Symptom-Based Approach to Pediatric Neurology

Deepak M. Kamat
Lalitha Sivaswamy
Editors

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Preface

The brain and its connections unarguably constitute the most complex of all human organ systems. While an adult brain weighs a little over a kilogram, it houses over 85 billion neurons and contains miles of axons. It can generate complex emotions, allows us to imagine, strategize, and carry out a myriad of functions, and controls every aspect of our awake or sleeping life. Given the complexity of the nervous system, it is natural that symptoms that refer to the central or peripheral nervous system can lead to concern on the part of the caregiver and the pediatrician.

This book was conceptualized by a child neurologist (LS) and an academic pediatrician (DK) with clinical experiences in a wide variety of settings. We bring the unique perspectives of both fields to this book. When a newborn or a child has a symptom that might have a neurological basis, it may be most reassuring to consult with a colleague in neurology. However, that may not be practical in all settings. Further, parents may do their own "research" and obtain information from non-medical sources that they bring to the discussion. While imaging has indeed revolutionized neurology as we know it, the primary care physician must still obtain a relevant history and conduct a pertinent physical examination to provide the best care. This book has been formulated keeping the primary care physician's workflow in mind. Dispensing with the traditional "where is the lesion" and "what is the lesion" model of neurology, where one presumes a thorough knowledge of neuroanatomy and clinical correlates, we chose to proceed with the more practical "what is the story" and "what do I see on my examination" to arrive at a diagnosis.

We invited experts in the field to contribute to each chapter and asked that they place themselves in the shoes of the primary care doctor. We tried to avoid jargon, cumbersome neuropathological correlates, and in-depth reviews of disease processes—making the assumption that after making a presumptive diagnosis, the physician may choose to refer the patient to a specialist and/or continue to provide care alongside a specialist. We have placed an introductory chapter on how to conduct a neurological examination in children of different age groups that we hope the primary care physician will review this before reading individual chapters. We also outlined common neurological investigations and their interpretation—as results of imaging and EEG are often reviewed by parents on the electronic portal—even

before the physician may have looked over them, leading to anxious calls! There are numerous tables that one can consult quickly. The differential diagnosis section is comprehensively laid out as the relevant question at the end of any clinical encounter (especially with a neurological symptom) is “did I miss an important condition?”

Conditions such as concussion, a child with febrile seizures or first-time seizures, cerebral palsy, and functional neurological disorders will be encountered by every primary care doctor. On the other hand, neurocutaneous syndromes and autoimmune encephalitis may not. Nonetheless, a working knowledge of such conditions will allow primary care doctors to triage, refer, and start the investigative process with confidence. Considering that most children with neurological conditions will be evaluated and managed by primary care physicians, we believe that this book may be helpful in providing comprehensive care to such families.

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Neurological Examination of Children

Lalitha Sivaswamy

1 Introduction

The neurological examination is often considered challenging [1]. Since the nervous system is the most complex of all systems, a comprehensive neurological examination involves many components which may be difficult to perform in an anxious/uncooperative child [2]. Further, the examination should be tailored to the age and developmental stage of the child. While the history can help the clinician focus on certain portions of the neurological examination, it is important to conduct a complete neurological examination on every child who presents with a symptom referable to the nervous system. The nervous system is traditionally divided into the examination of the upper motor neuron pathway, i.e., brain and spinal cord and the lower motor neuron pathway, i.e., the anterior horn cells, plexus, peripheral nerve, neuromuscular junction, and muscle.

This chapter will review salient aspects of the neurological examination in infants, young children, and adolescents. The older the child, the more the examination will resemble that of an adult and technically should be easier to perform. Nonetheless, adopting a streamlined approach will avoid overlooking important physical clues that can guide decision-making and further investigations or referrals.

In addition, one must also perform a thorough general physical examination including assessment of vital signs with emphasis on examination of the skin, facial appearance, and limbs as well as measuring the head circumference. Important clues on the general examination that can guide the clinician toward a neurological diagnosis are noted in Table 1.

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Table 1 Important clues on general physical examination for neurological diagnosis

Physical examination finding	Possible implications
Head circumference (large or small for age per CDC growth chart)	Microcephaly (see Chap. 25) Macrocephaly (see Chap. 25)
Large anterior fontanel for age Bulging fontanel in sitting posture	Genetic syndromes Raised intracranial pressure
Overlapping sutures	Craniosynostosis
Facial nevus	Sturge–Weber syndrome (see Chap. 31)
Differences in color of iris Ptosis	Congenital Horner's syndrome Congenital or acquired Horner's syndrome/myopathy/disorders of the neuromuscular junction
Skin Nevi (café au lait spots of hypopigmented macules)	Neurocutaneous syndromes (see Chap. 31)
Unusual hair texture	Menke syndrome
Facial appearance Midline defects (single central incisor, midline cleft lip) Facial dysmorphisms (widely spaced eyes, unusual eye folds) Tenting of upper lip	Brain malformations Genetic syndromes Myopathy or muscular dystrophy
Differences in size of the limbs Calf hypertrophy	Perinatal or in-utero stroke Genetic syndromes Muscular dystrophy
Organomegaly (hepatomegaly or splenomegaly)	Inborn errors of metabolism
Scoliosis /kyphosis	Neuromuscular disorders/cerebral palsy
Tuft of hair or sacral dimple	Tethered cord or other malformation of the spinal cord
Ptosis or facial weakness more prominent at the end of the day	Neuromuscular disorders

CDC Center for Disease Control and Prevention

One can gain useful information while observing the child during the history. Children may feel self-conscious when attention is focused on them (as during the physical examination). Therefore, observing the child while the parent or the child is providing the history allows the clinician to note any unusual mannerisms, language deficits, articulation problems, or gait disturbances. Last but not least, while the examination is described as separate components below, there is significant overlap and one must remain flexible and initially perform the components that are least intrusive to gain the trust of the child (and parent). Placing the child at ease at the outset by stating that there will be no pain during the process and allowing them to hold or play with the examination tools may save the clinician a significant amount of time and effort and yield more reliable results. Whenever possible and appropriate, the child should be seated on the parent's lap or next to the parent, at least at the beginning of the examination. Finally, video recordings of the child may prove invaluable in complementing the physical examination.

2 Neurological Examination of Infants

(a) Tools

Flexible measuring tape
Bright object that makes no sound
Tendon (reflex) hammer suitable for an infant
Bright light (pen light or ophthalmoscope)

(b) Steps

Higher mental functions:

Is the baby alert? If asleep does she arouse to tactile stimuli or noise? If crying is she consolable? Does she smile at the parent? Does she look around the room and at you when you speak? Does she coo and babble? Does she make eye contact?

Cranial nerves:

I (Olfactory): not typically examined

II (Optic): Examination of the fundus is not possible in most instances.

Look for red reflex in both eyes. Infants with vision should respond to rapid movement of a hand towards the eyes by closing them as a protective response (response to "threat").

III, IV, VI (Oculomotor, Trochlear, and Abducens): are classically examined together since they control eye movements. Observe if the eyes move horizontally and vertically by moving a bright object in front of them. It is important to stay silent during this portion as the baby may turn her head to sound rather than the object. Try to assess pupillary size. This is better performed in a dark room. Corneal light reflex can help to assess for symmetry of eyes.

V (Trigeminal): difficult to assess in infants but one can gently touch both sides of the face to see if the baby reacts.

VII (Facial): is easy to examine as most babies cry at some point during the examination. Look for facial symmetry at the angle of the mouth and forehead.

VIII (Vestibulocochlear): finger rub is the best way to assess hearing informally at the bedside. The baby should turn head to sound by 4–6 months of age.

IX, X (Glossopharyngeal, Vagus): should be left to the end as gagging the baby at the beginning of the examination may make the rest of the examination challenging.

XI (Accessory): cannot be reliably assessed.

XII (Hypoglossal): If the baby cries one may obtain a quick look but cannot be reliably assessed in most instances. One may assess for tongue fasciculations as that leads the clinician to certain disorders such as spinal muscular atrophy.

Motor Examination:

Bulk: Observe the baby when undressed. Look for asymmetry in bulk between the right and left sides.

Tone: passively flex and extend all joints. Look for increased or reduced tone. Place the baby in horizontal suspension (face down) across your arms and see if she can hold her head up. Hold the baby up while supporting her shoulders and see if she "slips through" or can hold herself up. Look for head lag by placing her on the table and drawing her up to sitting position.

Strength: cannot be formally assessed at this age. Place a bright object overhead and see if she can reach out with both hands. Can she hold her bottle? Does she have an equal pincer grasp in both hands? Can she sit independently?

Range of Motion: observe the baby kick her legs and move her arms. Observe her crawling on the floor.

Gait: if the baby is walking or cruising taking the time to observe the gait can be very helpful.

Sensory Examination:

Unreliable at this age.

Deep Tendon Reflexes/Plantar Response:

Swing the reflex hammer while holding it at the bottom of the handle. At this age, the patellar and brachioradialis tendon reflexes are easily elicitable. The baby should ideally be resting calmly while tendon reflexes are being assessed. At this age, most babies have a bilaterally positive Babinski sign, i.e., great toes go up while stroking the lateral aspect of the feet; however, it becomes a reliable sign after the infant starts walking.

Developmental Assessment and Primitive Reflexes:

The developmental assessment is a conglomerate of the above components. Table 2 outlines the important developmental milestones and developmental reflexes in an infant. The disappearance of certain reflexes is as important as their appearance. Using a standardized tool such as the Bayley Scale of Infant Development is important to ensure all aspects of development are on target [3].

Table 2 Developmental reflexes

Reflex	Appears/disappears	Possible implications of absence/persistence
Sucking/ rooting	Birth/2–4 months	Absence—hypotonia/Persistence—frontal lobe dysfunction
Moro	Birth/4 months	Asymmetry—brachial plexus injury/Persistence—inborn errors of metabolism[a]
ATNR	Birth/2–3 months	Absence—limb weakness/Persistence—upper motor neuron disease process
Parachute reflex	8 months/never disappears	Asymmetric—limb weakness/Absence—hypotonia or upper motor neuron disease
Spinal incurvature	Birth/2–4 months	Absence—spinal cord pathology
Palmar grasp	Birth/5–6 months	Absence—hand weakness/Persistence—upper motor neuron disease process
Plantar grasp	Birth/6–10 months	Absence—limb weakness/Persistence—upper motor neuron disease process

ATNR asymmetric tonic neck reflex

[a]Tay Sach's disease may have persistence of Moro and exaggerated startle response

3 Neurological Examination of a Preschool-Aged Child

(a) Tools

Flexible measuring tape
Bright toy that makes no sound
Tendon (reflex) hammer
Bright light
Ophthalmoscope
Crayon or pen

(b) Steps

Higher Mental Functions: Is the child making eye contact? Is she talking? Does she have stranger anxiety? Is she exploring her environment? Is she paying attention to the conversation?

Cranial Nerves:

I (Olfactory): not typically examined

II (Optic): Examination of the fundus maybe possible in certain instances. Have the child focus at a distant object and darken the room to attempt fundus examination.

Look for red reflex in both eyes.

III, IV, VI (Oculomotor, Trochlear, and Abducens): See if the eyes move horizontally and vertically by moving a bright object in front of them. Instruct the child to hold their head in the neutral position or hold the child's head steady with one hand while you test eye movements using a toy held in the other hand. Look for restriction of eye movements or nystagmus. Look for symmetry of pupillary light response in a dark room.

V (Trigeminal): one can gently touch both sides of the face to see if the child reacts.

VII (Facial): have the child show their teeth, shut their eyes tightly and wrinkle their forehead. Look for facial symmetry at the angle of the mouth and creases of the forehead. One should not be able to open the eyes of a child who is closing them tightly.

VIII (Vestibulocochlear): finger rub is the best way to assess hearing informally at the bedside.

IX, X (Glossopharyngeal, Vagus): gag reflex need not be tested in all cases. Having the child say "aah" and looking at palatal symmetry often suffices.

XI (Accessory): examine shoulder shrug and strength of the sternocleidomastoid muscles.

XII (Hypoglossal): have the child initially open their mouth but not stick their tongue out. Look for fasciculations or atrophy. Then have the child move the tongue side to side outside the mouth.

Motor Examination:

Bulk: Look for asymmetry in bulk between the right and left sides.

Tone/Range of Motion: passively flex and extend all joints. Look for increased or reduced tone. May have to distract the child by chatting with them as children tend to tense up during the examination. One must pay special atten-

tion to the ankle joint as tightness at this joint is often overlooked. The child must remove their shoes for this part of the examination.

Strength: can be formally assessed in major muscle groups by playing a game of "show me how strong you are" involving the major muscles of the arms and legs. In most instances, formal assessment is not required if one can observe the child moving around and using her limbs appropriately. Observe if the child can jump in place, stand on one foot, and hold a crayon to draw.

Finger to Nose and Finger to Finger Test: most children can participate in this test if the parent performs it first. Look for intention tremor i.e. tremor that worsens as the child's finger approaches a target, e.g., your finger. Having the child give "high 5" by holding your hand well above their head may achieve similar results.

Gait: observe the child walk into the examination room or walk out if they refuse to walk during the neurological examination. Does the child drag one foot? Does she hold an arm awkwardly when she walks?

Sensory Examination:

Use light touch to assess for sensory loss in the limbs and trunk. Romberg's sign is a test of sensory information that is being transmitted to the spinal cord from the lower limbs and can be assessed by asking the child to close their eyes and stand with their feet together. An unsteady child should be reassessed in a few minutes to ensure reproduction of the findings.

Deep Tendon Reflexes/Plantar Response:

Distract the child while checking the tendon reflexes or have her clench her teeth during examination of the upper extremity and lock their hands while checking reflexes in the lower extremities. Positive Babinski sign or upgoing plantar response is pathological beyond the age of 24 months (especially if asymmetric) but must be interpreted in the context of the rest of the neurological examination.

Developmental Assessment/Primitive Reflexes:

Most primitive reflexes should have disappeared by the age of 12 months except for the parachute response that persists throughout life.

4 Neurological Examination of a School-Aged Child

(a) Tools

Tendon (reflex) hammer

Ophthalmoscope

Grade Appropriate Reading Material (most magazines are at an 8th—9th grade level).

Pen/Pencil and Paper

(b) Steps

Higher Mental Functions:

Since the child may be a 1st grader or a senior in school this part of the examination needs to be modified per the grade and perceived cognitive abilities of the child.

Is the child oriented to time, place, and person? Does she participate in the history and interview? Does she have a general fund of knowledge that is age appropriate, e.g., does she know the capital of the state she lives in; does she know who the President of the United States is; or does she know her home address? Can she perform grade level arithmetic, e.g., addition or multiplication?

Affect: does she look sad or withdrawn?

Language: can she name common objects (glasses, watch, identification badge); can she comprehend multistep instructions and carry them out? Can she read grade level material and explain it to you? Are her sentences well-constructed and grammatically correct?

Memory: mention 3 objects and have her repeat them back to you at the end of the examination. Inform them that this is a test of memory and you will ask her to repeat them in the next 10–15 min.

Cranial Nerves:

I (Olfactory): not typically examined.

II (Optic): Examination of the fundus is possible in most instances. Have the child focus at a distant object and darken the room to attempt fundus examination. Bedside tests of visual fields can be performed in a cooperative child. The child should look only at your eyes during the test. Try to test each eye individually if you suspect any issues with the visual fields. Use a hand-held card to assess visual acuity in each eye. Make sure the child is wearing glasses if they normally do so.

III, IV, VI (Oculomotor, Trochlear, and Abducens): See if the eyes move smoothly in the horizontal and vertical plane by using a bright light or your finger. Instruct the child to hold their head in the neutral position or hold the child's head steady with one hand while you test eye movements using a light held in the other hand. Look for restriction of eye movements/unusual movements or nystagmus. Look for symmetry of pupillary light response in a dark room.

V (Trigeminal): gently touch both sides of the forehead, both cheeks, and angle of the mouth and ask if it feels the same on both sides. Do not touch the angle of the jaw as that part of the face is not supplied by the trigeminal nerve.

VII (Facial): have the child show their teeth, shut their eyes tightly and wrinkle their forehead. Look for facial symmetry at the angle of the mouth and creases of the forehead. One can also have them puff their cheeks up.

VIII (Vestibulocochlear): finger rub is the best way to assess hearing informally at the bedside.

IX, X (Glossopharyngeal, Vagus): Having the child say "aah" and look for palatal symmetry.

XI (Accessory): examine shoulder shrug and strength of the sternocleidomastoid muscles bilaterally.

XII (Hypoglossal): examine the tongue while resting in the mouth. Look for fasciculations or atrophy. Have the child move the tongue side to side outside the mouth and test formally for strength by having them nudge the inside of the cheek with the tongue.

Motor Examination:

Bulk: Look for asymmetry in bulk between the right and left sides. Have the child undress for a more formal assessment of bulk of the scapular muscles when appropriate.

Tone/Range of Motion: passively flex and extend all joints. Look for increased or reduced tone.

Strength: can be formally assessed in major muscle groups by demonstrating what you want the child to do: e.g., "flex your elbow and do not let me extend it" to assess for strength of the biceps and "raise your foot towards your nose and do not let me push it down" to assess for strength of the anterior compartment of the leg. If the child has cognitive impairment one can use the same techniques one uses for a younger child as noted in the section above.

Finger to Nose and Finger to Finger Test: provides useful information regarding all aspects of the motor examination of the upper extremity. It is important that your finger be sufficiently far away that the child must stretch out to touch it. Look for intention tremor, i.e., tremor that worsens as the child's finger approaches a target, e.g., your finger.

Gait: observe the child walk in the hallway and have them heel-walk, toe-walk, and tandem walk. Wide based gait or unsteady gait may be indicative of disorders of the cerebellum. Conversion disorders can present with unusual gait disturbances [3].

Sensory Examination:

Use light touch to assess for sensory loss in the limbs and trunk. One may use a disposable pin in cases of suspected neuropathy and vibrating tuning fork if the clinician has one handy. Romberg's sign should be assessed in all children of this age. A positive Romberg's sign is indicative of an abnormality in the sensory pathways [4]. Romberg's sign can be elicited by asking the child to close their eyes and stand with their feet together. The examiner must look for swaying movements or fall to one side. One must stand close to the patient to avoid any actual falls.

Deep Tendon Reflexes/Plantar Response:

Distract the child while checking the tendon reflexes or have her clench her teeth during examination of the upper extremity and lock their hands while checking reflexes in the lower extremities. Asymmetry in plantar response (upgoing toe with fanning of the remaining toes) is usually pathological at this age.

5 Special Maneuvers and Important Pointers

Drift: in cases of suspected stroke or limb weakness have the child extend their arms out as if holding a big box and have them close their eyes for about 30 s. The weak limb will drift downward and inward (pronator drift).

Tremors: have the child pour water from one cup to another to assess for tremors if tremors are not apparent during the general examination but it is a symptom of concern. Having the child hold their arms out and placing a sheet of paper on their outstretched hands can also bring out fine tremors.

Examination of the Cerebellum: wide-based gait, truncal ataxia, tremors of the outstretched fingers (intention tremors), clumsiness during rapid repetitive movements of the fingers and toes, inability to perform the heel-shin test, and articulation problems (have the patient repeat a sentence, e.g., "the red fox jumped over the lazy dog") may indicate a disorder of the cerebellum [5].

Maneuvers to assess for dizziness: Dix–Hallpike test as described in Chap. 28.

Plantar Reflex: use a tongue depressor to stroke the lateral aspect of the foot and across the foot pads. Look at the big toes and the rest of the toes. If Babinski's sign is present, it should be reproducible.

Abnormal Movements: look for unusual movements when the child is comfortable and possibly distracted. One may notice tics, tremors, or chorea. Seizures may be noted during any part of the examination and may consist of lip-smacking, staring off, or facial twitching.

Kernig's sign: have the patient lay flat. Flex the hip and knee. Try to extend the knee with the hip flexed. Resistance to knee straightening indicates meningeal irritation.

Brudzinski's sign: have the patient lay flat. If flexion of the neck causes flexion of the hip and knees it indicates meningeal irritation.

6 Clinical Pearls/Key Points

- The neurological examination should be tailored to the age of the child. The younger the child, the more unstructured the examination tends to be. However, care must be taken to incorporate all essential components, while ensuring the child does not feel threatened. Sometimes useful information can be obtained by viewing home videos recorded on mobile phones.
- Observation of the child during the interview and while she is playing can provide useful pointers.
- Proceeding in a methodical manner becomes easier as a child gets older and can participate in the process. The classic approach to a basic neurological examination is outlined above.

- Essential tools such as a measuring tape, bright light, colorful toys and a reflex hammer can ensure a comprehensive examination.
- Special maneuvers may be required depending on the history and circumstances.

References

1. Jan MM, Al-Buhairi AR, Baeesa SS. Concise outline of the nervous system examination for the generalist. Neurosciences (Riyadh). 2001;6(1):16–22.
2. Jan MMS. Neurological examination of difficult and poorly cooperative children. J Child Neurol. 2007;22(10):1209–13.
3. Bayley N, Aylward GP. Bayley scales of infant and toddler development screening test. 4th ed.
4. Baker JM. Gait disorder. Am. J. Med. 2018;131(6):602–7.
5. Fuller G. Neurological examination made easy. 4th ed. Churchill Livingston Elsevier.

Child with Altered Mental Status

Katherine Cashen, Amarillis Martin, and Ahmed Aly

1 Introduction

Altered mental status is a term used to describe alterations in a child's interaction with their environment. This broad term encompasses a variety of diagnoses—some of which cause transient alterations in mental status, and others that are permanent. Levels of consciousness can vary from subtle alterations with decreased awareness of self/environment to a state of coma in which a person is unresponsive to all stimuli. Alterations in consciousness include confusion (a loss of clear thinking or inappropriate response to the environment) and clouding of consciousness or reduced wakefulness or awareness [1]. Lethargy or somnolence is a sleeplike state in which a child can be aroused with moderate external stimulation. Stupor is a minimally conscious state in which a patient can only be aroused with vigorous and continued stimulation [2]. Finally, a child who is unresponsive even to painful stimulation with eyes closed is in a coma. If this state continues,

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the unresponsive patient usually develops periodic eye opening and progresses to a vegetative state.

This terminology for alterations in consciousness is not standardized and terms such as encephalopathy are used to describe altered states of consciousness, altered cognition with personality change, and even seizures. Delirium is a mental state characterized by reduced clarity or awareness of the environment, inability to focus, change in cognition, disorientation, and in some children mental and motor excitement and agitation [2]. Thus, the number of terms used to describe alterations in consciousness can be very confusing for clinicians. Normal consciousness and behavior are not only person-specific but also age-specific [1]. Assessing alterations in consciousness and behavior in children can be challenging for an examiner who is not familiar with the child. Parents and caregivers play a key role in this assessment. In this chapter, we discuss the epidemiology, etiology, differential diagnosis, diagnostic approach, treatment, and prognosis for children with altered mental status.

2 Epidemiology

Altered mental status is more common in the adult population with 1–5% of all emergency department visits noting this to be the chief complaint [3, 4]. In pediatric patients, the epidemiology is not well reported. The most common causes of altered mental status in children are infection, trauma, metabolic derangements, and toxic ingestions with different prevalence in different age groups. Even the epidemiology of altered mental status due to central nervous system (CNS) infection differs based on location, with children in low-income countries having higher incidence than children in high-income countries [5].

3 Etiology

The differential diagnosis for altered mental status is broad and separating the different causes into categories may aid the clinician. One way to categorize the causes of altered mental status is to think of the areas of the brain that are responsible for arousal and consciousness. The ascending reticular activating system mediates arousal. Neurons in the ascending reticular activating system located in the midbrain, pons, and medulla control arousal from sleep and stimuli processed through sensory input are controlled by the cerebral hemispheres. Alterations in consciousness are due to abnormalities in either the cerebral hemispheres, in the ascending reticular activating system, or global CNS dysfunction (abnormalities in both the ascending reticular activating system and the cerebral hemispheres) [2].

Two commonly used mnemonics for the differential diagnosis of altered mental status include VITAMINS and AEIOU TIPS (Table 1). In general, for pediatric patients, a primary intracranial disease process (structural cause or central nervous system infection), systemic disease affecting the central nervous system, and ingestion/toxins are most common. In Table 2, we differentiate the most common causes of altered mental status by age at presentation. Important considerations in the history and physical examination will help guide the clinician toward important etiologies.

Table 1 Mnemonics for altered mental status

Vitamins		Aeiou tips	
V	**Vascular** – Arteriovenous malformation – Systemic vasculitis	**A**	Alcohol Abuse of substances
I	**Infection** – Meningoencephalitis – Meningitis – Sepsis	**E**	Epilepsy Encephalopathy Electrolyte abnormalities Endocrine abnormalities
T	**Toxin** – Environmental – Medication **Trauma** – Accidental – Abusive	**I**	Insulin Intussusception Intracranial space occupying lesion
A	**Autoimmune/inflammatory disorders** – Lupus	**O**	Overdose Oxygen deficiency
M	**Metabolic** – Hypoglycemia – Diabetic ketoacidosis – Hyper/hypothyroidism – Metabolic encephalopathy	**U**	Uremia
I	**Intussusception** **Iatrogenic**	**T**	Trauma Temperature abnormality Tumor
N	**Neoplasm**	**I**	Infection
S	**Seizure** – Especially subclinical status epilepticus	**P**	Poisoning Psychiatric condition
		S	Shock Stroke

Table 2 Altered mental status: Common causes by age

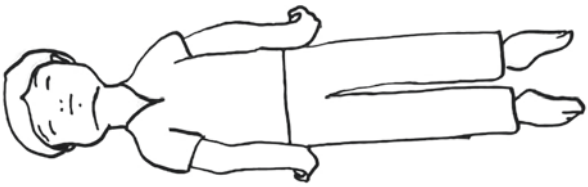
	Neonates—Infants	Toddlers—School-aged children	Adolescents	Any age
Primary intracranial process	Perinatal stroke Congenital malformation Hydrocephalus Cerebral vein thrombosis		Pseudotumor cerebri	Cerebral vein thrombosis Hemorrhagic stroke – Hypertensive crisis – Vascular malformation rupture Ischemic stroke Neoplasm Obstructive hydrocephalus Central nervous system vasculitis
Infectious/ inflammatory/ postinfectious	Sepsis Meningoencephalitis	Autoimmune encephalitis Meningoencephalitis	Autoimmune encephalitis Meningoencephalitis	Brain abscess Meningoencephalitis Acute demyelinating encephalomyelitis N-methyl-D-aspartate (NMDA) receptor antibody encephalitis Coronavirus disease 2019
Metabolic/endocrine	Hypoxia Kernicterus	Wernicke encephalopathy	Wernicke encephalopathy Diabetic ketoacidosis Hyperglycemic hyperosmolar syndrome Hepatic encephalopathy Hypo/hyperthyroidism	Acidosis Electrolyte imbalance Hyperammonemia Hypoglycemia Inborn errors of metabolism Uremia
Toxic ingestion/ exposure		Accidental ingestion Heavy metal poisoning	Intentional ingestion/overdose Substance use/abuse	Carbon monoxide poisoning Supratherapeutic levels of prescribed medications (seizure medications, psychiatric medications, etc.)
Trauma	Birth Abusive head trauma		Accidental trauma – Intracerebral, epidural, subdural bleeding – Diffuse axonal injury	Accidental/abusive – intracranial hemorrhage – concussion
Cardiovascular	Global hypoxia/ hypoperfusion – Congenital heart disease (CHD)	Hypertensive encephalopathy	Hypertensive encephalopathy	Global hypoxia/Hypoperfusion – Asphyxia or shock – Cardiopulmonary arrest Embolic stroke (child with CHD)
Environmental				Heat stroke/hypothermia High altitude cerebral edema
Other	Maternal drug use withdrawal	Intussusception	Psychiatric illness Psychogenic Drug withdrawal	Delirium Seizures/postictal state Posterior reversible encephalopathy with seizures (PRES)

4 Diagnostic Approach

4.1 Initial Approach and Acute Stabilization

The differential diagnosis for altered mental status is broad and the first steps in evaluating a child with altered mental status should focus on a determination of whether the situation is an emergent clinical scenario that requires basic life support (BLS) measures, or whether the patient is stable enough for a detailed history and physical examination. In a child with transient alteration in mental status who recovers to their baseline prior to or during clinical evaluation, the cause of alteration in mental status is likely benign. A detailed history and physical examination including a complete cardiac and neurologic examination are important. If the history is suggestive of a benign diagnosis and the detailed examination is normal, in most cases, the child can be discharged home. One example is a breath-holding spell in an infant or young child (6 months–6 years of age; most commonly around 18 months). These children usually present with transient alteration in mental status or brief period of unresponsiveness and are back to their baseline mental status during examination. The physical examination is otherwise normal and they may be sent home without a period of observation after parental counseling [6]. Other benign causes of transient alterations in mental status include simple febrile seizures and brief unexplained life-threatening events. In the child with simple febrile seizure, an evaluation of the cause of fever is important but if the child has returned to his/her baseline mental status and the physical examination is reassuring (depending on the age and evaluation for infection), the child does not require prolonged observation or admission [7]. Brief unexplained events (BRUE) are defined as a sudden, brief, now resolved episode in an infant <1 year of age who has one or more of the following: cyanosis or pallor, absent or decreased breathing, marked change in tone, or altered level of responsiveness without another explanation for the symptoms [8]. The American Academy of Pediatrics Clinical Practice Guideline suggests that infants who met criteria for being "lower-risk" (age >60 days, born >32 weeks gestation, no CPR by trained medical provider, event <1 min, first event) with reassuring physical examination and history should be monitored for a brief period and then discharged with education to caregivers and a scheduled follow-up visit [8]. In an older child, syncope is the most common cause of transient altered mental status and is usually benign [6]. Detailed history and cardiac examination is important for these patients because potentially fatal arrhythmias or undiagnosed structural or functional heart disease must be ruled out [6].

In children who are comatose with no response to painful stimulation initial measures include checking circulation, airway, and breathing [9]. If a child is unstable, activation of the emergency response system, initiation of BLS, and, if feasible, pediatric advanced life support (PALS) are the most critical first steps. Identification of signs of increased intracranial pressure (ICP) is very important in initial assessment of a child with altered mental status because treatment should be initiated immediately. Some of these signs include unilateral or bilateral midpoint or dilated



Decerebrate posturing

Decorticate posturing

Fig. 1 Depiction of decerebrate and decorticate posturing

unreactive pupils, papilledema, hyperventilation or slow irregular gasping respirations, child is unresponsive to pain, or has decorticate-flexor/decerebrate-extensor posturing (Fig. 1). Cushing's triad (bradycardia, hypertension, and irregular deep respirations (Cheyne–Stoke's breathing)) is a finding suggestive of impending herniation. The clinician should not be falsely reassured that a child has normal ICP if there is no bradycardia or hypertension [10].

For the child with adequate circulation and a stable airway, who is breathing comfortably without signs of increased intracranial pressure, a detailed history and physical examination should be performed to help guide evaluation and management.

4.2 History

Depending on the age and mental status of the child, the caregiver/parent will provide the majority of the history. In certain situations, the clinicians may need to reach out to caregivers who were with the child at the time of onset of the symptoms. Important questions including pre-existing neurological status, development, birth, and medical history should be asked [11]. Detailed timing of symptoms, exposures, medication history with details of medications or drugs that the patient has access to, and history regarding accompanying symptoms including fever, preceding viral illness, vomiting, headache, history of seizure, and trauma even if the parent considers it minor, should be elicited. Family history of neurologic, metabolic, vascular disease, and parental consanguinity is important. Social factors including who cares for the child and the temporal relationship with symptoms including other social risk factors for abusive head trauma may be important as well as any previous history of abuse.

4.3 Physical Examination

4.3.1 General Examination

The physical examination starts with observation of the child and the child's response to the environment. Next, review of the vital signs can help guide the clinician in development of a differential diagnosis. Fever often points to an infectious process but can be associated with anticholinergic poisoning too. Bradycardia may be seen with increased ICP but also with ingestion (clonidine, beta-blockers), hypoxia, and hypothermia. Tachycardia may be seen in shock, during seizures (which may be subclinical and not noted during the examination), with increased ICP, and associated with fever. Tachypnea can be a sign of acidosis (from shock, sepsis, diabetic ketoacidosis, or inborn errors of metabolism) or increased ICP. Apnea may be a sign of increased ICP, herniation, or toxic ingestion. Hypertension can be seen with increased ICP, hypertensive encephalopathy, posterior reversible encephalopathy, seizures, and toxic ingestions (e.g., amphetamines, cocaine). Complete physical examination should be performed. Findings of rash, neurocutaneous findings, signs of trauma, or hepatomegaly may focus the differential diagnosis on systemic illnesses. Findings of injection marks may guide the clinician toward a diagnosis of drug injection/ingestion as would findings such as diaphoresis or dry skin and the quality and frequency of bowel sounds may lead toward certain ingestions. Certain systemic diseases are characterized by distinctive body odors ("fruity breath" in patients with diabetic ketoacidosis, select inborn errors of metabolism {"sweet smell" in maple syrup urine disease or a "musty" odor in infants with phenylketonuria, etc.}). Thus, complete physical examination with a focus on specific nuances is important for children with altered mental status.

4.3.2 Neurologic Examination

The Glasgow Coma Scale (GCS) is the most widely used scale for assessing alterations in mental status [12]. Table 3 shows the scale and the modified scale for children less than 5 years old [13]. The GCS can be a more objective assessment of mental status than the previously described terms (stupor, confusion, etc.). This should be done almost simultaneously while assessing vital signs. Neurologic examination in a patient with delirium (agitation, hallucinations, exaggerated response to noise or pain) may be challenging. Complete neurologic examination should include assessment of level of consciousness in addition to mental status as described above. Mental status and sensory/motor testing that requires participation is typically not feasible in children with significant alterations in mental status. Next, cranial nerve examination should be performed with a special focus on pupillary, funduscopic examination, and eye movements. Pupillary examination should focus on shape, size, symmetry, and reactivity. Pupils that are poorly responsive to light, irrespective of size may suggest exposure to drugs or toxins. On the other

Table 3 Glasgow Coma Scale and modified Glasgow Coma Scale

>5 years of age	**1**	**2**	**3**	**4**	**5**	**6**
Eye opening	None	To pain	To voice	Spontaneous		
Verbal	No response to pain	Incomprehensible sounds	Inappropriate words	Confused	Oriented	
Motor	No response to pain	Extensor movements to pain	Flexor movements to pain	Withdraws to pain	Localizes to pain	Obeys commands
<5 years of age	**1**	**2**	**3**	**4**	**5**	**6**
Eye opening	None	To pain	To voice	Spontaneous		
Verbal	No response to pain	Moans to pain	Cries to pain	Less than usual ability, irritable cry	Alert, babbles, coos, words or sentences normal	
Motor	No response to pain	Extensor movements to pain	Flexor movements to pain	Withdraws to pain	Localizes to pain	Normal spontaneous movements

hand, unilateral pupillary dilation with poor response to light may be suggestive of uncal herniation. Papilledema suggests increased ICP. However, absence of papilledema does not rule out early increased ICP because it may take hours to develop [14]. Funduscopic examination may show retinal hemorrhages (concerning for abuse or other traumatic injury). Eye examination suggestive of nystagmus or deviation of the eyes may suggest subtle seizures or ingestion. Motor exam should focus on subtle weakness and determination of whether patterns of weakness can distinguish between specific etiologies (eg. stroke). Reflexes should be tested to determine if there are upper motor neuron signs. In an altered child, it may be difficult to assess cerebellar function; one method to detect truncal ataxia is to sit the child up in bed. Nonetheless, any child with altered mental status may demonstrate what appears to be truncal ataxia and therefore this finding must be placed in the context of the rest of the physical examination. Sensory examination is likely to be unreliable in a child with altered mental status. A prepubertal child with delirium should have organic encephalopathies (infection, ingestion, autoimmune, CNS lesions) ruled out prior to consideration of schizophrenia or a psychiatric diagnosis. Focal findings on neurologic examination are important to attempt to localize the lesion to a specific area of the brain. The goal of the clinician is to combine information from the history and physical examination to create a differential diagnosis and determine testing needed to diagnose and treat the condition.

