as double the number of patients with expressive speech abnormalities and triple the number of special education needs. It is unclear what the underlying mechanism is; treatment differences were apparently not a factor. In general, children with DP and without comorbid conditions are usually developmentally normal, healthy children. This development contrasts with craniosynostosis, in which increases in intracranial pressure may have deleterious effects on central nervous system function.

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Chapter 633

Seizures in Childhood

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An epileptic seizure is a sudden transient occurrence of signs and/or symptoms resulting from abnormal excessive or synchronous neuronal activity in the brain. The International League Against Epilepsy (ILAE) operational classification of seizure types divides epileptic seizures into four categories based on the presumed mode of seizure onset: focal, generalized, unknown onset, and unclassified (Figs. 633.1 and 633.2). In **focal** (formerly known as *partial*) **seizures**, the first clinical and electroencephalographic (EEG) changes suggest initial activation of a system of neurons limited to part of one cerebral hemisphere. Focal seizures can be described as motor or nonmotor and are further characterized by preserved or impaired consciousness, which is used synonymously with the term **awareness**. Simple partial seizure is an outdated term that refers to a focal seizure with no alteration in consciousness or awareness; the current term is **focal aware seizure**. Complex partial seizure is also an outdated term that denotes focal seizures with altered consciousness or awareness of the surroundings; they are currently referred to as **focal seizures with impaired awareness**. In **generalized seizures**, the first clinical and EEG changes indicate synchronous involvement of both hemispheres. A seizure may be labeled as being of **unknown onset** if there is not enough clinical information available to determine if the seizure is focal or generalized. If the clinical characteristics of a seizure are unusual and a determination of onset cannot be made despite an adequate evaluation, the seizure may be labeled as **unclassified**. Approximately 30% of patients who have a first afebrile seizure later develop epilepsy; the risk is approximately 20% if the neurologic exam, EEG, and neuroimaging are normal.

Febrile seizures are a separate category (see Chapter 633.1). **Acute symptomatic** or **provoked seizures** occur secondary to an acute problem affecting brain excitability, such as an electrolyte imbalance; most children with these types of seizures do well. However, sometimes these seizures signify major structural, inflammatory, or metabolic disorders of the brain, such as meningitis, encephalitis, acute stroke, or brain tumor. Consequently, the prognosis depends on the underlying disorder, including its reversibility or treatability and the likelihood of

developing epilepsy from it. An **unprovoked seizure** is one that is not an acute symptomatic seizure. A **remote symptomatic seizure** is one secondary to a distant brain injury, such as an old stroke.

Reflex seizures are a type of seizure precipitated by a sensory stimulus. These types of seizures can be caused by a variety of stimuli, including visual (flickering lights, patterns, reading), auditory (music), somatosensory, or proprioceptive stimuli; praxis; eating; bathing in hot water; or being startled (see Chapter 631.9).

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition (see Fig. 633.2). The clinical diagnosis of epilepsy usually requires the occurrence of at least one unprovoked epileptic seizure with either a second such seizure or enough EEG and clinical information to convincingly establish an enduring predisposition to develop recurrences. For epidemiologic and, commonly, for clinical purposes, epilepsy is considered present when two or more unprovoked seizures occur in a time frame of longer than 24 hours in between them. Approximately 4–10% of children experience at least one seizure (febrile or afebrile) in the first 16 years of life. The cumulative lifetime incidence of epilepsy is 3%, and more than half of the disorders start in childhood. The annual prevalence is 0.5–1.0%. Thus the occurrence of a single seizure or of febrile seizures does not necessarily imply the diagnosis of epilepsy. **Seizure disorder** is a general term that is usually used to include any one of several disorders, including epilepsy, febrile seizures, and, possibly, single seizures and symptomatic seizures secondary to metabolic, infectious, or other etiologies (e.g., hypocalcemia, meningitis).

An **epileptic syndrome** is a disorder that manifests as one or more specific seizure types and has a specific age of onset and a specific prognosis. Several types of epileptic syndromes can be distinguished (Tables 633.1–633.6; Fig. 633.3). This category must be distinguished from the category of epileptic seizures that refers to single events rather than to clinical syndromes. In general, the seizure type is the primary determinant of the medications to which the patient is likely to respond, and the epilepsy syndrome determines the prognosis one could expect. An **epileptic encephalopathy** is an epilepsy syndrome in which there is a severe EEG abnormality that is thought to result in cognitive and other impairments. **Developmental encephalopathy** denotes a disorder in which the underlying etiology (e.g., a specific gene variant) contributes to a developmental delay independently of the patient's seizure burden and/or EEG abnormalities. The terms *epileptic* and *developmental encephalopathy* can be combined (i.e., **developmental epileptic encephalopathy**) in specific situations where both the EEG abnormalities and the underlying etiology contribute to the patient's developmental delay.

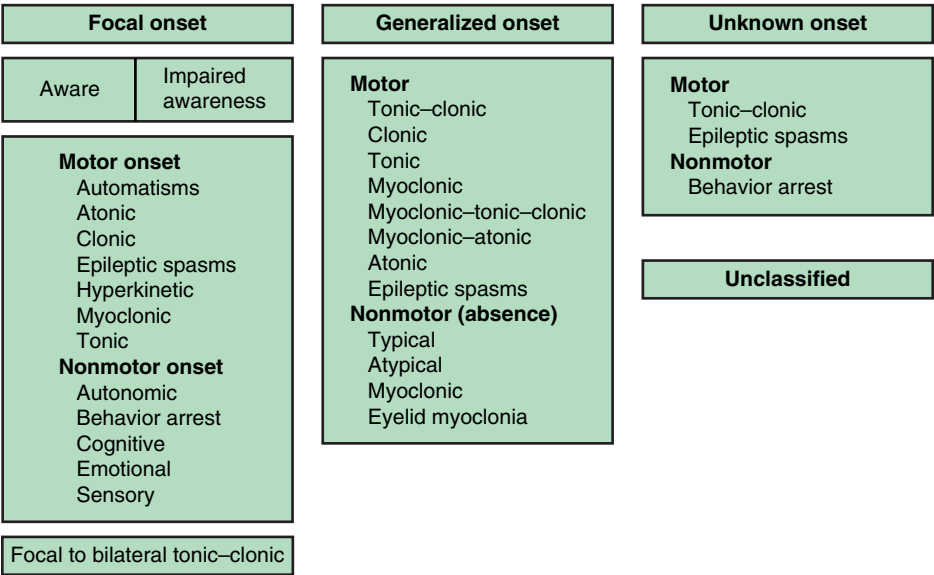


Fig. 633.1 International League Against Epilepsy classification of seizures. (Modified from Katayan A, Diaz-Medina G. Epilepsy: epileptic syndromes and treatment. *Neurol Clon.* 2021;39:779–794, Fig. 1, p. 780.)

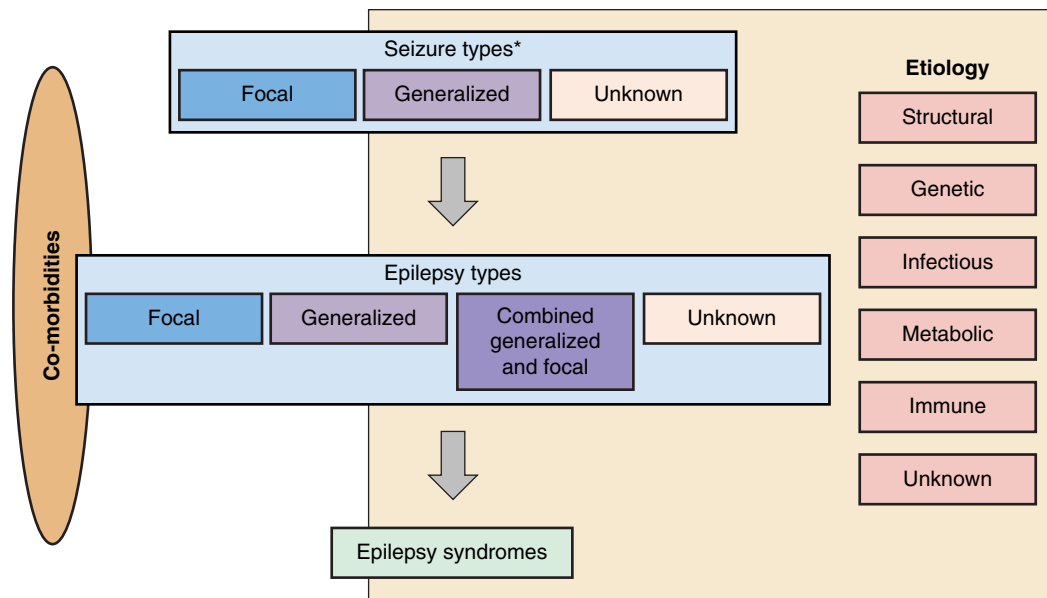


Fig. 633.2 ILAE classification of epilepsies. *Denotes onset of seizure. (From Katayayan A, Diaz-Medina G. *Epilepsy: epileptic syndromes and treatment*. Neurol Clin. 2021;39:779–794, Fig. 2, p. 781.)

The ILAE Task Force on Classification has proposed a multilevel framework for categorizing epilepsies (Table 633.7). This framework should help guide therapeutic decisions and assist with prognostication. At the most basic level (**level 1**), a patient's epilepsy can be classified by seizure type (focal, generalized, focal and generalized, or unknown). At the next level (**level 2**), based on available clinical data and known seizure types, an epilepsy type can be assigned (focal, generalized, focal and generalized, or unknown). At the next level (**level 3**), if further clinical data are available and based on supporting studies (e.g., EEG and/or MRI), the diagnosis of a specific epilepsy syndrome can be made (e.g., juvenile myoclonic epilepsy). Concurrent to this classification paradigm, the associated comorbidities and the underlying cause for the epilepsy must also be considered. If categorized by etiology, epilepsies are grouped into genetic, structural, metabolic, immune, infectious, or unknown categories. It is important to note that these categories are not mutually exclusive, and a patient's epilepsy may have multiple concurrent etiologies (e.g., genetic and structural). At the final level (**level 4**) of categorizing and diagnosing the epilepsy, the epilepsy syndrome, the underlying etiology, and associated comorbidities are considered.

Genetic epilepsy (previously also referred to as *idiopathic epilepsy*) implies that the epilepsy syndrome is the direct result of a known or presumed genetic defect(s) that is not causative of a brain structural or metabolic disorder other than the epilepsy. This category encompasses *genetic generalized epilepsies* (previously called *idiopathic generalized epilepsies*), such as childhood absence epilepsy, as well as epilepsies caused by a known gene defect (see Tables 633.1–633.6).

Structural epilepsy (previously called *symptomatic epilepsy*) refers to an epilepsy syndrome caused by an underlying structural brain disorder that may or may not be genetic. This includes etiologies such as old stroke or hypoxic-ischemic injury, as well as epilepsy secondary to tuberous sclerosis (which is also genetic). **Immune-mediated epilepsy** is an important category that describes epilepsies occurring secondary to immune-mediated central nervous system (CNS) inflammation. This group of disorders warrants special attention because immunotherapies such as steroids and intravenous immunoglobulin (IVIG) may be the first-line treatments. **Autoimmune encephalitis** such as anti-N-methyl-D-aspartate (NMDA) receptor encephalitis and anti-LG1 limbic encephalitis are examples of immune-mediated epilepsies. **Infectious epilepsy** describes epilepsies secondary to chronic

infectious conditions such as tuberculosis and HIV rather than acute infections such as bacterial meningitis or herpes simplex virus (HSV) encephalitis.

The older terms *cryptogenic epilepsy* and *presumed symptomatic epilepsy* refer to an epilepsy syndrome in which there is a presumed underlying brain disorder causing the epilepsy and affecting neurologic function, but the underlying disorder is not known; the disorder is now referred to as **unknown epilepsy**, designating that the underlying cause of the epilepsy is still unknown.

EVALUATION OF THE FIRST SEIZURE

The initial evaluation of an infant or a child during or shortly after a suspected seizure should include an assessment of the adequacy of the airway, ventilation, and cardiac function, as well as measurement of temperature, blood pressure, and glucose concentration. For acute evaluation of the first seizure, the physician should search for potentially life-threatening causes of seizures, such as meningitis, systemic sepsis, unintentional or intentional head trauma, and ingestion of drugs or medications or other toxins. The history should aim to determine if the event was a seizure or not and to define factors that might have promoted the convulsion and to provide a detailed description of the seizure and the child's postictal state.

The subsequent step in an evaluation is to determine whether the seizure has a focal onset or is generalized. **Focal seizures** could include forceful turning of the head and eyes to one side, unilateral clonic movements beginning in the face or extremities, or a sensory disturbance, such as paresthesia or pain localized to a specific area. Focal seizures in an adolescent or adult usually indicate a localized lesion, whereas these seizures during childhood are often either secondary to a lesion or the result of a genetic, formerly known as *idiopathic*, epilepsy. Focal seizures in a neonate may be seen because of focal lesions such as perinatal stroke or because of a metabolic abnormality such as hypocalcemia that results in focal seizures that may not generalize because of immaturity of the brain connections. Focal and generalized motor seizures may be tonic-clonic, tonic, clonic, myoclonic, or atonic. **Tonic seizures** are characterized by increased tone or rigidity (usually lasting 2 seconds up to several minutes), and **atonic seizures** are characterized by flaccidity and lack of movement. **Clonic seizures** consist of rhythmic, fast muscle contractions and slightly longer relaxations; **myoclonus** is a shocklike contraction of a muscle of <50 milliseconds that is often repeated. The duration of

Table 633.1 Classification of Epilepsy Syndromes with an Indication of Age of Onset, Duration of Active Epilepsy, Prognosis, and Therapeutic Options

SPECIFIC SYNDROMES	AGE RANGE AT ONSET	AGE AT REMISSION	PROGNOSIS	MONOTHERAPY OR ADD-ON*	POSSIBLE ADD-ON†	SURGERY‡
NEONATAL						
Benign neonatal seizures	Newborn	Newborn	Good	LEV, TPM, PB	—	No
Early myoclonic encephalopathy and Ohtahara syndrome	Newborn infant	Poor, Ohtahara syndrome evolves into West syndrome	Ominous	PB, steroids, VGB	BZD, ZON, TPM, LEV, ketogenic diet	No
Benign familial neonatal convulsions	Newborn to young infant	Newborn to young infant	Good	LEV, TPM, PB	—	No
INFANCY						
Benign infantile seizures (nonfamilial)	Infant	Infant	Good	LEV, TPM, PB	—	No
Benign familial infantile convulsions	Infant	Infant	Good	LEV, TPM, OXC, CBZ, PB	—	No
Epilepsy of infancy with migrating focal seizures	Infant	No remission	Ominous	LEV, PB, OXC, CBZ, PHT, TPM, QND	BZD, bromides, LAC, VPA, ZON	No
West syndrome	Infant	Variable	Variable	ACTH, steroids, VGB	BZD, FBM, IVIG, TPM, ZON, ketogenic diet	Lesionectomy ± cortical resection
Dravet syndrome (severe myoclonic epilepsy in infancy)	Infant	No remission	Severe	CLB, stiripentol, VPA (only after age 2yr)	BZD, TPM, LEV, ZON, ketogenic diet	No
Benign myoclonic epilepsy in infancy	3mo-3yr	3-5yr	Variable	LEV, TPM, BZD	VPA, ZON	No
CHILDHOOD						
Benign childhood epilepsy with centrotemporal spikes	3-13yr	16yr	Good	OXC, CBZ, LEV, VPA	LAC, PER	No
Early and late-onset idiopathic occipital epilepsy	2-8yr; 6-17yr	12yr or younger; 18yr	Good	OXC, CBZ, LEV, VPA	LAC, PER	No
Autosomal dominant nocturnal frontal lobe epilepsy	Childhood		Variable	OXC, CBZ, LEV	CLB, PB, PHT, LAC, PER, GBP, TPM	No
Familial lateral temporal lobe epilepsy	Childhood to adolescence		Variable	OXC, CBZ, LEV	CLB, PB, PHT, GBP, TPM, VPA, LAC, PER	No, except in rare cases
Generalized epilepsies with febrile seizures plus	Childhood to adolescence		Variable	ESM, LTG, LEV, VPA (depending on seizure type)	CLB, TPM, PER	No
Mesial temporal lobe epilepsy with hippocampal sclerosis	School-age or earlier	Long- lasting	Variable	OXC, CBZ, LEV	CLB, GBP, LAC, PB, PER, PHT, ZON, TPM, VPA	Temporal resection
Rasmussen syndrome	6-12yr	Progressive	Ominous	LEV, OXC, CBZ, plasmapheresis, immunoglobulins	LAC, PB, PER, PHT, TPM	Functional hemispherectomy
Hemiconvulsion-hemiplegia syndrome	1-5yr	Chronic	Severe	OXC, CBZ, LEV	CLB, GBP, LAC, PB, PER, PHT, ZON, TPM, VPA	Functional hemispherectomy
Epilepsy with myoclonic astatic seizures	3-5yr	Variable	Variable	ESM, TPM, VPA, LEV, ZON	BZD, ketogenic diet, LTG, PER, steroids	No
Childhood absence epilepsy	5-6yr	10-12yr	Good	ESM, LTG, VPA	Acetazolamide, CZP, ketogenic diet, ZON	No
Epilepsy with myoclonic absences	1-12yr	Variable	Guarded	ESM, VPA, CZP	ZON, LTG	No

Table 633.1 Classification of Epilepsy Syndromes with an Indication of Age of Onset, Duration of Active Epilepsy, Prognosis, and Therapeutic Options—cont'd

SPECIFIC SYNDROMES	AGE RANGE AT ONSET	AGE AT REMISSION	PROGNOSIS	MONOTHERAPY OR ADD-ON*	POSSIBLE ADD-ON†	SURGERY†
Lennox-Gastaut syndrome	3-10yr	No remission	Severe	CLB, LTG, RFD, TPM, VPA	BZD, FBM, IVIG, PER, steroids, ZON, ketogenic diet	Callosotomy
Landau-Kleffner syndrome	3-6yr	8-12yr	Guarded	Nocturnal DZP, steroids, VPA, LEV	CLB, ESM, IVIG, LTG, ketogenic diet	Multiple subpial transections, rarely lesionectomy
Epilepsy with continuous spike waves during slow-wave sleep	4-7yr	8-12yr	Guarded	Nocturnal DZP, steroids, VPA, LEV	CLB, ESM, IVIG, LTG, ketogenic diet	No
Other visual-sensitive epilepsies	2-5yr	Unclear	Variable	VPA	BZD, LEV, LTG, ZON	No
Febrile seizures	3-5yr	3-6yr	Good	BZD (only as needed for febrile periods if frequent febrile seizures)	—	No
JUVENILE ONSET						
Juvenile absence epilepsy	10-12yr	Usually lifelong	Good	ESM, LTG, VPA	Same as in childhood absence epilepsy	No
Juvenile myoclonic epilepsy	12-18yr	Usually lifelong	Good	LEV, TPM, VPA	BZD, LTG, PB, PER, PRM, ZON	No
Epilepsy with generalized tonic-clonic seizures only	12-18yr	Usually lifelong	Good	LEV, LTG, TPM, VPA	BZD, CBZ, PER, ZON	No
Idiopathic photosensitive occipital lobe epilepsy	10-12yr	Unclear	Variable	VPA, LEV	BZD, LTG, ZON	No
Progressive myoclonic epilepsies (e.g., Unverricht-Lundborg, Lafora, ceroid lipofuscinoses)	Late infant to adolescent	Progressive	Ominous	TPM, VPA, ZON, LEV	BZD, PB, CLB, PER, ketogenic diet	No
VARIABLE AGE OF ONSET						
Mesial temporal lobe epilepsy defined by location and cause	Variable	Long-lasting	Variable	LEV, OXC, CBZ, TPM, VPA	PHT, PB, CLB, GBP, LAC, PER, ZON	Lesionectomy ± cortical resection
Mesial temporal lobe epilepsy defined by specific causes	Variable	Long-lasting	Variable	LEV, OXC, CBZ, TPM, VPA	CLB, GBP, LAC, PB, PER, PHT, ZON	Temporal resection
Startle epilepsy	Variable	Long-lasting	Guarded	OXC, CBZ, LEV, TPM, VPA	CLB, LEV, PB, PHT, ZON, GBP	Lesionectomy ± cortical resection in some
Reflex seizures	Variable	n/a		LEV, VPA	LTG, ZON	No
Drug or other chemically induced seizures	Variable	n/a		Withdraw offending agent	—	No
Immediate and early posttraumatic seizures	Variable	n/a		LEV, PHT	—	No

*Reflects current trends in practice, which may be off-label and may not be FDA-approved for that indication. Order of listing does not necessarily imply preference of use in that order. See Table 633.13 for FDA indications.

†May apply to selected cases only. Vagus nerve stimulation has been used for all types of refractory seizures and epilepsy types but has been FDA-approved as an adjunct therapy in patients 4 yr or older with medically refractory partial-onset seizures.

ACTH, Adrenocorticotrophic hormone; BZD, benzodiazepine; CBZ, carbamazepine; CLB, clobazam; DZP, diazepam; ESM, ethosuximide; FBM, felbamate; GBP, gabapentin; IVIG, intravenous immunoglobulin; LAC, lacosamide; LEV, levetiracetam; LTG, lamotrigine; n/a, not applicable; OXC, oxcarbazepine; PB, phenobarbital; PER, perampanel; PHT, phenytoin; PRM, primidone; QND, quinidine; RFD, rufinamide; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; ZON, zonisamide.

Modified from Guerrini R. Epilepsy in children. *Lancet*. 2006;367:499-524; and Parisi P, Verrotti A, Paolino MC, et al. "Electro-clinical syndromes" with onset in the pediatric age group: the highlights of the clinical-EEG, genetic, and therapeutic advances. *Ital J Pediatr*. 2011;37:58.

Table 633.2 Ion Channel Pathogenic Gene Variants and Associated Epilepsy Syndromes/Seizure Types			
ION CHANNEL	GENE	EPILEPSY SYNDROMES/SEIZURE TYPES	SEIZURE ONSET
SODIUM α Subunit	SCN1A	DS, GEFS+, GTCs	Infancy, childhood
	SCN2A	Benign familial neonatal-infantile epilepsy, sporadic infantile spasm, sporadic neonatal epileptic encephalopathy	Neonatal, infancy
	SCN3A	Cryptogenic focal epilepsy, focal unaware to bilateral GTC, GTC, myoclonic	Neonatal, infancy, childhood
	SCN8A	GTC, tonic, myoclonic	Neonatal, infancy
β Subunit	SCN9A	Febrile seizures, focal unaware, GTC	Childhood
	SCN1B	GEFS+	Childhood, adolescence, adulthood
POTASSIUM Voltage dependent	KCNA2	GTC, focal unaware, alternating hemiclonic seizures, absence, juvenile myoclonic epilepsy	Infancy, childhood
	KCNB1	GTC, focal unaware, infantile spasm, West syndrome, Lennox-Gastaut	Infancy, childhood
	KCND2	GTC, focal unaware	Infancy, adolescence
	KCNQ2	Benign familial neonatal seizures, tonic	Neonatal, infancy
	KCNQ5	Focal unaware, infantile spasm	Infancy, childhood
	KCNH1	Temple-Baraitser syndrome, GTC, focal unaware, myoclonic, tonic, clonic	Neonatal, infancy
	KCNH5	GTC, hemiclonic	Infancy
	KCNMA1	GTC	Childhood
Non-voltage dependent	KCNT1	MMFSI, ADNFLE	Infancy, childhood
	KCNJ10	EAST syndrome, idiopathic generalized epilepsies, childhood absence epilepsy	Infancy, childhood
CHLORIDE K ⁺ /Cl ⁻ -co-transporter	CLCN1	Idiopathic generalized epilepsies	Infancy
	CLCN2	Idiopathic generalized epilepsies, childhood absence, juvenile absence, GTC, tonic	Infancy, childhood
	SLC12A5	Epileptic encephalopathy with focal migrating seizures, idiopathic generalized epilepsy, GTC, myoclonic, absence	Infancy
CALCIUM α Subunit	CACNA1H	Idiopathic generalized epilepsies	Infancy, childhood
	CACNA1A	Epileptic encephalopathy, absence	Infancy
β Subunit	CNCNB4	Myoclonic epilepsy, tonic, idiopathic generalized epilepsies	Infancy, childhood

ADNFLE, Autosomal dominant nocturnal frontal lobe epilepsy; EAST, epilepsy, ataxia, sensorineural deafness, and tubulopathy; GEFS+, genetic epilepsy with febrile seizures plus; GTCs, generalized tonic-clonic seizures; MMFSI, malignant migrating focal seizures of infancy.

Modified from Martinez LA, Lai YV, Holder JL Jr, Anderson AE. Genetics in epilepsy. *Neurol Clin.* 2021;39:743–777, Table 1, p. 745–747.

Table 633.3 Defects in Neurotransmitter Receptors and Associated Epilepsy Syndromes/Seizure Types			
RECEPTOR	GENE	EPILEPSY SYNDROMES/SEIZURE TYPES	SEIZURE ONSET
GABA	GABRA1	Absence, idiopathic generalized epilepsy, epileptic encephalopathy, juvenile myoclonic epilepsy	Infancy, childhood, adolescence
	GABRB3	Childhood absence, epileptic encephalopathy	Neonatal, infancy, childhood
	GABRG2	Childhood absence, GEFS+, idiopathic generalized epilepsy, epileptic encephalopathies	Neonatal, infancy
	GABRE	Infantile spasm, focal unaware, focal unaware to bilateral GTC, GTC	Infancy
Nicotinic acetylcholine	CHRNA4	ADSHE	Childhood, adolescence
	CHRN2	ADSHE	Childhood, adolescence
	CHRNA2	Benign infantile familial seizures	Infancy
Glutamate	GRIN1	Infantile spasm, tonic, atonic, hypermotor, focal dyscognitive, GTC	Neonatal, infancy, childhood
	GRIN2A	Childhood focal epilepsy, rolandic epilepsy, epileptic encephalopathy, absence, tonic, myoclonic	Infancy, childhood
	GRIN2B	West syndrome, childhood-onset focal epilepsy, epileptic encephalopathy	Infancy, childhood
	GRIN2D	Infantile spasm, focal unaware to bilateral GTC, GTC, myoclonic, atypical absence	Neonatal, infancy, childhood

ADSHE, Autosomal dominant sleep-related hypermotor epilepsy; GEFS+, genetic epilepsy with febrile seizures plus; GTC, generalized tonic-clonic seizure.

Modified from Martinez LA, Lai YV, Holder Jr. JL, Anderson AE. Genetics in epilepsy. *Neurol Clin.* 2021;39:743–777, Table 2, p. 748.

Table 633.4 Pathogenic Gene Variants of Synaptic Complexes and Associated Epilepsy Syndromes/Seizure Types

LOCATION	GENE	EPILEPSY SYNDROMES/SEIZURE TYPES	SEIZURE ONSET
Presynaptic	<i>DNM-1</i>	Infantile spasms, absence with eyelid myoclonia, atonic, myoclonic, tonic, focal, GTCs	Neonatal, infancy
	<i>NRXN1</i>	Absence, GTCs, myoclonic	Childhood
	<i>SNAP25</i>	Infantile spasms, GTCs, focal, absence, myoclonic, tonic	Neonatal, infancy, childhood
	<i>STX1B</i>	GTC, partial, absence, tonic, atonic, Ohtahara syndrome, West syndrome	Infancy, childhood, adolescence
	<i>SV2A</i> <i>TBC1D24</i>	Myoclonic, tonic Myoclonic, GTC, partial, absence, infantile spasms	Infancy Neonatal, infancy, childhood
Postsynaptic	<i>CNTNAP2</i>	Focal, tonic	Infancy, childhood
	<i>IQSEC2</i>	Atypical absence, GTCs	Infancy, childhood
	<i>PCDH19</i>	GTC, tonic, absence, atonic, partial, myoclonic	Infancy
	<i>SHANK3</i>	GTC, partial, absence, tonic, myoclonic, atonic	Infancy, childhood
	<i>SYNGAP1</i>	GTC, atonic, absence with eyelid myoclonia, myoclonic	Childhood
	<i>STXBP1</i>	Infantile spasms, myoclonic, GTC, atonic, absence, partial	Neonatal, infancy

GTCs, Generalized tonic-clonic seizures.

Modified from Martinez LA, Lai YV, Holder JL Jr, Anderson AE. Genetics in epilepsy. *Neurol Clin.* 2021;39:743–777, Table 3, p. 749.**Table 633.5** Defects in Intracellular Pathways/Organelles and Associated Epilepsy Syndromes/Seizure Types

	GENE	EPILEPSY SYNDROMES/SEIZURE TYPES	SEIZURE ONSET
mTOR pathway	<i>TSC1, TSC2</i>	Tuberous sclerosis	Infancy, childhood, adolescence, adulthood
	<i>MTOR</i>	Focal cortical dysplasia	Variable age of onset
	<i>RHEB</i>	Focal cortical dysplasia	Variable age of onset
	<i>DEPDC5</i>	Focal cortical dysplasia	Neonatal, infancy, childhood
	<i>NPRL2, NPRL3</i>	Nocturnal frontal lobe epilepsy, frontal lobe epilepsy, temporal lobe epilepsy	Infancy, childhood
	<i>AKT3</i>	Infantile spasm	Infancy
Mitochondria	<i>POLG</i>	Alpers-Huttenlocher syndrome	Childhood
	<i>MT-TK</i>	Myoclonic epilepsy with red, ragged fibers	Childhood, adolescence, adulthood
	<i>PDHA1</i>	Infantile spasm, myoclonic absence, atypical absence, West syndrome, Lennox-Gastaut	Neonatal, infancy
	<i>PDHB</i>	Infantile spasm, myoclonic absence, atypical absence, West syndrome, Lennox-Gastaut	Neonatal, infancy
Lysosome	<i>SCARB2</i>	AMRF	Adolescence, adulthood
	<i>CLN1–CLN8, CLN10–CLN14</i>	Myoclonic epilepsy, atypical absence	Variable age of onset depending on specific CLN gene defect
	<i>NEU1</i>	Progressive myoclonic epilepsy, GTC	Adolescence, adulthood

AMRF, Action myoclonus–renal failure, progressive myoclonic epilepsy; mTOR, mechanistic target of rapamycin; PDHB, pyruvate dehydrogenase complex E1-beta.

Modified from Martinez LA, Lai YV, Holder JL Jr, Anderson AE. Genetics in epilepsy. *Neurol Clin.* 2021;39:743–777, Table 4, p. 750.**Table 633.6** Metabolic Defects and Associated Epilepsy Syndromes/Seizure Types

	GENE	EPILEPSY SYNDROMES/SEIZURE TYPES	SEIZURE ONSET
Pyridoxine	<i>ALDH7A1</i>	Focal, GTC, infantile spasm, myoclonic	Neonatal, infancy, childhood
	<i>PNPO</i>	GTC, tonic, clonic, myoclonic, focal	Neonatal
Biotin	<i>BTD</i>	GTC, myoclonic, infantile spasm, Ohtahara syndrome	Neonatal, infancy
Folic acid	<i>FOLR1</i>	Myoclonic-astatic, myoclonic, GTC	Childhood
Glycine	<i>GLDC</i>	Nonketotic hyperglycinemia	Neonatal
	<i>AMT</i>	Nonketotic hyperglycinemia	Neonatal
Glutamate	<i>SLC2A1</i>	Focal, absence, myoclonic-astatic	Infancy
Uridine	<i>CAD</i>	GTC, focal	Infancy

GTC, Generalized tonic-clonic seizures.

Modified from Martinez LA, Lai YV, Holder JL Jr, Anderson AE. Genetics in epilepsy. *Neurol Clin.* 2021;39:743–777, Table 5, p. 751.

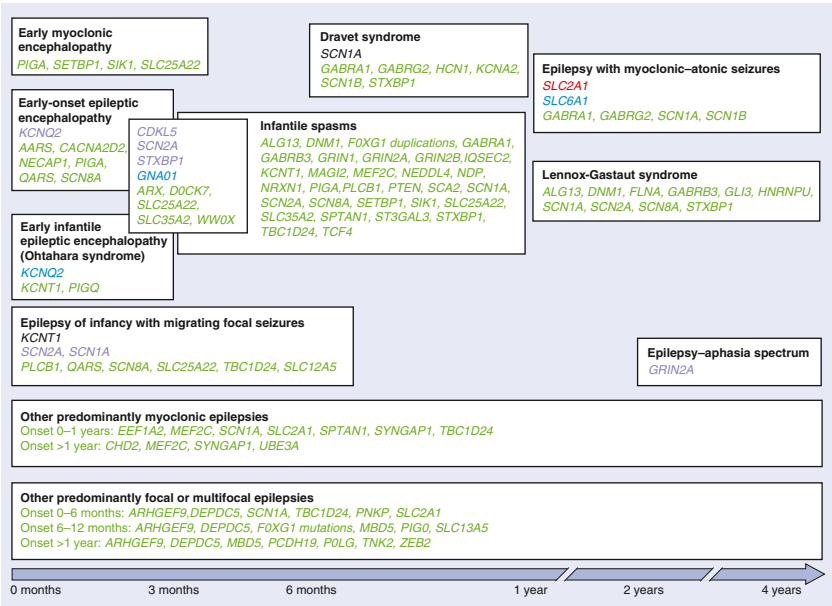


Fig. 633.3 Genetic causes, and proportion of cases caused by each gene, including only nonchromosomal, nonmalformative, and nonmetabolic disorders. Only genes with more than one case reported are included. *Black font* denotes genes that account for at least 50% of cases, *purple font* 10–50% of cases, and *red font* 5–10% of cases. *Blue font* denotes genes that account for less than 5% of cases, and *green font* denotes genes that account for an unknown percentage of cases. (From McTague A, Howell KB, Cross JH, et al. The genetic landscape of the epileptic encephalopathies of infancy and childhood. *Lancet*. 2016;15:304–316.)

Table 633.7	Diagnostic and Classification Scheme of Epilepsies
Level 1: Determine if the event was an epileptic seizure and, if so, characterize the seizure type or types based on available clinical information as focal, generalized, or unknown. (Refer to Fig. 633.1 for more detailed characterizations.)	
Level 2: Determine the type of epilepsy the patient has (focal, generalized, focal and generalized, or unknown).	
Level 3: Determine if the epilepsy fits into a particular epilepsy syndrome (refer to Table 633.2).	
Level 4: Establish a unifying diagnosis that takes into account the epilepsy syndrome, underlying etiologies, and associated comorbidities.	
The etiology for the epileptic seizures should be considered at all levels of an epilepsy diagnosis as listed earlier; etiologic categories include:	
Genetic	
Structural	
Metabolic	
Immune	
Infectious	
Unknown	
Comorbidities should be considered at all levels of an epilepsy diagnosis. These can include developmental delay, psychiatric symptoms, behavioral issues, academic difficulties, movement abnormalities, and many others.	

Modified from Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58(4):512–521.

the seizure and state of consciousness (retained or impaired) should be documented. The history should determine whether an **aura** preceded the convulsion and the behavior the child was exhibiting immediately preceding the seizure. Auras can take the form of a number of sensations, including visual (e.g., flashing lights or seeing colors or complex visual hallucinations), somatosensory (tingling), olfactory, auditory, vestibular, or experiential (e.g., déjà vu, déjà vécu feelings) sensations, depending on the precise localization of the origin of the seizures. The most common aura experienced by children consists of epigastric discomfort or pain and a feeling of fear. The posture of the patient, presence or absence and distribution of cyanosis, vocalizations, loss of sphincter control (more commonly of the urinary bladder), and postictal state (including sleep, headache, and hemiparesis) should be noted. The provider taking the history should

ask specifically about each of these symptoms as appropriate because caretakers may not spontaneously report them. Determination of focal versus generalized onset is sometimes difficult historically. A seizure may start focally and secondarily generalize too quickly to manifest observable early focal symptoms. In addition, a caregiver witnessing the seizure later in its evolution may describe only the more generalized-appearing signs.

In addition to clarifying the seizure semiology, a detailed history is crucial in identifying an underlying cause for the seizure. Reported personality changes or symptoms of increased intracranial pressure can suggest an intracranial tumor. Similarly, a history of cognitive regression can suggest a degenerative or metabolic disease. A history of prenatal or perinatal distress or of developmental delay can suggest etiologic congenital or perinatal brain dysfunction. Acute to subacute personality changes, psychiatric symptoms, and/or associated movement abnormalities may suggest an autoimmune etiology.

The examination of a child with a seizure disorder should also be geared toward the search for an organic cause. The child's head circumference, length, and weight are plotted on a growth chart and compared with previous measurements. A careful general and neurologic examination should be performed. A funduscopic exam should be performed to evaluate for the presence of papilledema, optic neuritis, retinal hemorrhages, uveitis, chorioretinitis, coloboma, or macular changes, as well as retinal phakoma. The finding of unusual facial features or of associated physical findings such as hepatosplenomegaly may point to storage disease or inborn error of metabolism as the cause of the neurologic disorder. The presence of a **neurocutaneous disorder** may be indicated by the presence of vitiliginous ash leaf-type lesions usually better seen using an ultraviolet light (Wood lamp); of adenoma sebaceum, shagreen patches, or retinal phakomas (tuberous sclerosis); of multiple café-au-lait spots (neurofibromatosis); or of V1- or V2-distribution nevus flammeus (Sturge-Weber syndrome) (see Chapter 636).

Localizing neurologic signs, such as a subtle **hemiparesis** with hyperreflexia, an equivocal or positive Babinski sign, and pronator drifting of an extended arm with eyes closed, might suggest a contralateral hemispheric structural lesion, such as a slow-growing glioma, as the cause of the seizure disorder. Unilateral growth arrest of the thumbnail, hand, or extremity in a child with a focal seizure disorder suggests a chronic condition, such as a porencephalic cyst, arteriovenous malformation, or cortical atrophy of the opposite hemisphere.

In an acute setting such as the emergency department, the decision to pursue further laboratory testing, including serum electrolytes, a

complete blood count, and/or urine toxicology tests, should be made on a case-by-case basis that considers the patient's clinical history and examination. ECG to rule out long QT or other cardiac dysrhythmias and other tests directed at disorders that could mimic seizures may be needed (see [Chapter 634](#)). A lumbar puncture is usually of limited value in an acute workup of a *nonfebrile* seizure unless the history or examination is concerning for an infectious or inflammatory process or if there is clinical concern for intracranial bleeding despite normal brain imaging. *A routine EEG should be performed in all cases of a first unprovoked nonfebrile seizure to help predict the risk of seizure recurrence.* If the patient's neurologic status has returned to baseline, the EEG can often be done on an outpatient basis even though the yield may be slightly lower because the EEG has been delayed beyond the first 12 hours. Emergent brain imaging with a head CT or brain MRI is usually performed if the seizure was focal, if there are postictal focal deficits on neurologic exam, or if the patient's status is not returning to baseline; in patients with trauma preceding the seizure; and in patients with a high-risk medical history. In other situations, the yield of emergent imaging identifying an abnormality that warrants emergent intervention is less than 1%. *Brain MRI is preferred over a CT scan, and performing it on a nonemergent basis should be considered in most patients.* CT is useful if a rapid study is needed to look for trauma, a mass, or signs of increased intracranial pressure. In select situations, such as when the clinical and EEG manifestations are consistent with a genetic generalized epilepsy such as childhood absence epilepsy, a brain MRI may not be necessary. Gadolinium (contrast) does not need to be routinely used when performing the brain MRI unless there is clinical suspicion of a neoplasm, vascular malformation, abscess, or another infectious or inflammatory process. Further details regarding the approach to a first seizure are included in [Chapter 633.2](#). The 2021 guidelines from the American College of Radiology provide recommendations in different clinical scenarios (variants) for pediatric patients presenting with seizures while taking into consideration the patient's age, precipitating events, clinical findings, EEG, and neurodevelopmental status. These address neonatal seizures, simple and complex febrile seizures, posttraumatic seizures, focal seizures, and primary generalized seizures ([Table 633.8](#)).

633.1 Febrile Seizures

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Febrile seizures are seizures that occur between the ages of 6 and 60 months of life (peak 12-18 months old) with a temperature of 38°C (100.4°F) or higher, that are not the result of CNS infection or any metabolic imbalance, and that occur in the absence of a history of prior afebrile seizures. A **simple febrile seizure** is a primary generalized, usually tonic-clonic, attack associated with fever, lasting for a maximum of 15 minutes, and not recurrent within a 24-hour period. A **complex febrile seizure** is more prolonged (>15 minutes), and/or is focal, and/or recurs within 24 hours. **Febrile status epilepticus** is a febrile seizure lasting longer than 30 minutes. Most patients with simple febrile seizures have a very short postictal state and usually return to their baseline normal behavior and consciousness within minutes of the seizure. **Febrile infection-related (or refractory) epilepsy syndrome (FIRES)** is a very different disorder seen predominantly in older (>5 years of age) usually male children and associated with an encephalitis-like illness but without an identifiable infectious agent. Children with FIRES were previously normal but subsequently develop difficult-to-treat epilepsy.

Between 2% and 5% of neurologically healthy infants and children experience at least one, usually simple, febrile seizure. Simple febrile seizures do not have an increased risk of mortality even though they are concerning to the parents. Complex febrile seizures may have an approximately twofold long-term increase in mortality rates as compared with the general population over the subsequent 2 years, probably secondary to a coexisting pathology. There are no long-term adverse effects of having one or more *simple* febrile seizures. Compared with age-matched controls, patients with febrile seizures do not have

Table 633.8 American College of Radiology Panel Summary of Recommendations for Imaging After a Seizure

- Variant 1:** MRI head without IV contrast is usually appropriate for the initial imaging of neonatal seizures.
- Variant 2:** Imaging is usually not appropriate for the assessment of simple febrile seizures in children 6 months to 5 years of age.
- Variant 3:** MRI head without IV contrast may be appropriate for the initial imaging of children 6 months to 5 years of age with complex febrile seizures.
- Variant 4:** CT head without IV contrast or MRI head without IV contrast is usually appropriate for the initial imaging of children with posttraumatic seizures (not including abusive head trauma). These procedures are equivalent alternatives (i.e., only one procedure will be ordered to provide the clinical information to effectively manage the patient's care).
- Variant 5:** MRI head without IV contrast is usually appropriate for the initial imaging of a child with focal seizures (not including abusive head trauma). The panel did not agree on recommending MRI head without and with IV contrast for this clinical scenario. There is insufficient medical literature to conclude whether or not these patients would benefit from this procedure in this clinical setting. Imaging in this patient population is controversial but may be appropriate.
- Variant 6:** MRI head without IV contrast may be appropriate for the initial imaging of children with primary generalized seizure (neurologically normal).
- Variant 7:** MRI head without IV contrast is usually appropriate for the initial imaging of children with generalized seizure (neurologically abnormal).
- Variant 8:** MRI head without IV contrast is usually appropriate for children with intractable seizures or refractory epilepsy. The panel did not agree on recommending MRI head without and with IV contrast for children with intractable seizures or refractory epilepsy. There is insufficient medical literature to conclude whether or not these patients would benefit from administration of IV gadolinium contrast in this clinical setting.

Modified from Expert Panel on Pediatric Imaging, Trofimova A, Milla SS, Ryan ME, et al. ACR appropriateness criteria seizures-child. *J Am Coll Radiol.* 2021;18(55):S199-S210 (Summary of Expectations, p. S208-S209).

any increase in the incidence of abnormalities of behavior, scholastic performance, neurocognitive function, or attention. Children who develop later epilepsy, however, might experience such difficulties. Febrile seizures recur in approximately 30% of those experiencing a first episode, in 50% after two or more episodes, and in 50% of infants younger than 1 year of age at febrile seizure onset. Several factors affect the recurrence risk ([Table 633.9](#)). Although approximately 15% of children with epilepsy have had febrile seizures, only 5% (range 1–33%, dependent on risk factors) of children who experience febrile seizures proceed to develop epilepsy later in life. There are several predictors of epilepsy after febrile seizures ([Table 633.10](#)).

GENETIC AND OTHER FACTORS LEADING TO FEBRILE SEIZURES

The genetic contribution to the incidence of febrile seizures is manifested by a positive family history for febrile seizures in many patients. In some families, the disorder is inherited as an autosomal dominant trait, and multiple single genes that cause the disorder have been identified in such families. However, in most cases the disorder appears to be polygenic, and many genes predisposing to it remain to be identified. Genes associated with febrile seizures include *SCN1A*, *SCN1B*, *SCN9A*, and *CPA6*. In terms of other etiologies, a dysregulation between the proinflammatory interleukin (IL)-1 β , IL-6, and IL-8 cytokines and antiinflammatory ILR-1A cytokines has been associated with **febrile status epilepticus**. A decreased ILR-1A/IL-8 ratio (suggestive of an overall proinflammatory state) is predictive of hippocampal abnormalities on MRI done after febrile status epilepticus. The ILR-1A/IL-8 ratio may thus prove to be a potential biomarker for identifying febrile seizure patients who may be at higher risk for developing mesial temporal lobe epilepsy later in life.

Table 633.9	Risk Factors for Recurrence of Febrile Seizures*
MAJOR	
Age <1 yr	
Duration of fever <24 hr	
Fever 38–39°C (100.4–102.2°F)	
MINOR	
Family history of febrile seizures	
Family history of epilepsy	
Complex febrile seizure	
Daycare	
Male gender	
Lower serum sodium at time of presentation	

*Having no risk factors carries a recurrence risk of approximately 12%; one risk factor, 25–50%; two risk factors, 50–59%; three or more risk factors, 73–100%.

Table 633.10	Risk Factors for Occurrence of Subsequent Epilepsy After a Febrile Seizure*
RISK FACTOR	RISK FOR SUBSEQUENT EPILEPSY
Simple febrile seizure	1%
Recurrent febrile seizures	4%
Complex febrile seizures (>15 min in duration or recurrent within 24 hr)	6%
Fever <1 hr before febrile seizure	11%
Family history of epilepsy	18%
Complex febrile seizures (focal)	29%
Neurodevelopmental abnormalities	33%

*Having more than one risk factor is at least in part additive.

Almost any type of epilepsy can be preceded by febrile seizures. A few epilepsy syndromes typically start with febrile seizures; these are **generalized epilepsy with febrile seizures plus (GEFS+)**, **severe myoclonic epilepsy of infancy (SMEI or Dravet syndrome)**, and, in many patients, temporal lobe epilepsy secondary to mesial temporal sclerosis. **GEFS+** is an autosomal dominant syndrome with a highly variable phenotype. Onset is usually in early childhood, and remission is usually in mid-childhood. It is characterized by multiple febrile seizures and by several subsequent types of afebrile generalized seizures, including generalized tonic-clonic, absence, myoclonic, atonic, or myoclonic astatic seizures with variable degrees of severity. A focal febrile seizure plus epilepsy variant, in which the seizures are focal rather than generalized, has also been described.

Dravet syndrome is the most severe of the phenotypic spectrum of febrile seizure-associated epilepsies. It constitutes a distinct entity, the onset of which is in infancy. It is initially characterized by febrile and afebrile unilateral clonic seizures that recur every 1 or 2 months. These early seizures are typically induced by fever, but they differ from the usual febrile convulsions in that they are more prolonged, more frequent, and focal and recur in clusters. Seizures subsequently start to occur with lower fevers and then without fever. During the second year of life, myoclonus, atypical absences, and focal seizures occur frequently, and developmental delay usually follows (Fig. 633.4). This syndrome is usually caused by a de novo pathogenic variant, although rarely it is inherited in an autosomal dominant manner or may be inherited from a nonaffected carrier parent. Variants in the *SCN1A* gene are the most common cause of Dravet syndrome (causing ~80% of all cases). The same gene is affected in the GEFS+ spectrum; however, in Dravet syndrome the variant leads to loss of function and

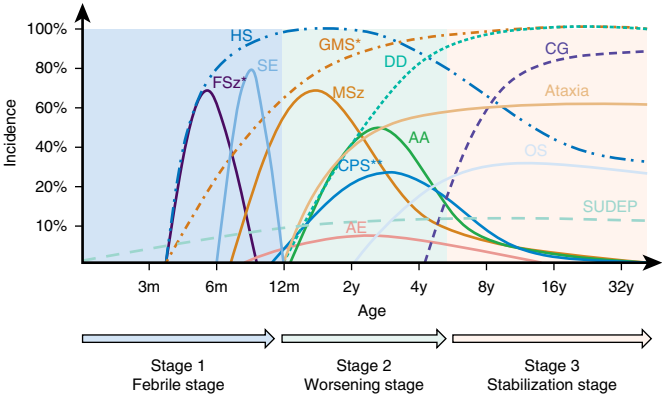


Fig. 633.4 Schematic representation of the varied clinical manifestations of Dravet syndrome and their relative incidence according to age. AA, Atypical absences; AE, acute encephalopathy; CG, crouching gait; CPS, complex partial seizures; DD, developmental delay; FSz, complex febrile seizures; GMS, generalized motor seizures; HS, hyperthermia sensitivity; MSz, myoclonic seizures; OS, obtundation status; SE, convulsive status epilepticus; Ataxia; SUDEP, sudden unexpected death in epilepsy. *Moderate fever for 60%; mostly clonic generalized and unilateral motor seizures. **Difficult distinction between atypical absences and complex partial seizures without ictal EEG recording, so their precise incidence is unknown; including generalized tonic-clonic and unilateral seizures. However, unilateral seizures are less frequent after the age of 7 yr, whereas sleep seizures increase after 6–7 yr and become predominant after age of 9–10 yr. (From Gataullina S, Dulac O. From genotype to phenotype in Dravet disease. *Seizure*. 2017;44:58–64, Fig. 1, p. 59.)

thus to a more severe phenotype. There are several *milder variants* of Dravet syndrome that manifest some, but not all, of the previous features and that are referred to as **Dravet syndrome spectrum** or SMEI-Borderland. Rarely the *GABRG2*, *SCN1B*, and *SCN2A* genes may cause Dravet syndrome; however, in 10–20% of the cases a specific gene variant is not identified.

The majority of patients who had prolonged febrile seizures and encephalopathy after vaccination and who had been presumed to have suffered from vaccine encephalopathy (seizures and psychomotor regression occurring after vaccination and presumed to be caused by it) turn out to have Dravet syndrome pathogenic gene variants, indicating that their disease is caused by the variant and not secondary to the vaccine. This has raised doubts about the very existence of the entity termed *vaccine encephalopathy*.

EVALUATION

Figure 633.5 delineates the general approach to the patient with febrile seizures. Each child who presents with a febrile seizure requires a detailed history and a thorough general and neurologic examination. Febrile seizures often occur in the context of otitis media; roseola and human herpesvirus (HHV) 6 infections; and infections with norovirus, parechovirus, enteroviruses, *Shigella*, or similar agents, making the evaluation more demanding. In patients with febrile status epilepticus, HHV-6B (more frequently) and HHV-7 infections may account for 30% of the cases.

Lumbar Puncture

Meningitis should be considered in the differential diagnosis, and lumbar puncture should be performed for all infants younger than 6 months of age who present with fever and seizure, if the child is ill-appearing, or at any age if there are clinical signs or symptoms of concern. A lumbar puncture is an option in a child 6–12 months of age who is deficient in *Haemophilus influenzae* type b and *Streptococcus pneumoniae* immunizations or for whom the immunization status is unknown. A lumbar puncture is an option in children who have been pretreated with antibiotics. In uninfected patients presenting with febrile status epilepticus, a nontraumatic lumbar puncture rarely shows cerebrospinal fluid (CSF) pleocytosis (96% have <3 nucleated cells in

the CSF) with a concurrently normal CSF protein and glucose. Pleocytosis suggests bacterial or viral infection.

Electroencephalogram

If the child is presenting with the first simple febrile seizure and is otherwise neurologically healthy, an EEG need not be performed as part of the evaluation. An EEG would not predict the future recurrence of febrile seizures or epilepsy even if the result is abnormal. Spikes during drowsiness are often seen in children with febrile seizures, particularly those older than age 4 years, and these do not predict later epilepsy. EEGs performed within 2 weeks of a febrile seizure often have non-specific slowing, usually posteriorly. Thus in many cases, if an EEG is indicated, it is delayed until or repeated after more than 2 weeks have passed. An EEG should therefore generally be restricted to special cases in which epilepsy is highly suspected (see Table 633.10), and, generally, it should be used to delineate the type of epilepsy rather than to predict its occurrence. If an EEG is done, it should be performed for at least 20 minutes in wakefulness and in sleep according to international guidelines to avoid misinterpretation and drawing of erroneous conclusions. At times, if the patient does not recover immediately from a seizure, an EEG can help distinguish between ongoing seizure activity and a prolonged postictal state. After febrile status epilepticus, focal EEG slowing over the temporal lobe increases the chance that the patient may have medial temporal sclerosis on follow-up.

Blood Studies

Blood studies (serum electrolytes, calcium, phosphorus, magnesium, and a complete blood count) are not routinely recommended in the workup of a child with a first simple febrile seizure. Blood glucose should be measured initially and with prolonged postictal obtundation or with poor oral intake (prolonged fasting). Serum electrolyte values may be abnormal in children after a febrile seizure, but this should be suggested by precipitating or predisposing conditions elicited in the history and reflected in the physical examination. If clinically indicated (e.g., dehydration), these tests should be performed. A low sodium level is associated with a higher risk of recurrence of the febrile seizure within the following 24 hours.

Neuroimaging

A CT or MRI is not recommended in evaluating the child after a first simple febrile seizure. The workup of children with complex febrile seizures needs to be individualized. This can include an EEG and neuroimaging, particularly if the child is neurologically abnormal. Approximately 10% of children with febrile status epilepticus are reported to have unilateral or, less frequently, bilateral swelling of their hippocampus acutely; subsequent long-term hippocampal atrophy is evident in about 71% of those who had the acute findings. Whether these patients will ultimately develop temporal lobe epilepsy remains to be determined.

TREATMENT

In general, antiepileptic therapy, continuous or intermittent, is not recommended for children with one or more simple febrile seizures. Parents should be counseled about the relative risks of recurrence of febrile seizures and recurrence of epilepsy, educated on how to handle a seizure acutely, and given emotional support. If the seizure lasts for longer than 5 minutes, acute treatment with lorazepam, midazolam, or diazepam is needed (see Chapter 633.8 for acute management of seizures and status epilepticus). Rectal diazepam is often prescribed to families to be used at home as a rescue medication if a febrile seizure lasts longer than 5 minutes (see Table 633.14 for dosing). Alternatively, buccal or intranasal midazolam or diazepam may be used. In cases of frequently recurring febrile seizures, intermittent oral clonazepam (0.01 mg/kg every 8–12 hours up to a maximum dose of 1.5 mg/day) or oral diazepam (0.33 mg/kg every 8 hours) can be given during febrile illnesses. Such therapies help reduce, but do not eliminate, the risks of recurrence of febrile seizures. Historically, continuous therapy with the antiepileptic drugs (AEDs) phenobarbital or valproic acid was occasionally used to prevent febrile seizures. However, in the vast majority

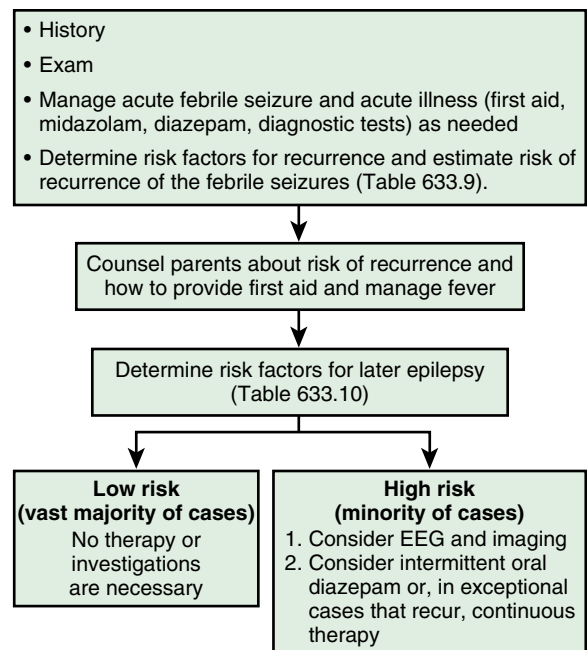


Fig. 633.5 Treatment algorithm for the management of febrile seizures. (Modified from Mikati MA, Rahi A. Febrile seizures: from molecular biology to clinical practice. *Neurosciences [Riyadh]*. 2004;10:14–22.)

of cases, use of continuous therapy is not justified because of the risk of side effects and lack of demonstrated long-term benefits, even if the recurrence rate of febrile seizures is expected to be decreased by these drugs.

Antipyretics can decrease the discomfort of the child but do not reduce the risk of having a recurrent febrile seizure. Chronic antiepileptic therapy may be considered for children with a high risk for later epilepsy. The possibility of future epilepsy does not change with or without antiepileptic therapy. Iron deficiency is associated with an increased risk of febrile seizures, and thus screening for that problem and treating it appear appropriate. A recent Delphi-type European study generated specific recommendations for providers to deliver to caretakers after a febrile seizure (reference provided later). These included the definition of febrile seizures, basis of this clinical diagnosis, acknowledging parental stress, risk of recurrence, and long-term care of the child, which also should include that the parents should avoid cosleeping, which is dangerous for their child and does not prevent febrile seizures.

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633.2 Unprovoked Seizures

Mohamad A. Mikati, Dmitry Tchapyjnikov, and Kevin M. Rathke

HISTORY AND EXAMINATION

Evaluation of a first-time seizure was discussed earlier in this chapter. It entails stabilization of the patient if the child presents during or shortly after the seizure. A careful history and examination are done to accurately characterize the seizure, exclude acute intervenable causes, and attempt to determine the underlying etiology of the seizure.

DIFFERENTIAL DIAGNOSIS

This involves consideration of nonepileptic paroxysmal events (see Chapter 634), determination of the seizure type as classified by the ILAE system (see Fig. 633.1), and consideration of potential underlying etiologies. Some seizures might begin with **auras**, which are sensory experiences reported by the patient and are not observed externally.

Motor seizures can be **tonic**, **clonic**, **myoclonic**, **atonic**, or **astatic**. **Astatic** seizures often follow myoclonic seizures and cause a momentary loss of tone with a sudden fall. **Atonic** seizures, on the other hand, are usually longer, and the loss of tone often develops more slowly. Sometimes it is difficult to distinguish among tonic, myoclonic, atonic, or astatic seizures based on the history alone when the family reports only that the patient falls; in such cases, the seizure may be described as a **drop attack**. Loss of tone or myoclonus in only the neck muscles results in a milder seizure referred to as a **head drop**. Tonic, clonic, tonic-clonic, myoclonic, and atonic seizures can be focal (including one limb or one side only), focal with secondary generalization, or primary generalized. Epileptic spasms, or **axial spasms** (these terms being preferred over infantile spasms because the spasms can occur beyond infancy), consist of flexion or extension of the truncal and extremity musculature that is sustained for 1-2 seconds, shorter than the duration seen in tonic seizures, which last longer than 2 seconds. Focal motor clonic and/or myoclonic seizures that persist for days, months, or even longer are termed **epilepsia partialis continua**.

Absence seizures are generalized seizures consisting of staring, unresponsiveness, and eye flutter lasting usually for a few seconds. **Typical absences** are associated with 3-Hz spike-and-slow-wave discharges and with childhood absence epilepsy, which has a good prognosis. **Atypical absences** are associated with 1- to 2-Hz spike-and-slow-wave discharges and with head atonia and myoclonus during the seizures. They occur in **Lennox-Gastaut syndrome** and similar syndromes, which have a poor prognosis. **Juvenile absences** are similar to typical absences but are associated with 4- to 5-Hz spike-and-slow-wave discharges and often occur in juvenile myoclonic epilepsy. Seizure type and other EEG and clinical manifestations determine the type of **epilepsy syndrome** with which a particular patient is afflicted (see [Tables 633.1-633.6](#); see also [Chapters 633.3 and 633.4](#)).

A family history of certain forms of epilepsy, such as benign familial neonatal seizures, can suggest the specific epilepsy syndrome. More often, however, different members of a family with a positive history of epilepsy have different types of epilepsy. Specific findings on physical exam may point to an underlying disorder causing the seizure, such as tuberous sclerosis, Sturge-Weber syndrome, neurofibromatosis, or other brain malformations.

LONG-TERM APPROACH TO THE PATIENT AND ADDITIONAL TESTING

The approach to the patient with epilepsy is based on the diagnostic scheme proposed by the ILAE Task Force on Classification and Terminology and presented in [Table 633.7](#). Most epilepsy syndromes are potentially caused by any one of multiple underlying or still undetermined etiologies. However, in addition, there are many epilepsy syndromes that are associated with specific gene mutations (see [Tables 633.1-633.6](#) and [Fig. 633.3](#)). Different pathogenic variants of the same gene can result in different epilepsy syndromes, whereas variants of different genes can cause the same epilepsy syndrome phenotype. The clinical use of gene testing in the diagnosis and management of childhood epilepsy is indicated in patients manifesting specific underlying malformational, metabolic, or degenerative disorders; patients with severe epilepsy syndromes (such as West and Dravet syndromes and progressive myoclonic epilepsies); and patients with syndromes of mendelian inheritance (see [Tables 633.1 and 633.6](#)). Gene testing is indicated in epilepsy encephalopathy syndromes and in patients with other organ involvement (hepatic, muscle, cardiac, intestinal) and in atypical phenotypes.

In patients with drug-resistant epilepsy or in infants with new-onset epilepsy in whom the initial testing did not reveal an underlying etiology, a full metabolic workup, including amino acids, organic acids, biotinidase, and CSF studies, is needed. Additional testing can include, depending on the case, some or most of the following:

1. Measurement of serum lactate, pyruvate, acyl carnitine profile, creatine, very long-chain fatty acids, ammonia, and guanidino-acetic acid.
2. Blood and serum sometimes need to be tested for white blood cell lysosomal enzymes, serum coenzyme Q levels, and serum copper and ceruloplasmin levels (for Menkes syndrome).

3. Serum immune isoelectric focusing (or gene panels) is performed for carbohydrate-deficient transferrin in disorders of glycosylation. CSF glucose testing looks for glucose transporter deficiency, and the CSF can be examined for cells and proteins (for parainfectious and postinfectious syndromes and for Aicardi-Goutières syndrome, which also shows cerebral calcifications and has a specific gene defect test available).

4. Other laboratory studies include CSF immunoglobulin (Ig) G index, NMDA receptor, and other autoimmune encephalitis-associated antibodies, as well as measles titers in serum and CSF.

5. CSF tests can also confirm, with the appropriate clinical setup, the diagnosis of cerebral folate deficiency, pyridoxine dependency, pyridoxal-5-phosphate dependency, mitochondrial disorders, nonketotic hyperglycinemia, neopterin/biopterin metabolism disorders, adenylosuccinate lyase deficiency, and neurotransmitter deficiencies.

In infants who do not respond immediately to antiepileptic therapy, vitamin B₆ (100 mg intravenously) is given as a therapeutic trial to help diagnose pyridoxine-responsive seizures, with precautions to guard against possible apnea. The trial is best done with continuous EEG monitoring, including a preadministration baseline recording period. Before the vitamin B₆ trial, a pipecolic acid level and serum, urine, or CSF α -amino adipic acid semialdehyde levels should be drawn because they are often elevated in this rare syndrome and the therapeutic trial result may not be definitive. Some patients are pyridoxal phosphate, rather than pyridoxine, dependent. Patients with cerebral folate deficiency can also have intractable seizures. Thus trials of pyridoxal phosphate given orally (up to 50 mg/kg/day given every 6 hours) and folinic acid (2.5-5 mg twice a day, if needed; can titrate up to a maximum dose of 8 mg/kg/day) over several weeks can help diagnose these rare disorders while one is waiting for the definitive diagnosis from CSF or genetic testing. Certain EEG changes such as continuous spike-and-slow-wave seizure activity and burst-suppression patterns may also suggest these vitamin-responsive syndromes.

6. Urine may also need to be tested for urinary sulfites indicating molybdenum cofactor deficiency and for oligosaccharides and mucopolysaccharides. MR spectroscopy can be performed for lactate and creatine peaks to rule out mitochondrial disease and creatine transporter deficiency.

7. Gene testing looks for specific disorders that can manifest with seizures, including *SCN1A* pathogenic variants in Dravet syndrome; *ARX* gene for West syndrome in males; *MECP2*, *CDKL5*, and protocadherin 19 for Rett syndrome and similar presentations; syntaxin-binding protein for Ohtahara syndrome; and polymerase G for West syndrome and other seizures in infants. Gene testing can also be performed for other dysmorphic or metabolic syndromes.

8. Muscle biopsy can be performed for mitochondrial DNA and oxidative enzymes as well as coenzyme Q10 levels, and skin biopsy for inclusion bodies seen in neuronal ceroid lipofuscinosis and Lafora body disease.

9. Genetic panels are available that include multiple genes that can cause epilepsy at specific ages; whole exome or genome sequencing is also available. The availability of gene panels, particularly ones that can test for amenably treatable conditions such as vitamin B₆-dependent epilepsy, and the rapid turnaround time have replaced the need for many of the tests listed in points 1-9.

10. MRI should also be performed to identify congenital disorders (cortical dysplasias, lissencephaly, schizencephaly), calcifications, focal lesions (basal ganglia), and myelinization disorders (acute disseminated encephalomyelitis [ADEM], leukodystrophies). MRI may identify specific disorders such as posterior reversible encephalopathy syndrome (PRES), stroke (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes [MELAS]), Rasmussen encephalitis, tumors, cerebral edema, hemorrhage, or venous thrombosis (see [Table 633.8](#)). It should also be noted that seizures alone may cause nonspecific-nondiagnostic transient MRI abnormalities; these may include transient gray matter and subcortical white matter signals or transient hippocampal and temporal lobe abnormalities.

Most patients do not require an extensive evaluation. The pace and extent of the workup must depend on the clinical epileptic and non-epileptic features, the family and antecedent personal history of the patient, the medication responsiveness of the seizures, the likelihood of identifying a treatable condition, and the wishes and need of the family to assign a specific diagnosis to the child's illness.

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633.3 Focal Seizures and Related Epilepsy Syndromes

Mohamad A. Mikati and Dmitry Tchapyjnikov

Focal seizures account for approximately 40% of seizures in children and can be divided into **focal seizures with preserved awareness**, in which consciousness is not impaired, and **focal seizures with impaired awareness**, in which consciousness is affected.

Focal seizures with preserved or impaired awareness can each occur in isolation, one can temporally lead to the other (usually from preserved to impaired awareness), and/or each can progress into secondary generalized seizures, called **focal to bilateral tonic-clonic seizures**, although less commonly, the secondary generalized seizure may also be tonic, clonic, or atonic.

FOCAL SEIZURES WITH PRESERVED AWARENESS

These can take the form of sensory seizures (auras, called *focal aware seizures*) or brief motor seizures, the specific nature of which gives clues as to the location of the seizure focus. Brief motor seizures are the most common and include focal tonic, clonic, or atonic seizures. Often there is a motor (Jacksonian) march from face to arm to leg, adverse head and eye movements to the contralateral side, or postictal (Todd) paralysis that can last minutes or hours, and sometimes longer. Unlike tics, motor seizures are not under partial voluntary control; seizures are more often stereotyped and are less likely than tics to manifest different types in a given patient.

FOCAL SEIZURES WITH IMPAIRED AWARENESS

These seizures usually last 1-2 minutes and are often preceded by an **aura**, such as a rising abdominal feeling, déjà vu or déjà vécu, a sense of fear, complex visual hallucinations, micropsia or macropsia (temporal lobe), generalized difficult-to-characterize sensations (frontal lobe), focal sensations (parietal lobe), or simple visual experiences (occipital lobe). Children younger than 7 years old are less likely than older children to report auras, but parents might observe unusual preictal behaviors that suggest the experiencing of auras. Subsequent manifestations consist of decreased responsiveness, staring, looking around seemingly purposelessly, and automatisms. **Automatisms** are automatic semipurposeful movements of the mouth (oral, alimentary such as chewing) or of the extremities (manual, such as manipulating the sheets; leg automatisms such as shuffling, walking, or bicycling movements). Often there is salivation, dilation of the pupils, and flushing or color change. The patient might appear to react to some of the stimulation around him or her but does not later recall the epileptic event. At times, walking and/or marked limb flailing and agitation occur, particularly in patients with frontal lobe seizures. Frontal lobe seizures often occur at night and can be very numerous and brief, but other complex partial seizures from other areas in the brain can also occur at night. There is often contralateral dystonic posturing of the arm and, in some cases, unilateral or bilateral tonic arm stiffening. Some seizures have these manifestations with minimal or no automatisms. Others consist of altered consciousness with contralateral motor, usually clonic, manifestations. After the seizure, the patient can have postictal automatisms, sleepiness, and/or other transient focal deficits such as weakness (Todd paralysis) or aphasia.

FOCAL TO BILATERAL TONIC-CLONIC SEIZURES

These can either start with generalized clinical phenomena (from rapid spread of the discharge from the initial focus) or as focal seizures with

subsequent clinical generalization. There is often adverse eye and head deviation to the side contralateral to the side of the seizure focus, followed by generalized tonic, clonic, or tonic-clonic activity. Tongue biting, urinary and stool incontinence, vomiting with risk of aspiration, and cyanosis are common. Fractures of the vertebrae or humerus are rare complications. Most such seizures last 1-2 minutes. Focal tonic or focal to bilateral tonic-clonic seizures often manifest as adverse head deviation to the contralateral side, fencing, hemi- or full figure-of-four arm, and/or Statue of Liberty postures. These postures usually suggest a frontal origin and, when awareness is preserved during them, favor that the seizure originated from the medial frontal supplementary motor area.

EEG in patients with focal/partial seizures usually shows focal spikes or sharp waves in the lobe where the seizure originates. A *sleep-deprived* EEG with recording during sleep increases the diagnostic yield and is advisable in all patients (Fig. 633.6). Despite that, approximately 15% of children with epilepsy initially have normal EEGs because the discharges are relatively infrequent or the focus is deep. If repeating the test does not detect paroxysmal findings, longer recordings in the laboratory or using ambulatory EEG or even inpatient 24-hour video EEG monitoring may be helpful. The latter is particularly helpful if the seizures are frequent enough because it then can allow visualization of the clinical events and the corresponding EEG tracing.

Brain imaging is critical in patients with focal seizures. MRI is preferable to CT, which misses subtle but, occasionally, potentially clinically significant lesions. MRI can show pathologies such as changes as a result of previous strokes or hypoxic injury, malformations, medial temporal sclerosis, arteriovenous malformations, inflammatory pathologies, or tumors (Fig. 633.7). Of note is that patients with focal seizures and epilepsies can have focal corresponding neuropsychologic deficits but also have patterns of network-related deficits such as impaired social cognition, deficits that are shared with generalized epilepsies.

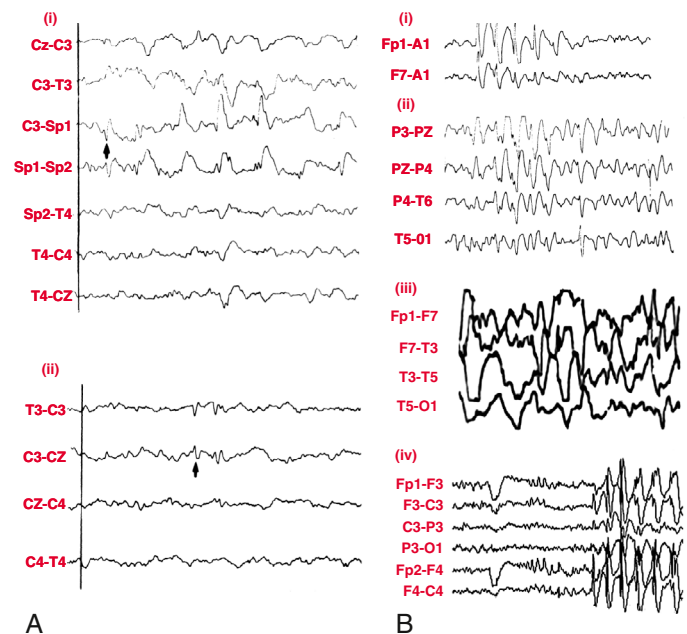


Fig. 633.6 A, Representative EEG associated with partial seizures: (i) Spike discharges from the left temporal lobe (arrow) in a patient with complex partial seizures caused by mesial temporal sclerosis; (ii) left central-parietal spikes (arrow) characteristic of benign partial epilepsy with centrotemporal spikes. B, Representative EEGs associated with generalized seizures: (i) 3/sec spike-and-wave discharge of absence seizures with normal background activity; (ii) 1-2/sec interictal slow spike waves in a patient with Lennox-Gastaut syndrome; (iii) hypsarrhythmia with irregular multifocal high-voltage spike-and-wave activity with a chaotic high-voltage slow background; (iv) juvenile myoclonic epilepsy EEG showing 4-6/sec spike and waves enhanced by photic stimulation.

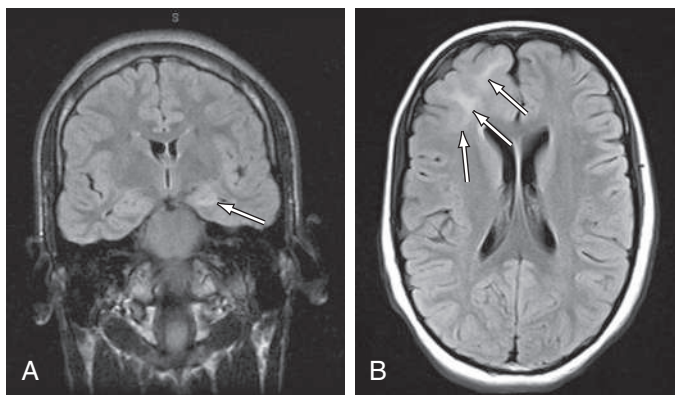


Fig. 633.7 A, Coronal fluid-attenuated inversion-recovery (FLAIR) MRI scan of a 13-yr-old with intractable seizures and mesial temporal sclerosis (MTS). The arrow points at the hippocampus with the high-intensity signal characteristic of MTS. B, Axial FLAIR MRI of a 7-yr-old with intractable seizures and right frontal cortical dysplasia. The arrows point at the high-intensity signal corresponding to the dysplasia. (A from Lee JYK, Adelson PD. *Neurosurgical management of pediatric epilepsy*. *Pediatr Clin North Am*. 2004;51:441–456.)

These observations support current thinking that not only generalized but also focal epilepsy involves network-related pathophysiology.

BENIGN EPILEPSY SYNDROMES WITH FOCAL SEIZURES

The most common such syndrome is **benign childhood epilepsy with centrotemporal spikes (BECTS)**, which typically starts during childhood (ages 3–10 years) and is outgrown by adolescence. The child typically wakes up at night because of a focal seizure with preserved awareness causing buccal and throat tingling and tonic or clonic contractions of one side of the face, with drooling and inability to speak but with preserved consciousness and comprehension. Focal seizures with impaired awareness and secondary generalized seizures can also occur. EEG shows typical wide-based centrotemporal spikes that are markedly increased in frequency during drowsiness and sleep. MRI is normal. Patients respond very well to AEDs such as oxcarbazepine and carbamazepine. In some patients who only have rare and mild seizures, treatment might not be needed. Traditionally patients with BECTS are considered to have normal neurocognitive development, but some studies have documented problems in memory and in other neuropsychologic functions and in attention. **Atypical BECTS** is a less common variant of the disorder characterized by often a younger age of onset, multiple seizure types including drop attacks, atypical EEG patterns including secondary bilateral synchrony, and/or other comorbidities such as developmental delay.

Benign epilepsy with occipital spikes can occur in early childhood (**Panayiotopoulos type**) and manifests with focal seizures with impaired awareness and with ictal vomiting; they may also first appear in later childhood (**Gastaut type**) as focal seizures with impaired awareness, visual auras, and migraine headaches that occur independently or postictally (epilepsy-migraine sequence). Both are typically outgrown in a few years.

In infants, several less common **benign infantile familial convulsion syndromes** have been reported. For some of these, the corresponding gene variant and its function are known (see Table 633.1), including **benign familial neonatal seizures** (*KCNQ2*, *KCNQ3*), **benign familial neonatal infantile seizures** (*SCN2A*), and **early familial neonatal infantile seizures** (*SCN2A*).

A number of **benign infantile nonfamilial syndromes** have been reported, including focal seizures with impaired awareness with temporal foci, focal to bilateral tonic-clonic seizures with variable foci, tonic seizures with midline foci, and focal seizures in association with mild gastroenteritis. All of these have a good prognosis and respond to treatment promptly; often, only short-term therapy (e.g., 6 months), if any therapy, is needed. **Nocturnal autosomal dominant frontal**

lobe epilepsy has been linked to acetylcholine-receptor and to *KCNT1* pathogenic variants. It manifests with nocturnal seizures with dystonic posturing, agitation, screaming, and kicking that respond promptly to carbamazepine. Several other less frequent familial benign epilepsy syndromes with different localizations have also been described, some of which occur exclusively or predominantly in adults.

SEVERE EPILEPSY SYNDROMES WITH FOCAL SEIZURES

Symptomatic structural/metabolic epilepsy secondary to focal brain lesions has a higher chance of being severe and refractory to therapy than genetic (idiopathic) epilepsy. Many patients with focal lesions, for example, old strokes or brain tumors, either never have seizures or have well-controlled epilepsy. In infants, **drug-resistant epilepsy** with focal seizures is often caused by severe metabolic problems, hypoxic-ischemic injury, or congenital malformations. In addition, in this age-group, a syndrome of multifocal severe partial seizures with progressive mental regression and cerebral atrophy called **epilepsy of infancy with migrating focal seizures** (EIMFS; previously called *malignant migrating partial seizures of infancy*) has been described. Some cases of EIMFS are secondary to pathogenic variants in the calcium-sensitive potassium channel *KCNT1*. Brain malformations causing focal epilepsy include focal cortical dysplasia, hemimegalencephaly, Sturge-Weber cutaneous lesion, tuberous sclerosis, and congenital tumors such as ganglioglioma and dysembryoplastic neuroepithelial tumors and others. The intractable seizures can be focal seizures with or without impaired awareness, focal to bilateral tonic-clonic seizures, or combinations thereof. If secondary generalized seizures predominate and take the form of absence-like seizures and drop attacks, the clinical picture can mimic the generalized epilepsy syndrome of Lennox-Gastaut syndrome and has been termed by some as **pseudo-Lennox-Gastaut syndrome**.

Temporal lobe epilepsy can be caused by any temporal lobe lesion. A common cause is **mesial** (also termed **medial**) **temporal sclerosis**, a condition often preceded by febrile seizures. They are rarely genetic in origin. Pathologically, these patients have atrophy, gliosis, or cortical dysplasia of the hippocampus and, in some these conditions, of the amygdala. Some patients with mesial temporal sclerosis have pathogenic variants in *SUCO*. Medial temporal lobe epilepsy is the most common cause of surgically remediable partial epilepsy in adolescents and adults. Occasionally, in patients with other structural or genetic focal or generalized epilepsies, the focal discharges are so continuous that they cause an epileptic encephalopathy. Activation of temporal discharges in sleep can lead to loss of speech and verbal auditory agnosia (**Landau-Kleffner epileptic aphasia syndrome**). Activation of secondary generalized and at times focal discharges in sleep leads to more global delay secondary to the **syndrome of continuous spike waves in slow-wave sleep** (>85% of the slow-wave sleep recording is dominated by discharges).

The syndrome of **Rasmussen encephalitis** is a form of chronic encephalitis that manifests with *unilateral* intractable partial seizures, *epilepsia partialis continua*, and progressive hemiparesis of the affected side, with progressive atrophy of the involved hemisphere. The etiology is usually unknown, although autoimmune etiologies have been hypothesized.

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633.4 Generalized Seizures and Related Epilepsy Syndromes

Mohamad A. Mikati and Dmitry Tchapyjnikov

ABSENCE SEIZURES

Typical absence seizures usually start at 5–8 years of age and are often, because of their brevity, overlooked by parents for many months even though they can occur up to hundreds of times per day. Unlike focal seizures with impaired awareness, they *do not* have an aura, usually last

for only a few seconds, and are sometimes accompanied by eyelid flutter or upward rolling of the eyes but typically not by the usually more florid automatisms seen in focal seizures with impaired awareness (absence seizures can have simple automatisms such as lip smacking or picking at clothing, and the head can very minimally fall forward). Absence seizures do not have a postictal period and are characterized by immediate resumption of what the patient was doing before the seizure. Hyperventilation for 3–5 minutes can precipitate the seizures and the accompanying 3-Hz spike-and-slow-wave discharges. The presence of eye closure eyelid myoclonia (**Jeavons syndrome**) and periorbital, perioral, or limb myoclonic jerks (the latter called **myoclonic absences**) with the typical absence seizures usually predicts difficulty in controlling the seizures with medications. Early-onset absence seizures (<4 years of age) or drug resistance should trigger evaluation for a glucose transporter defect, which is often associated with low CSF glucose levels and an abnormal sequencing test of the *SLC2A1* transporter gene.

Atypical absence seizures have associated myoclonic components and tone changes of the head (head drop) and body, usually last longer than typical absence seizures, and are also usually more difficult to treat. They are precipitated by drowsiness and are usually accompanied by 1- to 2-Hz spike-and-slow-wave discharges.

Juvenile absence seizures are similar to typical absences but occur at a later age and are accompanied by 4- to 6-Hz spike-and-slow-wave and polyspike-and-slow-wave discharges. These are usually associated with juvenile myoclonic epilepsy (see “Benign Generalized Epilepsies”).

GENERALIZED MOTOR SEIZURES

The most common generalized motor seizures are generalized tonic-clonic seizures that can be either primarily generalized (bilateral) or focal to bilateral tonic-clonic (as described in [Chapter 633.3](#)) from a unilateral focus. If there is no partial component, the seizure usually starts with loss of consciousness and, at times, with a sudden cry, upward rolling of the eyes, and a generalized tonic contraction with falling, apnea, and cyanosis. In some, a clonic or myoclonic component precedes the tonic stiffening. The tonic phase is followed by a clonic phase that, as the seizure progresses, shows slowing of the rhythmic contractions until the seizure stops, usually 1–2 minutes later. Incontinence and a postictal period often follow. The latter usually lasts for a few minutes up to several hours with semicomatose or obtundation and postictal sleepiness, weakness, ataxia, hyperreflexia or hyporeflexia, and headaches. There is a risk of aspiration and injury. First aid measures include positioning the patient on his or her side, clearing the mouth if it is open, loosening tight clothes or jewelry, and gently extending the head and, if necessary, insertion of an airway by a trained professional. The mouth should not be forced open with a foreign object (this could dislodge teeth, causing aspiration) or with a finger in the mouth (this could result in serious injury to the examiner's finger). Many patients have single **genetic generalized tonic-clonic seizures** that may be associated with a concurrent illness or with a cause that cannot be ascertained (see [Chapter 633.2](#)). Generalized tonic, atonic, and atonic seizures often occur in severe generalized pediatric epilepsies. Generalized myoclonic seizures can occur in either benign or difficult-to-control generalized epilepsies (see “Benign Generalized Epilepsies” and “Severe Generalized Epilepsies”).

BENIGN GENERALIZED EPILEPSIES

Childhood absence epilepsy typically starts in mid-childhood, and most patients outgrow it before adulthood. Approximately 25% of patients also develop generalized tonic-clonic seizures, half before and half after the onset of absences. **Benign myoclonic epilepsy of infancy** consists of the onset of myoclonic and other seizures during the first year of life, with generalized 3-Hz spike-and-slow-wave discharges. Often, it is initially difficult to distinguish this type from more severe syndromes, but follow-up clarifies the diagnosis. **GEFS+** manifests as febrile seizures and multiple types of generalized seizures in multiple family members, and at times different individuals within the same family manifest different generalized and febrile seizure types (see [Chapter 633.1](#)).

Juvenile myoclonic epilepsy (Janz syndrome) is the most common generalized epilepsy in young adults, accounting for 5% of all epilepsies. It has been linked to pathogenic variants in many genes, including *CACNB4*; *CLNC2*; *EJM2*, 3, 4, 5, 6, 7, 9; *GABRA1*; *GABRD*; and *myoclonin1/EFHC1*. Typically, it starts in early adolescence with one or more of the following manifestations: myoclonic jerks in the morning, often causing the patient to drop things; generalized tonic-clonic or clonic-tonic-clonic seizures upon awakening; and juvenile absences. Sleep deprivation, alcohol (in older patients), and photic stimulation or, rarely, certain cognitive activities can act as precipitants. The EEG usually shows generalized 4- to 5-Hz polyspike-and-slow-wave discharges.

There are other forms of generalized epilepsies such as **photoparoxysmal epilepsy**, in which generalized tonic-clonic, absence, or myoclonic generalized seizures are precipitated by photic stimuli such as strobe lights, flipping through TV channels, and viewing video games. Other forms of **reflex** (i.e., **stimulus-provoked**) **epilepsy** can occur; associated seizures are usually generalized, although some may be focal (see [Chapter 633.9](#)).

SEVERE GENERALIZED EPILEPSIES

Severe generalized epilepsies are associated with intractable seizures and developmental delay. **Early myoclonic encephalopathy (EME)** starts during the first 2 months of life with severe myoclonic seizures and a burst suppression pattern on EEG. It is usually caused by inborn errors of metabolism such as nonketotic hyperglycinemia. **Early infantile epileptic encephalopathy (Ohtahara syndrome)** has a similar age of onset and EEG but manifests as tonic seizures and is usually caused by brain malformations or various epileptogenic gene mutations. The term *early infantile epileptic encephalopathy* (EIEE) has also been applied to the increasing number (~36) of other genetic epileptic encephalopathies and developmental epileptic encephalopathies that are associated with an increasing number of specific genes with pathogenic variants ([Table 633.11](#)); these may or may not manifest as Ohtahara syndrome, but all share the characteristic of early-onset epileptic encephalopathy. For example, EIEE type 4 is Ohtahara syndrome caused by syntaxin-binding protein 1 pathogenic variants. **Severe myoclonic epilepsy of infancy (Dravet syndrome)**, most often caused by pathogenic variants in *SCN1A*, starts as focal febrile status epilepticus or focal febrile seizures and later manifests as myoclonic and other seizure types (see [Chapter 633.1](#)).

West syndrome starts between the ages of 2 and 12 months and consists of a triad of infantile epileptic spasms that usually occur in clusters (particularly in drowsiness or upon arousal), developmental regression, and a typical EEG picture called **hypsarrhythmia** (see [Fig. 633.6](#)). Hypsarrhythmia is a high-voltage, slow, chaotic background with multifocal spikes. Patients with *cryptogenic/idiopathic* (referred to as *unknown etiology*) West syndrome have normal development before onset, whereas patients with *symptomatic* West syndrome have preceding developmental delay owing to perinatal encephalopathies, malformations, underlying metabolic disorders, infections like with congenital Zika virus, or other etiologies (see [Chapter 633.2](#)). In males, West syndrome can also be caused by *ARX* gene variants (often associated with ambiguous genitalia and cortical migration abnormalities). West syndrome, especially in cases where the etiology is unknown (i.e., cases that are not explained by the presence of a gene variant or a structural brain anomaly), is a medical emergency because a delay in diagnosis of 3 weeks or longer can affect the long-term prognosis. The spasms are often overlooked by parents and by physicians, being mistaken for startles caused by colic or other benign paroxysmal syndromes (see [Chapter 634](#)).

Lennox-Gastaut syndrome typically starts between the ages of 2 and 10 years and consists of a triad of developmental delay, multiple seizure types that as a rule include atypical absences, and myoclonic, atonic, and tonic seizures, as well as specific EEG abnormalities. The tonic and/or atonic seizures occur either in wakefulness (causing falls and injuries, broadly termed **drop attacks**) or also, typically, in sleep. The third component is the EEG findings (see [Fig. 633.6](#)): 1- to 2-Hz spike and slow waves, polyspike bursts in sleep (also called *generalized*

Table 633.11 Early Infantile Epileptic Encephalopathy (EIEE)

GENE	PROTEIN
ARX (EIEE1)	Aristaless-related homeobox
CDKL5 (EIEE2)	Cyclin-dependent kinase-like 5
SLC25A22 (EIEE3)	Mitochondrial glutamate carrier 1
STXBP1 (EIEE4)	Syntaxin-binding protein 1
SPTAN1 (EIEE5)	α_2 -Spectrin
SCN1A (EIEE6)	Sodium-channel protein type 1 α
KCNQ2 (EIEE7)	Potassium voltage-gated channel
ARHGEF9 (EIEE8)	Rho guanine nucleotide exchange factor 9
PDCH19 (EIEE9)	Protocadherin-19
PNKP (EIEE10)	Bifunctional polynucleotide phosphatase/kinase
SCN2A (EIEE11)	Sodium-channel protein type 2 α
PLC β 1 (EIEE12)	Phospholipase C β 1
SCN8A (EIEE13)	Sodium-channel, voltage-gated, type VIII, alpha subunit
KCNT1 (EIEE14)	Potassium-channel subfamily T, member 1
ST3GAL3 (EIEE15)	ST3 beta-galactoside alpha-2,3-sialyltransferase 3
TBC1D24 (EIEE16)	TBC1 domain family, member 24
GNAO1 (EIEE17)	Guanine nucleotide-binding protein G(o) subunit alpha
SZT2 (EIEE18)	Seizure threshold 2 homolog
GABRA1 (EIEE19)	Gamma-aminobutyric acid receptor subunit alpha-1
PIGA (EIEE20)	Phosphatidylinositol N-acetylglucosaminyltransferase subunit A
NECAP1 (EIEE21)	Adaptin ear-binding coat-associated protein 2
SLC35A2 (EIEE22)	UDP-galactose translocator
DOCK7 (EIEE23)	Dedicator of cytokinesis 7
HCN1 (EIEE24)	Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 1
SLC13A5 (EIEE25)	Solute carrier family 13 (sodium-dependent citrate transporter), member 5
KCNB1 (EIEE26)	Potassium voltage-gated channel, Shab-related subfamily, member 1
GRIN2B (EIEE27)	NMDA receptor subtype 2B
WWOX (EIEE28)	WW domain-containing oxidoreductase
AARS (EIEE29)	Alanyl-tRNA synthetase
SIK1 (EIEE30)	Salt inducible kinase 1
DNM1 (EIEE31)	Dynamin-1
KCNA2 (EIEE32)	Potassium voltage-gated channel subfamily A member 2
EEF1A2 (EIEE33)	Elongation factor 1-alpha 2
SLC12A5 (EIEE34)	Potassium-chloride transporter member 5
ITPA (EIEE35)	Inosine triphosphate pyrophosphatase
ALG13 (EIEE36)	Asparagine-linked glycosylation 13 homolog

paroxysmal fast activity or GPFA), and a slow background in wakefulness. Most patients are left with long-term cognitive impairment and intractable seizures despite multiple therapies. Some patients start with Ohtahara syndrome, develop West syndrome, and then progress to Lennox-Gastaut syndrome. **Myoclonic astatic epilepsy (Doose**

syndrome) is a syndrome similar to, but milder than, Lennox-Gastaut syndrome and is characterized by seizures consisting of myoclonic jerking rapidly followed by an atonic (astatic) drop attack. Patients with Doose syndrome usually do not have tonic seizures or polyspike bursts in sleep. The prognosis is more favorable than that for Lennox-Gastaut syndrome. Another syndrome characterized by atonic seizures causing head nodding as well as tonic, clonic, and stimulus-sensitive seizures is **nodding syndrome**, which is seen in some African countries and is often associated with encephalopathy, stunted growth, and variable degrees of cognitive deficits. The underlying etiology is a likely autoimmune reaction to the parasitic worm *Onchocerca volvulus*. The head nodding is associated with generalized slow waves and electrodecrement, likely representing generalized ictal activity, but is commonly resistant to drug therapy.

Progressive myoclonic epilepsies (EPM) are a group of epilepsies characterized by progressive dementia and worsening myoclonic and other seizures. **Type I**, or **Unverricht-Lundborg disease**, is caused by pathogenic variants in the *CSTB* gene, is more slowly progressive than the other types, and usually starts in adolescence. **Type II**, or **Lafora body disease**, can have an early childhood onset but usually starts in adolescence, is more quickly progressive, and is usually fatal within the second or third decade of life. It can be associated with photosensitivity, manifests periodic acid-Schiff-positive Lafora inclusions on muscle or skin biopsy (in eccrine sweat gland cells), and has been shown to be caused by laforin (*EPM2A*) or malin (*EPM2B*) gene variants and possibly *PRDM8* in 90% of patients. Other causes of progressive myoclonic epilepsy include **myoclonic epilepsy with ragged red fibers (MERRF)**, caused by various pathogenic variants in mitochondrial DNA), **sialidosis type I** (caused by variants in *NEU1*), **neuronal ceroid lipofuscinoses** (lysosomal storage disorders caused by variants in *CLN1-CLN14*), **type 3 neuronopathic Gaucher disease** (caused by lysosomal glucocerebrosidase deficiency), **dentatorubral-pallidoluysian atrophy** (caused by unstable expansion of trinucleotide repeats on the *ATN1* gene), **action myoclonus-renal failure syndrome** (aka *EPM4*, caused by variants in *SCARB2*), **progressive myoclonus epilepsy-ataxia syndrome** (aka *EPM5*, caused by variants in *PRICKLE1*), and **North Sea progressive myoclonic epilepsy** (aka *EPM6*, caused by variants in *GOSR2*).

Myoclonic encephalopathy in nonprogressive disorders is an epileptic encephalopathy that occurs in some congenital disorders affecting the brain, such as Angelman syndrome, and consists of almost continuous and difficult-to-treat myoclonic and, at times, other seizures.

Landau-Kleffner syndrome is a rare condition of presumed autoimmune but sometimes also of genetic (*GRIN2A* variants) etiology. It is characterized by loss of language skills and by verbal auditory agnosia in a previously normal child; ~70% have associated clinical seizures. The seizures, when they occur, are of several types, including focal with preserved awareness, focal to bilateral tonic-clonic, atypical absence, focal with impaired awareness, and occasionally myoclonic seizures. High-amplitude spike-and-wave discharges predominate and tend to be bimodal. In the later evolutionary stages of the condition, the EEG findings may be normal. The spike discharges are always more apparent during non-rapid eye movement sleep; a child in whom Landau-Kleffner syndrome is suspected should have an EEG during sleep. CT and MRI studies typically yield normal results. In the related but clinically distinct epilepsy syndrome called **epileptic encephalopathy with continuous spike waves in slow-wave sleep (CSWS)**, the discharges occur in >85% of the slow-wave sleep, a finding termed **electrical status epilepticus in sleep (ESES)**. ESES can also occur in Landau-Kleffner syndrome, but in CSWS the discharges are usually frontal or generalized and the delays usually global. The approach to and therapy for the two syndromes are similar. Although valproic acid and benzodiazepines are often used first, the evidence favors that they address the seizures and that steroids and possibly nocturnal diazepam are the more effective agents for the aphasia. Some children respond to the combination of valproic acid and clobazam or to levetiracetam. Nocturnal diazepam (0.2-0.5 mg/kg orally at bedtime for several months) is often used as first- or second-line therapy, as are steroids used either

orally (more commonly studied) or intravenously. Oral prednisone is started at 2 mg/kg/day for 1-2 months, then weaned over a period of 1-3 months. Alternatively, monthly infusions of high-dose intravenous methylprednisolone have been used instead of oral steroids. Long-term therapy is often needed irrespective of which drug(s) elicit a patient response. If the seizures and aphasia persist after diazepam and steroid trials, then a course of IVIGs should be considered because many patients can respond to that. It is imperative to initiate speech therapy and maintain it for several years, because improvement in language function occurs over a prolonged period.

Amenably treatable metabolic epilepsies are well recognized (see Table 633.6). **Pyridoxine-dependent epilepsy** typically presents with a neonatal or infantile (and rarely childhood) onset of encephalopathy with, at times, reports of increased fetal movements (seizures) in utero. There are recurrent focal motor seizures, generalized tonic seizures, and myoclonus. Seizures progress to status epilepticus if no pyridoxine is used. Diagnosis is confirmed by the presence of elevated plasma, urine, and CSF α -aminoacidic semialdehyde and elevated plasma and CSF pipercolic acid levels. The presence of either homozygous or compound heterozygous pathogenic variants in *ALDH7A1* (which encode the protein antiquitin) confirms the diagnosis. The use of pyridoxine 100 mg daily orally (higher doses, up to 500-600 mg/day, have been used) or intravenously helps stop the seizures. Variants of *PROSC* can also cause pyridoxine-dependent epilepsy. **Pyridoxal phosphate-responsive neonatal epileptic encephalopathy** (pyridox[am]line 5'-phosphate oxidase [PNPO] deficiency) may present similarly in the absence of gastrointestinal symptoms sometimes seen with pyridoxine-dependent epilepsy. Diagnostically, there are reduced pyridoxal phosphate levels in the CSF with increased levels of CSF levodopa and 3-methoxytyrosine, along with decreased CSF homovanillic acid and 5-hydroxyindoleacetic acid. The EEG may show a burst suppression pattern. Treatment is by enteral administration of pyridoxal phosphate (up to 50 mg/kg/day every 6 hours). **Folinic acid-responsive seizures** may also present with neonatal or infantile epileptic encephalopathy and intractable seizures. Some of these patients have a diagnostic profile similar to that of pyridoxine-dependent epilepsy patients, and their disorder is caused by the same gene variants but responds to folinic acid supplementation in addition to pyridoxine. **Cerebral folate deficiency**, which also responds to high doses of folinic acid (1-3 mg/kg/day), may manifest with epilepsy, intellectual disability, developmental regression, dyskinesias, and autism. CSF 5-methyltetrahydrofolate levels are decreased, with normal plasma and red blood cell folate levels. There are usually pathogenic variants in the folate receptor (*FOLR1*) gene or blocking autoantibodies against membrane-associated folate receptors of the choroid plexus. **Tetrahydrobiopterin deficiencies** with or without hyperphenylalaninemia may present with epilepsies and symptoms resulting from deficiencies of dopamine (parkinsonism, dystonia), noradrenaline (axial hypotonia), serotonin (depression, insomnia, temperature changes), and folate (myelin formation, basal ganglia calcifications, and seizures). Treatment is by substitution therapy with tetrahydrobiopterin and neurotransmitter precursors started as early as possible. **Creatine deficiency syndromes** present typically with developmental delay, seizures, autistic features, and movement disorders and are diagnosed by gene sequencing and abnormal levels of urine creatine and guanidinoacetic acid and/or, particularly in the case of creatine transporter deficiency, an absent creatine peak on MR spectroscopy of the brain. Use of creatine monohydrate and dietary restrictions is helpful. **Biotinidase deficiency** presenting as developmental delay, seizures, ataxia, alopecia, and skin rash and often associated with intermittent metabolic acidosis and an organic acid profile of lactic and propionic acidemia, responds to the use of biotin. Serine biosynthesis defects with low serine levels in plasma or CSF amino acids often present with congenital microcephaly, intractable seizures, and psychomotor retardation and respond to supplemental serine and glycine. **Developmental delay, epilepsy, and neonatal diabetes** are caused by activating pathogenic variants in the adenosine triphosphate-sensitive potassium channels. Sulfonylurea drugs that block the potassium channel treat the neonatal diabetes and probably also favorably affect the CNS symptoms and affect seizures. **Hyperinsulinism-hyperammonemia**

syndrome is caused by activating variants of the glutamate dehydrogenase encoded by *GLUD1*. Patients present with hypoglycemic seizures after a protein-rich meal with hyperammonemia (ammonia levels 80-150 μ mol/L). They are managed with a combination of protein restriction, AEDs, and diazoxide (a potassium channel agonist that inhibits insulin release). **GLUT-1 deficiency syndrome** (caused by pathogenic variants in *SLC2A1*, which encodes for a glucose transporter) classically presents with infantile-onset epilepsy, developmental delay, acquired microcephaly, and complex movement disorders. It causes impaired glucose transport to the brain that is typically diagnosed by genetic testing or a finding of low CSF lactate and CSF glucose or low CSF-to-serum glucose ratios (<0.4). The manifestations of the disease are usually responsive to the ketogenic diet. **Thiamine transporter variants with acute basal ganglia disease** often presents with accompanying seizures and is responsive to biotin and thiamine supplementation. **Riboflavin transporter deficiency** can also manifest as a seizure in addition to the usual symptoms of neuromuscular (polyneuropathy) weakness; it is treated with high-dose riboflavin supplementation.

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633.5 Mechanisms of Seizures

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There are four distinct, often sequential, mechanistic processes in the pathophysiology of epilepsy. First is the **underlying etiology**, which is any pathology or pathologic process that can disrupt neuronal function and connectivity, leading to the second process (**epileptogenesis**), which makes the brain epileptic. Sometimes the underlying etiology can directly increase excitability even without the contribution of the downstream effects of epileptogenesis.

In some **genetic epilepsies**, a disorder in ion channel function and/or structure is the underlying etiology that leads to aberrant signal transduction, which can cause seizures (see Tables 633.2-633.4). These variants can involve voltage-gated channels (Na^+ , K^+ , Ca^{2+} , Cl^- , and HCN [hydrogen cyanide]), ligand-gated channels (nicotinic acetylcholine and γ -aminobutyric acid A receptors [GABA_A]), or other proteins. For example, in Dravet syndrome, the loss-of-function pathogenic variant in *SCN1A* encodes a voltage-gated sodium channel and causes decreased excitability in inhibitory GABAergic interneurons, leading to increased excitability and epilepsy. In human cortical dysplasia, the expression of the NR2B subunit of the NMDA receptor is increased, leading to excessive depolarizing currents. Gene variants can also affect neurotransmitter function through other mechanisms (see Table 633.3). For example, *ARX* variants can lead to dysfunction in GABAergic neurons and can cause X-linked West syndrome, among other epilepsies. In fragile X syndrome, it is hypothesized that variants in *FMR* cause enhanced glutamatergic signaling via the mGluR5 receptor. In Rett syndrome, variants in *MECP2* lead to increased NMDA receptor expression, which can cause epilepsy and other symptoms associated with the disorder.

In infantile spasms, animal models suggest that increases in the stress-related corticotropin-releasing hormone, sodium channel blockade, and NMDA receptor stimulation are contributing mechanisms.

Autoimmune etiologies for epilepsy are also recognized. Autoantibodies, sometimes generated because of cross-reactivity from a recent infection or secondary to a malignancy, can bind to extracellular receptors or other proteins expressed in neurons. This, in turn, leads to an inflammatory response and, in some cases, seizures. NMDA-receptor antibody encephalitis is probably the best-characterized autoimmune cause of epilepsy. Other epilepsy syndromes have been associated with autoantibodies targeting the voltage-gated potassium channel complex (anti-LGI2 and anti-CASPR2), GABA receptors (GABA_A and GABA_B), glycine receptors, and glutamic acid decarboxylase (GAD).

Abnormalities in the **structure** of the brain can be the underlying etiology for epilepsy. The structural abnormalities can be scarring from

previous injuries (hypoxic ischemic encephalopathy [HIE], stroke, cerebral hemorrhage), brain tumors, vascular malformations (cavernomas or arteriovenous malformations), and Sturge-Weber syndrome. In some cases where no identifying underlying etiology is found, epilepsy may be from the self-resolving maturational process of developing brains like BECTS and childhood occipital epilepsy syndromes (Gastaut and Panayiotopoulos types).

Second, **epileptogenesis** is the mechanism through which the brain, or part of it, turns epileptic. The role of large-scale molecular cell signaling pathways in epileptogenesis has been implicated in the mechanisms leading to epilepsy, namely, the mammalian target of rapamycin (mTOR), the Ras/ERK, and repressor element 1 (RE1)–silencing transcription factor (REST) pathways. The mTOR pathway is seen in tuberous sclerosis, hemimegalencephaly, and cortical dysplasia–related epilepsies; the Ras/ERK pathway in a number of syndromes; and the REST pathway in epileptogenesis after acute neuronal injury. Repeat seizures lead through the earlier and other mechanisms to rewiring of the brain and to long-term epilepsy.

The third process is the resultant **epileptic state of increased excitability** present in all patients irrespective of the underlying etiology or mechanism of epileptogenesis. A dysregulation of glutamatergic excitation versus GABAergic inhibition occurs in epileptogenic neurons, which creates a seizure focus or network.

The fourth process is **seizure-related neuronal injury**, as often is demonstrated by MRI in patients after prolonged status epilepticus or those with long-term drug-resistant epilepsy. Many patients show acute swelling in the hippocampus or other regions after status epilepticus and long-term hippocampal atrophy with sclerosis on MRI. There is evidence from surgically resected epileptic tissue that apoptotic pathways are activated in foci of drug-resistant epilepsy. There is evidence that the pathophysiology of epileptic seizures, whether focal or generalized, and of the coexisting comorbidities involves disruption of neural networks of the brain resulting not only in increased excitability but the often-associated abnormal neurologic dysfunction.

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633.6 Treatment of Seizures and Epilepsy

Mohamad A. Mikati, Muhammad S. Zafar, and
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DECIDING ON LONG-TERM THERAPY

After a first seizure, if the risk of recurrence is low, such as when the patient has a normal neurodevelopmental status, EEG, and MRI (risk ~20%), treatment is usually not started. If the patient has an abnormal EEG, MRI, developmental status, and/or neurologic exam and/or has a positive family history of epilepsy, the risk is higher, and often treatment is started. Other considerations are also important, such as motor vehicle driving status and type of employment in older patients or the parents' ability to manage recurrences or AED therapy in children. The decision is individualized and should be discussed with the family. [Figure 633.8](#) presents an overview of the approach to the treatment of seizures and epilepsy.

COUNSELING

An important part of the management of a patient with epilepsy is educating the family and the child about the disease, its management, and the limitations it might impose and how to live with them. Restrictions on driving (in adolescents), swimming, and certain sports are usually necessary ([Table 633.12](#)). In most states, the physician is not required to report the epileptic patient to the motor vehicle registry; this is the patient's responsibility. The physician is then requested to complete a specific form for patients who are being cleared to drive. In addition, in most states, a seizure-free period of 6 months, and in some states longer, is required before driving is allowed. Often swimming in rivers, lakes, or the sea and underwater diving are prohibited, but

swimming in pools may be allowable. When swimming, even patients with epilepsy under excellent control should be under the continuous supervision of an observer who is aware of the condition and capable of lifeguard-level rescue.

The physician, parents, and child should jointly evaluate the risk of involvement in athletic activities. To participate in athletics, proper medical management, good seizure control, and proper supervision are crucial to avoid significant risks. The ILAE Task Force on Sports and Epilepsy recommendations group sports into categories based on the potential risk of injury or death to the patient and to bystanders.

Group 1 sports are associated with no significant additional risk to patients with epilepsy and include most athletics (excluding pole vaulting), bowling, most collective contact sports such as judo and wrestling, most ground-based collective sports (e.g., baseball, basketball, cricket, field hockey, football, rugby), cross country skiing, curling, dancing, golf, and racquet sports, including tennis and table tennis. **Group 2 sports** are associated with moderate risk to patients with epilepsy but not to bystanders; they include alpine skiing, archery, pole vaulting, biathlon/triathlon/modern pentathlon, canoeing, collective sports that can potentially lead to serious injury (e.g., boxing, karate, kickboxing), cycling, fencing, gymnastics, horse riding, ice hockey, shooting, skateboarding, roller and ice skating, skiing and snowboarding, swimming, water skiing, and weightlifting. **Group 3 sports** are considered high risk for the patient and for bystanders; they include aviation, climbing, platform and springboard diving, horse racing, motorsports, parachuting and other forms of skydiving, rodeo, scuba diving, ski jumping, solitary sailing, and surfing and windsurfing (see [Table 633.12](#)). In general, there has been a shift toward encouraging safe sports participation in patients with epilepsy rather than indiscriminately restricting their participation; however, the decision has to be individualized to the patient and his or her family. Staying physically active has been shown to reduce the chance for neuropsychologic impairments that often are associated with epilepsy.

Counseling is helpful to support the family and to educate them about the resources available in the community. Educational and, in some cases, a psychologic evaluation may be necessary to evaluate for possible learning disabilities or abnormal behavioral patterns that might coexist with epilepsy. Epilepsy does carry a risk of increased mortality rates (2 or more times the standardized mortality rates of the general population) and of sudden unexpected death. This is mostly related to the conditions associated with or underlying epilepsy (e.g., tumor, metabolic diseases), to poor seizure control (e.g., in patients with severe epileptic encephalopathies or drug-resistant seizures), and to poor compliance with prescribed therapies. Thus it is recommended that family members be informed about this increased risk without inappropriately increasing their anxiety. Many family members feel they need to observe the patient continuously in wakefulness and sleep and have the patient sleep in the parents' room to detect seizures. There are advertised seizure-detection devices that use motion sensors placed under the mattress or worn on the wrist to detect seizures. Some are disappointing and ineffective in detecting seizures, whereas data from other equipment are encouraging. They are useful in detecting a majority of generalized tonic-clonic seizures during sleep; most have not been rigorously studied. Whether such measures can reduce the risk of **sudden unexpected death in epilepsy (SUDEP)** remains to be seen. The parents need to guard against being overprotective to avoid adversely affecting the child's psychology. Education about what to do in case of seizures, the choices of treatment or no treatment and medications and their side effects, and the potential complications of epilepsy should be provided to the parents and, if the child is old enough, to the child.

PRINCIPLE OF DRUG THERAPY

The clinical pharmacology of an AED consists of three important facets: pharmacokinetics, pharmacodynamics, and pharmacogenomics.

Pharmacokinetics describes how the body affects antiepileptics after administration through the mechanisms of absorption and distribution, as well as the metabolic changes of the substance in the body. The steps involved in pharmacokinetics are liberation (the process of release of a drug from the pharmaceutical formulation), absorption

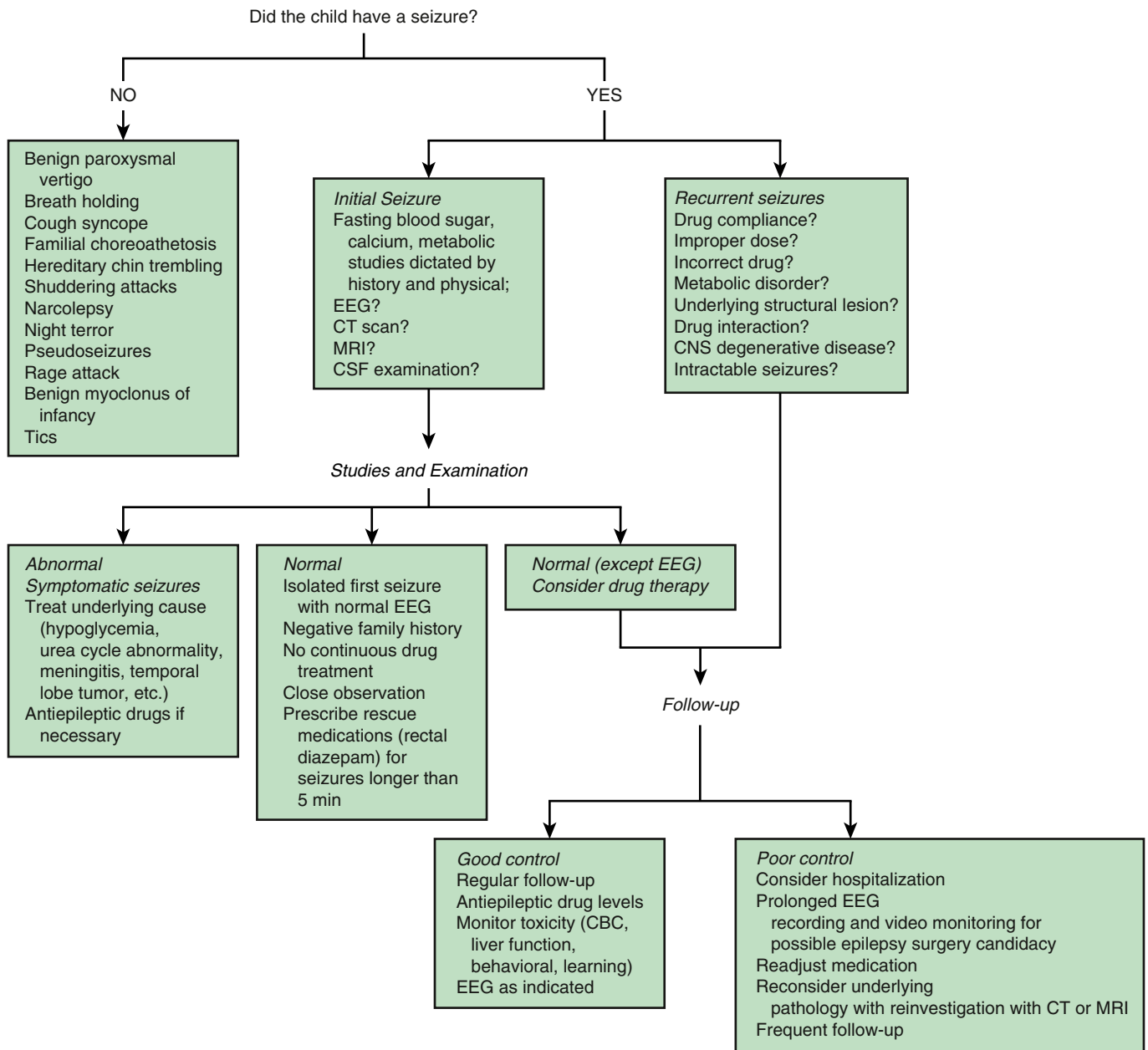


Fig. 633.8 Algorithm for the approach to the child with a suspected convulsive disorder.

Table 633.12 Sports and Special Considerations for the Child with Epilepsy*

CLINICAL SITUATION	GROUP 1	GROUP 2	GROUP 3
Acute symptomatic seizures (one or more)	Permitted	Neurologist's discretion	Neurologist's discretion
One unprovoked seizure	Permitted	Permitted if >12 mo of seizure freedom	Permitted if >12 mo of seizure freedom
Seizure freedom for >12 mo	Permitted	Permitted	Permitted
Sleep-related seizures	Permitted	Neurologist's discretion	Neurologist's discretion
Seizures without impaired awareness	Permitted	Neurologist's discretion	Not recommended
Seizures with impaired awareness	Neurologist's discretion	Neurologist's discretion	Not recommended
Resolved epilepsy with no seizures >10 yr and off AEDs >5 yr	Permitted	Permitted	Permitted
Medication withdrawal	Neurologist's discretion	Neurologist's discretion	Neurologist's discretion

*Specific advice should be individualized, depending on the patient's clinical condition. Group 1: low-risk sports; Group 2: moderate-risk sports; Group 3: high-risk sports. Refer to Chapter 633.6 for further details about the definition of each group.

Modified from Capovilla G, Kaufman KR, Perucca E, et al. Epilepsy, seizures, physical exercise, and sports: a report from the ILAE Task Force on Sports and Epilepsy. *Epilepsia*. 2016;57:6–12.

(the process of a substance entering the blood circulation), distribution (the dispersion or dissemination of substances throughout the fluids and tissues of the body), metabolism (the irreversible transformation of parent compounds into daughter metabolites), and excretion (the removal of the substances from the body).

Pharmacodynamics describes the biochemical and physiologic effect of AED dose or concentration. The response may be desirable (*effectiveness*) or untoward (*toxicity*). **Pharmacogenomics** is the study of how variant forms of human genes contribute to interindividual variability in drug response.

MECHANISMS OF ACTION OF ANTIEPILEPTIC DRUGS

AEDs reduce excitability by interfering with sodium, potassium, or calcium ion channels by reducing excitatory neurotransmitter release or function or enhancing GABAergic inhibition (Fig. 633.9). Most medications have multiple mechanisms of action, and the exact mechanism responsible for their activity in human epilepsy is usually not fully understood. Often, medications acting on sodium channels are effective against partial seizures, and medications acting on T-type calcium channels are effective against absence seizures. Voltage-gated sodium channels are blocked by felbamate, valproate, topiramate, carbamazepine, oxcarbazepine, lamotrigine, phenytoin, rufinamide, lacosamide, and zonisamide. T-type calcium channels found in the thalamus area

are blocked by valproate, zonisamide, and ethosuximide. Voltage-gated calcium channels are inhibited by gabapentin, pregabalin, lamotrigine, and felbamate. N-type calcium channels are inhibited by levetiracetam.

GABA_A receptors are activated by phenobarbital, benzodiazepines, topiramate, felbamate, and levetiracetam. Tiagabine, by virtue of its binding to GABA transporters 1 (GAT-1) and 3 (GAT-3), is a GABA reuptake inhibitor. GABA levels are increased by vigabatrin via its irreversible inhibition of GABA transaminases. Valproate inhibits GABA transaminases, acts on GABA_B presynaptic receptors (also done by gabapentin), and activates glutamic acid decarboxylase (the enzyme that forms GABA).

Glutaminergic transmission is decreased by felbamate that blocks NMDA and AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid)/kainate receptors. Topiramate also blocks AMPA/kainate receptors. Levetiracetam and brivaracetam bind to the presynaptic vesicle protein SV2A found in all neurotransmitter vesicles and possibly result in inhibition of presynaptic neurotransmitter release in a use-dependent manner. Perampanel blocks glutamate AMPA receptors.

The precise mechanisms by which cannabidiol (CBD) exerts its anticonvulsant effect in humans are unknown. CBD does not appear to exert its anticonvulsant effects through interaction with cannabinoid receptors. Fenfluramine increases extracellular levels of serotonin through interaction with serotonin transporter proteins and exhibits agonist activity at serotonin 5HT-2 receptors. Everolimus is

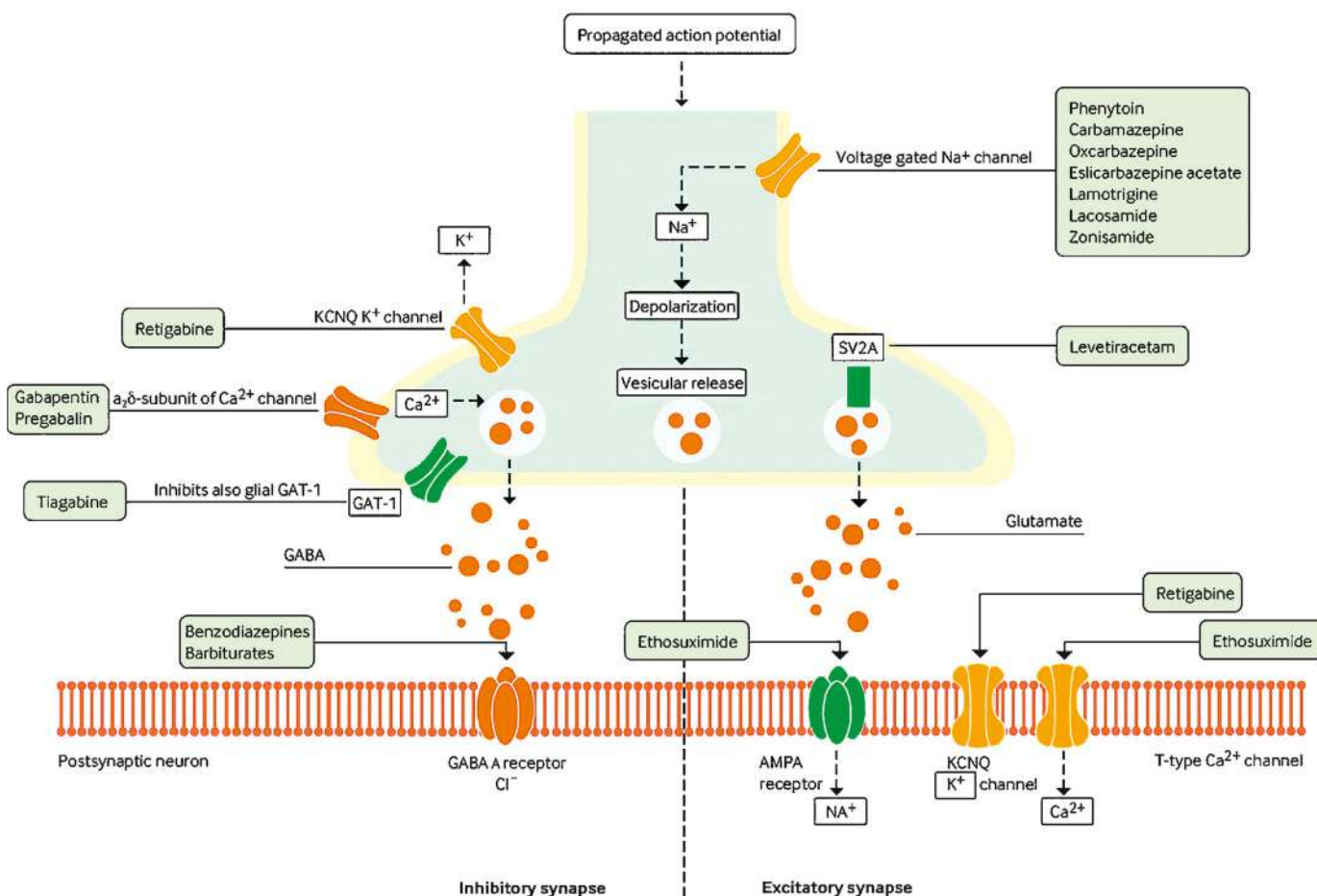


Fig. 633.9 Mechanisms of action of AEDs, which are diverse, mainly involving modulation of voltage-activated ion channels, potentiation of GABA, and inhibition of glutamate. Approved AEDs have effects on inhibitory (left-hand side) and excitatory (right-hand side) nerve terminals. The antiepileptic efficacy in trials of most of these drugs as initial add-ons does not differ greatly, indicating that seemingly similar antiseizure activity can be obtained by mechanisms aimed at diverse targets. However, putative mechanisms of action were determined only after discovering the antiseizure effects; mechanism-driven drug discovery has played only a minor role. AMPA, α -Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; GABA, γ -aminobutyric acid; GAT-1, sodium-dependent and chloride-dependent GABA transporter 1; SV2A, synaptic vesicle glycoprotein 2A. (From Schmidt D, Schachter SC. Drug treatment of epilepsy in adults. *BMJ*. 2014;348:g254.)

an inhibitor of mTOR, a serine-threonine kinase, downstream of the PI3K/AKT pathway. The mTOR pathway is dysregulated (too active) in tuberous sclerosis. Ganaxolone is a positive allosteric modulator of synaptic and extrasynaptic GABA_A receptors. It is being studied for long-term use in certain types of epilepsy and in acute treatment of status epilepticus.

There is also a role for immune modulation in treating epilepsy, as depicted by the use of adrenocorticotrophic hormone (ACTH), IVIG, oral prednisone, and intravenous methylprednisolone.

CHOICE OF DRUG ACCORDING TO SEIZURE TYPE AND EPILEPSY SYNDROME

Drug therapy should be based on the type of seizure and the epilepsy syndrome and on other individual factors. In general, the **drugs of first choice** for focal seizures and epilepsies are oxcarbazepine and levetiracetam; for absence seizures, ethosuximide; for juvenile myoclonic epilepsy, valproate (less so in women because of its hormonal and fetal side effects); other choices include levetiracetam (which is often the first drug to use in other primary generalized seizures), lamotrigine, zonisamide, topiramate, and perampamel. There is significant controversy about these choices, and therapy should always be individualized (see “Choice of Drug: Other Considerations”).

West syndrome is best treated with hormonal therapy in the form of either ACTH injections or, possibly, oral steroids. There are several protocols that range in dose from high to intermediate to low. The recommended regimen of ACTH (80 mg/mL) is a daily dose of 150 units/m² (divided into twice-daily intramuscular injections of 75 units/m²) administered over a 2-week period with a subsequent gradual taper over a 2-week period (30 units/m² in the morning for 3 days; 15 units/m² in the morning for 3 days; 10 units/m² in the morning for 3 days; and 10 units/m² every other morning for 6 days; then stop). Response is usually observed within the first 7 days. During the tapering period of any regimen, spasm relapse can occur. Remediation entails increasing the dose to the previously effective dose for 2 weeks and then beginning the taper again. Synthetic ACTH (tetracosactide/cosyntropin) can also be used as long as the long-acting (depot) preparation is chosen. Oral high-dose prednisolone is a lower-cost alternative to ACTH and does not necessitate families learning how to administer intramuscular injections; however, it may be inferior in efficacy to ACTH, particularly in those with cryptogenic (of unknown etiology) West syndrome.

Awake and asleep EEGs are often done 1, 2, and 4 weeks after the initiation of hormonal therapy to monitor the patient's response, with the aim of clearing the EEG from hypsarrhythmia and of stopping the seizures. Side effects, more common with the higher doses, include hypertension, electrolyte imbalance, infections, hyperglycemia and/or glycosuria, and gastric ulcers. Prophylactic therapy for ulcers with an H₂ blocker or protein pump inhibitor is desirable while the patient is receiving hormonal therapy. Also, live vaccines are contraindicated, and other vaccines are not effective during ACTH and steroid therapy because of the immune-suppressive effects of these hormonal agents. Thus all vaccines are not given during hormonal therapy and in the period after it (usually ≤3 months after the last dose).

Vigabatrin can be used as a first-line agent to treat **infantile spasms** in patients with tuberous sclerosis and is the second-line choice if hormonal therapy was unsuccessful in other cases of infantile spasms. Its principal side effect is retinal toxicity, seen in approximately 30% of patients, most often if the drug is used for longer than 6 months, with resultant visual field defects that persist despite the withdrawal of the drug. Because of this toxicity, vigabatrin is available only through a restricted distribution Risk Evaluation and Mitigation Strategy (REMS) program. The level of evidence for its efficacy is weaker than that for ACTH but stronger than that of other alternative medications. Emerging evidence suggests that dual treatment with vigabatrin and hormonal therapy at the onset of spasms may be superior to hormonal therapy alone but may predispose to the CNS neurotoxicity of vigabatrin associated with increased T2 signal in the basal ganglia. The ketogenic diet is probably the third-line therapy. Subsequent alternative treatment options for spasms include valproate, benzodiazepines such as nitrazepam and clonazepam, topiramate, lamotrigine, zonisamide,

pyridoxine, and IVIG. None of these alternative drugs offers uniformly satisfactory results. However, they are useful for decreasing the frequency and severity of seizures in patients with symptomatic infantile spasms and as adjunctive therapy in patients with idiopathic infantile spasms who do not respond completely to ACTH or vigabatrin.

Lennox-Gastaut syndrome is another difficult-to-treat epilepsy syndrome. Treatment of seizures in the syndrome varies according to the preponderant seizure type. For drop attacks (tonic, atonic, or myoclonic-astatic seizures), clobazam, valproate, lamotrigine, topiramate, felbamate, and rufinamide are considered effective. The FDA also approved CBD and fenfluramine to be used in Lennox-Gastaut syndrome. Fenfluramine is available only through a restricted distribution REMS program because of the risk of valvular heart disease and pulmonary arterial hypertension.

Felbamate is used as a last-resort medication because of its potential toxicity. These drugs might control other types of seizures (partial, generalized tonic-clonic, atypical absence, other tonic, myoclonic). For patients who have a preponderance of atypical absence seizures, valproate, lamotrigine, or ethosuximide are often suitable drugs to try because they are relatively less toxic than many alternative drugs. Clonazepam is often helpful but produces significant sedation, hyperactivity, and drooling and often tolerance to its antiepileptic effects develops in a few months. Consequently, in Lennox-Gastaut or other drug-resistant epilepsy syndromes, clonazepam is often used as a rescue medication for clusters of seizures (disintegrating tablet preparation) or as a bridge over a few days until dose changes of background medications take effect. In resistant cases of Lennox-Gastaut syndrome and related epilepsies, ketogenic diet, zonisamide, levetiracetam, acetazolamide, methsuximide, corticosteroids, or IVIG can be used.

Dravet syndrome is usually treated with benzodiazepines such as clobazam and with valproate. The ketogenic diet can also be useful in patients with this syndrome, including cases with refractory status. Stiripentol, which is available in some countries, is useful, particularly if used in combination with valproate and clobazam; doses need to be adjusted because stiripentol can increase clobazam levels, and valproate can increase stiripentol levels. Other medications include zonisamide and topiramate. Lamotrigine, carbamazepine, oxcarbazepine, and phenytoin are reported to exacerbate seizures in Dravet syndrome. Barbiturate use during status epilepticus in this syndrome is suspected to be associated with adverse outcomes; consequently, alternative acute therapies in such cases need to be considered.

The FDA has approved CBD and fenfluramine for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients ≥2 years. The starting dose is 2.5 mg/kg taken twice daily (5 mg/kg/day). After 1 week, the dose is usually increased to a maintenance dosage of 5 mg/kg twice daily (10 mg/kg/day). If it is tolerated and needed, the dose may be increased up to 10 mg/kg twice daily (20 mg/kg/day). It comes as an oral solution (100 mg/mL). Checking the package insert of all these medications before initiating their use is essential because of the frequent interactions with concurrent antiseizure and other medications.

Absence seizures are most often initially treated with ethosuximide, which is as effective as, but less toxic than, valproate; both are more effective than lamotrigine (which has fewer side effects than valproate). Alternative drugs of first choice are lamotrigine and valproate, especially if generalized tonic-clonic seizures coexist with absence seizures. These two medications are effective against the latter seizures, whereas ethosuximide is not. Patients resistant to ethosuximide might still respond to valproate or to lamotrigine. In absence seizures, the EEG is usually helpful in monitoring the response to therapy and is often more sensitive than the parents' observations in detecting these seizures. The EEG often normalizes when complete seizure control is achieved. This is usually not true for partial epilepsies. Other medications that could be used for absence seizures include acetazolamide, zonisamide, or clonazepam.

Benign myoclonic epilepsies are often best treated with valproate, particularly when patients have associated generalized tonic-clonic and absence seizures. Zonisamide, clonazepam, lamotrigine, and topiramate are alternatives.

Severe myoclonic epilepsies are treated with medications effective for Lennox-Gastaut syndromes, such as topiramate, clobazam, valproate, and zonisamide. Levetiracetam may also have efficacy in myoclonic epilepsies.

Focal and focal to bilateral tonic-clonic seizures can be treated with oxcarbazepine, levetiracetam, carbamazepine, phenobarbital, topiramate, lacosamide, zonisamide, valproic acid, lamotrigine, clobazam, perampanel, or clonazepam (see Table 633.1). Oxcarbazepine and levetiracetam are often used first.

Vigabatrin is the preferred treatment for infantile spasms due to **tuberous sclerosis**. The FDA also approved CBD and everolimus to treat a seizure in tuberous sclerosis in patients older than 2 years of age.

For children with ESES and SWS, nighttime benzodiazepine and daily or pulsed-dose steroids are preferentially used. Alternatively, other AEDs like valproate, clobazam, levetiracetam, and acetazolamide and ketogenic therapy have been used.

CHOICE OF DRUG: OTHER CONSIDERATIONS

Because there are many options for each patient, the choice of which drug to use is always an individualized decision based on comparative effectiveness data from randomized controlled trials and on several other considerations delineated next:

- **Comparative effectiveness** (Tables 633.13 and 633.14 list dosages) and the **potential for paradoxical seizure aggravation** by some AEDs (e.g., precipitation of myoclonic seizures by lamotrigine in Dravet syndrome and exacerbation of absence seizures by carbamazepine and tiagabine) must be considered. Although many antiseizure medications have not been studied in the pediatric population, off-label use of these medications in children is common, and there are studies that have shown that, in general, their efficacy in adults is predictive of their efficacy in children with the same seizure types.

- **Comparative tolerability** (Table 633.15): Adverse effects can vary according to the profile of the patient. The most prominent example is the increased risk of liver toxicity for valproate therapy in children who are younger than 2 years of age, taking polytherapy, and/or have metabolic disorders. Thus if metabolic disorders are suspected, other drugs should be considered first, and valproate should not be started until the metabolic disorders are ruled out by normal amino acids, organic acids, acylcarnitine profile, lactate, pyruvate, liver function tests, and perhaps gene testing for mitochondrial disorders (see the paragraph on the presence of comorbid conditions later). The choice of an AED can also be influenced by the likelihood of occurrence of nuisance side effects, such as weight gain (valproate, carbamazepine), gingival hyperplasia (phenytoin), alopecia (valproate), hyperactivity (benzodiazepines, barbiturates, levetiracetam, valproate, gabapentin), or irritability/anger (levetiracetam and perampanel). Children with behavior problems and/or with attention-deficit disorder can become particularly hyperactive with the GABAergic drugs mentioned earlier. This often affects the choice of medications. In general, newer-generation antiepileptic medications provide a better side effect profile than older medications.
- **Cost and availability**: The cost of the newer AEDs often precludes their use, particularly in developing countries. Many drugs are not available in all countries (1) because they are too expensive; (2) because, paradoxically, they are too inexpensive (lower profit margin); or (3) because of regulatory restrictions. AEDs have a narrow therapeutic range, and thus switching from brand name to generic formulations or from one generic to another can result in changes in levels that could result in breakthrough seizures or side effects.
- **Ease of initiation** of the AED: Medications started very gradually, such as lamotrigine and topiramate, should not be chosen in situations when there is a need to quickly achieve a therapeutic level. In such situations, medications that have intravenous preparations or

Table 633.13 Comparison of Recommendations for the Treatment of Pediatric Epilepsy

SEIZURE TYPE OR EPILEPSY SYNDROME	FDA APPROVED [†]	ILAE (2013)* [†]
Focal-onset	CBZ, ezogabine, lacosamide, LEV, LTG, OXC, PB, PER, PHT, TPM, VGB	A: OXC B: None C: CBZ, PB, PHT, TPM, VGB, VPA D: CLB, CZP, LTG, ZNS
BCECT	None	A, B: None C: CBZ, VPA D: GBP, LEV, OXC, STM
Childhood absence epilepsy	ESM, VPA	A: ESM, VPA B: None C: LTG D: None
Juvenile myoclonic epilepsy	LEV, LTG, TPM	A, B, C: None D: TPM, VPA
Lennox-Gastaut syndrome	CLB, FLB, LTG, rufinamide (atonic), TPM	Not reviewed
Infantile spasms	ACTH, VGB	Not reviewed
Primary generalized tonic-clonic seizures	LEV, LTG, TPM, PER	A: None B: None C: CBZ, PB, PHT, TPM, VPA D: OXC

*ILAE recommendations are listed according to levels of evidence supporting the efficacy of the options. Level A: one or more class I randomized controlled trials (RCTs) or two or more class II RCTs; Level B: one class II RCT or two or more class III RCTs; Level C: two or more class III RCTs; Level D: one class III double-blind or open-label study or one class IV clinical study or data from expert committee reports, opinions from experienced clinicians.

[†]More recent data are available after FDA approval and ILAE review, and the implications of these data have been incorporated as much as possible into Table 633.13. Together, these two tables aim to provide as complete a picture as possible of the state of the art and the approved indications for the therapy of pediatric epilepsy.

ACTH, Adrenocorticotrophic hormone; BCECT, benign childhood epilepsy with centrotemporal spikes; CBZ, carbamazepine; CLB, clobazam; CZP, clonazepam; ESM, ethosuximide; FDA, Food and Drug Administration; FLB, felbamate; GBP, gabapentin; ILAE, International League Against Epilepsy; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PER, perampanel; PHT, phenytoin; STM, sulthiame; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; ZNS, zonisamide.

Modified and updated from Puccia E, Tomson T. ILAE Subcommittee on AED Guidelines: updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia*. 2013;54(3):551–563.

Table 633.14 Dosages of Selected Antiepileptic Drugs

MEDICATION	FDA APPROVAL (AGE APPROVED)	MAINTENANCE ORAL DOSAGE (mg/kg/day) UNLESS OTHERWISE SPECIFIED	USUAL DOSING	THERAPEUTIC LEVELS	PREPARATIONS
Acetazolamide	Absence seizures (adults)	1-12 mo: 10 >1 yr: 20-30	bid or tid	10-15 mg/L	125, 250, 500 mg tabs
Brivaracetam	Focal sz (age >16 yr)	50-200 mg/day	bid		10, 25, 50, 75, 100 mg tabs; 10 mg/mL oral and IV solns
Bromide		50-100	bid or qd	10-15 mEq/L, other references 75- 352 mg/dL	Supplied as triple bromide soln (240 mg/mL or 500 mg/mL of bromide salt)
Carbamazepine*	Focal and GTC (all ages)	10-20	tid or qid SR usually bid	3-12 mg/L	150, 300 mg ER caps; 100, 200, 400 mg ER tabs 100 mg chewable tabs; 200 mg tabs; 100 mg/5 mL susp
Cenobamate	Focal in adults ≥18 yr	200-400 mg/day final dose	Once per day	—	12.5, 25, 50, 100, 150, 200 and 400 mg tabs
Clobazam†	LGS (all ages above 2 yr)	10-40 mg/day	bid	60-200 µg/L	10 mg, 20 mg tabs; 2.5 mg/mL soln
Clonazepam†	Absence sz, LGS, myoclonic sz (all ages)	0.05	bid or tid	25-85 µg/L	0.5, 1, 2 mg tabs; 0.125, 0.25, 0.5 mg orally disintegrating tabs
Diazepam	Focal sz (all ages >6 mo)	0.25-1.5 0.01-0.25 IV 0.2-0.5 mg/kg rectal (according to age)	bid or tid	100-700 µg/L	2, 5, 10 mg tabs 5 mg/mL, 5 mg/5 mL soln; rectal gel that can be dialed to dispense 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20 mg
Eslicarbazepine	Focal sz (adult)	800-1600 mg/day	qd		200, 400, 600, 800 mg tabs
Ethosuximide	Absence sz (>3 yr)	20-30	bid or tid	40-100 mg/L	250 mg caps; 250 mg/5 mL soln
Felbamate	LGS (>2 yr) Focal sz (>14 yr)	15-45	bid or tid	50-110 mg/L	400, 600 mg tabs; 600 mg/5 mL susp
Gabapentin‡	Focal sz (>3 yr)	30-60	tid	2-20 mg/L	100, 300, 400 mg caps; 300, 600, 800 mg tabs; 250 mg/5 mL soln; 25 mg/mL susp
Lacosamide	Focal sz (>17 yr)	4-12	bid	≤15 µg/L	50, 100, 150, 200 mg tabs 10 mg/mL oral soln
Lamotrigine	LGS, focal and tonic-clonic sz (age >2 yr)	5-15 [§] 1-5 [¶]	tid bid	1-15 mg/L	25, 100, 150, 200 mg tabs 5, 25 mg chewable dispersible tabs 25, 50, 100, 200 mg ODTs 25, 50, 100, 200, 250, 300 mg ER tabs
Levetiracetam†	Focal-onset (age ≥1 mo), tonic- clonic sz (age ≥6 yr), myoclonic (age ≥12 yr)	20-60	bid or tid	6-40 mg/L	250, 500, 750 mg tabs 100 mg/mL soln 500, 750 mg SR (ER) tabs
Lorazepam	Status epilepticus (all ages)	0.05-0.1	bid or tid	20-30 µg/L	0.5, 1, 2 mg tabs 2 mg/mL soln

Continued

Table 633.14 Dosages of Selected Antiepileptic Drugs—cont'd

MEDICATION	FDA APPROVAL (AGE APPROVED)	MAINTENANCE ORAL DOSAGE (mg/kg/day) UNLESS OTHERWISE SPECIFIED	USUAL DOSING	THERAPEUTIC LEVELS	PREPARATIONS
Methsuximide	Absence sz (children and older)	10-30	bid or tid	10-50 mg/L	150, 300 mg caps
Nitrazepam	—	0.25-1	bid or tid	<200 µg/L	5 mg tabs
Oxcarbazepine*	Focal sz (>2yr)	20-60	bid	13-35 mg/L	150, 300, 600 mg tabs 300 mg/5 mL susp
Perampanel	Focal sz (>12yr)	2-12 mg per day (>12yr)	qhs	20-800 ng/mL	2, 4, 6, 8, 10, 12 mg tabs; 0.5 mg/ mL soln
Phenobarbital	Myoclonic, focal and tonic-clonic sz and status (all ages)	<5 yr, 3-5 >5 yr, 2-3	bid or qd	10-40 mg/L	15, 30, 60, 90, 100 mg tabs 4 mg/mL soln
Phenytoin	Focal, tonic-clonic sz and status (all ages)	<3 yr, 8-10 >3 yr, 4-7	tabs, susp: tid caps: qd	5-20 mg/L	50 mg tabs 30, 100 mg caps 125 mg/5 mL susp
Pregabalin	Focal sz (adults)	2-14	bid	Up to 10 µg/mL	25, 50, 75, 100, 150, 200, 225, 300 mg caps 20 mg/mL soln
Primidone	Focal and tonic- clonic sz (all ages)	10-20	bid or tid	4-13 mg/L	50, 250 mg tabs, susp
Rufinamide†	LGS (age >4yr)	30-45	bid	<60 µg/mL	200, 400 mg tabs
Sulthiame**		5-15	bid or tid	1.5-20 µg/mL	50, 200 mg caps
Tiagabine	Focal sz (age >2yr)	0.5-2	bid, tid, qid	80-450 µg/L	2, 4, 12, 16 mg tabs
Topiramate‡	LGS, focal and tonic-clonic sz (all ages)	3-9, slow titration	bid or tid	2-25 mg/L	25, 100, 200 mg tabs 15, 25 mg sprinkle caps
Valproate	Absence, myoclonic, focal and tonic-clonic sz (age >2yr)	15-40; higher doses are used if patient is on enzyme inducers (≤60 mg/kg/day)	Sprinkle caps: bid Soln: tid	50-100 mg/L	250 mg caps 125 mg sprinkle caps 125, 250, 500 mg tabs 250 mg/5 mL soln
Vigabatrin	Infantile spasms and focal sz (age >1 mo)	50-150	bid	20-160 µg/mL (following levels is not useful for this drug)	500 mg tabs 500 mg powder for soln
Zonisamide	Focal sz (age >16yr)	4-8	bid or qd	10-40 mg/L	100 mg caps

*Usually start with one-fourth maintenance dose and increase by one-fourth every 2-3 days to full dose.

†Usually start with one-fourth maintenance dose and increase by one-fourth every 7 days to full dose.

‡Usually start with one-fourth maintenance dose and increase by one-fourth every day to full dose.

§Child receiving enzyme inducers.

**Available in some European countries.

††Child receiving valproate.

Unless specified otherwise earlier, one would usually target the lower range of the therapeutic dose and then adjust it as needed, depending on the response, side effects, and/or levels. The dosing schedule (e.g., bid or tid) can depend on if a sustained-release preparation is available and if the patient is taking enzyme inducers (e.g., carbamazepine) or inhibitors (e.g., valproic acid) that could affect the drug (as indicated in the dosing schedule in the table and in the text).

cap, Capsule; ER, extended release; GTC, generalized tonic-clonic; LGS, Lennox-Gastaut syndrome; ODT, orally disintegrating tablet; soln, solution; SR, sustained release; susp, suspension; sz, seizure(s); tab, tablet.

Table 633.15 Some Adverse Effects of Antiepileptic Drugs*

ANTIEPILEPTIC DRUG	SIDE EFFECTS
Acetazolamide	Nuisance: dizziness, polyuria, electrolyte imbalance Serious: Stevens-Johnson syndrome, renal calculi
Benzodiazepines	Nuisance: dose-related neurotoxicity (drowsiness, sedation, ataxia), hyperactivity, drooling, increased secretions Serious: apnea
Brivaracetam	Dizziness, nausea/vomiting, fatigue, depressed mood
Bromide	Nuisance: irritability, spurious hyperchloremia (falsely high chloride due to bromide) Serious: psychosis, rash, toxicity developing slowly owing to the very long half-life
Carbamazepine	Nuisance: tics, transient leukopenia; hyponatremia, weight gain, nausea; dizziness Serious: Stevens-Johnson syndrome, agranulocytosis, aplastic anemia, liver toxicity
Cenobamate	Drug reaction with eosinophilia and systemic symptoms (DRESS), short QT, sedation, H/A Contraindicated in familial short QT syndrome
Clobazam	Nuisance: drowsiness, sedation, drooling Serious: Stevens-Johnson syndrome, toxic epidermal necrolysis
Eslicarbazepine	Dizziness, ataxia, nausea/vomiting, diplopia, tremor, somnolence, headache, fatigue
Felbamate	Nuisance: anorexia, vomiting, insomnia, hyperactivity, dizziness Serious: major risks for liver and hematologic toxicity requiring close monitoring (1 in 500 in children >2 yr with complex neurologic disorders)
Gabapentin	In children: acute onset of aggression, hyperactivity In adults: euphoria and behavioral disinhibition, weight gain
Lacosamide	Nuisance: diplopia, headache, dizziness, nausea Serious: possibly cardiac arrhythmias (if predisposed)
Lamotrigine	Nuisance: CNS side effects: headache, ataxia, dizziness, tremor, but usually less than other AEDs Serious: Stevens-Johnson syndrome, ECG abnormalities (both have FDA warning about them), rarely liver toxicity
Levetiracetam	CNS adverse events: somnolence, asthenia, dizziness, but usually less than other AEDs In children: anger, irritability, other behavioral symptoms In adults: depressive mood
Oxcarbazepine	Somnolence, headache, dizziness, nausea, apathy, rash, hypertrichosis, gingival hypertrophy, hyponatremia
Perampanel	Aggression, homicidal ideation, suicidal thoughts/behavior
Phenobarbital and other barbiturates	Nuisance: neurotoxicity, insomnia, hyperactivity, signs of distractibility, fluctuation of mood, aggressive outbursts Serious: liver toxicity, Stevens-Johnson syndrome
Phenytoin and other hydantoins	Nuisance: gingival hyperplasia, coarsening of the facies, hirsutism, cerebellovestibular symptoms (nystagmus and ataxia) Serious: Stevens-Johnson syndrome, liver toxicity
Pregabalin	Nuisance: dizziness, peripheral edema, blurred vision, weight gain, thrombocytopenia Serious: hypersensitivity reactions
Primidone	Nuisance: CNS toxicity (dizziness, slurred speech, giddiness, drowsiness, depression) Serious: liver toxicity, Stevens-Johnson syndrome
Rufinamide	Nuisance: somnolence, vomiting Serious: contraindicated in familial short QT interval
Succinimides	Nuisance: nausea, abdominal discomfort, anorexia, hiccups Serious: Stevens-Johnson syndrome, drug-induced lupus
Tiagabine	Nuisance: dizziness, somnolence, asthenia, headache and tremor, precipitation of absence or myoclonic seizures Serious: precipitation of nonconvulsive status epilepticus
Topiramate	Nuisance: cognitive dysfunction, weight loss, hypohidrosis, fever Serious: precipitation of glaucoma, renal calculi
Valproic acid	Nuisance: weight gain, hyperammonemia, tremor, alopecia, menstrual irregularities Serious: hepatic and pancreatic toxicity
Vigabatrin	Nuisance: hyperactivity Serious: irreversible visual field deficits, retinopathy that requires frequent ophthalmologic evaluations and follow-up
Zonisamide	Fatigue, dizziness, anorexia, psychomotor slowing, ataxia, rarely hallucinations, hypohidrosis and fever, renal calculi

*Essentially all AEDs can cause CNS toxicity and potentially rashes and serious allergic reactions. For a full list of side effects, please review the drug's FDA-approved packet insert. AED, Antiepileptic drug; CNS, central nervous system.

that can be started and titrated more quickly, such as levetiracetam, phenytoin, lacosamide, or valproate, should be considered instead.