4.4 Evaluation

4.4.1 Laboratory

Initial testing should include serum glucose and electrolytes with blood urea nitrogen and creatinine. History and physical examination will dictate additional testing. In general, serum and urine toxicology, blood gas measurement, liver function tests, serum ammonia, complete blood count, blood culture, and urinalysis are indicated for a child with persistent altered mental status and unclear history [15]. If the child has other symptoms of infection, a more detailed evaluation for infection may be indicated. A lumbar puncture should be performed if there is concern for meningitis or encephalitis as long as there are no contraindications (unstable patient, coagulopathic or thrombocytopenic patient, signs of increased ICP, focal neurologic signs). In children with known seizure disorders on antiepileptic medications, drug levels should be measured.

4.4.2 Neuroimaging

Computed tomography (CT) is important to detect increased intracranial pressure, identify tumors, trauma, hydrocephalus, and hemorrhage. CT is not sensitive at identifying lesions in the posterior fossa, may not identify stroke or early diffuse injury, and exposes the child to radiation. Therefore, assessment of risks and benefits in the context of the clinical presentation, history, and physical examination are important.

Magnetic resonance imaging (MRI) should be performed in a child with coma or persistent alteration of mental status. MRI is useful in diagnosing stroke, encephalitis, demyelinating disease processes, smaller tumors, and posterior fossa tumors that may not have been detected by CT. Magnetic resonance spectroscopy can identify features of specific inborn errors of metabolism. Magnetic resonance venography (MRV) and magnetic resonance angiography (MRA) may be necessary in certain clinical situations. The main drawback of MRI testing is the longer duration required to perform the examination so the patient should be stabilized prior to transport to the MRI suite. In addition, uncooperative (due to age, delirium, etc.) children may need sedation to have an MRI performed.

4.4.3 Electroencephalogram

Electroencephalogram (EEG) can help in identification of subclinical status epilepticus in a child with altered mental status. EEG can help localize a focal area of slowing which may be indicative of certain disorders such as herpes simplex

encephalitis or focal pathology such as a tumor. EEG is noninvasive and usually well tolerated. The challenge is that pediatric EEGs may not be readily available in community settings and specialized interpretation is required.

5 Treatment/Management

After acute stabilization of a child with persistent alteration in mental status as described in the initial approach/acute stabilization section, treatment should focus on identifying the underlying cause of alteration in mental status. An important next step is determining whether the child can be cared for in an inpatient setting at the current facility or requires transfer to an acute care or tertiary care pediatric facility. Certain recommendations may dictate where the child would receive the best care. For example, many children require cardiac telemetry after toxic ingestion and this is not available in all settings even if the child's mental status is improving.

In a child with suspected narcotic ingestion with pinpoint pupils, slowed respiratory rate, and altered mental status, a dose of naloxone should be considered. The state poison control center can provide guidance in the evaluation and treatment for children with suspected ingestion. Correction of hypoglycemia, hypoxia, hypotension, and electrolyte disturbances are important for children with ingestion as well as children with altered mental status due to other systemic illness.

In children with signs of increased ICP with impending herniation, emergency treatment involves BLS and PALS in addition to manual hyperventilation (targeting pCO_2 of 30–35 mmHg), mannitol or hypertonic saline, elevation of head of bed, and intensive care along with neurosurgical consultation. If the child is stabilized, additional diagnostic testing will be performed and therapies to treat the underlying process will be carried out (shunt for hydrocephalus, evacuation of blood after traumatic injury, treatment for neoplasm, etc.).

An infectious etiology should be strongly considered in children with fever and altered mental status and neonates with altered mental status. Lumbar puncture (if not contraindicated) should be performed and meningitic dosing of antibiotics should be delivered as soon as possible. Empiric antibiotic therapy should be initiated based on age of patient, suspect pathogen, and local resistance patterns and via the intravenous route although intraosseus or intramuscular routes can be used if there is delayed intravenous access. Most treatment guidelines recommend the use of a third-generation cephalosporin (ceftriaxone (100 mg/kg/day in 2 divided doses

given every 12 h with a maximum dose of 4 g/day) or cefotaxime (300 mg/kg/day in 4 divided doses administered every 6 h with a maximum dose of 8–12 g/day)) in conjunction with vancomycin (60 mg/kg/day in 4 divided doses administered every 6 h with dose adjusted to achieve trough concentrations of 10–15 mg/L). In neonates and immunocompromised children at risk for *Listeria monocytogenes*, a benzylpenicillin (ampicillin 300 mg/kg/day in divided doses administered every 4–6 h with a maximum dose of 12 g/day) should be added [16, 17]. Empiric acyclovir should be started if herpes encephalitis is a concern based on age or other risk factors and physical/laboratory examination findings.

Inborn errors of metabolism should be considered in a neonate presenting with lethargy, seizure, and vomiting or feeding intolerance. Laboratory evaluation including blood gas analysis for acidosis or alkalosis, serum glucose, ammonia level, lactate, and urine for ketones or reducing substances may be helpful. Pediatric neurologic and genetic consultation is indicated for these children, and they usually require specialized management in a tertiary care center.

Children with known seizure disorders and witnessed seizures followed by an alteration in mental status should be assessed and observed to determine if they have responded to treatment and have improving mental status. Many of these children will be discharged home. If there is concern that the child is not having improvement in their mental status or if there is concern for ongoing seizures, they should be observed and determination of disposition in consultation with pediatric neurology and the parents could result in observation or transfer to a pediatric facility with pediatric neurology. In these patients, levels of their anticonvulsant medications should be sent and other precipitating factors that could lower their seizure should be considered (i.e., concurrent infection, missed medications, etc.). In children who present with continuous seizures, treatment of status epilepticus should be started. Many centers have pediatric-specific treatment guidelines based on availability and comfort with specific antiepileptics. Initial treatment with benzodiazepines is the mainstay of therapy and if alteration in mental status continues after treatment, the patient should be admitted in a monitored setting. A general treatment algorithm is shown in Fig. 2.

Treatment for systemic illnesses causing altered mental status is very disease specific. Hepatic encephalopathy, hypertensive encephalopathy, and uremia from renal failure all require individualized evaluation and treatments with pediatric subspecialty consultation. Most of these systemic illnesses will require admission in a monitored setting with multidisciplinary input.

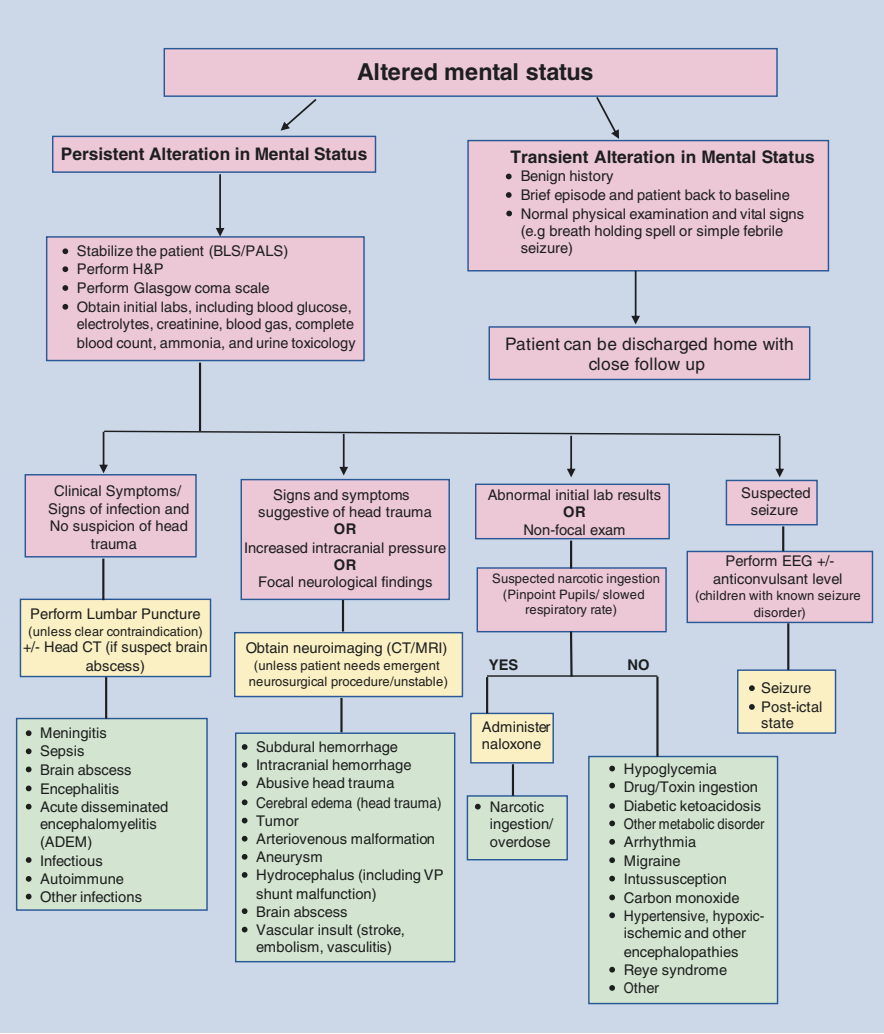


Fig. 2 Algorithm for diagnosis and treatment of common causes of altered mental status in children

6 Outcomes

Outcome depends on the etiology of altered mental status. Most transient alterations in mental status have benign causes and have excellent outcomes. Children with toxic ingestions usually have complete recovery with supportive care. Outcomes are variable for children with systemic illnesses causing altered mental status, traumatic brain injury, and primary intracranial pathologies.

7 When to Refer/Admit

Persistent alterations in mental status should be observed. The decision to refer to a tertiary care center versus a community hospital depends on the needs of the patient. A child who needs cardiac telemetry or intensive care should be transferred to a center that can provide those resources. If a child is improving and simply needs a period observation, they may be monitored in an emergency department or observation unit. Altered mental status has a broad differential diagnosis and referral or consultation with pediatric subspecialists (pediatric neurology, pediatric intensive care, poison control, etc.) should be considered depending on the clinical status of the child and may aid in the diagnostic evaluation and determination of disposition.

8 Clinical Pearls

- Altered mental status can be brief or persistent, and may present with subtle changes such as decreased self-awareness to frank coma or persistent vegetative state.
- Altered mental status has a broad differential diagnosis in the pediatric patient, which can be significantly narrowed based on the age of the patient, history, physical examination findings, and laboratory results.
- A focused history and physical examination with particular attention to neurologic, ophthalmologic, and cardiorespiratory assessment are key in differentiating patients who need emergent stabilization from those who can be monitored in a nonintensive setting.
- Initial management should focus on stabilization (circulation, airway, breathing) and identification of signs of increased intracranial pressure.
- Evaluation for electrolyte abnormalities and hypoglycemia are important initial tests, as they are relatively easy to treat but can have negative long-lasting neurologic consequences if not promptly treated.
- Evaluation for infection should be initiated for neonates and children with fever and altered mental status. Antibiotics should not be delayed in a child with suspected central nervous system infection, even if a lumbar puncture has to be delayed.

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References

1. Posner JB, Saper CB, Schiff ND, Plum F. Pathophysiology of signs and symptoms of coma. In: Posner JB, editor. Plum and Posner's diagnosis of stupor and coma. 4th ed. Oxford: Oxford University Press; 2007. p. 3–38.
2. American Psychiatric Association, editor. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Association; 2013.
3. Kanich W, Brady WJ, Huff JS, Perron AD, Holstege C, Lindbeck G, Carter CT. Altered mental status: evaluation and etiology in the ED. Am J Emerg Med. 2002;20(7):613–7.
4. Han JH, Wilber ST. Altered mental status in older patients in the emergency department. Clin Geriatr Med. 2013;29(1):101–36.
5. Robertson FC, Lepard JR, Mekary RA, Davis MC, Yunusa I, Gormley WB, Baticulon RE, Mahmud MR, Misra BK, Rattani A, Dewan MC, Park KB. Epidemiology of central nervous system infectious diseases: a meta-analysis and systematic review with implications for neurosurgeons worldwide. J Neurosurg. 2018:1–20.
6. MacNeill ED, Vashist S. Approach to syncope and altered mental status. Pediatr Clin North Am. 2013;60:1083–106.
7. Subcommittee on Febrile Seizures, American Academy of Pediatrics. Neurodiagnostic evaluation of the child with a simple febrile seizure. Pediatrics. 2011;127(2):389–94.
8. Tieder JS, Bonkowsky JL, Etzel RA, et al; Subcommittee on Apparent Life Threatening Events. Clinical practice guideline: brief resolved unexplained events (formerly apparent life-threatening events) and evaluation of lower-risk infants. Pediatrics. 2016;137(5):e20160590.
9. Berg MD, Schexnayder SM, Chameides L, Terry M, Donaghue A, Hickey RW, Berg RA, Sutton RM, Hazinski MF. Pediatric basic life support. Circulation. 2010;122:S862–75.
10. Cushing H. Concerning a definite regulatory mechanism of the vasomotor centre which controls blood pressure during cerebral compression. Bull Johns Hopkins Hosp. 1901;12:290–2.
11. Davies E, Connolly DJ, Mordekar SR. Encephalopathy in children: an approach to assessment and management. Arch Dis Child. 2012;97:452–8.
12. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. Lancet. 1974:81–4.
13. Tatman A, Warren A, Williams A. Development of a modified paediatric coma scale in intensive care practice. Arch Dis Child. 1997;77:519–21.
14. Jindal A, Singhi SC, Singhi P. Non-traumatic coma and altered mental status. Indian J Pediatr. 2012;70(3):367–75.
15. Royal College of Paediatrics and Child Health. The management of children and young people with an acute decrease in conscious level. A nationally developed evidence based guideline for hospital practitioners. 2015. http://www.rcpch.ac.uk/sites/default/files/2019-03/2016_decreased_conscious_level__full_clinical_guideline.pdf. Accessed 30 Dec 2020.
16. Le Saux N, Canadian Paediatric Society, Infectious Diseases and Immunization Committee. Guidelines for the management of suspected and confirmed bacterial meningitis in Canadian children older than one month of age. Paediatr Child Health. 2014;19(3):141–52.
17. Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, Whitely RJ. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis. 2004;39(9):1267–84.

Child with Global Developmental Delay

Leigh Anne Flore and Stephanie Campbell

1 Introduction

Through infancy and childhood, typical development is defined by the occurrence and timing of specific milestones. These milestones can be categorized into four domains: fine/gross motor, speech and language, personal/social, and cognitive development [1–3]. Children typically master these milestones in a specific order, and once a milestone is achieved, those skills should not be lost. There can be some mild variability in the timeframe that these milestones are achieved but if a child does not achieve the expected milestones at a rate comparable to similarly aged peers (and therefore has a developmental age significantly lower than the chronologic age), they are considered to have a developmental delay [2].

Global developmental delay (GDD) is defined as significant delay in two or more developmental domains, with "significant delay" being further defined as function that is greater than or equal to 2 standard deviations below similar aged peers, based on standardized developmental measures [1–3]. GDD is often associated with later development of intellectual disability (ID). ID is defined in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as deficits in intellectual functioning (with mental abilities scoring 2 standard deviations below

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average, such as an intelligence quotient (IQ) of less than 70), impairment in adaptive function, with deficits noted during the developmental period [2, 4]. While there is not a specific age requirement for the diagnosis of ID [4], it is challenging to diagnose a child with ID before 5 years of age, since it can be difficult to get reliable measures of developmental skills before that age. As a result, a diagnosis of GDD will often precede a diagnosis of ID, though there are children with GDD who do not later meet diagnostic criteria for ID. In addition, children with certain neurocognitive disorders such as autism may not necessarily have GDD. Since GDD and ID are often linked, the evaluation and workup for GDD and ID are nearly identical, and in the literature, they are often discussed interchangeably in regards to diagnostic approach and evaluation. Therefore, while the focus of this chapter will be on the diagnostic evaluation and management of children with GDD, the discussion will also frequently include patients with ID.

In many cases, a genetic or nongenetic etiology for the GDD can be found, though anywhere from 20 to 62% have an unknown etiology after diagnostic workup [5, 6]. More recent studies that incorporate newer genetic diagnostic tools do show an improved diagnostic yield, with one study showing only 29% of patients having an indeterminate cause of GDD after a thorough genetic and metabolic evaluation [7]. Correctly identifying an underlying genetic diagnosis for patients with GDD is beneficial for informing prognosis; identifying risks for other possible associated health concerns, especially when a syndromic diagnosis is made; providing understanding and closure to parents and providers [8]; accurately determining familial recurrence risks; and in some cases, revealing specific management and treatment modalities that could change the patient's clinical course. However, since the evaluation of GDD can be a drawn-out process, therapeutic intervention should be concurrent with evaluation, in order to achieve the full benefit from therapy.

2 Epidemiology

GDD is a relatively common clinical problem in the pediatric population. Up to 1–3% of children under the age of 5 years will have GDD [1, 8]. GDD and ID are found in every ethnic group and every demographic, with a meta-analysis showing a higher reported prevalence of ID in lower- and middle-income countries [9].

3 Etiology

There is a diverse array of genetic and/or environmental etiologies that can cause GDD (Table 1). There are also identifiable causes for GDD that may themselves be etiologically heterogeneous, such as perinatal stroke or certain brain malformations. A broad differential needs to be considered when evaluating any child with GDD. The following discussion includes many of the more common causes of

Table 1 Etiologies of global developmental delay/intellectual disability

Etiology	Percentages
Genetic – Aneuploidy/abnormal karyotype – Chromosomal CNV – Single gene pathogenic/likely pathogenic variant – (Fragile X syndrome)	Up to 47%[a] – 2.3–3%[b,c] – 6.7–33%[b,d] – 10–29%[b,d,e,f,g,h,n] – (2–6%)[d,i]
CNS abnormality	11–28%[a,d,j]
Prematurity, perinatal injury, neonatal complications	14–55%[a,j]
Teratogens	Up to 21%[a]
Environmental/trauma/neglect/toxins/infections	0.5–11%[a,j]
Inborn errors of metabolism	0.8–2.8%[k,l,o]
Unknown	29–62%[d,j,m]

CNV copy number variants, *CNS* central nervous system
[a]Jimenez et al. [10]
[b]Liao et al. [11]
[c]Miller et al. [12]
[d]Han et al. [7]
[e]Miclea et al. [13]
[f]de Ligt et al. [14]
[g]Hamdan et al. [15]
[h]The Deciphering Developmental Disorders study [16]
[i]Hersh et al. [17]
[j]Chen et al. [5]
[k]Sempere et al. [18]
[l]Engbers et al. [19]
[m]Srour et al. [6]
[n]Fragile X syndrome has an etiology of 2–6%
[o]Diagnostic yield was shown to increase with more specific metabolic testing in one study by Papavasiliou et al. [20]

GDD, as well as different categories that can be used to classify these common causes and help with evaluation. However, this is not a comprehensive list. New single gene syndromes and/or specific chromosomal disorders associated with GDD are being identified at a rapid pace, and an exhaustive list of these conditions is not possible. Up to 25–50% of identified causes of GDD are estimated to be genetic in origin [21]. It is also worth noting that 19–62% of cases of GDD had an unknown etiology even after extensive workup, highly dependent on the specific study methods [10, 11].

3.1 Prenatal/Perinatal Causes

It is well known that many prenatal or perinatal insults can predispose to developmental delay. Prenatal or perinatal asphyxia or hypoxic brain injury from other causes can lead to neuronal injury that prohibits normal development. Certain teratogenic exposures during pregnancy can also negatively impact brain development.

For example, maternal alcohol use during pregnancy can lead to Fetal Alcohol Spectrum Disorder, which is typically associated with behavior and learning difficulties including frank GDD/ID in some patients, in addition to causing characteristic facial features and growth deficiency. Certain prenatal infectious exposures such as congenital cytomegalovirus infection can impact the central nervous system and cause long-term developmental issues.

3.2 Postnatal Trauma/Illness

In the newborn or infant period, trauma and illness continue to be common causes for GDD. Examples include postnatal meningitis and traumatic brain injury [13].

Another risk factor for developmental delay is prolonged hospitalization [22]. For example, children with a congenital heart defect who require surgery and a prolonged intensive care unit (ICU) hospitalization can have subsequent developmental delay [22]. Other medically complex children who require frequent and/or prolonged hospitalizations or are frequently ill can similarly be at risk for GDD [22].

3.3 Lead Exposure

Lead exposure has long been known to have multiple negative health effects for children. Exposure to lead with levels as low as 10 μg/dL can lead to altered neuromotor and neurosensory function, as well as learning and behavior issues. They can have impaired function in their gross and fine motor skills, as well as hearing issues [23]. The American Academy of Pediatrics no longer recommends universal screening, but instead recommends targeted lead level screening for patients at high risk for lead exposure, including children that rely on Medicaid, and families that live in older houses [24]. If a child has symptoms of lead poisoning or a history concerning for lead exposure, diagnostic venous lead levels should be ordered [24].

3.4 Iron Deficiency

Iron deficiency is a very common mineral deficiency, and there is a suspected link between iron deficiency anemia and development [25]. However, there is not a clear etiologic link between iron deficiency and developmental delay because there are many other risk factors associated with anemia that also affect development (including low socio-economic status, low birth weight, malnutrition, and decreased caregiver stimulation) [26]. Still, given the association, this common deficiency is still an important factor and should be considered when there is developmental delay.

3.5 Hypothyroidism

Congenital hypothyroidism can present with developmental delay since thyroid hormone serves an important function in development of the central nervous system. The most common cause worldwide of congenital hypothyroidism and hypothyroidism, in general, is iodine deficiency. Other causes include defects in thyroid development, hypothalamic or pituitary disease (such as septo-optic dysplasia, among others), and anti-thyroid-stimulation hormone receptor antibodies from the mother, passed on to the fetus through the placenta [27]. Newborn screening programs can often identify neonatal congenital hypothyroidism. While evidence regarding the diagnostic yield of thyroid studies for GDD are lacking in the presence of newborn screen, advocates for testing argue that acquired hypothyroidism should remain on the differential after the newborn period, since it is easily treatable [28, 29].

3.6 Neglect

Since development is influenced by a child's environment and physical and social stimuli [2], it is important to be vigilant for signs of child abuse or neglect. Language milestones in particular are frequently delayed if there is decreased engagement with caretakers [30, 31], and neglecting to encourage gross and fine motor skills will also lead to a delay. These children typically show rapid developmental progress when they are placed in a more secure and nurturing environment [31], which would not be expected for most of the other discussed etiologies of GDD.

3.7 Brain/CNS Malformation

Malformation of the brain accounts for up to 28% of diagnosed cases of GDD [10]. This can be an isolated finding, or part of a syndromic presentation with other congenital anomalies and/or dysmorphic features. Recent genomic research has illustrated that even "isolated" cortical malformations can result from germline single gene pathogenic variants, or in some cases, from somatic mosaicism for a pathogenic variant, where a new mutation occurs after fertilization of the zygote, and therefore the pathogenic variant may be limited to certain tissues, such as the brain. It is also worth noting that an isolated central nervous system malformation can sometimes be found incidentally on imaging, and depending on the type of malformation, it is not always associated with developmental delay or cognitive impairment [1, 32].

3.8 Chromosome Abnormalities

Abnormalities of chromosome number, size, or more rarely, arrangement are the most common single genetic cause for GDD, accounting for an estimated 26–55% of genetic causes of developmental delay, depending on the study [7, 11]. One well-known category of chromosomal abnormalities is abnormalities of chromosome number, also known as chromosomal aneuploidy. The most common example is Trisomy 21, or Down syndrome, with a prevalence around 1:1200 in the United States [33]. Down syndrome is universally associated with GDD and hypotonia, as well as characteristic facial features. The phenotype also includes congenital anomalies such as congenital heart defects (in 40% of individuals) and gastrointestinal anomalies (such as duodenal atresia or Hirschsprung disease), single palmar crease (in 45%), ophthalmologic and hearing issues, thyroid disease, myeloproliferative disorders, sleep apnea, and other medical issues [34].

A less common but more phenotypically severe aneuploidy is Trisomy 18. Around 50% of these children die in the first week of life, and only 5–10% survive past the first year [34]. Those that survive can have many clinical manifestations, including severe intellectual disability, growth deficiency, clenched hands with overlapping fingers, rocker-bottom feet, cardiac defects (such as ventricular or atrial septal defects), and hypertonia after the newborn period. Trisomy 13 is another aneuploidy with a severe phenotype, with most children only surviving around 7 days, and over 91% dying within 12 months [34]. Clinical features include severe ID, holoprosencephaly, seizures, apneic spells, midline defects including cleft lip and/or palate, cardiac defects (in 80%), and cutis aplasia [34].

Other examples of chromosome aneuploidy that can sometimes present with GDD include sex chromosome aneuploidies. It is important to note that in contrast to Trisomy 21, 13, or 18, individuals with sex chromosome aneuploidy, with the exception of Turner syndrome, often have a subtle phenotype, with very few or no recognizable physical or developmental anomalies, especially in early childhood. Girls with Turner syndrome, associated with absence or abnormality of one of the X chromosomes (most commonly, 45, X), may have normal early development, but delays, especially in motor skills, are common, and GDD/ID occurs at a rate higher than in the general population. Common physical findings include characteristic dysmorphic features (low set ears, wide and short neck, low posterior hairline, downward slanting palpebral fissures, wide chest with widely spaced nipples), short stature with ovarian dysgenesis, congenital lymphedema, cardiac defects such as bicuspid aortic valve or coarctation of the aorta, and renal anomalies including horseshoe kidney. 47, XXY, also known as Klinefelter syndrome, can have a variable presentation. Developmental delays, if they are present, are often milder. Learning difficulties are common; there is a wide range of reported IQs, with most falling in the normal range. Other common features include tall stature, small penis and testes, low testosterone, gynecomastia, and infertility. Another aneuploidy is 47, XYY syndrome, which is likely under-recognized because many of these patients will be phenotypically normal well into adulthood. However, in these

patients, there is an increased incidence of speech delay, poor gross and fine motor coordination and weakness, learning difficulty, autism spectrum disorder, hyperactivity, and attention problems. These children will also often have a lower IQ than their siblings, though it is still usually in the normal range.

Another important group of chromosomal abnormalities that cause GDD is pathogenic copy number variants (CNVs), with chromosomal microdeletions and microduplications resulting in an abnormal amount of genetic material. There are numerous well-recognized microdeletion and microduplication syndromes that have GDD as an associated feature, often with other characteristic medical and physical anomalies. Some of the most common include 22q11.2 deletion (DiGeorge/Velocardiofacial syndrome), 22q11.2 duplication, 4p deletion (Wolf–Hirschorn syndrome), 5p deletion (Cri-du-Chat syndrome), 7q11.2 deletion (Williams syndrome), and 17p11.2 deletion (Smith–Magenis syndrome) [35]. Deletion, abnormal imprinting, or uniparental disomy of chromosome 15q11-q13 can result in either Prader–Willi syndrome or Angelman syndrome, depending on whether the affected chromosome is maternal or paternal in origin. Many other pathogenic microdeletions and –duplications exist, and the list of chromosomal CNVs causing GDD is constantly evolving.

While history and physical examination often provide clues for the diagnosis of well-known syndromes, nonspecific GDD may be the only feature of some pathogenic chromosomal microdeletions or microduplications.

Finally, structural chromosomal abnormalities can also lead to GDD if there is significant net gain or loss of genetic material, such as with unbalanced chromosome translocations or ring chromosomes. Even balanced chromosomal translocation could potentially result in GDD, if the structural change to the chromosome also interrupts an important gene.

3.9 Single Gene Disorders

Fragile X syndrome is a well-known, X-linked semi-dominant disorder caused by loss of function of the *FMR1* gene secondary to CGG trinucleotide repeat expansion near the gene promoter, leading to hypermethylation and silenced gene expression. It is considered one of the most common inherited causes of GDD/ID, and hence, is often considered separately from other single gene causes. Additional phenotypic findings include characteristic facial features (long face, prominent ears in older males), large testes, mitral valve prolapse, and behavioral problems (autistic features, overactivity, impulsivity). The methylation of the *FMR1* gene occurs when there are >200 CGG repeats present, and this is considered a full mutation. While Fragile X syndrome mostly affects males, females with the full mutation in FMR1 can also have behavioral issues or learning difficulties, usually to a milder degree compared to males, but overlapping with the male phenotypic spectrum [36]. Family members can have a premutation allele, with 59–200 trinucleotide repeats, which

can then expand to a full mutation during gametogenesis. Patients with a premutation allele can also present in late adulthood with Fragile-X associated tremor/ataxia syndrome, and women with a premutation allele can develop Fragile X-associated primary ovarian insufficiency. Therefore, if a patient with GDD has a family history of GDD following an X-linked pattern, ataxia/ early onset Parkinsonian features, or ovarian insufficiency, testing for Fragile X syndrome should be considered.

Other single gene disorders that cause GDD can be further divided into two categories: syndromic and nonsyndromic. Syndromic causes of GDD describe single gene conditions with clinical manifestations in several organ systems, often with dysmorphic features or other congenital anomalies that can be appreciated on physical examination. Genetic syndromes associated with GDD are too numerous to individually list here, and as with chromosomal CNVs, new syndromes associated with GDD are being identified at rapid pace. A few examples include Rett syndrome (MECP2-related disorder), Tuberous sclerosis complex, Smith–Lemli–Opitz syndrome, Noonan spectrum disorders, Cornelia de Lange syndrome, and hundreds to thousands of others [35].

Nonsyndromic causes of GDD/ID, by contrast, usually have GDD/ID as the primary clinical finding, without other associated anomalies beyond the neurocognitive features, or with only subtle physical findings that are easily missed. With advancement in genetic testing, there have been many newly identified genes that are associated with nonsyndromic GDD and/or ID. This growing list of genes associated with isolated GDD and/or ID includes genes that encode for proteins that play a role in central nervous system development or maintenance. When considering a patient with nonsyndromic GDD/ID, a genetic etiology is more likely to be identified in patients with more severe GDD/ID compared to mild GDD/ID [37].

3.10 Metabolic Disorders

While inborn errors of metabolism are overall a less common cause of GDD, they are an important group of conditions to consider because many of these conditions have a treatment, and early diagnosis can have a profound impact on morbidity (including developmental outcome) and in some cases, mortality. There are many classes of inborn errors of metabolism that are associated with GDD, including amino acidopathies, organic acidemias, carbohydrate metabolism disorders, lysosomal storage disorders, mitochondrial disorders, congenital disorders of glycosylation, and peroxisomal disorders.

There are several red flags on history and physical examination that should alert the clinician to consider a possible metabolic etiology. Children with inborn errors of metabolism usually have a progressive delay, with a widening gap in their development compared to their same age peers [38]. Concurrent behavioral problems or motor automatisms with or without stereotypic behaviors are also a concerning

finding [38]. Finally, many patients with an inborn error of metabolism will have a period of normal development, followed by regression [2]. Neurologic regression is always a major red flag that requires full evaluation, including laboratory and other assessment such as brain imaging for a possible inborn error of metabolism. Many inborn errors of metabolism will affect other organ systems as well, including the liver, spleen, endocrine, connective tissue, eyes and muscles [38]. These patients frequently have other neurologic features in addition to developmental delay, including seizures and abnormal muscle tone [38]. However, developmental delay might be the only presenting symptom, with subsequent neurologic and multi organ system involvement occurring later in the course [38].

4 Differential Diagnosis

While GDD can be readily identified using standardized tools [39], there are other conditions that can present similarly to GDD, but have different diagnostic workup or management. Autism spectrum disorder (ASD) can present very similarly to GDD, with defects with social and language skills, and sometime with developmental regression [2, 40]. However, properly identifying ASD can help with initiating effective management, including applied behavior analysis (ABA) therapy. Patients with hypotonia often have both gross and fine motor delay, thereby meeting criteria for GDD. However, the differential diagnosis for a child whose primary feature is hypotonia differs from a child with GDD and may require a different workup. The presence or absence of language or social delays can help with determining the next best diagnostic approach, but this can be difficult to differentiate in early infancy. Behavioral issues in older children, including attention-deficit/hyperactivity disorder (ADHD), can also be hard to differentiate from developmental delay, as it may be difficult to evaluate these children's performance in specific developmental skills.

5 Diagnostic Approach

Given the etiologic heterogeneity and the broad differential diagnosis for GDD, a comprehensive evaluation and workup is needed to make an accurate diagnosis (Table 2). A thorough clinical history and physical examination is critical for narrowing the differential diagnosis, and in certain instances could lead to a single likely diagnosis, sometimes more targeted testing can be offered. While there are many laboratory investigations, imaging, genetic tests, and other evaluations that can aid in diagnosing GDD, not all of these evaluations will be necessary or revealing in each individual case. Hence, the clinician's judgment is crucial to determine which work-up is appropriate for any individual patient.

Table 2 Diagnostic approach to evaluation of global developmental delay

History	Physical examination	Laboratory investigations to consider	Imaging	Other evaluations
– Pregnancy history – Birth history – Developmental milestones – +/− congenital anomalies – Other significant health issues – Formal diagnosis of ID and/or autism – +/− neuroregression – Family history including +/− consanguinity – Imaging: +/−structural brain defects, aberrant myelination – +/− seizures – Growth history (including growth chart)	– Growth parameters – Head circumference (macro- or microcephaly) – Dysmorphic features – Coarse facial features – Hepatosplenomegaly – Muscle tone (hypertonic or hypotonic?) – Reflexes (hyper or hyporeflexic?)	– Lead level – Thyroid levels – Chromosomal microarray – Fragile X DNA testing – Single gene testing for specific identifiable syndrome – Screening for inborn errors of metabolism – Multigene panel versus whole exome/ genome sequencing	– Consider MRI brain	– Hearing evaluation – Vision/ophthalmology evaluation – Neuropsychological evaluation

5.1 History

When evaluating a child for GDD, the following points should be covered in the clinical history:

- *Pregnancy:* Was there any concerns with growth during pregnancy? Was the pregnancy high risk? Were there any complications? Did mother have any health issues during pregnancy (hypertension, diabetes, maternal PKU, illness)? Was there any exposure during pregnancy to prescribed medications, supplements, alcohol etc.?
- *Birth history:* Was baby born term, preterm, post-term? Was the delivery emergent? Were there any complications with delivery (maternal blood loss, chorioamnionitis)? Was there any neonatal distress noted immediately after birth (low APGARS, intubation)? Did baby spend time in the NICU (neonatal intensive care unit)?
- *Developmental milestones:* What developmental milestones has the patient achieved? What age were these milestones achieved? At what age is the child functioning developmentally? Has there been any loss in milestones that were previously achieved? Has achievement of developmental milestones always been delayed, or was the patient initially on track, then stopped achieving new milestones?
- *ID*: For older patients, were they evaluated and found to have ID?
- *Past medical history:* Has the patient had hearing or vision evaluations in the past? Has the patient had any health issues that have required multiple hospitalizations (cardiac defect, cancer diagnosis, frequent infections)? Has patient undergone newborn screening?
- *Autism*: Is the child showing signs concerning for autism spectrum disorder? If older, has this child been evaluated for possible autism?
- *Family history*: Are there any other family members who have or had developmental delay or ID (parents, siblings, aunts/uncles, cousins)? Is there known consanguinity between the parents (increasing the risk for autosomal recessive conditions in the child)?
- *Social history:* Who does the child live with at home? How frequently has the child been taken to well-child visits for evaluation? Is the child at risk for lead exposure? Have family members been engaging the child and working with the child on developmental milestones (supervised tummy time, talking with baby, switching from bottle to cup, etc.)?
- *Structural birth defects:* Has the patient had any surgical corrections of birth defects in the past (cleft lip/palate, polydactyly)? Has the baby had previous imaging (x-ray, ultrasound, MRI, echocardiogram) that identified a structural defect?
- *Growth history:* Have there been any concerns with the child's growth? Failure to thrive? Is there macrocephaly or microcephaly, with head size either 2 SD above or below average, or significantly above or below the child's weight and height (relative macro or microcephaly)? Has the head circumference been increasing or decreasing at a higher or lower rate compared to other growth parameters (progressive macro-microcephaly)?

5.1.1 Physical Examination

General Examination:

- *Growth parameters*: Where does the child fall on the standardized growth curves? Some genetic conditions associated with GDD are also associated with poor growth or short stature. These findings might also necessitate a failure to thrive workup.
- *Head circumference:* Does the child have macrocephaly or microcephaly? The differential for macrocephaly and GDD/ID includes (but is not limited to) PTEN-related disorder, Sotos syndrome, Fragile X syndrome, and Noonan spectrum disorders, while the differential for microcephaly and GDD/ID includes Rett syndrome, Angelman syndrome, Mowat–Wilson syndrome, Smith–Lemli–Opitz syndrome, Cornelia de Lange syndrome, Ataxia-telangiectasia, Pitt–Hopkins syndrome, and Cohen syndrome [35].
- *Dysmorphic features:* Dysmorphic features are physical findings that are seen in <4% of the general population [41]. While these findings have no medical significance by themselves, they can act as a marker for an underlying genetic condition, especially if there are multiple dysmorphic findings. Be aware that some features are more common in certain ethnic groups (epicanthal folds in the Asian population, broad nasal bridge in the African population). Does the patient look like the parents? (For example, single palmar crease is a marker of Down syndrome, but most children with a single palmar crease have a parent with the same finding.)
- *Coarse facial features:* Coarse facial features include a broad forehead, and enlarged parts of the face including the nose, lips, and gums [42]. These findings might not be present initially, but rather develop as the child gets older. Coarse facial features are found in many lysosomal storage diseases (in which the coarse features emerge over time), but it can also be found in other metabolic or genetic conditions, including Coffin–Lowry and Coffin–Siris syndromes, where the coarse features are present from birth [42].
- *Hepatosplenomegaly:* Enlarged liver and spleen in the context of GDD can be another finding of many lysosomal storage diseases. A thorough cardiac examination can be helpful in certain situations as in children who have certain metabolic disorders (e.g., Pompe's disease).

5.1.2 Neurologic Examination:

- Is the child hypertonic (spastic)? Hypotonic? Spasticity raises concern for possible neurodevelopmental anomaly or brain injury. Hypotonia is associated with a long list of conditions, depending on whether it is central (due to central nervous system anomalies), peripheral (related to abnormalities in the spinal cord, peripheral nerves, and/or muscle), or combined. Many patients who have hypotonia as well as developmental delay, will have a central or combined hypotonia [43]. Also evaluate for the presence of developmental and deep tendon reflexes.

Is the patient hyper-reflexic, suggesting an upper motor neuron injury? Does the baby have upgoing plantars beyond the age of 2 years? Does the baby have decreased tendon reflexes (hypothyroidism, spinal muscular atrophy).

5.2 Laboratory Investigations/Imaging

After completing the history and physical examination, there are many additional evaluations that can be considered. If a specific condition is suspected, then targeted testing would be the first step. Initial blood work, including lead level and thyroid function tests, can be considered. If there is macrocephaly, microcephaly, or a history of seizures, then an MRI of the brain should be ordered to look for CNS anomalies [1, 10]. There are nonspecific central nervous system abnormalities found in 20–30% of children with isolated developmental delay [1, 29]. Careful consideration should be given before obtaining an MRI of the brain. There is conflicting recommendations about whether imaging should be ordered for nearly all patients with GDD/ID [44], or only for those with neurologic findings on examination [45]. The AAP recommends against routine ordering of imaging in patients without the above findings, since it often requires sedation or anesthesia, with the associated risks [1].

5.3 Other Evaluation

Any child who has language delays should undergo a formal hearing evaluation, regardless of if they have had a previously normal newborn hearing screen. A vision evaluation should also be considered in infants who are not meeting social developmental milestones such as tracking or reflexive smile. If there are behavioral findings concerning for autism spectrum disorder, then specific diagnostic evaluation is warranted. In many cases, neuropsychologic evaluation can be helpful in determining a child's specific cognitive strengths and weakness, and can better categorize ID in older children.

5.4 Genetic Testing

Since 25–50% of cases of GDD have an underlying genetic etiology [10, 13], genetic testing is a key component of the diagnostic workup, and GDD is a common reason for referral to a medical geneticist. It is recommended that any child with GDD without an identified etiology should have genetic testing [8], though one study reported that only 20.6% of surveyed pediatricians ordered genetic studies for this indication, if other findings were not present [46]. The American College of

Medical Genetics and Genomics (ACMG), the American Academy of Pediatrics (AAP), and the Canadian Paediatric Society (CPS) have provided guidelines for the recommended genetic testing for patients with GDD [1, 12, 28].

First, if the history and clinical features are consistent with a recognizable syndrome, or if there is a known family history of a heritable condition that can cause GDD, then direct and specific testing for that suspected condition or syndrome should be performed. An example would be an infant who has physical features consistent with Down syndrome, in which case the first test ordered should be chromosomal analysis with a karyotype.

If the findings are not suspicious for a specific condition, the recommended first genetic test is chromosomal microarray, a genetic test that uses either array-based comparative genomic hybridization (CGH) or single-nucleotide polymorphism array (SNP) to detect copy-number variants, and can identify microdeletions, microduplications, and aneuploidies [12]. The microarray is recommended as first tier testing for evaluation of GDD by the ACMG, the AAP, and the CPS [1, 12, 28].

The microarray has replaced the karyotype as a first tier evaluation in the workup for GDD. The karyotype allows direct visualization of the patient's chromosomes. Since chromosomes can be counted and visualized, aneuploidy can be readily detected, as well as chromosomal abnormalities, including translocations, inversions, insertions, and ring chromosomes. It can also detect large duplications and deletions within the chromosomes, but only at the level of ~5 Mb [12]. Comparatively, the microarray can detect microduplications and microdeletions of 20–50 kb in size [12]. As a result, the diagnostic yield of chromosomal microarray in the GDD/ID population is 15–20%, compared to a ~3% yield with karyotype [12]. Karyotyping is the initial test of choice in those with an identifiable syndrome consistent with a chromosomal aneuploidy (such as Down syndrome). A karyotype will also detect balanced rearrangements, and should be considered if there is a family history of multiple miscarriages or a known family history of a chromosomal rearrangement [12].

Fragile X trinucleotide repeat evaluation of FMR1 is also considered first-tier testing in both males and females with GDD/ID by the current ACMG guidelines [12] as well as the AAP and CPS [1, 28]. Fragile X has been reported as the most common genetic cause of ID, identified in 2–6% of affected boys and 1–4% of affected girls [28]. This recommendation has become somewhat controversial in recent years. Advances in genetic testing have identified many other common genetic etiologies of GDD and ID which approach the frequency of Fragile X syndrome in this population [47, 48]. In a study performed by Borch et al. [47], they found that 96% of individuals diagnosed with Fragile X showed either clinical features or family history of the disease, so these authors argue that Fragile X testing should be a second tier test, rather than an initial diagnostic evaluation, if the clinical suspicion for Fragile X is low. Despite the current discussion on whether Fragile X testing should be considered second tier testing based on these findings, at this time it is still generally considered a first-line test for genetic evaluation of GDD.

If both chromosomal microarray and Fragile X DNA testing are nondiagnostic, the next step is broad testing of single gene disorders, either through gene panels,

whole-exome sequencing (WES), or whole-genome sequencing (WGS). Gene panels are a type of genetic test that evaluates a large number of genes from a patient sample, and looks for variations in the sequence that could impact the gene function. These gene panels are categorized by a similar phenotype, such as ID or ASD. There are many clinical testing laboratories that offer multi-gene panels that include a growing list of genes found to be associated with GDD. Since these gene panels are made independently by each laboratory, there will be differences in which genes are tested, depending on the laboratory. These laboratories will use next-generation sequencing to identify variants in the genes on their gene panels. Depending on the laboratory, they can also provide options for identifying small deletions or duplications in the genes using a different methodology. Whole-exome sequencing is a test that also uses next-generation sequencing, but instead of focusing on a specific list of genes, whole-exome sequencing analyzes the entire coding region, or exons, of a patient's genome. Broad testing with WES has identified many novel genes [49], and increased understanding on the genetic etiology of GDD. Whole-genome sequencing also uses next-generation sequencing, but it sequences the entire genome, including both coding and noncoding regions, and can identify variants in noncoding regions that can nonetheless affect gene expression. WGS can also detect uniparental disomy (UPD) and trinucleotide repeats, depending on the laboratory performing the test, which can also increase the diagnostic yield. UPD is the inheritance of both homologous chromosomes from one parent; if the chromosome involved contains imprinted genes (i.e., genes expressed only if inherited from the father or from the mother), this can lead to an abnormal phenotype. For both WES and WGS, the clinical laboratory uses the provided clinical features of the patient to sort and interpret the many gene variants that are detected, to identify a likely cause for a patient's phenotype. WGS does have a slightly increased yield compared to WES, though in some studies the yield is comparable [50], and WGS is still typically more expensive than WES.

As WES and WGS have been more readily available, and the cost to perform these tests has decreased significantly since their initial availability [51], these tests have been increasingly used in evaluation of GDD. Several studies have been done to compare the diagnostic yield of WES or WGS compared to chromosomal microarray, with Clark et al. [50] showing increased clinical and diagnostic utility in WES and WGS over microarray. Another study did a meta-analysis that showed a diagnostic yield of 36% for WES for neurodevelopmental disorders (NDD), with a 31% yield in isolated NDD, and a 53% yield when there were associated findings in addition to NDD [52]. If the WES/WGS is negative, then the lab can perform a reanalysis in 1–3 years, which can sometimes lead to a diagnosis.

For both chromosomal microarray and WES/WGS genetic testing, a copy number or sequencing variant can be found that is not clearly pathogenic, but also not clearly benign, and these variants are classified as variants of uncertain significance (VUS). If a VUS is found, then further evaluation of that variant may need to be done, either through familial testing, examination of the expected effect of the variant on gene expression, and reviews of current medical literature. Interpretation and disclosure of a VUS to a family can be very challenging, because there is often

uncertainty about what these results mean for the patient and their family. As more and broader genetic testing is being ordered, VUS are being identified with increased frequency. Primary care providers will often consult or refer to medical genetics for help with interpreting and counseling in the event of a VUS. In many instances, primary care providers will refer patients to medical genetics before genetic testing is ordered so that appropriate pre- and post-test counseling can be provided about VUS.

5.5 Testing for Metabolic Disorders

Broad testing for metabolic disorders in children with isolated GDD is typically low yield, from 0 to 8.4% [7, 45]. Therefore, in countries where many of these inborn errors of metabolism are part of the newborn screen, further testing for these conditions should be dependent on the specific clinical features of the patient. In countries with more limited newborn screening, then workup for these conditions may be warranted [8]. Certain elements in the history (neuroregression, episodic decompensation, and delay with illness), physical examination findings (example: coarse facial features, hepatosplenomegaly), or imaging findings (examples: brain atrophy, white matter abnormalities on MRI) should increase suspicion for an inborn error of metabolism [10]. In these cases, biochemical and/or molecular testing for metabolic disorders may be first tier. Basic screening for inborn errors of metabolism often includes plasma lactic acid, liver function tests, plasma amino acids, ammonia levels, acylcarnitines, urine organic acid, and total and free carnitine levels [38]. These labs will evaluate for some, but not all, inborn errors of metabolism. Appropriate selection and interpretation of metabolic screening labs usually requires input from a metabolic specialist. Other laboratory workup can be considered that is more specific to certain groups of metabolic disorders, such as congenital disorders of glycosylation, peroxisomal disorders, or lysosomal storage diseases, depending on clinical suspicion. For discussion of diagnostic evaluation in patients with possible metabolic disease, please see Chap. 33.

6 Treatment/Management

Even if the etiology of the GDD cannot be ascertained, early intervention and treatment with therapies can lead to improved outcomes. Since the diagnostic odyssey for these patients can often be long, it is best for patients to receive educational and developmental intervention and therapies concurrent with the diagnostic evaluation, since the earlier the intervention and therapies are started, the more favorable the developmental outcome. Depending on the location, many services are available to get children the therapies they need to achieve their potential, whether it is physical

therapy, occupational therapy, speech therapy, or another intervention [2]. If a treatable condition is identified, such as an inborn error of metabolism, starting the recommended treatment or management can also affect the course of the patient's development, depending on the disorder and the age of diagnosis.

7 Prognosis/Outcomes

The prognosis for future development is largely dependent on the cause of the GDD. While some patients will have improvement with therapy and treatment, other patients may not have any improvement even with therapy. Still, since it is difficult to predict which children will respond to therapy, and since many patients will have some response to therapy, early and universal referral to early intervention programs leads to the best outcomes [53].

8 When to Refer/Admit

The timing of referral for GDD evaluation will often depend on the availability of subspecialists (developmental pediatrics, pediatric neurology, medical genetics). Primary care providers can order first line genetic testing and refer if the testing is negative, though many providers choose to refer even before sending first line testing [8, 46]. When there is consideration for next generation sequencing or genomic tests such as panels, WES or WGS, the provider who orders the test should be comfortable with obtaining informed consent from the family (including discussion of incidental or unexpected findings in both the patient and parents), obtaining prior authorization or otherwise making sure the test is covered by insurance, interpreting the results, and counseling the family [46]. For providers who do not order panel-based tests, WES or WGS frequently, then referral to a genetic specialist to facilitate further testing would be recommended. Other reasons to consider referral to medical genetics include multiple affected family members, dysmorphic features that do not match up to a clear etiology, multiple congenital anomalies, or other red flags, including neuroregression, encephalopathy, or seizures. Referral to a metabolic specialist, if available, should be considered if the patient has coarse facial features, hepatosplenomegaly, unexplained liver disease, and recurrent episodes of decompensation with illness, especially if accompanied by metabolic acidosis or hypoglycemia. If there is suspicion for a group of conditions that are diagnosed via a specialized, rarely ordered lab, this could be another reason for referral to medical genetics or a metabolic specialist. If there are other neurological features, including microcephaly, macrocephaly, seizures, hypo- or hypertonia, or abnormal movements, then referral to pediatric neurologist is warranted [8].

Long-standing GDD can typically be evaluated in the outpatient setting, and patients with GDD would usually only need admission to the hospital if other symptoms (example: uncontrolled or new-onset seizures, rapid loss of skills, failure to thrive) are present.

9 Prevention

If a specific genetic etiology for GDD is identified, then genetic counseling can be offered to parents, including reproductive risks and options. Potential options for families include prenatal testing for a future pregnancy, or preimplantation genetic diagnosis (PGD).

For etiologies related to toxins, reducing or eliminating exposure, such as avoiding alcohol during pregnancy, eliminating lead exposure in children, and providing supplemental iron for patients who are deficient, can help present developmental delay in these children.

10 Clinical Pearls/Key Points

- Watch for red flag symptoms, including neuroregression, seizures, and history of encephalopathy, which should prompt subspecialist referral.
- Since there is frequently a genetic etiology in patients with global developmental delay, diagnostic genetic testing should be considered for every child for which there is not a clearly identified etiology based on history or physical examination.
- Current first tier genetic testing includes chromosomal microarray and Fragile X testing. However, recommendations will continue to be evaluated, so watch for changes in clinical guidelines.
- If further testing beyond first tier genetic testing is being considered, or in a child with dysmorphic features and/or congenital anomalies, referral to medical genetics is often beneficial.
- Do not forget about child abuse and neglect as a potential etiology for global developmental delay.

References

1. Moeschler JB, Shevell M, Committee on Genetics. Comprehensive evaluation of the child with intellectual disability or global developmental delays. Pediatrics. 2014;134(3):e903–18.
2. Brown KA, Parikh S, Patel DR. Understanding basic concepts of developmental diagnosis in children. Transl Pediatr. 2020;9(Suppl 1):S9–22.
3. Shevell M, Ashwal S, Donley D, Flint J, Gingold M, Hirtz D, et al. Practice parameter: evaluation of the child with global developmental delay: report of the quality standards Subcommittee

of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2003;60(3):367–80.
4. American Psychiatric Association. Intellectual disabilities [Internet]. 2013. https://www.psychiatry.org/psychiatrists/practice/dsm/educational-resources/dsm-5-fact-sheets.
5. Chen I-C, Chen C-L, Wong M-K, Chung C-Y, Chen C-H, Sun C-H. Clinical analysis of 1048 children with developmental delay. Chang Gung Med J. 2002;25(11):743–50.
6. Srour M, Mazer B, Shevell MI. Analysis of clinical features predicting etiologic yield in the assessment of global developmental delay. Pediatrics. 2006;118(1):139–45.
7. Han JY, Jang W, Park J, Kim M, Kim Y, Lee IG. Diagnostic approach with genetic tests for global developmental delay and/or intellectual disability: single tertiary center experience. Ann Hum Genet. 2019;83(3):115–23.
8. Mithyantha R, Kneen R, McCann E, Gladstone M. Current evidence-based recommendations on investigating children with global developmental delay. Arch Dis Child. 2017;102(11):1071–6.
9. Maulik PK, Mascarenhas MN, Mathers CD, Dua T, Saxena S. Prevalence of intellectual disability: a meta-analysis of population-based studies. Res Dev Disabil. 2011;32(2):419–36.
10. Jimenez-Gomez A, Standridge SM. A refined approach to evaluating global developmental delay for the international medical community. Pediatr Neurol. 2014;51(2):198–206.
11. Liao L-H, Chen C, Peng J, Wu L-W, He F, Yang L-F, et al. Diagnosis of intellectual disability/global developmental delay via genetic analysis in a central region of China. Chin Med J. 2019;132(13):1533–40.
12. Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet. 2010;86(5):749–64.
13. Miclea D, Peca L, Cuzmici Z, Pop IV. Genetic testing in patients with global developmental delay/intellectual disabilities. A review. Clujul Med. 2015;88(3):288–92.
14. de Ligt J, Willemsen MH, van Bon BWM, Kleefstra T, Yntema HG, Kroes T, et al. Diagnostic exome sequencing in persons with severe intellectual disability. N Engl J Med. 2012;367(20):1921–9.
15. Hamdan FF, Srour M, Capo-Chichi J-M, Daoud H, Nassif C, Patry L, et al. De novo mutations in moderate or severe intellectual disability. PLoS Genet. 2014;10(10):e1004772.
16. The Deciphering Developmental Disorders Study. Large-scale discovery of novel genetic causes of developmental disorders. Nature. 2015;519(7542):223–8.
17. Hersh JH, Saul RA, Committee on Genetics. Health supervision for children with fragile X syndrome. Pediatrics. 2011;127(5):994–1006.
18. Sempere A, Arias A, Farré G, García-Villoria J, Rodríguez-Pombo P, Desviat LR, et al. Study of inborn errors of metabolism in urine from patients with unexplained mental retardation. J Inherit Metab Dis. 2010;33(1):1–7.
19. Engbers HM, Berger R, van Hasselt P, de Koning T, de Sain-van der Velden MGM, Kroes HY, et al. Yield of additional metabolic studies in neurodevelopmental disorders. Ann Neurol. 2008;64(2):212–7.
20. Papavasiliou AS, Bazigou H, Paraskevoulakos E, Kotsalis C. Neurometabolic testing in developmental delay. J Child Neurol. 2000;15(9):620–2.
21. Srour M, Shevell M. Genetics and the investigation of developmental delay/intellectual disability. Arch Dis Child. 2014;99(4):386–9.
22. Lehner DC, Sadler LS. Toddler developmental delays after extensive hospitalization: primary care practitioner guidelines. Pediatr Nurs. 2015;41(5):236–42.
23. US Department of Health and Human Services. Toxicological profile for lead. North Charleston: Createspace Independent Publishing Platform; 2014.
24. American Academy of Pediatrics Committee on Environmental Health. Lead exposure in children: prevention, detection, and management. Pediatrics. 2005;116(4):1036–46.
25. Stoltzfus RJ. Iron-deficiency anemia: reexamining the nature and magnitude of the public health problem. Summary: implications for research and programs. J Nutr. 2001;131(2S-2):697S–700S; discussion 700S–701S.

26. Saloojee H, Pettifor JM. Iron deficiency and impaired child development. BMJ. 2001;323(7326):1377–8.
27. Firth HV, Hurst JA, editors. Congenital hypothyroidism. In: Oxford desk reference: clinical genetics and genomics. 2nd ed. London: Oxford University Press; 2017. p. 116–8.
28. Bélanger SA, Caron J. Evaluation of the child with global developmental delay and intellectual disability. Paediatr Child Health. 2018;23(6):403–19.
29. Silove N, Collins F, Ellaway C. Update on the investigation of children with delayed development: investigation of developmental delay. J Paediatr Child Health. 2013;49(7):519–25.
30. Naughton AM, Maguire SA, Mann MK, Lumb RC, Tempest V, Gracias S, et al. Emotional, behavioral, and developmental features indicative of neglect or emotional abuse in preschool children: a systematic review: a systematic review. JAMA Pediatr. 2013;167(8):769–75.
31. McDonald JL, Milne S, Knight J, Webster V. Developmental and behavioural characteristics of children enrolled in a child protection pre-school: child development in maltreatment. J Paediatr Child Health. 2013;49(2):E142–6.
32. Murias K, Moir A, Myers KA, Liu I, Wei X-C. Systematic review of MRI findings in children with developmental delay or cognitive impairment. Brain Dev. 2017;39(8):644–55.
33. Presson AP, Partyka G, Jensen KM, Devine OJ, Rasmussen SA, McCabe LL, et al. Current estimate of Down Syndrome population prevalence in the United States. J Pediatr. 2013;163(4):1163–8.
34. Jones KL, Jones MC, del Campo M, editors. Recognizable patterns of malformation. In: Smith's recognizable patterns of human malformation: Expert consult—online and print. 7th ed. London: W B Saunders; 2013. p. 7–23.
35. Flore LA, Milunsky JM. Updates in the genetic evaluation of the child with global developmental delay or intellectual disability. Semin Pediatr Neurol. 2012;19(4):173–80.
36. Firth HV, Hurst JA, editors. Fragile X syndrome (FRAX). In: Oxford desk reference: clinical genetics and genomics. 2nd ed. London: Oxford University Press; 2017. p. 424–6.
37. Vissers LELM, Gilissen C, Veltman JA. Genetic studies in intellectual disability and related disorders. Nat Rev Genet. 2016;17(1):9–18.
38. Eun S-H, Hahn SH. Metabolic evaluation of children with global developmental delay. Korean J Pediatr. 2015;58(4):117–22.
39. Committee on Children with Disabilities. Developmental surveillance and screening of infants and young children. Pediatrics. 2001;108(1):192–6.
40. Riou EM, Ghosh S, Francoeur E, Shevell MI. Global developmental delay and its relationship to cognitive skills. Dev Med Child Neurol. 2009;51(8):600–6.
41. Hoyme HE. Minor malformations. Am J Dis Child. 1987;141:947.
42. Firth HV, Hurst JA, editors. Coarse facial features. In: Oxford desk reference: clinical genetics and genomics. 2nd ed. London: Oxford University Press; 2017. p. 106–8.
43. Lisi EC, Cohn RD. Genetic evaluation of the pediatric patient with hypotonia: perspective from a hypotonia specialty clinic and review of the literature: review. Dev Med Child Neurol. 2011;53(7):586–99.
44. Schaefer GB, Bodensteiner JB. Radiological findings in developmental delay. Semin Pediatr Neurol. 1998;5(1):33–8.
45. van Karnebeek CDM, Jansweijer MCE, Leenders AGE, Offringa M, Hennekam RCM. Diagnostic investigations in individuals with mental retardation: a systematic literature review of their usefulness. Eur J Hum Genet. 2005;13(1):6–25.
46. Tremblay I, Janvier A, Laberge A-M. Paediatricians underuse recommended genetic tests in children with global developmental delay. Paediatr Child Health. 2018;23(8):e156–62.
47. Borch LA, Parboosingh J, Thomas MA, Veale P. Re-evaluating the first-tier status of fragile X testing in neurodevelopmental disorders. Genet Med. 2020;22(6):1036–9.
48. Weinstein V, Tanpaiboon P, Chapman KA, Ah Mew N, Hofherr S. Do the data really support ordering fragile X testing as a first-tier test without clinical features? Genet Med. 2017;19(12):1317–22.

49. Stojanovic JR, Miletic A, Peterlin B, Maver A, Mijovic M, Borlja N, et al. Diagnostic and clinical utility of clinical exome sequencing in children with moderate and severe global developmental delay/intellectual disability. J Child Neurol. 2020;35(2):116–31.
50. Clark MM, Stark Z, Farnaes L, Tan TY, White SM, Dimmock D, et al. Meta-analysis of the diagnostic and clinical utility of genome and exome sequencing and chromosomal microarray in children with suspected genetic diseases. npj Genom Med [Internet]. 2018;3(1). https://doi.org/10.1038/s41525-018-0053-8
51. Wetterstrand KA. DNA sequencing costs: data from the NHGRI genome sequencing program (GSP) [Internet]. Genome.gov. [cited 2020 Dec 18]. http://www.genome.gov/sequencingcostsdata.
52. Srivastava S, Love-Nichols JA, Dies KA, Ledbetter DH, Martin CL, Chung WK, et al. Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders. Genet Med. 2019;21(11):2413–21.
53. Cloet E, Leys M, De Meirleir L. Access to early diagnostics, intervention, and support for children with a neurobiological developmental delay or disorder. Dev Med Child Neurol. 2017;59(12):1215–6.

Child with Suspected Autism

Aram Kim and Deepa S. Rajan

1 Introduction

Autism spectrum disorder (ASD) is a common, heterogeneous neurodevelopmental disorder characterized by impairments in language and social communication along with repetitive stereotypical behaviors. Since ASD is a behavioral diagnosis, the diagnostic criteria have evolved with time. The Diagnostic and Statistical Manual, third edition (DSM-III) included Autism, Asperger's syndrome, and Pervasive Developmental Disorders as possible diagnoses. But, due to the lack of clear diagnostic boundaries, the most recent International Classification of Diseases (ICD-11) and Diagnostic and Statistical Manual (DSM-V) merged these diagnoses under a single entity—Autism spectrum disorder [1]. The DSM-V criteria are listed below. While the diagnosis of ASD is primarily behavioral, it is crucial to obtain a comprehensive medical, developmental, and psychosocial history and perform a comprehensive physical examination. Finally, it is crucial to evaluate for a possible underlying etiology, in all cases.

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The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Criteria for Autism Spectrum Disorder (ASD)

(a) Persistent deficits in social communication and social interaction: In multiple settings in all 3 subdomains:
   - Social reciprocity
   - Non-verbal communication
   - Developing, maintaining, and understanding relationships

(b) Restricted, repetitive behaviors and interests: In 2 of 4 subdomains:
   - Stereotyped, repetitive behaviors
   - Insistence on monotony
   - Highly restricted, fixed interests
   - Altered sensitivity or interest in sensory inputs

(c) Symptoms must be present in early development but manifest later or masked later by learned techniques.
(d) Symptoms must cause clinically significant impairment in functioning
(e) Not better explained by intellectual disability or global developmental delay

2 Epidemiology

ASD has an estimated prevalence of 1 in 54 in children aged 8 years who are living in the United States [2]. There is a higher prevalence in males [2]. Prevalence is estimated to be equal among black and white children aged 8; however, black children are less likely to be evaluated by the age of 36 months when compared to their white counterparts despite a higher prevalence of intellectual disability. It is important to note that Hispanic children are less frequently identified as having ASD [2]. Both the prevalence and discrepancy among different racial groups are important for pediatricians to be knowledgeable about, to ensure equal screening and identification of all children at risk for ASD.

3 Diagnostic Approach

3.1 History

A comprehensive history is vital in the evaluation of a child with suspected ASD. The prenatal, birth, and postnatal history including maternal substance use, trauma during birth, or need for further evaluation in the neonatal intensive care unit

(NICU) are important. Along with providing an assessment of a child's development in comparison to his or her chronological age, a detailed history also enables risk stratification. A complete developmental history to understand achievement of milestones in different domains such as gross motor, fine motor, receptive language, expressive language, social interaction, and communication is essential. Isolated expressive language delay is important to differentiate from ASD. Children with developmental regression would benefit from a detailed neurological evaluation to distinguish from other neurodegenerative disorders. A comprehensive family history to understand the risks of an underlying genetic etiology would help guide diagnostic testing. A history should also include a complete review of systems to evaluate for risks of co-morbid conditions such as pica, attention-deficit/hyperactivity disorder (ADHD), intellectual disability, anxiety disorders, and epilepsy.

3.2 Physical Examination

A complete general physical examination in a child with suspected ASD should consider features that would point to the need for further diagnostic evaluation. Features concerning for dysmorphism or microcephaly should raise concerns for a possible underlying genetic disorder. While a larger head circumference has been described in children with ASD, those children who have a head circumference more than 2 standard deviations from mean would benefit from a genetics evaluation to rule out PTEN related abnormalities and other neurocutaneous mimics including neurofibromatosis and tuberous sclerosis. Any child being evaluated for ASD should have a dermatological examination for skin markers since neurocutaneous syndromes can be associated with ASD.

A comprehensive neurological examination evaluating tone, motor strength, deep tendon and developmental reflexes and coordination is crucial. Most children with ASD have a normal, nonlocalizing, neurological examination, and a deviation from such a norm would be concerning and likely require further evaluation by a neurologist. Additionally, observing how a child explores a new environment, how they interact with a stranger compared to a parent or caregiver, and how they play with caregiver and toys are extremely important when assessing a child for possible ASD.

3.3 Screening

Historically, diagnosing and screening for ASD was solely based on parental concerns and routine developmental screening done in a primary care setting. Despite parents reporting symptom onset at an average age of 2–3 years, the median age of diagnosing ASD in the United States was 4.25 years of age [2, 3]. Due to concerns for delays in making a diagnosis and evidence that earlier intervention improves

outcomes, the American Academy of Pediatrics (AAP) recommends screening all children during well child visits for developmental delays and disabilities at 9, 18, and 30 months and for ASD with specific screening tools at 18 and 24 months [4–8].

During routine developmental screening, all developmental milestones should be assessed through informal observations such as how a child interacts with parents or caregivers and when an unfamiliar adult enters the room, and during physical examination. Parents should be asked for concerns regarding their child's development and behaviors and in particular should be asked screening questions pertaining to symptoms concerning for ASD. Examples of "red flag" symptoms that should alert a pediatrician that a child may be at risk for ASD are: if a child does not respond to his or her name by 12 months or if a child does not point to items of interest by 14 months [9]. More symptoms can be found on the CDC website [9]. Pediatricians should be especially vigilant in children with siblings with ASD due to not only its heritability but also the fact that siblings of patients with ASD also have an increased risk of neurodevelopmental disorders [6, 10].

In addition to screening at every visit, specific screening tools for ASD should be employed at 18 and 24 months as developmental screening alone may not be sensitive enough to detect ASD (Fig. 1). There are several tools that can be used in the office, with the Modified Checklist for Autism in Toddlers—Revised and Follow up (MCHAT-R/F) being the most common tool used [4].

A child screened negative at 18 months needs to be screened again at 24 months since repeat screening at 24 months can identify children at risk despite an initial negative screen [15]. While children who are screened positive with the MCHAT may not be diagnosed with ASD, many of these children are at risk for other developmental disorders. Therefore, it is important for pediatricians to continue to monitor for symptoms that may lead to other diagnoses [11].

It is also important for clinicians to be aware that children with milder symptoms and typical cognition may not come to attention until they are older when the social demands of school tend to be challenging. In addition, some children with ASD have normal development to begin with before developing regression in developmental milestones. Therefore, vigilant surveillance is important even in school age children. Unfortunately, there is limited evidence for screening tools for children >30 months in a primary care setting [3, 4]. Despite limited evidence in the primary care setting, physicians can consider using the Social Communication Questionnaire (SCQ). Based on the cut off used, it can differentiate children who are developing normally compared to children with symptoms consistent with ASD rather than children who may also have symptoms concerning for ADHD [3, 16, 17].