- **Drug interactions** and the presence of background medications: An example is the potential interference of enzyme-inducing drugs with many chemotherapeutic agents. In those cases, medications such as gabapentin or levetiracetam are used. Also, valproate inhibits the metabolism and increases the levels of lamotrigine, phenobarbital, and felbamate; it also displaces protein-bound phenytoin from protein-binding sites, increasing the free fraction; and thus the free and not the total level needs to be checked when both medications are used together. Enzyme inducers such as phenobarbital, carbamazepine, phenytoin, and primidone reduce levels of lamotrigine, valproate, and, to a lesser extent, topiramate, zonisamide, and perampanel. Medications exclusively excreted by the kidney, such as levetiracetam and gabapentin, are not subject to such interactions.
- **The presence of comorbid conditions:** The presence of migraine in a patient with epilepsy can lead to the choice of a medication that is effective against both conditions, such as valproate, topiramate, or zonisamide. In an obese patient, a medication such as valproate might be avoided, and a medication that decreases the appetite, such as topiramate or zonisamide, might be used instead. In adolescent females of child-bearing potential, enzyme-inducing AEDs are often avoided because they can interfere with birth control pills; other AEDs, particularly valproate, can increase risks for fetal malformations. Valproic acid may unmask or exacerbate certain underlying metabolic disorders; these include nonketotic hyperglycinemia, DNA polymerase γ pathogenic variant (*POLG*) with mitochondrial DNA depletion (also known as **Alpers-Huttenlocher syndrome**), other mitochondrial disorders (Leigh syndrome; **MELAS**; myoclonic epilepsy with ragged red fibers; myoclonic epilepsy–myopathy–sensory ataxia syndrome), and hyperammonemic encephalopathies. Manifestations may include hepatotoxicity or encephalopathy. Attention-deficit/hyperactivity disorder (ADHD) is a common comorbid condition in children with epilepsy. The presence of epilepsy should not necessarily discourage treatment with stimulants if indicated.
- **Coexisting seizures:** In a patient with both absence and generalized tonic-clonic seizures, a drug that has a broad spectrum of antiseizure effects, such as lamotrigine or valproate, could be used rather than medications that have a narrow spectrum of efficacy, such as phenytoin and ethosuximide.
- **History of prior response** to specific AEDs: For example, if a patient or a family member with the same problem had previously responded to levetiracetam, levetiracetam could be a desirable choice.
- **Mechanism of drug actions:** At present, in most patients the current understanding of the pathophysiology of epilepsy does not allow a specific choice of AEDs based on the assumed pathophysiology of the epilepsy. However, it is believed that it is better to avoid combining medications that have similar mechanisms of action, such as phenytoin and carbamazepine (both work on sodium channels). A number of medications, such as lamotrigine and valproate or topiramate and lamotrigine, are reported to have synergistic effects, possibly because they have different mechanisms of action.
- **Ease of use:** Medications given once or twice a day are easier to use than medications given 3 or 4 times a day. Availability of a pediatric liquid preparation, particularly if palatable, also plays a role. Some drugs are also available as sprinkles and biofilm formulation for use in children.
- **Ability to monitor the medication** and adjust the dose: Some medications are difficult to adjust and to follow, requiring frequent blood levels. The prototype of such medications is phenytoin, but many of the older medications, such as valproate and phenobarbital, also require blood level monitoring for optimal titration. Monitoring can represent a practical or patient satisfaction disadvantage for the older drugs compared with the newer AEDs, which generally require less blood level monitoring most often to check for compliance.
- **Patient's and family's preferences:** The choice between two or more acceptable alternative AEDs might also depend on the patient's or family's preferences. For example, some patients might want to avoid

gingival hyperplasia and hirsutism as side effects but might tolerate weight loss or vice versa.

- **Genetics** and genetic testing: A genetic predisposition to developing AED-induced side effects is another factor that may be a consideration. There is a strong association between the human leukocyte antigen HLA-B*1502 allele and severe cutaneous reactions induced by carbamazepine, oxcarbazepine, phenytoin, or lamotrigine in Chinese Han patients and, to a lesser extent, Southeast Asian populations; hence, these AEDs should be avoided in genetically susceptible persons after testing for the allele. Pathogenic variants of the *SCN1A* sodium channel gene indicating Dravet syndrome could also lead to avoiding lamotrigine, carbamazepine, oxcarbazepine, and phenytoin and to the use of the more appropriate valproate, clobazam, or stiripentol.
- **Teratogenic profiles:** Based on available evidence, levetiracetam and lamotrigine are FDA pregnancy category C drugs and probably the safest AEDs to use during pregnancy. Valproate is a category X drug that is associated with neural tube defects, hypospadias, and cardiovascular malformations. *The use of valproate should thus be avoided during pregnancy if possible.* Topiramate, phenobarbital, and phenytoin are category D drugs with birth defects associated with their use reported in humans. The decision to transition to a less teratogenic AED rather than continuing with an existing regimen must be made on a case-by-case basis and consider the risk of seizures during pregnancy versus the risk of teratogenicity.
- **Underlying etiology:** The cause for the patient's epilepsy must be considered and can lead to more specific therapy choices, such as the use of immune-modulating therapy for autoimmune encephalopathy or personalized and precision therapies for specific epileptic channelopathies or vitamin-responsive epilepsies.

INITIATING AND MONITORING THERAPY

In nonemergency situations or when loading is not necessary, the **maintenance dose** of the chosen AED is started (see [Table 633.14](#)). With some medications (e.g., oxcarbazepine, carbamazepine, topiramate, and perampanel), even smaller doses are initially started and then **gradually increased** up to the maintenance dose to build a tolerance to adverse effects such as sedation. The starting dose of oxcarbazepine is usually 8–10 mg/kg/day. Increments of 5 mg/kg/day can be added every 3 days until a therapeutic level is achieved and therapeutic response is established or until unacceptable adverse effects occur. With other medications such as zonisamide, phenobarbital, phenytoin, or valproate, starting at the maintenance dose is usually tolerated. With some, such as levetiracetam and gabapentin, either approach can be used. Patients should be counseled about potential adverse effects, and these should be monitored during follow-up visits (see [Table 633.15](#)).

Titration

Levels of many AEDs should usually be determined after initiation to ensure compliance and therapeutic concentrations. Monitoring is most helpful for the older AEDs, such as phenytoin, carbamazepine, valproate, phenobarbital, and ethosuximide. After starting the maintenance dosage or after any change in the dosage, a steady state is not reached until 5 half-lives have elapsed, which, for most AEDs, is 2–7 days (half-life: 6–24 hours). For phenobarbital, it is 2–4 weeks (mean half-life: 69 hours). For zonisamide, it is 14 days during monotherapy and less than that during polytherapy with enzyme inducers (half-life: 63 hours in monotherapy and 27–38 hours during combination therapy with enzyme inducers). If a therapeutic level has to be achieved faster, a loading dose may be used for some drugs, usually with a single dose that is twice the average maintenance dose per half-life. For valproate, it is 20 mg/kg; for phenytoin, it is 20 mg/kg; and for phenobarbital, it is 10–20 mg/kg. A lower loading dosage of phenobarbital is sometimes given in older children (5 mg/kg, which may be repeated once or more in 24 hours) to avoid excessive sedation.

Only one drug should be used initially, and the dose increased until complete control is achieved or until side effects prohibit further increases. Then, and only then, may another drug be added and

the initial drug subsequently tapered. Control with one drug (**monotherapy**) should be the goal, although some patients eventually need to take multiple drugs. When appropriate, levels should also be checked upon addition (or discontinuation) of a second drug because of potential drug interactions. During follow-up, repeating the EEG every few months may be helpful to evaluate changes in the predisposition to seizures. This is especially true in situations where tapering off of medication is contemplated in any seizure type and during follow-up to assess the response for absence seizures because the EEG mirrors the response in such patients.

Monitoring

For the older AEDs, before starting treatment, baseline laboratory studies, including complete blood count, platelets, liver enzymes, and possibly kidney function tests and urinalysis, are often obtained and repeated periodically. Laboratory monitoring is more relevant early on because idiosyncratic adverse effects such as allergic hepatitis and agranulocytosis are more likely to occur in the first 3-6 months of therapy. These laboratory studies are usually initially checked once or twice during the first month, then every 3-4 months after that. Significant concerns have been raised about the usefulness of routine monitoring in the absence of clinical signs because the yield of significant adverse effects is low. There are currently many advocates of less frequent routine monitoring.

In approximately 10% of patients, a reversible dose-related leukopenia may occur in patients taking carbamazepine or phenytoin. This adverse effect responds to decreasing the dose or stopping the medication and is distinguished from the much less common idiosyncratic aplastic anemia or agranulocytosis. One exception requiring frequent (even weekly) monitoring of liver function and blood counts throughout the therapy is felbamate, owing to the high incidence of liver and hematologic toxicity (1 in 500 children under 2 years of age with complex neurologic disorders who are taking the drug). The gum hyperplasia that is seen with phenytoin necessitates good oral hygiene (brushing teeth at least twice per day and rinsing the mouth after taking the phenytoin); in a few cases, it may be severe enough to warrant surgical reduction and/or a change of medication. An allergic rash can occur with any medication but is probably most common with lamotrigine, carbamazepine, and phenytoin.

Because of the risk of valvular heart disease and pulmonary arterial hypertension with fenfluramine and irreversible peripheral vision loss with vigabatrin, these drugs are available only through a restricted distribution REMS program. In addition, the FDA has circulated a warning about factoring in the possibility of cardiac arrhythmias when deciding on lamotrigine use, particularly in cardiac patients and the need to monitor ECG during its use.

SIDE EFFECTS

Occasionally, a Stevens-Johnson-like syndrome develops, probably most commonly with lamotrigine but also with other medications like clobazam; it also has been found to be particularly common in Chinese patients who have the allele HLA-B*1502 and are taking oxcarbazepine, carbamazepine, and/or lamotrigine.

Other potential side effects are rickets from phenytoin, phenobarbital, primidone, and carbamazepine (enzyme inducers that reduce the 25-hydroxy-vitamin D level by inducing its metabolism) and hyperammonemia from valproate. Skeletal monitoring is warranted in patients taking chronic AED therapy because it is often associated with osteopenia independent of or secondary to vitamin D deficiency (low bone density, rickets, and hypocalcemia), particularly in patients taking enzyme-inducing medications. Thus counseling the patient about sun exposure and vitamin D intake, monitoring vitamin D levels, and, in most cases, giving vitamin D supplementation are recommended. There is currently no consensus on the dose to be used for supplementation or prophylaxis, but starting doses of 2,000 IU/day with follow-up of the levels are reasonable.

Irreversible hepatic injury and death are particularly feared in young children (<2 years old) who are receiving valproate in combination with other AEDs, particularly those who might have inborn errors of

metabolism such as aminoacidopathies and mitochondrial disease. Virtually all AEDs can produce sleepiness, ataxia, nystagmus, and slurred speech with toxic levels.

The FDA has determined that the use of AEDs may be associated with an increased risk of suicidal ideation and action and has recommended counseling about this side effect before starting these medications.

When adding a new AED, the doses used are often affected by the background medications. If the patient is receiving enzyme inducers, the doses needed of valproate, lamotrigine, topiramate, zonisamide, and perampanel are often higher, sometimes 1.5-2 times, than the usual maintenance doses. On the other hand, if the patient is taking valproate (an enzyme-inhibiting AED), the doses of phenobarbital or lamotrigine are approximately half of what is usually needed. Changes in the dosing of the background medication are often done as the interacting medication is being started or stopped. Genetic variability in enzymes that metabolize AEDs and in the presence of inducible multidrug-resistance genes (pharmacogenomics) might account for some of the variation among individuals in responding to certain AEDs and for the variability in the drug dose necessary for seizure control.

ADDITIONAL TREATMENTS

The principles of monotherapy indicate that a second medication needs to be considered after the first either is pushed as high as tolerated and still does not control the seizures or results in intolerable adverse effects. In those cases, a second drug is started and the first is tapered and then discontinued. The second drug is then again pushed to the dose that controls the seizure or that results in intolerable side effects. If the second drug fails, monotherapy with a third drug and **dual (combination) therapy** are considered.

Patients with **drug-resistant** (previously referred to as *intractable* or *refractory*) **epilepsy** (those who have failed at least two trials of appropriate medications) warrant a careful diagnostic reevaluation to look for degenerative, metabolic, or inflammatory underlying disorders (e.g., mitochondrial disease, Rasmussen encephalitis; see [Chapter 633.2](#)) and to investigate drug-resistant patients for candidacy for epilepsy surgery. Treatable metabolic disorders that can manifest as drug-resistant epilepsy include pyridoxine-dependent and pyridoxal-responsive epilepsy; cerebral folate deficiency; other vitamin-responsive conditions (such as biotin/thiamine-responsive basal ganglia disease and riboflavin-responsive epilepsy); neurotransmitter disorders; biotinidase deficiency; glucose transporter 1 deficiency (responds to the ketogenic diet); serine synthesis defects; creatine deficiency syndromes; untreated phenylketonuria; developmental delay, epilepsy, and neonatal diabetes; and hyperinsulinemia-hyperammonemia. Often patients who do not respond to AEDs are candidates for steroids, IVIG, or the ketogenic diet.

Steroids may be the first-line treatment in certain cases (e.g., ACTH use in West syndrome) but may also be used for other drug-resistant epilepsy syndromes such as Lennox-Gastaut, myoclonic-astatic, continuous spike waves in slow-wave sleep, and Landau-Kleffner syndromes. In these situations, steroid therapy is typically given as a monthly intravenous infusion (pulse steroids) or as daily oral prednisone 2 mg/kg/day (or equivalent). This dose is maintained for 1-2 months, then tapered off over 1-3 months. Pulse steroids are usually better tolerated than a daily steroid regimen, which can cause more weight gain, hyperglycemia, hypertension, immunosuppression, and other side effects. Because relapses occur commonly during tapering and in such syndromes as Landau-Kleffner and continuous spike waves in slow-wave sleep, therapy for longer than 1 year is often needed.

IVIG has also been reported to be similarly effective in nonimmunodeficient patients with West, Lennox-Gastaut, Landau-Kleffner, and continuous spike waves in slow-wave sleep syndromes and may also have efficacy in partial seizures. One should check the IgA levels before starting the infusions (to assess the risk for allergic reactions because these are increased in patients with complete IgA deficiency) and guard against allergic reactions during the infusion that can occur even in the absence of IgA deficiency. Low IgA, low IgG₂, and male sex are reported to predict a possibly favorable response. The usual regimen is 2 g/kg divided over 2-4 consecutive days followed by 1 g/kg once a month for 6 months.

The mechanisms of action of steroids and IVIG are not known but are presumed to be antiinflammatory because it has been demonstrated that seizures increase cytokines and that these, in turn, increase neuronal excitability by several mechanisms, including activation of glutamate receptors. Steroids and ACTH might also stimulate brain neurosteroid receptors that enhance GABA activity and might reduce corticotrophin-releasing hormone, which is known to be epileptogenic.

The ketogenic diet is considered effective in glucose transporter protein 1 deficiency (GLUT-1), pyruvate dehydrogenase deficiency, myoclonic-astatic epilepsy, tuberous sclerosis complex, Rett syndrome, severe myoclonic epilepsy of infancy (Dravet syndrome), and infantile spasms. There is also a suggestion of possible efficacy in selected mitochondrial disorders—glycogenosis type V, Landau-Kleffner syndrome, Lafora body disease, and subacute sclerosing panencephalitis. The diet is absolutely contraindicated in carnitine deficiency (primary), carnitine palmitoyltransferase I or II deficiency, carnitine translocase deficiency, β -oxidation defects, medium-chain acyl dehydrogenase deficiency, long-chain acyl dehydrogenase deficiency, short-chain acyl dehydrogenase deficiency, long-chain 3-hydroxyacyl-coenzyme A deficiency, medium-chain 3-hydroxyacyl-coenzyme A deficiency, pyruvate carboxylase deficiency, and porphyrias. Thus an appropriate metabolic workup, depending on the clinical picture, usually needs to be performed before starting the diet (e.g., acyl carnitine profile, total and free carnitine levels). The diet has been used for refractory seizures of various types (partial or generalized) and consists of an initial period of fasting followed by a diet with a 3:1 or 4:1 fat:nonfat calorie ratio, with fats consisting of animal fat, vegetable oils, or medium-chain triglycerides. Many patients do not tolerate it, owing to diarrhea, vomiting, hypoglycemia, dehydration, or lack of palatability. Diets such as the low-glycemic-index diet and the modified Atkins diet are easier to

institute, do not require hospitalization, and may also be effective in treating epilepsy.

CBD is a nonpsychoactive extract of the cannabis plant that has gained prominence as a possible adjunct (add-on) therapy for drug-resistant epilepsies such as Dravet and Lennox-Gastaut syndromes.

Precision genetic-based therapy is defined as a patient-specific, or more accurately physiology-specific, selection of therapy as determined by the available information regarding the underlying pathophysiology based on the primary specific genetic, metabolic, and/or other cause of epilepsy in that patient. The use of precision therapies (Table 633.16) has expanded as more epileptogenic gene pathogenic variants are identified as part of routine genetic screening for drug-resistant epilepsies. This has allowed for targeted therapy based on the specific gene variant (see Table 633.16). Examples include the use of quinidine for gain-of-function *KCNT1* variants and retigabine for loss-of-function *KCNQ2* variants. Gain-of-function *KCNQ2* variants do not respond to retigabine, a fact that emphasizes the need for careful gene analysis that accounts for the functional outcome of each particular gene. The same applies to pathogenic variants of sodium channels; patients with epilepsy caused by **gain-of-function** variants show good response to sodium channel-blocking agents, a response not shared by patients with epilepsy caused by *loss-of-function* variants in the sodium channel gene.

Vitamin-responsive epilepsies also warrant special attention because if they are diagnosed early and precision therapy is given for them, the therapy can significantly affect seizure control and neurodevelopmental outcomes. Examples include the use of pyridoxine for antiquitin deficiency-associated epilepsies, biotin for biotinidase deficiency, folate for cerebral folate deficiency, and biotin/thiamine for **biotin thiamine-responsive basal ganglia disease**, which can have coexisting epilepsy and is caused by defects in a cerebral thiamine transporter.

Table 633.16 Precision Therapy: Treatment Considerations for Genetic Epilepsies and Other Syndromes with a High Prevalence of Epilepsy

GENE MUTATION	EPILEPTIC DISORDER	TREATMENT CONSIDERATIONS
<i>ALDH7A1</i>	Pyridoxine-dependent epilepsy	Pyridoxine
<i>BTBD</i>	Biotinidase deficiency-associated epilepsy	Biotin
<i>FOLR1</i>	Cerebral folate deficiency	Folinic acid
<i>GRIN2A</i>	GRIN2A-related epilepsy	Memantine and dextromethorphan for gain-of-function variant
<i>KCNQ2</i>	Benign familial neonatal or infantile seizures; KCNQ2-related epileptic encephalopathy	Retigabine for loss-of-function variants*
<i>KCNT1</i>	Migrating focal seizures of infancy	Quinidine for gain-of-function variants
<i>PNPO</i>	Pyridoxal 5'-phosphate dependent epilepsy	Pyridoxal 5'-phosphate
<i>PRRT2</i>	Benign familial infantile epilepsy; paroxysmal dyskinesias; hemiplegic migraine; episodic ataxia	Oxcarbazepine and carbamazepine
<i>SCN1A</i>	Dravet syndrome; GEFS+; other SCN1A-related epilepsies	Avoid using sodium channel blockers (carbamazepine, oxcarbazepine, lamotrigine, lacosamide, phenytoin) and vigabatrin
<i>SCN2A</i>	Benign neonatal or infantile seizures; Dravet syndrome; GEFS+; infantile spasms; other early infantile epileptic encephalopathies	Phenytoin and carbamazepine
<i>SCN8A</i>	Early infantile epileptic encephalopathies; benign infantile seizures; movement disorders	High-dose phenytoin
<i>SLC2A1</i>	Glucose transporter-deficiency syndrome	Ketogenic diet
<i>SLC19A3</i>	Biotin thiamine-responsive basal ganglia disease	Biotin and thiamine
<i>TSC1; TSC2</i>	Tuberous sclerosis complex	Vigabatrin for infantile spasms; possibly everolimus for drug-resistant seizures

*Withdrawn from market.

Data from Hani A, Mikati MA. Current and emerging therapies of severe epileptic encephalopathies. *Semin Pediatr Neurol.* 2016;23(2):180–186; Mudigoudar B, Weatherspoon S, Wheelless JW. Emerging antiepileptic drugs for severe pediatric epilepsies. *Semin Pediatr Neurol.* 2016;23(2):167–179; and Smith LA, Ullman JFP, Olson HE, et al. A model program for translational medicine in epilepsy genetics. *J Child Neurol.* 2017;32(4):429–436.

APPROACH TO EPILEPSY SURGERY

If a patient has failed three drugs, the chance of achieving seizure freedom using AEDs is <10%. Therefore proper evaluation for surgery is necessary when a patient fails two or three AEDs, usually within 2 years of the onset of epilepsy and often sooner than 2 years. Performing epilepsy surgery in children at an earlier stage (e.g., <5 years of age) allows the transfer of function in the developing brain. Candidacy for epilepsy surgery requires proof of resistance to AEDs used at maximum, tolerably nontoxic doses; absence of expected unacceptable adverse consequences of surgery; and a properly defined **epileptogenic zone** (the area that needs to be resected to achieve seizure freedom). The epileptogenic zone is identified by careful analysis of the following parameters: seizure semiology, video-EEG long-term monitoring, neuropsychologic profile, and brain MRI. 7-Tesla MRI may, in some cases, have some advantage over 3-Tesla MRI. Other techniques, such as high-density EEG (HD-EEG), invasive EEG (depth electrodes, subdural grid or strips, intraoperative electrocorticography), single-photon emission CT (SPECT), magnetoencephalography (MEG), and positron emission tomography (PET), are also needed if the epileptogenic zone is difficult to localize or when it is close to the eloquent cortex. **Stereo-EEG** is a method of invasive EEG monitoring used to localize epileptic areas of the cortex. It involves the stereotactic implantation of depth electrodes through multiple burr holes in the skull using robot-assisted implantations and computer-based 3D localization. Several procedures can be used to avoid resection of eloquent cortex, including the **Wada test**, **functional MRI**, MEG, transcranial magnetic stimulation, and cortical stimulation with subdural and depth electrodes. Developmental delay or psychiatric diseases must be considered in assessing the potential impact of surgery on the patient. The usual minimal presurgical evaluation includes video-EEG monitoring, brain imaging, and age-specific neuropsychologic assessment.

Epilepsy surgery is often used to treat drug-resistant epilepsy of a number of etiologies, including cortical dysplasia, tuberous sclerosis, polymicrogyria, hypothalamic hamartoma, encephalomalacia

from prior cerebrovascular insult, mesial temporal sclerosis, Landau-Kleffner syndrome, and hemispheric syndromes such as Sturge-Weber syndrome, hemimegalencephaly, and Rasmussen encephalitis. Patients with drug-resistant epilepsy resulting from metabolic or degenerative problems are *not* candidates for resective epilepsy surgery. **Focal resection** of the epileptogenic zone is the most common procedure. **Hemispherectomy** is used for diffuse hemispheric lesions in cases such as Rasmussen encephalitis, hemimegalencephaly, large perinatal stroke, Sturge-Weber syndrome; **multiple subpial transections**, a surgical technique in which the horizontal connections of the epileptic focus are partially cut without resecting it, is sometimes used for unresectable foci located in the eloquent cortex, as in Landau-Kleffner syndrome. In Lennox-Gastaut syndrome, **corpus callosotomy** is used as a palliative procedure for drop attacks.

Laser interstitial thermal therapy (LITT) is a less invasive surgical technique that uses a laser to ablate relatively small (<3 × 3 cm) epileptic areas in the cortex; it has been used to treat mesial temporal sclerosis, tuberous sclerosis, and hypothalamic hamartomas and for corpus callosotomies. Other minimally invasive techniques include gamma knife stereotactic radiosurgery that uses gamma radiation. Focal resection and hemispherectomy result in a high rate (50–80%) of seizure freedom. Corpus callosotomy and vagal nerve stimulation result in lower rates of seizure freedom (5–10% for vagus nerve stimulation [VNS] and lower for callosotomy); however, these procedures do result in significant reductions in the frequency and severity of seizures, decreases in medication requirements, and meaningful improvements in the patient's quality of life in approximately half or more of eligible patients.

VNS is often used for drug-resistant epilepsies of various types (partial, generalized, Lennox-Gastaut) and for seizures of diffuse focal or multifocal anatomic origin that do not yield themselves to resective surgery (Fig. 633.10). VNS is approved for age 4 years and above but has also been used in even younger ages. This technique is considered palliative rather than curative because it most often leads to seizure

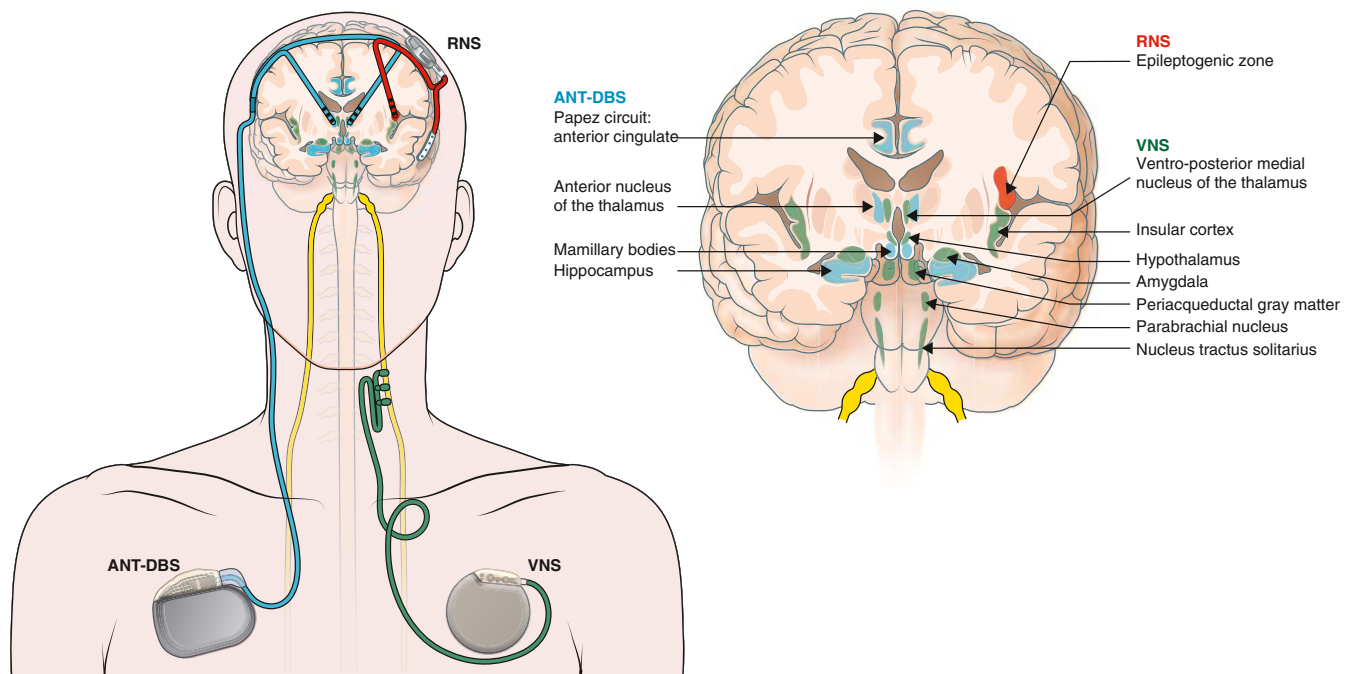


Fig. 633.10 Approved neuromodulation therapies in epilepsy. The brain targets for each neuromodulation approach according to sites of stimulation and known primary anatomic pathways. This illustration is not meant to be comprehensive. VNS is expected to activate the nucleus tractus solitarius, with downstream effects on its brainstem, subcortical, and cortical efferences; ANT-DBS stimulation is expected to modulate the activity of the anterior nucleus of the thalamus and the associated Papez circuit, and RNS stimulation is expected to inhibit the suspected cortical epileptogenic zone. ANT-DBS, Deep brain stimulation of the anterior nucleus of the thalamus; RNS, responsive neurostimulation; VNS, vagus nerve stimulation. (From Ryvlin P, Rheims S, Hirsch LJ, et al. *Neuromodulation in epilepsy: state-of-the art approved therapies*. *Lancet Neurol*. 2021;20[12]:1038–1047, Fig. 1, p. 1039.)

frequency *reduction* rather than seizure cessation. By producing low-amplitude current stimulations, usually once every 5 minutes, this device results in a reduction of seizures. Also, caretakers can activate the device by swiping a magnet over it at the time of the seizure, which can shorten seizure duration. Vagus nerve stimulators also have integrated heart rate monitoring that detects tachycardia patterns typically associated with seizures and then activates the stimulator during these times. **Responsive neurostimulation (RNS)** is a technique that has been used in adults with epilepsy; it requires the implantation of subdural or depth electrodes to directly monitor seizure activity on a long-term basis to detect and abort the seizures. Once a seizure is detected, electrical stimulation is delivered to that area of the brain to stop the seizure. **Deep brain stimulation (DBS)** is approved for refractory partial epilepsy in adults. In DBS, the electrical stimulation is provided by two stereotactically placed electrodes in bilateral thalamic nuclei (anterior nuclei for focal epilepsy and centromedian nuclei, as being studied, in generalized epilepsies).

DISCONTINUATION OF THERAPY

Discontinuation of AEDs is usually indicated when otherwise well children are free of seizures for at least 2 years. In more severe syndromes, such as temporal lobe epilepsy secondary to mesial temporal sclerosis, Lennox-Gastaut syndrome, or severe myoclonic epilepsy, a prolonged period of seizure freedom with treatment is often warranted before AEDs are withdrawn, if withdrawal is attempted at all. In self-limited (benign) epilepsy syndromes, the duration of therapy can often be as short as 6 months.

Many factors should be considered before discontinuing medications, including the likelihood of remaining seizure-free after drug withdrawal based on the type of epilepsy syndrome and etiology; the risk of injury in case of seizure recurrence (e.g., if the patient drives); and the adverse effects of AED therapy. Most children who have not had a seizure for 2 years or longer and who have a normal EEG when AED withdrawal is initiated remain free of seizures after discontinuing medication, and most relapses occur within the first 6 months.

Certain risk factors can help clinicians predict the prognosis after AED withdrawal. The most important risk factor for seizure relapse is an abnormal EEG before medication is discontinued. Children who have remote structural (symptomatic) epilepsy are less likely to be able to stop AEDs than are children who have a benign (idiopathic) epilepsy. In patients with absences or in patients treated with valproate or other medications for primary generalized epilepsy, the risk of relapse might be high despite a normal EEG because valproate (and less so other AEDs for primary generalized epilepsy) can normalize EEGs with generalized spike-wave abnormalities. Thus in these patients, repeating the EEG during drug tapering may help identify a recurrence of the EEG abnormality and associated seizure risk before clinical seizures recur. Older age of epilepsy onset, longer duration of epilepsy, presence of multiple seizure types, and need to use more than one AED are all factors associated with a higher risk of seizure relapse after AED withdrawal.

AED therapy should be discontinued gradually, often over a period of 3–6 months, but many advocate for shorter periods down to 6 weeks. Abrupt discontinuation can result in withdrawal seizures or in status epilepticus. Withdrawal seizures are especially common with phenobarbital and benzodiazepines; consequently, special attention must be given to a prolonged tapering schedule during the withdrawal of these AEDs. Seizures that occur more than 2–3 months after AEDs are completely discontinued indicate a relapse, and resumption of treatment is usually warranted. Seizures that occur before that, such as during or shortly after a medication taper, may be withdrawal seizures or may indicate a relapse.

The decision to attempt AED withdrawal must be assessed mutually by the clinician, the parents, and the child depending on the child's age. The American Academy of Neurology in collaboration with the American Epilepsy Society has developed guidelines regarding such withdrawals. In addition, there is an online risk calculator tool that has been generated based on clinical nomograms from an independent participant data meta-analysis. This tool can be used, with caution, as an aid to estimate risk of recurrence, but individualized decision based

Table 633.17 Measures in Clinical Practice to Reduce the Risk of SUDEP

Counseling: Explaining SUDEP and risk factors is imperative, even if the discussion may be uncomfortable. Emphasize modifiable risk factors, such as compliance with taking medication.
Reduction of tonic-clonic seizures: Optimum treatment, good drug compliance, lifestyle advice (e.g., alcohol intake, sleep deprivation).
Treatment changes: Change in a gradually staged manner; when switching drugs, introduce the new drug before withdrawing the old drug; the patient should have access to immediate advice in the event of worsening seizures during periods of change.
Supervision at night for patients at high risk: Attendance, use of alarms (balancing the benefits of independent living and the penalties of intrusive monitoring).
Choice of drugs: Caution with AEDs with potential cardiorespiratory adverse effects.
Act on ictal warning signs: Tonic-clonic seizures that are prolonged, associated with marked cyanosis, severe bradycardia or apnea, and postictal EEG suppression; complex partial seizures with marked atonia (drop attacks); seizure in those with preexisting cardiac or respiratory impairment.
Supervision after a tonic-clonic seizure: Continuous attendance until full consciousness is restored; call emergency services for high-risk seizures.

EEG, Electroencephalogram; SUDEP, sudden unexpected death in epilepsy.

From Shorvan S, Tomson T. Sudden unexpected death in epilepsy. *Lancet*. 2011;378:2028–2036.

on each case's particulars and on the discussions with the caretakers should be the final guide in planning the course of care. The patient and family should be counseled fully on what to expect, what precautions to take (e.g., cessation of driving for a period), and what to do in case of relapse. A prescription for rectal diazepam or intranasal midazolam to be given at the time of seizures that might occur during and after tapering is usually warranted (see [Table 633.23](#) for dosing).

SUDDEN UNEXPECTED DEATH IN EPILEPSY

SUDEP is the most common epilepsy-related cause of mortality and is responsible for up to 17% of deaths in patients with epilepsy. Risk factors include polytherapy with more than three AEDs, male gender, young age at epilepsy onset, developmental delay, poor AED compliance, nocturnal seizures, poorly controlled convulsive seizures (especially if >3 per year), high frequency of seizures (especially if >50 per year), and having epilepsy for >30 years in adults. Patients are usually found dead in their bed in a prone position, with evidence suggesting a recent seizure.

Respiratory, cardiogenic, and mixed respiratory/cardiogenic mechanisms have been hypothesized to cause SUDEP. Respiratory models include seizure-induced central hypoventilation, neurogenic pulmonary edema, and disturbances in the brainstem serotonergic system leading to respiratory arrest. Cardiogenic models include seizure-induced cardiac arrhythmia as well as **cardiocerebral channelopathies** in which ion channels are expressed in both the brain and heart, causing cardiac dysfunction concurrent with the seizures. *SCN1A*, *SNC8A*, *ATPIA3*, and *KCNQ1* are examples of genes that encode for cardio-cerebral ion channels known to cause epilepsy and that have also been associated with SUDEP. Mixed respiratory/cardiogenic models include seizure-induced dysautonomia, high adenosine levels during seizure causing cardiorespiratory collapse, and spreading depression in the brainstem causing dysautonomia. More data are needed to determine if safety pillows, seizure detection devices, or selective serotonin reuptake inhibitors may be of benefit in preventing SUDEP. *It is currently recommended to counsel the patients and family regarding SUDEP, even if the topic is not comfortable to talk about.* In addition to providing them with important information, such counseling may also encourage families to address modifiable risk factors such as AED compliance. [Table 633.17](#) lists other possible preventive measures.

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633.7 Neonatal Seizures

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Seizures are possibly the most important and common indicator of significant neurologic dysfunction in the neonatal period. Seizure incidence is higher during this period than in any other period of life: seizures occur in 57.5 per 1,000 in infants with birthweights <1,500 g and 2.8 per 1,000 in infants weighing between 2,500 and 3,999 g. The etiology of neonatal seizures depends on postnatal age of onset (Fig. 633.11, Table 633.18) as well as EEG and clinical features (Fig. 633.12, Table 633.18 and Table 633.19).

PATHOPHYSIOLOGY

The immature brain has many differences from the mature brain that render it more excitable and more likely to develop seizures. Based predominantly on animal studies, these include a delay in Na⁺, K⁺-adenosine triphosphatase maturation and increased NMDA and AMPA receptor density. In addition, the specific types of these receptors that are increased are those that are permeable to calcium (GLUR2 AMPA receptors). This contributes to increased excitability and to the long-term consequences associated with seizures, particularly those resulting from perinatal hypoxia. Medications that block AMPA receptors, such as topiramate, may thus prove useful in this clinical scenario.

Another difference is delay in the development of inhibitory GABA-ergic transmission. In fact, GABA in the immature brain has an excitatory function because the chloride gradient is reversed relative to the mature brain, with higher concentrations of chloride being present intracellularly than extracellularly. Thus opening of the chloride channels in the immature brain results in depolarizing the cell and not in hyperpolarizing it. How applicable this is to human neonates and, if so, at what conceptional ages, is not clear yet. This phenomenon, however,

appears to be more prominent in male neonates, perhaps explaining their greater predisposition to seizures.

TYPES OF NEONATAL SEIZURES

There are two main neonatal seizure types: electroclinical and electrographic only. Electroclinical seizures can be categorized as motor, nonmotor, and sequential. Motor seizures include automatisms, clonic seizures, epileptic spasms, myoclonic seizures, and tonic seizures. Non-motor seizures include autonomic seizures and behavioral arrest (see Fig. 633.12 and Table 633.19). Differentiating seizure types based on

Table 633.18 Causes of Neonatal Seizures According to Common Age of Presentation

AGES 1-4 DAYS

Hypoxic-ischemic encephalopathy
Drug withdrawal, maternal drug use of opiate or barbiturates
Drug toxicity: lidocaine, penicillin
Intraventricular hemorrhage
Sepsis
Acute metabolic disorders

- Hypocalcemia
- Maternal hyperthyroidism, or hypoparathyroidism
- Hypoglycemia
- Maternal diabetes
- Hyperinsulinemic hypoglycemia
- Hypomagnesemia
- Hyponatremia or hypernatremia
- Iatrogenic or inappropriate antidiuretic hormone secretion

Inborn errors of metabolism

- Galactosemia
- Hyperglycinemia
- Urea cycle disorders

Pyridoxine dependency and pyridoxal-5-phosphate dependency (must be considered at any age)

AGES 4-14 DAYS

Infection

- Meningitis (bacterial)
- Encephalitis (enteroviral, herpes simplex)

Metabolic disorders

- Hypocalcemia related to diet, milk formula
- Hypoglycemia, persistent
- Inherited disorders of metabolism
- Galactosemia
- Fructosemia
- Leucine sensitivity
- Hyperinsulinemic hypoglycemia, hyperinsulinism, hyperammonemia syndrome
- Anterior pituitary hypoplasia, pancreatic islet cell tumor
- Beckwith syndrome

Drug withdrawal, maternal drug use of narcotics or barbiturates
Benign neonatal convulsions, familial and nonfamilial
Kernicterus, hyperbilirubinemia
Developmental delay, epilepsy, neonatal diabetes syndrome

AGES 2-8 WK

Infection

- Herpes simplex or enteroviral encephalitis
- Bacterial meningitis

Head injury

- Subdural hematoma
- Child abuse

Inherited disorders of metabolism

- Aminoacidurias
- Urea cycle defects
- Organic acidurias
- Neonatal adrenoleukodystrophy

Malformations of cortical development

- Lissencephaly
- Focal cortical dysplasia

Tuberous sclerosis
Sturge-Weber syndrome

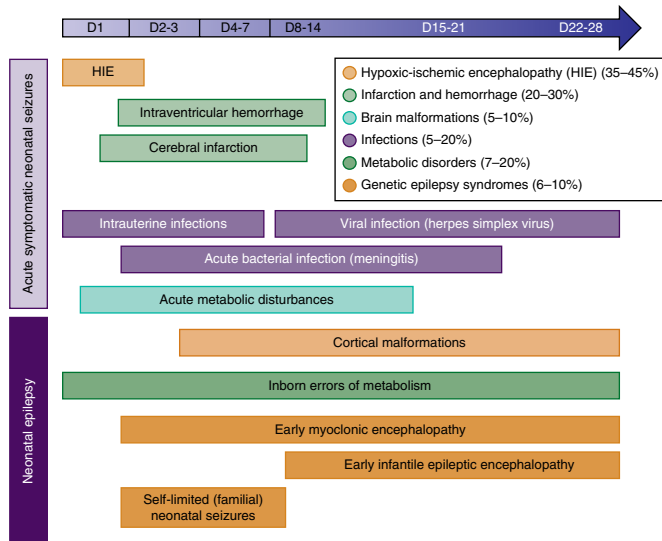


Fig. 633.11 Etiologies of neonatal seizures according to seizure onset timing. The most common causes of seizures occurring within the first 24 hr of life are hypoxic-ischemic encephalopathy or vascular etiologies, followed by acute metabolic disturbances such as hypoglycemia or inborn errors of metabolism such as pyridoxine dependency. Within the next 24-72 hr, the main etiologies include infection, cortical malformations, cerebral infarction, inborn errors of metabolism such as glycine encephalopathy, urea cycle disturbances, pyridoxine dependency, and benign familial neonatal seizures. Over the next 72 hr to a week, causes include cortical malformations, cerebral infarction or hemorrhage, or inborn errors of metabolism, such as urea cycle disturbances. In the next 1-4 wk, the differential includes cortical malformations, viral infections such as herpes simplex, or genetic epilepsy syndromes. (From Kim EH, Shin J, Lee BK. Neonatal seizures: diagnostic updates based on new definition and classification. *Clin Exp Pediatr*. 2022;65[8]:387-397, Fig. 1, p. 389.)

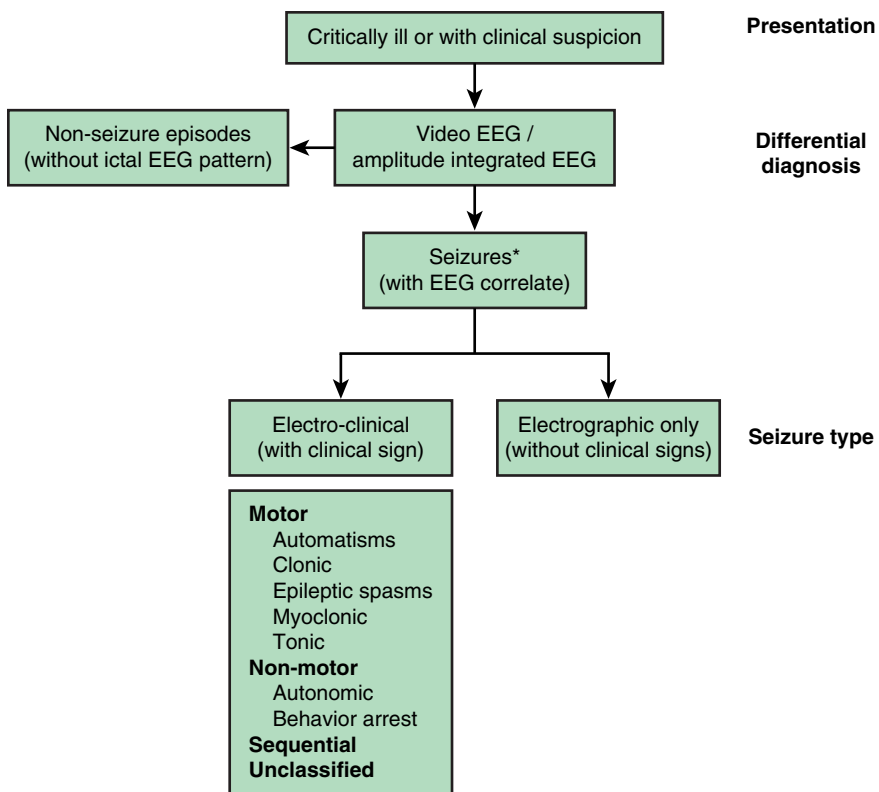


Fig. 633.12 Diagnostic framework of seizures in the neonatal period, including classification of seizures. Adapted from 2017 ILAE seizure classification. Neonates present with discrete events suspected to be epileptic seizures or are critically ill (often ventilated, sedated, and treated with muscle relaxants in intensive care). *If no EEG is available, refer to global alignment of immunization safety assessment in pregnancy levels of diagnostic certainty. (From Pressler RM, Cilio MR, Mizrahi EM, et al, The ILAE classification of seizures and the epilepsies: modification for seizures in the neonate. Position paper by the ILAE Task Force on Neonatal Seizures. *Epilepsia*. 2021;62[3]:615–628, Fig. 2.)

Table 633.19 Clinical Characteristics, Classification, and Presumed Pathophysiology of Neonatal Seizures			
CLASSIFICATION	CHARACTERIZATION	CLASSIFICATION	CHARACTERIZATION
Focal clonic	Repetitive, rhythmic contractions of muscle groups of the limbs, face, or trunk May be unifocal or multifocal May occur synchronously or asynchronously in muscle groups on one side of the body May occur simultaneously but asynchronously on both sides Cannot be suppressed by restraint Pathophysiology: epileptic	Spasms	May be flexor, extensor, or mixed extensor/flexor Unilateral or bilateral May occur in clusters Asymmetric or symmetric Cannot be provoked by stimulation or suppressed by restraint Pathophysiology: epileptic
Focal tonic	Sustained posturing of single limbs Sustained asymmetric posturing of the trunk Sustained eye deviation Cannot be provoked by stimulation or suppressed by restraint Pathophysiology: epileptic	MOTOR AUTOMATISMS (UNILATERAL, BILATERAL, ASYMMETRIC OR SYMMETRIC)	
Generalized tonic	Sustained symmetric posturing of limbs, trunk, and neck May be flexor, extensor, or mixed extensor/flexor May be provoked or intensified by stimulation May be suppressed by restraint or repositioning Presumed pathophysiology: nonepileptic	Ocular signs	Random and roving eye movements or nystagmus (distinct from tonic eye deviation) May be provoked or intensified by tactile stimulation Presumed pathophysiology: nonepileptic
Myoclonic	Random, single, rapid contractions of muscle groups of the limbs, face, or trunk: asymmetric or symmetric Typically not repetitive or may recur at a slow rate May be generalized, focal, multifocal, or fragmentary May be provoked by stimulation Presumed pathophysiology: may be epileptic or nonepileptic	Oral-buccal-lingual movements	Sucking, chewing, tongue protrusions May be provoked or intensified by stimulation Presumed pathophysiology: nonepileptic
		Progression movements	Rowing or swimming movements Pedaling or bicycling movements of the legs May be provoked or intensified by stimulation May be suppressed by restraint or repositioning Presumed pathophysiology: nonepileptic
		Complex purposeless movements	Sudden arousal with transient increased random activity of limbs May be provoked or intensified by stimulation Presumed pathophysiology: nonepileptic

clinical appearance alone is challenging. Thus in many cases, specifically in sick neonates with a history of suspected neurologic injury, continuous bedside EEG is necessary to make this distinction.

Motor Seizures Automatisms

Automatisms include transient eye deviations, nystagmus, blinking, mouthing, and abnormal extremity movements (rowing, swimming, bicycling, pedaling, and stepping). Automatisms occur more commonly in premature than in full-term infants.

Clonic Seizures

Clonic seizures can be focal or multifocal. Multifocal clonic seizures incorporate several body parts and are migratory in nature. The migration follows a non-Jacksonian trend; for example, jerking of the left arm can be associated with jerking of the right leg. Generalized clonic seizures that are bilateral, symmetric, and synchronous are uncommon in the neonatal period, presumably because of decreased connectivity associated with incomplete myelination at this age.

Epileptic Spasms

Epileptic spasms are sudden generalized jerks lasting 1–2 seconds that are distinguished from generalized tonic spells by their shorter duration and by the fact that spasms are usually associated with a single, very brief, generalized discharge.

Myoclonic Seizures

Myoclonic seizures are divided into focal, multifocal, and generalized types. Myoclonic seizures can be distinguished from clonic seizures by the rapidity of the jerks (<50 milliseconds) and by their lack of rhythmicity. Focal myoclonic seizures characteristically affect the flexor muscles of the upper extremities and are sometimes associated with seizure activity on EEG. Multifocal myoclonic movements involve asynchronous twitching of several parts of the body and are not commonly associated with seizure discharges on EEG. Generalized myoclonic seizures involve bilateral jerking associated with flexion of the upper and occasionally lower extremities. The latter type of myoclonic jerks is more commonly correlated with EEG abnormalities than the other types.

Tonic Seizures

Tonic seizures can be focal or generalized (generalized are more common). Focal tonic seizures include persistent posturing of a limb or posturing of the trunk or neck in an asymmetric way, often with persistent horizontal eye deviation. Generalized tonic seizures are bilateral tonic limb extensions or tonic flexions of the upper extremities often associated with tonic extension of the lower extremities and trunk.

Nonmotor Seizures Autonomic

Autonomic seizures involve fluctuations in autonomic system function, including alterations in the cardiovascular, vasomotor, pupillary, and thermoregulatory function. These seizures may include heart rate changes, hypertension episodes, and apnea. Autonomic seizures typically accompany additional seizure types and are rarely seen in isolation.

Behavioral Arrest

Behavioral arrest seizures include cessation of activity or immobilization. This seizure type is rarely seen in isolation and can be seen as a component of sequential seizures.

Sequential

Sequential seizures have been defined by the ILAE as a seizure type for “events with a sequent of signs, symptoms, and EEG changes at different times.” An example would be a sequence of tonic, then clonic, then automatisms, and autonomic manifestations with varying lateralization during one seizure. In these seizures, it can be challenging to define the predominant semiology, and features present in a sequence.

These are most commonly associated with genetic epilepsies, including KCNQ2 encephalopathy.

Seizures Versus Jitteriness

Jitteriness can be defined as rapid motor activities, such as a tremor or shake, that can be ended by flexion or holding the limb. Seizures generally do not end with tactile or motor suppression. Jitteriness, unlike most seizures, is usually induced by a stimulus. Unlike jitteriness, seizures often involve eye deviation and autonomic changes.

ETIOLOGY

Table 633.18 and Table 633.20 and Figure 633.11 list causes of neonatal seizures.

Hypoxic-Ischemic Encephalopathy

This is the most common cause of neonatal seizures, accounting for 50–60% of patients. Seizures secondary to this encephalopathy occur within 24 hours of birth. Abnormal EEG background, including excessive discontinuity, burst suppression, and extremely low voltage patterns, are strongly associated with the development of seizures.

Vascular Events

These include intracranial bleeds and ischemic strokes and account for 10–20% of patients. Three types of hemorrhage can be distinguished: primary subarachnoid hemorrhage, germinal matrix–intraventricular hemorrhage, and subdural hemorrhage. Patients with arterial strokes or venous sinus thrombosis can present with seizure, and these can be diagnosed by neuroimaging. Venous sinus thrombosis could be missed unless MR or CT venography studies are requested.

Intracranial Infections

Bacterial and nonbacterial infections account for 5–10% of the cases of neonatal seizures and include bacterial meningitis, TORCH (toxoplasmosis, other infections, rubella, cytomegalovirus, herpes simplex virus) infections, and, particularly, herpes simplex encephalitis.

Brain Malformations

Brain malformations account for 5–10% of neonatal seizure cases. An example is **Aicardi syndrome**, which affects girls only and consists of retinal lacunae, agenesis of the corpus callosum, and severe seizures, including subsequent infantile spasms with hypsarrhythmia that is sometimes initially unilateral on EEG.

Metabolic Disturbances

Metabolic disturbances include disturbances in glucose, calcium, magnesium, other electrolytes, amino acids, or organic acids and pyridoxine dependency (Table 633.21).

Hypoglycemia can cause neurologic disturbances and is common in small neonates and neonates whose mothers are diabetic or prediabetic. The duration of hypoglycemia is very critical in determining the incidence of neurologic symptoms.

Hypocalcemia occurs with two peaks. The first peak corresponds to low birthweight infants and is evident in the first 2–3 days of life. The second peak occurs later in neonatal life and often involves large, full-term babies who consume milk that has an unfavorable ratio of phosphorus to calcium and phosphorus to magnesium. **Hypomagnesemia** is often associated with hypocalcemia. **Hypонатremia** can cause seizures and is often secondary to inappropriate antidiuretic hormone secretion or water intoxication.

Local anesthetic intoxication seizures can result from neonatal intoxication with local anesthetics that are inadvertently administered into the infant's scalp.

Neonatal seizures can also result from disturbances in **amino acid or organic acid** metabolism. These are usually associated with acidosis and/or hyperammonemia. However, even in the absence of these findings, if a cause of the seizures is not immediately evident, then ruling out metabolic causes requires a full metabolic workup (see Chapter 633.2), including examination of serum amino acids, acyl carnitine profile, lactate, pyruvate, ammonia, very long-chain fatty acids (for neonatal adrenoleukodystrophy and Zellweger syndrome), examination of urine

Table 633.20 Clinical Characteristics and Genetic Variants of Neonatal Epilepsy Syndromes

SYNDROME	SEIZURE ONSET	TYPES OF SEIZURE	ETIOLOGY	EEG FEATURES	PROGNOSIS
Self-limited familial neonatal seizures	Days 2-3	Focal tonic seizures, often with apnea, vocalization, or autonomic change, frequent brief seizures	Autosomal dominant variants in <i>KCNQ2</i> , <i>KCNQ3</i> , <i>SCN2A</i>	Background: usually normal Interictal: a theta pointu alternant pattern or focal or multifocal epileptiform abnormalities	Favorable outcome, typically resolved seizures by 6 mo of age
Self-limited neonatal seizures	Days 4-6	Unilateral or bilateral clonic seizures, frequent seizure clusters	Most unknown, rare <i>KCNQ2</i> variant	Ictal: focal rhythmic spike or slow waves	Favorable outcome, usually decreased seizure within 48 hr
Early-infantile epileptic encephalopathy	First 2 wk, up to 3 mo	Tonic seizures, epileptic spasms	Structural brain malformations, genetic variants in <i>ARX</i> , <i>CDKL5</i> , <i>SLC25A22</i> , <i>STXBP1</i> , <i>KCNQ2</i> , <i>SPTAN1</i> , <i>SCN2A</i> , metabolic disorders	Background/interictal: suppression-burst patten: same asleep and awake Ictal: diffuse attenuation with emergency of low-voltage, high-frequency activity, or focal ictal rhythms	Frequent early-life mortality, severe developmental disabilities
Early myoclonic encephalopathy	Hours to months	Multifocal erratic myoclonus	Metabolic disorders, genetic variants in <i>STXBP1</i> , <i>TBC1D24</i> , <i>GABRA1</i>	Background/interictal: suppression-burst patten, enhanced by sleep Ictal: no ictal pattern but followed by bursts, or focal ictal rhythms	
Epilepsy of infancy with migrating focal seizures	Days to months	Nearly continuous focal clonic and/or tonic, autonomic, migrating seizures	Pathogenic variants in <i>KCNT1</i> , <i>SCN2A</i> , <i>SCN1A</i> , <i>SLC25A22</i> , <i>PLCB1</i> , <i>QARS</i>	Background: normal or diffuse slowing Interictal: multifocal discharges Ictal: rhythmic alpha or theta activities that evolve simultaneously from different brain regions and migrate to contiguous or contralateral regions	Generally poor with refractory seizures and severe developmental disabilities

From Kim EH, Shin J, Lee BK. Neonatal seizures: diagnostic updates based on new definition and classification. *Clin Exp Pediatr*. 2022;65(8):387–397. Table 1, p. 390.

for organic acids, α -aminoadipic acid semialdehyde, and sulfoxysteine, as well as examination of CSF for glucose, protein, cells, amino acids, lactate, pyruvate, α -aminoadipic acid semialdehyde, pyridoxal phosphate, 5-methyltetrahydrofolate (5-MTHF), succinyladenosine, and CSF neurotransmitter metabolites. This is because many inborn errors of metabolism, such as nonketotic hyperglycinemia, can manifest with neonatal seizures (often mistaken initially for hiccups, which these patients also have) and can be detected only by performing these tests. Definitive diagnosis of **nonketotic hyperglycinemia**, for example, requires measuring the ratio of CSF glycine to plasma glycine.

Pyridoxine- and **pyridoxal-dependency disorders** can cause severe seizures. These seizures, which are often multifocal clonic, usually start during the first few hours of life. Cognitive impairment is often associated if therapy is delayed (see [Chapter 633.4](#)).

Drug Withdrawal

Seizures can rarely be caused by the neonate's passive addiction and then drug withdrawal after birth. Such drugs include narcotic analgesics, sedative-hypnotics, and others. The associated seizures appear during the first 3 days of life.

Neonatal Seizure Genetic Syndromes

Seizure syndromes include **benign neonatal convulsions (fifth-day fits)**, which are usually apneic, and focal motor seizures that start around

the fifth day of life (see [Table 633.20](#)). Interictal EEG shows a distinctive pattern called *theta pointu alternant* (runs of sharp 4- to 7-Hz activity), and ictal EEG shows multifocal electrographic seizures. Patients have a good response to medications and a good prognosis. Autosomal dominant **benign familial neonatal seizures** have an onset at 2-4 days of age and usually remit at 2-15 weeks of age. The seizures consist of ocular deviation, tonic posturing, clonic jerks, and, at times, motor automatisms. Interictal EEG is usually normal. These are caused by pathogenic variants in *KCNQ2* and *KCNQ3*. Approximately 16% of patients develop later epilepsy. **Early myoclonic encephalopathy** and **early infantile epileptic encephalopathy (Ohtahara syndrome)** are discussed in [Chapter 633.4](#).

Miscellaneous Conditions

Miscellaneous conditions include benign neonatal sleep myoclonus and hyperekplexia, which are nonepileptic conditions (see [Chapter 634](#)).

DIAGNOSIS

Some cases can be correctly diagnosed by simply taking the pre-natal and postnatal history and performing an adequate physical examination; however, the *American Clinical Neurophysiology Society Guidelines for Neonatal EEG Monitoring* recommend EEG monitoring in cases where there is a clinical concern for seizure and/or when

Table 633.21 Overview of Diagnostic Findings in Inborn Errors of Metabolism Presenting with Isolated Neonatal Seizures

DISORDER	MRI AND MRS FINDINGS	CSF FINDINGS	FURTHER DIAGNOSTIC TESTING
Pyridoxine-dependent seizures	Normal or hypoplasia of corpus callosum and cerebellum	Increased levels of α -AASA, pipecolic acid, and neurotransmitter markers	Urinary and serum α -AASA or pipecolic acid, ALDH7A1 gene testing
Pyridoxal-phosphate-dependent seizures	Generalized atrophy	May be normal or nonspecific changes	Pyridoxamine-5-phosphate oxidase gene testing
Defects of serine biogenesis	Initially normal, progressing to profound hypomyelination	Low levels of serine; may also have low levels of glycine or 5-MTHF	Skin biopsy for 3-phosphoglycerate dehydrogenase activity
GLUT-1 deficiency	Normal or generalized atrophy	CSF glucose <40mg/dL or <half of serum glucose	FDG-PET; 3-OMG uptake in red blood cells; gene testing for SLC2A1
Nonketotic hyperglycinemia	Normal, or agenesis or thinning of the corpus callosum	Increased levels of glycine, and increased CSF/plasma glycine ratio	Liver glycine cleavage complex enzyme activity; gene testing for nonketotic hyperglycinemia
Sulfite oxidase/molybdenum cofactor deficiency	MRI findings can mimic those of hypoxic-ischemic injury; MRS reveals increased levels of lactate, myoinositol, and choline, with decreased levels of NAA	Normal or nonspecific changes in amino acid profile	Plasma homocysteine and uric acid; urine sulfites, sulfocysteine, and thiosulfates; sulfite oxidase enzyme activity in skin or liver biopsy
Congenital neuronal ceroid-lipofuscinosis	Generalized cerebral hypoplasia	Normal	Cathepsin D gene testing
γ -Aminobutyric acid transferase deficiency	MRI indicates leukodystrophy and agenesis of the corpus callosum; MRS indicates elevated levels of γ -aminobutyric acid in the basal ganglia	Increased levels of homocarnosine	Enzyme activity in lymphocytes
Dihydropyrimidine dehydrogenase deficiency	Diffuse atrophy	Increased levels of uracil and thymine	Dihydropyrimidine dehydrogenase gene testing
Creatine deficiency syndromes	MRI indicates delayed myelination MRS reveals absent creatine peak	Normal	Serum creatine and guanidinoacetate; urinary creatine, creatinine, and guanidinoacetate; fibroblast enzyme activity; specific genetic testing

For current information on the best locations to perform biochemical and genetic testing, see genereviews.org.

3-OMG, 3-O-methyl-D-glucose; 5-MTHF, 5-methyltetrahydrofolate; α -AASA, α -amino adipic semialdehyde; CSF, cerebrospinal fluid; FDG-PET, fluorodeoxyglucose–positron emission tomography; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA, N-acetylaspartate.

From Ficicioglu C, Bearden D. Isolated neonatal seizures: when to suspect inborn errors of metabolism. *Pediatric Neurol.* 2011;45:283–291. Table 2.

an infant has a condition that predisposes the infant to seizures. EEG monitoring can show epileptiform activity (e.g., sharp waves) between the seizures (suggesting an increased risk for seizures) and confirm electrographic seizure activity if a clinical seizure is recorded. Additionally, EEG monitoring is often necessary because electrographic seizures can occur without observed clinical signs (**electroclinical dissociation**). This is presumed to be caused by the immaturity of cortical connections, resulting, in many cases, in no or minimal clinical manifestations.

Continuous bedside EEG monitoring in the neonatal intensive care unit is the preferred clinical practice for neonates at risk for neonatal seizures and brain injury. Amplitude-integrated EEG (aEEG) monitoring is also used as an *adjunct* to conventional EEG monitoring and provides a bedside graphic representation of a neonate's electrocerebral activity, which may aid in earlier seizure identification. Appropriately trained nurses and providers can identify possible seizure activity using aEEG and can then contact the neurophysiologist to confirm the presence or absence of seizures. Examples of situations in which continuous EEG monitoring should be used include cases of **hypoxic-ischemic injury** (particularly if an infant is undergoing therapeutic hypothermia), intracranial infarct or hemorrhage, or CNS infection;

for seizure screening in infants receiving paralytics; in infants with congenital cerebral malformations; and/or in infants in whom clinical events suspected to be seizures need to be characterized.

Careful neurologic examination of the infant might uncover the cause of the seizure disorder. Examination of the retina might show the presence of chorioretinitis, suggesting a congenital TORCH infection, in which case titers of mother and infant are indicated. **Aicardi syndrome** is associated with coloboma of the iris and retinal lacunae. Inspection of the skin might show hypopigmented lesions characteristic of tuberous sclerosis (seen best on ultraviolet light examination) or the typical crusted vesicular lesions of incontinentia pigmenti; both neurocutaneous syndromes are often associated with generalized myoclonic seizures beginning early in life. An unusual body or urine odor suggests an inborn error of metabolism.

Blood should be obtained for determinations of glucose, calcium, magnesium, electrolytes, and blood urea nitrogen. If hypoglycemia is a possibility, bedside serum glucose testing is indicated so that treatment can be initiated immediately. Hypocalcemia can occur in isolation or in association with hypomagnesemia. A lowered serum calcium level is often associated with birth trauma or a CNS insult in the perinatal period. Additional causes include maternal diabetes, prematurity,

DiGeorge syndrome, and high-phosphate feedings. Hypomagnesemia (<1.5 mg/dL) is often associated with hypocalcemia and occurs particularly in infants of malnourished mothers. In this situation, the seizures are resistant to calcium therapy but respond to intramuscular magnesium 0.2 mL/kg of a 50% solution of MgSO_4 . Serum electrolyte measurement can indicate significant hyponatremia (serum sodium <115 mEq/L) or hypernatremia (serum sodium >160 mEq/L) as a cause of the seizure disorder.

A **lumbar puncture** may be indicated in neonates with seizures, unless the cause is obviously related to a metabolic disorder (such as hypoglycemia or hypocalcemia) or attributable to a structural etiology such as hypoxic-ischemic injury or intracranial hemorrhage. The CSF findings can indicate a bacterial meningitis or aseptic encephalitis. Prompt diagnosis and appropriate therapy improve the outcome for these infants. Bloody CSF indicates a traumatic tap or a subarachnoid or intraventricular bleed. Immediate centrifugation of the specimen can assist in differentiating the two disorders. A clear supernatant suggests a traumatic tap, and a xanthochromic color suggests a subarachnoid bleed. Mildly jaundiced normal infants can have a yellowish discoloration of the CSF that makes inspection of the supernatant less reliable in the newborn period.

Many **inborn errors of metabolism** cause generalized convulsions in the newborn period. Because these conditions are often inherited in an autosomal recessive or X-linked recessive fashion, it is imperative that a careful family history be obtained to determine if there is consanguinity or whether siblings or close relatives developed seizures or died at an early age. Serum ammonia determination is useful for screening for the hypoglycemic hyperammonemia syndrome and for suspected urea cycle abnormalities. In addition to having generalized clonic seizures, these latter infants present during the first few days of life with increasing lethargy progressing to coma, anorexia and vomiting, and a bulging fontanel. If the blood gases show an anion gap and a metabolic acidosis with the hyperammonemia, urine organic acids should be immediately determined to investigate the possibility of an **organic acidemia** such as methylmalonic or propionic acidemia.

Maple syrup urine disease should be suspected when a metabolic acidosis occurs in association with generalized clonic seizures, vomiting, a bulging fontanel, and muscle rigidity during the first week of life. The result of a rapid screening test using 2,4-dinitrophenylhydrazine that identifies keto derivatives in the urine is positive in maple syrup urine disease.

Additional metabolic causes of neonatal seizures include **nonketotic hyperglycinemia**, an intractable condition characterized by markedly elevated plasma and CSF glycine levels, prominent hiccups, persistent generalized seizures, and lethargy rapidly leading to coma; ketotic hyperglycinemia in which seizures are associated with vomiting, fluid and electrolyte disturbances, and a metabolic acidosis; and Leigh disease, suggested by elevated levels of serum and CSF lactate or an increased lactate:pyruvate ratio. **Biotinidase deficiency** should also be considered. A comprehensive description of the diagnosis and management of these metabolic diseases is discussed in Part IX, Metabolic Disorders.

Unintentional **injection of a local anesthetic** into a fetus during labor can produce intense tonic seizures. These infants are often thought to have had a traumatic delivery because they are flaccid at birth, have abnormal brainstem reflexes, and show signs of respiratory depression that sometimes require ventilation. Examination may show a needle puncture of the skin or a perforation or laceration of the scalp. An elevated serum anesthetic level confirms the diagnosis. The treatment consists of supportive measures and promotion of urine output by administering intravenous fluids with appropriate monitoring to prevent fluid overload.

Benign familial neonatal seizures, an autosomal dominant condition, begins on the second to third day of life, with a seizure frequency of 10–20/day. Patients are normal between seizures, which stop in 1–6 months. These are caused by pathogenic variants in the voltage-sensitive potassium channel genes *Kv7.2* and *Kv7.3* (*KCNQ2* and *KCNQ3*). Other variants in *Kv7.2* cause severe neonatal epileptic encephalopathy. **Fifth-day fits** occur on day 5 of life (4–6 days) in

normal-appearing neonates. The seizures are multifocal and are often present for <24 hours. The diagnosis requires exclusion of other causes of seizures and sequencing of the previously mentioned genes. The prognosis is good for the benign form.

Pyridoxine dependency, a rare disorder, must be considered when seizures begin shortly after birth with signs of fetal distress in utero and are resistant to conventional anticonvulsants such as phenobarbital or phenytoin even if there is an initial treatment response. The history may suggest that similar seizures occurred in utero. When pyridoxine-dependent seizures are suspected, 100 mg of pyridoxine should be administered intravenously during the EEG, which should be promptly performed once the diagnosis is considered. The seizures abruptly cease, and the EEG often normalizes in the next few hours or longer. Not all cases of pyridoxine dependency respond dramatically to the initial bolus of intravenous pyridoxine. Therefore a 6-week trial of oral pyridoxine (100–200 mg/day) or, preferably, pyridoxal phosphate (because pyridoxine does not help infants with the related but distinct syndrome of pyridoxal dependency) is recommended for infants in whom a high index of suspicion continues after a negative response to intravenous pyridoxine. Measurement of serum pipercolic acid and α -aminoadipic acid semialdehyde (elevated) and CSF pyridoxal-5-phosphate (decreased) needs to be performed before initiation of the trials without delay. These children require lifelong supplementation of oral pyridoxine (100 mg/day at times with folic acid) or pyridoxal phosphate (up to 50 mg/kg/day given every 6 hours). **Cerebral folate deficiency** should also be ruled out by a medication trial (folic acid 1–3 mg/kg/day) and by CSF levels of 5-methyltetrahydrofolate assay. Gene sequencing can confirm the diagnosis (see Chapter 633.4). The earlier the therapy is initiated in these vitamin-responsive disorders, the more favorable the outcome.

Drug withdrawal seizures can occur in the newborn nursery but can take several weeks to develop because of prolonged excretion of the drug by the neonate. Drugs include barbiturates, benzodiazepines, heroin, buprenorphine, fentanyl, and methadone. The infant may be jittery, irritable, and lethargic and can have myoclonus or frank clonic seizures. The mother might deny the use of drugs; a serum or urine drug screen might identify the responsible agent.

Infants with focal seizures, suspected stroke or intracranial hemorrhage, and severe **cytoarchitectural abnormalities** of the brain (including lissencephaly and schizencephaly) who clinically may appear normal or microcephalic should undergo MRI or CT scan. Indeed, it is appropriate to recommend imaging of all neonates with seizures unexplained by serum glucose, calcium, or electrolyte disorders.

PROGNOSIS

The prognosis of neonatal seizures has improved owing to advancements in obstetric and intensive neonatal care but depends on the etiology and other organ system injury. Prematurity and high seizure burden have been shown to be associated with early death. The correlation between EEG findings and prognosis is clear. An abnormal EEG background is a powerful predictor of a less favorable later outcome. In addition, prolonged electrographic seizures (>10 min/hr), multifocal periodic electrographic discharges, and spread of the electrographic seizures to the contralateral hemisphere are also correlated with a poorer outcome. Patients with seizures secondary to severe hypoxic-ischemic encephalopathy have a 50% chance of typical development, whereas those with seizures caused by primary subarachnoid hemorrhage or hypocalcemia have a much better prognosis.

TREATMENT

A mainstay in the therapy of neonatal seizures is the diagnosis and treatment of the underlying etiology (e.g., HIE, hypoglycemia, hypocalcemia, meningitis, drug withdrawal, trauma) whenever one can be identified. There are conflicting approaches regarding the control of neonatal seizures. Most experts advocate complete control of electroclinical and electrographic seizures. An important consideration before starting anticonvulsants is deciding, based on the severity, duration, and frequency of the seizures, if the patient needs to receive intravenous therapy and loading with an initial bolus or can simply

be started on maintenance doses of a long-acting drug. Patients may require assisted ventilation after receiving intravenous or oral loading doses of AEDs, and thus precautions for observations and for needed interventions are necessary.

Lorazepam and Other Benzodiazepines

Lorazepam is often used in the acute treatment of neonatal seizures; it is distributed to the brain very quickly and exerts its anticonvulsant effect in less than 5 minutes. It is not very lipophilic and does not clear out from the brain very rapidly. Its action can last 6-24 hours. Usually, it does not cause hypotension or respiratory depression. The dose is 0.1 mg/kg when used for acute treatment of seizures, and 0.05 mg/kg (range: 0.02-0.10 mg/kg) every 4-8 hours when used as a scheduled medication. Diazepam has also been used, and midazolam is often started as a continuous infusion for refractory cases of neonatal seizures. Midazolam doses used have been in the range of 0.05-0.15 mg/kg as an initial intravenous bolus, with a continuous infusion of 0.5-1 µg/kg/min intravenously that can then be gradually titrated upward, if tolerated, every 5 minutes or longer, to a maximum of approximately 33 µg/kg/min (2 mg/kg/hr).

Phenobarbital

Consensus guidelines and existing data support the use of phenobarbital as the first-choice treatment of neonatal seizures. The usual loading dose is 20 mg/kg. If this dosage is not effective, then additional doses of 10-20 mg/kg can be given until a cumulative dose of 40 mg/kg is reached. Respiratory support may be needed after phenobarbital loading. Twenty-four hours after starting the loading dose, maintenance dosing can be started at 3-6 mg/kg/day, usually administered in two separate doses. Phenobarbital is metabolized in the liver and is excreted through the kidneys. Thus any abnormality in the function of these organs alters the drug's metabolism and can result in toxicity. In infants with acidosis or critical illness that might alter the serum protein content, free (i.e., not protein bound) levels of the drug should be followed carefully. The use of phenobarbital can be associated with electroclinical dissociation, where electrographic seizures persist despite the resolution of clinical seizures, after the drug is given. Subsequent EEG monitoring is therefore imperative to rule out subclinical seizure activity.

Phenytoin and Fosphenytoin

Consensus guidelines support the use of fosphenytoin as a second line anti-seizure medication in neonatal seizures. The only randomized controlled trial to compare the efficacy of phenobarbital versus phenytoin did not find that one drug was superior to the other for the treatment of neonatal seizures. Because of its reduced solubility, potentially severe local cutaneous reactions, interactions with other drugs, and possible cardiac toxicity, intravenous phenytoin is not widely used, and fosphenytoin is the preferred agent. Phenytoin is given at a loading dose of 20 mg/kg at a rate not to exceed 0.5-1.0 mg/kg/min, so as to prevent cardiac problems; the medication should be used with caution or avoided in patients with significant heart disease. The heart rate should be monitored while the drug is administered. It is not possible to mix phenytoin or fosphenytoin with dextrose solutions. Additionally, phenytoin and fosphenytoin should not be used in conjunction with intravenous lidocaine owing to the concern that both drugs can increase the risk of cardiac arrhythmias and hypotension.

As stated earlier, fosphenytoin, which is a phosphate ester pro-drug, is preferable to phenytoin. It is highly soluble in water and can be administered safely intravenously and intramuscularly, without causing injury to tissues. Fosphenytoin is administered in phenytoin equivalents (PE). The usual loading dose of fosphenytoin is 15-20 PE/kg administered over 30 minutes. Maintenance doses of 4-8 PE/kg/day can be given. As is the case for phenobarbital, free levels of the drug should be monitored in neonates whose serum pH or protein content might not be normal.

Other Medications

Approximately 45% of neonates respond to the first drug used if it is phenobarbital or phenytoin, and an additional 15% respond to the

second agent. **Levetiracetam** (which can be given intravenously with a later convenient conversion to oral solution) is commonly used as a second- or third-line agent. In a randomized controlled trial of levetiracetam (40-60 mg/kg) versus phenobarbital (20-40 mg/kg) for neonatal seizures, 28% of infants responded to levetiracetam as a first-line agent, as compared with 80% of infants who received phenobarbital. The maintenance dosages used are 40-60 mg/kg/day of levetiracetam, dosed 3 times daily. Topiramate, a possible third line agent, can be given at a dose of 5-10 mg/kg/day (sometimes higher). There is growing evidence that lidocaine is an effective second- or third-line agent, and some studies suggest it may be superior to benzodiazepines in treating neonatal seizures. A bolus dose of 2 mg/kg is given, followed by an infusion at a rate of 4-6 mg/kg/hr. Cardiac arrhythmias and hypotension were not reported at this dosing range but are potential side effects at higher doses. Lidocaine should not be used in conjunction with phenytoin or fosphenytoin owing to concern for cardiac side effects. A randomized controlled trial suggested that bumetanide provided added reduction in seizure burden when used as an adjunct agent without an increased risk of adverse events. Studies of the efficacy and safety of lacosamide for neonatal seizures are ongoing. Primidone, carbamazepine, lamotrigine, or valproate use, although reported in some studies, is rarely warranted. Valproate, for example, is more likely to be toxic in children younger than 2 years of age than in older children.

Duration of Therapy

The duration of therapy is related to the risk of epilepsy developing later in infants suffering from neonatal seizures, a risk that ranges from 10% to 30% and depends on the individual neurologic examination and the etiology of the seizures. Existing data and consensus guidelines support the discontinuation of anticonvulsant medications before hospital discharge in neonates with acute symptomatic seizures.

ADDRESSING FAMILY NEEDS

Over half of parents of newborns with seizures experience symptoms of anxiety, one third experience symptoms of depression. Existing data suggest that parents of newborns with seizures experience consistent challenges, including prognostic uncertainty, concern about adapting their family life, and the physical and emotional toll of caring for a critically ill infant. Clinicians can help address these needs by attending to parent psychosocial needs, connecting parents to peer support, and communicating effectively.

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633.8 Status Epilepticus

Mohamad A. Mikati and Dmitry Tchapyjnikov

Status epilepticus (SE) is a medical emergency that should be anticipated in any patient who presents with an acute seizure. The ILAE has refined the definition of SE to reflect the time at which treatment should be initiated (t_1) and time at which continuous seizure activity leads to long-term sequelae (t_2) such as neuronal injury, depending on the type of SE. For generalized tonic-clonic seizures, SE is defined as continuous convulsive activity or recurrent generalized convulsive seizure activity without regaining consciousness ($t_1 = 5$ minutes, $t_2 \geq 30$ minutes). The definition differs for SE consisting of focal seizures with impaired awareness ($t_1 = 10$ minutes, $t_2 = 30$ minutes) and absence SE ($t_1 = 10-15$ minutes, $t_2 =$ unknown). The most common type of SE is **convulsive status epilepticus** (generalized tonic, clonic, or tonic-clonic), but other types do occur, including **nonconvulsive status** (focal with impaired awareness, absence), myoclonic status, *epilepsia partialis continua*, and neonatal SE. The incidence of SE ranges between 10 and 60 per 100,000 population in various studies. SE is most common in children younger than 5 years of age, with an incidence in this age-group of ~100 per 100,000 children.

Approximately 30% of patients presenting with SE are having their first seizure, and approximately 40% of these later develop epilepsy.

Febrile status epilepticus is the most common type of SE in children. Currently, with the recognition of SE as a medical emergency, the mortality rate is 4–5%, most of it secondary to the underlying etiology rather than to the seizures. SE carries an approximately 14% risk of new

Table 633.22	Clinical Features of Febrile Infection–Related Epilepsy Syndrome (FIRES)
Age of onset: 2–17 (median 8) yr	
Medical history: febrile seizures in rare cases, no epilepsy or other chronic disease, normal psychomotor development	
Family history: uninformative (e.g., no allergies and especially no other family member with FIRES)	
Prodromal phase:	
• Different types of febrile infections, often flulike • Frequently followed by an afebrile and asymptomatic interval of 1–2 days resulting in a consistent neurologic syndrome	
Neurologic syndrome:	
• Peracute/explosive onset of multifocal or generalized seizures of different types directly evolving into superrefractory status epilepticus • Without other neurologic features (pure seizure phenotype)	
EEG: global slowing or multifocal discharges with bilateral frontotemporal predominance, or both	
CSF: normal or pleocytosis, normal protein concentration, no oligoclonal bands	
MRI (during the acute phase of status epilepticus):	
• No or nonextensive bitemporal or diffuse abnormalities • Sporadic involvement of the basal ganglia, diffuse cortical edema, and/or hydrocephalus	
Cause: extensive infectiologic (e.g., brain biopsies), metabolic (e.g., muscle biopsy), and genetic investigations (e.g., <i>POLG</i> , <i>SCN1A</i> , <i>PCDH19</i> genes, CNVs, exome sequencing) without causative findings	
Coexisting autoimmunities: some patients with autoantibodies (e.g., TPO or GluR antibodies)	
Treatment: resistance to nearly all drugs and even anesthetics	
Outcome:	
• Almost always chronic epilepsy without silent period • Often global brain atrophy after a few weeks with mild to severe neuropsychologic impairments	

CNVs, Copy number variants; GluR, glutamate receptor; TPO, thyroid peroxidase. From van Baalen A, Vezzani A, Hauser M, et al. Febrile infection-related epilepsy syndrome: clinical review and hypotheses of epileptogenesis. *Neuropediatrics*. 2017;48:5–18, Table 1, p.6.

neurologic deficits, most of them (12.5%) secondary to the underlying pathology.

Nonconvulsive status epilepticus (NCSE) can manifest as a confusional state, dementia, fluctuating mental status, hallucinations, paranoia, aggressiveness, catatonia, and/or psychotic symptoms. It should be considered in all children who present to the hospital in an encephalopathic state or in the intensive care unit when a child’s mental status fails to improve. **Epilepsia partialis continua** has been defined previously and can be caused by tumor, vascular etiologies, mitochondrial disease (MELAS), and Rasmussen encephalitis.

Refractory status epilepticus is SE in which a child’s seizures fail to resolve despite therapy with both a benzodiazepine and a non-benzodiazepine medication. **Superrefractory status epilepticus** is SE that has failed to resolve, or recurs, within 24 hours or more despite therapy that includes a continuous infusion such as midazolam and/or pentobarbital.

New-onset refractory status epilepticus (NORSE) is defined as SE without a clear etiology after initial investigations (typically brain imaging as well as blood and CSF analysis) have ruled out common causes for SE, including stroke, infection, and toxic/metabolic derangements. Children presenting with NORSE may sometimes have a prodromal flulike illness before developing seizures but are otherwise often previously healthy with no history of seizures. A clear etiology is ultimately determined only 50% of the time and includes inflammatory and autoimmune causes (such as anti-NMDA receptor encephalitis), rare infectious disorders, or genetic causes that predispose the child to having prolonged seizures (such as pathogenic variants in *PCDH19*). Children with NORSE almost always develop superrefractory status epilepticus, and the prognosis is often poor with >10% mortality and up to two thirds developing long-term neurologic disability. **Febrile infection-related epilepsy syndrome (FIRES)** is a subtype of NORSE in which the child also has a febrile illness 1–14 days preceding seizure onset (Table 633.22 and Fig. 633.13). A fever does not have to be present at the time of seizure onset as long as a fever was present in the preceding period. FIRES was thought to be a condition mostly affecting children; however, it is recognized that NORSE and FIRES can occur in both adults and children. An international group of pediatric epileptologists, pediatric neurointensivists, rheumatologists, and basic scientists with interest and expertise in FIRES published recommendations regarding the approach to and management of FIRES (Figs. 633.14 and 633.15). FIRES should be considered in all previously healthy patients older than 2 years of age who present with sudden-onset refractory SE within 2 weeks of a prior febrile illness (see Table 633.22). They also recommended early use of the ketogenic diet and the IL-1 receptor

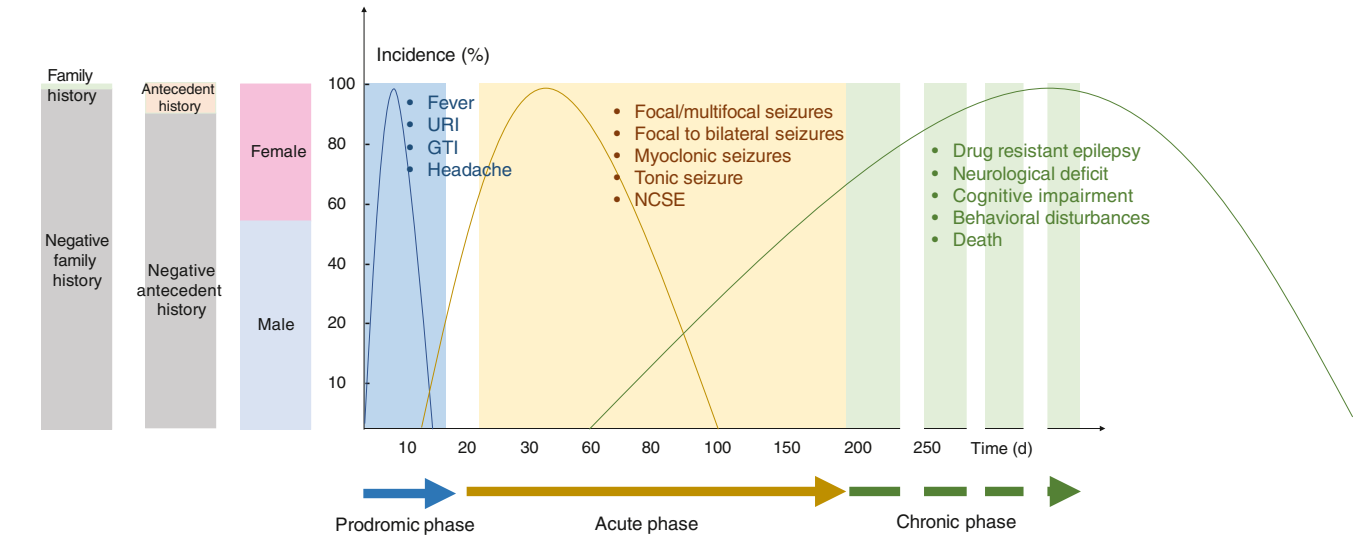


Fig. 633.13 Clinical findings in FIRES and NORSE, including family history, antecedents, and sex predominance. The graph shows the symptoms during the prodromic phase, type of seizures in the acute phase, and clinical findings during the chronic phase. GTI, Gastrointestinal tract infections; NCSE, nonconvulsive status epilepticus; URI, upper respiratory infection. (From Specchio N, Pietrafusa N. New-onset refractory status epilepticus and febrile infection-related epilepsy syndrome. *Dev Med Child Neurol*. 2020;62:897–905, Fig. 1, p. 899.)

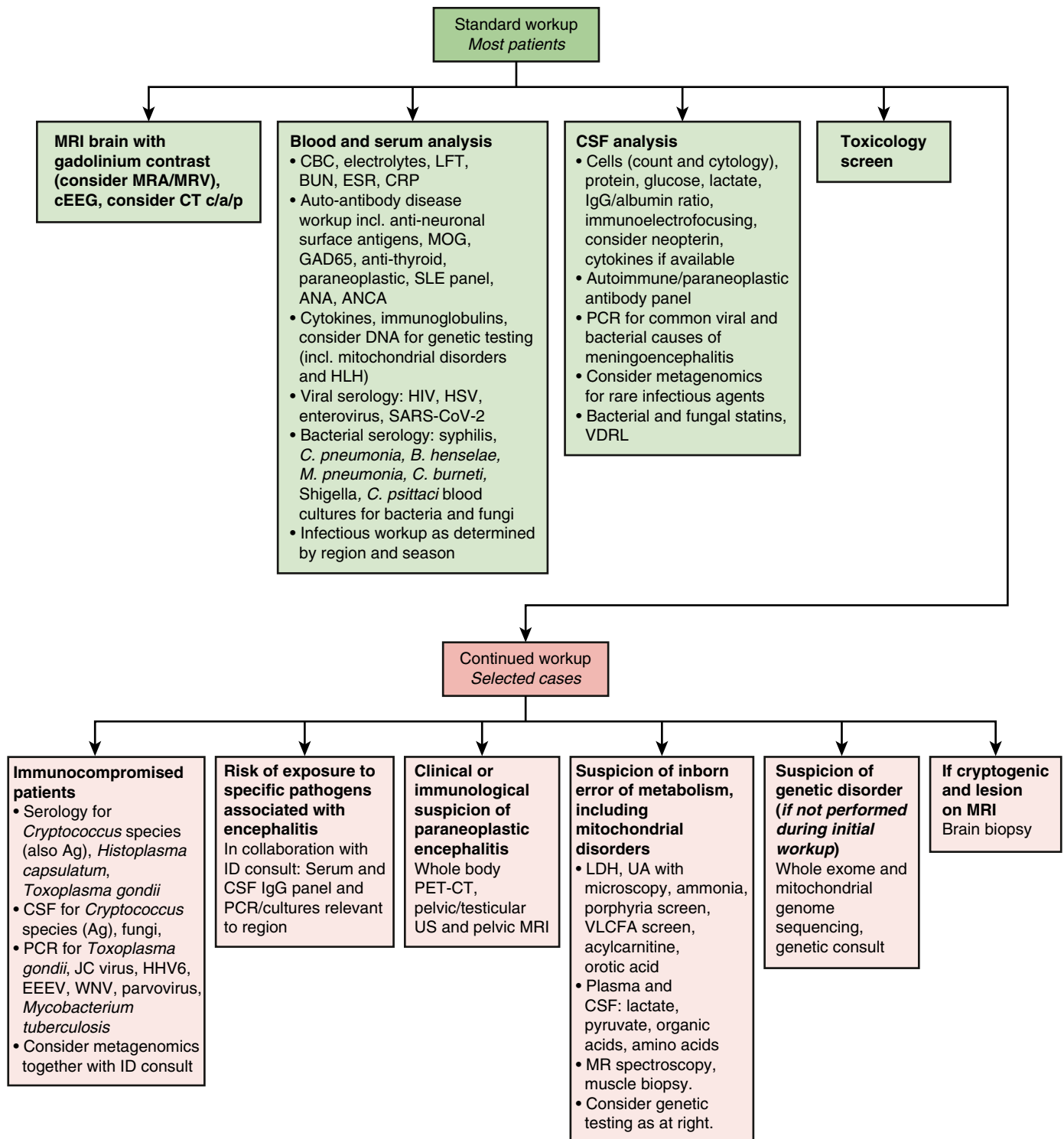
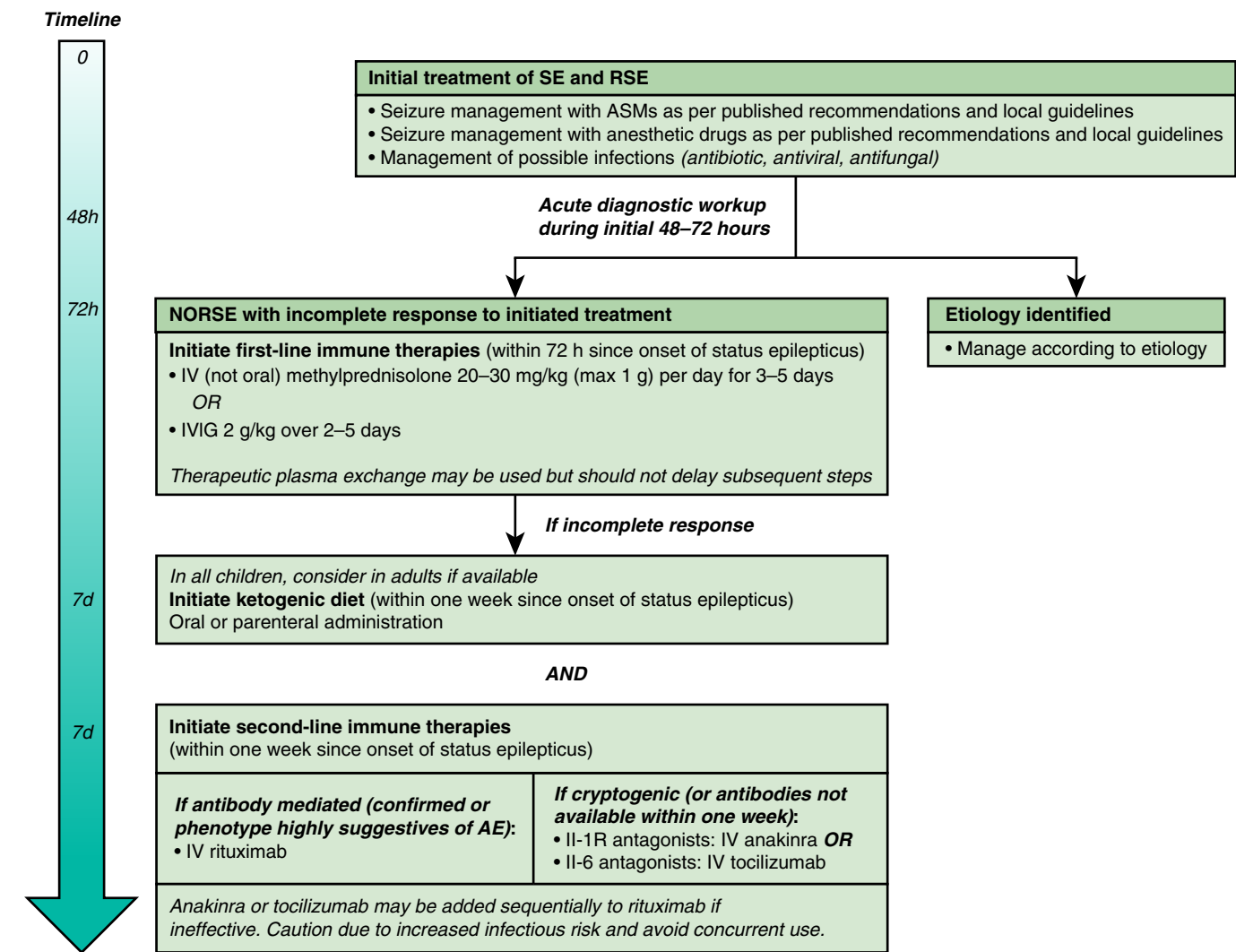


Fig. 633.14 Algorithm for diagnostic workup in NORSE, including FIRES. Ag, Antigen; ANA, anti-nuclear antibodies, ANCA, anti-neutrophil cytoplasmic antibodies; *B. henselae*, *Bartonella henselae*; BUN, blood urea nitrogen; *C. burnetii*, *Coxiella burnetii*; *C. pneumoniae*, *Chlamydia pneumoniae*; *C. psittaci*, *Chlamydia psittaci*; CBC, complete blood count; cEEG, continuous EEG; CRP, C-reactive protein; CSF, cerebrospinal fluid; DNA, deoxyribonucleic acid; EEEV, eastern equine encephalitis virus; EEG, electroencephalography; ESR, erythrocyte sedimentation rate; GAD, glutamic acid decarboxylase; HHV, human herpesvirus; HIV, human immunodeficiency virus; HLH, hemophagocytic lymphohistiocytosis; HSV, herpes simplex virus; ID, infectious disease; IgG, immunoglobulin G; JC, John Cunningham; LDH, lactate dehydrogenase; LFT, liver function test; *M. pneumoniae*, *Mycoplasma pneumoniae*; MOG, myelin oligodendrocyte glycoprotein; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; MRV, magnetic resonance venography; PCR, polymerase chain reaction; PET-CT, positron emission tomography-computed tomography; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; SLE, systemic lupus erythematosus; UA, urine analysis; US, ultrasound; VLCFA, very long-chain fatty acid; VDRL, Venereal Disease Research Laboratory; VZV, varicella-zoster virus; WNV, West Nile virus. (Adapted from NORSE Institute website norseinstitute.org; and from Sculier C, Gaspard N. New onset refractory status epilepticus [NORSE]. *Seizure*. 2019;68:72–78, Fig. 1.)



Try to minimize the exposure to anesthetic drugs, especially barbiturates, and monitor the patient closely for complications of prolonged sedation

Fig. 633.15 Suggested treatment algorithm for NORSE, including FIRES (expert opinion). AE, Autoimmune encephalitis; ASM, antiseizure medication; IV, intravenous; IVIG, intravenous immunoglobulins; RSE, refractory status epilepticus; SE, status epilepticus. (From Wickström R, Taraschenko O, Dilella R, et al. International consensus recommendations for management of new onset refractory status epilepticus [NORSE] including febrile infection-related epilepsy syndrome [FIRES]: summary and clinical tools. *Epilepsia*. 2022;63:2827–2839, Fig. 2, p. 2836.)

antagonist that blocks IL-1 β activity, anakinra, in FIRES patients (see Fig. 633.15).

ETIOLOGY

Etiologies of SE include new-onset epilepsy of any type; drug intoxication (e.g., tricyclic antidepressants) in children and drug and alcohol misuse in adolescents; drug withdrawal or overdose in patients taking AEDs; hypoglycemia; hypocalcemia; hyponatremia; hypomagnesemia; acute head trauma; encephalitis; meningitis; autoimmune encephalitis (anti-NMDA receptor; steroid-responsive encephalopathy associated with autoimmune thyroiditis [SREAT], and anti-voltage-gated potassium channel complex antibody syndromes); ischemic (arterial or venous) stroke; intracranial hemorrhage; folinic acid and pyridoxine- and pyridoxal-phosphate dependency (these usually present in infancy, but childhood onset is also possible); inborn errors of metabolism (see Chapter 633.2) such as nonketotic hyperglycinemia in neonates and MELAS in infants, children, and adolescents; ion channel-related epilepsies (e.g., sodium and potassium channel mutations reviewed in the sections earlier); hypoxic-ischemic injury (e.g., after cardiac arrest); systemic conditions (such as hypertensive encephalopathy, posterior reversible encephalopathy, renal or hepatic encephalopathy); brain

tumors; and any other disorder that can cause epilepsy (such as brain malformations, neurodegenerative disorders, different types of progressive myoclonic epilepsy, and storage diseases).

A rare condition called **hemiconvulsion-hemiplegia-epilepsy syndrome** consists of prolonged febrile SE presumably caused by focal acute encephalitis with resultant atrophy in the involved hemisphere, contralateral hemiplegia, and chronic epilepsy. It should be suspected early on to attempt to control the seizures as early as possible. This and the somewhat similar condition FIRES are likely to have a parainfectious-autoimmune etiology. In addition, hemophagocytic lymphocytic histiocytosis has been reported to cause FIRES. **Rasmussen encephalitis** often causes *epilepsia partialis continua* (see Chapter 633.3) and sometimes convulsive SE. Several types of infections are more likely to cause encephalitis with SE, such as herpes simplex (complex partial and convulsive status), *Bartonella* (particularly nonconvulsive status), Epstein-Barr virus, and mycoplasma (postinfectious encephalomyelitis with any type of status epilepticus). Postinfectious encephalitis and acute disseminated encephalomyelitis are common causes of SE, including refractory SE. HHV-6 can cause a distinct epileptic syndrome with limbic SE in immunosuppressed patients.

MECHANISMS

The mechanisms leading to the establishment of sustained seizure activity seen in SE appear to involve (1) failure of desensitization of AMPA glutamate receptors, thus causing the persistence of increased excitability, and (2) reduction of GABA-mediated inhibition as a result of intracellular internalization of GABA_A receptors. This explains the clinical observation that SE is often less likely to stop in the next specific period the longer the seizure has lasted and why benzodiazepines appear to be decreasingly effective the longer seizure activity lasts. During SE, there is an increased cerebral metabolic rate and a compensatory increase in cerebral blood flow that, after approximately 30 minutes, is not able to keep up with the increases in cerebral metabolic rate. This leads to a transition from adequate to inadequate cerebral oxygen tensions and, together with other factors, contributes to neuronal injury resulting from SE.

THERAPY

SE is a medical emergency that requires initial and continuous attention to securing the airway, breathing, and circulation (with continuous monitoring of vital signs including ECG) and determination and management of the underlying etiology (e.g., hypoglycemia). Laboratory studies,

including glucose, sodium, calcium, magnesium, complete blood count, basic metabolic panel, CT scan, and continuous EEG, are needed for all patients. Blood and spinal fluid cultures, toxic drug screens, and tests for inborn errors of metabolism are often needed. AED levels need to be determined in all patients known already to be taking these drugs. EEG is helpful in ruling out **pseudo-status epilepticus** (psychologic functional neurologic disorder mimicking SE) or other movement disorders (chorea, tics), rigors, clonus with stimulation, and decerebrate/decorticate posturing. The EEG can also be helpful in identifying the type of SE (generalized vs focal), which can guide further testing for the underlying etiology and further therapy. EEG can also help distinguish between postictal depression and later stages of SE in which the clinical manifestations are subtle (e.g., minimal myoclonic jerks) or absent (electroclinical dissociation) and can help in monitoring the therapy, particularly in patients who are paralyzed and intubated. Neuroimaging must be considered after the child has been stabilized, especially if it is indicated by the clinical manifestations, by an asymmetric or focal nature of the EEG abnormalities, or by lack of knowledge of the underlying etiology.

The initial emergent therapy should be started for convulsive seizures lasting longer than 5 minutes and involves the use of a benzodiazepine medication (Fig. 633.16). The American Epilepsy Society SE

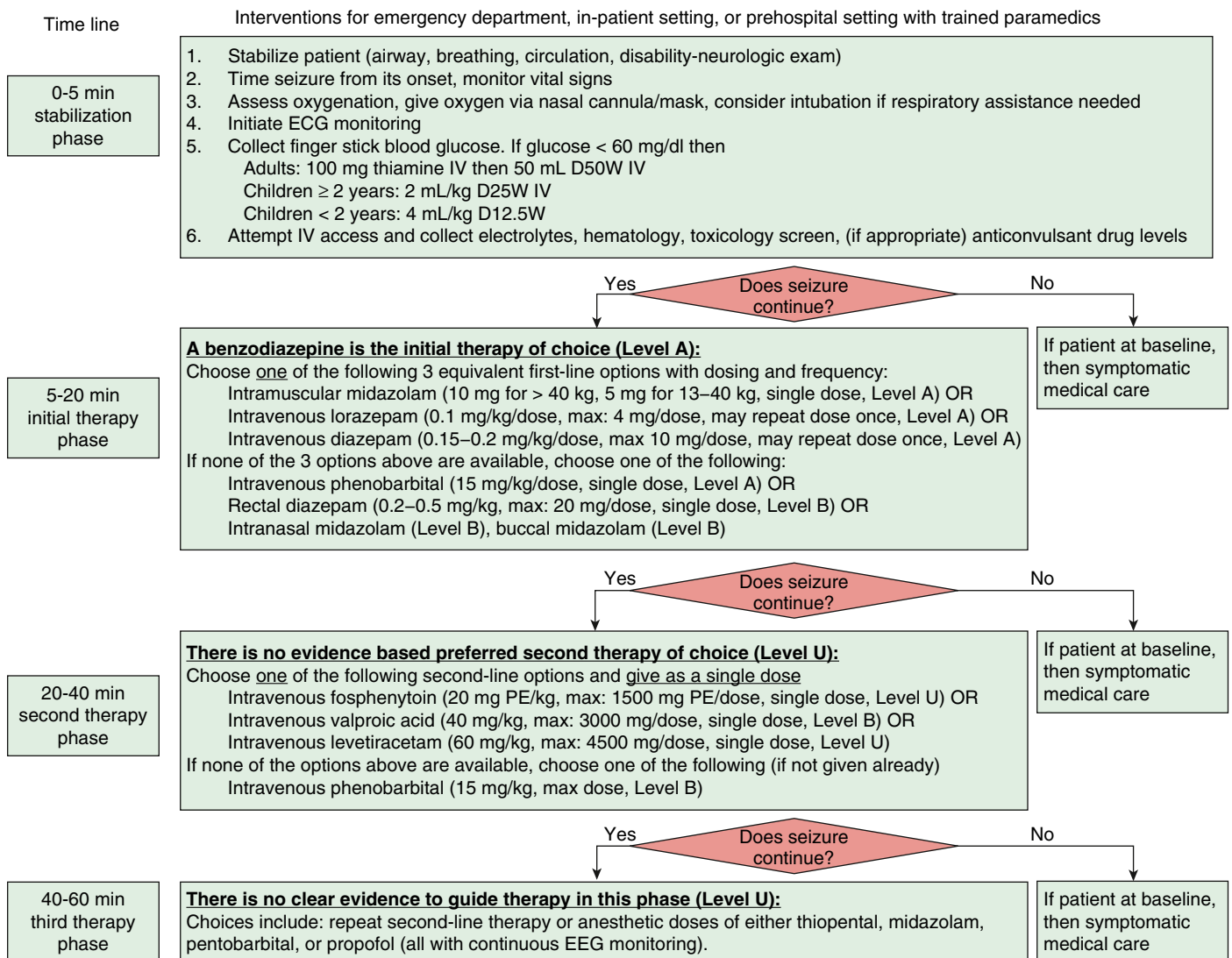


Fig. 633.16 Proposed treatment algorithm for status epilepticus. Disclaimer: This clinical algorithm/guideline is designed to assist clinicians by providing an analytic framework for evaluating and treating patients with status epilepticus. It is not intended to establish a community standard of care, replace a clinician's medical judgment, or establish a protocol for all patients. The clinical conditions contemplated by this algorithm/guideline will not fit or work with all patients. Approaches not covered in this algorithm/guideline may be appropriate. (From Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline committee of the American Epilepsy Society. *Epilepsy Curr.* 2016;16[1]:48–61, Fig. 1.)

Table 633.23 Doses of Commonly Used Antiepileptic Drugs in Status Epilepticus

DRUG*	ROUTE	DOSAGE
Lorazepam	Intravenous Intranasal	0.1 mg/kg up to maximum of 4 mg, may repeat in 5-10 min 0.1 mg/kg up to maximum of 5 mg
Midazolam	Intravenous Intramuscular Intranasal Buccal	0.2 mg/kg up to 10 mg total dose, may repeat in 5-10 min Continuous infusion maintenance: 0.05-2 mg/kg/hr 0.2 mg/kg 0.2 mg/kg 0.5 mg/kg
Diazepam	Intravenous Rectal	0.15 mg/kg up to a maximum total dose of 10 mg; may repeat in 5-10 min 2-5 yr: 0.5 mg/kg 6-11 yr: 0.3 mg/kg ≥12 yr: 0.2 mg/kg
Fosphenytoin	Intravenous	Loading: 20 mg/kg PE, infusion rate maximum 50 mg PE/min Maintenance: 4-8 mg/kg/24 hr divided tid
Ketamine	Intravenous	Loading: 1 mg/kg Maintenance: 0.5-2 mg/kg/hr
Phenobarbital	Intravenous	Loading: 15-20 mg/kg (maximum 1,000 mg) Maintenance: 3-5 mg/kg/24 hr divided bid
Pentobarbital coma	Intravenous	Loading: 5-15 mg/kg Maintenance: 1-5 mg/kg/hr
Propofol	Intravenous	Loading: 1-2 mg/kg Maintenance infusion: 1.2-3.9 mg/kg/hr
Thiopental	Intravenous	Loading: 2-7 mg/kg, infusion rate maximum 50 mg/min Maintenance infusion: 0.5-5 mg/kg/hr
Valproate	Intravenous	Loading: 20-40 mg/kg Maintenance: 30-60 mg/kg/24 hr divided bid
Lacosamide†	Intravenous	Loading: 4-8 mg/kg (maximum 400 mg) Maintenance: 4-12 mg/kg/day divided bid (maximum 400 mg/day)
Levetiracetam	Intravenous	Loading: 30-60 mg/kg (maximum 4,500 mg) Maintenance: 30-60 mg/kg/24 hr divided bid (maximum 3,000 mg/day)
Topiramate	Enterally	Loading: 5-10 mg/kg Maintenance: 5-12 mg/kg/day divided bid (maximum 400 mg/day)

*Reflects current trends in use that may not be FDA approved. For FDA indications, see [Table 633.13](#).

†May cause PR prolongation.

PE, Phenytoin sodium equivalents.

Guidelines recommend using either intravenous lorazepam, intravenous diazepam, or intramuscular midazolam as a first-line agent. The Neurocritical Care Society SE Guidelines recommend intravenous lorazepam as a first-line agent and, if the patient does not have intravenous access, using intramuscular midazolam. [Table 633.23](#) outlines the drugs and dosages typically used in SE. If intravenous access is not available, other options besides intramuscular midazolam include buccal or intranasal midazolam, intranasal lorazepam, or rectal diazepam. With all options, respiratory depression is a potential side effect for which the patient should be monitored and managed as needed. If seizures persist 5 minutes after the initial benzodiazepine dose, a second dose of the drug should be given. Less evidence supports the use of phenytoin/fosphenytoin, phenobarbital, valproate, or levetiracetam as alternative first-line agents. Additionally, in some infants, a trial of pyridoxine may be warranted.

If the emergency therapy with a benzodiazepine is unsuccessful (persistent seizures 5 minutes after the second benzodiazepine dose), fosphenytoin, valproate, or levetiracetam is the recommended option for urgent therapy. Fosphenytoin is given at a loading dose of 20 mg/kg, and a level is usually taken 2 hours later to ensure achievement of a therapeutic concentration. Depending on the level and response, a maintenance dose can be started right away or, more commonly, 6 hours after the initial bolus. Valproate

is given at a loading dose of 40 mg/kg, but its use should be avoided in patients younger than 2 years of age and in those with hepatic dysfunction or mitochondrial disease. Levetiracetam is given at loading doses of 60 mg/kg and is well tolerated. Several prospective studies have compared the efficacy of these second-line agents in treating SE that failed to respond to benzodiazepines. One demonstrated the noninferiority of levetiracetam, fosphenytoin, and valproate. Others demonstrated the noninferiority of levetiracetam to phenytoin. In all of these studies, roughly half the patients have seizure resolution with a second-line agent.

Intravenous phenobarbital is an alternative option if valproate, fosphenytoin, or levetiracetam is not available but is not recommended as a first-line urgent therapy because of its side effects. The phenobarbital dose used in neonates is usually 20 mg/kg as a loading dose, but in infants and children the dose is often lower to avoid respiratory depression, with the dose repeated if there is not an adequate response. If seizures persist after administration of the urgent therapy medication, a decision must be made regarding redosing with another second-line agent or proceeding to a continuous infusion. This decision is case-dependent. The Neurocritical Care Society Guidelines on SE suggest that definitive seizure control should be achieved within 60 minutes of seizure onset, which may prompt opting for the more aggressive therapy (i.e., proceeding to continuous infusion and intubation) in a

patient who has already had convulsive seizures for more than 30-60 minutes.

After the second or third medication is given, and sometimes before that, the patient might need to be intubated. All patients with SE, even the ones who respond, need to be admitted to the intensive care unit for completion of therapy and monitoring. Ideally, emergent and urgent therapies should have been received within less than 30 minutes so as to initiate the subsequent therapy soon, thus reducing the chances of sequelae. For **refractory status epilepticus treatment**, an intravenous bolus followed by continuous infusion of midazolam, propofol, pentobarbital, or thiopental is used. Subsequent boluses and adjustment of the rate of the infusion are usually made, depending on clinical and EEG responses. Because most of these patients need to be intubated and paralyzed, the EEG becomes the method of choice by which to monitor response to therapy. The goal is to stop electrographic seizure activity before reducing the therapy. Usually this implies achievement of complete flattening of the EEG, a pattern called **burst suppression**. Some consider that achieving a burst suppression pattern may be enough, and the periods of flattening in such a case need to be 8-20 seconds to ensure interruption of electrographic seizure activity. Evidence suggests that patients who receive higher doses of intravenous anesthetic therapy earlier and achieve EEG voltage suppression sooner are more likely to have fewer complications and shorter duration for need for mechanical ventilation.

Patients receiving these therapies require careful attention to blood pressure and to systemic complications, and some develop multiorgan failure. It is not unusual for patients put into pentobarbital coma to have to be given multiple vasopressors to maintain their blood pressure during therapy.

The choice among these options to treat refractory and superrefractory SE often depends on the experience of the specific center. Midazolam probably has fewer side effects but is less effective, and barbiturate coma is more effective but carries a higher risk of side effects. Some patients taking propofol develop propofol infusion syndrome with lactic acidosis, hemodynamic instability, and rhabdomyolysis with higher infusion rates ($>67 \mu\text{g/kg/min}$). This limits the use of propofol in the pediatric population. Electrolytes, creatine phosphokinase, and organ function studies need to be monitored if a patient is being given propofol infusion therapy. Often, barbiturate coma and similar therapies are maintained for one or more days before it is possible to gradually taper the therapy, usually over a few days. However, in some cases, including cases of NORSE, such therapies need to be maintained for several weeks or even months. Even though the prognosis in NORSE (and FIRES) cases is often poor and many patients do not survive, meaningful recovery despite a prolonged course is still possible.

Patients with **superrefractory status epilepticus (SRSE)** have persistent seizure activity or seizure recurrence despite 24 hours of general anesthesia with medications such as midazolam, pentobarbital, and/or propofol. In addition to these continuous infusions, polytherapy with other AEDs is usually initiated, although data are lacking regarding the optimal treatment strategy. The most commonly used drugs are fosphenytoin, valproate, phenobarbital, levetiracetam, topiramate, and lacosamide.

Ketamine infusion is a recognized treatment option for SRSE. It is an NMDA receptor antagonist and may be of particular benefit because NMDA receptors are upregulated in SE. The **ketogenic diet** has also been found to be effective in children, although the response may take up to a week after diet initiation and ketosis may be more difficult to achieve if the patient is receiving pentobarbital, which has a carbohydrate-rich carrier fluid. Immunotherapy with intravenous steroids, immunoglobulins, and/or plasma exchange is often used in cases of SRSE of unclear etiology. In specific situations such as **anti-NMDA receptor encephalitis** or **CNS vasculitis**, immunotherapy may be the first-line therapy. Because it can take some time to definitively diagnose autoimmune encephalitis, immunotherapy is often initiated empirically if the clinical history is consistent with the diagnosis. **Inhaled anesthetics** such as isoflurane have been used for SRSE but are associated with a number of adverse reactions and require the presence of an anesthesiologist at bedside,

which limits their use. **Induced hypothermia** has also been used, but further studies are needed to assess its safety and efficacy. In select cases of lesional SRSE, emergent neurosurgery may be an option. Such cases include performing hemispherectomy for **Rasmussen encephalitis** or focal resection if the seizures are secondary to an area of cortical dysplasia. The use of VNS, electroconvulsive therapy, and transcranial magnetic stimulation (for epilepsy partialis continua) has also been reported. Allopregnanolone, a neurosteroid, has shown promise in the treatment of pediatric and adult SRSE, and clinical trials are currently underway to better determine its efficacy.

For **nonconvulsive status epilepticus** and **epilepsia partialis continua**, therapy needs to be tailored according to the clinical manifestations and often consists of trials of sequential oral or sometimes parenteral AEDs without resorting to barbiturate coma or overmedication that could result in respiratory compromise. The approach to focal SE with impaired awareness is sometimes similar to the approach to generalized convulsive SE and sometimes intermediate between the approach for epilepsy partialis and that for convulsive status, depending on severity.

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633.9 Reflex Seizures (Stimulus-Precipitated Seizures)

Mohamad A. Mikati, Dmitry Tchapyjnikov, and Kevin M. Rathke

Many patients with epilepsy can identify precipitating or provoking events that predispose them to having a seizure. Common precipitants in these patients include stress, lack of sleep, fever, or fatigue.

However, there is another group of patients who have seizures in response to a specifically identifiable sensory stimulus or activity and are considered to have reflex seizures. Because no known reflex may be involved, more appropriate terms may be *sensory-precipitated* or *stimulus-sensitive seizures*. Stimuli may be external (light, patterns, music, brushing teeth) or internal (math, reading, thinking, self-induced). Reflex seizures may be generalized, focal, nonconvulsive, absence, or myoclonic. One pattern is photosensitive seizures in which repetitive **photic stimulation** induces photoparoxysmal epileptogenic discharges on EEG and sometimes seizures.

Photosensitive seizures are a well-recognized disorder stimulated by bright or flashing lights (TV, video games, discotheques, concert light shows) or by patterns (TV, video games, lines on the road while traveling). Visual sensitivity may occur in 0.3-3% of the population, whereas photosensitive or pattern-induced seizures may occur in 1 in 4,000 people in the at-risk age-group of 5-25 years. When Japanese children were exposed to a Pokémon cartoon that induced seizures in many, only 24% of those had a history of prior spontaneous seizures. Some children with photosensitive epilepsies stimulate seizures purposefully by rapidly blinking or waving a hand in front of their face (sunflower syndrome). Patients tend to outgrow photosensitive or pattern-induced seizures in their 30s. Photoparoxysmal responses, with an abnormal EEG response to photic stimulation, are more common than photic-induced seizures.

For patients with isolated photosensitive or pattern-induced seizures, avoidance or modification of stimuli is the initial approach. Such activities may include wearing blue or polarized sunglasses, avoiding high-contrast flashing-light video games, avoiding discotheques, watching television in a well-lit room at a distance of >8 feet, and covering one eye when in a provocative situation. A number of genes have been associated with certain patients with reflex epilepsy such as *CHD2* with photosensitive or self-induced seizures caused by fixation-off sensitivity, *LGII* or *SCN1A* with musicogenic seizures, *MECP2* with eating seizures in Rett syndrome, and *SYN1*, *GPR56*, or *SYNGAP1* with hot water or bathing epilepsy. Not all patients with these reflex seizures have these pathogenic variants, nor do all patients with variants in these genes have reflex seizures.

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633.10 Nodding Syndrome

Michael J. Boivin and Itziar Familiar-Lopez

Nodding syndrome (NS) is form of epilepsy that mainly affects children between 3 and 18 years of age who live in distinct regions of Uganda, Liberia, Tanzania, the Democratic Republic of Congo, and southern Sudan. The prevalence is approximately 6.8 per 1,000 children. The first clinical symptom is usually an involuntary nodding of the head in a previously healthy child. These nodding episodes are characterized by at least daily rapid, paroxysmal, forward head-bobbing spells lasting several minutes; some patients are unresponsive, whereas others may respond to commands or continue what they were doing before the episode. Nodding episodes may be triggered during meals while eating hot foods or drinking cold liquids; cold environmental temperatures may also trigger a nodding episode. Head nodding has been determined to be a type of atonic seizure, although other types of seizures, including generalized tonic-clonic or *absence* seizures, may develop. Given the extent of the brain pathogenesis in NS, it is not surprising that it is accompanied by lifelong profound cognitive neurodisability, severe behavior and psychiatric difficulties, growth stunting, delayed puberty, and high mortality rates (Table 633.24 lists case definitions).

Although the diagnosis remains largely based on clinical presentation, the EEG demonstrates a disorganized slow background and interictal generalized 2.5- to 3.0-Hz spike-and-slow waves, with generalized electrodecrement and paraspinal electromyography dropout suggestive of an atonic seizure. NS is characterized by stunted brain growth, which includes significant brain atrophy near the hippocampal and glial matter of the brain and significant cerebellar involvement. Routine CSF analyses are usually negative, but brain MRI shows cerebral and cerebellar atrophy. An MRI study of Tanzanian nodding disease patients revealed that the most frequent abnormality was generalized atrophy, followed by intraparenchymal pathologies such as changes in the hippocampus, gliotic lesions, and subcortical signal abnormalities.

Treatment of seizures is indicated, and choice of AED should be based on the type of seizure presented. Sodium valproate is indicated for atonic seizures and may be a good option to simultaneously treat behavioral difficulties like aggression and impulsive behavior. The suggested starting dose is 10 mg/kg/day in two divided doses and increase the dose by 5 mg/kg/day until seizure control is achieved or

the maximum dose is reached (40 mg/kg/day). Other antiepileptic medications used for NS include phenytoin and phenobarbitone, either individually or combined. Management of behavioral and psychiatric difficulties, nursing care, nutritional, and subsequently, physical and cognitive rehabilitation should also be considered.

Despite extensive investigations, the etiology of NS remains unknown. A systematic review using the Bradford Hill criteria for causality identified *Onchocerca volvulus* as the most likely trigger of NS and other forms of onchocerciasis-associated epilepsy. *O. volvulus* is a nematode carried by the blackfly, the bites of which can cause onchocerciasis, a highly prevalent type of blindness caused by infection. High prevalence of NS overlaps with onchocerciasis-endemic areas with high rates of *O. volvulus* transmission and low or no coverage of community-directed treatment with ivermectin. However, the pathophysiologic mechanism through which *O. volvulus* could directly cause the neurologic damage observed in NS patients remains unknown, as microfilariae are not known to invade the brain.

Studies in Uganda support the hypothesis that NS may be an autoimmune epileptic disorder caused by molecular mimicry with *O. volvulus* antigens. Histologic postmortem examination of brains has revealed polarizable material in the majority of specimens, but it has proved difficult to characterize or identify. There is evidence of autoantibodies to leiomodulin-1 in both the sera and CSF of Ugandan patients with nodding syndrome. Because leiomodulin-1 antibodies cross react with *O. volvulus* proteins, nodding syndrome may be an autoimmune epilepsy initiated by the infection caused by this parasite. Therefore it may be preventable by treatment with antiparasitic strategies, such as the drug ivermectin. It may also perhaps be treatable in its early stages with immunomodulatory therapies.

Onchocerciasis tends to have the highest prevalence in rural east and central African areas with poorly developed healthcare and social service infrastructures. Because of this, families with children affected by nodding disease, often existing on the margins of their resources in impoverished areas, have little in the way of caregiving resources needed to cope with the profound disability that results from this disease. This further diminishes the prognosis for these children because of further risk to their health from accidental injury (e.g., burns from cooking fires), malnutrition because of difficulty in feeding, and/or neglect.

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Table 633.24 Consensus Case Definition and Modified Consensus Case Definition for Nodding Syndrome, Uganda, 2012–2013*

TYPE OF CASE	CONSENSUS CASE DEFINITION	MODIFIED CONSENSUS CASE DEFINITION
Suspected case	Reported head nodding (repetitive involuntary drops of the head toward the chest on two or more occasions) in a previously normal person	Reported head nodding (repetitive involuntary drops of the head toward the chest on two or more occasions) in a previously normal person
Probable case	Suspected case of head nodding, with both major criteria: Age of onset of nodding ranging from 3 to 18 yr Frequency of nodding 5–20 per min Plus at least one of the following minor criteria: Other neurologic abnormalities (cognitive decline, school dropout because of cognitive or behavioral problems, other seizures or neurologic abnormalities) Clustering in space or time with similar cases Triggering by food or cold weather Stunting or wasting Delayed physical development/absence of development of secondary sexual characteristics Psychiatric symptoms	Suspected case of head nodding, with one major criterion: Age of onset of nodding ranging from 3 to 18 yr Plus at least one of the following minor criteria: Other neurologic abnormalities (cognitive decline, school dropout because of cognitive or behavioral problems, other seizures or neurologic abnormalities) Clustering in space or time with similar cases Triggering by food or cold weather Stunting or wasting Psychiatric symptoms
Confirmed case	Probable case, with documented nodding episode Observed and recorded by a trained healthcare worker, or Videotaped nodding episode, or Video/EEG/EMG documenting head nodding as atonic seizures	Probable case, with documented nodding episode Observed and recorded by a trained healthcare worker, or Videotaped nodding episode, or Video/EEG/EMG documenting head nodding as atonic seizures

*The consensus case definition was drafted at the first International Scientific Meeting on Nodding Syndrome, held July 30 to August 1, 2012, in Kampala, Uganda. Meeting report available at http://www.who.int/neglected_diseases/diseases/Nodding_syndrome_Kampala_Report_2012.pdf. The modified consensus case definition was developed during the March 2013 single-stage cluster survey conducted by the Centers for Disease Control and Prevention (CDC) and the Ugandan Ministry of Health to assess the prevalence of nodding syndrome in Uganda.

EEG, Electroencephalographic; EMG, electromyographic.

From Iyengar PJ, Wamala J, Ratto J, et al. Prevalence of nodding syndrome—Uganda, 2012–2013. *MMWR Morb Mortal Wkly Rep*. 2014;63:603–606, Table 1.

Chapter 634

Conditions That Mimic Seizures

Mohamad A. Mikati and Makram M. Obeid

The misdiagnosis of epilepsy is estimated to be as high as 5–40%. Often all that is needed to differentiate nonepileptic paroxysmal disorders from epilepsy is a careful and detailed history in addition to a thorough clinical examination, but sometimes an electroencephalogram (EEG) or more advanced testing may be necessary. The ready availability of video recording on mobile phones can provide invaluable information. Nonepileptic paroxysmal disorders can be classified according to the age at presentation and the clinical manifestations: (1) syncope and other generalized paroxysms, (2) movement disorders and other paroxysmal movements and postures, (3) oculomotor and visual abnormalities and visual hallucinations, and (4) sleep-related disorders (Table 634.1 and Fig. 634.1).

SYNCOPE AND OTHER GENERALIZED PAROXYSMS

Apnea

Apneic episodes (cessation of breathing >20 seconds) in neonates and apnea caused by brainstem compression are usually associated with

bradycardia. In contrast, apnea associated with seizures is usually accompanied by tachycardia. Exceptions are seen because bradycardia can occur during some epileptic seizures, and severe apnea of any cause can be followed by anoxic seizures. The term **brief resolved unexplained event (BRUE)** is defined as an event in an infant reported as a sudden, brief, self-resolving episode consisting of one or more of the following: (1) cyanosis or pallor; (2) absent, decreased, or irregular breathing; (3) a marked change in tone (hyper- or hypotonia); and (4) an altered level of responsiveness (see Chapter 424). A BRUE, which usually lasts less than 1 minute, is diagnosed only when no explanation is evident after an appropriate history and physical examination have been conducted. **Apnea** can either be obstructive or central, most commonly in premature neonates. Central apnea also occurs in the context of certain neurogenetic syndromes, the prototype of which is congenital central hypoventilation syndrome secondary to pathogenic variants in *PHOX2B*. **Ondine's curse** (idiopathic congenital central alveolar hypoventilation syndrome) consists of an inadequate respiratory drive in sleep with periods of prolonged apnea requiring tracheostomy and mechanical ventilation (see Chapter 468.2). Apnea can also be secondary to near cerebral herniation and intermittent brainstem compression in the context of increased intracranial pressure or Chiari malformations.

Breath-Holding Spells

The term *breath-holding spells* is actually a misnomer, because they are not necessarily self-induced but result from the immaturity of the autonomic system and occur in two different forms. The first type is the **pallid breath-holding spell**, which is caused by reflex vagal-cardiac bradycardia and asystole. The second type is the **cyanotic, or blue, breath-holding spell**, which does not occur during inspiration but results from prolonged expiratory

Table 634.1 Conditions that Mimic Seizures According to Age of Presentation

AGE	SYNCOPE AND OTHER GENERALIZED PAROXYSMS	MOVEMENT DISORDERS AND OTHER ABNORMAL MOVEMENTS	OCULOMOTOR AND VISUAL ABNORMALITIES	SLEEP DISORDERS
Neonate	Apnea Paroxysmal extreme pain disorder	Jitteriness, tremor, increased startle reflex, hiccups Hyperekplexia, paroxysmal dystonic choreoathetosis	Paroxysmal tonic upgaze Alternating hemiplegia of childhood, staring, daydreaming, and time-out “unresponsiveness”	Benign neonatal sleep myoclonus Sleep transition disorders, REM
Infants	Reflex anoxic seizures Breath-holding spells Benign paroxysmal vertigo Paroxysmal extreme pain disorder	Jitteriness Sandifer syndrome Paroxysmal dystonic choreoathetosis Benign myoclonus of early infancy Pathologic startle Shuddering attacks, infantile head atonic attacks Benign paroxysmal torticollis Psychologic disorders Alternating hemiplegia of childhood Jactatio capitis (head banging) Drug reactions	Paroxysmal tonic upgaze Oculomotor apraxia Spasmus nutans Opsoclonus-myoclonus syndrome, staring, daydreaming, and time-out “unresponsiveness”	Non-REM partial arousal disorders REM sleep disorders Narcolepsy Sleep transition disorders (somnambulism, somniloquy)
Children and adolescents	Benign paroxysmal vertigo Compulsive Valsalva-like maneuver Familial hemiplegic migraine Syncope (long QT, vasovagal, orthostatic, migraine-induced) Psychogenic seizures Transient global amnesia Hyperventilation spells, factitious disorder	Tics Tremor Pathologic startle Paroxysmal dyskinesias Alternating hemiplegia of childhood Benign paroxysmal torticollis Episodic ataxia Psychologic disorders, including factitious disorder imposed on another, malingering Masturbation Psychogenic seizures Cataplexy Jactatio capitis (head banging) Episodic rage, drug reactions, factitious disorder	Staring, daydreaming, and time-out “unresponsiveness” Drug reactions, hallucinations, visual snow Conversion reactions, factitious disorder	Non-REM partial arousal disorders REM sleep disorders Narcolepsy Sleep transition disorders (somnambulism, somniloquy) Sleep myoclonus Restless legs syndrome, conversion reactions, factitious disorder

REM, Rapid eye movement.

From Obeid M, Mikati MA. Expanding spectrum of paroxysmal events in children: potential mimickers of epilepsy. *Pediatr Neurol.* 2007;37(5):309–316.

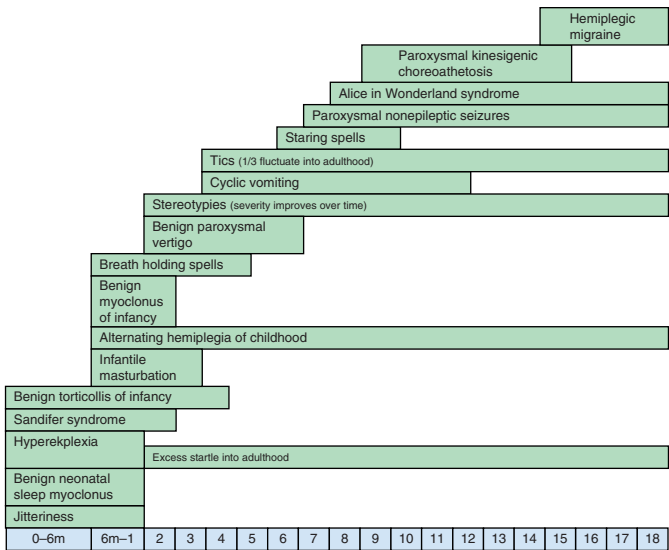


Fig. 634.1 Age ranges (months and years) of seizure mimics, typical onset, and resolution. (From Stainman RS, Kossoff EH. *Seizure mimics in children: an age-based approach*. *Curr Probl Pediatr Adolesc Health Care*. 2020;50:100894, Fig. 1.)

apnea and intrapulmonary shunting (see [Chapter 43](#)). Episodes usually start with a cry (often, in the case of the pallid type, a silent cry with marked pallor) and progress to apnea and cyanosis. Spells usually begin between 6 and 18 months of age. Syncope, tonic posturing, and even reflex anoxic seizures may follow the more severe episodes, particularly in breath-holding spells of the pallid type. Injury (such as even a minor bump on the head), pain, and frustration, particularly with surprise, are common triggers. There usually is a family history of vasovagal syncope or breath-holding spells. Education and reassurance of the parents are usually all that is needed because these episodes are, as a rule, self-limited and are outgrown within a few years. However, screening for anemia and for electrical cardiac disturbances with an electrocardiogram is recommended because the spells are worsened by iron-deficiency anemia and can rarely be the presenting sign of long QT (LQT) syndromes. Anticholinergic drugs, for the selected cases of pallid breath-holding spells (e.g., atropine sulfate 0.03 mg/kg/day in two to three divided doses with a maximum daily dose of 1.2 mg) or antiseizure drug therapy for coexisting anoxic seizures that are recurrent, prolonged, and not responding to other measures may rarely be needed. If antiseizure medications are needed, it is ill-advised to use medications that may increase irritability, such as levetiracetam. It is important also to educate parents on how to handle more severe spells with first aid measures or even basic cardiopulmonary resuscitation when needed. Extremely severe episodes resulting in marked bradycardia and asystole have been reported to respond to a cardiac pacemaker. All parents should be taught not to provide secondary gain when the episodes occur, because this can reinforce them. Also, preparation for unpleasant experiences (such as receiving a shot) rather than surprising the child with them can help limit the number of spells.

Compulsive Valsalva-Like Maneuver

In children with intellectual disability, including Rett syndrome, syncopal convulsions may be self-induced by maneuvers such as the Valsalva maneuver. In this case, true breath holding occurs, and it usually lasts for approximately 10 seconds during inspiration. Some clinicians advocate the use of naloxone in such cases. In the authors' experience, a compulsive Valsalva-like maneuver can rarely be a feature of a panic attack or conversion disorder. When clinically stereotyped, a prolonged EEG and a careful workup by a pediatric epileptologist are needed in order to rule out epileptic seizures.

Neurally Mediated Syncope

Syncope can present with drop attacks and can also lead to generalized convulsions, termed *anoxic seizures*. These convulsions, triggered by a sudden reduction of oxygen to the brain, are clinically similar to, and can

be misdiagnosed as, generalized epileptic seizures. **Vasovagal (neurocardiogenic) syncope** is usually triggered by dehydration, heat, standing for a long time without movement, hot showers, the sight of blood, pain, swallowing, vomiting, sudden exposure to cold as with cold water immersion, and a sudden episode of stress (see [Chapter 84](#)). The history is usually the clue to distinguishing syncope from epileptic seizures: there is initially pallor and sweating followed by blurring of vision, dizziness, and nausea and then a gradual collapse with loss of consciousness. Of importance is the fact that such prodromal features have an insidious onset and build up gradually, often arising from a state of malaise when they precede syncope. However, in epilepsy, when auras with similar features precede an epileptic seizure, such features are usually sudden, short in duration, and followed by other manifestations of complex partial seizures such as stereotyped automatisms. Abdominal pain, a common aura in temporal lobe epilepsy, occurs in vasovagal syncope and can be a trigger or a consequence of that process (intestinal vagal hyperactivity). Urinary incontinence and a brief period of convulsive jerks are not uncommon in vasovagal syncope. These occur with a frequency of 10% and 50%, respectively. Postictal confusion only rarely occurs, and the rule is the occurrence of only brief postictal tiredness with a subsequent remarkable ability to resume planned activities. Most children with vasovagal syncope have an affected first-degree relative; reports demonstrate autosomal dominant inheritance at least in some families. The EEG is normal, and the tilt test has been used for diagnostic purposes in selected cases. In most cases with a typical history, this test is not needed. In addition, **exercise-induced anaphylaxis** has rarely been reported. In **stretch syncope**, which occurs mostly in adolescents while stretching the neck and the trunk backward and the arms outward or during flexion of the neck, the presumed mechanism is mechanical disruption of brain perfusion caused by compression of the vertebral arteries. In some other cases, this may be associated with an abnormally prolonged stylohyoid process compressing the carotids. If the latter condition is suspected, neuroimaging with cranial CT or MRI is required for proper diagnosis of the stylohyoid anomaly. **Migraine** can also induce vasovagal syncope. Other causes of syncope include primary autonomic failure, which is rare in children, and familial dysautonomia is the only relatively common form. **Familial dysautonomia**, a disease found in Ashkenazi Jews, is characterized by absence of overflow emotional tears, depressed patellar reflexes, and lack of a flare reaction after intradermal histamine. **Dopamine β-hydroxylase deficiency** is a rare cause of primary autonomic failure and is characterized by a complicated perinatal course (hypotension, hypotonia, hypothermia), ptosis, highly arched palate, hyperflexible joints, nocturia, and later impaired ejaculation.

Postural Tachycardia Syndrome

See [Chapter 84.1](#).

Cardiac Syncope

See [Chapters 84 and 485](#).

LQT syndromes can cause life-threatening pallid syncope. Accompanying this are ventricular arrhythmias and, usually, torsades de pointes or even ventricular fibrillation. When accompanied by congenital deafness, it is part of the autosomal recessive Jervell and **Lange-Nielsen syndrome** (type 1, LQT 1, associated with the *KvLQT1* potassium channel pathogenic variant). **Romano-Ward syndrome** is an autosomal dominant syndrome with incomplete penetrance (LQT 2 associated with an *HERG* potassium channel variant). LQT 3 is associated with an *SCN5A* sodium channel variant, LQT 4 with an ankyrin protein mutation, LQT 5 (milder form) with *KCNE1* variants, LQT 6 with *KCNE2* potassium channel gene variants, LQT 9 with caveolin sodium channel-related protein variants, and LQT 10 with *SCN4B* sodium channel variants. LQT 7 and LQT 8 have associated clinical and neurologic manifestations. LQT 7 (**Andersen-Tawil**) syndrome is associated with periodic paralysis, skeletal developmental abnormalities, clinodactyly, low-set ears, and micrognathia (variants in *KCNJ2*). LQT 8, or **Timothy syndrome** (variants in the calcium channel gene *CACNA1C*), manifests with congenital heart disease, autism, syndactyly, and immune deficiency. All family members of an affected child should be investigated. Affected individuals

need insertion of cardiac defibrillators, and their families should be taught cardiopulmonary resuscitation. Children with a new-onset seizure disorder of unclear etiology should get an electrocardiogram to rule out LQT syndrome masquerading as a seizure disorder. Cardiac syncope is usually sudden, without the gradual onset and symptoms that accompany vagal syncope. Aortic stenosis can cause sudden syncope at the height of exercise (usually hypertrophic) or directly at the end (usually valvular) and, if suspected, warrants an echocardiogram.

Migraine and Migraine Variants

Familial hemiplegic migraine (FHM) is a rare type of autosomal dominant migraine with the prominent feature of transient motor weakness. Attacks begin as early as 5-7 years of age. In a genetically susceptible child, attacks may be precipitated by head trauma, exertion, or emotional stress. The three genes commonly identified are *CACNA1A* in FHM1 (neuronal calcium channel subunit), *ATP1A2* in FHM2 (sodium potassium adenosine triphosphatase subunit), and *SCN1A* in FHM3 (neuronal sodium channel subunit). Pathogenic variants of other genes such as *PRRT2* may also cause FHM. However, at least a quarter of the affected families and most of the sporadic patients do not carry a pathogenic variant in these genes. Headaches occur in all attacks in most patients. The presence of negative phenomena (e.g., numbness, visual scotomas) in addition to positive phenomena (pins and needles, flickering lights) and the progressive and successive occurrence of visual, sensory, motor, aphasic, and basilar signs and symptoms, in that order, help differentiate these attacks from epileptic seizures. Persistent cerebellar deficits (e.g., nystagmus, ataxia) may be present. Verapamil, acetazolamide, and lamotrigine have been successfully used to prevent attacks, and verapamil and ketamine have been used for the acute episode; ergot derivatives, nimodipine, Midrin (isometheptene mucate, dichloralphenazone, and paracetamol), and probably triptans and propranolol are to be avoided because of concerns of exacerbating the attacks. Interestingly, the co-occurrence of epileptic seizures has been reported in a minority of patients with hemiplegic migraine. It is important also to note that recurrent attacks akin to hemiplegic migraine can be symptomatic of Sturge-Weber syndrome or various metabolic diseases (e.g., mitochondrial encephalopathy with lactic acidosis and strokelike episodes, as well as alternating hemiplegia of childhood).

Benign paroxysmal vertigo of childhood is a common migraine equivalent that consists of brief seconds-to-minutes episodes of vertigo that are often accompanied by postural imbalance and nystagmus. It is important to note that vertigo does not always refer to a spinning motion; it can also refer to a backward or forward motion (vertigo titubans) where children sometimes report that objects seem to be moving toward them. The child appears frightened during the episode. Diaphoresis, nausea, vomiting, and, rarely, tinnitus may be present. Episodes usually remit by 6 years of age. MRIs and EEGs are normal, but caloric testing, if done, can show abnormal vestibular function. Diphenhydramine 5 mg/kg/day (maximum of 300 mg/day) may be used for a cluster of attacks. Preventive therapy with cyproheptadine may rarely be needed for frequent attacks.

Cyclic vomiting syndrome (CVS) is another related periodic migraine variant that can respond to antimigraine or antiepileptic drugs. Recurrent vomiting can also be caused by neuromyelitis optica, juvenile Alexander disease, brainstem pathology, inborn errors of metabolism with intermittent presentations, and seizures, usually from the nondominant temporal lobe. With the latter, there is, as a rule, impaired consciousness. Prophylaxis for CVS has included medications such as amitriptyline, propranolol, cyproheptadine, sumatriptan, erythromycin, coenzyme Q, fluoxetine, or antiepileptics. Acute therapy usually consists of 10% dextrose intravenously with ondansetron and an antihistamine or benzodiazepine.

Alice in Wonderland syndrome (see “Visual Hallucinations,” later), confusional migraine, and abdominal migraine are also migraine variants. One should note that many patients with migraine or migraine variants (including FHM) have coexisting epilepsy, and children with

epilepsy have a higher incidence of migraine headaches compared with the general population, so providers should be aware that such patients may have symptoms attributable to either.

Nonepileptic Seizures (Formerly, Functional Disorders)

Nonepileptic seizures are a form of functional neurologic disorder that can be diagnosed clinically based on the characteristics of the spells (Tables 634.2 and 634.3). A video of the event is usually possible because most of the events are witnessed and tend to be more prolonged than epileptic seizures. If needed, a diagnosis can be confirmed by video-EEG with capture of an episode to eliminate any residual doubts about its nature because these functional paroxysms can often occur in patients who also have epileptic seizures. A social history is very important because psychogenic nonepileptic seizures (PNESs) are often a reaction to physical or sexual abuse or to the inability to cope with psychosocial tasks. They are best managed acutely by reassurance about their relatively benign nature and by a supportive attitude while at the same time avoiding positive reinforcement of the episodes; an early accurate diagnosis and timely management result in more favorable outcomes. The use of terms such as *nonepileptic stress seizures* facilitates communication with families, given the often-perceived negative connotation of the term *psychogenic*. Psychiatric evaluation and follow-up are needed to uncover an underlying psychopathology and to establish continued support because psychogenic seizures can persist over long periods. Malingering and factitious disorder imposed on another (formerly called *Munchausen syndrome by proxy*) are often difficult to diagnose, but an approach similar to that for psychogenic seizures, including video-EEG monitoring, is often helpful. Sad cases of loss of consciousness related to suffocation by caregivers in infants and toddlers have also been reported.

Paroxysmal Extreme Pain Disorder

Paroxysmal extreme pain disorder, previously called *familial rectal pain syndrome*, is caused by an autosomal dominant gain-of-function variant in a sodium channel (Nav1.7) encoded by the *SCN9A* gene. Paroxysmal extreme pain disorder usually starts in infancy and persists throughout life. Autonomic manifestations predominate initially, with skin flushing in all cases and harlequin color change and tonic attacks in most. Dramatic syncope with bradycardia and sometimes asystole occurs. Later, the disorder is characterized by attacks of excruciating, deep burning pain often in the rectal, ocular, or jaw areas, but also diffusely in some. Attacks are triggered by defecation, cold, wind, eating, and emotion. Carbamazepine is used, but the response is often incomplete. Neurologically impaired children can often have irritability without clear etiology even after investigations, and this has been reported to respond to gabapentin (for neurologic irritability).

Autonomic Storms

Autonomic storms are also referred to as diencephalic seizures, paroxysmal sympathetic hyperactivity, sympathetic storms, paroxysmal autonomic instability with dystonia, dysautonomia, and central autonomic dysfunction. Spells of hyperhidrosis and changes in blood pressure, temperature, and autonomic instability occur in patients with severe diffuse brain injury or localized hypothalamic injury and have been termed autonomic storms. The term diencephalic seizures is discouraged because the episodes are not truly seizures. Therapy is difficult and has included, with mixed results, clonidine, propranolol, baclofen (oral or intrathecal), benzodiazepines (particularly clonazepam), bromocriptine, chlorpromazine, hydralazine, methadone, cyproheptadine, morphine, and sympathectomy.

Serotonin syndrome caused by antidepressants, stimulants, opioids, certain herbs such as St. John's wort, and some other medications can produce similar symptoms, and if not recognized, can at times be fatal, as can the similar **neuroleptic malignant syndrome** caused by antipsychotic medications.

Table 634.2 Comparison of Generalized Seizures and Some Disorders That Can Mimic Them

CONDITION	PRECIPITANTS (MAY NOT APPLY TO ALL PATIENTS)	PRODROME	ICTAL SYMPTOMS	POSTICTAL SYMPTOMS
Generalized seizures	Sleep deprivation, television, video games, visual patterns, and photic stimulation	Rarely irritability or nonspecific behavioral changes	Usually 2-3 min Consciousness might be preserved if atonic or, in some, tonic seizures Synchronous bilateral movements Tongue biting	Delayed recovery with postictal depression, incontinence (may be ictal also)
Syncope: vasovagal	Fatigue, emotional stress, dehydration, vomiting, choking, swallowing	Blurring of vision, tinnitus, dizziness, nausea, sweating	Loss of consciousness for seconds, pallor, and rarely reflex anoxic seizures	Rapid recovery with no postictal depression
Syncope with reflex anoxic seizures	Minor bump to head, upsetting surprises	Crying in breath-holding spells		
Syncope: trigeminal vagal	Cold water on face			
Syncope: orthostatic	Standing up, bathing, awakening			
Hyperekplexia	Auditory and tactile stimuli	None	Tonic stiffening, cyanosis if severe, nonfatigable nose-tap-induced startles	Depending on severity, may have postictal depression
Cardiac	Exercise	None	Loss of consciousness, often only for a few seconds, pallor	Rarely
Nonepileptic seizures (formerly, functional disorders)	Suggestion, stress	None; some have headache, nausea, palpitations, poor concentration, panic-like attack	Eyes closed, with active opposition to attempts to open them Asynchronous (nonrhythmic) flailing or tremulous limb movements that vary between attacks Motor activity stops and starts during a spell Weeping and crying No injury May respond to suggestion during “loss of consciousness” Usually longer than 5 min, decrease in intensity when provider places hand on patient’s shoulder	No postictal depression

Adapted from Obeid M, Mikati MA. Expanding spectrum of paroxysmal events in children: potential mimickers of epilepsy. *Pediatr Neurol.* 2007;37(5):309–316.

Table 634.3 Positive Diagnostic Features and Biomarkers of Nonepileptic Seizures and Functional Movement Disorder

ESTABLISHED DIAGNOSTIC FEATURES		NEW DIAGNOSTIC FEATURES*
NONEPILEPTIC SEIZURES		
Seizures	Eyes closed; prolonged attacks; hyperventilation; awareness during generalized shaking; ictal or postictal weeping	Suggestive seizure induction; qualitative conversation analysis; use of smartphone video; wrist-worn accelerometers; postictal plasma proteins
FUNCTIONAL MOVEMENT DISORDER		
Tremor	Tremor entrainment or cessation to externally cued rhythm; variability of frequency and amplitude of tremors	“Whack-a-mole” sign: holding down a tremulous body part induces tremor in another body part; coherence between antagonist muscles measured with standard coherence or wavelets
Dystonia	Fixed inverted or plantar flexed ankle; fixed clenched fist	Dystonia of the face: downward lip pulling, orbicularis oculi spasm, platysma spasm; sustained facial movement to evoke a spasm; functional hemifacial spasm lacks the “other Babinski sign” (i.e., raising of eyebrow on affected side)
Gait and balance	Variability of gait performance; gait performance shows excellent balance; “walking-on-ice” gait, dragging monoplegic gait, or knee-buckling gait	Classification of gait types into seven types: ataxic, spastic, weak gait, antalgic, parkinsonian, hemiparetic, and dystonic; “huffing and puffing” sign: huffing, grunting, grimacing, and breath holding after small amounts of exercise; posturographic improvement with distraction (guessing numbers written on back or cognitive task)
Jerks or myoclonus	Truncal jerking, especially with facial movement†; positive Bereitschaftspotential before movement using back averaging	Increased startle; event-related desynchronization using back averaging
Limb weakness and generic motor dysfunction	Hoover sign; hip abductor sign; drift without pronation	Absence of amplitude suppression of median nerve somatosensory evoked potential; decreased prepulse inhibition of the blink reflex by stimulation of the index finger; absence of contingent negative variation in reaction time task

*Described in the past 10 years.

†The diagnosis of functional jerks can be difficult, but 104 (58%) of 179 patients with truncal myoclonus had functional neurologic disorder in one series.

From Hallett M, Aybek S, Dworetzky BA, et al. Functional neurological disorder: new subtypes and shared mechanisms. *Lancet Neurol.* 2022;21:537–550, p. 539.

MOVEMENT DISORDERS AND OTHER PAROXYSMAL MOVEMENTS AND POSTURES

Neonatal Jitteriness and Clonus

Jitteriness consists of recurrent tremors. These movements manifest as equal backward-and-forward movements of the limbs, either occurring spontaneously or triggered by touch or loud sounds. Movement suppression by stimulus removal or by relaxing the affected limbs, the lack of autonomic symptoms, and the clear difference from the two-phased (fast contraction, slow relaxation) clonic activity and the very quick myoclonic jerks point to a nonepileptic event. Hypocalcemia, hypoglycemia, drug withdrawal, and hypoxic-ischemic encephalopathy are possible etiologies, but jitteriness is also often seen in normal neonates. Clonus as a result of corticospinal tract injury usually occurs in later infancy and childhood and can be stopped by a change in position. Two to three beats of clonus can be within normal in some neonates.

Hyperekplexia (Stiff Baby Syndrome) and Pathologic Startles

Hyperekplexia is a rare, sporadic, or dominantly inherited (less often recessive or X-linked) disorder with neonatal onset of life-threatening episodes of tonic stiffening that precipitate apnea and convulsive hypoxic seizures. It is characterized by a triad of generalized stiffness, nocturnal myoclonus, and later a pathologic startle reflex. Stiffness may result in difficulty in swallowing, choking spells, hip dislocations, umbilical or inguinal hernias, and delayed motor development. Stiffness in the neonatal form improves by 1 year of age and may disappear during sleep. The genetic cause is a defect in the α or β subunits of the strychnine-sensitive glycine receptors. However, other less common pathogenic variants that disrupt the glycine receptor signaling complex have also been described. Pathogenic variants in *GLRA1* or *SLC6A5* are the most common genes followed by *GLRB*, *GPHM*, and *ARHGEF9* (X-linked). A specific diagnostic sign can be elicited by tapping the nose, which produces a nonfatigable startle reflex with head retraction. Bathing, sudden awakening, and auditory or tactile stimuli can induce attacks. The differential diagnosis includes congenital stiff person syndrome, startle epilepsy, myoclonic seizures, neonatal tetany, phenothiazine toxicity, and Schwartz-Jampel syndrome. Making a prompt diagnosis is extremely important so that treatment with clonazepam can be initiated, because hypoxic brain injury can result from a prolonged episode. Other antiepileptics have also been effective. Repeatedly flexing the baby at the neck and hips (the Vigevano maneuver) can abort the episodes. Rare challenging cases of children with hyperekplexia and concomitant epileptic seizures (including myoclonic seizures) have been reported. In other children after brain injury, and in many patients with cerebral palsy, an **exaggerated startle reflex** can occur; this is more common than hyperekplexia. In Tay-Sachs disease and similar gangliosidoses, an exaggerated startle to sound occurs and has been inappropriately interpreted as hyperacusis. **Hiccups** can occur normally in newborns but can be a feature of nonketotic hyperglycinemia, citrullinemia, and neuromyelitis optica syndromes, with the latter presenting during later childhood and adolescence rather than in neonates. In addition, in children with neurologic diseases, a related limited repertoire of movements and behaviors, startle, arousal, or signs of distress may be clinically expressed with stereotyped movements that can mimic epileptic seizures.