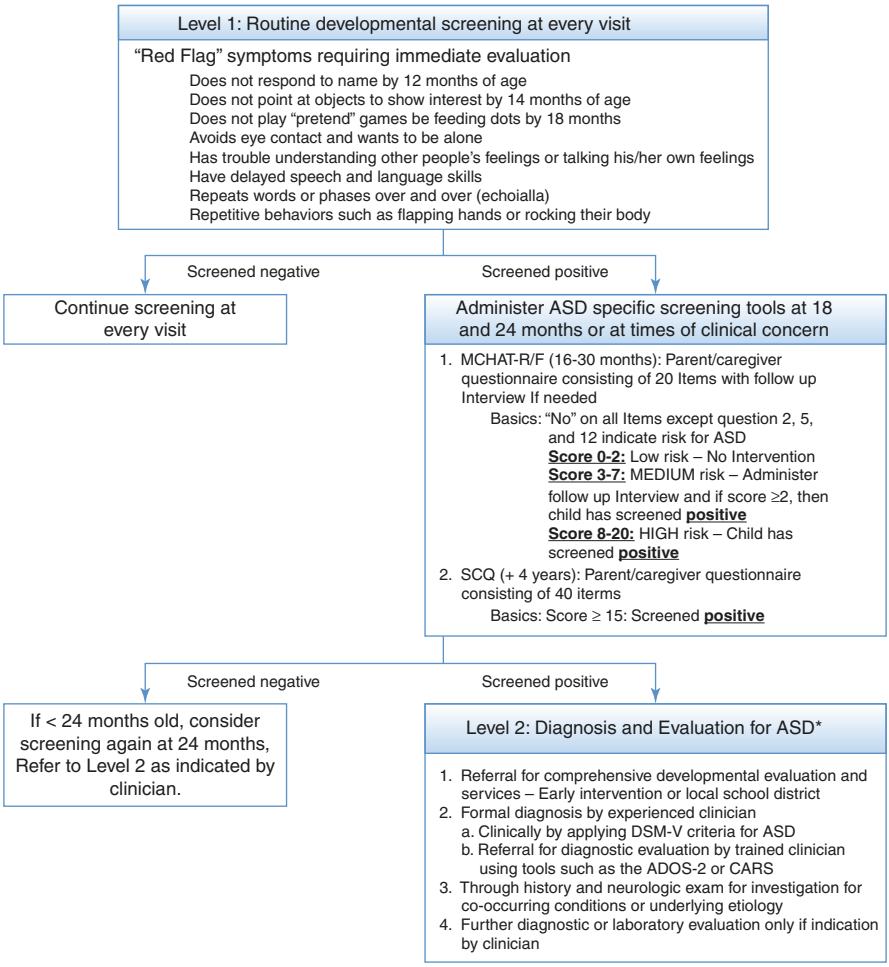

Fig. 1 Screening and diagnostic algorithm for autism spectrum disorder. *ASD* autism spectrum disorder, *MCHAT R/F* Modified Checklist for Autism in Toddler Revised and Follow up, *SCQ* Social Communication Questionnaire, *DMS V* Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, *ADOS 2* Autism Diagnostic Observation Schedule, Second Edition, *CARS 2* Childhood Autism Rating Scale, Second Edition. (Adapted from American Academy of Neurology, Practice Parameter: Screening and Diagnosis of Autism [4, 9, 11–14])

3.4 Diagnosis

Screening is meant to detect children who are at risk for ASD and not as a means of diagnosis. Once there is concern for ASD, a pediatrician can diagnose a child with ASD if he or she is comfortable with the application of the DSM-V criteria, as it has been shown that children as young at 18 months old can be diagnosed with ASD accurately by a skilled professional [18]. This is especially advantageous as it may expedite the implementation of appropriate interventions. However, it is important to note that children with ASD can have co-occurring conditions and other developmental concerns that often require multidisciplinary care from developmental behavioral pediatricians, neurologist, neurodevelopmental pediatricians, and psychiatrists. Referral to an audiologist is also an important step in the diagnostic process.

Validated tools for diagnosing ASD exist. Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) and Childhood Autism Rating Scale, Second Edition (CARS 2) are diagnostic tools based on observation of symptoms, while measures such as the Autism Diagnostic Inventory-Revised (ADI-R) are based on parent interview. The current diagnostic tools are time consuming and require a trained administrator, making implementation challenging in a primary care setting. Diagnoses by a combination of clinical observation and caregiver reports are more reliable than those made with diagnostic tools such as the ADI-R alone [19]. Therefore, pediatricians, despite making a referral for further evaluation, play an important role in supporting a diagnosis.

3.5 Etiologic Investigations and Differential Diagnoses

As emphasized before, a thorough history including prenatal, birth, family and medical history and a detailed general and neurological examination should be the initial step in guiding a clinician through a diagnostic evaluation of a child with ASD.

Laboratory and imaging studies to identify an underlying etiology should be tailored for the child being evaluated. Routine laboratory testing is not recommended. There are no neuroimaging findings that are specific to patients with ASD. Therefore, unless there are historical or clinical concerns, neuroimaging is not currently recommended in children with ASD as part of an initial evaluation. Red flags signs/symptoms that should point toward neuroimaging include the presence of microcephaly, macrocephaly, abnormal neurologic examination, concern for genetic disorder known to cause structural abnormalities in the central nervous system and atypical motor delays [12, 20–22].

Additionally, while patients with ASD are at an increased risk for developing seizures, electroencephalograms (EEG) are not recommended as part of the initial evaluation unless there are historical or clinical concerns. Atypical language regression should prompt a pediatrician to consult a neurologist or order an overnight EEG as it can be concerning for electrical status epilepticus of sleep (ESES). ESES is a childhood onset encephalopathy, characterized by developmental regression, where there is an activation and abundance of epileptiform discharges which become near continuous in nonrapid eye movement sleep.

The American Academy of Pediatrics, American College of Medical Genetics, and American Academy of Child and Adolescent Psychiatry recommend genetic testing for all children with ASD starting with chromosomal microarray (CMA) [4, 20, 21, 23]. The yield of definite pathogenic variants, or alterations known to be causative, is about 5.4–14% in patients with ASD and increases to 17–42% when variants of unknown significance (VUS) are added [24–27]. VUS are important to note as many times these variants can be reclassified as either benign or pathogenic.

Pediatricians should also consider investigating for Fragile X syndrome, as it is the most common monogenic cause of ASD and a common cause of intellectual disability (ID). Patients with fragile X syndrome may have a family history of males with intellectual disability and are characterized by a long narrow face, large ears, enlarged testicles in males, lax joints, and a prominent jaw. Both females and males may have ID or ASD due to Fragile X syndrome [28]. As Fragile X syndrome is caused by a CGG trinucleotide repeat on the FMR1 gene, it is not detected by a CMA and needs to be ordered separately.

However, if both the CMA and Fragile X testing are not revealing, nondiagnostic, or difficult to interpret and there is continued suspicion of a genetic diagnosis, medical genetics or neurogenetics referral is recommended (Table 1).

Lastly, as the yield of metabolic testing is low, testing for inborn errors of metabolism not recommended routinely for all patients with ASD. However, symptoms that suggest a need for further metabolic evaluation include atypical regression such as regression past 2 years of age, family history notable for metabolic diseases, sudden death in the family, dysmorphic features, hearing or visual compromise or other systemic signs such as poor weight gain. Initial metabolic evaluation can include a complete blood count, comprehensive metabolic panel, blood lead level, plasma amino acids, urine organic acids, acylcarnitine profile, as well pyruvate, and lactate levels. Additionally, AAP recommends serum creatine kinase and thyroid studies in children with motor delays [29–32]. Though many children at this point of evaluation will likely be referred to a specialist, pediatricians in resource limited areas may need to complete bulk of the diagnostic evaluation given the treatment implications in some disorders involving inborn errors of metabolism (Fig. 2).

Table 1 Genetic syndromes associated with ASD

Condition	Examination findings	Gene and additional testing
Fragile X syndrome	Long face, large ears, prominent forehead and jaw, joint laxity	*FMR1* (CGG trinucleotide repeat) via targeted mutation analysis (Southern blot)
Neurofibromatosis 1	Café au lait spots, axillary and inguinal freckling, cutaneous neurofibromas, Lisch nodules in iris, hypertension	*NF1*
PTEN hamartoma tumor syndrome	Macrocephaly; dermatologic findings such as lipomas, oral papilloma, trichilemmomas, pigmented macules on glans penis	*PTEN*; high risk for both benign and malignant tumors
Rett syndrome	Microcephaly, loss of purposeful hand movement, stereotypical hand movements such as hand wringing, apraxia, hyperventilation, seizures, developmental regression	*MECP2*
Smith–Lemil–Opitz syndrome	Microcephaly, cleft palate, toe syndactyly, hypospadias in males, growth stagnation, typical facial features—ptosis, low set ears, epicanthal folds, short nose, micrognathia, anteverted nares	*DHCR7*; can additionally test for 7-dehydrocholesterol which will be elevated
Timothy syndrome	Low set ears, flat nasal bridge, thin upper lip, round facies, baldness first 2 years then thin scalp hair, dental abnormalities, frequent infections, abnormalities on EKG—long QT interval, AV block, macroscopic T wave alterans	*CACNA1C*
Tuberous sclerosis	Shagreen patches, angiofibromas, retinal hamartomas, hypopigmented macules, ungula fibromas, seizures	*TSC1, TSC2*; associated conditions may need monitoring such as renal angiomyolipomas and CNS tumors

Adapted from Myers SM, Challman TD. Autism Spectrum Disorders. In: Voight RG, Macias MM, Myers SM, eds. Developmental and Behavioral Pediatrics. Elk Grove Village, IL: American Academy of Pediatrics; 2011: 249–291

Disorders of amino acid metabolism
PKU untreated
Homocystinuria
Branched chain ketoacid dehydrogenase kinase deficiency
Disorders of cholesterol metabolism
Smith Lemli Opitz syndrome
Disorders associated with folate deficiency
Folate receptor 1 gene mutations
Dihydrofolate reductase deficiency
Disorders of creatine transport or metabolism
Ariginine-glycine amidinotransferase deficiency
Guanidinoacetate methyltransferase deficiency
X-linked creatine transporter deficits
Disorders of carnitine biosynthesis
6-N-terimethyllysine dioxygenase deficiency
Adenosine deaminase deficiency
Cytosolic 5' nucleotidase superactivity
Lysosomal storage disorders
Sanfilippo syndrome
Mitochondrial disorders
Others
Biotinidase deficiency
Urea cycle defects

Fig. 2 Treatable metabolic disorders associated with ASD [21, 33–40]

4 Management

The pediatrician's role primarily starts with universal clinical screening during well-child visits with the goal of early recognition. A patient- and family-centered approach is helpful in establishing trust and helping families navigate this challenging diagnosis. The Autism Speaks Network maintains a toolkit that is recommended by the AAP as a useful resource to guide physicians leading families through this diagnosis.

Once children are identified through screening, the goals of intervention in children should aim to minimize deficits and maximize the patient's ability to function independently. In the United States, the Individuals with Disabilities Act (IDEA) of 2004 and Every Student Succeeds Act of 2015 require the use of practices supported by scientific evidence. Early Intervention services under part C IDEA ensure that children under 3 years of age who are identified through screening are assessed and receive appropriate therapies and services.

The interventions available for children with ASD include educational strategies, developmental therapies, and behavioral interventions. These should be individualized to each child's need and developmental stage and reassessed periodically.

4.1 Interventional Therapies

Evidence-based interventions are categorized into comprehensive treatment models and focused interventions [41]. Applied behavior analysis (ABA) is one of the most commonly utilized comprehensive and individualized treatment approaches based on the principles of learning theory. ABA is centered on methods such as reinforcement to improve communication through language. ABA may also decrease challenging behaviors [42]. It has been associated with achievement of individualized goals and optimal developmental outcomes [43, 44]. Other interventions including Developmental Relationship are focused on interventions that work on caregiver child relationships. As integrating parents in the intervention process is important, many interventions are now based on parent support and many are parent mediated [45].

There are certain other interventions that focus on educational therapies including classroom-based models and social skill instruction.

Directing appropriate diagnostic evaluation, advocating for community-based and psychosocial interventions, identifying co-morbidities, recognizing red flags signs/symptoms that indicate need for further investigation and considering psychopharmacology when the need arises would help in providing comprehensive care for children identified with ASD.

A large number of complementary, integrative, and alternative therapies have emerged over the years for children with ASD but unfortunately lack supporting scientific evidence. The National Center for complementary and Integrative Health maintains a list of current evidence on these therapies and can serve as a useful resource in the primary care setting to help pediatricians lead meaningful discussions with patient families.

4.2 Comorbidities: Identification and Management

For patients who are diagnosed with ASD, it is considered standard of care that they undergo a comprehensive developmental evaluation since many patients have co-occurring disorders. Language delays that include up to 30% being non-verbal, motor issues, difficulty with sleep and eating, and epilepsy are more common in preschool children [46]. Conversely, mood disorders, anxiety, externalizing behaviors, ADHD, and intellectual disability are more commonly seen in school-aged children [10]. In fact, it has been reported that as much as 33% of school aged children with ASD have ID [2]. Many times, referral to the school system or appropriate services such as early intervention will expedite this process.

4.2.1 ADHD

ADHD is one of the most common co-occurring condition in individuals with ASD, and is known to further compromise social skill functioning [47]. Individuals with ASD, especially with language delay may appear to be inattentive or hyperactive and hence a full comprehensive evaluation and implementation of appropriate educational support are important before assigning a diagnosis [4]. Also, interventions for ASD do not target symptoms of ADHD, making it crucial to screen for symptoms and signs concerning for ADHD.

4.2.2 Epilepsy

Patients with ASD are at an increased risk for developing epilepsy especially those with ID, female patients, and those born at a lower gestational age [10, 48]. It is also important to note that many patients with ASD, who do not have seizures, can still have interictal abnormalities (abnormalities on EEG that indicate a predisposition to seizures in the future) [49]. Therefore, EEGs should be ordered only if there is a clinical concern for seizures. Atypical regression such as a late speech regression, especially among children with genetic disorders like tuberous sclerosis, could be sign of seizures in sleep and will need referral to a neurologist.

4.2.3 Sleep

Disturbances of sleep are a common problem in patients with ASD and are reported in about 50–80% of children with ASD [50]. In younger children, it is more common to see bedtime resistance and parasomnias, whereas in older children, delayed sleep onset and shorter sleep duration are more common. Unfortunately, these symptoms can cause worsening of daytime behaviors [50, 51]. Therefore, it is important for pediatricians to screen for issues with sleep including a thorough environmental history—household noise and appliance placement such as electronic tablets can disrupt sleep hygiene—and sleep habits such as snoring and restless sleeping. Other etiologies that can disrupt sleep such as iron deficiency anemia, sleep apnea, seizures, and reflux should also be considered.

The most successful interventions include behavioral interventions and parental education. Anticipatory guidance for parents, recommendations about behavioral interventions such as establishing regular bedtime routines and attempts at improving sleep hygiene such as removing all tablets from vicinity are helpful [52, 53]. Though there are no FDA-approved medications for improving sleep in children, melatonin can be considered in conjunction with behavioral interventions to aid in sleep at a dose of 1–6 mg [54, 55].

4.2.4 Visual Problems

The AAP and the American Academy of Ophthalmology recommend that children have their vision evaluated as a newborn, at 6 months of age and yearly until 5 years of age with follow up annually or biannually after 5 years of age [56]. However, patients with ASD have increased risk of having vision problems that may not only hinder progress despite. Common clinical findings in children with ASD are significant refractive error, strabismus and amblyopia with even higher rates in children with concurrent ID. Therefore, any abnormalities on routine visual screening or clinical concerns should prompt pediatricians to make appropriate referrals to ophthalmology [57].

4.2.5 Gastrointestinal Symptoms and Feeding Issues

Children with ASD have multiple gastrointestinal symptoms including feedings issues and pica. Generalized abdominal pain, constipation, diarrhea and reflux are more commonly reported in children with ASD. The diagnoses of these disorders in nonverbal children or those who have delays in expressive language can be challenging. They may present with irritability, difficulty with sleep, or worsening behavioral outbursts [58, 59]. Additionally, children with ASD can also have food selectivity based on texture or color along with rumination and volitional gagging [60, 61].Though many times an etiologic cause for these behaviors may not be elucidated, it is important to ensure that delays in oromotor skills, dental pain, significant constipation, food allergies, and lactose intolerance are not contributing to these behaviors. The AAP recommends that pediatricians should get a detailed dietary history especially if parents or caregivers report concerns about restrictive eating. Like many children in the United States, children with ASD are also at risk for nutritional deficiencies such as Vitamin D deficiency [62]. Parental education encouraging routine meals and snacks along with promotion of self-feeding and distraction free eating is recommended. It is also important to let parents know that children with ASD may need to be offered new food items several times before they are familiar with it. Additionally, with concerns for pica, educating parents on possible toxic ingestions and safeguarding the house along with constant adult supervision, if deemed necessary is extremely important. If there are severe gastrointestinal issues causing weight loss or nutritional deficiencies referral to a specialist may be warranted at that time.

4.2.6 Obesity

Individuals with ASD are at an increased risk for being overweight or obese due to their food habits and higher prevalence of sedentary lifestyles since they may have minimal interest in activities such as sports [63]. Additionally, side effects from medications can increase the risk of obesity. Therefore, parental education and

careful monitoring of an individual's body mass index (BMI) is recommended with referrals to programs that promote healthy choices if needed.

4.2.7 Dental

There are several barriers precluding individuals with ASD from getting proper timely dental care including lack of cooperation from the child and lack of comfort from the dental care provider [64]. Therefore, it is important for pediatricians to provide anticipatory guidance on brushing and fluoride application and to ensure that when changes in behaviors or sleep patterns occur, dental pain is evaluated as a potential cause and ruled out. Referral to a pediatric dentist who has expertise and interest in managing children with developmental challenges may be beneficial.

4.2.8 Disruptive Behavior Disorders

Disruptive behaviors such as aggression, self-injurious behaviors, and tantrums have been reported in children with ASD. New onset of these behaviors should prompt evaluation for commonly co-occurring medical conditions that may cause discomfort such as constipation, dental pain, or eye pain. However, if a thorough review of systems does not reveal an etiology, assessments such as a functional behavioral analyses should be considered so that behavioral interventions can be implemented both at school and home to maximize the child's environment [65]. Children who have concomitant ADHD, lower cognitive skills, sleep issues and internalizing behaviors such as anxiety have higher rates of aggressive behaviors. Similarly, children with limited cognitive abilities, hyperactivity, lower language skills, or impulsivity can also display persistence of self- injurious behaviors such as head banging and self-picking [66, 67]. This again highlights the importance of screening for these co-occurring medical conditions. If behaviors cannot be managed through conservative interventions such as behavioral strategies, the pediatrician can consider referral to a child psychiatrist/neurologist for possible initiation of medication. Additionally, the safety of the child and family should always be assessed and appropriate referrals should be made if pediatrician deems a certain environment to be unsafe [4].

4.2.9 Psychiatric Disorders

There is an increased frequency of anxiety and depressive disorders in individuals with ASD [10]. Anxiety is more commonly reported in school aged children and adults with ASD with typical cognitive and language abilities and can manifest as hyperactivity, gastrointestinal symptoms, inattention, or worsening sensory seeking behaviors [68, 69]. Similarly, depressive disorders are also more common in the same population. Individuals with ASD have an increased rate of attempted suicide

[70]. This risk is higher among males, minority race or ethnicity, lower education level, those subjected to peer victimization and have behavioral issues [4, 71]. It is important for pediatricians to screen for depression risk by obtaining a family history, asking about environmental stressors, and about home and school environment. The AAP recommends screening adolescents for depression starting at 12 years of age [4]. Interventions include supportive therapy, medications, and cognitive behavioral therapy.

4.3 Psychopharmacology

Identifying comorbidities like ADHD, behavioral issues, and mood disorders should help direct the need and effective use of psychopharmacology in children with ASD. Pediatricians will need to carefully consider the benefits and risks of psychotropic medications and always use these as only as part of a comprehensive care plan. Risperidone and aripipazole are the only two medications approved by the Food and Drug Administration for irritability in individuals with ASD [4]. The recommended doses, per the American Academy of Child and Adolescent Psychiatry, are 0.5–3.5 mg per day for risperidone and 5, 10, or 15 mg per day for aripipazole. Common adverse effects of for both these medications are weight gain and dyslipidemia that may be improved with metformin along with extrapyramidal symptoms [4, 20]. Children with epilepsy should be treated in collaboration with a child neurologist (Table 2).

Table 2 When to refer/admit

When to refer:	
1.	Refer to Developmental Specialist for red flag signs in Table 1
2.	History of motor regression
3.	History suggestive of metabolic disorders, dysmorphism, or a genetic syndrome
4.	Abnormal neurological examination
5.	Co-morbidities not addressed by first line interventions—seizures, failure to thrive despite dietary changes, visual abnormalities, significant sleep disorders or behavior problems or mental health concerns not responding to first-line interventions
When to admit:	
1.	Severe malnutrition
2.	Concern for frequent untreated seizures
3.	Severe behavioral issues with concerns for safety of the child or family

4.4 Outcomes/Prognosis

Though the course cannot be fully predicted at time of diagnosis, in general when the diagnosis is made prior to 3 years of age after a complete evaluation, ASD tends to have a nonprogressive course [72]. Studies have shown that a small percentage of children diagnosed at early childhood may not meet the diagnostic criteria in the future; these children tended to have participated in early intervention, had higher cognitive skills at age 2 years, and had a reduction in repetitive behaviors. In fact, in both groups—children who were more cognitively abled and those who were less so—parent participation in early intervention has shown to predict positive outcomes during adulthood with regards to IQ and adaptive skills [73]. Skills earlier in life predict the potential progress a child with ASD can make in the future. However, ASD tends to be a lifelong diagnosis and a trajectory of one child with ASD cannot predict that of another [10]. However, this highlights the importance of early screening for improving outcomes of children with ASD (Table 3).

Resources for Pediatricians and Families ATN/AIPR-P Guide to Providing Feedback to Families Affected by Autism. https://www.autismspeaks.org/tool-kit/atnair-p-guide-providing-feedback-families-affected-autism

Center for Disease Control and Prevention: Autism Spectrum Disorder. https://www.cdc.gov/ncbddd/autism/index.html

National Center for Complementary and Integrative Health: Autism. https://www.nccih.nih.gov/health/autism

Table 3 Clinical pearls/key points table

ASD is a common neurodevelopmental disorder. All children should be screened with screening tools at 18 and 24 months
Early intervention such as participation in EI or ABA impacts overall outcome. Hence early identification is important
Appropriate referral for a complete developmental assessment and further diagnostic evaluations is recommended in a child, identified as being at risk for ASD
Children with ASD are at a higher risk of developing multiple co-occurring conditions such as seizures, intellectual disability, sleep issues, ADHD and psychiatric issues. Recognizing and addressing these is essential to the care of these children
Parental education, continued symptom management, and early intervention are important

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub; 2013.
2. Maenner MJ, Shaw KA, Baio J. Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2016. MMWR Surveill Summ. 2020;69(4):1.
3. Levy SE, Wolfe A, Coury D, Duby J, Farmer J, Schor E, et al. Screening tools for autism spectrum disorder in primary care: a systematic evidence review. Pediatrics. 2020;145(Suppl 1):S47–59.
4. Hyman SL, Levy SE, Myers SM. Identification, evaluation, and management of children with autism spectrum disorder. Pediatrics. 2020;145(1):e20193447.
5. Baio J. Prevalence of autism spectrum disorder among children aged 8 years-autism and developmental disabilities monitoring network, 11 sites, United States, 2010. 2014.
6. Zwaigenbaum L, Bauman ML, Fein D, Pierce K, Buie T, Davis PA, et al. Early screening of autism spectrum disorder: recommendations for practice and research. Pediatrics. 2015;136(Supplement 1):S41–59.
7. Dawson G, Rogers S, Munson J, Smith M, Winter J, Greenson J, et al. Randomized, controlled trial of an intervention for toddlers with autism: the Early Start Denver Model. Pediatrics. 2010;125(1):e17–23.
8. Kasari C, Gulsrud AC, Wong C, Kwon S, Locke J. Randomized controlled caregiver mediated joint engagement intervention for toddlers with autism. J Autism Dev Disord. 2010;40(9):1045–56.
9. Centers for Disease Control and Prevention. Autism spectrum disorder (ASD)—signs and symptoms 2019. https://www.cdc.gov/ncbddd/autism/signs.html.
10. Lord C, Brugha TS, Charman T, Cusack J, Dumas G, Frazier T, et al. Autism spectrum disorder. Nat Rev Dis Primers. 2020;6(1):1–23.
11. Robins D, Fein D, Barton M. Modified checklist for autism in toddlers, revised with follow-up. https://www.mchatscreen.com; 2009.
12. Filipek PA, Accardo PJ, Ashwal S, Baranek G, Cook E, Dawson G, et al. Practice parameter: screening and diagnosis of autism: report of the quality standards Subcommittee of the American Academy of Neurology and the Child Neurology Society. Neurology. 2000;55(4):468–79.
13. Shulman C, Rice CE, Morrier MJ, Esler A. The role of diagnostic instruments in dual and differential diagnosis in autism spectrum disorder across the lifespan. Child Adolesc Psychiatr Clin. 2020;29(2):275–99.
14. Eaves LC, Wingert HD, Ho HH, Mickelson EC. Screening for autism spectrum disorders with the social communication questionnaire. J Dev Behav Pediatr. 2006;27(2):S95–S103.
15. Dai YG, Miller LE, Ramsey RK, Robins DL, Fein DA, Dumont-Mathieu T. Incremental utility of 24-month autism spectrum disorder screening after negative 18-month screening. J Autism Dev Disord. 2020;50(6):2030–40.
16. Mouti A, Dryer R, Kohn M. Differentiating autism spectrum disorder from ADHD using the social communication questionnaire. J Atten Disord. 2019;23(8):828–37.
17. Schwenck C, Freitag CM. Differentiation between attention-deficit/hyperactivity disorder and autism spectrum disorder by the social communication questionnaire. ADHD Attent Deficit Hyperactivity Disord. 2014;6(3):221–9.
18. Zwaigenbaum L, Bryson SE, Brian J, Smith IM, Roberts W, Szatmari P, et al. Stability of diagnostic assessment for autism spectrum disorder between 18 and 36 months in a high-risk cohort. Autism Res. 2016;9(7):790–800.
19. Havdahl KA, Bishop SL, Surén P, Øyen AS, Lord C, Pickles A, et al. The influence of parental concern on the utility of autism diagnostic instruments. Autism Res. 2017;10(10):1672–86.
20. Volkmar F, Siegel M, Woodbury-Smith M, King B, McCracken J, State M. Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry. 2014;53(2):237–57.

21. Schaefer GB, Mendelsohn NJ. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. Genet Med. 2013;15(5):399–407.
22. Moeschler JB, Shevell M. Comprehensive evaluation of the child with intellectual disability or global developmental delays. Pediatrics. 2014;134(3):e903–18.
23. Manning M, Hudgins L. Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. Genet Med. 2010;12(11):742–5.
24. Ho KS, Wassman ER, Baxter AL, Hensel CH, Martin MM, Prasad A, et al. Chromosomal microarray analysis of consecutive individuals with autism spectrum disorders using an ultra-high resolution chromosomal microarray optimized for neurodevelopmental disorders. Int J Mol Sci. 2016;17(12):2070.
25. Tammimies K, Marshall CR, Walker S, Kaur G, Thiruvahindrapuram B, Lionel AC, et al. Molecular diagnostic yield of chromosomal microarray analysis and whole-exome sequencing in children with autism spectrum disorder. JAMA. 2015;314(9):895–903.
26. Shen Y, Dies KA, Holm IA, Bridgemohan C, Sobeih MM, Caronna EB, et al. Clinical genetic testing for patients with autism spectrum disorders. Pediatrics. 2010;125(4):e727–35.
27. McGrew SG, Peters BR, Crittendon JA, Veenstra-VanderWeele J. Diagnostic yield of chromosomal microarray analysis in an autism primary care practice: which guidelines to implement? J Autism Dev Disord. 2012;42(8):1582–91.
28. Stone WL, Basit H, Los E. Fragile X syndrome. StatPearls. Treasure Island: StatPearls Publishing. Copyright © 2020, StatPearls Publishing LLC; 2020.
29. Shevell M, Ashwal S, Donley D, Flint J, Gingold M, Hirtz D, et al. Practice parameter: evaluation of the child with global developmental delay: report of the quality standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2003;60(3):367–80.
30. Schiff M, Benoist J-F, Aïssaoui S, Boepsflug-Tanguy O, Mouren M-C, De Baulny HO, et al. Should metabolic diseases be systematically screened in nonsyndromic autism spectrum disorders? PLoS One. 2011;6(7):e21932.
31. Hadjixenofontos A, Schmidt MA, Whitehead PL, Konidari I, Hedges DJ, Wright HH, et al. Evaluating mitochondrial DNA variation in autism spectrum disorders. Ann Hum Genet. 2013;77(1):9–21.
32. Campistol J, Díez-Juan M, Callejón L, Fernandez-De Miguel A, Casado M, Garcia Cazorla A, et al. Inborn error metabolic screening in individuals with nonsyndromic autism spectrum disorders. Dev Med Child Neurol. 2016;58(8):842–7.
33. García-Cazorla A, Oyarzabal A, Fort J, Robles C, Castejón E, Ruiz-Sala P, et al. Two novel mutations in the BCKDK (branched-chain keto-acid dehydrogenase kinase) gene are responsible for a neurobehavioral deficit in two pediatric unrelated patients. Hum Mutat. 2014;35(4):470–7.
34. van Karnebeek CD, Stockler S. Treatable inborn errors of metabolism causing intellectual disability: a systematic literature review. Mol Genet Metab. 2012;105(3):368–81.
35. Cario H, Smith DE, Blom H, Blau N, Bode H, Holzmann K, et al. Dihydrofolate reductase deficiency due to a homozygous DHFR mutation causes megaloblastic anemia and cerebral folate deficiency leading to severe neurologic disease. Am J Hum Genet. 2011;88(2):226–31.
36. Ziats MN, Comeaux MS, Yang Y, Scaglia F, Elsea SH, Sun Q, et al. Improvement of regressive autism symptoms in a child with TMLHE deficiency following carnitine supplementation. Am J Med Genet A. 2015;167(9):2162–7.
37. Flinn AM, Gennery AR. Adenosine deaminase deficiency: a review. Orphanet J Rare Dis. 2018;13(1):1–7.
38. Legido A, Jethva R, Goldenthal MJ, editors. Mitochondrial dysfunction in autism. Seminars in pediatric neurology. Elsevier; 2013.
39. Jiang Y-H, Wang Y, Xiu X, Choy KW, Pursley AN, Cheung SW. Genetic diagnosis of autism spectrum disorders: the opportunity and challenge in the genomics era. Crit Rev Clin Lab Sci. 2014;51(5):249–62.

40. Frye RE. Metabolic and mitochondrial disorders associated with epilepsy in children with autism spectrum disorder. Epilepsy Behav. 2015;47:147–57.
41. Wong C, Odom SL, Hume KA, Cox AW, Fettig A, Kucharczyk S, et al. Evidence-based practices for children, youth, and young adults with autism spectrum disorder: a comprehensive review. J Autism Dev Disord. 2015;45(7):1951–66.
42. Smith T, Eikeseth SO. Ivar Lovaas: pioneer of applied behavior analysis and intervention for children with autism. J Autism Dev Disord. 2011;41(3):375–8.
43. Linstead E, Dixon DR, French R, Granpeesheh D, Adams H, German R, et al. Intensity and learning outcomes in the treatment of children with autism spectrum disorder. Behav Modif. 2017;41(2):229–52.
44. Orinstein AJ, Helt M, Troyb E, Tyson KE, Barton ML, Eigsti I-M, et al. Intervention for optimal outcome in children and adolescents with a history of autism. J Dev Behav Pediatr. 2014;35(4):247–56.
45. Bearss K, Johnson C, Smith T, Lecavalier L, Swiezy N, Aman M, et al. Effect of parent training vs parent education on behavioral problems in children with autism spectrum disorder: a randomized clinical trial. JAMA. 2015;313(15):1524–33.
46. Tager-Flusberg H, Kasari C. Minimally verbal school-aged children with autism spectrum disorder: the neglected end of the spectrum. Autism Res. 2013;6(6):468–78.
47. Lord C, Elsabbagh M, Baird G, Veenstra-Vanderweele J. Autism spectrum disorder. Lancet. 2018;392(10146):508–20.
48. El Achkar CM, Spence SJ. Clinical characteristics of children and young adults with co-occurring autism spectrum disorder and epilepsy. Epilepsy Behav. 2015;47:183–90.
49. Ghacibeh GA, Fields C. Interictal epileptiform activity and autism. Epilepsy Behav. 2015;47:158–62.
50. Miano S, Ferri R. Epidemiology and management of insomnia in children with autistic spectrum disorders. Pediatr Drugs. 2010;12(2):75–84.
51. Cohen S, Conduit R, Lockley SW, Rajaratnam SM, Cornish KM. The relationship between sleep and behavior in autism spectrum disorder (ASD): a review. J Neurodev Disord. 2014;6(1):44.
52. Blackmer AB, Feinstein JA. Management of sleep disorders in children with neurodevelopmental disorders: a review. Pharmacotherapy. 2016;36(1):84–98.
53. Malow BA, Adkins KW, Reynolds A, Weiss SK, Loh A, Fawkes D, et al. Parent-based sleep education for children with autism spectrum disorders. J Autism Dev Disord. 2014;44(1):216–28.
54. Tordjman S, Najjar I, Bellissant E, Anderson GM, Barburoth M, Cohen D, et al. Advances in the research of melatonin in autism spectrum disorders: literature review and new perspectives. Int J Mol Sci. 2013;14(10):20508–42.
55. Malow B, Adkins KW, McGrew SG, Wang L, Goldman SE, Fawkes D, et al. Melatonin for sleep in children with autism: a controlled trial examining dose, tolerability, and outcomes. J Autism Dev Disord. 2012;42(8):1729–37.
56. Loh AR, Chiang MF. Pediatric vision screening. Pediatr Rev. 2018;39(5):225.
57. Swanson MW, Lee SD, Frazier MG, Bade A, Coulter RA. Vision screening among children with autism spectrum disorder. Optom Vis Sci. 2020;97(11):917–28.
58. Buie T, Campbell DB, Fuchs GJ, Furuta GT, Levy J, VandeWater J, et al. Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. Pediatrics. 2010;125(Suppl 1):S1–S18.
59. Chaidez V, Hansen RL, Hertz-Picciotto I. Gastrointestinal problems in children with autism, developmental delays or typical development. J Autism Dev Disord. 2014;44(5):1117–27.
60. Bandini LG, Anderson SE, Curtin C, Cermak S, Evans EW, Scampini R, et al. Food selectivity in children with autism spectrum disorders and typically developing children. J Pediatr. 2010;157(2):259–64.
61. Sharp WG, Berry RC, McCracken C, Nuhu NN, Marvel E, Saulnier CA, et al. Feeding problems and nutrient intake in children with autism spectrum disorders: a meta-analysis and comprehensive review of the literature. J Autism Dev Disord. 2013;43(9):2159–73.

62. Hyman SL, Stewart PA, Schmidt B, Lemcke N, Foley JT, Peck R, et al. Nutrient intake from food in children with autism. Pediatrics. 2012;130(Suppl 2):S145–53.
63. Zuckerman KE, Hill AP, Guion K, Voltolina L, Fombonne E. Overweight and obesity: prevalence and correlates in a large clinical sample of children with autism spectrum disorder. J Autism Dev Disord. 2014;44(7):1708–19.
64. Du RY, Yiu CK, King NM. Oral health behaviours of preschool children with autism spectrum disorders and their barriers to dental care. J Autism Dev Disord. 2019;49(2):453–9.
65. Doehring P, Reichow B, Palka T, Phillips C, Hagopian L. Behavioral approaches to managing severe problem behaviors in children with autism spectrum and related developmental disorders: a descriptive analysis. Child Adolesc Psychiatr Clin. 2014;23(1):25–40.
66. Chen C, Shen YD, Xun GL, Cai WX, Shi LJ, Xiao L, et al. Aggressive behaviors and treatable risk factors of preschool children with autism spectrum disorder. Autism Res. 2017;10(6):1155–62.
67. Fitzpatrick SE, Srivorakiat L, Wink LK, Pedapati EV, Erickson CA. Aggression in autism spectrum disorder: presentation and treatment options. 2016.
68. Sukhodolsky DG, Scahill L, Gadow KD, Arnold LE, Aman MG, McDougle CJ, et al. Parent-rated anxiety symptoms in children with pervasive developmental disorders: frequency and association with core autism symptoms and cognitive functioning. J Abnorm Child Psychol. 2008;36(1):117–28.
69. Vasa RA, Mazurek MO, Mahajan R, Bennett AE, Bernal MP, Nozzolillo AA, et al. Assessment and treatment of anxiety in youth with autism spectrum disorders. Pediatrics. 2016;137(Suppl 2):S115–23.
70. Segers M, Rawana J. What do we know about suicidality in autism spectrum disorders? A systematic review. Autism Res. 2014;7(4):507–21.
71. De-la-Iglesia M, Olivar J-S. Risk factors for depression in children and adolescents with high functioning autism spectrum disorders. ScientificWorldJournal. 2015;2015:127853.
72. Ozonoff S, Young GS, Landa RJ, Brian J, Bryson S, Charman T, et al. Diagnostic stability in young children at risk for autism spectrum disorder: a baby siblings research consortium study. J Child Psychol Psychiatry. 2015;56(9):988–98.
73. Anderson DK, Liang JW, Lord C. Predicting young adult outcome among more and less cognitively able individuals with autism spectrum disorders. J Child Psychol Psychiatry. 2014;55(5):485–94.

Child with Attention Deficit Disorder/Child with Attention Deficit Hyperactivity Disorder (ADHD)

Kimberley Levitt and Barbara Felt

1 Background

1.1 Introduction

Attention-deficit/hyperactivity disorder or ADHD is the most common neurodevelopmental disorder in children and adolescents. The term, ADHD, describes individuals with levels of inattention, and/or motoric activity and impulsivity that are greater than for other same-age and gender peers. The *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) [1] lists the following three categories of ADHD: predominantly inattentive, predominately hyperactive/impulsive, and combined. It may be challenging, however, to differentiate ADHD from other co-occurring or alternative conditions affecting areas of development, learning, behavior, mental health, and/or psychosocial concerns. The purpose of this chapter is to provide a review of our current understanding of ADHD, as well as, guidance regarding the identification, evaluation and management of this common disorder. It is important that primary care physicians and other health providers in general practice, consider ADHD often and feel comfortable evaluating for this condition.

1.2 Epidemiology

The prevalence of ADHD has increased overtime, thought to be related to improvements in the education of physicians and other primary care providers and the availability of tools for screening and assessment [2]. The estimated prevalence of

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ADHD varies depending on the study and methods used. Data from the United States (US) National Survey of Children's Health (NSCH) suggest that between 2003 and 2011, using phone survey of parents, the percent of individuals ever being diagnosed with ADHD increased by 42% from 5 to 11% [2, 3]. More recently, the 2016 NSCH survey used online and mail methods and expanded the age of interest to children 2–17 years. The 2016 survey demonstrated that 9.4% of US children had ever received a diagnosis of ADHD and 8.4% had a current ADHD diagnosis [4]. In the 2016 NSCH survey, a number of demographic factors were associated with having an ADHD diagnosis, including Black race, male gender, age 12–17 years, and living in poverty, rural areas or the Midwest or Southern US. Reports estimate the prevalence of ADHD for males as 2–4:1 compared to females [4–6]. Co-occurring conditions were common among children with current ADHD, affecting nearly 64%. Behavior and conduct problems were reported for over half of the children, and anxiety problems for nearly one-third [4]. The United States is not alone with regard to ADHD prevalence; a 2013 World Health Organization report of the global burden of diseases noted that about 39 million people worldwide were estimated to have been affected by ADHD [7, 8].

1.3 Etiology

The etiology of attention-deficit and hyperactivity disorder (ADHD) is multifactorial. In discussing the various risk factors for ADHD, we will consider genetic, neurobiological, neurochemical, and environmental etiologies.

The hereditary nature of ADHD has been well described in the literature [9]. Immediate family members, such as parents and siblings, of children with ADHD have been reported to have a two to eight times higher risk [10]. No specific gene or genome-wide associations have been identified, though the literature includes descriptions of potential candidate genes [11]. ADHD has also been associated with a number of genetic conditions including Fragile X syndrome, Klinefelter syndrome, Turner syndrome, Prader–Willi syndrome, Williams syndrome, neurofibromatosis, and 22q11.2 deletion syndrome [12].

Alterations in morphology and structural connectivity have been described in regards to anatomical brain variations associated with ADHD [11]. Findings include decreased cerebral and cerebellar volumes, gray matter reduction, and cortical thinning [11]. Additionally, frontostriatal circuitry differences have been implicated in children with ADHD [11].

In regards to the neurochemical etiology of ADHD, involvement of the dopaminergic and adrenergic systems, as well as potentially serotoninergic and cholinergic systems, have been implicated [11]. Pharmacologic therapies target these neurochemical systems, as stimulant medications (methylphenidate and amphetamine salts) block presynaptic reuptake of dopamine and norepinephrine [11].

Environmental risk factors account for approximately 20–25% of ADHD [11]. Significant prenatal and perinatal environmental factors associated with ADHD

include maternal smoking and alcohol consumption, prematurity, and low birth weight [8, 11, 12]. Postnatal risk factors for ADHD symptoms include lead exposure, thyroid disorder, viral illness (particularly post viral encephalitis), sleep disorders, and traumatic brain injury [12].

2 Diagnosis

2.1 Presentation

At health supervision visits, a parent might present his/her concern(s) about their child's progress in preschool or school and/or behavioral dysregulation at home, school or in community settings. Even without a parent prompting; however, the high prevalence of ADHD suggests that it would be prudent to take the opportunity at health care visits to ask questions that might allow for earlier identification of the problems. Screening questions might include: "have you or your child's teacher had concerns about your child's learning, attention or work completion at school?"; "have there been behavioral concerns at school or home?"

Compared to same-aged peers, individuals with primarily inattentive type ADHD may present with difficulties listening, sustaining attention, being forgetful and distractible and/or having trouble getting organized and completing tasks. Individuals with ADHD predominantly hyperactive/impulsive type often present with concerns such as restlessness, being fidgety, hyperactive, talking excessively, interrupting others and blurting out answers before being asked. Of the nine symptoms listed in the DSM-5 for each ADHD category, six are necessary at an "often" or "very often" level within each category for children and teens 16 years or younger; at least five symptoms are required for adolescents 17 years and older. Several symptoms should have onset before age 12 years that are inappropriate for developmental level, demonstrated across settings and time (for at least 6 months), have associated functional impairments, and are not be better explained by another condition. Combined type ADHD requires that criteria are met in both categories (see full criteria: DSM-5) [1].

2.2 Evaluation

2.2.1 History

The approach to evaluating behavioral and developmental concerns for children and teens can proceed similarly to the evaluation of other medical concerns. Ask about the age of onset of concerns in the areas of inattention, and hyperactive-impulsive behaviors. Inquire about the type, frequency, and degree of these behaviors and whether they occur across settings (e.g., home, school, other). Have the concerns persisted for at least 6 months? Is there a time of day or setting when the concerns

are more likely (e.g., around nap or bed times, mealtimes or visits to a nonpreferred setting)? Other questions to consider include:

- Has the child's language, academic and social development progressed normally?
- Have vision and hearing screens been checked and are they normal?
- Have there been psychosocial changes that the caretaker suspects could have played a role in the initiation or evolution of the child's behavioral concerns across settings?
- Is there concern about autism spectrum disorder, anxiety or moodiness?
- For the school-age child, how have grades progressed within and across subjects?
- Has the school or another entity conducted an evaluation for these concerns and if yes, what were the results?

Consider the child's past medical history. A history of prematurity or low birth weight increases risk for ADHD. Alcohol exposure in-utero, and a history of lead intoxication both increase the risks for presentation with symptoms of ADHD. A family history of ADHD is common. If as least one parent has ADHD, the risk for the child is increased [5].

2.2.2 Physical Examination

A complete physical examination should be conducted and include height, weight, heart rate, blood pressure, vision, and hearing screens (if not previously done and found to be normal) along with a thorough cardiovascular and neurological examination.

Data collection: If the child is 6–12 years of age, consider a screening tool such as the Vanderbilt Assessment Scales (VAS), which is available available for use on line through the National Initiative for Children's Healthcare Quality (https://www.nichq.org/resource/nichq-vanderbilt-assessment-scales). This can be administered to parents in the office to screen for ADHD from their perspective [13]. Based on the history and parent screening, the decision might be to pursue further evaluation.

To evaluate for ADHD further, schedule a follow-up visit and ask for the parent to collect the following: VAS for parents and teachers or other informants (e.g., grandparent or coach/other reporter who knows the child well); past report cards/progress reports; and any previous evaluations. While not diagnostic, behavioral ratings like the nonproprietary VAS can assess for consistency of significant concerns across settings. Other forms which are proprietary span broader age-ranges are normed by age and gender and provide options for self-report for older age groups (e.g., Conners Comprehensive Behavior Rating Scales™, 8–18 years for the self-report form) [14].

Medical testing beyond history and physical examination is based on the findings. Examples include referral to ophthalmology for failed vision screen, endocrinology for elevated TSH in the context of altered growth parameters and daytime tiredness/inattention, or psychiatry for elevated conduct disorder concerns. Review these findings at the follow-up visit.

2.3 Differential Diagnosis

The primary care provider is in the optimal position to screen for, evaluate and diagnose ADHD. Knowing the patient over time, the developmental trajectory, risk factors, symptom history and having the trust of the family are important available resources that allow a timely and accurate evaluation and diagnosis. Children with a history of low birth weight or prematurity, and those with a family history of ADHD are at greater risk of having this diagnosis. It is not unusual, however, to have co-occurring medical, mental health or psychosocial problems to consider as associated factors that make the presentation more complex or offer alternative diagnoses. For instance, children with some genetic disorders (e.g., Fragile X syndrome, Down syndrome, 22q deletion syndrome), and history of toxic exposures (e.g., lead exposure, fetal alcohol spectrum disorders) often present with a pattern of behavioral concerns for which ADHD might be considered. Other conditions are also highly associated with ADHD and are important to consider in the context of the evaluation such as learning, mental health, and sleep disorders. For instance, the child with daytime hyperactive and irritable behavior who snores heavily might benefit from a referral to sleep medicine to evaluate for sleep disordered breathing which can contribute to poor sleep quality and daytime behavioral dysregulation [5, 15, 16]. Less commonly, seizures are important considerations. Among co-occurring conditions, if ADHD is considered primarily, the management for ADHD may proceed while the evaluations for associated conditions occur. Examples of potentially co-occurring or alternative conditions are reviewed in Table 1 [5, 15, 16].

Table 1 Potential co-occurring or alternative diagnoses for ADHD symptom presentation and considerations for referral

Symptom	History/screening	Referral to	Concern
Anxiety	History of anxiousness, include separate patient interview; SCARED [8–18 years] [17], GAD-7 [11 years+] [18]	Psychology; psychiatry	Anxiety disorder
Fatigue	Poor growth/elevated TSH	Endocrinology	Hypothyroidism
Moodiness	History depressed mood include separate patient interview; PHQ-9 [11–17 years] [19]	Psychology; psychiatry	Depression
Poor grades	History of learning problems and poor grades	School evaluation [20]	Intellectual disability; specific learning disability
Poor hearing	Fail hearing screen	Audiology	Hearing loss
Poor vision	Fail vision screen	Ophthalmology	Vision loss
Restless sleep	Leg symptoms in evening (urge to move, unusual sensations); leg kicks in sleep	Sleep medicine	Restless legs/periodic limb movements, iron deficiency
Snoring	Daytime hyperactivity and tiredness; restless/sweaty sleep	Sleep medicine	Sleep-disordered breathing
Staring spells	History	Neurology	Seizures
Substance use, behavior changes	History; include separate teen interview and S2BI [21]	Psychiatry	Substance use disorder

3 Management

3.1 Overview

Current pediatric ADHD treatment practices are informed by the American Academy of Pediatrics 2019 clinical practice guideline [22], as well as the Society for Developmental and Behavioral Pediatrics' (SDBP) 2020 complementary clinical practice guideline regarding complex ADHD [23]. In reviewing the current treatment guidelines, we will first discuss ADHD treatment based on age, as organized in the 2019 AAP guideline, and then follow with a discussion of complex ADHD.

Among preschool-aged children, 4 years of age until 6 years of age, behavioral interventions, including behavioral therapy and school based interventions, are considered first line treatments [22]. Despite an increased occurrence of side effects in this age group, the AAP supports the use of methylphenidate for moderate to severe ADHD, if behavioral interventions alone have not been sufficient, or if behavioral interventions are unavailable and the benefit of medication management outweighs the risk [22].

Among school-aged children, 6–12 years of age, medication management in conjunction with behavioral interventions is recommended [22]. The Multimodal Treatment of Attention Deficit Hyperactivity Disorder (MTA) study among 7–9-year-old children found that at 14-month follow-up, stimulant medication management with methylphenidate was superior to behavioral treatments. In terms of ADHD core symptoms, combined (medication and behavioral) treatment was not associated with significantly greater benefits as compared to stimulant medication management alone, though a positive effect was appreciated in terms of functioning [24]. Therefore, concomitant behavioral interventions, including behavioral therapies and school based supports, may also be therapeutic for school age children.

Among adolescents, 12 years of age until 18 years of age, medication management is recommended, in addition to training and/or behavioral interventions [22]. In a 2016 NCHS parent survey, 62% of children and teens with a current ADHD diagnosis were taking medication and 46.7% had received behavioral treatment in the preceding year [4].

The 2020 SDBP Complex ADHD guideline defines complex ADHD as symptomatic presentation less than 4 years of age or greater than 12 years of age, coexisting conditions or psychosocial factors, moderate/severe functional impairment, diagnostic uncertainty, and/or inadequate treatment response [23]. The guideline recommends a comprehensive evaluation, including history taking, physical examination, and psychological assessment, with particular care to evaluate for coexisting conditions, by a specialist or clinician with expertise, in conjunction with an interprofessional consultation. Similar to the 2019 AAP ADHD guideline, it recommends implementation of behavioral interventions, at parental, classroom and peer levels, as well as educational interventions. The 2020 SDBP Complex ADHD guideline emphasizes the importance of a treatment plan aimed at addressing the functional impairment(s), with incorporation of skill development and prevention of

negative sequelae, rather than simply the reduction of ADHD symptoms. Lastly, the SDBP Complex ADHD guideline recommends providing a family-centered approach to care and highlights the chronic nature of ADHD, noting the importance of preparation surrounding life transitions [23].

3.2 Medications

There is strong evidence to support the use of stimulant medications (effect size 1.0) for treatment of ADHD symptoms, while there is sufficient evidence for the use of nonstimulant medications (effect size 0.7) [22]. Stimulant medications consist of two classes: methylphenidate and amphetamine salts. Nonstimulant medications include, in order of decreasing strength of supporting evidence in treatment of ADHD: atomoxetine (selective norepinephrine reuptake inhibitor (SNRI)), extended-release guanfacine (α-2 adrenergic agonist), and extended-release clonidine (α-2 adrenergic agonist) [22]. Additional information is presented in Table 2.

Table 2 General characteristics of ADHD medications

Group	Medications	Characteristics/considerations
Stimulants	Methylphenidate [25] Enantiomer: Dexmethylphenidate	Immediate release (short acting): approximately 3–6 h of duration depending on the formulation Extended release (long acting): approximately 8–12 h of duration depending on the formulation Notable side effects: sleep disturbance, appetite changes, headache, abdominal discomfort, irritability and tics[a] Recommended monitoring: linear growth, weight, heart rate and blood pressure (due to potential increase) FDA Boxed Warning: medication abuse and dependence
	Amphetamine (mixed amphetamine salts) [26] Enantiomer: Dextroamphetamine Prodrug (converted to Dextroamphetamine): Lisdexamfetamine	Short acting: approximately 5–7 h of duration depending on the formulation Long acting: approximately 6–16 h of duration depending on the formulation Notable side effects: sleep disturbance, appetite changes, headache, abdominal discomfort, irritability and tics[a] Recommended monitoring: linear growth, weight, heart rate and blood pressure (due to potential increase) FDA-boxed warning: medication abuse and dependence

(continued)

Table 2 (continued)

Group	Medications	Characteristics/considerations
Nonstimulants	Atomoxetine [27]	Duration of action: approximately 24 h Notable side effects: gastrointestinal upset (nausea, vomiting, abdominal pain) and somnolence, which are improved by starting at one-half target dose for a week before advancing Recommended monitoring: linear growth, weight, heart rate and blood pressure (due to potential increase) Risks: hepatic injury (routine monitoring of LFTs not recommended) FDA-boxed warning: suicidality
	Extended release Guanfacine [28]	Duration of action: approximately 24 h Notable side effects: sedation, hypotension, bradycardia, syncope, dizziness, and abdominal pain Risks: rebound hypertension if abruptly terminated (requires titration); heart block
	Extended release clonidine [29]	Duration of action: approximately 24 h Notable side effects: sedation, hypotension, bradycardia, dry mouth, nasal congestion, sore throat, and constipation Risks: rebound hypertension if abruptly terminated (requires titration); heart block

[a] Despite an association between stimulant medications and tics, stimulant medications can be used for medication management among children with ADHD and concomitant tic disorder, such as Tourette syndrome, as stimulant medications have not been found to worsen tics for most patients [30]. For individuals who experience increased tic frequency with stimulant treatment, nonstimulant medications may be considered [30], particularly α-2 adrenergic agonists which are used in treatment of tic disorders

In addition to medication class, selection of medication may be dependent on intended duration of action, administration, cost, and side effect profile. In regards to stimulant medications, 40% of children are reported to respond to either methylphenidate or amphetamine salts, with another 40% responding to both [22]. There is evidence, though effect sizes were small to medium [31], to support the use of an α-2 adrenergic agonist as an adjunct to stimulant medication management [22]. In terms of duration of action, medications can generally be grouped into immediate-release (short acting) and extended-release (long acting) formulations. Selection of immediate versus extended-release or a combination there of, is often based on the need for adequate symptom coverage throughout the academic day, homework completion, and potential extracurricular activities, as well as the side effects of the medication. Psychosocial circumstances and/or a personal or family history of drug abuse/dependence may also be a factor that leads to selecting an extended-release

formulation due to the decreased abuse potential and risk of medication diversion. Additional considerations regarding psychosocial factors and medication selection may include the need for consistent administration compliance with an α-2 adrenergic agonist, due to the associated risk of rebound hypertension if abruptly stopped, as compared to stimulant medications from which the family may decide to take a "holiday."

Another consideration, particularly among pediatric patients, is the route of administration, such as tablets, capsules, oral solution, disintegrating tablet, chewable tablet, or patch. Cost may also be considered, as the cost of a 1-month supply of stimulant medications may range from tens to hundreds of dollars. Age is another factor, as the 2019 AAP guidelines includes a discussion of the insufficient evidence to support the use of ADHD medications other than methylphenidate among preschool age children, including amphetamine, which is FDA-approved for use under 6 years of age, and nonstimulants, which are not FDA-approved for preschoolers [22]. Methylphenidate has the greatest empirical support among preschool-aged children in part due to its use in the Preschool ADHD Treatment Study (PATS) [32]. Of note, the 2019 AAP guideline does not recommend the use of pharmacogenetic tools to aid in selecting medication management [22]. For more information about FDA-approved ADHD medications, the 2019 AAP guideline references The ADHD Medication Guide© (www.ADHDMedicationGuide.com) [22, 33].

The side effect profiles of medications used to treat ADHD inform their monitoring and use; for further information regarding medication side effects, risks, and FDA-boxed warnings, refer to Table 2. Stimulant medications have been associated with decreased linear growth without subsequent linear growth rebound, on the order of 1–2 cm below predicted height [22, 34]. Atomoxetine has been associated with delayed growth but with subsequent catch up growth noted [22]. The risk of decreased linear growth and decreased weight, in the setting of appetite changes, associated with stimulant medications informs the practice of close growth chart monitoring. The literature is mixed in regards to whether medication "holidays" may counteract stimulant medications' impact on height and weight, though there have been reports of positive growth during longer breaks, such as over the summer [35]. Per the 2019 AAP Guidelines, "stimulant medications have not been shown to increase the risk of sudden death beyond that observed in children who are not receiving stimulants" [22]. However due to potential cardiovascular changes associated with both stimulant and nonstimulant medications, family and/or personal cardiovascular history, including cardiac arrhythmias (Wolff–Parkinson–White, Long QT syndrome), hypertrophic cardiomyopathy (previously HOCM), and/or sudden/unexplained death, warrants further evaluation, such as obtaining an electrocardiogram and/or referral to be evaluated by a pediatric cardiologist [22]. A relationship between stimulant medications and tic disorders has been described; refer to Table 2 for additional information. Stimulants and atomoxetine have been associated with priapism [36], warranting counseling for male pediatric patients.

3.3 Behavioral Treatment

In regards to behavioral therapy, the 2019 AAP guideline recommends "parent training in behavior management (PTBM)," such as parent–child interaction therapy (PCIT) [22]. Parental satisfaction associated with behavioral treatment has been found to be superior compared to medication treatment [24]. The 2019 AAP guideline states that behavioral management can be recommended even prior to an ADHD diagnosis being made, due to its effectiveness for many behavioral challenges [22]. School-based supports may include accommodations, as well as, implementation of 504 plan or an Individual Education Plan (IEP). The primary care provider can help the caretaker construct a letter requesting evaluation for school services, a process supported by Federal Law. Training interventions to target improvements in organizational skills, have been found to be effective among school-aged children and adolescents with ADHD, though the frequency of practice and degree of feedback are important factors [37]. The 2019 AAP guidelines do not recommend the following modalities for ADHD treatment: external trigeminal nerve stimulation, electroencephalogram biofeedback, cannabidiol (CBD) oil, modified diets, mindfulness, cognitive training, social skills training, or supportive counseling [22].

3.4 When to Refer

While the primary care provider may be the first to screen and evaluate for ADHD, it is not unusual to have co-occurring medical, mental health, or psychosocial considerations that make the patient's presentation more complex. Children or teens with co-occurring genetic, neurologic, or psychiatric disorders will benefit from the comprehensive management that a primary care provider provides. However, more complex ADHD may additionally benefit from subspecialty referral(s). Complex ADHD, defined above, may benefit from subspecialty referral to a developmental-behavioral pediatrician, pediatric psychologist or child and adolescent psychiatrist to assist in evaluation and care coordination [23]. Referral recommendations for potentially co-occurring or alternative conditions are reviewed in Table 1 [5, 15, 16].

4 Prognosis

In general, having ADHD is associated with poorer high school completion rates, poor adult job performance and poorer long-term health outcomes [38]. Among school children treated for ADHD in Scotland, there were increased odds of lower academic attainment, and a greater likelihood of leaving school before age 16 years

[39]. Children with ADHD have greater social functioning difficulties with peers and more trouble understanding emotions [40]. Individuals with ADHD have more reactive and negative emotions and poorer emotion regulation particularly at older ages [41].

In a follow-up from the Multimodal Treatment study of Attention-Deficit/Hyperactivity Disorder, the MTA study in the United States, it was suggested that adult height was affected by the cumulative stimulant dose given over the years of ADHD treatment [42]. In the Scotland study, children with ADHD were more likely than their peers to have injury requiring hospitalization and for overall number of hospitalizations [39]. Individuals with ADHD may be at higher risk for alcohol and other substance use disorders in later adolescence and adulthood [43]. However, treatment of ADHD with stimulants has not been causally related to disorders of substance use [44]. Due to high rates of drug diversion, education for patients with ADHD and their families about the need to monitor stimulant use is very important [45].

Experts underscore the life-long nature of ADHD for many individuals and the associations with poor academic progress, and mental health disorders [23]. At follow-up at age 25 years of the children participating in the US MTA study at 7–9 years of age, ADHD symptoms persisted into adulthood for those with more severe symptoms and co-occurring mental health conditions including conduct and depressive disorders at school age. However, some investigations suggest that the continuity of ADHD from childhood to adulthood is quite variable [46], and that the overlap between childhood and adult ADHD may be less than previously thought [47]. This is an area of ongoing research.

5 Prevention

As the etiology of ADHD is often multifactorial and interrelated, the prevention of ADHD is therefore an equally complex topic. In regards to environmental associations with ADHD, limiting exposure to potential toxins is one means of prevention, such as limiting alcohol and nicotine exposure in utero, as well as limiting lead exposure postnatally. Sleep is another area of potential intervention, as disordered sleep can worsen behavioral dysregulation and executive functioning [48]. The parent–child relationship can be complicated by the presence of ADHD, associated with parental stress, ineffective parenting practices, and parental psychiatric comorbidity [49]. However, the parent–child interaction may also serve as a protective shaping force related to ADHD [49], as maternal positive parenting has been associated with better functioning among preschoolers with less severe hyperactivity/impulsivity [50]. Overall, ADHD is a complex entity that is impacted by genetic, environmental, relational, cultural, and systematic factors [8]; therefore, prevention may be as multifaceted as its treatment.

6 Pearls/Key Points

- Early identification and management of ADHD improves engagement with learning, school completion rates, and emotional development.
- It is important to have high index of suspicion when child present with symptoms of inattention, externalizing behaviors and learning.
- Prematurity, low birth weight, in-utero exposure of alcohol, lead intoxication and family members with ADHD are risk factors for ADHD.
- Screening tools such as Vanderbilt Assessment Scale and Conners Comprehensive Behavior Rating Scale can be used for screening for ADHD.
- Among preschool aged children behavioral intervention is primary mode of therapy.
- In school age children, medication in conjunction with behavioral intervention is recommended.
- For adolescents medications in addition to behavioral intervention is recommended.
- Complex ADHD needs to be evaluated and managed by specialist or clinician with expertise in managing complex ADHD.
- Stimulant medications are not associated with increased rate of sudden death.
- Children with ADHD with family history of arrhythmia or cardiomyopathy need evaluation by cardiologist.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub; 2013.
2. Visser SN, Danielson ML, Bitsko RH, Holbrook JR, Kogan MD, Ghandour RM, et al. Trends in the parent-report of health care provider-diagnosed and medicated attention-deficit/hyperactivity disorder: United States, 2003–2011. J Am Acad Child Adolesc Psychiatry. 2014;53(1):34–46.e2.
3. Perou R, Bitsko RH, Blumberg SJ, Pastor P, Ghandour RM, Gfroerer JC, et al. Mental health surveillance among children—United States, 2005–2011. MMWR Suppl. 2013;62(2):1–35.
4. Danielson ML, Bitsko RH, Ghandour RM, Holbrook JR, Kogan MD, Blumberg SJ. Prevalence of parent-reported ADHD diagnosis and associated treatment among US children and adolescents, 2016. J Clin Child Adolesc Psychol. 2018;47(2):199–212.
5. Thapar A, Cooper M. Attention deficit hyperactivity disorder. Lancet. 2016;387(10024):1240–50.
6. Willcutt EG. The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. Neurotherapeutics. 2012;9(3):490–9.
7. Vos T, Barber RM, Bell B, Bertozzi-Villa A, Biryukov S, Bolliger I, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;386(9995):743–800.
8. Hinshaw SP. Attention deficit hyperactivity disorder (ADHD): controversy, developmental mechanisms, and multiple levels of analysis. Annu Rev Clin Psychol. 2018;14:291–316.
9. Faraone SV, Mick E. Molecular genetics of attention deficit hyperactivity disorder. Psychiatr Clin North Am. 2010;33(1):159–80.

10. Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, et al. Molecular genetics of attention-deficit/hyperactivity disorder. Biol Psychiatry. 2005;57(11):1313–23.
11. Cortese S. The neurobiology and genetics of attention-deficit/hyperactivity disorder (ADHD): what every clinician should know. Eur J Paediatr Neurol. 2012;16(5):422–33.
12. Millichap JG. Etiologic classification of attention-deficit/hyperactivity disorder. Pediatrics. 2008;121(2):e358–65.
13. Wolraich ML, Lambert W, Doffing MA, Bickman L, Simmons T, Worley K. Psychometric properties of the Vanderbilt ADHD diagnostic parent rating scale in a referred population. J Pediatr Psychol. 2003;28(8):559–68.
14. Conners CK. Rating scales in attention-deficit/hyperactivity disorder: use in assessment and treatment monitoring. J Clin Psychiatry. 1998;59:24–30.
15. Feldman HM, Reiff MI. Attention deficit–hyperactivity disorder in children and adolescents. N Engl J Med. 2014;370(9):838–46.
16. Becker SP. ADHD and sleep: recent advances and future directions. Curr Opin Psychol. 2020;34:50–6.
17. Birmaher B, Khetarpal S, Brent D, Cully M, Balach L, Kaufman J, et al. The screen for child anxiety related emotional disorders (SCARED): scale construction and psychometric characteristics. J Am Acad Child Adolesc Psychiatry. 1997;36(4):545–53.
18. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166(10):1092–7.
19. Johnson JG, Harris ES, Spitzer RL, Williams JB. The patient health questionnaire for adolescents: validation of an instrument for the assessment of mental disorders among adolescent primary care patients. J Adolesc Health. 2002;30(3):196–204.
20. Lipkin PH, Okamoto J. The individuals with disabilities education act (IDEA) for children with special educational needs. Pediatrics. 2015;136(6):e1650–62.
21. Levy S, Weiss R, Sherritt L, Ziemnik R, Spalding A, Van Hook S, et al. An electronic screen for triaging adolescent substance use by risk levels. JAMA Pediatr. 2014;168(9):822–8.
22. Wolraich ML, Hagan JF, Allan C, Chan E, Davison D, Earls M, et al. Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics. 2019;144(4):e20192528.
23. Barbaresi WJ, Campbell L, Diekroger EA, Froehlich TE, Liu YH, O'Malley E, et al. Society for Developmental and Behavioral Pediatrics clinical practice guideline for the assessment and treatment of children and adolescents with complex attention-deficit/hyperactivity disorder. J Dev Behav Pediatr. 2020;41:S35–57.
24. Jensen PS. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Arch Gen Psychiatry. 1999;56(12):1073–86.
25. RITALIN® (methylphenidate hydrochloride) tablets, RITALIN-SR® (methylphenidate hydrochloride) extended-release tablets [Internet]. [updated 1/2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/010187s071s082,018029s041s051lbl.pdf.
26. Adderall® CII (Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate and Amphetamine Sulfate Tablets) [Internet]. U.S. Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/011522s043lbl.pdf.
27. Strattera (atomoxetine hydrochloride) capsules [Internet]. U.S. Food and Drug Administration (FDA) [updated 07/2010]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021411s035lbl.pdf.
28. INTUNIV (guanfacine) extended-release tablets [Internet]. U.S. Food & Drug Administration (FDA) [updated 02/2013]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022037s009lbl.pdf.
29. KAPVAY (clonidine hydrochloride) extended-release tablets [Internet]. U.S. Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022331s001s002lbl.pdf.
30. Osland ST, Steeves TD, Pringsheim T. Pharmacological treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders. Cochrane Database Syst Rev. 2018;6(6):CD007990.

31. Hirota T, Schwartz S, Correll CU. Alpha-2 agonists for attention-deficit/hyperactivity disorder in youth: a systematic review and meta-analysis of monotherapy and add-on trials to stimulant therapy. J Am Acad Child Adolesc Psychiatry. 2014;53(2):153–73.
32. Kollins S, Greenhill L, Swanson J, Wigal S, Abikoff H, McCracken J, et al. Rationale, design, and methods of the preschool ADHD treatment study (PATS). J Am Acad Child Adolesc Psychiatry. 2006;45(11):1275–83.
33. Adesman A. The ADHD medication guide© [Internet]. Cohen Children's Medical Center Northwell Health. http://www.adhdmedicationguide.com/.
34. Swanson JM, Elliott GR, Greenhill LL, Wigal T, Arnold LE, Vitiello B, et al. Effects of stimulant medication on growth rates across 3 years in the MTA follow-up. J Am Acad Child Adolesc Psychiatry. 2007;46(8):1015–27.
35. Ibrahim K, Donyai P. Drug holidays from ADHD medication: international experience over the past four decades. J Atten Disord. 2015;19(7):551–68.
36. Eiland LS, Bell EA, Erramouspe J. Priapism associated with the use of stimulant medications and atomoxetine for attention-deficit/hyperactivity disorder in children. Ann Pharmacother. 2014;48(10):1350–5.
37. Evans SW, Owens JS, Wymbs BT, Ray AR. Evidence-based psychosocial treatments for children and adolescents with attention deficit/hyperactivity disorder. J Clin Child Adolesc Psychol. 2018;47(2):157–98.
38. Stein DS, Blum NJ, Barbaresi WJ. Developmental and behavioral disorders through the life span. Pediatrics. 2011;128(2):364–73.
39. Fleming M, Fitton CA, Steiner MF, McLay JS, Clark D, King A, et al. Educational and health outcomes of children treated for attention-deficit/hyperactivity disorder. JAMA Pediatr. 2017;171(7):e170691.
40. Ros R, Graziano PA. Social functioning in children with or at risk for attention deficit/hyperactivity disorder: a meta-analytic review. J Clin Child Adolesc Psychol. 2018;47(2):213–35.
41. Graziano PA, Garcia A. Attention-deficit hyperactivity disorder and children's emotion dysregulation: a meta-analysis. Clin Psychol Rev. 2016;46:106–23.
42. Swanson JM, Arnold LE, Molina BS, Sibley MH, Hechtman LT, Hinshaw SP, et al. Young adult outcomes in the follow-up of the multimodal treatment study of attention-deficit/hyperactivity disorder: symptom persistence, source discrepancy, and height suppression. J Child Psychol Psychiatry. 2017;58(6):663–78.
43. Levy S, Katusic SK, Colligan RC, Weaver AL, Killian JM, Voigt RG, et al. Childhood ADHD and risk for substance dependence in adulthood: a longitudinal, population-based study. PLoS One. 2014;9(8):e105640.
44. Molina BS, Hinshaw SP, Arnold LE, Swanson JM, Pelham WE, Hechtman L, et al. Adolescent substance use in the multimodal treatment study of attention-deficit/hyperactivity disorder (ADHD)(MTA) as a function of childhood ADHD, random assignment to childhood treatments, and subsequent medication. J Am Acad Child Adolesc Psychiatry. 2013;52(3):250–63.
45. Clemow DB, Walker DJ. The potential for misuse and abuse of medications in ADHD: a review. Postgrad Med. 2014;126(5):64–81.
46. Caye A, Swanson J, Thapar A, Sibley M, Arseneault L, Hechtman L, et al. Life span studies of ADHD—conceptual challenges and predictors of persistence and outcome. Curr Psychiatry Rep. 2016;18(12):111.
47. Moffitt TE, Houts R, Asherson P, Belsky DW, Corcoran DL, Hammerle M, et al. Is adult ADHD a childhood-onset neurodevelopmental disorder? Evidence from a four-decade longitudinal cohort study. Am J Psychiatr. 2015;172(10):967–77.
48. Owens JA. The ADHD and sleep conundrum: a review. J Dev Behav Pediatr. 2005;26(4):312–22.
49. Modesto-Lowe V, Danforth JS, Brooks D. ADHD: does parenting style matter? Clin Pediatr. 2008;47(9):865–72.
50. Healey DM, Flory JD, Miller CJ, Halperin JM. Maternal positive parenting style is associated with better functioning in hyperactive/inattentive preschool children. Infant Child Dev. 2011;20(2):148–61.