Benign Paroxysmal Torticollis of Infancy

This condition typically presents as morning episodes of painless retrocollis and, later, torticollis, often triggered by changes in posture. Attacks may start with abnormal ocular movements and progress to stillness in an abnormal posture. Vomiting, malaise, irritability, and ataxia may be present during the spells that usually last minutes (paroxysmal) or, more commonly, hours and, at times, days (periodic). Neurologic exam between attacks, EEG, and neuroimaging studies are normal. The condition affects girls more than boys (3:1), often begins in infancy, and spontaneously remits before

the age of 5 years. However, some children, particularly those with migrainous features during attacks, develop migraine later in life. Indeed, this condition is considered to be a migraine equivalent and cosegregates with migraine in families. Medical therapy is supportive during the attacks, especially when vomiting is a prominent feature.

Sandifer Syndrome and Rumination

Gastroesophageal reflux in infants may cause paroxysmal episodes of generalized stiffening and opisthotonic posturing that may be accompanied by apnea, staring, and minimal jerking of the extremities. Episodes often occur 30 minutes after a feed. In older children, this syndrome manifests with episodic dystonic or dyskinetic movements consisting of laterocollis, retrocollis, or torticollis, the exact pathophysiology of which remains elusive. Reflux can also present with rumination consisting of contraction of abdominal muscles followed by mouthing and swallowing movements and at times vomiting.

Alternating Hemiplegia of Childhood

This is a rare, often severe, disorder that consists of attacks of flaccid hemiplegia affecting one or both sides lasting minutes to days, starting in the first 18 months of life. Earlier manifestations include paroxysmal nystagmus, which is often monocular and ipsilateral to the hemiplegia or dystonia. Dystonic spells are the rule also. Patients can have episodes of reduced consciousness and confusion that are not epileptic. Most affected children also have ataxia and developmental delay, and many have choreoathetosis and behavioral problems. Most of the patients are initially misdiagnosed as having refractory focal epilepsy with Todd paralysis. About half of them also have epileptic seizures, which makes the differential diagnosis even more difficult. Flunarizine 2.5–20 mg/day reduces the frequency and severity of the attacks. This condition is most commonly caused by variants in *ATP1A3*, but it can also result from variants in *ATP1A2* or the glucose transporter 1 (*GLUT-1/SLC2A1*), variants that are notoriously associated with diagnostically challenging protean manifestations ranging from epilepsy, usually in early life, to movement disorders thereafter. The *ATP1A3* gene has also been reported in a syndrome of **relapsing encephalopathy with cerebellar ataxia (RECA)** during febrile illnesses. Another syndrome is benign nocturnal alternating hemiplegia, which manifests during sleep and is generally outgrown and has been linked to *PRRT2* variants.

Paroxysmal Dyskinesias and Other Movement Disorders

These disorders are characterized by sudden attacks that consist of choreic, dystonic, ballistic, or mixed movements (Table 633.4 and see Table 634.3). Despite their historical classification into distinct entities, emerging insight into their clinical features and their underlying genetic causes is revealing a significant overlap with phenotypic pleiotropy whereby a pathogenic variant in a single gene may be associated with multiple types of dyskinesias and paroxysms, including epileptic seizures even in the same child. A sensation of fatigue or weakness confined to one side may herald an attack. Consciousness is preserved and patients may be able to perform a motor activity, such as walking, despite the attack. The variability in the pattern of severity and localization between different attacks may also help in differentiating them from seizures. The frequency of attacks increases in adolescence and steadily decreases in the third decade. Neurologic examination between attacks, laboratory investigations, and imaging studies are usually normal. Because the co-occurrence of movement disorders and epileptic seizures is not uncommon, the nature of each type of paroxysmal event has to be characterized as epileptic or not, often with a cautiously analyzed video-EEG, as movement-related artifact may be misread as epileptiform. **Chorea** consists of involuntary rapid fast movements that are slower than myoclonus and not rhythmic. Common causes are poststreptococcal Sydenham chorea, antiphospholipid antibody syndrome, and systemic lupus erythematosus. Action

Table 634.4 Differential Diagnoses of Various Types of Paroxysmal Dyskinesia

FEATURES	PKD	PNKD			PHD (EPILEPSY WITH DYSTONIC EPILEPTIC SEIZURES)
		PNKD1 (MR1+ VE)	PNKD2 (MR1- VE)	PED	
Nomenclature	PKC	PDC, FPC	PDC, FPC	PEDt	ADNFLE
Inheritance	AD-16q	AD-2q35	AD-2q13	AD/AR	AD-20q13, 15q24, 1q21, 8p21
Gene	<i>PRRT2</i> (most common), <i>SCN8A</i> , <i>DEPDC5</i>	<i>MR1</i> (now called <i>PNKD</i>)	Not well characterized <i>KCNMA1</i> , <i>ATP1A3</i>	<i>SLC2A1</i>	<i>CHRNA4</i> , <i>CHRNA2</i> , <i>KCNT1</i>
Age at onset (yr)	1-20	<1-12	1-23	Usually childhood	Usually childhood
Triggers	Sudden whole-body movement	Coffee, alcohol, stress	Exercise	After 10-15 min of exercise	Sleep
Clinical features	Chorea, athetosis, ballismus, dystonia	Chorea, athetosis, dystonia, ballismus	Chorea, athetosis, dystonia, ballismus	Mainly leg dystonia	Wakes up with dystonic posture
Usual duration	<1-5 min	10 min to 1 hr	10 min to 2-3 hr	10-15 min	<1 min
Frequency	1-20/day	1/wk	1/wk	Daily, weekly, or monthly	Several/night
Associations	Infantile seizures (ICCA), migraine, writer's cramp, essential tremor	Migraine	Epilepsy	RE-PED-WC	
Medication	Carbamazepine Phenytoin Oxcarbazepine	Benzodiazepines, mainly clonazepam	Benzodiazepines, mainly clonazepam	Acetazolamide L-DOPA Antiepileptics Trihexyphenidyl Ketogenic diet in <i>SLC2A1</i> mutation cases	Carbamazepine Oxcarbazepine
Prognosis	Excellent	Excellent, worse than PKD	Minimally worse than PNKD MR1+	Poor medication response	Excellent

AD, Autosomal dominant; ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; AR, autosomal recessive; FPC, familial paroxysmal choreoathetosis; ICCA, infantile convulsions choreoathetosis syndrome; MR1+, myofibrillogenesis regulator 1-positive; MR1-, myofibrillogenesis regulator 1-negative; PDC, paroxysmal dystonic choreoathetosis; PED, paroxysmal exercise-induced dyskinesia; PEDt, paroxysmal exercise-induced dystonia; PHD, paroxysmal hypnogenic dyskinesia; PKC, paroxysmal kinesigenic choreoathetosis; PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal nonkinesigenic dyskinesia; RE-PED-WC, rolandic epilepsy-paroxysmal exercise-induced dystonia-writer's cramp. From Friedman NR, Ghosh D, Moodley M. Syncope and paroxysmal disorders other than epilepsy. In: Swaiman KF, Ashwal S, Ferriero DM, et al, eds. *Swaiman's Pediatric Neurology*, 5th ed. Philadelphia: WB Saunders; 2012: Table 65-1.

myoclonus and paroxysmal lower body action dystonia occur in children with myoclonus dystonia—a syndrome caused by pathogenic variants in *SGCE* or *RELN*. **Drug reactions** can result in abnormal movements; they include **oculogyric crisis** with many antiemetics and lamotrigine toxicity, choreoathetosis with phenytoin, dystonia and facial dyskinesias with antidopaminergic drugs, and tics with carbamazepine. Strokes, focal brain lesions, connective tissue disorders (e.g., systemic lupus erythematosus), vasculitis, or metabolic and genetic disorders can also cause movement disorders. Indeed, paroxysmal dyskinesia may be secondary to basal ganglia lesions, and various forms of nonepileptic paroxysms, including dystonic posturing, bicycling, and rhythmic boxing, may occur in children with decompensated maple syrup urine disease.

Episodic Ataxias

Episodic ataxias form a clinically and genetically heterogeneous group of diseases that manifest with recurrent truncal ataxia and incoordination. Of the nine syndromes described so far, only two (types 1 and 2) have been reported in a large number of families from different ethnic groups. **Type 1** is caused by pathogenic variants in *KCNA1* that encodes the voltage-gated potassium channel Kv1.1. It consists of brief episodes (seconds to minutes) of cerebellar ataxia and occasional seizures with interictal myokymia as a main diagnostic feature. **Type 2** is characterized by longer attacks (minutes to hours) and interictal cerebellar signs. It is caused by variants in the voltage-gated calcium channel gene *CACNA1A*. This type is more

responsive than type 1 to acetazolamide; the drug can reduce the frequency and severity of attacks but not the interictal signs and symptoms. The other types of episodic ataxia are not well-characterized, but types 5, 6, and 9 have been associated with variants in *CACNB4*, *SLC1A3*, and *FGF14*, respectively. Spells of episodic ataxia may also occur in children with paroxysmal dyskinesia secondary to variants in *CACNA1A* or *PRRT2*, in line with the previously discussed phenotypic pleiotropy of these conditions. Although epileptic seizures have been primarily described in episodic ataxia type 1, they have also been reported with the other types, specifically types 2 and 6. Glucose transporter deficiency can at times present as episodic ataxia.

Motor Tics

These are movements that are under partial control and are associated with an urge to do them and with subsequent relief. They are usually exacerbated by emotions and often change in character over time. **Simple tics**, which occur at some time in about one in five children, involve one or two muscle groups; **complex tics** involve multiple tics or muscle groups; and **Tourette syndrome** consists of multiple motor tics and vocal tics for more than a year. In patients with tics who have Tourette syndrome, there is often a family history of tics and/or obsessive-compulsive disorder or personality traits. Some rare cases appear to occur after preceding streptococcal infections and have been termed **PANDAS** (pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections). **PANS**, on the other hand, refers to an acute onset of obsessive-compulsive symptoms

with other behavioral problems and often with tics but without the association of streptococcal infections (acute-onset neuropsychiatric syndrome).

Benign Motoric Paroxysms in Infancy

Benign myoclonus of infancy consists of myoclonic jerks of the extremities in wakefulness and sometimes also in sleep with no concurrent epileptic EEG changes in a neurologically normal child. **Shuddering attacks** are characterized by rapid tremors of the head, shoulder, and trunk lasting a few seconds, often associated with eating, and recurring many times a day. Others have considered shuddering as an early manifestation of essential tremor because a family history of essential tremor is often present. **Infantile head atonic attacks** consist of repeated head drops, hundreds to thousands per day, usually appearing at 3-6 months of life and spontaneously subsiding by the first year of life, without concurrent EEG epileptic activity. Spontaneous remission occurs in all three syndromes, usually within a few months. Video-EEG is normal ictally and interictally in these syndromes but should be performed to differentiate them from infantile spasms and epileptic myoclonus. **Hereditary chin trembling** at a frequency faster than 3 Hz starting shortly after birth and precipitated by stress has been described in several families.

Brainstem Dysfunction

Decorticate or decerebrate posturing that mimics epileptic tonic seizures may be secondary to decompensated hydrocephalus, intracranial hemorrhage, brainstem tumors, Chiari malformation, or other causes of sudden rises in intracranial pressure that lead to brainstem dysfunction. The term *cerebellar fits* has been used to describe drop attacks, extensor posturing with varying degrees of altered consciousness and respiratory compromise secondary to crowding of the posterior fossa, and near herniation in decompensated cerebellar tumors and certain cases of Chiari malformation.

Behavioral Conditions

Many behavioral disorders can be mistaken for epileptic seizures. Pleasurable behaviors similar to masturbation may occur from infancy onward and may consist of rhythmic rocking movements in the sitting or lying position or rhythmic hip flexion and adduction. **Infantile gratification** (masturbation), which is more common in females, usually occurs at 2-3 years of age and is often associated with perspiration, irregular breathing, and grunting but no loss of consciousness. Occasionally this is associated with child abuse or with other psychopathology. **Stereotypies**, or repetitive movements that are more complex than tics and do not change and wax and wane as do tics (e.g., head banging, head rolling, body rocking, and hand flapping), usually occur in neurologically impaired children. A **mannerism** is a pattern of socially acceptable, situational behavior that is seen in particular situations such as gesturing when talking. Mannerisms should not be confused with stereotypies, which are generally pervasive over almost every other activity, such as head shaking or hand flapping in multiple situations. Stereotypies, unlike mannerisms, increase with stress. Unlike tics and mannerisms, stereotypies usually start before the age of 3 years, involve more body parts, are more rhythmic, and most importantly occur when a child is engrossed with an object or activity of interest; children rarely try to suppress stereotypies. **Panic and anxiety attacks** have been described in children; at times, these may be clinically indistinguishable from actual epileptic seizures and therefore may necessitate video-EEG monitoring. **Rage attacks** usually occur in patients with a personality disorder and are usually not seizures, although rare cases of partial seizures can manifest as rage attacks. **Hyperventilation spells** can be precipitated by anxiety and are associated with dizziness, tingling, and, at times, carpopedal spasm. **Transient global amnesia** consists of isolated short-term memory loss for minutes to hours that occurs mostly in adults but has been reported in children. The etiology can be emotional

stress, an epileptic disorder, migraine, a vascular disorder, or a drug-related reaction.

OCULOMOTOR AND VISUAL ABNORMALITIES

Paroxysmal Tonic Upgaze of Childhood

This usually starts before 3 months of age and consists of protracted attacks (hours to days) of continuous or episodic upward gaze deviation, during which horizontal eye movements are preserved. A downbeating nystagmus occurs on downward gaze. Symptoms are reduced or relieved by sleep, exacerbated by fatigue and infections, and spontaneously remit after a few years. Up to 50% of patients may have psychomotor and language delay. Although imaging and laboratory tests were nonrevealing in the seminal cases, white matter lesions have been later reported in some patients. An association with *CACNA1A* gene variants in a few patients who also suffered from ataxia has been reported, pointing to etiologic and clinical heterogeneity. The differential diagnosis includes drug reactions, tics, Chediak-Higashi disease, Rett syndrome, and Wilson disease. Most of those, however, occur at a later age. Therapy with carbonic anhydrase inhibitors or low-dose levodopa/carbidopa may be helpful in severe cases. Concomitant absence epilepsy has been reported in few cases.

Oculomotor Apraxia and Saccadic Intrusions

In oculomotor apraxia, saccadic eye movements are impaired. Sudden head turns compensating for lateral gaze impairment mimic seizures. This disorder may be idiopathic (Cogan congenital oculomotor apraxia) or may occur in the context of Joubert syndrome, ataxia telangiectasia, spinocerebellar ataxias, or lysosomal storage diseases. A selective loss of Purkinje cells required to suppress omnipause neurons and initiate saccadic eye movement is believed to occur in some of the disorders. Saccadic intrusions are involuntary, sudden, conjugate eye movements away from the desired eye position. These are not necessarily pathologic.

Spasmus Nutans

This disorder presents with a triad of nystagmus, head tilt, and head nodding. If diurnal fluctuation occurs, symptoms may look like those of epileptic seizures. A brain MRI should be performed because the triad has been associated with masses in the optic chiasm and third ventricle. Retinal disease should also be ruled out. In the absence of these associations, remission occurs before 5 years of age.

Opsoclonus-Myoclonus Syndrome

In opsoclonus-myoclonus syndrome, the term *dancing eyes* refers to continuous, random, irregular, and conjugate eye movements that may fluctuate in intensity. The finding usually accompanies myoclonus and ataxia (dancing feet). Neuroblastoma (more commonly), encephalitis, and a presumed postinfectious etiology are possible causes. In addition to treating the underlying etiology, adrenocorticotrophic hormone (ACTH), corticosteroids, rituximab, and clonazepam are often needed. Recurrences are not infrequent, and developmental delay is common. The opsoclonus and myoclonus may recur after treatment. The long-term neurologic prognosis remains poor, yet the presence of this syndrome is associated with a favorable treatment response of a coexisting neuroblastoma. Opsoclonus with epileptic myoclonus has also been described in a child with GLUT-1 deficiency.

Daydreaming and Behavioral Staring

Staring may be a manifestation of absence seizures, which should be differentiated from daydreaming and from behavioral staring because of fatigue and inattention. This is common in children with **attention-deficit disorder** because these patients are often referred to rule out absence seizures. Hyperventilation in the office precipitates absences and is a useful clinical test. Episodes of staring only in certain settings

(e.g., school) are unlikely to be seizures. In addition, responsiveness to stimulation such as touch and lack of interruption of playing activity characterize nonepileptic staring. **Daydreaming** occurs often in children, and **time-out staring** occurs in children when they are overwhelmed with external stimuli or with demands and shut down, ignoring their surroundings and staring.

Visual Hallucinations

Temporal lobe seizures can be associated with complex visual auras, such as seeing people and places, often with subsequent focal seizure manifestations. **Occipital lobe seizures** usually cause simple visual hallucinations and may occur as isolated auras or may be accompanied by headache and nausea (**Gastaut type** of benign occipital epilepsy), making them difficult to differentiate from **migraine**. Hallucinations in occipital seizures are characterized by colorful shapes, circles, and spots seen for seconds and confined to one hemifield, whereas migrainous auras usually last minutes and consist of black-and-white lines, scotomas, and/or fortification spectra that start in the center of the vision. **Visual snow** is a phenomenon that can be confused with occipital seizures and a migraine aura. It consists of dynamic continuous tiny dots in all of the visual field lasting >3 months with at least two to four additional specific visual symptoms (afterimages [i.e., palinopsia], enhanced visual phenomena [i.e., entoptic phenomena such as excessive floaters and photopsias], photophobia, and impaired night vision [i.e., nyctalopia]). Although it can occur in patients with migraine or with psychologic stress, the underlying pathology is not clear. Unlike migraine, it is associated with increased, rather than decreased, metabolism on PET scans of the lingual gyrus, which is the visual memory area, and patients usually do not respond to antimigraine therapies. **Alice in Wonderland syndrome** consists of the visual distortion of one's body or surroundings (bigger, smaller, closer, or more distant) and has been associated with migraine, epilepsy, acute infection such as Epstein-Barr virus, or fever. Hallucinations can also be **secondary to other causes**: drug exposure, midbrain lesions, and psychiatric illnesses. In addition, retinal-associated hallucinations can occur in the form of flashes of light in the context of inflammatory etiologies, trauma, or optic nerve edema. **Charles Bonnet syndrome** is the occurrence of visual hallucinations caused by ocular-origin visual loss or, at times, intracranial pathology.

SLEEP-RELATED DISORDERS (SEE ALSO CHAPTER 31)

Paroxysmal nonepileptic sleep events are more common in epileptic patients than in the general population, which makes their diagnosis difficult. The EEG pattern of frontal lobe epileptic seizures may be similar to the one seen in normal arousals, making their diagnosis challenging, especially because they have nonspecific hypermotor manifestations such as thrashing, body rocking, kicking, boxing, pedaling, bending, running, and various vocalizations. The diagnosis of such epileptic seizures is made on the basis of highly stereotyped, usually brief (<1 minute) events arising several times a night from non-rapid eye movement sleep.

Benign Sleep Myoclonus and Neonatal Sleep Myoclonus

Physiologic sleep myoclonus consists of repetitive, usually bilateral, rhythmic jerks involving the upper and lower limbs during non-rapid eye movement (REM) sleep, sometimes mimicking clonic seizures. Although the rule is that it is not stimulus sensitive, a slow (1-Hz) rocking of the infant in a head-to-toe direction is a specific diagnostic test that may sometimes reproduce the neonatal sleep myoclonus. The lack of autonomic changes, occurrence only in sleep, and suppression by awakenings may help in differentiating these events from epileptic seizures. Remission is spontaneous, usually at 2-3 months of age. In older children and adults, sleep myoclonus consists of random myoclonic jerks of the limbs.

Non-Rapid Eye Movement Partial Arousal Disorders

Brief **nocturnal confusional arousals** occur during slow-wave sleep and are normal in children. Such episodes can vary from chewing, sitting up, and mumbling to agitated sleepwalking and usually last for 10-15 minutes. With **somnambulism**, there is often a positive family history, and it usually occurs 1-3 hours after sleep onset. **Night terrors** similarly occur in deep sleep, most often at 2-7 years of age and more so in males. Stress increases the risk of both. In night terrors, the child screams; appears terrified; has dilated pupils, tachycardia, tachypnea, unresponsiveness, agitation, and thrashing that increase with attempts to be consoled; is difficult to arouse; and may have little or no vocalization. In older children with persistent night terrors, an underlying psychologic etiology may be present. The diagnosis is based on the history. However, rarely, video-EEG monitoring may be needed, especially if stereotyped motoric features are suggested by the history. At times, the use of bedtime diazepam (0.2-0.3 mg/kg) or clonazepam (0.125-0.5 mg) may help control the problem while psychologic factors are being investigated. **Restless legs syndrome** can cause painful leg dysesthesias that cause nocturnal arousals and insomnia. It can be either genetic or associated with iron deficiency, systemic illness, or some drugs such as antidepressants. Therapy depends on treating the underlying cause and, if needed, on dopaminergic drugs, such as levodopa/carbidopa, or antiepileptics, such as gabapentin.

Rapid Eye Movement Sleep Disorders

Unlike night terrors, **nightmares** tend to occur later during the night and the child has a memory of the event. **REM sleep behavior disorder** consists of loss of atonia during REM sleep, enabling patients to act out their dreams and thus mimicking nocturnal frontal or temporal lobe seizures. It is more common in adults. Children with autism and developmental delay are more likely to have it than other children.

Sleep Transition Disorders

Nocturnal head banging (**jactatio capitis nocturna**), rolling, repetitive limb movements, or body rocking often occur in infants and toddlers as they are trying to fall asleep and can be mistaken for seizures or spasms. They usually remit spontaneously by 5 years of age. No specific therapy is needed, but in exceptional cases, clonazepam at bedtime may be used.

Narcolepsy-Cataplexy Syndrome

Narcolepsy is characterized by excessive daytime sleepiness, cataplexy, sleep paralysis, hypnagogic hallucinations, and disturbed nighttime sleep (see [Chapter 31](#)). The persistence of REM sleep atonia upon awakening or its intrusion during wakefulness leads to sleep paralysis or cataplexy, respectively. Loss of tone in cataplexy occurs in response to strong emotions and spreads from the face downward, leading to a fall in a series of stages rather than a sudden one. Consciousness is maintained in cataplexy. A selective loss of hypocretin-secreting neurons in the hypothalamus is at the origin of this disorder. The fact that DQB1*0602 is a predisposing human leukocyte antigen (HLA) allele identified in 85-95% of patients with narcolepsy-cataplexy suggests an autoimmune-mediated neuronal loss. Secondary narcolepsy has also been described in children with brain lesions affecting the brainstem or hypothalamic regions subserving wakefulness. The diagnosis is based on the multiple sleep latency test. Therapy relies on scheduled naps; medications such as amphetamines, methylphenidate, tricyclic antidepressants, modafinil, or sodium oxybate; and counseling about precautions in work and driving.

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Chapter 635

Headaches

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Headache is a common complaint in children and adolescents. Headaches can be a *primary* problem or occur as a symptom of another disorder (a *secondary* headache). Recognizing this difference is essential for choosing the appropriate evaluation and treatment to ensure successful management of the headache. Primary headaches should be thought of as a disease themselves and are most often present as recurrent, episodic headaches, and for most children are sporadic in their presentation. This oftentimes creates confusion when patients and providers focus on the events (i.e., the headache, calling it a “migraine”) rather than the disease itself.

The most common forms of *primary headache* in childhood are migraine and tension-type headache (Table 635.1). Other forms of primary headache, including the trigeminal autonomic cephalalgias and cluster headaches, occur much less commonly. Primary headache disorders can progress to very frequent or even daily headaches, with chronic migraine and chronic tension-type headache being recognized as a problem for children and adolescents. These more frequent headaches can have an enormous impact on the life of the child and adolescent, as reflected in school absences and decreased school performance, social withdrawal, and changes in family interactions. To reduce this impact, a treatment strategy that incorporates acute treatments, preventive treatments, and biobehavioral therapies must be implemented.

Secondary headache is a headache that is a symptom of an underlying illness (see Table 635.1). The underlying illness should be clearly present as a direct cause of the headaches with close association of timing and symptomatology. This is often difficult when two or more common conditions occur in close temporal association. This frequently leads to the misdiagnosis of a primary headache as a secondary headache. This is the case when the headaches caused by migraine are misdiagnosed as sinus headaches. The key components of a secondary headache are the likely direct cause-and-effect relationship between the headache and the precipitating condition. In this regard, when the presumed cause of the secondary headache has been treated (antibiotics) or given adequate time to recover (posttraumatic headache), the headache symptoms should resolve. If this does not occur, either the diagnosis must be reevaluated or the effectiveness of the treatment reassessed.

In all instances of primary headaches, the neurologic examination should be normal. If it is not normal or a secondary headache is suspected, this raises a red flag. *The presence of an abnormal neurologic examination (including fundoscopic) or unusual neurologic symptoms is a key clue that additional investigation is warranted.*

635.1 Migraine

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Joanne Kacperski

Migraine is a disease that has a genetic basis (Table 635.2) and represents the most frequent reason recurrent headaches are brought to the attention of parents and primary care providers, but it remains under-recognized and undertreated, particularly in children and adolescents. Migraine is characterized by episodic attacks. These attacks are typically thought of as headaches, but in children there are also periodic syndromes that may represent attacks of migraine. The headaches may be moderate to severe in intensity, be focal in location, have a throbbing quality, and be associated with nausea, vomiting, light sensitivity, and/or sound sensitivity. Compared with migraine in adults, migraine

in children and adolescents may be shorter in duration and has a bilateral, often bifrontal, location. The headaches can also be associated with an aura that may be typical (visual, sensory, or dysphasic) or atypical (hemiplegic, Alice in Wonderland syndrome) (Tables 635.3-635.7). Migraine may present with a number of variants in children, including abdominally related symptoms without headache and components of the periodic syndromes of childhood—also called *episodic disorders associated with migraine* (see Table 635.1). Treatment of migraine requires the incorporation of an acute treatment plan, a preventive treatment plan if the migraine occurs frequently or is disabling or long lasting, and a biobehavioral plan to help cope with both the acute attacks and frequent or persistent attacks if present.

EPIDEMIOLOGY

Up to 75% of children report having a significant headache by the time they are 15 years of age. Recurrent headaches are less common but remain highly frequent. Migraine has been reported to occur in up to 10.6% of children between the ages of 5 and 15 years and up to 28% of older adolescents. When headaches are occurring more than 15 days per month, they are termed *chronic migraine* and may occur in up to 1% of children and adolescents. The risk of conversion to a daily headache becomes more likely as the frequency increases or ineffective acute treatments are used. This explains the necessity to treat the headaches aggressively or prevent the headaches altogether, trying to block transformation to chronic migraine.

Migraine can affect a patient's life through school absences, limitation of home activities, and restriction of social activities. This can be assessed through simple tools such as PedMIDAS (pediatric migraine disability assessment tool). When headaches become more frequent, their negative impact increases in magnitude. This can lead to further complications, including anxiety and school avoidance, requiring a more extensive treatment plan.

CLASSIFICATION AND CLINICAL MANIFESTATIONS

Criteria have been established to guide the clinical and scientific study of headaches; these are summarized in *The International Classification of Headache Disorders*, 3rd edition (ICHD-3). Table 635.1 contrasts the different clinical types of migraine; Tables 635.3-635.7 list the specific criteria for migraine types.

Migraine Without Aura

Migraine without aura is the most common form of migraine in both children and adults. The ICHD-3 (see Table 635.3) requires this to be recurrent (at least five headaches that meet the criteria, typically over the past year, but no firm period is required). The recurrent episodic nature helps differentiate this from a secondary headache and separates migraine from tension-type headache. Because headaches may first start in young childhood, this may limit the diagnosis in children as they are just beginning to develop headaches.

The duration of the headache is defined as 4-72 hours for adults. It has been recognized that children may have shorter-duration headaches, so an allowance has been made to reduce this duration to 2-72 hours in children and adolescents under the age of 18 years. Note that this duration is for the untreated or unsuccessfully treated headache. Furthermore, if the child falls asleep with the headache, the entire sleep period is considered part of the duration. These duration limits help differentiate migraine from both short-duration headaches, including the trigeminal autonomic cephalalgias, and prolonged headaches, such as those caused by idiopathic intracranial hypertension (pseudotumor cerebri). Some prolonged headaches may still be migraine, but a migraine that persists beyond 72 hours is classified as a variant termed **status migrainosus**.

The quality of migraine pain is often, but not always, throbbing or pounding. This may be difficult to elicit in young children, and drawings or demonstrations may help confirm the throbbing quality.

The location of the pain has classically been described as **unilateral (hemicrania)**; in young children it is more commonly bilateral. A more appropriate way to think of the location would therefore be focal to differentiate it from the diffuse pain of tension-type headaches.

Table 635.1 Classification of Headaches (ICHD-3 Code Diagnosis)

MIGRAINE Migraine with or without aura Migraine with typical aura (with or without headache) Migraine with brainstem aura Hemiplegic migraine (sporadic or familial types 1, 2, 3 or other genetic loci) Retinal migraine Chronic migraine Complications of Migraine Status migrainosus Persistent aura without infarction Migrainous infarction Migraine aura–triggered seizure Episodic Syndromes that May Be Associated with Migraine Recurrent gastrointestinal disturbance Cyclical vomiting syndrome Abdominal migraine Benign paroxysmal vertigo Benign paroxysmal torticollis Episodic colic TENSION-TYPE HEADACHE (TTH) Infrequent episodic TTH associated with or without pericranial tenderness Frequent episodic TTH associated with or without pericranial tenderness Chronic TTH associated with or without pericranial tenderness Probable TTHs TRIGEMINAL AUTONOMIC CEPHALALGIAS (TACS) Cluster headache (episodic or cluster) Paroxysmal hemicrania (episodic or cluster) Short-lasting unilateral neuralgiform headache attacks with or without conjunctival injection and tearing (SUNCT) Episodic SUNCT Chronic SUNCT Short-lasting unilateral neuralgiform headache attacks with or without cranial autonomic symptoms (SUNA) Episodic SUNA Chronic SUNA Hemicrania continua Probable trigeminal autonomic cephalalgias OTHER PRIMARY HEADACHE DISORDERS Primary cough headache Primary exercise headache Primary headache associated with sexual activity Primary thunderclap headache Cold-stimulus headache (external application, ingestion, or inhalation) External-pressure headache External-compression headache External-traction headache Primary stabbing headache Nummular headache Hypnic headache New daily persistent headache (NDPH) HEADACHE ATTRIBUTED TO TRAUMA OR INJURY TO THE HEAD AND/OR NECK Acute headache attributed to traumatic (mild, moderate, or severe) injury to the head Persistent headache attributed to traumatic (mild, moderate, or severe) injury to the head Acute or persistent headache attributed to whiplash Acute or persistent headache attributed to craniotomy	HEADACHE ATTRIBUTED TO CRANIAL OR CERVICAL VASCULAR DISORDER Headache attributed to ischemic stroke or transient ischemic attack Headache attributed to nontraumatic intracerebral hemorrhage Headache attributed to nontraumatic subarachnoid hemorrhage Headache attributed to nontraumatic acute subdural hemorrhage Headache attributed to unruptured vascular malformation Headache attributed to unruptured saccular aneurysm Headache attributed to arteriovenous malformation Headache attributed to dural arteriovenous fistula Headache attributed to cavernous angioma Headache attributed to encephalotrigeminal or leptomeningeal angiomatosis (Sturge-Weber syndrome) Headache attributed to arteritis Headache attributed to giant cell arteritis Headache attributed to primary angiitis of the central nervous system Headache attributed to secondary angiitis of the central nervous system Headache attributed to cervical carotid or vertebral artery disorder Headache or facial or neck pain attributed to cervical carotid or vertebral artery dissection Postendarterectomy headache Headache attributed to carotid or vertebral angioplasty Headache attributed to cerebral venous thrombosis Headache attributed to other acute intracranial arterial disorder Headache attributed to an intracranial endovascular procedure Angiography headache Headache attributed to reversible cerebral vasoconstriction syndrome Headache attributed to intracranial arterial dissection Headache attributed to genetic vasculopathy Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) Headache attributed to another genetic vasculopathy Headache attributed to pituitary apoplexy HEADACHE ATTRIBUTED TO NONVASCULAR INTRACRANIAL DISORDER Headache attributed to increased cerebrospinal fluid pressure Headache attributed to idiopathic intracranial hypertension Headache attributed to intracranial hypertension secondary to metabolic, toxic, or hormonal causes Headache attributed to intracranial hypertension secondary to hydrocephalus Headache attributed to low cerebrospinal fluid pressure Post–dural puncture headache Cerebrospinal fluid fistula headache Headache attributed to spontaneous intracranial hypotension Headache attributed to noninfectious inflammatory disease Headache attributed to neurosarcoidosis Headache attributed to aseptic (noninfectious) meningitis Headache attributed to other noninfectious inflammatory disease Headache attributed to lymphocytic hypophysitis Syndrome of transient headache and neurologic deficits with cerebrospinal fluid lymphocytosis (HaNDL) Headache attributed to intracranial neoplasm Headache attributed to colloid cyst of the third ventricle Headache attributed to carcinomatous meningitis Headache attributed to hypothalamic or pituitary hypersecretion or hyposecretion Headache attributed to intrathecal injection Headache attributed to epileptic seizure Hemicrania epileptica Postictal headache Headache attributed to Chiari malformation type I Headache attributed to other nonvascular intracranial disorder
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Table 635.1 Classification of Headaches (ICHD-3 Code Diagnosis)—cont'd

HEADACHE ATTRIBUTED TO A SUBSTANCE OR ITS WITHDRAWAL Headache attributed to use of or exposure to a substance Nitric oxide donor–induced headache Phosphodiesterase inhibitor–induced headache Carbon monoxide–induced headache Alcohol–induced headache Monosodium glutamate–induced headache Cocaine–induced headache Histamine–induced headache Calcitonin gene-related peptide–induced headache Headache attributed to exogenous acute pressor agent Headache attributed to occasional or long-term use of non-headache medication Headache attributed to exogenous hormone Medication-Overuse Headache (MOH) Ergotamine-overuse headache Triptan-overuse headache Simple analgesic–overuse headache Paracetamol (acetaminophen)-overuse headache Acetylsalicylic acid–overuse headache Other nonsteroidal antiinflammatory drug–overuse headache Opioid-overuse headache Combination analgesic–overuse headache Headache Attributed to Substance Withdrawal Caffeine-withdrawal headache Opioid-withdrawal headache Estrogen-withdrawal headache HEADACHE ATTRIBUTED TO INFECTION Acute or chronic headache attributed to bacterial meningitis or meningoencephalitis Persistent headache attributed to past bacterial meningitis or meningoencephalitis Acute or chronic headache attributed to intracranial fungal or other parasitic infection Headache attributed to brain abscess Headache attributed to subdural empyema Headache attributed to systemic infection (acute or chronic) HEADACHE ATTRIBUTED TO DISORDER OF HOMEOSTASIS Headache attributed to hypoxia and/or hypercapnia High-altitude headache Headache attributed to airplane travel Diving headache Sleep apnea headache Dialysis headache Headache attributed to arterial hypertension Headache attributed to pheochromocytoma Headache attributed to hypertensive crisis with or without hypertensive encephalopathy Headache attributed to preeclampsia or eclampsia Headache attributed to autonomic dysreflexia Headache attributed to hypothyroidism Headache attributed to fasting Cardiac cephalgia Headache attributed to other disorder of homeostasis	HEADACHE OR FACIAL PAIN ATTRIBUTED TO DISORDER OF THE CRANIUM, NECK, EYES, EARS, NOSE, SINUSES, TEETH, MOUTH, OR OTHER FACIAL OR CERVICAL STRUCTURE Headache attributed to disorder of cranial bone Headache attributed to retropharyngeal tendonitis Headache attributed to craniocervical dystonia Headache attributed to acute glaucoma Headache attributed to refractive error Headache attributed to heterophoria or heterotropia (latent or persistent squint) Headache attributed to ocular inflammatory disorder Headache attributed to tracheitis Headache attributed to disorder of the ears Headache attributed to acute or chronic or recurring rhinosinusitis Headache attributed to temporomandibular disorder Head or facial pain attributed to inflammation of the stylohyoid ligament Headache or facial pain attributed to other disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structure HEADACHE ATTRIBUTED TO PSYCHIATRIC DISORDER Headache attributed to somatization disorder Headache attributed to psychotic disorder PAINFUL CRANIAL NEUROPATHIES AND OTHER FACIAL PAINS Classical trigeminal neuralgia Classical trigeminal neuralgia, purely paroxysmal or with concomitant persistent facial pain Painful trigeminal neuropathy Painful trigeminal neuropathy attributed to acute herpes zoster Postherpetic trigeminal neuropathy Painful posttraumatic trigeminal neuropathy Painful trigeminal neuropathy attributed to multiple sclerosis (MS) plaque Painful trigeminal neuropathy attributed to space-occupying lesion Painful trigeminal neuropathy attributed to other disorder Glossopharyngeal neuralgia Classical nervus intermedius (facial nerve) neuralgia Nervus intermedius neuropathy attributed to herpes zoster Occipital neuralgia Optic neuritis Headache attributed to ischemic ocular motor nerve palsy Tolosa-Hunt syndrome Paratrigeminal oculosympathetic (Raeder) syndrome Recurrent painful ophthalmoplegic neuropathy Burning mouth syndrome (BMS) Persistent idiopathic facial pain (PIFP) Central neuropathic pain Central neuropathic pain attributed to multiple sclerosis Central post-stroke pain (CPSP)
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From Headache Classification Committee of the International Headache Society (IHS). *The International Classification of Headache Disorders*, 3rd ed. Cephalalgia. 2018;38(1):1–211.

Of particular concern is the exclusively occipital headache because although these can be migraines, they are more frequently secondary to another more proximate etiology such as posterior fossa abnormalities.

The headaches of migraine, when allowed to fully develop, often worsen with activity. Worsening of the pain occurs classically in adults when going up or down stairs. This history is often not elicited in children. A change in the child's activity pattern can be easily observed as a reduction in play or physical activity. Older children may limit or restrict their sports activity or exercise during a headache attack.

The attacks may have a variety of associated symptoms. In younger children, nausea and vomiting may be the most obvious symptoms and

often outweigh the headache itself. This often leads to the overlap with several of the gastrointestinal periodic diseases, including recurrent abdominal pain, recurrent vomiting, cyclic vomiting, and abdominal migraine. The common feature among all of these related conditions is an increased propensity among children with them for the later development of a typical description of a headache caused by migraine. Early childhood recurrent vomiting may in fact be migraine, but the child is not asked about or is unable to describe headache pain. This may occur as early as infancy because babies with colic have a higher incidence of migraine once they are able to express their symptoms. Once a clear head pain becomes evident, the earlier diagnosis of a gastrointestinal disorder is no longer appropriate.

Table 635.2 Genetics in Migraine**KEY FACTS**

- Based on studies with twins, the heritability of migraine has been estimated as 42%
- A genome-wide association meta-analysis identified 38 genomic loci that affect migraine risk
- The relative risk of migraine without aura is 1.9 in first-degree relatives of probands with migraine without aura
- The relative risk of migraine with aura is 3.8 in first-degree relatives of probands with migraine with aura

GENETIC BIOMARKERS FOR MONOGENIC SUBTYPES OF MIGRAINE OR MIGRAINE-RELATED SYNDROMES

- Familial hemiplegic migraine
 - Type 1 (CACNA1A gene)
 - Type 2 (ATP1A2 gene)
 - Type 3 (SCN1A gene)
 - Possible association with PRRT2 gene
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (NOTCH3 gene)
- Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (TRESX1 gene)
- Familial advanced sleep phase syndrome (CSNK1D gene)

Modified from Ashina M, Terwindt GM, Al-Mahdi Al-Karagholi M, et al. Migraine: disease characterization, biomarkers, and precision medicine. *Lancet*. 2021;397:1496–1504, Panel 2, p. 1498.

Table 635.3 Migraine Without Aura

- At least five attacks fulfilling criteria B-D
- Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)
- Headache has at least two of the following four characteristics:
 - Unilateral location
 - Pulsating quality
 - Moderate or severe pain intensity
 - Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
- During headache at least one of the following:
 - Nausea and/or vomiting
 - Photophobia and phonophobia
- Not better accounted for by another ICHD-3 diagnosis

From Headache Classification Committee of the International Headache Society (IHS). *The International Classification of Headache Disorders*, 3rd ed. Cephalalgia. 2018;38(1):1–211, Table 4.

Table 635.4 Migraine with Typical Aura

- At least two attacks fulfilling criteria B and C
- One or more of the following fully reversible aura symptoms:
 - Visual
 - Sensory
 - Speech/language symptoms
 - Motor
 - Brainstem
 - Retinal
- At least three of the following six characteristics:
 - At least one aura symptom spreads gradually over 5 or more minutes
 - Two or more symptoms occur in succession
 - Each individual aura symptom lasts 5-60 min
 - At least one aura symptom is unilateral
 - At least one aura symptom is positive
 - The aura is accompanied, or followed within 60 minutes, by headache
- Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded

From Headache Classification Committee of the International Headache Society (IHS). *The International Classification of Headache Disorders*, 3rd ed. Cephalalgia. 2018;38(1):1–211, Table 6.

Table 635.5 Migraine with Brainstem Aura

- At least two attacks fulfilling criteria for migraine with aura and criterion B
- Aura with both of the following
 - At least two of the following brainstem symptoms:
 - Dysarthria
 - Vertigo
 - Tinnitus
 - Hyperacusis
 - Diplopia
 - Ataxia
 - Decreased level of consciousness
 - No motor or retinal symptoms

From Headache Classification Committee of the International Headache Society (IHS). *The International Classification of Headache Disorders*, 3rd ed. Cephalalgia. 2018;38(1):1–211, Table 7.

Table 635.6 Vestibular Migraine with Vertigo

- At least five episodes fulfilling criteria C and D
- A current or past history of *migraine without aura* or *migraine with aura*
- Vestibular symptoms of moderate or severe intensity, lasting between 5 min and 72 hr
- At least 50% of episodes are associated with at least one of the following three migrainous features:
 - Headache with at least two of the following four characteristics:
 - Unilateral location
 - Pulsating quality
 - Moderate or severe intensity
 - Aggravation by routine physical activity
 - Photophobia and phonophobia
 - Visual aura
- Not better accounted for by another ICHD-3 diagnosis or by another vestibular disorder

From Headache Classification Committee of the International Headache Society (IHS). *The International Classification of Headache Disorders*, 3rd ed. Cephalalgia. 2018;38(1):1–211, Table 8.

Table 635.7 Chronic Migraine

- Headache (tension-type-like and/or migraine-like) on 15 or more days/mo for more than 3 mo and fulfilling criteria B and C
- Occurring in a patient who has had at least five attacks fulfilling criteria B-D for *migraine without aura* and/or criteria B and C for *migraine with aura*
- On 8 or more days/mo for more than 3 mo, fulfilling any of the following:
 - Criteria C and D for *migraine without aura*
 - Criteria B and C for *migraine with aura*
 - Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
- Not better accounted for by another ICHD-3 diagnosis

From Headache Classification Committee of the International Headache Society (IHS). *The International Classification of Headache Disorders*, 3rd ed. Cephalalgia. 2018;38(1):1–211, Table 9.

When headache is present, vomiting raises the concern of a secondary headache, particularly related to increased intracranial pressure. *One of the red flags for this is the daily or near-daily early morning vomiting or headaches waking the child up from sleep or with the Valsalva maneuver.* When the headaches associated with vomiting episodes are sporadic and not worsening, it is more likely that the diagnosis is migraine. Vomiting and headache caused by increased intracranial pressure are frequently present on first awakening and remit with maintenance of upright posture. In contrast, if a migraine is present on

first awakening (*a relatively infrequent occurrence in children*), getting up and going about normal, upright activities usually makes the headache and vomiting worse.

When the child matures, light and sound sensitivity (**photophobia** and **phonophobia**) may become more apparent. This is either by direct report of the patient or the interpretation by the parents of the child's activity because the parent may become aware of this symptom before the child. These symptoms are likely a component of the hypersensitivity that develops during an acute migraine attack and may also include smell sensitivity (**osmophobia**) and touch sensitivity (**cutaneous allodynia**). Although only the photophobia and phonophobia are components of the ICHD-3 criteria, these other symptoms are helpful in confirming the diagnosis and may be helpful in understanding the underlying pathophysiology and determining the response to treatment. The final ICHD-3 requirement is the exclusion of causes of secondary headaches, and this should be an integral component of the headache history.

Migraine typically runs in families, with reports of up to 90% of children having a first- or second-degree relative with recurrent headaches. Given the underdiagnoses and misdiagnosis in adults, this is often not recognized by the family, and a headache family history is required. When a family history is not identified, this may be the result of either a lack of awareness of migraine within the family or an underlying secondary headache in the child. *Any child whose family, upon close and both direct and indirect questioning, does not include individuals with migraine or related syndromes (e.g., motion sickness, cyclic vomiting, menstrual headache) should have an imaging procedure performed to look for anatomic etiologies for headache.*

In addition to the classifying features, there may be additional markers of a migraine disorder. These include such things as **triggers** (skipping meals, inadequate or irregular sleep, dehydration, and weather changes are the most common), **pattern recognition** (associated with menstrual periods in adolescents or Monday-morning headaches resulting from changes in sleep patterns over the weekend and non-physiologic early waking on Monday mornings for school), and **prodromal symptoms** (a feeling of irritability, tiredness, and food cravings before the start of the headache) (Fig. 635.1). Although these additional features may not be consistent, they do raise the index of suspicion for migraine and provide a potential mechanism of intervention. In the past, food triggers were considered widely common, but the majority have either been discredited with scientific study or represent such a small number of patients that they only need to be addressed when consistently triggering the headache.

Migraine with Aura

The aura associated with migraine is a neurologic warning that a migraine is going to occur. In the common forms, this can be the start of a typical headache without migraine, or it may even occur in isolation. For a typical aura, the aura needs to be visual, sensory, or dysphasic, lasting longer than 5 minutes and less than 60 minutes, with the headache starting within 60 minutes (see Table 635.4). The importance of the aura lasting longer than 5 minutes is to differentiate the migraine aura from a seizure with a postictal headache, whereas the 60-minute maximal duration is to separate migraine aura from the possibility of a more prolonged neurologic event such as a transient ischemic attack. The ICHD-3 criteria have also added the requirements that for a diagnosis of aura, there needs to be a positive symptom and not just a loss of function (i.e., flashing lights, tingling, not just blurring of vision).

The most common type of visual aura in children and adolescents is **photopsia** (flashes of light or light bulbs going off everywhere). These photopsias are often multicolored, and when gone, the child may report not being able to see where the flash occurred. Less likely in children are the typical adult auras, including *fortification spectra* (brilliant white zigzag lines resembling a starred pattern castle) or *shimmering scotoma* (sometimes described as a shining spot that grows or a sequined curtain closing). In adults, the auras typically involve only half the visual field, whereas in children they may be randomly dispersed. Blurred vision is often confused as an aura but is difficult to separate from photophobia or difficulty concentrating during the pain of the headache.

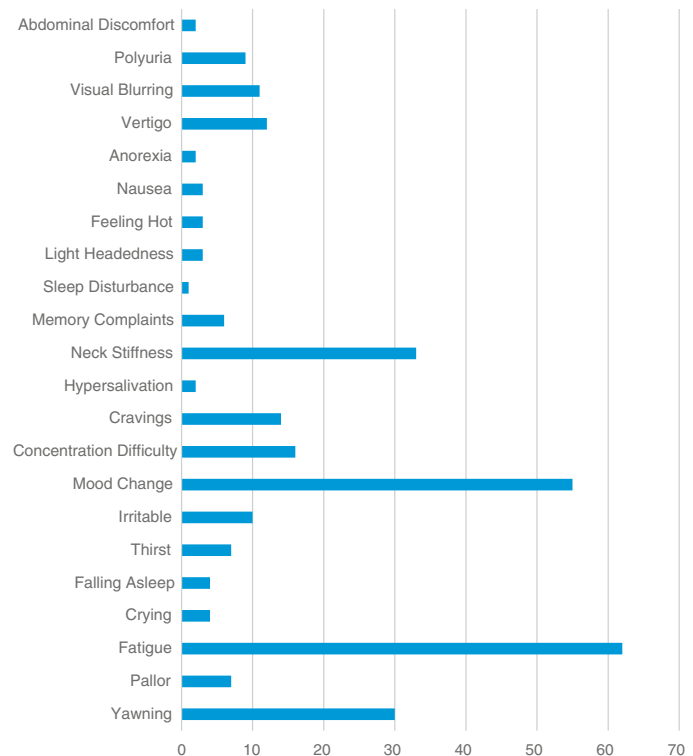


Fig. 635.1 Frequency of different premonitory symptoms reported. (From Karsan N, Prabhakar P, Goadsby PJ. Characterizing the premonitory stage of migraine in children: a clinic-based study of 100 patients in a specialist headache service. *J Head Pain*. 2016;17:94, Fig. 1.)

Sensory auras are less common. They typically occur unilaterally. Many children describe this sensation as insects or worms crawling from their hand, up their arm, to their face with a numbness following this sensation. Once the numbness occurs, the child may have difficulty using the arm because they have lost sensory input, and a misdiagnosis of hemiplegic migraine may be made.

Dysphasic auras are the least common type of typical aura and have been described as an inability or difficulty to respond verbally. The patient afterward will describe an ability to understand what is being asked but cannot answer back. This may be the basis of what in the past has been referred to as *confusional migraine*, and special attention needs to be paid to asking the child about this possibility and their degree of understanding during the initial phases of the attack. Most of the time, these episodes are described as a motor aphasia, and they are often associated with sensory or motor symptoms.

Much less commonly, *rarer forms of aura can occur*, including hemiplegia (true weakness, not numbness, and may be familial), vertigo or lower cranial nerve symptoms–brainstem aura (formerly called *basilar-type* and once thought to be caused by basilar artery dysfunction, now thought to be a more brainstem-based migraine with brainstem aura) (see Table 635.4), and distortion (Alice in Wonderland syndrome). Whenever these rarer forms of aura are present, further investigation is warranted. Not all motor auras can be classified as hemiplegic migraine spectrum, and they should be differentiated from those specific migrainous events, because the diagnosis of hemiplegic migraine has genetic, pathophysiologic, and therapeutic implications.

Hemiplegic migraine is one of the better-known forms of rare auras. This transient unilateral weakness usually lasts only a few hours but may persist for days. Both familial and sporadic forms have been described. The familial hemiplegic migraine is an autosomal dominant disorder with pathogenic variants in three separate genes: *CACNA1A*, *ATP1A2*, and *SCN1A* (see Table 635.2). Some patients with familial hemiplegic migraine have other yet-to-be-identified genetic variants. Multiple polymorphisms have been described for these genes. Hemiplegic migraines may be triggered by minor head

trauma, exertion, or emotional stress. The motor weakness is usually associated with another aura symptom and may progress slowly over 20-30 minutes, first with a visual aura and then, in sequence, with sensory, motor, aphasic, and basilar auras. Headache is present in more than 95% of patients and usually begins during the aura; headache may be unilateral or bilateral and may have no relationship to the motor weakness. Some patients may develop attacks of coma with encephalopathy, cerebrospinal fluid (CSF) pleocytosis, and cerebral edema. Long-term complications may include seizures, repetitive daily episodes of blindness, cerebellar signs with the development of cerebellar atrophy, and mental disabilities.

Migraine with brainstem aura (basilar-type migraine) was formerly considered a disease of the basilar artery because many of the unique symptoms were attributed to dysfunction in this area of the brainstem. Some of the symptoms described include vertigo, tinnitus, diplopia, blurred vision, scotoma, ataxia, and an occipital headache. The pupils may be dilated, and ptosis may be evident.

Syndrome of transient headache and neurologic deficits with CSF lymphocytosis (HaNDL) describes transient migraine-like headaches associated with neurologic deficits (motor, sensory, language impairments) and CSF showing pleocytosis. It is considered a self-limited migraine-like syndrome of unknown etiology and is rarely reported in the pediatric population.

Childhood periodic syndromes are a group of potentially related symptoms that occur with increased frequency in children with migraine. The hallmark of these symptoms is the recurrent episodic nature of the events. Some of these have included gastrointestinal-related symptoms (colic, motion sickness, recurrent abdominal pain, recurrent vomiting including cyclic vomiting, and abdominal migraine), sleep disorders (sleepwalking, sleep talking, and night terrors), unexplained recurrent fevers, and even seizures.

The **gastrointestinal symptoms** span the spectrum from the relatively mild (motion sickness on occasional long car rides) to severe episodes of uncontrollable vomiting that may lead to dehydration and the need for hospital admission to receive fluids. These latter episodes may occur on a predictable time schedule and are called **cyclic vomiting**. During these attacks, the child may appear pale and frightened but does not lose consciousness. After a period of deep sleep, the child awakens and resumes normal play and eating habits as if the vomiting had not occurred. Many children with cyclic vomiting have a positive family history of migraine and as they grow older have a higher-than-average likelihood of developing migraine. Cyclic vomiting may be responsive to migraine-specific therapies; careful attention is needed for fluid replacement if the vomiting is excessive. **Cyclic vomiting of migraine** must be differentiated from gastrointestinal disorders, including intestinal obstruction (malrotation, intermittent volvulus, duodenal web, duplication cysts, superior mesenteric artery compression, and internal hernias), peptic ulcer, gastritis, giardiasis, chronic pancreatitis, and Crohn disease. Abnormal gastrointestinal motility and pelviureteric junction obstruction can also cause cyclic vomiting. Metabolic causes include disorders of amino acid metabolism (heterozygote ornithine transcarbamylase deficiency), organic acidurias (propionic acidemia, methylmalonic acidemia), fatty acid oxidation defects (medium-chain acyl-coenzyme A dehydrogenase deficiency), disorders of carbohydrate metabolism (hereditary fructose intolerance), acute intermittent porphyria, and structural central nervous system lesions (posterior fossa brain tumors, subdural hematomas, or effusions). The diagnosis is a diagnosis of exclusion, and children will need a full workup to be labeled as having cyclic vomiting syndrome. Cyclic vomiting syndrome is more frequent in younger children and will gradually transform into a typical migraine attack by puberty (see [Chapter 390](#)).

The diagnosis of **abdominal migraine** can be confusing but can be thought of as a migraine without the headache. Like a migraine, it is an episodic disorder characterized by midabdominal pain with pain-free periods between attacks. At times this pain is associated with nausea and vomiting (thus crossing into the recurrent abdominal pain or cyclic vomiting spectrum). The pain is usually described as dull and may be moderate to severe. The pain may persist from 1 to 72 hours, and although it is usually in the midline, it may be periumbilical or

poorly localized by the child. To meet the criteria of abdominal migraine, the child must complain at the time of the abdominal pain of at least two of the following: anorexia, nausea, vomiting, or pallor. Similar to cyclic vomiting, a thorough history and physical examination with appropriate laboratory studies must be completed to rule out an underlying gastrointestinal disorder as a cause of the abdominal pain. Careful questioning about the presence of headache or head pain needs to be addressed directly to the child because many times, this is truly a migraine but in the child's mind (and the parents' observation), the abdominal symptoms are paramount.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

A thorough history and physical examination, including a neurologic examination with special focus on headache, has been shown to be the most sensitive indicator of an underlying etiology. The history needs to include a thorough evaluation of the prodromal symptoms, any potential triggering events or timing of the headaches, associated neurologic symptoms, and a detailed characterization of the headache attacks, including frequency, severity, duration, associated symptoms, use of medication, and disability. The disability assessment should include the impact on school, home, and social activities and can easily be assessed with tools such as PedMIDAS. A family history of headaches and any other neurologic, psychiatric, and general health conditions is also important both for identification of migraine within the family and the identification of possible secondary headache disorders. The familial penetrance of migraine is so robust that the absence of a family history of migraine or its equivalent phenomena should raise the concern that the diagnosis may not be migraine and warrants further history taking, referral to a headache specialist, or investigation. The lack of a family history may be the result of a lack of awareness of the family of the migraine ("doesn't everybody get headaches?"). When headaches are refractory, a history of potential comorbid conditions, which includes mood disorders and illicit substance use, especially in teenagers, that may influence adherence and acceptability of the treatment plan, may also need to be addressed. Patients with difficult-to-treat chronic migraines may have raised intracranial pressure; a lumbar puncture with lowering of the pressure may resolve the migraine. These patients may not have papilledema. In addition, disorders such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Moyamoya disease, reversible cerebral vasoconstriction syndrome, and stroke-like migraine attacks after radiation therapy (SMART) may initially present with migraines ([Table 635.8](#)).

Neuroimaging is warranted when the neurologic examination is abnormal or unusual neurologic features occur during the migraine; when the child has headaches that awaken the child from sleep or that are present on first awakening and remit with upright posture; when the child has brief headaches that only occur with cough or bending over; when the headache is mostly in the occipital area; and when the child has migrainous headache with an absolutely negative family history of migraine or its equivalent (e.g., motion sickness, cyclic vomiting; [Table 635.9](#)). In this case, an MRI is the imaging method of choice because it provides the highest sensitivity for detecting posterior fossa lesions and does not expose the child to radiation.

In the child with a headache that is instantaneously at its worst at onset, a CT scan looking for blood is the best initial test; if it is negative, a lumbar puncture should be done looking especially for xanthochromia of the CSF. There is no evidence that laboratory studies or an electroencephalogram is beneficial in a typical migraine without aura or migraine with aura.

TREATMENT

[Table 635.10](#) outlines the drugs used to manage migraine headaches in children. The American Academy of Neurology established useful practice guidelines for the management of migraine as follows:

- Reduction of headache frequency, severity, duration, and disability
- Reduction of reliance on poorly tolerated, ineffective, or unwanted acute pharmacotherapies
- Improvement in quality of life
- Avoidance of acute headache medication escalation

Table 635.8 Migraine Mimics and Secondary Migraine

Trigeminal autonomic cephalgias (TACs)
Cluster headache
Hemicrania continua
Short-lasting unilateral neuralgiform headache attacks with or without conjunctival tearing (injection) (SUNCT/SUNA)
Ophthalmoplegic (CN III, IV, VI) migraine
Arterial dissection
Vasculitis/vasculopathies
Giant cell arteritis
Moyamoya
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (<i>NOTCH 3</i>)
Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) (<i>HTRA1</i>)
SLE
Granulomatosis with polyangiitis
Primary CNS vasculitis
Reversible cerebral vasoconstriction syndrome (RCVS)
Antiphospholipid antibody syndrome
MELAS
Idiopathic intracranial hypertension (pseudotumor cerebri)
Occipital epilepsy
Sudden vision loss
Transient ischemic attack
Acute glaucoma
Sinusitis with intracranial extension
Epilepsy with aura
Transient headache and neurologic deficits with CSF lymphocytosis (HaNDL)
Alternating hemiplegia of childhood (<i>ATP1A3</i>)
Fabry disease
SMART syndrome

CN, Cranial nerve; CNS, central nervous system; CSF, cerebrospinal fluid; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; SMART, stroke-like migraine attack after radiation therapy.
 Modified from Lauck SM, Gage S. Headaches. In: Kliegman RM, Toth H, Bordini BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 34.17, p. 560.

Table 635.9 Indications for Neuroimaging in a Child with Headaches

Abnormal neurologic examination
Abnormal or focal neurologic signs or symptoms
• Focal neurologic symptoms or signs developing during a headache (i.e., complicated migraine)
• Focal neurologic symptoms or signs (except classic visual symptoms of migraine) develop during the aura, with fixed laterality; focal signs of the aura persisting or recurring in the headache phase
Seizures or very brief auras (<5 min)
Unusual headaches in children
• Atypical auras, including basilar-type, hemiplegic
• Trigeminal autonomic cephalgia, including cluster headaches in child or adolescent
• An acute secondary headache (i.e., headache with known underlying illness or insult)
Headache in children younger than 6 yr old or any child who cannot adequately describe his or her headache
Brief cough headache in a child or adolescent
Headache worst on first awakening or that awakens the child from sleep
Migrainous headache in the child with no family history of migraine or its equivalent

- Education and enabling of patients to manage their disease to enhance personal control of their migraine
- Reduction of headache-related distress and psychologic symptoms

To accomplish these goals, three components need to be incorporated into the treatment plan: (1) an acute treatment strategy should be developed for stopping a headache attack on a consistent basis with return to function as soon as possible, with the goal being 2 hours maximum; (2) a preventive treatment strategy should be considered when the headaches are frequent (one or more per week) and disabling; and (3) biobehavioral therapy should be started, including a discussion of adherence, elimination of barriers to treatment, and healthy habit management.

Acute Treatment

Management of an acute attack is designed to provide headache freedom as quickly as possible with return to normal function. This mainly includes two groups of medicines: nonsteroidal antiinflammatory drugs (NSAIDs) and triptans. Small-molecule calcitonin gene-related peptide modulator (CGRP receptor antagonists) therapies are approved for patients 18 and older for acute headache treatment, but they are still under investigation for efficacy and tolerability in children and adolescents. Most headaches caused by migraine in children will respond to appropriate doses of NSAIDs when they are administered at the *onset* of the headache attack. Ibuprofen has been well documented to be effective at a dose of 7.5–10.0 mg/kg and is often preferred; however, acetaminophen (15 mg/kg) can be effective in those with a contraindication to NSAIDs. Special concern for the use of ibuprofen or other NSAIDs includes ensuring that the children can recognize and respond to onset of the headache. This means discussing with the child the importance of telling the teacher when the headache starts at school and ensuring that proper dosing guidelines and permission have been provided to the school. In addition, medication overuse needs to be avoided, limiting NSAIDs and other pain medications for headache (or any combination of nonprescription analgesics) to not more than 2–3 times per week. The limitation of any analgesic to not more than three headaches per week is necessary to prevent the transformation of the migraines into **medication-overuse headaches (MOHs)**. If a patient has maximized the weekly allowance of analgesics, the patient's next step is to only use hydrating fluids for the rest of the week as an abortive approach. If ibuprofen is not effective, naproxen sodium also may be tried in similar doses. Aspirin is also a reasonable option but is usually reserved for older children (>16 years). Use of other NSAIDs has yet to be studied in pediatric migraine. The goal of the acute medication should be relief of headache and associated symptoms within 1 hour, with return to function in 10 of 10 headaches.

When an attack of migraine is especially severe, NSAIDs alone may not be sufficient. In this case, a triptan may be considered. Multiple studies have demonstrated their effectiveness and tolerability. There are currently three triptans that are approved by the U.S. Food and Drug Administration (FDA) for the treatment of episodic migraine in the pediatric population. Almotriptan is approved for the treatment of acute migraine in adolescents (ages 12–17 years). Rizatriptan is approved for the treatment of migraine in children as young as age 6 years. The intranasal formulation of zolmitriptan is also approved by the FDA in the United States for use in children ages 12 and over. Several studies have shown it to provide rapid and effective relief, and it has been demonstrated to be well tolerated for treatment of acute migraine in patients 12 years and older. Zolmitriptan nasal spray may be of particular benefit to those with nausea and in patients who have difficulty swallowing tablets.

The combination of naproxen sodium and sumatriptan has been studied and may be effective in children. Controlled clinical trials demonstrate that intranasal sumatriptan is safe and effective in children older than age 8 years with moderate to severe migraine. At present, pediatric studies showing the effectiveness of oral sumatriptan are lacking, and there is insufficient evidence to support the use of subcutaneous sumatriptan in children. For most adolescents, dosing is the same as for adults; a reduction in dose is made for children weighing less than 40 kg. The triptans vary by rapidity of onset and biologic half-life. This is related to both their variable lipophilicity and dose. Clinically, 60–70% of patients respond to the first triptan tried, with 60–70% of

Table 635.10 Drugs Used in the Management of Migraine Headaches in Children				
DRUG	DOSE	MECHANISM	SIDE EFFECTS	COMMENTS
ACUTE MIGRAINE				
Analgesics				
Acetaminophen	15 mg/kg/dose	Analgesic effects	Overdose, fatal hepatic necrosis	Effectiveness limited in migraine
Ibuprofen	7.5-10 mg/kg/dose	Antiinflammatory and analgesic	GI bleeding, stomach upset, kidney injury	Avoid overuse (2-3 times per wk)
Triptans				
Almotriptan* (ages 12-17 yr)	12.5 mg	5-HT _{1b/1d} agonist	Vascular constriction, serotonin symptoms such as flushing, paresthesias, somnolence, GI discomfort	Avoid overuse (>4-6 times per mo)
Eletriptan	40 mg	Same	Same	Avoid overuse (>4-6 times per mo)
Frovatriptan	2.5 mg	Same	Same	May be effective for menstrual migraine prevention Avoid overuse (>4-6 times per mo)
Naratriptan	2.5 mg	Same	Same	May be effective for menstrual migraine prevention Avoid overuse (>4-6 times per mo)
Rizatriptan* (ages 6-17 yr)	5 mg for child weighing <40 kg, 10 mg	Same	Same	Available in tablets and melts Avoid overuse (>4-6 times per mo)
Sumatriptan	Oral: 25, 50, 100 mg Nasal: 10 mg SC: 6 mg	Same	Same	Avoid overuse (>4-6 times per mo)
Zolmitriptan (NS ages 12+)	Oral: 2.5, 5 mg Nasal: 5 mg*	Same	Same	Available in tablets and melts Avoid overuse (>4-6 times per mo)
PROPHYLAXIS (NONE APPROVED BY FDA FOR CHILDREN)				
Calcium Channel Blockers				
Flunarizine†	5 mg hs	Calcium channel blocking agent	Headache, lethargy, dizziness	May ↑ to 10 mg hs
Anticonvulsants				
Valproic acid	20 mg/kg/24 hr (begin 5 mg/kg/24 hr)	↑ Brain GABA	Nausea, pancreatitis, fatal hepatotoxicity	↑ 5 mg/kg every 2 wk
Topiramate* (12-17 yr)	100-200 mg divided bid	↑ Activity of GABA	Fatigue, nervousness	Increase slowly over 12-16 wk
Levetiracetam	20-60 mg/kg divided bid	Unknown	Irritability, fatigue	Increase every 2 wk starting at 20 mg/kg divided bid
Gabapentin	900-1800 mg divided bid	Unknown	Somnolence, fatigue, aggression, weight gain	Begin 300 mg, ↑ 300 mg/wk
Antidepressants				
Amitriptyline	1 mg/kg/day	↑ CNS serotonin and norepinephrine	Cardiac conduction, abnormalities and dry mouth, constipation, drowsiness, confusion	Increase by 0.25 mg/kg every 2 wk Morning sleepiness reduced by administration at dinnertime
Antihistamines				
Cyproheptadine	0.2-0.4 mg/kg divided bid; max: 0.5 mg/kg/24 hr	H ₁ -receptor and serotonin agonist	Drowsiness, thick bronchial secretions	Preferred in children who cannot swallow pills; not well tolerated in adolescents
Antihypertensive				
Propranolol	10-20 mg tid	Nonselective β-adrenergic blocking agent	Dizziness, lethargy	Begin 10 mg/24 hr ↑ 10 mg/wk (contraindicated in asthma and depression)
Others				
Coenzyme Q10	1-3 mg/kg/day	Increases fatty acid oxidation in mitochondria	No adverse effects reported	Fat soluble; ensure brand contains small amount of vitamin E to help absorption
Riboflavin	50-400 mg daily	Cofactor in energy metabolism	Bright yellow urine, polyuria and diarrhea	

Table 635.10 Drugs Used in the Management of Migraine Headaches in Children—cont'd

DRUG	DOSE	MECHANISM	SIDE EFFECTS	COMMENTS
Magnesium	9 mg/kg divided tid	Cofactor in energy metabolism	Diarrhea or soft stool	
Butterbur	50-150 mg daily	May act similar to a calcium channel blocker	Burping	
OnabotulinumtoxinA	100 units (age 11-17 yr)	Inhibits acetylcholine release from nerve endings	Ptosis, blurred vision, hematoma at injection site	Used off-label in children
SEVERE INTRACTABLE				
Prochlorperazine	0.15 mg/kg/IV; max dose 10 mg	Dopamine antagonist	Agitation, drowsiness, muscle stiffness, akinesia and akathisia	May have increased effectiveness when combined with ketorolac and fluid hydration
Metoclopramide	0.2 mg/kg IV; 10 mg max dose	Dopamine antagonist	Drowsiness, urticaria, agitation, akinesia and akathisia	Caution in asthma patients
Ketorolac	0.5 mg/kg IV; 15 mg max dose	Antiinflammatory and analgesic	GI upset, bleeding	
Valproate sodium injection	15 mg/kg IV; 1,000 mg max dose	↑ Brain GABA	Nausea, vomiting, somnolence, thrombocytopenia	Would avoid in hepatic disease
Dihydroergotamine IV	0.5 mg/dose every 8 hr (<40 kg) 1.0 mg/dose every 8 hr (>40 kg)		Nausea, vomiting, vascular constriction, phlebitis	Dose may need to be adjusted for side effects (decrease) or limited effectiveness (increase)
Nasal spray	0.5-1.0 mg/dose 0.5 mg/spray			

*FDA approved in the pediatric population.

†Available in Europe.

↑, Increase; CNS, central nervous system; GABA, γ -aminobutyric acid; GI, gastrointestinal; hs, at night; SC, subcutaneous.

the patients who did not respond to the first triptan responding to the next triptan. Therefore in the patient who does not respond to the first triptan in the desired way (rapid reproducible response without relapse or side effects), it is worthwhile to try a different triptan. The most common side effects of the triptans are caused by their mechanism of action—tightness in the jaw, chest, and fingers as a result of vascular constriction and a subsequent feeling of grogginess and fatigue from the central serotonin effect. The vascular constriction symptoms can be alleviated through adequate fluid hydration during an attack.

The most effective way to administer acute treatment is with the recognition that NSAIDs and triptans have different mechanisms of action. NSAIDs are used for all headaches, mild to severe, with their use being restricted to fewer than two to three attacks per week; the triptans are added for moderate to severe headaches, with their use being restricted to not more than six to eight attacks per month. For an acute attack, the NSAIDs can be repeated once in 3-4 hours, if needed for that specific attack, and the triptans can be repeated once in 2 hours if needed. It is important to consider the various formulations available, and these options should be discussed with pediatric patients and their parents, especially if a child is unable to swallow pills or take an oral dose because of nausea and/or vomiting.

Because vascular dilation is a common feature of migraine that may be responsible for some of the facial flushing, followed by paleness and the lightheaded feeling accompanying the attacks, fluid hydration should be integrated into the acute treatment plan. For oral hydration, this can include the sports drinks that combine electrolytes and sugar to provide the intravascular rehydration.

Antiemetics are used for acute treatment of the nausea and vomiting. Further study has identified that their unique mechanism of effectiveness in headache treatment is related to their antagonism of dopaminergic neurotransmission. Therefore the antiemetics with the most robust dopamine antagonism (i.e., prochlorperazine and

metoclopramide) have the best efficacy. These can be very effective for status migrainosus or a migraine that is unresponsive to NSAIDs and triptans. They require intravenous administration because other forms of administration of these drugs are less effective than the NSAIDs or triptans. When combined with ketorolac and intravenous fluids in the emergency department or an acute infusion center, intravenous antiemetics can be highly effective. When they are not effective, further inpatient treatment may be required using dihydroergotamine (DHE), which will mean an admission to an inpatient unit for more aggressive therapy of an intractable attack.

There are also a growing number of devices that appear to be effective for the acute treatment of headache attacks caused by migraine. Currently both a remote electrical neuromodulation (REN) device and a vagal nerve stimulator are approved for the acute treatment of attacks down to age 12. These devices have the benefit of improving the adolescent's locus of control, as they can modulate the degree and duration of treatment, without the need to swallow a pill.

Emergency Department Treatments for Intractable Headaches

When an acute migraine attack does not respond to the recommended outpatient regimen and the headache is disabling, more aggressive therapeutic approaches are available and may be necessary to prevent further increase in the duration and frequency of headaches. These migraines fall into the classification of status migrainosus (migraine attack lasting more than 72 hours), and patients may need to be referred to an infusion center, the emergency room, or an inpatient unit.

Available specific treatments for migraine headache in an emergency room setting include the following: antidopaminergic medications such as prochlorperazine and metoclopramide, NSAIDs such as ketorolac, vasoconstrictor medications such as DHE, and antiepileptic drugs such as sodium valproate.

Antidopaminergic Drugs: Prochlorperazine and Metoclopramide

The use of antidopaminergic medications is not limited to controlling the nausea and vomiting often present during a migraine headache. Their potential pharmacologic effect may be a result of their antidopamine property and the underlying pathologic process involving the dopaminergic system during a migraine attack. Prochlorperazine is highly effective in aborting an attack in the emergency room when given intravenously with a bolus of intravenous fluid. Results show a 75% improvement with 50% headache freedom at 1 hour and 95% improvement with 60% headache freedom at 3 hours. Prochlorperazine may be more effective than metoclopramide. The average dose of metoclopramide is 0.13-0.15 mg/kg, with a maximum dose of 10 mg given intravenously over 15 minutes. The average dose of prochlorperazine is 0.15 mg/kg, with a maximum dose of 10 mg. These medications are usually well-tolerated, but *extrapyramidal reactions* are more frequent in children than in older persons. An acute extrapyramidal reaction can be controlled in the emergency room with 25-50 mg of diphenhydramine given intravenously. There is no need for premedication with diphenhydramine to prevent side effects. Diphenhydramine should only be used if needed when side effects are present.

Nonsteroidal Antiinflammatory Drugs: Ketorolac

It is known that an aseptic inflammation occurs in the central nervous system as a result of the effect of multiple reactive peptides in patients with migraines, including the CGRP molecules. Ketorolac is often used in the emergency department as monotherapy for a migraine attack or in combination with other drugs. In monotherapy, the response to ketorolac is 55.2% improvement. When ketorolac is combined with prochlorperazine, the response rate jumps to 93%.

Antiepileptic Drugs: Sodium Valproate

Antiepileptic drugs have been used as prophylactic treatment for migraine headache for years with adequate double-blinded, controlled studies on their efficacy in adults. The mechanism by which sodium valproate acutely aborts migraine headaches is not well understood. Sodium valproate is given as a bolus of 15-20 mg/kg push (over 10 minutes). This intravenous load is followed by an oral dose (15-20 mg/day) in the 4 hours after the injection. Patients may benefit from a short-term preventive treatment with an extended-release form after discharge from the emergency room for 2 weeks to keep the level in the therapeutic range. Sodium valproate is usually well tolerated. Patients should receive a fluid load during the procedure to prevent a possible hypotensive episode.

Triptans

Subcutaneous sumatriptan (0.06 mg/kg) has an overall efficacy of 72% at 30 minutes and 78% at 2 hours, with a recurrence rate of 6%. Because children tend to have a shorter duration of headache, a recurrence rate of 6% would seem appropriate for this population. DHE, if recommended for the recurrences, should not be given in the 8 hours after triptan use. Triptans are contraindicated in patients treated with ergotamine within 24 hours and within 2 weeks of treatment with monoamine oxidase inhibitors. Triptans may rarely produce serotonin syndrome in patients taking a serotonin receptor reuptake inhibitor. *Both triptans and ergotamine are contraindicated in hemiplegic migraines.*

Dihydroergotamine

DHE is a medication used as a vasoconstrictor to abort the vascular phase of migraine headache. The effectiveness is discussed in detail in the section "Inpatient Management of Intractable Migraine and Status Migrainosus," next. One dose of DHE can be effective for abortive treatment in the emergency department. Emergency room treatment of migraine shows a recurrence rate of 29% at 48-72 hours, with 6% of patients needing even more aggressive therapy in an inpatient unit.

Inpatient Management of Intractable Migraine and Status Migrainosus

About 6-7% of patients fail acute treatment in the emergency department. These patients are usually admitted for 3-5 days to an inpatient

unit and receive extensive parenteral treatment. Admission is reserved for patients who are disabled by their acute migraine attack and those who did not experience relief from all other abortive approaches as discussed earlier: (1) for acute status migrainosus, (2) for exacerbation of an underlying chronic migraine when the episode fits the criteria for a status migrainosus occurring on top of their continuous baseline headache, and (3) for severe analgesic overuse headache that did not respond to any other recommended abortive therapy. The goal of inpatient treatment is to control a headache that has been unresponsive to other outpatient abortive therapies and is disabling to the child. Treatment protocols include the use of DHE, antiemetics, sodium valproate, and other drugs.

Dihydroergotamine

Ergots are one of the oldest treatments for migraine headache. DHE is a parenteral form used for acute exacerbations. Its effect stems from the 5HT_{1A-1B-1D-1F} receptor agonist affinity and central vasoconstriction. DHE has greater α -adrenergic antagonist activity and is less vasoconstrictive peripherally. Before initiation of an intravenous ergot protocol, a full history should be obtained and a neurologic examination performed to rule out any possibility of secondary headache before the initiation of the treatment, keeping in mind that patients with migraine can still develop a secondary headache. Females of childbearing age should be evaluated for pregnancy before ergots are administered.

The DHE protocol consists of the following: Patients are premedicated with 0.13-0.15 mg/kg of prochlorperazine 30 minutes before the DHE dose (maximum of three prochlorperazine doses to prevent extrapyramidal syndrome; after three doses of prochlorperazine, a non-dopamine antagonist antiemetic should be used, such as ondansetron). A dose of 0.5-1.0 mg of DHE is used (depending on age and tolerability) every 8 hours until headache freedom is achieved or headache returns back to baseline for those with a continuous headache. The first dose should be divided into two half-doses separated by 30 minutes if the patient is naïve to treatment with DHE. When the headache ceases, an extra dose of DHE is given in an attempt to prevent recurrence after discharge. The response to this protocol is a 97% improvement and 77% headache freedom. The response is noticeable by the fifth dose; the drug can reach its maximum effects after the tenth dose. Common side effects of DHE include nausea, vomiting, abdominal discomfort, a flushed face, muscle cramping, and increased blood pressure. The maximum dose used in this protocol is 15 mg total of DHE.

Sodium Valproate

Sodium valproate is used when DHE is contraindicated or has been ineffective. One adult study recommends the use of valproate sodium as follows: bolus with 15 mg/kg (maximum of 1,000 mg), followed by 5 mg/kg every 8 hours until headache freedom or up to a maximum of 10 doses. An extra dose is recommended after the headache ceases to prevent recurrence. This protocol was studied in adults with chronic daily headaches and showed an 80% improvement. It is well tolerated and is useful in children when DHE is ineffective, contraindicated, or not tolerated.

Other Inpatient Therapies

During an inpatient admission for status migrainosus, other services such as behavioral medicine and holistic medicine should be involved if they are available. The behavioral medicine staff can play a major role in talking to patients about their specific triggers and can also evaluate school, as well as home and social stressors. The staff would also initiate some coping skills training during the admission and evaluate the necessity for further outpatient follow-up for cognitive-behavioral therapy, biofeedback, or treatment for other comorbidities. The holistic medicine staff, when consulted, can offer holistic approaches to pain control, including relaxation techniques, medical massage, and craniosacral therapy.

Preventive Therapy

When the headaches are frequent (more than one headache per week) or disabling (causing the patient to miss school, home, or social activities or with a PedMIDAS score >20), preventive or **prophylactic**

therapy may be warranted. The goal of this therapy should be to reduce the frequency to one headache or fewer per week and level of disability (PedMIDAS score <10). Prophylactic agents should be given for at least 4-6 months at an adequate dose and then weaned over several weeks. Evidence in adult studies has begun to demonstrate that persistent frequent headaches foreshadow an increased risk of progression with decreased responsiveness and increased risk of refractoriness in the future. It is unclear whether this also occurs in children and/or adolescents and whether early treatment of headache in childhood prevents development of refractory headache in adulthood.

Multiple preventive medications have been used for migraine prophylaxis in children. When analyzed as part of a practice parameter, one medication, **flunarizine** (a calcium channel blocking agent), demonstrated a level of effectiveness viewed as substantial; it is not available in the United States. Flunarizine is typically given at 5 mg orally daily and increased after 1 month to 10 mg orally daily, with a month off the drug every 4-6 months.

A commonly used preventive therapy for headache and migraine is amitriptyline. Typically, a dose of 1 mg/kg daily at dinner or in the evening is effective. However, this dose needs to be reached slowly (i.e., over weeks, with an increase every 2 weeks until the goal is reached) to minimize side effects and improve tolerability. Side effects include sleepiness and those related to amitriptyline's anticholinergic activity. Weight gain has been observed in adults using amitriptyline but is a less frequent occurrence in children. Amitriptyline does have the potential to exacerbate prolonged QT syndrome, so it should be avoided in patients with this diagnosis and looked for in patients taking the drug who complain of a rapid or irregular heart rate.

Antiepileptic medications are also used for migraine prophylaxis, with topiramate, valproic acid, and levetiracetam having been demonstrated to be effective in adults. There are limited studies in children for migraine prevention, but all of these medications have been assessed for safety and tolerability in children with epilepsy.

Topiramate has become widely used for migraine prophylaxis in adults. Topiramate was also demonstrated to be effective in an adolescent study. This study demonstrated that a 25-mg dose twice a day was equivalent to placebo, whereas a 50-mg dose twice a day was superior. Thus it appears that the adult dosing schedule is also effective in adolescents with an effective dosage range of 50 mg twice a day to 100 mg twice a day. This dose needs to be reached slowly to minimize the cognitive slowing associated with topiramate use. Side effects include weight loss, paresthesias, kidney stones, lowered bicarbonate levels, decreased sweating, and rarely glaucoma and changes in serum transaminases. In addition, in adolescent females taking birth control pills, the lowering of the effectiveness of the birth control by topiramate needs to be discussed.

A comparative effectiveness study in children (8-17 years) of the two most common treatments (amitriptyline and topiramate) compared with placebo (the CHAMP study) demonstrated that all three treatments were effective, but there was not statistical superiority for amitriptyline or topiramate over placebo.

Valproic acid has long been used for epilepsy in children and has been demonstrated to be effective in migraine prophylaxis in adults. The effective dose in children appears to be 10 mg/kg orally twice a day. Side effects of weight gain, ovarian cysts, and changes in serum transaminases and platelet counts need to be monitored. Other antiepileptics, including lamotrigine, levetiracetam, zonisamide, gabapentin, and pregabalin, are also used for migraine prevention.

β Blockers have long been used for migraine prevention. The studies on β blockers have a mixed response pattern with variability both between β blockers and between patients with a given β blocker. Propranolol is the best studied for pediatric migraine prevention with unequivocally positive results. The contraindication for the use of propranolol in children with asthma or allergic disorders or diabetes and the increased incidence of depression in adolescents using propranolol limit its use somewhat. It may be effective for a mixed subtype of migraine (basilar-type migraine with postural orthostatic tachycardia syndrome). This syndrome has been reported to be responsive to propranolol. α -Blockers and calcium channel blockers, aside from

flunarizine, also have been used in pediatric migraine; their effectiveness, however, remains unclear.

In very young children, cyproheptadine may be effective in the prevention of migraine or the periodic syndromes of childhood. Young children tend to tolerate the increased appetite induced by the cyproheptadine and tend not to be subject to the lethargy seen in older children and adults; the weight gain is limiting once children start to enter puberty. Typical dosing is 0.1-0.2 mg/kg orally twice a day.

Nutraceuticals are popular choices, especially among families who prefer a more natural approach to headache treatment. Despite studies showing success of these therapies in adults, few studies have shown effectiveness in pediatric headaches. Riboflavin (vitamin B₂), at doses ranging from 25 to 400 mg, is the most widely studied with good results. Side effects are minimal and include bright yellow urine, diarrhea, and polyuria. Coenzyme Q10 supplementation may be effective in reducing migraine frequency at doses of 1-2 mg/kg/day. Butterbur is also effective in reducing headaches, with minimal side effects, including burping. Use in children has been limited to avoid the potential toxicity of butterbur-containing pyrrolizidine alkaloids, which are naturally contained and are a known carcinogen and toxic to the liver.

OnabotulinumtoxinA is the first medication FDA-approved for chronic migraine in adults. There are studies in children indicating its effectiveness; use in children is considered off-label. The limited available studies revealed the following: The average dose used was 188.5 units $\pm$ 32 units with a minimum dose of 75 units and maximum of 200 units. The average age of patients receiving the treatment was 16.8 $\pm$ 2.0 years (minimum 11 years; maximum 21 years). OnabotulinumtoxinA injections improved disability scores (PedMIDAS) and headache frequency in pediatric chronic daily headache patients and chronic migraine in this age-group. OnabotulinumtoxinA not only had a positive effect on the disability scoring for these young patients with headache but was also able to transform the headaches from chronic daily to intermittent headaches in more than 50% of the patients.

Eptinezumab, erenumab, galcanezumab, and fremanezumab—humanized monoclonal antibodies against the CGRP or its receptor—have demonstrated safety and efficacy in adult patients with migraine. The FDA has approved these agents for use in adults with migraine, including chronic migraine. There are no completed studies in children and adolescents.

Biobehavioral Therapy

Biobehavioral evaluation and therapy are essential for effective migraine management. This includes identification of behavioral barriers to treatment, such as a child's shyness or limitation in notifying a teacher of the start of a migraine or a teacher's unwillingness to accept the need for treatment. Additional barriers include a lack of recognition of the significance of the headache problem and reverting to bad habits once the headaches have responded to treatment. Adherence is equally important for acute and preventive treatment. The need to have a sustained response long enough to prevent relapse (to stay on preventive medication) is often difficult when the child starts to feel better. Establishing a defined treatment goal (one or two or fewer headaches per month for 4-6 months) helps with acceptance.

Because many of the potential triggers for attacks of migraine (skipping meals, dehydration, decreased or altered sleep) are related to a child's daily routine, a discussion of healthy habits is a component of biobehavioral therapy. This should include adequate fluid intake without caffeine, regular exercise, not skipping meals and making healthy food choices, and adequate (8-9 hours) sleep on a regular basis. Sleep is often difficult in adolescents because middle and high schools often have very early start times, and the adolescent's sleep architecture features a shift to later sleep onset and waking. This has been one of the explanations for worsening headaches during the school year in general and at the beginning of the school year and week.

Biofeedback-assisted relaxation and cognitive-behavioral therapy (usually in combination with amitriptyline) are effective for both acute and preventive therapy and may be incorporated into this multiple treatment strategy. This provides the child with a degree of self-control over the headaches and may further help the child cope with frequent headaches.

Young Adults and the Transition of Headache Care from a Pediatric to an Adult Provider

Migraine is a chronic condition that may first present in childhood. Males are diagnosed at a younger age than females; however, during development, the prevalence becomes highest among women, starting at puberty. Some adolescents and women report migraine associated with menses; the pain symptoms are described as lasting longer and having a higher intensity. The role of oral contraceptive pills (OCPs) is often a topic of discussion among female adolescents and young women. Studies have shown improvement of menstrual migraine in adult patients taking oral estrogens and progesterone; similar studies have not been done in adolescents. OCPs are not approved by the FDA for treatment of menstrual migraine; they have been associated with an increased risk of stroke among women with migraine aura. Therefore their use in adolescents as a prophylactic agent is not advised.

Comorbid conditions such as anxiety and depression are seen with a high prevalence among adults with migraine; however, the prevalence among adolescent patients remains unclear. Diagnostic tools capable of differentiating mood disorders from pain symptoms in the pediatric population are limited, which makes identifying those at risk challenging. However, it is important to keep in mind the potential of mood disorders, especially in young adults.

Remission of migraine is seen in up to 34% of adolescents, and almost 50% continue to have migraine persisting into adulthood. Successful transition of care from a pediatric to an adult provider has been shown to improve outcomes in patients with chronic disease.

Early diagnosis and treatment of migraine can help minimize the progression of the disease in adults. This, together with careful screening for comorbid conditions, may help identify those at risk for refractory migraine, minimize disability, and improve overall headache outcomes.

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635.2 Secondary Headaches

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Headaches can be a common symptom of other underlying illnesses. In recognition of this, the ICHD-3 has classified potential secondary headaches (see [Table 635.1](#)). The key to the diagnosis of a secondary headache is to recognize the underlying cause and demonstrate a direct cause and effect. Until this has been done, the diagnosis is speculative. This is especially true when the suspected etiology is common.

Headache is a common occurrence after concussion or mild traumatic brain injury (mTBI), reported in as many as 86% of high school and college athletes who have suffered from head trauma (see [Chapter 729](#)). Although there are no strict criteria for determining who will develop persistent headache after concussion, it is important to gather information to rule out other secondary headaches and significant primary headache disorders and to identify those who may be at risk for persistent headache after concussion.

Chronic or persistent headaches are headaches that last for more than 3 months after head trauma. This definition is consistent with the classification of persistent posttraumatic headaches in the ICHD-3. Although concussion and posttraumatic headache are rapidly evolving areas of study, there is an unfortunate lack of definitive scientific evidence at this time on these topics in pediatrics. The ICHD-3 classifies posttraumatic headaches as acute if they last less than 3 months and persistent if they last more than 3 months after injury. This period is consistent with ICHD-II diagnostic criteria, although the term *persistent* has been adopted in place of *chronic*. Although the ICHD-3 criteria state that posttraumatic headaches begin within 7 days after injury to the head or after regaining consciousness, this 7-day cutoff is arbitrary, and some experts believe that headaches may develop after a longer interval. Some studies have shown that ~50% of children with

posttraumatic headache 3 months after concussion had a history of preexisting headaches, and 31% had a history of migraine or probable migraine before the injury. Furthermore, 56% of patients with headaches at 3 months after injury had a family history of migraine. Based on clinical experiences of patients with prolonged postconcussion symptoms, those with *prior* concussion and *persistent* posttraumatic headaches, preexisting anxiety and/or depression, and maladaptive coping styles may also be at higher risk for persistent posttraumatic headache.

Despite being classified as a secondary headache, a posttraumatic headache generally presents with clinical features that are observed in primary headache disorders, including tension-type, migraine, and cervicogenic headaches. The few reports that have thus far assessed the characteristics of posttraumatic headache in the pediatric population have also reported various proportions of migraine or tension-type characteristics, with the reported prevalence of each varying among individual studies.

Although headache is reported to be the most common symptom after concussion, there is a paucity of studies regarding the safety and efficacy of headache treatments for persistent posttraumatic headaches. Posttraumatic headaches may be difficult to treat. There are currently no established guidelines for their treatment, especially when persistent, and practices can vary widely. Most treatment algorithms proposed have been extrapolated from the primary headache literature and small noncontrolled trials of posttraumatic headache regimens. When posttraumatic headaches become problematic or persistent, a multidimensional management approach, including pharmacologic intervention, physical rehabilitation, and cognitive-behavioral therapies, are often used. Management should therefore be relevant to the type of headache and focused on the clinical needs of the child.

Like primary headache disorders, these headaches can have a substantial effect on the child's life, leading to lost school days and withdrawal from social interactions. Referral for biobehavioral therapy and coping strategies may be necessary. Adherence should be promoted and can be optimized by educating both the patient and the family about the proper use of acute and prophylactic medications, establishing realistic expectations (including expectations for recovery), and emphasizing compliance at the initiation of treatment.

Children with persistent posttraumatic headaches may require frequent analgesics. Rebound headaches are common and can complicate treatment. The excessive use of symptomatic headache medicines, most commonly simple analgesics, can cause MOHs in susceptible patients and has been well-described in patients with primary headache disorders. Medication overuse can be a contributing factor in headache chronicity in 20–30% of children and adolescents, with chronic daily headache unrelated to concussion. Because analgesics are commonly recommended for the treatment of acute headaches after concussion, some susceptible patients with concussion are at risk for developing a medication-overuse pattern that causes a chronic headache syndrome.

There is no clear evidence to help guide the clinician on the timing of initiation of preventive therapy in children to decrease the likelihood of developing persistent posttraumatic headaches. Although many medications are being used to manage persistent posttraumatic headaches, most have supporting data for the management of migraine or chronic migraine, and few have been studied for the treatment of persistent posttraumatic headaches in a systematic manner.

Sinus headache is the most overdiagnosed form of recurrent headache. Although no studies have evaluated the frequency of misdiagnosis of an underlying migraine as a sinus headache in children, in adults, it has been found that up to 90% of adults diagnosed as having a sinus headache either by themselves or their physician appear to have migraine. When headaches are recurrent and respond within hours to analgesics, migraine should be considered first. In the absence of purulent nasal discharge, fever, or chronic cough, the diagnosis of sinus headache should not be made.

MOHs frequently complicate primary and secondary headaches. An MOH is defined as a headache present for more than 15 days/month for longer than 3 months and intake of a simple analgesic on

Table 635.11 History-Related Red Flags for Secondary Headache**QUALITY**

“Thunderclap” rapid-onset headache or the “worst headache of my life”

Recent worsening in severity or frequency

Change in quality

New-onset symptoms consistent with cluster headache

LOCATION

Unilateral without alteration of sides

Chronic or recurrent occipital headache

TIMING

Awakens from sleep

Occurs in morning or causes morning vomiting

Acute or chronic progressive pattern

POSITIONAL OR ACTIVITY-RELATED VARIATIONS

Worsened in the recumbent position or when bending over

Headache experienced or worsened with cough or the Valsalva maneuver

ASSOCIATED NEUROLOGIC HISTORY

Neurologic dysfunction other than typical aura

Altered sensorium during headache

Sensory deficits or changes in vision, gait, or coordination

Other focal neurologic deficits

Seizures or syncope

Decreased visual acuity

Mental status changes (e.g., confusion or disorientation)

Regression in fine or gross motor developmental skills

Decline in cognition or school performance

Change in mood, behavior, or personality

ASSOCIATED GENERAL HISTORY

Vomiting without nausea and morning/fasting nausea or vomiting

Polyuria or polydipsia

Preschool or younger age

History of head trauma

Neck pain

Medical comorbidities

History of ventriculoperitoneal shunt

Certain medications

Signs of systemic or localized head/neck infection

Negative family history of primary headache disorders

From Lauck SM, Gage S. Headaches. In: Kliegman RM, Toth H, Bordini BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 34.5, p. 553.

more than 15 days/month and/or prescription medications, including triptans or combination medications, on more than 10 days/month. Some of the signs that should raise suspicion of medication overuse are the increasing use of analgesics (nonprescription or prescription) with either decreased effectiveness or frequent wearing off (i.e., analgesic rebound). An MOH can be worsened by ineffective medications or misdiagnosis of the headache. Patients should be cautioned against the frequent use of antimigraine medications, including combination analgesics or triptans.

Serious causes of secondary headaches are likely to be related to **increased intracranial pressure**. This can be caused by a mass (tumor, vascular malformation, cystic structure) or an intrinsic increase in pressure (idiopathic intracranial hypertension, also known as *pseudotumor cerebri*). In the former case, the headache is caused by the mass effect and local pressure on the dura; in the latter case, the headache is caused by diffuse pressure on the dura. The etiology of idiopathic intracranial hypertension may be the intake of excessive amounts of fat-soluble compounds (e.g., vitamin A, retinoic acid, and minocycline), hormonal changes (increased incidence in females), or blockage of

Table 635.12 Physical Examination Red Flags for Secondary Headaches**ABNORMAL VITAL SIGNS**

Hypertension

Growth failure

Increased head circumference or bulging fontanel

Fever

Meningeal signs with or without fever

Evidence of cranial trauma

Cranial bruit

Frontal bony tenderness

Macrocephaly

ABNORMAL OPHTHALMOLOGIC FINDINGS

Papilledema

Abnormal ocular movements

Squinting

Pathologic pupillary response

Visual field defects

ABNORMAL NEUROLOGIC FINDINGS

Impaired mental status

Cranial nerve palsy

Ataxia

Abnormal gait

Abnormal coordination

Abnormal reflexes

Asymmetric motor or sensory examination

Hemiparesis

Developmental regression

Precocious, delayed, or arrested puberty

SKIN FINDINGS

Café-au-lait or ash leaf macules

Petechiae or purpura

Facial hemangioma

Malar rash

From Lauck SM, Gage S. Headaches. In: Kliegman RM, Toth H, Bordini BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 34.6, p. 553.

venous drainage (as with inflammation of the transverse venous sinus from mastoiditis). When increased pressure is suspected, either by historical suspicion or the presence of papilledema, an MRI with magnetic resonance angiography and magnetic resonance venography should be performed, followed by a lumbar puncture if no mass or vascular anomaly is noted. The lumbar puncture can be diagnostic and therapeutic of idiopathic intracranial hypertension but must be performed with the patient in a relaxed recumbent position with legs extended, because abdominal pressure can artificially raise intracranial pressure. If headache persists or there are visual field changes, pharmaceutical treatment with a carbonic anhydrase inhibitor, optic nerve fenestration, or a shunt needs to be considered.

Additional causes of secondary headaches in children that may not be associated with increased intracranial pressure include arteriovenous malformations, berry aneurysm, collagen vascular diseases affecting the central nervous system, hypertensive encephalopathy, infectious or autoimmune etiologies, acute subarachnoid hemorrhage, and stroke. The management of secondary headache depends on the cause. Helpful laboratory tests and neuroradiologic procedures depend on the clues provided by the history (Table 635.11) and physical (Table 635.12) examination. By definition, a secondary headache has a specific cause and should resolve once this cause is treated. If the headache persists, the diagnosis and treatment should be questioned because either the diagnosis, which may include a primary headache, or the treatment, or both, may be incorrect.

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635.3 Tension-Type Headaches

Andrew D. Hershey, Marielle Kabbouche, and Joanne Kacperski

Tension-type headaches (TTHs) may be common in children and adolescents, with a prevalence in some studies as high as 48%, with those having a combination of migraine and TTH around 20%. Because of their mild to moderate nature, relative lack of associated symptoms, and lower degree of associated disability, they are often ignored or have minimal impact. The ICHD-3 subclassifies TTHs as infrequent (<12 headaches/year) (Table 635.13), frequent (1-15 headaches/month), and chronic (>15 headaches/month). They can further be separated into headaches with or without pericranial muscle tenderness. The classification of TTH can be likened to the opposite of migraine. Whereas migraines are typically moderate to severe, are focal in location, are worsened by physical activity or limit physical activity, and have a throbbing quality, TTHs are mild to moderate in severity, are diffuse in location, are not affected by activity (although the patient may not feel like being active), and are nonthrobbing (often described as a constant pressure). TTH is much less frequently associated with nausea, photophobia, or phonophobia and is never associated with more than one of these at a time or with vomiting. TTH must be recurrent, but at least 10 headaches are required, and the duration can be 30 minutes to 7 days. Secondary headaches with other underlying etiologies must be ruled out.

Evaluation of patients with suspected TTHs requires a detailed headache history and complete general and neurologic examination. This is to establish the diagnosis and ensure exclusion of secondary etiologies. When secondary headaches are suspected, further directed evaluation is indicated.

Treatment of TTHs can require acute therapy to stop attacks, preventive therapy when frequent or chronic, and behavioral therapy. It is often suspected that there may be underlying psychologic stressors (hence, the misnomer as a stress headache), but this is often difficult to identify in children, and although it may be suspected by the parents, it cannot be confirmed in the child. Studies of and conclusive evidence to guide the treatment of TTH in children are lacking, but the same general principles and medications used in migraine can be applied to children with TTHs (see Chapter 635.1). Oftentimes, simple analgesics (ibuprofen or acetaminophen) can be effective for acute treatment. Flupirtine is a nonopioid analgesic that has been approved in Europe for the treatment of TTH in children as young as age 6 years but is not available in the United States. Amitriptyline has the most evidence of effective prevention of TTH; biobehavioral intervention, including biofeedback-assisted relaxation training and coping skills, can be useful as well.

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Table 635.13	Infrequent Episodic Tension-Type Headache
A. At least 10 episodes of headache occurring on <1 day/mo on average (<12 days/yr) and fulfilling criteria B-D	
B. Lasting from 30 min to 7 days	
C. At least two of the following four characteristics:	
1. Bilateral location	
2. Pressing or tightening (nonpulsating) quality	
3. Mild or moderate intensity	
4. Not aggravated by routine physical activity, such as walking or climbing stairs	
D. Both of the following:	
1. No nausea or vomiting	
2. No more than one of photophobia or phonophobia	
E. Not better accounted for by another ICHD-3 diagnosis	

From Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd ed. Cephalalgia. 2018;38(1):1–211, Table 10.

Chapter 636

Neurocutaneous Syndromes

Mustafa Sahin, Nicole Ullrich, Siddharth Srivastava, and Anna L. Pinto

The neurocutaneous syndromes include a heterogeneous group of disorders characterized by abnormalities of both the integument and central nervous system (CNS) of variable severity (Table 636.1). Many of the disorders are hereditary and believed to arise from a defect in differentiation of the primitive ectoderm (nervous system, eyeball, retina, and skin). Disorders classified as neurocutaneous syndromes include neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), tuberous sclerosis complex (TSC), Sturge-Weber syndrome (SWS), von Hippel-Lindau disease (VHL), PHACE (posterior fossa malformations, hemangiomas, arterial anomalies, coarctation of the aorta, cardiac defects, eye abnormalities) syndrome, ataxia-telangiectasia (AT), linear nevus syndrome, hypomelanosis of Ito, and incontinentia pigmenti.

636.1 Neurofibromatosis

Nicole Ullrich

NF refers to a group of autosomal dominant genetic conditions that cause tumors to grown on nerves throughout the body. The types of NF include neurofibromatosis type 1 (NF1) and all types of schwannomatosis (SWN), including NF2-related schwannomatosis (NF2-SWN, formerly called neurofibromatosis type 2, or NF2).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

NF1 has an incidence of 1 in 2,500 live births and is caused by autosomal dominant loss-of-function pathogenic variants in the NF1 gene. Approximately 50% are inherited from an affected parent, and the other 50% result from a sporadic gene variant. The diagnostic criteria for NF1 were updated in 2021 by an international expert panel. The disease is clinically diagnosed when any two of the following manifestations are present: (1) Six or more café-au-lait macules (CALMs) >5 mm in greatest diameter in prepubertal individuals and >15 mm in greatest diameter in postpubertal individuals (Fig. 636.1). CALMs are the hallmark of neurofibromatosis and are present in almost 100% of patients. They are present at birth but increase in size, number, and pigmentation, especially during the first few years of life. The CALMs are scattered over the body surface, with predilection for the trunk and extremities. CALMs are not specific for NF1 and may be observed in other disorders (Table 636.2). (2) Axillary or inguinal freckling consisting of multiple hyperpigmented areas 2-3 mm in diameter; at least one of the two pigmentary findings (café-au-lait macules or freckling) must be bilateral (Fig. 636.2). Skinfold freckling usually appears between 3 and 5 years of age. The frequency of axillary and inguinal freckling is reported to be >80% by 6 years of age. (3) Two or more iris Lisch nodules, which are hamartomas located within the iris and are best identified by a slit-lamp examination, or two or more choroidal abnormalities (Fig. 636.3). They are present in more than 74% of patients with NF1. The prevalence of Lisch nodules increases with age, from only 5% of children younger than 3 years of age, to 42% among children 3-4 years of age, and virtually 100% of adults older than 21 years of age. (4) Two or more neurofibromas or one plexiform neurofibroma. Neurofibromas are most visible on the skin, but they may occur on any peripheral nerve in the body, including along peripheral nerves and blood vessels and within viscera, including the gastrointestinal

Table 636.1 Genetic and Clinical Features Associated with Neurocutaneous Syndromes

SYNDROME	GENE(S)	INHERITANCE	CLINICAL FEATURES
Tuberous sclerosis complex	<i>TSC1</i> (tuberous sclerosis 1; hamartin) <i>TSC2</i> (tuberous sclerosis 2; tuberin)	Autosomal dominant	Angiofibromas, hypomelanotic macules, shagreen patches, ungual fibromas, cortical dysplasias, subependymal giant cell astrocytomas, subependymal nodules, intellectual disability, epilepsy including infantile spasms, autism spectrum disorder, retinal hamartomas, cardiac rhabdomyomas, lymphangi leiomyomatosis, renal angiomyolipomas
Neurofibromatosis type 1	<i>NF1</i> (neurofibromin)	Autosomal dominant	
Schwannomatosis		Autosomal dominant	
NF2-related schwannomatosis	<i>NF2</i>		Vestibular schwannoma, meningioma, ependymoma, schwannoma, juvenile subcapsular or cortical cataract, retinal hamartoma, epiretinal membrane, affected parent, <i>NF2</i> pathogenic variant in at least two distinct tumors (formerly called NF2)
Non-NF2-related schwannomatosis			Two or more schwannomas or hybrid nerve sheath tumors AND pathogenic variant identified; no vestibular schwannomas identified
<i>SMARCB1</i> -related schwannomatosis	<i>SMARCB1</i>		
<i>LZTR1</i> -related schwannomatosis	<i>LZTR1</i>		
22q-related schwannomatosis	LOH of chromosome 22		
Schwannomatosis NOS (not otherwise specified): For those who have not had genetic testing			
Schwannomatosis NEC (not elsewhere classified): For those in whom genetic testing of blood/saliva and tumors failed to detect a pathogenic variant			
Von Hippel-Lindau	<i>VHL</i> (von Hippel-Lindau tumor suppressor)	Autosomal dominant	Cerebellar hemangioblastomas, retinal angiomas, endolymphatic sac tumors, pancreatic neuroendocrine tumors, renal cysts, renal cell carcinomas, pheochromocytomas
Linear nevus sebaceous	<i>HRAS</i> (<i>HRas</i> proto-oncogene, GTPase) <i>KRAS</i> (<i>KRAS</i> proto-oncogene, GTPase) <i>NRAS</i> (neuroblastoma RAS viral oncogene homolog)	Somatic mosaicism	Linear sebaceous nevus, hemimegalencephaly, ventriculomegaly, intellectual disability, epilepsy, ocular defects (e.g., strabismus), cardiac defects (e.g., coarctation of the aorta), urogenital defects (e.g., horseshoe kidney), skeletal defects (e.g., fibrous dysplasia)
PHACE	Unknown		Posterior fossa malformations, hemangiomas, arterial lesions (e.g., dysplasia of cerebral arteries), cardiac defects (e.g., coarctation of the aorta), ocular defects (e.g., microphthalmia), ventral defects (e.g., sternal clefting)
Incontinentia pigmenti	<i>IKBKG</i> (inhibitor of kappa B kinase gamma)	X-linked dominant	Distinctive skin lesion appearing in four stages (bullous, verrucous, pigmentary, atretic), alopecia, dental anomalies (e.g., hypodontia), intellectual disability, epilepsy, ocular defects (e.g., retinal neovascularization), nail defects (e.g., dystrophic nails)

tract. These lesions appear characteristically during adolescence or pregnancy, suggesting a hormonal influence. They are usually small, rubbery lesions with a slight purplish discoloration of the overlying skin. Plexiform neurofibromas are typically congenital and result from diffuse thickening of nerve trunks and surrounding soft tissues. The skin overlying a plexiform neurofibroma may be coarse and associated

with hyperpigmentation. Plexiform neurofibromas may produce overgrowth of an extremity and a deformity of the corresponding bone. (5) A distinctive osseous lesion such as sphenoid dysplasia (which may cause pulsating exophthalmos), anterolateral bowing of tibia (tibial dysplasia), or pseudarthrosis of a long bone. (6) Optic pathway gliomas are present in approximately 15–20% of individuals with NF1;



Fig. 636.1 Neurofibromatosis type 1 (NF1). The presence of six or more café-au-lait (CAL) spots larger than 0.5 cm in diameter in children and 1.5 cm in adolescents suggests the possibility of NF1, although having CAL spots alone does not allow for definitive diagnosis. (From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology*, 5th ed. Philadelphia: Elsevier; 2016, Fig. 11-44.)

however, only ~30% of these are clinically symptomatic and require tumor-directed therapy. They are the most frequently observed CNS tumor in NF1. Because of visual acuity compromise, it is recommended that all children with NF1 undergo at least annual ophthalmologic examinations, or more frequent ones if there is a concern. The most common time to develop symptoms is between the ages of 2 and 6 years; they manifest as a change in visual acuity, a change in the visual fields, or pallor of the optic nerve. Extension into the hypothalamus can lead to precocious puberty. The brain MRI findings of an optic glioma include diffuse thickening, localized enlargement, or a distinct focal mass originating from the optic nerve or chiasm (Fig. 636.4). (7) A parent with NF1 whose diagnosis was based on the aforementioned criteria. (8) A pathogenic *NF1* gene variant. It is important to note that genetic testing is not required to make a diagnosis of NF1, but it may allow for an earlier diagnosis. In addition, presence of a genetic variant *alone* is not sufficient to diagnose NF1; a second diagnostic feature is required.

Children with NF1 are susceptible to **neurologic complications**. MRI studies of selected children have shown abnormal hyperintense T2-weighted signals in the optic tracts, brainstem, globus pallidus, thalamus, internal capsule, and cerebellum (Fig. 636.5). These signals, **unidentified bright objects** or focal areas of signal abnormality (FASI), tend to disappear with age; most have disappeared by 30 years of age. It is unclear what the unidentified bright objects represent pathologically, and there is disagreement as to the relationship between the presence and number of unidentified bright objects and the occurrence of learning disabilities, attention-deficit disorders, behavioral and psychosocial problems, and abnormalities of speech among affected children. Therefore imaging studies such as brain MRIs should be reserved for patients with clinical symptoms only.

One of the most common complications is a learning disability affecting more than half of individuals with NF1. Seizures are observed in approximately 8% of NF1 patients. The cerebral vessels may develop aneurysms or stenosis consistent with moyamoya syndrome (see Chapter 641). Neurologic sequelae of these vascular abnormalities include transient cerebrovascular ischemic attacks, hemiparesis, and cognitive defects. Precocious puberty may become evident in the presence or absence of lesions of the optic pathway tumors. Malignant peripheral nerve sheath tumors are in the family of aggressive sarcomas and occur either *de novo* or as the result of malignant degeneration of an existing plexiform neurofibroma. The lifetime risk is 8–13%. Additionally, the incidence of pheochromocytoma, rhabdomyosarcoma, leukemia, and Wilms tumor is higher than in the general population. Scoliosis is a common complication found in approximately 10% of the patients. Patients with NF1 are at risk for hypertension, which may be present in isolation or result from renal vascular stenosis or a pheochromocytoma.

Table 636.2 Diseases Associated with Multiple Café-Au-Lait Macules

DISEASE	MAJOR FEATURES
Ataxia telangiectasia	Progressive ataxia, lymphoreticular malignancy
Bannayan-Riley-Ruvalcaba syndrome	Macrosomia, megalencephaly, lipomas, intestinal polyps
Basal cell nevus syndrome	Multiple basal cell epitheliomas, jaw cysts, skeletal anomalies
Bloom syndrome	Short stature, photosensitivity, chromosome breaks, malignancy
Fanconi anemia	Limb anomalies, renal anomalies, pancytopenia
Gaucher disease	Jewish predilection, ataxia, mental retardation
Hunter syndrome	Thickened skin, coarse facies, skin papules, joint contractures
Jaffe-Campanacci syndrome	Fibromas of long bones, hypogonadism, mental retardation, ocular/cardiac anomalies
Legius syndrome	Axillary freckling, macrocephaly, a Noonan-like facial dysmorphism, lipomas
Maffucci syndrome	Venous malformations, enchondromas
McCune-Albright syndrome	Polyostotic fibrous dysplasia, precocious puberty
Multiple lentigines syndrome	Multiple lentigines, hypertelorism, pulmonic stenosis
Multiple mucosal neuroma syndrome	Mucosal neuromas, thyroid carcinoma, pheochromocytoma, parathyroid adenoma, dysautonomia
Neurofibromatosis type 1	Neurofibromas, optic pathway glioma, central nervous system tumors, iris hamartomas, axillary freckles, skeletal anomalies, learning disabilities
Neurofibromatosis type 2-related schwannomatosis	Vestibular schwannoma, meningioma, subcapsular cataracts, skin plexiform schwannomas, ependymoma
Schwannomatosis	Multiple schwannomas or hybrid nerve sheath tumors; subtypes distinguished by the molecular phenotype of the tumor. No vestibular schwannomas present.
Russell-Silver syndrome	Short stature, asymmetry, limb anomalies
Tuberous sclerosis	White macules, multiple hamartomas, central nervous system anomalies
Watson syndrome	Pulmonic stenosis, axillary freckles, low intelligence

From Marcoux DA, Duran-McKinster C, Baselga E, et al. Pigmentary abnormalities. In: Schachner LA, Hansen RC, eds. *Pediatric Dermatology*, 4th ed. Philadelphia: Mosby; 2011: Table 10-2.

Mosaic NF1 (also called *segmental NF1*) results from a pathogenic variant that occurs after conception, leading to a mixture of cells with and without the gene variant. The manifestations are therefore limited to one or more body segments secondary to somatic (or gonadal) variants expressed in those locations. Lesions may be unilateral or bilateral, asymmetric or symmetric, and confined to a narrow band or a single quadrant. Neurologic manifestations are rare but have been reported.



Fig. 636.2 Neurofibromatosis. Axillary freckling (Crowe's sign) is a pathognomonic sign. (From Habif TP, ed. *Clinical Dermatology*, 4th ed. Philadelphia: Mosby; 2004: Fig. 26-11.)

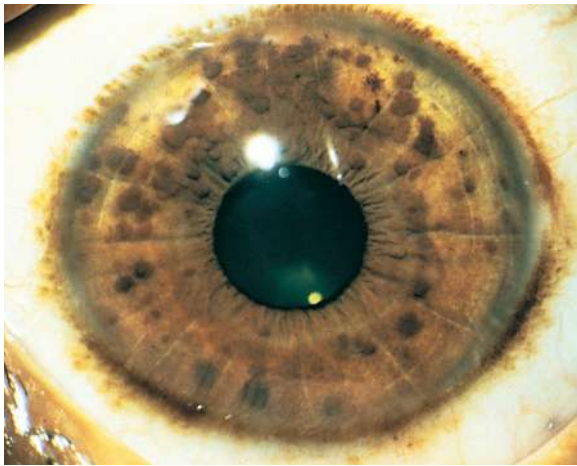


Fig. 636.3 Neurofibromatosis type 1 (NF1). Pigmented hamartomas of the iris (Lisch nodules). (From Zitelli BJ, McIntire S, Nowalk AJ, eds. *Zitelli and Davis' Atlas of Pediatric Physical Diagnosis*, 6th ed. Philadelphia: Mosby; 2012: Fig. 15-9.)

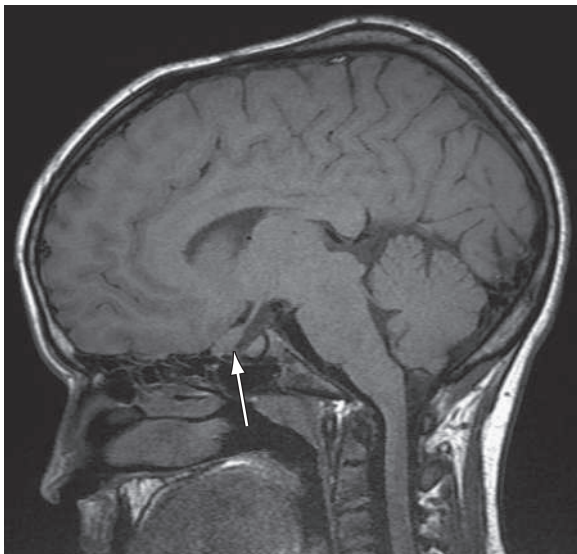


Fig. 636.4 Optic glioma. Sagittal T1-weighted MRI scan of a patient with NF1 shows thickening of the optic nerve (arrow).

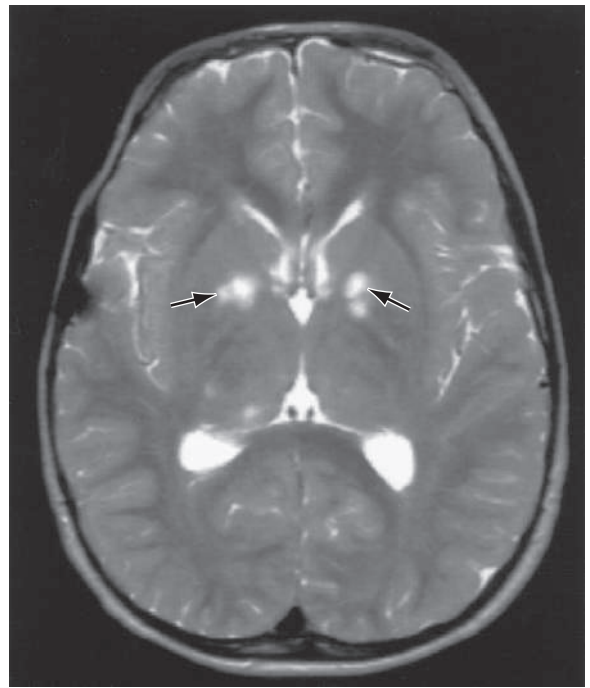


Fig. 636.5 T2-weighted MRI scan of a patient with NF1. Note the high-signal areas (unidentified bright objects or focal areas of signal abnormality [FASIs]) in the basal ganglia (arrows).

MANAGEMENT

Because of the diverse and unpredictable complications associated with NF1, close multidisciplinary follow-up is necessary. Patients with NF1 should have regular clinical assessments at least yearly, focusing the history and examination on the potential problems for which they are at increased risk. These assessments include yearly ophthalmologic examination, neurologic assessment, blood pressure monitoring, and scoliosis evaluation. Neuropsychologic and educational testing should be considered as needed. The National Institutes of Health (NIH) Consensus Development Conference has advised against routine imaging studies of the brain and optic tracts because treatment in these *asymptomatic* NF1 children is rarely required. However, all symptomatic cases (i.e., those with changes in visual acuity, optic pallor, proptosis, precocious puberty) should undergo MR imaging. Selumetinib, an oral inhibitor of mitogen-activated protein kinase kinase (MEK) 1 and 2, has been demonstrated in children (≥ 2 years of age) with NF1-related inoperable plexiform neurofibromas to be effective in inducing partial responses and reducing tumor progression.

GENETIC COUNSELING

Although NF1 is an autosomal dominant disorder, more than half the cases are sporadic, representing *de novo* pathogenic variants. The *NF1* gene on chromosome region 17q11.2 encodes for a protein also known as *neurofibromin*. Neurofibromin acts as an inhibitor of the oncogene Ras (Fig. 636.6). The diagnosis of NF1 is based on the clinical features; molecular testing for the *NF1* gene variants is available and now is included as one of the diagnostic criteria. Some scenarios in which genetic testing is particularly helpful include patients who meet only one of the criteria for clinical diagnosis, those with unusually severe disease, and those seeking prenatal/preimplantation diagnosis.

An international consensus group of NF experts updated the diagnostic criteria for neurofibromatosis type 2 and **schwannomatosis** (SWN). SWN is the umbrella term used to describe the group of overlapping conditions in which a patient has multiple schwannomas. The criteria also address the discovery of the genes involved, assists in distinguishing the types of neurofibromatosis and SWN using classification according to

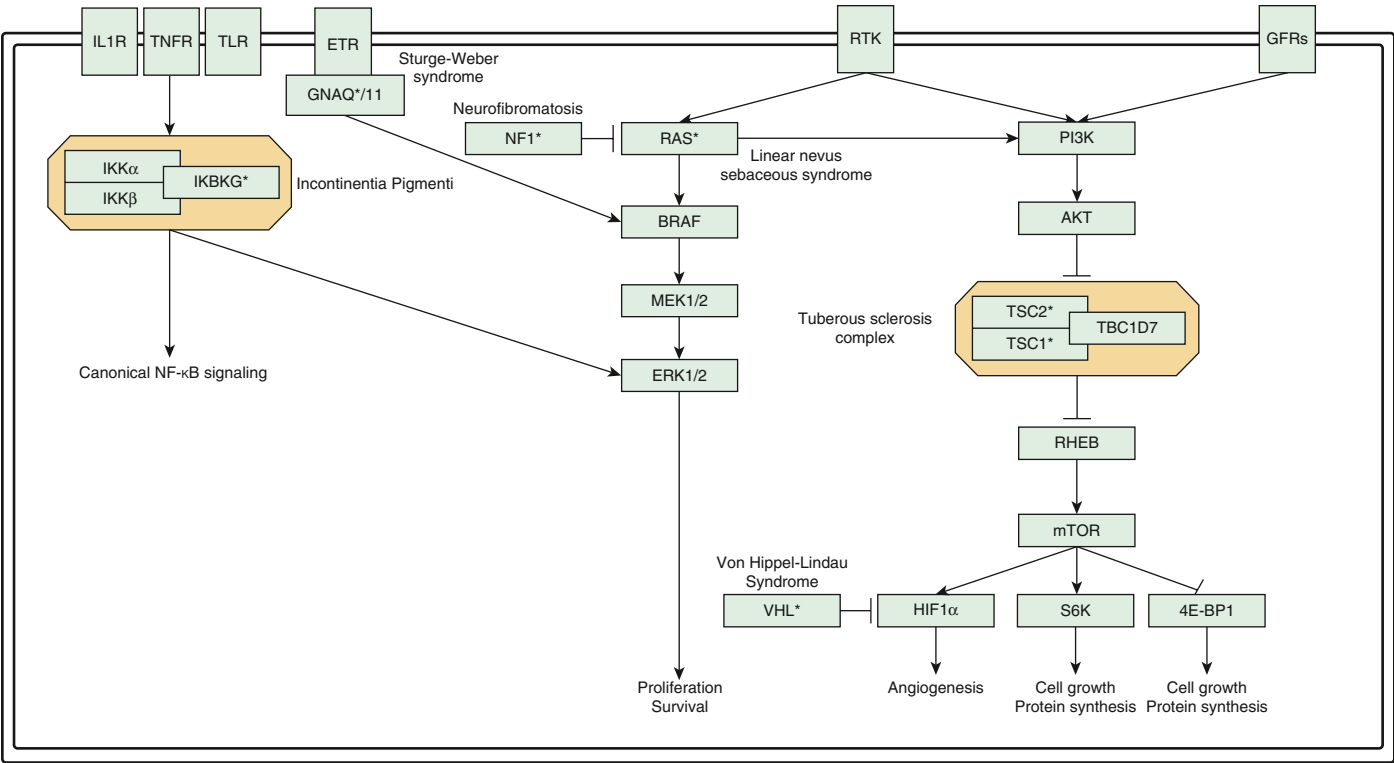


Fig. 636.6 Schematic representation of the cellular pathways affected by pathogenic variants in the genes associated with neurocutaneous disorders, such as NF1, TSC, and SWS. The asterisks denote genes with associated syndromes discussed in the chapter.

the pathogenic variant identified, and minimizes the misdiagnosis with NF1. Genetic testing for the variants involved in all subtypes of SWN is available and should be completed whenever possible for a patient suspected of having this diagnosis. This can be performed on a blood or saliva sample, but often requires tumor tissue. There are several key updates to the former NF2 diagnostic criteria: *NF2* pathologic variant added; clarification of first-degree relative with “other than sibling”; cataract clarified as juvenile cataract; retinal hamartoma added as a criterion; glioma and neurofibroma removed; and ependymoma added (Table 636.3).

Genetic testing identifies pathogenic variants in the *NF2* gene in 66-90% of individuals with *NF2*-schwannomatosis (*NF2*-SWN), which has an incidence of 1:25,000 worldwide. The *NF2* gene (which codes for a protein known as merlin or schwannomin) is located on chromosome 22q1.11. Table 636.4 notes the frequency of lesions in *NF2*. Testing is *not* required for the diagnosis and it remains possible to diagnose *NF2*-SWN based on clinical criteria. Genetic testing is required for the diagnosis of a specific type of schwannomatosis (except *NF2*-related or NOS). Excluding *NF2*-SWN, the other types of SWN affect 1:70,000 individuals. Genetic testing alone is not sufficient to make a diagnosis and there must also be a clinical feature. In most cases, tissue from schwannoma or hybrid nerve sheath tumor is required to diagnose the type of SWN and to distinguish between *LZTR1*-related SWN, *SMARCB1*-related SWN, *22q*-related SWN and SWN NOS/NEC.

Individuals with *NF2*-SWN may present with tinnitus, hearing loss, facial weakness, headache, and gait instability. Although this may present in childhood, VS are more likely to appear in the second and third decades of life. In the pediatric age group, café au lait macules and cutaneous plexiform schwannomas are the most common presentation and can be confused with the skin findings in NF1.

Workup should include ophthalmologic evaluation (assessing for subcapsular or cortical cataracts), MRI of the brain and spine, and audiology evaluation. These are all important components of ongoing surveillance and management of individuals with suspected or confirmed *NF2*-related SWN. The goal is to preserve hearing related to VS. Other forms of SWN should be suspected when an individual has two or more schwannomas in the absence

Table 636.3	Diagnostic Criteria for <i>NF2</i> -Related Schwannomatosis (Formerly Called Neurofibromatosis Type 2 [NF2])
A diagnosis of <i>NF2</i> -related schwannomatosis can be made when a patient has one of the following :	
• Bilateral vestibular schwannomas (VS) • An identical <i>NF2</i> pathogenic variant in at least two anatomically distinct <i>NF2</i>-related tumors (schwannoma, meningioma, and/or ependymoma)	
Either two major OR one major and two minor criteria are present as follows:	
MAJOR CRITERIA	
• Unilateral vestibular schwannoma • First-degree relative other than a sibling with <i>NF2</i>-related schwannomatosis • Two or more meningiomas • <i>NF2</i> pathogenic variant in an unaffected tissue, such as blood	
MINOR CRITERIA	
Can count more than one of a type (e.g. two schwannomas = two minor criteria)	
• Ependymoma • Schwannoma (note that if the major criterion is a unilateral VS, at least one schwannoma must be dermal in location)	
Can count only once	
• Juvenile subcapsular or cortical cataract • Retinal hamartoma • Epiretinal membrane in a person aged less than 40 years • Single meningioma (meningioma cannot be used as both a major and a minor criteria)	

Table 636.4 Frequency of Lesions Associated with Neurofibromatosis Type 2-Related Schwannomatosis*

	FREQUENCY OF ASSOCIATION WITH NF2-RELATED SCHWANNOMATOSIS
NEUROLOGIC LESIONS	
Bilateral vestibular schwannomas	90–95%
Other cranial nerve schwannomas	24–51%
Meningioma	45–58%
Spinal schwannomas	63–90%
Spinal ependymoma	20%
Peripheral neuropathy	Up to 66%
OPHTHALMOLOGIC LESIONS	
Juvenile subcapsular or cortical cataract	60–81%
Epiretinal membranes (age less than 40 years)	12–40%
Retinal hamartomas	6–22%
CUTANEOUS LESIONS	
Cutaneous schwannomas	59–68%
Subcutaneous tumors	43–48%
Intradermal tumors	Rare

*Formerly known as NF2.

Modified from Asthagiri AR, Parry DM, Butman JA, et al. Neurofibromatosis type 2. *Lancet*. 2009;373:1974–1984, Table 1.

of bilateral vestibular schwannomas. Evaluation also includes imaging of the brain and spine to exclude VS and to distinguish from NF2-related SWN.

Legius syndrome (caused by *SPRED1* pathogenic variants) is an autosomal dominant disorder with skin findings that resemble and may be hard to distinguish from NF1 in younger individuals. Persons with Legius syndrome present with multiple CALMs and macrocephaly, with and without skinfold freckling. However, other typical features of NF1, such as Lisch nodules, neurofibromas, optic nerve gliomas, long bone dysplasia, plexiform neurofibromas, and malignant peripheral nerve sheath tumors, are not seen in individuals with *SPRED1* variants.

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636.2 Tuberous Sclerosis

Siddharth Srivastava and Mustafa Sahin

Tuberous sclerosis complex (TSC) is a multisystem disease characterized by an autosomal dominant mode of inheritance, variable expressivity, and a prevalence of 1 in 6,000–10,000 newborns. Spontaneous pathogenic variants occur in 65% of the cases. Molecular genetic studies have identified two foci for TSC: the *TSC1* gene (located on chromosome 9q34) and the *TSC2* gene (located on chromosome 16p13). The *TSC1* gene encodes a protein called *hamartin*, and the *TSC2* gene encodes a protein called *tuberin*. Within a cell, these two molecules form a complex along with a third protein, TBC1D7 (Tre2-Bub2-Cdc16 1 domain family, member 7). Consequently, a pathogenic variant in either the *TSC1* gene or the *TSC2* gene results in a similar disease in patients, though individuals with *TSC2* variants tend to be more severely affected.

Tuberin and hamartin are involved in a key pathway in the cell that regulates protein synthesis and cell size (see Fig. 636.6). One of the ways

cells regulate their growth is by controlling the rate of protein synthesis. A protein called *mechanistic target of rapamycin* (mTOR) is one of the master regulators of cell growth (mTOR has additional roles in the CNS, where it helps regulate neuronal development and synaptic plasticity). mTOR, in turn, is controlled by Ras homolog enriched in brain (RHEB), a small cytoplasmic guanosine triphosphatase. When RHEB is activated, the protein synthesis machinery is turned on, most likely via mTOR signaling, and the cell grows. Under normal conditions, the tuberin/hamartin complex keeps RHEB in an inactive state. However, in TSC, there is disinhibition of RHEB and subsequent overactivation of the mTOR pathway. Accordingly, the *TSC1* and *TSC2* genes can be considered tumor-suppressor genes. The loss of either tuberin or hamartin protein results in the formation of numerous benign tumors (hamartomas).

TSC is an extremely heterogeneous disease with a wide clinical spectrum varying from severe intellectual disability and intractable epilepsy to normal intelligence and a lack of seizures. This variation is often seen within the same family, that is, with individuals within a family carrying the same variant. The disease affects many organ systems other than the skin and brain, including the heart, kidney, eyes, lungs, and bone (Fig. 636.7).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Definite TSC is diagnosed when at least two major or one major plus two minor features are present (Tables 636.5 and 636.6 list the major and minor features). In addition, carrying a pathogenic variant in *TSC1* or *TSC2* is sufficient for the diagnosis of TSC.

The hallmark of TSC is the involvement of the CNS. The characteristic brain lesion is a cortical tuber (Fig. 636.8). Brain MRI is the best way of identifying cortical tubers, which can form before birth.

Subependymal nodules are lesions found along the wall of the lateral ventricles, where they undergo calcification and project into the ventricular cavity, producing a candle-dripping appearance. These lesions do not cause any problems; however, in 5–10% of cases, these benign lesions can grow into **subependymal giant cell astrocytomas (SEGAs)**. These tumors can grow and block the circulation of cerebrospinal fluid around the brain and cause hydrocephalus, which requires immediate neurosurgical intervention. Thus it is recommended that all asymptomatic TSC patients undergo brain MRI every 1–3 years to monitor for new occurrences of SEGA. Patients with large or growing SEGAs, or with SEGAs causing ventricular enlargement without other manifestations, should undergo MRI scans more frequently, and the patients and their families should be educated regarding the potential of new symptoms caused by increased intracranial pressure. Surgical resection should be performed for acutely symptomatic SEGA. For growing but otherwise asymptomatic SEGAs, either surgical resection or medical treatment with an mTOR inhibitor (sirolimus, everolimus) may be used. Treatment with everolimus can be effective in slowing the growth or even reducing the size of SEGAs. Everolimus is also effective in treating renal angiomyolipomas. Sirolimus is also effective in treating lymphangiomyomatosis, renal angiomyolipomas, and cardiac rhabdomyomas.

The most common neurologic manifestations of TSC are epilepsy, intellectual disability, and autism spectrum disorder. TSC may present during infancy with infantile spasms and a hypsarrhythmic electroencephalogram pattern. However, it is important to remember that TSC patients can have infantile spasms without hypsarrhythmia. The seizures may be difficult to control, and at a later age, they may develop into other seizure types such as focal-onset seizures or generalized myoclonic seizures (see Chapter 633). Vigabatrin is the first-line therapy for infantile spasms. Adrenocorticotrophic hormone (ACTH) or prednisolone can be used if treatment with vigabatrin fails. Anticonvulsant therapy for other seizure types in TSC should generally follow that of other epilepsies, and epilepsy surgery can be considered for medically refractory TSC patients. Everolimus (adjunctive) has received U.S. Food and Drug Administration (FDA) approval for treatment-refractory focal seizures in TSC. Studies on prevention of epilepsy with preemptive treatment with vigabatrin have yielded mixed results so far. However, it is recommended that infants with TSC should undergo baseline EEG to enable early detection and treatment

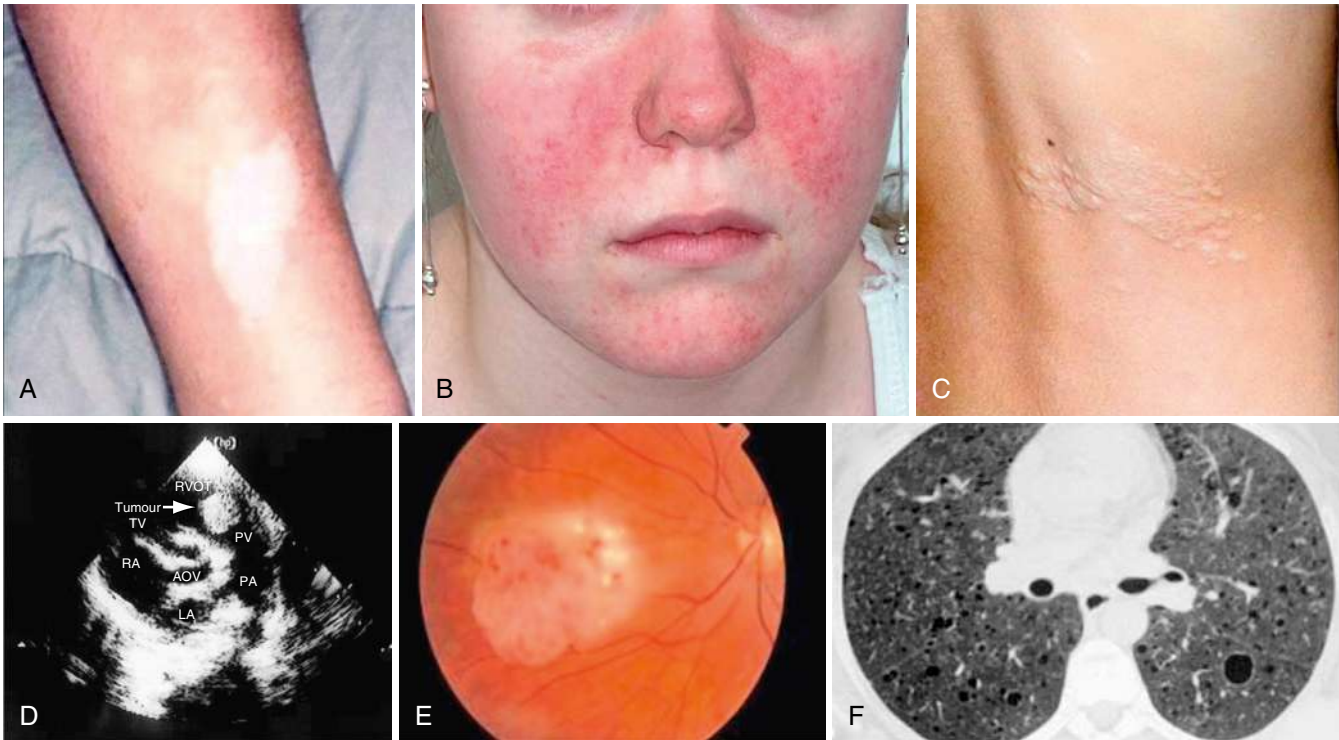


Fig. 636.7 Dermatologic, cardiac, and pulmonary manifestations of tuberous sclerosis. A, Hypomelanotic macules. B, Facial angiofibromas. C, Shagreen patch. D, Hyperechoic rhabdomyoma detected by echocardiography. E, Retinal hamartoma. F, Lymphangioleiomyomatosis. (From Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. *Lancet*. 2008;372:657–668, Fig. 7.)

Table 636.5	Major Features of Tuberous Sclerosis Complex
Cortical dysplasias (including tubers and cerebral white matter migration lines)	
Subependymal nodules	
Subependymal giant cell astrocytoma	
Facial angiofibromas (≥3) or forehead plaque	
Ungual fibromas (≥2)	
Hypomelanotic macules (≥3, ≥5mm in diameter)	
Shagreen patch	
Multiple retinal nodular hamartomas	
Cardiac rhabdomyoma	
Renal angiomyolipoma	
Pulmonary lymphangioleiomyomatosis	

Table 636.6	Minor Features of Tuberous Sclerosis Complex
Dental enamel pits (>3)	
Intraoral fibromas (≥2)	
Retinal achromic patch	
Confetti skin lesions	
Nonrenal hamartomas	
Multiple renal cysts	

of seizures, and this should be repeated every 6 weeks until 12 months of age. In addition to epilepsy, about 90% of individuals with TSC have a spectrum of cognitive, behavioral, psychiatric, and academic impairments termed *tuberous sclerosis–associated neuropsychiatric disorders (TANDs)*, which include intellectual disability, autism spectrum disorder, attention-deficit/hyperactivity disorder, anxiety, and depression. About 45% of individuals with TSC have intellectual disability, and up to 25–50% have autism spectrum disorder.

Skin Lesions

More than 90% of patients show the typical hypomelanotic macules that have been likened to an ash leaf on the trunk and extremities.

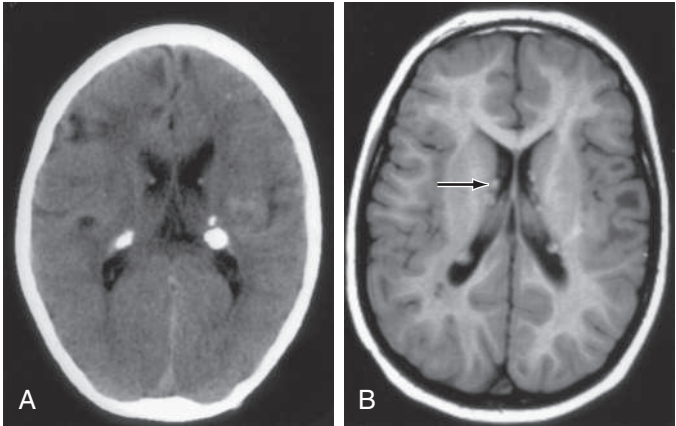


Fig. 636.8 Tuberous sclerosis. A, CT scan with subependymal calcifications characteristic of tuberous sclerosis. B, The MRI demonstrates multiple subependymal nodules in the same patient (arrow). Parenchymal tubers are also visible on both the CT and the MRI scan as low-density areas in the brain parenchyma.

Visualization of the hypomelanotic macule is enhanced by using a Wood ultraviolet lamp (see Chapter 694). To count as a major feature, at least three hypomelanotic macules must be present (see Fig. 636.7). Facial angiofibromas develop between 4 and 6 years of age; they appear as tiny red nodules over the nose and cheeks and are sometimes confused with acne (see Fig. 636.7). Later, they enlarge, coalesce, and assume a fleshy appearance. Topical rapamycin is approved for treatment of facial angiofibromas. A shagreen patch is also characteristic of TSC and consists of a roughened, raised lesion with an orange-peel consistency located primarily in the lumbosacral region (see Fig. 636.7). Forehead fibrous plaques usually occur on one side of the forehead. They are characteristically raised, yellow-brown or flesh-colored, and soft to hard in consistency. Forehead plaques are histologically similar to facial angiofibromas, though the former can appear at any point. During adolescence or later, small fibromas or nodules of skin may form around fingernails or toenails (ungual fibromas) in 15–20% of TSC patients (Fig. 636.9).



Fig. 636.9 Periungual fibroma in a patient with tuberous sclerosis complex (TSC).

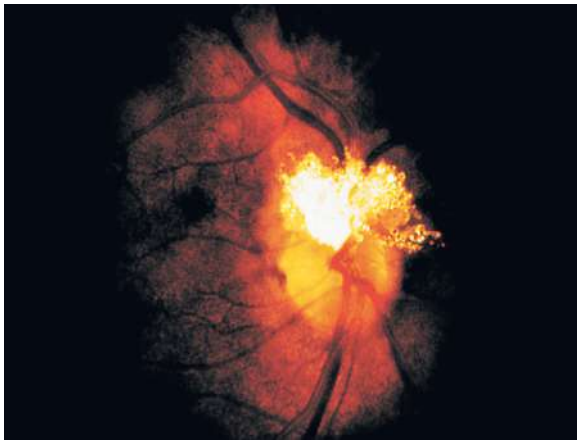


Fig. 636.10 A mulberry lesion involving the superior part of the optic nerve in a patient with tuberous sclerosis. (From Yanoff M, Sassani JW. *Ocular Pathology*, 7th ed. Philadelphia: WB Saunders; 2015: Fig. 2-7.)

Other Organ Involvement

Retinal lesions consist of two types: hamartomas (elevated mulberry lesions or plaque-like lesions (Fig. 636.10) and white depigmented patches (similar to the hypopigmented skin lesions). Approximately 50% of children with TSC have cardiac rhabdomyomas, which may be detected in the fetus by an echocardiogram, usually by 20–30 weeks of gestation. The rhabdomyomas may be numerous and located throughout the ventricular myocardium, and although they can cause congestive heart failure and arrhythmias in a minority of patients, they tend to slowly resolve spontaneously. In 75–80% of patients older than 10 years of age, the kidneys display angiomyolipomas that are usually benign tumors. Angiomyolipomas begin in childhood in many individuals with TSC, but they may not be problematic until young adulthood. By the third decade of life, they may cause lumbar pain and hematuria from slow bleeding, and rarely they may result in sudden retroperitoneal bleeding. Embolization followed by corticosteroids to alleviate postembolization syndrome is first-line therapy for angiomyolipoma presenting with acute hemorrhage. Nephrectomy should be avoided as a way of maintaining renal function, because lesions can be numerous and bilateral. For asymptomatic, growing angiomyolipomas measuring larger than 3 cm in diameter, an mTOR inhibitor, everolimus, is approved for treatment by the FDA. Selective embolization or kidney-sparing resection is an alternative therapy for asymptomatic angiomyolipoma. Single or multiple renal cysts are also commonly present in TSC; renal cell carcinoma, on the other hand, is rare. Lymphangioleiomyomatosis is the classic pulmonary lesion in TSC and only affects women, beginning in late adolescence (≥ 15 years). Sirolimus is approved by the FDA for lymphangioleiomyomatosis. Topical rapamycin should be considered for treatment of facial angiofibromas.

Diagnosis of TSC relies on a high index of suspicion, especially when assessing a child with infantile spasms. A careful evaluation for the typical skin and retinal lesions should be completed in all patients with a seizure disorder or autism spectrum disorder. Brain MRI can confirm the clinical diagnosis in many cases. Genetic testing for pathogenic *TSC1* and *TSC2* variants is available and should be considered when the individual patient does not meet all the clinical criteria, or in order to provide molecular confirmation of a clinical diagnosis. Prenatal testing may be offered when a known pathogenic *TSC1/TSC2* variant exists in that family.

MANAGEMENT

The following are recommended for routine follow-up of individuals with TSC in addition to physical examination: brain MRI every 1–3 years; abdominal MRI to evaluate the kidneys every 1–3 years; echocardiogram every 1–3 years in patients with cardiac rhabdomyomas until there is regression of the rhabdomyomas; electrocardiogram every 3–5 years; high-resolution chest CT every 5–10 years in females older than 18 years; dental examination twice a year; skin examinations once a year; detailed ophthalmic examination once a year in patients with vision concerns or retinal lesions (sooner if they are receiving treatment with vigabatrin); neurodevelopmental testing at the beginning of first grade or sooner based on concerns; and screening for TAND at each clinic visit. Based on the complications of the disease, additional follow-up testing may be required for each individual. Symptoms and signs of increased intracranial pressure suggest obstruction of the foramen of Monro by a SEGA and warrant immediate investigation and surgical intervention.

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636.3 Sturge-Weber Syndrome

Anna L. Pinto

Sturge-Weber syndrome (SWS) is a segmental vascular neurocutaneous disorder with a constellation of symptoms and signs characterized by capillary malformation in the face (port-wine birthmark [PWB]) and brain (leptomeninges), as well as abnormal blood vessels of the eye leading to glaucoma. Low flow of the leptomeningeal capillary malformation appears to result in a chronic hypoxic state leading to cortical atrophy and calcifications. Patients present with seizures, hemiparesis, stroke-like episodes, headaches, and developmental delay. Approximately 1 in 20,000–50,000 live births are affected with SWS.

ETIOLOGY

The nonsyndromic PWBs and SWS are caused by a pathologic somatic single-nucleotide variant (c.548G→A, p.Arg183Gln) in the *GNAQ* gene (see Fig. 636.6). Brain tissue from SWS patients also demonstrates the same change in the *GNAQ* gene. These results strongly suggest that SWS occurs as a result of a *mosaic pathologic genetic variant* in *GNAQ*.

The *GNAQ* p.R183Q variant is enriched in endothelial cells in SWS brain lesions, thereby revealing endothelial cells as a source of aberrant Gαq signaling. The timing of the somatic variant in *GNAQ* during development likely affects the clinical phenotype. Mosaic-activating *GNA11* and *GNB2* gene variants have been described in atypical SWS cases. The aberrant G-protein signaling provides a molecular basis to explain SWS lesions.

CLINICAL MANIFESTATIONS

Facial PWBs are present at birth, but not all are associated with SWS (Table 636.7). In fact, the overall incidence of SWS has been reported to be 20–40% in those with a PWB involving the forehead and upper eyelid. High-risk PWB for SWS includes hemifacial, median, and forehead phenotypes (Fig. 636.11), along with large segmental PWB. The PWB tends to be unilateral and ipsilateral to the brain involvement (Fig. 636.12). The capillary malformation may also be evident over the lower face and trunk and in the mucosa of the mouth and pharynx. Buphthalmos and glaucoma of the ipsilateral eye are common

Table 636.7	Port-Wine Birthmark–Associated Syndromes
Sturge-Weber syndrome	
Klippel-Trénaunay syndrome	
Parkes Weber syndrome	
Phakomatosis pigmentovascularis	
Proteus syndrome	
CLOVES syndrome	
Macrocephaly–capillary malformation (M-CM) syndrome	
Capillary malformation–arteriovenous malformation (CM-AVM) syndrome	
Cobb syndrome	
Bannayan-Riley-Ruvalcaba syndrome	
Beckwith-Wiedemann syndrome	
Von Hippel-Lindau disease	
Rubinstein-Taybi syndrome	
Wyburn-Mason syndrome	
Roberts syndrome	
Coat disease	
Nonsyndromic, idiopathic, neurologically asymptomatic	

CLOVES, Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/skeletal and spinal anomalies.
From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology*, 5th ed. Philadelphia: Elsevier; 2016: Box 12-2.

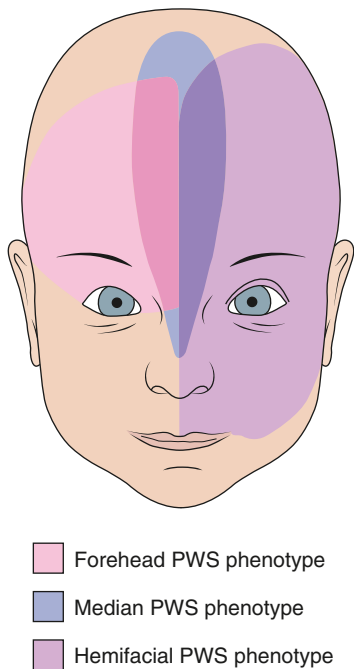


Fig. 636.11 Port-wine stain (birthmark) phenotypes associated with highest risk of Sturge-Weber syndrome. (From Zallmann M, Mackay MT, Leventer RJ, et al. Retrospective review of screening for Sturge-Weber syndrome with brain magnetic resonance imaging and electroencephalography in infants with high-risk port-wine stains. *Pediatr Dermatol*. 2018;35:575–581, Fig.1, p. 576.)

complications. Seizures occur in 75–80% of all SWS patients and in over 90% of those with bilateral brain involvement. Early onset of seizures will likely occur during the first year of life but rarely during the first month of life, and they are typically focal clonic and contralateral to the side of the facial PWB. They may become refractory to anticonvulsants, and status epilepticus is often associated. One third of children with intractable epilepsy associated with SWS experience episodes of *prolonged postictal deficits*, which would last from 1 day to a few years, until recovering back to baseline. Some patients also develop slowly progressive hemiparesis. Transient strokelike episodes or visual field defects persisting for several days and unrelated to seizure activity are common and probably result from thrombosis of cortical veins in the affected region. Although neurodevelopment appears to be normal in the first year of life, intellectual disability



Fig. 636.12 Port-wine birthmark involving both the V1 and V2 dermatomes. (Courtesy Dr. Anne W. Lucky, Cincinnati Children's Hospital.)

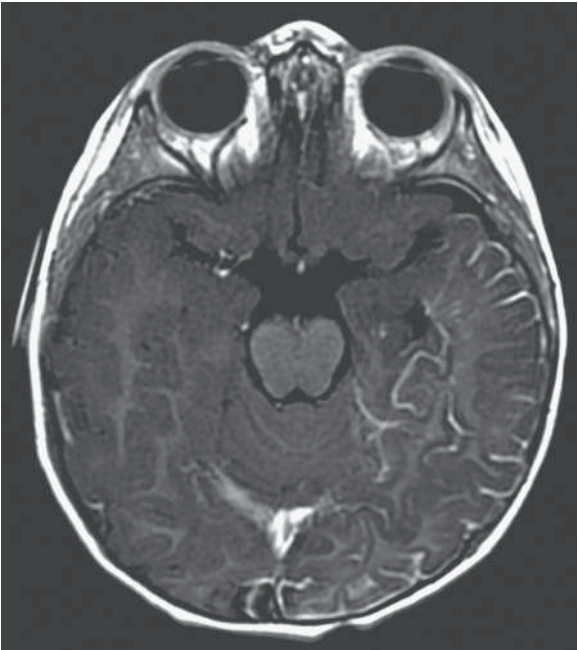


Fig. 636.13 Gadolinium-enhanced axial T1 fluid-attenuated inversion recovery (FLAIR) images of a 15-mo-old with Sturge-Weber syndrome show leptomeningeal enhancement in the left hemisphere.

or severe learning disabilities are present in at least 50% of patients in later childhood, probably the result of intractable epilepsy and increasing cerebral atrophy. The degree of visual field defect, hemiparesis, seizure frequency, and cognitive function (based on age-group: infant/preschooler, child, and adult) can be rated using a validated SWS neurologic rating system.

DIAGNOSIS

Brain MRI with contrast is the imaging modality of choice for demonstrating the extension of pial capillary malformation in SWS (Fig. 636.13). White matter abnormalities are common and are thought to be a result of chronic hypoxia. Often, atrophy is noted ipsilateral to the leptomeningeal capillary malformation. Calcifications can be seen best with a head CT (Fig. 636.14). The choroid plexus is frequently enlarged, and the degree of plexal enlargement shows a positive correlation with the extent of the leptomeningeal capillary malformation. Positron emission tomography using 18 F-deoxyglucose has been used to study cerebral metabolism in patients with SWS, and it has been useful for the surgical planning and prognosis. Ophthalmologic evaluation examining for glaucoma is also necessary and is a lifelong concern because ocular complications can occur at any moment during a lifetime. Based on the involvement of the brain and the face, there are three types of SWS in the Roach Scale:

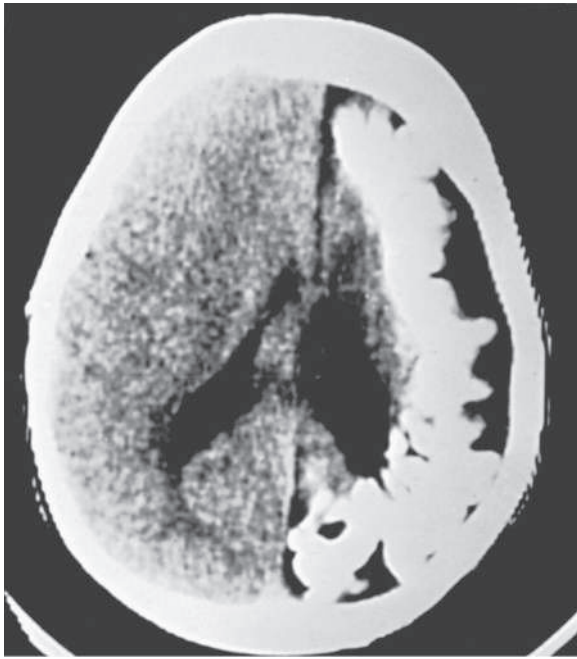


Fig. 636.14 CT scan of a patient with Sturge-Weber syndrome showing unilateral calcification and underlying atrophy of a cerebral hemisphere.

Type I: Classic facial and leptomeningeal capillary malformation present; often with glaucoma.

Type II: Facial capillary malformation alone (no CNS involvement); may have glaucoma.

Type III: Isolated leptomeningeal capillary malformation; usually no glaucoma.

In addition, there is an overlap syndrome between SWS and **Klippel-Trénaunay syndrome** (mixed capillary, venous, or lymphatic malformations involving bone and muscle in one limb).

MANAGEMENT

The management of SWS is primarily symptomatic and multidisciplinary but not well studied by prospective studies. Treatment is aimed at seizure control, relief of headaches, and prevention of stroke-like episodes, as well as monitoring of glaucoma and laser therapy for the cutaneous capillary malformations. Most infants with SWS brain involvement have seizure onset by 2 years of age. Presymptomatic treatment in high-risk babies may prevent or delay seizure onset. For patients with well-controlled seizures and normal or near-normal development, management consists of anticonvulsants and surveillance for complications, including glaucoma and behavioral abnormalities. If the seizures are refractory to anticonvulsant therapy, especially in infancy and the first 1-2 years and arise from primarily one hemisphere, most medical centers advise a hemispherectomy or, if well indicated, focal disconnections. The use of low-dose aspirin is controversial. The medication is not used routinely, but patients with stroke-like events and frequent refractory seizures may benefit from this form of treatment. Because of the risk of glaucoma, regular measurement of intraocular pressure is indicated. The facial PWB is often a target of ridicule by classmates, leading to psychologic trauma. Pulsed-dye laser therapy often provides excellent clearing of the PWB, particularly if it is located on the forehead.

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636.4 Von Hippel-Lindau Disease

Siddharth Srivastava and Mustafa Sahin

von Hippel-Lindau disease affects many organs, including the cerebellum, spinal cord, retina, endolymphatic sac of the inner ear, kidney, pancreas, adrenal glands, epididymis, and broad ligament of the

uterus. Its incidence is around 1 in 36,000 newborns. It results from an autosomal dominant pathogenic variant affecting a tumor suppressor gene, *VHL*. Approximately 80% of affected individuals have an inherited variant, and approximately 20% have a de novo variant. Molecular testing is available and detects pathogenic variants in most probands.

The major neurologic feature of the condition is CNS hemangioblastomas, including brain hemangioblastomas and spinal hemangioblastomas. In affected individuals, brain hemangioblastomas commonly affect the cerebellum. Patients with cerebellar hemangioblastoma can present in early adult life with symptoms and signs of increased intracranial pressure. A brain CT or MRI scan typically shows a cystic cerebellar lesion with a vascular mural nodule. A smaller number of patients have hemangioblastoma of the spinal cord, producing pain as well as sensory and motor changes. Syringomyelia often accompanies symptomatic spinal hemangioblastomas in von Hippel-Lindau disease. Surgical intervention for symptomatic CNS hemangioblastomas and syringomyelia is often warranted.

Approximately 70% of individuals with von Hippel-Lindau disease have retinal angiomas (also known as *retinal hemangioblastomas*), which have identical histology as CNS hemangioblastomas. Retinal angiomas, which can present in childhood, are characterized by small masses of thin-walled capillaries that are fed by large and tortuous arterioles and venules. They are usually located in the peripheral retina so that vision is unaffected. Exudation in the region of the angiomas may lead to retinal detachment and visual loss. Retinal angiomas are treated with photocoagulation and cryocoagulation, though outcomes can vary depending on the characteristics of the lesions, and complications such as retinal edema can occur.

Cysts (affecting the kidneys, pancreas, and liver), as well as tumors/malignancies (including endolymphatic sac tumors, pheochromocytoma, paragangliomas, neuroendocrine tumors of the pancreas, renal cell carcinomas, epididymis cystadenomas, and broad ligament cystadenomas) are associated with von Hippel-Lindau disease. Renal carcinoma and CNS hemangioblastomas can be causes of death in affected individuals. Regular follow-up and appropriate imaging studies are necessary to identify lesions that may be treated at an early stage. In affected individuals ≥ 1 year, there should be yearly ophthalmology evaluation for retinal angiomas. Beginning in the first decade of life, there should be yearly clinical assessment for neurological concerns, vision concerns, and hearing concerns, as well as measurement of blood pressure. At age 5 years, laboratory screening for pheochromocytoma should begin. Beginning at age 11 years, there should be brain and complete spine MRI every 2 years to evaluate for CNS lesions, with particular focus on the inner/petrous temporal bone and posterior fossa. Beginning at age 11 years, there should also be formal audiology assessment every 2-3 years to screen for endolymphatic sac tumors. Formal audiological assessment should occur sooner and more frequently if symptoms such as hearing loss, tinnitus, and vertigo are present. Beginning at age 15 years, there should be MRI of the abdomen (including kidney, pancreas, and adrenal glands) every 2 years to evaluate for visceral lesions. At age 15-20 years in asymptomatic individuals, there should be an MRI of internal auditory canals to screen for endolymphatic sac tumor.

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636.5 Linear Nevus Sebaceous Syndrome

Siddharth Srivastava and Mustafa Sahin

This sporadic condition is characterized by a large facial nevus, neurodevelopmental abnormalities, and systemic defects. The nevus is usually located on the forehead and nose and tends to be midline in its distribution, although it may affect other locations, such as the scalp and neck. It may be quite faint during infancy but later becomes hyperkeratotic, with a yellow-brown appearance.

The most common associated CNS finding is unilateral hemimegalencephaly (enlargement of one cerebral hemisphere), which affects

about half of patients. Other structural brain abnormalities include enlargement of the lateral ventricles, white matter hyperintensity on T2-weighted imaging, cortical dysplasia, pachygyria, agyria, agenesis of the corpus callosum, and Dandy-Walker malformation. The incidence of epilepsy and intellectual disability is as high as 75% and 60%, respectively. Focal neurologic signs, including hemiparesis and homonymous hemianopia, may occur.

Other organ systems may be involved, including the eyes (strabismus, retinal abnormalities, coloboma, cataracts, corneal revascularization, ocular hemangiomas, and lipodermoid scleral tumors); heart (aortic coarctation, ventricular septal defect); kidneys (horseshoe kidney); and skeleton (fibrous dysplasia, skeletal hypoplasia, scoliosis/kypthoscoliosis, and vitamin D-resistant hypophosphatemic rickets).

The syndrome is associated with somatic variants in members of the Ras family of oncogenes, including *HRAS* (HRas proto-oncogene, GTPase), *KRAS* (KRAS proto-oncogene, GTPase), and *NRAS* (neuroblastoma RAS viral oncogene homolog) (see Fig. 636.6).

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636.6 PHACE Syndrome

Siddharth Srivastava and Mustafa Sahin

See also Chapter 691.

The syndrome denotes posterior fossa malformations, hemangiomas, arterial anomalies, coarctation of the aorta and other cardiac defects, and eye abnormalities (see Chapter 691). It is also referred to as *PHACES syndrome* when ventral developmental defects, including sternal clefting and/or a supraumbilical raphe, are present. The hallmark of the disorder is infantile hemangiomas affecting the face, neck, and/or scalp. The underlying pathogenesis of PHACE syndrome remains unknown, though evidence that infantile hemangiomas may result from abnormal growth and differentiation of hemogenic endothelium highlights some avenues for further investigation. Overall, there is a female predominance, but the reasons for this association are unclear.

Other organ systems besides the skin are commonly affected in PHACE syndrome. Posterior fossa anomalies affect up to 80% of patients and encompass Dandy-Walker malformation and cerebellar hypoplasia/dysplasia. Less common structural brain anomalies include neuronal migration defects (polymicrogyria, heterotopia, cortical dysplasia), dysgenesis of the corpus callosum or septum pellucidum, and pituitary defects. Congenital heart disease affects up to two thirds of patients, and common defects are aortic anomalies (coarctation of aorta, dysplasia of aortic arch) and aberrant left subclavian artery. The facial hemangioma is typically ipsilateral to the aortic arch anomalies. Arterial anomalies include hypoplasia/dysplasia/altered anatomic course of cervical, cerebral, and brachiocephalic arteries. Cerebrovascular anomalies can result in progressive arterial stenosis and acute ischemic stroke. Ophthalmologic findings include persistent fetal vasculature (also known as *persistent hyperplastic primary vitreous*), retinal vascular anomalies, morning glory disc anomaly, optic nerve hypoplasia, peripapillary staphyloma, coloboma, cataracts, and microphthalmia. Endocrinopathies (such as hypopituitarism, hypogonadism, hypothyroidism, ectopic thyroid gland, growth hormone deficiency, and diabetes insipidus) can occur. Midline defects of the chest and abdomen encompass sternal defect, sternal pit, sternal cleft, and supraumbilical raphe. Dental abnormalities, specifically enamel hypoplasia, can be associated with PHACE syndrome.

There can be an assortment of neurologic symptoms, the most common of which is headaches, specifically migraines. Other reported neurologic symptoms are seizures, cyclical vomiting, developmental delay (language, gross motor, fine motor), hypotonia, tremor, dysphagia, opisthotonus, hearing loss (conductive, sensorineural, or mixed), and cranial nerve deficits. New onset of headaches in an individual with PHACE syndrome should prompt further evaluation for vessel disease and cerebral ischemia. Development can be affected: according to a

case series of 29 children with PHACE syndrome, 69% had abnormal neurodevelopment, including 44% with language delay, 36% with gross motor delay, and 8% with fine motor delay. Certain medical comorbidities like posterior fossa malformations and oropharyngeal hemangiomas increase the risk for dysphagia. Sensorineural hearing loss may be caused by involvement of the cranial nerve VIII that is on the same side as the infantile hemangioma; similarly, conductive hearing loss may be caused by compression of the eustachian tube that is on the same side as the infantile hemangioma.

There are clinical diagnostic criteria for PHACE syndrome that delineate definite PHACE syndrome and possible PHACE syndrome. Definite PHACE syndrome is defined by either of the following: (1) infantile hemangioma (>5 cm in diameter) affecting the head/scalp in combination with one major or two minor criteria or (2) segmental infantile hemangioma of the neck, upper trunk, or trunk/proximal arm in combination with two major criteria. Possible PHACE syndrome is defined by one of the following: (1) infantile hemangioma (>5 cm in diameter) affecting the head/scalp in combination with one minor criteria; (2) segmental infantile hemangioma of the neck, upper trunk, or trunk/proximal arm in combination with one major or two minor criteria; and (3) absence of hemangioma but presence of two major criteria. Major and minor criteria pertain to arterial, structural brain, cardiovascular, ocular, and ventral/midline features of the syndrome.

Children newly diagnosed with PHACE syndrome should undergo a complete physical examination, screening echocardiogram, ophthalmologic examination, hearing screening, and MRI with and without gadolinium of the brain/neck as well as MRA of the brain/neck/aortic arch. Results of these baseline evaluations steer further management. The presence of a severe midline defect would prompt evaluation with pediatric surgery. Abnormalities on echocardiogram would require expertise from pediatric cardiology. Anomalies on ophthalmologic exam would likely require ongoing care. Hearing loss can be a risk factor for language delay, so affected children should have hearing screening if not already performed. If there are structural brain abnormalities identified on MRI, evaluation by pediatric neurology and neurosurgery (in the case of Dandy-Walker malformation or hydrocephalus) would be necessary. Pituitary defects would require endocrinologic evaluation. Results from MRA of cervical and cerebral arteries would classify patients into one of three risk tiers for cerebrovascular changes and stroke (low risk, intermediate risk, high risk), each with varying levels of need for follow-up neuroimaging and ongoing neurologic care.

Treatments in PHACE syndrome are symptom targeted. The β blocker propranolol can be used for infantile hemangiomas associated with PHACE syndrome, though there must be careful consideration in the presence of cerebrovascular abnormalities predisposing to stroke. Treatment of headaches is per standard clinical care, but certain vasoconstrictive medications, like triptans and ergotamine derivatives, should be avoided if there are arterial abnormalities. Dysphagia would require referral for feeding evaluation. Developmental delays should prompt neurodevelopmental assessment and developmental therapies such as physical therapy and speech-language therapy.

LUMBAR syndrome (lower-segment hemangioma, urogenital defects, myelopathy of spinal cord, bony deformities, arterial and anorectal defects, renal anomalies), also called **SACRAL syndrome** (spinal dysraphism, anogenital anomalies, cutaneous anomalies, renal-urologic anomalies, angioma of lumbosacral localization), is a possible variant of PHACES syndrome in the lumbosacral region.

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636.7 Incontinentia Pigmenti

Siddharth Srivastava and Mustafa Sahin

Incontinentia pigmenti (IP) is a rare, heritable, multisystem ectodermal disorder that features dermatologic, dental, ocular, and CNS abnormalities. The phenotype is produced by defects in the X-linked

dominant gene *IKBK*G (previously *NEMO*), which plays a role in activating the antiapoptotic signaling molecule NF-kappaB (NF-κB). In the majority of males, IP causes embryonic lethality, so affected males who survive have *somatic mosaicism* for a pathogenic *IKBK*G variant or a 47,XXY karyotype. With respect to a male with IP, some of his daughters may inherit a pathogenic *IKBK*G variant and hence be affected, but all of his sons would be unaffected. Among affected females, an abnormal gene product causes apoptosis in cells; therefore highly skewed X-inactivation can be a result. With respect to a female with IP, one third of her offspring are expected to be unaffected females, one third are expected to be affected females, and one third are expected to be unaffected males; this ratio accounts for the high rate of miscarriages in pregnancies with a male conceptus carrying a pathogenic variant in *IKBK*G.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

This disease has four stages, not all of which may occur in a given patient. The **first (bullous) stage** is evident at birth or in the first few weeks of life and consists of erythematous linear streaks and plaques of vesicles (Fig. 636.15) that are most pronounced on the limbs and circumferentially on the trunk. The lesions may be confused with those of herpes simplex, bullous impetigo, or mastocytosis, but the linear configuration is unique. Histopathologically, epidermal edema and eosinophil-filled intraepidermal vesicles are present. Eosinophils also infiltrate the adjacent epidermis and dermis. Blood eosinophilia as high as 65% of the white blood cell count is common. The **first stage** generally resolves by 4 months of age, but mild, short-lived recurrences of blisters may develop during febrile illnesses. In the **second (verru-cous) stage**, as blisters on the distal limbs resolve, they become dry and hyperkeratotic, forming verrucous plaques. The verrucous plaques rarely affect the trunk or face and generally involute within 6 months. Epidermal hyperplasia, hyperkeratosis, dyskeratosis, and papillomatosis are characteristic. The **third (pigmentary) stage** is the hallmark of IP. It generally develops over weeks to months and may overlap the earlier phases or, more commonly, begin to appear in the first few months of life. Hyperpigmentation is more often apparent on the trunk than the limbs and is distributed in macular whorls, reticulated patches, flecks, and linear streaks that follow Blaschko lines. The axillae and groin are characteristically affected. The sites of involvement are not necessarily those of the preceding vesicular and warty lesions. The pigmented lesions, once present, persist throughout childhood. They generally begin to fade by early adolescence and often disappear by age 16 years. Occasionally, the pigmentation remains permanently, particularly in the groin. Histopathologically, the lesion shows vacuolar degeneration of the epidermal basal cells and melanin in melanophages of the upper dermis as a result of incontinence of pigment. In the **fourth (atretic) stage**, hairless, anhidrotic, hypopigmented patches or streaks occur as a late manifestation of IP; they may develop, however, before the hyperpigmentation of stage 3 has resolved. The lesions develop mainly on the flexor aspect of the lower legs and less often on the arms and trunk. On



Fig. 636.15 Whorled vesicular phase of incontinentia pigmenti.

histology, there are decreased rete ridges (epidermal protrusions) and sweat gland secretory coils during this stage.

A large percentage of affected children have other dermal/dental defects. Alopecia, which may be scarring and patchy or diffuse, is most common on the vertex and occurs in up to 40% of patients. Hair may be coarse and wooly or sparse and brittle. Fingernails and toenails may demonstrate pigmentary or dystrophic changes (ridging, pitting), as well as painful subungual and periungual keratotic tumors. Dental anomalies consist of late dentition, hypodontia, conical teeth, malocclusion, and impaction.

CNS manifestations are found in up to 30% of affected children and include seizures, intellectual disability, learning disabilities, microcephaly, hemiplegia/hemiparesis (in the setting of stroke), spasticity, and cerebellar ataxia. Brain MRI in patients can be notable for periventricular and subcortical white matter changes, ischemic/hemorrhagic infarcts, hemorrhagic necrosis, dysgenesis of the corpus callosum, cerebral atrophy, cerebellar hypoplasia, cystic changes, and ventricular enlargement.

Ocular anomalies, such as retinal neovascularization, microphthalmos, strabismus, optic nerve atrophy, cataracts, and retrolenticular masses, occur in up to 77% of affected individuals. Nonetheless, >90% of patients have normal vision. Notably, retinal neovascularization could herald abnormalities in the CNS vasculature that predispose the patient to ischemic or hemorrhagic stroke.

Other medical issues have been reported in IP. Leukocytosis with eosinophilia can occur. Primary pulmonary hypertension is seen in some affected individuals.

Diagnosis of IP is made on clinical grounds, although major and minor criteria have been established to aid in the diagnosis. Satisfaction of the sole major criteria (pertaining to the characteristic skin lesions in the varying stages) is needed for a clinical diagnosis; lack of fulfillment of any of the minor criteria may direct the clinician toward the possibility of another diagnosis. Wood lamp examination may be useful in older children and adolescents to highlight pigmentary abnormalities. Clinical molecular testing is available, and around 65% of affected females and 16% of affected males have a recurrent pathogenic variant, an 11.7-kb deletion of exons 4-10 of *IKBK*G. Skin biopsy may be helpful if the patient has unclear clinical findings and negative genetic testing. For male patients with negative genetic testing from blood, a variant may be detectable in skin cells from an affected region, increasing the utility of a skin biopsy. The differential diagnosis includes hypomelanosis of Ito, which presents with similar skin manifestations and is often associated with chromosomal mosaicism.

MANAGEMENT

The choice of investigative studies and the plan of management depend on the occurrence of particular noncutaneous abnormalities. Medical genetics and genetic counseling can help establish a molecular diagnosis in addition to providing family counseling. Dermatology may be involved to characterize the nature of skin lesions and to manage skin manifestations that are extensive. Dentistry can provide teeth implants along with routine care. If dental issues affect speech or feeding, then input from speech pathologists and nutritionists may be necessary. Ophthalmology is important for delineating the presence and extent of retinal neovascularization (which can be treated with cryotherapy and laser photocoagulation) and other ocular abnormalities. Cardiology may be necessary if there is pulmonary hypertension. Neurology can help evaluate and treat relevant concerns such as microcephaly, seizures, and motor abnormalities. A brain MRI is useful if there are focal neurologic deficits or retinal neovascularization. Finally, developmental medicine can formulate recommendations regarding developmental and behavioral concerns. Surveillance includes regular ophthalmologic assessment (monthly until age 4 months, then every 3 months until age 1 year, then every 6 months until age 3 years, then annually thereafter). Regular evaluation with dentistry and neurologic/neurodevelopmental assessments are appropriate.

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Chapter 637

Movement Disorders

Jonathan W. Mink

INTRODUCTION

Movement disorders are characterized by impaired voluntary movements or excessive involuntary movements that may result in abnormalities in posture, tone, balance, or fine motor control. Most movement disorders in children are characterized by involuntary movements. These involuntary movements can represent the sole disease manifestation, or they may be one of many signs and symptoms.

Evaluation of movement disorders begins with a comprehensive history and careful neurologic examination. It is often difficult for children and caregivers to describe abnormal movements, which makes observation of the movements by the clinician an essential component of the evaluation. If the movements are not apparent at the time of the examination, video examples from home or school can be invaluable.

There is no specific diagnostic test to differentiate among movement disorders. The category of movement assists in localizing the pathologic process, whereas the onset of the disorder, age of the patient, and degree of abnormal motor activity and associated neurologic findings help organize the investigation.

When considering the type of movement disorder, the following questions concerning the history and examination of the movement are helpful:

- What is the distribution of the movements across body parts?
- Are the movements symmetric?
- What is the speed of the involuntary movements? Are they rapid and fast or slow and sustained?
- When do the movements occur? Are they present at rest? Are they present with maintained posture or with voluntary actions?
- Are the movements seen in relation to certain postures or body positions?
- Do the abnormal movements occur only with specific tasks?
- Can the child voluntarily suppress the movements, even for a short time?
- Are the movements stereotyped?
- Are the movements rhythmic?
- What is the temporal pattern of the movements? Are they continuous or intermittent? Do they occur in discrete episodes?
- Are the involuntary movements preceded by an urge to make the movement?
- Do the movements persist during sleep?
- Are the movements associated with impairment of motor function?
- What factors aggravate or alleviate the movements?

The first decision to be made is whether the movement disorder is **hyperkinetic** (characterized by excessive and involuntary movements) or **hypokinetic** (characterized by slow voluntary movements and a general paucity of movement). Hyperkinetic movement disorders are much more common than hypokinetic disorders in children. Once the category of movement disorder is recognized, the etiology can be considered. The clinical history, including the birth history, medication/toxin exposure, trauma, infections, family history, progression of the involuntary movements, developmental progress, and behavior, should be explored as the underlying cause is established. Table 637.1 lists the types and clinical characteristics of selected hyperkinetic movement disorders. A diagnostic approach to paroxysmal movement disorders is noted in Figure 637.1; age-related presentations of paroxysmal movement disorders are noted in Figure 637.2.

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637.1 Ataxias

Peter E. Morrison and Jonathan W. Mink

Ataxia is the inability to make smooth, accurate, and coordinated movements. It occurs because of a dysfunction of the cerebellum, its inputs or outputs, its sensory pathways in the posterior columns of the spinal cord, or a combination of these. Ataxias may be generalized but can also primarily affect the gait, the hands and arms, or the trunk; they may be acute or chronic, or acquired or genetic (Tables 637.2-637.8).

Signs and symptoms of ataxia include clumsiness, difficulty walking or sitting, falling to one side, slurred speech, low muscle tone, intention tremor, dizziness, delayed motor development, or a combination of these. Genetic or chronic causes of cerebellar ataxia are often characterized by a long duration of symptoms, a positive family history, muscle weakness and abnormal gait, abnormal tone and strength, abnormal deep tendon reflexes, pes cavus, and sensory defects. Distinguishing ataxia from vestibular dysfunction may be difficult; however, labyrinth disorders are often characterized by severe vertigo, nausea and vomiting, position-induced vertigo, and a severe sense of unsteadiness.

Congenital anomalies of the posterior fossa, including Dandy-Walker malformation, Chiari malformation, and encephalocele, are prominently associated with ataxia because of their destruction or abnormal development of the cerebellum (see Chapter 631.8). MRI

Table 637.1 Selected Types of Involuntary Movement in Childhood	
TYPE	CHARACTERISTICS
Stereotypies (see Chapter 37)	Involuntary, patterned, coordinated, repetitive, rhythmic movements that occur in the same fashion with each repetition
Tics (see Chapter 37)	Involuntary, sudden, rapid, abrupt, repetitive, nonrhythmic, simple or complex motor movements or vocalizations (phonic productions). Tics are usually preceded by an urge that is relieved by carrying out the movement.
Tremor (see Chapter 637.2)	Oscillating, rhythmic movements about a fixed point, axis, or plane
Dystonia (see Chapter 637.4)	Intermittent and sustained involuntary muscle contractions that produce abnormal postures and movements of different parts of the body, often with a twisting quality
Chorea (see Chapter 637.2)	Involuntary, continual, irregular movements or movement fragments with variable rate and direction that occur unpredictably and randomly
Ballism	Involuntary, high-amplitude, flinging movements typically occurring proximally. Ballism is essentially a large-amplitude chorea
Athetosis (see Chapter 637.2)	Slow, writhing, continuous, involuntary movements
Myoclonus (see Chapter 637.3)	Sudden, quick, involuntary muscle jerks

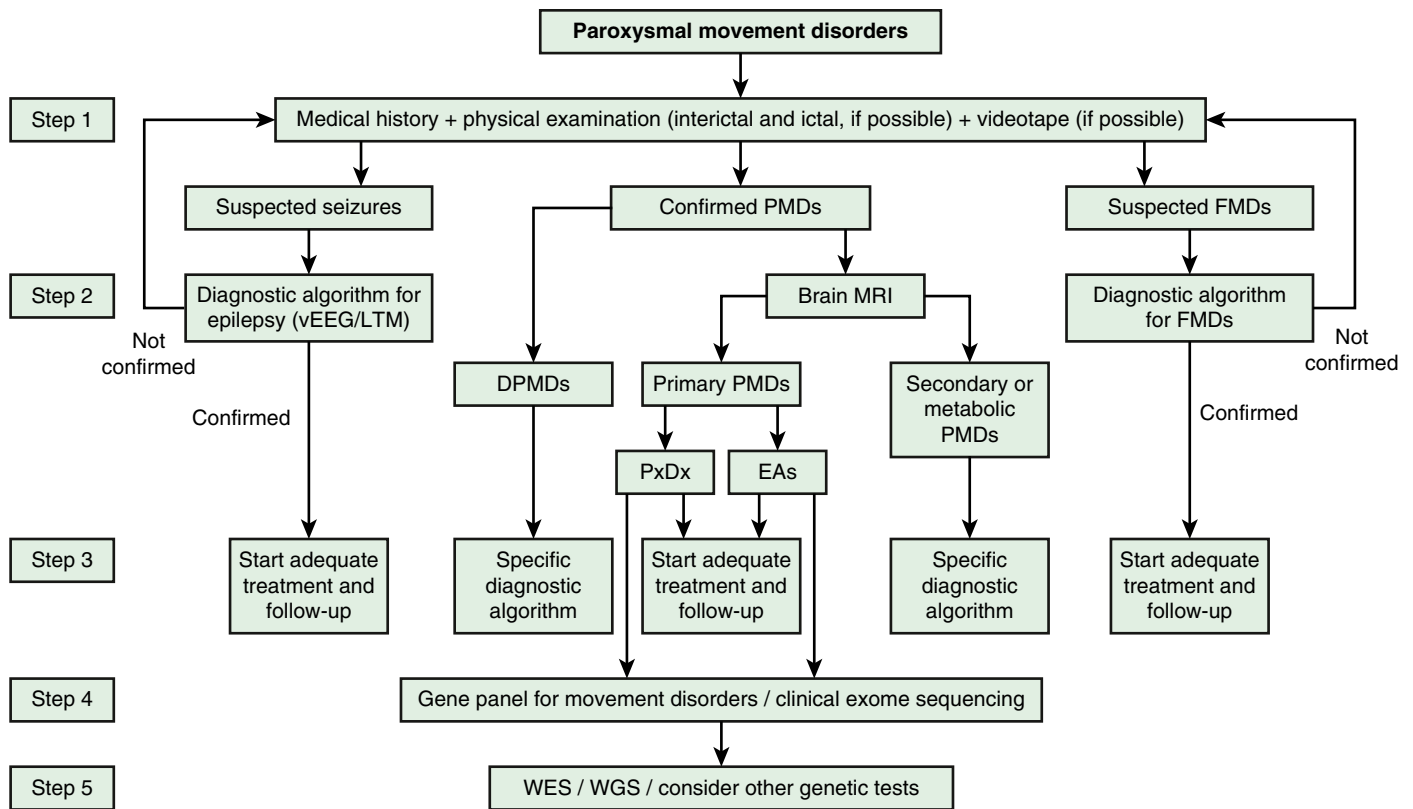


Fig. 637.1 Operative algorithm for pediatric-onset PMDs. DPMDs, developmental PMDs; EAs, episodic ataxias; FMDs, functional movement disorders; LTM, long-term EEG monitoring; PxDx, paroxysmal dyskinesias; vEEG, video electroencephalogram; WES, whole exome sequencing; WGS, whole genome sequencing. (Modified from Garone G, Capuano A, Travaglini L, et al. *Clinical and genetic overview of paroxysmal movement disorders and episodic ataxias*. *Inter J Mol Sci*. 2020;21:3603, Fig. 5.)

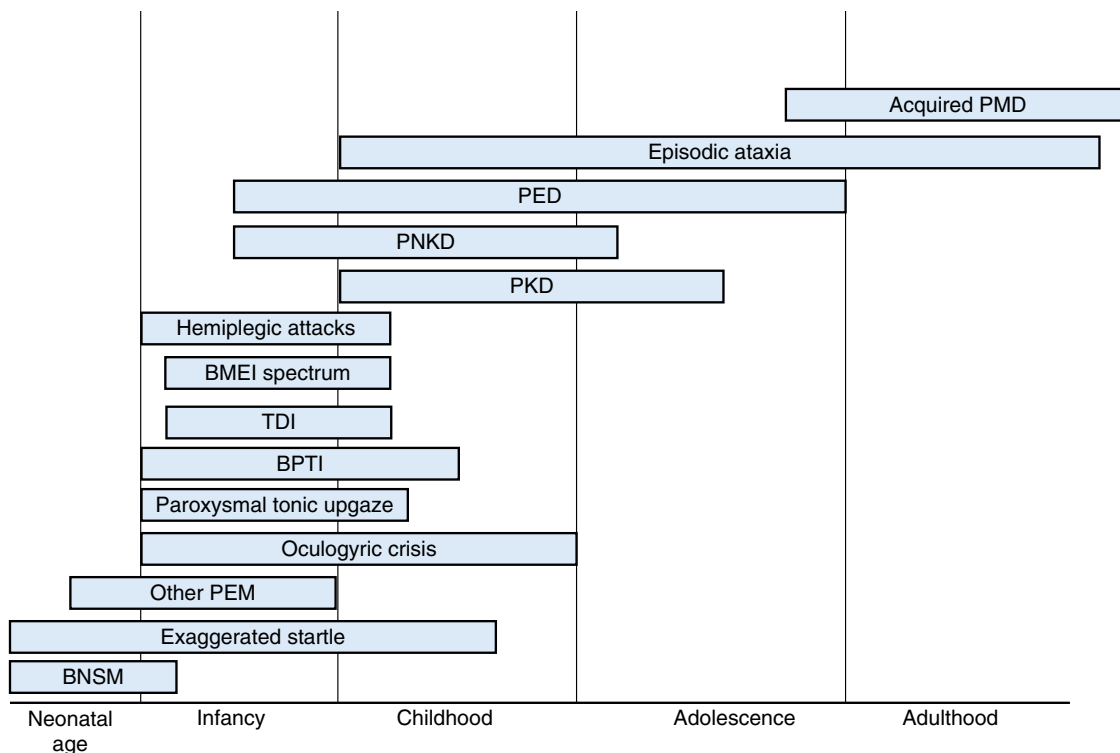


Fig. 637.2 Onset of different paroxysmal movement disorders (PMDs) according to age. BNSM, benign neonatal sleep myoclonus; BMEI, benign myoclonus of early infancy; BPTI, benign paroxysmal torticollis of infancy; PEM, paroxysmal eye movements; PED, paroxysmal exercise-induced dyskinesia; PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal nonkinesigenic dyskinesia. (From Garone G, Capuano A, Travaglini L, et al. *Clinical and genetic overview of paroxysmal movement disorders and episodic ataxias*. *Inter J Mol Sci*. 2020;21:3603, Fig. 1.)

Table 637.2 Selected Causes of Ataxia in Childhood**CONGENITAL CAUSES**

Agenesis of vermis of the cerebellum
 Aplasia or dysplasia of the cerebellum
 Basilar impression
 Cerebellar dysplasia with microgyria, macrogyria, or agyria
 Cervical spinal bifida with herniation of the cerebellum (Chiari malformation type 3)
 Chiari malformation
 Dandy-Walker syndrome
 Encephalocele
 Hydrocephalus (progressive)
 Hypoplasia of the cerebellum

DEGENERATIVE AND/OR GENETIC CAUSES

Acute intermittent cerebellar ataxia
 Ataxia, retinitis pigmentosa, deafness, vestibular abnormality, and intellectual deterioration
 Ataxia-telangiectasia
 Biemond posterior column ataxia
 Cerebellar ataxia with deafness, anosmia, absent caloric responses, nonreactive pupils, and hyporeflexia
 Cockayne syndrome
 Dentate cerebellar ataxia (dyssynergia cerebellaris progressiva)
 Familial ataxia with macular degeneration
 Friedreich ataxia
 Hereditary cerebellar ataxia, intellectual retardation, choreoathetosis, and eunuchoidism
 Hereditary cerebellar ataxia with myotonia and cataracts
 Hypertrophic interstitial neuritis
 Marie ataxia
 Marinesco-Sjögren syndrome
 Multiple system atrophy
 Pelizaeus-Merzbacher disease
 Periodic attacks of vertigo, diplopia, and ataxia: autosomal dominant inheritance
 Posterior and lateral column difficulties, nystagmus, and muscle atrophy
 Progressive cerebellar ataxia and epilepsy
 Ramsay Hunt syndrome (myoclonic seizures and ataxia)
 Roussy-Lévy disease
 Spinocerebellar ataxia (SCA); olivopontocerebellar ataxias
 Vanishing white matter syndrome

ENDOCRINOLOGIC CAUSES

Hypothyroidism (acquired or congenital)

INFECTIOUS, POSTINFECTIOUS, AND IMMUNE INFLAMMATORY CAUSES

Acute cerebellar ataxia
 Acute disseminated encephalomyelitis
 Autoimmune (anti-glutamic acid decarboxylase, anti- γ -aminobutyric acid-B receptor antibodies, idiopathic, gluten ataxia, Miller-Fisher syndrome, Hashimoto encephalopathy, lupus)
 Cerebellar abscess
 Cerebellitis
 Coxsackievirus
 Diphtheria
 Echovirus
 Fisher syndrome
 Infectious mononucleosis (Epstein-Barr virus infection)
 Infectious polyneuropathy
 Japanese B encephalitis
 Multiple sclerosis
 Mumps encephalitis
Mycoplasma pneumoniae
 Paraneoplastic (opsoclonus-myoclonus-ataxia syndrome)
 Pertussis
 Polio
 Postbacterial meningitis
 Rubella
 Tuberculosis
 Typhoid
 Varicella

METABOLIC CAUSES

Abetalipoproteinemia
 Argininosuccinic aciduria
 Ataxia with vitamin E deficiency (AVED)
 Congenital disorders of glycosylation
 GM₂ gangliosidosis (late)
 Hartnup disease
 Hyperalaninemia
 Hyperammonemia I and II (urea cycle defects)
 Hypoglycemia
 Kearns-Sayre syndrome
 Leigh disease
 Maple syrup urine disease (intermittent)
 Myoclonic epilepsy with ragged red fibers (MERRF)
 Metachromatic leukodystrophy
 Mitochondrial complex defects (I, III, IV)
 Multiple carboxylase deficiency (biotinidase deficiency)
 Neuronal ceroid-lipofuscinosis
 Neuropathy, ataxia, retinitis pigmentosa (NARP)
 Niemann-Pick disease (late infantile)
 5-Oxoprolinuria
 Pyruvate decarboxylase deficiency
 Refsum disease
 Sialidosis
 Triose-phosphate isomerase deficiency
 Tryptophanuria
 Wernicke encephalopathy

NEOPLASTIC CAUSES

Frontal lobe tumors
 Hemispheric cerebellar tumors
 Midline cerebellar tumors
 Neuroblastoma
 Pontine tumors (primarily gliomas)
 Spinal cord tumors

PRIMARY PSYCHOGENIC CAUSES

Functional disorder

TOXIC CAUSES

Alcohol
 Benzodiazepines
 Carbamazepine
 Clonazepam
 Dextromethorphan
 Lead encephalopathy
 Neuroblastoma
 Phenobarbital
 Phenytoin
 Primidone
 Tic paralysis poisoning

TRAUMATIC CAUSES

Acute cerebellar edema
 Acute frontal lobe edema

VASCULAR CAUSES

Angioblastoma of the cerebellum
 Basilar migraine
 Cerebellar embolism
 Cerebellar hemorrhage
 Cerebellar thrombosis
 Posterior cerebellar artery disease
 Vasculitis
 von Hippel-Lindau disease

Table 637.3 Treatable Causes of Inherited Ataxia

DISORDER	METABOLIC ABNORMALITY	DISTINGUISHING CLINICAL FEATURES	TREATMENT
Acute disseminated encephalomyelitis	Demyelination	Positive MRI findings	Steroids, IVIG, rituximab
Ataxia with vitamin E deficiency	Pathogenic variants in α -tocopherol transfer protein	Ataxia, areflexia, retinopathy	Vitamin E
Bassen-Kornzweig syndrome	Abetalipoproteinemia	Acanthocytosis, retinitis pigmentosa, fat malabsorption	Vitamin E
Hartnup disease	Tryptophan malabsorption	Pellagra rash, intermittent ataxia	Niacin
Familial episodic ataxia type 1 and type 2	Pathogenic variants in potassium channel (KCNA1) and α_{1A} voltage-gated calcium channel, respectively	Episodic attacks, worse with pregnancy or birth control pills	Acetazolamide
Multiple carboxylase deficiency	Biotinidase deficiency	Alopecia, recurrent infections, variable organic aciduria	Biotin
Mitochondrial complex defects	Complexes I, III, IV	Encephalomyelopathy	Possibly riboflavin, CoQ10, dichloroacetate
Opsoclonus-myoclonus-ataxia syndrome	Paraneoplastic or spontaneous autoimmune	Underlying neuroblastoma or autoantibodies	Steroids, IVIG, rituximab
Primary CoQ10 deficiency (multiple types)	Mitochondrial dysfunction	Seizures, sensorineural hearing loss, lactic acidosis, cardiomyopathies	Possibly CoQ10
Pyruvate dehydrogenase deficiency	Block in E-M and Krebs cycle interface	Lactic acidosis, ataxia	Ketogenic diet, possibly dichloroacetate
Refsum disease	Phytanic acid, α -hydroxylase	Retinitis pigmentosa, cardiomyopathy, hypertrophic neuropathy, ichthyosis	Dietary restriction of phytanic acid
Urea cycle defects	Urea cycle enzymes	Hyperammonemia	Protein restriction, arginine, benzoate, α -ketoacids

CoQ10, Coenzyme Q10; E-M, mitochondrial electron transport; IVIG, intravenous immunoglobulin.

Modified from Stumpf DA. The inherited ataxias. *Pediatr Neurol*. 1985;1:129–133, Table 1; and from Jafar-Nejad P, Maricich SM, Zoghbi HY. The cerebellum and the hereditary ataxias. In: Swaiman KF, Ashwal S, Ferriero DM, et al., eds. *Swaiman's Pediatric Neurology*, 5th ed. Philadelphia: WB Saunders; 2012: Table 67-1.

Table 637.4 Hereditary Ataxias Caused by Nucleotide Repeat Expansions: Clinical Findings

GENE*	DISORDER	MOI	DISTINGUISHING NONATAXIC CLINICAL FEATURES	COMMENT
MOST COMMONLY INVOLVED GENES				
ATN1	DRPLA	AD	Chorea, dementia, myoclonus, seizures; mimics Huntington disease	• Anticipation is prominent • More common in Japan
ATXN1	SCA1	AD	Peripheral neuropathy, pyramidal signs; early bulbar features; occasional cognitive decline	• Anticipation is more likely with paternal transmission.
ATXN2	SCA2	AD	↓ DTRs, dementia, peripheral neuropathy, slow saccadic eye movements	• Anticipation is more likely with paternal transmission • Large Cuban founder population
ATXN3	SCA3	AD	Amyotrophy, fasciculations, sensory loss; lid retraction, nystagmus, and ↓ saccade velocity; pyramidal and extrapyramidal signs; shortened life span	• Anticipation may be more likely with paternal transmission • Large Portuguese founder population • Also known as Machado-Joseph disease
ATXN7	SCA7	AD	Visual loss with retinopathy; often rapidly progressive; shortened life span	Anticipation is prominent with more marked repeat expansions with paternal transmission
ATXN8 ATXN8OS	SCA8	AD	Slowly progressive, sometimes brisk DTRs, ↓ vibration sense; rarely, cognitive impairment in persons with earlier onset	Anticipation is more likely with maternal transmission

Continued

Table 637.4 Hereditary Ataxias Caused by Nucleotide Repeat Expansions: Clinical Findings—cont'd

GENE*	DISORDER	MOI	DISTINGUISHING NONATAXIC CLINICAL FEATURES	COMMENT
ATXN10	SCA10	AD	Seizures in certain families	- Anticipation can occur with paternal transmission - Large Mexican founder population
CACNA1A	SCA6	AD	May begin with episodic ataxia, very slow progression; onset often after age 50 yr; normal life span	- Anticipation is not seen - See Table 637.6 for ataxia caused by missense variants
FXN	Friedreich ataxia	AR	Generally childhood onset with slowly progressive ataxia, absent tendon reflexes, Babinski responses, posterior column sensory loss, cardiomyopathy, scoliosis, pes cavus, and diabetes; in some: onset ≥ 25 yr, slower progression, and retained reflexes	Anticipation is not seen
RFC1	RFC1 CANVAS/ spectrum disorder	AR	Spectrum ranges from typical cerebellar ataxia, neuropathy, and vestibular areflexia syndrome (CANVAS), to cerebellar, sensory, and vestibular impairment, to more limited phenotypes involving predominantly or exclusively one of the systems involved in balance control	Anticipation is not seen
TBP	SCA17	AD	Mental deterioration; occasional chorea, dystonia, myoclonus, epilepsy	Anticipation is infrequently observed
LESS COMMONLY INVOLVED GENES				
BEAN1	SCA31 (OMIM 117210)	AD	Normal sensation	Common in Japan
FMR1	Fragile X-associated tremor/ataxia syndrome (FXTAS)	XL		- Anticipation occurs almost exclusively with maternal transmission - Most common X-linked ataxia; occurs in male and female premutation carriers
NOP56	SCA36	AD	Hyperreflexia, muscle fasciculations, tongue atrophy	Insufficient evidence for anticipation
PPP2R2B	SCA12 (OMIM 604326)	AD	Action tremor in the fourth decade, cognitive/psychiatric disorders, including dementia, hyperreflexia, slowly progressive ataxia, subtle parkinsonism possible	Insufficient evidence for anticipation

*Genes are listed in alphabetic order within prevalence categories.

DRPLA, Dentatorubral-pallidoluysian atrophy; DTR, deep tendon reflex; SCA, spinocerebellar ataxia.

From Perlman S. Hereditary ataxia overview. 1998 Oct 28 [Updated 2022 Jun 16]. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023, Table 1.

Table 637.5 Hereditary Ataxias Caused by Nucleotide Repeat Expansions: Molecular Genetics

GENE ¹	PATHOGENIC VARIANTS (%)	NUCLEOTIDE REPEAT (AMINO ACID)	REPEAT LOCATION	NORMAL REPEAT NUMBER	FULL-PENETRANCE PATHOGENIC REPEAT NUMBER	COMMENT
ATN1	100	CAG (Gln)	Exon 5	6-35	≥ 48	
ATXN1	100	CAG (Gln)	Exon 8	6-35	≥ 39	
ATXN2	100	CAG (Gln)	Exon 1	≤ 31	≥ 33	
ATXN3	100	CAG (Gln)	Exon 8	12-44	60-87	
ATXN7	100	CAG (Gln)	Exon 1	4-19	≥ 36	
ATXN8	100	CAG (Gln)	Exon 1	~ 80	Unknown	
ATXN8OS	100	CTG	3' UTR	15-50 CTA/CTG	≥ 71 -1300 CTA/CTG ²	Penetrance is $<100\%$ ²
ATXN10	100	ATTCT	Intron 9	10-32	≥ 800	Repeat interruptions are associated with presence of seizures

Table 637.5 Hereditary Ataxias Caused by Nucleotide Repeat Expansions: Molecular Genetics—cont'd

GENE ¹	PATHOGENIC VARIANTS (%)	NUCLEOTIDE REPEAT (AMINO ACID)	REPEAT LOCATION	NORMAL REPEAT NUMBER	FULL-PENETRANCE PATHOGENIC REPEAT NUMBER	COMMENT
<i>BEAN1</i>	100	TGGAA	Intron 6	0	2.5- to 3.8-kb insertion	
<i>CACNA1A</i> ³	>99	CAG (Gln)	Exon 7	≤18	20-33	See Table 637.6 for phenotype associated with variants that are not nucleotide repeat disorders
<i>FMR1</i>	>99	CGG	5' UTR	5-44	≥200	Premutation alleles: 55-200 CGG repeats
<i>FXN</i>	~98	GAA	Intron 1	5-33	≥66	In about 5% of affected persons one <i>FXN</i> allele is an expanded GAA repeat and one is a pathogenic missense variant
<i>NOP56</i>	100	GGCCTG	Intron 1	3-14	≥650	
<i>PPP2R2B</i>	100	CAG	Promoter	7-31	51-78	
<i>RFC1</i>	100	AAGGG ⁴	Intron 2	Unknown	~400 to ~2000	ACAGG repeat expansion has been reported in three persons from Asian and Asian Pacific populations ⁴
<i>TBP</i>	100	CAG or CAA (Gln)	Exon 3	25-40	≥49	

Based on Resources for Genetics Professionals — Genetic Disorders Caused by Nucleotide Repeat Expansions and Contractions

¹Genes are listed in alphabetic order.²Although penetrance less than 100% has been reported at all repeat sizes, higher penetrance is reported for CTA/CTG repeat sizes of 80-250.³The majority of *CACNA1A* pathogenic variants are CAG repeat expansions associated with spinocerebellar ataxia type 6. Heterozygous *CACNA1A* missense, nonsense, splice site, frameshift, and exon/multiexon deletions have been reported in individuals with episodic ataxia type 2 and progressive cerebellar ataxia.⁴*RFC1* intron 2 contains a microsatellite region with variable benign AAAAG repeats (range: 11-200 repeats) and/or benign AAAGG repeats (range: 40-1000 repeats). Interruption of the benign AAAAG/AAAGG repeated units with biallelic pathogenic AAGGG expansions has been identified in individuals with *RFC1* CANVAS/spectrum disorder.

From Perlman S. Hereditary Ataxia overview. 1998 Oct 28 [Updated 2022 Jun 16]. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023, Table 2.

Table 637.6 Most Common Hereditary Ataxias (Excluding Nucleotide Repeat Disorders)

GENE ¹	MOI	PHENOTYPE		OTHER PHENOTYPIC FEATURES/COMMENTS	DESIGNATION/GENEREVIEW/OMIM
		ATAXIA	SPASTICITY		
<i>AFG3L2</i>	AD	+	+	Ophthalmoparesis, slow saccades, ptosis ³	SCA28 (OMIM 610246)
	AR				SCAR5 (OMIM 614487)
<i>ANO10</i>	AR	+	+	Downbeat nystagmus, fasciculations	SCAR10 (OMIM 613728)
<i>APTX</i>	AR	+		Early-onset ataxia, oculomotor apraxia, extrapyramidal features, sensorimotor neuropathy, hypoalbuminemia; secondary coenzyme Q10 deficiency (see primary coenzyme Q10 deficiency)	Ataxia with oculomotor apraxia type 1
<i>ATM</i>	AR	+		Early-onset ataxia, oculomotor apraxia, extrapyramidal features, immunodeficiency, cancer risk, ↑ alpha-fetoprotein	Ataxia-telangiectasia
<i>CACNA1A</i> ²	AD	+			Episodic ataxia type 2 (OMIM 108500)

Continued

Table 637.6 Most Common Hereditary Ataxias (Excluding Nucleotide Repeat Disorders)—cont'd

GENE ¹	MOI	PHENOTYPE		OTHER PHENOTYPIC FEATURES/COMMENTS	DESIGNATION/GENEREVIEW/OMIM
		ATAXIA	SPASTICITY		
ITPR1	AD	+		Adult onset, slowly progressive	SCA15/16 (OMIM 606658)
	AD ³	+		Congenital, nonprogressive	SCA29 (OMIM 117360)
KCNC3	AD ³	+		Adult onset, slowly progressive	SCA13
				Congenital, nonprogressive	
KCND3 ⁴	AD	+			SCA19/22 (OMIM 605411)
PRKCG	AD	+			SCA14
SACS	AR	+	+	Early-onset ataxia with spastic paraparesis and axonal-demyelinating sensorimotor neuropathy; hypointense pontine stripes on T2-weighted MRI ⁵	ARSACS (SPAX6)
SETX ⁶	AR	+	+	Early-onset ataxia, oculomotor apraxia with ↑ alpha-fetoprotein ⁵	Ataxia with oculomotor apraxia type 2 (SCAR1)
SPG7	AR	+	+	Variable spasticity and cerebellar ataxia ⁵	Spastic paraplegia 7
SPTBN2	AD	+			SCA5 (OMIM 600224)
	AR				SCAR14 (OMIM 615386)
SYNE1 ⁷	AR	+	+	Cerebellar ataxia, variable spasticity, and further multisystemic neurologic damage ⁵	ARCA1 (SCAR8) (see SYNE1 deficiency)

Based on Synofzik & Schüle [2017] and Galatolo et al. [2018].

¹Genes are listed in alphabetic order.

²Allelic disorders include familial hemiplegic migraine and spinocerebellar ataxia type 6.

³The disorder may occur as the result of a de novo pathogenic variant.

⁴Allelic disorder: Brugada syndrome.

⁵Synofzik and Schüle [2017].

⁶Allelic disorder: amyotrophic lateral sclerosis.

⁷Allelic phenotype: arthrogryposis multiplex congenita (see SYNE1 deficiency).

AD, Autosomal dominant; AR, autosomal recessive; ARCA, autosomal recessive cerebellar ataxia; MOI, mode of inheritance; OMIM, Online Mendelian Inheritance in Man; SCA, spinocerebellar ataxia; SCAR, spinocerebellar ataxia, autosomal recessive.

From Perlman S. Hereditary Ataxia overview. 1998 Oct 28 [Updated 2022 Jun 16]. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023, Table 3.

Table 637.7 The Hereditary Spastic Ataxias

SPASTIC ATAXIA (MIM#)	GENE	MODE OF INHERITANCE	AGE OF ONSET (YR)	FEATURES
SPAX1 (108600)	VAMP1		10-20yr	Progressive leg spasticity, dysarthria, ocular movement abnormalities
SPAX2 (611302)	KIF1C		1-16yr	Frequent falls, ataxia, head tremor, hyperreflexia, fasciculations
SPAX3/ARSAL (611390)	MARS2	AR	2-59yr; mean 15yr	Ataxia and spasticity
SPAX4 (613672)	MTPAP	AR	Early childhood	Ataxia, spastic paraparesis, dysarthria, optic atrophy, upper limb hypertonia
SPAX5 (614487)	AFG3L2	AR	Childhood	Spasticity, ataxia, oculomotor apraxia, dystonia, myoclonic epilepsy
SPAX6/SACS/ARCSACS (270660)	SACS	AR	Childhood	Spasticity and ataxia, very slow course, stops progressing after age 20
SPAX7	Unknown	AD	Infancy to 20yr	Symmetric ataxia, dysarthria, pyramidal signs, optic atrophy
SPAR (607565)	Unknown	—	15-35yr	Later onset: spastic paraplegia Early onset + ataxia, mental retardation

From Jafar-Nejad P, Maricich SM, Zoghbi H. The cerebellum and the hereditary ataxias. In: Swaiman KF, Ashwal S, Ferriero DM, et al., eds. *Swaiman's Pediatric Neurology*, 6th ed. Philadelphia: WB Saunders; 2018: Table 91-5.

Table 637.8 Genetic and Metabolic Disorders that Can Cause a Spastic-Ataxic Syndrome

	AGE AT ONSET	TREATMENT AVAILABLE	DIAGNOSTIC TESTS, IN ADDITION TO METABOLIC TESTS	MODE OF INHERITANCE	GENES
Abetalipoproteinemia (MIM #200100)	C	Yes	Blood lipid profile, vitamin E	AR	<i>MTP</i>
Adrenomyeloneuropathy (MIM #300100)	A	Yes	MRI spinal cord, blood VLCFA	X-linked	<i>ABCD1</i>
Ataxia with (primary) vitamin E deficiency (MIM #277460)	C	Yes	Blood vitamin E	AR	<i>TTPA</i>
CAMOS (also SCAR5; MIM #606937)*	C	No	—	AR	<i>ZNF592</i>
CARASIL (MIM #600142)	A	No	MRI	AR	<i>HTRA1</i>
Cerebral amyloid angiopathy: presenile dementia with spastic ataxia (MIM #176500)*	A	No	MRI	AD	<i>ITM2B</i>
Cerebral folate deficiency (MIM #613068)	C	Yes	CSF folates	AR	<i>FOLR1</i>
Childhood-onset spastic ataxia with optic atrophy and mental retardation (MIM #270500)*	C	No	—	AR	Unknown
Coenzyme Q10 deficiency (MIM #607426)	C	Yes	—	AR	>3 different genes
Female carriers of EIEE1 (MIM #308350)*	A	No	—	X-linked	<i>ARX</i>
Gaucher disease type III (MIM #231000)	C-A	Yes	—	AR	<i>GBA</i>
Glutaric acidemia II (MIM #231680)	C	Yes	MRI	AR	<i>ETFA, ETFB, ETFDH</i>
GM2 gangliosidosis (MIM #272800)	A	No	MRI	AR	<i>HEXA, HEXB, GM2A</i>
Hereditary spastic ataxia with congenital miosis (MIM #108650) (SPAX7)*	C	No	—	AD	Unknown
Krabbe disease (MIM #245200)	C-A	No	MRI	AR	<i>GALC</i>
LBSL (MIM #611105)*	C-A	No	MRI	AR	<i>DARS2</i>
Megalencephalic leukoencephalopathy with subcortical cysts (MIM #604004)*	C	No	MRI	AR	<i>MLC1</i>
Metachromatic leukodystrophy (MIM #250100)	C-A	Yes	MRI	AR	<i>ARSA</i>
Nonketotic hyperglycinemia (MIM #605899)	C-A	Yes	CSF amino acids	AR	>3 different genes
Optic atrophy ± deafness, ophthalmoplegia, myopathy, ataxia, neuropathy (MIM #605290)*	C	No	—	AD	<i>OPA1</i>
PHARC (MIM #612674)*	C	No	—	AR	<i>ABHD12</i>
Triple H syndrome (MIM #238970)*	C-A	Yes	Blood ammonia, amino acids	AR	<i>SLC25A15</i>
Type III 3-methylglutaconic aciduria (MIM #258501)*	C	No	Urine organic acids	AR	<i>OPA3</i>
Vanishing white matter leukodystrophy (#603896)*	C	No	MRI	AR	>3 different genes

*OMIM (Online Mendelian Inheritance in Man).

A, Adult onset; C, childhood onset; C-A, all ages possible, predominantly onset in adolescence; CAMOS, cerebellar ataxia with mental retardation, optic atrophy, and skin abnormalities; CARASIL, cerebral arteriopathy with subcortical infarcts and leukoencephalopathy; EIEE1, early infantile epileptic encephalopathy 1; LBSL, leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation; MIM#, phenotype description or locus, molecular basis unknown; MIM%, phenotype description, molecular basis known; MRI, brain MRI unless otherwise stated; when MRI is indicated, a typical or pathognomonic pattern can be recognized; PHARC, polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract; triple H, hyperornithinemia-hyperammonemia-homocitrullinuria; VLCFA, very long-chain fatty acids.

Modified from deBot ST, Willemsen MAA, Vermeer S, et al. Reviewing the genetic causes of spastic-ataxias. *Neurology*. 2012;79:1507–1514, Table 2.

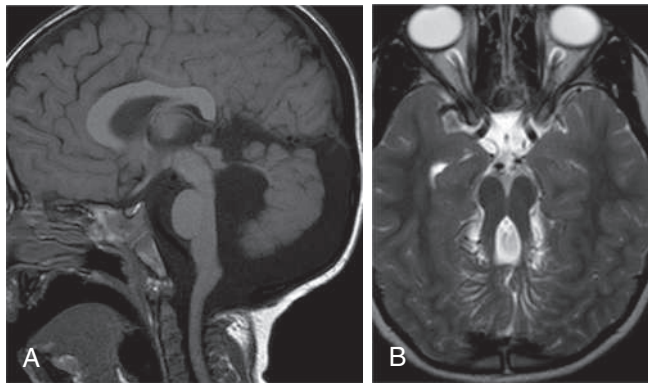


Fig. 637.3 Molar tooth syndrome. A, Sagittal T1-weighted MR image shows hypoplasia of the superior cerebellar vermis with upward bowing of the roof of the fourth ventricle. B, Axial T2-weighted image shows the molar tooth at the level of the midbrain, the hallmark of Joubert syndrome and related disorders (JSRD). (From Rollins N. *Congenital brain malformations*. In: Coley BD, ed. *Caffey's Pediatric Diagnostic Imaging*, 13th ed. Philadelphia: Elsevier; 2019, Fig. 31.29AB, p. 286.)

is the method of choice for investigating congenital abnormalities of the cerebellum, vermis, and related structures. **Agenesis of the cerebellar vermis** presents in infancy with generalized hypotonia and decreased deep tendon reflexes. Delayed motor milestones and truncal ataxia are typical. **Joubert syndrome and related disorders** are autosomal recessive disorders marked by developmental delay, hypotonia, abnormal eye movements, abnormal respirations, and a distinctive malformation of the cerebellum and brainstem that manifests as the “molar tooth sign” on axial MRI (Fig. 637.3). Pathogenic variants in more than 21 different genes are associated with Joubert syndrome, but only approximately 50% of patients have demonstrated a pathogenic variant.

The major **infectious or postinfectious causes of ataxia** include acute cerebellar ataxia, infectious cerebellitis, immune-mediated cerebellitis, and acute labyrinthitis. **Acute cerebellar ataxia** occurs primarily in children 1-3 years of age and is a diagnosis of exclusion. The condition often follows a viral illness, such as varicella virus, coxsackievirus, or echovirus infection, by 2-3 weeks. It is thought to represent an autoimmune response to the viral agent affecting the cerebellum (see Chapter 643). The onset is typically sudden, and the truncal ataxia can be so severe that the child is unable to stand or sit. Vomiting may occur initially, but fever and nuchal rigidity are absent because of the lack of meningeal involvement. Horizontal nystagmus is evident in ~50% of cases; if the child is able to speak, dysarthria may be impressive. Examination of the cerebrospinal fluid is typically normal at the onset of ataxia, but a mild lymphocytic pleocytosis (10-30/mm³) is not unusual. Later in the course, the cerebrospinal fluid protein undergoes a moderate elevation. The ataxia begins to improve in a few weeks but may persist for as long as 3 months, and rarely longer than that. The incidence of acute cerebellar ataxia appears to have declined with increased rates of vaccination against varicella. The prognosis for complete recovery is excellent. A small number of patients have long-term sequelae, including behavioral and speech disorders, as well as ataxia and incoordination. **Acute cerebellitis**, in contrast, is a more severe form of cerebellar ataxia characterized by abnormalities on MRI scans, more severe symptoms, and a worse long-term prognosis. Infectious agents include Epstein-Barr virus, mycoplasma, mumps, and influenza virus. An inflammatory process such as hemophagocytic lymphohistiocytosis may involve the cerebellum. Cerebellar abscesses can also occur with bacterial infections. In many, the etiology is unknown, but autoimmune cerebellitis may represent some of these unknown cases. Clinically, patients may present with ataxia, increased intracranial pressure from obstructive hydrocephalus, headache, and fever. **Acute labyrinthitis** may be difficult to differentiate from acute cerebellar ataxia in a toddler. The condition is associated with middle ear infections and presents with intense vertigo, vomiting, and abnormalities in labyrinthine function.

Toxic causes of ataxia include alcohol, thallium (which is used occasionally in homes as a pesticide), dextromethorphan, and



Fig. 637.4 Conjunctival telangiectasia in a patient with ataxia-telangiectasia. (From Daroff RB, Jankovic J, Mazziotta JC, et al., eds. *Bradley's Neurology in Clinical Practice*, 7th ed. Philadelphia: Elsevier; 2016, Fig. 97.6, p. 1468.)

anticonvulsants, particularly phenytoin and carbamazepine, when serum levels exceed the usual therapeutic range.

Brain tumors (see Chapter 546), including tumors of the cerebellum and frontal lobe, may present with ataxia. Cerebellar tumors cause ataxia because of direct disruption of cerebellar function or indirectly because of increased intracranial pressure from compression of the fourth ventricle. Frontal lobe tumors may cause ataxia as a consequence of destruction or interruption of the associated fibers connecting the frontal lobe with the cerebellum or because of increased intracranial pressure. Neuroblastoma (see Chapter 547) may be associated with a paraneoplastic encephalopathy characterized by progressive ataxia, myoclonic jerks, and opsoclonus (nonrhythmic, conjugate horizontal and vertical oscillations of the eyes).

Several **metabolic disorders** are characterized by ataxia, including abetalipoproteinemia, arginosuccinic aciduria, and Hartnup disease (see Table 637.2). **Abetalipoproteinemia** (Bassen-Kornzweig disease) is an autosomal recessive disorder caused by a pathogenic variant in the microsomal triglyceride transfer protein (MTP). This disorder begins in childhood with steatorrhea and failure to thrive. A blood smear shows acanthocytosis, which consists of spiculated red blood cells. Serum chemistries reveal decreased levels of cholesterol and triglycerides and absent serum β -lipoproteins. Neurologic signs become evident by late childhood and consist of ataxia, retinitis pigmentosa, peripheral neuritis, abnormalities of position and vibration sense, muscle weakness, and intellectual disability. Vitamin E is undetectable in the serum of patients with neurologic symptoms. In addition, ataxia may be one manifestation of a **mitochondrial disorder**; these include myoclonic epilepsy with ragged red fibers (MERFF), Kearns-Sayre syndrome, *POLG1* pathogenic variants, and Charlevoix-Saguenay syndrome.

Degenerative diseases of the central nervous system represent an important group of ataxic disorders of childhood because of the genetic consequences and poor prognosis. **Ataxia-telangiectasia**, an autosomal recessive condition, is the most common of the degenerative ataxias and is heralded by ataxia beginning at approximately age 2 and progressing to loss of ambulation by adolescence. Ataxia-telangiectasia is caused by pathogenic variants in *ATM*. *ATM* is a phosphatidylinositol-3 kinase that phosphorylates proteins involved in DNA repair and cell-cycle control. Oculomotor apraxia of horizontal gaze, defined as difficulty shifting the gaze from one object to another and overshooting the target with lateral movement of the head, followed by refixating the eyes, is a frequent finding. In addition, strabismus, hypometric saccade pursuit abnormalities, and nystagmus are often seen. Ataxia-telangiectasia may also present with chorea (see Chapter 637.2) rather than ataxia. The telangiectasia becomes evident by mid-childhood and is found on the bulbar conjunctiva, over the bridge of the nose, and on the ears and exposed surfaces of the extremities (Fig. 637.4). Examination of the skin shows a loss of elasticity. Abnormalities of

immunologic function that lead to frequent sinopulmonary infections include decreased serum and secretory immunoglobulin (Ig) A, as well as diminished IgG2, IgG4, and IgE levels in more than 50% of patients. Children with ataxia-telangiectasia have a 50- to 100-fold increased risk of developing lymphoreticular tumors (lymphoma, leukemia, and Hodgkin disease) and brain tumors. Additional laboratory abnormalities include an increased incidence of chromosome breaks, particularly of chromosome 14, and elevated levels of α -fetoprotein. Death typically results from infection or tumor dissemination.

Friedreich ataxia is inherited as an autosomal recessive disorder involving the spinocerebellar tracts, dorsal columns in the spinal cord, pyramidal tracts, and cerebellum and medulla. Most patients are homozygous for a GAA trinucleotide repeat expansion in the noncoding region of the gene coding for the mitochondrial protein frataxin. Pathogenic variants cause oxidative injury associated with excessive iron deposits in mitochondria. The onset of ataxia is somewhat later than in ataxia-telangiectasia but usually occurs before the age of 10. The ataxia is slowly progressive and involves the lower extremities to a greater degree than the upper extremities. Examination will demonstrate a positive Romberg test and absent deep tendon reflexes (particularly at the ankle); the plantar response is typically extensor (Babinski sign). Patients develop a characteristic explosive, dysarthric speech; nystagmus is present in most children. Although patients may appear apathetic, their intelligence is preserved. They may have significant weakness of the distal musculature of the hands and feet. Marked loss of vibration and joint position sense is common and is caused by degeneration of the posterior columns. Friedreich ataxia is also characterized by skeletal abnormalities, including high-arched feet (pes cavus) and hammer toes, as well as progressive kyphoscoliosis. Results of electrophysiologic studies, including visual, auditory brainstem, and somatosensory-evoked potentials, are often abnormal. Hypertrophic cardiomyopathy with progression to intractable congestive heart failure is the cause of death for most patients.

In addition to ataxia-telangiectasia and Friedreich ataxia, there are more than 40 other known inherited causes of either autosomal dominant or recessive forms of ataxia (Fig. 637.5; see Tables 637.4–637.8). More specifically, there are more than 20 dominantly inherited spinocerebellar ataxias (SCAs), some of which are also repeat expansion

disorders and can present in childhood. These include those associated with CAG (polyglutamine) trinucleotide repeats and noncoding microsatellite expansions. There is also a separate group of dominantly inherited episodic ataxias (EAs) caused by potassium or calcium channel dysfunction. These disorders present as episodes of ataxia and muscle weakness and at times may respond to acetazolamide. The dominantly inherited **olivopontocerebellar atrophies** include ataxia, cranial nerve palsies, and abnormal sensory findings in the second or third decade, but can present in children with rapidly progressive ataxia, nystagmus, dysarthria, and seizures. **Roussy-Levy disease** has, in addition to ataxia, atrophy of the muscles of the lower extremity with a pattern of wasting similar to that observed in Charcot-Marie-Tooth disease. **Ramsay Hunt syndrome** has an associated myoclonic epilepsy.

Additional degenerative ataxias include **Pelizaeus-Merzbacher disease**, **neuronal ceroid lipofuscinoses**, and late-onset **GM₂ gangliosidosis** (see Chapter 639). Rare forms of progressive cerebellar ataxia have been described in association with **vitamin E deficiency**.

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637.2 Chorea, Athetosis, and Tremor

Jennifer A. Vermilion and Jonathan W. Mink

Chorea, meaning “dance-like” in Greek, refers to rapid, chaotic movements that seem to flow unpredictably from one body part to another. Affected individuals often appear restless, and movements exhibit randomness. They often demonstrate motor impersistence on neurologic examination, showing classic signs such as “darting tongue” (difficulty maintaining tongue protrusion) or “milkmaid grip” (difficulty maintaining grip). Chorea tends to occur both at rest and with action, although certain actions or postures can exacerbate chorea. Patients often attempt to incorporate the involuntary movements into more purposeful-seeming movements, making them appear fidgety. *Chorea increases with stress and disappears in sleep.* Chorea has traditionally been divided into primary and secondary forms; however, this classification scheme in movement disorders can cause confusion given the recent explosion of genetic discoveries in the field. Rather, it may be more helpful to classify chorea causes by etiology: acquired or inherited (Tables 637.9 and 637.10).

Sydenham chorea (St. Vitus dance; rheumatic chorea) is the most common acquired chorea of childhood, although the prevalence varies worldwide. It occurs in 10–20% of patients with **acute rheumatic fever**, typically weeks to months after a group A β -hemolytic streptococcal infection (see Chapter 194). Peak incidence is at age 8–9 years, with a female predominance of 2:1. There is evidence that group A β -hemolytic streptococci promote the generation of cross-reactive or polyreactive antibodies through molecular mimicry between streptococcal and host antigens. Specifically, antibodies against the N-acetyl- β -D-glucosamine epitope (GlcNAc) of streptococcal group A carbohydrate appear to target intracellular β -tubulin and extracellular lysoganglioside GM₁ in human caudate-putamen preparations. These antibodies are also capable of causing calcium/calmodulin-dependent protein kinase II activation, which may cause the neurologic manifestations of Sydenham chorea by increasing dopamine release into the synapse.

The clinical hallmarks of Sydenham chorea are chorea, hypotonia, and emotional lability. Onset of the chorea is typically over hours to days, but it may be more abrupt. Chorea is typically generalized, although often asymmetric; up to 20% have hemichorea. Parents may describe the child as seeming clumsy and dropping items while awake with cessation of adventitious movements during sleep. Hypotonia manifests with the *pronator sign* (arms and palms turn outward when held overhead) and the *choreic hand* (spooning of the extended hand by flexion of the wrist and extension of the fingers). When chorea and hypotonia are severe, the child may be incapable of feeding, dressing, or walking without assistance. Speech is often involved, sometimes to the point of being unintelligible. Periods of uncontrollable crying and extreme mood

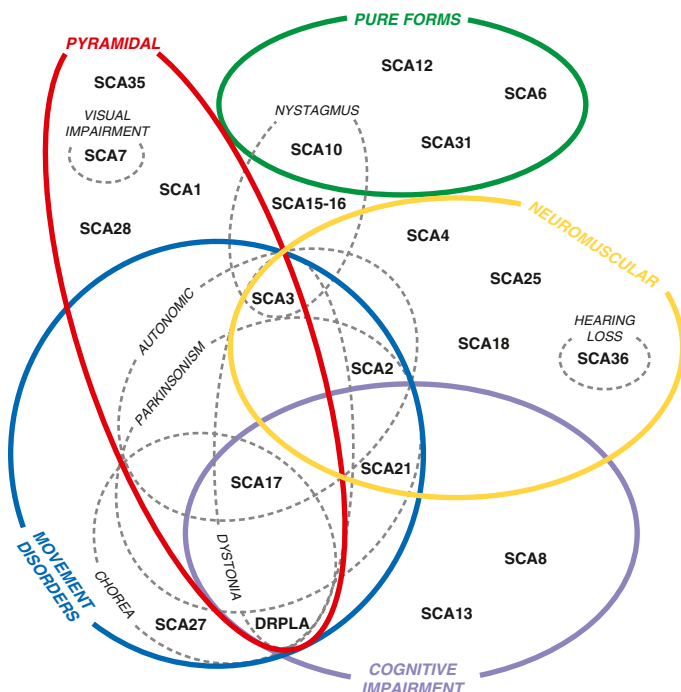


Fig. 637.5 Organization of spinocerebellar ataxias (SCA) according to main clinical features. (From Rossi M, Perez-Lloret S, Doldan L, et al. Autosomal dominant cerebellar ataxias: a systematic review of clinical features. *Eur J Neurol*. 2014;21:607–615, Fig. 2.)

Table 637.9 Acquired Causes of Chorea

STRUCTURAL-BASAL GANGLIA LESIONS	
Stroke	
Moyamoya disease	
Vascular malformations	
Hemorrhage	
Choreoathetoid cerebral palsy (dyskinetic cerebral palsy)	
Postcardiac transplant (postpump chorea)	
Mass lesions (CNS lymphoma, metastatic brain tumors)	
Multiple sclerosis plaque	
Extrapontine myelinolysis	
Trauma	
PARAINFECTIOUS AND AUTOIMMUNE DISORDERS	
Poststreptococcal Sydenham chorea	
Chorea secondary to systemic lupus erythematosus	
Chorea secondary to antiphospholipid antibody syndrome	
Acute disseminated encephalomyelitis	
Anti-NMDA receptor encephalitis	
Rasmussen encephalitis	
Chorea gravidarum	
Postinfectious or postvaccinal encephalitis	
Paraneoplastic choreas	
Celiac disease	
INFECTIOUS DISORDERS	
HIV encephalopathy	
Toxoplasmosis	
Cysticercosis	
Diphtheria	
Bacterial endocarditis	
Neurosyphilis	
Scarlet fever	
Viral encephalitis (mumps, measles, varicella)	
METABOLIC OR TOXIC DISORDERS	
Acute intermittent porphyria	
Hyponatremia/hypermnatremia	
Hypocalcemia	
Hyperthyroidism	
Hypoparathyroidism	
Hepatic/renal failure	
Carbon monoxide poisoning	
Methyl alcohol	
Toluene	
Manganese poisoning	
Mercury poisoning	
Organophosphate poisoning	
Pheochromocytoma	
PSYCHOGENIC DISORDERS	
DRUG-INDUCED DISORDERS	
<i>Dopamine-blocking agents</i> (upon withdrawal or as a tardive syndrome)	Phenothiazines Butyrophenones Benzamides
<i>Antiparkinsonian drugs</i>	L-DOPA Dopamine agonists Anticholinergics
<i>Antiepileptic drugs</i>	Phenytoin Carbamazepine Valproic acid
<i>Psychostimulants</i>	Amphetamines Methylphenidate Cocaine
<i>Calcium channel blockers</i>	Cinnarizine Flunarizine Verapamil
<i>Others</i>	Lithium Baclofen Digoxin Tricyclic antidepressants Cyclosporine Steroids/oral contraceptives Theophylline Propofol

swings are characteristic and may precede the onset of the movement disorder. Patients may also demonstrate inattention, anxiety, obsessive-compulsive symptoms, paranoia, and a reluctance to speak. It is not clear if these psychiatric symptoms represent an increased susceptibility to developing Sydenham chorea or if they are part of the disorder.

Sydenham chorea is a clinical diagnosis; a combination of acute and convalescent serum antistreptolysin O titers may help to confirm an acute streptococcal infection. Negative titers do not exclude the diagnosis. All patients with Sydenham chorea should be evaluated for carditis and treated with long-term antibiotic prophylaxis to decrease the risk of rheumatic heart disease with recurrence (see [Chapter 487](#)). This prophylaxis should be continued until the patient is 21 years old. For patients with chorea that is impairing, treatment options include valproate, carbamazepine, and dopamine receptor antagonists. There have been conflicting data regarding the efficacy of prednisone, intravenous immunoglobulin (IVIG), and other immunomodulatory agents in Sydenham chorea, making it difficult to recommend their routine use. One study compared high-dose prednisone (2 mg/kg/day, max: 60 mg) for 4 weeks to placebo and found that steroids reduced the time to remission. Another trial of IVIG, plasma exchange, and low-dose prednisone demonstrated an overall decreased severity of chorea in the IVIG and plasma exchange groups at 1-month follow-up. There is no evidence that prednisone, IVIG, or plasma exchange *alters the recurrence rate or long-term outcome*. Given the lack of impact on long-term outcome and the potential for side effects, immunomodulatory treatments are optional.

Sydenham chorea usually resolves spontaneously within 1 year, but symptoms may recur in about 20% of patients despite penicillin prophylaxis. Remote recurrence of chorea is rare, but may be provoked by streptococcal infections, pregnancy (**chorea gravidarum**), or oral contraceptive use.

Although less common than Sydenham chorea, **systemic lupus erythematosus (SLE)** and **antiphospholipid antibody syndrome (APS)** (see [Chapter 199](#)) are known causes of chorea in children. In some cases, chorea may be the presenting sign of these disorders and clinically may be indistinguishable from Sydenham chorea.

Anti N-methyl-D-aspartic acid (anti-NMDA) receptor encephalitis is an immune-mediated encephalitis with movement disorder as a prominent feature. Abnormal movements, including chorea, may be the presenting feature in some cases. Other commonly reported abnormal movements include dystonia, stereotypies (limb and oral), and motor perseveration. In addition to abnormal movements, psychiatric symptoms, seizures, and autonomic instability commonly occur. Treatment includes removal of the tumor, if present, and immune therapies such as steroids, IVIG, plasma exchange, and rituximab.

Additional causes of acquired chorea include metabolic (hyperthyroidism, hypoparathyroidism), infectious (Lyme disease), vascular (stroke, moyamoya disease, postpump chorea), hereditary degenerative disorders (Wilson disease), and drugs (see [Table 637.9](#)). Although chorea is a hallmark of Huntington disease in adults, children who develop Huntington disease tend to present with rigidity and bradykinesia (**Westphal variant**) or dystonia rather than chorea.

Various genetic diseases may manifest with chorea; some present with predominantly chorea, but most have a combination of neurologic, psychiatric, and systemic manifestations that accompany the movement disorder (see [Table 637.10](#)). **Benign hereditary chorea** is a relatively rare cause of chorea in childhood. It typically presents before age 5 years; the chorea is either stable or slowly progressive. Chorea tends to improve in the late teen to young adult years and often remits by mid-adulthood. It is most commonly secondary to a pathogenic variant in *NKX2-1*, which encodes for the protein thyroid transcription factor-1 (TTF1). The majority of patients (80%) also have hypothyroidism or neonatal respiratory distress syndrome (**brain-lung-thyroid syndrome**). Variants in *NKX2-1* confer increased risk of lung cancer or emphysema in adulthood. Although children are considered cognitively normal, there are reports of an increased incidence of learning disabilities and attention-deficit/hyperactivity disorder (ADHD) in this population.

In **ADCY5-related dyskinesia**, chorea is a core feature. There is a phenotypic variability to this disorder, but some patients present with a form of familial benign chorea with onset of paroxysmal movements starting

Table 637.10 Inherited Causes of Childhood-Onset Chorea

DISEASE NAME	INHERITANCE	ASSOCIATED GENE	AGE OF ONSET	NEUROLOGIC OR PSYCHIATRIC MANIFESTATIONS	SYSTEMIC SYMPTOMS
CHOREA PROMINENT FEATURE					
Ataxia-telangiectasia	AR	ATM	18 mo to 3 yr	Chorea often initial symptom; also have oculomotor apraxia, ataxia, and dystonia	Telangiectasias, increased sinopulmonary infections, increased incidence of cancer
Ataxia with oculomotor apraxia 1 and 2 (especially type 1)	AR	APTX	Onset later than ataxia-telangiectasia	Chorea, dystonia, oculomotor apraxia, ataxia, distal sensory axonal neuropathy	
Friedreich ataxia	AR	GAA in <i>FRDA</i>	Over 2 yr, usually teenagers	Gait ataxia, axonal neuropathy, areflexia, extensor plantar response. Can have various movements (tremor, dystonia, chorea, myoclonus). Cases of chorea without cerebellar signs described.	Cardiomyopathy, diabetes
GNAO1-related dyskinesias	AR	GNAO1	Infancy	Ballismus, chorea, orofacial dyskinesias; can alternatively cause Ohtahara syndrome	
FOXP1-related dyskinesias	AD	FOXP1	Infancy	Chorea, dystonia, athetosis, hand-mouthing stereotypies, postnatal microcephaly, epilepsy, severe developmental delay	
Benign hereditary chorea	AD	NKX2-1	Before age 5 yr	Chorea; can have myoclonus, learning disability	Thyroid disease, lung disease
ADCY5-associated dyskinesias	AD	ADCY5	Infancy to late adolescence	Chorea, choreic facial twitches (previously called myokymia); can have myoclonus or dystonia	Some reports of congestive heart failure
PDE10A-associated dyskinesias	AD or AR	PDE10A	AD: childhood AR: infancy	Chorea, MRI striatal changes in AD form	
Paroxysmal nonkinesigenic dyskinesias	AD	PNKD	Infancy to 10 yr	Dystonia, chorea, or a combination	
3-methylglutaconic aciduria type III (Costeff syndrome)	AR	OPA3	Infancy	Bilateral optic atrophy and chorea early; spasticity, ataxia, and dementia later	
Congenital cataracts, facial dysmorphism, and neuropathy	AR	CTDP1	Infancy or childhood	Progressive neuropathy, delayed psychomotor development, mild chorea, hypomyelination, hearing loss	Skeletal abnormalities, dysmorphic face, congenital cataracts, microcornea, hypogonadism
Dentatorubral-pallidoluysian atrophy	AD	CAGn in <i>atrophin-1</i>	Mostly adults but seen in a few children	Neurodegeneration, chorea, tics, dementia, seizures, ataxia, psychiatric symptoms	
Huntington chorea/disease	AD	CAGn in <i>HTT</i>	Adolescence to 40s	Younger onset <i>without</i> chorea and with parkinsonism, but later, teenagers can manifest chorea, emotional disturbances similar to adult form	
Huntington disease-like-3 (HDL3)	AR	Linked to chromosome 4p15.3	Childhood	Neurodegeneration, chorea, dystonia, ataxia, dementia, seizures	
Idiopathic basal ganglia calcification (IBGC), childhood onset (bilateral striopallidodentate calcinosis)	AR or AD	SLC20A2 or PDGFRB	Infancy to second decade of life	Tetraplegia, chorea, severe cognitive impairment, microcephaly, basal ganglia calcifications	Early death

Continued

Table 637.10 Inherited Causes of Childhood-Onset Chorea—cont'd

DISEASE NAME	INHERITANCE	ASSOCIATED GENE	AGE OF ONSET	NEUROLOGIC OR PSYCHIATRIC MANIFESTATIONS	SYSTEMIC SYMPTOMS
Choreoacanthocytosis	AR	VPS13A	Mean age 20 yr but described in childhood	Psychiatric symptoms (e.g., obsessive-compulsive disorder) can precede neurologic symptoms. Neurodegeneration, progressive hyperkinetic movements (limb chorea, orofacial dyskinesias, tics, dystonia), dementia, seizures, cognitive decline, sensorimotor polyneuropathy.	Acanthocytosis, increased CK and/or liver transaminases
Spinocerebellar ataxia 1	AD	CAGn in ATXN1	Childhood	Neurodegeneration, progressive ataxia, mild cognitive impairment, dysarthria, ophthalmoplegia, optic atrophy, spasticity, dystonia or chorea	
Spinocerebellar ataxia 17	AD	CAGn or CAA n in TBP	Mostly early adulthood but some teenagers reported	Neurodegeneration, psychiatric symptoms (depression, hallucinations), frontal release signs, chorea, dystonia, and parkinsonism; may have ocular movement abnormalities	
Leigh syndrome	X-linked	PDHA1	Infancy or childhood	Neurodegeneration, psychomotor delay, hypotonia and chorea and other hyperkinetic movements can be prominent, progresses to feeding and swallowing defects, nystagmus, ophthalmoplegia, optic atrophy, seizures Lesions in basal ganglia, cerebrum, cerebellum, spinal cord	Lactic acidemia, respiratory failure
Nonketotic hyperglycemia (glycine encephalopathy)	AR	GLDC, GCST, or GCSH	Neonates/infancy	Hypotonia, severe myoclonic epilepsy, profound cognitive impairment, restlessness	Hyperglycemia
Infantile bilateral striatal necrosis	AR	NUP62	Infancy	Developmental regression, intellectual disability, pendular nystagmus, optic atrophy, dysphagia, dystonia, choreoathetosis, spasticity, and severe bilateral striatal atrophy	
CHOREA SOMETIMES PRESENT					
Spinocerebellar ataxia 7	AD	CAGn in ATXN7	Childhood	Neurodegenerative mitochondrial disorder, progressive ataxia, dysarthria, dysphagia, optic atrophy, ophthalmoplegia, spasticity, dystonia or chorea may occur	Retinal degeneration
Wilson disease	AR	ATP7B	12 yr to early 20s	Dysarthria, drooling, pharyngeal dysmotility, clumsiness, tremor ("wing-beating"), psychiatric symptoms (decline in school, anxiety, depression, psychosis); chorea and dystonia variable	Hepatic dysfunction (asymmetric hepatomegaly, acute transient or fulminant hepatitis), Kayser-Fleischer rings of cornea
Lesch-Nyhan disease	X-linked	HPRT	Early childhood	Self-injurious behaviors, intellectual disability, motor disability, pyramidal signs, dystonia superimposed on hypotonia, may have chorea or ballismus, abnormal ocular motility	Hyperuricemia, nephrolithiasis, gout
Pantothenate kinase-associated neurodegeneration (PKAN), classic form	AR	PANK2	Before 6 yr old (in classic onset)	Progressive motor difficulties, personality changes, cognitive decline, dysarthria, spasticity; later onset of movements (dystonia most common, chorea or tremor may also be present); "eye of the tiger" sign on MRI of brain	Pigmentary retinal degeneration, acanthocytosis

Table 637.10 Inherited Causes of Childhood-Onset Chorea—cont'd

DISEASE NAME	INHERITANCE	ASSOCIATED GENE	AGE OF ONSET	NEUROLOGIC OR PSYCHIATRIC MANIFESTATIONS	SYSTEMIC SYMPTOMS
Paroxysmal kinesigenic dyskinesia (PKD)	AD	<i>PRRT2</i>	1-20 yr	Short episodes triggered by sudden movement; dystonia is most common movement but can have chorea	
Bioprotein-dependent hyperphenylalaninemia (group of disorders)	Usually AR	Multiple genetic causes	Neonate	Initially hypotonic with poor suck, decreased movements, and microcephaly; months later, oculogyric crises, swallowing difficulties, variable hypokinetic and hyperkinetic movements, seizures, cognitive impairment	Elevated phenylalanine level at birth; autonomic symptoms start several months later
Glutaric aciduria	AR	<i>GCDH</i>	First 6 mo	Hypotonia and jitteriness at birth; at 6-18 mo, progressive hyperkinetic movements (dystonia, choreoathetosis); may have seizures	
Alternating hemiplegia of childhood	AR	<i>ATP1A-3</i>	Neonate to <18 mo	Transient episodes of alternating hemiplegia/hemiparesis, dystonic attacks, paroxysmal abnormal ocular movements, seizures, episodes of autonomic dysfunction; between attacks, may have ataxia, dystonia, and/or choreoathetosis; most have intellectual disability	
Succinate semialdehyde dehydrogenase deficiency	AR	<i>ALDH5A</i>	Infancy to early childhood	Intellectual disability, pronounced language dysfunction, autistic traits, hypotonia, aggression, ataxia, anxiety, hallucinations, can have choreoathetosis	

anywhere from infancy to late adolescence. Although chorea is the most commonly described movement, there are reports of myoclonic or dystonic movements as well. Movements are more common in the arms and face and less common in the legs. *ADCY5*-related dyskinesia has commonly been associated with choreic facial twitches that were previously considered facial myokymia (known as **familial dyskinesia with facial myokymia**). Interestingly, movements in this form can persist in sleep. Symptoms can fluctuate such that chorea may be paroxysmal; they tend to be worsened by specific actions and anxiety. These patients also tend to have a stable or very slowly progressive course that tends to stabilize and even improve in middle age. *ADCY5*-related dyskinesia can have a more severe presentation with infantile onset of axial hypotonia and developmental delay. *ADCY5*-related dyskinesia has not been associated with thyroid or lung disease; however, heart failure has been reported in five patients. Although these conditions are called benign, these movements can be disabling and progressive in some patients. Therefore some patients may warrant symptomatic treatment. Although there is no proven symptomatic treatment for these conditions, there have been reports of benefit with dopamine receptor–blocking or –depleting agents. In a few cases, low-dose levodopa has provided benefit.

A pure, benign, and nonprogressive childhood-onset chorea has been described in a few patients with pathogenic variants in *PDE10A*, which encodes for a phosphodiesterase. Children with de novo dominant variants characteristically have symmetric T2 hyperintensities in the bilateral striatum on brain MRI. Children with recessive homozygous variants have been described with an earlier age of onset and a more severe clinical course.

Paroxysmal dyskinesias can present with chorea or dystonia, or both; chorea is most commonly associated with **paroxysmal nonkinesigenic dyskinesia (PNKD)**. This disorder presents in the first decade of life, with ~30% of patients manifesting symptoms in the first year of life. Patients often have both chorea and dystonia, although some patients manifest only dystonia. Episodes can last minutes to hours, and children are normal between episodes. The episodes are not triggered by sudden movement but can be precipitated by alcohol, caffeine, or emotional stress. About half of patients report a premonitory sensation

or a sense of anxiety before an episode. Although various genes have been implicated in this disorder, *PNKD* (formerly known as *MR-1*) is most commonly associated with PNKD. Patients with a *PNKD* pathogenic variant often respond to benzodiazepines; avoidance of triggers is also important. Symptoms typically improve with age. Variants in *KCNMA1* can also cause a PNKD phenotype, although these children often have other neurologic abnormalities.

Some inherited disorders classified as ataxia syndromes also manifest with significant chorea. **Ataxia-telangiectasia** typically presents as a mixed movement disorder with ataxia, dystonia, and chorea in early childhood (18 months to 3 years). These symptoms present before the appearance of telangiectasias. Over time, children have progression of limb and gait involvement and typically become nonambulatory in childhood. Children also present with oculomotor apraxia (difficulty in initiating horizontal and vertical saccades). Ataxia-telangiectasia is an autosomal recessive disorder secondary to pathogenic variants in *ATM*. Because this gene encodes for a protein involved in DNA repair mechanisms, affected children are at increased risk of sinopulmonary infections and lymphoreticular neoplasms. When this disease is suspected, the initial workup involves testing the alpha-fetoprotein (AFP) level, which is abnormally increased in this population. **Ataxia with oculomotor apraxia type 1 (AOA1)** is also associated with a mixed movement disorder and is caused by variants in *APTX*, which encodes for the aprataxin protein. Up to 80% of children have chorea and dystonia as their initial symptoms. Other neurologic symptoms include oculomotor apraxia, ataxia, and a distal sensory axonal neuropathy. The movement disorder tends to be most severe early in the disease and improves as the disease progresses. Unlike ataxia-telangiectasia, this disorder is not associated with skin findings or an increased incidence of cancer.

Chorea can also be a major manifestation in children with inherited conditions that have a progressive, severe course. **Pontocerebellar hypoplasia type 2A (PCH-2A)** is associated with chorea present from a young age. The majority of patients have chorea within the first 6 months of life. PCH-2A is associated with an acquired microcephaly, extrapyramidal dyskinesias, and spasticity. These children have significant psychomotor delay with early death. Although various genes have

been implicated in the different forms of pontocerebellar hypoplasia, PCH-2A is associated with pathogenic variants in *TSEN54*, which encodes for a protein involved in transfer RNA (tRNA) splicing. Variants in *GNAO1*, which encodes for the alpha subunit of G proteins, have been described as causing a particular movement disorder in affected children. This gene has previously been described as a cause of early infantile epileptic encephalopathy (**Ohtahara syndrome**). However, affected children may instead manifest with hypotonia, developmental delay without epilepsy, and a movement disorder characterized by chorea and ballismus in the first decade of life. Chorea tends to start acutely during an illness. Some children with *GNAO1* variants have a severe movement disorder without seizures. Orofacial dyskinesias are common. Children often have periods of movement exacerbations that can be accompanied by autonomic changes. These movements can be refractory to treatment and led to death in two of the children in a study. Deep brain stimulation has been proposed as a potential treatment for these medically refractory children. *FOXG1* variants are associated with postnatal microcephaly, an early epileptic encephalopathy, and abnormal movements. Chorea is commonly reported and may involve the upper extremities and orolingual muscles. Dystonia, athetosis, and stereotypies are also reported.

Athetosis is characterized by slow, continuous, writhing movements that repeatedly involve the same body part(s), usually the distal extremities, face, neck, or trunk. Like chorea, athetosis may occur at rest and is often worsened by voluntary movement. Because athetosis tends to occur with other movement disorders, such as chorea (**choreoathetosis**) and dystonia, it is often difficult to distinguish as a discrete entity. Choreoathetosis is common in dyskinetic cerebral palsy, which can result from hypoxic ischemic encephalopathy, kernicterus, or other basal ganglia injuries. Cerebral palsy is a static disturbance in the developing brain that results in motor impairment. Dyskinetic cerebral palsy, the second most common form after spastic cerebral palsy, typically presents with dystonia and choreoathetosis. The choreoathetosis is typically more common in the upper body. Choreoathetosis is often seen in conjunction with **rigidity**—increased muscle tone that is equal in the flexors and extensors in all directions of passive movement regardless of the velocity of the movement. This is to be differentiated from **spasticity**, a velocity-dependent (clasp-knife) form of hypertonia that is seen with upper motor neuron dysfunction. Case reports in dyskinetic cerebral palsy report chorea improvement with levetiracetam. In addition, a small study of risperidone in children with dyskinetic cerebral palsy reported improvement in abnormal movements and behavior.

Tremor is a rhythmic, oscillatory movement around a central point or plane that results from the action of antagonist muscles. Tremor can affect the extremities, head, trunk, or voice and can be classified by both its frequency (slow [4 Hz], intermediate [4–7 Hz], and fast [≥7 Hz]) and by the context in which it is most pronounced. **Rest tremor** is maximal when the affected body part is inactive and supported against gravity, whereas **postural tremor** is most notable when the patient sustains a position against gravity. **Action tremor** occurs with performance of a voluntary activity and can be subclassified into **simple kinetic tremor**, which occurs with limb movement, and **intention tremor**, which occurs as the patient's limb approaches a target and is a feature of cerebellar disease.

Essential tremor (ET) is the most common movement disorder in adults, and 50% of persons diagnosed with ET report an onset in childhood; thus ET may be the most common tremor disorder in children as well. Clinical experience in a pediatric movement disorders clinic suggests that ET is more common in the pediatric population than the literature would suggest. ET is an autosomal dominant condition with variable expressivity but complete penetrance by the age of 60 years. Although the genetics of ET are not fully understood, at least five genes (*EMT1*, *EMT2*, *EMT3*, *EMT4*, and *EMT5*) are linked to this condition. In addition, polymorphisms in the gene *LINGO1* (also known as *LRRN6A*) have been associated with ET.

ET is characterized by a slowly progressive, bilateral, 4- to 9-Hz postural tremor that involves the upper extremities and occurs in the absence of other known causes of tremor. Face, neck, and voice tremors are less common but can occur. Mild asymmetry in the

upper extremities is common, but ET is rarely unilateral. ET may be worsened by actions, such as trying to pour water from cup to cup. Affected adults may report a history of ethanol responsiveness. In the adult literature, there is a consensus on diagnostic criteria; there are no specific criteria in children. Unlike adults, children do not require a 5-year duration of symptoms to make the diagnosis of ET. Most young children come to medical attention once a parent, teacher, or therapist notices the tremor, rather than because the tremor causes impairment. Most children with ET do not require pharmacologic intervention. If they are having difficulty with their handwriting or self-feeding, an occupational therapy evaluation and/or assistive devices, such as wrist weights and weighted silverware, may be helpful. Teenagers tend to report more impairment from ET. Teenagers who do warrant pharmacotherapy usually respond to the same medications that are used in adults—propranolol and primidone. Propranolol, which is generally considered the first-line treatment, can be started at 10–40 mg daily and titrated to effect, with most patients responding to doses of 60–80 mg/day. Propranolol should not be used in patients with reactive airway disease. Primidone can be started at 12.5–25 mg at bedtime and increased gradually in a twice-daily schedule. Most patients respond to doses of 50–200 mg/day. Other treatment options for ET reported in the adult literature include atenolol, gabapentin, pregabalin, topiramate, and alprazolam. Surgical treatments, which include deep brain stimulation of the thalamus and unilateral thalamotomy, are generally reserved for adults with medically refractory disabling tremor.

Enhanced physiologic tremor is one of the most common etiologies of tremor in adolescents. This tremor occurs in healthy people and is characterized by a symmetric hand tremor that is often of faster frequency and lower amplitude than an ET. Triggers include increased emotions, fatigue, fever, hunger, and waking from sleep. Substances such as caffeine may enhance a tremor. Weighted objects may decrease tremor frequency.

In children 3–7 years old, coordination difficulties due to developmental delay can present with nonprogressive tremor. Many children with motor delays will have a hand and possibly truncal tremor that is most apparent with fine motor tasks, such as drawing, using scissors, or playing with small toys. The history often shows that these children are behind typically developing children in terms of fine and/or gross motor skills and speech articulation. Examination shows that the movement tends to be a small-amplitude, regular or irregular postural or intention tremor. Walking and running may be clumsy. Evidence-based treatment has not been established for tremor related to developmental delay; however, referral to occupational therapy may help to identify strategies to improve coordination in these children.

Infantile tremor syndrome is a disorder of unknown etiology that presents at age 6–18 months with regression or plateaued development, coarse tremor, and anemia. Potential etiologies include deficiencies in vitamin B₁₂, iron, zinc, or magnesium.

There are numerous secondary etiologies of tremor in children (Table 637.11). **Holmes tremor**, previously referred to as *midbrain* or *“rubral”* tremor, is characterized by a slow-frequency, high-amplitude tremor that is present at rest and with intention. It is a symptomatic tremor, which usually results from lesions of the brainstem, cerebellum, or thalamus. **Functional (psychogenic) tremor** is distinguished by its variable appearance, abrupt onset and remission, nonprogressive course, and association with selective but not task-specific disabilities.

In some cases, tremor may even occur as a manifestation of another movement disorder, as is seen with position- or task-specific tremor (e.g., writing tremor), dystonic tremor, and myoclonic tremor.

When evaluating a child with tremor, it is important to screen for common metabolic disturbances, including electrolyte abnormalities and thyroid disease, assess the child's caffeine intake, and review the child's medication list for known tremor-inducing agents. It is also critical to exclude Wilson disease in teenagers with characteristic “wing-beating” tremor (low-frequency/high-amplitude posture initiated with horizontal position and abduction of arms, flexed elbows, and downward-facing palms with resultant shoulder and hand tremors) because this is a treatable condition.

Table 637.11 Selected Causes of Tremor in Children**BENIGN TREMORS**

Enhanced physiologic tremor
Developmental delay
Shuddering attacks
Jitteriness
Spasmus nutans

STATIC INJURY/STRUCTURAL TREMORS

Cerebellar malformation
Stroke (particularly in the midbrain or cerebellum)
Multiple sclerosis

HEREDITARY/DEGENERATIVE TREMORS

Familial essential tremor
Fragile X premutation
Wilson disease
Huntington disease
Juvenile parkinsonism (tremor is rare)
Pallidonigral degeneration

METABOLIC TREMORS

Hyperthyroidism
Hyperadrenergic state (including pheochromocytoma and neuroblastoma)
Hypomagnesemia
Hypocalcemia
Hypoglycemia
Hepatic encephalopathy
Vitamin B12 deficiency
Inborn errors of metabolism
Mitochondrial disorders

DRUGS/TOXINS

Valproate, phenytoin, carbamazepine, lamotrigine, gabapentin, lithium, tricyclic antidepressants, stimulants (cocaine, amphetamine, caffeine, thyroxine, beta agonist, bronchodilators), neuroleptics, cyclosporine, toluene, mercury, thallium, amiodarone, nicotine, lead, manganese, arsenic, cyanide, naphthalene, ethanol, lindane, serotonin reuptake inhibitors

PERIPHERAL NEUROPATHIES**FUNCTIONAL (PSYCHOGENIC) TREMORS****637.3 Myoclonus**

Jonathan W. Mink

Myoclonus refers to brief, abrupt, involuntary, nonsuppressible, jerky contractions (or interruption of contractions) involving a single muscle or muscle group. The rapidity of these movements is often described as *shocklike*. In some cases, myoclonus can be elicited by a sensory stimulus (reflex myoclonus; the most common example is the acoustic startle response in infancy) or volitional movement (action myoclonus). It is present in normal and pathologic situations, both epileptic and non-epileptic. Epileptic myoclonus is discussed in [Chapter 633](#). Etiologic classification of myoclonus is summarized in [Table 637.12](#).

Physiologic myoclonus occurs in healthy individuals in specific settings. It includes such entities as hiccups, sleep starts, and sleep myoclonus. Sleep starts, also known as *hypnic* or *hypnagogic myoclonus*, occur with sleep initiation. They are often accompanied by a sense of falling. Sleep starts are normal physiologic phenomena, and no treatment is required. Sleep myoclonus (nocturnal myoclonus) is also a part of normal sleep physiology. It typically occurs during rapid eye movement (REM) sleep owing to transient failure of brainstem inhibition. Sleep myoclonus tends to persist throughout life. No treatment is required.

Benign myoclonus may occur in association with specific developmental stages. Benign neonatal sleep myoclonus is characterized by repetitive myoclonic jerks occurring during sleep. The myoclonus is typically more distal than proximal and is more prominent in the upper than the lower extremities. The myoclonus can be focal, multifocal, unilateral, or bilateral. Typically, the movements occur in clusters of jerks at 1–5 Hz over a period of several seconds. Benign neonatal sleep myoclonus

begins during the first week of life, diminishes in the second month, and is usually gone before 6 months of age. The movements are most likely to occur during quiet (non-REM) sleep but have been described in all sleep stages. Waking the baby causes the movements to abruptly cease. Neurologic examination and outcome are normal.

Myoclonus also can occur with fever in otherwise normal children. The myoclonic jerks may be quite frequent, but they are self-limited, ceasing when the fever resolves. Febrile myoclonus may be more common in younger children. No treatment is required.

Opsoclonus myoclonus (ataxia) syndrome (OMS/OMAS) is characterized by a combination of rapid, chaotic involuntary eye movements (opsoclonus), multifocal myoclonus, and ataxia. Irritability is a common feature. It typically begins abruptly in early childhood, most often before age 5 years. A common misdiagnosis is acute cerebellar ataxia (ACA) because both ACA and OMAS have subacute, progressive disturbances in gait, truncal instability, and behavioral irritability. Irritable toddlers are difficult to examine thoroughly, adding to the challenge of discerning the presence of multifocal mini-myoclonus and action myoclonus plus ataxia in a toddler with OMAS versus titubation, gait, and limb ataxia in ACA. At its peak, OMAS can cause marked disability for the child.

OMAS is an autoimmune condition in which there is abnormal B-cell trafficking in the central nervous system. It may follow a viral infection in many cases. A large proportion of children (40% by one estimate) with OMAS have a neuroblastoma, a potentially fatal neural crest tumor (see [Chapter 547](#)). Conversely, only a small proportion of children with neuroblastoma (probably <5%) have OMAS. The subacute onset of OMAS and the association with neural crest tumors support an autoimmune paraneoplastic etiology. Intensive research into multiple circulating auto-antibodies, including antibodies to Purkinje cell targets, has not, to date, identified any unique, consistently present, disease-associated antibody.

OMAS is a clinical diagnosis. In the presence of subacute irritability, tremor, and ataxia, a diagnosis of OMAS must be considered, and children diagnosed with ACA should continue to be monitored for the emergence of symptoms characteristic of OMAS. The presence of opsoclonus has a high positive predictive value for OMAS, but its absence does not have a high negative predictive value. That is because opsoclonus can be subtle, intermittent, or late, so clinicians and parents need to continue to watch for it. Brain MRI should be normal, and cerebrospinal fluid unremarkable. No immune studies are clinically established for this diagnosis. The search for a neuroblastoma should be thorough and persistent in this clinical setting. MRI with gadolinium or CT with contrast of the chest and abdomen has the highest yield. Nuclear medicine ¹³¹I-MIBG (metaiodobenzylguanidine) or ¹¹¹In-pentetreotide (somatostatin receptor ligand) PET scans and urine collection for elevated 24-hour urine catecholamines and serum neuron-specific enolase may be considered but have a lower yield.

Multimodal treatment is required for OMAS. If related to neuroblastoma, the child will likely need immune-modulating treatments even if a tumor is identified and resected. Adrenocorticotrophin (ACTH) protocols are recommended based on expert consensus and clinical experience. In addition to ACTH, combination treatment with IVIG, plasmapheresis, rituximab, or other immune-modulating therapies may be needed. Symptomatic pharmacologic and behavioral therapy for myoclonus, behavioral problems, aggression, and insomnia may also be beneficial. Physical therapy, occupational therapy, and speech therapy may be beneficial. Suboptimal cognitive outcomes occur in most cases.

Causes of other types of myoclonus are listed in [Table 637.12](#). Differentiating myoclonus and other movement disorders from a functional neurologic disorder may be difficult. Clues to a functional disorder are noted in [Table 637.13](#).

Treatment of myoclonus is symptomatic and may be ineffective in many cases. Cortical myoclonus may respond to benzodiazepines and is commonly treated with clonazepam (although sleep myoclonus may worsen). Valproic acid is sometimes helpful, but it must be used with caution because of its ability to cause tremor as a side effect, with consequent confusion of symptoms. Other epilepsy medications, including levetiracetam and zonisamide, may be effective in some forms of myoclonus. Carbamazepine can worsen myoclonus.

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Table 637.12 Etiologic Classification of Myoclonus

I. Physiologic myoclonus (normal subjects) A. Sleep jerks (hypnic jerks) B. Anxiety-induced C. Exercise-induced D. Hiccup (singultus) E. Benign infantile myoclonus with feeding II. Essential myoclonus (no known cause other than genetic and no other gross neurologic deficit) A. Hereditary (autosomal dominant and most are likely myoclonus dystonia) B. Sporadic III. Epileptic myoclonus (seizures dominate and no encephalopathy, at least initially) A. Fragments of epilepsy - Isolated epileptic myoclonic jerks - Photosensitive myoclonus - Myoclonic absences in petit mal - Epilepsia partialis continua B. Childhood myoclonic epilepsies - Infantile spasms - Myoclonic astatic epilepsy (Lennox-Gastaut) - Cryptogenic myoclonus epilepsy (Aicardi) - Juvenile myoclonus epilepsy of Janz C. Benign familial myoclonic epilepsy (Rabot) D. Progressive myoclonus epilepsy (Unverricht-Lundborg) IV. Symptomatic myoclonus (progressive or static encephalopathy dominates) A. Storage disease - Lafora body disease - Lipidoses (e.g., GM1 and GM2 gangliosidosis, Krabbe) - Ceroid-lipofuscinosis (Batten) - Sialidosis ("cherry-red spot") B. Spinocerebellar degeneration - Unverricht-Lundborg disease - Ataxia telangiectasia - Adult-onset cerebellar ataxias - Some spinocerebellar ataxias (SCAs) - Multiple system atrophy type C C. Basal ganglia degenerations - Wilson disease - Dystonia - Pantothenate kinase-associated neurodegeneration - Progressive supranuclear palsy - Multiple system atrophy type P - Huntington disease - Corticobasal ganglionic degeneration - Dentatorubro-pallidolusian atrophy - Parkinson disease	D. Dementias - Creutzfeldt-Jakob disease - Alzheimer disease E. Viral encephalopathies - Subacute sclerosing panencephalitis (SSPE) - Encephalitis lethargica - Arbor virus encephalitis - Herpes simplex encephalitis - Postinfectious encephalitis - Whipple disease - AIDS - SARS-CoV-2 F. Autoimmune - Opsoclonus-myoclonus syndrome - Celiac disease G. Metabolic - Hepatic failure - Renal failure - Dialysis syndrome - Hyponatremia - Hypoglycemia - Infantile myoclonic encephalopathy - Nonketotic hyperglycemia - Mitochondrial encephalomyopathy - Multiple carboxylase deficiency - Biotin deficiency H. Toxic encephalopathies - Bismuth - Heavy metal poisons - Methyl bromide, DDT - Drugs, including levodopa - Serotonin syndrome (e.g., SSRIs) I. Physical encephalopathies - Posthypoxic (Lance-Adams) - Posttraumatic - Heat stroke - Electric shock - Decompression injury J. Focal central nervous system damage - Poststroke - Postthalamotomy - Tumor - Trauma - Dentato-olivary lesions (palatal myoclonus/tremor) K. Functional
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From Jankovic J, Hallett M, Okun MS, et al., eds. *Principles and Practice of Movement Disorders*, 3rd ed. Philadelphia: Elsevier; 2022: Table 18.2, p. 498.

637.4 Dystonia

Shannon L. Dean and Erika F. Augustine

Dystonia is a disorder of movement characterized by sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures (Table 637.14). Major causes of dystonia include primary generalized dystonia, medications, metabolic disorders, and perinatal asphyxia (Tables 637.15 and 637.16).

INHERITED PRIMARY DYSTONIAS

Primary generalized dystonia, also referred to as *primary torsion dystonia* or *dystonia musculorum deformans*, is caused by a group of genetic disorders with onset in childhood (Fig. 637.6). Many of these disorders are autosomal dominant with incomplete penetrance, but genetic dystonias may also appear sporadically or be inherited in an autosomal recessive, X-linked, or mitochondrial pattern. Children are more likely to manifest with or progress to generalized dystonia, whereas segmental or focal dystonia is more common in adolescents and adults.

One form, which occurs more commonly in the Ashkenazi Jewish population, is caused by a dominant change in *DYT1* coding for the adenosine triphosphate (ATP)-binding protein torsinA. The initial manifestation of ***DYT1* dystonia** is often intermittent unilateral posturing of a lower extremity, which assumes an extended and rotated position. Ultimately, all four extremities and the axial musculature can be affected, but the dystonia may also remain localized to one limb. Cranial involvement can occur in *DYT1* dystonia, but it is uncommon compared with non-*DYT1* dystonias. There is a wide clinical spectrum, varying even within families. If a family history of dystonia is absent, the diagnosis should still be considered, given the intrafamilial variability in clinical expression.

More than two dozen loci for genes for **torsion dystonia** have been identified (*DYT1-DYT31*). More sophisticated genetic testing and genotype-phenotype correlation have eliminated some of these designations, and others have been linked to specific chromosomal regions but not yet to a specific gene. In this text we review only those linked definitively to a specific gene.

One is the autosomal dominant disorder **dopa-responsive dystonia** (DRD, *DYT5a*), also called *Segawa syndrome*. The gene for DRD codes

for guanosine triphosphate cyclohydrolase 1, the rate-limiting enzyme for tetrahydrobiopterin synthesis, which is a cofactor for synthesis of the neurotransmitters dopamine and serotonin. Thus the genetic alteration results in dopamine deficiency. The hallmark of the disorder, particularly in adolescents and adults, is diurnal variation: symptoms worsen as the day progresses and may transiently improve with sleep. Early-onset patients, who tend to present with delayed or abnormal gait from dystonia of a lower extremity, can easily be confused with patients with dystonic cerebral palsy. It should be noted that in the presence of a progressive dystonia, diurnal fluctuation, or loss of previously achieved motor skills, a prior diagnosis of cerebral palsy should be reexamined. **DRD responds dramatically to small daily doses of levodopa.** The responsiveness to levodopa is a sustained benefit, even if the diagnosis is delayed several years, as long as

contractures have not developed. More rarely, an autosomal recessive form of this disorder is caused by alterations in the *TH* gene.

Myoclonus dystonia (DYT11), caused by alterations in the *SCGE* gene, is characterized by dystonia involving the upper extremities, head, and/or neck, as well as myoclonic movements in these regions. Although a combination of myoclonus and dystonia typically occurs, each manifestation can present in isolation. When repetitive, the myoclonus may take on a tremor-like appearance, termed *dystonic tremor*. Improvement in symptoms after alcohol ingestion, reported by affected adult family members, may be a helpful clue to this diagnosis.

Common to the inherited dystonias, there is considerable intrafamilial variability in clinical manifestations, distribution, and severity of dystonia. In primary dystonias, although the main clinical features are motor, there may be an increased risk for major depression. Anxiety, obsessive-compulsive disorder, and depression have all been reported in myoclonus-dystonia syndrome. Screening for psychiatric comorbidities should not be overlooked in this population.

Table 637.13 Clues Relating to the Signs and Symptoms That Suggest a Functional Movement Disorder

1. Abrupt onset
2. Inconsistent movements (changing characteristics over time; pattern, body distribution, rapidly varying severity)
3. Incongruous movements and postures (movements that do not fit with recognized patterns or with normal physiologic patterns)
4. Presence of certain types of abnormal movements that are fairly common among individuals with functional movement disorders, such as:
 - Rhythmical shaking
 - Bizarre gait
 - Deliberate slowness carrying out requested voluntary movement
 - Bursts of verbal gibberish
 - Excessive startle (bizarre movements in response to sudden, unexpected noise or threatening movement)
5. Presence of additional types of abnormal movements that are not known to be part of the primary or principal movement pattern that the patient manifests
6. Manifesting exhaustion, excessive fatigue
7. Delayed, often excessive, startle response to a stimulus
8. Spontaneous remissions
9. Decrease or disappearance of movements with distraction
10. Disappearance of tremors when handling treasured objects
11. Entrainment of the tremor to the rate of the requested rapid successive movement the patient is asked to perform
12. Response to placebo, suggestion, or psychotherapy
13. Dystonia beginning as a fixed posture
14. Twisting facial movements that move the mouth to one side or the other (note that organic dystonia of the facial muscles usually does not move the mouth sideways)

From Jankovic J, Hallett M, Okun MS, et al., eds. *Principles and Practice of Movement Disorders*, 3rd ed. Philadelphia: Elsevier; 2022: Table 27.2, p. 598.

DRUG-INDUCED DYSTONIAS

A number of medications are capable of inducing involuntary movements or drug-induced movement disorders in children and adults. Dopamine-blocking agents, including antipsychotics (e.g., haloperidol) and antiemetics (e.g., metoclopramide, prochlorperazine), as well as atypical antipsychotics (e.g., risperidone, aripiprazole) can produce acute dystonic reactions or delayed (tardive) drug-induced movement disorders.

Acute dystonic reactions, occurring in the first days of exposure, typically involve the face and neck and manifest as torticollis, retrocollis, oculogyric crisis, or tongue protrusion. Life-threatening presentations with laryngospasm and airway compromise can also occur, requiring prompt recognition and treatment of this entity. Intravenous diphenhydramine 1-2 mg/kg/dose (maximum dose 50 mg) may rapidly reverse the drug-related dystonia. The degree of potency of the dopamine blocker, young age, and prior dystonic reactions may be predisposing factors. Acute dystonic reactions have also been described with cetirizine.

Severe rigidity combined with high fever, autonomic symptoms (tachycardia, diaphoresis), delirium, and dystonia are signs of **neuroleptic malignant syndrome**, which typically occurs a few days after starting or increasing the dose of a neuroleptic drug or in the setting of withdrawal from a dopaminergic agent. In contrast to acute dystonic reactions, which take place within days, neuroleptic malignant syndrome typically occurs within a month of medication initiation or dose increase.

Delayed-onset involuntary movements, **tardive dyskinesias**, develop in the setting of chronic neuroleptic use, usually longer than 3 months. Involvement of the face, particularly the mouth, lips, and/or jaw with chewing or tongue thrusting, is characteristic. The risk of tardive dyskinesia, which is much less frequent in children compared with adults, increases as the medication dose, duration of treatment, and polypharmacy increase. There are data to suggest that children

Table 637.14 Classification of Dystonias by Affected Body Part

TYPE OF DYSTONIA	NO. OF BODY PARTS AFFECTED	DETAIL
Focal*	1	• Eyelids (blepharospasm) • Mouth (oromandibular dystonia, musician's cramp) • Larynx (dystonic adductor dysphonia, "whispering dysphonia") • Neck (cervical dystonia, previously known as spasmodic torticollis) • Hand and arm (writer's cramp)
Segmental	≥2 contiguous body parts	• Axial (neck and trunk) • Brachial (1 arm and trunk; both arms ± neck ± trunk) • Crural (1 leg and trunk; both legs ± trunk)
Multifocal	≥2 noncontiguous body parts	Faciobrachial (blepharospasm and writer's cramp)
Hemidystonia	≥2	Ipsilateral arm and leg
Generalized	≥3	Trunk and ≥2 other sites ± leg involvement

*Some localized dystonias may spread and eventually generalize.

From Klein C, Lohmann K, Marras C, et al. Hereditary dystonia overview. 2003 Oct 28 [Updated 2017 Jun 22]. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. *GeneReviews* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023, Table 1.

Table 637.15 Causes of Dystonia in Childhood

STATIC INJURY/STRUCTURAL DISORDERS Cerebral palsy Hypoxic-ischemic injury Kernicterus Head trauma Encephalitis Tumors Stroke in the basal ganglia (which may be a result of vascular abnormalities or varicella) Congenital malformations	METABOLIC DISEASE Glutaric aciduria types 1 and 2 Acyl-coenzyme A (CoA) dehydrogenase deficiencies Dopa-responsive dystonia Aromatic l-amino acid decarboxylase deficiency Aminolevulinic acid dehydrase Biotin-responsive basal ganglia disease Mitochondrial disorders Wilson disease Vitamin E deficiency Homocystinuria Methylmalonic aciduria Tyrosinemia
HEREDITARY/DEGENERATIVE DISORDERS DYT1 (early-onset primary torsion dystonia, <i>TOR1A</i>) DYT2 (early-onset dystonia with craniocervical involvement, autosomal recessive) DYT3 (adult-onset dystonia-parkinsonism, X-linked <i>TAF1</i>) DYT4 (adult-onset spasmodic dysphonia, <i>TUBB4A</i>) DYT5 (dopa-responsive dystonia, <i>GCH1</i>) DYT6 (adult-onset torsion dystonia with craniocervical and laryngeal involvement, <i>THAP1</i>) DYT7 (adult-onset cervical dystonia) DYT8 (paroxysmal nonkinesigenic dyskinesia, <i>MR1</i>) DYT10 (paroxysmal kinesigenic dyskinesia, <i>PRRT2</i>) DYT11 (myoclonus dystonia, <i>SGCE</i>) DYT12 (rapid-onset dystonia-parkinsonism, <i>ATP1A3</i>) DYT16 (early-onset dystonia-parkinsonism, autosomal recessive, <i>PRKRA</i>) DYT18 (paroxysmal exercise-induced dyskinesia, <i>SLC2A1</i>) DYT23 (adult-onset cervical dystonia and myoclonus, <i>CACNA1B/CIZ1</i>) DYT24 (craniocervical dystonia with limb tremor, <i>ANO3</i>) DYT26 (early-onset myoclonic dystonia, <i>KCTD17</i>) DYT27 (early-onset segmental dystonia, autosomal recessive, <i>COL6A30</i>) DYT 28 (early-onset generalized dystonia, <i>KMT2B</i>) DYT29 (early-onset dystonia with optic atrophy and basal ganglia abnormalities, <i>MECR</i>) DYT30 (progressive early-onset dystonia, <i>VPS16</i>) DYT31 (early-onset multifocal or generalized dystonia, autosomal recessive, <i>AOPEP</i>) Fahr disease (often caused by hypoparathyroid disease) Neurodegeneration with brain iron accumulation Huntington disease (particularly the Westphal variant, IT15-4p16.3) Spinocerebellar ataxias (SCAs, including SCA3/Machado-Joseph disease) Neuronal ceroid-lipofuscinoses (NCLs) Rett syndrome Striatal necrosis Leigh disease Leber hereditary ocular neuropathy (LHON) Neuroacanthocytosis HARP syndrome (hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration) Ataxia-telangiectasia <i>POLG1</i> gene alterations Tay-Sachs disease Sandhoff disease Niemann-Pick type C GM ₁ gangliosidosis Mitochondrial membrane protein-associated neurodegeneration (MPAN) Metachromatic leukodystrophy (MLD) Lesch-Nyhan disease Pantothenate kinase-associated neurodegeneration (PKAN)	DRUGS/TOXINS Neuroleptic and antiemetic medications (haloperidol, chlorpromazine, olanzapine, risperidone, prochlorperazine) Calcium channel blockers Stimulants (amphetamine, cocaine, ergot alkaloids) Anticonvulsants (carbamazepine, phenytoin) Thallium Manganese Carbon monoxide Ethylene glycol Cyanide Methanol Wasp sting
	PAROXYSMAL DISORDERS Paroxysmal kinesigenic choreoathetosis (PKD) Paroxysmal nonkinesigenic choreoathetosis (PNKD) Paroxysmal exercise-induced dystonia (PED) Complex migraine Alternating hemiplegia of childhood (AHC) Paroxysmal torticollis of infancy
	DISORDERS THAT MIMIC DYSTONIA Tonic seizures (including paroxysmal nocturnal dystonia caused by nocturnal frontal lobe seizures) Arnold-Chiari malformation type II Atlantoaxial subluxation Syringomyelia Posterior fossa mass Cervical spine malformation (including Klippel-Feil syndrome) Skew deviation with vertical diplopia causing neck twisting Juvenile rheumatoid arthritis Sandifer syndrome (associated with hiatal hernia in infants) Spasmus nutans Tics Infant masturbation Spasticity Myotonia Rigidity Stiff-person syndrome Isaac syndrome (neuromyotonia) Startle disease (hyperekplexia) Neuroleptic malignant syndrome Central herniation with posturing Psychogenic dystonia

From Sanger TD, Mink JW. Movement disorders. In: Swaiman KF, Ashwal S, Ferriero DM, et al., eds. *Swaiman's Pediatric Neurology*, 5th ed. Philadelphia: Saunders; 2012: Box 68-2.

with autism spectrum disorders may also be at increased risk for this drug-induced movement disorder. Unlike acute dystonic reactions and neuroleptic malignant syndrome, discontinuation of the offending agent may not result in clinical improvement. In these patients, use of dopamine-depletors, such as reserpine, tetrabenazine, or valbenazine, may prove helpful.

Therapeutic doses of phenytoin, carbamazepine, or valproate rarely cause progressive dystonia in children with epilepsy, particularly in those who have an underlying structural abnormality of the brain.

During evaluation of new-onset dystonia, a careful history of prescriptions and potential medication exposures is critical

Table 637.16 Examples of Primary and Secondary Dystonia in Childhood

DIAGNOSIS	ADDITIONAL CLINICAL FEATURES	DIAGNOSIS	ADDITIONAL CLINICAL FEATURES
Aicardi-Goutières syndrome	Encephalopathy, developmental regression Acquired microcephaly Sterile pyrexias Lesions on the digits, ears (chilblain) Epilepsy CT: calcification of the basal ganglia	Kernicterus	Jaundice in infancy Hearing loss Impaired upgaze Enamel dysplasia MRI: hyperintense lesions in the globus pallidus
Alternating hemiplegia of childhood	Episodic hemiplegia/quadruplegia Abnormal ocular movements Autonomic symptoms Epilepsy Global developmental impairment Environmental triggers for spells	Leigh syndrome	Motor delays, weakness, hypotonia Ataxia, tremor Elevated lactate MRI: bilateral symmetric hyperintense lesions in the basal ganglia or thalamus
Aromatic amino acid decarboxylase deficiency (AADC)	Developmental delay Oculogyric crises Autonomic dysfunction Hypotonia	Lesch-Nyhan syndrome (X-linked)	Male Self-injurious behavior Hypotonia Oromandibular dystonia, inspiratory stridor Oculomotor apraxia Cognitive impairment Elevated uric acid
ARX gene alteration (X-linked)	Male Cognitive impairment Infantile spasms, epilepsy Brain malformation	Myoclonus dystonia	Myoclonus Head, upper limb involvement
Benign paroxysmal torticollis of infancy	Episodic Cervical dystonia only Family history of migraine	Niemann-Pick type C	Hepatosplenomegaly Hypotonia Supranuclear gaze palsy Ataxia, dysarthria Epilepsy Psychiatric symptoms
Complex regional pain syndrome	Lower limb involvement Prominent pain	Neuroacanthocytosis	Oromandibular and lingual dystonia
Dopa-responsive dystonia (DRD)	Diurnal variation	Neurodegeneration with brain iron accumulation	Cognitive impairment Retinal pigmentary degeneration, optic atrophy
Drug-induced dystonia		Rapid-onset dystonia parkinsonism (DYT12)	Acute onset Distribution face > arm > leg Prominent bulbar signs
Dystonia-deafness optic neuropathy syndrome	Sensorineural hearing loss in early childhood Psychosis Optic atrophy in adolescence	Rett syndrome	Female Developmental regression after a period of normal development Stereotypic hand movements Acquired microcephaly Epilepsy
DYT1 dystonia	Lower limb onset followed by generalization	Spinocerebellar ataxia 17 (SCA17)	Ataxia Dementia, psychiatric symptoms Parkinsonism
Glutaric aciduria type 1	Macrocephaly Encephalopathic crises MRI: striatal necrosis	Tics	Stereotyped movements Premonitory urge, suppressible
GM ₁ gangliosidosis type 3	Short stature, skeletal dysplasia Orofacial dystonia Speech/swallowing disturbance Parkinsonism MRI: putaminal hyperintensity	Tyrosine hydroxylase deficiency	Infantile encephalopathy, hypotonia Oculogyric crises, ptosis Autonomic symptoms Less diurnal fluctuation than DRD
Huntington disease	Parkinsonism Epilepsy Family history of Huntington disease		

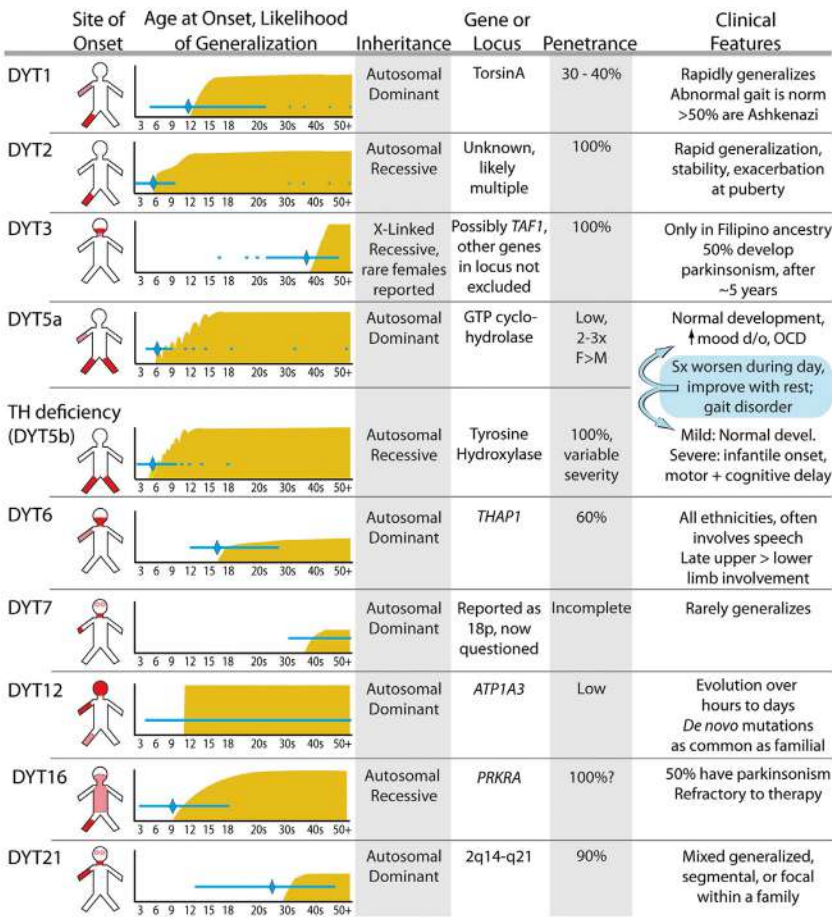
CEREBRAL PALSY

See Chapter 638.1.

METABOLIC DISORDERS

Disorders of monoamine neurotransmitter metabolism, of which dopa-responsive dystonia is one, present in infancy and early childhood with dystonia, hypotonia, oculogyric crises, and/or autonomic

symptoms. Common comorbidities such as epilepsy, developmental delay, and microcephaly, which are also found in cerebral palsy and other more common disorders, likely contribute to underdiagnosis of this group of rare diseases. The more common disorders in this group include DRD, tyrosine hydroxylase deficiency, and aromatic amino acid decarboxylase deficiency. With the exception of aromatic amino acid decarboxylase deficiency, most do respond at least partially to



levodopa. Abnormalities of the dopamine transporter (DAT) can also present in infancy with dystonia.

Wilson disease is an autosomal recessive inborn error of copper transport characterized by cirrhosis of the liver and degenerative changes in the central nervous system, particularly the basal ganglia (see Chapter 405.2). It has been determined that there are multiple alterations in the Wilson disease gene (*WND*), accounting for the variability in presentation of the condition. The neurologic manifestations of Wilson disease rarely appear before age 10 years, and the initial sign is often progressive dystonia. Tremors of the extremities develop, unilaterally at first, but they eventually become coarse, generalized, and incapacitating. Other neurologic signs of Wilson disease relate to a progressive basal ganglia disease, such as parkinsonism, dysarthria, dysphonia, and choreoathetosis. Less frequent are ataxia and pyramidal signs. The MRI or CT scan shows ventricular dilation in advanced cases, with atrophy of the cerebrum, cerebellum, and/or brainstem, along with signal intensity change in the basal ganglia, thalamus, and/or brainstem, particularly the midbrain.

Pantothenate kinase-associated neurodegeneration is a rare autosomal recessive neurodegenerative disorder. Many patients have alterations in pantothenate kinase 2 (*PANK2*) localized to mitochondria in neurons. The condition usually begins before 6 years of age and is characterized by rapidly progressive dystonia, rigidity, and choreoathetosis. Spasticity, extensor plantar responses, dysarthria, and intellectual deterioration become evident during adolescence, and death usually occurs by early adulthood. MRI shows lesions of the globus pallidus, including low signal intensity in T2-weighted images (corresponding to iron pigments) and an anteromedial area of high signal intensity (tissue necrosis and edema), or *eye-of-the-tiger* sign (Fig. 637.7). Neuropathologic examination indicates excessive accumulation of iron-containing pigments in the globus pallidus and substantia nigra. Similar disorders of high brain iron content without *PANK2* gene alterations, including phospholipase

Fig. 637.6 Syndromes with dystonia as the presenting or a predominant feature; primary dystonias or dystonia-plus syndromes that commonly begin with dystonia are listed. The most common sites of dystonia onset are indicated on the homunculus in red, with less common sites of onset in pink. The distribution in age of onset is indicated by a blue bar, with the mean age indicated by a blue diamond, and rare but reported outliers indicated by extralinear blue dashes. Typical rates of progression and the likelihood of generalization are indicated by yellow plots. Note that homunculi and plots represent the most common clinical presentations, but variations on these axes are not uncommon. (From Waugh JL, Sharma N. Clinical neurogenetics: dystonia from phenotype to genotype. *Neurol Clin.* 2013;31:969–986, Fig. 1.)

A2-associated neurodegeneration (PLAN), mitochondrial membrane protein-associated neurodegeneration (MPAN), beta-propeller protein-associated neurodegeneration (BPAN), neuroferritinopathy, aceruloplasminemia, and others, have been grouped as disorders of **neurodegeneration with brain iron accumulation** (Table 637.17). Patterns of iron deposition visualized by brain MRI have shown utility in differentiating these disorders.

Biotin-responsive basal ganglia disease manifests with episodes of acute dystonia, external ophthalmoplegia, and encephalopathy. *SLC19A3* is the responsible mutated gene. MRI demonstrates involvement of the basal ganglia, with vasogenic edema and the *bat-wing* sign (Fig. 637.8). **Treatment with biotin and thiamine results in improvement in 2–4 days** (Table 637.18).

Although dystonia may present in isolation as the first sign of a metabolic or neurodegenerative disorder, this group of diseases should be considered mainly in those who demonstrate signs of systemic disease (e.g., organomegaly, short stature, hearing loss, vision impairment, epilepsy) and those with episodes of severe illness, evidence of regression, or cognitive impairment. Table 637.16 outlines additional features suggestive of specific disorders.

OTHER DISORDERS

Although uncommon, movement disorders, including dystonia, may be part of the presenting symptoms of **complex regional pain syndrome**. Onset of involuntary movements within 1 year of the traumatic event, an affected lower limb, pain disproportionate to the inciting event, and changes in the overlying skin and blood flow to the affected area suggest complex regional pain syndrome. Although sustained dystonia can produce pain or discomfort, complex regional pain syndrome should be considered in those who have a prominent component of pain and a recent history of trauma to the affected limb.

Paroxysmal dyskinesias can cause a combination of dystonic posturing and choreoathetoid movements (Table 637.19). By far the most

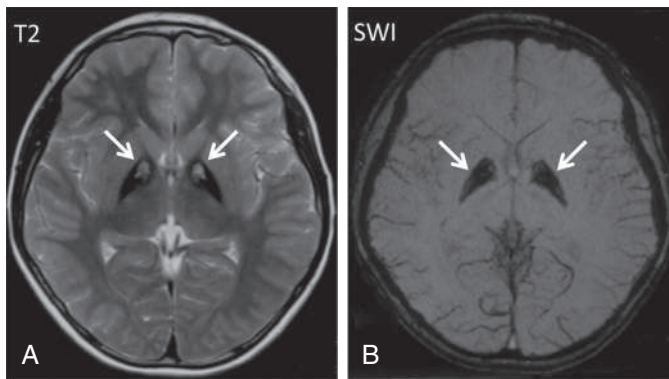


Fig. 637.7 Pantothenate kinase-associated neurodegeneration (PKAN). A, Axial T2-weighted image showing symmetric hypointensity in the bilateral globi pallidi with central hyperintensity (eye-of-the-tiger sign, arrows). B, Axial susceptibility-weighted image (SWI) image showing hypointensity in the globi pallidi representing increased iron accumulation (arrows). (From Bosemani T, Meoded A, Poretti A. Susceptibility-weighted imaging in pantothenate kinase-associated neurodegeneration. *J Pediatr*. 2014;164:212.)

common is **paroxysmal kinesigenic dyskinesia** (PKD), which most commonly presents around the age of 10 years with attacks of chorea or dystonic posturing lasting seconds to minutes. The movements are most commonly precipitated by voluntary movements and are often easily controlled by low doses of carbamazepine or other antiepileptic medications. Many patients have a gene alteration in *PRRT2*, a trans-membrane protein that interacts with SNAP 25. **Paroxysmal nonkinesigenic dyskinesia** (PNKD) is characterized by prolonged attacks precipitated by emotional stress or alcohol rather than voluntary movement. The attacks are less frequent, perhaps a few times per year or less, but they may last hours. PNKD is less responsive to treatment than PKD. The rarest form of paroxysmal dyskinesia is **exercise-induced dystonia**. Dystonia in this disorder occurs after periods of prolonged exercise and tends to last between 10 and 30 minutes. Patients may also suffer from migraines and epilepsy. This disorder is caused by gene alteration in *SLC2A1*, which encodes the glucose transporter type 1 protein and is part of GLUT-1 deficiency syndrome. Dystonia may be present in classic GLUT-1 deficiency, although it is generally not the presenting sign. Case reports indicate some patients may have improvement in dystonia with the ketogenic diet.

There are disorders unique to childhood that warrant exploration in this section as well. **Benign paroxysmal torticollis of infancy** is

Table 637.17 Overview of NBIA Conditions and Genes (If Known)

CONDITION (ACRONYM)	SYNONYM	GENE	CHROMOSOMAL POSITION	AREAS OF HIGHEST IRON DENSITY	PATHOLOGIC MANIFESTATIONS
PKAN	NBIA1	<i>PANK2</i>	20p13	GP, eye of the tiger sign (central hyperintensity within a surrounding area of hypointensity).	GP with variable involvement of adjacent structures (putamen and internal capsule). Spheroid bodies. Only occasional peripheral manifestation.
PLAN	NBIA2, PARK14	<i>PLA2G6</i>	22q12	GP. Additional SN involvement in some.	Widespread cortical alpha-synuclein-positive Lewy body pathology. Presence of tau. Degeneration of the cerebellum, optic pathway and of brainstem and spinal cord long tracts.
FAHN	SPG35	<i>FA2H</i>	16q23	GP. Often white matter changes.	No human brain data. In animal models, cerebellar abnormalities, demyelination, and profound axonal loss in the CNS.
MPAN	—	<i>C19orf12</i>	19q12	GP and SN.	GP and SN iron-containing deposits, axonal spheroids, Lewy body-like inclusions, and tau-positive inclusions.
Kufor-Rakeb disease	PARK9	<i>ATP13A2</i>	1p36	Putamen and caudate.	No human brain data. On peripheral nerve biopsy cytoplasmic inclusion bodies resembling irregular primary lysosomes.
Aceruloplasminemia	—	<i>CP</i>	3q23	Basal ganglia, thalamus, dentate nuclei, and cerebral and cerebellar cortices. Liver, pancreas.	Basal ganglia and dentate nuclei, extending to the cerebral cortex.
Neuroferritinopathy	—	<i>FTL</i>	19q13	Caudate, GP, putamen, SN, and red nuclei.	Ferritin-positive spherical inclusions in iron-rich areas, mainly in the posterior putamen and cerebellum. Spheroids immunoreactive to ubiquitin and tau. Hepatic iron deposits may be present.
SENDA syndrome	—	n.k.	n.k.	GP and SN. White matter changes.	n.k.
Idiopathic late-onset cases	—	Probably heterogeneous	Probably heterogeneous	Heterogeneous.	n.k.

CP, Ceruloplasmin; FA2H, fatty acid 2-hydroxylase; FTL, ferritin light chain; GP, globus pallidus; MPAN, mitochondrial-associated neurodegeneration; NBIA, neurodegeneration with brain iron accumulation; PANK2, pantothenate kinase 2; PKAN, pantothenate kinase-associated neurodegeneration; PLA2G6, phospholipase A2; PLAN, phospholipase A2-associated neurodegeneration; SENDA, static encephalopathy of childhood with neurodegeneration in adulthood; SN, substantia nigra; SPG, spastic paraplegia; n.k., not known. From Schneider SA, Bhatia KP. Syndromes of neurodegeneration with brain iron accumulation. *Sem Pediatr Neurol*. 2012;19:57–66, Table 1, p. 58.

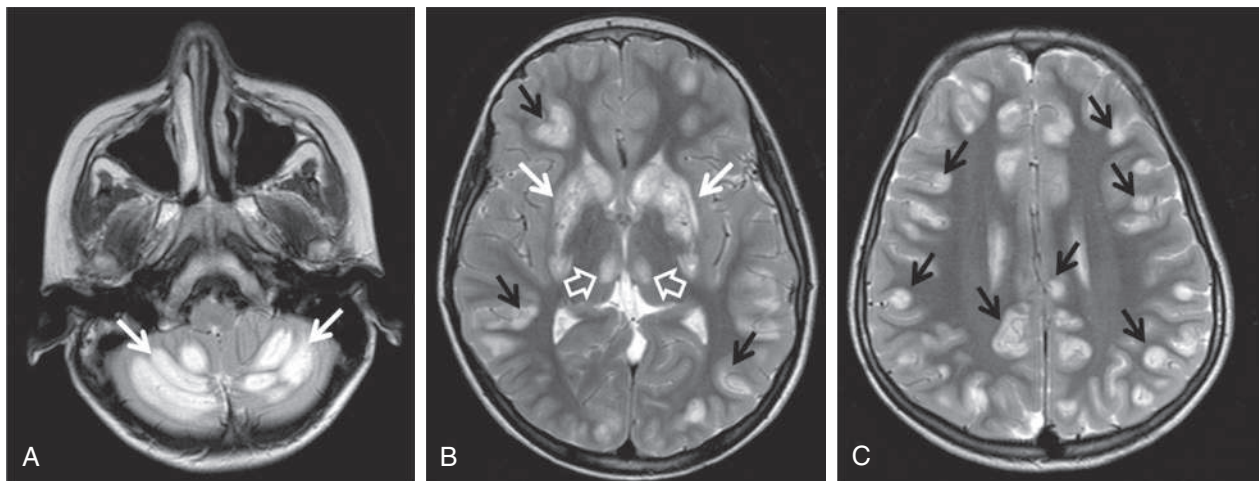


Fig. 637.8 Biotin-responsive basal ganglia disease. An initial brain MRI showed high signal intensity alterations on T2-weighted images bilaterally involving the (A) cerebellum (arrows), (B) basal ganglia (white arrows), and medial nucleus of the thalamus (open arrows) and (B, C) cerebral cortex (black arrows). (Modified from Tabarki B, Al-Sheikh F, Al-Shahwan S, Zuccoli G. Bilateral external ophthalmoplegia in biotin-responsive basal ganglia disease. *J Pediatr*. 2013;162:1291–1292.)

Table 637.18 Dystonia Treatment	
Nonspecific dystonia management	Trial of carbidopa/levodopa Botulinum toxin injection Also consider: neuroleptics, dopamine depletors Surgical options: baclofen pump, deep brain stimulation
Neurotransmitter disorders, including Segawa syndrome	Carbidopa/levodopa (except aromatic L-amino acid decarboxylase deficiency, which may worsen), dopamine agonists
Acute drug-induced dystonic reaction	Diphenhydramine, removal of offending agent
Tardive dyskinesia	Dopamine depletors, removal of offending agent
Paroxysmal dyskinesias	Carbamazepine, other AEDs (especially paroxysmal kinesogenic dyskinesia), acetazolamide (paroxysmal nonkinesogenic dyskinesia), ketogenic diet (exercise-induced dyskinesia)
Biotin-responsive basal ganglia disease	Biotin and thiamine
Complex regional pain syndrome and functional movement disorders	Physical therapy, occupational therapy, cognitive behavioral therapy

characterized by recurrent episodes of cervical dystonia beginning in the first few months of life. The torticollis may alternate sides from one episode to the next and may also persist during sleep. Associated signs and symptoms include irritability, pallor, vomiting, vertigo, ataxia, and occasionally limb dystonia. The family history is often notable for migraine and/or motion sickness in first-degree relatives. Despite the high frequency of spells, imaging studies are normal, and the outcome is uniformly benign with resolution by 3 years of age.

In **alternating hemiplegia of childhood (AHC)**, episodic hemiplegia affecting either side of the body is the hallmark of the disorder. However, patients are also affected by episodes of dystonia, ranging from minutes to days in duration. On average, both features of the disorder commence at approximately 6 months of age. Episodic abnormal eye movements are observed in a large proportion of patients (93%) with onset as early as the first week of life. AHC is associated with pathogenic variants in *ATP1A2* and *ATP1A3*. The disorder can be triggered

by fluctuations in temperature, certain foods, or water exposure. Over time, epilepsy and cognitive impairment emerge, and the involuntary movements change from episodic to constant. Infantile onset and the paroxysmal nature of symptoms early in the disease course are key features to this diagnosis. Another disorder linked to variants in *ATP1A3*, **rapid-onset dystonia parkinsonism (RODP)**, often presents in adolescents with acute to subacute progressive dystonia and bradykinesia, often after a stressor such as recent illness. Although the classic forms of these two disorders, AHC and RODP, are generally caused by non-overlapping gene alterations, molecular genetics has allowed the identification of patients with intermediate phenotypes.

Although it is a diagnosis of exclusion, the presence of odd movements or selective disability may indicate a functional dystonia in older children. There is considerable overlap in features of organic and **functional movement disorders**, making the diagnosis difficult to establish. Both organic and psychogenic movement disorders have the potential to worsen in the setting of stress and may dissipate with relaxation or sleep. The history should include a review of recent stressors, psychiatric symptoms, and exposure to others with similar disorders. On examination, a changing movement disorder, inconsistent motor or sensory exam, or response to suggestion is supportive of a possible psychogenic movement disorder. Early recognition of this disorder may lessen morbidity caused by unnecessary diagnostic and interventional procedures (see Table 637.13).

Practice guidance had once involved targeted, single-gene testing; currently the most appropriate approach to a child with dystonia not explained by a clear mechanism of injury will be a dystonia gene sequencing panel, followed by a microarray and then whole exome or genome sequencing if the panel was unrevealing. This includes children previously diagnosed with cerebral palsy but without severe perinatal distress and/or with injury solely confined to the basal ganglia on brain imaging. In families with a known history of a specific genetic dystonia, single-gene testing is the most appropriate initial approach. Because dystonia panels may vary in which genes they include, a knowledge of phenotypic features expected in various disorders can ensure that the dystonia panel selected is appropriate to a given patient. An approach to diagnostic testing is noted in Table 637.20 and Figure 637.9.

TREATMENT

Acute Treatment

Status dystonicus, or “dystonic storm,” is a rare but potentially life-threatening emergency that often requires management in an intensive care setting. It is characterized by severe frequent dystonic posturing leading to vital sign instability, exhaustion, and/or muscle breakdown. It is likely underrecognized. About half of patients have

Table 637.19 Classification of Primary and Epilepsy Paroxysmal Dyskinesias

	PKD	PNKD	PED	PHD*
Inheritance	AD	AD	AD	Usually sporadic
Gender M:F	4:1	2:1	2:3	7:3
Age at onset, yr	<1-20	<1-20s	2-30	4-20s
Phenomenology of abnormal movements	Dystonia with or without chorea/ballism, unilateral or bilateral	Dystonia with or without choreoathetosis, unilateral or bilateral, rarely spasticity	Dystonia, sometimes in combination with choreoathetosis, unilateral or bilateral	Dystonia, chorea, ballism
Triggers	Sudden movement, change in direction, acceleration, startle	Alcohol, caffeine, emotions, fatigue	Prolonged exercise, muscle vibration	Sleep
Duration of paroxysms	Seconds up to 5 min	2 min to 4 hr	5 min to 2 hr	30 min up to 50 min
Frequency of paroxysms	1 per month to 100 per day	Few per week to few in a lifetime	Few per month	Few per year to few per night
Genetics	1. EKD1: 16p11.2-q12.1 (DYT10) with <i>PRRT2</i> gene within this region 2. EKD2: 16q13-q22.1 (DYT19) 3. EKD3: no variant on chromosome 16	1. <i>PNKD</i> : 2q35 (DYT8) 2. <i>SCL2A1</i> : chromosome 1 (DYT9) 3. <i>KCNMA1</i> : 10q22 4. Locus on 2q31 (DYT20)	1. <i>SCL2A1</i> : 1p35-p31.3 (DYT18)	1. <i>CHRNA4</i> : 20q13.2-q13.3 2. <i>CHRNA2</i> : chromosome 1q21 3. Locus on chromosome 15q24 4. Locus on chromosome 8p21
Treatment	Anticonvulsants (carbamazepine, phenytoin, others)	Avoiding triggers, benzodiazepines (clonazepam)	Avoiding triggers, ketogenic diet (in GLUT-1 deficiency)	Anticonvulsants

*Also known as autosomal dominant nocturnal frontal lobe epilepsy.