Child with Alterations of Mood

Richard Dopp, Priyanka Reddy, and Gregory Hanna

1 Introduction

Depression was recognized as the third leading cause of burden of disease (as measured by the costs caused by loss of health and death due to an illness) by the World Health Organization in 2008 with predictions that depression would be the number one cause by 2030. Since that disclosure in 2008, the prevalence rates of depression and suicide-related outcomes have risen dramatically especially among adolescents and young adults [1]. Furthermore, the stressors associated with the global coronavirus pandemic have added even more challenges for youth including the demands of online schooling and limited in-person socialization, and these contributed to increases in anxiety, depression, and post-traumatic stress disorder [2].

There is a shortage of child and adolescent psychiatrists in all countries [3]. It is important, therefore, for primary care providers to have familiarity with screening, referring, and perhaps providing some treatments for depressive disorders in youth.

2 Epidemiology

Depressive symptoms are common in children and adolescents, with most reporting depressive symptoms at some point before adulthood [4]. A meta-analysis conducted in 2006 estimated the point prevalence of depressive disorders was 2.8% for children younger than 13 years old and 5.6% for 14–18-year-olds [5]. In contrast,

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another community study of children aged 5–8 years found that less than 1% met criteria for major depressive disorder (MDD) [6].

Subsequent epidemiologic studies estimated the 12-month prevalence of MDD at 2.7% for 8–15-year-olds and 8.2% for 12–17-year-olds [7, 8].

A recent epidemiologic study estimated the prevalence of MDD in adolescents aged 13–18 years using data from the National Comorbidity Survey-Adolescent Supplement [9]. Lifetime and 12-month prevalence of MDD were 11.0% and 7.5%, respectively. The corresponding rates of severe MDD were 3.0% and 2.3%. MDD prevalence increased significantly across adolescence, with markedly greater increases among females than males. Most cases were associated with psychiatric comorbidity and severe role impairment, with a substantial minority reporting suicidality. The Sheehan Disability Scale was used to assess the degree of role impairment, i.e., the extent to which the depression interfered with functioning in the worst month of the past year in the areas of household chores, school/work, family relationships, and social roles [10]. More than 25% of depressed adolescents had severe MDD as indicated by high levels of distress and impairment that was also associated with higher rates of suicidality and comorbidity.

An epidemiologic study of adolescents aged 13–18 years found that 2.5% met criteria for lifetime bipolar I or II disorder and 1.7% met criteria for mania only [11]. There was nearly a twofold increase in rates of mania from early to late adolescence. The increasing prevalence of bipolar disorder with increasing age and the comparable rate of bipolar disorder within those of adult samples highlight adolescence as the peak period of mania onset. More than one of every five youth who had both manic and depressive episodes had made at least one suicide attempt, which is alarming given the young age and community setting of the sample. Although about half of the youth with bipolar disorder had sought help, less than half had been treated in the mental health sector.

A study of the developmental epidemiology of normative irritability in youth found that, at any given point in childhood or adolescence, 51.4% of participants reported phasic irritability, 28.3% reported tonic irritability, and 22.8% reported both [12]. Tonic irritability was defined as a persistently angry, grumpy, or grouchy mood; phasic irritability was defined as behavioral outbursts of intense anger. The items used to operationalize the tonic and phasic components were assessed with the Child and Adolescent Psychiatric Assessment interview completed with a parent figure and the child [13]. Even low levels of either tonic or phasic irritability increased risk for disrupted functioning including service use, school suspensions, parental burden, and emotional symptoms both concurrently and at 1-year follow-up. Although relatively common, irritability decreased with age but did not vary by sex.

3 Etiology

3.1 Genetic Factors

Twin and family studies have determined that liability to MDD has a nondeterministic genetic component in its etiology, with a twin heritability estimate of ~37% [14]. Genome-wide association studies (GWASs) have identified 102 common genetic variants associated with MDD—of which 87 replicated in an independent sample—providing further evidence that the underlying liability to depression is polygenic [15]. A recent study of large (≥100 kb), rare copy number variants (CNVs) found that three neurodevelopmental CNVs (1q21.1 duplication, Prader–Willi syndrome duplication, and 16p11.2 duplication) were associated with depression [16]. Similarly, a recent meta-analysis found a greater burden of short (<100 kb) deletions in MDD that were enriched for likely enhancer elements, suggesting that CNVs may contribute to depression risk through disruption of gene expression [17]. Although whole-exome and whole-genome sequencing studies of rare genetic variants are necessary to further delineate the genetic architecture of MDD, extremely large sample sizes may be required to yield confident results [18].

Several family and clinical follow-up studies suggest there are etiological differences between child-onset and adolescent-onset MDD [19, 20]. The epidemiologic factors associated with child-onset MDD differ from those of MDD with onset in mid to late adolescence in the sex ratio of affected individuals (with an equal sex ratio in child-onset cases and female predominance in adolescent-onset cases) and long-term psychiatric outcomes [21, 22]. Neurodevelopmental problems, including speech abnormalities and poor motor skills, are associated particularly with child-onset rather than adolescent-onset or adult-onset affective illness [23, 24]. Furthermore, clinical evidence demonstrates that children with attention-deficit hyperactivity disorder (ADHD) have an elevated risk of subsequent depressive symptoms, suicide attempt, and emotional problems in adult life [25, 26].

The results from those studies are consistent with a recent genetic study that found onset of depressive symptoms after puberty with persistence into adulthood was associated with an elevated genetic risk for depression indexed by an MDD polygenic risk score (PRS); however, depressive symptoms with onset by age 12 years were associated with the MDD PRS, as well as with the schizophrenia PRS, ADHD PRS, and a childhood history of ADHD and neurodevelopmental problems, including pragmatic language and social communication difficulties [27]. A polygenic risk score provides information about a person's risk of illness compared to that of others with a different genetic constitution. Pragmatic language difficulties included deficits in using communication for social purposes in a manner that is appropriate for the social context, impairment in the ability to change

communication to match context or the needs of the listener, difficulties following rules for conversation and storytelling, and difficulties understanding what is not explicitly stated and nonliteral or ambiguous meanings of language. The etiological heterogeneity of MDD was also supported by a recent cross-disorder genetic analysis of eight psychiatric disorders that found MDD had somewhat higher genetic correlations with ADHD and autism spectrum disorder (r_g = 0.44 and 0.45, respectively) than with bipolar disorder (r_g = 0.36), indicating that MDD may be more closely associated with these two neurodevelopmental disorders than previously thought [28]. It has been speculated that the response to tricyclic antidepressants may differ between prepubertal and postpubertal depression because prepubertal depression may be more closely associated with neurodevelopmental disorders [27, 29].

From the perspective of pediatric neurology, it is worth noting that a large cross-disorder genetic analysis of ten psychiatric disorders and seven neurological disorders found that migraine has a significant genetic correlation with MDD as well as with ADHD and Tourette syndrome (TS) [30]. The results suggest migraine may share some of its genetic architecture with those three psychiatric disorders, but the modest correlations of migraine with MDD, ADHD, and TS indicate only limited shared etiologic overlap (r_g values = 0.19–0.32).

3.2 Nongenetic Factors

Cognitive, interpersonal, and other psychosocial and biological factors involved in the etiology, pathogenesis, or maintenance of depressive disorders in youth are discussed in the sections on prognosis and outcome.

4 Differential Diagnosis

Symptoms of major depression may be seen in individuals with other primary psychiatric disorders such as anxiety, obsessive compulsive disorder, eating disorders, neurodevelopmental disorders, autism spectrum disorders, ADHD, and substance use disorders. Several medical illnesses may present with depressive symptoms including hypothyroidism, autoimmune disorders, inflammatory bowel disease, anemia, sleep apnea, and chronic fatigue syndrome. Grief and bereavement may also be associated with depressive symptoms. Some individuals may develop a complicated grief reaction after loss that may warrant treatment for depression and grief processing.

The diagnosis of bipolar I disorder requires manic symptoms lasting at least one week including elevated, expansive, or irritable mood, distractibility, and excessive

involvement in certain activities. The diagnosis of bipolar II disorder requires less severe manic symptoms lasting fewer than 4 days. Many individuals who develop bipolar disorder may initially present with symptoms of distractibility and hyperactivity, which may be misdiagnosed as ADHD, or mood changes that present as unipolar depression. Additionally, adults with bipolar disorder commonly report episodes of depression during childhood or adolescence [31]. In the Clinical Outcomes of Bipolar Youth (COBY) study, those who eventually met criteria for bipolar I/II disorder were more likely to have a first- or second-degree relative with bipolar disorder, prior psychiatric hospitalization, and elevated Mania Rating Scale score [32, 33].

5 Diagnostic Approach

5.1 History and Physical Examination

The presentation of depression in young children may include physical (somatic) symptoms such as stomachache, headache, weakness, or fatigue. Other children with depression may present with defiance, poor school performance, and morbid thoughts or drawings. Some adolescents with depression may be withdrawn, quiet, and distant, while others may have mood changes with sadness or irritability.

It is important to obtain information from multiple sources including the patient, parents, therapists, educators, and other individuals involved with the patient. In a study of 287 parents with depression, parental reports of depressive symptoms were better at predicting new onset mood disorders in their children when compared to the child reports [34]. In a large study of adolescents with suicidal behavior, there were more reports of suicidal ideation, plans, and attempts from patients compared with parents' reports [35]. A family history of depression may be present and should be sought from the parents.

A complete general and neurological examination should be performed on every child who presents with symptoms of depression or anxiety. A validated screening tool such as the Childhood Depression Inventory may be useful in cases where there is clinical suspicion.

5.2 Laboratory Assessment

Consider checking vitamin D level by checking 25(OH)D level and assessing thyroid stimulating hormone (TSH) as a marker of thyroid function [36] as abnormalities in these levels can be associated with depressive symptoms. Neuroimaging is not usually indicated unless abnormalities are noted on neurological examination.

6 Treatment/Management

6.1 Evidence-Based Psychotherapy

The empirical support and importance of psychotherapy to treat depression in youth are greater today than at any other time in history. Cognitive behavioral therapy (CBT) has been a cornerstone of depression treatment for decades. Behavioral strategies include an emphasis on coping skills, interpersonal relationships, social problem solving, and engagement in pleasurable activities [37]. Cognitive approaches in CBT work to identify and change negative beliefs about ourselves, the world, and the future. For adolescents, understanding these cognitive and behavior approaches within a familial context is also critical.

Garber and colleagues identified a cohort of adolescents whose parents had a current or prior depressive disorder. They recruited 316 adolescents who themselves had a prior diagnosis of depression or had elevated but sub-diagnostic depressive symptoms. Participants were randomly assigned to an 8-week cognitive behavior (CB) group intervention or usual care. The researchers followed the adolescents over the next year to better understand the development of future major depressive episodes, finding that adolescents in the CB prevention program showed greater reductions in depressive symptoms than those in usual care, but that the presence of parental depression was a moderator of this effect. More specifically, for adolescents whose parents were not depressed, the CB intervention was more effective at preventing future depressive episodes than usual care. For those youth with a currently depressed parent, the CB prevention program was less effective in preventing incident depression. The presence of parental depression was a greater predictor of child's future depressive episodes than the adolescent's participation in the CB prevention program [38].

In addition to CBT, there are many other evidence-based psychotherapeutic approaches including dialectical behavior therapy (DBT), acceptance and commitment therapy (ACT), interpersonal therapy (IPT), mindfulness-based cognitive behavioral therapy (MBCT), and other self-compassion and mindfulness-based interventions. The use of manualized therapy materials may be helpful to enhance the fidelity of treatment.

Majority of adolescents with MDD receive health care services but only a small proportion receive treatment that is disorder-specific or from the mental health sector. Service use is classified as "any treatment" if either the adolescent or parent endorsed treatment in a mental health specialty, general medical clinic, human services, complementary and alternative medicine, juvenile justice, or school setting. Service use is classified as "mental health specialty" if either the adolescent or parent reported using services rendered by a psychiatrist, psychologist, social worker, or family counselor in inpatient or outpatient settings.

6.2 Antidepressant Medications

6.2.1 Selective Serotonin Reuptake Inhibitors (SSRIs)

Fluoxetine (Prozac) is approved by the FDA to treat depression in children age 8 years and up. Escitalopram (Lexapro) is approved by the FDA to treat depression in children age 12 years and up [39]. Other SSRI medications, even in the absence of specific FDA approval, are also effective at treating depression in children and adolescents including sertraline (Zoloft), citalopram (Celexa), fluvoxamine (Luvox), and paroxetine (Paxil).

6.2.2 Prozac (Fluoxetine)

Starting at low doses and planning several dose increases in small increments can help to reduce side effects including those associated with suicidal ideation. Fluoxetine can be started at 5 or 10 mg once daily and increased every 1–2 weeks by 5 or 10 mg. Adolescents may respond at a variety of doses, but it is not uncommon to continue slow increases over time up to 40 or 60 mg a day. Side effects may include diarrhea, nausea, appetite changes, dry mouth, dizziness, insomnia, somnolence, or tremor.

6.2.3 Lexapro (Escitalopram)

Emslie and colleagues reported data from a multisite randomized placebo-controlled trial observing 312 adolescents with MDD and comparing 8 weeks of escitalopram 10–20 mg daily with 8 weeks of placebo [40]. They report response rates following 8 weeks of treatment as 62% for escitalopram and 51.6% for placebo. Rates of remission at the endpoint were 41.6% for escitalopram and 35.7% for placebo. Adolescents receiving escitalopram more commonly reported headache, menstrual cramps, insomnia, nausea, and flu-like symptoms.

For adolescents with MDD who continued taking escitalopram as part of a 16-week extension of this randomized placebo controlled trial, response rates rose to 66% and remission rates to 51% at week 24 of treatment [41]. This data highlights the benefits of observing the effects of SSRI medications over several months. Escitalopram can be started at 2.5 or 5 mg once daily and increased every 1–2 weeks by 2.5 or 5 mg up to 10 or 20 mg daily.

6.2.4 Celexa (Citalopram)

In a randomized controlled trial comparing citalopram with placebo, the response rate was 36% for those taking citalopram and 24% in the placebo condition [42]. In the Treatment of Resistant Depression in Adolescent study, 19/34 (55.9%) demonstrated response to treatment with citalopram with or without psychotherapy at 12 weeks [43]. Citalopram can be initiated at 5 or 10 mg once daily and increased every 1–2 weeks by 5 or 10 mg. Adolescents may respond at a variety of doses, but it is not uncommon to continue slow increases over time up to 40 mg daily. Consider an EKG to check QT interval in dosing greater than 40 mg per day.

6.2.5 Zoloft (Sertraline)

In addition to the safety and tolerability established in an open-label multisite trial of adolescents with MDD who were treated with sertraline for 10 weeks, pooled samples from two multicenter randomized controlled trials showed evidence of improved response to sertraline (69%) compared with placebo (59%) after 10 weeks of treatment [42]. Sertraline, like other SSRI medications, is also effective at treating social anxiety disorder in children and adolescents [44].

6.3 Other Antidepressant Medications

6.3.1 Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)

Venlafaxine (Effexor) demonstrated beneficial effects in treating adolescent depression especially when used in combination with cognitive behavioral therapy [43]. In the Treatment of Resistant Depression in Adolescents (TORDIA study), participants with elevated suicidal ideation at baseline reported more suicide-related adverse events when randomized to venlafaxine versus SSRI. There have been no randomized controlled trials demonstrating efficacy for duloxetine (Cymbalta) in the treatment of depression in adolescents [45]. It would be prudent to monitor for hypertension, as an added side effect for SNRIs compared to SSRIs.

6.3.2 Mirtazapine

Mirtazapine has suggestive evidence from an open-label study for its efficacy and safety in treating MDD in adolescents with dose ranges between 30 and 45 mg each evening with report of rapid onset of sleep [46]. Remeron may enhance central serotonergic and noradrenergic activity.

6.3.3 Buspirone

Buspirone is a serotonin agonist. It has limited evidence for treating anxiety in youth and adults. In the STAR*D trial, buspirone demonstrated evidence as an augmenting agent with SSRI medications in the treatment of major depressive disorder in adults [47]. Additionally, buspirone often has few side effects that include low rates of nausea, dizziness, headache, and somnolence.

6.4 Mood-Stabilizing and Antipsychotic Medications

Lamictal (lamotrigine) has evidence to support its use to treat both major depressive disorder and bipolar disorder in youth [48]. Lithium has also demonstrated safety and effectiveness in the treatment of children and adolescents with bipolar disorder [49]. For children and adolescents whose depressive symptoms have not improved significantly with psychotherapy and antidepressant treatments, the use of antipsychotic medications can also be considered [50].

6.5 TADS Study

The Treatment for Adolescents with Depression Study (TADS) randomized 429 adolescents with MDD to either pill placebo, fluoxetine, cognitive behavioral therapy, or fluoxetine plus CBT [51]. The response rate to fluoxetine plus CBT was 71% compared with 61% for fluoxetine alone, 43% for CBT alone, and 35% for placebo. There was a significant decrease in suicidal ideation, as measured by the Suicide Ideation Questionnaire—Junior, in all 4 groups with the greatest reduction seen in the fluoxetine plus CBT condition. It is worth noting that the TADS study excluded youth with higher levels of dangerous behavior including recent hospitalization or suicide attempt. At the same time, this landmark study demonstrated the importance of 6–9 months of combined treatment with antidepressant medication and psychotherapy in order to maximize benefits and minimize harm to adolescent patients.

6.6 TORDIA Study

The Treatment of Resistant Depression in Adolescents (TORDIA) study recruited 334 adolescents with MDD who had not responded to a 2-month initial treatment with an SSRI medication [43]. In TORDIA, the adolescents with depression were

randomized to one of four treatment groups for 12 weeks: (1) different SSRI than previously prescribed, (2) different SSRI plus CBT, (3) venlafaxine, or (4) venlafaxine plus CBT. Treatment response rates were higher for CBT and a switch to a different medication (54.8%) when compared with a medication switch alone (40.5%). There was no significant difference in rate of response when comparing venlafaxine (48.2%) and SSRIs (47.0%).

Although the TADS study excluded adolescents with recent hospitalization or suicide attempt due to concerns of randomization to 12 weeks of pill placebo, TORDIA consisted of four active treatment arms and included individuals with more chronic depression and higher levels of suicidal ideation. Similar to the results of most studies in depression and other psychiatric disorders, results of the TORDIA study affirmed that the combination of CBT and medication was more effective than medications alone.

6.7 Prescribing Antidepressant Medications After the FDA Black Box Warnings

A June 2003 report to the Food and Drug Administration (FDA) by the makers of paroxetine, showed evidence of an increased risk for possible suicide-related adverse events in pediatric patients with MDD treated with paroxetine compared with those treated with placebo [52]. In response, the FDA reviewed 23 placebo-controlled drug development clinical trials involving antidepressant treatment for pediatric patients as well as the placebo-controlled multicenter trial investigating fluoxetine for adolescents with depression which was funded by the National Institute of Mental Health (NIMH) [51]. Based on these data of pediatric patients with depression treated with SSRIs, 1–3 out of 100 treated patients might have a suicidal risk that surpasses inherent risk associated with depression [52].

In response, the FDA issued a 2003 public health advisory regarding the possible risk for increased suicidal thoughts and behaviors associated with the initiation of antidepressant medications in children and adolescents. In 2005, this advisory was strengthened by FDA requirements of a black box warning in labeling for antidepressants [53]. In 2007, this black box warning regarding suicidal thoughts was expanded to include young adults ages 18–24 years [54].

These FDA warnings added to the concerns of patients, parents, and providers regarding the risks associated with treatment such as SSRIs and other antidepressant medications. In the period following these official warnings in 2007, many clinicians had concerns about the risks associated with prescribing antidepressant medications to youth and young adults. Data from primary care providers showed reductions in new diagnoses of depression, decreased by 44% for pediatric patients, 37% for young adults, and 29% for adults [54]. These reductions were concerning as higher SSRI prescription rates are associated with lower suicide rates in child and adolescents [55].

6.8 Self-care Strategies

Disturbed sleep has been clearly identified as a factor in depression throughout the lifespan. Persistent sleep problems in childhood predict the risk of later onset of mood disorders [56] and difficulty with sleep is one of the most robust findings in early onset depression [57]. In adolescents with depression, sleep polysomnographic abnormalities have been found, including shorter sleep latency and shortened REM latency, as well as more REM sleep and less Stage 3 non REM sleep [58]. Melatonin and trazodone are the medications more commonly used by primary care physicians and psychiatrists to treat sleep disturbance in children with depression [59].

Despite treatment for depression including medications and evidence-based psychotherapies, many adolescents continue to have depressive symptoms. Higher levels of residual sleep disturbance (insomnia) increased the odds of depression relapse (OR = 6.74, $p = 0.006$) [60]. Exercise has been identified as a contributor to improved sleep outcomes [61].

Exercise is also an effective treatment for depression. Adolescents with MDD showed significant reductions in depressive symptoms with exercise [62]. One mechanism may be associated with increases in brain-derived neurotrophic factor (BDNF) related to engagement in consistent physical activity and exercise [63].

7 Prognosis/Outcomes

Psychosocial mediators and moderators including adolescent and familial cognitions, stress, and interpersonal interactions can influence the trajectory of adolescent depression. Per Ginsburg and her team, cognitive theories contribute to the development of constructs that can explain the development of depression. As compared to nondepressed adolescents, depressed adolescents exhibit increased cognitive distortions such as overgeneralizing, catastrophizing, and personalizing. Moreover, their propensity for critical thoughts of self and others can influence attitudes, self-esteem, and sense of control [64]. Ginsburg and her group investigated cognitive measures including the Beck Hopelessness Scale, Children's Negative Cognitive Error Questionnaire, and Children's Depression Rating Scale—Revised with depressed adolescents enrolled in TADS. Their outcome measures and analyses suggested that the predominant depression-related cognitions in clinical research could be separated into four constructs of Cognitive Distortions and Negative Beliefs, Cognitive Avoidance, Positive Outlook, and Solution-Focused Thinking. They further supported that adolescents who had increased cognitive distortions, unrealistic self-standards, and self-worth based on acceptance of others, had increased depressive symptoms, contributing to 30% of the variance in self-reported depression scores [64].

Cognitive distortions not only pertain to the adolescents but also extend to members of the family. This in turn can influence interactions with the adolescent. As described by Lohoff, genetics play a crucial role in the development of major depression with an increased risk by two- to fourfold for individuals with first-degree relatives with unipolar recurrent major depression [65]. Adult major depression similar to that of adolescents is inclusive of distorted thinking and when considering dyadic factors amidst parent and adolescent, it is suspected that negative cognitions contribute to the development and characterization of adolescent depression. As supported by Sander and McArty, parent pathology, lack of involvement, and lack of warmth as well as parental negative attribution and maladaptive cognitive styles are risk factors for adolescent depression. Additional considerations surrounding the family factors contributing to adolescent pathology include the family emotional climate, cohesion, level of discord, and individual coping styles [66].

Adolescence, a time of transition in itself, is a critical time period for onset of depression, with elevated risk for stress from a neurobiological, cognitive, emotional, and interpersonal perspective. As discussed by Auerbach and his group, stressful life events as well as recurrent chronic stress are significant predictors of onset, severity, and continuation of major depression. For adolescents, it is critical to consider the interpersonal stressors they are confronted with while also transitioning to greater autonomy from caregivers and investing more readily in peer relationships [67]. A core feature of adolescence includes development of brain reward circuitry amidst prefrontal cortex maturation. Auerbach supports that with consideration of a stress generation framework, reward dysfunction can negatively contribute to interpersonal stressors [67].

In summary, it is prudent to take into consideration several mediating and moderating factors including adolescent development, individual and familial cognitive styles, and interpersonal interactions, when evaluating and treating adolescent major depression.

8 When to Refer/Admit

Although there are no validated criteria to assess exact risk, there are several known risk factors such as acute suicidal or homicidal intent or plan, recent suicide attempt, history of self-harm or harm to others, impulsivity, aggression, active substance use, thought or behavior disorganization, functional compromise, and severity of psychosocial stressors that need to be gauged to determine the level of care that is needed. With adolescents who may have risk factors such as those above, and additional refusal or inability to engage in meaningful safety planning or when caregivers cannot be reasonably accountable to ensure safety, inpatient admission to a psychiatric facility would be recommended following medical clearance [68]. If there are acute comorbid medical concerns, such as in the case of sequelae from a

medication overdose, it may be more appropriate to admit to, medical facility with utilization of psychiatric consultation services.

If the patient's symptoms do not meet the most restrictive criteria for inpatient treatment, elevated outpatient treatment options such as partial hospitalization programs or intensive outpatient programs can be utilized, which can allow for significant medication and therapeutic interventions, though reduced supervision and monitoring from a safety perspective [68]. Adolescents and their families who may have complex psychiatric needs as well as significant psychosocial needs may be candidates for community mental health level of care, which may afford wraparound services to include in-home services. Adolescents deemed at lower risk would benefit from outpatient treatment with either a psychiatric or medical provider, with frequency of follow-up pending presentation. Referrals to an outpatient psychiatrist would be appropriate for diagnostic or treatment assessments, increased complexity of presenting factors, and need for more specialized interventions. As evaluation initiation with a psychiatrist may be delayed, it would be critical for medical providers to continue to bridge the adolescent with follow-up appointments and safety checks with additional support from case management and therapists. Outpatient psychiatry consultation services, which may be available in collaborative care models, would be a crucial resource for expedited psychiatric intervention.

8.1 Suicidal Behavior: Assessment and Management

Suicide contributes to about 24% of the top 10 causes of death for persons aged 15–24 years old, according to data from the CDC in 2008. Suicide rates for youth between the ages of 10 and 24 years old increased from 6.8 per 100,000 in 2007 to 10.7 per 100,000 in 2008 (https://www.cdc.gov/nchs/data/nvsr/nvsr69/nvsr-69-11-508.pdf). The escalating rates of suicidal thoughts, plans, attempts, and completions highlight the ever-growing importance of accurate, consistent suicide assessments. It is prudent to utilize a standard method for assessing suicidal thinking and behavior. Delineating passive versus active suicidal ideation, which is important for acuity of immediate risk, should include details about preparatory acts, gestures, and attempts. Posner and her group highlight definitions as well as risk factors including history of past suicidal behavior, at least one prior psychiatric diagnosis, family history of suicide, history of trauma and abuse, aggression and impulsivity, and demographic factors such as age, gender and gender identity [69]. Protective factors include absence of active intent or plan, greater parental supervision, positive school engagement, and low parent/family conflict. These protective factors are critical to consider as they will play a key role in management [70]. For clinicians, assessment strategies should include directly interviewing the adolescent, the primary informant, as well as use of assessment tools like the Columbia—Suicide Severity Rating Scale or Suicide Assessment Scale. It would be prudent to also interview the parent or caregiver separately for further information regarding the

adolescent's symptoms, behaviors, and suicidality, as well as for safety planning and treatment implementation [69].

Regarding management of a suicidal adolescent, initial considerations rest on the severity of acute risk. Evaluation would encompass review of risk and protective factors, intent and lethality of behaviors, and reliability and effectiveness of safety planning with the adolescent and their family or caregivers. For example, adolescents with elevated immediate risk include those with an intended, aborted, or failed suicide attempt, with ongoing active intent and access to lethal means. Other high-risk factors include active depressive disorder, substance use, psychosis, recent stressors or trauma, impulsivity, and poor social support [71]. For such adolescents with increased acute risk, elevated level of treatment is warranted including emergency department evaluation for inpatient psychiatric treatment. With reduced immediate risk although with several risk factors, an intermediate option such as a day program or partial hospitalization program would allow for elevated medication and therapeutic treatment as well as supervision, structure and routine. In the case of adolescents considered lower to moderate risk, management steps may include referrals for either medication or therapy, or both, and closer follow-up with primary care providers, case managers, and therapists for ongoing risk assessments and interventions.

Regardless of the acuity of risk, with any concerns surrounding self-harm, suicide, or homicide, safety planning should be implemented with the adolescent and their family. Safety planning includes identification of warning signs such as exacerbation of mood, suicidal thoughts and behaviors; planning should include review of effective coping skills, access to crisis contacts like the emergency department and National Suicide Prevention Line, and most importantly environmental safety with means restriction. The depth of safety planning would vary based on the acuity of risk, but it is critical to ensure that these core components are discussed with all adolescents with risk factors.

9 Prevention

Primary prevention may be considered by providing all children lessons on social and emotional learning [72]. Secondary prevention may be considered by identifying at-risk individuals and targeting treatments by expert clinicians guiding psychotherapy, medication management and self-care strategies. For example, children who have parents who are depressed have shown benefits from early interventions [73, 74]. Youth with subsyndromal depressive symptoms demonstrated positive response to cognitive behavioral therapy [75].

In summary, there are safe and effective strategies for using SSRIs and other antidepressants in the treatment of depression in children and adolescents. Moreover, there is substantial evidence supporting cognitive behavioral treatment of depression in children and adolescents. However, depressive disorders in youth remain underdiagnosed and undertreated.

10 Clinical Pearls/Key Points

- Childhood and adolescent depression is treatable with the use of evidence-based psychotherapies, medications, and self-care strategies.
- Psychosocial mediators and moderators inclusive of adolescent and familial cognitions, stress, and interpersonal interactions can all influence the trajectory of adolescent depression.
- Suicide is a leading cause of adolescent death. Suicide risk assessments inclusive of review of risk and protective factors and safety planning are critical for all patients. This will contribute to determining level of care needed.
- The prevalence of major depressive disorder (MDD) increases across adolescence, with markedly greater increases among females.
- Twin, family, and genome-wide association studies of MDD have shown that it has a nondeterministic genetic component in its etiology that is highly polygenic.

References

1. Twenge JM, Cooper AB, Joiner TE, Duffy ME, Binau SG. Age, period, and cohort trends in mood disorder indicators and suicide-related outcomes in a nationally representative dataset, 2005–2017. J Abnorm Psychol. 2019;128(3):185–99.
2. Miranda DM, Athanasio B, Oliveira AC, Simoes-e-Silva AC. How is COVID-19 pandemic impacting mental health of children and adolescents? Int J Disaster Risk Reduct. 2020;51:101845.
3. World Health Organization, et al. Mental health atlas. 2017. 2018.
4. Ollendick TH, Shortt AL, Sander JB. Internalizing disorders of childhood and adolescence. In: Maddux JE, Winstead BA, editors. Psychopathology: foundations for a contemporary understanding. Mahwah: Lawrence Erlbaum Associates; 2005. p. 353–76.
5. Costello EJ, Erkanli A, Angold A. Is there an epidemic of child or adolescent depression? J Child Psychol Psychiatry. 2006;47:1263–71.
6. Keenan K, Hipwell A, Duax J, Stouthamer-Loeber M, Loeber R. Phenomenology of depression in young girls. J Am Acad Child Adolesc Psychiatry. 2004;43:1098–106.
7. Merikangas KR, He JP, Brody D, Fisher PW, Bourdon K, Koretz DS. Prevalence and treatment of mental disorders among US children in the NHANES. Pediatrics. 2010;125:75–81.
8. Results from the 2007 National Survey on Drug Use and Health: national findings (DHHS publication no. SMA 08–4343, NSDUH series H-34). Rockville: Office of Applied Studies. 2008.
9. Avenevoli S, Swendse J, He J-P, Burstein M, Merikangas KR. Major depression in the National Comorbidity Survey-Adolescent Supplement: prevalence, correlates, and treatment. J Am Acad Child Adolesc Psychiatry. 2015;54:37–44.
10. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. Int Clin Psychopharmacol. 1996;11(Suppl 3):89–95.
11. Merikangas KR, Cui L, Kattan G, Carlson GA, Youngstromg EA, Angst J. Mania with and without depression in a community sample of US adolescents. Arch Gen Psychiatry. 2012;69:943–51.
12. Copeland WE, Brotman MA, Costello EJ. Normative irritability in youth: developmental findings from the Great Smoky Mountains study. J Am Acad Child Adolesc Psychiatry. 2015;54:635–42.
13. Angold A, Costello E. The child and adolescent psychiatric assessment (CAPA). J Am Acad Child Adolesc Psychiatry. 2000;39:39–48.

14. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry. 2000;157:1552–62.
15. Howard DM, Adams MJ, Clarke TK, Hafferty JD, Gibson J, Shirali M, et al. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nat Neurosci. 2018;22:343–52.
16. Kendall KM, Rees E, Bracher-Smith M, Legge S, Riglin L, Zammit S, et al. Association of rare copy number variants with risk of depression. JAMA Psychiatry. 2019;76:818–25.
17. Zhang X, Abdellaoui A, Rucker J, de Jong S, Potash MB, Weissman MM, et al. Genome-wide burden of rare short deletions is enriched in major depressive disorder in four cohorts. Biol Psychiatry. 2019;85:1065–73.
18. Zuc O, Schaffner SF, Samocha K, Do R, Hechter E, Kathiresa S, et al. Searching for missing heritability: designing rare variant association studies. Proc Natl Acad Sci U S A. 2014;111:E455–64.
19. Weissman MM, Wolk S, Wickramaratne P, Goldstein RB, Adams P, Greewald S, et al. Arch Gen Psychiatry. 1999;56:794–801.
20. Wickramaratne PJ, Weissman MM. Onset of psychopathology in offspring by developmental phase and parental depression. J Am Acad Child Adolesc Psychiatry. 1998;37:933–42.
21. Harrington R, Rutter M, Fombone E. Developmental pathways in depression: multiple meanings, antecedents, and endpoints. Dev Psychopathol. 1996;8:601–16.
22. Harrington R, Rutter M, Weissman M, Fudge H, Groothues C, Bredenkamp D, et al. Psychiatric disorders in the relatives of depressed probands I. Comparison of prepubertal, adolescent and early adult onset cases. J Affect Disord. 1997;42:9–22.
23. Jaffee SR, Moffitt TE, Caspi A, Fombonne E, Poulton R, Martin J. Differences in early childhood risk factors for juvenile-onset and adult-onset depression. Arch Gen Psychiatry. 2002;59:215–22.
24. van Os J, Jones P, Lewis G, Wadsworth M, Murray R. Developmental precursors of affective illness in a general population birth cohort. Arch Gen Psychiatry. 1997;54:625–31.
25. Ljung T, Chen Q, Lichtenstein P, Larsson H. Common etiological factors of attention-deficit/hyperactivity disorder and suicidal behavior: a population-based study in Sweden. JAMA Psychiatry. 2014;71:958–64.
26. Nock MK, Green JG, Hwang I, McLaughlin KA, Sampson MA, Zaslavsky AM, et al. Prevalence, correlates, and treatment of lifetime suicidal behavior among adolescents: results for the National Comorbidity Survey Replication Adolescent Supplement. JAMA Psychiatry. 2013;70:3000–310.
27. Rice F, Riglin L, Thapar AK, Heron J, Anney R, O'Donovan MD, et al. Characterizing developmental trajectories and the role of neuropsychiatric genetic risk variants in early-onset depression. JAMA Psychiatry. 2019;76:306–13.
28. Cross-Disorder Group of the Psychiatric Genomics Consortium. Genomic relationships, novel loci, and pleiotropic mechanisms across eight psychiatric disorders. Cell. 2019;179:1469–82.
29. Hazell P, Mirzaie M. Tricyclic drugs for depression in children and adolescents. Cochrane Database Syst Rev. 2013;2013:CD002317.
30. Brainstorm Consortium. Analysis of shared heritability in common disorders of the brain. Science. 2018;360(6395):eaap8757.
31. Strober M, Carlson G. Bipolar illness in adolescents with major depression: clinical, genetic, and psychopharmacologic predictors in a three- to four-year prospective follow-up investigation. Arch Gen Psychiatry. 1982;39:549–55.
32. Axelson D, Birmaher B, Strober M, et al. Course of subthreshold bipolar disorder in youth: diagnostic progression from bipolar disorder not otherwise specified. J Am Acad Child Adolesc Psychiatry. 2011;50:1001–16.
33. DelBello MP. A risk calculator for bipolar disorder in youth: improving the odds for personalized prevention and early intervention? J Am Acad Child Adolesc Psychiatry. 2018;57(10):725–7.
34. Lewis K, Mars B, Lewis G, Rice F, Sellers R, Thapar A, Craddock N, Collishaw S, Thepar A. Do parents know best? Parent-reported vs. child-reported depression symptoms as pre-

dictors of future child mood disorder in a high-risk sample. J Affect Disord. 2012;141(2–3, 233):–236.
35. Klaus NM, Mobilio A, King CA. Parent-adolescent agreement concerning adolescents' suicidal thoughts and behaviors. J Clin Child Adolesc Psychol. 2009;38(2):245–55.
36. Erensoy H. The association between anxiety and depression with 25(OH)D and thyroid stimulating hormone levels. Neuroscience (Riyadh). 2019;24(4):290–5.
37. Kazdin AE, Weisz JR. Identifying and developing empirically supported child and adolescent treatments. J Consult Clin Psychol. 1988;66(1):19–36.
38. Garber J, Clarke GN, Weersing VR, Beardslee WR, Brent DA, Gladstone TRG, et al. Prevention of depression in at-risk adolescents: a randomized controlled trial. JAMA. 2009;301(21):2215–24.
39. Dwyer JB, Bloch MH. Antidepressants for pediatric patients. Curr Psychiatr. 2019;18:26–42F.
40. Emslie GJ, Ventura D, Korotzer A, Tourkodimitris S. Escitalopram in the treatment of adolescent depression: a randomized placebo-controlled multisite trial. J Am Acad Child Adolesc Psychiatry. 2009;48(7):721–9.
41. Findling RL, Robb A, Bose A. Escitalopram in the treatment of adolescent depression: a randomized, double-blind, placebo-controlled extension trial. J Child Adolesc Psychopharmacol. 2013;23(7):468–80.
42. Wagner KD, Ambrosini P, Rynn M, Wohlberg C, Yang R, Greenbaum MS, et al. Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: two randomized controlled trials. JAMA. 2003;290(8):1033–41.
43. Brent D, Emslie G, Clarke G, Wanger K, Asarnow JR, Keller M, et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. JAMA. 2008;299(8):901–13.
44. Compton SN, Grant PJ, Chrisman AK, Gammon PJ, Brown VL, March JS. Sertraline in children and adolescents with social anxiety disorder: an open trial. J Am Acad Child Adolesc Psychiatry. 2001;40(5):564–71.
45. Emslie GJ, Prakash A, Zhang Q, Pangallo BA, Bangs ME, March JS. A double-blind efficacy and safety study of duloxetine fixed doses in children and adolescents with major depressive disorder. J Child Adolesc Psychopharmacol. 2014;24(4):170–9.
46. Haapasalo-Pesu K, Vuola T, Lahelma L, Marttunen M. Mirtazapine in the treatment of adolescents with major depression: an open-label, multicenter pilot study. J Child Adolesc Psychopharmacol. 2004;14(2):175–84.
47. Rush AJ, Warden D, Wisniewski SR, et al. STAR*D: revising conventional wisdom. CNS Drugs. 2009;23(8):627–47.
48. Shon S, Joo Y, Lee J, Kim H. Lamotrigine treatment of adolescents with unipolar and bipolar depression: a retrospective chart review. J Child Adolesc Psychopharmacol. 2014;24(5):258–87.
49. Amerio A, Ossola P, Scagnelli F, Odone A, Allinovi M, Cavalli A, et al. Safety and efficacy of lithium in children and adolescents: a systematic review in bipolar illness. Eur Psychiatry. 2018;54:85–97.
50. Dwyer JB, Stringaris A, Brent DA, Bloch MH. Annual research review: defining and treating pediatric treatment-resistant depression. J Child Psychol Psychiatry. 2020;61(3):312–32.
51. March J, Silva S, Petrycki S, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: treatment for adolescents with depression study (TADS) randomized controlled trial. JAMA. 2004;292(7):807–20.
52. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry. 2006;63(3):332–9.
53. Morrato EH, Libby AM, Orton HD, deGruy FV, Brent DA, Allen R, et al. Frequency of provider contact after FDA advisory on risk of pediatric suicidality with SSRIs. Am J Psychiatry. 2008;165:42–50.
54. Libby AM, Brent DA, Morrato EH, Orton HD, Allen R, Valuck RJ. Decline in treatment of pediatric depression after FDA advisory on risk of suicidality with SSRIs. Am J Psychiatry. 2007;164:884–91.

55. Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Erkins JA, et al. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. Am J Psychiatry. 2007;164:1356–63.
56. Ong SH, Wickramaratne P, Tang M, Weissman MM. Early childhood sleep and eating problems as predictors of adolescent and adult mood and anxiety disorders. J Affect Disord. 2006;96(1–2):1–8.
57. Dahl RE, Ryan ND, Birmaher B, al-Shabbout M, Williamson DE, Kupfer DJ. Sleep onset abnormalities in depressed adolescents. Biol Psychiatry. 1996;39(6):400–10.
58. Emslie GJ, Rush AJ, Weinberg WA, Rintelman JW, Roffwarg HP. Sleep EEG features of adolescents with major depression. Biol Psychiatry. 1994;36(9):573–81.
59. Boaffo A, Greenham S, Sullivan M, Bazaid K, Suntharalingam S, Silbernagel L, et al. Medications for sleep disturbance in children and adolescents with depression: a survey of Canadian child and adolescent psychiatrists. Child Adolesc Psychiatry Ment Health. 2020;14:10.
60. Kennard BD, Mayes TL, Chahal Z, Nakonezny PA, Moorehead A, Emslie GJ. Predictors and moderators of relapse in children and adolescents with major depressive disorder. J Clin Psychiatry. 2018;79(2):15m10330.
61. Youngstedt SD. Effects of exercise on sleep. Clin Sports Med. 2005;24(2):355–65.
62. Dopp RR, Mooney AJ, Armitage R, King C. Exercise for adolescents with depressive disorders: a feasibility study. Depress Res Treat. 2012;2012:257472.
63. Dopp R, Miklja Z, Jurries E, Mooney A. Exercise in adolescent depression: fitness, clinical outcomes, and BDNF. J Neurol Neurobiol. 2020;6(3).
64. Ginsburg GS, Silva SG, Jacobs RH, Tonev S, Hoyle RH, Kingery JN, Reinecke MA, Curry JF, March JS. Cognitive measures of adolescent depression: unique or unitary constructs? J Clin Child Adolesc Psychol. 2009;38(6):790–802.
65. Lohoff FW. Overview of the genetics of major depressive disorder. Curr Psychiatry Rep. 2010;12(6):539–46.
66. Sander JB, McCarty CA. Youth depression in the family context: familial risk factors and models of treatment. Clin Child Fam Psychol Rev. 2005;8(3):203–19.
67. Auerbach RP, Admon R, Pizzagalli DA. Adolescent depression: stress and reward dysfunction. Harv Rev Psychiatry. 2014;22(3):139–48.
68. Chun T, Mace S, Katz E. Evaluation and management of children and adolescents with acute mental health and/or behavioral emergencies. Pediatrics. 2016;138(3).
69. Posner K, Melvin GA, Stanley B, Oquendo MA, Gould M. Factors in the assessment of suicidality in youth. CNS Spectr. 2007;12(2):156–62.
70. Janiri D, Doucet GE, Pompili M, Sani G, Luna B, Brent DA, Frangou S. Risk and protective factors for childhood suicidality: a US population-based study. Lancet Psychiatry. 2020;7(4):317–26.
71. Shain B, Committee on Adolescence. Suicide and Suicide attempts in adolescents. Pediatrics. 2016;138(1):e20161420.
72. Oberle E, Schonert-Reicht KA. Social and emotional learning: recent research and practical strategies for promoting children's social and emotional competence in schools. In: Matson J, editor. Handbook of social behavior and skills in children. Autism and child psychopathology series. Cham: Springer. 2003. p. 175–197.
73. Beardslee WR, Versage EM, Van de Velde P, Swatlin S, Hoke L. Preventing depression in children through resiliency promotion: the prevention intervention project. In: McMahon RJ, Peters R, editors. The effects of parental dysfunction on children. New York: Kluwer Academic/Plenum; 2003. p. 71–86.
74. Clark GN, Hornbrook M, Lynch F, Polen M, Gale J, Beardslee W, O'Connor E, Seeley J. A randomized trial of a group cognitive intervention for preventing depression in adolescent offspring of depressed parents. Arch Gen Psychiatry. 2001;58(12):1127–34.
75. Brent DA, Birmaher B, Kolko D, Baughter M, Bridge J. Subsyndromal depression in adolescents after a brief psychotherapy trial: course and outcome. J Affect Disord. 2001;63(1–3):51–8.

Child with New Onset Convulsive Seizure

Amanda Weber and Aimee F. Luat

1 Introduction

An epileptic seizure is defined as a transient occurrence of signs and/or symptoms due to abnormal, excessive, or synchronous neuronal activity in the brain [1]. If it occurs in the presence of a provoking factor, it is referred to as provoked seizure or acute symptomatic seizure while, unprovoked seizures occur without any provoking factors [2]. Provoked seizures are estimated to account for 25–30% of first time seizures [3]. Seizures are very common, occur in 10% of the population (adults and children), and account for approximately 1% of all pediatric emergency department visits [4]. However, only half of children with a first seizure experience seizure recurrence and, thus, many may not need a daily antiseizure treatment. Hence, proper assessment and evaluation for risk of recurrence is needed. The focus of this chapter is on the evaluation and management of new onset unprovoked seizure, specifically generalized tonic–clonic seizures, formerly called grand mal seizures and popularly called convulsive seizures.

2 Epidemiology

The reported incidence of a single unprovoked seizure is 23–61 per 100,000 persons per year [2, 5]. Relative peaks occur in patients younger than 12 months and in individuals older than 65 years of age at 130.2 and 110.5 per 100,000 person-years, respectively [2]. Considering that about 10% of the population will have at least one

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seizure in his or her lifetime, but half or fewer will develop multiple seizures, it is important to comprehensively evaluate the patient to determine risk of recurrence [5]. People considered to be at high (more than 60%) risk for seizure recurrence based on EEG and imaging results, can be considered to have epilepsy, and may benefit from treatment with an antiseizure medication [1].

3 Etiology

A first seizure can be classified as (1) provoked immediate: caused by toxin, medication or metabolic disturbances; (2) acute symptomatic: occurring at the time of acute insult or in close association with a documented brain insult (i.e., traumatic brain injury or central nervous system infection); (3) remote symptomatic: associated with preexisting brain pathology (i.e., cortical dysplasia); (4) seizure associated with epilepsy syndrome (i.e., juvenile myoclonic epilepsy); (5) unidentified etiology; or (6) unprovoked [6, 7].

An unprovoked seizure is defined as a seizure or seizure cluster occurring within 24 h in a person >1 month of age in the absence of precipitating stimulus or beyond the interval estimated for the occurrence of acute symptomatic seizure [7]. In 15% of children, it may occur in a cluster [8].

The International League Against Epilepsy (ILAE) defines epilepsy as (1) at least two unprovoked seizures occurring >24 h apart, (2) one unprovoked seizure, and a probability of seizure recurrence over the next 10 years of at least 60%, or (3) the diagnosis of epilepsy syndrome [1].

The distinction between a provoked and unprovoked seizure is important in clinical practice as treatment approach and prognosis differ between the two (see subsection on outcome).

4 Provoked Seizures

Provoked seizures, as noted above, may occur in the context of an acute febrile illness such as upper respiratory infection, urinary tract infection, pneumonia, meningitis, or encephalitis. Interestingly, seizures may occur in these situations even without an actual fever [9]. Other situations when a seizure may occur are following a closed head injury, intracranial hemorrhage, and toxin ingestion. Electrolyte disturbances such as hypoglycemia, hypocalcemia, hypomagnesemia, hypo, or hypernatremia may also precipitate seizures [10]. These situations usually occur in children in response to a specific underlying condition such as hyponatremia following incorrect constitution of baby formula or hypernatremia in the context of dehydration [10]. Finally, a child may experience remote symptomatic seizures wherein an underlying brain malformation or remote event such as ischemic stroke

may serve as a seizure focus later on in life. Children with cerebral palsy can be considered to have remote symptomatic epilepsy [11].

5 Differential Diagnoses

The differential diagnosis of a child presenting with a first unprovoked convulsive seizure is broad (Table 1). The diagnosis significantly relies on the description of the event and its accurate interpretation. It is important to obtain witness accounts when available, as most seizures are too short to be identified by the first responders, are unwitnessed by the physician and the patient suspected to have had a seizure may be postictal or encephalopathic and thus unable to provide helpful information. This

Table 1 Differential diagnosis for new onset convulsive seizures in a child

Differential diagnoses	Distinguishing features from epileptic seizures
Syncope: transient loss of consciousness and postural tone due to transient global cerebral hypoperfusion marked by rapid onset, brief duration, and spontaneous complete recovery [12]; peaks at 15–19 years, higher rate in girls; neurally mediated syncope (vasovagal, situational, carotid sinus, atypical forms) is the most common type [13, 14]	**Provoking stimulus** (stress, pain, fear, injury, situational); **Prodrome:** pallor, diaphoresis, and warmth **Unconsciousness:** typically brief (<1 min), eye deviation is fixed or upward, uncommon tongue biting ("tongue tip"); uncommon incontinence, asynchronous myoclonic muscle movement follows loss of consciousness (epileptic seizure-jerking occurs immediately); **Post-ictal fatigue** not confusion [13]; EKG may show bradycardia or brief asystole associated with slowing on EEG during the episode (see Fig. 1a–c).
Cataplexy: one of the symptoms of narcolepsy type 1; history of excessive daytime sleepiness, hypnagogic and hypnopompic hallucinations, and sleep paralysis	Laugher/joke can trigger sudden antigravity tone loss starting in the face, then head falls forward, child crumples to the floor and is immobile but fully conscious [15]; deep tendon reflexes transiently are lost [13]
Parasomnias: undesirable physical or mental events occurring exclusively during sleep include NREM-related (confusional arousal, sleep terror) and REM-related parasomnias, (nightmare, and REM sleep behavior disorder) and may mimic frontal lobe seizures; sleep terrors and nightmares peak at age 3–8 years [16]	Sleep terrors occur within the first third of the night (seizures occur throughout the night) sudden arousals and various motor activities (in contrast to the stereotyped pattern in frontal lobe seizures) and screaming, crying, vocalizations and autonomic activation with inconsolability lasting several minutes (seizures are short seconds to <3 min). Nightmares occur in the last third of the night; lack motor behavior, absence of confusion on awakening with memory of the dream distinguish this from seizures [16].
Breath-holding spells: occurs between ages 6 months to 4 years, with characteristic sequence of events [17]	Provoking factors (emotion, stress, minor trauma) cause emotional upset, lead to "silent scream," color change, loss of consciousness and tone [17] some may evolve into a convulsive seizure

(continued)

Table 1 (continued)

Differential diagnoses	Distinguishing features from epileptic seizures
Psychogenic nonepileptic seizures (PNES): may be better called **functional seizures** [18] paroxysmal episodes of altered awareness, movement, or sensation that mimic epileptic seizures but are not associated with epileptiform abnormalities on EEG [19]	Episodes in the doctor's office or waiting room [20, 21] gradual onset, undulating motor activity, side-to-side (lateral) head shaking, closed eyes, resisted eyelid opening; >2 min; lack of cyanosis; partial responsiveness during the episode; rapid postictal re-orientation [22], tongue biting and oral lacerations may occur in both PNES and epileptic seizure but lateral tongue biting is highly specific for generalized tonic–clonic seizure [23]
Panic attacks: paroxysmal manifestations of anxiety or panic disorder (associated with intense autonomic symptoms)	Abrupt surge of intense fear or intense discomfort that reaches peak within minutes, in which at least 4 of the 13 symptoms (palpitations, pounding heart rate; sweating; trembling or shaking; shortness of breath or smothering; feeling of choking; chest pain or discomfort, nausea or abdominal distress; feeling dizzy, unsteady, or faint; feelings of unreality (derealization) or being detached from oneself (depersonalization; fear of losing control or going crazy; fear of dying; numbness or tingling; chills or hot flushes) enumerated on the DSM-V criteria are present [24]
Gastroesophageal reflux disorder (GERD): a digestive disorder that can cause laryngospasms, bradycardia, apneic episodes, and involuntary movements; common in children with neurological impairments	Recurrent regurgitation, with or without vomiting, heartburn, abdominal or chest pain, crying, head/eye version, contractions of the trunk, torticollis, flexor and extensor spasm, and stiffening movements typically associated with feeding [25]
Migraine may mimic focal seizures (occipital lobe seizures): both can present with visual hallucinations, and prominent autonomic symptoms including vomiting and pallor	As a rule, occipital lobe seizures are brief (<1 min), elementary visual hallucinations (seizure: colored and circular patterns; migraine: black and white; linear patterns), maybe followed by severe headache and vomiting [26]. Eye deviation, altered mental state including confusion as well as progression to focal motor seizures (convulsion) are features suggestive of seizures

EEG electroencephalogram, *EKG* electrocardiogram, *NREM* non-rapid eye movement, *REM* rapid eye movement

challenge is especially magnified in infants and younger children. During history taking, specific features of the spell including the presence of body stiffening, limb jerking, pattern or sequence of clinically observed behavior (semiology), and duration should be noted [27]. The detailed description of the semiology can provide localizing and diagnostic value that can aid in the management (Table 2). Although witnesses are often able to identify the key elements that can aid the physician in the diagnosis of seizures, routine questions, restricting the witness to provide "yes" or "no" responses may lead to misleading information [28]. It may sometimes be helpful for the physician to imitate, mimic, and demonstrate physically the symptoms when asking questions. Home video recording is always useful.

Table 2 Localization of common seizure manifestations

Seizure semiology	Localization
Forced head and eye deviation	Contralateral hemisphere
Focal clonic jerking	Contralateral frontal and perirolandic area
Focal tonic (stiffening)	Contralateral hemisphere
Ictal paresis or postictal Todd's paralysis	Contralateral hemisphere
Somatosensory symptoms	Contralateral primary sensory cortex
Unilateral limb automatism	Ipsilateral hemisphere
Hypermotor behavior	Frontal lobe
Gelastic (laughter)	Hypothalamus or mesial temporal lobe
Speech arrest	Temporal lobe, language dominant hemisphere
Visual symptoms	Occipital lobe
Ictal fear	Amygdala, hippocampus
Postictal nose wiping	Contralateral frontal or temporal

Common features in epileptic convulsive seizures include prodromal cry (ictal cry, vocalization) at the onset of the generalized convulsions, bilateral movements that are often synchronous, duration of <2–3 min, commonly associated with injury (lateral tongue biting) and frequent incontinence as well as amnesia of the event [19].

6 Diagnostic Approach

6.1 History

A detailed event history helps to narrow the differential diagnosis and identify potential triggers. It is imperative to obtain the history from both the patient and a direct observer when possible. The physician should determine whether the patient has actually had other seizures in the past. It is common for parents to seek medical attention following first generalized tonic–clonic seizure but they may have not have recognized early morning body jerking, nocturnal tongue biting, or brief staring episodes as seizures in the past [6]. Clinicians should review video footage of events and encourage families to video record recurrent episodes. Recently, outpatient smartphone video review by experts has been found to have a diagnostic accuracy in 89% for epileptic seizures and in 86% for psychogenic nonepileptic attacks suggesting its added value in routine history and physical examination [29]. Particular attention should be paid to the sequence of events beginning with the setting immediately before the event, the onset and core clinical features, and finally with event end and postictal symptomatology. Presence of aura should also be inquired about, but may be difficult, if not impossible, to elicit from preverbal children. Likelihood of aura in those cases may be inferred by fearful behavior, or other responses before a seizure. Rarely, young children may be able to describe

nonspecific symptoms of aura such as abdominal pain or headache [30, 31]. Adolescents with focal seizures may be able to describe their sensation or feeling prior to the seizure.

Precipitating factors may include recent febrile illnesses, vaccinations, trauma, ingestions, medications, sleep deprivation, exposure to strobe lights, and hyperventilation. Knowledge of this information may provide clues about the seizure type and may dictate management. Febrile seizures, for example, occur in children from about 6 months through 5 years of age, and daily antiseizure medications are not recommended in the majority of cases. Similarly, acute symptomatic seizures do not typically require long-term antiseizure medications. Sleep deprivation and illness are common provoking factors in children who have an underlying risk for seizures. Strobe lights and hyperventilation may induce seizures more commonly in patients with a generalized epilepsy type.

Information about the circumstance may help narrow the differential diagnosis (Table 1 and Fig. 1a–c). Recent food and fluid intake prior to the event may give insight regarding risks for events related to hypoglycemia or dehydration. Events in young children that consistently occur in the context of crying raise suspicion for breath-holding events. If events consistently occur in stressful settings, this may raise suspicion for nonepileptic events. It is important to question further regarding other subtle events from sleep such as recent nocturnal enuresis or tongue biting, which may suggest prior unwitnessed seizures.

The history of event onset begins with inquiry about the presence or absence of an aura. Generalized seizure types typically begin abruptly without warning. In contrast, focal seizures may begin with an aura of variable duration. If present, the type of aura may provide clues about localization. Auras may include a variety of symptoms with motor, sensory, autonomic, or cognitive features. These represent brief focal seizures with intact awareness. Common auras in patients with temporal lobe epilepsy, for example, may involve an unpleasant abdominal rising sensation, a feeling of panic, feelings of familiarity (déjà vu), or unfamiliarity (jamais vu), or abnormal smell [32]. The aura is often followed by progression of the seizure to include loss of awareness. Features of the clinical seizure including direction of head and eye turning, stiffening, or clonic jerking of one limb or side of the body are all helpful to lateralize which hemisphere may be involved, and sometimes to localize more specifically from which part of the hemisphere the seizure arises (Table 2). Having the observer mime the movements may be very helpful to understand the seizure semiology. Additional information should include duration, assessment of

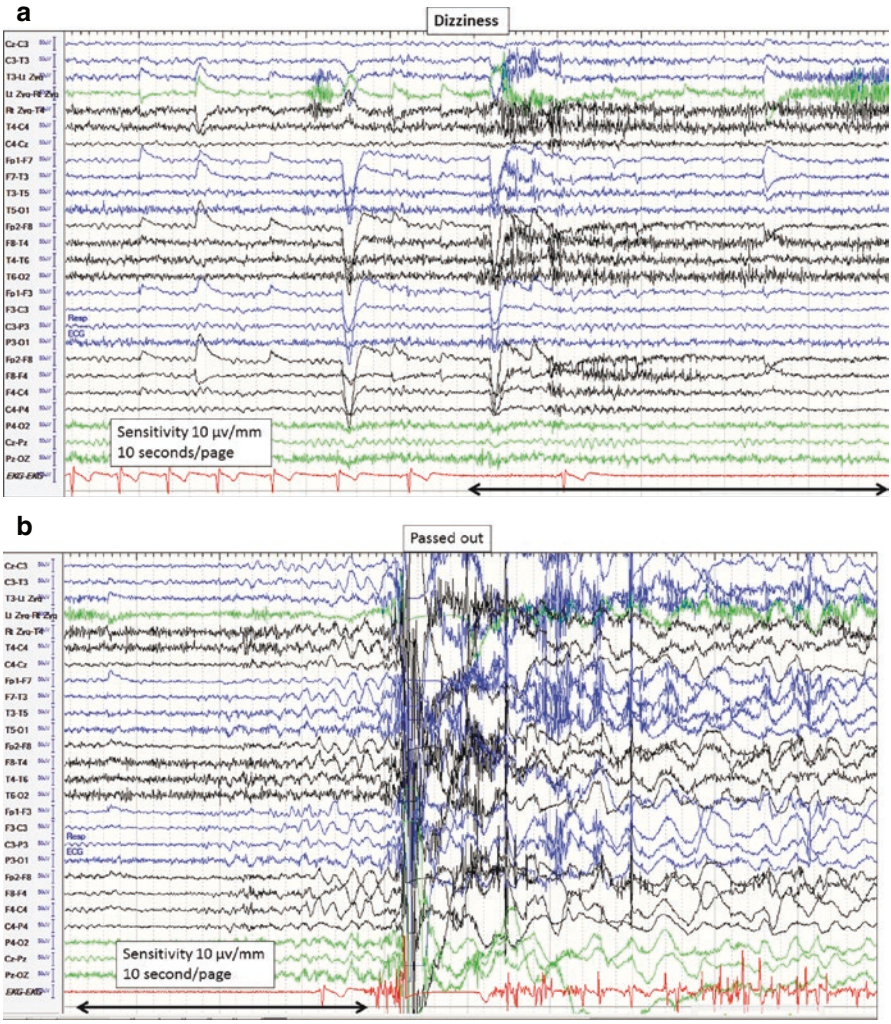

Fig. 1 A 15-year-old male who presented with recurrent dizziness, passing-out episodes occurring while in upright position followed by asynchronous myoclonic jerking. (**a**) Electroencephalogram (EEG) is shown. Habitual spell was captured during his prolonged video-EEG monitoring. (**b**) Patient was standing and urinating and, prior to the onset of the passing-out episode, felt dizzy (**box**); electrocardiogram (EKG) demonstrated an 8-s asystolic pause (**double headed arrow**) followed by generalized slow wave noted on EEG. (**b**, **c**) No epileptiform discharges were noted. Echocardiogram, tilt-table test, and cardiac electrophysiologic study were all negative. A diagnosis of vasovagal syncope was made

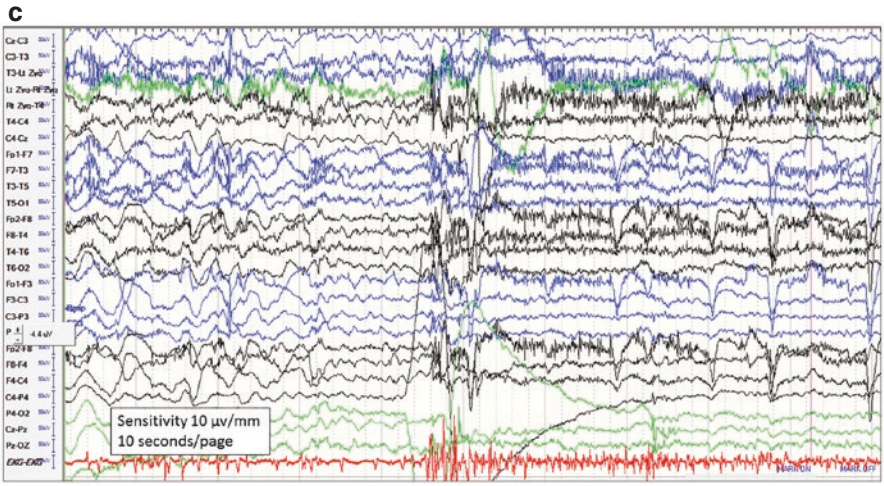

Fig. 1 (continued)

awareness, tongue biting, incontinence, presence of cyanosis, length of postictal period, and postictal focal neurologic abnormalities.

6.2 Physical Examination

(a) **General Physical Examination:** General examination should include measurement of vital signs, evaluation of fontanelle and head circumference, evaluation for evidence of trauma, evaluation for dysmorphic features, as well as thorough cardiac abdominal examination (hepatosplenomegaly), and skin examination with attention to features of neurocutaneous disorders. Figure 2a illustrates a port wine birth mark seen in a child with Sturge–Weber Syndrome, Fig. 2b demonstrates an ash leaf hypomelanotic macule in a child with Tuberous Sclerosis Complex and whorls/streaks of linear hypopigmentation following the lines of Blaschko are seen in a child with Linear Sebaceous Nevus who presented with new onset seizure is shown in Fig. 2c. A bulging fontanelle is associated with increased intracranial pressure. Neck rigidity raises suspicion for meningitis.

(b) **Neurological Examination**: Examination of higher mental functions should be performed to assess for alertness, appropriate interaction with family members and ability to talk and respond fluently. Persistent encephalopathy following a seizure raises concern for ongoing nonconvulsive seizures, structural abnormalities, or toxic/metabolic derangements. New onset psychotic features may be associated with ingestion, infectious or autoimmune encephalitis. The cranial nerve examination including a funduscopic assessment may identify retinal hemorrhages in the setting of trauma or optic disc edema associated with increased intracranial pressure. Asymmetry of motor function or deep tendon reflexes may be caused by the postictal state or related to a focal structural abnormality including a tumor or

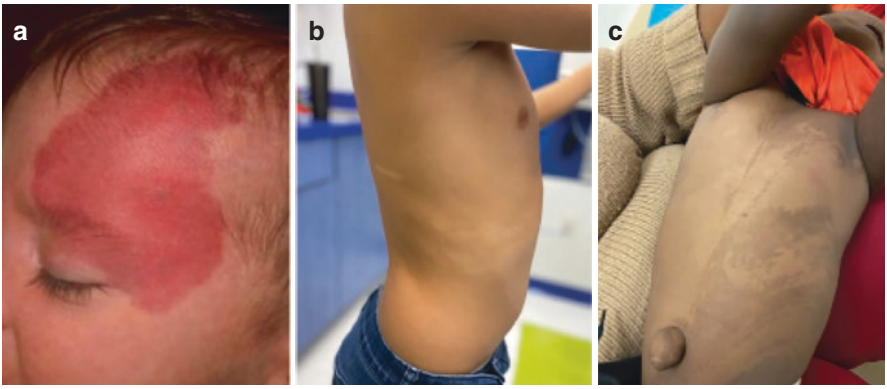

Fig. 2 (**a**) One-year-old girl who presented with new-onset right-sided jerking. A port-wine birth mark was noted on the left forehead region including the upper eyelid, suggesting the diagnosis of Sturge-Weber syndrome with intracranial involvement confirmed by brain magnetic resonance imaging (MRI). (**b**) Hypopigmented macules (also known as "ash leaf spot") are seen in this boy with tuberous sclerosis complex (TSC) and new-onset seizure. (**c**) Congenital birth mark in a 23-month-old child with developmental delay and linear sebaceous nevus syndrome characterized by whorls or streaks of hyperpigmentation following the lines of Blaschko predominantly on the left trunk who presented with new-onset seizure at age 10 months

stroke. The child may be ataxic shortly after a seizure. The examination of active or apprehensive infants and young children may need to be modified to consist primarily of observation of play, object manipulation, hand preference and gait. Hand preference is typically established after 2 years of age. When children are examined days or weeks after the event, the neurological examination is likely to be normal.

6.3 Evaluation

6.3.1 Laboratory Investigations

A variety of laboratory investigations are commonly performed for first time unprovoked seizure including complete blood count, serum electrolytes, serum calcium, magnesium, glucose levels and, toxin screening. The yield of such tests in children over 6 months of age, without a compelling clinical history is low. A retrospective study of 308 pediatric patients, including 105 children presenting to the ER for first unprovoked seizures, was performed to analyze how many had laboratory tests done, and the yield of actionable abnormalities. In the study, 104 patients had at least one laboratory study performed, and none of the laboratory findings were found to be contributory to the diagnosis [33]. Several other studies have reported similar findings.

The American Academy of Neurology Practice Parameter for the evaluation of a first time unprovoked seizure recommends consideration of laboratory investigations on a case by case basis as needed based on clinical history and physical

examination [34]. Lumbar puncture should be considered if there are concerns of meningitis or encephalitis.

6.4 Electroencephalogram (EEG)

A 20–30-min sleep-deprived EEG should be performed after a first time unprovoked seizure to evaluate for risk of recurrence. Epileptiform abnormalities, such as sharp waves and spikes, are predictive of seizure recurrence, and slowing of the EEG background in one brain region may suggest an underlying focal structural lesion [34]. The EEG is most helpful when sleep, wakefulness, photic stimulation, and hyperventilation are recorded. If abnormal, the routine EEG may be diagnostic of a specific epilepsy syndrome, or in other cases may support the diagnosis of an epileptic seizure over a seizure mimic and may help determine the need for imaging and an antiseizure medication. Focal slowing, for example, can be seen in association with structural lesions, and imaging is then imperative. On the other hand, specific classical epilepsy syndromes, such as childhood absence epilepsy, do not always require brain imaging [35].

6.5 Neuroimaging

Emergent neuroimaging is typically not required for evaluation of a first unprovoked seizure if the patient is well-appearing and has returned to baseline. Factors that prompt urgent imaging include prolonged encephalopathy, persistent focal weakness or deficit, signs or symptoms of trauma or increased intracranial pressure, the presence of a ventriculoperitoneal (VP) shunt, or patients with bleeding disorders. A head computed tomography (CT) is typically utilized as the imaging modality of choice in emergency circumstances because of the ability to quickly visualize fractures, large tumors, blood products, and hydrocephalus without the need for sedation.

The yield of head CT in a stable patient with a normal neurological examination who is back to baseline after an unprovoked seizure is low, and most typically is either normal or identifies unactionable findings [36–38]. Additionally, a head CT exposes a young brain to radiation, and children are more vulnerable to the carcinogenic effects of radiation [39]. In contrast, brain MRI is more sensitive than CT scan when evaluating for non-urgent epileptogenic lesions such as focal cortical dysplasias, vascular malformations, and mesial temporal sclerosis (Fig. 3). The yield of MRI abnormalities in children with first unprovoked seizure is about 33%, of which 4% or fewer require emergent intervention [40, 41].