AD, Autosomal dominant; PED, paroxysmal exercise-induced dyskinesia; PHD, paroxysmal hypogenetic dyskinesia (a seizure disorder); PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal nonkinesigenic dyskinesia.

From Joseph SA. Movement disorders in childhood. In: Kliegman RM, Toth H, Bordini BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 40.2, p. 719.

Table 637.20 Genetic Testing

All patients with early-onset dystonia without a clear family history or clear mechanism of injury, including those with “cerebral palsy” in the setting of only mild perinatal insults: comprehensive dystonia panel, consider microarray and whole exome sequencing if unrevealing

If the following features are present, ensure the appropriate gene is included in panel testing:

Limb-onset dystonia in early adolescence: *torsinA* (DYT1), especially with Ashkenazi ancestry

Cervical/cranial onset in mid-adolescence: *THAP1* (DYT6), especially with strained speech (spasmodic dysphonia)

Normal gait in the morning, disabled by the evening: give levodopa; if symptoms improve, check guanosine triphosphate (GTP) cyclohydrolase 1 (DYT5a); tyrosine hydroxylase (DYT5b)

Mixed myoclonus and dystonia with onset throughout childhood: ϵ -sarcoglycan (DYT11), especially if symptoms are alcohol responsive in family members

Onset of dystonia $\pm$ parkinsonism over hours to days: *ATP1A3* (DYT12), especially if symptoms progress in a rostral to caudal fashion

Paroxysmal dystonia $\pm$ chorea triggered by:

- Sudden movement: *PRRT2* (DYT10), especially if there is a family history of complex migraines or benign seizures/chorea in infancy
- Caffeine or alcohol: *PNKD* (DYT8), especially if symptoms are rare but last many minutes to hours
- Exertion or if the ratio of cerebrospinal fluid/serum glucose is less than 0.5, *SLC2A1* (DYT18), especially in families with unexplained cognitive delay or seizure disorder

Modified from Waugh JL, Sharma N. Clinical neurogenetics: dystonia from phenotype to genotype. *Neurol Clin*. 2013;31:969–986, Box, p. 975.

an underlying known cause of dystonia, such as cerebral palsy. Infections and changes in medications are frequently cited triggers. In addition, dystonic storm can also present in children with no prior history of movement disorders secondary to neurologic insults such as encephalitis or stroke. There are no consensus guidelines on treatment, but in general aggressive management with antidystonic agents such as anticholinergics, trihexyphenidyl, benzodiazepines, and baclofen is recommended. Midazolam infusion is generally chosen when sedation is needed because of its muscle relaxing properties. Intubation and other critical care supportive measures are commonly needed during treatment.

Chronic Treatment

Treatment strategy is summarized in Table 637.18. Children with Segawa syndrome and other neurotransmitter disorders generally have a robust response to low-dose carbidopa-levodopa. The evidence for efficacy in other causes of dystonia such as cerebral palsy is mixed. However, because neurotransmitter disorders are underdiagnosed and low-dose carbidopa-levodopa is generally well tolerated, a treatment trial is recommended unless there is a clear family history of a non-dopa-responsive dystonia.

Children with generalized dystonia, including those with involvement of the muscles of swallowing, may respond to the anticholinergic agent trihexyphenidyl. Titration occurs slowly over the course of months in an effort to limit untoward side effects, such as urinary retention, mental confusion, or blurred vision. Oral baclofen may also be used, although sedation may be a problem at higher doses. Dopamine depletors may be considered in treatment-refractory cases. Additional drugs that may be effective include benzodiazepines, neuroleptics, and antiepileptic drugs such as carbamazepine.

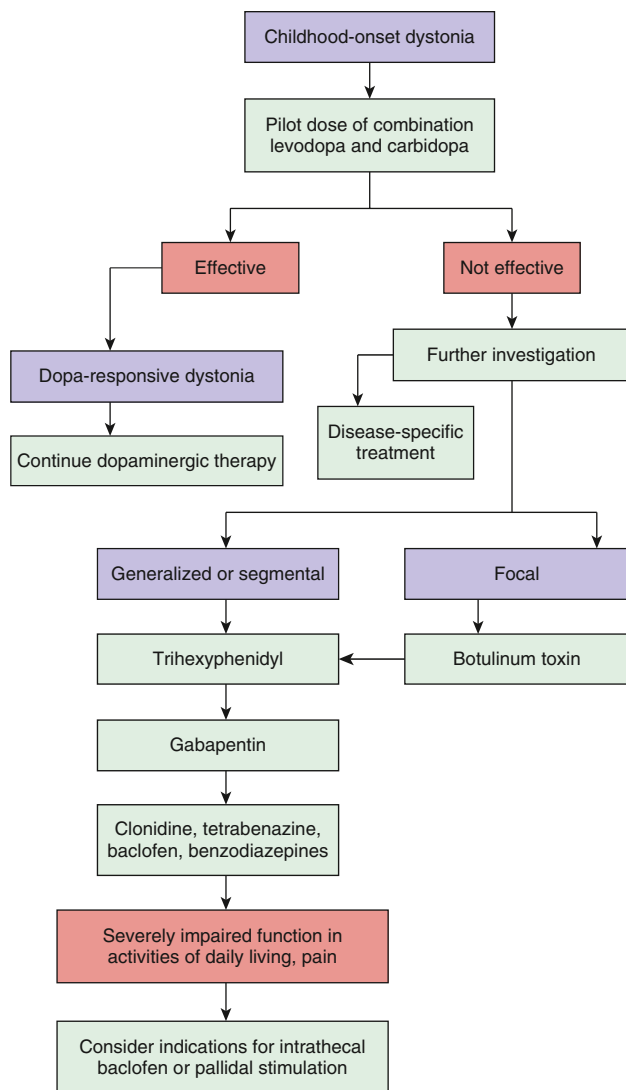


Fig. 637.9 Algorithm showing therapeutic approaches to the management of childhood-onset dystonia. Pharmacologic agents should be used sparingly where possible. High doses and polypharmacy inevitably arise when dystonia is severe enough to cause pain and interferes with daily cares, sitting comfort, and sleep. As with intractable epilepsy, consideration for functional neurosurgery should be considered when two or more drugs have failed to control dystonia. (From Lin JP. *Advances in pharmacotherapies for movement disorders in children: current limitations and future progress*. *Curr Opin Pediatr*. 2017;29:652–664, Fig. 6.)

Oral medications are not the only options for treatment. Segmental dystonia, such as torticollis, often responds well to botulinum toxin injections. Safe dosage restrictions limit the use of botulinum toxin in generalized dystonia, but it may be used as a supplemental treatment if symptoms in particular muscle groups are the most bothersome or functionally impairing.

Intrathecal baclofen delivered through an implantable constant-infusion pump may be helpful in some patients. It is often more effective in the lower extremities than the upper extremities.

Deep brain stimulation with leads implanted in the globus pallidus is most helpful for children with severe primary generalized dystonia. Deep brain stimulation may also be of benefit in children with secondary dystonias, such as cerebral palsy, although the effect is not as robust. A combination of factors are thought to reduce the efficacy in cerebral palsy, including a lack of normal neural substrate, reduced opportunity for motor learning during critical developmental windows, and the frequent presence of other neurologic impairments such as spasticity and weakness. It should only be considered if a trial of two to three oral agents has been unsuccessful.

DRUG-INDUCED DYSTONIAS

In the case of drug-induced dystonias, removal of the offending agent and treatment with intravenous diphenhydramine typically suffice. For neuroleptic malignant syndrome, dantrolene may be indicated. As tardive symptoms may not always respond to removal of the offending agent, dopamine depletors may be necessary.

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Chapter 638

Encephalopathies

Elizabeth Barkoudah

Encephalopathy is a generalized disorder of cerebral function that may be acute or chronic, progressive or static. The etiologies of the encephalopathies in children include infectious, toxic (carbon monoxide, drugs, lead), metabolic, genetic, and ischemic causes. Hypoxic-ischemic encephalopathy is discussed in [Chapter 122.4](#).

638.1 Cerebral Palsy

Elizabeth Barkoudah

See also [Chapters 56 and 637.4](#).

Cerebral palsy (CP) is a complex and heterogeneous disorder denoting a group of permanent motor conditions that cause physical disability in human development, chiefly in the various areas of body movement. It can be defined as a central motor dysfunction affecting muscle tone, posture, and movement that is attributed to *nonprogressive* disturbances in the developing fetal or infant brain. Despite being described as a nonprogressive disorder (historically referred to as *static encephalopathy* by some), the clinical expression of brain injury or insult changes over time. Therefore the condition should be viewed as a dynamic disorder that evolves because of factors such as growth, nervous system maturation, and aging.

Several classification systems are used to describe CP, which reflects the complexity underlying the heterogeneity of cause, distribution, type of motor involvement, and severity. Consideration of associated manifestations such as cognitive deficits, seizures, communication difficulties, visual impairment, and so on, as well as addressing the medical, surgical, and psychosocial needs requires a multidisciplinary approach.

EPIDEMIOLOGY AND ETIOLOGY

Cerebral palsy is the most common neuromotor disorder in childhood, with an overall incidence of 2.6–2.9 cases per 1,000 live births in the United States. Within developed countries, both cross-sectional and cohort-based studies estimate prevalence of CP as nearly 1–4 per 1,000 live births. In developing countries, available estimates of prevalence are similar. The estimated lifetime cost to care for someone with CP in 2003, according to the Centers for Disease Control and Prevention (CDC), was \$1 million. Adjusting for inflation, this is now \$1.2 million per individual and will continue to increase over time.

CP is caused by a broad group of developmental, genetic, metabolic, ischemic, infectious, and other etiologies that produce a common group of neurologic phenotypes. Thus CP should be based on phenotype rather than etiology. The prevalence of CP is higher for children born preterm or at a low birthweight, though this is influenced by sex, ethnicity, and socioeconomic status. There is a 30–40% greater prevalence in males. Prevalence is higher in low- and middle- versus

high-income communities. Rates of CP have only recently begun to decrease in developed countries, though direct interpretation of trends is complicated by changing patterns of neonatal care and survivorhood. Although overall prevalence has fluctuated, the specific etiologies and injury patterns have shifted over time given advances in perinatal and neonatal management.

In addition to prematurity and birthweight, numerous other prenatal and perinatal risk factors have been reported, though for many of these, a causal relationship has not been established. These risk factors include antenatal infection (chorioamnionitis, urinary tract infection), multiple pregnancy, and neonatal infection. Infertility treatments are also associated with a higher rate of CP, probably because these treatments are often associated with multiple pregnancies. CP is most often multifactorial, and multiple risk factors coexist.

The cerebral disruption associated with CP can occur prenatally, perinatally, or postnatally in the first 2 years of life given that brain development is ongoing during this critical period. Congenital CP (due to cerebral injury/maldevelopment before or during birth) accounts for 85–90% of total cases, whereas acquired CP (due to cerebral injury after 1 month of life) is responsible for the remaining cases.

One can also consider different etiologies based on premature versus term births. The major lesions that contribute to CP in preterm infants are **intracerebral hemorrhage** and **periventricular leukomalacia** (PVL). Although the incidence of intracerebral hemorrhage has declined significantly, PVL remains a major problem. The incidence of cystic PVL caused by a more diffuse injury pattern is being replaced by focal necrosis. PVL reflects the enhanced vulnerability of immature oligodendroglia in premature infants to oxidative stress caused by ischemia or infectious/inflammatory insults. White matter abnormalities (loss of volume of periventricular white matter, extent of cystic changes, ventricular dilation, thinning of the corpus callosum) present on MRI at 40 weeks of gestational age in former preterm infants are a predictor of later CP. MRI with diffusion tensor imaging is being used to map white matter tracts more precisely in patients with spastic diplegia, and this technique has shown that thalamocortical sensory pathways are often injured as severely as motor corticospinal pathways (Fig. 638.1).

In term births, causes historically have primarily been thought to be by events during labor and delivery causing hypoxia. The mechanisms are predominately the result of cerebral ischemia and excitotoxicity. The cause can be obvious (i.e., placental abruption, meconium aspiration), though at other times the etiology can be difficult to pinpoint. Risk factors can include eclampsia, hypercoagulability, and placental pathology. For some, no predisposing clinical factors are identified. **Hypoxic-ischemic encephalopathy (HIE)** may be decreasing as an apparent cause of CP in developed countries. Therapeutic hypothermia may reduce the risk of CP in term patients with HIE.

There are several causes of acquired CP. The most common cause in this category is perinatal stroke, which can be ischemic, hemorrhagic, or thromboembolic in nature. The second most common cause is meningitis or encephalitis during infancy. Kernicterus is a rare cause of CP in developed countries, though cases (particularly in very preterm infants) persist.

Cryptogenic CP traditionally refers to an individual in which no clear perinatal etiology has been identified and accounts for ~30% of cases. Chromosomal copy number variants and single gene disorders have been identified in ~30% of patients with CP. Monogenic genetic variants have been identified in ~30% of cases who met diagnostic criteria for CP. A wide range of genes have been implicated in CP phenotypes, though a few are relatively more frequently seen including *TUBA1A*, *TUBB4A*, *COL4A1*, *SPAST*, *CTNBN1*, *GNAO1*, *STXBPI*, and *KIF1A*. Factors associated with exome sequencing–identified gene variants include patients without a perinatal risk factor, those with a positive family history, and patients with intellectual disability, epilepsy, or autism spectrum disorders.

CLINICAL MANIFESTATIONS

There are several classification systems to describe CP, a reflection of the complexity underlying the heterogeneity of cause, distribution, type of motor involvement, and severity (Table 638.1). Classification aids in understanding cause, coordinating care, monitoring comorbidities, treatment offerings and their prognosis, and long-term outcomes. One such classification system starts by determining the type of motor involvement: spastic or extrapyramidal. **Spastic CP** can then be

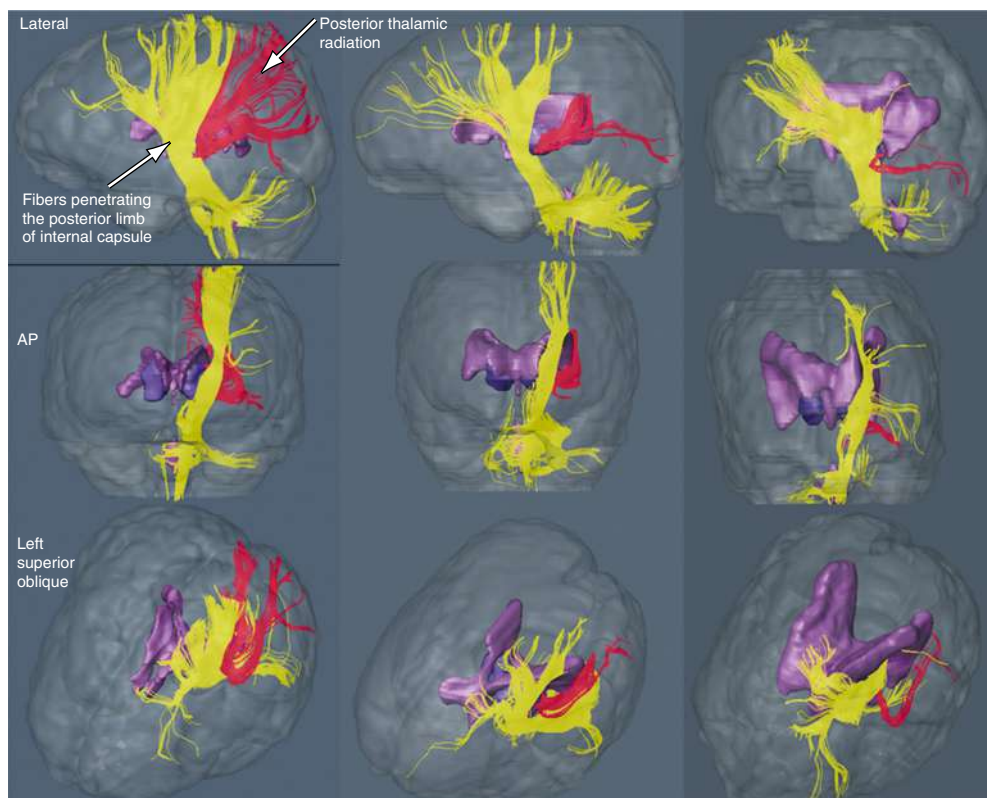


Fig. 638.1 Diffusion tensor image of white matter pathways in the brains of two patients with spastic diplegia on the right compared with a normal child on the far left. Yellow fibers are corticospinal pathways projected from the motor cerebral cortex at the top downward into the brainstem, whereas red fibers are thalamocortical sensory fibers projected from the thalamus upward to the cortex. In children with spastic diplegia, both the corticospinal and thalamocortical pathways are reduced in size but the ascending thalamocortical pathways are more affected. (From Nagae LM, Hoon AH Jr, Stashenko E, et al. Diffusion tensor imaging in children with periventricular leukomalacia: variability of injuries to white matter tracts. *AJNR Am J Neuro-radiol.* 2007;28:1213–1222.)

Table 638.1 Classification of Cerebral Palsy and Major Causes

MOTOR SYNDROME (APPROX % OF CP)	NEUROPATHOLOGY/MRI	MAJOR CAUSES
Spastic diplegia (35%)	Periventricular leukomalacia Periventricular cysts or scars in white matter, enlargement of ventricles, squared-off posterior ventricles	Prematurity Ischemia Infection Endocrine/metabolic (e.g., thyroid)
Spastic quadriplegia (20%)	Periventricular leukomalacia Multicystic encephalomalacia Cortical malformations	Ischemia, infection Endocrine/metabolic, genetic/developmental
Hemiplegia (25%)	Stroke: in utero or neonatal Focal infarct or cortical, subcortical damage Cortical malformations	Thrombophilic disorders Infection Genetic/developmental Periventricular hemorrhagic infarction
Extrapyramidal (athetoid, dyskinetic) (15%)	Asphyxia: symmetric scars in putamen and thalamus Kernicterus: scars in globus pallidus, hippocampus Mitochondrial: scarring of globus pallidus, caudate, putamen, brainstem No lesions: ? dopa-responsive dystonia	Hypoxia Kernicterus Mitochondrial Genetic/metabolic

further truncated topographically (Fig. 638.2), whereas extrapyramidal is further categorized based on the type of involuntary movement seen. In **extrapyramidal** CP, the brain injury or insult spares the pyramidal tracts that cause spasticity resulting in disorders of movement, coordination, and balance. Clinically, these patients exhibit dystonia and/or choreoathetosis (collectively referred to as *dyskinetic*) or ataxia associated with lesions in the cerebellum or its connections. Spastic CP accounts for 80% of cases, whereas extrapyramidal makes up 20% of cases (15% dyskinetic and 5% ataxic).

Historically, CP has been classified as mild, moderate, and severe without specified criteria for each group and primarily used for diagnostic purposes. The Gross Motor Function Classification System (GMFCS) was developed to categorize CP based on abilities and limitations in motor functioning. Goals included improved communication for treatment decisions, research into treatment outcomes, improved understanding and communication of the development of a child with CP, and anticipated future ambulatory needs. The emphasis is on *usual* rather than *best* motor performance in a variety of settings: home, school, and community.

Spastic hemiplegia has decreased spontaneous movements on the affected side and shows hand (handedness) preference at a very early age. The arm is often more involved than the leg, and difficulty in hand manipulation is evident by 1 year of age. Walking is usually delayed until 18–24 months, and a circumductive gait is apparent. Examination of the extremities may show growth arrest leading to shortened limbs and decreased muscle bulk on the affected side. Spasticity refers to the quality of increased muscle tone, which increases with the speed of passive muscle stretching and is greatest in antigravity muscles. It is apparent in the affected extremities, particularly at the ankle, causing an equinovarus deformity of the foot. An affected child often walks on tiptoe (toe-walking) because of the increased tone in the antigravity gastrocnemius muscles and tight contracted Achilles tendon; the affected upper extremity assumes a flexed posture when the child runs. Ankle clonus and a Babinski sign may be present, the deep tendon reflexes are increased, and weakness of the hand and foot dorsiflexors is evident. Difficulty in selective motor control is also present.

Spastic monoplegia is when only one limb is affected and may not be as obvious as other types of CP. Depending on which limb is affected, the child's motor disability ranges from challenges with either fine or gross motor skills. A monoplegia that affects the arm may result in challenges with bimanual tasks, whereas when the legs are involved, toe walking may be seen.

Spastic diplegia is bilateral spasticity of the legs that is greater than in the arms. Spastic diplegia is strongly associated with injury to the immature white matter during the vulnerable period of immature

oligodendroglia between 20 and 34 weeks of gestation, hence seen in those born prematurely. The first clinical indication of spastic diplegia is often noted when an affected infant begins to crawl. The child uses the arms in a normal reciprocal fashion but tends to drag the legs behind more as a rudder (commando crawl) rather than using the normal four-limbed crawling movement. If the spasticity is severe, application of a diaper is difficult because of the excessive adduction of the hips. Examination of the child reveals symmetric spasticity in the legs with brisk reflexes, ankle clonus, and a bilateral Babinski sign. When the child is suspended by the axillae, an extended scissoring posture of the lower extremities is maintained. Walking can be significantly delayed, the feet are held in a position of equinovarus, and the child walks on tiptoes. Severe spastic diplegia is characterized by disuse atrophy, impaired growth of the lower extremities, and disproportionate growth with normal development of the upper torso.

Spastic quadriplegia is the most severe form of CP because of marked motor impairment of all extremities and the high association with other comorbidities, including intellectual disabilities, seizure disorders, communication and visual impairment, and feeding difficulties. Swallowing difficulties are common as a result of supranuclear bulbar palsies, often leading to aspiration pneumonia and growth failure. Neurologic examination shows increased tone and spasticity in all extremities, decreased spontaneous movements, brisk reflexes, and plantar extensor responses. Flexion contractures of the knees, elbows, and wrists are often present by late childhood. Children with spastic quadriparesis can also have extrapyramidal findings given the diffuse involvement of the brain injury.

Extrapyramidal CP can be divided into the two main types of involuntary movement seen: ataxia and dyskinesias. In this type of CP, injury is typically to the subcortical areas, which are centers for coordination in movement and balance. Injury may not produce weakness, but rather the inability to voluntarily control movements. This type is less common than spastic CP and makes up approximately 15–20% of patients with CP.

Ataxic CP is the rarest form whose clinical picture is variable ranging from hypotonia to mild spasticity in addition to incoordination depending on the other systems involved. Walking gait is often very wide and sometimes irregular. Control of eye movements and depth perception can be impaired. Often, fine motor skills requiring coordination of the eyes and hands, such as writing, are difficult. Other causes of ataxia in infancy and childhood, including hydrocephalus, neoplasms, and degenerative disorders, should be ruled out before CP is diagnosed (see Chapter 637.1).

Dyskinetic CP is further divided into two groups: athetoid and dystonic. **Athetoid** CP includes cases with involuntary movement,

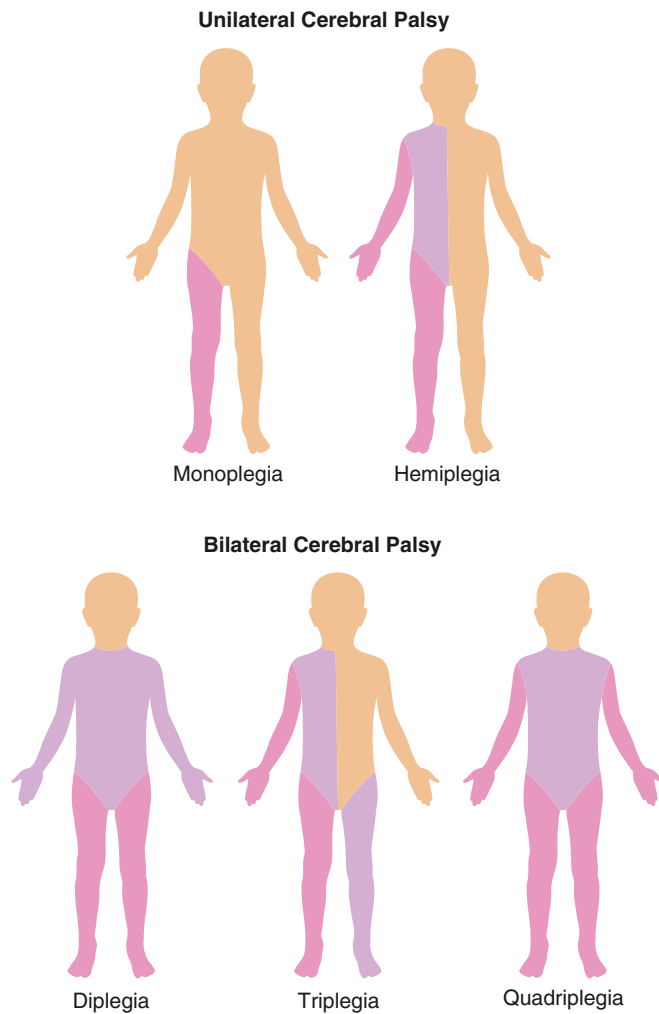


Fig 638.2 Topographical description in spastic cerebral palsy. Spastic cerebral palsy accounts for 70–80% of cases and is caused by an injury of the pyramidal tracts affecting voluntary movement. Monoplegia and hemiplegia affect one side of the body; in monoplegia one limb is affected, whereas in hemiplegia both the arm and leg on one side are affected. Hemiplegia can be asymmetric, affecting the arm or leg greater than the other extremity. Diplegia, triplegia, and quadriplegia affect both sides of the body. In diplegia, the predominant picture is involvement of the lower extremities. However, the arms can be affected though not to the same degree. In triplegia, both lower extremities and one arm are affected. A common picture is diplegia from periventricular leukomalacia and hemiplegia from an intraventricular hemorrhage. This results in one lower extremity being more severely affected because of a dual mechanism of injury. In quadriplegia, all extremities are involved. (From Graham HK, Rosenbaum P, Paneth N, et al. *Cerebral palsy*. *Nat Rev Dis Primers*. 2016;2:15082, Fig. 2.)

especially in the arms, legs, and hands. With the current management of Rh and ABO incompatibility, the incidence of CP characterized by athetosis has markedly decreased (see [Chapter 637](#)). Athetoid CP is often caused by **kernicterus** secondary to high levels of bilirubin, and in this case the MRI scan shows lesions in the globus pallidus bilaterally, or it may be normal. Cases are still seen as a result of HIE as well. The affected infant is initially hypotonic, but a tendency toward arching and opisthotonus (dystonia) is noted, and obligatory tonic neck reflexes are present. These primitive motor patterns preclude orderly motor development such as reaching, rolling, and sitting. **Dystonic CP** encompasses cases that affect the trunk muscles more than the limbs and results in a fixed, twisted posture. Toward the end of the first year, repetitive, involuntary movements become more consistent with the full-blown picture of dystonic CP. Dystonia in CP presents as hypertonia, involuntary postures and movements, or a combination.

Nearly all individuals with CP will have one or more medical, neurologic, or psychiatric comorbidities. Neuropsychiatric comorbidities that occur at higher rates with CP include intellectual disability, anxiety, depression, and attention-deficit/hyperactivity disorder (ADHD) compared with the general population. Other associated comorbidities are common and include chronic pain, sleep difficulties, urinary dysfunction, decreased bone health, sialorrhea, respiratory disorders, feeding and growth challenges, gastrointestinal disorders including constipation and dysmotility, speech/communication difficulties, visual impairment, and hearing loss.

DIAGNOSIS

CP is a clinical diagnosis that considers elements from the history, physical examination, and ancillary testing including neuroimaging. The history should focus on whether there was perinatal or postnatal injury to the brain, what factors led to this injury, and contributory pregnancy factors. Another important factor is the developmental trajectory. It is important to quantify rates of development in the various domains and whether that trajectory has been one of continued acquisition of skills, plateauing, or regression. This—especially no loss of acquired milestones (regression)—helps preclude a **progressive disorder** of the central nervous system (CNS), including degenerative diseases, metabolic disorders, spinal cord tumor, or muscular dystrophy.

Multiple components to the physical examination are necessary to characterize abnormalities of tone, reflexes, movements, posture, and balance that may be consistent with the diagnosis of CP. The physical examination should focus on the following features: presence of any limb deformities, curvature of the spine, range of motion of joints, muscle tone, muscle strength, reflexes, presence of any movement disorders, and gait.

An MRI scan of the brain is indicated to determine the location and extent of structural lesions or associated congenital malformations; an MRI scan of the spinal cord is indicated if there is any question about spinal cord pathology. An MRI with abnormalities consistent with CP supports the diagnosis and increases the level of certainty, but the diagnosis remains a clinical one. An early diagnosis of CP is desirable to initiate appropriate services and therapies and to provide a definitive diagnosis for families.

Additional studies may include tests of hearing and visual function. Genetic evaluation should be considered in patients with congenital malformations, evidence of metabolic disorders (e.g., amino acids, organic acids, MR spectroscopy), clinical features atypical of CP, or when there are no perinatal risk factors especially in term infants ([Fig. 638.3](#), [Tables 638.2 and 638.3](#)).

The differential diagnosis must include disorders that may **mimic** the various types of CP (see [Fig. 638.3](#)). These may include the hereditary spastic diplegias ([Table 638.4](#)), monoamine transmitter disorders such as dihydroxyphenylalanine (DOPA)-responsive dystonia (**Segawa disease**) ([Table 638.5](#) and [Fig. 638.4](#)), and many treatable inborn errors of metabolism, including disorders of amino acids, creatine, fatty acid oxidation, lysosomes, mitochondria, organic acids, and vitamin cofactors.

TREATMENT

The treatment strategy for CP is best developed in a multidisciplinary patient-centered setting, where medical interventions are embedded in a rehabilitation context considering the patient's individual goals (see [Chapter 752](#)). The overarching goal for patients with CP is to maximize functioning by improved biomechanics resulting from abnormal tone, musculoskeletal deformities, and muscle weakness. Other goals outside of those related to the neuromotor component can be equally important when they pertain to quality of life, comfort, and social stigmatization. Clear communication and coordination among the multidisciplinary team (physiatry, orthopedic, neurology/neurodevelopmentalists, neurosurgery) as well as physical and occupational therapy, speech pathology, social work, primary care physicians, developmental pediatricians, and educators maximize the chances of success.

Parents should be taught how to work with their child in daily activities such as feeding, carrying, dressing, bathing, and playing in ways that reduce the effects of abnormal muscle tone. Families and children also need to be instructed in the performance of a series of exercises designed to promote developmental progress, prevent long-term complications such as the development of contractures, preserve range of motion,

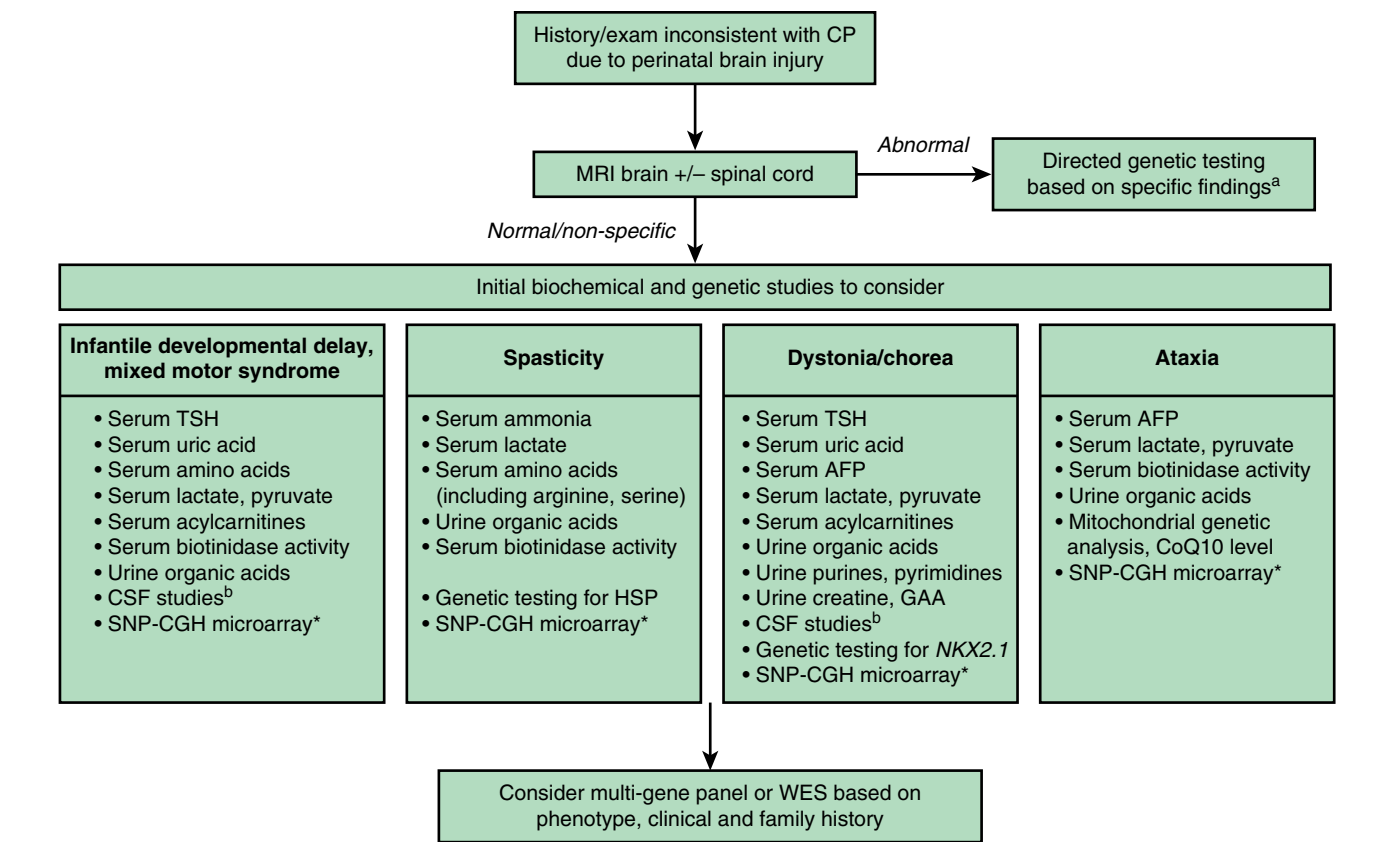


Fig. 638.3 Genetic mimics of cerebral palsy. Algorithm showing the general diagnostic approach to the patient with an infantile-onset, apparently nonprogressive motor disorder. Studies are grouped by predominant clinical presentation; it may be appropriate to consider investigations from more than one group depending on the specific clinical context. *In many situations WES has replaced microarray testing. ^aSee examples in Tables 638.2 and 638.3 ^bCSF studies: glucose (+ serum glucose), lactate, pyruvate, neurotransmitter metabolites (biogenic amines + GABA), pterins, 5-methyltetrahydrofolate; HSP, hereditary spastic paraplegia. (From Pearson TS, Pons R, Ghaoui R, Sue CM. Genetic mimics of cerebral palsy. *Mov Disord.* 2019;34:625–636, Fig. 1, p. 627.)

Table 638.2	Clinical Features That Should Prompt Evaluation for Genetic and Metabolic Conditions in a Patient Presenting with Symptoms of CP
Absent history of any perinatal risk factor for brain injury	
Family history of sibling with similar neurologic symptoms	
Motor symptom onset after an initial period of normal development	
Developmental regression	
Progressive neurologic symptoms	
Paroxysmal motor symptoms or marked fluctuation of motor symptoms	
Clinical exacerbation in the setting of a catabolic state (e.g., febrile illness)	
Isolated generalized hypotonia	
Prominent ataxia	
Signs of peripheral neuromuscular disease (reduced or absent reflexes, sensory loss)	
Eye movement abnormalities (e.g., oculogyria, oculomotor apraxia, or paroxysmal saccadic eye-head movements)	

From Pearson TS, Pons R, Ghaoui R, et al. Genetic mimics of cerebral palsy. *Mov Disord.* 2019;34:625–636, Table. 1, p. 628.

and strengthen weak muscles. Therapists help children to achieve their full potential and often recommend further evaluations and adaptive equipment.

Rehabilitative strategies include orthotics, casting, and physiotherapy (see Chapter 752). Adaptive equipment can help individuals with CP achieve a greater level of independence and autonomy. Equipment such as braces, wheelchairs, and walkers can significantly improve mobility and increase self-confidence. Orthotics are devices that are used to help prevent foot and ankle deformities, improve stability during walking, and

Table 638.3	Brain MRI Findings Suggestive of Selected Genetic CP Mimics
FINDING	SELECTED CONDITIONS
Hypomyelination	PLP1-related dysmyelinating disorders H-ABC (<i>TUBB4A</i> variant) AGS (may also have basal ganglia and WM calcification) GM1 gangliosidosis
Demyelination	Krabbe disease Metachromatic leukodystrophy
Thin corpus callosum	HSP (i.e., SPG4, SPG11, SPG15, and others)
Globus pallidus lesions	T ₂ -hypointense: NBIA (SN also involved in BPAN, MPAN), fucosidosis T ₂ -hyperintense: MMA, PDH deficiency, creatine deficiency syndromes
Focal atrophy or hypoplasia	Glutaric aciduria type 1 (frontotemporal) H-ABC (cerebellum ± putamen) Joubert syndrome (cerebellum)

AGS, Aicardi-Goutières syndrome; BPAN, beta-propeller protein-associated neurodegeneration; H-ABC, hypomyelination with atrophy of the basal ganglia and cerebellum; HSP, hereditary spastic paraplegia; MMA, methylmalonic aciduria; MPAN, mitochondrial membrane protein-associated neurodegeneration; NBIA, neurodegeneration with brain iron accumulation; PDH, pyruvate dehydrogenase; WM, white matter.

From Pearson TS, Pons R, Ghaoui R, et al. Genetic mimics of cerebral palsy. *Mov Disord.* 2019;34:625–636, Table 2, p. 628.

Table 638.4 Clinical and Neuroimaging Findings in Hereditary Spastic Paraplegias (HSP) with Pediatric Onset*

HSP FORM	HSP TYPE	INHERITANCE	GENE	CHILDHOOD ONSET	DISEASE CHARACTERISTICS [†]	NEUROIMAGING FINDINGS (BRAIN)
Pure	SPG3A	AD	<i>ATL1</i>	+++	None	Normal
Pure	SPG4	AD	<i>SPAST</i>	++	None	Leukoencephalopathy, thin corpus callosum
Pure	SPG6	AD	<i>NIPA1</i>	+	None	Normal
Pure	SPG10	AD	<i>KIF5A</i>	+++	Neuropathy	Normal
Pure	SPG12	AD	<i>RTN2</i>	+++	None	Normal
Pure	SPG31	AD	<i>REEP1</i>	++	None	Normal
Complicated	SPG1	X-linked	<i>L1CAM</i>	++	Intellectual disability, adducted thumb	Thin corpus callosum
Complicated	SPG2	X-linked	<i>PLP1</i>	+++	Intellectual disability, epilepsy	Normal
Complicated	SPG7	AR	<i>SPG7</i>	+	Optic atrophy, neuropathy, cerebellar ataxia	Cerebellar atrophy
Complicated	SPG11	AR	<i>KIAA1840</i>	+++	Intellectual disability, neuropathy	Leukoencephalopathy, thin corpus callosum
Complicated	SPG15	AR	<i>ZFYVE26</i>	+++	Intellectual disability, retinopathy, cerebellar ataxia	Leukoencephalopathy, thin corpus callosum
Complicated	SPG17	AR	<i>BSCL2</i>	+	Neuropathy	Normal

*Onset before 18yr of age.

[†]Other than the classic HSP symptoms, including spastic paraparesis, atrophy of the distal lower extremities, and neurogenic bladder dysfunction.

AD, autosomal dominant; AR, autosomal recessive; +, occasional; ++, common; +++, characteristic.

From Lee RW, Poretti A, Cohen JS, et al. A diagnostic approach for cerebral palsy in the genomic era. *Neurol Med.* 2014;16:821–844, Table 5, p. 832.**Table 638.5** Clinical Features of the Monoamine Neurotransmitter Disorders

ENZYME DEFICIENCY	AGE AT PRESENTATION	MOTOR AND COGNITIVE DELAY	EXTRAPYRAMIDAL HYPERKINETIC FEATURES	EXTRAPYRAMIDAL HYPOKINETIC FEATURES	PYRAMIDAL TRACT FEATURES	EPILEPSY	AUTONOMIC FEATURES	NEUROPSYCHIATRIC FEATURES
AD GTPCH-D	Childhood (but can occur at any age)	Not common	Yes	Yes	No	No	No	Yes
SR-D	Infancy	In most	Yes	Yes	Yes	Yes	Yes	Yes
AR GTPCH-D	Infancy	Yes	Yes	Yes	Yes	Yes	Yes	Yes
PTPS-D	Infancy to childhood	In most	Yes	Yes	Yes	Yes	Yes	Yes
DHPR-D	Infancy to childhood	Yes	Yes	Yes	Yes	Yes	Yes	Yes
PCD-D	Infancy	No	No	No	No	No	No	No
TH-D	Infancy to early childhood	In most	Yes	Yes	Yes	Yes	Yes	No
AADC-D	Mainly infancy (but can occur at any age)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
PLP-DE	Infancy to early childhood	In most	Yes	Yes	Yes	Yes	Yes	Yes
DTDS	Infancy	Yes	Yes	Yes	Yes, in older children	No	Yes	No

AD GTPCH-D, autosomal dominant GTP cyclohydrolase deficiency; SR-D, D-Serine; AR GTPCH-D, autosomal recessive GTP cyclohydrolase deficiency; PTPS-D, 6-pyruvoyl tetrahydropterin synthase deficiency; DHPR-D, dihydropteridine reductase deficiency; PCD-D, pterin-4 α carbinolamine dehydrase deficiency; TH-D, tyrosine hydroxylase deficiency; AADC-D, aromatic L-amino acid decarboxylase deficiency; PLP-DE, pyridoxal 5 phosphate dependent enzymes; DTDS, dopamine transporter deficiency syndrome.From Kurian MA, Gissen P, Smith M, et al. The monoamine neurotransmitter disorders: an expanding range of neurological syndromes. *Lancet Neurol.* 2011;10:721–731, Table, p. 722.

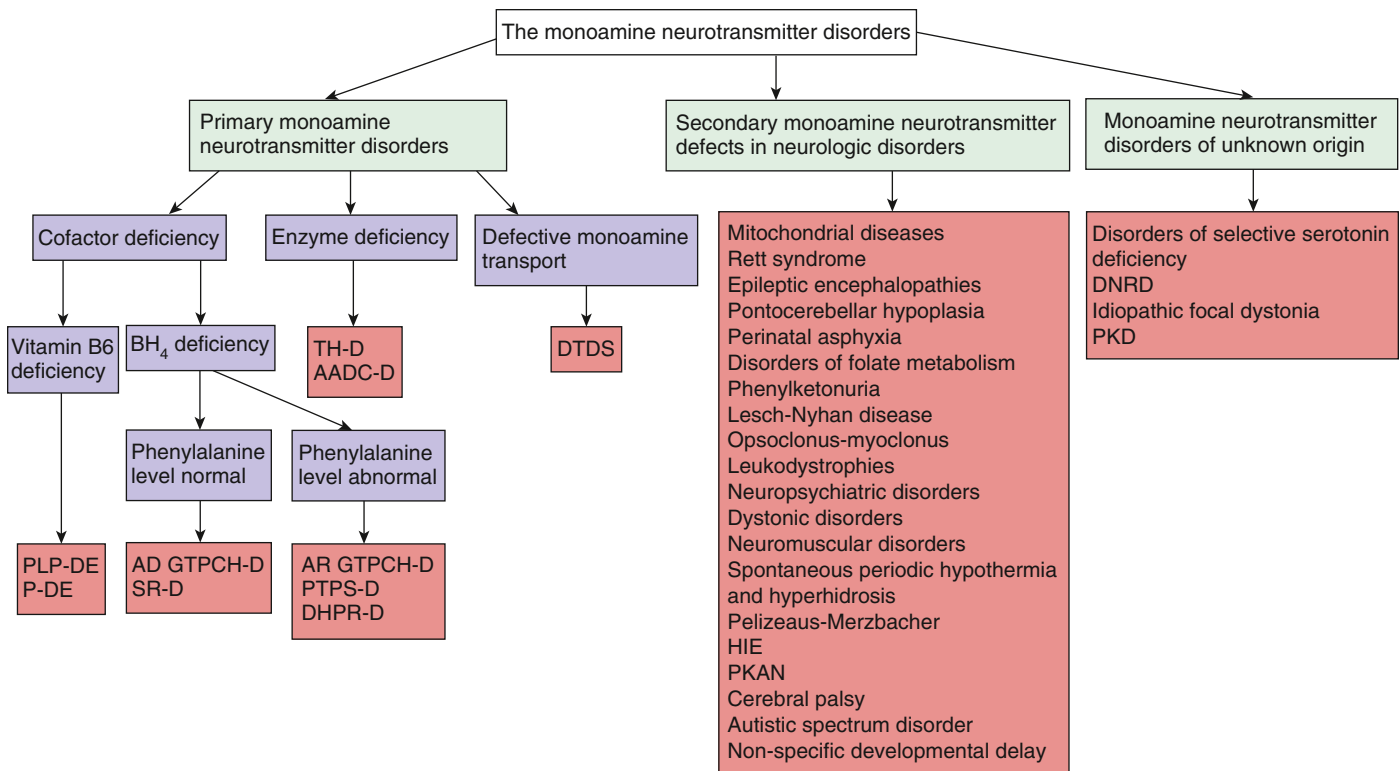


Fig. 638.4 Classification of the monoamine neurotransmitter disorders. BH₄, Tetrahydrobiopterin; TH-D, tyrosine hydroxylase deficiency; AADC-D, aromatic L-amino acid decarboxylase deficiency; DTDS, dopamine transporter deficiency syndrome; PLP-DE, pyridoxal-phosphate-dependent epilepsy; P-DE, pyridoxine-dependent epilepsy; AD GTPCH-D, autosomal dominant GTP cyclohydrolase 1 deficiency; SR-D, sepiapterin reductase deficiency; AR GTPCH-D, autosomal recessive GTP cyclohydrolase 1 deficiency; PTPS-D, 6-pyruvoyltetrahydropterin synthase deficiency; DHPR-D, dihydropteridine reductase deficiency; HIE, hypoxic-ischemic encephalopathy; PKAN, pantothenate kinase associated neurodegeneration; DNRD, dopa-nonresponsive dystonia; PKD, paroxysmal kinesigenic dyskinesia. (From Kurian MA, Gissen P, Smith M, et al. *The monoamine neurotransmitter disorders: an expanding range of neurological syndromes*. *Lancet Neurol*. 2011;10:721–731, Fig. 1.)

sometimes relieve pain. Additional equipment needs address activities of daily living such as bathing and hygiene, communication, and driving.

Pharmacotherapy is often the first-line approach used to manage the various tone abnormalities seen in CP and includes both enteral options and targeted injections. Systemic medications are often chosen for more widespread management of spasticity and dyskinesias. Although baclofen is routinely favored, other antispasticity medications such as tizanidine, dantrolene, and benzodiazepines are also available. Second-line medications such as clonidine or gabapentin may provide dual benefit for both tone management and other neurologic associations, including sleep disruption, dysautonomia, pain, and neuroirritability. Medications used to treat dystonia include enteral baclofen, benzodiazepines, trihexyphenidyl, clonidine, dantrolene, levodopamine, and gabapentin, but practice varies widely. Tetrabenazine can be useful for hyperkinetic movement disorders, including athetosis or chorea.

The management of focal/segmental spasticity or dystonia includes chemodenervation agents that target these specific locations. Targeted injections are often used in combination with systemic medications to augment tone management in specific areas that are more problematic. Examples include **botulinum toxin A** (BoNT-A), phenol, and ethyl alcohol. Targeted injections combined with rehabilitative therapies can allow for improved motor functioning and delay or avoid orthopedic surgery; these injections require repeat administration. Typically repeat injections are performed every 4–6 months, primarily to avoid the development of resistance; 3 months may be necessary. Injections into salivary glands may also help reduce the severity of drooling if it is not adequately treated with anticholinergic agents.

Neurosurgical options include intrathecal baclofen (ITB), selective dorsal rhizotomy (SDR), and deep brain stimulation (DBS). ITB can be considered in patients whose spasticity is not adequately treated with enteral baclofen or who are experiencing side effects such as sedation,

weakness, or gastrointestinal (GI) symptoms. Baclofen is delivered with an implanted pump in children with severe spasticity; it is useful because it delivers the drug directly around the spinal cord, where it reduces neurotransmission of afferent nerve fibers. Direct delivery to the spinal cord overcomes the problem of CNS side effects caused by the large oral doses needed to penetrate the blood-brain barrier. ITB may reduce dystonia with evidence for benefit with higher catheter placement.

The main goal of **SDR** is to improve the gait or functioning in those that function at GMFCS I–III with good selective motor control and minimal weakness. However, SDR is being looked at for management of tone, minimizing pain, and ease of caregiving in patients functioning on a GMFCS IV–V level. Because SDR is an irreversible treatment for spasticity, optimal selection of ideal candidates from a multidisciplinary approach is necessary to avoid short- and long-term complications. SDR's spasticity benefits are caused by a partial sensory deafferentation of the spinal cord. This is achieved by resection of dorsal nerve rootlets based on abnormal motor responses to electrical stimulation (Fig. 638.5). The total number of nerve rootlets resected ranges from 25% to 40%, though in some institutions it exceeds >40%. Combining both ventral and dorsal rhizotomies can help manage both spasticity and dystonia. SDR manages lower extremity tone equally as the ITB pump, may provide more upper-extremity tone control compared with the ITB pump, and improves bladder function.

DBS can be considered if there is severe hypertonia with combined spasticity and dystonia. DBS is a neurosurgical procedure that evolved from the recognition that pallidotomies and thalamotomies could help patients with medically refractory dystonia. It involves the introduction of stimulating electrodes in areas of the brain such as the globus pallidus and the subthalamic nucleus, which are connected to an extracranial pulse generator (see Chapter 637). After the surgical procedure, the beneficial effects are not immediately

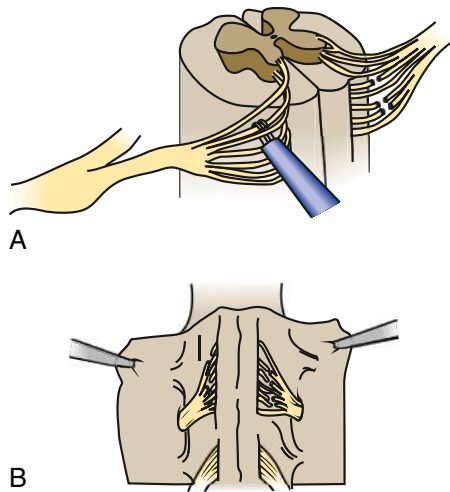


Fig. 638.5 Schematic of the technique of selective dorsal rhizotomy. **A**, After laminectomy, the dura is opened and the dorsal spinal rootlets are exposed. The rootlets are stimulated so that abnormal rootlet activity can be identified. **B**, A proportion of rootlets is transected. (From Koman LA, Smith BP, Shilt JS. *Cerebral palsy*. *Lancet*. 004;363:1619–1631. Reproduced with permission from Wake Forest University Orthopaedic Press.)

visible, often taking several months. The procedure is associated with perioperative risks as well as infection and hardware complications. Therefore patient selection and consideration of the appropriate target for stimulation for DBS are key. Most agree that the presence of spasticity, contractures/deformities, and myelopathy are poor predictors of response and that neurosurgical expertise, anatomic factors, and severity/time of dystonic symptoms may influence response.

Orthopedic interventions address musculoskeletal pathology, including fixed muscle contractures, torsion of long bones, hip displacement, and spine deformities. Several surgical methods exist for lengthening the muscle-tendon units for contraction management, though these are rarely necessary before 6 years of age. Before this, prevention of contracture development is key and often is a combination of tone management, bracing, and stretching exercises. Femoral and tibial torsion occur, respectively, because of failure of remodeling fetal anteversion and mostly as a response to abnormal biomechanical forces during walking. Derotational osteotomies are ideally performed between 6 and 12 years of age. With increasing GMFCS level comes increased risk of developing hip displacement and neuromuscular scoliosis. Monitoring and prevention strategies are paramount, as both hip displacement and scoliosis may progress with age. Conservative treatment and surgical approaches can be challenging when balancing the complexity of these surgical interventions and outcome goals defined presurgically.

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638.2 Mitochondrial Encephalomyopathies

Shamima Rahman

Mitochondrial encephalomyopathies are complex neurologic disorders caused by disturbed mitochondrial function. Mitochondria are dynamic cellular organelles with multitudinous roles, most notably energy generation via oxidative phosphorylation (OXPHOS), but other mitochondrial functions include intermediary metabolism (the Krebs cycle, fatty acid beta oxidation, and part of the urea cycle are housed in the mitochondrion), calcium homeostasis, intracellular signaling, apoptosis, and biosynthesis of coenzyme Q₁₀, heme, iron-sulfur

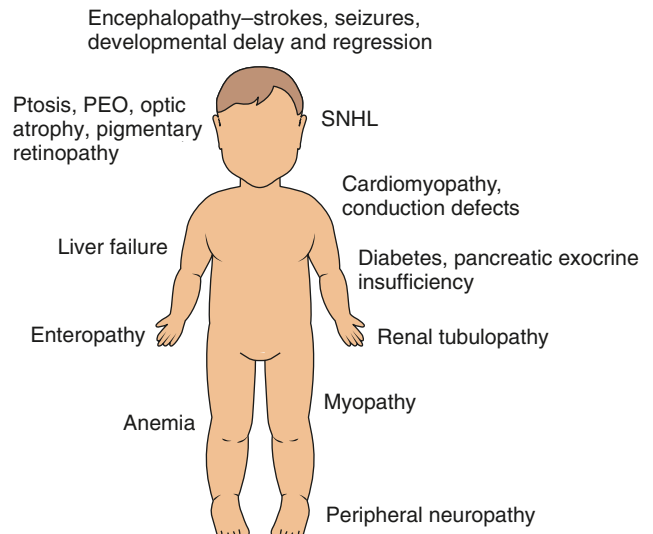


Fig. 638.6 Clinical features of mitochondrial encephalomyopathies. PEO, progressive external ophthalmoplegia; SNHL, sensorineural hearing loss. (Adapted from Rahman S. *Mitochondrial disease in children*. *J Intern Med*. 2020;287[6]:609–633.)

clusters, and lipoic acid. Aberrant mitochondrial function most commonly involves disturbed energy generation via the OXPHOS system, but other mechanisms include oxidative stress mediated by increased production of reactive oxygen species (ROS), alterations of other metabolic processes within the mitochondria (such as pyruvate dehydrogenase, the Krebs cycle, vitamin metabolism and transport, and cofactor biosynthesis) and of the mitochondrial lipid membranes, protein quality control, import system, and organelle dynamics (disturbed fission and fusion).

Mitochondria are unique among cellular organelles in that they contain their own genome: the maternally inherited circular mitochondrial DNA (mtDNA) molecule comprising 16,569 base pairs in humans encoding 37 genes: 13 protein-coding genes, 22 transfer RNAs (tRNAs), and 2 ribosomal RNAs (rRNAs). The mitochondrial genome is present in multiple copies within each mitochondrion, and there are hundreds to thousands of mtDNA molecules per cell. mtDNA gene variants may be heteroplasmic (only a percentage of the mtDNA is mutated) or homoplasmic (100% of the mtDNA is mutated). Primary mitochondrial disease may be caused by maternally inherited or sporadic variants affecting the mtDNA or by recessive, dominant, X-linked, or de novo variants in nearly 400 nuclear genes involved in mitochondrial function and structure.

Mitochondrial disorders, especially those presenting in childhood, have a predilection for high-energy-consuming organs: the brain, skeletal muscle, eyes, ears, heart, kidneys, and liver. Neurologic features of primary mitochondrial disease in childhood include hypotonia, dystonia, spasticity, ptosis, progressive external ophthalmoplegia (PEO), seizures, and ataxia. Multisystem features that may be observed in children with mitochondrial disease are illustrated in Figure 638.6. Some mitochondrial syndromes with characteristic constellations of symptoms and signs were recognized many decades before their genetic basis was understood; several of these syndromes are summarized in Table 638.6.

Mitochondrial encephalomyopathies can be considered according to age at onset of symptoms. In early **infancy** the most frequent presentations include Leigh syndrome, the mtDNA depletion syndromes (MDDS), disorders of coenzyme Q₁₀ (CoQ₁₀) biosynthesis, and reversible infantile respiratory chain disease (RIRCD). Clinical syndromes observed later in **childhood** include Kearns-Sayre syndrome (KSS), mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy with ragged red fibers (MERRF), and neurogenic muscle weakness, ataxia, and retinitis pigmentosa (NARP). However, many children presenting with mitochondrial disease have overlapping features not specific to an individual

Table 638.6 Clinical Manifestations of Syndromic Mitochondrial Encephalomyopathies

TISSUE	SYMPTOMS/SIGNS	LSS	KSS	MELAS	MERRF	NARP	LHON
CNS	Regression	+	+	+	+		
	Seizures	±		+	+		
	Ataxia	±	+	+	+	+	
	Cortical blindness	±		+			
	Deafness	±		+		+	
	Migraine			+			
	Hemiparesis			+			
	Myoclonus			+	+		
	Movement disorder	+		+	+		±
Nerve	Peripheral neuropathy	±	+	+	+	+	
Muscle	Ophthalmoplegia	±	+				
	Weakness	+	+	+	+	+	
	RRF on muscle biopsy	±	+	+	+		
	Ptosis	±	+				
Eye	Pigmentary retinopathy	±	+			+	
	Optic atrophy	+	+				+
Heart	Conduction block		+				±
	Cardiomyopathy	±	+				
	Lactic acidosis	+	+	+	+	+	
Endocrine	Diabetes mellitus		+	+			
	Short stature	+	+	+	+		
Kidney	Tubulopathy	±	+	+	+		

KSS, Kearns-Sayre syndrome; LHON, Leber hereditary optic neuropathy; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; NARP, neuropathy, ataxia, and retinitis pigmentosa; RRF, ragged red fibers.

Courtesy Prof. Shamima Rahman, Great Ormond Street Institute of Child Health, London, United Kingdom.

syndrome, whereas others may present with a single clinical feature, such as an epileptic encephalopathy, leukoencephalopathy, myopathy, or isolated optic atrophy.

LEIGH SYNDROME

Leigh syndrome, or subacute necrotizing encephalomyelopathy, is a clinical syndrome of neurodevelopmental delay and/or regression and variable other neurologic features, including dystonia, hypotonia, spasticity, ataxia, and seizures, with characteristic MRI brain appearances and biochemical evidence of mitochondrial dysfunction. Peak onset is usually in the first 2 years of life (mean 7 months), although longer surviving cases and adult onset are both recognized. Initial symptoms may be nonneurologic, including feeding difficulties, vomiting, and poor weight gain in infancy. Eye involvement is a frequent finding, including nystagmus, ptosis, PEO, optic atrophy, and retinitis pigmentosa. MRI reveals bilateral, usually symmetric T2-weighted hyperintense lesions variably affecting the basal ganglia, thalamus, midbrain, and brainstem structures (Fig. 638.7). These imaging lesions reflect the neuropathology, which consists of spongiform lesions with cavitation, neuronal loss, demyelination, and capillary proliferation.

Biochemical features are variable in Leigh syndrome and include elevated lactate in blood and/or cerebrospinal fluid (CSF) and isolated or combined deficiency of one or more OXPHOS enzymes. Normal biochemical findings do not exclude the diagnosis. Leigh syndrome is genetically heterogeneous, and more than 100 monogenic causes have been identified, including variants in both mtDNA-encoded

genes (responsible for 25–30% of cases) and nuclear genes. Modes of inheritance include maternal (for mtDNA variants), autosomal recessive, X-linked, and de novo dominant. **MEGDEL** (3-methylglutaconic aciduria with deafness and encephalopathy, Leigh-like) syndrome is a subtype of Leigh syndrome caused by biallelic variants in *SERAC1* encoding a protein involved in remodeling mitochondrial membrane lipids. Affected infants typically fail the newborn hearing screen and have problems with hypoglycemia and hyperammonemia related to hepatic dysfunction. Some infants succumb to liver failure, but hepatic function improves in most affected individuals, who later progress to a neurodegenerative course with prominent dystonia and loss of skills.

A few causes of Leigh syndrome are potentially treatable. These include deficiencies of biotinidase (an enzyme required for biotin recycling within the cell), the thiamine transporter SLC19A3 (also associated with biotin-thiamine-responsive basal ganglia disease), and proteins required for biosynthesis of CoQ₁₀, a mobile electron carrier in the mitochondrial respiratory chain. All other forms of Leigh syndrome have no curative treatments and are associated with a progressive neurodegenerative course with early death, usually caused by respiratory failure secondary to brainstem lesions affecting the respiratory center. Median age at death was reported as 2.4 years in one cohort, but this is variable and related to the underlying genetic cause. Longer survival has been reported in some forms of Leigh syndrome, including MEGDEL and deficiencies of SURF1 (an assembly factor for OXPHOS complex IV) and SUCLA2 (a subunit of the Krebs cycle enzyme succinyl-CoA ligase).

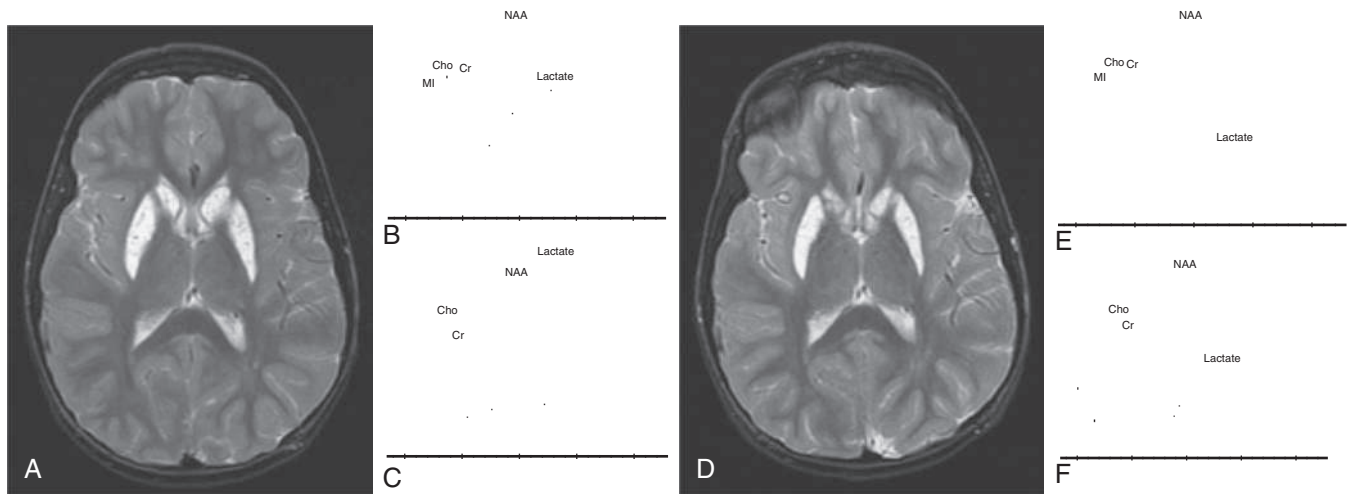


Fig. 638.7 Complex I deficiency in an 8-yr-old child with magnetic resonance examinations acquired approximately 3 mo apart. Axial T2-weighted (A), short echo magnetic resonance spectroscopy (MRS) (B), and long echo MRS (C) images were obtained. The imaging reveals a pattern characteristic of Leigh syndrome with an abnormal hyperintense signal bilaterally within the caudate and globus pallidus. The MRS image acquired in the left basal ganglia at a period of clinical exacerbation caused by febrile illness demonstrates a dramatic elevation of lactate compared with her routinely observed levels as shown in axial T2-weighted (D), short echo MRS (E), and long echo MRS (F) images. The spectra acquired 3 mo later demonstrate a significant reduction in lactate. A comparison of the imaging data is unremarkable between the examinations. The dramatic elevation of lactate revealed on MRS in (B) and (C) corresponds to worsening clinical symptoms (seizures and leg stiffening). The lactate levels observed in (E) and (F) are typical and consistent with this mitochondrial defect. (From Cecil KM. MR spectroscopy of metabolic disorders. *Neuroimaging Clin N Am.* 2006;16:87–116.)

Table 638.7 Mitochondrial DNA Depletion Syndromes

GENE*	FUNCTION	CLINICAL FEATURES	mtDNA DEPLETION	MULTIPLE DELETIONS
<i>POLG</i>	mtDNA replication	Alpers, juvenile epilepsy syndromes, ataxia, PEO	+	+
<i>TWINK</i>	mtDNA replication	Hepatocerebral disease, IOSCA, juvenile epilepsy syndromes, PEO	+	+
<i>TFAM</i>	mtDNA replication	Hepatocerebral disease	+	
<i>MGME1</i>	mtDNA replication	Encephalomyopathic	+	+
<i>SLC25A4</i>	Nucleoside metabolism	Encephalomyopathic, cardiac	+	+
<i>DGUOK</i>	Nucleoside metabolism	Hepatocerebral disease	+	+
<i>TK2</i>	Nucleoside metabolism	Progressive myopathy	+	+
<i>MPV17</i>	Nucleoside metabolism	Hepatocerebral disease	+	+
<i>RRM2B</i>	Nucleoside metabolism	Encephalomyopathic, SNHL, renal tubulopathy	+	+
<i>SUCLA2</i>	Nucleoside metabolism	Encephalomyopathic (LSS), SNHL	+	
<i>SUCLG1</i>	Nucleoside metabolism	Encephalomyopathic, hepatocerebral disease	+	
<i>TYMP</i>	Nucleoside metabolism	MNGIE	+	+

*All are recessive disorders, but, in addition, de novo dominant variants of *SLC25A4* may also present as MDDS.

IOSCA, Infantile-onset spinocerebellar ataxia; LSS, Leigh syndrome spectrum; MNGIE, mitochondrial neurogastrointestinal encephalopathy; PEO, progressive external ophthalmoplegia.

Courtesy Prof. Shamima Rahman, Great Ormond Street Institute of Child Health, London, United Kingdom.

MITOCHONDRIAL DNA DEPLETION SYNDROMES

The most prevalent MDDS is **Alpers-Huttenlocher syndrome** (progressive neuronal degeneration of childhood with epilepsy, PNDE) caused by recessively inherited gene variants in *POLG* encoding the catalytic subunit of DNA polymerase γ , the polymerase responsible for replicating the mtDNA. Affected individuals frequently present with intractable epilepsy, particularly *epilepsia partialis continua*, around 12 months of age. A characteristic EEG finding in the early stages of the disease is rhythmic high amplitude with delta spikes (RHADS).

Repeated episodes of status epilepticus frequently lead to a median age of death of around 16 months (there is typically a median of 4 months between presentation with seizures and death). Sodium valproate is absolutely contraindicated in Alpers-Huttenlocher syndrome and other presentations of *POLG* disease because exposure to valproate may trigger fatal hepatic failure.

Recessive pathologic variants of at least 12 genes have been linked to infantile- and childhood-onset MDDS (Table 638.7). There is often a period of normal development lasting weeks to months before clinical

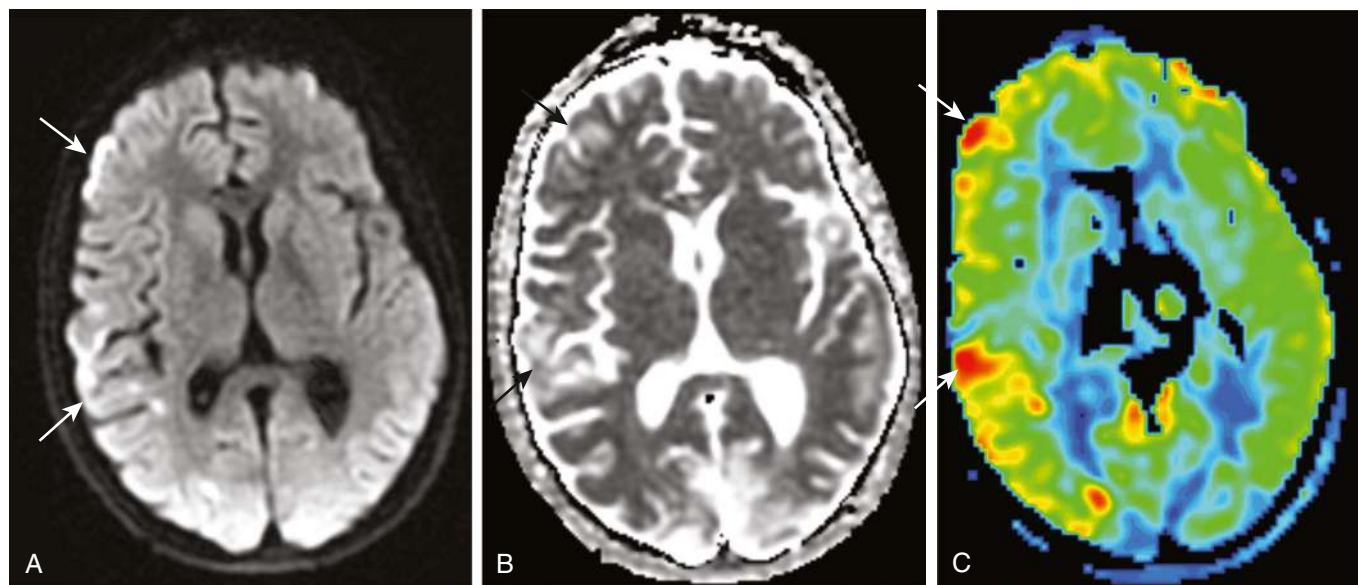


Fig. 638.8 Mitochondrial encephalomyopathy, lactic acidosis, and strokelike symptoms (MELAS) in a 13-yr-old male. Axial diffusion-weighted imaging (A), axial apparent diffusion coefficient (ADC) map (B), and an axial arterial spin labeling color map (C) are shown. Scattered foci of vasogenic edema denoted by arrows corresponding to increased perfusion are identified in the acute phase of the disease in the right cerebral hemisphere. (From Zuccoli G, Cecil KM. *Inherited metabolic and neurodegenerative disorders*. In: Coley BD, ed. *Caffey's Pediatric Diagnostic Imaging*, 13th ed. Philadelphia: Elsevier; 2019: Fig. 33.8, p. 312.)

manifestations become apparent. Associated organ involvement may provide a clue to the underlying genetic diagnosis: sensorineural hearing loss (SNHL) and methylmalonic aciduria occur in *SUCLA2* defects, SNHL and renal tubular involvement in *RRM2B* defects, and hepatic involvement is associated with *DGUOK*, *MPV17*, *POLG*, *TWINK*, *TFAM*, and *SUCLG1* gene variants. **Thymidine kinase 2 (TK2) deficiency** appears to be a special case because this disorder leads to a pure myopathic presentation in most affected cases. Clinical response to nucleoside supplementation has been reported for TK2 deficiency but not for any other form of MDDS.

DISORDERS OF COENZYME Q₁₀ BIOSYNTHESIS

CoQ₁₀ functions as a mobile electron carrier and antioxidant in the mitochondrial inner membrane. CoQ₁₀ is synthesized by a complex biosynthetic pathway, 10 defects of which have been linked to human disease. Clinical presentations of these recessive disorders include an infantile encephalomyopathy with prominent seizures and dystonia variably associated with multisystem features: SNHL, optic atrophy, pigmentary retinopathy, cardiomyopathy, and renal disease. Other presentations include ataxia, myopathy, and steroid-resistant nephrotic syndrome. Affected patients should be treated with high-dose CoQ₁₀ supplementation, although clinical response is variable.

REVERSIBLE INFANTILE RESPIRATORY CHAIN DEFICIENCY

RIRCD, also known as *benign reversible mitochondrial myopathy*, typically presents after a period of normal development lasting 3–6 weeks with profound lactic acidosis and progressive muscle weakness, often leading to a need for enteral tube feeding and, in some cases where the respiratory muscles are severely affected, artificial ventilation. A ventilatory requirement may persist for up to 18 months. Muscle biopsy reveals ragged red and cytochrome *c* oxidase negative fibers with multiple OXPHOS enzyme deficiencies on spectrophotometric assay. This condition is linked to two homoplasmic variants at the same nucleotide in mtDNA: m.14674T>G and m.14674T>C. Although all maternally related individuals are homoplasmic for the variant, only a small proportion are clinically affected. Studies have also identified potential modifying variants in several nuclear-encoded genes involved in mitochondrial translation, particularly *EARS2*. Spontaneous recovery of muscle strength is associated with excellent neurodevelopmental outcomes. Because it is not possible to distinguish RIRCD

from fatal infantile mitochondrial myopathies, rapid testing for the m.14674T>G/C variants is recommended in all infants presenting with severe muscle weakness and lactic acidosis, so that ventilatory support can be provided to affected infants if needed.

Another form of RIRCD is a reversible hepatopathy caused by recessive variants in the *TRMU* gene encoding a protein required to modify mitochondrial tRNAs. Affected infants present with acute liver failure, variably associated with encephalomyopathic features.

KEARNS-SAYRE SYNDROME

KSS is defined by a *clinical triad* of PEO, pigmentary retinopathy, and heart block, with age of onset <20 years. Other neurologic features include cerebellar ataxia, elevated CSF protein levels, progressive myopathy, and cognitive decline. A peculiar feature of KSS is white matter disease associated with cerebral folate deficiency. Low levels of CSF 5-methyltetrahydrofolate (5-MTHF) and clinical response to folinic acid supplementation have been documented in some patients. Variable associated multisystem disease features include SNHL, renal tubulopathy, endocrine dysfunction (diabetes mellitus, hypoparathyroidism, and short stature with growth hormone deficiency in some cases), and cardiomyopathy. KSS is usually a sporadic condition caused by single large-scale mtDNA deletions (SLSMDs); many individuals have a common 4.9kb mtDNA deletion. SLSMDs are associated with a continuous clinical spectrum ranging from infantile-onset Pearson syndrome to adult-onset isolated PEO without systemic features.

MITOCHONDRIAL ENCEPHALOMYOPATHY WITH LACTIC ACIDOSIS AND STROKELIKE EPISODES

MELAS is a maternally inherited disorder that typically presents toward the end of the first decade with migraine headache, vomiting, and seizures, which may lead to a strokelike episode. MRI of the brain reveals focal lesions with a parieto-occipital predilection not confined to a vascular territory (Fig. 638.8). Other clinical features include hemianopia during the strokelike episodes, ptosis, optic atrophy, pigmentary retinopathy, SNHL, exercise intolerance, cognitive decline, GI dysmotility, cardiomyopathy, renal impairment, and diabetes mellitus. Eighty percent of cases have a common maternally inherited mtDNA gene variant m.3243A>G in the *MT-TL1* gene encoding a tRNA for leucine. This gene variant is present in 1 in 400 of the general population, yet MELAS is a rare disorder. Most individuals harboring the

m.3243A>G variant are asymptomatic or oligosymptomatic or have non-MELAS presentations, including **maternally inherited diabetes and deafness (MIDD)**, cardiomyopathy, sudden unexpected death, or isolated renal involvement (focal segmental glomerulosclerosis). Other causes of MELAS include other mtDNA variants, particularly in the *MT-TL1* gene or in mtDNA-encoded subunits of complex I (especially ND5), and occasionally *POLG* disease can mimic MELAS.

MYOCLONIC EPILEPSY WITH RAGGED RED FIBERS

MERRF is a maternally inherited syndrome characterized by progressive myoclonic epilepsy and cerebellar ataxia with nystagmus and dysarthria. Onset may be in late childhood or adult life, and the disorder may be rapidly progressive or have a more indolent course. Other neurologic features include other seizure types, spasticity, peripheral neuropathy, SNHL, ptosis, PEO, optic atrophy, cognitive decline, and psychiatric manifestations. MERRF can also mimic MELAS, including strokelike episodes. MERRF is typically a multisystemic disorder; extraneurologic features include multiple symmetric lipomatosis, endocrine disturbance (growth hormone deficiency, hypothyroidism, adrenal insufficiency), and cardiomyopathy. A common mtDNA pathologic variant, m.8344A>G in the *MT-TK* gene encoding the tRNA for lysine, accounts for 80% of cases of MERRF. Patients with a very high percentage of this variant (typically >90%) present with **Leigh syndrome** in infancy. The remaining patients with MERRF have other mtDNA tRNA gene variants; occasionally *POLG* disease may mimic MERRF.

NEUROGENIC MUSCLE WEAKNESS, ATAXIA, AND RETINITIS PIGMENTOSA

NARP is a maternally inherited disorder caused by a relatively common mtDNA gene variant, m.8993T>G, in the *MT-ATP6* gene encoding the ATP6 subunit of ATP synthase (OXPHOS complex V). Patients usually have a gene variant load of ~70%, but those with a higher variant load (typically >90%) of the same variant present with maternally inherited Leigh syndrome. Clinical presentation of NARP is usually in late childhood or early adult life with numbness and paresthesias caused by the sensory neuropathy associated with muscle weakness and ataxia. Retinitis pigmentosa initially causes poor night vision and progresses slowly to severe visual loss. Other clinical features include developmental delay, learning disability, dementia, seizures, SNHL, diabetes mellitus, and cardiac conduction defects. *MT-ATP6* variants have also been reported to cause axonal **Charcot-Marie-Tooth disease** without CNS or other features.

MITOCHONDRIAL NEUROGASTROINTESTINAL ENCEPHALOMYOPATHY

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a late-onset MDDS characterized by widespread demyelinating polyneuropathy leading to predominant GI symptoms and peripheral neuropathy with a relatively asymptomatic leukoencephalopathy. Onset of symptoms is usually toward the end of the second decade, but presentation in early childhood may occur. Major symptoms relate to GI dysmotility and pseudo-obstruction (nausea, vomiting, early satiety, abdominal pain, diarrhea) leading to severe weight loss and cachexia. Other clinical features include ptosis, PEO, SNHL, painful paresthesias, and foot drop. The disorder is caused by recessive variants in the *TYMP* gene encoding thymidine phosphorylase, a cytosolic enzyme whose function is essential to the maintenance of intramitochondrial nucleotide pools. Allogeneic hematopoietic stem cell or liver transplantation may be beneficial if performed early in the disease course.

JUVENILE POLG SYNDROMES

POLG variants may also present in later childhood or adult life with a range of clinical presentations, including PEO, proximal or distal myopathy, and juvenile and adult-onset epilepsy syndromes. Myoclonic epilepsy, myopathy, and sensory ataxia (MEMSA), incorporating an entity previously known as *spinocerebellar ataxia with epilepsy (SCAE)*, typically presents with cerebellar ataxia in adolescence or young adult life, with later development of epilepsy. The seizures are

focal initially, often affecting the right hand. Later they become generalized, including *epilepsia partialis continua* (EPC), and are refractory to therapy. The ataxia neuropathy spectrum (ANS) is characterized by ataxia and neuropathy and includes the previous acronyms MIRAS (mitochondrial recessive ataxia syndrome) and SANDO (sensory ataxia, neuropathy, dysarthria, ophthalmoplegia). ANS also frequently leads to an encephalopathy with seizures, so there is some overlap between MEMSA and ANS. *POLG* disease may also mimic MELAS, MERRF, and MNGIE. Variants in the *MT-ATP6* gene have also been linked to this condition.

MITOCHONDRIAL LEUKOENCEPHALOPATHIES

Several recessive mitochondrial disorders cause *cavitating* leukoencephalopathies (Table 638.8) that typically present in infancy or early childhood with acute- or subacute-onset of motor regression. Other clinical features include epileptic encephalopathy, hemiparesis, spastic paraparesis, bulbar problems, and visual loss (optic atrophy). Mitochondrial leukoencephalopathies may also present later in childhood or in adult life. Some of the mitochondrial tRNA aminoacyl synthetase deficiencies appear to cause specific white matter changes. Other genetic causes of mitochondrial leukoencephalopathy include variants in subunits of complexes I and II and defects of iron-sulfur cluster biosynthesis (see Table 638.8).

LEBER HEREDITARY OPTIC NEUROPATHY AND AUTOSOMAL DOMINANT OPTIC ATROPHY

Leber hereditary optic neuropathy (LHON) and autosomal dominant optic atrophy (ADOA) are two mitochondrial optic neuropathies that may occasionally present with additional encephalomyopathic features. **LHON** is maternally inherited and typically presents in the second or third decade of life (mean onset ~20 years, but childhood presentation is well-recognized) with subacute or acute visual loss sequentially affecting *both* eyes. Three common mtDNA variants in genes encoding complex I subunits (m.3460G>A in *MT-ND1*, m.11778G>A in *MT-ND4*, and m.14484T>C in *MT-ND6*) account for 90% of cases. Penetrance is incomplete, and there is an extreme male preponderance, which may be explained by a protective effect of estrogen in females with LHON variants. In most cases LHON presents as an isolated optic neuropathy, but other clinical manifestations in occasional cases include dystonia (with bilateral striatal necrosis), peripheral neuropathy, or cardiac conduction defects.

ADOA, also known as *Kjer disease*, is the most frequent genetic optic neuropathy and is caused by dominant variants of *OPA1*, encoding a protein needed for mitochondrial fusion. Usually this is an isolated optic neuropathy but may be associated with SNHL. In some patients there are biallelic variants of *OPA1* leading to multiple mtDNA deletions and additional manifestations, including PEO, RRF myopathy and white matter lesions, and cerebellar atrophy associated with ataxia, pyramidal signs, spasticity, and learning disability.

NONSYNDROMIC MITOCHONDRIAL DISORDERS

In childhood, many patients affected by mitochondrial disease present with complex multisystem features that do not align closely with any of the specific known mitochondrial syndromes or with nonsyndromic features, such as isolated epilepsy, leukoencephalopathy, or myopathy. These patients may lack biochemical features of mitochondrial disease such as lactic acidosis and are identified by exome and genome sequencing as a first-line diagnostic strategy in children with encephalomyopathies.

APPROACH TO DIAGNOSIS

When a mitochondrial disease is suspected, it is important to take a thorough personal and family history, including enquiring about early deaths within the extended family, and to screen for multisystemic involvement. This may include formal ophthalmologic, audiologic, and cardiac evaluation. There is no single diagnostic test that can detect all mitochondrial diseases. There are some characteristic MRI appearances, such as bilateral symmetric involvement of the basal ganglia and/or brainstem in Leigh syndrome, strokelike lesions

Table 638.8 Mitochondrial Leukoencephalopathies

GENE DEFECT(S)	CLASS OF MITOCHONDRIAL DISORDER	TYPE OF LEUKOENCEPHALOPATHY
NDUFV1	Complex I deficiency	Cystic leukoencephalopathy
NDUFA2	Complex I deficiency	Cystic leukoencephalopathy with tigroid-like changes
NUBPL	Complex I deficiency	Complex leukoencephalopathy involving deep cerebral white matter, basal ganglia, thalami and corpus callosum, with progressive cerebellar atrophy
SDHA, SDHB, SDHAF1	Complex II deficiency	Cystic leukoencephalopathy with succinate peak on MRS
LYRM7	Complex III deficiency	Cystic leukoencephalopathy
COA7	Complex IV deficiency	Cystic leukoencephalopathy with spinal cord hypotrophy
COA8	Complex IV deficiency	Cystic leukoencephalopathy with posterior predominance
TYMP	Disorder of mtDNA maintenance	Demyelinating leukoencephalopathy
mtDNA deletion	Disorder of mitochondrial translation	T2-hyperintense abnormalities of subcortical cerebral white matter, globus pallidus and substantia nigra (Kearns-Sayre syndrome)
DARS2	Disorder of mitochondrial translation	Leukoencephalopathy with Brainstem and Spinal cord involvement and Lactate elevation on proton MRS (LBSL)
EARS2	Disorder of mitochondrial translation	Leukoencephalopathy (sparing periventricular rim) with Thalamus and Brainstem involvement and Lactate elevation on proton MRS (LTBL)
IBA57, ISCA2, NFU1	Iron-sulfur cluster biosynthesis defect	Cystic leukoencephalopathy

Courtesy Prof. Shamima Rahman, Great Ormond Street Institute of Child Health, London, United Kingdom.

in MELAS, and the specific leukoencephalopathies outlined in [Tables 638.6 and 638.8](#). However, brain MRI rarely leads to a specific genetic diagnosis other than in these distinctive leukoencephalopathies. Metabolic investigations that may provide diagnostic clues include blood lactate, plasma amino acids and acylcarnitines, urine organic acids, and CSF lactate, amino acids, neurotransmitters, and 5-MTHF. The traditional approach to diagnose a mitochondrial disease included a muscle biopsy, which was subject to histologic, histochemical, and electron microscopic analysis, as well as spectrophotometric or polarographic assay of the individual OXPHOS enzyme complexes. However, in most centers muscle biopsy has been replaced by first-line genetic approaches that utilize next-generation sequencing to sequence the mtDNA, a large panel of nuclear genes, the exome or the whole genome. Muscle biopsy still retains a place in the investigation of critically unwell children with suspected mitochondrial disease and to provide functional validation of variants of unknown significance identified by genetic testing.

MANAGEMENT

There are no curative therapies for most mitochondrial encephalomyopathies, but there are a few notable exceptions. Leigh syndrome caused by deficiency of the SLC19A3 thiamine transporter may respond to a combination of biotin and thiamine, and some patients with disorders of CoQ₁₀ biosynthesis may improve with high-dose CoQ₁₀ supplementation. High-dose CoQ₁₀ supplementation appears to be particularly effective in preventing (but not reversing) the renal manifestations of CoQ₁₀ deficiency but has proved ineffective in treating the CNS manifestations of this disorder in prenatal/neonatal-onset CoQ₁₀ biosynthesis disorders associated with *COQ4* and *COQ9* variants.

Symptomatic therapies are the mainstay of management for children with mitochondrial encephalomyopathies. Supportive measures may include antiepileptic drugs, hearing aids, cochlear implantation, pto-sis surgery, enteral feeding, pancreatic enzyme supplements, hormone replacement (thyroxine, cortisol, growth hormone, insulin, estrogen),

cardiac pacing (which can be lifesaving in heart block caused by KSS), and medical management of heart failure.

Emerging therapies under investigation for mitochondrial encephalomyopathies can be divided broadly into pharmacologic and genetic approaches. Pharmacologic therapies under development include redox modulation and strategies to replenish reduced nicotinamide adenine dinucleotide (NAD) boost mitochondrial biogenesis, and stabilize cardiolipin, the membrane lipid unique to mitochondria. A successful trial of adeno-associated virus (AAV) gene replacement has been published for LHON caused by *MT-ND4* variants, and gene therapy has been reported for mouse models of several nuclear-encoded mitochondrial diseases but has yet to be translated to the clinic.

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638.3 Other Encephalopathies

Michael Perry and Cheryl Hemingway

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

Posterior reversible encephalopathy syndrome (PRES) is a rare clinical syndrome of acute neurologic dysfunction in the presence of vasogenic subcortical brain edema.

The pathophysiologic mechanisms underlying PRES are poorly understood. Endothelial injury, however, with subsequent blood-brain barrier breakdown and vasogenic edema, appears to be a critical factor. Sudden increases in blood pressure exceeding capacity for cerebral blood flow autoregulation, direct cytokine effects, and cytotoxic drugs are all plausible mediators of the endothelial dysfunction. The posterior circulation may be more vulnerable to increased blood pressure because of a relative lack of sympathetic innervation. Children taking immunosuppressant or cytotoxic drugs (e.g., calcineurin inhibitors,

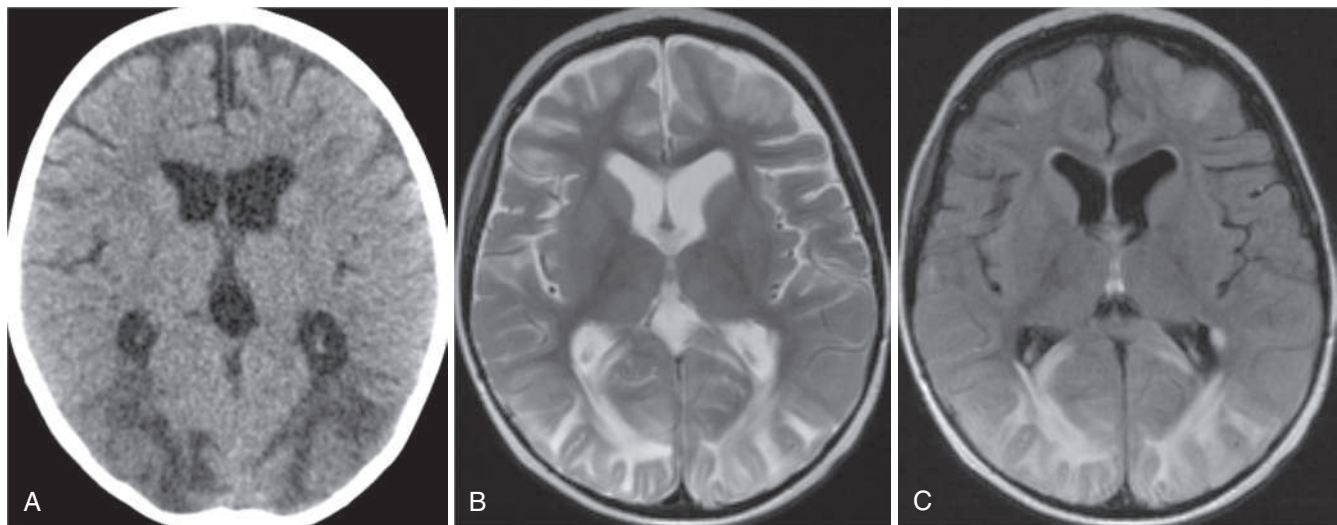


Fig. 638.9 Posterior reversible encephalopathy syndrome (PRES). A, Emergent head CT was performed for acute hypertension in this 2-yr-old female with a history of severe aplastic anemia undergoing bone marrow transplantation. A symmetric pattern of posterior-predominant vasogenic edema was evident. Also noteworthy is the moderate parenchymal volume loss, likely related to the patient's other underlying medical conditions. Subsequently obtained T2-weighted (B) and FLAIR (C) MRIs showed a symmetric abnormally high signal in the posterior cerebral white matter. (From Nazarian JP, Wolansky L, Gupta A, Coffey M. Demyelinating disease and leukoencephalopathies. In: Haaga JR, Boll DT, eds. *CT and MRI of the Whole Body*, 6th ed. Philadelphia: Elsevier; 2017: Fig. 19.18, p. 580.)

cyclosporine, tacrolimus) in the context of organ transplantation, cancer, and autoimmune disease are at highest risk of developing PRES; renal disease (e.g., glomerulonephritis, IgA vasculitis) is also a risk factor.

Neurologic symptoms in PRES (i.e., seizures, encephalopathy, headache, and visual disturbances) develop over hours to days. Seizures occur almost universally; a focal onset with subsequent generalization is common, and status epilepticus may occur. Encephalopathy can range from mild alteration of mental state to coma. Focal deficits (e.g., hemiparesis) are seen in a small minority of patients.

MRI characteristically shows asymmetric T2/FLAIR high-signal intensities corresponding to vasogenic edema predominantly in the parieto-occipital regions (Fig. 638.9). The basal ganglia, cerebellar hemispheres, and brainstem may also be involved. The changes are almost always seen bilaterally and invariably involve the subcortical white matter with or without hemorrhage (intraparenchymal, petechial, or subarachnoid), restricted diffusion, or contrast enhancement (leptomeningeal, cortical, or nodular). Radiologic resolution typically occurs in days to weeks.

There are no PRES-specific treatments. Care is therefore supportive and should be directed at restoration of a normotensive state, control of seizures with appropriate anticonvulsants, and discontinuation of any offending agent (e.g., cytotoxic drugs). Continuous infusions of antihypertensives may be useful to prevent dramatic fluctuations of blood pressure.

Contrary to what its name suggests, PRES is not always reversible (nor does it always occur posteriorly). Despite this, the prognosis is generally favorable with complete recovery seen in up to 85% of children. Clinical and radiologic improvement becomes evident days to weeks after symptom onset. Hemorrhage is most often responsible for permanent disability.

ACUTE NECROTIZING ENCEPHALOPATHY

Acute necrotizing encephalopathy (ANE) is a rare severe encephalopathy characterized by a rapid and fulminant course. It is seen most often in children under 2 years old in East Asian countries, particularly Japan and Taiwan. Most cases are monophasic and sporadic. However, a familial and recurrent form has been reported in White children in North America and Europe. Approximately half of these cases are associated with pathogenic variants in the mitochondria-related RAN-binding protein 2 (RANBP2) gene; this variant is termed ANE1. The pathogenesis is not well understood but may be driven by hyper-cytokinemias (e.g., interleukin [IL]-6) triggered by a preceding

Table 638.9	Diagnostic Criteria for Acute Necrotizing Encephalopathy of Childhood
1. Acute encephalopathy after (1-3 days) a febrile disease. Rapid deterioration in the level of consciousness. Seizures. 2. No cerebrospinal fluid pleocytosis. Increase in cerebrospinal fluid protein. 3. CT or MRI evidence of symmetric, multifocal brain lesions. Involvement of the bilateral thalami. Lesions also common in the cerebral periventricular white matter, internal capsule, putamen, upper brainstem tegmentum, and cerebellar medulla. No involvement of other central nervous system regions. 4. Elevation of serum aminotransferases of variable degrees. No increase in blood ammonia. 5. Exclusion of mimics. A. Differential diagnosis from clinical viewpoints. Overwhelming bacterial and viral infections, and fulminant hepatitis; toxic shock, hemolytic-uremic syndrome, and other toxin-induced diseases; Reye syndrome, hemorrhagic shock and encephalopathy syndrome, and heat stroke B. Differential diagnosis from radiologic viewpoints. Leigh encephalopathy and related mitochondrial cytopathies; glutaric acidemia, methylmalonic acidemia, and infantile bilateral striatal necrosis; Wernicke encephalopathy and carbon monoxide poisoning; acute disseminated encephalomyelitis, acute hemorrhagic leukoencephalitis, other types of encephalitis, and vasculitis; arterial or venous infection, and the effects of severe hypoxia or head trauma	

Modified from Hoshino A, Saitoh M, Oka A, et al. Epidemiology of acute encephalopathy in Japan, with emphasis on the association of viruses and syndromes. *Brain Dev.* 2012;34:337–343, Table 1.

viral infection (e.g., influenza, rotavirus, respiratory syncytial virus [RSV], parainfluenza virus, enterovirus, human herpesvirus [HHV]-6, SARS-CoV-2) in a genetically susceptible host.

ANE presents with a dramatic encephalopathy after a febrile, “viral” prodrome. Neurologic deficits are profound with rapid progression to coma. Seizures are normally present, and progression of systemic inflammatory dysregulation such as shock, organ failure, and disseminated intravascular coagulation is common. Elevated hepatic enzymes without hyperammonemia are a unique feature. MRI is characterized by bilateral symmetric thalamic lesions with or without lesions in the tegmentum, cerebellar medulla, internal capsule, or periventricular white matter (Fig. 638.10). Table 638.9 lists the diagnostic criteria.

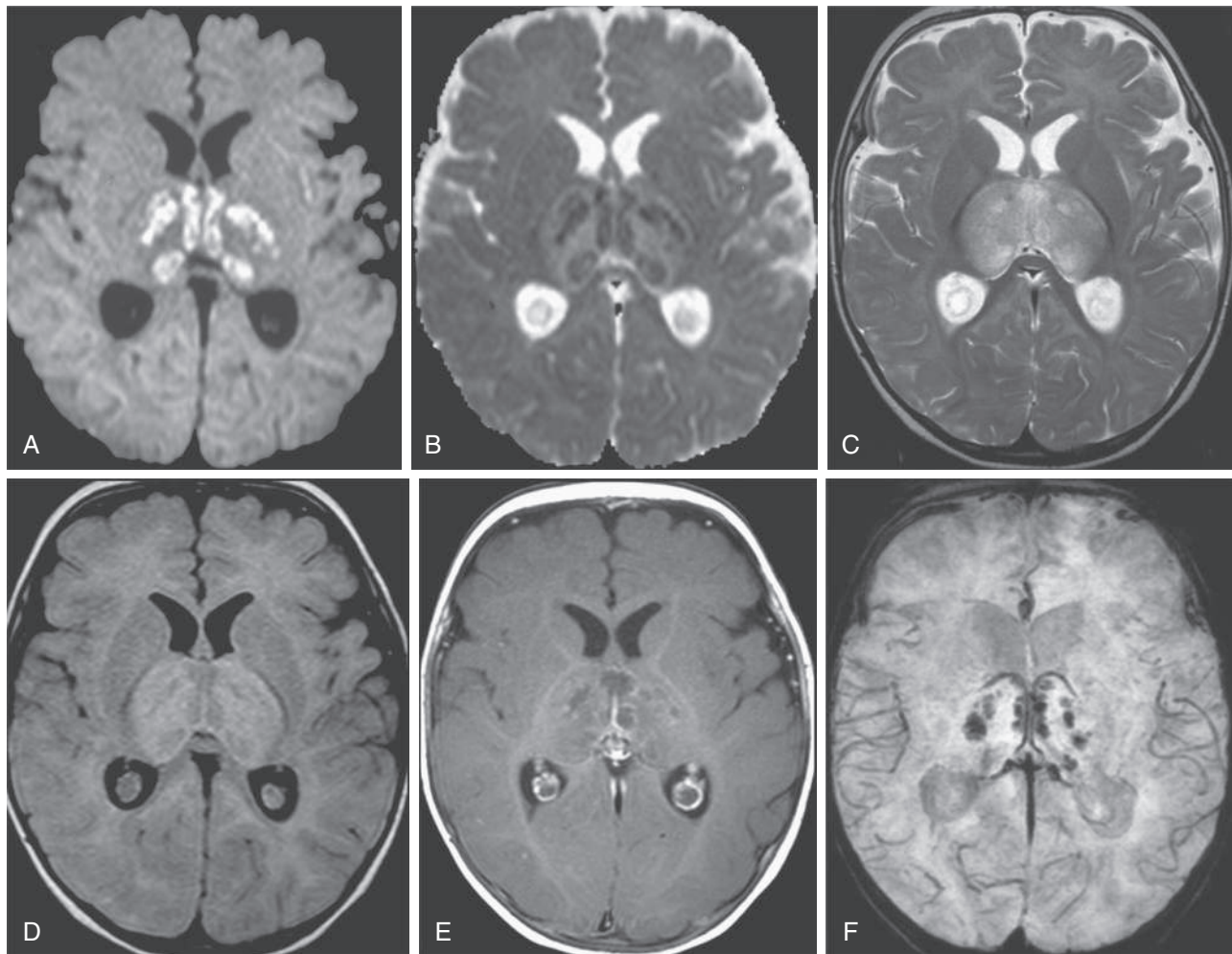


Fig. 638.10 Acute necrotizing encephalopathy. MRI at presentation. A, Axial diffusion-weighted image. B, Axial apparent diffusion coefficient (ADC) map. C, Axial T2-weighted image. D, Axial fluid-attenuated inversion recovery (FLAIR) image. E, Contrast-enhanced axial T1-weighted image. F, Axial susceptibility weighted image. Diffusion-weighted images (A) and corresponding ADC map (B) clearly show multiple areas of restricted diffusion against a background of increased diffusion involving both thalami, which are swollen. On T2-weighted (C) and FLAIR (D) images, the thalami are markedly swollen and hyperintense. On T1-weighted images obtained after intravenous gadolinium chelate injection (E), multiple necrotic portions are well delineated by peripheral faint, linear enhancement. Incidental choroid plexus cysts are detected. Susceptibility weighted image (F) shows multiple hypointense spots, consistent with petechial hemorrhage. (From Bergamino L, Capra V, Biancheri R, et al. Immunomodulatory therapy in recurrent acute necrotizing encephalopathy ANE1: is it useful? *Brain Dev.* 2012;34:384–391, Fig. 1.)

There are no formal treatment guidelines. There is limited evidence from small case series demonstrating some response to early (<24 hours from symptom onset) and aggressive high-dose pulsed IV methylprednisolone. Intravenous immunoglobulin (IVIG) may also be of some benefit. Treatment is otherwise supportive, usually in an intensive care setting. Prognosis in ANE is poor, particularly in children with brainstem involvement. Mortality rates approach 40%, and severe neurologic sequelae are typical in surviving children.

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638.4 Autoimmune Encephalitis

Thaïs Armangué and Josep Dalmau

Autoimmune encephalitis comprises an expanding group of clinical syndromes that can occur at all ages (<1 year to adult) but preferentially affect children and younger adults. Some of these disorders are associated with antibodies against neuronal cell surface proteins and synaptic receptors involved in synaptic transmission, plasticity, or neuronal excitability. The syndromes vary according to the

associated antibody, with phenotypes that resemble those in which the function of the target antigen is pharmacologically or genetically modified.

Most of these disorders are severe and potentially fatal, but patients frequently respond to immunotherapy with good outcomes. Moreover, because of the broad spectrum of symptoms—including alterations of behavior, psychosis, catatonia, insomnia, memory deficits, seizures, abnormal movements, and autonomic dysregulation—patients usually require a multidisciplinary treatment approach.

The identification of autoimmune mechanisms has provided a definitive diagnosis to many cases of encephalitis previously considered idiopathic, infectious, or postinfectious even though no causative agents were found. More than half of cases previously defined as encephalitis lethargica or choreoathetosis post-herpes simplex encephalitis are currently known to be anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis.

The mechanisms that trigger the production of the antibodies are unknown. In a small subgroup of adolescent or young adult patients, the presence of a tumor that expresses the target neuronal antigen likely contributes to the triggering of the immune response. In addition, the high prevalence of prodromal viral-like symptoms has suggested that nonspecific viral infections may contribute to altering the

immune tolerance for neuronal proteins and increasing the permeability of the blood-brain barrier to antibodies. Nonetheless, in many of these diseases the blood-brain barrier appears intact, and there is evidence that the autoantibodies are synthesized within the CNS by plasma cells that form part of the local brain and meningeal inflammatory infiltrates.

GENERAL DIAGNOSTIC APPROACH TO AUTOIMMUNE ENCEPHALITIS

Most autoimmune encephalitides have a rapid presentation of multiple symptoms, usually in less than 3 months, including neurologic and/or psychiatric alterations frequently associated with seizures or abnormal EEG, and CSF or MRI evidence of inflammatory changes.

Depending on the combination of clinical features and presence of neuronal-specific antibodies, three diagnostic categories have been established: possible autoimmune encephalitis, probable antibody-negative autoimmune encephalitis, and definite antibody-positive autoimmune encephalitis (Table 638.10).

In the pediatric population, the number of autoimmune encephalitis cases associated with well-defined antibodies is substantially lower than that affecting the adult population (Table 638.11).

ANTI-N-METHYL-D-ASPARTATE RECEPTOR ENCEPHALITIS

In this disease, the immunoglobulin G antibodies target the GluN1 subunit of the NMDA receptor. The estimated annual incidence of this disorder is 1.2–1.5 cases per million persons, and it is considered the second most common cause of autoimmune encephalitis after acute disseminated encephalomyelitis (ADEM) in children and adolescents. Overall, the disease predominates in females (80%); in patients younger than 12 years, the frequency of males is >40%. The resulting syndrome is highly predictable and usually evolves in stages. In teenagers and young adults, the disorder usually presents with *prominent psychiatric manifestations* that may include rapidly progressive anxiety, agitation, delusional thoughts, bizarre behavior, labile affect, mood disturbances (mania), catatonic features, memory deficit, language disintegration, aggression, and insomnia or other sleep disturbances. In many cases, these symptoms had been preceded by a few days of prodromal headache, fever, or viral infection–like symptoms. Patients are often misdiagnosed with new-onset psychosis or a primary psychiatric disorder. However, in a few days or weeks, additional symptoms occur, including a decreased level of consciousness, seizures (including status epilepticus), limb or oral dyskinesias, choreoathetoid movements, and *autonomic instability* that usually includes tachycardia, bradycardia, fluctuation of blood pressure, hypoventilation, hyperthermia, and sialorrhea. In rare instances, bradycardia and cardiac pauses occur, at times requiring the transient use of a pacemaker. The disorder also occurs in toddlers and infants (the youngest patient identified to date was 2 months old), and although the evolution of the syndrome is similar to that of adults, young patients more frequently present with seizures and movement disorders. Because of the age of patients, the psychiatric-behavioral features may be missed. In this young age-group, behavior changes include irritability, new-onset temper tantrums, agitation, aggression, reduced speech, mutism, and autistic-like regression. Moreover, compared with adults, some children also develop cerebellar ataxia and hemiparesis; in contrast, autonomic dysfunction is usually milder and less severe in children.

Brain MRI studies are abnormal in approximately 35% of patients, usually showing nonspecific cortical and subcortical T2–fluid-attenuated inversion recovery (FLAIR) signal abnormalities, sometimes with transient cortical or meningeal enhancement; nonspecific white matter abnormalities can occur. However, if white matter changes are predominant, an overlapping syndrome with a demyelinating disease should be suspected (Fig. 638.11A). The CSF is initially abnormal in approximately 80% of patients, showing moderate lymphocytic pleocytosis and, less frequently, increased protein synthesis and oligoclonal bands. The EEG is abnormal in *virtually all* patients; it usually shows focal or diffuse slow activity in the delta and theta ranges, which does not correlate with abnormal movements. In addition, many patients

develop epileptic activity, requiring video monitoring for adequate clinical management. A distinctive EEG pattern called *extreme delta brush*, characterized by beta-delta complexes, occurs in 30% of adults and less frequently in children (Fig. 638.12).

The diagnosis of the disorder is established by demonstrating NMDAR antibodies in CSF. The sensitivity is higher in CSF compared with serum (100% vs 85%), and the levels of antibodies in CSF appear to correlate better with the outcome. Antibodies may remain detectable, albeit at lower titers, after patients recover.

The presence of an underlying tumor, usually a teratoma, is age and sex dependent. Whereas 40% of females older than 12 years have an underlying teratoma of the ovary, the presence of a tumor is unusual in young males and females or young adult male patients. In children, an MRI of the abdomen and pelvis and abdominal and testicular ultrasound are the preferred tumor screening tests.

In a small number of patients, anti-NMDAR encephalitis occurs simultaneously with or after infections with a variety of pathogens, including *Mycoplasma pneumoniae*, herpes simplex virus (HSV), human herpesvirus 6, enterovirus, COVID-19, and influenza virus. With the exception of HSV1, a pathogenic link with most of these infections has not been established. There is evidence that about 50% of patients with HSV encephalitis develop antibodies against the GluN1 subunit of the NMDAR and other neuronal cell surface proteins and receptors, and of these about half the patients develop new or relapsing neurologic symptoms 2–12 weeks after completing treatment for HSV encephalitis. In children younger than 4 years, this type of autoimmune encephalitis usually manifests with choreoathetosis and dyskinesias (known as *choreoathetosis post-HSV encephalitis*; see Videos 638.1, 638.2, and 638.3). In contrast, older children and adults more often develop predominantly behavioral symptoms. A similar complication has been reported in patients with Japanese encephalitis, who develop autoimmune encephalitis (usually with NMDAR antibodies) after the viral encephalitis has subsided.

There is evidence that tumor removal, when appropriate, and prompt immunotherapy improve the outcome. Most children receive first-line immunotherapies, including corticosteroids, IVIG, or plasma exchange. However, because these treatments fail in ~50% of patients, and with multiple reports showing that rituximab is effective, this treatment is increasingly being used in combination with IVIG and steroids or after first-line immunotherapies fail. Cyclophosphamide can be effective when there has been no response to these treatments.

Approximately 80% of patients recover substantially or fully; mortality is estimated to be ~5%, usually as a result of infections or autonomic dysregulation during the acute phase of the disease. Recovery is usually slow and can take as long as 2 years after symptom onset. The last symptoms to improve are problems in social interactions and language and executive functions. **Relapses** occur in approximately 15% of patients; they can develop as partial syndromes, are usually milder than the initial episode, and respond equally well to immunotherapy. Initial comprehensive immunotherapy and rituximab appear to prevent or reduce the number of relapses. The efficacy of chronic immunosuppression with drugs such as azathioprine or mycophenolate mofetil in preventing relapses is unknown. Young children with autoimmune encephalitis, post-HSV encephalitis, and NMDAR antibodies have a poorer prognosis than patients with classical anti-NMDAR encephalitis (see Fig. 638.11B).

The differential diagnosis of anti-NMDAR encephalitis is extensive and varies according to the stage of the disease (Table 638.12). The most frequently considered disorders are viral encephalitis, neuroleptic malignant syndrome, acute psychosis, and drug misuse.

OTHER TYPES OF ENCEPHALITIS ASSOCIATED WITH ANTIBODIES AGAINST NEURONAL CELL SURFACE ANTIGENS

Encephalitis with antibodies against the γ -aminobutyric acid A receptor (GABA_AR) is a rare autoimmune encephalitis that can affect

Table 638.10 Classification Criteria for Possible and Definite Antibody-Positive Autoimmune Encephalitis and Probable Antibody-Negative Pediatric Autoimmune Encephalitis

CATEGORICAL FEATURES OF AUTOIMMUNE ENCEPHALITIS	SPECIFIC DIAGNOSTIC FEATURES	DIAGNOSTIC CATEGORIES		
		POSSIBLE AE	PROBABLE ANTIBODY-NEGATIVE AE	DEFINITE ANTIBODY-POSITIVE AE
1. Evidence of acute or subacute symptom onset	Onset of neurologic and/or psychiatric symptoms over ≤ 3 mo in a previously healthy child	Yes	Yes	Yes
2. Clinical evidence of neurologic dysfunction	Features include:	≥ 2 features present	≥ 2 features present	≥ 2 features present
	Altered mental status/level of consciousness or EEG with slowing or epileptiform activity (focal or generalized)			
	Focal neurologic deficits			
	Cognitive difficulties ^a			
	Acute developmental regression			
	Movement disorder (except tics)			
	Psychiatric symptoms			
	Seizures not explained by a previously known seizure disorder or other condition			
3. Paraclinical evidence of neuroinflammation	Features include:	Not available [*]	≥ 1 feature present	$\geq 1^b$ feature present
	CSF inflammatory changes (leukocytosis > 5 cells/ mm^3 and/or oligoclonal banding)			
	MRI features of encephalitis			
	Brain biopsy showing inflammatory infiltrates and excluding other disorders			
4. Autoimmune encephalitis serology	Presence in serum and/or CSF of well-characterized autoantibodies associated with autoimmune encephalitis ^b	Not available	No	Yes
5. Exclusion of other etiologies	Reasonable exclusion of alternative causes, including other causes of CNS inflammation	Yes	Yes	Yes

^aSevere cognitive dysfunction that is not attributable to a primary psychiatric syndrome as documented by a qualified clinician (e.g., neurologist, psychiatrist, and neuropsychologist) or a significant drop in IQ (> 20 points).

^bWhen antibodies against *N*-methyl-D-aspartate receptor (NMDAR), gamma-aminobutyric acid A receptor (GABA_AR), or glutamic acid decarboxylase 65 (GAD65) are present in the CSF, further paraclinical biomarkers of neuroinflammation are not required to diagnose definite autoimmune encephalitis. When only serum antibodies are present, one or more paraclinical marker(s) of neuroinflammation is required.

^{*}If clinical criteria of possible AE are met, the authors recommend proceeding with paraclinical and antibody testing and consider initiating immune therapy if the paraclinical tests are abnormal.

AE, Autoimmune encephalitis.

Adapted from Cellucci T, Van Matter H, Graus F, et al. Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. *Neurol Neuroimmunol Neuroinflamm*. 2020;7:e663.

Table 638.11 Autoimmune Encephalitis in Children

DISEASE	ANTIBODIES AND/OR MECHANISMS	SYNDROME	ANCILLARY TEST	TREATMENT/PROGNOSIS
Anti-NMDAR encephalitis	Antibodies against the GluN1 subunit of the NMDAR. In children, most cases are idiopathic. In a subgroup of patients, the disease is triggered by the presence of a tumor. In another subgroup, the disease is triggered by HSV encephalitis.	Psychiatric symptoms, decreased verbal output, sleep disorder (mainly insomnia), seizures, dyskinesias (orofacial, limbs), dystonia, rigidity and other abnormal movements, autonomic dysfunction, hypoventilation	EEG: almost always abnormal (epileptic and/or slow activity). In some patients it shows the pattern of extreme delta brush. Brain MRI: nonspecific abnormal findings in ~35% CSF: pleocytosis and/or increased proteins in ~80%	80% substantial or complete recovery after immunotherapy and tumor removal (if appropriate). About 50% of patients need second-line immunotherapies.* Relapses in ~15% of patients. Worse outcome when post-HSV encephalitis
Encephalitis associated with GABA _A R antibodies	Antibodies against $\alpha 1$, $\beta 3$, or $\gamma 2$ subunits of the GABA _A R. ~40% of adults have an underlying tumor (thymoma). Children usually do not have tumor association.	Refractory seizures, epilepsy partialis continua. Patients may develop limb or orofacial dyskinesias.	EEG: almost always abnormal; frequent epileptic activity MRI: multifocal corticosubcortical FLAIR/T2 hyperintensities in 77% of patients CSF: pleocytosis and/or increased proteins	80% show moderate or good recovery after immunotherapy.
Encephalitis with mGluR5 antibodies** (Ophelia syndrome)	Antibodies against mGluR5 Frequent association with Hodgkin lymphoma	Abnormal behavior, seizures, memory deficits	EEG: frequently abnormal with nonspecific findings MRI: normal or nonspecific findings CSF: frequent pleocytosis and/or increased proteins	Good recovery after tumor treatment and immunotherapy
Other autoimmune encephalitis** (very infrequent in children)	Antibodies against neuronal cell surface (GABA _B R, DPPX, GlyR, mGluR2, LGI1, Caspr2, GluK2) or intraneuronal antigens (Hu, Ma2, GAD65 amphiphysin) All these antibodies rarely associate with tumors in children.	The syndrome varies depending on the autoantibody, and the phenotypes are often different from those reported in adults. GABA _B R: encephalitis, seizures, cerebellar ataxia DPPX: CNS hyperexcitability, PERM GlyR: PERM, stiff person syndrome*** mGluR2: paraneoplastic cerebellar ataxia LGI1: similar syndrome as that of the adults but without FBDS and hyponatremia. Caspr2: similar syndrome as that of the adults and hypertensive encephalopathy, hormonal dysfunction, palmoplantar erythema GluK2: cerebellitis and/or autoimmune encephalitis with prominent ataxia Hu: brainstem or limbic encephalitis GAD65****: encephalitis with epilepsy	MRI: variable changes depending on the syndrome. CSF: frequent pleocytosis and/or increased proteins	Disorders with antibodies against cell surface antigens are substantially more responsive to immunotherapy than those with antibodies against intracellular antigens.
Encephalitis associated with MOG antibodies	In children the most common clinical manifestation is ADEM	Seizures, motor deficits, ataxia, or visual dysfunction accompanied by encephalopathy	MRI with T2/FLAIR large, hazy abnormalities, with or without involvement of the deep gray matter Some patients develop encephalitis with predominant cortical involvement CSF: frequent pleocytosis and/or increased proteins	In ~70-80% of patients, the disease is monophasic and shows good response to steroids. Some patients develop relapsing disease (with prolonged detection of serum MOG antibodies).

Continued

Table 638.11 Autoimmune Encephalitis in Children—cont'd

DISEASE	ANTIBODIES AND/OR MECHANISMS	SYNDROME	ANCILLARY TEST	TREATMENT/PROGNOSIS
NMOSD	Patients can have AQP4 or MOG antibodies; some patients are seronegative.	Typical involvement of optic nerves and spinal cord Encephalopathy in the context of diencephalic or area postrema syndromes	Characteristic involvement of brain areas rich in AQP4 (periaqueductal gray matter, hypothalamus, optic nerve and central involvement of the spinal cord)	High risk of relapses and long-term disability. Requires chronic immunotherapy. Patients with MOG antibodies have better long-term outcome than those with AQP4 antibodies or seronegative cases.
Acute cerebellar ataxia and acute cerebellitis	Frequently triggered by infections. Most patients do not have detectable autoantibodies (a few patients have GluK2 antibodies).	Ataxia and dysmetria. Some patients present with headache, vomiting, and decreased level of consciousness caused by intracranial hypertension	MRI: normal in acute cerebellar ataxia; several MRI patterns in acute cerebellitis: diffuse (more frequent) or focal bihemispheric acute cerebellitis with T2/FLAIR hyperintensities in the cerebellar parenchyma; hemocerebellitis (only one hemisphere involved).	Usually self-limiting and benign course in acute cerebellar ataxia; Immunotherapy is usually effective in acute cerebellitis, but some patients may need urgent decompressive craniectomy, and residual neurologic symptoms are frequent.
Opsoclonus-myoclonus and other cerebellar-brainstem encephalitis	Most patients do not have detectable autoantibodies (a few patients with neuroblastoma have Hu antibodies). Neuroblastoma occurs in 50% of children <2yr old; teratoma in teenagers and young adults.	Opsoclonus often accompanied by irritability, ataxia, falling, myoclonus, tremor, and drooling	MRI: usually normal; it may show cerebellar atrophy over time. EEG: Normal. CSF: may be normal or show abnormalities suggesting B-cell activation.	Neuroblastoma treatment (if it applies). Partial neurologic response to immunotherapy in many young children regardless of presence or absence of neuroblastoma. (Better outcomes if aggressive immunotherapy is used.) Good response to treatment in teenagers with teratoma-associated opsoclonus.
Bickerstaff encephalitis	GQ1b antibodies (~65%, nonspecific for this disorder)	Ophthalmoplegia, ataxia, and decreased level of consciousness. Frequent hyperreflexia. Patients may develop hyporeflexia and overlap with Miller-Fisher syndrome.	MRI: abnormal in ~30% (T2-signal abnormalities in the brainstem, thalamus, and cerebellum) Nerve conduction studies: abnormal in ~45% (predominant axonal degeneration, and less often demyelination)	Good response to steroids, IVIG, or plasma exchange
Steroid responsive encephalopathy with autoimmune thyroiditis (SREAT) (Hashimoto encephalitis)	TPO antibodies [†] (nonspecific for this disorder)	Strokelike symptoms, tremor, myoclonus, aphasia, seizures, ataxia, sleep and behavioral problems	48% hypothyroidism (usually subclinical), MRI often normal EEG: slow activity CSF: elevated protein	Steroid-responsive. Partial responses are frequent.
Rasmussen encephalitis	Most likely immune mediated (unclear mechanism)	Progressive refractory partial seizures, cognitive decline, focal deficits, and brain hemiatrophy	MRI: progressive unilateral hemispheric atrophy	Limited response to immunotherapy. The most effective treatment is functional hemispherectomy.
Basal ganglia encephalitis	Infrequent antibodies against D2R	Lethargy, abnormal movements, behavioral change, agitation, psychosis	MRI: Basal ganglia T2/FLAIR abnormalities, but may be normal in up to 50% CSF: frequently, elevated protein	Mostly monophasic, variable outcome; 40% complete recovery with immunotherapy.
CLIPPERS	No specific autoantibody association Probably represents different diseases. Important differential diagnosis with lymphoma	Episodic diplopia or facial paresthesias with subsequent development of symptoms of brainstem and occasionally spinal cord dysfunction	MRI: symmetric curvilinear gadolinium enhancement peppering the pons and extending variably into the medulla, brachium pontis, cerebellum, midbrain, and, occasionally, spinal cord	Steroid-responsive but patients may require chronic steroid or other immunosuppressive therapy.

Table 638.11 Autoimmune Encephalitis in Children—cont'd

DISEASE	ANTIBODIES AND/OR MECHANISMS	SYNDROME	ANCILLARY TEST	TREATMENT/PROGNOSIS
ROHHAD	Postulated autoimmune or genetic; some patients have antibodies against ZSCAN1. Frequently associated with neural crest tumors	Rapid-onset obesity, hyperphagia, abnormal behavior, autonomic dysfunction, and central hypoventilation	Brain MRI, usually normal	Symptomatic treatment. In some patients, limited response to immunotherapy.

*Includes rituximab and cyclophosphamide.

**Commercial testing panels do not include GluK2, D2R, or mGluR antibodies. Therefore when one of these conditions is suspected, the samples should be investigated in a research laboratory.

***Low titers of GlyR ab have been reported in the serum of multiple different disorders, and their clinical significance is unclear; demonstration of antibodies in CSF has higher disease-specificity and is found usually associated with PERM.

****Lower titers of GAD65 antibodies in serum are found in patients with diabetes mellitus (~100-fold lower titers than those associated with GAD-antibody-associated neurologic disorders), other non-neurologic autoimmune conditions, and healthy persons.

[†]Diagnosis of exclusion, after ruling out relevant autoantibodies (e.g., NMDAR, AMPAR, among others).

AQP4, Aquaporin 4; CLIPPERS, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; Caspr2, contactin-associated protein-like 2; CSF, cerebrospinal fluid; D2R, dopamine 2 receptor; DPPX, dipeptidyl-peptidase-like protein-6; EEG, electroencephalography; FBDS, faciobrachial dystonic seizures; FLAIR, fluid-attenuated inversion recovery; GABA_AR, γ -aminobutyric acid-A receptor; GABA_BR, γ -aminobutyric acid-B receptor; GAD65, glutamic acid decarboxylase 65; GluK2, glutamate kainate receptor 2; HSV, herpes simplex virus; IVIG, intravenous immunoglobulin; LGI1, leucine-rich glioma-inactivated 1; mGluR, metabotropic glutamate receptor; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; NMDAR, N-methyl-D-aspartate receptor; NMOSD, neuromyelitis optica spectrum disorder; PERM, progressive encephalomyelitis with rigidity and myoclonus; ROHHAD, rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation; TPO, thyroid peroxidase; ZSCAN1, Zinc finger and SCAN domain-containing protein 1.

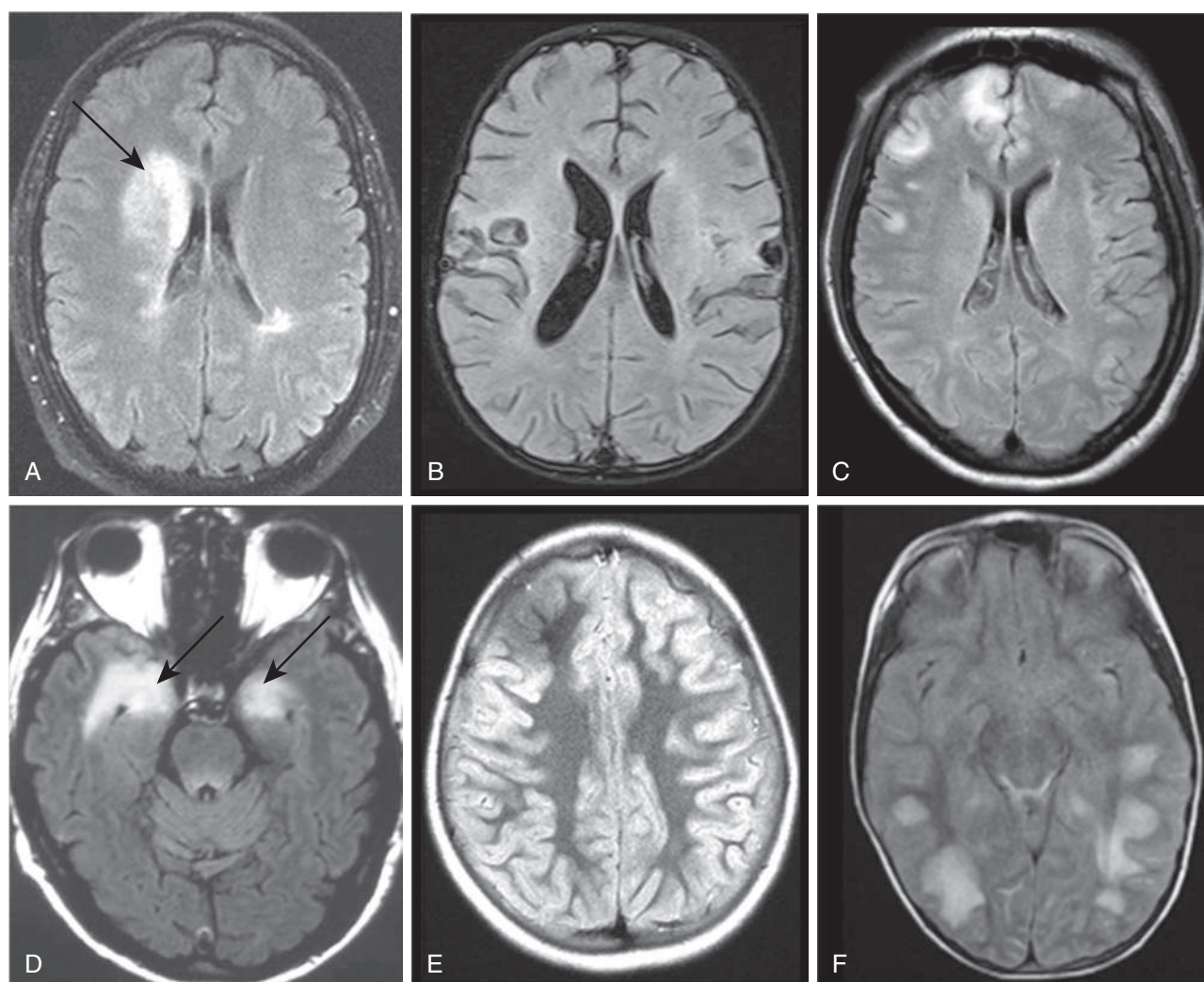


Fig 638.11 Brain MRI patterns in autoimmune encephalitis. A, FLAIR MRI image of a patient with anti-NMDAR encephalitis and concurrent MOG antibodies; it shows a prominent right frontal abnormality compatible with demyelination. B, T1-weighted MRI image of a 2-yr-old male with anti-NMDAR encephalitis after herpes simplex encephalitis. There are extensive necrotic areas in temporal regions that are residual from the viral encephalitis, without new MRI lesions produced by the autoimmune encephalitis. C, FLAIR MRI image from a patient with anti-GABA_AR encephalitis; it shows multiple cortical-subcortical bilateral right frontal predominant hyperintensities. D, FLAIR MRI image showing typical features of limbic encephalitis with bilateral medial temporal lobe abnormalities; this adult patient with autopsy-proven limbic encephalitis did not have serum or CSF antineuronal antibodies. E, FLAIR MRI image showing extensive cortical involvement in a 9-yr-old with fatal encephalitis associated with MOG antibodies and severe intracranial hypertension. F, Typical FLAIR MRI findings in a 4-yr-old female with acute disseminated encephalomyelitis associated with MOG antibodies; it shows bilateral large abnormalities in the white matter. Left side of images = right side of brain. (A and D from Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol*. 2016;15:391–404. Fig. 2.; C courtesy Dr. Mateus Mistieri Simabukuro; B, E, and F courtesy Drs. Thaïs Armangué and Josep O. Dalmau.)

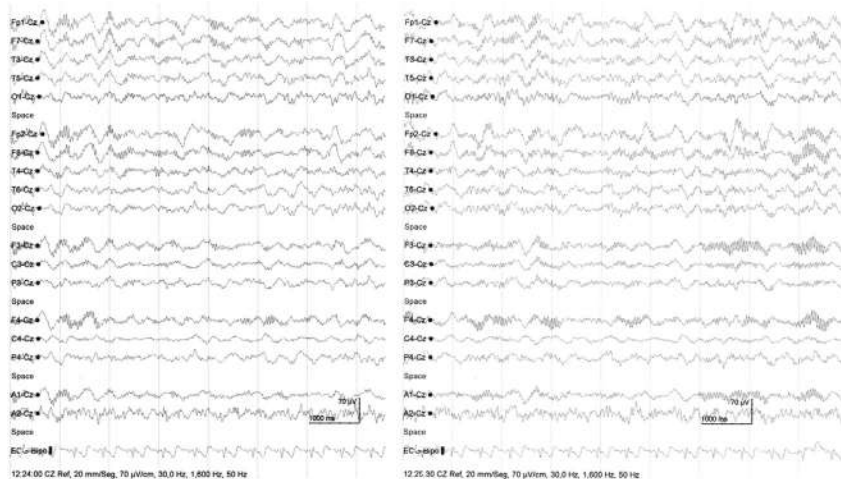


Fig. 638.12 Electroencephalogram showing a pattern called extreme delta brush in a 14-yr-old female with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. This pattern has been found to be characteristic of anti-NMDAR encephalitis. It consists of a nearly continuous combination of delta activity with superimposed fast activity, usually in the beta range, symmetrically involving all regions, with a frontal preference in patients who are not under sedation or anesthesia. (From Armangue T, Titulaer MJ, Málaga I, et al. *Pediatric anti-N-methyl-D-aspartate receptor encephalitis: clinical analysis and novel findings in a series of 20 patients*. *J Pediatr*. 2012;162:850–856, Fig. 2.)

children (40% of patients are <18 years) and develops with status epilepticus, refractory seizures, or *epilepsia partialis continua* in association with antibodies against the $\alpha 1$, $\beta 3$, or $\gamma 2$ subunits of the GABA_AR. Young children can develop abnormal movements suggestive of anti-NMDAR encephalitis but with studies negative for NMDAR antibodies. Unlike other types of autoimmune encephalitis in which the brain MRI is usually normal or shows nonspecific findings, pediatric and adult patients with this disorder frequently develop multifocal hyperintense cortical-subcortical FLAIR/T2 abnormalities (see Fig. 638.11C). In adults, this encephalitis may occur with thymoma, but children rarely have an underlying tumor.

Ophelia syndrome is a form of encephalitis that occurs in association with Hodgkin lymphoma and predominantly affects young adults, teenagers, or children. Some patients develop antibodies against mGluR5, a receptor involved in learning and memory. Neurologic symptoms are highly responsive to treatment of the tumor and immunotherapy.

Autoimmune limbic encephalitis refers to an inflammatory process of the limbic system, including the medial temporal lobes, amygdala, and cingulate gyri (see Fig. 638.11D). In adults, the most frequent immune-mediated limbic encephalitis occurs in association with antibodies against proteins that were once thought to be voltage-gated potassium channels (VGKCs) but which, in fact, target a secreted neuronal protein called *leucine-rich glioma-inactivated 1* (LGI1) and a protein called *Caspr2* expressed in the brain and the juxtaparanodal regions of myelinated nerves. Adult patients with LGI1 antibody-associated limbic encephalitis often develop *hyponatremia*; in some patients, the disorder is preceded by dystonic or myoclonic-like movements, described as *faciobrachial dystonic seizures*. Adult patients with Caspr2 antibodies can develop limbic encephalitis, neuromyotonia, or **Morvan syndrome**, which includes encephalopathy, seizures, a sleep disorder, autonomic dysfunction, and neuromyotonia. In children, encephalitis with LGI1 or Caspr2 antibodies is extremely rare. Children with LGI1 antibodies do not develop hyponatremia or faciobrachial dystonic seizures. Younger children with Caspr2 antibodies often have similar symptoms to those of the adults, which can also be accompanied by generalized weakness, flaccid paresis, hypertensive encephalopathy, hormonal dysfunction, and palmoplantar erythema or eczema that has been attributed to sweating and itching. Children with Caspr2 antibodies do not have associated tumors.

VGKC-complex antibodies have very limited clinical utility unless they are specifically characterized as antibodies against LGI1 or Caspr2 proteins. Thus a positive test for VGKC-complex antibodies without further information on LGI1 or Caspr2 specificity should be interpreted with caution because it does not necessarily indicate autoimmune encephalitis.

Excluding patients with anti-NMDAR- or GABAAR antibody-associated encephalitis, an exceptionally low number of children with

limbic and other types of neuronal antibody-associated encephalitis have been reported in the English literature, some of them with antibodies against neuronal cell surface proteins (GABA_BR, DPPX, GlyR) or intracellular proteins (Hu, Ma2, GAD65, amphiphysin). In some patients, an underlying malignancy was identified, including leukemia, ganglioneuroblastoma, neuroblastoma, or small cell carcinoma of the ovary.

Determination of the type of autoantibodies and location of the target antigens is important because an encephalitis in which the antigens are on the cell surface (e.g., NMDAR or GABAAR) responds better to immunotherapy than one in which the antigens are intracellular (e.g., GAD65).

ACQUIRED DEMYELINATING SYNDROMES WITH ENCEPHALOPATHY

ADEM is the most frequent autoimmune encephalitis in children (see [Chapter 640.1](#)). Symptoms may include seizures, motor deficits, ataxia, and visual dysfunction, among others. The brain MRI typically shows multifocal demyelinating lesions that can also involve the basal ganglia, brainstem, or cerebellum, with variable contrast enhancement (see [Fig. 638.11F](#)). Antibodies against myelin oligodendrocyte glycoprotein (MOG) occur in 50–60% of patients with ADEM and have a negative predictive value for evolution to multiple sclerosis in children with a first demyelinating event (see [Chapter 640.1](#)). Some children with MOG antibodies develop a clinical picture resembling autoimmune encephalitis with MRI FLAIR/T2 increased signal involving cortical regions, with variable contrast enhancement, or presenting as nondemyelinating focal or diffuse lesions (see [Fig. 638.11E](#)). MOG antibodies may also coexist with NMDAR antibodies; these patients usually develop overlapping syndromes related to these autoimmuneities.

Neuromyelitis optica spectrum disorder (NMOSD) can present as an encephalopathy with predominant involvement of diencephalic and area postrema regions. These patients often harbor aquaporin 4 (AQP4) antibodies or MOG antibodies. Determination of these antibodies should be considered in patients with encephalopathy and MRI findings showing involvement of AQP4-rich regions, such as the periaqueductal gray matter, hypothalamus, optic nerves, and central region of the spinal cord (see [Chapter 640.2](#)).

HASHIMOTO ENCEPHALOPATHY

Hashimoto encephalopathy, also known as **steroid-responsive encephalopathy with autoimmune thyroiditis (SREAT)**, is a controversial disorder defined by the detection of thyroid peroxidase (TPO) antibodies in patients with acute or subacute encephalitis that responds to corticosteroids. Clinical features are not specific and may include strokelike episodes, tremor, myoclonus, transient aphasia, sleep and behavior abnormalities, hallucinations, seizures, and ataxia. The CSF, MRI, and EEG findings are not specific. The diagnosis of this disorder should be based on the exclusion of other inflammatory and autoimmune diseases. Pretreatment criteria of Hashimoto encephalopathy do

Table 638.12 Differential Diagnosis of Anti-NMDAR and Other Types of Autoimmune Encephalitis in Children

DISORDER	COMMENTS
Viral encephalitis	Viral encephalitis is often suggested by the acute onset of symptoms, CSF pleocytosis, and hyperthermia. Most viral encephalitides (except rabies) occur with higher levels of CSF pleocytosis and protein concentration. Psychosis and dyskinesias are significantly less frequent in viral encephalitis than in anti-NMDAR encephalitis.
New neurological symptoms post-HSV encephalitis	Occurs ~2-12 wk after successful treatment of HSV encephalitis. This may represent a true viral relapse of encephalitis (CSF PCR-positive, progression of necrotic MRI changes, response to acyclovir) or an autoimmune disorder (CSF PCR-negative, no new necrotic lesions on MRI, lack of response to acyclovir). In a proportion of the latter patients, the disorder is anti-NMDAR encephalitis.
New-onset psychosis	Because most patients with anti-NMDAR encephalitis present with psychosis, a psychiatric disorder is frequently considered. When the disease evolves, the development of neurologic symptoms usually reveals the diagnosis.
Drugs/toxins	The acute development of personality and behavioral changes and symptoms suggesting involvement of dopaminergic pathways (rigidity, dystonia, orofacial movements) usually leads to a suspicion of drug use (e.g., ketamine, phencyclidine, synthetic cannabinoids, among others).
Neuroleptic malignant syndrome (NMS)	The occurrence of an altered level of consciousness, episodes of rigidity, hyperthermia, and autonomic instability often suggest NMS. In addition, some patients with anti-NMDAR encephalitis have elevated serum creatine kinase and rhabdomyolysis (in the absence of antipsychotic medication). The frequent use of neuroleptics to control the abnormal behavior adds further confusion between both syndromes. The presence of dyskinesias and catatonia suggest anti-NMDAR encephalitis.
Limbic encephalitis (LE)	Criteria of LE are well defined. Patients with LE do not have dyskinesias or central hypoventilation; the MRI usually shows abnormalities restricted to the medial temporal lobes, and the EEG findings (epileptic or slow activity) are largely restricted to the temporal lobes.
Encephalitis lethargica	This is an ill-defined entity, likely representing multiple disorders. Criteria include acute or subacute encephalitis with at least three of the following: signs of basal ganglia involvement; oculogyric crises; ophthalmoplegia; obsessive-compulsive behavior; akinetic mutism; central respiratory irregularities; and somnolence and/or sleep inversion. Many patients categorized as encephalitis lethargica hyperkinetica have anti-NMDAR encephalitis.
Childhood disintegrative disorder/late-onset autism	Children with anti-NMDAR encephalitis often show cognitive regression, rapid loss of language function, autistic features, and seizures, suggesting a childhood disintegrative disorder. Although the prognosis of CDD is poor, most patients with anti-NMDAR encephalitis respond to immunotherapy and have a substantial clinical recovery.
Kleine-Levin syndrome	Symptoms of hypersomnia, compulsive hyperphagia, hypersexuality, apathy, and childlike behavior, which are typical components of Kleine-Levin syndrome, may occur transiently during the process of recovery of anti-NMDAR encephalitis or as permanent sequelae. However, different from the Kleine-Levin syndrome, the symptoms in anti-NMDAR encephalitis are not relapsing-remitting
Inborn errors of metabolism	Glutaric aciduria type I can present in previously asymptomatic patients as episodes of encephalopathy with dystonia, coinciding with an infection or febrile process. Several inborn errors of metabolism can also occur with acute or subacute encephalopathy with extrapyramidal signs, including 3-methylglutaconic aciduria, creatine transport deficiency, mitochondrial disorders (Leigh syndrome), Wilson syndrome, and Lesch-Nyhan syndrome. Pantothenate kinase-associated neurodegeneration, porphyria, and urea cycle defects should also be considered.
Genetic disorders that can manifest as autoimmune encephalitis	HLH (often initial presentation as primary CNS with later 1-2 yr onset of systemic features) RANBP2 variants, interferonopathies, autoinflammatory syndromes including cryopyrin-associated periodic syndromes, Aicardi-Goutières syndrome, and CTLA4 deficiency can present with clinical features mimicking ADEM or autoimmune or infectious encephalitis. MRI often shows hyperintense T2/FLAIR abnormalities involving white matter with contrast enhancement in HLH and CTLA4 deficiency; both thalami in RANBP2 variants; and may show striatal necrosis with or without associated hypomyelination in ADAR1 interferonopathy. CSF is abnormal in most patients. Some patients develop systemic symptoms (e.g., fever, arthralgias or rash in autoinflammatory syndromes, or autoimmune cytopenias or hypogammaglobulinemia in CTLA4 deficiency) that can help to make the diagnosis, which is confirmed by genetic testing.
Monoamine neurotransmitter disorders	Deficiency of dopamine or serotonin, or both, can result in encephalopathy, epilepsy, and pyramidal and extrapyramidal symptoms. The diagnosis is established by examining the CSF for levels of these neurotransmitters.
Acquired demyelinating disorders	ADEM and NMOSD are immune-mediated inflammatory and demyelinating disorders of the central nervous system. These disorders should be considered in the differential diagnosis of multifocal neurologic abnormalities and encephalopathy in children. As with anti-NMDAR encephalitis, these disorders may be preceded by an infection and can show pleocytosis. The diagnosis is suggested by the MRI findings. In NMOSD, the presence of AQP4 antibodies in serum or CSF is associated with relapses and poor prognosis. MOG antibodies occur in ~50% of children with ADEM and some patients with NMOSD.

Continued

Table 638.12 Differential Diagnosis of Anti-NMDAR and Other Types of Autoimmune Encephalitis in Children—cont'd

DISORDER	COMMENTS
CNS vasculitis	CNS vasculitis (including RVCLS: <i>TREX1</i>) results in neurologic deficits and psychiatric manifestations. The diagnosis is established by angiography in large-vessel angiitis and brain biopsy in small vessel angiitis. In the latter, serum inflammatory markers (erythrocyte sedimentation rate, C-reactive protein, Complement 3, von Willebrand factor antigen) are usually elevated, and the MRI shows FLAIR/T2 abnormalities in the white and/or gray matter suggesting ischemia and microhemorrhages, but are not restricted to vascular territories and frequent leptomeningeal and/or local enhancement.
Systemic rheumatic disorders	Systemic lupus erythematosus and other rheumatic disorders can result in encephalopathy and multifocal neurologic and psychiatric manifestations. These disorders are usually suggested by the presence of signs and symptoms of involvement of systemic organs: skin, joints, kidneys, blood-forming cells, and blood vessels.

ADEM, Acute disseminated encephalomyelitis; CDD, childhood disintegrative disorder; CNS, central nervous system; CSF, cerebrospinal fluid; HSV, herpes simplex virus; EEG, electroencephalography; FLAIR, fluid-attenuated inversion recovery; HLH, hemophagocytic lymphohistiocytosis; LE, limbic encephalitis; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; NMDAR, N-methyl-D-aspartate receptor; NMOSD, neuromyelitis optica spectrum disorders; NMS, neuroleptic malignant syndrome; PCR, polymerase chain reaction; RANBP2, Ras-related nuclear protein-binding protein 2; RVCLS, retinovasculopathy and cerebral leukodystrophy with systemic features, CTLA4, cytotoxic T-lymphocyte-associated protein 4; ADAR1, adenosine deaminase acting on RNA 1.

not predict steroid responsiveness. Because TPO antibodies occur in approximately 10% of asymptomatic children (i.e., nonencephalopathic and, in most cases, euthyroid) and can also be found in some patients who have more relevant antibody-associated diseases, the detection of TPO antibodies should be viewed as a marker of autoimmunity rather than a disease-specific or pathogenic antibody. Therefore detection of TPO antibodies should not prevent testing for more relevant antibodies, such as NMDAR antibodies.

Acute cerebellar ataxia and acute cerebellitis are the most frequent causes of cerebellar dysfunction in children. Ataxia and dysmetria are usually the main presenting symptoms, but some patients present with headache, vomiting, and decreased level of consciousness caused by intracranial hypertension. Brain MRI is normal in patients with acute cerebellar ataxia, but in cases of cerebellitis it shows T2/FLAIR hyperintensities in the white and gray matter of the cerebellum along with edema that may cause obstruction of the fourth ventricle and hydrocephalus. Treatment with steroids is usually effective, but some patients may need decompressive craniectomy. Whereas acute cerebellar ataxia with normal MRI is often self-limiting and has a benign course, cerebellitis with MRI abnormalities associates with a less favorable prognosis and almost half of them have residual neurologic deficits. The most frequent cause of acute cerebellar ataxia and cerebellitis is a viral infection; much less frequently, they may occur after bacterial infections or vaccines. A few cases with antibodies against the glutamate kainate 2 (GluK2) receptor have been reported.

OPSOCLONUS-MYOCLONUS AND OTHER TYPES OF RARE BRAINSTEM-CEREBELLAR ENCEPHALITIS

Opsoclonus-myoclonus occurs in infants, teenagers, and adults, although it probably represents different diseases and pathogenic mechanisms. In infants, the syndrome usually develops in the first 2 years of life (mean: 20 months), and at least 50% of patients have an underlying neuroblastoma. The child often presents with irritability, ataxia, falling, myoclonus, tremor, and drooling. Additional symptoms may include a refusal to walk or sit, speech problems, hypotonia, and the typical features of opsoclonus characterized by rapid, chaotic, multidirectional eye movements without saccadic intervals. Because opsoclonus may be absent at symptom presentation, patients may initially be diagnosed with acute cerebellitis. Typically, CSF abnormalities suggest B-cell activation, and the presence of antibodies against neuronal proteins has been demonstrated in rare instances, but the identification of a specific autoantigen has been elusive.

Immunotherapy, including corticosteroids and IVIG, often improves the abnormal eye movements, but residual behavioral, language, and cognitive problems persist in the majority of patients.

In addition, insomnia and an abnormal response to pain are common. Relapses occur in 50% of patients, usually as a result of an intercurrent infection or drug tapering. Patients treated with more aggressive immunosuppression (often including rituximab) have better outcomes compared with historic control series or patients who did not receive these treatments. Delay in treatment appears to be associated with a poorer neurologic outcome; therefore in cases with neuroblastoma, removal of the tumor should not delay the start of immunotherapy.

In teenagers and young adults, opsoclonus-myoclonus and brainstem-cerebellar encephalitis without opsoclonus are often considered idiopathic or postinfectious; however, there is evidence that some of these patients have an underlying **teratoma**, usually in the ovaries. These patients do not harbor NMDAR antibodies, and compared with those with anti-NMDAR encephalitis, they are less likely to present with psychiatric symptoms or dyskinesias. Although these patients do not appear to have neuronal antibodies, the CSF often shows pleocytosis and an elevated protein concentration. Treatment with immunotherapy (corticosteroids, IVIG, and/or plasma exchange) and removal of the ovarian teratoma frequently associate with full recovery. The prognosis of opsoclonus-myoclonus in teenagers and young adults seems better than that of young children (with or without neuroblastoma) or of the paraneoplastic opsoclonus of older patients, usually related to breast, ovarian, or lung cancer.

BICKERSTAFF ENCEPHALITIS

This term is used to describe patients with rapid progression (<4 weeks) of bilateral external ophthalmoplegia, ataxia, and decreased level of consciousness. Although this entity has been described more frequently in adults, children as young as 3 years old have been identified. Most patients are treated with steroids, IVIG, or plasma exchange; they often have a good outcome. Serum GQ1b immunoglobulin G antibodies are found in 66% of patients. Brain MRI abnormalities occur in 30% of patients and usually include increased T2-signal abnormalities in the brainstem, thalamus, and cerebellum and sometimes in the cerebral white matter. Some patients develop hyporeflexia and limb weakness, with predominant axonal involvement, overlapping with symptoms of Miller-Fisher syndrome and the axonal subtype of Guillain-Barré syndrome.

CHRONIC LYMPHOCYTIC INFLAMMATION WITH PONTINE PERIVASCULAR ENHANCEMENT RESPONSIVE TO STEROIDS

This is a clinically and radiologically distinct pontine-predominant encephalomyelitis. Patients usually present with episodic diplopia or facial paresthesias with subsequent development of symptoms of

brainstem, cerebellum, and, occasionally, spinal cord dysfunction. A brain MRI shows symmetric curvilinear gadolinium enhancement peppering the pons and extending variably into the medulla, brachium pontis, cerebellum, and midbrain and occasionally into the spinal cord. The clinical and radiologic findings usually respond to high-dose steroids but may worsen after steroid tapering, requiring chronic steroid or other immunosuppressive therapy. The differential diagnosis is extensive and includes infections, acquired demyelinating syndromes, granulomatous disease, lymphoma, or vasculitis. Biopsy studies may be needed to exclude these and other conditions.

AUTOIMMUNE ENCEPHALOPATHIES ASSOCIATED WITH EPILEPSY AND STATUS EPILEPTICUS

Rasmussen encephalitis is an inflammatory encephalopathy characterized by progressive refractory focal seizures, cognitive deterioration, and focal neurologic deficits that occur with gradual atrophy of one brain hemisphere. The disorder frequently presents in children 6–8 years old, although adolescents and adults can be affected. The etiology is unknown, and therefore multiple theories are proposed, including the presence of neuronal antibodies and T-cell-mediated mechanisms triggered by a viral infection. None of these mechanisms satisfactorily explain the unilateral brain involvement characteristic of the disorder. Treatment with high-dose steroids, plasma exchange, or IVIG can ameliorate symptoms in early stages of the disease. Multiple different approaches with immunotherapy, including rituximab, tacrolimus, azathioprine, adalimumab, mycophenolate mofetil, natalizumab, or anakinra have not substantially changed the poor outcome of most patients. The most effective treatment for control of the seizures is functional hemispherectomy, which consists of surgical disconnection of the affected hemisphere.

OTHER SUSPECTED TYPES OF AUTOIMMUNE ENCEPHALITIS

Vasculitis of the CNS and rheumatic diseases associated with autoimmune mechanisms that can result in encephalitis are discussed in [Chapter 642](#).

Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) is discussed in [Chapter 468.3](#).

The term **basal ganglia encephalitis** is used to describe patients with predominant or isolated involvement of the basal ganglia. These patients typically have abnormal movements such as dystonia, chorea, or parkinsonism and neuropsychiatric disease. Although these clinical manifestations may have multiple etiologies, including metabolic, toxic, genetic, and infectious processes, an immune-mediated etiology has been postulated in some patients. There have been no clinical trials, but case reports and small noncontrolled case series describe the potential benefit of immunotherapy. Antibodies against the dopamine-2 receptor have been infrequently identified in these patients.

Pseudomigraine syndrome with CSF pleocytosis (PMP) or headache with neurologic deficits and CSF lymphocytosis (HaNDL) is an ill-defined entity that predominantly affects young male adults with a family history of migraine, although adolescents can be affected. This syndrome is characterized by repeat episodes of severe headache with transient neurologic deficits, accompanied by aseptic CSF lymphocytosis and a normal brain MRI. Patients frequently show a high CSF opening pressure, an elevated CSF protein concentration, and focal EEG slowing, which normalize after the episodes of headache. Because of the inflammatory characteristics of the CSF and the high prevalence of prodromal viral-like symptoms, an infectious-immune-mediated mechanism has been proposed. Other theories include spreading cortical depression and trigeminal-vascular activation.

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Chapter 639

Neurodegenerative Disorders of Childhood

Kristin A. Seaborg and Jennifer M. Kwon

Neurodegenerative disorders of childhood encompass a large, heterogeneous group of diseases caused by specific genetic and biochemical defects. Although many children with neurodegenerative disorders first present with developmental delay or seizures, the hallmark of a neurodegenerative disease is **regression and progressive deterioration** of neurologic function with loss of speech, vision, hearing, locomotion, feeding difficulties, and cognitive decline. The age of onset, rate of progression, and principal neurologic findings determine whether the disease affects primarily the white or the gray matter. Upper motor neuron signs and progressive spasticity are the hallmarks of white matter disorders; convulsions and intellectual and visual impairments that occur early in the disease course are the hallmarks of gray matter disorders. A precise history confirms regression or delay of developmental milestones, and the neurologic examination localizes the process within the nervous system. At that point, modern neuroimaging techniques and specific biochemical and molecular diagnostic tests are used to arrive at a diagnosis. Although available therapies are often limited, it is important to make the correct diagnosis so that genetic counseling may be offered and prevention strategies can be implemented. Bone marrow transplantation, enzyme replacement therapies, cell-based gene therapy, immune modulation, and dietary restrictions may prevent the progression of disease in certain individuals who are either presymptomatic or very early in their disease course. For all conditions in which the specific genetic defect is known, prevention by prenatal diagnosis through chorionic villus sampling or amniocentesis is possible, as is carrier detection. [Table 639.1](#) summarizes selected inherited neurodegenerative and metabolic disorders by their usual age of onset.

639.1 Sphingolipidoses

Kristin A. Seaborg and Jennifer M. Kwon

The sphingolipidoses are characterized by intracellular storage of lipid substrates resulting from defective catabolism of the sphingolipids comprising cellular membranes ([Fig. 639.1](#)). Poorly degraded sphingolipids accumulate in neuronal lysosomes leading to cellular dysfunction and death. There are multiple sphingolipidoses, including Niemann-Pick disease, Gaucher disease, GM₁ gangliosidosis, GM₂ gangliosidosis, Krabbe disease (KD), and metachromatic leukodystrophy. Niemann-Pick disease and Gaucher disease are discussed in [Chapter 106.4](#).

GANGLIOSIDOSSES

See also [Chapter 106.4](#).

Gangliosides are sphingolipids consisting of an oligosaccharide chain attached to a hydroxyl group of ceramide and sialic acid bound to galactose. The gangliosides are catabolized by sequential cleavage of the sugar molecules by specific exoglycosidases. Abnormalities in catabolism result in an accumulation of the ganglioside within the cell, resulting in disease. Defects in ganglioside degradation include GM₁ gangliosidosis and the GM₂ gangliosidoses.

GM₁ Gangliosidosis

GM₁ gangliosidosis is an autosomal recessive condition caused by deficiency of acid β -galactosidase from pathogenic variants in *GLB1*. It is further classified by age at presentation: infantile (type I), juvenile (type II), and adult (type III), where the age of onset and severity

Table 639.1 Selected Metabolic Conditions Associated with Developmental Regression

AGE AT ONSET (YR)	CONDITIONS	COMMENTS
<2, often with hepatomegaly or hepatic effects	Fructose intolerance	Vomiting, hypoglycemia, poor feeding, failure to thrive (when given fructose)
	Galactosemia	Lethargy, hypotonia, icterus, cataract, hypoglycemia (when given lactose)
	Glycogenosis (glycogen storage disease) types I-IV	Hypoglycemia, cardiomegaly (type II)
	Mucopolysaccharidosis types I and II	Coarse facies, stiff joints
	GM ₁ gangliosidosis	Coarse facies, macroglossia, cherry-red spot in macula
	Niemann-Pick disease, infantile type	Gray matter disease, failure to thrive
	Zellweger syndrome	Hypotonia, high forehead, flat facies
	Gaucher disease (neuronopathic form)	Extensor posturing, irritability
	Carbohydrate-deficient glycoprotein syndromes	Dysmyelination, cerebellar hypoplasia
<2, without hepatomegaly	Krabbe disease	Irritability, extensor posturing, optic atrophy, and blindness
	Rett syndrome	Girls with deceleration of head growth, loss of hand skills, hand wringing, impaired language skills, gait apraxia
	Maple syrup urine disease	Poor feeding, tremors, myoclonus, opisthotonos
	Phenylketonuria	Light pigmentation, microcephaly
	Menkes kinky hair disease	Hypertonia, irritability, seizures, abnormal hair
	Tay-Sachs disease, GM ₂ gangliosidosis	Seizures, cherry-red spot of macula, increased startle response
	Subacute necrotizing encephalopathy or Leigh disease	White matter disease, basal ganglia, brainstem lesions
	Canavan disease	White matter disease, macrocephaly
	Neurodegeneration with brain iron accumulation disease (see Table 639.4)	Cerebellar atrophy, optic atrophy, iron accumulation in basal ganglia, movement disorder
2-5	Niemann-Pick disease types III and IV	Hepatosplenomegaly, gait difficulty
	Wilson disease	Liver disease, Kayser-Fleischer ring; deterioration of cognition is late
	Neuronal ceroid lipofuscinosis	Gray matter disease
	Mitochondrial encephalopathies (e.g., myoclonic epilepsy with ragged red fibers [MERRF])	Gray matter disease
	Ataxia-telangiectasia	Basal ganglia disease
	Neurodegeneration with brain iron accumulation syndrome	Basal ganglia disease
	Metachromatic leukodystrophy	White matter disease
	Adrenoleukodystrophy	White matter disease, behavior problems, deteriorating school performance, vision loss
5-15	Adrenoleukodystrophy	Same as for adrenoleukodystrophy in 2- to 5-yr-olds
	Neuronal ceroid lipofuscinosis, juvenile and adult forms	Gray matter disease
	Refsum disease	Peripheral neuropathy, ataxia, retinitis pigmentosa
	Sialidosis II, juvenile form	Cherry-red macula, myoclonus, ataxia, coarse facies

Adapted from Kliegman RM, Greenbaum LA, Lye PS, eds. *Practical Strategies in Pediatric Diagnosis and Therapy*, 2nd ed. Philadelphia: Elsevier; 2004:542.

depends on the degree of β -galactosidase deficiency. Diagnosis can be made by enzyme assay or by identification of biallelic pathogenic variants in *GLB1* by molecular genetic testing. Prenatal diagnosis is possible by enzyme or direct molecular testing of cultured amniotic cells.

Infantile GM₁ gangliosidosis presents during the neonatal period with poor sucking and inadequate weight gain. Development is delayed,

and generalized seizures are prominent. The phenotype is characterized by coarse facial features, prominent forehead, depressed nasal bridge, large tongue (macroglossia), and gum hypertrophy. There is early hepatosplenomegaly from intracellular accumulation of foamy histiocytes and kyphoscoliosis from anterior beaking of the vertebral bodies. The neurologic examination is notable for progressive blindness, deafness,

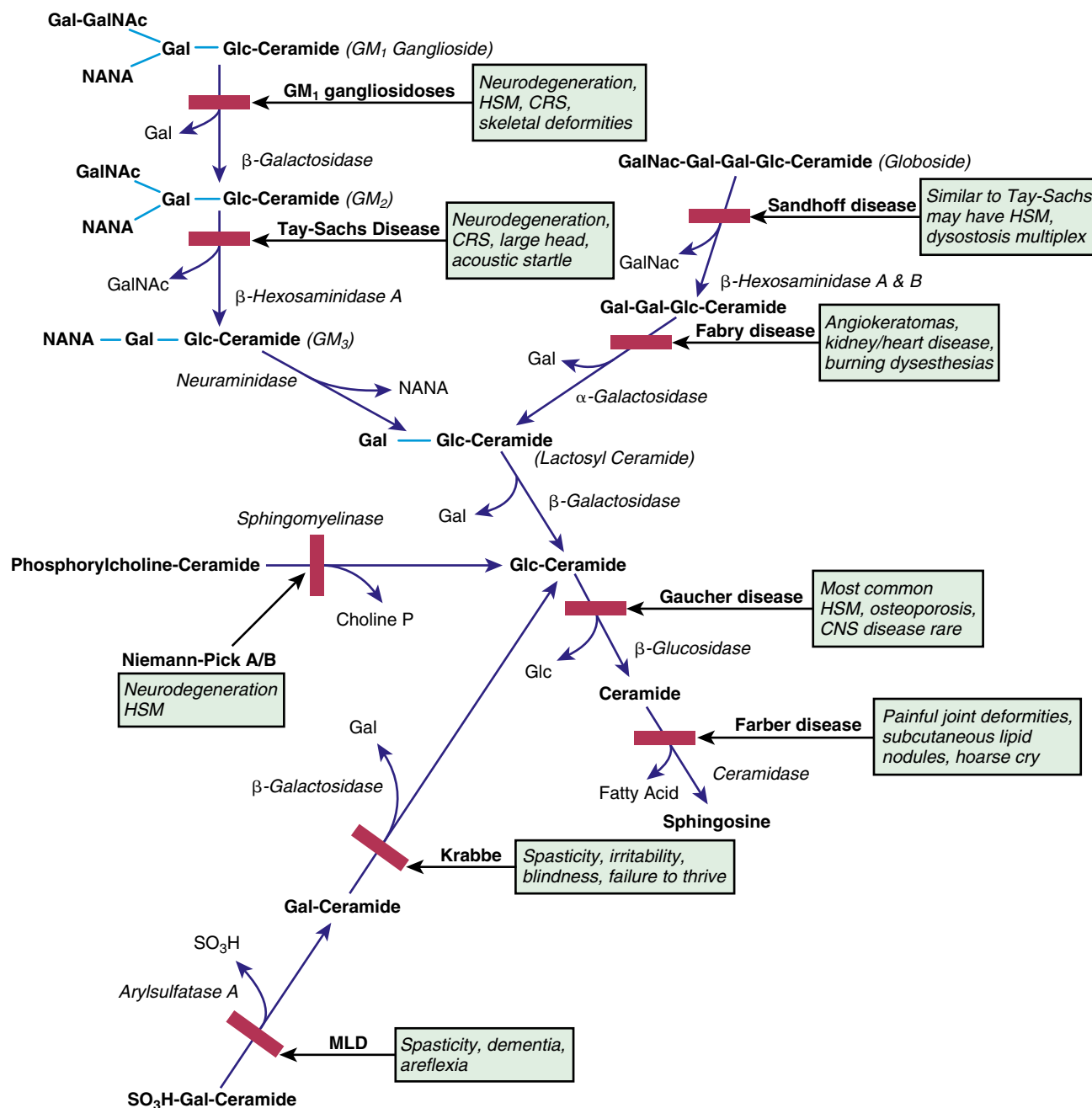


Fig. 639.1 Sphingolipid degradation pathway showing the sites of enzyme deficiencies and their associated disorders. Sphingolipids are composed of a ceramide backbone with oligosaccharide side chains. CRS, cherry-red spot (retinal); Gal-, galactosyl-; GalNAc, N-acetyl-galactose; Glc-, glucosyl-; HSM, hepatosplenomegaly; MLD, metachromatic leukodystrophy; NANA, N-acetyl-neuraminic acid.

spastic quadriplegia, and decerebrate rigidity. A cherry-red spot in the macula is visualized in approximately 50% of cases (Fig. 639.2). Treatment is supportive, and children rarely survive beyond age 2-3 years. Death is often from aspiration pneumonia.

Type II GM₁ gangliosidosis presents later in infancy, before 3 years. Initial symptoms consist of weakness, ataxia, and regression of language. Thereafter, convulsions, spasticity, decerebrate rigidity, and blindness are the major findings. Unlike type I, coarse facial features and hepatosplenomegaly are not usually seen. Lumbar vertebrae may show minor beaking. Children rarely survive beyond 10 years of age. **Adult GM₁ gangliosidosis** is a slowly progressive disease with onset between ages 3 and 30 years consisting of spasticity, ataxia, dysarthria, cardiomyopathy, and a gradual loss of cognitive function.

GM₂ Gangliosidoses

The GM₂ gangliosidoses are a heterogeneous group of autosomal recessive disorders caused by abnormal catabolism of the GM₂ ganglioside, which accumulates in neuronal lysosomes. GM₂ catabolism requires functional isoenzymes β -hexosaminidase and GM₂ activator protein. Tay-Sachs disease (TSD), Sandhoff disease, juvenile GM₂ gangliosidosis, and adult GM₂ gangliosidosis are caused by genetic variants in the genes that encode the alpha and beta subunits of β -hexosaminidase and lead to decreased or absent β -hexosaminidase activity with subsequent accumulation of GM₂.

TSD is most prevalent in the Ashkenazi Jewish population, with an approximate carrier rate of 1 in 30 Jews in the United States. TSD is caused by pathogenic variants in *HEXA* on chromosome 15q23, which

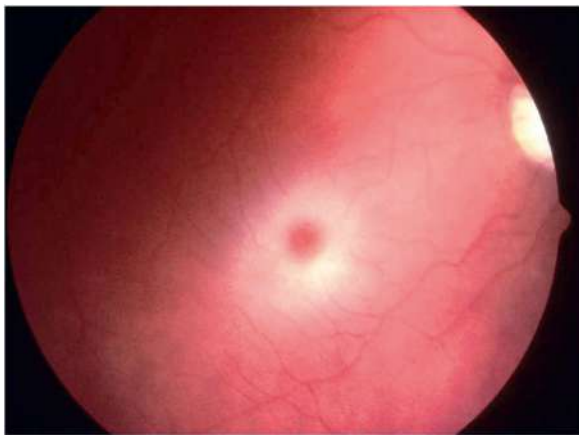


Fig. 639.2 A cherry-red spot in a patient with GM₁ gangliosidosis. Note the whitish ring of sphingolipid-laden ganglion cells surrounding the fovea. (From Leavitt JA, Kotagal S. The “cherry red” spot. *Pediatr Neurol.* 2007;37:74–75, Fig. 1.)

encodes the α subunit of β -hexosaminidase. Affected infants often have a *marked startle reaction* to noise that is evident soon after birth but otherwise have normal development until ~6 months of age. They then begin to lag in developmental milestones and gradually lose the ability to stand, sit, and vocalize by age 1. Children with TSD have earlier onset of dysphagia than children with other GM₂ gangliosidoses. Early hypotonia develops into progressive spasticity and relentless deterioration follows, with convulsions, blindness, deafness, and cherry-red spots in almost all patients (see Fig. 639.2). Macrocephaly becomes apparent by 1 year of age and results from the 200- to 300-fold normal content of GM₂ ganglioside deposited in the brain. Few children live beyond 3–4 years of age, and death is usually associated with aspiration or bronchopneumonia.

To diagnose TSD or any of the GM₂ gangliosidoses, a deficiency of the isoenzyme β -hexosaminidase is found in blood, serum, or fibroblasts. In addition, molecular genetic testing may be done to evaluate for variants in the *HEXA* or *HEXB* gene to confirm the diagnosis.

Sandhoff disease occurs secondary to a variant *HEXB* gene located on chromosome 5q13. Affected infants present very similar to TSD, including progressive loss of motor and language milestones beginning at 6 months of age. Unlike children with TSD, children with Sandhoff disease may also have visceromegaly. The visual evoked potentials (VEPs) are normal early in the course of Sandhoff disease and TSD but become abnormal or absent as the disease progresses. The auditory brainstem responses show prolonged latencies. The diagnosis of Sandhoff disease is established by finding deficient levels of hexosaminidases A and B in serum and leukocytes. Children usually die by 3 years of age.

Juvenile GM₂ gangliosidosis develops in mid-childhood, initially with clumsiness followed by ataxia. Signs of spasticity, athetosis, loss of language, and seizures gradually develop. Progressive visual loss is associated with optic atrophy, but cherry-red spots rarely occur in juvenile GM₂ gangliosidosis. A deficiency of hexosaminidase is variable (total deficiency to near normal) in these patients. Death occurs around 15 years of age.

Although the genetic etiologies of the gangliosidoses are well-established, there is currently no known treatment for these disorders other than supportive management and palliative care. An adeno-associated virus-*HEXA*/*HEXB*-directed gene therapy proof-of-concept trial has been performed in two children with TSD.

KRABBE DISEASE (GLOBOID CELL LEUKODYSTROPHY)

Krabbe disease (KD) is a rare autosomal recessive neurodegenerative disorder characterized by severe myelin loss and the presence of globoid bodies in the white matter. The gene for KD (*GALC*) is located on chromosome 14q24.3–q32.1. The disease results from a marked deficiency of the lysosomal enzyme galactocerebroside β -galactosidase

(*GALC*). KD is a disorder of myelin destruction rather than abnormal myelin formation. Normally, myelination begins in the third trimester, corresponding with a rapid increase of *GALC* activity in the brain. In patients with KD, galactocerebroside cannot be metabolized during the normal turnover of myelin because of deficiency of *GALC*. Nonmetabolized galactocerebroside stimulates the formation of globoid cells, which can be cytotoxic to oligodendrocytes. Because oligodendroglial cells are responsible for the elaboration of myelin, their loss results in myelin breakdown, thus producing additional galactocerebroside and causing a vicious circle of myelin destruction.

Myelin exists in both the central and peripheral nervous system and allows for rapid conduction along axons. With *GALC* deficiency and associated rapid and severe demyelination, the symptoms of KD become evident in the first few months of life and include excessive irritability and crying, poor head control, episodes of hyperpyrexia, vomiting, and difficulty feeding. In the initial stage of KD, children are often treated for colic or milk allergy with frequent formula changes. Generalized seizures may appear early in the course of the disease. Alterations in body tone with rigidity and opisthotonos as well as visual inattentiveness caused by optic atrophy become apparent as the disease progresses. In the later stages of the illness, blindness, deafness, absent deep tendon reflexes, autonomic instability, and decerebrate rigidity constitute the major physical findings. Most patients die by 2 years of age. MRI and magnetic resonance spectroscopy are useful for evaluating the extent of demyelination in KD. Umbilical cord blood (stem cell) transplantation from unrelated donors in asymptomatic babies may favorably alter the natural history but will not help patients who already have neurologic symptoms. Recombinant *GALC* triggers an immune reaction, and the large protein does not efficiently cross the blood-brain barrier.

Late-onset KD has been described beginning in childhood or adolescence. Patients present with pes cavus, sensorimotor demyelinating neuropathy, optic atrophy, and cortical blindness; their condition may be confused with adrenoleukodystrophy. Slowly progressive gait disturbances, including spasticity and ataxia, are prominent. Globoid cells are abundant in the white matter, and leukocytes are deficient in *GALC*. MRI may reveal white matter lesions. An examination of the cerebrospinal fluid shows an elevated protein content, and the nerve conduction velocities are markedly delayed as a result of segmental demyelination of the peripheral nerves.

METACHROMATIC LEUKODYSTROPHY

This disorder of myelin metabolism is inherited as an autosomal recessive trait and is characterized by a deficiency of arylsulfatase A activity. The *ARSA* gene is located on chromosome 22q13.33. The absence or deficiency of arylsulfatase A leads to accumulation of cerebroside sulfate within the myelin in both the central and peripheral nervous systems, and the excessive cerebroside sulfate is thought to cause myelin breakdown. Prenatal diagnosis of metachromatic leukodystrophy (MLD) is made by assaying arylsulfatase A activity in chorionic villi or cultured amniotic fluid cells. Those affected with MLD are generally classified according to age of onset: late infantile, juvenile, and adult.

Late infantile MLD begins with insidious onset of gait disturbances between 1 and 2 years of age. The child initially appears awkward and frequently falls, but locomotion is gradually impaired significantly and support is required to walk. The extremities are hypotonic, and the deep tendon reflexes are absent or diminished. Within the next several months, the child can no longer stand, and deterioration in intellectual function becomes apparent. The speech is slurred and dysarthric, and the child appears dull and apathetic. Visual fixation is diminished, nystagmus is present, and examination of the retina shows optic atrophy. Within 1 year from the onset of the disease, the child is unable to sit unsupported, and progressive decorticate postures develop. Feeding and swallowing are impaired because of pseudobulbar palsies. Affected children develop seizures and painful muscle spasms and generalized irritability. Patients ultimately become stuporous and die of aspiration or bronchopneumonia by age 5–6 years. Neurophysiologic evaluation shows slowing of peripheral nerve conduction velocities caused by

peripheral myelin damage and progressive changes in the VEPs, auditory brainstem responses, and somatosensory evoked potentials. CT and MRI images of the brain indicate diffuse symmetric attenuation of the cerebellar and cerebral white matter, and examination of the cerebrospinal fluid shows an elevated protein content.

Late infantile MLD is characterized by little to no functional aryl-sulfatase A, resulting in rapid accumulation of sulfatides and disease progression. Bone marrow transplant or lentiviral autologous hematopoietic stem cell gene (ARSA-cDNA) therapy is a promising experimental therapy for the management of late infantile MLD patients identified very early in the course of their disease.

Juvenile MLD has many features in common with late infantile MLD, but the onset of symptoms is delayed to 5-10 years of age. Deterioration in school performance and alterations in personality may herald the onset of the disease. This is followed by incoordination of gait, urinary incontinence, and dysarthria. Muscle tone becomes increased, and ataxia, dystonia, tremor, or diminished deep tendon reflexes may be present. In the terminal stages, generalized tonic-clonic convulsions are prominent and are difficult to control. Patients rarely live beyond mid-adolescence. Patients with juvenile MLD usually have one functional copy of ARSA with some residual enzyme activity.

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639.2 Neuronal Ceroid Lipofuscinoses

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The neuronal ceroid lipofuscinoses (NCLs) are a group of inherited, neurodegenerative, **lysosomal storage disorders** characterized by visual loss, progressive dementia, seizures, motor deterioration, and early death. The NCLs are named because of the intracellular accumulation of fluorescent lipopigments ceroid and lipofuscin. They comprise a genetically and phenotypically heterogeneous group of disorders (currently there are at least 14 NCL types) that have traditionally been subclassified by age of onset, among other clinical features. With the exception of CLN4 (Parry disease), which is transmitted as an autosomal dominant trait, all other types of NCL are autosomal recessive. They differ from one another in the associated ultrastructural patterns of the inclusions as seen by electron microscopy. With the advent of enzymatic and molecular testing methods, clinicians can make specific NCL diagnoses using genetic and biochemical testing (Table 639.2).

Table 639.2 NCL of Childhood Onset: Clinical Classification and Major Diagnostic Procedure

CLINICAL FORM	AGE OF ONSET	DISEASE	GENE	DIAGNOSIS	MAJOR SYMPTOMS AT ONSET
Congenital	Birth	CLN10	CLN10/CTSD	NGS Enzymatic assay	Microcephaly, dysmorphic features, seizures, hyperkinetic movements
Infantile	6-18 mo	CLN1	CLN1/PPT1	NGS enzymatic assay	Decreased head growth, neurodevelopmental regression, seizures
		CLN10	CLN10/CTSD	NGS enzymatic assay	Decreased head growth, neurodevelopmental regression
		CLN14	CLN14/KCDT7	NGS	Decreased head growth, seizures (myoclonus)
		LATE INFANTILE			
Classical	2-4 yr	CLN2	TPP1	NGS enzymatic assay	Seizures, ataxia, visual loss, delayed language development
Variant	2-5 yr	CLN1	CLN1/PPT1	NGS enzymatic assay	Seizures, neurodevelopmental regression, behavioral disturbances
		CLN5	CLN5	NGS	Impaired learning and cognition
		CLN6	CLN6	NGS	Seizures, ataxia, delayed language development
		CLN7	CLN7/MFSD8	NGS	Seizures, visual loss, motor and cognitive regression
		CLN8	CLN8	NGS	Seizures, visual loss, motor and cognitive regression
JUVENILE					
Classical	3-5 yr	CLN3	CLN3	NGS	Visual loss, behavioral problems, cognitive decline
	5-7 yr	CLN5	CLN5	NGS	Motor and cognitive regression, behavioral problems
	5-7 yr	CLN1	CLN1/PPT1	NGS enzymatic assay	Visual loss, cognitive decline
Late	8-12 yr	CLN6 CLN10	CLN6 CLN10/CTSD	NGS NGS enzymatic assay	Myoclonic seizures, cognitive decline; ataxia, cognitive decline, visual loss
	13-16 yr	CLN12	ATP13A2	NGS	Rigidity, hypokinesia

NSG, Next-generation sequencing.

From Simonati A, Williams RE. Neuronal ceroid lipofuscinosis: the multifaceted approach to the clinical issues, an overview. *Frontiers Neurol.* 2022;13:Article 811686, Table 1.

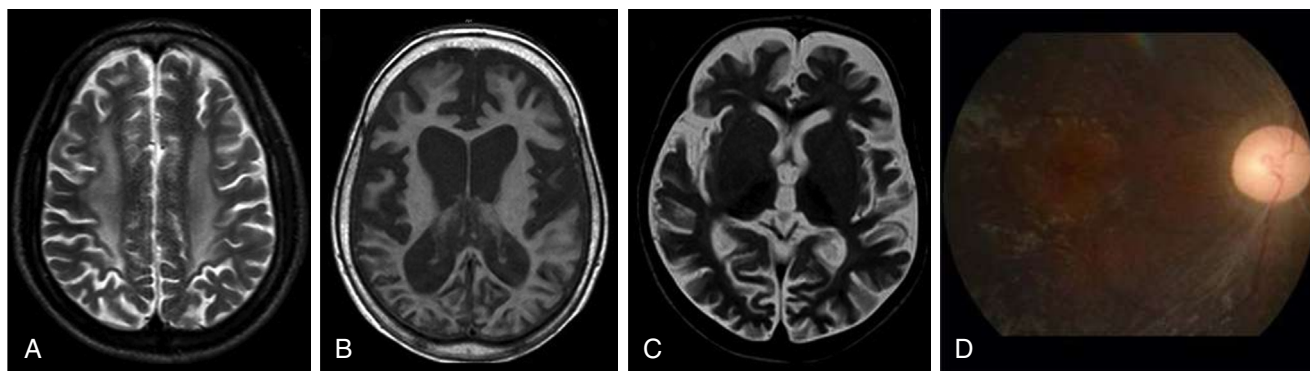


Fig. 639.3 A, T2-weighted (axial) image showing leukoencephalopathy in a child with late infantile neuronal ceroid lipofuscinoses (NCL). B, T1-weighted (axial) sequence revealing diffuse atrophy in a child with late infantile NCL. C, A child with late infantile NCL with cerebellar atrophy in T2-weighted axial section of the brain. D, Fundus photograph showing atypical retinitis pigmentosa with optic atrophy in a child with juvenile NCL. (Modified from Jadav RH, Sinha S, Yasha TC, et al. *Clinical, electrophysiological, imaging, and ultrastructural description in 68 patients with neuronal ceroid lipofuscinoses and its subtypes*. *Pediatr Neurol*. 2014;50:85–95, Fig. 1, p. 88.)

Infantile-type neuronal ceroid lipofuscinosis (ICLN, Santavuori disease) begins in the first year of life with developmental delay, myoclonic seizures, intellectual deterioration, and blindness. Optic atrophy and brownish discoloration of the macula are evident on examination of the retina, and cerebellar ataxia is prominent. The infantile form is caused by recessive pathogenic variants of the gene for the lysosomal enzyme palmitoyl-protein thioesterase-1 (PPT1) on chromosome 1p32. A number of cell types in INCL patients show characteristic intracellular fine granular osmiophilic deposits discernible by electron microscopy.

Although death typically occurs during early childhood, a subset of children with PPT1 enzyme deficiency has a much less severe course with clinical features resembling those of the juvenile-onset NCL patients. Clinically, these variant INCL patients have a course that is often quite distinct from the typical, classic, rapidly degenerating infantile form, yet they have PPT1 deficiency and granular osmiophilic deposits on pathology. There is no clear *CLN1* genotype that predicts severity of phenotype.

Late infantile-type neuronal ceroid lipofuscinosis (LINCL, Jansky-Bielschowsky) is the second most common type of NCL and generally presents with myoclonic seizures beginning between 2 and 4 years of age in a previously normal child. Dementia and ataxia are combined with a progressive loss of visual acuity and microcephaly. Examination of the retina shows marked attenuation of vessels, optic atrophy, and a subtle brown pigment in the macular region, with associated visual changes early in the course of disease (Fig. 639.3). The autofluorescent material is deposited in neurons, fibroblasts, and secretory cells.

LINCL can be caused by autosomal recessive variants of several different genes: *CLN2* gene, which codes for a tripeptidyl peptidase-1 (TPP1) that is essential for the degradation of cholecystokinin-8, as well as the *CLN5*, *CLN6*, *CLN8*, and *CLN14* genes, which code for membrane proteins that have not been completely characterized. *CLN8* is also known as *locus of northern epilepsy syndrome*, which is often called *progressive epilepsy with cognitive impairment*.

At this time, there is only one clinically approved treatment for all types of NCL. *CLN2* can be treated with *intraventricular* cerliponase alfa, a recombinant human proenzyme of TPP1. Treatment with cerliponase alfa can attenuate motor and language decline but does not alter visual symptoms. Stem cell therapy, gene therapy, and immunomodulatory therapy to repair genetic variants or alter adaptive immunoresponses are all in preclinical studies for adjunctive treatment of NCL.

Juvenile-type neuronal ceroid lipofuscinosis (JNCL, Spielmeier-Vogt or Batten disease) is the most common form of NCL disease and is generally caused by autosomal recessive variants in *CLN3*. Children affected with JNCL tend to develop normally for the first 5 years of life. Their initial symptom is usually progressive visual loss, and their retinal pigmentary changes often result in an initial diagnosis of retinitis pigmentosa. The fundoscopic changes are similar to those for LINCL. After disease onset, there may be a rapid decline with changes in cognition and personality, motor incoordination, and seizures. Myoclonic seizures are not as prominent as in LINCL, but parkinsonism can

develop and impair ambulation. Patients die in their late 20s to early 30s. In JNCL caused by *CLN3*, the electron microscopy of tissues shows deposits called *fingerprint profiles*, and routine light microscopy of a peripheral blood smear may show lymphocyte vacuoles.

A possible mimic of JNCL is **Lafora disease (LD)** caused by pathogenic variants in *EPM2A* and *EPM2B*. LD also has skin (eccrine) inclusion bodies in addition to seizures, myoclonus, ataxia, dysarthria, progressive loss of milestones, and death within 10 years of onset. The diseases can be distinguished by specific gene sequencing.

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639.3 Adrenoleukodystrophy

See Chapter 106.2.

639.4 Sialidosis

Kristin A. Seaborg and Jennifer M. Kwon

Sialidosis is the result of lysosomal sialidase deficiency secondary to an autosomal recessive pathogenic variant in the sialidase (α -neuraminidase, *NEU1*) gene on chromosome 6p21.3. Up to 40 pathologic variants of *NEU1* have been identified. The accumulation of sialic acid–oligosaccharides with markedly increased urinary excretion of sialic acid–containing oligosaccharides is associated with clinical presentations that range from the milder sialidosis type I to the more severe sialidosis type II.

Sialidosis type I, cherry-red spot myoclonus syndrome, usually presents in the second decade of life, when a patient complains of visual deterioration. Inspection of the retina shows a cherry-red spot, but, unlike patients with TSD, visual acuity declines slowly in individuals with cherry-red spot myoclonus syndrome. Myoclonus of the extremities is gradually progressive and eventually renders patients nonambulatory. The myoclonus is triggered by voluntary movement, touch, and sound and is not controlled with anticonvulsants. Generalized convulsions responsive to antiseizure medications occur in most patients.

Sialidosis type II patients present at a younger age and have cherry-red spots and myoclonus, as well as somatic involvement, including coarse facial features, hepatosplenomegaly, corneal clouding (rarely), and dysostosis multiplex, producing anterior beaking of the lumbar vertebrae. Type II patients may be further subclassified into congenital and infantile (childhood) and juvenile forms, depending on the age of onset and severity. Examination of lymphocytes shows vacuoles in the cytoplasm, biopsy of the liver demonstrates cytoplasmic vacuoles in Kupffer cells, and membrane-bound vacuoles are found in Schwann cell cytoplasm, all attesting to the multiorgan nature of sialidosis type II. Identification of genetic variants in the *NEU1* gene can confirm the diagnosis.

Some cases of what appears to be sialidosis type II are the result of combined deficiencies of β -galactosidase and α -neuraminidase resulting from deficiency of protective protein/cathepsin A that prevents premature intracellular degradation of these two enzymes. These patients have galactosialidosis, and they are clinically indistinguishable from those with sialidosis type II. Consequently, patients who have features of sialidosis type II with marked urinary excretion of oligosaccharides should be tested for protective protein/cathepsin A deficiency as well as sialidase deficiency.

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639.5 Miscellaneous Neurodegenerative Disorders

Kristin A. Seaborg and Jennifer M. Kwon

PELIZAEUS-MERZBACHER DISEASE

Pelizaeus-Merzbacher disease (PMD) is an X-linked recessive disorder characterized by nystagmus and abnormalities of myelin. PMD is caused by gene variants in the *PLP1* gene on chromosome Xq22, which is essential for CNS myelin formation and oligodendrocyte differentiation. Different variants in the same gene can cause a spectrum of disorders, ranging from the milder **familial spastic paraparesis** (progressive spastic paraparesis type 2, SPG2) to the more severe congenital form associated with rapid neurologic decline from an early age and death in the first decade of life. *PLP1* variants causing disease include point changes, deletions, gene duplications, and other gene dosage variants.

Classic PMD is the most common type, clinically recognized by nystagmus and roving eye movements along with head nodding during infancy. Developmental milestones are delayed; ataxia, choreoathetosis, and spasticity ultimately develop. Optic atrophy and dysarthria are associated findings, and death occurs in the second or third decade. The major pathologic finding is a loss of myelin with intact axons, suggesting a defect in the function of oligodendroglia. An MRI scan shows a symmetric pattern of delayed myelination. The final diagnosis can be made through genetic testing for variants in the *PLP1* gene.

Other PMD-like, hypomyelinating leukodystrophies continue to be identified and should be considered in the differential diagnosis of PMD. These include Allan-Herndon-Dudley syndrome, *TUBB4A*-related disorders, and hypomyelinating leukodystrophy 7 or 8.

ALEXANDER DISEASE

This is a rare disorder that causes progressive macrocephaly and leukodystrophy. Alexander disease is caused by dominant pathogenic variants in the *GFAP* gene on chromosome 17q21; cases are usually sporadic. Pathologic examination of the brain discloses deposition of eosinophilic hyaline bodies called *Rosenthal fibers* in astrocyte processes. In the classic infantile form of Alexander disease (**type I**), degeneration of white matter is most prominent frontally. The diagnosis may be suggested by MRI (Fig. 639.4) and MR spectroscopy demonstrating abnormal metabolic substrates. Affected children develop progressive loss of intellect, spasticity, and treatment-resistant seizures causing death by 5 years of age. Patients with **type II** Alexander disease present later in life and may not have the characteristic frontal predominance or megalencephaly. Most patients with type II Alexander disease develop ataxia, and approximately 50% develop difficulty with speech or swallowing.

CANAVAN SPONGY DEGENERATION

See Chapter 105.15.

OTHER LEUKODYSTROPHIES

Metabolic and degenerative disorders can present with significant cerebral white matter changes, such as some mitochondrial disorders (see Chapters 106.1 and 108) and glutaric aciduria type 1. In addition, the broader use of brain MRI has brought to light new leukodystrophies.

One example is vanishing white matter disease or childhood ataxia with central nervous system (CNS) hypomyelination characterized by ataxia and spasticity (Fig. 639.5). Some patients also have optic

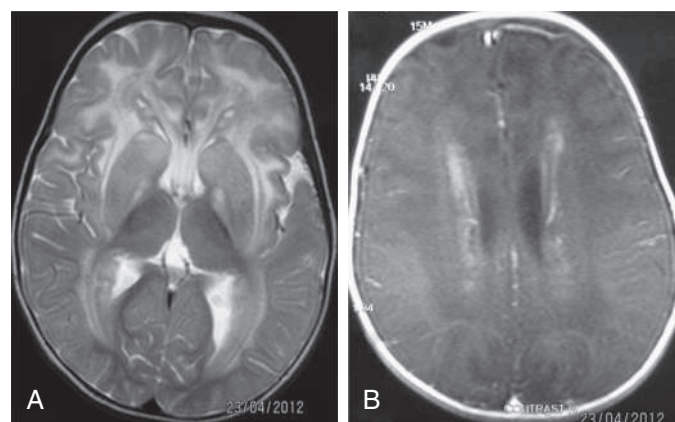


Fig. 639.4 Alexander disease. MRI of the index patient at the age of 15 mo. A, Axial T2-weighted sequences (TR/TE: 4000/99) at the basal ganglia and thalamus level demonstrating diffuse bilateral, symmetric increased signal predominantly of the frontal periventricular but also of the subcortical, white matter and the basal ganglia. B, Significant periventricular rim after intravenous gadolinium infusion (T1-weighted sequences; TR/TE: 400/88). (From Zafeiriou DI, Dragoumi P, Vargiami E. Alexander disease. *J Pediatr*. 2013;162:648.)

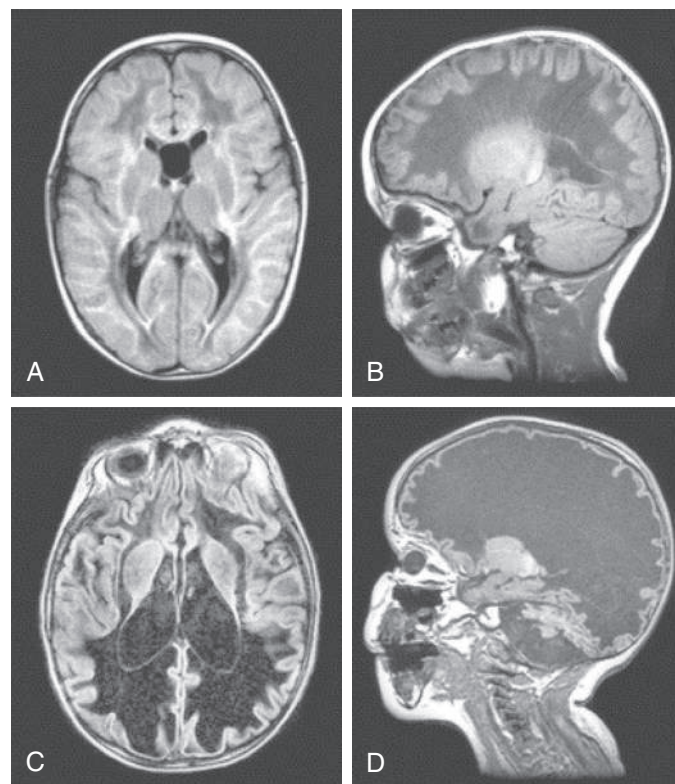
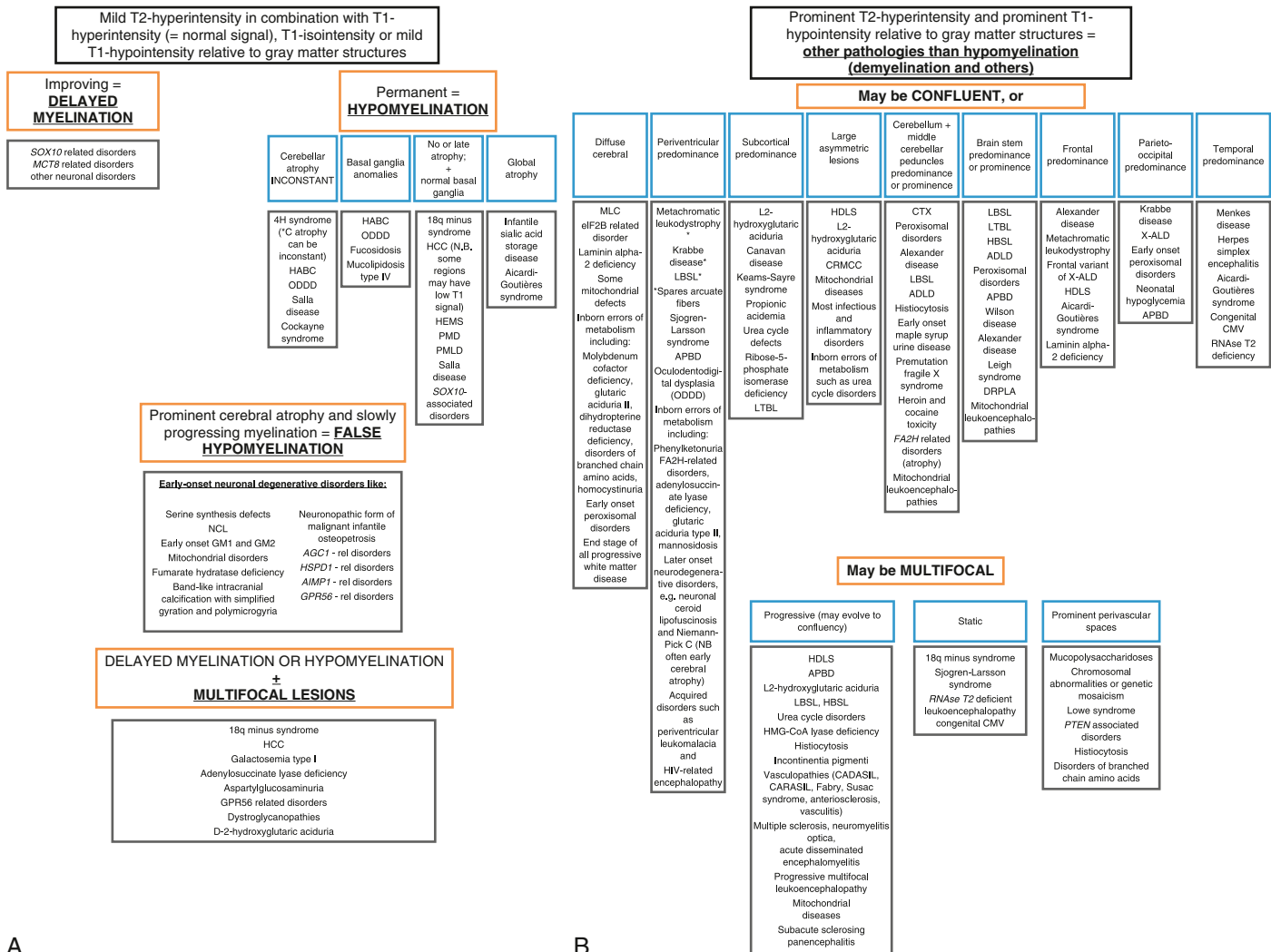


Fig. 639.5 T1-weighted and FLAIR images of a patient with vanishing white matter disease. Axial FLAIR (A, C) and sagittal T1-weighted (B, D) images of a patient at ages 1½ and 2½ yr. The first MRI (A, B) was obtained soon after the onset of symptoms. The initial FLAIR image (A) shows diffuse abnormality and partial cystic degeneration of the cerebral white matter, whereas the follow-up FLAIR image (C) shows that all of the cerebral white matter has been replaced by fluid. The initial T1-weighted sagittal image (B) shows the typical striplike pattern within the abnormal white matter, whereas the follow-up image (D) shows that all of the cerebral white matter has disappeared and that only the cerebral cortex and ependymal lining are preserved. The cerebellum has become highly atrophic. (A, C from Van der Knaap MS, Valk J. *Magnetic Resonance of Myelination and Myelin Disorders*, 3rd ed. Heidelberg: Springer; 2005, Fig 65.3; B, D from van der Knaap MS, Pronk JC, Scheper GC. Vanishing white matter disease. *Lancet Neurol*. 2006;5:413-423. Fig. 3.)

atrophy, seizures, and cognitive deterioration. Symptoms worsen rapidly after episodes of fever, head trauma, or external stressors. The age of presentation and the rapidity of decline in leukodystrophies can be quite variable. In the early-onset forms, decline is usually rapid and followed quickly by death; in the later-onset forms, mental decline is usually slower and milder. Interestingly, acute demyelination in these disorders can be triggered by fever or fright. The diagnosis of vanishing white matter disease or childhood ataxia with CNS hypomyelination is

based on clinical findings, characteristic abnormalities on cranial MRI, and autosomal recessive gene variants in one of five causative genes (*EIF2B1*, *EIF2B2*, *EIF2B3*, *EIF2B4*, and *EIF2B5*) encoding the five subunits of the eukaryotic translation initiation factor, eIF2B, which regulates cellular protein synthesis. An approach to leukodystrophies based on MRI findings is noted in Figure 639.6 and associated clinical features in Figure 639.7, and the diagnostic evaluation is noted in Table 639.3.



A

B

Fig. 639.6 MRI pattern recognition in the leukodystrophies and genetic leukoencephalopathies (gLEs). Three major MRI characteristics help to discriminate between the different types of leukodystrophy and gLE. The first discriminator is the presence or absence of *hypomyelination* (A). Within this subset, the presence of improvement of myelination or atrophy directs the clinician toward a series of gLEs. Within the true hypomyelinating leukodystrophies, the presence of basal ganglia and cerebellar involvement further helps refine the diagnosis. If the pattern is not one of hypomyelination, then the second discriminator is whether the white matter abnormalities are *confluent* or *isolated* and *multifocal* (B). If the white matter abnormalities are confluent, then the third discriminator is the *predominant localization of the abnormalities* (B). 4H, Hypomyelination, hypodontia, and hypogonadotropic hypogonadism; HABC, hypomyelination with atrophy of the basal ganglia and cerebellum; HEMS, hypomyelination of early myelinating structures; ODDD, oculodentodigital dysplasia; HCC, hypomyelination with congenital cataract; PMD, Pelizaeus-Merzbacher disease; PMLD, Pelizaeus-Merzbacher-like disease; NCL, neuronal ceroid lipofuscinosis; APBD, adult polyglucosan body disease; ADLD, autosomal dominant leukodystrophy with autonomic symptoms; CRMCC, cerebrotendinous microangiopathy with calcifications and cysts; CTX, cerebrotendinous xanthomatosis; DRPLA, dentatorubral pallidolysian atrophy; HDLS, hereditary diffuse leukoencephalopathy with spheroids/neuroaxonal leukodystrophy with spheroids; HBSL, hypomyelination with brainstem and spinal cord and leg involvement; LTBL, leukoencephalopathy with thalamic and brainstem involvement and high lactate; LBSL, leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation; MLC, megalencephalic leukodystrophy with subcortical cysts; X-ALD, X-linked adrenoleukodystrophy. (Pattern recognition reprinted with permission from GeneReviews; from Parikh S, Bernard G, Leventer RJ, et al. A clinical approach to the diagnosis of patients with leukodystrophies and genetic leukoencephalopathies. *Mol Gen Metab*. 2018;114:501–515, Fig. 2, pp. 508–509.)

Leukodystrophies: “special” clinical features

Peripheral neuropathy	Ophthalmologic	Hearing loss	Endocrine	Skin	Dental	Skeletal	Other
MLD Krabbe PMDL PMD (mutations leading to loss of both PLP1 and DM20) HCC LCC SOX10-related disorder APBD CTX ALD and variants MNGIE	Early-onset VWM (cataracts) HCC (cataracts) 4H leukodystrophy (severe myopia) Aicardi-Goutières (glaucoma) Cockayne (retinitis pigmentosa) HSMD (retinitis pigmentosa) CTX (cataracts) SLS (macular degeneration, retinitis pigmentosa, white glistering spots) Coats plus (retinal telangiectasia and exudates) SOX10-related disorder (iris heterochromia) AMACR deficiency (retinitis pigmentosa) Early-onset peroxisomal disorders (retinitis pigmentosa) Mitochondrial LDs (cataracts, retinitis pigmentosa) Late stage of many LDs (optic atrophy)	SOX10-related disorder Cockayne 18q minus Early-onset peroxisomal disorders Fabry Mitochondrial LDs	VWM (premature ovarian failure) AARS2-related LD (premature ovarian failure) ALD and variants (adrenal failure, testicular failure) 4H leukodystrophy (delayed puberty, growth hormone deficiency) Cockayne (hypothyroidism) 18q minus (growth hormone deficiency) KSS (growth hormone deficiency, diabetes, hypoparathyroidism)	Generalized pigmentation (ALD and variants) Aicardi-Goutières (chilblains) Cockayne (photosensitivity) Trichothiodystrophy (photosensitivity) CTX (tendon xanthomas) SLS (ichthyosis) Fabry (angiokeratoma) Fucosidosis (angiokeratoma) Hyperpigmentation (Addison in ALD and variants) Linear pigment alterations (chromosomal mosaicism)	4H leukodystrophy (delayed dentition, hypodontia, abnormal tooth shape, caries) ODDD (hypodontia, abnormal tooth shape, caries) Cockayne (caries) Early-onset peroxisomal disorders (enamel hypoplasia) Periodontal Ehlers Danlos (premature loss of teeth)	HSMD (spondylo-metaphyseal dysplasia) 4H leukodystrophy (osteosclerosis) Fucosidosis (dysostosis multiplex) ODDD (syndactyly of 4th and 5th fingers) Coats plus (osteopenia with poor bone healing) Early-onset peroxisomal disorders (skeletal dysplasia)	MLD (gallbladder) Early-onset VWM (liver, pancreas, kidneys) Salla (hepatosplenomegaly) Fucosidosis (hepatosplenomegaly) Early-onset peroxisomal disorders (liver, kidney) CTX (neonatal cholestasis, diarrhea) Congenital muscular dystrophies 18q minus (congenital heart defects) Coats plus (gastrointestinal bleeding and portal hypertension) SOX10-related disorder (Hirschsprung disease; white lock of hair) MNGIE (intestinal pseudo-obstruction) NRF2-related LD (immune deficiency) PUS3-related LD (nephropathy)

Fig. 639.7 Leukodystrophies: “Special” clinical features. MLD, Metachromatic leukodystrophy; PMDL, Pelizaeus-Merzbacher-like disease; PMD, Pelizaeus-Merzbacher disease; HCC, hypomyelination with congenital cataracts; LCC, leukodystrophy with calcifications and cysts; APBD, adult polyglucosan body disease; CTX, cerebrotendinous xanthomatosis; ALD, adrenoleukodystrophy; MNGIE, myoneurogastrointestinal encephalopathy; VWM, vanishing white matter; HSMD, X-linked hypomyelination with spondylometaphyseal dysplasia; SLS, Sjögren-Larsson syndrome; AMACR, alpha-methylacyl-CoA racemase; KSS, Kearns-Sayre syndrome; ODDD, oculodentodigital dysplasia; LD, leukodystrophy. (From van der Knaap MS, Schiffmann R, Mochel F, Wolf NI. *Diagnosis, prognosis, and treatment of leukodystrophies*. *Lancet Neurol*. 2019;18:962–972, Appendix Fig. 2.)

MENKES DISEASE

Menkes disease (kinky hair disease) is a progressive neurodegenerative condition inherited as an X-linked recessive trait. The Menkes gene, *ATP7A*, on Xq21.1, codes for a copper-transporting, P-type adenosine triphosphatase, and mutations in the protein are associated with low serum copper and ceruloplasmin levels, as well as a defect in intestinal copper absorption and transport. The clinical symptoms of Menkes disease depend on the activity of different enzymes that use copper as a cofactor, such as superoxide dismutase, cytochrome *c* oxidase, and dopamine β hydroxylase, among others. Symptoms begin in the first few months of life and include hypothermia, hypotonia, and generalized myoclonic seizures. The facies are distinctive, with chubby, sagging, rosy cheeks and kinky, colorless, friable hair. Microscopic examination of the hair shows several abnormalities, including **trichorrhexis nodosa** (fractures along the hair shaft) and **pili torti** (twisted

hair). Feeding difficulties are prominent and lead to failure to thrive. Severe cognitive impairment, vascular tortuosity, and optic atrophy are constant features of the disease. Neuropathologic changes include tortuous degeneration of the gray matter and marked changes in the cerebellum with loss of the internal granule cell layer and necrosis of the Purkinje cells. Death can occur by 3 years of age in untreated patients. Very rarely does Menkes disease manifest in females, and when it does, symptoms are milder.

Copper histidine therapy may be effective in preventing neurologic deterioration in some patients with Menkes disease, particularly when treatment is begun in the neonatal period or, preferably, with the fetus. These presymptomatic children are identified because of a family history of an affected brother and confirmed by target analysis for variants in the *ATP7A* gene. Infants diagnosed presymptotically in the first 10 days of life can be started on an experimental protocol of daily

Table 639.3 Clinical and Laboratory Tests that Aid in the Diagnosis of Leukodystrophies and Genetic Leukoencephalopathies

CLINICAL/LABORATORY TEST*	DIAGNOSTIC TARGET
Brain and spinal MRI (± gadolinium, ± MRS)	Establish white matter disease; ± evidence of leaky blood-brain barrier and metabolite accumulation (mitochondrial disorders, Canavan disease, Sjögren-Larson syndrome, peroxisomal biogenesis disorders)
Ophthalmologic exam	Document ophthalmologic signs in several leukodystrophies
Head CT	Assess for calcifications
Plasma very long-chain fatty acids	X-linked adrenoleukodystrophy and adrenomyeloneuropathy and peroxisomal biogenesis disorders
Lysosomal enzymes (leukocytes)	Metachromatic leukodystrophy, Krabbe disease, multiple sulfatase deficiency, galactosialidosis, sialidosis
Blood lactate, pyruvate, amino acids	Mitochondrial disorders
Lumbar puncture (cell count, protein, ± CSF neopterin, ± interferon-α)	Nonspecific marker of demyelination; ± pleocytosis and markers for Aicardi-Goutières syndrome
Urine sulfatides	Metachromatic leukodystrophy, multiple sulfatase deficiency
Urine organic acids	L-2-hydroxyglutarate; N-acetyl aspartic acid for Canavan disease; Krebs cycle intermediates (mitochondrial disorders)
Neurophysiologic studies (BAER, EMG/NCV, VEP, SSEP)	Characterize involvement of cranial and peripheral nerves, optic tracts, and spinal tracts
Genetic analyses	As indicated for each leukodystrophy or genetic leukoencephalopathy

*Additional tests may be indicated for patients with certain distinctive clinical presentations or extraneurologic features suggestive of one or more specific leukodystrophies.
BAER, Brainstem auditory evoked response test; CSF, cerebrospinal fluid; CT, computed tomography; EMG, electromyogram; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NCV, nerve conduction velocity test; SSEP, somatosensory evoked potential test; VEP, visual evoked potential test.
From Parikh S, Bernard G, Leventer RJ, et al. A clinical approach to the diagnosis of patients with leukodystrophies and genetic leukoencephalopathies. *Mol Gen Metab*. 2018;114:501–515, Table 6.

copper-histidine subcutaneous injections. Optimal response to treatment appears to occur only in patients who are identified in the newborn period and whose mutations permit residual copper transport activity.

RETT SYNDROME

This syndrome is characterized as a disorder of early brain development marked by a period of developmental regression and deceleration of

brain growth after a relatively normal neonatal course. It is an X-linked disease that occurs predominantly in females and is one of the most common causes of cognitive disability in females. The frequency is approximately 1 in 10,000–15,000 live births. Rett syndrome is caused by pathogenic variants in *MeCP2* on Xq28, which codes for a transcription factor that binds to methylated CpG islands and silences transcription.

Clinically, development may proceed normally until 1 year of age, when regression of language and motor milestones and acquired microcephaly become apparent. Some atypical forms of Rett syndrome are congenital and can be associated with early-onset seizures and developmental impairment within the first months of life. An ataxic gait or fine tremor of hand movements is an early neurologic finding. Most children develop peculiar sighing respirations with intermittent periods of apnea that may be associated with cyanosis. The hallmark of Rett syndrome is repetitive hand-wringing movements and a loss of purposeful and spontaneous use of the hands; these features may not appear until 2–3 years of age. Autistic behavior is a typical finding in all patients. Generalized tonic-clonic convulsions occur in the majority but may be well controlled by anticonvulsants. Feeding disorders and poor weight gain are common. After the initial period of neurologic regression, the disease process appears to plateau, with persistence of the autistic behavior. Cardiac arrhythmias may result in sudden, unexpected death at a rate that is higher than the general population. Females usually survive into adulthood.

Although very few males survive with the classic Rett syndrome phenotype, genotyping of males without the classic Rett syndrome phenotype but with intellectual disability and other atypical neurologic features has detected patients with variants in *MeCP2*. Gene variants in *MeCP2* have been demonstrated in normal female carriers, females with Angelman syndrome, and males with fatal encephalopathy, Klinefelter (47,XXY) syndrome, and familial X-linked cognitive impairment. Males may present with a Rett-like syndrome if they have an *MECP2* duplication.

Classic Rett syndrome has been treated with trofinetide, an analog of the amino-terminal tripeptide of insulin-like growth factor 1. Its potential antiinflammatory and trophic properties may be the mechanisms that produce a positive clinical effect. It is approved for patients ≥2 years of age.

Some females have an atypical Rett phenotype associated with severe myoclonic seizures in infancy, slowing of head growth, and developmental arrest and have variants in another X-linked gene encoding for cyclin-dependent kinase–like 5 (*CDKL5*), which may interact with *MeCP2* and other proteins regulating gene expression.

NEURODEGENERATION WITH BRAIN IRON ACCUMULATION

Neurodegeneration with brain iron accumulation represents multiple age-of-onset–dependent disorders characterized by extrapyramidal symptoms and intellectual deterioration and regression, with iron deposition in the basal ganglia. There is significant phenotypic variability of these disorders; however, a characteristic finding on MRI demonstrates symmetric T2-signal homogeneous *hypointensity*. Common neurodegeneration with brain iron accumulation disorders are distinguished in Table 639.4, and an approach to their diagnosis is noted in Figure 639.8. Clinical features, which are highly variable, may include dystonia, parkinsonism, ataxia, spasticity, psychiatric symptoms, and intellectual impairment. Treatment should focus on the specific disorder and is usually symptomatic relief rather than curative. Iron chelation has been attempted without major long-term benefit.

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Table 639.4 Overview of Neurodegeneration with Brain Iron Accumulation Conditions and Genes (If Known)

CONDITION (ACRONYM)	SYNONYM	GENE	CHROMOSOMAL POSITION	LB PATHOLOGY	CHILDHOOD-ONSET VARIANT		LATE-ONSET VARIANT	
					AGE OF ONSET	CLINICAL PRESENTATION	AGE OF ONSET	CLINICAL PRESENTATION
PKAN	NBIA1	<i>PANK2</i>	20p13	No	Early childhood, around age 3	Typical PKAN	Teens or early adulthood	Atypical PKAN
PLAN	NBIA2, PARK14	<i>PLA2G6</i>	22q12	✓	Infancy	Infantile neuroaxonal dystrophy	Teens or early adulthood	Dystonia parkinsonism
FAHN	SPG35	<i>FA2H</i>	16q23	Not known	Childhood	Leukodystrophy, hereditary spastic paraplegia	Adulthood (age range up to 30yr)	May resemble idiopathic Parkinson disease
MPAN	—	<i>C19orf12</i>	19q12	✓	—	Pyramidal extrapyramidal syndrome		
Kufor-Rakeb disease	PARK9	<i>ATP13A2</i>	1p36	✓	Childhood- teens	Parkinsonism, pyramidal tract signs, eye movement disorder		
BPAN	SENDA syndrome	<i>WDR45</i>	Xp11.23	Not known	Childhood	Encephalopathy with psychomotor regression, then static	Then: 20s to 30s	Sudden-onset progressive dystonia parkinsonism
Aceruloplasminemia	—	<i>CP</i>	3q23	No	—	—	50s (range: 16-70)	Extrapyramidal, diabetes, dementia
Neuroferritinopathy	—	<i>FTL</i>	19q13	No	—	—	40s	Chorea, dystonia, dementia
Idiopathic late-onset cases	—	Probably heterogeneous	Probably heterogeneous	Heterogeneous	—	—	Heterogeneous	Parkinsonism; it may resemble idiopathic Parkinson disease

✓, Present; BPAN, beta-propeller-associated neurodegeneration; CP, ceruloplasmin; FA2H, fatty acid 2-hydroxylase; FAHN, fatty acid 2-hydroxylase-associated neurodegeneration; FTL, ferritin light chain; LB, Lewy body; MPAN, mitochondrial membrane-associated neurodegeneration; NBIA, neurodegeneration with brain iron accumulation; PANK2, pantothenate kinase 2; PKAN, pantothenate kinase-associated neurodegeneration; PLA2G6, phospholipase A2; PLAN, PLA2G6-associated neurodegeneration; SENDA, static encephalopathy of childhood with neurodegeneration in adulthood; SPG, spastic paraplegia.

From Schneider SA, Zorzi G, Nardocci N. Pathophysiology and treatment of neurodegeneration with brain iron accumulation in the pediatric population. *Curr Treat Option Neurol*. 2013;15:652-667, Table 1.

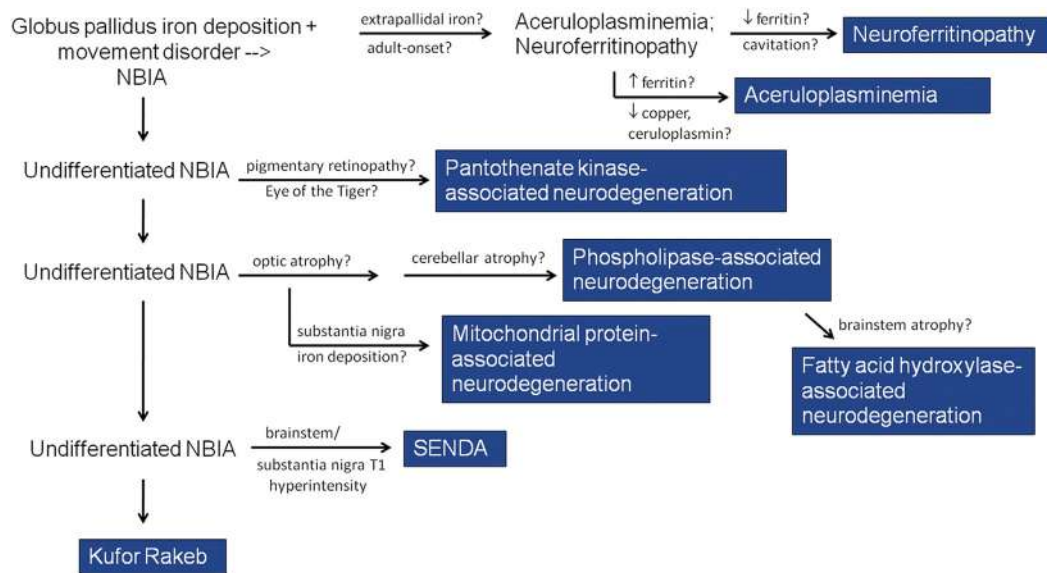


Fig. 639.8 Algorithm showing the clinical and radiographic approach to neurodegeneration with brain iron accumulation. NBIA, neurodegeneration with brain iron accumulation; SENDA, static encephalopathy of childhood with neurodegeneration in adulthood. (From Kruer MC, Boddaert N. Neurodegeneration with brain iron accumulation: a diagnostic algorithm. *Semin Pediatr Neurol*. 2012;19:67–74, Fig. 1.)

Chapter 640

Demyelinating Disorders of the Central Nervous System

Michael Perry and Cheryl Hemingway

Acquired demyelinating syndromes (ADSs) of the central nervous system (CNS) are rare disorders, occurring with an approximate annual incidence of 9.8 per million children per year. They present with neurologic dysfunction caused by immune-mediated injury to the myelin sheath of the brain, optic nerves, and spinal cord. In contrast to genetically determined **leukodystrophies** (sometimes called *dysmyelinating disorders*) that produce disrupted white matter, acquired demyelinating disorders target normally formed white matter. They can be monophasic or relapsing.

The pathogenesis often involves demyelination together with B cells and CNS antibodies. Two immunoglobulin G (IgG) antibodies recognized as playing an important part in demyelination are aquaporin 4-antibody (AQP4-Ab) and myelin oligodendrocyte glycoprotein antibody (MOG-Ab). The aquaporins are plasma membrane water-transporting proteins expressed in astrocytes and are primarily involved in water movement, cell migration, and neuroexcitation. Myelin oligodendrocyte glycoprotein (MOG) is exclusively expressed in the CNS. Although MOG comprises only a minor component of the myelin sheath, its location on the outermost lamellae and on the cell surface of oligodendrocytes makes it available for antibody binding. Increasing knowledge of the importance of these antibodies in disease, together with available disease-modifying treatments (DMTs) has made accurate diagnosis in demyelinating disorders

crucial. Pediatric demyelinating syndromes may be clinically characterized by:

1. Localization of neurologic deficits: monofocal vs polyfocal
2. Presence or absence of encephalopathy
3. Disease course: monophasic vs polyphasic
4. Presence or absence of specific antibodies

MRI of the brain and spine is essential to characterize both symptomatic and *clinically silent* demyelinating lesions, aid in the diagnosis of the specific demyelinating syndrome, predict likelihood of recurrence, and rule out other etiologies. Serial MRIs may be needed to confirm the diagnosis and can also be used to monitor the treatment response and guide DMT use. The presence of **oligoclonal bands (OCBs)** in cerebrospinal fluid (CSF) analysis is useful to help confirm the diagnosis of multiple sclerosis (MS) (Table 640.1); their absence may suggest an alternative diagnosis. OCBs, matched or unmatched (to blood OCB), may also be seen in other CNS inflammatory diseases. Additional laboratory studies, including an autoimmune profile, antibody testing, metabolic testing, genetic testing, catheter angiography, and less often, brain biopsy, may be required to evaluate for mimics of demyelination. These mimics may include conditions such as migraine, systemic rheumatologic disorders, mitochondrial disorders, primary CNS angiitis, infection, neoplasm, and genetic conditions such as the inherited white matter disorders (e.g., leukodystrophies) and primary CNS hemophagocytic lymphohistiocytosis (HLH) (Tables 640.2 and 640.3).

Most children presenting with a first episode of demyelination will experience a monophasic course and do not relapse. Monophasic demyelinating disorders of childhood may include acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), and transverse myelitis (TM); relapsing forms of demyelination include MS, MOG, multiphasic disseminated encephalomyelitis (MDEM), relapsing ON, and AQP4-Ab-associated demyelination and neuromyelitis optica spectrum disorder (NMOSD). Relapsing disease is often characterized by gradual accrual of physical disability and cognitive impairment.

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Table 640.1 Acute Demyelinating Disorders of the Central Nervous System

DISORDER	DEFINITION
Acute disseminated encephalomyelitis (ADEM)	A first polyfocal CNS event with presumed inflammatory cause Encephalopathy present that cannot be explained by fever MRI often showing bilateral diffuse, poorly demarcated T2 lesions No new symptoms, signs, or MRI findings after initial 3 mo
Multiphasic ADEM	New event of ADEM 3 mo or more after the initial event that can be associated with new or reemerging clinical and MRI findings Frequently associated with the presence of MOG-Ab
Clinically isolated syndrome (CIS)	A first monofocal or multifocal CNS demyelinating event Encephalopathy is absent, unless caused by fever
Multiple sclerosis (MS)	MS can be diagnosed in those for whom there is no better explanation if both dissemination in time (DIT) and dissemination in space (DIS) can be demonstrated. DIS Demonstrated by one or more T2 lesions affecting at least two of the following CNS sites: • Periventricular • Juxtacortical or cortical • Infratentorial • Spinal cord DIT Demonstrated by one of the following: • Simultaneous presence on MRI of one or more gadolinium-enhancing lesions AND one or more nonenhancing lesions • CSF oligoclonal bands • Follow-up MRI (>30 days from previous scan) with one or more new enhanced OR nonenhanced lesions • Two or more acute episodes typical of MS each lasting >24 hr and at least 30 days apart
Primary progressive MS (PPMS)	PPMS is exceedingly rare in childhood, and therefore in cases of suspected PPMS, or diagnostic uncertainty, specialist advice should be obtained. Biopsy and/or further genetic investigation may be appropriate to rule out mimics.
MOG-Ab–associated demyelination	MDEM: recurrent ADEM (see earlier) ADEM-ON: ADEM or MDEM followed by optic neuritis (ON) NMOSD: ON and acute transverse myelitis (ATM), either sequentially or simultaneously Relapsing inflammatory ON (RION) Brainstem demyelination: recurrent episodes of demyelination often involving the posterior fossa and brainstem
Neuromyelitis optica spectrum disorder (NMOSD)	If AQP4–positive, one of the following core criteria is required: • Optic neuritis • Acute myelitis • Area postrema syndrome (nausea, vomiting, hiccups) • Acute brainstem syndrome • Narcolepsy, acute diencephalic syndrome with MRI lesions • Symptomatic cerebral syndrome with MRI lesions If AQP4–negative or unavailable, two core criteria and all the following: 1. At least one core criteria must be optic neuritis, longitudinally extensive TM, or area postrema syndrome 2. Dissemination in space (≥2 different core criteria) 3. Exclusion of alternative diagnoses If MOG-Ab–positive with both ON and TM, then MOG + NMOSD may be diagnosed

640.1 Acute Disseminated Encephalomyelitis

Michael Perry and Cheryl Hemingway

Acute disseminated encephalomyelitis is an inflammatory, demyelinating event of early childhood presenting with acute-onset *polyfocal* neurologic deficits, accompanied by *encephalopathy* and MRI changes consistent with demyelination (see [Table 640.1](#)).

EPIDEMIOLOGY

Although ADEM can occur at any age, most studies report a mean age between 5 and 8 years with a slight male predominance and an incidence of 0.1–0.6 per 100,000 children per year. ADEM is usually *monophasic*, but recurrence can occur; this is termed **multiphasic disseminated**

encephalomyelitis (MDEM) if the recurrence is 3 months or longer after the incident episode. Approximately 50% of ADEM cases are associated with serum MOG-Ab positivity (MOGAD) (see [Chapter 640.5](#)). MDEM patients are almost exclusively MOG-Ab positive. An episode of ADEM can also be followed by non-ADEM demyelination in a new location. If ADEM is followed by a relapse in a specific location, such as the optic nerve, then **ADEM-ON** is diagnosed. If the optic nerve and spinal cord are involved, then **NMOSD** (see [Table 640.1](#)) is diagnosed. Both ADEM-ON and NMOSD are associated with MOG-Ab positivity.

PATHOGENESIS

Molecular mimicry induced by infectious exposure has long been thought to trigger the production of CNS autoantigens, though causality has never been proven. Many patients experience a transient febrile

illness in the month before ADEM onset. Preceding infections associated with ADEM include influenza, Epstein-Barr virus (EBV), cytomegalovirus, varicella, enterovirus, measles, mumps, rubella, herpes simplex, *Mycoplasma pneumoniae*, and COVID-19.

Table 640.2	Differential Diagnosis of Demyelinating Disorders
Multifocal white matter lesions	Demyelination (e.g., ADEM, MS, CIS, NMOSD, AHL) Autoantibody (e.g., NMDAR-Ab, Hashimoto encephalopathy) Migraine Prior insult and residual gliosis (e.g., congenital infections or hypoxic damage) Primary and secondary vasculitides (e.g., primary angiitis of the CNS, neurosarcoidosis, SLE, Behçet syndrome, scleroderma) Mitochondrial (e.g., Leber hereditary optic neuropathy [LHON], POLG) Leukoencephalopathy (e.g., DARS) X-linked Charcot-Marie-Tooth disease
Bilateral or diffuse white matter lesions	Leukodystrophy (e.g., X-linked adrenoleukodystrophy, Alexander disease, metachromatic LD, Krabbe disease) Leukoencephalopathy (e.g., Aicardi-Goutières syndrome) Mitochondrial (e.g., LHON, Leigh disease, MELAS, MERFF) Infection Tumor (e.g., gliomatosis cerebri, astrocytoma, lymphoma) Hemophagocytic lymphohistiocytosis (HLH)
Deep gray, thalamic, and striatal lesions	Infection (e.g., mycoplasma, Epstein-Barr virus, West Nile virus, Japanese B encephalitis, enterovirus) Biotin-responsive basal ganglia disease (e.g., SLC19A3) Acute necrotizing encephalopathy (ANE) and RANBP2 pathogenic variant

CLINICAL MANIFESTATIONS

Initial symptoms of ADEM may include lethargy, fever, headache, vomiting, meningeal signs, and seizures, including status epilepticus. Encephalopathy is the hallmark of ADEM. It can range from behavioral change and persistent irritability to coma. Common neurologic signs include visual loss, ataxia, motor and sensory deficits, and cranial neuropathies. In cases with concurrent spinal cord involvement, bladder/bowel dysfunction may be seen. Focal neurologic deficits, however, can be difficult to ascertain in the obtunded or very young child. The clinical course is usually rapidly progressive over days, and intensive care may be required, particularly for patients with brainstem dysfunction or raised intracranial pressure.

NEUROIMAGING

Brain MRI typically shows large (sometimes confluent), bilateral, multifocal, edematous, masslike T2 lesions of the cerebral hemispheres, cerebellum, and brainstem. Deep gray matter structures (e.g., thalami, basal ganglia) are often involved (Figs. 640.1 and 640.2). Contrast enhancement is variable. The spinal cord may have an abnormal T2 signal or enhancement, with or without clinical signs of myelitis. ADEM lesions will typically appear to be of similar age on MRI, but their evolution often lags the clinical presentation. Serial MRI imaging 3-12 months after ADEM frequently demonstrates near-complete resolution of T2 abnormalities, though residual gliosis may remain.

Severe involvement may progress to an **acute hemorrhagic leukoencephalopathy** (Weston-Hurst disease). This leukodystrophy-like picture is characterized by large lesions, edema with mass affect, and a polymorphonucleated cell pleocytosis; this contrasts with the CSF lymphocytic pleocytosis typically noted in ADEM.

LABORATORY FINDINGS

There is no biologic marker for ADEM, and laboratory findings can vary widely. CSF studies are often normal or can exhibit pleocytosis with lymphocytic or monocytic predominance. CSF protein can be elevated, especially on repeat studies. Elevated CSF immunoglobulin production can be present, but true OCB positivity is rare. Electroencephalograms often show generalized slowing, consistent with encephalopathy. Polyregional demyelination of ADEM can also cause focal slowing or epileptiform discharges.

Table 640.3	MR Imaging Red Flags for the Diagnosis of Children with Acquired Demyelinating Syndromes	
LEPTOMENINGEAL ENHANCEMENT	SVC-PACNS Infection Tumor HLH	Leptomeningeal enhancement is not a feature of MS in adults; it has emerged as a red flag for vasculitic or malignant processes in the pediatric cohort.
LESION EXPANSION	Tumor Lymphoma PML Sarcoidosis	Increased size of T2 lesions on serial imaging is well recognized in MS, although this should always prompt consideration of malignancy. Increasing size of a white matter–predominant lesion without lesion enhancement in a patient treated with immunosuppressant therapy (or a patient with known HIV) should prompt consideration of PML. PML is a risk for MS patients exposed to more intense immunosuppressive therapies.
HEMORRHAGE	ANE Stroke Cerebellitis AHLE Large-vessel CNS vasculitis SVC-PACNS	Although susceptibility-weighted imaging reveals tiny microfoci of hemosiderin in MS patients, hemorrhage large enough to be visible on conventional MRI sequences is not a feature of ADS or MS and should prompt consideration of disorders in which the cerebral vasculature is specifically involved.

ADS, Acquired demyelinating syndrome; AHLE, acute hemorrhagic leukoencephalitis; CNS, central nervous system; HIV, human immunodeficiency virus; HLH, hemophagocytic lymphohistiocytosis; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy; SVC-PACNS, small-vessel childhood primary angiitis of the central nervous system. From O’Mahony J, Shroff M, Banwell B. Mimics and rare presentations of pediatric demyelination. *Neuroimaging Clin North Am.* 2013;23:321–336, Table 2.

DIFFERENTIAL DIAGNOSIS

ADEM is a clinical diagnosis supported by MRI, CSF, and serum findings. The differential diagnoses for ADEM are broad; empirical antibiotic and antiviral treatment should be considered while infectious evaluations are pending. Follow-up MRI examinations 3–12 months after typical ADEM should show improvement; new or enlarging T2 lesions should prompt reevaluation for other etiologies such as MS, antibody-associated disorders, leukodystrophies, tumor, vasculitis, mitochondrial, metabolic, or rheumatologic disorders (Table 640.4 and see Tables 640.1–640.3).

TREATMENT

High-dose intravenous steroids are often prescribed (most commonly methylprednisolone 20–30 mg/kg/day for 5 days with a maximum dose of 1,000 mg/day) followed by an oral prednisolone taper of 1–2 mg/kg/day (maximum 40–60 mg/day) over 4–6 weeks. In refractory or severe cases, additional treatment options include intravenous

immunoglobulin (2 g/kg administered over 2–5 days) or plasmapheresis (5–7 exchanges administered every other day). There is no consensus about the timing of these treatments for ADEM.

PROGNOSIS

Most children experience full motor recovery after ADEM, but residual deficits can be seen. Cognitive impairment or behavioral changes are not uncommon. Recovery starts within days to weeks, but symptoms can fluctuate throughout the course.

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640.2 Optic Neuritis

Michael Perry and Cheryl Hemingway

Optic neuritis (ON) is inflammation of one or both optic nerves. It presents with visual dysfunction. ON can occur in three phenotypes: (1) as a clinically isolated monophasic syndrome; (2) recurrently in isolation; or (3) as part of other multifocal systemic or CNS-specific inflammatory conditions such as ADEM, MS, or antibody-associated demyelination (e.g., AQP-4-Ab NMOSD or MOGAD).

EPIDEMIOLOGY AND CLINICAL PRESENTATION

ON is one of the most common of the acquired demyelinating syndromes, accounting for ~25% of all demyelinating presentations in childhood. The typical presentation is unilateral or bilateral visual loss over hours to days with abnormal color vision (typically red-green desaturation), visual field loss, and sometimes a relative afferent pupillary defect. The visual loss is often severe, with most children at 20/200 visual acuity (VA) or worse. Periocular pain and painful eye movements (often reported as headache in young children) are common. Bilateral ON is more common in younger children and frequently associated with MOG-Ab disease. Unilateral ON is more common in older children and more likely to be associated with MS. Funduscopic examination in over half of children reveals acute optic nerve head swelling (papillitis). However, when the inflammation occurs in the retrobulbar optic nerve portion, the appearance of the optic nerve may be normal. Optic nerve pallor is more often noted in the chronic stage after an initial episode or in those with relapsing ON. Bilateral ON, longitudinally extensive (>50% of the optic nerve), perineural optic sheath enhancement (perineuritis), and optic disc edema are features suggestive of ON caused by MOG-Ab disease. ON without papillitis and that involves the optic chiasm or tract is more typical of AQP4-Ab (NMOSD) disease.

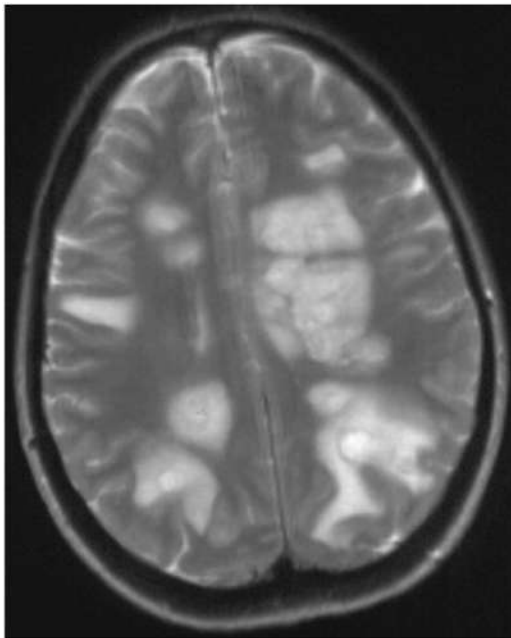


Fig. 640.1 6-year-old patient diagnosed with ADEM presenting with encephalopathy, ataxia, and motor deficits after mild viral infection. Axial T2-weighted MRI shows bilateral, diffuse, poorly demarcated lesions. Gray matter involvement, including the thalamus and basal ganglia, is commonly seen.

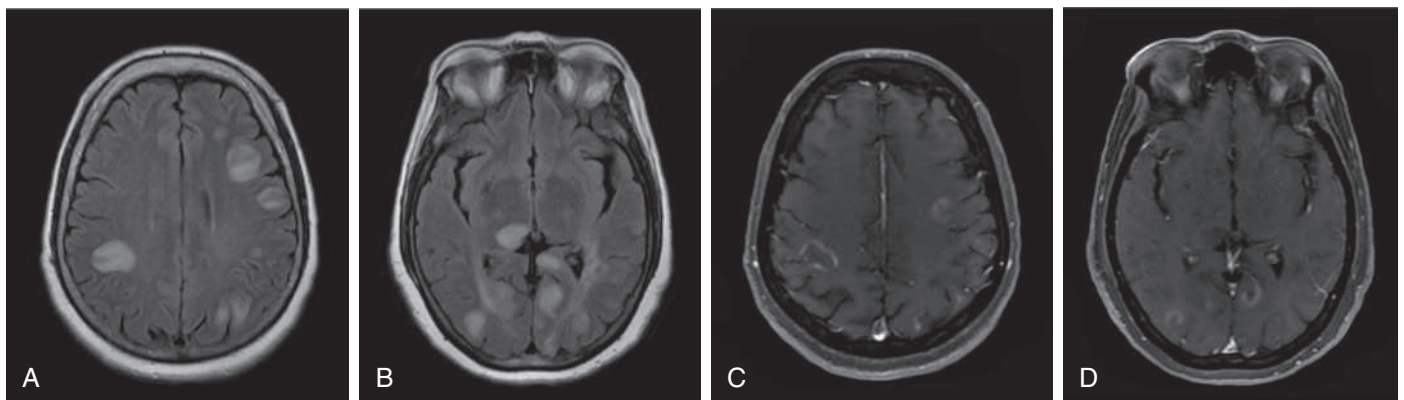


Fig. 640.2 Acute disseminated encephalomyelitis (ADEM). A and B, T2-weighted FLAIR images show numerous asymmetric, rounded, hyperintense, predominantly subcortical white matter lesions. Some lesions involve the cortex. A right pulvinar lesion is also seen. C and D, Postcontrast T1-weighted image demonstrates incomplete ring enhancement associated with these lesions. All the lesions show similar imaging features. Marked improvement was seen after steroid therapy. (From Lerner A, Rajamohan A, Shiroishi MS, et al. *Cerebral infections and inflammation*. In: Haaga JR, Boll DT, eds. *CT and MRI of the Whole Body*, 6th ed. Philadelphia: Elsevier; 2017: Fig. 10-15, p. 280.)

Table 640.4	Features that May Distinguish ADEM from a First Attack of MS	
	ADEM WITH OR WITHOUT MOG-AB	MS
Age and sex	<10yr Males and females equal	>10yr Female preponderance
Seizures	+	–
Encephalopathy	+ /+/- for MOG-Ab	–
Fever/vomiting	+	–
Family history	No	20%
Optic neuritis	Bilateral	Unilateral
Manifestations	Polysymptomatic	Monosymptomatic
CSF	Pleocytosis (lymphocytosis) OCBs negative	Acellular OCBs positive
MRI	Large, fluffy, poorly demarcated T2 lesions involving white and gray matter	Ovoid T2 lesions involving juxtacortical, periventricular, or infratentorial areas or spinal lesions; T1 hypointense lesions
MRI follow-up after 30 days	No new lesions	New lesions seen

+, More likely to be present; –, less likely to be present; ADEM, acute disseminated encephalomyelitis; CSF, cerebrospinal fluid; MS, multiple sclerosis; MOG-Ab, myelin oligodendrocyte glycoprotein antibody; OCBs, oligoclonal bands.

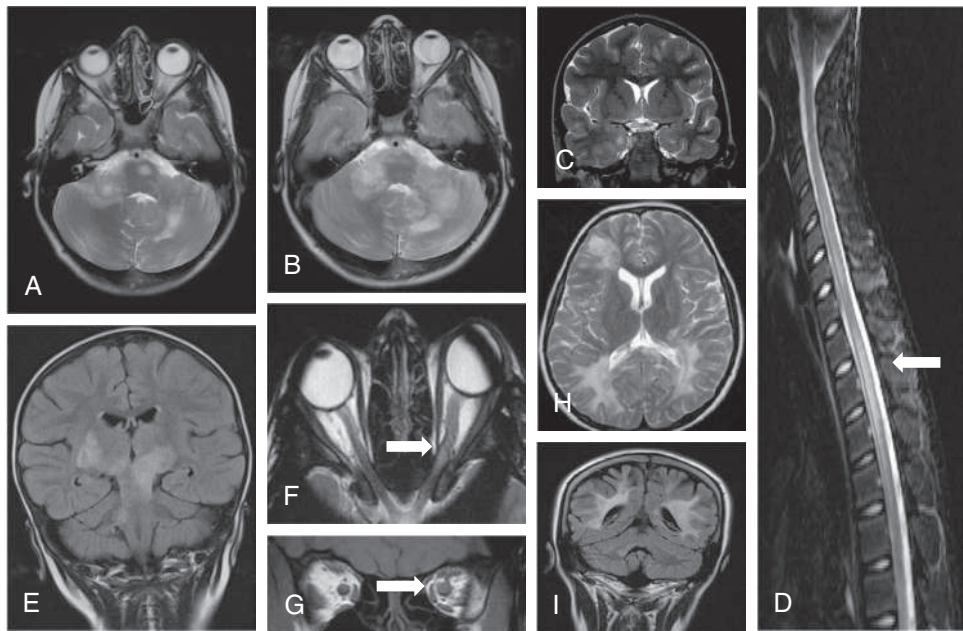


Fig. 640.3 MRI images highlighting the spectrum of possible phenotypes in relapsing myelin oligodendrocyte glycoprotein (MOG) antibody-associated disorders. **A**, Axial T2-weighted FLAIR MRI of brain from a 6-yr-old female with bilateral ON, ataxia, and lethargy, initially diagnosed with ADEM until her relapse (**B**) with further multiple brainstem lesions associated with MOG-Ab positivity. **C**, Coronal T2-weighted MRI with longitudinally extensive ON with both pre- and post-chiasm involvement and (**D**) sagittal MRI of spine with longitudinally extensive TM from a 9-yr-old female diagnosed with MOG-Ab-associated NMOSD after simultaneous presentation of bilateral visual impairment and paraparesis requiring ventilatory support. **E**, T2-weighted FLAIR MRI of brain demonstrating asymmetric, bilateral, poorly defined lesion involving the brainstem and extending into the middle cerebellar peduncle. **F** and **G**, Orbital MRI shows a thickened left optic nerve in a 13-yr-old female with recurrent left ON associated with positive MOG-Ab. **H**, Axial T2-weighted image shows diffuse, bilateral, asymmetric leukodystrophy-like phenotype associated with MOG-Ab. **I**, Coronal T2-weighted FLAIR MRI of brain similarly showing the leukodystrophy-like appearance seen over time in those with young-onset relapsing MOG-Ab-associated demyelination.

DIAGNOSTIC EVALUATION

MRI, optical coherence tomography (OCT), and visual evoked potentials (VEPs) are useful for evaluating and quantifying the functional and structural integrity of the optic nerve of a child with suspected ON. Orbital MRI is useful but not required for a diagnosis of ON. Though sometimes normal, it will usually show optic nerve thickening on T1-weighted images with T2 hyperintensities and contrast enhancement. (Fig. 640.3F, G). Longitudinally extensive ON

involving the chiasm is thought to be more commonly associated with antibody-mediated demyelination (see Fig. 640.3C). **Optical coherence tomography** can detect structural neuronal and retinal change, such as retinal nerve fiber layer (RNFL) thinning and may be helpful in monitoring the young child experiencing recurrent disease. In acute ON, VEPs may detect prolonged latency. VEPs in children may also detect clinically silent episodes of ON in the seemingly unaffected contralateral eye.

CSF OCB analysis is not always indicated; however, in the context of a normal MRI brain scan, negative OCBs predict a very low risk of subsequent MS development.

Many conditions can both mimic and be associated with ON. Therefore although a detailed ophthalmologic review is essential, other investigations must be carefully considered to exclude systemic rheumatologic disorders (e.g., systemic lupus erythematosus [SLE], sarcoidosis, celiac disease, Behçet disease), infectious diseases (viral disease, Lyme disease, syphilis, tuberculosis), mitochondrial disorders (e.g., Leber hereditary optic neuropathy), vascular events, toxic (methanol, ethylene glycol, chloroquine, hydroxychloroquine), nutritional (folate, vitamin B12, copper deficiencies), or metabolic disorders, and optic nerve sheath meningioma or optic nerve glioma. Antibody testing in serum with live cell-based assays (CBAs) for both AQP4-Ab and MOG-Ab is recommended to ensure that prophylactic treatment can be provided if indicated (e.g., AQP4-Ab positive) or to provide counseling on the risk of recurrence (MOG-Ab positivity).

TREATMENT

The standard of care is based on expert clinical opinion and adult trials and typically includes high-dose intravenous steroids (e.g., methylprednisolone 20–30 mg/kg/day for 3–5 days, maximum 1000 mg/day). In adults, steroid administration leads to faster recovery, but with no difference in long-term visual outcome. As with other severe episodes of demyelination, further treatment options include intravenous immunoglobulin (usually 2 g/kg administered over 2–5 days) or plasmapheresis (typically 5–7 exchanges administered every other day); there is neither definitive trial evidence of their benefit nor consensus about when to use them in isolated ON. Trials in adults have concentrated on neuroprotection; phenytoin has a beneficial effect on RNFL thinning in acute ON.

The initiation of chronic immunotherapy is dependent on etiology, the presence or absence of glial antibodies (e.g., MOG-Ab), and risk of relapse (i.e., ON caused by AQP4 + NMOSD) and is best considered by a multidisciplinary team experienced in the treatment of pediatric neuroinflammatory disorders.

PROGNOSIS

Although it is reassuring that full recovery of high-contrast visual acuity (HCVA) does usually occur in children, irreversible damage is often detected in the structural integrity of affected optic nerves. This may be evidenced by RNFL thinning on OCT, defective color vision, and impairments in low-contrast visual acuity (LCVA). Pediatric patients with AQP4-antibody-associated optic nerve demyelination are more commonly left with long-term visual disability than patients with other causes of ON.

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640.3 Transverse Myelitis

Michael Perry and Cheryl Hemingway

Transverse myelitis (TM) is a condition characterized by the rapid development of both motor and sensory deficits of the spinal cord. It presents acutely as either partial or complete cord involvement at any level with bilateral neurologic signs; in adults and older children, there will usually be a clear sensory level. TM has multiple causes (Tables 640.5 and 640.6). It can be secondary to an immune-mediated condition (postinfectious or antibody-driven), a result of direct infection (e.g., infectious myelitis), or idiopathic. In TM, evidence of spinal cord inflammation can be demonstrated by an enhancing lesion on MRI, CSF pleocytosis (>10 cells), or an increased IgG index. The progression is rapid. Time to maximal disability typically occurs 5–6 days after symptom onset.

EPIDEMIOLOGY

TM is more common in adults but is estimated to affect ~2 children/million per year. A bimodal age distribution is observed in those

Table 640.5 Reported Cases of Transverse Myelitis

1. Acquired demyelinating disorders
 - a. Multiple sclerosis
 - b. NMO
 - c. ADEM
 - d. MOGAD
2. Systemic inflammatory autoimmune disorders
 - a. SLE
 - b. SS
 - c. Antiphospholipid syndrome
 - d. Behçet disease
 - e. Vogt-Koyanagi-Harada disease
 - f. Ankylosing spondylitis
 - g. Mixed connective tissue disease
 - h. Others: systemic sclerosis, anti-Jo-1 antibody, urticarial vasculitis, psoriatic arthritis, perinuclear ANCA systemic vasculitis, graft-versus-host disease, common variable immunodeficiency, celiac disease
3. Neurosarcoidosis
4. Parainfectious TM
 - a. Viral: hepatitis A, hepatitis B, hepatitis C, hepatitis E, measles, mumps, rubella, varicella zoster, Epstein-Barr, cytomegalovirus, herpes simplex, influenza A/B, lymphocytic choriomeningitis virus, chikungunya, hantavirus, HIV, human T-cell lymphotropic virus, human herpes virus 6, Japanese encephalitis, Murray Valley encephalitis, St. Louis encephalitis, tickborne encephalitis, vaccinia, Rocky Mountain spotted fever, dengue virus, enterovirus 71, coxsackievirus A and B, West Nile virus, parvovirus B19, human corona virus, and echovirus
 - b. Bacterial: *Mycoplasma pneumoniae*, *Campylobacter jejuni*, *Borrelia burgdorferi*, *Acinetobacter baumannii*, *Coxiella burnetii*, *Bartonella henselae*, *Chlamydia psittaci*, *Leptospira*, *Chlamydia pneumoniae*, *Legionella pneumoniae*, *Orientia tsutsugamushi* (scrub typhus), *Salmonella paratyphi B*, *Mycobacterium tuberculosis*, *Treponema pallidum*, *Brucellosis melitensis*, and groups A and B streptococci
 - c. Fungal: *Actinomyces*, *Blastomyces*, *Coccidioides*, *Aspergillus*, *Cryptococcus*, and *Cladophialophora bantiana*
 - d. Parasitic: *Toxocara* species, *Schistosoma* species, *Gnathostoma spinigerum*, *Echinococcus granulosus*, *Taenia solium*, *Toxoplasma gondii*, *Acanthamoeba* species, *Paragonimus westermani*, and *Trypanosoma brucei*
5. Paraneoplastic syndromes
 - a. Anti-Ri (ANNA-2) antibody
 - b. CRMP-5-IgG antibody
 - c. Anti-amphiphysin IgG antibody
 - d. Anti-GAD65 antibody
 - e. NMDAR antibody
6. Atopic myelitis
7. Drugs and toxins
 - a. Tumor necrosis factor-alpha inhibitors
 - b. Sulfasalazine
 - c. Epidural anesthesia
 - d. Chemotherapeutic agents: gemcitabine, cytarabine, cisplatin
 - e. Heroin
 - f. Benzene
 - g. Brown recluse spider toxin
8. Idiopathic TM

MOGAD, MOG antibody disease.

From Beh SC, Greenberg BM, Frohman T, et al. Transverse myelitis. *Neurol Clin*. 2013;31:79–138, Box 5, p. 88–89.

younger than 5 years and older than 10 years. Children less than 5 years of age develop spinal cord dysfunction over hours to a few days. They often have a history of an infectious disease (e.g., viral or mycoplasma) in the weeks preceding development of neurologic symptoms. The motor dysfunction is often severe, approaching a complete loss of function. Recovery is slow (weeks to months) and usually incomplete, most commonly with residual bowel and bladder dysfunction (15–50%). Pathologic findings of perivascular infiltration with mononuclear cells suggest an infectious or inflammatory basis. Overt necrosis of the spinal cord may occur.

The syndrome may differ in older children, and outcomes vary by etiology. Although the onset is also rapid, recovery is faster and more

Table 640.6 Mimics of Transverse Myelitis

ETIOLOGY	DESCRIPTION
Vitamin B ₁₂ deficiency	May present as an isolated myelopathy or in combination with neuropathy, encephalopathy, and/or behavioral changes. Dorsal column impairment is the most common manifestation, followed by pyramidal dysfunction (the classic subacute combined degeneration of the cord). Hematologic manifestations may be absent in up to 30% of patients with neurologic manifestations. MRI reveals T2-hyperintense signal in the posterior columns (the “inverted V” or “inverted rabbit ear” sign on axial views). In severe cases, MRI shows the “anchor” sign (because of involvement of the posterior, anterior, and pyramidal tracts).
Vitamin E deficiency	May cause a predominantly dorsal column syndrome associated with a peripheral neuropathy because of axonal degeneration. Preferentially affects the cervical cord. Clinically and radiologically similar to B ₁₂ deficiency.
Copper deficiency	May cause both myelopathy and optic neuropathy. Causes of acquired copper deficiency include malnutrition, zinc toxicity, Menke disease, bariatric surgery, gastrectomy, malabsorption syndromes, and use of copper chelating agents. Clinically and radiologically indistinguishable from B ₁₂ deficiency.
Nitrous oxide (N ₂ O) toxicity	Analgesic gas commonly abused because of euphoric effects. N ₂ O inactivates vitamin B ₁₂ by irreversible oxidation of the cobalt center of methylcobalamin, thereby inhibiting the methionine synthesis pathway. In healthy subjects, this does not cause clinical manifestations. In subclinically B ₁₂ -deficient individuals, N ₂ O exhausts residual stocks of vitamin B ₁₂ , leading to neurologic manifestations.
Neurolathyrism and neurocassivism	Neurolathyrism is caused by consumption of grass pea. Neurocassivism (konzo) is caused by bitter cassava root consumption. Both are found in malnourished populations and are characterized by subacute paraparesis with prominent UMN features.
Intramedullary primary spinal cord tumors	May be ependymomas, astrocytomas, or hemangioblastomas. Typically cause an insidious, progressive myelopathy. Hemorrhage or infarction of the tumor may result in an acute presentation and radiologic appearance mimicking TM.
Primary CNS lymphoma	May give rise to a clinical and radiologic picture mimicking TM compounded by its corticosteroid responsiveness. Congenital or acquired immunodeficiency is the only established risk factor. More common in middle-age and older men. Insidious onset of myelopathy with back pain and constitutional symptoms. Serum lactate dehydrogenase may be elevated. CSF: lymphocytic pleocytosis, markedly elevated protein, and hypoglycorrhachia. OCBs and IgG index are absent. Cytologic analysis may demonstrate malignant cells (large-volume CSF examination can increase the diagnostic yield). MRI: T2 hyperintensity, gadolinium enhancement, cord swelling, conus medullaris involvement, and concomitant brain lesions.
Intravascular lymphoma	Predominantly affects vessels in the skin and neurologic system. May mimic TM and even LETM. CSF: lymphocytic pleocytosis and increased protein, but no malignant cells. MRI: affects the conus medullaris (unlike TM).
Radiation myelitis	Early radiation myelopathy: begins 10-16 wk after starting radiotherapy with predominantly sensory phenomena (including Lhermitte sign) and typically resolves spontaneously. Delayed radiation myelopathy: begins months or years after radiation exposure and manifests as a subacute or insidious myelopathy. Concurrent use of chemotherapeutic agents may cause widespread white matter necrosis owing to synergistic toxicity. Preexisting myelopathy from any cause may be risk factors for radiation myelitis. MRI: cord swelling on T1-weighted images, intramedullary T2 hyperintensity, ringlike gadolinium enhancement.

CNS, Central nervous system; CSF, cerebrospinal fluid; Ig, immunoglobulin; LETM, longitudinally extensive transverse myelitis; MRI, magnetic resonance imaging; OCB, oligoclonal bands; TM, transverse myelitis; UMN, upper motor neuron.

Modified from Beh SC, Greenberg BM, Frohman T, et al. Transverse myelitis. *Neural Clin*. 2013;31:79–138, Table 10, p. 102–103.

likely to be complete. Necrosis and irreversible injury may occur in a small but important number of cases. Potentially associated underlying etiologies include systemic vasculitic entities (e.g., SLE), antibody-mediated CNS disorders (e.g., AQP4-Ab- or MOG-Ab-associated NMOSD), infectious etiologies (e.g., mycoplasma, enterovirus), or idiopathic disease. Pathology and imaging studies show acute inflammation with demyelination in some cases.

Acute Flaccid Myelitis

Acute flaccid myelitis (AFM) is an idiopathic neurologic disorder presenting with acute weakness and/or paralysis in previously healthy children. It is predominantly of infectious etiology. Although many viruses have been implicated, the recent biennial outbreaks since 2014 are likely to have been caused by enterovirus-D68. Abnormalities are often seen in the lower motor neurons of the anterior horn gray matter

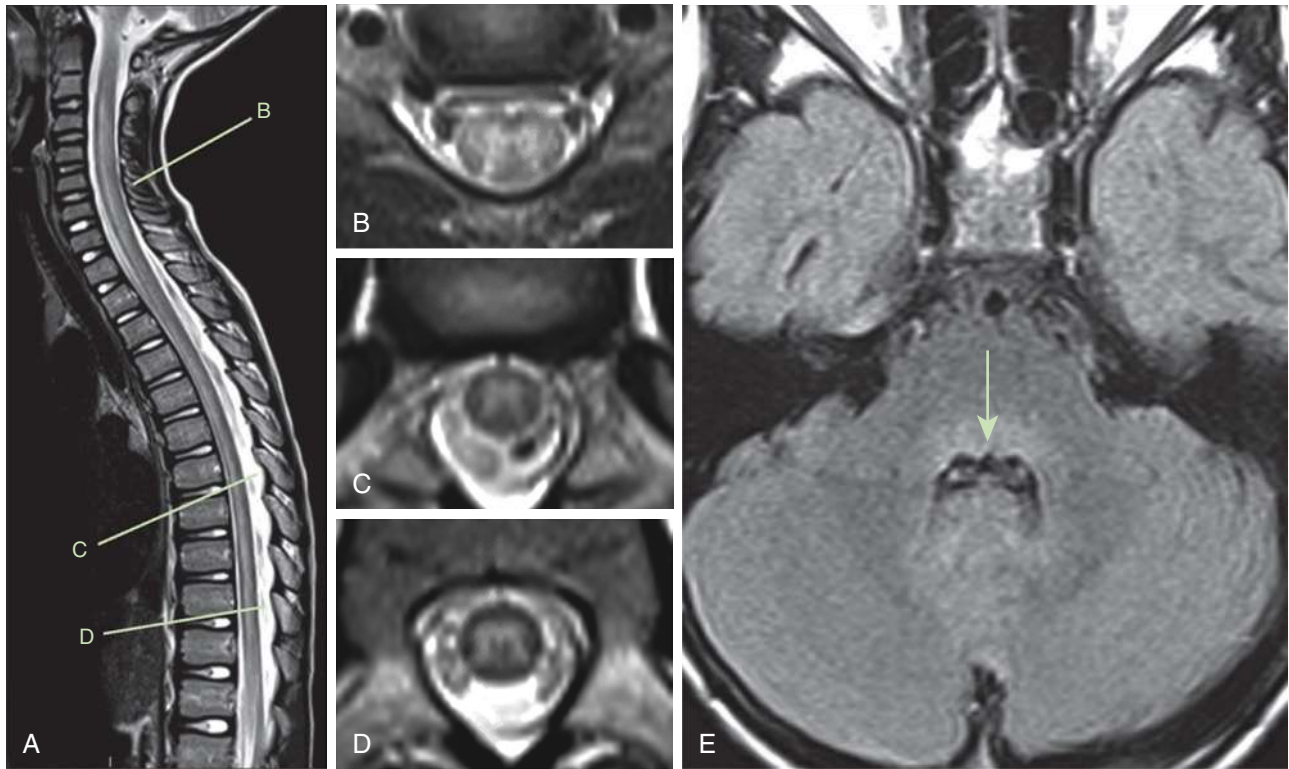


Fig. 640.4 Typical MRI findings in the acute phase of AFM. Spinal MRIs are shown of an 8-yr-old child with AFM, acquired 24 hr after onset of neurologic symptoms. **A**, Sagittal T2-weighted image showing an ill-defined, longitudinally extensive central/anterior spinal cord lesion. **B**, Axial T2-weighted image from C5–C6 shows hyperintensity of the entire gray matter of the spinal cord, with associated edema and some surrounding white matter hyperintensity. **C**, Axial T2-weighted image from T7 shows asymmetric hyperintensity of the gray matter (right more than left). **D**, Axial T2-weighted image from T10 shows hyperintensity of the entire gray matter. **E**, Axial FLAIR image at the level of the middle cerebellar peduncle demonstrates hyperintensity of the dorsal pons (arrow). AFM, acute flaccid myelitis. (From Murphy OC, Messacar K, Benson L, et al. Acute flaccid myelitis: cause, diagnosis, and management. *Lancet*. 2021;397:334–344, Fig. 1, p. 338.)

(Fig. 640.4). Symptoms can progress rapidly; paralysis is often asymmetric and is not usually accompanied by a sensory deficit; cranial nerve involvement may include facial weakness, dysarthria, and dysphagia (Table 640.7).

In the United States, AFP is considered a generalized “umbrella” term for multiple clinical entities, including paralytic poliomyelitis, transverse myelitis, AFM, Guillain-Barré syndrome, toxic neuropathy, and muscle disorders. Essentially, this grouping helps with case ascertainment of AFM, but the individual diagnoses still remain important because each has its own differential diagnoses to consider.

A pragmatic case definition of AFP is “a clinical syndrome with rapid onset of weakness that frequently involves the respiratory and bulbar muscles.” Whenever these criteria are met and poliomyelitis is a possibility, thorough investigation and reporting of potential poliomyelitis is required. Two diagnostic stool samples more than 24 hours apart should be collected within 14 days of onset of paralysis and then processed in a World Health Organization–approved laboratory. If poliomyelitis is confirmed, it may be caused by *wild poliovirus* (serotypes 1–3) or *vaccine-associated paralytic poliomyelitis*, and it will need full epidemiologic investigation. In the individual patient, disease progression with paralysis (with sensory preservation) is rapid, asymmetrical, and involves proximal more than distal muscles.

Other potential viral causes of AFP include coxsackie and echoviruses, Japanese B encephalitis, Murray Valley encephalitis, St. Louis encephalitis, and Russian spring encephalitis, tickborne viruses, and herpes virus. These causes vary by geography with, for example, EV-A71 being the cause in parts of Southeast Asia and West Nile virus being a cause in the United States. Therefore consider the following investigations for possible viral causes of AFP, as well as other conditions in the differential diagnosis:

- Imaging with MRI of the spine (and possibly brain)
- CSF sampling for differential cell counts, glucose, and protein;

microbiology and diagnostic polymerase chain reaction (PCR) testing for enteroviruses and other infectious diseases; and for autoantibodies such as anti-myelin oligodendrocyte glycoprotein (anti-MOG, see later)

- Respiratory/nasopharyngeal secretion samples for viral PCR testing (e.g., enterovirus)
- Peripheral neurophysiology with nerve conduction studies (NCS) if differentiation from GBS is needed or botulism is suspected
- Studies for identification of possible metabolic disease (e.g., acute hypokalemic periodic paralysis, thyrotoxic periodic paralysis, acute intermittent porphyria) and/or toxin exposures (e.g., sporadic hypokalemic paralysis secondary to licorice, barium, or cottonseed oil exposure)
- Investigations to exclude paralytic syndromes that mimic or are misdiagnosed as AFP, such as vitamin B₁₂ deficiency, which may be exacerbated by chronic cycad poisoning from evergreens, cyanide toxicity from cassava ingestion, and lathyrism.

CLINICAL MANIFESTATIONS OF TM

TM is often preceded within the previous 1–3 weeks by a mild nonspecific illness or minimal trauma. Discomfort or overt pain in the neck or back is common. Depending on its severity, the condition progresses to numbness, anesthesia, ataxia, areflexia, and motor weakness in the truncal and appendicular musculature at or distal to the lesion. Paralysis begins as flaccidity (paraparesis, tetraparesis). Spasticity then develops over weeks, accompanied by hyperreflexia and clonus. Weakness may rarely be unilateral, but usually such a finding suggests a hemicord lesion, which is most often associated with MS (particularly in adolescence). Urinary retention is a common early symptom; incontinence occurs later in the course. Early sensory findings may be isolated to the posterior column, necessitating evaluation of vibratory sensation. Progressive sensory loss may manifest as anesthesia, paresthesia, or

Table 640.7 Diagnostic Criteria for AFM

Diagnostic items	Definite	Probable	Possible	Uncertain
H1: Acute onset of limb(s) weakness (period from onset to nadir: hours to 10 days)	P	P	P*	P
H2: Prodromal fever or illness [†]	P/A	P/A	P/A	P
E1: Weakness involving one or more limbs, neck, face, or cranial nerves	P	P	P*	P
E2: Decreased muscle tone in at least one weak limb	P	P	P/A	P
E3: Decreased or absent deep tendon reflexes in at least one weak limb [‡]	P	P	P/A	P
MRI: Spinal cord lesion with predominant gray matter involvement, with or without nerve root enhancement [§]	P	P	P	ND
CSF: Pleocytosis (white cell count >5 cells/L)	P	A or ND	P/A or ND	P/A or ND
Factors that might suggest an alternative diagnosis 1. Encephalopathy that cannot be explained by fever, illness, respiratory distress, metabolic abnormalities, or medications 2. Presence of sensory deficits on examination 3. Presence of lesions in supratentorial white matter or cortex, which should prompt consideration of ADEM, MOG-antibody associated disease, neuromyelitis optica spectrum disorder, encephalomyelitis, and others 4. Absence of CSF pleocytosis, which should prompt consideration of Guillain-Barré syndrome, botulism, ischemic cord lesions, and others 5. Positive serum aquaporin-4 (AQP-4) antibody, which would exclude AFM 6. Positive serum MOG antibody, which would suggest MOG-antibody associated disease				

From Murphy OC, Messacar K, Benson L, et al. Acute flaccid myelitis: cause, diagnosis, and management. *Lancet*. 2021;397:334–344, Fig. 2, p. 339.

allodynia. Other potential findings include priapism, respiratory compromise, and spinal shock with subsequent autonomic dysreflexia. Rarely an overlap syndrome of TM with features of Guillain-Barré syndrome may occur.

DIAGNOSTIC EVALUATION

TM is a diagnosis of exclusion, and a thorough evaluation should be completed in all cases. The differential diagnoses include, among others, Guillain-Barré syndrome, demyelinating disorders, systemic rheumatologic conditions, meningitis, infectious myelitis, spinal cord infarction, arteriovenous malformations, trauma, mass lesions, bony and intervertebral disk distortion, abscess, and tumors of the spine and spinal cord (see [Tables 640.5 and 640.6](#)).

MRI with and without contrast enhancement is essential to rule out a mass lesion. T1-weighted images of the spine at the anatomic level of involvement may be normal or show spinal cord distension. In the infantile form, T2-weighted images show high signal intensity over multiple spinal segments. In the adolescent form, the high signal is often centrally located and involves both gray and white matter. It may be limited to one or two segments but is frequently more extensive. A limited degree of gadolinium contrast enhancement is expected (especially in the infantile form) and is indicative of an inflammatory condition. Cervical and cervicothoracic lesions represent most acute TM lesions. Axial cuts of the spinal cord are invaluable and can help to establish potential etiologies. Hemicord involvement may indicate MS. Holocord involvement with typical brain and optic nerve involvement suggests NMO. If

gray matter involvement predominates, consider a vasculitic or infectious process (e.g., SLE or enterovirus). Nerve root enhancement is occasionally seen and should raise suspicion for a mixed picture (central and peripheral demyelination) or anterior horn cell involvement ([Fig. 640.5](#)). Up to 6% of cases do not show spinal cord lesions on MRI. Repeat imaging at 7 days may reveal atrophy in these cases. *MRI of the brain is also indicated.* Evidence of other foci of demyelination is seen in at least 40% of patients; lesion localization should guide further consideration for MS, ADEM, NMO, SLE, and enterovirus-associated acute flaccid myelitis. In any child with *encephalopathy*, ADEM must be considered.

Lumbar puncture is indicated after exclusion of a mass on MRI and should be analyzed for cells, protein, immunoglobulin index, OCBs, and infectious pathogens. Mononuclear cells are usually elevated in TM. Protein may be elevated or normal. The presence of CSF inflammatory cells is essential for the diagnosis of TM.

Because one of the most important possibilities for this condition is NMO, the serum and CSF of all patients should be analyzed for both AQP-4 and MOG antibodies. Older children should also have serum studies sent for other autoimmune disorders, particularly SLE.

TREATMENT

Treatment of childhood TM has not been standardized. Available evidence suggests immune response modulation may be effective in reducing the severity and duration of disease. High-dose steroids (i.e., methylprednisolone) are used acutely in TM. In cases of poor response to high-dose steroids, other acute therapeutic approaches include

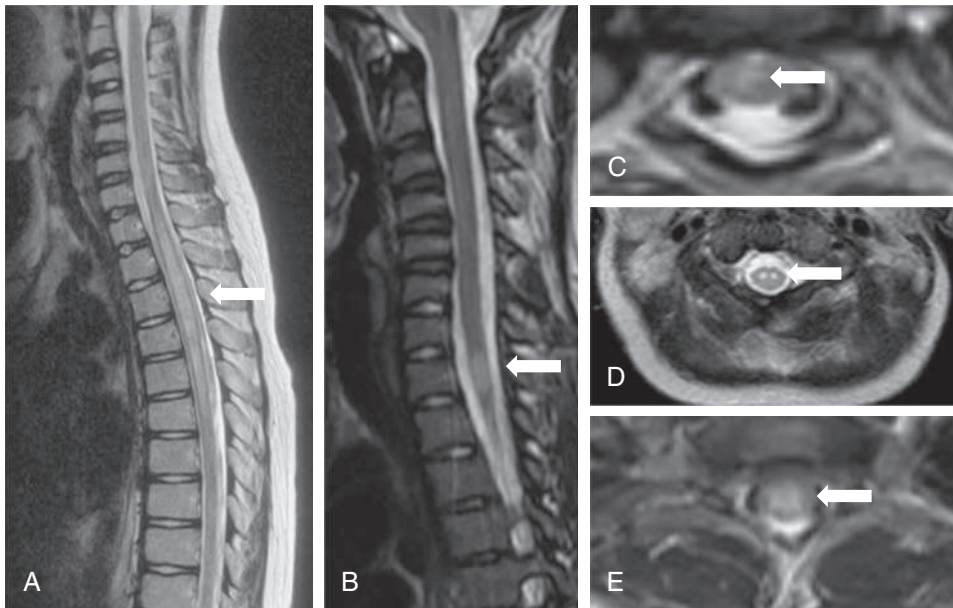


Fig. 640.5 Transverse myelitis. A, Sagittal T2-weighted image demonstrates a longitudinal hyperintense spinal cord lesion in a 12-yr-old female with first presentation of AQP4-Ab-positive NMOSD (arrow). B, Sagittal T1-weighted image shows a short segment at T1-weighted (arrow) in a 14-yr-old female with ON and MS. Axial T2-weighted images of the spine with different etiologies showing typical hemicord appearance in MS (C), anterior horn cell involvement in polio (D), and holocord involvement in NMOSD (E). (C–E courtesy Dr. Felice D’Arco, Great Ormond Street Hospital, London.)

intravenous immunoglobulin (IVIG) and plasma exchange (PLEX). Rituximab may be considered if an antibody-driven TM is suspected. Long-term prophylactic therapy is recommended for children with either relapsing disease or biomarkers indicating a risk for recurrence.

PROGNOSIS

Older children with acute TM have a better outcome than adults, with nearly 50% making a good recovery by 2 years. This may reflect the higher likelihood of MOG-Ab-associated disorders in the older child. The most common sequelae in the remaining 50% are sensory problems and bladder dysfunction. Outcomes in younger children with TM are comparatively poor. Recovery is slow and usually incomplete; the likelihood of independent ambulation is approximately 40%.

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640.4 Multiple Sclerosis

Michael Perry and Cheryl Hemingway

Multiple sclerosis (MS) is a chronic demyelinating autoimmune disorder of the brain, spinal cord, and optic nerves. It exhibits a relapsing-remitting course of neurologic events *without* encephalopathy separated in time (i.e., more than one episode of at least 24 hours at least 30 days apart) and space (i.e., in more than one CNS region). When occurring in those under 18 years, it is known as **pediatric-onset MS (POMS)**. Recurrent events lead to a characteristic accumulation of physical disability, cognitive impairment, and brain atrophy.

EPIDEMIOLOGY AND RISK FACTORS

MS is rare in childhood. In northern countries such as the United Kingdom and Canada, the annual incidence is estimated at 2 children per million. Interestingly, 5% of adult MS patients report in retrospect that they first experienced symptoms before age 18. POMS affects pre-pubescent males and females equally, but after puberty there is a 2:1 female predominance. Childhood MS is almost invariably relapsing-remitting in nature; features suggestive of primary progressive MS should prompt careful specialist evaluation for alternative conditions (Table 640.8).

In adults, a complex interplay of environmental (e.g., low sun-light exposure, low vitamin D, obesity, toxins), infectious (e.g., EBV

exposure), and genetic/epigenetic factors (e.g., HLA-DRB1*15:01 homozygosity) are thought to synergistically influence MS susceptibility. Studies in pediatric MS have so far confirmed the role of some of the earlier factors; however, the rarity of MS, the modest effects of a multitude of candidate risk factors, and the near ubiquity of EBV in the general population have made identification of causality and quantification of risk challenging. A landmark study of U.S. military service members, however, has provided the best evidence yet that EBV infection, long postulated as a putative cause of MS, precedes the onset of disease and confers a 32-fold increase in the risk of disease development. B cells, then, a reservoir of latent EBV infection, may help to explain the effectiveness of anti-CD20 DMTs in MS and provide a target for future therapeutics or vaccines.

PATHOGENESIS

Dysregulation of both the innate and adaptive immune systems is at the heart of MS pathogenesis. The precise sequence of events leading to aberrant production of autoreactive immune cells is not well understood. Restriction of inflammation to the CNS suggests the presence of a CNS autoantigen. How and where an immune response (i.e., B- and T-cell activation) to a purported autoantigen is initiated is unclear; it is possible that CNS antigens migrate into the peripheral lymph nodes (via antigen-presenting cells) where autoreactive T and B cells become activated or that the triggering antigen is derived from the periphery itself (e.g., systemic infection). Clonal cells targeting the brain and spinal cord initiate a self-perpetuating deleterious cycle of inflammation, axonal demyelination, and astrocytic gliosis, and eventual axonal degeneration occurs in both white and gray matter. It is this axonal degeneration that directly contributes to permanent disability. DMTs target inflammatory infiltrates within actively demyelinating lesions of relapsing-remitting MS in an attempt to attenuate this cycle before axonal loss.

CLINICAL MANIFESTATIONS

Presenting symptoms are polyregional in more than half of patients. These include focal sensory loss or other paresthesia (39–63%); cerebellar symptoms such as ataxia or dysarthria (50%); unilateral (and sometimes bilateral) painful eye movement and reduced visual acuity (ON) (37%); brainstem symptoms in 30%; and motor deficits in up to 50%. Such motor dysfunction can manifest as focal deficits, hemiparesis, paraparesis, and bowel/bladder dysfunction (from TM or other spinal lesions). Except in cases of significant brainstem involvement, encephalopathy is not a feature.

Table 640.8 Differential Diagnosis of Multiple Sclerosis: Selected Disorders with a Progressive Course				
	CLINICAL FEATURES	MRI FINDINGS	CSF FINDINGS	OTHER INVESTIGATIONS
HTLV1-associated myelopathy	Progressive myelopathy; residence or travel to an endemic area (especially West Indies or Japan)	Spinal cord atrophy (thoracic more than cervical); T2-hyperintense brain lesions in some patients	OCBs sometimes present	CSF HTLV1 antibody testing
Tumor	Progressive, variable features; headache, nonlocalizing symptoms of raised intracranial pressure; encephalopathy, vomiting, seizures, motor and/or sensory disturbances	Progressive enhancing and nonenhancing T2 lesions on serial imaging	OCBs absent	MRI; biopsy ± genetic investigations
Nutritional myelopathy (vitamin B ₁₂ or copper deficiency)	Subacute progressive myelopathy or myeloneuropathy; optic atrophy (severe vitamin B ₁₂ deficiency); anemia or pancytopenia	T2 hyperintensity of upper cervical cord classically affecting posterior columns; brain MRI normal	OCBs absent	Serum B ₁₂ , methylmalonic acid; serum copper levels, ceruloplasmin
Leukodystrophies: adrenomyeloneuropathy; Krabbe disease; Alexander disease; hereditary diffuse leukoencephalopathy with axonal spheroids	Progressive myelopathy (adrenomyeloneuropathy, Krabbe disease); bulbar symptoms, ataxia (Alexander disease); early cognitive impairment (hereditary diffuse leukoencephalopathy with axonal spheroids)	Highly variable; diffuse, symmetric T2 hyperintensity sparing subcortical U-fibers; with posterior hemispheric predominance (adrenomyeloneuropathy); spinal cord MRI normal or showing atrophy	OCBs absent	Very long-chain fatty acids (adrenomyeloneuropathy); genetic testing available for some leukodystrophies
Hereditary spastic paraplegia (especially SPG5)	Slowly progressive myelopathy (spasticity greater than weakness) with or without other neurologic symptoms and family history	Spinal cord atrophy; supratentorial and infratentorial white matter lesions (SPG5); atrophy of corpus callosum	OCBs absent	Genetic testing
Spinocerebellar ataxias	Progressive cerebellar ataxia, with or without other neurologic symptoms and family history	Early, prominent cerebellar findings, with or without spinal cord atrophy	OCBs absent	Genetic testing

CSF, Cerebrospinal fluid; HTLV1, human T-lymphotropic virus type 1; OCB, oligoclonal band.
From Brownlee WJ, Hardy TA, Fazekas F, et al. Multiple sclerosis 1: diagnosis of multiple sclerosis: progress and challenges. *Lancet*. 2017;389:1336–1346, Table 2, p. 1341.

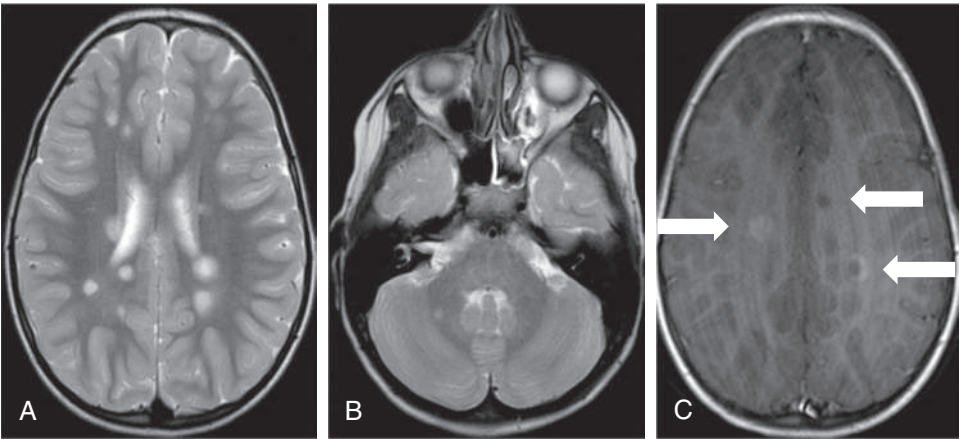


Fig. 640.6 5-year-old patient diagnosed on imaging with MS after presentation with left-sided weakness. **A**, Axial T2-weighted MRI of brain shows multiple discrete, ovoid white matter lesions in the periventricular region and cortical, juxtacortical, and infratentorial lesions (**B**). **C**, Axial T1-weighted area of hypointensity and two contrast-enhancing lesions (arrows).

IMAGING AND LABORATORY FINDINGS
Brain MRI exhibits typically discrete, ovoid, asymmetric T2 lesions in cerebral white matter, particularly periventricular, juxtacortical, cortical, brainstem and cerebellar. Less commonly, lesions are noted in the deep gray matter (Fig. 640.6). When involved, spine MRI typically

reveals partial-width cord lesions restricted to one to two spinal segments. Longitudinally extensive lesions are more likely to occur in NMOSD (associated with MOG-Ab and AQP4-Ab) than in MS. CSF may be normal or exhibit mild lymphocytosis. OCBs are positive in CSF but not in serum (type 2 pattern) in more than 90% of pediatric

MS patients. In NMOSD, OCBs are usually either negative (type 1 pattern) or present in both CSF and serum (type 4 pattern). Evoked potential studies can localize disruptions in visual, auditory, or somatosensory pathways.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Pediatric MS can usually be diagnosed after two demyelinating episodes *without* encephalopathy. Episodes must localize to one of four distinct CNS regions, last longer than 24 hours, and be separated by more than 30 days. Importantly in pediatric MS, there must exist no other plausible explanation for the symptoms. MRI may serve as a surrogate for recurrent demyelination, thereby enabling MS diagnosis after the first clinical event so long as it demonstrates dissemination in space (at least two T2 lesions involving juxtacortical, periventricular, infratentorial, or spine regions) and time (presence of gadolinium-enhancing lesion and nonenhancing T2 lesion in the same scan). A 10-year longitudinal study demonstrated that 96% of children diagnosed with POMS met 2017 McDonald criteria at presentation. Alternatively, MS can be diagnosed with a follow-up MRI at any time interval that exhibits accumulation of T2 or gadolinium-enhancing lesions in the brain or spine. The 2017 McDonald diagnostic criteria allow the presence of intrathecal OCBs to substitute for dissemination in time (see Table 640.1). Challenges may arise in distinguishing a first attack of pediatric MS from other acquired demyelinating syndromes, particularly those associated with antibodies (e.g., AQP4-Ab, MOG-Ab) or ADEM (Table 640.9 and see Table 640.4). Although irritability and lethargy may be present (particularly with brainstem lesions), encephalopathy is a highly atypical feature of MS, and one should be extremely cautious in making this diagnosis in a child with such symptoms. Indeed, the 2017 McDonald criteria's positive predictive value (PPV) was shown to be reduced because of the relative predominance of ADEM compared with MS in the under-12-years cohort. The absence of encephalopathy is therefore required to make a diagnosis of MS in this age-group.

TREATMENT

Relapses causing functional disability may be treated with intravenous methylprednisolone 20–30 mg/kg/day (maximum 1000 mg/day) for 3–5 days, with or without prednisolone taper. It should be noted that a study in adults demonstrated noninferiority of oral vs intravenous methylprednisolone in acute relapses in MS.

DMTs reduce both relapse frequency and T2 lesion load by targeting elements of the inflammatory response that predominates during the relapsing-remitting phase of MS. There is an increasing number of immunomodulatory and immunosuppressive treatment options available. They include injectables, oral medications, and infusions. The choice and sequencing of medications are becoming increasingly highly specialized (Table 640.10). Nearly all DMT use in pediatrics is currently off-label, though several randomized controlled trials are in progress. The only medication with FDA approval at the present time is fingolimod. One trial comparing oral fingolimod with intramuscular interferon-beta-1 α demonstrated that fingolimod reduced the annualized relapse rate by 82% when compared with interferon-beta-1 α in children between 10 and 18 years of age. This efficacy is greater than that seen in adults, possibly because of the greater inflammatory burden in POMS. This is but one of the reasons that prompt initiation of treatment is recommended for all those diagnosed with POMS.

An ongoing debate about DMT use concerns escalation vs induction—that is, whether to start with safer, less efficacious first-line agents and only escalate if treatment fails or whether remission should first be induced with the more aggressive and effective treatments before then maintaining on safer medications. Adult trials to answer this question are underway, and currently, the more efficacious treatments are generally reserved only for those with highly active MS. However, the increased inflammatory activity, higher relapse rate, and young age at which disability occurs in POMS has inspired research to investigate the theorized benefits of high-efficacy early treatment (HEET). One effectiveness study of DMTs in pediatric MS provided evidence in favor of HEET, having demonstrated marked superiority of high-efficacy medications in preventing both relapses and new brain lesions.

PROGNOSIS

Reliable prognostication in POMS remains a challenge for several reasons. The first is the long time over which the disease progresses. The second is the disconnect between inflammatory activity (e.g., lesion accumulation, relapse rate) and neuronal/axonal degeneration, which more directly corresponds to disability. Pediatric MS studies before widespread DMT use suggested a higher relapse rate but slower rate of disability accumulation compared with adults. Despite this longer interval to irreversible disability (20–30 years), pediatric MS patients acquire disability at a younger age than adults owing to the earlier age of onset of disease. Indeed, emerging evidence suggests the plasticity of the young brain likely accounts for the relative delays in disability accumulation and cognitive impairment. Nonetheless, like adults with MS, pediatric MS patients can acquire fixed neurologic deficits affecting the visual and other cranial nerves, motor and sensory function, balance, and bowel/bladder function. Children with MS have also been shown to have an overall smaller head size and brain volume that can be attributed to gray matter degeneration. Despite the marked reduction in annualized relapse rate (ARR), lesion load, and overall inflammatory burden compared with interferon-beta-1 α , children treated with fingolimod still lost brain volume and failed to achieve age-expected brain volume increase. This underscores the difficulty in addressing cognitive impairment, which is increasingly recognized and present in up to 50% of young people with POMS, more than that seen in adult-onset MS.

Fatigue is also a major symptom in pediatric MS that can lead to a poor quality of life. It is important to address this in a multidisciplinary setting together with other factors, such as mood, sleep quality, and sleep hygiene. Pharmacologic management of fatigue is challenging, but psychology-based therapy with cognitive-behavioral therapy and pacing has been shown to be effective.

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640.5 Myelin Oligodendrocyte Glycoprotein–Associated Disorders

Michael Perry and Cheryl Hemingway

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) encompasses a group of demyelinating disorders characterized by IgG autoantibodies to the MOG glycoprotein expressed in the outer layer of the myelin sheath. MOG antibodies are present in about 40% of all children with acquired demyelinating syndromes at first presentation. This increases to half of children with ADEM and nearly all those with relapsing ADEM (MDEM).

There is considerable *phenotypic* overlap between MOGAD, MS, and AQP4-Ab–positive NMOSD. Children with MOG-Ab seropositivity have often been classified as early MS or NMOSD; emerging evidence is drawing lines of demarcation between these entities. This paradigm is owed primarily to improved MOG-Ab assay techniques and specific clinical phenotypic description; differences in symptomatology, epidemiology, disease course, treatment response, prognosis, and histopathology between MOGAD, MS, and AQP4-Ab–positive NMOSD have been described. MOGAD may be either monophasic or relapsing; both MS and AQP4-NMOSD are characterized by a relapsing course. MOGAD has also demonstrated age-dependent variation of phenotype not seen in either MS or AQP4-NMOSD. Indeed, a minority of children with MOG antibodies may fit strict clinical and imaging criteria for a diagnosis of NMOSD with MOG (see Chapter 640.6). Most MOG-positive children (~60%) previously classified as NMOSD would no longer fit this criterion and thus represent a cohort distinct from NMOSD.

CLINICAL PRESENTATION

There are four main clinical phenotypes of MOGAD: (1) ADEM, (2) ON, (3) TM (NMOSD: ON and TM sequentially or simultaneously), and (4) cortical encephalitis. These may be monophasic or relapsing in nature, such as is seen with relapsing inflammatory optic neuritis (RION) or ADEM followed by

Table 640.9 Differential Diagnosis of Multiple Sclerosis: Clinical, MRI, and Serologic Findings of the Main Disorders that Can Resemble Relapsing-Remitting Disease

	NEUROLOGIC FEATURES	MRI FEATURES	BLOOD TEST AND CSF FINDINGS
Acute disseminated encephalomyelitis (most typically found in pediatric cohorts)	Similar to MS symptoms but encephalopathy is typical; frequently multifocal symptoms	Large spectrum from small punctate lesions to tumefactive lesions with mass effect, in the supratentorial or infratentorial white matter, bilateral, and asymmetric; involvement of cerebral cortex, deep gray matter, brainstem, and spinal cord; enhancement	CSF pleocytosis; serum antibody to MOG
Antibody-associated disease (e.g., AQP-4 NMOSD, MOG-Ab ON)	ON or TM (often concomitant and/or severe in NMOSD); nausea and vomiting	Variable depending on etiology; longitudinally extensive spinal cord lesion (>3 vertebral segments) (NMOSD); longitudinally extensive optic nerve lesions (MOG); posterior optic nerve or chiasmal involvement (NMOSD); spinal lesions with prominent gray matter involvement (H-sign) (MOG); pencil-thin ependymal enhancement and cloudlike enhancement	Serum antibody to AQP4 or MOG; possible mild pleocytosis; CSF OCBs infrequent
Neurosarcoidosis	Cranial nerve involvement (primarily facial and optic nerve); headache; raised intracranial pressure; meningitis; seizures; myelopathy	Meningeal enhancement with pituitary, hypothalamic, and cranial nerve involvement; brain white matter lesions; simultaneous enhancement of all lesions	Raised serum and CSF ACE (not sensitive or specific for sarcoidosis); CSF OCBs sometimes present
CNS vasculitis	Confusion, headache, personality change; seizures; stroke-like symptoms	Ischemic, multiple lesions; predominance of lesions at cortico-subcortical junction; intracranial hemorrhage; meningeal enhancement; simultaneous enhancement of all lesions; microbleeds	Serum antineutrophil cytoplasmic antibodies; CSF OCBs sometimes present
Susac syndrome	Visual loss; sensorineural hearing loss; encephalopathy; headache; memory loss; behavioral disturbances	Focal and small lesions in supratentorial and infratentorial regions (both white matter and gray matter); involvement of corpus callosum (snowball lesions); leptomeningeal enhancement	CSF OCBs usually absent
Hypoxic-ischemic vasculopathies (particularly small-vessel disorder)	Stroke events; cognitive decline; focal neurologic signs; gait disturbance	Punctate and peripheral white matter lesions, sparing U-fibers; symmetric and confluent periventricular lesions; lacunar infarcts; involvement of central transverse fibers in pons; microbleeds	Serum testing for vascular risk factors (diabetes, hypercholesterolemia); CSF OCBs absent
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)	Migraine; stroke events; psychiatric problems and dementia	Temporal pole lesions; external capsule and U-fiber lesions; microbleeds	CSF OCBs absent; testing for <i>NOTCH3</i> gene variant
Connective tissue disorders (SLE, Sjögren syndrome, antiphospholipid antibodies syndrome)	Optic nerve, brain, and spinal cord involvement; neuropsychiatric symptoms; seizures; ischemic episodes	Brain infarcts and hemorrhage; basal ganglia lesions; punctate (subcortical) lesions; spinal cord lesions; cerebral venous sinus thrombosis; parotid gland involvement in Sjögren syndrome	Serum antinuclear antibody; extractable nuclear antigens (in particular, anti SS-A(Ro) and SS-B(La) antibodies for Sjögren syndrome, and anti-Sm for SLE); CSF OCBs usually absent
Neuro-Behçet disease	Brainstem syndrome; myelopathy; meningoencephalitis	Large brainstem lesions; basal ganglia, subcortical white matter, and spinal cord lesions; gadolinium enhancement; cerebral venous sinus thrombosis	HLA-B5; CSF pleocytosis; CSF OCBs usually absent
Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS)	Cranial nerve dysfunction and long-tract signs; symptoms referable to brainstem or cerebellar dysfunction; spinal cord syndrome; cognitive dysfunction	Multiple punctate, patchy, and linear regions of gadolinium enhancement relatively confined to pons; lesions also involving cerebellum, basal ganglia, supratentorial white matter, brainstem, and spinal cord	CSF OCBs sometimes present; consider testing for primary CNS hemophagocytic lymphohistiocytosis even if meeting criteria for CLIPPERS (see later)

Table 640.9 Differential Diagnosis of Multiple Sclerosis: Clinical, MRI, and Serologic Findings of the Main Disorders that Can Resemble Relapsing-Remitting Disease—cont'd

	NEUROLOGIC FEATURES	MRI FEATURES	BLOOD TEST AND CSF FINDINGS
Primary CNS hemophagocytic lymphohistiocytosis (HLH)	Mimic of CLIPPERS, MDEM, and small vessel CNS vasculitis with a treatment-resistant and steroid-dependent disease pattern; symptoms include seizures, encephalopathy, weakness, ataxia, nystagmus, vomiting	Multifocal cerebral and cerebellar matter lesions with variable T2 hyperintensities; homogeneous enhancing nodules and curvilinear and punctate lesions of pons like that seen in CLIPPERS; diffuse cerebellar cortical edema	Genetic testing (e.g., <i>PRF1</i> , <i>UNC13D</i>); natural killer (NK)-cell function; CSF proteinosis or pleocytosis; neopterin may be a useful biomarker of disease activity
Fabry disease	Stroke events; vertigo	Posterior infarcts; multiple white matter lesions with pulvinar involvement (T1 hypointense lesions)	Reduced activity of GLA enzyme; analysis of GLA gene
Leber hereditary optic neuropathy	Bilateral sequential optic neuropathies with poor visual recovery; more common in men than women	Normal or might show white matter lesions (Harding disease)	OCBs absent; mitochondrial DNA (mtDNA) genetic testing for three most common (~90%) variants in first instance: MTND1m.3460G>A, MTND4m.11778G>A, MTND6m.14484T>C; full mtDNA sequencing indicated if targeted sequencing negative and clinical suspicion remains high

Infectious diseases are not included in this table but should be considered, especially in cases of atypical demyelinating lesions. CSF, Cerebrospinal fluid; ACE, angiotensin-converting enzyme; GLA, α galactosidase A; OCB, oligoclonal band. Modified from Thompson AJ, Baranzini SE, Geurts J, et al. Multiple sclerosis. *Lancet*. 2018;391:1622–1636, Table 3, pp. 1628–1629.

Table 640.10 Overview of Available and Emerging Therapies Used in Pediatric Multiple Sclerosis and Other Relapsing Demyelinating Disorders

MEDICATION AND ROUTE OF ADMINISTRATION	MEDICATION CLASS	MECHANISM IN MS	COMMONLY REPORTED OR SERIOUS SIDE EFFECTS	EFFICACY
FIRST-LINE THERAPIES APPROVED FOR MS IN ADULTS				
Interferon- β -1a and β -1b (subcutaneous or intramuscular injection on alternate days, 3 times weekly, weekly or bimonthly depending on preparation)	Immunomodulator	Modulates T cells and cytokine production	Injection site reaction; flu-like symptoms; headache, muscle aches, transaminitis; leukopenia; tissue necrosis at injection site (rare)	~33% decrease in ARR and slows progression of disability
Glatiramer acetate (daily or 3 times weekly, subcutaneous injection)	Immunomodulator	Stimulation of Th-2 regulatory T-cells	Injection site reactions; transient flushing, chest tightness and shortness of breath. Lipodystrophy at injection sites	~33% decrease in ARR and slows progression of disability
Dimethyl fumarate (DMF) (oral medication 12 hourly with food, i.e., twice a day)	Immunomodulator	Unclear mechanism; likely antiinflammatory promotion via modulation of nuclear factor κ B; modulates cytokine production and reduces lymphocyte count. neuroprotectant; antioxidant	Flushing; viral URTI; dysmenorrhea; GI upset; headache; proteinuria, leukopenia. Rare reports of PML in those with severe prolonged lymphopenia	Reduces number of relapses by ~ 50% compared with placebo in adults; this has recently been shown to remain stable over 10 yr of treatment (ENDORSE). Small single-arm pediatric phase 2 + extension study (FOCUS + CONNECTED) demonstrates favorable safety and efficacy profile. Phase 3 pediatric RCT (CONNECT) ongoing
SECOND-LINE THERAPIES APPROVED FOR MS IN ADULTS				
Teriflunomide	Immunomodulator	Pyrimidine synthesis impairment via dihydroorotate dehydrogenase inhibition; reduction of T and B cells proliferation	Infections (respiratory tract); pancreatitis; headaches; diarrhea; liver inflammation or injury; alopecia; nail and skin disorders; teratogenicity	43% reduction in combined risk of clinical relapse or high MRI activity vs placebo; 55% reduction in new or enlarged T2 lesions vs placebo (TERIKIDS trial)

Continued

Table 640.10 Overview of Available and Emerging Therapies Used in Pediatric Multiple Sclerosis and Other Relapsing Demyelinating Disorders—cont'd

MEDICATION AND ROUTE OF ADMINISTRATION	MEDICATION CLASS	MECHANISM IN MS	COMMONLY REPORTED OR SERIOUS SIDE EFFECTS	EFFICACY
Natalizumab (infusion over 2-3 hr every 4 wk; alternatively subcutaneous injection every 4 wk)	Monoclonal antibody	Targets α_4 -integrin on vascular endothelium, preventing T- and B-cell migration into CNS	Infusion reactions with headache, dizziness, rash; rare anaphylaxis. May affect liver function. Risk of PML able to be stratified by JC virus status, length of treatment, and previous treatments. Immune reconstitution syndrome after discontinuation; melanoma	Reduces number of relapses by ~70% in adults
Fingolimod (daily oral medication: first dose, cardiac monitoring required and need to ensure good compliance because of risks of first-dose bradycardia and heart block)*	Immunomodulator	Modulates sphingosine-1-phosphate receptors; causes T-cell sequestration in lymphoid compartments	First-dose bradycardia; cardiac arrhythmia; systemic viral infection; persistent lymphopenia with risk of severe herpetic and varicella infection; macular edema; transaminitis; basal cell carcinoma. Rare cases of PML	FDA approved for pediatrics May 2018 after first prospective RCT in children with POMS (PARADIGMS) showing 82% decrease in ARR compared with interferon β
Alemtuzumab (infusions 2 courses: first for 5 consecutive days; second 12 mo later for 3 consecutive days) [†]	Monoclonal antibody	Anti-CD52 antibody target; depletes mature B and T cells	Vascular disorders (see footnotes re: FDA black box warning: ischemic stroke, arterial dissection); Infusion reactions within first 2-3 hr; opportunistic infection, secondary autoimmune disorders, including thyroiditis (50% risk), hemophagocytic lymphohistiocytosis (HLH), autoimmune hepatitis, immune thrombocytopenia (1%); glomerular nephropathies including anti-glomerular basement membrane disease (Goodpasture syndrome). Monthly blood tests required for 4 yr after last course	Highly effective in adults; ~ 55% decrease in ARR compared with interferons. Pediatric single-arm, before and after switch study (LemKids) ongoing.
Cladribine (oral tablets two courses: first for 4-5 consecutive days during mo 1 and 2; second as before 12 mo later)	Immunomodulator	Selective activity against CD4 and CD8 T cells and CD19 B cells via adenosine deaminase activity	Neutropenia, lymphopenia, infection, oral herpes, GI disorders, and rash	Reduced relapses by ~58% vs placebo in adults and delay in disability progression. No pediatric trials conducted to date
Rituximab (infusions given 2 wk apart ~every 6 mo)	Monoclonal antibody	Targets CD20, a marker of immature B cells; depletes B-cell populations	Infusion-related side effects; hepatitis, PML (rate undefined)	Used off-label for adult MS; no efficacy assessments available in pediatric MS
Ocrelizumab (infusions given 2 wk apart ~every 6 mo)	Monoclonal antibody	Targets CD20, a marker of immature B cells; depletes B-cell populations	Headache; infusion-related side effects; theoretic risk of PML (undefined) and, possibly, malignancy	In adult MS showed 50% reduction in ARR compared with interferons; a phase 3 pediatric trial (OPRETTA 2) is ongoing
OTHER MEDICATIONS USED FOR DEMYELINATING DISORDERS				
Azathioprine (intravenous infusion or oral tablets daily)	Chemotherapeutic	Disrupts purine metabolism; effects include cytotoxic immune cell depletion	GI side effects, alopecia, bone marrow suppression, and blood dyscrasias, transaminitis, infections, secondary malignancy, alopecia. Increased side effects with low TPMT enzyme activity	No efficacy assessments available in pediatric MS; small retrospective studies for NMOSD

Table 640.10 Overview of Available and Emerging Therapies Used in Pediatric Multiple Sclerosis and Other Relapsing Demyelinating Disorders—cont'd

MEDICATION AND ROUTE OF ADMINISTRATION	MEDICATION CLASS	MECHANISM IN MS	COMMONLY REPORTED OR SERIOUS SIDE EFFECTS	EFFICACY
Intravenous immunoglobulin (IVIG)	Immunotherapy	Inhibits complement binding; promotes antiinflammatory interleukin secretion; promotes regulatory T cells	Generally better tolerated than PLEX; headache; rash; allergic reaction	Limited class C evidence (small pediatric case series) suggests improved outcomes in severe and/or relapsing cases of ADS
Mycophenolate mofetil (MMF) (intravenous infusion or oral tablets twice daily)	Immunosuppressant	Disrupts purine synthesis and impairs B- and T-lymphocyte proliferation	GI side effects, alopecia, bone marrow suppression and blood dyscrasias, transaminitis, infections, secondary malignancy, alopecia. Teratogenic.	
Plasma exchange (PLEX)	Extracorporeal immunotherapy	Removal of pathogenic autoantibodies and proinflammatory macromolecules	Electrolyte abnormalities (particularly hypocalcemia); infection; hypotension; allergic reaction; anemia	Limited pediatric case series and adult studies available support use as rescue and/or second-line therapy
Vitamin D	Vitamin/hormone	Modulates immune cell expression	Hypercalcemia and kidney stones at serum 25(OH) vitamin D level > 100 ng/mL	Prospective trials in pediatric and adult MS are currently underway

*Additional S1P inhibitors with more specific receptor selectivities (i.e., less cardiac cross reactivity) are coming to market; pediatric trials are currently ongoing.

[†]U.S. FDA black box warning regarding rare but serious vascular side effects including ischemic and hemorrhagic stroke and cervicocephalic dissection. To be used with caution only in specialist centers.

CNS, Central nervous system; ARR, annualized relapse rate; MS, multiple sclerosis; JC virus, John Cunningham virus; PML, progressive multifocal leukoencephalopathy; TPMT, thiopurine methyltransferase; GI, gastrointestinal.

optic neuritis (ADEM-ON) (see Table 640.1). Tumefactive lesions, cerebellar demyelination, cranial neuropathies, monofocal or polyfocal cerebral motor deficits, and occasionally a widespread progressive leukodystrophy-like pattern may also be seen. Children with cortical encephalitis may present with seizures, headache, fever, and cortical symptoms with cortical hyperintensities on T2-weighted MRI sequences. Symptoms may be preceded by a viral prodrome, but no pathogens have been causally linked.

The diagnostic guideline of the International MOGAD Panel requires fulfillment of three criteria (Table 640.11):

1. Presence of one of six core clinical demyelinating events: optic neuritis, myelitis, ADEM, cerebral monofocal or polyfocal deficits, brainstem or cerebellar deficits, or cerebral cortical encephalitis
2. Serum MOG-Ab positivity
3. Exclusion of MS and other demyelinating syndromes

IMAGING AND LABORATORY FINDINGS

MRI findings are atypical for MS (Fig. 640.7 and see Fig. 640.3). Brain MRI may show widespread involvement of the supratentorial and infratentorial white matter that can over time develop into a leukodystrophy-like pattern. This may extend into the pons, middle cerebellar peduncle, medulla, or deep gray matter. Spinal imaging suspicious for MOG-Ab disease may show longitudinally extensive myelitis, a characteristic H-sign of the central cord, or a lesion of the conus medullaris. Accrual of MRI lesions in the absence of relapse (i.e., clinically silent), a hallmark of MS, is not a typical feature of MOGAD. MRI of the optic nerves can be particularly useful in discrimination of phenotype and may show specific findings that together may indicate MOG-Ab disease. These include perineural sheath enhancement, papilledema, bilateral ON, and longitudinal nerve involvement. Previously attributed to those with POMS, these findings are now recognized as hallmarks of MOG-Ab-associated disease.

Suspected cases should have serum tested for MOG antibodies via live CBA for the IgG Fc or IgG1 secondary antibodies; importantly, laboratories should ideally report both quantitative (i.e., titers) and qualitative results (i.e., low-positive or high-positive) (Fig. 640.8). Despite variation in assay protocols across laboratories

globally, high positivity is reliably predictive of true MOG-Ab positivity. Low-positive or borderline results less reliably differentiate MOG-Ab disease from other entities and should prompt reconsideration of other diagnoses, particularly MS. Fixed CBAs may be used with some caution if live CBA is not available, but enzyme-linked immunosorbent assay (ELISA) should be avoided. Although useful for diagnostic purposes, MOG-Ab titer levels are unhelpful in predicting risk of relapse.

Intrathecal OCBs are not normally present. However, OCB positivity should not preclude a diagnosis of MOG in the presence of supportive clinical features (particularly TM) and high MOG-IgG antibodies. Elevated CSF white blood cells with pleocytosis is often present.

TREATMENT

Treatment of acute attacks is similar to other demyelinating disorders: high-dose methylprednisolone, PLEX, and IVIG. Most children with MOGAD will experience a monophasic course and thus should not be offered DMT after a first event.

There is currently no clarity about DMTs that may be helpful over the long term and in relapsing disease. A complicating factor is the potential for long intervals between relapses. This makes it exceedingly difficult to determine the true efficacy of DMTs and guide early decisions about initiating treatment. Some studies have even demonstrated an exacerbation of MOG-Ab disorders treated with traditional MS medications, highlighting again the importance of an accurate clinical diagnosis.

The decision to use long-term immunosuppressive agents after induction therapy can be difficult. Unlike MS and AQP4-NMOSD, MOGAD may be monophasic or relapsing. At present, reliable predictors for risk of relapse do not exist. Therefore children with MOGAD are assessed holistically to determine the appropriateness of chronic therapy based on the risk:benefit ratio of each individual patient. This may include the severity of initial presentation, response to acute treatment, recovery from index attack, and likelihood of relapse. In children assessed as likely to benefit from DMTs, medications such as mycophenolate mofetil and azathioprine are frequently

Table 640.11		Proposed Diagnostic Criteria for MOGAD*	
(A) Core clinical demyelinating event	• Optic neuritis • Myelitis • ADEM • Cerebral monofocal or polyfocal deficits • Brainstem or cerebellar deficits • Cerebral cortical encephalitis often with seizures		
(B) Positive MOG-IgG test	Cell-based assay: serum	Clear positive	No additional supporting features required
		Low positive Positive without reported titer Negative but CSF positive	AQP4-IgG seronegative AND ≥1 supporting clinical or MRI feature
Supporting clinical or MRI features	Optic neuritis	• Bilateral simultaneous clinical involvement • Longitudinal optic nerve involvement (> 50% length of the optic nerve) • Perineural optic sheath enhancement • Optic disc edema	
	Myelitis	• Longitudinally extensive myelitis • Central cord lesion or H-sign • Conus lesion	
	Brain, brainstem, or cerebral syndrome	• Multiple ill-defined T2 hyperintense lesions in supratentorial and often infratentorial white matter • Deep gray matter involvement • Ill-defined T2-hyperintensity involving pons, middle cerebellar peduncle, or medulla • Cortical lesion with or without lesional and overlying meningeal enhancement	
(C) Exclusion of better diagnoses including multiple sclerosis			

*Requires fulfillment of A, B, and C.
Modified from Banwell B, Bennett JL, Marignier R et al. Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: International MOGAD Panel proposed criteria. *Lancet Neurol.* 2023;22(3):268-282.

offered. This can be done with or without steroids. Rituximab has been used with some reports of benefit. However, there have also been concerning cases of severe exacerbations despite B-cell depletion, particularly in those with relapsing brainstem demyelination. It is important to remember that although both AQP4 and MOG disorders are antibody-driven, the former is an astrocytopathy, whereas the latter is an oligodendrocytopathy. Therefore extrapolation of treatment effects from one condition to the other is not necessarily possible. Monthly IVIG is the only treatment to date to consistently have shown benefit in high-risk individuals. However, there is great promise in new treatments such as satralizumab, an anti-IL-6 antibody, and anti-neonatal Fc receptor antibodies, which aim to reduce levels of pathogenic autoantibody by blocking IgG recycling.

PROGNOSIS

MOGAD is generally associated with a more benign course and favorable recovery compared with AQP4-Ab demyelination. Dramatic resolution is often seen in as little as 30 days on follow-up MRIs. MOGAD is particularly heterogenous, however, and certain phenotypes such as brainstem demyelination can have a very high relapse rate. Progression of disability is directly related with relapse rate, and therefore predictors of relapse rate is a focus of intense research. Approximately one third of MOG-positive children will relapse within 8 years of the first presentation. This risk is slightly higher in MOG-related ON and lower in isolated TM. Relapses can also occur many years after the first event, with intervals of more than 10 years having been reported. Cognitive deficits are seen frequently in those with young onset and frequent relapses.

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640.6 Neuromyelitis Optica Spectrum Disorders

Michael Perry and Cheryl Hemingway

The neuromyelitis optica spectrum disorders (NMOSDs) are severe autoimmune inflammatory diseases classically characterized by episodes of ON and/or longitudinally extensive TM. The discovery of pathogenic antibodies to the astrocyte water channel protein aquaporin-4 (AQP4) and the incorporation of these antibodies into the 2015 revised diagnostic criteria for NMOSDs have helped to distinguish AQP4-Ab-related disorders from other demyelinating conditions; it has also widened the spectrum of the group of disorders to include brainstem syndromes (e.g., area postrema syndrome) and recurrent forms of ON and TM (see Table 640.1). MOG-Ab has also been identified in many cases that were initially thought to have been AQP4-antibody-negative presentations. Reports of both antibodies being simultaneously present in a single individual are exceedingly rare; in these circumstances, a diagnosis of AQP4-Ab-positive NMOSD should take precedence and guide management.

EPIDEMIOLOGY

AQP4-Ab-positive NMOSD typically presents in older adults, whereas MOG-Ab NMOSD is much more common in children and young people. Both, however, can occur across a wide age spectrum. Population studies vary significantly but suggest a pediatric incidence for NMOSDs of 0.5–4.5% of all ADS presentations. AQP4-Ab-driven NMOSD is significantly more common in females than in males. NMOSD appears to have a higher mortality rate in Black people. Most cases of NMOSD are idiopathic; only occasionally have familial cases have been reported. Several genetic risk factors have been described, including the HLA-DRB1*0301 allele and a single-nucleotide polymorphism in CD58.

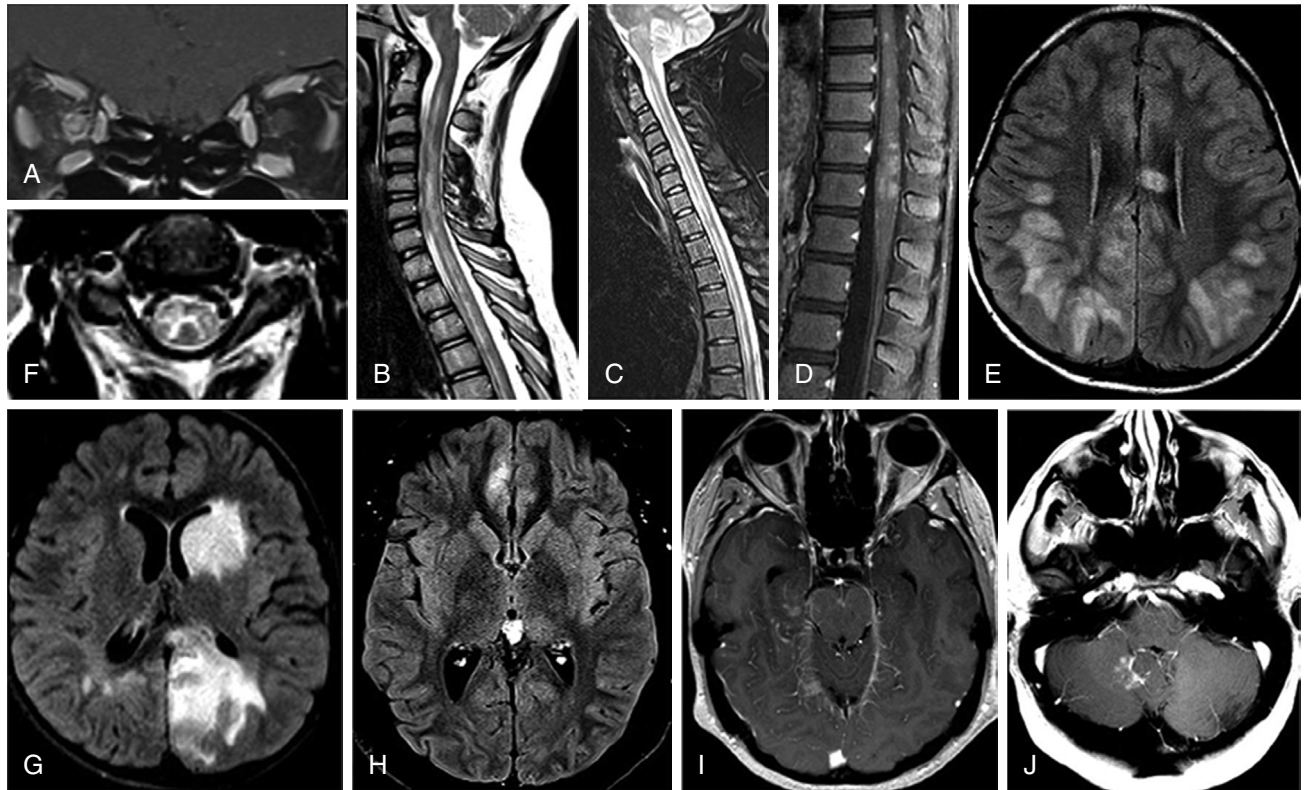


Fig. 640.7 Spectrum of anti-MOG-associated diseases. A, Coronal T1-weighted MRI of brain post-gadolinium contrast showing contrast enhancement of bilateral optic nerves and right optic nerve sheath consistent with peri-optic neuritis. B, Sagittal STIR MRI of spine showing longitudinal extensive patchy lesion spanning from cervical to thoracic cord. C, Sagittal T2-weighted MRI of spine showing hyperintense, longitudinally extensive "pseudo-dilation" of central canal. D, Sagittal T1-weighted MRI of spine post-gadolinium contrast showing patchy enhancement of the conus medullaris. E, Axial FLAIR MRI of brain showing large subcortical and septal white matter lesions in a pediatric patient presenting with ADEM. F, Axial T2-weighted MRI of brain with hyperintense "H" sign outlining the central gray matter of the upper cervical cord in a teenager with myelitis. G, Axial T2-weighted MRI of brain with "fluffy" hyperintense lesion of gray and white matter of the left caudate and left occipital parietal regions in a pediatric patient who presented with ADEM. H, Axial T2-weighted MRI of brain showing unilateral FLAIR hyperintensity and edema of the right mesial frontal cortex in a patient with FLAMES syndrome. I, Axial T1-weighted MRI of brain post-gadolinium contrast showing leptomenigeal enhancement of the midbrain and right mesial temporal lobe. J, Axial T1-weighted MRI of brain post-gadolinium contrast showing a lesion adjacent to the cerebellar vermis and dorsal medulla in a patient with brainstem syndrome and no other lesions. (From Parrotta E, Kister I. The expanding clinical spectrum of myelin oligodendrocyte glycoprotein [MOG] antibody associated diseases in children and adults. *Front Neurol*. 2020;11:Article 960, Fig. 1.)

PATHOGENESIS

The water channels against which the AQP4-IgG antibody is directed are most abundant on the astrocyte foot processes within the periventricular regions, brainstem, optic nerves, and spinal cord; thus strictly speaking, NMOSD can be characterized as an autoimmune *astrocytopathy* with secondary demyelination. Antibody (primarily IgG1 subtype) binding occurs at the extracellular loops of the AQP4 protein. This activates the classical complement pathway with C5b-C9 component, stimulating leukocyte migration and degranulation, ultimately resulting in astrocytic death. Chemokine secretion from the dying astrocytes and activated leukocytes further attract additional macrophages, leading to oligodendrocyte and neuronal death. Subsequent necrosis or cavitation may occur.

CLINICAL MANIFESTATIONS

AQP4-positive NMOSD presents most commonly with ON, TM, or area postrema syndrome (i.e., hiccups, nausea, and/or intractable vomiting); vomiting is highly unusual in MOG-Ab NMOSD. The symptoms and signs of TM depend on the spinal level and completeness of the inflammatory changes. ON or TM may occur simultaneously or may be separated in time by weeks or even years. Some patients, particularly in MOG-Ab NMOSD, present with seizures and encephalopathy mimicking ADEM. Others exhibit endocrinopathies such as the syndrome of inappropriate antidiuretic hormone secretion (SIADH),

diabetes insipidus (DI), hyperinsulinemia, disrupted puberty, or obesity. NMOSD may also be associated with other autoimmune conditions, such as SLE, Sjögren syndrome, diabetes mellitus (DM), and thyroiditis.

IMAGING AND LABORATORY FINDINGS

Neuroimaging studies must include the entire spine, optic nerves if visual symptoms are present, and brain. Although often manifesting with large, hazy, ill-defined white matter lesions and/or gray matter involvement, such as thalamic lesions, brain imaging may have only subtle white matter changes, or even be normal. Brain lesions most frequently localize to areas of high AQP4-Ab expression such as the periaqueductal gray matter, dorsal brainstem, and diencephalon (Fig. 640.9). Spinal imaging may reveal short or longitudinally extensive TM; longitudinally extensive ON involving the chiasm is more common in MOG-Ab disease. Imaging does not reliably differentiate AQP4-Ab and MOG-Ab. Both, however, are readily distinguished from MS by the absence of discrete, well-defined oval lesions in the periventricular white matter.

Although AQP4-Ab and MOG-Ab can be found in both the serum and CSF, their relative increased prevalence in the serum suggests extrathecal production of antibody. There are several different methods of varying sensitivity for antibody testing; the gold standard is the live CBA. Repeat testing is advised in cases of high clinical suspicion of an antibody-driven

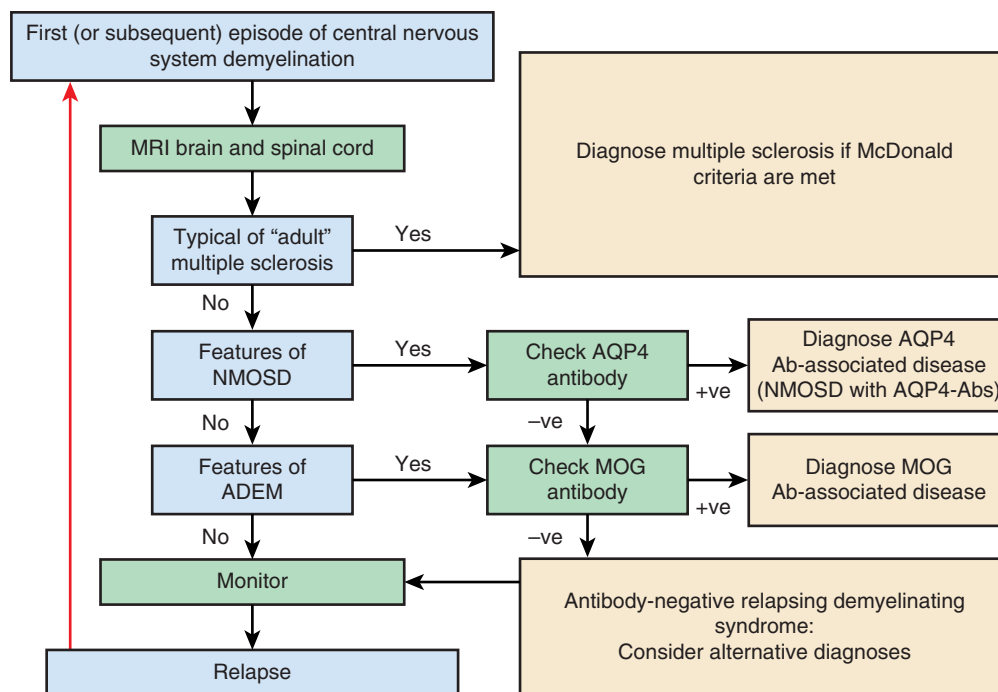


Fig. 640.8 Diagnostic algorithm that can be applied to any episode of CNS demyelination in children. The first recommended diagnostic test is brain and spinal cord MRI. If MRI findings are considered to be typical or suggestive of adult MS, then the McDonald diagnostic criteria should be applied. In children whose MRI is not typical or suggestive of MS but who have clinical and radiologic features suggestive of NMOSD, AQP4-Ab testing is recommended. In particular, this test is advised in children presenting with an area postrema syndrome, MRI abnormalities localized to the brainstem and hypothalamus, and destructive lesions. If AQP4-Ab is negative, then MOG-Ab should be tested. In children whose MRI is not typical of MS or NMOSD but the clinical and radiologic presentation has features of ADEM, MOG-Ab testing is recommended. Supporting features for MOG-Ab-associated disease include lesions in the cerebellar peduncle and leukodystrophy-like MRI pattern in the very young. Alternative diagnoses should be considered in the remaining Ab-negative patients. (From Hacohen Y, Mankad K, Chong WK, et al. *Diagnostic algorithm for relapsing acquired demyelinating syndromes in children*. *Neurology*. 2017;89:269–287, Fig. 2.)

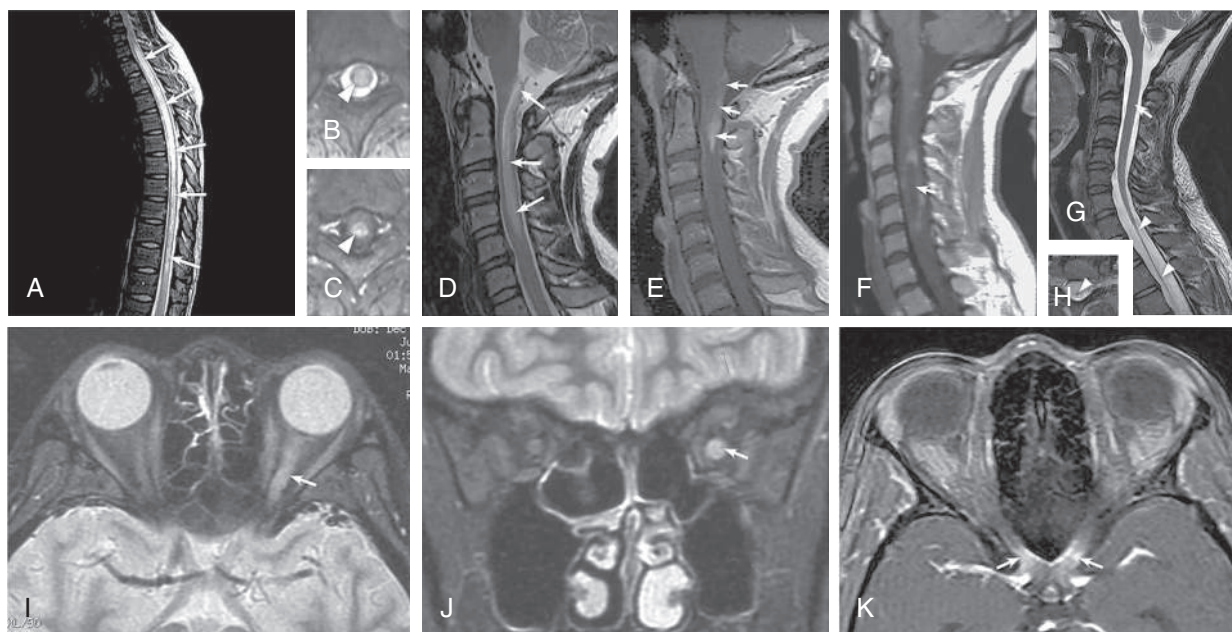


Fig. 640.9 Spinal cord and optic nerve MRI patterns in NMOSD. Spinal cord imaging in the context of acute myelitis in NMOSDs usually reveals a longitudinally extensive transverse myelitis (LETM) lesion extending over three or more vertebral segments. A, Sagittal T2-weighted MRI of the thoracic spinal cord demonstrates a typical LETM lesion involving most of the thoracic spinal cord (arrows). LETM lesions have a predilection for the central cord, as shown by axial T2-weighted (B; arrowhead) and T1-weighted MRIs with gadolinium (C; arrowhead). Cervical LETM may extend into the medulla, a characteristic NMOSD pattern demonstrated in D (arrows; sagittal T2-weighted MRI) and E (arrows; sagittal T1-weighted MRI with gadolinium). Acute LETM lesions can be associated with intralesional hypointensity, as shown by sagittal T1-weighted MRI (F; arrow); in this example, a rim of gadolinium enhancement surrounds the hypointense region. Chronic sequelae of LETM may include longitudinally extensive segments of spinal cord atrophy, as shown by T2-weighted MRI using the sagittal plane (G; the two arrowheads indicate the atrophic segment, and the top arrow indicates the normal diameter of unaffected cervical spinal cord) and axial plane (H; arrowhead shows an atrophic spinal cord). Fast spin echo fat-suppressed T2-weighted MRI in the axial (I) and coronal (J) planes shows increased signal throughout most of the length of the left optic nerve, especially its posterior portion (arrows). K, Axial T1-weighted MRI with gadolinium shows enhancement of the optic chiasm (arrows). These images are from two different patients experiencing acute ON in the setting of NMOSD. (From Wingerchuk DM, Banwell B, Bennett JL, et al. *International consensus diagnostic criteria for neuromyelitis optica spectrum disorders*. *Neurology*. 2015;85:177–189, Fig. 1.)

disorder despite a negative test. CSF typically reveals elevated white blood cells (WBCs) and, unlike in MS, is usually negative for OCBs.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The International Panel for NMO Diagnosis (IPND) published new criteria for NMOSD in 2015. Emphasis is now placed on the presence or absence of AQP4 antibody (see Table 640.1). In seropositive patients (after exclusion of alternative diagnoses), only one core clinical criterion is required from the following six: (1) ON, (2) TM, (3) area postrema syndrome, (4) acute brainstem syndrome, (5) narcolepsy or diencephalic syndrome with compatible MRI lesions, and (6) symptomatic cerebral syndrome with typical brain lesions. If AQP4-Ab negative, the diagnosis is more stringent and two core clinical criteria are required, one of which must be ON, longitudinally extensive transverse myelitis (LETM), or area postrema syndrome. The heterogenous nature of this seronegative cohort suggests that further antibodies are yet to be discovered and likely represent multiple subgroups.

The differential diagnoses include other demyelinating disorders, such as MS or ADEM; vasculitis and rheumatologic disorders, including SLE, Behçet disease, and neurosarcoidosis (usually accompanied by other nonneurologic manifestations); idiopathic TM, tropical spastic paraparesis, and viral encephalomyelitis (none of which have NMO antibodies in the serum or CSF); genetic disorders such as familial HLH or pathogenic variants in *DARS*; metabolic causes such as biotinidase deficiency and riboflavin-responsive conditions; idiopathic causes of isolated ON; or other acute forms of monocular or binocular visual loss (Table 640.12; see also Chapter 671). Additional considerations include lymphoma, Langerhans cell histiocytosis, tuberculosis, and vitamins B₁₂ and E deficiencies.

TREATMENT

In principle, treatment of NMOSD involves acute treatment with early aggressive antiinflammatory therapy (e.g., steroids) and removal of the antibody (PLEX or monoclonal) and longer-term relapse prevention with DMTs.

Initial episodes and relapses may be treated acutely with methylprednisolone 20–30 mg/kg/day (maximum 1,000 mg/day) usually for 5 days; this can be extended for severe attacks. An oral taper (though there is no consensus regarding length) is recommended, particularly if antibody results are not available at the time of discharge. In certain circumstances, treatment escalation in the acute phase may be indicated: for example, when minimal or no improvement is seen with steroids, or even initially in patients deemed to be high-risk (i.e., brainstem symptoms or ON in a child with preexisting deficit in the contralateral eye). In these cases, PLEX either before or after IVIG (2 g/kg over 2–5 days) with a repeat course of steroids may be considered. Rituximab can be used both acutely and to prevent further relapses.

In adults, AQP4-Ab-positive NMOSD has historically been treated with a range of DMTs, including azathioprine, mycophenolate mofetil (MMF), and rituximab. A study of satralizumab (interleukin [IL]-6 reuptake inhibitor of T- and B-cell activation, Th17 differentiation, and plasmablast survival) in NMOSD demonstrated clear benefit in pediatric patients, particularly those who were AQP4-Ab-positive, and it is licensed for use in children in the United States and Canada. Preliminary evidence in adults suggests that eculizumab, a monoclonal antibody against the C5 complement protein, reduces recurrence and may improve disability in patients with severe NMOSD. A pilot study of tocilizumab, an anti-IL-6 monoclonal antibody, demonstrated efficacy in AQP4-NMOSD in adults. Inebilizumab, an anti-CD19 antibody, has been shown to effectively ameliorate multiple NMOSD endpoints (time to relapse, disability scores, new MRI lesions) in adults and is now in pediatric clinical trials. Importantly, medications used for the treatment of MS are ineffective and can even exacerbate relapses, again highlighting the criticality of accurate diagnosis.

PROGNOSIS

The relapsing and aggressive nature of AQP4-positive NMOSD in pediatric patients very often results in poor recovery and a progressive accrual of disability. MOG-Ab-positive NMOSD is more likely to be monophasic. In relapsing phenotypes (either AQP4-Ab or MOG-Ab), the relapse

Table 640.12 Red Flags: Findings Atypical for NMOSD and TM*

RED FLAGS (CLINICAL AND LABORATORY)

- Clinical features and laboratory findings
 - Progressive overall clinical course (neurologic deterioration unrelated to attacks; consider MS)
 - Atypical time to attack nadir: less than 4 hr (consider cord ischemia/infarction); continual worsening for more than 4 wk from attack onset (consider sarcoidosis or neoplasm)
 - Partial TM, especially when not associated with LETM MRI lesion (consider MS)
 - Presence of CSF OCBs (OCBs occur in <20% of NMO cases vs >80% of MS cases)
- Comorbidities associated with neurologic syndromes that mimic NMOSD
 - Sarcoidosis, established or suggestive clinical, radiologic, or laboratory findings thereof (e.g., mediastinal adenopathy, fever and night sweats, elevated serum angiotensin-converting enzyme or interleukin-2 receptor levels)
 - Cancer, established or with suggestive clinical, radiologic, or laboratory findings thereof; consider lymphoma or paraneoplastic disease (e.g., collapsin response mediator protein-5–associated optic neuropathy and myelopathy or anti-Ma–associated diencephalic syndrome)
 - Chronic infection, established or with suggestive clinical, radiologic, or laboratory findings thereof (e.g., HIV, syphilis)

RED FLAGS AND MIMICS (CONVENTIONAL NEUROIMAGING)

- Brain
 - Imaging features (T2-weighted MRI) suggestive of MS (MS typical)
 - Lesions with orientation perpendicular to a lateral ventricular surface (Dawson fingers)
 - Lesions adjacent to lateral ventricle in the inferior temporal lobe
 - Juxtacortical lesions involving subcortical U-fibers
 - Cortical lesions
 - Imaging characteristics suggestive of diseases other than MS and NMOSD
 - Lesions with persistent (>3 mo) gadolinium enhancement
- Spinal cord
 - Spinal nerve root inflammation (e.g., Guillain-Barré syndrome)
 - Tumor (e.g., neuroblastoma, Wilms tumor, Ewing sarcoma)
 - Destructive lesions (e.g., tuberculosis, lymphoma, Langerhans cell histiocytosis)
 - Vascular disorders (e.g., arteriovenous infarct, arteriovenous malformation, cavernomas, Cobb syndrome, spinal cord infarction)
 - Vasculitis (e.g., SLE, Behçet disease)
 - Characteristics more suggestive of MS than TM/NMOSD:
 - Lesions in <3 complete vertebral segments on sagittal T2-weighted sequences
 - Lesions located predominantly (>70%) in the peripheral cord on axial T2-weighted sequences
 - Diffuse, indistinct signal change on T2-weighted sequences (as sometimes seen with long-standing or progressive MS)

*These are some common or key findings that should prompt a thorough investigation for competing differential diagnoses before making a diagnosis of NMOSD or isolated TM.

LETM, Longitudinally extensive transverse myelitis lesions; TM, transverse myelitis; MS, multiple sclerosis; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorders.

Modified from Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 2015;85:177–189, Table 2, p. 180 and 182; with data from Thomas T, Branson HM. Childhood transverse myelitis and its mimics. *Neuroimaging Clin North Am*. 2013;23:267–278, Box 1.

rate is higher in those with AQP4-Ab, with emerging consensus for a better recovery and long-term prognosis for MOG-Ab-associated disorders. Like adults with NMOSD, pediatric patients are often (>50%) left with fixed neurologic deficits affecting VA, visual fields, color vision, motor and sensory function, balance, and bowel/bladder function, and the best outcomes are achieved with prompt treatment by a multidisciplinary team experienced in pediatric neuroinflammatory care.

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Chapter 641

Pediatric Stroke

Nomazulu Dlamini and Gabrielle A. deVeber

Stroke is an important cause of acquired brain injury in newborns, children, and adolescents. The ischemic varieties of arterial ischemic stroke (AIS) and cerebral sinovenous thrombosis (CSVT) are, together, more common than brain malignancy (incidence ~5 in 100,000 children per year). Perinatal ischemic stroke is especially common (1 in 2,500-4,000 live births) and is the leading cause of hemiparetic cerebral palsy. Beyond ischemic stroke, a similar number of children have hemorrhagic stroke (HS) and other forms of cerebrovascular disease. Acute stroke is a neurologic emergency; unfortunately, delays in recognition are common, and delayed treatment worsens outcomes. In comparison with stroke in adults, there is a more diverse group of disorders producing stroke in neonates and children.

641.1 Arterial Ischemic Stroke

Nomazulu Dlamini and Gabrielle A. deVeber

Arterial blood reaches the brain via the anterior (internal carotid) and posterior (vertebrobasilar) circulations, converging at the circle of

Willis. Strokes most often involve the middle cerebral artery territory but can occur in any cerebral artery of any size. AIS is the focal brain infarction that results from occlusion of these arteries.

The diagnosis of stroke in children is frequently delayed. This is a consequence of subtle and nonspecific clinical presentations, poor awareness by primary care physicians, a complicated differential diagnosis for hemiparesis (see Chapter 641.5), and a high frequency (>50%) of negative initial brain CT scans in true AIS. *The acute onset of a focal neurologic deficit in a child is stroke until proven otherwise.* The most common focal presentation is hemiparesis, but acute visual, speech, sensory, or balance deficits also occur. Importantly, new-onset seizures, especially focal motor seizures, frequently herald stroke, especially in infants and younger children. Children with these presentations require urgent neuroimaging and consultation with a child neurologist because emergency interventions may be indicated. AIS is a clinical and radiographic diagnosis. Although CT imaging can demonstrate mature AIS and exclude hemorrhage, cerebral MRI is required to identify early and small infarcts and disorders of the cerebral arteries. **Diffusion-weighted MRI** demonstrates AIS from minutes to 7 days after the onset; MR angiography can confirm vascular occlusion and suggest possible arteriopathy (Fig. 641.1). Diffusion-weighted MRI can also demonstrate Wallerian degeneration in the descending corticospinal tract, which correlates with chronic hemiparesis.

Many possible risk factors for childhood AIS are recognized (Tables 641.1-641.3), although their specific pathophysiologic mechanisms remain poorly understood. Half of children with AIS are healthy before stroke onset. Three main categories of etiology should be considered: **arteriopathy**, **cardiac disease**, and **hematologic disease** (see Table 641.1). Hence, in addition to a careful history taking and physician examination, a full investigation (including vascular imaging,

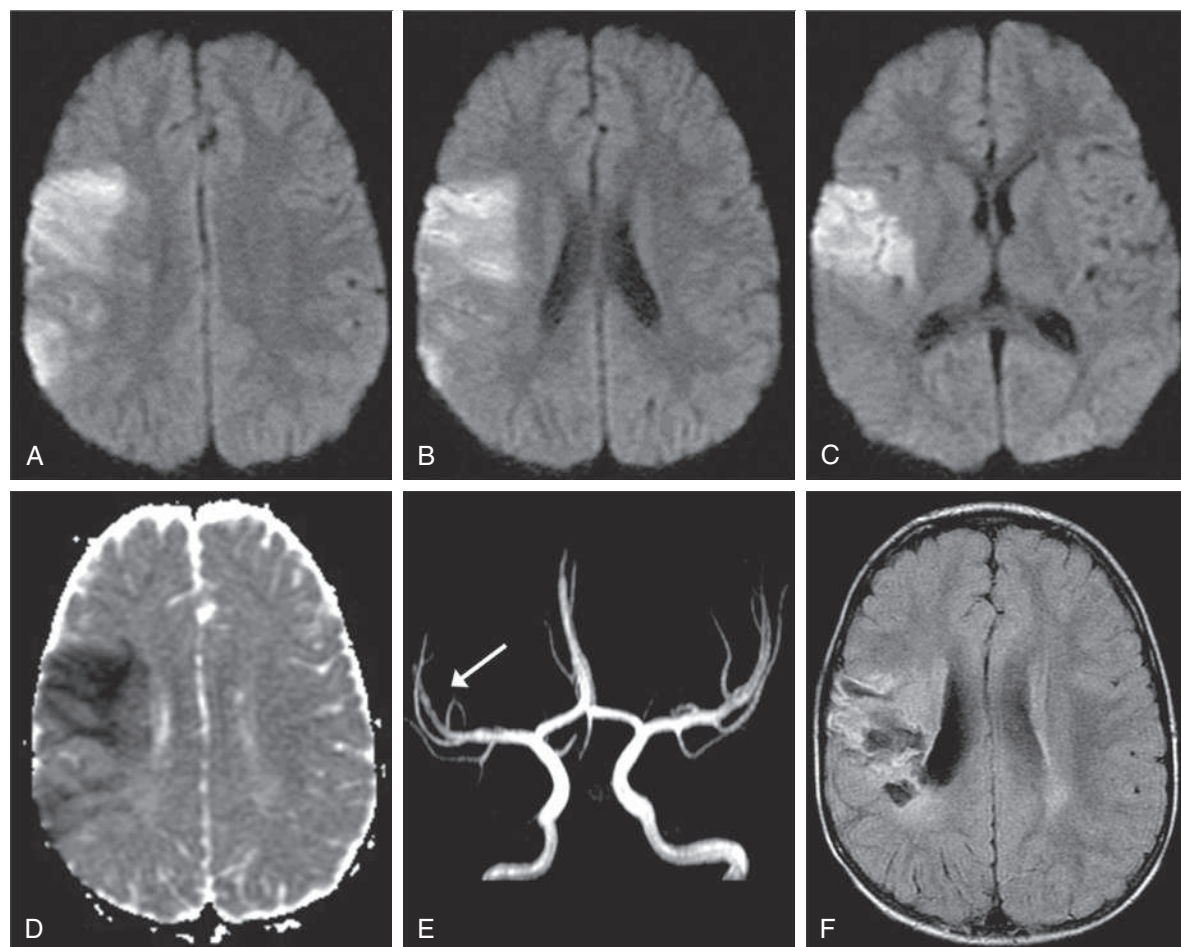


Fig. 641.1 Arterial ischemic stroke. A healthy 3-yr-old male had sudden onset of left-sided weakness. Examination also demonstrated left-sided hemisensory loss and neglect. A-C, Diffusion-weighted MRI shows focal increased signal in the right temporal-parietal region in the territory of the middle cerebral artery (MCA). D, Apparent diffusion coefficient map confirms restricted diffusion consistent with infarction (ischemic stroke). E, MR angiogram shows decreased flow in the corresponding branch of the MCA. F, Follow-up MRI at 3 mo shows atrophy and gliosis in the same region.

Table 641.1 Risk Factors and Causes of Stroke in Children

ARTERIOPATHIES Focal or transient cerebral arteriopathy Craniocervical arterial dissection Fibromuscular dysplasia Moyamoya disease or syndrome Sickle cell arteriopathy Primary CNS angiitis HANAC syndrome Genetic variants (see text and Table 641.2)	SYSTEMIC DISORDERS Meningitis • Viral • Bacterial • Tuberculous Systemic infection • Viremia • Bacteremia • Local head and neck infections, including Lemierre syndrome • Postinfectious (including varicella and other viruses) Drug-induced inflammation and vasoconstriction • Amphetamine • Cocaine • Ergot alkaloids Autoimmune disease • Systemic lupus erythematosus • Juvenile idiopathic arthritis • Takayasu arteritis • Mixed connective tissue disease • Polyarteritis nodosa • Primary CNS vasculitis Trisomy 21
CARDIOVASCULAR DISEASE Congenital Aortic stenosis Mitral stenosis Ventricular septal defects Patent ductus arteriosus Patent foramen ovale PHACE syndrome Cyanotic congenital heart disease	METABOLIC DISEASES Hyperhomocysteinemia/homocystinuria/elevated homocysteine levels Fabry disease Pseudoxanthoma elasticum Sulfite oxidase deficiency (see Table 641.2)
Acquired Endocarditis Kawasaki disease Cardiomyopathy Atrial myxoma Arrhythmia Rheumatic heart disease Prosthetic heart valve Catheterization/surgery ECMO	MITOCHONDRIAL DISORDERS MELAS Leigh syndrome
HEMATOLOGIC ABNORMALITIES Hemoglobinopathies Polycythemia Leukemia/lymphoma Thrombocytopenia including TTP Disorders of coagulation • Protein C deficiency • Protein S deficiency • Antithrombin III deficiency • Factor V (Leiden) resistance to activated protein C • Lupus anticoagulant • Oral hormonal contraception • Pregnancy and the postpartum state • Disseminated intravascular coagulation • Paroxysmal nocturnal hemoglobinuria • Inflammatory bowel disease • Protein-losing enteropathy • Nephrotic syndrome • L-Asparaginase • Prothrombin G20210A variant • MTHFR deficiency • Lipoprotein(a) elevation • Antiphospholipid antibody syndrome • PNH	INTRACEREBRAL VASCULAR PROCESSES Ruptured aneurysm Arteriovenous malformation Migraine headache Post-subarachnoid hemorrhage vasospasm Hereditary hemorrhagic telangiectasia Sturge-Weber syndrome Carotid or vertebral artery dissection Neurofibromatosis type 1 CADASIL CARASIL
	TRAUMA AND OTHER EXTERNAL CAUSES Nonaccidental trauma Head and neck trauma Oral trauma Placental embolism Neck hyperextension (carotid dissection) Lollipop stroke (pharyngeal trauma)

CADASIL, Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASIL, cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; CNS, central nervous system; ECMO, extracorporeal membrane oxygenation; HANAC, hereditary angiopathy with nephropathy aneurysms, muscle cramps; MELAS, mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes; MTHFR, methylenetetrahydrofolate reductase; PHACE, posterior fossa brain malformations, hemangiomas of the face, neck, and scalp, arterial anomalies, coarctation of the aorta and cardiac anomalies, and eye defects; PNH, paroxysmal nocturnal hemoglobinuria; TTP, thrombotic thrombocytopenic purpura.

Modified from Farias-Moeller R. Stroke. In: Kliegman RM, Toth H, Bordini BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 37.15, p. 652.

echocardiography, and blood tests for inflammatory, infectious, and prothrombotic disorders) are important because these tests often reveal multiple predispositions and triggering risk factors.

Arteriopathy, a disorder of the cerebral arteries, is a leading cause of childhood AIS, present in more than 50% of children. One common arteriopathy that affects healthy school-age children features unilateral irregular stenosis of the proximal middle cerebral artery

and neighboring arteries with associated basal ganglia infarction. **Transient cerebral arteriopathy** is monophasic, nearly always self-limited, and may be the result of focal inflammation. This entity has been published under multiple names—**transient cerebral arteriopathy**, post-varicella angiopathy (Fig. 641.2), and nonprogressive childhood primary angiitis of the central nervous system (CNS). The term *focal cerebral arteriopathy (FCA)* is now used, reflecting uncertainty

Table 641.2 Genetic Associations with Thrombotic, Hemorrhagic, or Vascular Stroke

LIPID AND OTHER DISORDERS WITH ATHEROSCLEROSIS Hereditary dyslipoproteinemias Familial hypercholesterolemia Familial hypertriglyceridemia Hyperlipoproteinemia (types III and IV) Familial hypoalphalipoproteinemia Tangier disease Progeria (de Lange, Seckel, Bloom, Cockayne syndromes) ARTERIOPATHY, ANGIOPATHY, VASCULITIS Ehlers-Danlos (type IV) syndrome Pseudoxanthoma elasticum Menkes syndrome Marfan syndrome Rendu-Osler-Weber syndrome (hereditary hemorrhagic telangiectasia) Sturge-Weber syndrome Neurofibromatosis 1 Tuberous sclerosis complex Polycystic kidney disease (autosomal dominant type 1, 2) Fibromuscular dysplasia von Hippel-Lindau syndrome Bannayan-Zonana syndrome Moyamoya disease (<i>GUCY1A3</i>, <i>RNF213</i>, unknown) Fabry disease CARASIL (<i>HTRA1</i>) CADASIL (<i>NOTCH3</i>) RVCL (<i>TREX-1</i>) DADA2 (<i>CECR1</i>) COL4A1/A2 angiopathies, including: - Hereditary angiopathy nephropathy and cramps (HANAC) - Autosomal dominant porencephaly with infantile hemiplegia (POREN1) FOXC1/PITX2: Digenetic inheritance CARASAL (<i>CTSA</i>) HCHWA – Dutch type HCHWA – Icelandic type FAP ADA2 deficiency ACTA2 gene variant HEMATOLOGIC DISORDERS Antithrombin deficiency Protein C and S deficiency Thrombomodulin deficiency Activated protein C resistance Factor V Leiden variant Prothrombin G20210A variant Sickle cell disease	Factor V, VII, VIII, IX, X, XI, XII, XIII deficiency Hemoglobinopathies (hemoglobin C or S disorders) Prekallikrein deficiency C2 deficiency β-thalassemia Disorders of fibrinogen - Afibrinogenemia - Hypofibrinogenemia - Dysfibrinogenemia Elevated thrombin-activatable fibrinolysis inhibitor Elevated factor VIII Elevated factor IX Elevated factor XI Disorders of the fibrinolytic system - Hypoplasminogenemia - Tissue plasminogen activator defects MTHFR gene variant Heparin cofactor II deficiency Hereditary platelet defects CARDIAC DISORDERS Familial atrial myxomas Rhabdomyomas (tuberous sclerosis) Mitral valve prolapse Cardiac papillary fibroelastoma Hereditary cardiac conduction disorders Hereditary cardiomyopathies INBORN ERRORS OF METABOLISM Mitochondrial abnormalities - MELAS - Leigh disease - MERRF Organic acidemia - Methylmalonic acidemia - Propionic acidemia - Isovaleric acidemia Homocystinuria Glutaric aciduria type II Sulfite oxidase deficiency 11β-hydroxylase deficiency, 11β-ketoreductase deficiency, 17α-hydroxylase deficiency 3-Methylcrotonyl-CoA carboxylase 3-hydroxy-3-methylglutaryl-CoA lyase deficiency OTHER DISORDERS CCM1 (<i>KRIT1</i>) CCM2 (<i>CCM2</i>) CCM3 (<i>PDCD10</i>)
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CADASIL, Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASAL, cathepsin A–related arteriopathy with strokes and leukoencephalopathy; CARASIL, cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; CCM, cerebral cavernous malformation; DADA2, deficiency of adenosine deaminase 2; FAP, familial amyloid polyneuropathy; HCHWA, hereditary cerebral hemorrhage with amyloidosis; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; MERRF, mitochondrial encephalopathy with ragged red fibers; RVCL, retinal vasculopathy with deficiency of adenosine deaminase 2.

Modified from Farias-Moeller R. Stroke. In: Kliegman RM, Toth H, Bordini BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 37.17, p. 655.

regarding AIS pathogenesis at the time of presentation because it may be indistinguishable from intracranial dissection or early moyamoya disease. FCA can be subclassified as FCA inflammation type, FCA dissection type, and undetermined FCA.

Arterial dissection can be spontaneous or posttraumatic and involves extracranial (carotid, vertebral) arteries more frequently than intracranial arteries. **Moyamoya** demonstrates progressive occlusion of the distal internal carotid arteries. It may be idiopathic (**moyamoya disease**) or associated with other conditions (**moyamoya syndrome**) such as sickle cell anemia, neurofibromatosis type 1, trisomy 21, William syndrome, Alagille syndrome, chromosomal microdeletions/microduplications, and disorders after irradiation (Fig. 641.3). Diffuse, bilateral, progressive **vasculitis** is rare and can represent progressive

childhood primary angiitis of the CNS or occur in association with systemic vasculitides (Table 641.4; see also Chapter 642). Cranial infections (e.g., bacterial or tuberculous meningitis) also produce **infectious arteritis** and thrombophlebitis of surface vessels. **Congenital/genetic disorders** of craniocervical arteries include PHACES (posterior fossa abnormalities, hemangioma, and arterial, cardiac, eye, and sternal abnormalities) syndrome, fibromuscular dysplasia, or CADASIL (cerebral autosomal dominant arteriopathy, subcortical infarcts, and leukoencephalopathy). *ACTA2*, *COL4A1*, and *ADA2* gene variants may be associated with AIS, and new genetic arteriopathic conditions are steadily being added to this list. Hence, targeted genetic testing and whole exome sequencing are recommended (see Table 641.2). Vaso-spasm, as occurs in migraine, subarachnoid hemorrhage, or reversible

Table 641.3 Risk Factors for Perinatal Arterial Ischemic Stroke (AIS)

TYPE OF RISK FACTOR	RISK FACTORS
TERM INFANTS WITH NEONATAL AIS	
Maternal	Thrombophilia Infertility Prolonged rupture of membranes Preeclampsia or gestational hypertension Smoking Intrauterine growth restriction Infection Maternal fever during delivery Smoking
Fetal	Thrombophilia (MTHFR variant, FVL, prothrombin gene variant, protein C/S deficiency) Congenital heart disease Arteriopathy Twin-twin transfusion syndrome Hypoglycemia Perinatal asphyxia Infection (sepsis/meningitis) Need for resuscitation Apgar score of <7 at 5 min
Placental	Chorioamnionitis Placental infarcts Distal villous immaturity Placenta weighing <10th percentile
PRETERM INFANTS WITH NEONATAL AIS	
Maternal	Infection Gestational bleeding
Fetal	Maternal smoking Maternal drug use Twin-twin transfusion syndrome Twin demise Abnormal fetal heart rate Hypoglycemia Thrombophilia (MTHFR variant, FVL)
PRESUMED PERINATAL AIS	
Maternal	Preeclampsia Infection
Fetal	Gestational bleeding Gestational diabetes Thrombophilia Congenital heart disease

MTHFR, Methylene tetrahydrofolate reductase deficiency; FVL, factor V Leiden deficiency.

Modified from Lehman LL, Rivkin MJ. Perinatal arterial ischemic stroke: presentation, risk factors, evaluation, and outcome. *Pediatr Neurol*. 2014;51:760–768.

cerebral vasoconstriction syndrome (sometimes called *Call-Fleming syndrome*), can cause AIS. Metabolic strokes are seen in organic acidemia, methylmalonic acidemia, propionic acidemia, isovaleric acidemia, glutaric aciduria type II, mitochondrial encephalomyopathies, MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes), MERRF (mitochondrial encephalopathy with ragged red fibers), MERRF/MELAS overlap syndrome, and Kearns-Sayre syndrome.

Cardioembolic stroke makes up approximately 25% of childhood AIS cases, with the maximal embolic risk concurrent with interventional catheterization, surgical repair, or ventricular assist device use. AIS complicates approximately 0.5% of pediatric cardiac surgeries, and reoperation increases the risk. Although **complex congenital heart diseases** are most frequently associated with AIS, acquired conditions, including arrhythmia, cardiomyopathy, and infective endocarditis, should also be considered. A **patent foramen ovale**

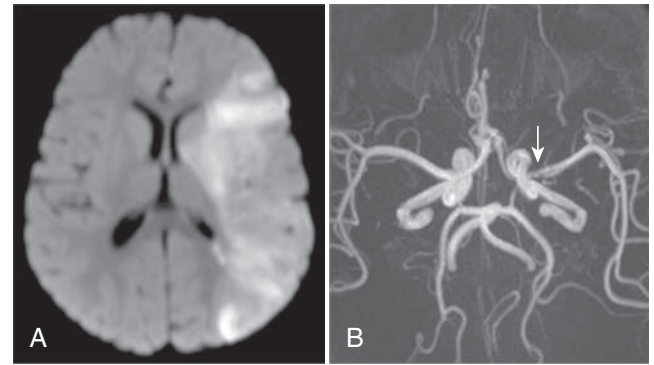


Fig. 641.2 A, Axial diffusion-weighted magnetic resonance imaging demonstrating hyperintense signal in the left middle cerebral artery distribution consistent with acute infarct. B, Magnetic resonance angiography axial maximum intensity projection images demonstrating narrowing of the left middle cerebral artery M1 segment (arrow). (From Vora SB, Amlie-Lefond C, Perez FA, et al. Varicella-associated stroke. *J Pediatr*. 2018;199:281, p. 281.)

provides a possible conduit for paradoxical venous thromboembolism to the brain. All children with suspected AIS require a thorough cardiovascular examination, an electrocardiogram, and an echocardiogram. Prothrombotic coagulation disorders and infection identified at the time of the index cardiogenic stroke increase the stroke recurrence risk.

Hematologic disorders associated with AIS include **sickle cell anemia**, in which the stroke risk is increased 400-fold, although effective screening (using transcranial Doppler) and transfusion therapy have reduced the incidence. Iron-deficiency anemia also increases the risk and is easily treatable. **Coagulation disorders** are associated with childhood AIS. They include hereditary (e.g., factor V Leiden) and acquired (e.g., antiphospholipid antibodies, lipoprotein-a elevation) **prothrombotic states** and **prothrombotic medications**, including oral contraceptives and asparaginase chemotherapy. Additional AIS risk factors include migraine, acute childhood illnesses, chronic systemic illnesses, illicit drugs and toxins, and rare inborn errors of metabolism.

Treatment of childhood AIS is multifaceted, and multiple consensus-based guidelines are available. The safety and efficacy of thrombolysis and/or thrombectomy in children with AIS has only been reported anecdotally. Nonetheless, some pediatric stroke centers offer thrombolysis with or without thrombectomy for pediatric patients with AIS. Most candidates are preteen or adolescent patients with AIS; younger children may also be candidates for thrombolysis but often have mimics of stroke and must be evaluated carefully for other diagnoses. In adults, treatment with both thrombolysis (~4.5 hours) and endovascular thrombectomy (~16–24 hours) results in improved functional outcome. Pending additional data, for younger children (e.g., <5 years age who often have comorbidities, e.g., congenital heart disease), thrombectomy treatment should probably be avoided.

Early initiation of antithrombotic strategies is paramount to prevent early reinfarction. Depending on the suspected cause, this includes anticoagulation with heparin or antiplatelet strategies, usually aspirin. Hyperacute neuroprotective strategies are essential to initiate within minutes in suspected stroke because they prevent progressive ischemic brain injury. These include control of blood glucose (avoid hypoglycemia and hyperglycemia) and temperature (avoid hyperthermia, maintain normal temperature) and maintenance of adequate cerebral perfusion (avoid hypotension and hypertension) and oxygenation. Urgent treatment of seizures is an important neuroprotective strategy, including possible monitoring with continuous electroencephalography (EEG). Early malignant infarct edema is life-threatening, more common in children, and predictable, and emergency surgical decompression can be lifesaving. Disease-specific treatments include transfusion therapy in sickle cell disease, immunosuppression in vasculitis, and revascularization surgery in moyamoya. Long-term

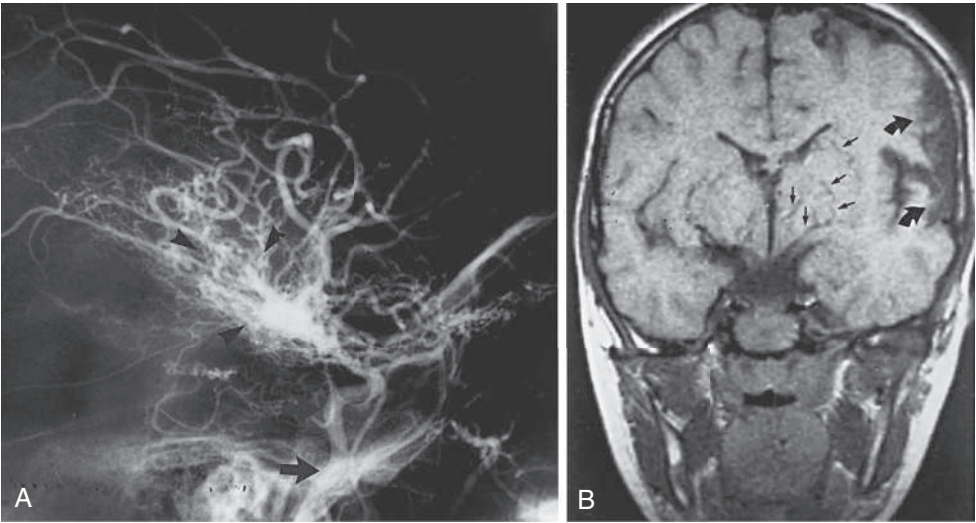


Fig. 641.3 Sudden onset of right hemiparesis in a 6-yr-old male. **A**, Cerebral angiogram shows the left internal carotid artery (arrow) leading to a highly arborized, telangiectatic network of vessels (arrowheads) characteristic for moyamoya disease. The typical middle cerebral artery vascular tree is absent. **B**, Cranial coronal MRI scan shows region of low signal in the middle cerebral artery territory and denotes infarction (curved arrows). Flow voids in the basal ganglia (straight arrows) are radiographic manifestations of the basilar collateral circulation typical of this vascular anomaly. (From Farias-Moeller R. Stroke. In Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023, Fig. 37.17, p. 653.)

Table 641.4	Classification of Cerebral Vasculitis
INFECTIOUS VASCULITIS BACTERIAL, FUNGAL, PARASITIC Spirochetal (syphilis, Lyme disease, leptospirosis) Viral, rickettsial, mycobacterial, free-living amebae, cysticercosis, other helminths	
NECROTIZING VASCULITIDES CLASSIC POLYARTERITIS NODOSA Granulomatosis with polyangiitis Eosinophilic granulomatosis with polyangiitis Necrotizing systemic vasculitis overlap syndrome Lymphomatoid granulomatosis	
VASCULITIS ASSOCIATED WITH COLLAGEN VASCULAR DISEASE Systemic lupus erythematosus Rheumatoid arthritis Scleroderma Sjögren syndrome	
VASCULITIS ASSOCIATED WITH OTHER SYSTEMIC DISEASES Behçet disease Ulcerative colitis Sarcoidosis Relapsing polychondritis Kohlmeier-Degos disease Takayasu arteritis	
HYPERSENSITIVITY VASCULITIDES IgA vasculitis Drug-induced vasculitides	
CHEMICAL VASCULITIDES MISCELLANEOUS VASCULITIDES VASCULITIS ASSOCIATED WITH NEOPLASIA Vasculitis associated with radiation Cogan syndrome Dermatomyositis–polymyositis X-linked lymphoproliferative syndrome Kawasaki disease Primary central nervous system vasculitis	

From Biller J, Mathews KD, Love BB. *Stroke in Children and Young Adults*. Boston: Butterworth-Heinemann; 1994.

treatment goals include **secondary stroke prevention**, for example with antiplatelet therapy in arteriopathy and anticoagulation in cardiogenic causes. Multimodal, family-centered rehabilitation programs are required for most survivors, targeting motor deficits, language

and intellectual impairments, behavioral and social disabilities, and epilepsy. Long-term attention to arterial health lifestyle factors is also important. Outcomes after childhood AIS include recurrent stroke in 10–50%, depending on the cause and preventive treatment, death in 2–6%; neurologic deficits in 60–70% (usually mild); and seizure disorders long-term in 30%.

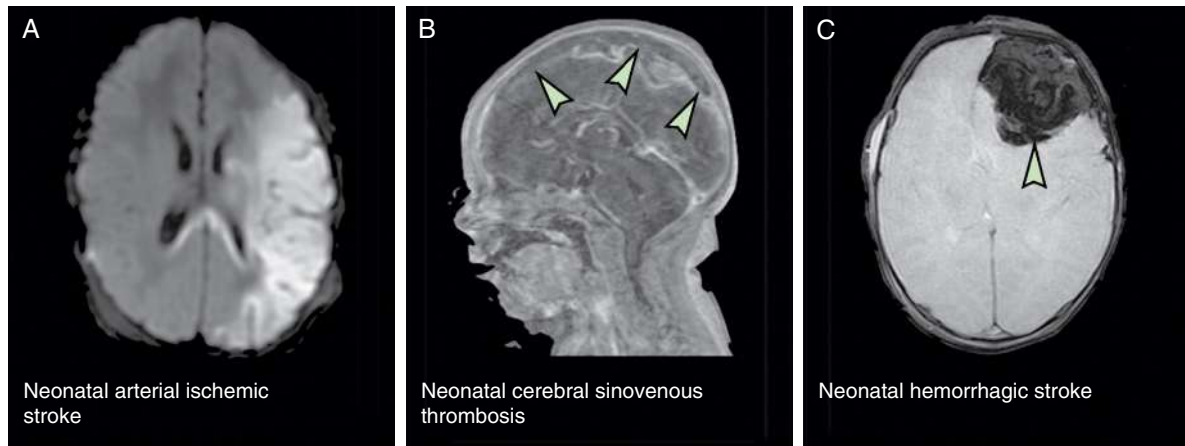
Adolescents and young adults with idiopathic (cryptogenic) AIS and a patent foramen ovale (PFO) may benefit from percutaneous PFO closure to prevent a recurrent stroke.

PERINATAL ARTERIAL ISCHEMIC STROKE

Perinatal stroke is common. It differs from childhood stroke, and it has two distinct clinical presentations. Acute symptomatic neonatal AIS presents with focal seizures within 24–28 hours of birth (Fig. 641.4 and see Table 641.3). Cranial ultrasound frequently misses the diagnosis of AIS. MRI diffusion abnormalities in an arterial territory confirm recent infarction. Alternatively, some affected neonates are asymptomatic at birth and present in later infancy with signs of early hand preference and congenital hemiparesis. Hand dominance within the first year of life is abnormal and may be the result of perinatal stroke. Imaging reveals focal encephalomalacia in an arterial territory, typically porencephaly in the middle cerebral artery territory.

In acute neonatal AIS, seizure control is important, but anti-thrombotic agents are rarely required because recurrent stroke is rare; the exceptions are neonates with congenital heart disease and cardiac embolism, prothrombotic disorders, and, perhaps, those with congenital arterial anomalies (stenosis, hypoplasia). The pathophysiology is complex and poorly understood. Most are idiopathic, although established causes include congenital heart disease, thrombotic placental pathology, and meningitis. The role of prothrombotic conditions in noncardiac neonatal AIS is controversial, but they likely play an additive role alongside other risk factors. Many other maternal, prenatal, perinatal, obstetric, and neonatal factors have been investigated with several strong associations found (e.g., chorioamnionitis, infertility, primiparity, monozygotic twins). Outcomes include normal or mild deficit in ~50% of children; however, ~25% of children have significant long-term disabilities. Perinatal stroke accounts for most cases of hemiparetic cerebral palsy (congenital hemiplegia, see Chapter 638.1). Additional morbidity, seen in ~25%, includes disorders of language, learning, cognition, and behavior and longer-term epilepsy. Stroke recurrence rates in subsequent pregnancies are extremely low in the absence of a familial prothrombotic disorder.

Acute symptomatic perinatal stroke



Presumed perinatal stroke

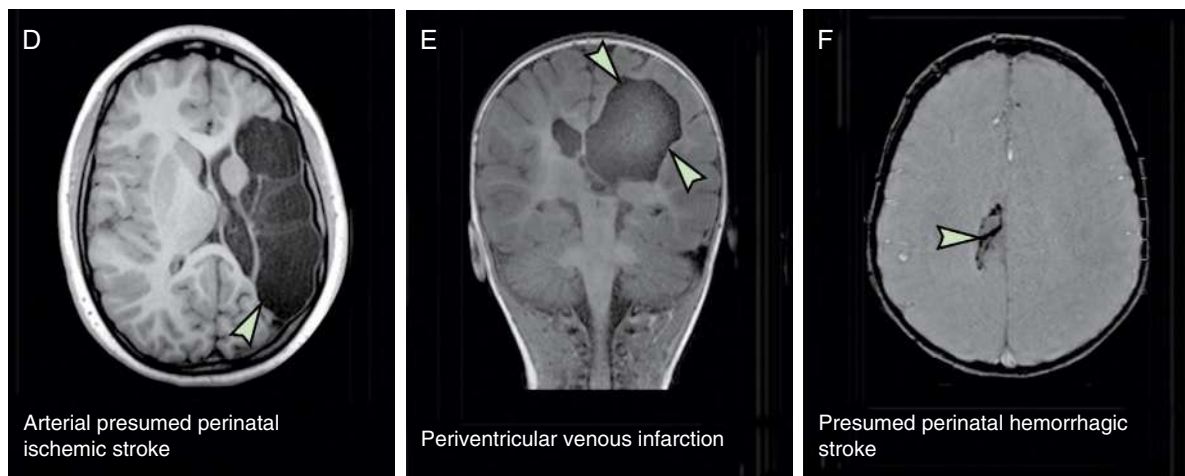


Fig. 641.4 Perinatal stroke diseases by MRI. **A**, Neonatal arterial ischemic stroke features acute restriction on axial diffusion-weighted MRI in an arterial territory; diaschisis of the splenium of the corpus callosum is also evident. **B**, Neonatal cerebral sinovenous thrombosis is evident as a filling defect on sagittal MR venogram (shown), in this case, in the superior sagittal sinus (arrows). **C**, Neonatal hemorrhagic stroke detectable on gradient echo or susceptibility-weighted MRI (arrow). **D**, Arterial presumed perinatal ischemic stroke in a child with hemiparesis is diagnosed by focal encephalomalacia on CT or MRI (axial T1-weighted MRI shown) in an arterial territory (arrow). **E**, Periventricular venous infarction presents with congenital hemiparesis with a focal lesion affecting the periventricular white matter with sparing of the cortex and basal ganglia, shown on coronal T1-weighted MRI (porencephaly indicated with arrows). **F**, Presumed perinatal hemorrhagic stroke with a focal area of remote parenchymal injury showing hemorrhage (gradient echo, arrow). (From Dunbar M, Kirton A. Perinatal stroke: mechanisms, management, and outcomes of early cerebrovascular brain injury. *Lancet*. 2018;2:666–676, Fig. 2, p. 668.)

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641.2 Cerebral Sinovenous Thrombosis

Nomazulu Dlamini and Gabrielle A. deVeber

Cerebral venous drainage occurs via the cerebral sinovenous system. The superficial system (i.e., cortical veins, superior sagittal sinus) and deep system (i.e., internal cerebral veins, straight sinus) converge at the torcula to exit the cranial vault via the paired transverse and sigmoid sinuses and jugular veins. In cerebral sinovenous thrombosis (CSVT), thrombotic occlusion of these venous structures can create regional or diffuse increased intracranial pressure, cerebral edema, and, in 50% of cases, venous infarction or hemorrhage (venous stroke). CSVT is more common in children than in adults, and risk is greatest in the neonatal period (Table 641.5).

Clinical presentations are typically gradual, variable, and nonspecific compared with AIS. Neonates often present with encephalopathy and seizures. Children may present with symptoms mimicking

idiopathic intracranial hypertension, including progressive headache, papilledema, diplopia secondary to sixth cranial nerve palsy, or acute focal deficits. Seizures, lethargy, and confusion are common. Diagnosis requires a high clinical suspicion and specifically requested imaging of the cerebral venous system. Nonenhanced CT is insensitive in detecting CSVT, and so either contrast **CT venography** or MR venography is necessary to demonstrate filling defects in the cerebral venous system (Fig. 641.5). MRI offers superior parenchymal imaging compared with CT.

Table 641.5 lists the risk factors for CSVT. **Prothrombotic states** associated with childhood CSVT include inherited conditions (e.g., prothrombin gene mutation of 20210A) and acquired conditions (e.g., antiphospholipid antibodies), prothrombotic medications (e.g., asparaginase, oral contraceptives), and common childhood illnesses (e.g., otitis media, iron-deficiency anemia, and dehydration). **Systemic diseases** associated with increased risk of CSVT include leukemia, inflammatory bowel disease, and nephrotic syndrome.

Head and neck disorders can directly involve cerebral veins and sinuses thereby causing CSVT. Common infections, including

Table 641.5 Causes of Cerebral Venous Thrombosis

IDIOPATHIC PROTHROMBOTIC STATE Protein C or S deficiency Antithrombin deficiency Factor V Leiden variant Activated protein C resistance Prothrombin G20210A variant Variants in thrombomodulin Platelet glycoprotein IIIa (β_3) variant Heparin cofactor II deficiency Variants in plasminogen gene MTHFR C677 variant Dysfibrinogenemia Elevated plasminogen activator inhibitor Tissue plasminogen activator deficiency Increased factors VIII, IX, X; von Willebrand factor Variants in tissue factor pathway inhibitor Sickle cell disease and trait Reactive thrombocytosis and essential thrombocythemia Pregnancy and puerperium	INFECTIONS Herpes zoster virus Myeloidosis Mucormycosis Aspergillosis Pneumococcal meningitis Syphilis HIV Otitis media Mastoiditis Sinusitis Peritonsillar abscess Endotoxemia Trichinosis Sepsis
POSTOPERATIVE STATE Antiphospholipid antibody syndrome Hyperhomocysteinemia Homocystinuria Cancer Inflammatory bowel diseases Dehydration Congestive heart failure Paroxysmal nocturnal hemoglobinuria Marasmus Iron-deficiency anemia Nephrotic syndrome Thrombocytopenia Essential thrombocythemia Disseminated intravascular coagulation Thrombotic microangiopathies Polycythemia vera and secondary polycythemia Hyperlipidemia Familial histidine-rich glycoprotein deficiency	VASCULITIDES Behçet disease Sarcoidosis Polyangiitis with granulomatosis Systemic lupus erythematosus Polyarteritis nodosa
DRUGS Asparaginase Estrogen and oral contraceptives Androgen ϵ -Aminocaproic acid Cisplatin and etoposide Medroxyprogesterone Heparin (heparin-induced thrombocytopenia) Immunoglobulin G (intravenous immunoglobulin)	TRAUMA Head trauma Neurosurgical procedures Strangulation Intravenous catheters Cardiac pacemakers
	OTHERS Osteopetrosis Malignant atrophic papulosis (Kohlmeier-Degos disease) Chronic lung disease Diabetes mellitus Budd-Chiari syndrome Arteriovenous malformation Sturge-Weber syndrome Cerebral arterial occlusions Neoplasm (meningioma, metastasis, glomus tumors)

From Biller J. *Stroke in Children and Young Adults*. 2nd ed. Philadelphia: Saunders; 2009: Table 12-3, p. 237.

meningitis, otitis media, and mastoiditis, can cause **septic thrombophlebitis** of venous channels. CSVT can complicate head trauma especially in veins/venous sinuses adjacent to skull fractures. Neurosurgical procedures in proximity to cerebral venous structures may also lead to injury and CSVT. Finally, obstruction of the jugular veins and proximal stasis may result in CSVT. In neonates, because the cranial sutures are unfused, mechanical distortion of the underlying venous sinuses may occur and predispose to CSVT either during labor and delivery or with supine lying because of occipital bone compression of the posterior sagittal sinus.

Anticoagulation therapy plays an important role in childhood CSVT treatment. Substantial indirect evidence has led to a consensus recommendation for anticoagulation with unfractionated or low molecular weight heparins in most children. The presence of hemorrhagic venous infarcts is not an absolute contraindication. Treatment is usually planned for 6 months, although if reimaging at 3 months confirms recanalization, treatment is usually discontinued. However, anticoagulation of neonates is more controversial, and guidelines differ. Evidence

suggests that 30% of untreated neonates and children will extend their thrombosis in the first week after diagnosis, and additional venous infarction can result. Therefore if anticoagulation is withheld, early (e.g., 5-7 days) repeat venous imaging is paramount. Protocols supporting initial anticoagulation recommend shorter treatment durations (i.e., 6 weeks to 3 months) in neonates. Children with persistent risk factors may require prophylactic long-term anticoagulation. At initial diagnosis, supportive interventions include management of infection, detection and treatment of seizures, and neuroprotective measures (e.g., normothermia, normotension, normovolemia, normoglycemia). **Compressive optic neuropathy** secondary to prolonged increased intracranial pressure after CSVT is an important complication that can lead to permanent visual loss. Regular funduscopic examination by an ophthalmologist and treatment directed at reducing intracranial pressure (e.g., acetazolamide, serial lumbar puncture) may be required. Most neurologic morbidity is suffered by those incurring venous infarction. Consistent with other forms of childhood stroke, a comprehensive neurorehabilitation program is required.

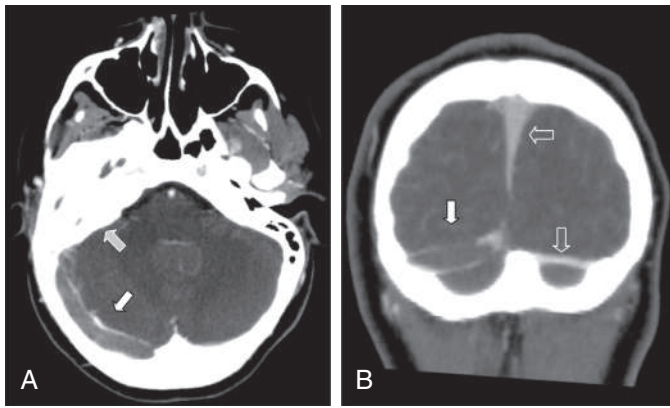


Fig. 641.5 Cerebral sinovenous thrombosis. A 9-yr-old female presented with fever and progressive right-sided headache. She complained of double vision and had papilledema on examination. Axial (A) and coronal (B) CT venography demonstrates a large thrombus in the right transverse sinus that fails to opacify with contrast (solid arrows). Note normal filling in superior sagittal sinus and smaller left transverse sinuses (open arrows, right) and opacification of the mastoid air cells (hatched arrow, left). The cause was otitis media/mastoiditis with septic thrombophlebitis of transverse sinus.

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641.3 Spinal Cord Lesions Associated with Vascular Processes

Nomazulu Dlamini and Gabrielle A. deVeber

Most cases of **transverse myelitis** (TM) in childhood are postinfectious or, if recurrent, are associated with underlying demyelinating processes, such as multiple sclerosis (see [Chapter 640.4](#)) or neuromyelitis optica (see [Chapter 640.2](#)). However, in a small proportion of children presenting with acute spinal cord symptoms, infarction and necrosis may occur. This pathology may be associated with disease of the vessels, such as systemic lupus erythematosus (SLE)-associated **vasculitis** (see [Chapter 199](#)) or other vascular events such as **embolism** (including nucleus propulsus embolism-fibrocartilaginous embolism). Rarely, **arteriovenous malformations** of the spinal cord may exist and may cause myelopathy and infarction with hemorrhage in the spinal cord. An acute onset and a peak of symptoms over minutes to hours suggest a vascular process.

VASCULITIC PROCESSES: SYSTEMIC LUPUS ERYTHEMATOSUS

Most cases of SLE-associated **myelitis** are longitudinally extensive, and although reports in pediatric populations are rare, the disorder can occur. In 23–60% of cases, myelitis may be the first clinical manifestation of lupus and in many cases occurs at times of low systemic SLE disease activity. Poor recovery is frequent in these cases, with only 14% of patients experiencing complete recovery. In children, other vasculitic etiologies of cord disease, such as Behcet disease, exist.

SPINAL CORD EMBOLISM

Other rare etiologies of an acute increased T2 signal on a spinal cord MRI presenting clinically as TM include cord infarction caused by thromboembolism, either the result of fibrocartilaginous embolism or originating from a lower segment vertebral artery dissection or aortic dissection at the artery of Adamkiewicz. Ischemic myelopathy caused by a **vertebral artery dissection** occurs in the cervical spine; however, fibrocartilaginous embolism may occur anywhere in the spinal cord. A hyperacute onset and lesion appearance (wedge-shaped distribution) together with MRI diffusion-weighted imaging showing diffusion

restriction may be helpful in distinguishing ischemic thromboembolic abnormalities from inflammatory TM.

Clinical Manifestations

Similar to *inflammatory* TM, patients present with acute onset of motor weakness accompanied by sensory abnormalities. The weakness progresses over minutes to hours. Pain or discomfort localized to the back or neck, depending on lesion localization, is frequent, with rapid progression of motor weakness and early areflexia reflecting **spinal shock**. Spasticity, hyperreflexia, and clonus occur in the ensuing weeks. A sensory level and motor weakness are present distal to the lesion, with urinary symptoms, including urinary retention, a frequent occurrence.

Investigations

MRI of the spinal cord, including T1- and T2-weighted axial as well as sagittal cuts with gadolinium, are necessary to evaluate for the presence of a focal spinal cord lesion. Given the frequency of longitudinally extensive lesions in myelopathy in pediatric populations, both cervical and thoracic spine imaging should be included in all patients presenting with acute TM. Inclusion of imaging sequences sensitive for hemorrhage (gradient echo sequences) may help, as will diffusion sequences. The inclusion of brain MRI scans, including associated vascular imaging of head and neck vessels, are useful to evaluate the possibility of large-vessel disease. In the event of a cervical spine lesion combined with ischemic brain lesions in the distribution of the posterior circulation, vertebral artery dissection should be investigated.

Lumbar puncture can be performed once MRI evaluation has ruled out a severe cord expansion or mass leading to complete spinal column block. Although inflammatory TM may be associated with elevations in the CSF white blood cells (WBCs) and protein, ischemic myelopathy caused by embolism does not show an acute pleocytosis. However, in a vasculitic event such as myelopathy associated with SLE, increased CSF protein and WBCs may be present.

Serum testing for the presence of underlying rheumatologic disorders should be performed in patients presenting with TM. A workup for hypercoagulable states should also be performed in cases with a high suspicion for ischemic myelopathy.

TREATMENT

In addition to supportive care, treatment is directed at the suspected underlying disease process. Given the low likelihood of complete recovery in ischemic lesions of the spinal cord and the significant disability associated with spinal cord injury, when underlying etiologies such as SLE are found, prophylactic treatment is recommended. Supportive care, including pain control for neuropathic pain, spasticity management, and management of urinary symptoms, is frequently required in this population. When vascular abnormalities are identified or if ischemic myelitis is the suspected cause, low-dose aspirin (2–4 mg/kg/day) for prevention of recurrence may be indicated.

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641.4 Hemorrhagic Stroke

Nomazulu Dlamini and Gabrielle A. deVeber

HS includes nontraumatic intracranial hemorrhage and is classified by the intracranial compartment containing the hemorrhage. Intraparenchymal bleeds may occur in any location within the brain's substance. Intraventricular hemorrhage may be isolated within ventricles or an extension of intraparenchymal hemorrhage. Bleeding outside the brain may occur in the subarachnoid, subdural, or epidural spaces.

Clinical presentations vary according to location, cause, and rate of bleeding. Acute hemorrhages may feature instantaneous or **thunderclap headache**, loss of consciousness, and nuchal rigidity in addition to focal neurologic deficits and seizures. HS can be rapidly fatal. In bleeds associated with vascular malformations, pulsatile tinnitus,

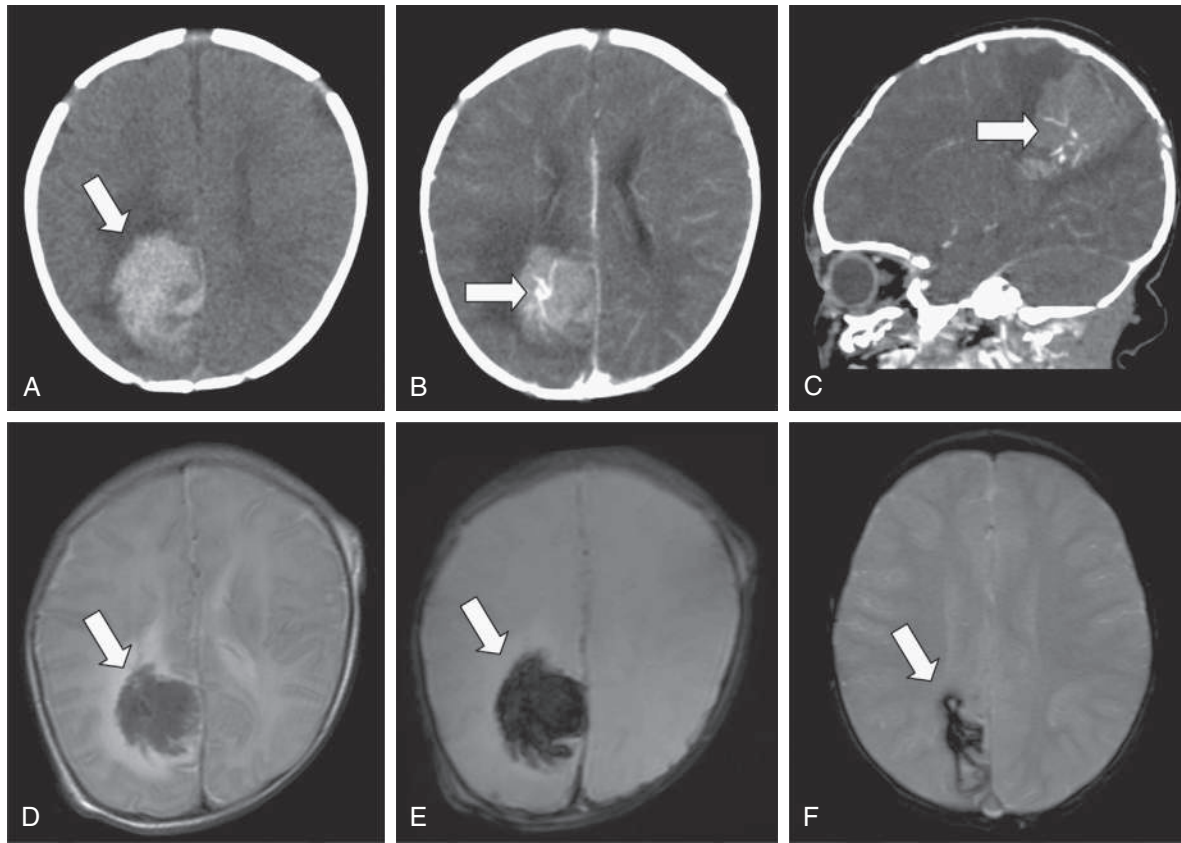


Fig. 641.6 Hemorrhagic stroke. A healthy 1-mo-old presented with sudden-onset irritability followed by focal left body seizures. Plain CT scan of head demonstrates a large hyperdense lesion in the right parietal region with surrounding edema, consistent with acute hemorrhage (A). Axial (B) and sagittal (C) contrast CT scans suggest an abnormal cluster of vessels in the center of the hemorrhage, consistent with an arteriovenous malformation. T2-weighted MRI differentiates the acute hemorrhage from surrounding edema (D). Gradient echo MRI, both acutely (E) and at 3 mo (F), demonstrates the presence of blood product.

cranial bruit, macrocephaly, and high-output heart failure may be present. The diagnosis relies on imaging, and CT scanning is highly sensitive to acute HS. However, lumbar puncture may be required to exclude subarachnoid hemorrhage. MRI is highly sensitive to even small amounts of both acute and chronic hemorrhage and offers improved diagnostic accuracy (Fig. 641.6). Angiography by CT, MR, or conventional catheterization means is often required to exclude underlying vascular abnormalities (e.g., vascular malformations, aneurysms).

Abusive head trauma with intracranial bleeding in children may present as primary subdural or parenchymal hemorrhage with no apparent history of trauma. Clinicians should search for the following: subtle scalp, suborbital, or ear bruising; retinal hemorrhages in multiple layers; and chronic failure to thrive. In infants with subdural bleeds, x-rays should be performed to rule out fractures. Epidural hematoma is nearly always caused by trauma, including middle meningeal artery injury typically associated with skull fracture. Subdural hematoma can occur spontaneously or with trivial trauma in children with brain atrophy because of stretching of bridging veins.

Causes of and risk factors for HS (Table 641.6) include vascular malformations and systemic disorders. **Arteriovenous malformations** are the most common cause of childhood subarachnoid and intraparenchymal HS and may occur anywhere. Neonates with vein of Galen malformations may present with heart failure, progressive macrocephaly, or, rarely, hemorrhage. In older children with arteriovenous malformations, the risk of bleeding is approximately 2–4% per year throughout life. Somatic gene variants in *KRAS* have been noted in some patients with arteriovenous malformations of the

brain. Other vascular malformations leading to HS include cavernous angiomas (**cavernomas**), dural arteriovenous fistulas, and vein of Galen malformations (Fig. 641.7). Cerebral cavernous malformations may be sporadic or familial (autosomal dominant) and associated with gene variants in the *CCM1*, *CCM2*, or *CCM3* genes. Cerebral aneurysms are a less common cause of subarachnoid hemorrhage in children and may suggest an underlying disorder (e.g., polycystic kidney disease, infective endocarditis) (Fig. 641.8 and Table 641.7). A common cause for HS is bleeding from a preexisting brain tumor. Arterial diseases that usually cause ischemic stroke, including fibromuscular dysplasia, vasculitis, intracranial dissection, and moyamoya, can also predispose to HS. Additional causes of parenchymal HS include hypertensive hemorrhage and hematologic disorders such as thrombocytopenic purpura, hemophilia, acquired coagulopathies (e.g., disseminated intravascular coagulopathy, liver failure), anticoagulant therapy (e.g., warfarin), or illicit drug use. Ischemic infarcts may undergo hemorrhagic transformation, particularly in CSVT, and may be difficult to differentiate from primary HS.

Management of acute childhood HS requires emergency neurosurgical intervention for a large or rapidly expanding hemorrhage. The same principles of neuroprotection for vulnerable brain suggested in the AIS sections also apply to HS. Reversal of anticoagulant therapy (with, for example, vitamin K, fresh-frozen plasma) may be required. The recurrence risk for those with structural lesions is significant, and serial imaging may be required. Definitive repair or removal of the vascular malformation may require a combined approach with interventional endovascular methods and neurosurgery. Outcomes from childhood HS are not well studied but likely depend on lesion size,

Table 641.6 Causes of Spontaneous Intracerebral Hemorrhage in Young Adults

VASCULAR MALFORMATIONS AVMs Capillary telangiectasias (HTT) Cavernous malformations Developmental venous anomalies	ICELANDIC FORM OF CAA ARTERITIS/ARTERIOPATHIES Infectious vasculitides Multisystem vasculitides Isolated CNS angiitis Moyamoya disease HANAC syndrome
ANEURYSMS Saccular Infective Traumatic Neoplastic	DRUG RELATED Amphetamines Cocaine Phenylpropanolamine Pentazocine (Talwin)– tripeleminamine (Pyribenzamine) Phencyclidine Heroin Monoamine oxidase inhibitor Other drugs
ARTERIAL HYPERTENSION Secondary Primary	INTRACRANIAL TUMORS Primary malignant or benign Metastatic
BLEEDING DIATHESSES Leukemia Thrombocytopenia Disseminated intravascular coagulation Polycythemia Hyperviscosity syndromes Hemophilia Hypoprothrombinemia Afibrinogenemia Selective factor deficiencies von Willebrand disease Sickle cell anemia Antiplatelet therapy Anticoagulant therapy Thrombolytic therapy Vitamin K deficiency	CEREBRAL VENOUS OCCLUSIVE DISEASE MISCELLANEOUS Post-carotid endarterectomy Post-selective neurosurgical procedures Post-spinal anesthesia Postmyelography Cold related Post-painful dental procedures Protracted migraine Methanol intoxication

AVM, Arteriovenous malformation; CAA, cerebral amyloid angiopathy; CNS, central nervous system; HANAC, hereditary angiopathy with nephropathy, aneurysms, muscle cramps; HTT, hereditary hemorrhagic telangiectasia.

From Farias-Moeller R. Stroke. In: Kliegman RM, Toth H, Bordini BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 37.2, p. 633.

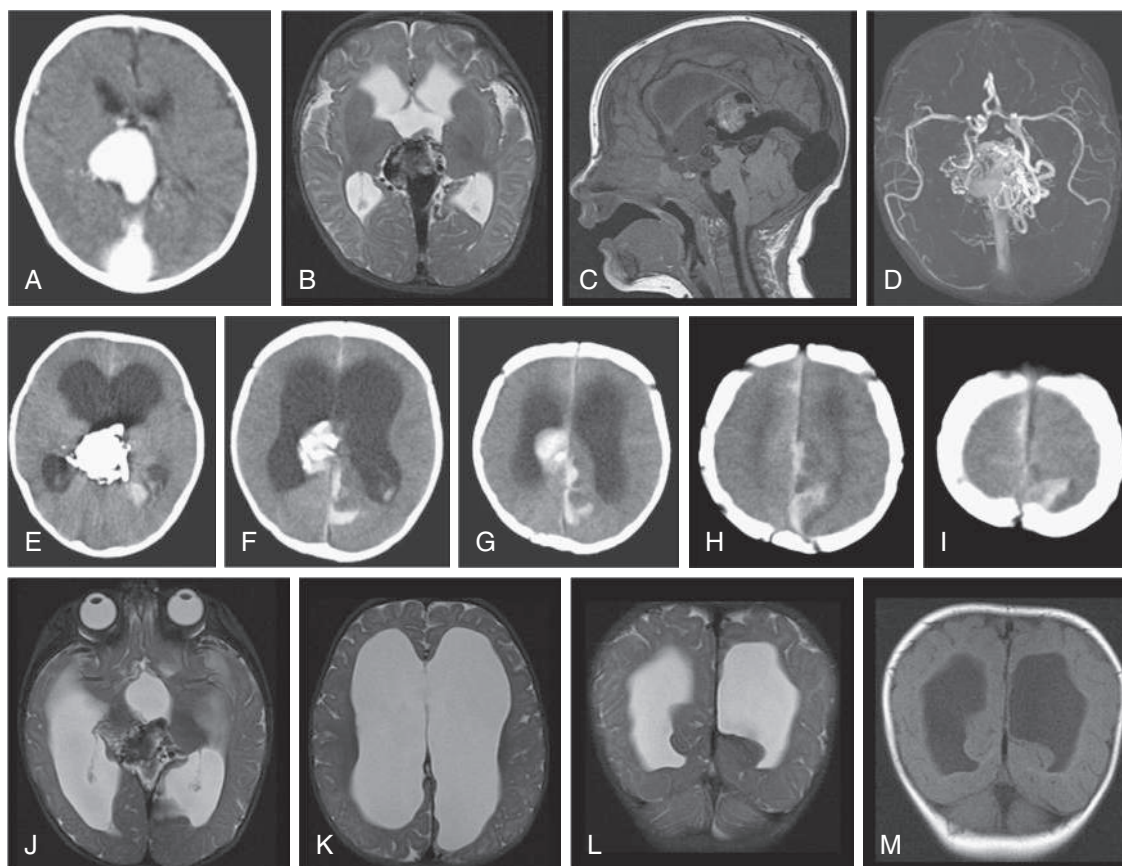


Fig. 641.7 Neonatal vein of Galen malformation and intraventricular hemorrhage. A 5-day-old female born at 38 weeks was noted to be drowsy with poor feeding. She had signs of cardiac failure. A CT scan (A) demonstrates vein of Galen aneurysmal malformation, which was partly treated by transarterial glue embolization without complication but with significant residual arteriovenous shunting (B-D). After a second embolization procedure, there was acute clinical deterioration with signs of raised intracranial pressure (E-I). CT shows acute intraventricular hemorrhage and hydrocephalus and a left parieto-occipital lobe low-density lesion (E-G) with adjacent subarachnoid and subdural hematoma (H and I). Some linear hyperdensity was believed to be the result of thrombus within the persistent falcine sinus (H and I). Follow-up imaging shows maturation of the focal left parieto-occipital lesion in keeping with an infarct (J-M), which is probably venous in origin. (From Gunny RS, Lin D. *Imaging of pediatric stroke*. *Magn Reson Imaging Clin North Am*. 2012;20:1–33, Fig. 18.)

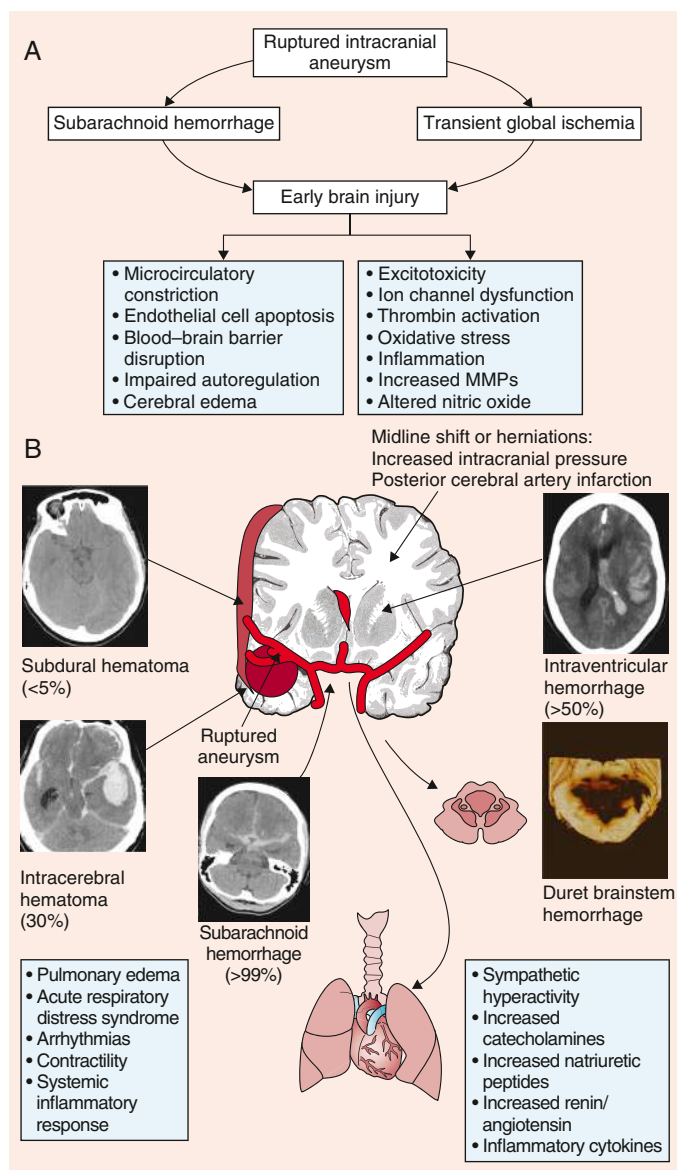


Fig. 641.8 Pathophysiology of subarachnoid hemorrhage. Hemorrhage into various compartments (subarachnoid, intraventricular, intracerebral, subdural) can cause brain shift, increased intracranial pressure, herniation, Duret brainstem hemorrhages, and death. Systemic effects of subarachnoid hemorrhage include cardiac and pulmonary complications. Brain injury from this condition initially is the result of transient global ischemia and effects of the hemorrhage. Delayed neurologic complications can ensue. MMPs, Matrix metalloproteinases. (From Macdonald RL, Schweizer TA. Spontaneous subarachnoid haemorrhage. *Lancet*. 2017;389:655–666, Fig. 2.)

location, and etiology. Compared with AIS, the HS mortality rate is higher, but long-term deficits are less common.

Neonatal HS has unique features. Cranial ultrasound can detect many neonatal parenchymal bleeds, especially in the preterm infant, where bleeds are located centrally within the cranium including germinal matrix bleeding and intraventricular hemorrhage, and in the cerebellum (see Chapter 122.3). Germinal matrix injury or bleeding may also occur in utero, resulting in periventricular venous infarction that presents in later infancy as chronic hemiparesis. Subarachnoid and subdural blood are common postpartum in normal-term newborns and may be detected by imaging in up to 25%. Term newborn HS is poorly studied and includes the etiologies listed earlier, although HS may be idiopathic in more than 50% of cases. Term intraventricular bleeding is often secondary to deep CSVT with specific management implications.

Table 641.7 Causes of Spontaneous Subarachnoid Hemorrhage in Young Adults

Cerebral aneurysm rupture
Perimesencephalic hemorrhage
Vascular malformation rupture (arteriovenous malformation, arteriovenous fistula, cavernous malformations)
Other
Congenital disorders
Coarctation of the aorta
Pseudoxanthoma elasticum
Menkes kinky hair syndrome
Sturge-Weber syndrome
Tuberous sclerosis complex
Neurofibromatosis 1 (von Recklinghausen disease)
Hereditary hemorrhagic telangiectasia (Rendu-Osler disease)
Ehlers-Danlos syndrome
Klinefelter syndrome
Autosomal dominant polycystic kidney disease
Systemic vascular disease
Hypertension
Cerebral embolism
Moyamoya disease
Cerebral venous occlusive disease
Eclampsia
Hematologic disorders
Hemophilia
Aplastic anemia
Sickle cell anemia
Leukemias
Thrombocytopenic purpura
Anticoagulant therapy
Thrombolytic therapy
Infectious diseases
Infective endocarditis
Tuberculous meningitis
Luetic meningoencephalitis
Fungal central nervous system infections
Infectious mononucleosis
Tickborne relapsing fever
Autoimmune disorders
Systemic lupus erythematosus
Polyarteritis nodosa
Henoch-Schönlein purpura
Poststreptococcal glomerulonephritis
Kawasaki disease
Other systemic diseases
Heat stroke
Conn syndrome
Thyrotoxicosis
Wolman disease
Spinal endometriosis
Neoplasms
Gliomas
Meningiomas
Acoustic neuromas
Choroid plexus papillomas
Pituitary adenomas
Pineocytomas
Chordomas
Subependymomas
Metastatic carcinoma
Intraspinal neoplasms
Drugs
Amphetamines
Cocaine
Ephedrine
Monoamine oxidase inhibitors
Oral contraceptive pills
Phencyclidine
Alcohol
Miscellaneous
α -Galactosidase deficiency
α_1 -Antitrypsin deficiency
Cystic fibrosis
Klippel-Trénaunay-Weber syndrome
Parry-Romberg syndrome
3-M syndrome

From Biller J. Stroke in Children and Young Adults. 2nd ed. Philadelphia: Saunders, 2009. Table 15-1. p. 290.

641.5 Differential Diagnosis of Strokelike Events

Nomazulu Dlamini and Gabrielle A. deVeber

The diagnosis of stroke in childhood requires a high index of suspicion balanced with awareness of the differential diagnosis for strokelike events (Table 641.8). An acute onset of a focal neurologic deficit should be considered a stroke until proven otherwise and assessed with urgent neuroimaging. However, pediatric stroke must also be differentiated from other strokelike disorders that may require their own urgent specific treatment.

MIGRAINE

A careful history and examination can often suggest migraine as the cause of acute focal deficits (see Chapter 635.1). Neurologic deficits

associated with migraine typically evolve slowly compared with stroke, with sensory disturbance or weakness marching across body areas over minutes. Migraine auras should last between 5 and 60 minutes and resolve completely. Although evolution into a headache is expected in migraine, headache may also accompany true AIS. Furthermore, a group of uncommon “acephalic” migraine subtypes can occur without headache and can more closely mimic stroke in children. These entities include familial hemiplegic migraine, basilar migraine, and migraine aura without headache. Migraine can also (rarely) cause a stroke, referred to as *migrainous infarction*.

Reversible cerebral vasoconstriction syndrome (RCVS) presents in patients with a history of migraine, pregnancy, or exposure to drugs (sympathomimetic agents, SSRIs, migraine abortive agents). There is both multifocal arterial constriction and dilation producing intense (thunderclap) headache, migraine-like symptoms, seizures, or focal

Table 641.8 Distinguishing Clinical and Imaging Features of Stroke Mimics

DISORDER	CLINICAL DISTINCTION FROM STROKE	IMAGING DISTINCTION FROM STROKE
Migraine	Evolving or “marching” symptoms, short duration, complete resolution, headache, personal or family history of migraine	Typically normal Migrainous infarction is extremely rare
Seizure*	Positive symptoms, Todd paralysis is postseizure and time limited	Normal or may identify source of seizures (e.g., malformation, old injury)
Infection	Fever, encephalopathy, gradual onset, meningismus	Normal or signs of encephalitis/cerebritis, which are typically diffuse and bilateral. Arterial ischemic stroke and cerebral sinovenous thrombosis can occur in bacterial meningitis.
Demyelination	Gradual onset, multifocal symptoms, encephalopathy Accompanying optic neuritis or transverse myelitis	Multifocal lesions, characteristic appearance (e.g., patchy in acute disseminated encephalomyelitis, ovoid in multiple sclerosis), typical locations (e.g., pericallosal in multiple sclerosis), less likely to show restricted diffusion
Hypoglycemia	Risk factor (e.g., insulin therapy), related to meals, additional systemic symptoms	Bilateral, symmetric May see restricted diffusion Posterior dominant pattern
Hypertensive encephalopathy (posterior reversible leukoencephalopathy syndrome)	Documented hypertension, bilateral visual symptoms, encephalopathy	Posterior dominant, bilateral, patchy lesions involving gray and white matter; usually no restricted diffusion
Inborn errors of metabolism	Preexisting delays/regression, multisystem disease, abnormal biochemical profiles	May have restricted diffusion lesions but bilateral, symmetric, not conforming to established vascular territories. Magnetic resonance spectroscopy changes (e.g., high lactate in mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes).
Vestibulopathy	Symptoms limited to vertigo, imbalance (i.e., no weakness); gradual onset	Normal
Acute cerebellar ataxia	Sudden-onset bilaterally symmetric ataxia; postviral	Normal
Channelopathy	Syndromic cluster of symptoms not localizing to single lesion; gradual onset, progressive evolution	Normal
Alternating hemiplegia	History of contralateral events Choreoathetosis/dystonia	Normal
Functional neurologic disorders	Recent psychosocial stressors Failure of signs and symptoms to localize to a specific lesion within the neural axis Presence of inconsistent examination findings Positive Hoover sign (when being evaluated for supposed lower extremity weakness, the patient with a functional disorder will exert downward pressure at the heel of the unaffected limb if the examiner holds the heel while asking the patient to raise the affected leg off the bed)	Normal

*Seizures, however, can also herald the onset of true stroke.

From Farias-Moeller R. Stroke. In: Kliegman RM, Toth H, Bordini BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 37.5, p. 636.

neurologic deficits (stroke). MRI is useful in differentiating RCVS from other disorders, especially primary angiitis of the central nervous system.

SEIZURE

Prolonged focal motor seizure activity is typified by stiffening or jerking movements, termed *positive* symptoms frequently followed by a period of focal neurologic deficit (so-called **Todd paresis**), which typically resolves rapidly over hours after the seizure (see [Chapter 633](#)). Very rarely, focal seizures can manifest with only “negative” symptoms producing only hemiparesis or other acute-onset focal neurologic deficits. A known history of seizures and epileptiform EEG findings may be helpful. Urgent brain imaging should be considered in new cases of prolonged or recurrent focal seizure with persisting Todd paresis because stroke in children is often associated with seizures at onset.

INFECTION

Life-threatening and treatable brain infections, including abscess, bacterial meningitis, and herpes encephalitis, can be mistaken for stroke (see [Chapter 643](#)). However, symptom onset in primary CNS infection is typically more gradual and less focal with fever as a consistent feature. Children with bacterial meningitis are at risk for both venous and arterial stroke.

DEMYELINATION

Acute disseminated encephalomyelitis, clinically isolated syndrome, multiple sclerosis, and other demyelinating conditions can present with acute focal neurologic deficits (see [Chapter 640](#)). The symptom onset and initial progression are, however, more gradual compared with stroke onset (i.e., typically hours or days versus minutes). Multifocal deficits, or concurrent encephalopathy in the case of acute disseminated encephalomyelitis, decreases the probability of stroke.

HYPOGLYCEMIA

Acute lowering of blood glucose levels can produce focal deficits mimicking stroke. New-onset hypoglycemia in otherwise healthy children is rare, but predisposing conditions include insulin-dependent diabetes, adrenal insufficiency, steroid withdrawal, and ketogenic diet.

GLOBAL HYPOXIC-ISCHEMIC ENCEPHALOPATHY

Generalized reduction in cerebral perfusion can produce focal areas of watershed brain infarction, which, when asymmetric, can mimic vasooclusive forms of stroke. Watershed ischemic injury should be accompanied by recognized hypotension or conditions predisposing to low cerebral perfusion, such as sepsis, dehydration, or cardiac dysfunction. Clinical presentations tend to be generalized and include bilateral cerebral dysfunction compared with stroke, and the anatomic location of the infarct on MRI or CT scanning is in typical bilateral watershed zones rather than conforming to an established arterial territory.

HYPERTENSIVE ENCEPHALOPATHY

Posterior reversible leukoencephalopathy syndrome is seen in children with hypertension, often in the context of an acute rise in blood pressure. The posterior regions are selectively involved, possibly resulting in symptoms of bilateral cortical visual dysfunction in addition to encephalopathy and seizures.

INBORN ERRORS OF METABOLISM

Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS; see [Chapter 638.2](#)) is the classic example of a metabolic strokelike condition, though other mitochondrial diseases can mimic stroke. Features favoring MELAS include a history of developmental regression, deafness, posterior (and often bilateral) lesions not respecting vascular territories on MRI, and elevated serum or CSF lactate on MR spectroscopy. In contrast to these types of metabolic infarctions, children with Fabry disease (see [Chapter 653.6](#)), hyperhomocysteinemia, and homocystinuria (see [Chapter 105.4](#)) are at risk of true ischemic stroke.

VESTIBULOPATHY AND ATAXIA

Acute-onset vertigo and/or ataxia can be confused with brainstem or cerebellar stroke. Simple bedside tests of vestibular function with otherwise intact brainstem functions are reassuring. This differential diagnosis includes acute vestibular neuronopathy, viral labyrinthitis, and the benign paroxysmal vertigos, as well as acute postviral cerebellar ataxia and episodic ataxias.

CHANNELOPATHIES

An increasing number of nervous system ion channel mutations are described that feature sudden focal neurologic deficits, thereby mimicking stroke. These include the migraine syndromes, as well as a growing list of episodic ataxias. A strong family history raises suspicion, but most require additional investigation.

ALTERNATING HEMIPLEGIA OF CHILDHOOD

Alternating hemiplegia of childhood typically presents in late infancy with acute intermittent episodes of hemiplegia that alternate from one side of the body to the other. The hemiplegia persists for minutes to weeks and then resolves spontaneously. Choreoathetosis and dystonic movements are commonly observed in the hemiparetic extremity. Signs spontaneously regress with sleep but recur with awakening. Affected children may also experience sudden attacks of redness and warmth (i.e., flushing) or unusual paleness (i.e., pallor) of the skin occurring during or separately from episodes of hemiplegia. Almost all affected individuals have some level of developmental delay and intellectual disability that typically progresses over time. Neuroimaging, including MRA, should be completed to exclude moyamoya disease. Alternating hemiplegia of childhood is linked to variants in the *ATP1A3* gene.

Chapter 642

Central Nervous System Vasculitis

Sona Narula

Autoimmune-mediated inflammatory brain diseases include primary central nervous system (CNS) vasculitis, secondary CNS vasculitis, and autoimmune encephalitis ([Fig. 642.1](#); see [Chapter 638.4](#)).

Primary vasculitis or angiitis of the CNS (PACNS) is recognized as an underlying etiology of a broad spectrum of neurologic and psychiatric symptoms in children. Criteria characteristic of primary angiitis of the CNS in childhood (cPACNS) include (1) newly acquired focal and/or diffuse neurologic deficits and/or psychiatric symptoms in a child 18 years of age or younger, **plus** (2) angiographic and/or histologic evidence of vasculitis **in the absence of** (3) a systemic underlying condition known to cause or mimic the findings. Two broad categories of cPACNS are recognized based on the predominant vessel size affected: large-/medium-vessel cPACNS and small-vessel cPACNS. Large-/medium-vessel cPACNS is diagnosed by angiography demonstrating features of vessel wall inflammation, such as wall thickening and resulting luminal stenosis. Based on the clinical course and the corresponding distribution of vessel stenosis within the vascular tree of the CNS, children with large-/medium-vessel cPACNS are classified as having a monophasic, nonprogressive subtype (NPcPACNS) or a progressive subtype (PcPACNS). The latter is characterized by chronic, progressive vessel wall inflammation affecting both proximal and distal vessel segments in one or both hemispheres. In contrast, NPcPACNS is a monophasic illness; vessel inflammation occurs in a characteristic distribution and is limited to

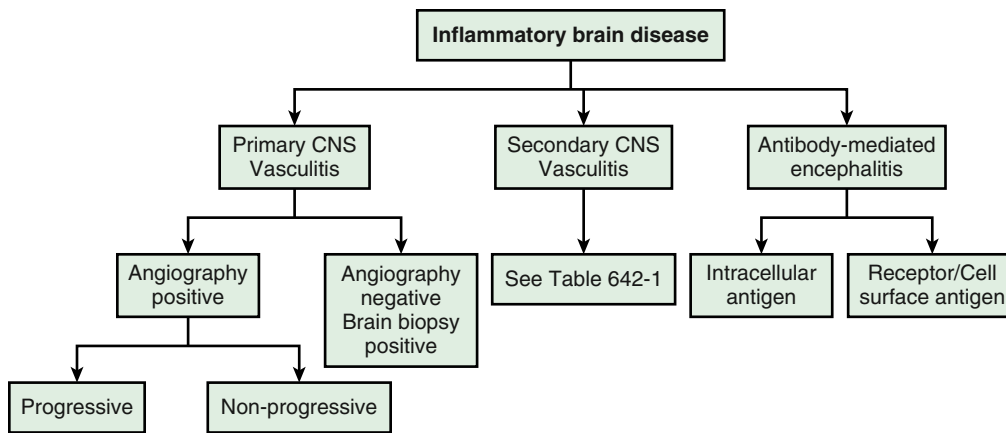


Fig. 642.1 Classification algorithm for CNS vasculitis within the spectrum of immune-mediated inflammatory brain diseases.

the proximal vessel segments of the anterior and/or middle cerebral artery and/or distal internal carotid artery of one hemisphere. Small-vessel cPACNS (SVcPACNS) is considered a progressive illness; the diagnosis is confirmed by brain biopsy, as angiography is typically normal.

Secondary childhood CNS vasculitis can affect all cerebral vessel segments and can occur in the context of infections, or rheumatic or other inflammatory conditions, or as a result of systemic or local vascular irritation (Table 642.1). The neuropsychiatric manifestations of secondary CNS vasculitis are the same as those of primary CNS vasculitis. Secondary CNS vasculitis is distinguished from primary CNS vasculitis largely by the non-CNS manifestations of the underlying systemic vasculitic disease.

EPIDEMIOLOGY

The incidence and prevalence of primary CNS vasculitis are undetermined. Increased physician awareness, improved diagnostic markers, sensitive neuroimaging techniques, and utilization of brain biopsies have led to dramatically increased recognition and decreased mortality rates. The disease has many names, including *isolated angiitis of the CNS*, *transient cerebral angiitis*, *postvaricella angiopathy*, and *focal cerebral arteriopathy*. Furthermore, children are frequently diagnosed with their presenting clinical phenotype, such as stroke, movement disorder, psychosis, or cognitive decline. Within clinical phenotypes such as arterial ischemic stroke or status epilepticus in children without preexisting epilepsy, cPACNS should be considered an important etiology.

CLINICAL MANIFESTATIONS

Recognition of childhood CNS vasculitis requires a very high level of suspicion because any neurologic or psychiatric presentation can be the result of an underlying CNS vasculitis. The clinical phenotype may provide clues to the size of the primarily affected vessel segments and resulting cPACNS subtype: the majority of children with large/medium cPACNS present with arterial ischemic stroke. Focal neurologic deficits, such as hemiparesis, facial droop, aphasia, or any other distinct gross or fine motor deficits, may be the result of large-vessel inflammation causing stenosis and a decreased blood supply to the specific functional areas of the brain. Initially, these focal deficits wax and wane; they may even briefly resolve without therapeutic intervention and can therefore be easily overlooked. Headaches can be a symptom of vascular disease and are commonly reported in cPACNS. New-onset headaches in children without any family history of migraine can serve as a diagnostic clue. Cognitive dysfunction in cPACNS often includes loss of higher executive function, concentration difficulties, learning and memory problems, atypical behavior or personality changes, and loss of social and emotional control. Seizures are a hallmark of SVcPACNS, as more than 80% of children with

Table 642.1 Causes of Secondary CNS Vasculitis

VIRAL INFECTIONS

Varicella-zoster virus, HIV, hepatitis C virus, cytomegalovirus, parvovirus B19

BACTERIAL INFECTIONS

Treponema pallidum, *Borrelia burgdorferi*, *Mycobacterium tuberculosis*, *Mycoplasma pneumoniae*, *Bartonella henselae*, *Rickettsia* spp.

FUNGAL INFECTIONS

Aspergillosis, mucormycosis, coccidioidomycosis, candidiasis

PARASITIC INFECTIONS

Cysticercosis

SYSTEMIC VASCULITIDES

Granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, Behçet disease, polyarteritis nodosa, IgA vasculitis, Kawasaki disease, giant-cell arteritis, Takayasu arteritis, Degos disease, ADA2 deficiency, TREX1-associated diseases

CONNECTIVE TISSUE DISEASES

Systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, dermatomyositis, mixed connective tissue disease

MISCELLANEOUS

Antiphospholipid antibodies syndrome, Hodgkin and non-Hodgkin lymphomas, neurosarcoidosis, inflammatory bowel disease, graft-versus-host disease, bacterial endocarditis, acute bacterial meningitis, **drug-induced CNS vasculitis** (cocaine, amphetamine, ephedrine, phenylpropanolamine, immune checkpoint inhibitors), hemophagocytic lymphohistiocytosis, reversible vasoconstriction syndrome, Fabry disease, migrainous infarction, primary (RNF213) and secondary moyamoya disease, NOTCH3 and HTRA1 vasculopathies, genetic structural disorders (COL4A1, ACTA2, MOPD2).

From Salvarani C, Brown RD Jr, Hunder GG. Adult primary central nervous system vasculitis. *Lancet*. 2012;380:767–776.

SVcPACNS present with seizures. In many centers, refractory status epilepticus is increasingly recognized as the presenting phenotype of SVcPACNS. Optic neuritis and spinal cord disease can also occur in the setting of SVcPACNS.

Constitutional features of fever or fatigue may point toward an underlying systemic illness causing a secondary CNS vasculitis. All children with suspected or confirmed CNS vasculitis require a careful assessment for a systemic illness.

DIAGNOSIS

The first step is considering vasculitis as a possible underlying etiology of newly acquired neurologic deficits and/or psychiatric symptoms (Table 642.2). The likelihood of CNS vasculitis in general and a specific

Table 642.2 Proposed Diagnostic Evaluation of Suspected Childhood Primary CNS Vasculitis

1. Clinical evaluation: Newly acquired symptom or deficit in a previously healthy child • Focal neurologic deficit: hemiparesis, hemisensory loss, aphasia, ataxia, movement abnormality, paresthesia, facial droop, ataxia, vision loss, spinal cord symptoms, others • Seizures or status epilepticus • Diffuse neurologic deficit, including cognitive decline with loss of higher executive function, concentration difficulties, learning or memory problems, behavior or personality changes, loss of social skills or emotional/impulse control, others • Headaches • Meningitis symptoms, abnormal level of consciousness • Psychiatric symptoms, including hallucinations <i>Differential diagnosis approach:</i> • Underlying illness known to cause, be associated or mimic CNS vasculitis: check all potential clinical features
2. Laboratory tests • Blood inflammatory markers: C-reactive protein, erythrocyte sedimentation rate and complete blood counts • Endothelial markers: von Willebrand factor (vWF) antigen • Cerebrospinal fluid (CSF) inflammatory markers: opening pressure, cell count, protein, oligoclonal bands <i>Differential diagnosis approach:</i> • Infections/postinfectious inflammation: cultures, serologies, Gram stain • Autoimmune encephalitis: check neuronal antibodies in CSF and blood • Systemic inflammation/rheumatic disease: characteristic laboratory markers such as complement, autoantibodies • Thromboembolic conditions: procoagulatory profile
3. Neuroimaging • Parenchymal imaging on MRI • Inflammatory lesions: T2/fluid attenuated inversion recovery sequences plus gadolinium • Ischemic lesions: diffusion-weighted images/apparent diffusion coefficient mapping • Vessel imaging
4. Brain biopsy

subtype of CNS vasculitis in particular depends on the demographic characteristics of the patient, the CNS and non-CNS features of the clinical presentation, the preceding symptoms, and the mode of onset of the disease. SVcPACNS is more commonly seen in females, whereas large/medium cPACNS has a clear male predominance. Seizures are a hallmark of SVcPACNS, whereas strokes often reflect large/medium-vessel inflammation. Laboratory markers of vasculitis typically include C-reactive protein, erythrocyte sedimentation rate, and complete blood counts. *However, inflammatory markers lack sensitivity and specificity in cPACNS, particularly when the CNS is involved in isolation.* More than 50% of children with large/medium-vessel cPACNS have normal inflammatory markers at diagnosis. In contrast, the majority of children with SVcPACNS present with mild to moderately raised markers. Von Willebrand factor antigen, an endothelial cell-derived protein, is a proposed biomarker of vasculitis correlating closely with disease activity in cPACNS. It may be of particular importance for distinguishing SVcPACNS from demyelinating disorders. Cerebrospinal fluid (CSF) analysis is abnormal in up to 90% of SVcPACNS patients and less than half of large/medium-vessel cPACNS patients. Within the latter group, children with the progressive subtype have a higher likelihood of presenting with abnormal CSF findings, including elevated opening pressure, raised CSF cell count (typically with lymphocyte predominance), and raised CSF protein. Oligoclonal bands are positive in 20% of children with SVcPACNS. They are rarely seen in other subtypes. Autoimmune encephalitis (see [Chapter 638.4](#)) and anti-myelin oligodendrocyte glycoprotein (MOG)-associated

encephalitis are two of the key neuroinflammatory differential diagnoses of SVcPACNS.

Neuroimaging is a valuable diagnostic modality for cPACNS. Parenchymal lesions may be inflammatory or ischemic in nature and are best viewed on MRI, including T2/fluid-attenuated inversion recovery (FLAIR) sequences and diffusion-weighted images (DWIs) ([Fig. 642.2](#)). CNS lesions in children with large/medium-vessel cPACNS are predominantly ischemic in nature and restricted to large vascular territories. In contrast, MRI lesions in children with SVcPACNS are not restricted to major vascular territories; lesions are primarily inflammatory and may enhance with contrast. In this subtype, focal or generalized meningeal enhancement is commonly seen if children are imaged before initiation of immunosuppressive therapy.

Evidence of vessel stenosis confirms the diagnosis in large/medium-vessel cPACNS subtypes; brain biopsies are not required. Important information about the disease activity can be obtained from post-gadolinium contrast studies of the vascular wall. The vessel wall of an inflamed cerebral vessel in active large/medium-vessel cPACNS subtypes is thickened and enhances contrast. Vessel wall enhancement may also be useful for the assessment of ongoing disease activity. Conventional angiography, when compared with MR angiography, has a higher sensitivity in detecting vessel stenosis in the distal vessel segments, the posterior circulation, and in very young children. Vessel wall imaging is often normal in children with SVcPACNS, often mandating a brain biopsy to definitively confirm the diagnosis. Studies of regional blood flow or therapeutic trials of antiinflammatory or immunosuppressive agents are nonsurgical alternatives that do not afford specific diagnostic information.

If a biopsy is pursued, a targeted lesional biopsy is preferred if an accessible lesion is identified on imaging. Biopsies should target low-risk, nonfunctional areas identified on MRI. In the appropriate clinical context, nonlesional biopsies can also be done to confirm the diagnosis of SVcPACNS and are typically taken from the nondominant frontal lobe. Diagnostic yield is improved if the biopsy is full thickness and includes the meninges and gray and white matter and if it is done before initiation of immunosuppression. In adults, one study reported the diagnostic yield of biopsies for PACNS to be 11%, with an identified alternative diagnosis reported in about 30% of cases. In this study, smaller biopsies and closed procedures were less likely to be diagnostic, and biopsy-related complications occurred in 16% of patients.

Characteristic findings on biopsy in SVcPACNS include an intramural and/or perivascular lymphocytic infiltrate, evidence of endothelial activation, and reactive astrocyte activation. Gliosis and perivascular demyelination are hallmarks of long-standing disease. Hemorrhagic lesions have also been reported. Findings typically seen in adult PACNS, including granulomas or vessel wall necrosis, are less commonly seen in children with SVcPACNS. Disorders that may be seen in adolescents and young adults that produce the reversible vasoconstriction syndrome must also be considered. These include migraine, drug-induced vasospasm, and postpartum angiopathy. Differentiating vasculitis from these other etiologies is important for therapy and prognosis ([Table 642.3](#)).

TREATMENT

Corticosteroids are the mainstay of acute immunosuppressive management of cPACNS. Usually pulse therapy is initially given. Antithrombotic therapy is equally important, particularly in large/medium-vessel cPACNS subtypes, because children are at high risk for recurrent ischemic events. For the distinct cPACNS subtypes, different treatment regimens should be considered. Nonprogressive cPACNS is a monophasic inflammatory illness with the highest risk of poor neurologic outcome. Vessel wall inflammation causes severe proximal stenosis and a high risk of stroke recurrence. High-dose corticosteroid pulses are commonly given,

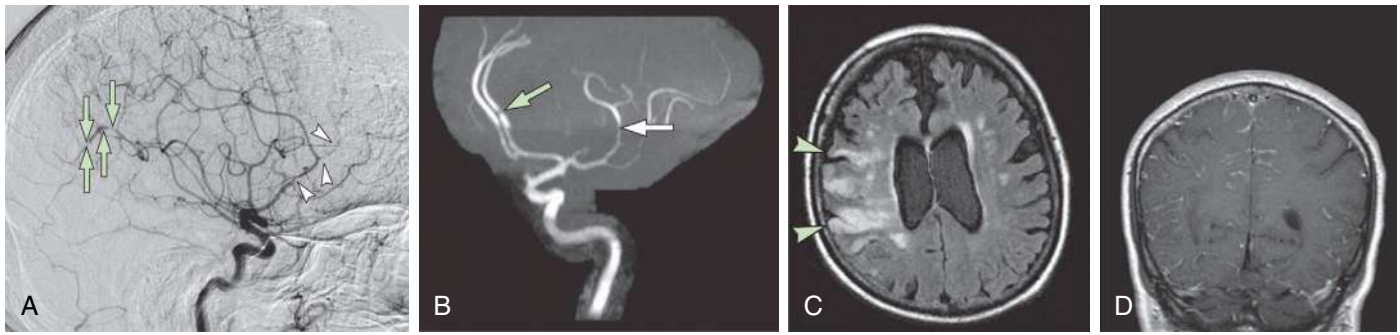


Fig. 642.2 Imaging of patients with primary CNS vasculitis. **A**, Cerebral angiogram shows alternating stenosis and dilation of the distal middle cerebral artery (arrows) and the anterior cerebral artery (arrowheads). **B**, MR angiography of the brain shows a short-segment stenosis of the anterior cerebral artery (green arrow) and stenosis of the distal middle cerebral artery (white arrow). **C**, Fluid attenuation inversion recovery-weighted MRI shows a large abnormality within the right cerebral hemisphere consistent with ischemia (arrowheads). **D**, MRI shows diffuse, asymmetric, nodular, and linear leptomeningeal enhancement, with the dura only slightly affected. (From Salvarani C, Brown RD Jr, Hunder GG. Adult primary central nervous system vasculitis. *Lancet*. 2012;380:767–776, Fig. 2.)

Table 642.3 Characteristics of Primary CNS Vasculitis and Reversible Cerebral Vasoconstriction Syndrome

	PCNSV	RCVS
Precipitating factor	None	Postpartum onset or onset after exposure to vasoactive substances
Onset	More insidious, progressive course	Acute onset followed by a monophasic course
Headaches	Chronic and progressive	Acute, thunderclap type
CSF findings	Abnormal (leukocytosis and high total protein concentration)	Normal to near normal
MRI	Abnormal in almost all patients	Initially may be normal or demonstrate vasogenic edema, vasospasm, or sequelae of vasospasm
Angiography	Possibly normal; otherwise, diffuse abnormalities are often indistinguishable from RCVS; irregular and asymmetric arterial stenoses or multiple occlusions are more suggestive of PCNSV; abnormalities might be irreversible	Always abnormal, strings-of-beads appearance of cerebral arteries; abnormalities reversible within 6–12wk
Cerebral biopsy	Vasculitis	No vasculitic changes
Drug treatment	Prednisone with or without cytotoxic agents	Nimodipine

CSF, Cerebrospinal fluid; PCNSV, primary CNS vasculitis; RCVS, reversible cerebral vasoconstriction syndrome.

From Salvarani C, Brown RD Jr, Hunder GG. Adult primary central nervous system vasculitis. *Lancet*. 2012;380:767–776, Table 2.

followed by a 6- to 12-week course of oral steroids at tapering doses. Second-line immunosuppressive agents are uncommonly used. All children require antithrombotic therapy, though no unifying regimen exists. Many centers initially use low molecular weight heparin followed by long-term antiplatelet therapy. When reimaged at 3 months, children should have stable or improved vessel disease, no newly affected vessel segments, and no evidence of vessel wall enhancement. At this point, the immunosuppressive therapy is commonly discontinued, and children are only kept on antiplatelet therapy.

Progressive cPACNS and SVcPACNS are considered chronic progressive vasculitis subtypes requiring a prolonged course of combination immunosuppression. High-dose corticosteroids are initially used, followed by long-term oral corticosteroids with a slow taper. Many centers use an induction-maintenance protocol, adding cyclophosphamide to corticosteroids (for 6 months), followed by mycophenolate mofetil or other oral second-line agents during maintenance therapy (usually 18 months). Symptomatic therapy is essential, including anticonvulsants or psychotropic medication if required. Supportive

therapy includes bone protection with calcium and vitamin D, prophylaxis against *Pneumocystis pneumonia*, and gastric mucosal protection as required.

PROGNOSIS

The mortality rate of cPACNS has significantly improved. In large-vessel cPACNS, the risk of stroke recurrence is thought to be high in patients who are found to have progression on vascular imaging at 12 months (especially if there was simultaneous progression and improvement occurring across multiple vessels).

Some treatment protocols for SVcPACNS report a good outcome, defined as no functional neurologic deficits, in two thirds of children. Children presenting with status epilepticus and SVcPACNS have the poorest cognitive outcome. Multidisciplinary care involving neurology, rheumatology, hematology, and rehabilitation is ideal and may improve outcomes.

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Chapter 643

Central Nervous System Infections

Andrew B. Janowski and David A. Hunstad

Infection of the central nervous system (CNS) is a significant cause of morbidity and mortality in children. Identification of CNS infections can be problematic for clinicians because symptoms can be nonspecific in younger infants, and delayed or missed diagnosis can amplify the morbidity and mortality rates associated with these diseases. Implementation of multiple conjugate vaccines has greatly reduced the incidence of bacterial infections of the CNS. Nonetheless, bacterial and viral infections remain a significant cause of CNS disease, with atypical bacterial, fungal, and parasitic pathogens also causing a smaller number of cases.

Independent of etiology, many patients with CNS infection have similar clinical manifestations. **Common symptoms** include headache, nausea, vomiting, anorexia, photophobia, restlessness, altered state of consciousness, and irritability. **Common signs** of CNS infection include fever, neck pain, nuchal rigidity, focal neurologic deficits, seizures, obtundation, and coma. The severity and constellation of signs are determined by host-pathogen interactions and the affected region of the CNS. **Meningitis** describes primary involvement of the meninges, and **encephalitis** indicates brain parenchymal involvement. However, these anatomic boundaries may be indistinct during infection, and many patients have clinical or imaging evidence of both meningeal and parenchymal involvement. Terms such as *meningoencephalitis* may better describe diffuse infections of the CNS by pathogens such as viruses. Brain abscess is the most common example of a focal infection of the CNS (see Chapter 644).

The diagnosis of CNS infection depends on a combination of imaging of the brain, testing the cerebrospinal fluid (CSF) by culture, polymerase chain reaction (PCR), and serologic methods and, in rare situations, biopsy of brain tissue. Pending many of these tests, standard CSF studies provide initial data to help guide selection of empiric antimicrobials. Table 643.1 provides an overview of the typical CSF abnormalities with various CNS disorders.

643.1 Acute Bacterial Meningitis Beyond the Neonatal Period

Andrew B. Janowski and David A. Hunstad

Bacterial meningitis is one of the most serious pediatric infections because it is associated with a high rate of acute complications and a risk of long-term morbidity and mortality. However, the use of antibiotics and vaccines against the most common causes of bacterial meningitis has significantly altered the spectrum of disease. In the 1980s, the most common causes of bacterial meningitis in children older than 1 month of age in the United States were *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and *Neisseria meningitidis*. The incidence of meningitis caused by all three organisms has been significantly reduced in countries that have introduced universal immunization against these pathogens. *S. pneumoniae* is now the most common cause of bacterial meningitis in the United States. Demonstrating the impact of vaccination in the United States, invasive *H. influenzae* disease occurred in 67–129 cases per 100,000 children under 5 years of age in the 1980s. By 2019, *H. influenzae* type b–associated diseases were exceptionally rare; there were only 18 invasive cases in the United States, with a calculated national rate of 0.08 cases per 100,000 children under 5 in the year 2017. Nonetheless, other serotypes of *H. influenzae* (particularly type a and, rarely, other serotypes have emerged as a cause of meningitis).

EPIDEMIOLOGY

A major risk factor for bacterial meningitis is the lack of preexisting immunity to specific pathogens and serotypes, reflected in a higher incidence of meningitis in young infants. Additional risk factors include recent colonization with pathogenic bacteria, close contact (household, daycare centers, college dormitories, military barracks) with individuals having invasive disease caused by *N. meningitidis* or *H. influenzae* type b, crowding, poverty, and male sex. The mode of transmission of these pathogens is through contact with respiratory tract secretions or droplets. The risk of meningitis is increased among infants and young children with occult bacteremia; the odds ratio is greater for meningococcus (85 times) and *H. influenzae* type b (12 times) relative to that for pneumococcus.

Indigenous Nation and Eskimo populations exhibit a higher incidence of bacterial meningitis because these populations have altered immunoglobulin production in response to encapsulated pathogens. Defects of the complement system (C5–C8) are associated with recurrent meningococcal infection, and defects of the properdin system are associated with a significant risk of lethal meningococcal disease. Splenic dysfunction (e.g., in sickle cell anemia) or asplenia (caused by trauma or a congenital defect) is associated with an increased risk of pneumococcal, *H. influenzae* type b, and meningococcal sepsis and meningitis. T-lymphocyte defects (congenital or acquired by chemotherapy, AIDS, or malignancy) are associated with an increased risk of *Listeria monocytogenes* infections of the CNS.

The risk of pneumococcal meningitis is increased in children with congenital or acquired CSF leak across a mucocutaneous barrier, such as a lumbar dural sinus, cranial or midline facial defects (cribriform plate), fistulas of the middle ear (stapedial foot plate) or inner ear (oval window, internal auditory canal, cochlear aqueduct), or CSF leakage as a result of basilar or other skull fracture. The risk of pneumococcal bacterial meningitis was historically increased by more than 30-fold in children with cochlear implants, though advances in implant design have reduced this risk. Lumbosacral dermal sinus and myelomeningocele are associated with staphylococcal, anaerobic, and gram-negative enteric bacterial meningitis. CSF shunt infections increase the risk of meningitis caused by *Pseudomonas aeruginosa*, *Staphylococcus* spp. (*S. aureus* and coagulase-negative species), *Cutibacterium* spp. (formerly *Propionibacterium* spp.), and other lower-virulence bacteria that typically colonize the skin.

Streptococcus pneumoniae

See also Chapter 228.

Although the incidence of pneumococcal meningitis has been reduced, *S. pneumoniae* remains the most frequently identified pathogen from cases of bacterial meningitis in the United States and in other countries that have adopted similar vaccination strategies. The seven-valent pneumococcal conjugate vaccine (PCV7) was included in the routine U.S. vaccination schedule in 2000 and contained serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, responsible for ~85% of invasive pneumococcal infections in the country. A dramatic decrease in the rate of pneumococcal meningitis followed, from 8.2 cases per 100,000 in 1998–1999 to 0.59 cases per 100,000 in 2004–2005. Similar reductions were also identified in other nations that introduced this vaccine. However, this was followed by an increased incidence of invasive disease caused by serotypes not contained in the original vaccine, known as *serotype replacement*. In response, a 13-valent pneumococcal conjugate vaccine (PCV13) was licensed in the United States in 2010, containing the serotypes in PCV7 plus serotypes 1, 3, 5, 6A, 7F, and 19A. Post-marketing surveillance data suggest the rate of invasive pneumococcal infections has decreased further, though there are conflicting data as to whether the rate of pneumococcal meningitis has decreased. Based on data from the Centers for Disease Control and Prevention (CDC) Active Bacterial Surveillance system, the incidence of invasive pneumococcal infections has fallen from 142.9 per 100,000 children under age 1 in 1977 to 13.3 per 100,000 children under age 1 in 2018. Children with anatomic or functional asplenia secondary to sickle cell disease and those infected with HIV have infection rates that are 20- to 100-fold higher than those of healthy children in the first 5 years of

Table 643.1 Cerebrospinal Fluid Findings in Central Nervous System Disorders

CONDITION	PRESSURE (cm H ₂ O)	LEUKOCYTES (mm ³)	PROTEIN (mg/dL)	GLUCOSE (mg/dL)	COMMENTS
Normal	<28	<5, ≥75% Lymphocytes in neonates: <20	20-45	>50 (or 75% serum glucose)	
COMMON FORMS OF MENINGITIS					
Acute bacterial meningitis	Usually elevated	100-10,000 or more; usually 300-2,000; PMNs predominate	Usually 100-500	Decreased, usually <40 (or <50% of serum glucose)	Organisms usually seen on Gram stain and isolated by culture or identified by PCR
Partially treated bacterial meningitis	Normal or elevated	5-10,000; PMNs usual, but mononuclear cells may predominate if pretreated for extended period	Usually 100-500	Normal or decreased	Organisms may be seen on Gram stain. Pretreatment may render CSF sterile. PCR-based assays may detect bacterial DNA.
Viral meningitis or meningoencephalitis	Normal or slightly elevated	Rarely >1,000 cells. Eastern equine encephalitis and lymphocytic choriomeningitis may have cell counts of several thousand. PMNs early, but mononuclear cells predominate through most of the course,	Usually 50-200	Generally normal; may be decreased to <40 in some viral diseases, particularly mumps (15-20% of cases)	HSV encephalitis is suggested by focal seizures or by focal findings on MRI or CT scans or EEG. Most arboviruses detected by PCR of CSF or urine and serology.
UNCOMMON FORMS OF MENINGITIS					
Tuberculous meningitis	Usually elevated	10-500; PMNs early, but lymphocytes predominate through most of the course	100-3,000; may be higher in presence of obstruction	<50 in most cases; decreases with time if treatment is not provided	Acid-fast organisms rarely seen on smear. Large volumes of CSF required for recovery of organisms. <i>Mycobacterium tuberculosis</i> can be detected by PCR of CSF.
Fungal meningitis	Usually elevated	5-500; PMNs early, but mononuclear cells predominate for most of the course. Cryptococcal meningitis may lack pleocytosis. Coccidioidal meningitis may have eosinophilia	25-500	<50; decreases with time if treatment is not provided	Budding yeast may be seen. Organisms may be recovered by culture. Cryptococcal antigen (CSF and serum) may be positive in cryptococcal infection.
Syphilis (acute), Lyme disease, and leptospirosis	Usually elevated	50-500; lymphocytes predominate	50-200	Usually normal	Positive CSF serology. Spirochetes not demonstrable by smear or culture; dark-field examination may be positive. Positive Lyme serology.
Amebic (<i>Naegleria</i>) meningoencephalitis	Elevated	1,000-10,000 or more; PMNs predominate	50-500	Normal or slightly decreased	Mobile amoebas may be seen by wet-mount microscopy of CSF
BRAIN ABSCESSSES AND PARAMENINGEAL FOCUS					
Brain abscess	Usually elevated	5-200; CSF rarely acellular; lymphocytes predominate; if abscess ruptures into ventricle, PMNs predominate and cell count may reach >100,000	75-500	Normal unless abscess ruptures into ventricular system	CSF cultures are only positive in 24% of cases unless abscess ruptures into ventricular system

Continued

Table 643.1 Cerebrospinal Fluid Findings in Central Nervous System Disorders—cont'd

CONDITION	PRESSURE (cm H ₂ O)	LEUKOCYTES (mm ³)	PROTEIN (mg/dL)	GLUCOSE (mg/dL)	COMMENTS
Subdural empyema	Usually elevated	100-5,000; PMNs predominate	100-500	Normal	No organisms on smear or culture of CSF unless meningitis also present; organisms found on tap of subdural fluid
Cerebral epidural abscess	Normal to slightly elevated	10-500; lymphocytes predominate	50-200	Normal	No organisms on smear or culture of CSF
Spinal epidural abscess	Usually low, with spinal block	10-100; lymphocytes predominate	50-400	Normal	No organisms on smear or culture of CSF
Chemical (drugs, dermoid cysts, myelography dye)	Usually elevated	100-1,000 or more; PMNs predominate	50-100	Normal or slightly decreased	Epithelial cells may be seen within CSF by use of polarized light in some children with ruptured dermoids
NONINFECTIOUS CAUSES					
Sarcoidosis	Normal to elevated slightly	0-100; mononuclear	40-100	Normal	No specific findings
Systemic lupus erythematosus with CNS involvement	Slightly elevated	0-500; PMNs usually predominate; lymphocytes may be present	100	Normal or slightly decreased	No organisms on smear or culture. Positive neuronal and ribosomal P protein antibodies in CSF.
Tumor, leukemia	Slightly elevated to very high	0-100 or more; mononuclear or blast cells	50-1,000	Normal to decreased (20-40)	Cytology may be positive
Acute disseminated encephalomyelitis	Normal or elevated	~100 lymphocytes	Normal to elevated	Normal	MRI adds to diagnosis
Autoimmune encephalitis	Normal	~100 lymphocytes	Normal to elevated	Normal	Anti-NMDAR or other autoimmune antibody-positive (CSF is often more sensitive than serum)

CSF, Cerebrospinal fluid; EEG, electroencephalogram; HSV, herpes simplex virus; NMDAR, N-methyl-D-aspartate receptor; PCR, polymerase chain reaction; PMN, polymorphonuclear neutrophils.

life. Additional risk factors for contracting pneumococcal meningitis include endocarditis, otitis media, mastoiditis, sinusitis, pneumonia, CSF otorrhea or rhinorrhea, the presence of a cochlear implant, and immunosuppression.

Neisseria meningitidis

See also Chapter 237.

Six serogroups of meningococcus (A, B, C, X, Y, and W-135) are responsible for invasive disease in humans. Meningococcal meningitis may be sporadic or may occur in major epidemics, particularly in the African meningitis belt, where serogroup A accounts for 80–85% of outbreaks. In the United States, serogroup B is the most common cause of meningitis in infants and is also a cause of outbreaks on college campuses. Meningococcal cases are more common in the winter and spring, likely because of associations with viral infections, including influenza. Nasopharyngeal carriage of *N. meningitidis* occurs in up to 15% of adults. Most infections in children are acquired from a contact in a daycare facility, a colonized adult family member, or an ill patient with meningococcal disease. Colonization may last weeks to months; recent colonization places nonimmune younger children at greatest risk for meningitis. The incidence of disease occurring in association with an index case in the family is 1%, a 1,000-fold increase in risk in comparison to the general population. The risk of secondary cases occurring in contacts at daycare centers is approximately 1 in 1,000. Children under 5 years of age have the highest rates of meningococcal infection, and a second peak in incidence occurs in persons between

15 and 24 years of age. First-year college students living in dormitories have an increased incidence of infection compared with non-college-attending, age-matched controls.

Haemophilus influenzae Type b

See also Chapter 240.

Before universal *H. influenzae* type b vaccination in the United States, approximately 70% of cases of bacterial meningitis occurring in the first 5 years of life were caused by this pathogen. Invasive infections occurred primarily in infants 2 months to 2 years of age, the peak incidence was at 6-9 months of age, and 50% of cases occurred in the first year of life. The risk to children was markedly increased among household or daycare contacts of patients with *H. influenzae* type b disease. Global vaccination efforts have also led to remarkable declines in the incidence of this disease. Incompletely vaccinated individuals, those in underdeveloped countries who are not vaccinated, and those with immune-compromising conditions remain at risk for *H. influenzae* type b meningitis. Other serotypes of *H. influenzae* (a, f) have been associated with meningitis.

PATHOLOGY AND PATHOPHYSIOLOGY

A purulent exudate of varying thickness may be distributed around the cerebral veins, venous sinuses, convexity of the brain, and cerebellum and in the sulci, sylvian fissures, basal cisterns, and spinal cord. Ventriculitis with bacteria and inflammatory cells in ventricular fluid may be present (more often in neonates) in addition to subdural effusions

and empyema. Perivascular inflammatory infiltrates may also be evident, and the ependymal membrane may be disrupted. Vascular and parenchymal cerebral changes have been described at autopsy, including polymorphonuclear infiltrates extending to the subintimal region of small arteries and veins, vasculitis, thrombosis of small cortical veins, occlusion of major venous sinuses, necrotizing arteritis producing subarachnoid hemorrhage, and cerebral cortical necrosis in the absence of identifiable thrombosis. Cerebral infarction is a frequent sequela that is caused by vascular occlusion from inflammation, vasospasm, or thrombosis. The extent of an infarct may range from microscopic to an entire hemisphere.

Inflammation of spinal nerves and roots produces meningeal signs, and inflammation of the cranial nerves produces cranial neuropathies of optic, oculomotor, facial, and auditory nerves. Increased intracranial pressure (ICP) also produces oculomotor nerve palsy because of temporal lobe compression of the nerve during tentorial herniation. Abducens nerve palsy may be an early nonlocalizing sign of elevated ICP.

Increased ICP is a result of cell death (cytotoxic cerebral edema), cytokine-induced increased capillary vascular permeability (vasogenic cerebral edema), and increased hydrostatic pressure (interstitial cerebral edema) after obstructed reabsorption of CSF in the arachnoid villus or obstruction of the flow of fluid from the ventricles. ICP may exceed 30 cm H₂O and cerebral perfusion may be further compromised if the cerebral perfusion pressure (mean arterial pressure minus mean ICP) falls below 50 mm Hg as a result of systemic hypotension. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) may produce excessive water retention and potentially increase the risk of elevated ICP (see Chapter 597). Hypotonicity of brain extracellular spaces may cause cytotoxic edema with cell swelling and lysis. Tentorial, falcine, or cerebellar herniation does not usually occur, because the increased ICP is transmitted to the entire subarachnoid space and there is little structural displacement. Furthermore, if the fontanels are still patent, increased ICP is not always dissipated.

Hydrocephalus can occur as an acute complication of bacterial meningitis because it is often caused by adhesive thickening of the arachnoid villi around the cisterns at the base of the brain. Thus this thickening leads to interference with the normal resorption of CSF and development of hydrocephalus. Less often, obstructive hydrocephalus develops after fibrosis and gliosis of the cerebral aqueduct or the foramina of Magendie and Luschka.

Elevated CSF protein levels are partly a result of increased vascular permeability of the blood-brain barrier (BBB) and the loss of albumin-rich fluid from the capillaries and veins traversing the subdural space. Continued transudation may result in subdural effusions, usually observed in the later phase of acute bacterial meningitis. **Hypoglycorrhachia** (reduced CSF glucose level) is attributable to altered glucose transport by the cerebral tissue.

Damage to the cerebral cortex may be a result of the focal or diffuse effects of vascular occlusion (infarction, necrosis, lactic acidosis), hypoxia, bacterial invasion (cerebritis), toxic encephalopathy (bacterial toxins), elevated ICP, ventriculitis, and/or transudation (subdural effusions). These pathologic factors result in the clinical manifestations of impaired consciousness, seizures, cranial nerve deficits, motor and sensory deficits, and later, psychomotor retardation.

PATHOGENESIS

Bacterial meningitis outside the neonatal period is typically the result of bacterial colonization of the nasopharynx with subsequent invasion into the bloodstream, causing bacteremia. Circulating bacteria then breach the BBB to cause CNS infection and inflammation.

Meningitic pathogens frequently colonize the nasopharynx of asymptomatic children, but rapid invasion after recent colonization may also occur. Bacterial proteins termed *adhesins* act to enhance colonization by enabling *N. meningitidis* and *H. influenzae* type b to attach to mucosal epithelial cell receptors. The microbiome of the nasopharynx is a complex community of bacteria that may enhance or inhibit colonization by other bacteria. *S. pneumoniae* can synthesize hydrogen peroxide, which can inhibit growth of *H. influenzae* type b; conversely, *H. influenzae* type b can invoke a specific immune response that targets

clearance of *S. pneumoniae*. Other bacteria may alter the microbiome of the nasopharynx, and studies after implementation of PCVs have identified alterations to the composition of nasopharyngeal bacterial populations. Viruses can also enhance bacterial adherence by a combination of expression of viral factors that interact with host adhesion proteins.

After attachment to epithelial cells, bacteria may breach the mucosa and enter the bloodstream. Various models of invasion have been developed; *N. meningitidis* can be transported across the mucosal surface within a phagocytic vacuole after ingestion by the epithelial cell. Expression of the polysaccharide capsule in relevant bacteria also appears to be tightly regulated, as it can enhance or inhibit the efficiency of bacterial translocation across the mucosal barrier. Viral infection can disrupt the mucosal barrier, thereby facilitating bacterial invasion; specifically, there is a significant association between recent influenza infection and development of meningococcemia. Once bacteria reach the bloodstream, the capsule is a critical component for survival because it interferes with opsonic phagocytosis. Host-related immune defects in bacterial opsonic phagocytosis can also allow bacteremia. In nonimmune hosts, the defect may be from an absence of preformed IgM or IgG anticapsular antibodies (as in an unimmunized toddler), whereas deficiencies in components of the complement or properdin system may preclude effective opsonic phagocytosis. Asplenia may also hamper opsonic phagocytosis by the reticuloendothelial system.

There is a positive correlation between the bloodstream bacterial titer and the accompanying risk of developing meningitis, suggesting that a critical threshold may be necessary for breaching the BBB. Bacterial factors, including the capsule, play a role in crossing the BBB through transcellular, paracellular, or Trojan horse (within infected phagocytes) mechanisms. Bacteria gain entry to the CSF through the choroid plexus of the lateral ventricles and the meninges and then circulate to the extracerebral CSF and subarachnoid space. Bacteria multiply rapidly because CSF concentrations of complement and antibodies are inadequate to contain bacterial proliferation. Chemotactic factors then incite a local inflammatory response characterized by polymorphonuclear cell (neutrophil) infiltration. The presence of lipopolysaccharide (endotoxin) from gram-negative bacteria (*H. influenzae* type b, *N. meningitidis*) or of pneumococcal cell wall components (teichoic acid, peptidoglycan) stimulates a marked inflammatory response, with local production of tumor necrosis factor, interleukin-1, prostaglandin E, and other inflammatory mediators. The subsequent inflammatory response is characterized by neutrophilic infiltration, increased vascular permeability, further compromise of the BBB, and vascular thrombosis. Meningitis-associated brain injury is not simply caused by bacterial-derived factors but also occurs as a consequence of the host inflammatory cascade triggered by bacterial components.

Uncommonly, meningitis may follow bacterial invasion from a contiguous focus of infection such as paranasal sinusitis, otitis media, mastoiditis, orbital cellulitis, or cranial or vertebral osteomyelitis; or it may occur after introduction of bacteria via penetrating cranial trauma, dermal sinus tracts, or myelomeningocele.

CLINICAL MANIFESTATIONS

The onset of acute meningitis has two predominant patterns. Most often, meningitis is preceded by several days of fever accompanied by upper respiratory tract or, less often, gastrointestinal symptoms, followed by nonspecific signs of CNS infection, such as lethargy and irritability. Fortunately, the more dramatic presentation is less common and features sudden and progressive shock, purpura, disseminated intravascular coagulation, and reduced levels of consciousness, often resulting in progression to coma or death within 24 hours.

The signs and symptoms of meningitis reflect the nonspecific findings associated with any systemic infection and the manifestations of meningeal irritation. Nonspecific findings include fever, anorexia or poor feeding, headache, upper respiratory symptoms, myalgias, arthralgias, tachycardia, hypotension, and various cutaneous signs, such as petechiae, purpura, or an erythematous macular rash. The rash of meningococcemia is typified by an initial petechial rash that evolves into ecchymotic and purpuric lesions. Meningeal irritation is manifested as nuchal rigidity, back pain, **Kernig sign** (flexion of

the hip 90 degrees with subsequent pain upon extension of the leg), and **Brudzinski sign** (involuntary flexion of the knees and hips after passive flexion of the neck while supine). In children, particularly in those younger than 12–18 months, Kernig and Brudzinski signs are not consistently present. In adults, fever, headache, and nuchal rigidity are present in only 40% of cases of bacterial meningitis. Increased ICP is suggested by headache, emesis, bulging fontanelle or diastasis (widening) of the sutures, oculomotor (anisocoria, ptosis) or abducens nerve paralysis, hypertension with bradycardia, apnea, or hyperventilation, decorticate or decerebrate posturing, stupor, coma, or signs of herniation. Papilledema is more common in complicated meningitis and is suggestive of a chronic process, such as the presence of an intracranial abscess, subdural empyema, or occlusion of a dural venous sinus. Focal neurologic signs usually are a result of vascular occlusion. Cranial neuropathies of the ocular, oculomotor, abducens, facial, and auditory nerves may also be the result of focal inflammation. Overall, 10–20% of children with bacterial meningitis have focal neurologic signs.

Seizures (focal or generalized) related to cerebritis, infarction, or electrolyte disturbances occur in 20–30% of patients with meningitis. Seizures that occur on presentation or within the first 4 days of onset usually are of little prognostic significance. Poorer prognosis is suggested when seizures persist after the fourth day of illness, as these can be refractory to treatment.

Alteration in mental status is common among patients with meningitis and may be the consequence of increased ICP, cerebritis, or hypotension; manifestations include irritability, lethargy, stupor, obtundation, and coma. Comatose patients have a poor prognosis. Additional manifestations of meningitis include photophobia and tache cérébrale, which is elicited by stroking the skin with a blunt object and observing a raised red streak within 30–60 seconds.

DIAGNOSIS

Lumbar puncture (LP), to obtain CSF for Gram stain and culture, is the most important step in the diagnosis of meningitis. Testing of the CSF for neutrophilic pleocytosis, elevated protein, and/or reduced glucose concentrations can yield results within a few hours and can indicate bacterial meningitis (see [Table 643.1](#)). **Contraindications** to immediate LP include (1) evidence of increased ICP (other than a bulging fontanel), such as third or sixth cranial nerve palsy with a depressed level of consciousness, or the Cushing reflex (hypertension and bradycardia associated with respiratory abnormalities; see [Chapter 630](#)); (2) severe cardiopulmonary compromise requiring prompt resuscitative measures for shock or in patients in whom positioning for the LP would further compromise cardiopulmonary function; or (3) infection of the skin overlying the site of the LP. Thrombocytopenia is a relative contraindication for LP. **If LP is delayed, empiric antibiotic therapy should be initiated.**

Some clinicians obtain a head CT scan before LP to evaluate for evidence of increased ICP because an LP in the setting of elevated ICP may promote brain herniation. However, a head CT scan may delay diagnosis of meningitis and initiation of antimicrobials, and it does not always rule out increased ICP. Therefore **head CT scans before LP are not routinely recommended** unless the patient has clinical signs or is at risk for elevated ICP, including papilledema, focal neurologic findings, coma, history of hydrocephalus, or prior neurosurgical procedures including shunt placement. However, if a CT scan is to be obtained before LP, antimicrobial therapy should not be delayed. LP can safely be performed after increased ICP (if present) has been appropriately treated.

Blood cultures should be performed in all patients with suspected meningitis. Blood cultures reveal the responsible bacteria in up to 80–90% of cases of meningitis. Elevations of C-reactive protein, erythrocyte sedimentation rate, and procalcitonin can be seen in both bacterial and viral meningitis, but some clinical prediction tools include these tests to determine risk for bacterial meningitis.

Lumbar Puncture

See also [Chapter 630](#).

The CSF leukocyte count in bacterial meningitis often is elevated to $>1,000/\text{mm}^3$ and, typically, there is a neutrophilic predominance (75–95%). Turbid CSF is observed when the leukocyte count exceeds $200\text{--}400/\text{mm}^3$. Healthy neonates may have as many as 20 leukocytes/ mm^3 , but older children without viral or bacterial meningitis have <8 leukocytes/ mm^3 in the CSF, and these should be nearly all lymphocytes or monocytes.

The CSF leukocyte count is $<250/\text{mm}^3$ in as many as 20% of patients with acute bacterial meningitis. Pleocytosis may be absent in patients with severe overwhelming sepsis associated with meningitis; this is a poor prognostic sign. Of note, neutrophilic pleocytosis may be present in the early stages of acute viral meningitis. The shift to lymphocytic-monocytic predominance in viral meningitis invariably occurs within 8–24 hours of an initial LP. In the absence of CNS infection or inflammatory disease, children with seizures (including febrile seizures) *do not* exhibit CSF pleocytosis.

A diagnostic conundrum in the evaluation of children with suspected bacterial meningitis is the analysis of CSF obtained from children who have already received antibiotic therapy. This is a common clinical scenario, as 25–50% of children undergoing evaluation for bacterial meningitis have received antibiotics before a CSF sample is obtained. CSF from children with bacterial meningitis can be negative on Gram stain and culture as early as 2–4 hours after administration of antibiotics, especially in situations of *N. meningitidis* and sensitive *S. pneumoniae* meningitis. However, pleocytosis with a predominance of neutrophils, an elevated protein level, and a reduced concentration of CSF glucose will usually persist for several days after initiation of appropriate parenteral antibiotics. Therefore despite negative cultures, the presumptive diagnosis of bacterial meningitis can be made on the basis of an abnormal CSF cell count, protein, and glucose. A multiplex PCR test for common CNS bacterial and viral pathogens is available for testing on CSF samples, with turnaround times of only a few hours. This test is often used as an adjunct (and rapid) diagnostic test, as its current sensitivity and specificity have not supplanted the use of routine bacterial cultures; in particular, its highest false-positive rate is for *S. pneumoniae*. PCR of bacterial 16S ribosomal RNA sequences may be useful in diagnosing the cause of culture-negative meningitis caused by prior antibiotic therapy or for the detection of nonculturable or fastidious pathogens.

A traumatic LP may also complicate the interpretation of CSF tests, as CSF leukocyte count and protein concentration are significantly affected by blood in the sample. However, the Gram stain, culture, and glucose level are unlikely to be influenced by blood in a CSF sample. Repeat LP at a higher interspace may produce fluid that is less hemorrhagic, but this fluid usually still contains red blood cells. Although methods for correcting for the presence of red blood cells have been proposed for red blood cell counts $<10,000$ cells/ mm^3 , these corrections can be imprecise and unreliable, so empiric treatment with antibiotics pending any bacterial culture result might be indicated.

DIFFERENTIAL DIAGNOSIS

Most bacterial meningitis is caused by *S. pneumoniae* and *N. meningitidis*, whereas *H. influenzae* type b is relatively rare in nations with high immunization rates. However, other pathogens less frequently identified in meningitis can cause similar clinical manifestations. These organisms include other bacteria, including non-type-b *H. influenzae*, *Mycobacterium tuberculosis*, *Nocardia* spp., *Treponema pallidum* (syphilis), and *Borrelia burgdorferi* (Lyme disease); fungi, such as those endemic to specific geographic areas (*Coccidioides*, *Histoplasma*, and *Blastomyces*) and those responsible for infections in compromised hosts (*Candida*, *Cryptococcus*, and *Aspergillus*); parasites, such as *Toxoplasma gondii* and *Taenia solium*; and most frequently, viruses ([Tables 643.2 and 643.3](#) and see [Chapter 643.2](#)). Focal infections of the CNS, including brain abscess and parameningeal abscess (subdural empyema, cranial and spinal epidural abscess), may also be confused with meningitis. In addition, noninfectious illnesses can cause generalized inflammation of the CNS; relative to infections, these disorders are very uncommon and include malignancy (lymphoma), immunologic diseases (CNS vasculitis, sarcoidosis, autoimmune encephalitis), and exposure to toxins (see [Table 643.3](#)).

Table 643.2 Causes of Aseptic Meningitis and Encephalitis Including Differential Diagnosis at Different Ages

AGE	INFECTIOUS	INFLAMMATION	AUTOIMMUNE	MIMICS
0-24 mo	Enteroviruses Parechovirus HSV Congenital infections Arboviruses HIV	Cryopyrin disorders Interferonopathies Complement disorders (HUS/TTP) Aicardi-Goutieres syndrome	Paraneoplastic rare under 12 mo	- Bacterial meningitis - Urea cycle disorders, maple syrup urine disease, MCAD deficiency, CPT2, mitochondrial disorders (Leigh) - Brain malformations - Intoxication - Epilepsy - Dravet (SCNA1) and other epilepsy encephalopathy syndromes - Acute adrenal crisis - Hydrocephalus - HLH - Glioma
2-5 yr	Enteroviruses HSV Influenza Arboviruses Adenovirus <i>Bartonella</i> <i>Ehrlichia</i> and <i>Borrelia</i> spp. Rabies	Complement disorders (HUS/TTP)	ADEM NMOSD VZV AFP TM	- Bacterial meningitis - Intoxication - MCAD deficiency - Epilepsy - Dravet (SCNA1) and other epilepsy encephalopathy syndromes - Infectious HUS - HLH - Mitochondrial disorders (MELAS) - Glioma; CNS lymphoma
5-18 yr	Enteroviruses HSV Influenza Arboviruses Adenovirus <i>Bartonella</i> <i>Ehrlichia</i> and <i>Borrelia</i> spp. Rabies		ADEM NMDAR NMOSD VZV AFP SLE TM	- Bacterial meningitis - Epilepsy - Intoxication - Psychosis - Wilson disease - Pseudotumor cerebri - Multiple sclerosis - Dravet (SCNA1) and other epilepsy encephalopathy syndromes - HLH - Mitochondrial disorders (MELAS) - Vasculitis (primary, rickettsia, VZV) - Tumors: Glioma; CNS lymphoma; Metastatic
Young adult	Enteroviruses HSV Influenza Arboviruses <i>Ehrlichia</i> and <i>Borrelia</i> spp. HIV Rabies		ADEM NMDAR NMOSD SLE Paraneoplastic AFP TM	- Bacterial meningitis - Intoxication - Psychosis - Wilson disease - HLH - Periarteritis nodosa, Takayasu, giant cell, ANCA + arteritis - Acute intermittent porphyria - Multiple sclerosis - Vasculitis (primary, rickettsia, VZV) - Tumors: Glioma; CNS lymphoma; metastatic
Older adult	Enteroviruses HSV Influenza Arboviruses <i>Ehrlichia</i> and <i>Borrelia</i> spp. HIV Rabies		Limbic encephalitis SLE AFP NMOSD NMDAR	- Bacterial meningitis - Intoxication - TTP - Neurodegeneration - Tumor metastases - HLH - Periarteritis nodosa, Takayasu, giant cell, ANCA + arteritis - Multiple sclerosis - Mitochondrial disorders (MELAS) - Vasculitis (primary, rickettsia, VZV) - Tumors: Glioma; CNS lymphoma; metastatic

ADEM, Acute disseminated encephalomyelitis; AFP, acute flaccid paralysis; ANCA, antineutrophil cytoplasmic antibody; CNS, central nervous system; CPT2, carnitine palmitoyltransferase-2; HLH, hemophagocytic lymphohistiocytosis; HSV, herpes simplex virus; HUS, hemolytic uremic syndrome; MCAD, medium-chain acylcarnitine deficiency; MELAS, mitochondrial encephalopathy lactic acidosis syndrome; NMDAR, N-methyl-D-aspartate receptor encephalitis; NMOSD, neuromyelitis optica spectrum disorder; SCNA1, sodium voltage-gated channel alpha subunit 1; SLE, systemic lupus erythematosus; SMA, spinal muscular atrophy; TM, transverse myelitis; TTP, thrombotic thrombocytopenic purpura; VZV, varicella-zoster virus

Modified from Kliegman RM. Encephalitis. In: Kliegman RM, Toth H, Bordini BJ, et al, eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier, 2023: Table 42.2, p. 768.

Table 643.3 Exposures Associated with Agents Causing Aseptic Meningitis, Encephalitis, and Encephalitis-Like Syndrome

EXPOSURE	AGENT	RISK FACTORS AND EPIDEMIOLOGY
ARTHROPODS Mosquitoes		
	<i>Togaviridae</i>	
	Chikungunya virus	Humans and other vertebrates serve as reservoirs. Vertical transmission has been reported.
	Eastern equine encephalitis virus	Like Western equine encephalitis, birds are the primary reservoir, exposure to horses is not a risk factor. High frequency of symptomatic infections in children and elderly.
	Semliki Forest virus	Cases are rare; one reported death attributed as part of a possible laboratory accident
	Venezuelan equine encephalitis virus	Equids and small mammals are the primary reservoir. Children are at higher risk for development of long-term neurological sequelae.
	Western equine encephalitis (WEE) virus	Birds are the primary reservoir. Viremia is too low in humans or horses to infect mosquitoes, so horse exposure is not a true risk factor for disease.
	<i>Flaviviridae</i>	
	Dengue virus	The primary reservoir is humans and other primates. Vertical transmission has been reported, as well through organ transplant and blood transfusion
	Japanese encephalitis virus	Primary reservoir is birds and pigs. Bats may also contribute to circulation of the virus.
	Murray Valley encephalitis virus	Waterfowl are the primary reservoir
	St. Louis encephalitis virus	Birds are the primary reservoir
	West Nile virus	Birds are the primary reservoir. Transmission has also been reported through organ transplantation or blood transfusions.
	Zika virus	Humans and non-human primates are the like primary reservoir. Transmission has also been reported through sexual contact and vertical transmission.
	<i>Reoviridae</i>	
	Banna virus	Unknown reservoir
	<i>Bunyavirales</i>	
	Jamestown Canyon virus	The primary reservoir is deer and other ungulates (moose and bison)
	La Crosse encephalitis virus	Small mammals (chipmunks and squirrels) serve as the primary reservoir. Peak incidence in school-age children
	Rift Valley fever virus	Mosquitos are the vector and reservoir. Further viral amplification occurs in livestock and other domestic ruminants. Small mammals and bats may also contribute to persistence. Transmission may also occur from handling infected animal tissue or drinking unpasteurized milk.
Ticks		
	<i>Anaplasma phagocytophilum</i>	White-footed mouse is hypothesized the primary reservoir, with other sources including various mammals including deer. Rare reports of transmission through blood transfusion.
	<i>Borrelia burgdorferi</i>	White-footed mouse and other small mammals are the primary reservoir. Deer serve to support the tick population but not <i>Borrelia</i> .
	<i>Ehrlichia chaffeensis</i>	Primary reservoir is white-tailed deer. Transmission also reported through blood transfusion or solid organ transplantation.
	<i>Ehrlichia ewingii</i>	Dogs and deer are hypothesized to be the primary reservoirs.
	Powassan virus	Small mammals are the primary reservoir.
	<i>Rickettsia rickettsii</i>	Transmission may occur with very short tick attachment times. Ticks serve as both the vector and reservoir. Rare reports of transmission through blood transfusion.
	Kyasanur Forest disease virus	Transmission may also occur from contact with an infected animal. While it can infect livestock, there are no reports of transmission through unpasteurized milk
Sandflies	Tickborne encephalitis virus	Reservoirs include ticks, birds, and small mammals. Transmission may also occur via direct contact, consuming unpasteurized dairy products, blood transfusion, organ transplantation, and breastfeeding.
	<i>Bartonella bacilliformis</i>	Reservoir is unknown. Most infections occur at sunrise or sundown as the flies are most active during these time periods.

Table 643.3 Exposures Associated with Agents Causing Aseptic Meningitis, Encephalitis, and Encephalitis-Like Syndrome—cont'd

EXPOSURE	AGENT	RISK FACTORS AND EPIDEMIOLOGY
	Chandipura vesiculovirus	Mosquitos may also play a role in transmission. No other vertebrate has been identified as a potential reservoir. Cases described from India and West Africa.
	Toscana virus	Reservoir is presumed to be sandflies; very little data exist as to whether other mammals could serve as a source of the virus.
Tsetse flies	<i>Trypanosoma brucei gambiense</i>	Humans are the primary reservoir although it can also be identified in primates and ungulates. Vertical transmission has been reported.
	<i>Trypanosoma brucei rhodesiense</i>	Livestock such as cattle and other large mammals are considered to be the primary reservoir
WILD OR DOMESTIC ANIMALS		
Bats	Australian bat lyssavirus	It is assumed that any bat in Australia could carry this virus.
	<i>Histoplasma capsulatum</i>	Guano promotes fungal growth. Bats can develop chronic and disseminated infection with <i>Histoplasma</i> , but risk of transmission is likely highest through guano exposure.
	Nipah virus	Reports of transmission via direct contact with bats or coming into contact with bat bodily fluids on food. Human to human transmission has been reported.
	Rabies virus	Some bat bites are too small to be detected, often post-exposure prophylaxis is offered to anyone with direct contact with bats or if contact cannot be ruled out (e.g., an individual waking up to a bat flying in the same room). Transmission has been reported via solid organ transplant
Cattle	<i>Brucella abortus</i>	Many large mammals can be infected. Nearly eradicated from cattle in the US, Canada, Europe, Australia, New Zealand, and some Asian countries including Japan and Israel.
Dogs	Rabies virus	Many countries have been declared rabies-free in dogs, including Europe, Japan, the US, Australia, and New Zealand. Other countries remain at high risk for transmission from dogs.
	<i>Toxocara canis</i>	Dogs (especially puppies) shed eggs in feces, and organism survives in soil for prolonged period
Cats	<i>Bartonella henselae</i>	Typically follows scratch or bite from cat or kitten; highest incidence in children, in the fall, and around holidays (when cats are given as gifts)
	Rabies virus	In the US, more rabid cats are detected than dogs. In other countries, cats are second to dogs in prevalence.
	<i>Toxoplasma gondii</i>	Cats and other felines are reservoir hosts; they shed oocytes in feces, and the soil becomes contaminated. Sheep, goats, swine, cattle serve as intermediate hosts. Transmission may also occur vertically or through blood transfusion or solid organ transplantation. Worldwide distribution
	<i>Toxocara cati</i>	Cats, (specially kittens) shed eggs in feces, and organism survives in soil for prolonged period
Rodents	<i>Leptospira</i> spp.	Rodents (and many other animals) excrete organism in urine, and the organism remains viable in soil or water for weeks to months
	Lymphocytic choriomeningitis virus	Peak incidence in fall and winter; chronic infection in mice, hamsters, and guinea pigs; humans infected by inhalation or ingestion of dust or food contaminated by urine, feces, blood, nasopharyngeal secretions of infected rodents. Transmission has also occurred by vertical transmission and solid organ transplant,
Raccoons	<i>Baylisascaris procyonis</i>	Young children at risk due to pica, particularly near raccoon latrines. Other animal handlers, including hunters, at risk.
	Rabies virus	"Raccoon strain" extends along Eastern seaboard of the USA and has reached northward into Canada
Sheep, goats	<i>Brucella melitensis</i>	Direct contact with infected animals or their secretions. Present world-wide but has been eradicated in some countries including Northern and Central Europe, US, Canada, Australia, New Zealand, and Japan. Transmission has also occurred from sexual intercourse, vertical transmission, solid organ transplantation and transfusions.
	<i>Coxiella burnetii</i>	Inhalation; either direct exposure to animal or exposure to contaminated materials particularly dust or during birth. Rare reports of vertical transmission, through blood transfusions, or sexual intercourse
Birds	<i>Chlamydophila psittaci</i>	Birds can harbor and transmit organism to humans; usually acquired via inhalation of fecal dust/sections of birds. Rare cases have been reported in exposures to other non-avian livestock.

Continued

Table 643.3 Exposures Associated with Agents Causing Aseptic Meningitis, Encephalitis, and Encephalitis-Like Syndrome—cont'd

EXPOSURE	AGENT	RISK FACTORS AND EPIDEMIOLOGY
	<i>Cryptococcus neoformans</i>	Primarily in immunocompromised individuals. Some association with exposure to soil contaminated with bird droppings, particularly pigeons
Old World monkeys	B virus	Bite of Old World macaques. Present in both wild and captive settings.
Horses	Hendra virus	Endemic in Australia; associated with excretions/tissues from horses
Swine	Nipah virus	Close contact with pigs was the primary cause of an outbreak in Malaysia
	<i>Brucella suis</i>	Prevalent in many locations in the world, some countries have achieved eradication including Europe, Canada, US, and Australia.
Skunks	Rabies virus	Skunk populations are the primary reservoir in the central US and California
Squirrels	Variegated squirrel bornavirus 1	Detected in Germany, particularly in captive squirrels originating from Latin America or Asia. Unclear if this virus originates in Europe or was imported.
INGESTION OR INHALATION		
Fresh water	<i>Leptospira</i> spp.	Organisms from animal urine or placental tissue can remain viable for weeks to months in soil or water; recreational exposure associated with wading or swimming in contaminated water (particularly after floods or hurricanes)
	<i>Naegleria fowleri</i>	Swimming in warm, natural bodies of water (rarely poorly chlorinated pools reported). Not found in salt water. Cases also linked to nasal rinses or neti pot usage.
Soil	<i>Acanthamoeba</i> spp.	Found in soil and water. Transmission through inhalation or inoculation; cases of keratitis associated with contact lens usage
	<i>Balamuthia mandrillaris</i>	Soil living organism, transmission presumably occurs through inhalation or inoculation into cuts or wounds. Transmission has also been reported via solid organ transplantation.
	<i>Baylisascaris procyonis</i>	Widespread in the US; export of raccoons has led to spread to Europe and Asia.
	<i>Blastomyces dermatitidis</i>	Present in the eastern half of the US (particularly along the Mississippi, Ohio, and St. Lawrence Rivers), Canada, Africa, and India.
	<i>Coccidioides</i> spp.	Also known as valley fever. Infection is seasonal and is acquired by inhalation of soil or dust. Transmission has occurred from solid organ transplantation.
	<i>Histoplasma capsulatum</i>	Inhalation of airborne spores from soil. Outbreaks have occurred in endemic areas with exposure to bird, chicken, or bat droppings or recently contaminated soil. Globally distributed, with as many as 80% of children have been infected.
	<i>Toxocara canis</i> / <i>Toxocara cati</i>	Eggs in sandboxes and playgrounds; organisms survive long periods in soil
Spelunking	<i>Histoplasma capsulatum</i>	Reports of infections due to indirect exposure near the entrance of bat caves
	Rabies virus	Aerosol transmission has been implicated in very rare cases after exploring caves with large bat populations
Undercooked pork, lamb, or beef	<i>Toxoplasma gondii</i>	Cook meats to a minimum of 145-160°F. Meat color is an insufficient marker to kill tissue cysts
Undercooked freshwater fish, birds, reptiles, or amphibians	<i>Gnathostoma</i> spp.	Marinating in lime juice (ceviche) does not kill the parasite.
Freshwater crayfish or crabs	<i>Paragonimus westermani</i>	Mostly in Asia. Related species present in Africa, North and South America.
Raw or undercooked meat	<i>Trichinella</i> spp.	Mostly associated with pigs but has been found in other wild game meat. Worldwide distribution
Raw or undercooked snails, slugs, freshwater prawns, crabs, or frogs,	<i>Angiostrongylus cantonensis</i>	Worldwide distribution. Snails and slugs can be accidentally chopped up with vegetables and consumed, leading to infection.

Table 643.3 Exposures Associated with Agents Causing Aseptic Meningitis, Encephalitis, and Encephalitis-Like Syndrome—cont'd		
EXPOSURE	AGENT	RISK FACTORS AND EPIDEMIOLOGY
Unpasteurized milk	Tickborne encephalitis virus	Unpasteurized milk or cheeses from cows, sheep, or goats have been implicated
	<i>Coxiella burnetii</i>	Highly prevalent in many types of raw milk, pasteurization reduces risk
	<i>Listeria monocytogenes</i>	Also found in various raw dairy, vegetable, and meat products
	<i>Toxoplasma gondii</i>	Consumption of raw goat, sheep, or camel milk
SEASONAL	Arthropod-borne pathogens	Prevalence mirrors insect populations, infections nadir during the winter in temperate regions.
	Common viral infections (influenza, coronaviruses, adenoviruses, astroviruses, and other respiratory or gastrointestinal viruses); mycoplasma	Many viral and atypical bacterial infections predominant in the winter in temperate regions. Unclear if SARS-CoV-2 will follow the same seasonality.
	Enteroviruses and parechoviruses	Peak incidence in late summer and early fall in temperate regions. In tropical regions, enteroviruses circulate year round. Hypothesized that humidity may stabilize viral particles in the environment.
	Enterovirus D68	Reemergence in 2014 in causing acute flaccid paralysis. Outbreaks occurred every two years until 2020.
	<i>Naegleria fowleri</i>	Thrives in warmer water temperatures, leading to increased incidence of disease during the summer and early fall.
SEXUAL ACTIVITY	Herpes simplex virus 1/2	Primary HSV-2 infection can cause meningitis particularly in young females.
	HIV	Highest risk with unprotected sex with viremic subjects. Undetectable viral load equals untransmittable.
	<i>Treponema pallidum</i>	Resurgence in cases over the past decade particularly in the US
	Zika virus	Reports of sexual transmission. Virus is present in saliva, semen, vaginal fluids, urine, and breast milk. Virus may persist longer in semen than other bodily fluids.
FOREIGN TRAVEL		
Global	Chikungunya virus	Spread to the Africa, Americas, Asia, and Europe. Large outbreak in Latin America in the mid 2010's.
	Dengue virus	Cases occur on most continents. In the US, occasional local transmission reported in Florida, Texas, Arizona, Hawaii, and US territories
	Rabies virus	Prevalent worldwide but most cases occur in Asia and Africa. Dog bites are the most common mode of acquisition in developing countries
	West Nile virus	Outbreaks have been reported on all continents except Antarctica. In the US, most cases now occur west of the Mississippi River. A few thousand cases are diagnosed each year in the US.
	Zika virus	Worldwide distribution including North/South America, Africa, Asia
	Measles	Most cases now occur in South America, Africa, and Asia, including the Malay Archipelago and the Philippines. Secondary spread has led to outbreaks in many other countries.
	Mumps	Remains prevalent worldwide and a frequent cause of viral meningitis
	Rubella	Endemic in the Eastern Hemisphere, particularly in Asia and Africa.
	<i>Gnathostoma</i> spp	Worldwide distribution of different species. Most cases have occurred in Asia and Latin America.
	<i>Plasmodium</i> spp.	Tropical and subtropical areas in most continents
	<i>Taenia</i> spp.	Endemic to most countries. Most cases are travel associated when they occur in the US, Canada, and Australia.
Africa	Poliovirus	Africa was declared polio free in 2020, but in 2023, transmission of poliovirus type 1 was detected in Mozambique
	Rift Valley fever virus	Most prevalent in southern and eastern Africa, most countries report cases or isolation of virus
	Toscana virus	Reported in Morocco, Tunisia, and Algeria

Continued

Table 643.3 Exposures Associated with Agents Causing Aseptic Meningitis, Encephalitis, and Encephalitis-Like Syndrome—cont'd

EXPOSURE	AGENT	RISK FACTORS AND EPIDEMIOLOGY
	<i>Blastomyces dermatitidis</i>	Rare cases described throughout Africa. Other related <i>Blastomyces</i> spp. present in Africa.
	<i>Trypanosoma brucei gambiense</i>	West and central Sub-Saharan Africa
	<i>Trypanosoma brucei rhodesiense</i>	East Africa, predominantly Uganda, Kenya, Tanzania, Zambia, Malawi, Zimbabwe, and Mozambique
Asia	Banna virus	Detected in mosquitoes in China, Vietnam, Indonesia
	Japanese encephalitis virus	Mostly southern and eastern Asia, Malay archipelago, and Australia
	Kyasanur Forest disease virus	Detected so far only in India
	Nipah virus	Southeast Asia, particularly Malaysia
	Poliovirus	Wild type continues to circulate in Pakistan and Afghanistan.
	Tickborne encephalitis virus	Central Europe to eastern Asia, includes Japan
	<i>Borrelia burgdorferi</i>	Temperate forested regions throughout northern Asia
Australia	Australian bat lyssavirus	Exclusive to Australia, spread by bats. Closely related to rabies virus.
	Hendra virus	Exposure to body fluids and excretions of infected horses is the primary risk for transmission. Most cases reported in Queensland
	Japanese encephalitis virus	Cases reported in northern and eastern regions
	Murray Valley encephalitis virus	Cases throughout Australia, many have occurred in the Northern Territory. Also in New Guinea
Europe	Tickborne encephalitis virus	Central Europe to Japan
	Toscana virus	Endemic in most Mediterranean countries
	<i>Anaplasma phagocytophilum</i>	Temperate zones, particularly western and central Europe
	<i>Borrelia burgdorferi</i>	Temperate forested regions, particularly eastern and central Europe
North America	California/La Crosse virus	Most cases in Ohio, West Virginia, Tennessee, and North Carolina, but many other cases reported in the Midwest and South. From 2003-2022, a total of 1,431 cases have been reported to the CDC.
	Eastern equine encephalitis	A total of 189 cases reported to the CDC from 2003-2022. Most cases east of the Mississippi River, particularly Michigan, Florida, New Hampshire, and Massachusetts.
	Jamestown canyon virus	Majority of cases in Wisconsin and Minnesota, with other Midwest and Eastern states reporting cases. A total of 282 cases reported in the past decade to the CDC.
	Powassan virus	Wisconsin Minnesota, northeastern US, Canada. A total of 290 cases have been reported to the CDC between 2004-2002.
	St. Louis encephalitis virus	Most cases in Arizona, California and Texas, but many other states have sporadic cases. A total of 284 cases reported to the CDC in the past two decades
	Venezuelan equine encephalitis virus	Sporadic cases in Florida and along the Mexican border
	Western equine encephalitis virus	Most cases occurred west of the Mississippi River extending into Latin America. Cases are now rare; no infections reported to the CDC in over a decade.
	<i>Anaplasma phagocytophilum</i>	Majority of cases in Wisconsin, Minnesota and northeastern US. Cases also occur in mid-Atlantic, Midwest, West coast
	<i>Borrelia burgdorferi</i>	Eastern USA as far south as Ohio, West Virginia, Virginia, and North Carolina. Also includes Wisconsin and Minnesota, with cases occurring less commonly in California, Oregon, and Washington state. Nearly 500,000 Americans are diagnosed with Lyme disease each year.
	<i>Ehrlichia chaffeensis</i>	Southern and central USA and Mid-Atlantic and coastal states
	<i>Rickettsia rickettsii</i>	Majority of cases in a central band of the US including Kansas, Missouri, Arkansas, Kentucky, Tennessee, Mississippi, Alabama, Virginia and North Carolina. Other cases identified throughout the US.
	<i>Blastomyces dermatitidis</i>	Predominates along the Mississippi, Ohio, and St Lawrence Rivers, but many cases reported throughout the eastern US and Canada. Estimated ~2 cases per 100,000 each year in the US.

Table 643.3 Exposures Associated with Agents Causing Aseptic Meningitis, Encephalitis, and Encephalitis-Like Syndrome—cont'd

EXPOSURE	AGENT	RISK FACTORS AND EPIDEMIOLOGY
	<i>Coccidioides</i> spp.	Semiarid regions of southwestern US (California, Nevada, Utah, Arizona, New Mexico, Texas, and southern portions of Colorado and Oklahoma. Extends south into much of Mexico and central America. Around 20,000 cases diagnosed each year in the US.
South America	St. Louis encephalitis virus	Sporadic cases in Argentina, Brazil, and Peru, but far more prevalent in the US.
	Venezuelan equine encephalitis virus	Tropical latitudes, particularly Colombia, Venezuela, Peru, and Ecuador. Sporadic cases reported in Brazil, Bolivia, and Argentina.
	Western equine encephalitis virus	Rare cases in Brazil and Colombia.
	<i>Rickettsia rickettsii</i>	Cases reported in Colombia, Brazil, and Argentina.
	<i>Coccidioides</i> spp.	Many countries in Latin America, including Brazil, Argentina, Colombia, Venezuela, and Paraguay
	<i>Bartonella bacilliformis</i>	Predominantly occurs in the Andes at elevations of 3,000 to 10,000 feet above sea level. Most cases in Peru, but has been reported in Colombia and Ecuador.

Modified from Kliegman RM. Encephalitis. In: Kliegman RM, Toth H, Bordoni BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier, 2023: Table 42.3, p. 770-775.

Determining the specific cause of CNS infection is facilitated by careful examination of the CSF with specific stains (e.g., Kinyoun carbol fuchsin for mycobacteria, India ink for fungi), cytology, antigen detection (*Cryptococcus*), CSF serology (syphilis, West Nile virus [WNV], arboviruses), and PCR (bacteria and viruses). Other potentially valuable diagnostic tests include blood cultures, CT or MRI of the brain, serum serologic tests, and, rarely, meningeal or brain biopsy.

Acute viral meningoencephalitis is the most likely infection to be confused with bacterial meningitis (see Table 643.2 and Table 643.3). Although children with viral meningoencephalitis typically appear less ill than those with bacterial meningitis, both types of infection have a spectrum of severity. Some children with bacterial meningitis may have relatively mild signs and symptoms, whereas some with viral meningoencephalitis may be critically ill. Although classic CSF profiles associated with bacterial versus viral infection tend to be distinct (see Table 643.1), these cases can overlap in the number of CSF leukocytes and glucose and protein levels. Quite often, children are empirically treated with antibiotics for >48 hours to await CSF culture and PCR results to distinguish these two groups of pathogens.

TREATMENT

Essential to improving clinical outcomes in patients with bacterial meningitis is prompt recognition, diagnostic testing, and initiation of appropriate antimicrobial therapy. Several studies have demonstrated that delays in initiating antimicrobial therapy, even a few hours, are significantly associated with adverse clinical outcomes and death. If focal neurologic findings, papilledema, or increased ICP is present, antibiotics should be given before obtaining a head CT scan (and subsequent LP), and the increased ICP should be treated simultaneously (see Chapter 82). Some patients with meningitis will develop multisystem organ failure, shock (see Chapter 85), and acute respiratory distress syndrome (see Chapter 86), requiring further management in an intensive care unit.

Initial Antibiotic Therapy

The initial (empiric) choice of antibiotic therapy for meningitis in immunocompetent infants and children should achieve bactericidal levels in the CSF and have excellent activity against the typical bacterial causes of meningitis (Table 643.4). Although there is substantial geographic variation in the frequency of resistance of *S. pneumoniae* to β -lactam antibiotics, rates are increasing throughout the world. In the United States, 25–50% of meningitic strains of *S. pneumoniae* have some level of resistance to penicillin; relative resistance (minimal inhibitory concentration = 0.1–1.0 μ g/mL) is more common than high-level resistance

(minimal inhibitory concentration = 2.0 μ g/mL). Resistance to ceftriaxone and cefepime is globally variable, but in some studies can be as high as 25%. Resistance to cephalosporins declined in the United States after the introduction of PCV13 because of the reduction in disease caused by serotype 19A, which is commonly associated with resistance. However, current surveillance suggests rising rates of cephalosporin resistance in non-PCV13 serotypes. In contrast, most strains of *N. meningitidis* are sensitive to penicillin and cephalosporins, although rare resistant isolates have been reported. Approximately 30–40% of isolates of *H. influenzae* type b and 10% of *H. influenzae* type a produce β -lactamases and therefore are resistant to ampicillin. These β -lactamase-producing strains remain sensitive to third- and fourth-generation cephalosporins.

The recommended empiric antibiotic regimen in suspected bacterial meningitis beyond the neonatal period is a third-generation cephalosporin (ceftriaxone) plus vancomycin. Because of the efficacy of third-generation cephalosporins in the therapy of meningitis caused by sensitive *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* type b, ceftriaxone (50 mg/kg/dose given every 12 hours) should be part of initial therapy. Based on the current incidence of cephalosporin-resistant strains of *S. pneumoniae*, vancomycin is also recommended as part of empiric therapy. Vancomycin dosing guidelines have shifted from trough-based dosing to area under the curve/minimum inhibitory concentration (AUC/MIC; see Chapter 225). Although current clinical data are limited, vancomycin dosing for meningitis should attain a target AUC/MIC of 400–600 mg $\cdot$ h/L (previous vancomycin trough goals were 15–20 mg/L). Patients allergic to penicillin and cephalosporin antibiotics can be treated with meropenem (40 mg/kg/dose every 8 hours); other alternatives include fluoroquinolones or chloramphenicol, if available. Alternatively, allergic patients can be desensitized to the preferred antibiotic (see Chapter 193).

If *L. monocytogenes* infection is suspected, as in young infants or those with a T-lymphocyte deficiency, ampicillin (300 mg/kg/day, divided every 6 hours) also should be given because cephalosporins are inactive against *L. monocytogenes*. Intravenous trimethoprim-sulfamethoxazole is an alternative treatment for *L. monocytogenes* and has documented clinical efficacy.

If a patient is immunocompromised and gram-negative bacterial meningitis is suspected, initial therapy might include cefepime or meropenem.

Duration of Antibiotic Therapy

The duration of antibiotic therapy for meningitis had been based on experience and expert opinion rather than randomized clinical trials.

Table 643.4 Antibiotics Used for the Treatment of Bacterial Meningitis*

DRUGS	NEONATES (TERM)		
	0-7 DAYS	8-28 DAYS	INFANTS AND CHILDREN
Amikacin ^{††}	15 divided q24h	18 divided q24h	15-22.5 divided q8h, q12h, or q24h
Ampicillin	300 divided q8h	300 divided q6h	300-400 divided q4h, max 12 g/day
Cefepime	100 divided q12h	100 divided q12h	150 divided q8h, max 6 g/day
Ceftriaxone [§]	—	—	100 divided q12h or q24h, max 4 g/day
Ceftazidime	100 divided q12h	150 divided q8h	150-200 divided q8h, max 6 g/day
Gentamicin ^{††}	4 divided q24h	5 divided q24h	7.5 divided q8h
Meropenem	60 divided q8h	90 divided q8h for days 14-28	120 divided q8h, max 6 g/day
Nafcillin	75 divided q8h	100 divided q6h	200 divided q4h-q6h, max 12 g/day
Penicillin G	450,000 divided q8h	500,000 divided q6h	300,000-400,000 divided q4h, max 24 million U/day
Rifampin	—	10 q24h	15-20 divided q12h or q24h, max 600 mg/day
Tobramycin ^{††}	4 divided q24h	5 divided q24h	7.5 divided q8h
Vancomycin ^{†##}	40 divided q12h	60 divided q8h	age 3 mo-12: 60-80 divided q6h age >12 yr: 60-70 divided q6h-q8h

*Dosages in mg/kg (units/kg for penicillin G) per day.

[†]Smaller doses and longer dosing intervals, especially of aminoglycosides and vancomycin for very low-birthweight neonates, may be advisable.

^{††}Monitoring of serum levels is recommended to ensure safe and therapeutic values.

[§]Use in neonates is not routinely recommended because of inadequate experience in neonatal meningitis and concerns of displacement of bilirubin from albumin, leading to worsening of hyperbilirubinemia. Some centers use ceftriaxone in term neonates older than 7 days of age who are not receiving calcium-containing solutions or total parenteral nutrition and have normal albumin level and total serum bilirubin <5 mg/dL.

[#]Goal vancomycin AUC/MIC of 400-600 mg*hr/L or trough of 15-20 mg/L.

Adapted from Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis*. 2004;39:1267-1284. Table 6; with updated data from Kimberlin DW, Barnett ED, Lynfield R, et al. Red Book (2021): Report of the Committee on Infectious Diseases, 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021.

In the past, the standard of care for the treatment of meningitis included repeating an LP before the end of antimicrobial therapy. The total length of therapy would be determined according to whether the CSF parameters (white blood cell count, protein, and glucose) had normalized or not. However, further studies showed that abnormal CSF parameters did not predict which patients would develop relapsed infection after stopping antibiotics. Therefore repeat LP before discontinuation of antibiotics for typical bacterial meningitis is not recommended.

Currently, the recommended treatment duration for uncomplicated *S. pneumoniae* meningitis is 10-14 days with a third-generation cephalosporin, or intravenous penicillin (300,000-400,000 units/kg/day, divided every 4 hours) for penicillin-sensitive isolates, or vancomycin if the isolate is resistant to penicillins and cephalosporins. For *N. meningitidis* meningitis, the recommended treatment duration is 5-7 days with intravenous penicillin for strains with an MIC of penicillin <0.1 µg/mL, or ceftriaxone for strains with an MIC of 0.1-1 µg/mL. Uncomplicated *H. influenzae* type b meningitis should be treated for 7-10 days with ampicillin for β-lactamase-negative strains or with a third-generation cephalosporin for β-lactamase-positive isolates. Patients who receive intravenous or oral antibiotics before LP and do not have an identifiable pathogen from cultures but do have evidence of bacterial meningitis based on their CSF profile and PCR should receive therapy with ceftriaxone for 7-10 days. Shorter durations of antibiotics for meningitis might be effective; one double-blinded, randomized study of children with meningitis demonstrated equivalent outcomes when treating with ceftriaxone for 5 versus 10 days. In addition, during epidemics of meningococcal meningitis in Africa, single intramuscular dosages of ceftriaxone or chloramphenicol can be used.

Meningitis caused by *Escherichia coli* or *P. aeruginosa* may require therapy with a third- or fourth-generation cephalosporin or carbapenem active against the isolate in vitro. Many isolates of *E. coli* are sensitive to ceftriaxone, and isolates of *P. aeruginosa* are often sensitive to ceftazidime. Repeat examination of CSF should be considered in some neonates and in patients with meningitis from gram-negative bacilli or β-lactam-resistant *S. pneumoniae*. The CSF in most cases will be sterile within 24-48 hours of initiation of appropriate antibiotic therapy. Gram-negative bacillary meningitis should be treated for 3 weeks, or at least 2 weeks after CSF sterilization, if documented.

Side effects of antibiotic therapy for meningitis include phlebitis, drug fever, rashes, emesis, oral or vaginal candidiasis, and diarrhea. Ceftriaxone may cause reversible gallbladder pseudolithiasis, detectable by abdominal ultrasonography. This is usually asymptomatic but may be associated with emesis and upper right quadrant pain.

Corticosteroids

Rapid killing of bacteria in the CSF by the host's immune response and antibiotics leads to release of inflammatory agents (e.g., endotoxin) that precipitate a cytokine-mediated inflammatory cascade. The resultant edema and neutrophilic infiltration may aggravate neurologic injury with worsening of CNS signs and symptoms. Therefore agents that restrain production of inflammatory mediators could be of benefit in bacterial meningitis.

In a Cochrane review of corticosteroid use in meningitis, steroids reduced hearing loss in children with meningitis caused by *H. influenzae* type b but not by other pathogens. The use of adjunctive steroids in children did not reduce mortality; however, steroids did improve survival rates in adults with pneumococcal meningitis. These data support

the use of intravenous dexamethasone 0.15 mg/kg/dose given every 6 hours for 2 days in the treatment of *H. influenzae* type b meningitis in children over 6 weeks of age. Corticosteroids appear to have maximum benefit if given 1-2 hours before antibiotics are initiated, which is difficult to operationalize; steroids may also be effective if given concurrently with or soon after the first dose of antibiotics. Pediatric data regarding benefits, if any, of corticosteroids in the treatment of meningitis caused by other bacteria remain inconclusive.

COMPLICATIONS

Treatment of meningitis can be accompanied by acute CNS complications, including seizures, increased ICP, cranial nerve palsies, stroke, cerebral or cerebellar herniation, SIADH, and thrombosis of dural venous sinuses.

Collections of fluid in the subdural space develop in 10–30% of patients with meningitis and are asymptomatic in 85–90% of patients. Subdural effusions are especially common in infants. Symptomatic subdural effusions may result in a bulging fontanel, diastasis of sutures, enlarging head circumference, emesis, seizures, fever, or abnormal results of cranial transillumination. CT or MRI scanning can confirm the presence of subdural effusion. In the presence of increased ICP or depressed level of consciousness, symptomatic subdural effusion should be treated by aspiration through the open fontanel (see [Chapters 82 and 630](#)). Fever alone is not an indication for aspiration.

SIADH occurs in some patients with meningitis, resulting in hyponatremia and reduced serum osmolality. This may exacerbate cerebral edema or result in hyponatremic seizures (see [Chapter 82](#)).

Fever associated with bacterial meningitis usually resolves within 5–7 days of the onset of therapy. Prolonged fever (>10 days) is noted in approximately 10% of patients. Prolonged fever is usually related to intercurrent viral infection, nosocomial or secondary bacterial infection, thrombophlebitis, or drug reaction. In meningitis caused by *N. meningitidis*, pericarditis or arthritis may occur during treatment (sometimes accompanied by recrudescence fever) and is caused by either bacterial dissemination or immune complex deposition. In general, infectious pericarditis or arthritis occurs earlier in the course of treatment than immune-mediated disease.

Thrombocytosis, eosinophilia, and anemia may develop during therapy for meningitis. Anemia may be a result of hemolysis or bone marrow suppression. Disseminated intravascular coagulation is most often associated with the rapidly progressive pattern of presentation and is observed most commonly in patients with shock and purpura. The combination of endotoxemia and severe hypotension initiates the coagulation cascade; coexistence of ongoing thrombosis may produce symmetric peripheral gangrene.

PROGNOSIS

Appropriate antibiotic therapy and supportive care have reduced the mortality rate of bacterial meningitis beyond the neonatal period to under 10%. The highest mortality rates are observed with pneumococcal meningitis. Severe neurodevelopmental sequelae may occur in 10–20% of patients recovering from bacterial meningitis, and as many as 50% have some neurologic sequelae. The prognosis is poorer among infants under 6 months of age and in those with high CSF bacterial burden. Those with seizures occurring later than 4 days into therapy or with coma or focal neurologic signs on presentation also have increased risk of long-term sequelae. There does not appear to be a correlation between the duration of symptoms before a diagnosis of meningitis and the subsequent outcome.

The most common neurologic sequelae of meningitis include hearing loss, cognitive impairment, recurrent seizures, delay in acquisition of language, visual impairment, and behavioral problems. Sensorineural hearing loss is most frequently detected and is often already present at the time of initial presentation. It results from cochlear or auditory nerve inflammation and occurs in as many as 30% of patients with pneumococcal meningitis, 10% with meningococcal meningitis, and 5–20% of those with *H. influenzae* type b meningitis. All patients with bacterial meningitis should undergo careful audiologic assessment before or soon after discharge from the hospital. Frequent reassessment

in the outpatient setting is indicated for patients who develop a hearing deficit.

PREVENTION

Vaccination and antibiotic prophylaxis of susceptible at-risk contacts represent two opportunities to reduce the transmission and development of secondary cases of bacterial meningitis.

Neisseria meningitidis

See also Chapter 237.

Chemoprophylaxis is recommended for all close contacts of patients with meningococcal meningitis, regardless of age or immunization status. Close contacts >1 month of age should be treated with rifampin 15–20 mg/kg/dose every 12 hours (maximum dose 600 mg) for 2 days as soon as possible after identification of a case of suspected meningococcal meningitis or sepsis. Alternative options include intramuscular ceftriaxone (125 mg once for children under age 15 years, or 250 mg once for persons older than 15 years) or ciprofloxacin 20 mg/kg as a single oral dose (maximum 500 mg). Close contacts include household, day-care, and nursery school contacts and healthcare workers who have direct exposure to oral secretions (mouth-to-mouth resuscitation, suctioning, intubation). If there is a high suspicion of meningococcemia in the index patient, exposed contacts should be prophylaxed immediately. In addition, all contacts should be educated about the early signs of meningococcal disease and the need to seek prompt medical attention if these signs develop.

Many countries have included quadrivalent conjugate meningococcal vaccine (types A, C, Y, and W-135) as part of routine immunization schedules. The Advisory Committee on Immunization Practices (ACIP) of the U.S. CDC recommends a two-dose vaccine series for all children, with the first dose administered at the age of 11–12 years and a second dose at age 16–18 years. Vaccination is also recommended for persons 2 months to 18 years of age who are at increased risk for meningococcal disease, including those with anatomic or functional asplenia or complement deficiencies or who are receiving a terminal complement inhibitor (e.g., eculizumab). Two meningococcal vaccines against serogroup B have been developed. In the United Kingdom, the vaccine is administered to all infants at 2, 4, and 12 months of age. This differs from the United States, where currently meningococcal B vaccine is recommended for children 10 years and older at increased risk for invasive disease and is optional for persons 16–23 years of age.

Haemophilus influenzae Type b

See also Chapter 240.

Rifampin prophylaxis should be given to all household contacts of patients with invasive disease caused by *H. influenzae* type b if any close family member younger than 48 months has not been fully immunized or if an immunocompromised child of any age resides in the household. A household contact is one who lives in the residence of the index case or who has spent a minimum of 4 hours with the index case for at least 5 of the 7 days preceding the patient's hospitalization. Family members should receive rifampin prophylaxis immediately after the diagnosis is suspected in the index case, because over 50% of secondary cases occur in the first week after the index patient is hospitalized. The dose of rifampin is 20 mg/kg/day (maximum dose 600 mg) given once daily for 4 days.

Three conjugate monovalent vaccines for *H. influenzae* type b are licensed in the United States along with two other multivalent vaccines that include *H. influenzae* type b components. Although each vaccine elicits different profiles of antibody response in infants immunized at 2–6 months of age, all result in protective levels of antibody with a 93% efficacy rate against invasive infections after the primary series. Thus all children should be immunized with *H. influenzae* type b conjugate vaccine beginning at 2 months of age. Efficacy is not as consistent in Indigenous Nation populations, a group recognized as having a higher incidence of *H. influenzae* disease.

Streptococcus pneumoniae

See also Chapter 228.

Antibiotic prophylaxis should not be administered to contacts of children diagnosed with pneumococcal meningitis. Routine administration of pneumococcal conjugate vaccine is recommended for children under 5 years of age. The initial dose of the series is given at 2 months of age. Children who are at high risk for invasive pneumococcal infection, including those with functional or anatomic asplenia (including sickle cell disease), cochlear implants, CSF leaks, chronic illnesses (chronic heart disease, chronic lung disease, or diabetes mellitus), and underlying immunodeficiency (such as infection with HIV, primary immunodeficiency, and those receiving immunosuppressive therapy) should receive pneumococcal conjugate vaccine and the 23-valent pneumococcal polysaccharide vaccine (PPSV23).

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643.2 Viral Meningoencephalitis

Andrew B. Janowski and David A. Hunstad

Viral meningoencephalitis is an acute inflammatory process involving the meninges and/or brain parenchymal tissue. These infections are caused by a number of different pathogens, and quite often, no pathogen can be identified from the CSF or brain tissue specimens after routine clinical testing. The CSF is characterized by pleocytosis and the absence of microorganisms on Gram stain and routine bacterial culture. Outcomes are quite variable because cases of meningoencephalitis caused by some pathogens are self-limited, whereas others cause significant long-term neurologic sequelae.

ETIOLOGY

Among the most common causes of viral meningoencephalitis are viruses of the family Picornaviridae, including the **enteroviruses** (poliovirus, coxsackievirus, enterovirus, and echovirus) and **parechoviruses** (see Chapters 296 and 297) (see Tables 643.2 and 643.3). Meningoencephalitis caused by these viruses is often self-limited but can be severe in neonates or chronic in immunocompromised hosts (particularly X-linked agammaglobulinemia; see Chapter 166). Human coxsackievirus A7 and enteroviruses D68 and 71 have been associated with neurologic symptoms, including acute flaccid paralysis. Parechoviruses are an important cause of meningoencephalitis in infants and rarely cause disease in older children. Clinical manifestations in infants are generally similar to those of enteroviral infection, but infants with parechovirus infection may also exhibit abdominal signs or a sepsis-like syndrome. In addition, parechovirus infection is associated with more severe MRI lesions of the cerebral cortex, and CSF pleocytosis may be minimal or absent.

The term **arbovirus** refers to a broad range of viruses from multiple viral families that are transmitted by arthropod vectors, typically mosquitoes or ticks (see Chapters 314 and 315). Most of these viral infections are considered zoonotic, as their primary reservoir is in birds or small animals. Humans often represent dead-end hosts because sufficient viremia does not develop to enable transmission back to arthropod vectors. However, humans are the primary reservoir for viruses such as Zika, chikungunya, and dengue. The arboviruses that most often cause meningoencephalitis include WNV, Japanese encephalitis virus, and La Crosse virus; other arboviruses are described in Table 643.3. WNV made its appearance in the Western Hemisphere in 1999 and is now the most common arbovirus causing meningoencephalitis in the United States. WNV may also be transmitted by blood transfusion, organ transplantation, or vertically across the placenta. Most children with WNV are either asymptomatic or have nonspecific viral-like illness. Approximately 1% of infected humans develop CNS disease; adults are more severely affected than children.

Several members of the viral family Herpesviridae can cause meningoencephalitis (see Chapters 299-304). Herpes simplex virus (HSV) type 1 is an important cause of severe, sporadic encephalitis in children and adults, with progression to coma and death in 70% of cases without antiviral therapy. In neonates, severe encephalitis with diffuse

brain involvement can be caused by HSV type 2, transmitted vertically at delivery. A mild transient (and sometimes recurrent) form of meningoencephalitis with HSV-2 may accompany genital herpes infection in sexually active adolescents and adults. Varicella-zoster virus (VZV) may cause CNS infection in a close temporal relationship with clinical manifestations of chickenpox. The most common manifestation of CNS involvement by VZV is cerebellar ataxia, whereas the most severe form is acute encephalitis. After primary infection, VZV establishes latency in spinal and cranial nerve roots and ganglia, and reactivation is evidenced by herpes zoster that can be accompanied by mild meningoencephalitis. Epstein-Barr virus is associated with various CNS syndromes (see Chapter 301). Cytomegalovirus (CMV) infection of the CNS can occur with congenital infection or disseminated disease in immunocompromised hosts, but it is an exceptionally rare cause of meningoencephalitis in immunocompetent infants and children (see Chapter 302). Human herpesvirus 6 is associated with encephalitis, but detection of the virus can also be reflective of latency in lymphocytes with reactivation caused by inflammation (see Chapter 303).

Mumps can cause meningoencephalitis and has a higher incidence in regions where the mumps vaccine is not implemented (see Chapter 295). Mumps meningoencephalitis is typically mild, but deafness from damage of the eighth cranial nerve can occur. Meningoencephalitis is also associated with acute infection with measles, rubella, respiratory viruses (adenovirus, coronaviruses, influenza virus, parainfluenza virus, respiratory syncytial virus), rotavirus, astroviruses, lymphocytic choriomeningitis virus, or rabies. HIV is associated with acute meningoencephalitis and can cause chronic encephalopathy leading to neurocognitive decline (see Chapter 322). In exceptionally rare situations, meningoencephalitis may follow live virus vaccination against polio, measles, mumps, rubella, or varicella.

EPIDEMIOLOGY

Meningoencephalitis has a seasonal pattern, with a peak incidence in the summer and late fall caused by a spike in circulation of enteroviruses and arboviruses. In 2018, the most common identifiable arbovirus responsible for meningoencephalitis in the United States was WNV, with a total of 2,647 cases; fewer than 200 combined cases were caused by the La Crosse, Jamestown Canyon, Powassan, St. Louis, and eastern equine encephalitis viruses (see Chapter 314). In 2019, an outbreak of 39 cases of eastern equine encephalitis occurred across the eastern United States, and 15 cases of St. Louis encephalitis were present in the western and central United States. In Asia, the most common cause is Japanese encephalitis virus, with an estimated >60,000 cases per year. Epidemiologic considerations in aseptic meningitis caused by agents other than enteroviruses also include the season, location of residence, recent travel, animal exposures, mosquito or tick bites, and additional factors related to specific pathogens.

Several studies have attempted to describe the causative pathogens associated with meningoencephalitis, including the California Encephalitis Project. Despite extensive testing, however, no pathogen can be identified in up to 63% of cases. Newer assays such as next-generation sequencing have the potential to identify novel or previously unrecognized pathogens in causing meningoencephalitis. Occult meningoencephalitis cases caused by pathogens such as *Leptospira*, astroviruses, and *Cutibacterium* (formerly *Propionibacterium*) *acnes* have been identified through this methodology. In addition to infectious agents, autoimmune encephalitis is a common cause of encephalitis-like illness (see Chapter 638.4).

PATHOGENESIS AND PATHOLOGY

Neurologic damage is caused by direct invasion and destruction of neural cells and tissues by actively multiplying viruses and by the host reaction to viral antigens. Tissue sections of the brain generally are characterized by meningeal congestion and mononuclear infiltration, perivascular cuffs of lymphocytes and plasma cells, some perivascular tissue necrosis with myelin breakdown, and neuronal disruption in various stages, including, ultimately, neuronophagia and endothelial proliferation or necrosis. A marked degree of demyelination with preservation of neurons and their axons is considered to represent

predominantly “postinfectious” or autoimmune encephalitis. In HSV encephalitis, the cerebral cortex (classically the temporal lobes in HSV-1 infection) is often severely affected. Arboviruses tend to affect the entire brain, whereas rabies has a predilection for the basal structures. The involvement of the spinal cord, nerve roots, and peripheral nerves can be variable with these viruses.

CLINICAL MANIFESTATIONS

The progression and severity of disease are related to the relative degree of meningeal and parenchymal involvement, which, in part, is determined by the specific etiology. The clinical course of infection varies from case to case, even with the same causative pathogen. Some children may have mild symptoms at onset, only to lapse into a coma and rapidly die. In others, the illness may be ushered in by high fever, violent convulsions interspersed with bizarre movements, and hallucinations, followed by complete recovery.

The onset of meningoencephalitis is generally acute, although CNS signs and symptoms are often preceded by a nonspecific febrile illness of a few days' duration. The presenting manifestations in older children include headache and hyperesthesia and, in infants, irritability and lethargy. Headache is most often frontal or generalized; adolescents frequently complain of retrobulbar pain. Fever, nausea and vomiting, photophobia, and pain in the neck, back, and legs are common. With high fevers, patients may develop altered mental status that progresses to encephalopathy in combination with uncontrolled body movements and seizures. Focal neurologic signs may be persistent, fluctuating, or migratory. WNV and nonpolio enteroviruses, including enterovirus D68, may cause anterior horn cell injury and acute flaccid paralysis. Encephalitis is more common than aseptic meningitis in WNV infection, whereas acute flaccid paralysis may be noted in approximately 5% of patients. Loss of bowel and bladder control and unprovoked emotional outbursts may also occur. Nonetheless, many patients have a nonspecific febrile illness caused by WNV infection and may never seek medical attention. Specific conditions associated with CNS viral infection include Guillain-Barré syndrome, transverse myelitis, hemiplegia, and cerebellar ataxia.

Exanthems can precede or accompany CNS signs, especially with enteroviruses, VZV, measles, rubella, and WNV.

During the pandemic caused by SARS-CoV-2, neurologic diseases were uncommonly associated with this infection in children, including encephalitis, Guillain-Barré syndrome, and stroke. In addition, in the multisystem inflammatory syndrome of children (MIS-C), encephalopathy is often observed, with some case series describing neurologic symptoms in over 50% of patients with MIS-C. Similar neurologic conditions have been observed in adults with SARS-CoV-2 infection, and persistent symptoms and impairments can be observed months after acute infection. It is unclear if the constellation of symptoms are the result of direct infection of the CNS by SARS-CoV-2 or if the inflammatory response to viral infection also contributes to the development of acute and chronic neurologic symptoms.

A syndrome of **mild encephalopathy with a reversible splenic lesion** (of the corpus callosum) has been associated with various pathogens, including rotavirus, respiratory syncytial virus (RSV), salmonella, CMV, adenovirus, and influenza virus.

DIAGNOSIS

CSF findings in viral meningoencephalitis are characterized by a pleocytosis of leukocytes with counts typically $<1,000/\text{mm}^3$ (see [Table 643.1](#)). In the initial hours of disease, the cells may be polymorphonuclear, whereas mononuclear cells predominate for the remainder of the illness. CSF protein concentration tends to be elevated, especially if brain destruction is extensive, as with HSV encephalitis. The glucose level is typically normal, although hypoglycorrachia can occur with certain viruses (e.g., mumps). With parechoviruses, the CSF glucose, protein, and cell counts may be normal.

Identification of an infectious cause relies on analysis of the CSF for the presence of pathogens by PCR and serology and, in rare situations, identification of pathogens in brain biopsy material. CSF metagenomic sequencing is available in limited centers. A commercial multiplex

PCR assay combines testing for common bacterial and viral pathogens in CNS infections. However, this assay does exhibit false-positive and false-negative results, so many clinicians still order individual PCR tests for common viral pathogens. In WNV meningoencephalitis, by the time patients present for medical care, viral nucleic acid may be absent in the CSF. Therefore the test of choice for detection of WNV and other arboviruses is serologic (on both blood and CSF). If initial CSF PCRs and serology are not diagnostic, serologic testing should be repeated 2-3 weeks later. A fourfold increase in titers for a specific virus or other pathogen would suggest the etiology of the patient's presentation.

Viruses detected in blood, nasopharyngeal, stool, and urine specimens can be used to suggest a potential viral etiology. However, caution must be practiced when viruses are detected in locations outside the CSF, because detection of these viruses may be incidental and not explain the patient's CNS symptoms. Other tests of potential value in the evaluation of patients with suspected viral meningoencephalitis include an electroencephalogram (EEG) and MRI. EEG typically shows diffuse slow-wave activity, although focal changes in temporal regions can be observed in HSV meningoencephalitis. MRI of the brain may demonstrate focal brain lesions that correlate with clinical disease, including temporal lobe involvement to suggest HSV-1 disease. Hyperdense lesions may also be identified on T2 and FLAIR imaging ([Fig. 643.1](#)).

A diagnostic approach is noted in [Table 643.5](#).

DIFFERENTIAL DIAGNOSIS

Meningoencephalitis is not exclusively caused by viruses, as other pathogens are also associated with this condition (see [Table 643.3](#)). The most important diagnosis to differentiate from meningoencephalitis is bacterial meningitis, given the consequences if that disease is untreated. Most children with acute bacterial meningitis are more critically ill than those with CNS viral infection (with HSV as an exception). Parameningeal bacterial infections, such as brain abscess or subdural or epidural empyema, may have features similar to viral CNS infections. Infections caused by *M. tuberculosis* (see Chapter 261), *T. pallidum* (syphilis, see Chapter 264), and *B. burgdorferi* (Lyme disease, see Chapter 268) may exhibit more indolent clinical courses. *Bartonella henselae* is associated with cat exposure, a papule at the site of inoculation, regional lymphadenopathy, and new-onset seizures (see Chapter 255). *Mycoplasma pneumoniae* has been suggested as a causative pathogen in meningoencephalitis, either as a direct pathogen or a trigger of postinfectious symptoms (see Chapter 269). However, serologic testing for *Mycoplasma* can be nonspecific, and IgM titers can be elevated for several months after infection, leading to incorrect interpretation of a positive result.

Infections caused by fungi, rickettsiae, protozoa, and other parasites may also need to be included in the differential diagnosis. Consideration of these agents usually arises as a result of exposure history, accompanying symptoms, local geographic epidemiology, and host immune factors.

Nonetheless, a significant proportion of patients will have a presentation and clinical testing that is consistent with a diagnosis of encephalitis, but despite exhaustive testing for pathogens, including metagenomic sequencing, no etiology will be identified. In this situation, many clinicians would agree that an infectious cause is less likely but still cannot be fully ruled out. Various noninfectious disorders may be associated with CNS inflammation and have manifestations overlapping with those associated with viral meningoencephalitis. Some of these disorders include malignancy, autoimmune diseases, intracranial hemorrhage, and exposure to certain drugs or toxins. Attention to the history and other organ involvement usually allows elimination of these diagnostic possibilities. Autoimmune encephalitis caused by anti-N-methyl-D-aspartate (anti-NMDA) receptor antibodies is an important cause of noninfectious encephalitis in adolescents and young adults (see [Chapter 638.4](#)). Detection of these antibodies in the serum and CSF confirms this diagnosis. Anti-NMDA receptor encephalitis has also been associated with recent HSV encephalitis, but a mechanism explaining this posited association is unknown. Acute

disseminated encephalomyelitis (ADEM) may also initially be confused with encephalitis (see [Chapter 640](#)).

TREATMENT

For most causes of viral meningoencephalitis, no effective antiviral agents exist; therefore treatment is primarily supportive care. Intravenous fluids are typically administered because of poor oral intake. NSAIDs are often used for symptomatic relief of headache. It is important to monitor patients with severe encephalitis closely for seizures, cerebral edema, disturbed fluid and electrolyte balance, aspiration, respiratory failure, and cardiac arrest.

Members of the herpesvirus family can be treated with antivirals, with acyclovir, ganciclovir, cidofovir, and foscarnet having variable activities against these viruses (see [Chapters 299-304](#)). Parenteral acyclovir has been specifically shown to dramatically reduce morbidity and mortality rates in HSV-associated meningoencephalitis. When no

pathogens are identified and a postinfectious or autoimmune etiology is suspected, patients are in some cases treated with a combination of steroids, intravenous immunoglobulin, and plasmapheresis (see [Chapters 638 and 640](#)).

PROGNOSIS

Supportive and rehabilitative efforts are very important after patients recover from the acute phase of illness. Motor incoordination, seizures, total or partial deafness, and behavioral disturbances may follow viral meningoencephalitis. Visual disturbances from chorioretinopathy and perceptual amblyopia may also occur. Some sequelae of infection may be subtle; therefore neurologic, developmental, and audiologic evaluations should be part of the routine follow-up of children who have recovered from viral meningoencephalitis.

Recovery from viral infections of the CNS depends on the severity of the clinical illness, the specific causative agent, and the age of

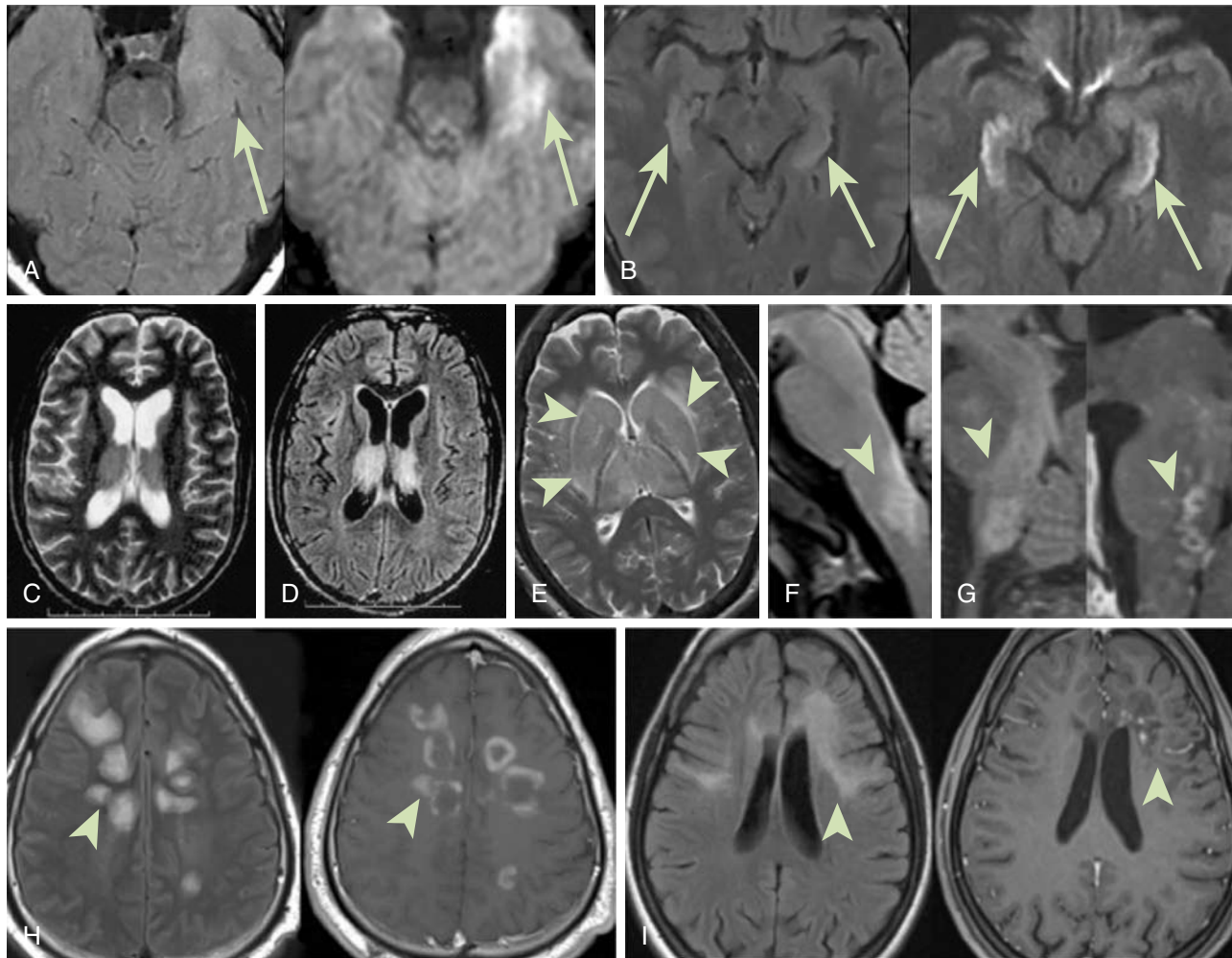


Fig. 643.1 MRI findings in acute encephalitis. Representative images from infectious and autoimmune encephalitides are shown. **A**, Early herpes simplex encephalitis; left temporal lobe abnormalities are more clearly seen on diffusion-weighted imaging (DWI) (*right*) than fluid-attenuated inversion recovery (FLAIR) (*left*). **B**, Autoimmune limbic encephalitis; bilateral mesial temporal lobe abnormalities seen on both DWI (*right*) and FLAIR (*left*)—note the symmetric nature of the lesions. **C-E**, Arboviral encephalitis; T2-weighted image of a patient with Japanese encephalitis shows hyperintensities in bilateral thalamus (**C**). The hyperintensities are better visualized in FLAIR image (**D**). T2-weighted image of patient with (**E**) Eastern equine encephalitis shows increased signal intensity and swelling in the deep gray matter. **F**, Neuromyelitis optica; FLAIR image of a patient who presented with brainstem encephalitis and found to have antibodies to aquaporin-4. **G**, *Listeria* brainstem encephalitis; FLAIR (*left*) and post-gadolinium (*right*) images show T2 abnormalities similar to neuromyelitis optica (NMO) but also multiple rim-enhancing brainstem lesions typical of *Listeria*. **H**, In acute disseminated encephalomyelitis, multifocal areas of T2 hyperintensity are seen on FLAIR (*left*) with characteristic incomplete rims of enhancement after gadolinium administration (*right*). **I**, In myelin oligodendrocyte glycoprotein encephalomyelitis, multifocal and confluent lesions can be seen on FLAIR imaging (*left*), and post-gadolinium imaging (*right*) shows patchy areas of enhancement. (**A**, **B**, and **F-H**, Modified from Venkatesan A, Michael BD, Probasco JC, et al. Acute encephalitis in immunocompromised adults. *Lancet*. 2019;393:702–716, Fig. 1, p. 709; **C** and **D**, Modified from Misra UK, Kalita J, Phadke RV, et al. Usefulness of various MRI sequences in the diagnosis of viral encephalitis. *Acta Trop*. 2010;116[3]:206–211, Fig 1ab; **E**, From Harvala H, Bremner J, Kealey S, et al. Case report: Eastern equine encephalitis virus imported to the UK. *J Med Virol*. 2009;81[2]:305–308; **I**, Courtesy Dr Michael Levy, Harvard Medical School.)

Table 643.5 Laboratory Testing and Neuroimaging Characteristics of Selected Pathogens

	LABORATORY TESTING	CHARACTERISTIC BRAIN MRI FINDINGS
VIRUSES		
HSV	CSF PCR (false negative can occur in first 72 hours). PCR of skin lesions may also be helpful if they occur in conjunction with neurological disease. Blood PCR in neonates. In neonatal CNS disease, CSF PCR is completed near the end of therapy to guide final treatment duration.	For HSV-1: Asymmetric abnormalities in mesiotemporal lobes, orbitofrontal lobes, and insular cortex with edema, possible restricted diffusion or hemorrhage (late stage) HSV-2 in neonates can appear like HSV-1. In adults, HSV-2 meningitis has variable findings (including no abnormalities) or may mimic HSV-1 encephalitis.
Varicella-zoster virus	CSF PCR; skin lesion PCR, biopsy, or DFA for VZV	Could affect temporal lobes, similar to HSV-1; lesions can occur in cerebellum and brainstem; ischemic or hemorrhagic lesions in white matter or gray-white matter junction suggest vasculopathy
Enteroviruses	CSF PCR; Blood PCR; nasopharyngeal swabs can be difficult to interpret as asymptomatic rhino/enterovirus infections are frequently detected. Stool testing only recommended for epidemiological tracing, including for poliovirus or enterovirus D68.	Wide range of findings from normal to diffuse white matter changes. EV 71 causes lesions in the dorsal brainstem, dentate nuclei of cerebellum, and anterior horns of spinal cord. EV D68 often causes lesions of the brainstem, spinal cord with involvement of the central gray matter, and of anterior horn cells.
Parechoviruses	CSF PCR; blood PCR	Variable findings from normal to restricted diffusion of thalami, corpus callosum, subcortical, and periventricular white matter, predominating in the frontal and parietal regions.
Measles*	Serum IgG and IgM; PCR of nasopharyngeal, throat, or urine samples in early infection	Cerebral edema, multifocal lesions, can resemble ADEM in acute setting
Mumps*	CSF and serum IgM and IgG; PCR from throat swab	Lesions in brainstem, hippocampus, and splenium of corpus callosum
Influenza virus	PCR or antigen testing of respiratory secretions; CSF PCR is infrequently positive	Neuroimaging is often normal, although abnormalities can include reversible splenial lesions, deep gray T2 abnormalities, diffuse edema, and hemorrhagic and necrotizing lesions of thalami, brainstem, and cerebellum
Arboviruses (many including alphaviruses such as eastern equine encephalitis, and flaviviruses, such as Japanese encephalitis or West Nile)	CSF and serum IgM and IgG (some viruses will have serological cross-reactivity with related viruses and further confirmation is needed through plaque reduction neutralization testing); CSF PCR (low sensitivity because viral nucleic acid is often absent by the time the patient presents for medical care. Can be useful in immunocompromised individuals); serum PCR (Zika); urine PCR (Zika, West Nile virus)	Up to half will have normal brain MRI; abnormalities might involve deep gray matter (i.e., thalamus, basal ganglia) and brainstem
Rabies virus*	PCR from saliva; PCR and immunofluorescent staining from nuchal skin biopsy or brain tissue; serum and CSF rabies virus neutralizing antibodies	Multifocal abnormalities in temporal cortex, hippocampi, deep gray nuclei, substantia nigra, brainstem, cerebral white matter, gray matter >> white matter
BACTERIA		
<i>Borrelia</i> spp.	Serology (serial EIA and Western blot); VlsE C6 ELISA; CSF antibody index; and CSF PCR (low sensitivity and specificity)	Multifocal lesions in subcortical white matter, potentially mimicking multiple sclerosis
<i>Brucella</i> spp.	Serum and CSF IgG and IgM; CSF culture	Variably enhancing lesions with marked surrounding edema
<i>Listeria monocytogenes</i>	Blood and CSF culture	In rhombencephalitis, multiple small rim-enhancing lesions with variable restriction of diffusion
<i>Mycobacterium tuberculosis</i> *	CSF AFB smear, culture, and PCR; sputum and blood AFB smear, culture, and PCR (in young children gastric aspirates are obtained instead of sputum). Often testing needs to be repeated (≥ 3) from the same site to enhance sensitivity; Tuberculin skin test or interferon-gamma release assay	Basilar meningeal enhancement, hydrocephalus, rim-enhancing lesions, and strokes in deep gray matter or internal capsule
<i>Rickettsia</i> and related diseases (i.e., <i>Anaplasma</i> spp., <i>Coxiella burnetii</i> , <i>Ehrlichia</i> spp., and <i>Rickettsia</i> spp.)	Serum IgG and IgM; whole blood PCR (useful for <i>Ehrlichia</i> and <i>Anaplasma</i>); if rash, PCR or immunohistochemical staining of skin biopsy	Reversible splenial lesions; punctate areas of restricted diffusion
<i>Treponema pallidum</i>	Diagnosed via combination of serum and CSF treponemal (e.g., FTA-ABS) and non-treponemal (e.g., serum RPR, CSF VDRL) antibodies, CSF white count, protein	Variable mesial temporal lobe involvement has been described

Continued

Table 643.5 Laboratory Testing and Neuroimaging Characteristics of Selected Pathogens—cont’d		
LABORATORY TESTING		CHARACTERISTIC BRAIN MRI FINDINGS
FUNGI		
Cryptococcus spp.	CSF and serum cryptococcal antigen, CSF culture and PCR. Opening pressure from the lumbar puncture may also be significantly elevated.	Basilar meningeal enhancement and hydrocephalus; cryptococcomas are T1 hypointense and T2 hyperintense lesions in basal ganglia and midbrain
Others (<i>Coccidioides</i> spp., <i>Histoplasma</i> spp., and <i>Blastomyces</i> spp.)	CSF and serum serology; large volume CSF culture; serum and urine antigen	Basilar meningeal enhancement, hydrocephalus, and rim-enhancing lesions
PARASITES AND FREE-LIVING AMEBAE*		
Acanthoameba spp.	Brain histopathology; CSF and brain tissue PCR and culture; serology	Hemorrhagic and necrotic rim-enhancing lesions
<i>Balamuthia mandrillaris</i>	Brain histopathology; CSF and brain tissue PCR; serology	Multifocal T2-weighted hyperintensities with rim enhancement, surrounding edema, and leptomeningeal extension
<i>Baylisascaris procyonis</i>	CSF and serum antibodies; peripheral or CSF eosinophilia	Multifocal or confluent white matter abnormalities and nodular enhancement
<i>Naegleria fowleri</i>	Wet mount preparation of warm CSF; brain histopathology; CSF and brain PCR and culture	Necrotic and hemorrhagic lesions often in CSF and brain PCR frontal lobes

*Coordinate testing with local, state, and national health departments. When serum IgM/IgG testing is performed, acute and convalescent titers are typically obtained 1-4 weeks apart. Seroconversion and fourfold or greater rise in titer using paired sera are supportive of infection. ADEM, Acute disseminated encephalomyelitis; AFB, acid-fast bacillus; CSF, cerebrospinal fluid; DFA, direct fluorescent antibody; EIA, enzyme immunoassay; EV, enterovirus; FTA-ABS, fluorescent treponemal antibody absorption; HSV, herpes simplex virus; RPR, rapid plasma reagin; VDRL, venereal disease research laboratory; VZV, varicella-zoster virus. Adapted From Venkatesan A, Michael BD, Probasco JC, et al. Acute encephalitis in immunocompromised adults. *Lancet*. 2019;393:702-716, Table 3, p. 708.

the child. If the clinical illness is severe and substantial parenchymal involvement is evident, the prognosis is poor, with potential deficits being intellectual, motor, psychiatric, epileptic, visual, or auditory in nature. Severe sequelae should also be anticipated in those with infection caused by HSV if it was not diagnosed and treated early in the disease. Overall, several studies have found that most children will have persistent symptoms years after the diagnosis of meningoencephalitis. These poor outcomes are likely reflective of a combination of suboptimal diagnostics for identifying pathogens that cause meningoencephalitis and a lack of specific therapies for most viral pathogens.

PREVENTION

For some viruses that cause meningoencephalitis, vaccines are available for prevention. Widespread use of effective viral vaccines for polio, measles, mumps, rubella, and varicella has almost eliminated CNS complications from these diseases in the United States. Vaccination against Japanese encephalitis virus is also available, but because of high costs, this vaccine has not been widely distributed in Asia. The availability of domestic animal vaccine programs against rabies has reduced the frequency of rabies encephalitis.

Control of encephalitis caused by arboviruses has been less successful because specific vaccines are only in various stages of development for clinical trials. The primary method for reducing arbovirus infections is vector control, through methods that include insecticides and eradicating insect breeding sites. Furthermore, minimizing mosquito and tick bites through the application of N,N-diethyl-3-methylbenzamide (DEET)—containing insect repellents on exposed skin and wearing long-sleeved shirts, long pants, and socks when outdoors, especially at dawn and dusk, reduces risk for arboviral infection.

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643.3 Eosinophilic Meningitis

Andrew B. Janowski and David A. Hunstad

Eosinophilic meningitis is defined as >10 eosinophils/mm³ of CSF or a finding that at least 10% of leukocytes in the CSF are eosinophils. The most common cause worldwide of eosinophilic CSF pleocytosis is CNS

infection with helminthic parasites. Nonetheless, the differential diagnosis of CSF eosinophilic pleocytosis is broad, especially in countries where helminthic infestation is uncommon, such as the United States (Table 643.6).

ETIOLOGY

Although any tissue-migrating helminth may cause eosinophilic meningitis, the most common worldwide cause is human infection with the rat lungworm, *Angiostrongylus cantonensis* (see Chapter 343). Other parasites that can cause eosinophilic meningitis include *Gnathostoma spinigerum* (dog and cat roundworm; see Chapter 343), *Baylisascaris procyonis* (raccoon roundworm), *Ascaris lumbricoides* (human roundworm, see Chapter 337), *Toxocara canis* (see Chapter 344), *Trichinella spiralis* (see Chapter 345), *Toxoplasma gondii* (see Chapter 336), *Paragonimus westermani*, *Paragonimus kellicotti*, *Echinococcus granulosus* (see Chapter 350), *Schistosoma japonicum* (see Chapter 346), *Onchocerca volvulus*, and *Taenia solium* (see Chapter 349). Eosinophilic meningitis may also occur as an unusual manifestation of more common viral, bacterial, or fungal infections of the CNS; for example, coccidioidomycosis has been particularly associated with eosinophilic meningitis. Noninfectious causes of eosinophilic meningitis include multiple sclerosis, malignancy, hypereosinophilic syndrome, or a reaction to medications or ventriculoperitoneal shunt materials.

EPIDEMIOLOGY

A. cantonensis is found in Southeast Asia, the South Pacific, Japan, Taiwan, Egypt, the Ivory Coast, and Cuba. Infection is acquired by eating raw or undercooked freshwater snails, slugs, prawns, or crabs containing infectious third-stage larvae. *Gnathostoma* infections are found in Japan, China, India, Bangladesh, and Southeast Asia. *Gnathostomiasis* is acquired by eating undercooked or raw fish, frog, bird, or snake meat. *B. procyonis* is endemic in the United States and is acquired by children playing outdoors where raccoons may deposit the organisms (raccoon latrines).

CLINICAL MANIFESTATIONS

Patients with eosinophilic meningitis from helminthic infestation typically become ill 1-3 weeks after exposure, as this reflects the transit time for parasites to migrate from the gastrointestinal tract to the CNS. Concomitant findings include fever, vomiting, abdominal pain, creeping skin eruptions, pleurisy, or peripheral eosinophilia. Neurologic symptoms may include headache, meningismus, ataxia, cranial nerve

Table 643.6 Common Infectious Etiologies of Eosinophilic Meningitis

DISEASE	ETIOLOGIC AGENT	SOURCE	LOCATION	SYMPTOMS	DIAGNOSIS	TREATMENT	PROGNOSIS
<i>Angiostrongyliasis</i> (rat lung worm)	<i>Angiostrongylus cantonensis</i> <i>Angiostrongylus costaricensis</i>	Definitive host: rats Intermediate hosts: mollusks (snails, slugs) Paratenic hosts: crustaceans, frogs, vegetables	Thailand, China, South America, Caribbean Islands, United States (Hawaii, Louisiana), Australia, Egypt, Nigeria, Côte d'Ivoire	Severe headache Neck stiffness Nausea, vomiting Low-grade fever Hyperesthesia, paresthesia Rarely have focal neurologic deficits Children: more systemic symptoms (fever, abdominal pain)	CSF: eosinophilia, normal glucose, elevated protein, elevated opening pressure, symptomatic relief after lumbar puncture Peripheral blood eosinophilia ELISA (epitopes 29 kDa and 31 kDa) CT head: normal MRI brain: leptomeningeal enhancement, micronodular enhancement	Supportive interventions (repeat lumbar puncture, analgesics) Prednisolone 60 mg/day divided three times a day for 2 weeks Albendazole 15 mg/kg/day orally in two divided doses for 2 weeks	Self-limiting within 3–6 weeks Severe disease can cause coma, respiratory failure, and death (case fatality 5%) Children and elderly may have more severe disease
<i>Gnathostomiasis</i> (neurognathostomiasis)	<i>Gnathostoma spinigerum</i>	Definitive host: dogs, cats, pigs, fish-eating mammals Intermediate hosts: freshwater crustaceans Secondary intermediate hosts: freshwater fish, frogs Paratenic hosts: birds, reptiles, mammals	Southeast Asia (Thailand), China, India, Zambia, Botswana, Mexico, Central America, South America	Prodrome: abdominal pain, nausea, vomiting, diarrhea, cutaneous larvae migrans, fever Severe headache Neck stiffness Radicular pain Paresis Paralysis Cranial nerve deficits Seizures	CSF: eosinophilia, xanthochromia, elevated protein, normal glucose Peripheral blood eosinophilia ELISA (24 kDa epitope, immunoglobulin subclasses) CT head: nodular lesions, hemorrhage MRI brain: diffuse or segmental hyperintense micronodules, hemorrhagic tracts, intracerebral hemorrhage, subarachnoid hemorrhage, subdural hemorrhage	Supportive (repeat lumbar punctures, analgesics) Use of anthelmintics is controversial Steroids may help CNS inflammation Monitor closely for intracranial hemorrhage	Long-term neurologic disability 23–46% of survivors, including paraplegia, paresis, radicular pain, cranial nerve Case fatality rate 7–25%
	<i>Baylisascaris procyonis</i>	Definitive host: raccoons, domesticated dogs, kinkajou Paratenic hosts: small mammals (rabbits, rodents), birds	North America	Lethargy Seizures Sensory loss Ataxia Paralysis Spasticity Cranial nerve deficits Paresis Concurrent ocular involvement Rarely have fever More common in young children	CSF: eosinophilia, variable protein, normal glucose Variable peripheral blood eosinophilia ELISA (epitopes 33 kDa, 45 kDa, BpRAG1 protein) CT head and MRI brain: parenchyma inflammation, cerebral atrophy	Exposure: albendazole (2550 mg/kg per day orally for 1020 days) Treatment: albendazole (2550 mg/kg per day orally for 14 weeks) Corticosteroids	Fulminant eosinophilic meningoencephalitis Severe neurologic impairment Case fatality rate 38%

Continued

Table 643.6 Common Infectious Etiologies of Eosinophilic Meningitis—cont'd							
DISEASE	ETIOLOGIC AGENT	SOURCE	LOCATION	SYMPTOMS	DIAGNOSIS	TREATMENT	PROGNOSIS
CNS coccidioidomycosis (valley fever)	<i>Coccidioides immitis</i> , <i>Coccidioides posadasii</i>	Colonized soil in southwestern United States, Mexico, South America	Southwestern United States, Mexico, South America	Additional organ system involvement (lungs, skin, bone, soft tissue) Prodrome: febrile respiratory infection Gradual neurologic symptom onset Headache Vomiting Lethargy Fever	CSF: pleocytosis, elevated protein, decreased glucose, elevated opening pressure, culture CSF complement fixation antibodies	Lifelong fluconazole Ventriculoperitoneal shunt placement	Long-term neurologic sequelae (hydrocephalus, fatal without treatment)

CSF, Cerebrospinal fluid; CT, computed tomography; ELISA, enzyme-linked immunosorbent assay; MRI, magnetic resonance imaging.
From Weatherhead J, Mejia R. Eosinophilic meningitis. In Cherry J, Demmler-Harrison GJ, Kaplan SL, Steinbach W, Hotez PJ, eds. *Feigin and Cherry's Textbook of Pediatric Infectious Diseases*. 8th ed, vol 1, Philadelphia: Elsevier; 2019, Table 34.1. pp 350-351.

palsies, and paresthesias. Paraparesis or incontinence can result from radiculitis or myelitis.

DIAGNOSIS

The presumptive diagnosis of helminth-induced eosinophilic meningitis is most often based on travel and exposure history in the presence of typical clinical and laboratory findings. Direct visualization of helminths in CSF is difficult because there typically is a low burden of organisms. Serologic assays for helminthic infections are also of limited utility because they are not readily available commercially and there is substantial cross-reactivity among different helminth species.

TREATMENT

Treatment is supportive, but anthelmintic drugs with or without steroids may be indicated (see Table 643.6). Anthelmintic drugs may provoke an inflammatory response because dying organisms can exacerbate symptoms. However, **treatment of *B. procyonis* should be initiated with albendazole and corticosteroids**. Steroids may decrease the duration of headaches in adults with eosinophilic meningitis. Analgesics should be given for headache and radiculitis, and CSF removal or shunting should be performed to relieve hydrocephalus, if present.

PROGNOSIS

Overall, up to 70% of patients improve significantly within 4 weeks after the onset of symptoms. The mortality rate associated with eosinophilic meningitis is <5%; untreated *Baylisascaris* infection may be fatal or associated with severe sequelae.

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Chapter 644

Brain Abscess

Andrew B. Janowski and David A. Hunstad

Annually, approximately 0.3–1.3 cases of brain abscess per 100,000 people are diagnosed. Development of brain abscess is most often associated with an underlying etiology, including contiguous spread from an associated infection (meningitis, otitis media, mastoiditis, sinusitis, soft tissue infection of the face or scalp, orbital cellulitis, or dental infections); direct compromise of the blood-brain barrier due to penetrating head injuries or surgical procedures; embolic phenomena (endocarditis); right-to-left shunts (congenital heart disease or pulmonary arteriovenous malformation); immunodeficiency; or infection of foreign material inserted into the central nervous system (CNS), including ventriculoperitoneal shunts (Table 644.1).

PATHOLOGY

Cerebral abscesses occur in both hemispheres in children, but in adults, left-sided abscesses are more common, likely because of penetrating injuries from right-handed assailants. Nearly 80% of abscesses occur in the frontal, parietal, and temporal lobes, whereas abscesses in the occipital lobe, cerebellum, and brainstem account for the remainder of cases. In 18% of cases, multiple brain abscesses are present, and in nearly 20% of cases, no predisposing risk factor can be identified. Abscesses in the frontal lobe are often caused by extension from sinusitis or orbital cellulitis, whereas abscesses located in the temporal lobe or cerebellum are frequently associated with otitis media and mastoiditis.

Table 644.1 Predisposing Conditions and Microbiology of Brain Abscess

PREDISPOSING CONDITION	USUAL MICROBIAL ISOLATES
Otitis media or mastoiditis	Streptococci, <i>Bacteroides</i> spp., <i>Haemophilus</i> spp., Enterobacteriales, <i>Pseudomonas aeruginosa</i>
Sinusitis (frontoethmoid or sphenoid)	Streptococci, <i>Bacteroides</i> spp., Enterobacteriales, <i>Staphylococcus aureus</i> , <i>Haemophilus</i> spp., <i>Fusobacterium</i> spp.
Dental infection	Streptococci, <i>Fusobacterium</i> spp., <i>Prevotella</i> spp., <i>Actinomyces</i> spp., <i>Bacteroides</i> spp., <i>Haemophilus</i> spp.
Penetrating trauma or postneurosurgical	<i>Staphylococcus</i> spp., streptococci, Enterobacteriaceae, <i>Clostridium</i> spp., <i>Cutibacterium</i> spp.
Lung abscess, empyema, bronchiectasis	Streptococci, <i>Fusobacterium</i> spp., <i>Actinomyces</i> spp., <i>Nocardia</i> spp.
Bacterial endocarditis	<i>Staphylococcus</i> spp., streptococci
Congenital heart disease	Streptococci, <i>Haemophilus</i> spp.
Neonates	<i>Streptococcus agalactiae</i> and other streptococci, Enterobacteriales including <i>Citrobacter koserii</i> , <i>Cronobacter sakazakii</i> , <i>Serratia marcescens</i> , <i>Proteus mirabilis</i> , <i>Listeria monocytogenes</i> , <i>Candida</i> spp.
Neutropenia or after hematopoietic cell transplant	Streptococci, Enterobacteriales, <i>Aspergillus</i> spp., Mucorales, <i>Candida</i> spp., <i>Nocardia</i> spp., <i>Cryptococcus neoformans</i> , <i>Coccidioides immitis</i> , <i>Blastomyces dermatitidis</i> , dematiaceous fungi and other mycoses, <i>Toxoplasma gondii</i> , <i>Mycobacterium tuberculosis</i>
Solid organ transplantation	Streptococci, Enterobacteriales, <i>Aspergillus</i> spp., Mucorales, <i>Candida</i> spp., <i>Cryptococcus neoformans</i> , <i>Coccidioides immitis</i> , <i>Blastomyces dermatitidis</i> , dematiaceous fungi and other mycoses, <i>Nocardia</i> spp., <i>Toxoplasma gondii</i> , <i>Mycobacterium tuberculosis</i> , <i>Listeria monocytogenes</i>
HIV infection	<i>Toxoplasma gondii</i> , <i>Nocardia</i> spp., <i>Mycobacterium</i> spp., <i>Listeria monocytogenes</i> , <i>Cryptococcus neoformans</i> , <i>Coccidioides immitis</i> , <i>Blastomyces dermatitidis</i>

Adapted from Gea-Banacloche JC, Tunkel AR. Brain abscess. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 9th ed. Philadelphia: Elsevier; 2020: Table 90.1, p. 1249.

ETIOLOGY

The predominant organisms that cause brain abscesses are streptococci, which account for one third of all cases in children, with members of the *Streptococcus anginosus* group (*S. anginosus*, *Streptococcus constellatus*, and *Streptococcus intermedius*) being the most common streptococci. Other important streptococci include *Streptococcus pneumoniae*, *Enterococcus* spp., and other viridans streptococci. *Staphylococcus aureus* is the second most common organism in pediatric brain abscesses, accounting for 11% of cases, and is most often associated with penetrating injuries. Other bacteria isolated from brain abscesses include gram-negative bacilli (*Haemophilus* spp., *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus* spp., and other Enterobacteriales) and anaerobic bacteria (gram-positive organisms, *Bacteroides* spp., *Fusobacterium* spp., *Prevotella* spp., and *Actinomyces* spp.). In neonates with meningitis, abscess

formation is a complication in 13% of cases, with *Citrobacter koseri*, *Cronobacter sakazakii*, *Serratia marcescens*, and *Proteus mirabilis* being special considerations in this age group. In up to 27% of all cases, more than one organism is isolated on routine bacterial cultures. Metagenomics sequencing has revealed that this percentage is likely a significant underestimate, as DNA from additional uncultured species has been detected from purulent abscess fluid, including rare case reports of detection of archaea. Abscesses associated with mucosal infections (sinusitis or dental infections) are more frequently polymicrobial and include anaerobic pathogens. Atypical bacteria, including *Nocardia*, *Mycobacterium*, and *Listeria* spp., and fungi (*Aspergillus*, *Candida*, *Cryptococcus*) are more common in children with impaired host defenses.

CLINICAL MANIFESTATIONS

Often the early stages of cerebritis and abscess formation are asymptomatic or are associated with nonspecific symptoms, including low-grade fever, headache, and lethargy. As the inflammatory process proceeds, vomiting, severe headache, seizures, papilledema, focal neurologic signs (hemiparesis), and coma may develop. The classic triad of headache, fever, and a focal deficit is noted in <50% of patients. A cerebellar abscess is characterized by nystagmus, ipsilateral ataxia and dysmetria, vomiting, and headache. If an abscess ruptures into the ventricular cavity, overwhelming shock and death may occur.

DIAGNOSIS

The key to diagnosis of brain abscesses is prompt imaging of the CNS. Brain MRI with contrast is the diagnostic test of choice because it can aid in differentiating abscesses from cysts and necrotic tumors (Fig. 644.1). As an alternative, cranial CT can provide more rapid imaging results but cannot provide the fine parenchymal detail offered by MRI (Fig. 644.2). Both MRI and CT scans with contrast can demonstrate a ring-enhancing abscess cavity. CT findings of cerebritis are characterized by a parenchymal low-density lesion, whereas T2-weighted MRI images feature increased signal intensity. Other abnormalities in common laboratory tests can be observed in children with brain abscesses. The peripheral white blood cell count is elevated in 60% of cases, and blood cultures are positive in 28% of cases. Lumbar puncture is not routinely recommended in cases of brain abscess, because the procedure could cause brain herniation from elevated intracranial pressure. When tested, the cerebrospinal fluid (CSF) is normal in 16% of cases, 71% of cases exhibit CSF pleocytosis, and 58% will have an elevated CSF protein level. CSF cultures are positive in only 24% of cases; therefore a culture obtained from the abscess fluid is essential for identifying bacterial pathogens. In some cases, culture of the abscess fluid can be sterile, and alternative testing, including 16S ribosomal RNA sequencing, may be used to identify organisms. An electroencephalogram (EEG) may identify corresponding focal slowing.

TREATMENT

The initial management of brain abscess includes prompt diagnosis and initiation of an antibiotic regimen that is based on the most likely pathogens (Table 644.2). Empiric therapy consists of a combination of a third-generation cephalosporin and metronidazole; often, vancomycin is added to provide coverage of methicillin-resistant *S. aureus* and resistant *S. pneumoniae*. Pharmacokinetics and penetration of the blood-brain barrier are essential considerations when using alternative agents. If resistant gram-negative organisms are suspected, as in cases of infected ventriculoperitoneal shunts, cefepime or meropenem may be used as the β -lactam in the initial regimen. *Listeria monocytogenes* may cause brain abscess in the neonate, and if this etiology is suspected, penicillin G or ampicillin with gentamicin is recommended. In immunocompromised patients, broad-spectrum antibiotic coverage is used, and

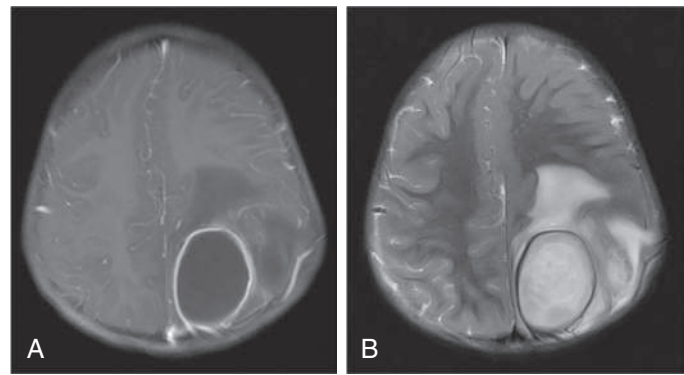


Fig. 644.1 Brain MRI in a 2-yr-old child with an atrial septal defect and brain abscess caused by MRSA. A, T1 fl2D postcontrast axial image demonstrating enhancement of the rim of the abscess. B, T2 TSE axial image showing a large fluid-filled lesion with surrounding edema.



Fig. 644.2 Brain abscess shown on CT with contrast. Note the large, wall-enhancing abscess in the left frontal lobe causing a rightward parenchymal shift. The patient had no neurologic signs until just before the CT scan, likely because the frontal lobe is a relatively “silent” area of the brain.

amphotericin B or azole therapy should be considered for coverage of potential fungi.

Neurosurgical procedures for brain abscess have been greatly enhanced by stereotactic MRI or CT systems, allowing for optimized approaches to minimize morbidity. Aspiration of the abscess is recommended for diagnostic cultures and decompression unless contraindicated based on its location or the patient's condition. There are limited data regarding injection of antibiotics into the abscess cavity, and this technique is not routinely recommended. Small abscesses (under 2.5 cm in diameter) or multiple abscesses may be treated initially with antibiotics and without surgical drainage, with follow-up neuroimaging studies to ensure a decrease in abscess size. Surgical excision of an abscess is rarely required, because such a procedure may be

Table 644.2 Antimicrobial Therapy for Brain Abscess

ORGANISM	STANDARD THERAPY	ALTERNATIVE THERAPIES
BACTERIA^{1,2}		
<i>Actinomyces</i> spp.	Penicillin G	Ampicillin, ceftriaxone
<i>Bacteroides fragilis</i>	Metronidazole	Meropenem
<i>Enterobacterales</i>	Ceftriaxone or ceftazidime	Cefepime, meropenem, fluoroquinolones
<i>Fusobacterium</i> spp.	Metronidazole	Meropenem
<i>Haemophilus</i> spp.	Ampicillin or ceftriaxone/ceftazidime	Cefepime, meropenem
<i>Listeria monocytogenes</i>	Ampicillin or penicillin G + gentamicin	Trimethoprim-sulfamethoxazole, fluoroquinolones
<i>Mycobacterium tuberculosis</i>	Isoniazid + rifampin + pyrazinamide + ethionamide or streptomycin	Consultation with an expert at TB Centers of Excellence is recommended for drug-resistant TB
<i>Nocardia</i> spp.	Trimethoprim-sulfamethoxazole + imipenem + amikacin (if involvement outside of the brain)	Minocycline, doxycycline, clarithromycin, ceftriaxone, linezolid
<i>Prevotella melaninogenica</i>	Metronidazole	Meropenem
<i>Pseudomonas aeruginosa</i>	Ceftazidime or cefepime	Meropenem, ciprofloxacin, aztreonam
<i>Staphylococcus aureus</i>		
Methicillin-sensitive	Nafcillin or oxacillin	Vancomycin, linezolid
Methicillin-resistant ³	Vancomycin	Linezolid, trimethoprim-sulfamethoxazole
<i>Streptococcus anginosus</i> (milleri) group, other Penicillin G streptococci	Penicillin G or ceftriaxone	Vancomycin
SELECTED FUNGI		
<i>Aspergillus</i> spp.	Voriconazole	Liposomal amphotericin B, amphotericin B lipid complex, amphotericin B deoxycholate, or salvage therapy ⁴
<i>Candida</i> spp.	Liposomal amphotericin B, amphotericin B lipid complex, amphotericin B deoxycholate (recommended in neonates) + flucytosine (in non-neonates)	Fluconazole, voriconazole
<i>Cryptococcus neoformans</i>	Liposomal amphotericin B, amphotericin B lipid complex, amphotericin B deoxycholate + flucytosine	Fluconazole
<i>Mucorales</i>	Liposomal amphotericin B, amphotericin B lipid complex, amphotericin B deoxycholate	Salvage therapy ⁴
PROTOZOA		
<i>Toxoplasma gondii</i>	Pyrimethamine + sulfadiazine with folinic acid	Pyrimethamine + clindamycin; other options: trimethoprim-sulfamethoxazole; atovaquone

¹Choice of specific antimicrobial agents for standard therapy, or consideration of alternative therapies, should be based on in vitro susceptibility testing for pathogens for which testing can be performed.

²Depending on the pathogenesis of bacterial brain abscess (see text), these bacteria may be isolated as part of a mixed infection.

³Other antibiotics with activity against methicillin-resistant *Staphylococcus* spp., daptomycin and ceftaroline, have limited data regarding penetration into the central nervous system. These drugs have been used in cases of salvage therapy.

⁴There is limited evidence for use of alternative anti-fungals for the central nervous system (CNS). Isavuconazole may have good CNS penetration but is understudied. Posaconazole and itraconazole have poor penetration, but successful usage has been reported. Echinocandins, in general, do not penetrate into the CNS.

Adapted from Gea-Banacloche JC, Tunkel AR. Brain abscess. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th ed. Philadelphia: Elsevier; 2020: Table 90.4, p. 1257

associated with greater morbidity compared with aspiration of a cavity. Administration of glucocorticoids can reduce edema, though evidence for improved outcomes with steroids is lacking.

The antibiotic regimen may be narrowed or made more specific once abscess culture data are available; importantly, most abscesses are polymicrobial, and not all organisms present may be isolated in culture. The duration of parenteral antibiotic therapy depends on the causative organism(s) and response to treatment (clinically and by imaging) but is typically 6 weeks. There has been interest in shorter regimens or use of oral antibiotics as an alternative to parenteral antibiotics, but clinical data are currently insufficient to support these alternative approaches.

PROGNOSIS

Mortality rates with contemporary use of CT and MRI, improved microbiologic techniques, and prompt antibiotic and surgical management are <10%. Factors associated with high mortality rate at the time of admission include delayed administration of antimicrobials, age <1 year, multiple abscesses, and coma. Long-term sequelae occur in about one third of patients and include hemiparesis, seizures, hydrocephalus, cranial nerve abnormalities, and behavioral and learning difficulties.

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Chapter 645

Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)

Alasdair P.J. Parker and Pooja D. Harijan

Idiopathic intracranial hypertension (IIH), or pseudotumor cerebri, is frequently considered a potential cause of headache *with* papilledema in children with normal findings on standard brain MRI. A false-positive diagnosis is common, and strategies are needed to avoid this. The pathophysiology remains poorly understood, particularly in children.

IIH is rare, affecting 1 in 100,000-150,000 children, but accurate diagnosis is essential because of the risk of loss of vision. Previously, normal levels of intracranial pressure (ICP) were unclear, leading to overdiagnosis of IIH. Studies in children with ICP monitoring show an upper limit of normal as 10 mm Hg (13.5 cm H₂O) between the ages of 2 and 5 years, with the adult level of cerebrospinal fluid (CSF) pressure being reached by 8 years of age. Currently, the 90th percentile of CSF pressure on lumbar puncture (LP) has been reported to be 28 cm CSF (22 mm Hg) in children age 5 to 18 years, without a significant age effect. Other normal parameters include CSF cell count, protein content, and ventricular size (although this could be slightly decreased on brain MRI). Papilledema may be overdiagnosed. With the advent of orbital coherence tomography (OCT), B-ultrasound, and MRI/venography, identification has improved (Figs. 645.1-645.3). Great care should be taken before the diagnosis of IIH, as there is a high rate of misdiagnosis (Fig. 645.4) and management is challenging.

ETIOLOGY

IIH, by definition, will not have an identifiable cause, despite typical findings. A large proportion of children referred to the pediatrician with possible/probable IIH after a thorough history, examination, and careful investigation will have *secondary IH* with an underlying cause

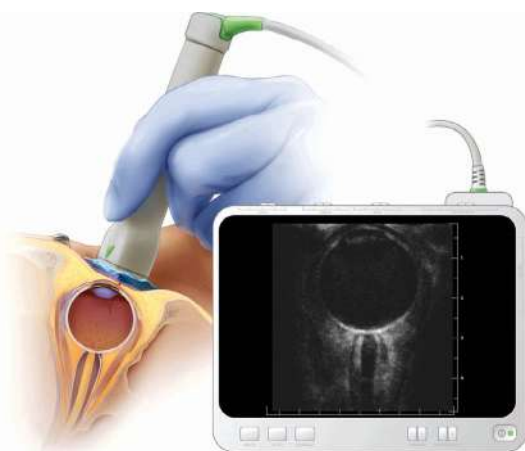


Fig. 645.1 Optic nerve ultrasonography. Left, A sagittal schematic view of gel applied on top of the closed right eyelid with the orientation of the operator hand and ultrasonography probe to the orbit. Right, An ultrasonography machine screen showing a coronal section of the orbit and optic nerve sheath. The distance between the stars represents the diameter of the optic nerve sheath. (From Koziarz A, Sne N, Kegel F, et al. Bedside optic nerve ultrasonography for diagnosing increased intracranial pressure. *Ann Intern Med.* 2019;171[12]:896–905, Fig. 1, p. 897.)

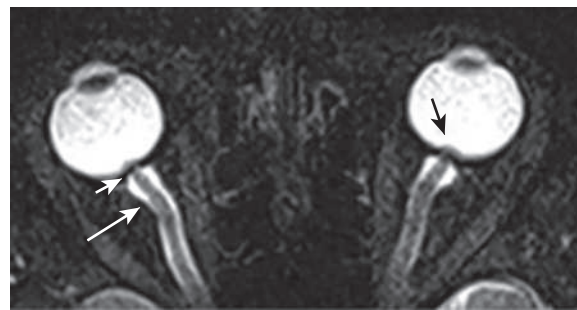


Fig. 645.2 Papilledema. Axial T2-weighted image with fat saturation of the orbits shows enlargement of the optic nerve sheaths (long white arrow), flattening of the posterior sclera (short white arrow), and protrusion of the optic disc head into the globe (black arrow). (Modified from Guarnizo A, Albreiki D, Cruz JP, et al. Papilledema: a review of the pathophysiology, imaging findings, and mimics. *Can Assoc Radiol J.* 2022;73[3]:557–567, Fig. 3a, p.561.)

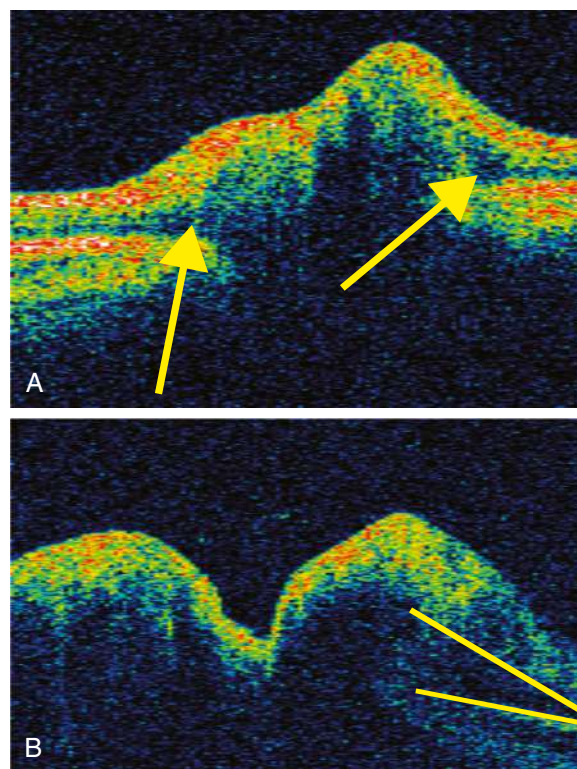


Fig. 645.3 A, Optical coherence tomogram (cross-sectional image) through an optic disc with drusen showing the typically irregular tissue underlying the elevated surface of the disc with no extension of the subretinal hyporeflective layer (arrows) beyond the optic nerve head. B, Optical coherence tomogram (cross-sectional image) of a papilledematous optic disc showing a smoothly elevated disc with underlying hyporeflective fluid extending beyond the disc into the subretinal space in a lazy-V pattern (illustrated by yellow lines). (Courtesy Louise Allen, MD, FRCOphth, Cambridge, United Kingdom.)

identified. Table 645.1 lists some of the many disorders that cause IH with no obstructive lesion on MRI. Research in adults suggests abnormal CSF androgen profiles/endocrine dysfunction leading to abnormal CSF pressure; glucagon-like peptide-1 and 11 β -hydroxysteroid dehydrogenase type 1 have been implicated.

CLINICAL MANIFESTATIONS

IIH is rare under the age of 10 years. In postpubertal children, there is a female sex preponderance, and for reasons that are poorly understood, patients are much more likely to be obese. However, most obese children with headache do not have IH and are at risk of false-positive

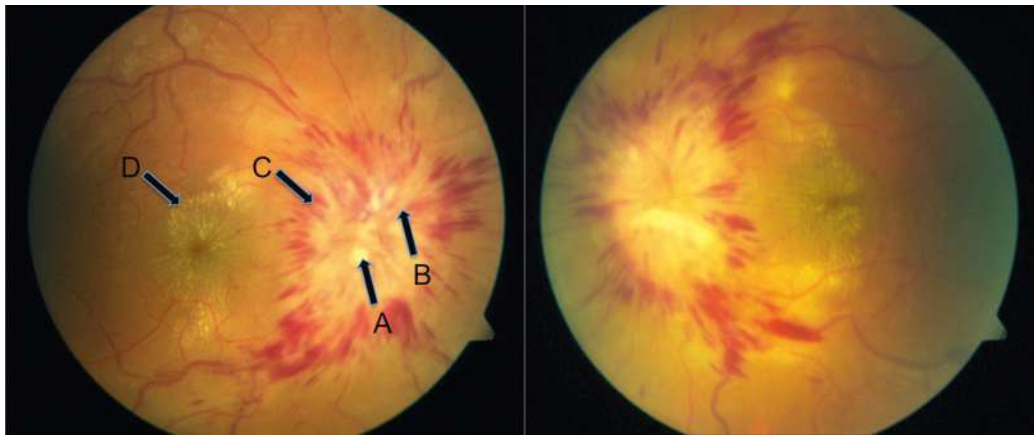


Fig. 645.4 Optic nerve photos of the right and left eyes, respectively, demonstrating grade 5 optic nerve head edema with characteristics, including (A) total obscuration of the optic cup, (B) total obscuration of a segment of a major blood vessel, (C) total obscuration of the disc margin, and (D) macular star. (From Vickers AL, El-Dairi MA. Subacute vision loss in young, obese female. *J Pediatr*. 2013;163:1518–1519, Fig. 1.)

Table 645.1 Secondary Intracranial Hypertension Without an Obstructive Lesion on MRI

HEMATOLOGIC DISORDERS Wiskott-Aldrich syndrome Iron-deficiency anemia Aplastic anemia Sickle cell disease Polycythemia Bone marrow transplantation and associated treatments Prothrombotic states Fanconi anemia Hemolytic anemia	NUTRITIONAL DISORDERS Hypovitaminosis A Vitamin A intoxication Hyperalimentation in malnourished patient Refeeding syndrome Vitamin D-dependent rickets
INFECTIONS Acute sinusitis Otitis media (lateral sinus thrombosis) Mastoiditis Tonsillitis Measles Roseola Varicella, recurrent varicella-zoster virus infection Lyme disease HIV or associated treatment complications	CONNECTIVE TISSUE DISORDERS Antiphospholipid antibody syndrome Systemic lupus erythematosus Behçet disease
DRUG-RELATED CONDITIONS Tetracyclines Sulfonamides Nalidixic acid Fluoroquinolones Corticosteroid therapy and withdrawal Nitrofurantoin Cytarabine Cyclosporine Phenytoin Mesalamine Isotretinoin Amiodarone Oral contraceptive pills/implants Valproic acid	ENDOCRINE DISORDERS Polycystic ovarian syndrome Hypothyroidism Hypoparathyroidism/hyperparathyroidism Pseudohypoparathyroidism Congenital adrenal hyperplasia Addison disease Recombinant growth hormone Menarche
RENAL DISORDERS Nephrotic syndrome Chronic renal insufficiency Post-renal transplantation Peritoneal dialysis	OTHER CONDITIONS Dural sinus thrombosis Transverse sinus stenosis Obesity (in pubertal patients) Superior vena cava syndrome Sleep apnea Guillain-Barré syndrome Crohn disease Ulcerative colitis Turner syndrome Galactosemia Atrial septal defect repair Moebius syndrome Sarcoidosis Hypophosphatasia Pregnancy

misdiagnosis. The most frequent symptom is chronic (weeks to months), progressive, frontal headache that may worsen with postural changes or a Valsalva maneuver. The headache phenotype attributed to IIH may mimic and/or coexist with chronic migraine and chronic tension-type headache. Calcitonin gene-related peptide has been implicated in the headache attributed to IIH (and in migraine). Although vomiting may occur, it is rarely as persistent and insidious as that associated with a posterior fossa tumor. **Transient visual**

obscuration (TVO) lasting seconds and diplopia (secondary to dysfunction of the abducens nerve) may also occur, as may pulsatile tinnitus. TVO is a transient graying out or vision loss often associated with postural changes or Valsalva maneuvers. Children are alert and lack constitutional symptoms. **Papilledema** with an enlarged blind spot is the most consistent sign. It is frequently misdiagnosed. Optic nerve head drusen and/or optic neuritis may be mistaken for papilledema, and failure/delay on treating the latter can lead to irreversible visual

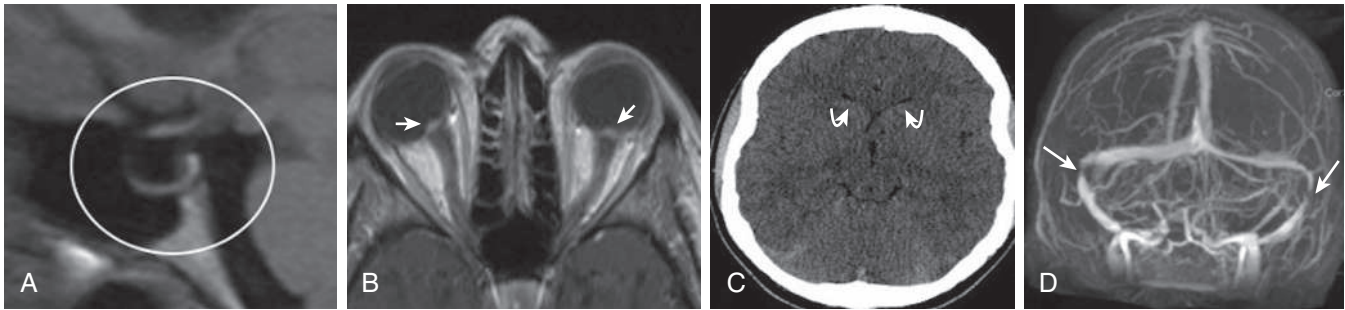


Fig. 645.5 Female with idiopathic intracranial hypertension. **A**, Sagittal T1-weighted image shows a partially empty sella. The pituitary gland is flattened against the floor of the sella, and the rest of the sella is filled with CSF (circle). **B**, Axial T1-weighted postgadolinium image of the orbits demonstrates protrusion of the optic disc heads into the vitreous, with associated enhancement (arrows). **C**, Axial head CT (shows slitlike appearance of the lateral ventricles (arrows). **D**, Coronal CE-MRV MIP image shows focal stenosis at the junction of the transverse and sigmoid venous sinuses (arrows). (From Guarnizo A, Albreiki D, Cruz JP, et al. Papilledema: a review of the pathophysiology, imaging findings, and mimics. *Can Assoc Radiol J.* 2022;73:557–567, Fig. 2, p. 560.)

impairment. OCT (see Fig. 645.3), B-ultrasound, and autofluorescence studies are strongly advised in all cases, as these will identify drusen and image the swelling. Inferior nasal or peripheral visual field defects may be detected. The presence of other focal neurologic signs prompts investigations to uncover a process other than IIH. All children should undergo cranial MRI, which may show any of the following: empty sella (in postpubertal children), posterior pituitary stalk displacement, meningoceles, posterior globe flattening, optic nerve head protrusion, optic nerve enhancement, optic nerve sheath distension, optic nerve tortuosity, slitlike ventricles, tight subarachnoid spaces, and inferior position of cerebellar tonsils (Fig. 645.5 and see Fig. 645.2). Absence of these findings does not rule out the diagnosis.

MR venography is essential, both to exclude venous thromboses/stenoses and to identify the tapering of the transverse sinuses that is commonly seen in intracranial hypertension (see Fig. 645.5). All children require measurement of their CSF pressure. Standard opening pressures in cm H₂O using a manometer can be falsely raised when the child is distressed or overflexed. More accurate recording will be achieved using an electronic transducer (similar equipment routinely attaches onto an arterial line), which will give a computer-aided recording with waveform analysis, both on opening and in steady state for 20 minutes (when the child is relaxed, happy, in the lateral decubitus position, and not held tightly or in an overflexed position). Cooperation of the child is required and is helped by the presence of a play specialist or use of nitrous oxide during needle insertion, thereby minimizing factors that may artificially alter ICP such as pain, crying, Valsalva maneuver, or abnormal respiration.

When LP opening pressure is measured under general anesthesia, it is important to record a normal end-tidal partial pressure of carbon dioxide (ET-PCO₂). Because secondary IH is more common, renal, liver, thyroid, hematologic, inflammatory, and autoimmune profiles should be obtained on venous blood testing. CSF infusion studies can also be helpful, particularly in borderline cases. Sterile fluid is infused via the spinal needle, and the resultant pressure-volume data can be analyzed to give the CSF dynamics and variables such as the pulse amplitude of ICP, the compensatory reserve, and the magnitude of slow waves of CSF pressure. Typically in IIH, the CSF pressure is elevated, the resistance to CSF outflow is low, and there is a depleted compensatory reserve. A summary of diagnostic criteria is noted in Table 645.2.

TREATMENT

Any causes of secondary IH should be treated (e.g., withdrawal of a drug). There are no randomized clinical trials (RCTs) to guide the treatment of IIH. The initial diagnostic LP may be therapeutic. The spinal needle produces a small hole in the dura that allows CSF to escape the subarachnoid space, thus reducing ICP. An additional LP and the removal of sufficient CSF to reduce the opening pressure by 50% occasionally lead to resolution of the process. Obese children with IIH need a weight-loss regimen, but the success rate is low. Medical management may include acetazolamide and topiramate. Acetazolamide (10–30 mg/kg/24 hours) has been found effective in adult RCT studies:

Table 645.2	Diagnostic Criteria for Idiopathic Intracranial Hypertension (IIH)
DIAGNOSIS OF IIH	DIAGNOSIS OF IIH WITHOUT PAPILLEDEMA
Diagnosis of IIH is definite if the patient fulfils A-E: A. Papilledema B. Normal neurologic examination except for sixth cranial nerve abnormalities C. Neuroimaging: Normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion and no abnormal meningeal enhancement on MRI, venous thrombosis excluded in all (best done on MRV) D. Normal CSF composition E. Elevated lumbar puncture opening pressure (≥250 mm CSF in adults; ≥280 in children or obese adults) in an appropriately performed lumbar puncture	In the absence of papilledema, a diagnosis of IIH can be made if B-E are satisfied and in addition the patient has unilateral or bilateral abducens nerve palsy In the absence of papilledema or sixth nerve palsy, a diagnosis of IIH can be suggested, but not made, if B-E are satisfied and in addition at least three of the following are present on neuroimaging: 1. Empty sella 2. Flattening of the posterior aspect of the globe 3. Distention of the perioptic subarachnoid space ± a tortuous optic nerve 4. Transverse venous sinus stenosis

From Mollan SP, Davies B, Silver NC, et al. Idiopathic intracranial hypertension: consensus guidelines on management. *J Neurol Neurosurg Psychiatry.* 2018;89(10):1088–1100.

some authors have recommended using topiramate, which has the added benefits of possible migraine prophylaxis and, in obese children, of being an appetite suppressant. Corticosteroids are not routinely administered because there is no benefit. When the symptoms such as headache and, in particular, visual deterioration, do not improve with an LP and acetazolamide or topiramate, then consideration of surgical management is necessary. In children first-line surgical management is currently CSF diversion (e.g., ventriculoperitoneal [VP] shunt, LP shunt); risks include obstruction and infection. There is a potential role for endovascular management of dural sinus stenosis (the technique of inserting a catheter to direct a self-expanding stent over a guide wire across a venous sinus stenosis)—this is increasingly first-line surgical treatment in adults; pediatric experience is limited. Repeated LP is likely to be traumatic for the child and unlikely to produce a longer-term solution. The value of optic nerve sheath fenestration (a decompressive procedure) is debated and is rarely performed; risks include ischemia and hemorrhage.

Any child whose ICP proves to be refractory to treatment warrants repeat full investigation. Serial monitoring of visual function (i.e., visual acuity, color vision, and visual fields) is required in children old enough to participate but remains a challenge in younger children. Serial optic nerve examination is also essential. OCT is useful to serially follow changes in papilledema. Serial visual-evoked potentials are useful if the visual acuity cannot be reliably documented.

Multidisciplinary management, including a pediatrician, pediatric neurologist, ophthalmologist, orthoptist, radiologist, specialist nurses, and, as needed, dietician, psychologist, interventional radiologist, and neurosurgeon, is helpful both in diagnosis and ongoing management.

The majority of adults with IIH continue to have headache after normalization of ICP and hence require continued headache management. Permanent visual function loss in IIH is rare; data from small studies suggest reduced visual acuity in up to 10% and permanent visual field defects in less than 17% of children.

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Chapter 646

Spinal Cord Disorders

Katie P. Fehnel and Mark R. Proctor

646.1 Tethered Cord

Katie P. Fehnel and Mark R. Proctor

Normally, as the spine flexes and extends, the spinal cord is free to move up and down within the spinal canal. If the spinal cord is fixed at any point, its movement is restricted, and the spinal cord and nerve roots can become stretched. This fixing of the spinal cord, regardless of the underlying cause, is called a *tethered cord*. When pain, neurologic deterioration, or bladder and bowel dysfunction occurs in response to the fixation, it is called **tethered cord syndrome**.

By full gestational age, the spinal cord ends, on average, at the lumbar L1-2 disk space, although there is a normal bell-shaped distribution from thoracic T12-L3. Spinal cord tethering cannot be determined by position of the conus medullaris alone, but a position below L3 is concerning for tethering, especially when associated with an abnormality that connects the cord to the bones or soft tissues around the spine. Similarly, the spinal cord can be tethered even if it terminates in a normal position if a tethering lesion is present. This can occur from a variety of causes.

In its simplest form, tethered cord syndrome results from a thickened filum terminale, which normally extends as a thin, very mobile structure from the tip of the conus to the sacrococcygeal region, where it attaches. When this structure is thickened and/or shortened, the cord can become tethered. This stretching between two points can cause symptoms later in life. Fatty infiltration is often seen in the thickened filum (Fig. 646.1).

Other conditions that are well-established as causes of symptomatic tethering include various forms of occult dysraphism, such as lipomyelomeningocele, myelocystocele, and diastematomyelia. These conditions can be associated with cutaneous manifestations such as midline lipomas, asymmetry of the gluteal fold (Fig. 646.2), dimples, and hairy patches called *hypertrichosis* (Fig. 646.3). Probably the most commonly known type of symptomatic tethered cord involves patients who had previously undergone closure of an open myelomeningocele and later become symptomatic with pain or neurologic deterioration. Tethered cord syndrome can also be iatrogenic and associated with scarring of

the spinal cord in patients who have undergone surgical procedures that disrupt the pial surface of the spinal cord.

CLINICAL MANIFESTATIONS

Patients at risk for the subsequent development of tethered cord syndrome can often be identified at birth by the presence of an open myelomeningocele or by cutaneous manifestations of dysraphism (see Chapter 631). It is important to examine the back of the newborn for cutaneous midline lesions (lipoma, dermal sinus, tail, or hairy patch) that may signal an underlying form of occult dysraphism. Dermal sinuses are almost always located *above* the gluteal fold, and dimples in the gluteal cleft directly overlying the coccyx are generally benign fibrous tracts called *coccygeal pits* that are not associated with spinal tethering. However, cutaneous abnormalities may be absent in patients



Fig. 646.1 Sagittal T1-weighted MRI showing thickening and fatty infiltration of the filum terminale (arrow) in a patient with a symptomatic tethered spinal cord.



Fig. 646.2 Child with a lipomyelomeningocele demonstrating an extraspinal mass and an asymmetry of the gluteal fold indicative of underlying occult dysraphism. (Used with permission from Barrow Neurological Institute.)



Fig. 646.3 Hairy patch or hypertrichosis usually associated with diastematomyelia. (Used with permission from Barrow Neurological Institute.)

with tethered spinal cord, and these patients present later in life with clinical manifestations.

Patients who become symptomatic later in life generally present with one of four clinical manifestations, including neurologic, orthopedic, bowel/bladder, and/or pain symptoms. One orthopedic presentation is asymmetry of the feet, with a smaller, high-arched foot with clawing of the toes (Fig. 646.4), sometimes referred to as **neuroorthopedic syndrome**. Characteristically, there is no ankle jerk on the involved side and the calf is atrophied. Scoliosis can also be a presenting sign. Another clinical presentation is increasing urinary urgency, which may progress to incontinence. Constipation progressing to incontinence can affect the gastrointestinal system as well. Finally, severe generalized back pain, often radiating into the lower extremities, can occur, particularly in older adolescents and adults.

DIAGNOSTIC EVALUATION

When patients present with symptoms related to tethered cord syndrome, a thorough motor and sensory examination of the patient must be documented. Assessment of bladder function with an ultrasound of the bladder and urodynamic studies is useful in analyzing bladder innervation. Magnetic resonance imaging (MRI) is the diagnostic study of choice for the anatomy of the tethering lesion and to provide information about the risks of surgical intervention.

TREATMENT

There are no nonsurgical options for the management of tethered cord syndrome. Because the presence of asymptomatic tethering is most likely to be at least suspected in the newborn, prophylactic surgery to prevent late deterioration has been advocated by some neurosurgeons. This strategy remains controversial and depends to some extent on a careful assessment of the risks compared with the benefits. If surgical intervention is chosen, microsurgical dissection with release of the spinal cord attachment to the overlying dura and soft tissues is the goal of treatment.

OUTCOME

The outcome of surgery depends on the complexity of the underlying lesion and the presenting condition of the child because existing deficits are generally not reversed. Releasing a thickened filum terminale or detethering of patients with diastematomyelia generally yields a good outcome, and the chance of recurrent symptoms is quite low. Patients with symptomatic tethered cord who undergo repair of a myelomeningocele or a lipomyelomeningocele have a significant possibility of recurrent tethering and recurrent symptoms. In this cohort, the



Fig. 646.4 Example of neuropathic changes to the right foot as a result of spinal cord tethering, with a smaller high-arched foot and absent ankle jerk on exam. (Used with permission from Barrow Neurological Institute.)

potential need for reoperation and sometimes even multiple reoperations is high. Given the technical challenges and increased neurologic risk in a patient multiply reoperated on for tethered cord, in adolescent patients for whom axial growth has completed, spinal column shortening procedures have been proposed as an alternative treatment modality. As opposed to surgery at the site of tethering, the tension is released by actual shortening of the vertebral column.

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646.2 Diastematomyelia (Split-Cord Malformation)

Katie P. Fehnel and Mark R. Proctor

Diastematomyelia is a relatively rare form of occult dysraphism in which the spinal cord is divided into two halves and can present as tethered spinal cord. In **type 1** split-cord malformation, there are two spinal cords, each in its own dural tube and separated by a spicule of bone and cartilage (Fig. 646.5). In a **type 2** split-cord malformation, the two spinal cords are enclosed in a single dural sac with a fibrous septum between the two spinal segments (Fig. 646.6). In both cases, the anatomy of the outer half of the spinal cord is essentially normal but the medial half is extremely underdeveloped. Underdeveloped nerve roots and dentate ligaments terminate medially into the medial dural tube in type 1 cases and terminate in the membranous septum in type 2 cases. Both types have an associated defect in the bony spinal segment. In the case of type 2 lesions, this defect can be quite subtle.

CLINICAL MANIFESTATIONS

Patients with both type 1 and type 2 split-cord malformations will have presentations similar to other types of spinal tethering lesions. This may include subtle signs of neurologic involvement, such as unilateral calf atrophy and a high arch in one or both feet early in life, but they are more likely to be neurologically normal. These patients are tethered by the adherence of the spinal cord, so they may develop progressive loss of bowel and bladder function and sensory and motor difficulties in the lower extremities. Back pain is a common symptom in adolescents and adults with split-cord malformation but is uncommon in small children.

Cutaneous manifestations of dysraphism are present in 90% of patients with split-cord malformations. Large, hairy, midline patches called **hypertrichosis**, the most common cutaneous manifestations, are present in approximately 60% of the cases.

DIAGNOSTIC EVALUATION

MRI, the study of choice, shows the two spinal cords. The frequent association of bony abnormalities in this condition may require further evaluation with computed tomography (CT).

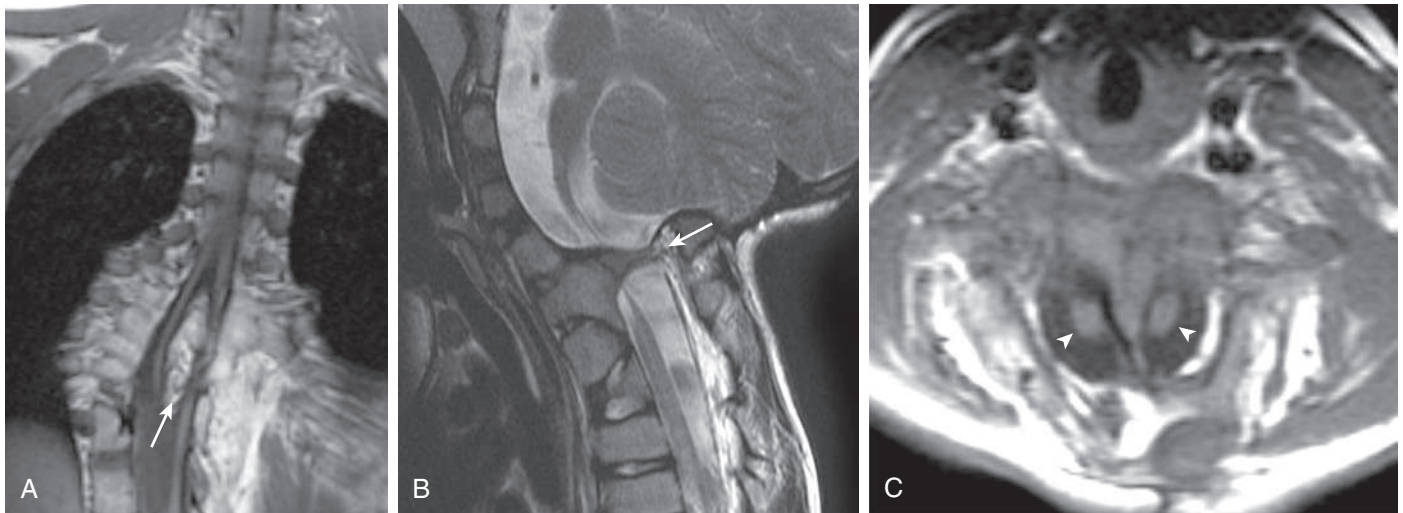


Fig. 646.5 Diastematomyelia type 1. A, Coronal T1-weighted MRI in a patient with type 1 DSM shows a large ossified spur (arrow) that splits the thoracic spinal cord. Numerous vertebral segmentation anomalies with posterior rib fusions are present. Sagittal T2-weighted (B) and axial T1-weighted (C) MRI of a different patient shows a type 1 cervical DSM with ossified spur (arrow in B) and two hemicords (arrowheads in C). (From Moore KR. *Congenital abnormalities of the spine*. In: Coley BD, ed. *Caffey's Pediatric Diagnostic Imaging*, 13th ed. Philadelphia: Elsevier; 2019: Fig. 43-12.)

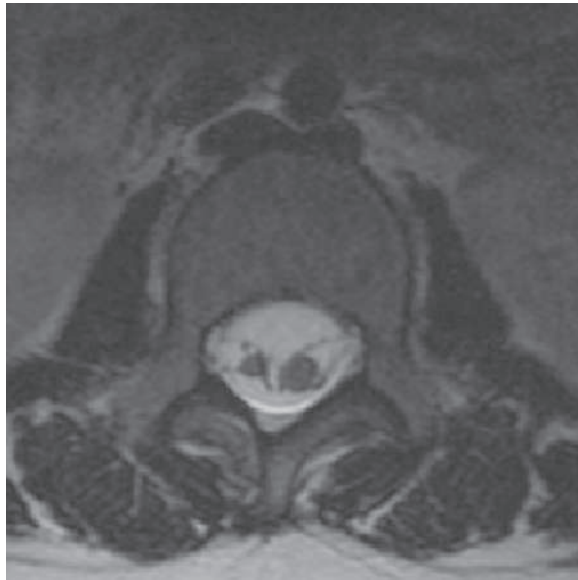


Fig. 646.6 Diastematomyelia type 2. Axial T2-weighted MRI in a patient with type 2 DSM shows the spinal cord split into two hemicords within a single dural tube. No fibrous or osseous septum was identified. (From Moore KR. *Congenital abnormalities of the spine*. In: Coley BD, ed. *Caffey's Pediatric Diagnostic Imaging*, 13th ed. Philadelphia: Elsevier; 2019: Fig. 43-13.)

TREATMENT

The treatment of split-cord malformation is surgical. This abnormality is a form of tethered cord syndrome, and its treatment is to release the spinal cord to move freely with movement of the spine. In type 1 split-cord malformations, the two half-cords are in separate dural sacs with medial attachment to the dura and bony septum. In this case, the dura needs to be opened, the bony septum removed, the medial attachments to the dura lysed, and a single dural tube created. For type 2 lesions, the membranous septum should be lysed. An attachment of this membrane to the anterior dura should be explored and lysed as well. Retethering of this type is rare, as there is no reason to disrupt the pia layer of the spinal cord.

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646.3 Syringomyelia

Katie P. Fehnel and Mark R. Proctor

Syringomyelia is a cystic distention of the spinal cord caused by obstruction of the flow of spinal fluid from within the spinal cord to its point of absorption. There are three recognized forms of syringomyelia, depending on the underlying cause. Communicating syringomyelia implies that cerebrospinal fluid (CSF) from within the ventricles communicates with the fluid within the spinal cord and is assumed to be the source of the CSF that distends the spinal cord. Noncommunicating syringomyelia implies that ventricular CSF does not communicate with the fluid within the spinal cord. It primarily occurs in the context of intramedullary tumors and obstructive lesions. In the final form of syringomyelia, that is, posttraumatic syringomyelia, spinal cord injury results in damage and subsequent softening of the spinal cord. This softening, combined with the scarring of the surrounding spinal cord tissue, results in progressive distention of the cyst. Syringomyelia is highly associated with Chiari malformation and can also be seen after infection or trauma, but many cases seen on imaging are normal anatomic variants unassociated with syndromes or any symptoms. It is also associated with connective tissue disorders (Ehlers-Danlos syndrome).

CLINICAL MANIFESTATIONS

Signs and symptoms of syringomyelia develop insidiously over years or decades. The classic presentation is **central cord syndrome**. Syringomyelia affects the spinal cord beginning from the central region, where the cervical and thoracic nerve fibers are located, so it less commonly affects the lumbar and sacral fibers, which are more laterally located in the spinal cord. Therefore in syringomyelia the patient develops numbness beginning in the shoulder in a capelike distribution followed by the development of atrophy and weakness in the upper extremities. Trophic ulcers of the hands are characteristic of advanced cases.

Other forms of presentation include scoliosis that may be rapidly progressive and often can be presumed from the absence of superficial abdominal reflexes. Urgency and bladder dysfunction as well as lower extremity spasticity also may be part of the presentation.

In patients with syringomyelia related to significant prior spinal cord injury, the presentation is usually severe pain in the area of the spinal cord distention above the level of the initial injury. There is also an ascending level of motor and sensory dysfunction.

DIAGNOSTIC EVALUATION

MRI is the radiologic study of choice (Figs. 646.7 and 646.8). The study should include the entire spine, and gadolinium-enhanced sequences should be a part of it if there is a suspicion for tumor. Specific attention should be paid to the craniovertebral junction because of the frequent association of syringomyelia with Chiari malformations. Obstruction to the flow of CSF from the fourth ventricle can cause syringomyelia; therefore most patients also should undergo imaging of the brain if a Chiari malformation is seen on the cervical imaging.

TREATMENT

The treatment of syringomyelia should be tailored to the underlying cause, and rarely is the syringomyelia addressed directly. If that cause can be removed or ameliorated, the syrinx should improve. Direct surgery on the syrinx is associated with a much higher surgical risk profile.

Communicating syringomyelia is most frequently seen in the context of abnormalities at the craniovertebral junction, often associated with Chiari malformations (see Fig. 646.7). In such cases, decompression of the craniovertebral junction is usually effective in the management of the syringomyelia. In the context of Chiari II malformation associated with spina bifida, syringomyelia usually results from an insidious failure of the shunt used to treat the hydrocephalus. This distention of the spinal cord results in a rapid development of scoliosis and occasionally spasticity in the lower extremities. Repair of the shunt is often effective treatment, and only rarely is surgical decompression at the craniovertebral junction necessary. Other conditions that can cause obstruction at the craniocervical junction include inflammatory conditions such as chronic meningitis, as seen in tuberculosis or meningeal carcinomatosis.

Noncommunicating syringomyelia results from blocking the flow of spinal cord extracellular fluid or CSF within the central canal by an intramedullary spinal cord tumor or severe external compression of the spinal cord. In such cases, management should be directed to tumor resection or to decompression of constricting elements.

Traumatic syrinxes result from hematomyelia in the substance of the spinal cord coupled with severe arachnoidal scarring around the circumference of the spinal cord. When progressive, this form of syringomyelia is treated by exploration and lysis of the adhesions that fix the spinal cord to the overlying dura. Microscopic lysis of the scar surrounding the spinal cord at the point of injury allows the spinal cord to collapse and prevents it from being distorted by a hydrostatic column of spinal fluid pulsations.

In rare cases, direct drainage procedures must be employed and can result in symptomatic and radiographic improvement. Syrinx-to-subarachnoid or pleural shunting with a small piece of silicone tubing is the treatment option. These procedures often have short-lived success because the tubing tends to become obstructed, so they should be reserved for cases with obstructive symptoms.

In the current era, where many children are undergoing spinal MRI, some children who demonstrate no neurologic deficits are being referred to pediatric neurosurgeons with the diagnosis of syringomyelia. Many of these children were scanned because of back pain or as part of a screening for scoliosis. They are found on MRI to have a **persistent central canal**, and the diagnosis of syringomyelia is made. These syrinxes are 1-3 mm in diameter and may extend over several segments (see Fig. 646.8). There is no distortion of the spinal cord in the region and no change in signal of the surrounding spinal cord. These syrinxes have been called “idiopathic” syrinxes. Follow-up of significant numbers of such children has shown them to be benign in nature and probably represent a normal variant. There does not seem to be a need for routine follow-up imaging without new symptoms. They need no treatment and do not require limitations of activity.

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Fig. 646.7 Sagittal MRI of patient with a Chiari I malformation and a holocord syrinx. (Used with permission from Barrow Neurological Institute.)

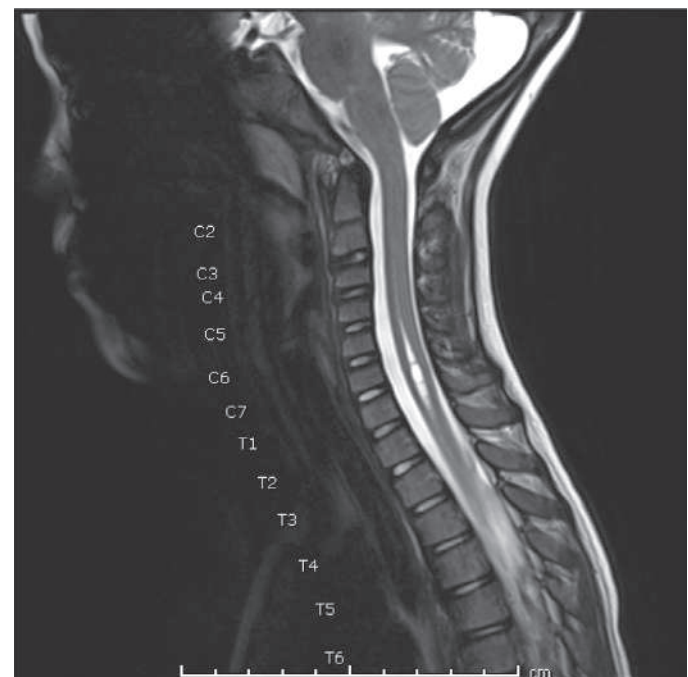


Fig. 646.8 T2-weighted MRI scan of the cervical and thoracic spinal cord showing dilation of the central canal (C5-T1) in the absence of a Chiari malformation or other pathology.

646.4 Spinal Cord Tumors

Katie P. Fehnel and Mark R. Proctor

Tumors of the spine and spinal cord are rare in children. Different types of tumors have different relationships with the spinal cord, meninges, and bony elements of the spine (Fig. 646.9). Intramedullary spinal cord tumors arise within the substance of the spinal cord itself (Fig. 646.10). They represent between 5% and 15% of primary central nervous system tumors. This percentage may well reflect the relative volume of spinal cord compared with brain. Approximately 10% of intramedullary spinal cord tumors are malignant astrocytic tumors, but most are World Health Organization grade I or II tumors of glial or ependymal origin. In children, low-grade astrocytomas and gangliogliomas represent the most common tumor types, with ependymomas being less common than in adults.

Except in the context of neurofibromatosis (NF-1 and NF-2; see Chapter 636.1), intradural extramedullary tumors are extremely rare in children. Most are nerve sheath tumors, either schwannomas or neurofibromas. Intraspinous meningiomas in children are essentially found only in patients with NF-2 or those who have undergone prior irradiation for some reason. The intradural extramedullary compartment is also a site for metastatic tumors from primary cancers such as leukemia or primitive neuroectodermal tumors. Myxopapillary ependymoma, a benign subtype found in the filum terminale, is another extramedullary tumor seen in children.

Extradural spinal tumors characteristically begin in the bones of the spine. Primary tumors in this location include aneurysmal bone cysts, Langerhans cell histiocytosis (formerly called *eosinophilic granuloma*), osteoid osteoma, and giant cell tumors. In infants, the extradural space is often the site of neuroblastomas or ganglioneuroblastomas, which tend to extend from a paraspinal location into the epidural space through the intervertebral foramen. In older patients, the bones of the spine may be the site of multiple myeloma and metastases from common malignant tumors, such as chordoma and sarcomas.

CLINICAL MANIFESTATIONS

With the exception of the uncommon malignant glial tumors of the spinal cord, which tend to present precipitously, intramedullary spinal cord tumors present in a very insidious manner. Back pain related to the level of the tumor is a common presenting complaint. It is likely that this pain will awaken the child from sleep and improve as the day progresses. Before the use of MRI became routine, the time from the first onset of symptoms to diagnosis of the tumor could be very prolonged, extending years. Weakness, gait disturbance, and sensory deficits are usually subtle but detectable on formal neurologic examination. Scoliosis, limb asymmetry, and bowel or bladder disturbance may be the presenting complaints associated with intramedullary spinal cord tumors.

Nerve sheath tumors primarily arise from the sensory rootlet of the exiting spinal nerve. They are very slow-growing tumors and present with symptoms and signs relative to the nerve root involved. Pain in a bandlike distribution around the chest or into an extremity is the most common presenting complaint. Tumor growth eventually leads to spinal cord compression and involvement of adjacent nerve roots, but pain is the more likely presenting symptom.

Extradural extramedullary tumors have a tendency to present more acutely owing to rapid growth within a confined space. Such children may present with acute paresis and urinary retention. They can also present abruptly with severe pain and neurologic deficit at the time of pathologic fracture of the vertebral body. Benign tumors such as giant cell tumors and aneurysmal bone cysts present more insidiously as the tumor slowly grows and begins to compress neural structures. Osteoid osteomas present with severe pain relieved by nonsteroidal antiinflammatory drugs.

DIAGNOSTIC EVALUATION

MRI with and without gadolinium enhancement of the spinal cord is the diagnostic study of choice and is essential in the diagnosis of spinal cord tumors, especially intramedullary spinal cord tumors. Most

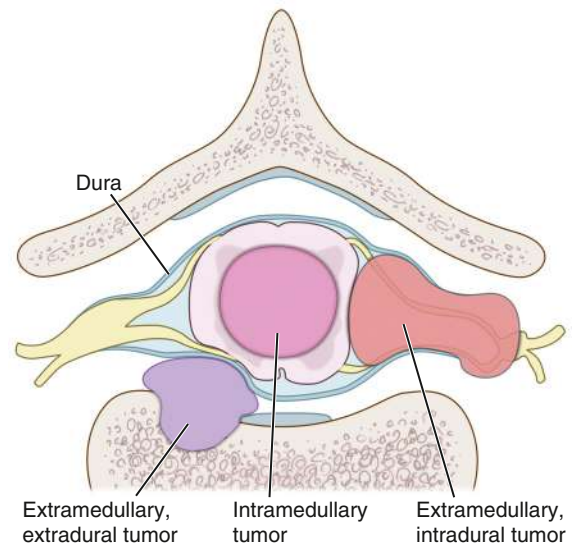


Fig. 646.9 Diagram of the relationship of various tumors to the spine, nerve roots, and spinal cord. (Used with permission from Barrow Neurological Institute.)



Fig. 646.10 T1 weighted MRI scan of a spinal cord tumor (arrow). The fusiform expansion of the cervical cord enhances after intravenous gadolinium injection.

astrocytic tumors of the spinal cord and most ependymomas show diffuse enhancement and will distend the spinal cord focally. These tumors may involve the entire length of the spinal cord (holocord astrocytomas), although much of the change might be due to the associated syrinx. Nerve sheath tumors characteristically enhance and are focal. They may exit through the neural foramen and distend the canal, as can be seen on MRI. They also may be visualized on plain radiographs of the affected area of the spine because of their chronic effect on the bones.

Plain radiographs of the spine are helpful in defining the relationship of extradural tumors to the bony spine and in documenting evidence of instability in the case of pathologic compression fractures. When a pathologic fracture occurs, CT is essential to determine the effect of the tumor on the bone. Because many of these tumors occur as metastatic lesions, a general staging of the extent of disease is essential. In the

case of Langerhans cell histiocytosis, a thorough bone survey should be conducted to look for other lesions. Radionuclide bone scanning, rapid STIR MRI, or PET MRI scans are useful in determining the extent of the disease.

TREATMENT

The primary treatment of both intramedullary and extramedullary intradural tumors is surgical removal. For both low-grade astrocytomas and ependymomas, microsurgical removal with the intent of total removal is the treatment of choice. This goal should be attainable in most patients with ependymomas and gangliogliomas and in many patients with low-grade astrocytomas. Though the majority of intramedullary spinal cord tumors are benign, the extent of resection may be limited in tumors that are diffusely infiltrating midline gliomas because of tumor invasion and infiltration of gray and white matter tracts. The invasive nature of these tumors is a leading cause of the poor prognosis for many of these patients, resulting in symptom progression and ultimately loss of neurologic function with profound implications on both quality and extent of life and is one of the most significant problems in spinal neurooncology. With the advent of routine molecular genetic testing, targetable pathogenic variants have been identified in some intramedullary spinal cord tumors, which will potentially expand nonsurgical and chemotherapeutic treatment options in as of now unresectable spinal cord tumors. Adjunctive treatment is often unnecessary in patients treated with adequate surgical resection. Likewise, schwannomas should be resectable. Occasionally, however, the nerve root must be resected. Doing so may be of no consequence in the thoracic spinal cord, but an attempt to remove the tumor while salvaging the motor root in the cervical and lumbosacral region is critical to preserve movement. Malignant astrocytic tumors cannot be resected without major morbidity and, in any case, carry an extremely poor prognosis. In the case of grades III and IV astrocytomas of the spinal cord, decompression and biopsy followed by radiation therapy and possibly chemotherapy are used.

The diagnosis and treatment of extramedullary spinal cord tumors must be individualized. Patients with bony involvement may be at risk of instability, and treatment will therefore involve both tumor resection and stabilization of the spine. For extramedullary tumors with soft tissue components such as neuroblastomas, treatment is determined by the nature of the tumor and degree of spinal cord compression and may require needle biopsy of the lesion to direct treatment. In the absence of significant neurologic compression, surgical intervention may not be indicated if adjuvant therapies might be effective.

OUTCOME

The prognosis for patients with benign intramedullary spinal cord tumors depends, to some extent, on the patient's condition at the time of surgical intervention. It is very unlikely that nonambulatory patients will improve after surgery, and most patients will have at least transient worsening with surgery. If, however, patients are ambulatory at the time of surgery, they are likely to recover at least to their preoperative level of function. The majority of intramedullary tumors in children are benign and behave like tumors with the same histologic findings in the brain. The evidence would point to the fact that intramedullary ependymomas act in a more benign fashion than they do in the fourth ventricle. Gross total removal without adjuvant treatment is the preferred method of treatment and carries not only a much longer progression-free survival time but an improved quality of life as well.

Malignant spinal cord tumors are usually lethal, with death resulting from diffuse metastases via the CSF pathways. Successful resection of nerve sheath tumors should be curative. In the context of neurofibromatosis, however, many more tumors can be found at other levels or can be expected to develop later in life. Surgical intervention in the context of neurofibromatosis should be performed only for clearly symptomatic lesions.

The outcome of treatment of extramedullary tumors depends on the cell type and, in most cases, on the efficacy of nonsurgical, adjunctive



Fig. 646.11 T2 weighted MRI showing an extensive thoracic spinal arteriovenous malformation.

therapies. For aneurysmal bone cysts and giant cell tumors, resection of the tumor and fusion of the spine are the treatments of choice.

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646.5 Spinal Arteriovenous Malformations

Katie P. Fehnel and Mark R. Proctor

Arteriovenous malformations of the spinal cord are rare lesions in children. Only about 60 patients younger than age 18 years are treated in the United States each year. These lesions are complex, and despite their rarity there are multiple subtypes, which require different treatment strategies. Patients commonly present with back or neck pain, depending on the segments of the spinal cord involved, and they may experience the insidious onset of motor and sensory disturbances. Sudden onset of paraplegia secondary to hemorrhage has been reported. Occasionally, patients present with subarachnoid hemorrhage without overt neurologic deficits, similar to the presentation associated with cerebral aneurysms. In some cases, bruits are audible upon auscultation over the bony spine.

DIAGNOSTIC EVALUATION

When a spinal arteriovenous malformation is suspected, MRI of the spinal cord is first needed to make the diagnosis and to obtain a general idea of the location of the lesion (Fig. 646.11). MR angiography or CT angiography may provide further information, but formal catheter angiography of the spinal cord is needed to obtain an adequate understanding of the complex anatomy of the lesion and to plan the intervention.

TREATMENT

Open microsurgery had been the mainstay of treatment for spinal cord arteriovenous fistulas and arteriovenous malformations. With the rapid development of interventional techniques, the percentage of patients undergoing microsurgery has decreased from 70% to approximately 30%. Stereotactic radiosurgery may be used adjunctively. Treatment of these complex lesions requires the commitment of an organized neurovascular treatment program.

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