A brain MRI, however, may take an hour or more to complete and thus in many young children do require sedation. If emergent imaging is not performed,

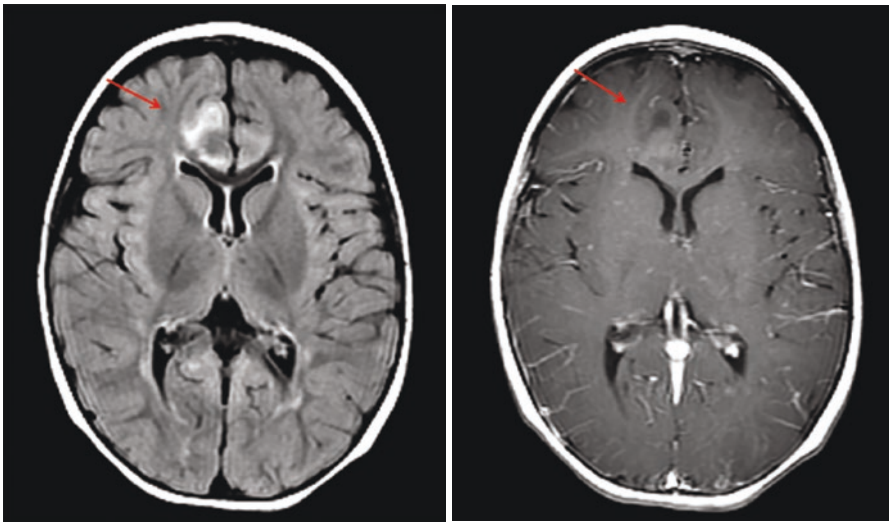

Fig. 3 Two-year-old girl who presented with the first episode of unprovoked seizure described as staring followed by body stiffening and jerking. Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) demonstrates a focal cortical dysplasia in the right anterior medial frontal region (**arrow**), which showed gadolinium enhancement on T1-weighted MRI

nonurgent brain MRI is preferred over head CT scan (unless contraindicated), and should be considered if there is a focal seizure, a prolonged seizure, significant cognitive or motor impairment of undetermined etiology, a focal EEG abnormality that is not consistent with a described benign epilepsy syndrome or primary epilepsy, and in children less than 12 months of age with new onset seizure [34, 35]. Due to concerns about the safety of gadolinium-based contrast agents [42], routine use of contrast-enhanced MRI for new onset seizure evaluations should be avoided and the decision regarding contrast injection should be made on an individual basis.

6.6 Treatment/Management

The decision regarding the use of a daily prophylactic antiseizure medication after a first time seizure must weigh the risks and benefits of treatment, while keeping in mind the likelihood of seizure recurrence after first time unprovoked seizure may be as low as 14–50% [34, 43]. While antiseizure medications may reduce the risk for seizure recurrence, long-term remission rate is similar in patients who were started on a prophylactic medication after the first or second unprovoked seizure [43]. Additionally, antiseizure medications may cause undesirable side effects including behavior changes, sedation, weight changes, and rash, among others. As such, the American Academy of Neurology practice parameter states that treatment with a

Table 3 Food and Drug Administration (FDA)-approved medications for intermittent use in epilepsy to control bouts of increased seizure activity (rectal diazepam) [45] and acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) distinct from the patient's usual seizure pattern (nasal diazepam, nasal midazolam) [46, 47, 49]

(a) **Rectal Diazepam** [45]**: 2.5, 5, 7.5, 10, 12.5, 15, 17.5, and 20 mg: Ages 2 years and older with epilepsy**

Note: dose may be repeated in 4–12 h if needed; do not use more than five times per month or more than once every 5 days

Recommended dosage

2–5 years (0.5 mg/kg)		**6–11 years (0.3 mg/kg)**		**12+ years (0.2 mg/kg)**	
Weight (kg)	**Dose (mg)**	**Weight (kg)**	**Dose (mg)**	**Weight (kg)**	**Dose (mg)**
6–10	5	10–16	5	14–25	5
11–15	7.5	17–25	7.5	26–37	7.5
16–20	10	26–33	10	38–50	10
21–25	12.5	34–41	12.5	51–62	12.5
26–30	15	42–50	15	63–75	15
31–35	17.5	51–58	17.5	76–87	17.5
36–44	20	59–74	20	88–111	20

(b) **Diazepam nasal spray** [46]**: 5 mg, 7.5 mg, 10 mg/0.1 mL doses**: **Ages 6 years and older with epilepsy**

Second dose (if needed): A second dose, when required, may be administered after at least 4 h after the initial dose

Maximum dose and frequency: Do not use >2 doses to treat a single episode; it is recommended to use no more than one episode every 5 days and to treat no more than five episodes per month

Recommended dosage

Dose based on age and weight			**Administration**	
6–11 years (0.3 mg/kg)	**12 years and older (0.2 mg/kg)**	**Dose (mg)**	**Number of nasal spray devices**	**Number of sprays**
Weight (kg)	**Weight (kg)**			
10–18	14–27	5	One 5 mg device	One spray in one nostril
19–37	28–50	10	One 10 mg device	One spray in one nostril
38–55	51–75	15	Two 7.5 mg devices	One spray in each nostril
56–74	76 and up	20	Two 10 mg devices	One spray in each nostril

(c) **Midazolam nasal spray** [47] **5 mg/0.1 mL: Ages 12 years and older with epilepsy**

Recommended dosage

Initial dose: Administer one spray (5 mg dose) into one nostril

Second dose: One additional dose (5 mg dose) into the opposite nostril maybe administered after 10 min if the patient has not responded to the initial dose

Maximum dose and frequency: Do not use >2 doses to treat seizure cluster; it is recommended to use no more than one dose every 3 days and to treat no more than five episodes per month

preventative antiseizure medication is not indicated for the prevention of the development of epilepsy, and that treatment with an antiseizure medication may be considered when risks of further seizures outweigh the potential risks of adverse effects from medication.

While the risk of recurrent seizures after a first time prolonged seizure is no greater than if the initial seizure is short [43], there is a correlation between a prolonged first seizure, and an increased risk of having a prolonged second seizure [44]. Patients who have experienced a prolonged (>30 min) first time seizure, therefore, may benefit from an abortive therapy to prevent a second episode of status epilepticus. There are currently multiple Food and Drug Administration (FDA)-approved abortive medications (Table 3) for the treatment of prolonged seizures, or seizure clusters, including rectal diazepam [45], intranasal diazepam [46], and intranasal midazolam [47] formulations. If an abortive medication is prescribed, parents should be trained regarding how and when to use it. Additional training should include seizure first aid techniques, seizure safety precautions, and an emergency seizure action plan for home and school, which will detail the management of a seizure emergency for that child. Laws with respect to driving may vary by state and country.

6.7 Outcome

The risk of seizure recurrence following a first unprovoked seizure is about 20–50% in untreated individuals within 2 years of the initial seizure [48] with cumulative risk of 29% at 1 year, 37% at 2 years, and 42% at 3 years [49]. In individuals with acute symptomatic seizures, though the risk of short-term mortality was reportedly higher than in those with unprovoked seizure, they were 80% less likely to experience subsequent seizure compared to those with an unprovoked seizure [50].

Adults with multiple seizures within a 24-h period as their first seizure manifestation were found no more likely to have seizure recurrence than those presenting with a single seizure [51]. However, conflicting data are reported in children. Metsaranta and colleagues demonstrated that the recurrence of seizures in children <16 years even if the initial presentation was status epilepticus was only 21% [52]. Conversely, a study which included a cohort of 490 children comparing "same day (≥2 seizures in 24 h)" with "different day" group (interval between 2 seizures >24 h) showed risk of subsequent seizure at 80% in the "same day" group. Hence, the authors suggested that if there are ≥2 seizures on the same day, the child has epilepsy [8].

Children whose first seizure occurred during sleep have a higher chance of seizure recurrence by 2 years compared to those who had seizure while awake [53].

7 When to Hospitalize?

Failure to return to baseline especially in terms of level of alertness, waxing and waning mental state and new onset focal neurological deficits (such as hemiparesis) raise concern for ongoing subclinical seizures, or new focal structural lesions and are thus indications for hospitalization after new onset seizure. Continuous video-EEG monitoring should be considered in those who are suspected to have subclinical seizures. Urgent brain imaging should be performed in the setting of new focal neurological deficits.

8 When to Refer to a Pediatric Neurologist?

All patients who present with new onset seizure should be referred to pediatric neurology to further assist in the evaluation and investigation of the underlying etiology, assess the recurrence risk and determine the need for anti-seizure drug therapy.

9 Clinical Pearls/Key Points

- First seizure is a common diagnosis in children, but only 20–50% will experience recurrence.
- The recurrence risk for a subsequent seizure is increased in those with an abnormal neurological examination, abnormal MRI, epileptiform EEG, those who experienced a seizure in sleep and those with a remote symptomatic cause.
- The differential diagnosis is broad and epileptic seizures should be distinguished from nonepileptic events.
- EEG and brain MRI are standard tests required for the evaluation of first unprovoked seizure in a child.

10 Conclusion

First time unprovoked seizures are a common cause of acute neurological emergencies in children. The differential diagnosis is broad, and history should focus on potential provoking factors, aura, event semiology, duration, and postevent symptomatology. While the typical recurrence rate is estimated to be 20–50%, evaluation should include a sleep-deprived EEG and brain MRI to better estimate the risk of recurrence in each individual. Laboratory evaluations should be considered on a case-by-case basis to evaluate for provoking causes. Prophylactic antiseizure medications are not routinely recommended after first time unprovoked seizures, unless

a particularly high risk for recurrence, or a specific epilepsy syndrome is identified. Abortive medications should be considered in patients who have experienced a prolonged seizure, or a cluster of seizures.

References

1. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55(4):475–82.
2. Hauser WA, Beghi E. First seizure definitions and worldwide incidence and mortality. Epilepsia. 2008;49(Suppl 1):8–12.
3. Pohlmann-Eden B, Beghi E, Camfield C, Camfield P. The first seizure and its management in adults and children. BMJ. 2006;332(7537):339–42.
4. Pallin DJ, Goldstein JN, Moussally JS, Pelletier AJ, Green AR, Camargo CA. Seizure visits in US emergency departments: epidemiology and potential disparities in care. Int J Emerg Med. 2008;1(2):97–105.
5. Olafsson E, Ludvigsson P, Gudmundsson G, Hesdorffer D, Kjartansson O, Hauser WA. Incidence of unprovoked seizures and epilepsy in Iceland and assessment of the epilepsy syndrome classification: a prospective study. Lancet Neurol. 2005;4(10):627–34.
6. Bergey GK. Management of a first seizure. Continuum (Minneap Minn). 2016;22(1 Epilepsy):38–50.
7. Rizvi S, Ladino LD, Hernandez-Ronquillo L, Téllez-Zenteno JF. Epidemiology of early stages of epilepsy: risk of seizure recurrence after a first seizure. Seizure. 2017;49:46–53.
8. Camfield P, Camfield C. Epilepsy can be diagnosed when the first two seizures occur on the same day. Epilepsia. 2000;41(9):1230–3.
9. Lee WL, Ong HT. Afebrile seizures associated with minor infections: comparison with febrile seizures and unprovoked seizures. Pediatr Neurol. 2004;31(3):157–64.
10. Nardone R, Brigo F, Trinka E. Acute symptomatic seizures caused by electrolyte disturbances. J Clin Neurol. 2016;12(1):21–33.
11. Shorvon S. The concept of symptomatic epilepsy and the complexities of assigning cause in epilepsy. Epilepsy Behav. 2014;32:1–8.
12. Moya A, Sutton R, Ammirati F, Blanc JJ, Brignole M, Dahm JB, et al. Guidelines for the diagnosis and management of syncope (version 2009). Eur Heart J. 2009;30(21):2631–71.
13. Cheshire WP. Syncope. Continuum (Minneap Minn). 2017;23(2, Selected Topics in Outpatient Neurology):335–58.
14. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res. 2011;21(2):69–72.
15. Stephenson JB. Syncopes and other paroxysmal events. Handb Clin Neurol. 2013;112:861–6.
16. Tinuper P, Provini F, Bisulli F, Vignatelli L, Plazzi G, Vetrugno R, et al. Movement disorders in sleep: guidelines for differentiating epileptic from non-epileptic motor phenomena arising from sleep. Sleep Med Rev. 2007;11(4):255–67.
17. Luat AF, Kamat D, Sivaswamy L. Paroxysmal nonepileptic events in infancy, childhood, and adolescence. Pediatr Ann. 2015;44(2):e18–23.
18. Loewenberger A, Cope SR, Poole N, Agrawal N. An investigation into the preferred terminology for functional seizures. Epilepsy Behav. 2020;111:107183.
19. Hopp JL. Nonepileptic episodic events. Continuum (Minneap Minn). 2019;25(2):492–507.
20. Benbadis SR. Psychogenic nonepileptic "seizures" or "attacks"? It's not just semantics: attacks. Neurology. 2010;75(1):84–6.
21. Benbadis SR. Nonepileptic behavioral disorders: diagnosis and treatment. Continuum (Minneap Minn). 2013;19(3 Epilepsy):715–29.

22. Doss RC, LaFrance WC. Psychogenic non-epileptic seizures. Epileptic Disord. 2016;18(4):337–43.
23. Benbadis SR, Wolgamuth BR, Goren H, Brener S, Fouad-Tarazi F. Value of tongue biting in the diagnosis of seizures. Arch Intern Med. 1995;155(21):2346–9.
24. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
25. Bayram AK, Canpolat M, Karacabey N, Gumus H, Kumandas S, Doğanay S, et al. Misdiagnosis of gastroesophageal reflux disease as epileptic seizures in children. Brain Dev. 2016;38(3):274–9.
26. Panayiotopoulos CP. Visual phenomena and headache in occipital epilepsy: a review, a systematic study and differentiation from migraine. Epileptic Disord. 1999;1(4):205–16.
27. Nowacki TA, Jirsch JD. Evaluation of the first seizure patient: key points in the history and physical examination. Seizure. 2017;49:54–63.
28. Muayqil TA, Alanazy MH, Almalak HM, Alsalman HK, Abdulfattah FW, Aldraihem AI, et al. Accuracy of seizure semiology obtained from first-time seizure witnesses. BMC Neurol. 2018;18(1):135.
29. Tatum WO, Hirsch LJ, Gelfand MA, Acton EK, LaFrance WC, Duckrow RB, et al. Assessment of the predictive value of outpatient smartphone videos for diagnosis of epileptic seizures. JAMA Neurol. 2020;77(5):593–600.
30. Fogarasi A, Janszky J, Faveret E, Pieper T, Tuxhorn I. A detailed analysis of frontal lobe seizure semiology in children younger than 7 years. Epilepsia. 2001;42(1):80–5.
31. Fogarasi A, Boesebeck F, Tuxhorn I. A detailed analysis of symptomatic posterior cortex seizure semiology in children younger than seven years. Epilepsia. 2003;44(1):89–96.
32. Rossetti AO, Kaplan PW. Seizure semiology: an overview of the 'inverse problem'. Eur Neurol. 2010;63(1):3–10.
33. Nypaver MM, Reynolds SL, Tanz RR, Davis AT. Emergency department laboratory evaluation of children with seizures: dogma or dilemma? Pediatr Emerg Care. 1992;8(1):13–6.
34. Hirtz D, Ashwal S, Berg A, Bettis D, Camfield C, Camfield P, et al. Practice parameter: evaluating a first nonfebrile seizure in children: report of the quality standards subcommittee of the American Academy of Neurology, the Child Neurology Society, and the American Epilepsy Society. Neurology. 2000;55(5):616–23.
35. Gaillard WD, Chiron C, Cross JH, Harvey AS, Kuzniecky R, Hertz-Pannier L, et al. Guidelines for imaging infants and children with recent-onset epilepsy. Epilepsia. 2009;50(9):2147–53.
36. McAbee GN, Barasch ES, Kurfist LA. Results of computed tomography in "neurologically normal" children after initial onset of seizures. Pediatr Neurol. 1989;5(2):102–6.
37. Stroink H, Brouwer OF, Arts WF, Geerts AT, Peters AC, van Donselaar CA. The first unprovoked, untreated seizure in childhood: a hospital based study of the accuracy of the diagnosis, rate of recurrence, and long term outcome after recurrence. Dutch study of epilepsy in childhood. J Neurol Neurosurg Psychiatry. 1998;64(5):595–600.
38. Veerapandiyan A, Aravindhan A, Takahashi JH, Segal D, Pecor K, Ming X. Use of head computed tomography (CT) in the Pediatric Emergency Department in evaluation of children with new-onset afebrile seizure. J Child Neurol. 2018;33(11):708–12.
39. Kleinerman RA. Cancer risks following diagnostic and therapeutic radiation exposure in children. Pediatr Radiol. 2006;36(Suppl 2):121–5.
40. Shinnar S, O'Dell C, Mitnick R, Berg AT, Moshe SL. Neuroimaging abnormalities in children with an apparent first unprovoked seizure. Epilepsy Res. 2001;43(3):261–9.
41. Al-Shami R, Khair AM, Elseid M, Ibrahim K, Al-Ahmad A, Elsetouhy A, et al. Neuro-imaging evaluation after the first afebrile seizure in children: a retrospective observational study. Seizure. 2016;43:26–31.
42. Guo BJ, Yang ZL, Zhang LJ. Gadolinium deposition in brain: current scientific evidence and future perspectives. Front Mol Neurosci. 2018;11:335.
43. Hirtz D, Berg A, Bettis D, Camfield C, Camfield P, Crumrine P, et al. Practice parameter: treatment of the child with a first unprovoked seizure: report of the quality standards Subcommittee

of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2003;60(2):166–75.
44. Shinnar S, Berg AT, Moshe SL, Shinnar R. How long do new-onset seizures in children last? Ann Neurol. 2001;49(5):659–64.
45. Valeant Pharmaceuticals North America LLC. Diastat (diazepam) [package insert]. www.accessdata.fda.gov/drugsatfda_docs/label/2014/020648s012lbl.pdf. Revised December 2014. Accessed 13 Dec 2020.
46. Neurelis. Valtoco (diazepam intranasal) [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211635s000lbl.pdf. Revised January 2020. Accessed 13 Dec 2020.
47. Proximagen, LLC. Nayzilam (versed) [package insert]. U.S. Food and Drug Administration website https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211321s000lbl.pdf Revised May 2019. Accessed 13 Dec 2020.
48. Berg AT. Risk of recurrence after a first unprovoked seizure. Epilepsia. 2008;49(Suppl 1):13–8.
49. Shinnar S, Berg AT, O'Dell C, Newstein D, Moshe SL, Hauser WA. Predictors of multiple seizures in a cohort of children prospectively followed from the time of their first unprovoked seizure. Ann Neurol. 2000;48(2):140–7.
50. Hesdorffer DC, Benn EK, Cascino GD, Hauser WA. Is a first acute symptomatic seizure epilepsy? Mortality and risk for recurrent seizure. Epilepsia. 2009;50(5):1102–8.
51. Kho LK, Lawn ND, Dunne JW, Linto J. First seizure presentation: do multiple seizures within 24 hours predict recurrence? Neurology. 2006;67(6):1047–9.
52. Metsäranta P, Koivikko M, Peltola J, Eriksson K. Outcome after prolonged convulsive seizures in 186 children: low morbidity, no mortality. Dev Med Child Neurol. 2004;46(1):4–8.
53. Ramos Lizana J, Cassinello Garciá E, Carrasco Marina LL, Vázquez López M, Martín González M, Muñoz Hoyos A. Seizure recurrence after a first unprovoked seizure in childhood: a prospective study. Epilepsia. 2000;41(8):1005–13.

Neonate/Infant with Seizures

Arnold J. Sansevere and Chellamani Harini

1 Neonatal Onset Seizures

1.1 Introduction

Neonatal seizures (NS) are common in the neonatal intensive care unit. Seizures in the newborn period vary in semiology, have subtle features, and clinical identification is difficult without the use of continuous video EEG (cvEEG). In addition, many NS are electrographic only or subclinical and would go undetected without cvEEG monitoring. Early identification of NS is important as seizures typically suggest an underlying disorder that requires immediate identification and attention.

1.2 Important Definitions

NS have been classified as clinical only, electroclinical, electrographic only, or subclinical. The term electrographic seizures (ES) describes both electroclinical and electrographic only seizures. ES are defined as a sudden abnormal EEG event that has a repetitive and evolving pattern lasting a minimum of 10 s. Clinical only seizures are paroxysmal clinical events without an associated EEG change and

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overtime most are considered nonepileptic. Electroclinical seizures have a clinical change associated with the EEG pattern. Electrographic only also called subclinical seizures have an abnormal EEG pattern without a clear clinical change [1].

1.3 Epidemiology

Establishing the true incidence of neonatal seizures has proven difficult based on variability among methods of seizure detection, with some studies focusing solely on a clinical diagnosis of seizure without confirmation with cvEEG. The modality of seizure detection is also variable with some studies relying on amplitude integrated EEG (aEEG), a limited channel EEG reliant upon the amplitude of the background and seizures, and not cvEEG. The incidence of NS approximates 1–5 per 1000 live births [2–4]. Estimates are higher in preterm and low birth weight and very low birth weight (LBW/VLBW) neonates. A recent population based study included 112 neonates over a 13-year period, the majority of whom had EEG confirmed NS. In this study the incidence of NS was 2.29 per 1000 live births, with higher rates in preterm neonates (14.28/1000 live births), as compared to term (1.10/1000 live births). The incidence increased with decreasing gestational age and decreasing birth weight [2].

1.4 Seizure Semiology in the Neonate [5]: Table 1

Table 1 Seizure semiology in the neonate

Seizure semiology	Description
Focal clonic seizures	Unilateral and rhythmic in nature. Fast contraction phase and slower relaxation phase. Involves face, upper and lower extremity, neck or trunk Neonates are often conscious during the spells
Focal tonic seizures (Generalized tonic seizures are extremely rare in neonates)	Sustained posturing of the limb and asymmetric tonic contraction of the trunk
Focal myoclonic seizures	Faster than clonic seizures. Involve flexor muscles of the upper extremity
Generalized myoclonic seizures	Involves bilateral upper extremity more so than the lower extremity
Subtle seizures (more common in preterm neonates)	Subtle ocular phenomena (i.e., horizontal eye deviation), orobuccal movements such as chewing, autonomic spells (i.e., tachycardia, pupillary dilation), apnea, and other limb movements like pedaling

Table 2 Neonates at high risk for subclinical seizures[a]

Neonatal encephalopathy	Hypoxic ischemic encephalopathy
Cardiopulmonary risk factors	ECMO, pulmonary hypertension, congenital heart disease status postsurgery using cardiopulmonary bypass
Infections	Meningitis, encephalitis
Trauma	Non-accidental trauma
Premature neonates	Acute high-grade intraventricular hemorrhage, VLBW with encephalopathy
Cerebrovascular disorders	Perinatal stroke, cerebral sinous venous thrombosis
CNS genetic syndromes	Confirmed cerebral dysgenesis, dysmorphic features with microcephaly

ECMO extracorporeal membrane oxygenation, *VLBW* very low birth weight
[a]Adapted from the American Clinical Neurophysiology Society (ACNS) guidelines on Continuous EEG monitoring in Neonates

1.5 Electrographic Only or Subclinical Seizures

Subclinical seizures are common in the neonatal ICU with estimates of up to 80% of NS being subclinical in nature [6, 7]. This is in part due to a phenomena seen commonly in neonates referred to as "electroclinical dissociation" or "uncoupling." This is a well-documented effect in which treated electroclinical seizures become subclinical [8]. The American Clinical Neurophysiology Society (ACNS) has identified several neonatal populations as being high risk for subclinical seizures [9] (Table 2).

1.6 Common Etiologies of Neonatal Seizures

1.6.1 Hypoxic Ischemic Encephalopathy (HIE)

HIE is the most common cause of NS in term infants accounting for 50%–75% of cases [6, 7]. Approximately 40–80% of neonates with HIE have NS [7]. NS in the setting of HIE tend to present early within the first 12–24 h after birth, with the majority presenting within the first 12 h. The seizures are often times subclinical and hard to treat. The majority of NS will be identified within the first 24 h of cvEEG and the background activity of the EEG can help stratify neonates at highest risk of seizures [10, 11].

Therapeutic hypothermia is considered standard of care in neonates with HIE and has been shown to decrease the overall seizure burden in patients with moderate HIE. Neonates that develop seizures during hypothermia are at risk of a rebound effect or worsening of seizures during rewarming.

1.6.2 Perinatal Stroke

Perinatal ischemic stroke is the second most common cause of NS and accounts for approximately 20% of cases [5]. NS are typically the first indication of stroke in 69–90% of term neonates. NS in the setting of perinatal stroke tend to occur within the first 3 days after birth. The initial seizure type tends to be focal clonic and often times the neonate appears well. Other common presentations may include encephalopathy, abnormalities of tone, and apnea [12]. EEG in babies with NS may have a background that is attenuated over the affected hemisphere and sharp waves may be persistently focal or periodic. Hemiparesis or other focal examination findings are not always present in the neonatal period. Venous infarctions and cerebral sinus venous thrombosis should be considered when the area of cerebral injury does not conform to a typical arterial pattern. Once identified, NS should be treated. Seizures in the acute phase typically remit. It is estimated that approximately 40% of patients with perinatal stroke presenting with NS will go on to develop epilepsy [12].

1.6.3 Intracranial Hemorrhage

Intracranial hemorrhage accounts for 10–15% of NS [4, 5]. *Subarachnoid hemorrhage (SAH)* in isolation can present with NS at around the second day of life. Neonates tend to look well between seizures. When uncomplicated and not associated with hypoxic ischemic injury or intraventricular hemorrhage, neonates with SAH tend to have a good prognosis and seizures remit with treatment. *Subdural hemorrhage* (SDH) may be seen after a traumatic birth, breech delivery, and if there is a need for instrumentation (i.e., forceps, vacuum assist). NS with SDH tend to occur in the first 48 h of life. *Intraventricular hemorrhage (IVH)* is a common cause of seizures of NS in the preterm neonate. NS tend to be due to grade 3 IVH or IVH associated with parenchymal extension and present within the first 3 days of life. It is uncommon for lower grades of IVH (i.e., germinal matrix hemorrhage) to cause NS.

1.6.4 Infections of the Central Nervous System (CNS)

CNS infections are responsible for 5% of neonatal seizures [5]. Intrauterine infections such as cytomegalovirus (CMV), herpes simplex virus (HSV), rubella, and toxoplasmosis present early, i.e., in the first 1–2 days of life. Neonates with intrauterine infections are often times microcephalic, have intrauterine growth restriction, and ophthalmic findings. CNS infections with group B streptococcus and *Escherichia coli* may also present within the first 48–72 h. The neonate typically looks well initially and then develops signs of sepsis.

1.6.5 Metabolic Disturbances

This category accounts for approximately 5% of NS [4, 5].

Hypoglycemia may occur in isolation or along with other causes of NS such as HIE. Risk factors for hypoglycemia include being small for gestational age and neonates born to diabetic mothers. Seizures associated with hypoglycemia typically present on the second day of life. Other symptoms include jitteriness, hypotonia, poor feeding, encephalopathy, and apnea. There are several causes of neonatal hypoglycemia. These include decreased glucose supply especially in premature neonates and those babies who are small for gestational age. Increased glucose utilization occurs in neonates born to diabetic mothers. Finally, hypoglycemia can be seen in the setting of inborn errors of metabolism affecting gluconeogenesis. *Hypocalcemia* may occur within the first 2–3 days after birth or occasionally later in the neonatal period. Neonates born to mothers with maternal diabetes and those that are small for gestational age are at higher risk for developing hypocalcemia. Hypocalcemia of later onset is typically associated with maternal hyperparathyroidism, hypoparathyroidism, high phosphate formula, hypomagnesemia, and DiGeorge syndrome (chromosome 22q11.2 deletion). Whole blood ionized calcium (iCa) tends to be the best measure of calcium status in the neonate. *Hypomagnesemia* may be seen the first 2 weeks of life.

1.6.6 Inborn Errors of Metabolism

Inborn errors of metabolism are rare accounting for approximately 1% of NS. This class of disorders is secondary to enzyme defects necessary for processing of carbohydrates, proteins, and fats. Despite being rare, these disorders must be considered early in the differential diagnosis, as a subset of inborn errors of metabolism is treatable with vitamin replacements.

Nonketotic hyperglycinemia or glycine encephalopathy is due to an inability to breakdown the nonessential amino acid glycine. There are several potential enzymatic defects in the glycine cleavage system. Accumulation of this substrate in the brain leads to severe neonatal encephalopathy, ineffective suck, apnea, hypotonia, multifocal myoclonus, hiccups, and myoclonic neonatal seizures. Mothers of neonates with NKH may describe abnormal in-utero movements or “hiccups” suggestive of intrauterine seizures. NS in this instance tend to occur in the first 2 days of life. The seizures are intractable and the EEG background shows a burst suppression pattern. The diagnosis of NKH relies on evaluation of glycine in the serum and cerebrospinal fluid (CSF). An increase in glycine in CSF, serum, and a CSF to serum glycine ratio > 0.8 is typically seen in this disorder. Treatment with sodium benzoate, dextromethorphan, and a low protein diet can decrease plasma levels of glycine. Although rare, a transient form of this disorder does exist with normalization of glycine levels 2–8 weeks after birth.

Pyridoxine-dependent epilepsy is a rare disorder presenting with refractory seizures soon after birth. The EEG traditionally shows a burst suppression pattern. Pyridoxine-dependent epilepsy is caused by homozygous variants in the ALDH7A1/Antiquitin gene, which encodes the enzyme alpha-aminoadipic semialdehyde dehydrogenase, which is important to the breakdown of lysine, which is thought to affect the metabolism of glutamate and GABA. Deficiency of this enzyme leads to the buildup of alpha-amino semialdehyde (α-AASA) and other molecules, which deactivates the active form of pyridoxine, which is pyridoxal-5-phosphate. Treatment should include 100–200 mg of IV pyridoxine while the patient is on EEG. In the classic description, the EEG should normalize and the seizures should abate in the next few hours. The diagnosis can be made through assessing levels of α-AASA in the blood, urine, and CSF. A separate disorder with a deficiency of the enzyme pyridoxamine-5-phosphate oxidase (PNPO) that directly influences the active form of pyridoxine has a similar clinical presentation. This disorder may not respond completely to IV pyridoxine and if suspected pyridoxal-5-phosphate should be supplemented. Levels of pyridoxal-5-phosphate can be tested in the CSF to confirm the diagnosis.

Folinic acid responsive seizures should also be considered when seizures present within the first day of life, when the seizures are refractory to medications and in the absence of a readily identifiable etiology. The EEG background may be described as discontinuous and seizures are reported to respond to folinic acid at a dose of 3–5 mg/kg/day given enterally.

Glucose transporter deficiency is another rare etiology of NS not to be overlooked. This is related to a defect in the glucose transporter GLUT-1 which is responsible for glucose entry to the brain across the blood brain barrier. This disorder affects neonates between 2 and 5 months of age. In this disorder, the CSF glucose is low while the serum glucose is normal. Diagnosis is made by obtaining serum and CSF glucose concurrently and at least 4 h postprandial. In this disorder, the CSF glucose is typically <40 mg/dL and the ratio of CSF:plasma glucose is <0.4 [13]. Neonates with Glut-1 deficiency respond well to the ketogenic diet.

1.7 Neonatal Genetic Epilepsy

The field of genetic epilepsy is expanding rapidly and there are several genetic causes of epilepsy that have been identified recently. One approach that has been adopted is to categorize genetic causes into malformations of cortical development, metabolic causes, vascular causes, syndromic associations, and cellular etiologies [13]. In some cases, the degree to which the abnormality is expressed plays a role in the severity of the phenotype of some genes. A classic example of this is the association of KCNQ2 with both benign neonatal convulsions, but also with Ohtahara syndrome—a more severe epilepsy type.

1.8 Genetic Epilepsy Syndromes in the Neonate

Early Infantile Epileptic Encephalopathy(EIEE) also referred to as Ohtahara syndrome presents with tonic spasms that may present as early as the first 10 days of life [14]. Other seizure types include focal motor seizures, and generalized tonic seizures. Myoclonic seizures are rarely seen and if they are, EME should be considered. The seizure burden tends to be high with up to 300 seizures per day noted in some cases. The EEG shows a classic suppression burst pattern present in both awake and asleep state that tends to diminish by 3 months and disappears by 6 months. This EEG pattern may then transition to hypsarrythmia between 2 and 6 months of age. Neonates with EIEE often times transition to West Syndrome and/or Lennox Gastaut. Classically, EIEE is associated with an underlying brain malformation such as megalencephaly, hemimegalencephaly, pachygyria, and cortical dysplasias. Common genetic abnormalities that can present with this phenotype include ARX, CDKL5, SLC25A22, and STXBP1 all of which have distinct phenotypic variability [14]. Other documented genetic abnormalities include KCNQ2, STXB1, and SCN2A. Metabolic disorders associated with EIEE include mitochondrial disorders and glycine encephalopathy [14]. EIEE phenotype may also be seen in the setting of HIE. In other words, EIEE is a phenotypic description that may have several underlying etiologies and is not a single entity.

EMEE (early myoclonic epileptic encephalopathy) presents within the first 3 months of life and is characterized by myoclonic seizures as the main seizure type that may not have a clear EEG correlate, frequent partial seizures, and tonic spasms. The EEG background also shows a suppression-burst pattern however, this tends to appear more prominently in sleep. The EEG background tends to transition to hypsarrythmia transiently before returning to a burst suppression pattern. Classically, EMEE has been associated with inborn errors of metabolism such as NKH and vitamin dependent epilepsies. The distinction between EIEE and EMEE is at times challenging due to overlapping features that define the spectrum of these severe neonatal epilepsy syndromes.

Self-limited benign neonatal epilepsy is also referred to as *benign neonatal convulsions*, benign idiopathic neonatal seizures, and fifth-day fits. Typically, the seizure is focal clonic or focal tonic and presents in the first 2–3 days of life. Overall, the neonate appears well between episodes and the EEG background is normal. This is a self-limited entity and seizures remit by 1–6 months [5]. This syndrome has been associated with variants of potassium and sodium channel subunits present in the brain that have autosomal dominant inheritance. These channelopathies include KCNQ2, KCNQ3, and SCN2A. Family history is important and may be overlooked as the parent themselves may not realize they had seizures in the first few weeks of life.

1.9 Diagnostic Approach

When a neonate presents with a suspected seizure, the history and physical examination are of utmost importance when determining the likelihood of whether the event was a seizure or not and while evaluating for the potential cause.

1.9.1 History

Key features of the history to focus on include the prenatal history, maternal history, perinatal events, intrapartum, and immediate postnatal course (Table 3).

If the parents can record the seizures, the time spent in reviewing the videos is often well worth it.

1.9.2 Physical Examination

Details of both the general pediatric examination and neurologic examination can help to narrow the differential diagnosis.

The *head, ears, eyes, nose, and throat (HEENT) examination* should not be overlooked, as in some cases, it is key to determining the underlying etiology of a suspected NS. The *head circumference* is a bedside measure of brain development and can give insight to likelihood of a prenatal injury, genetic etiology, or in some cases metabolic etiologies. Additionally, a dysmorphic appearing infant can increase the index of suspicion of an underlying genetic epilepsy, although it is often-times the case that neonates who ultimately have a genetic diagnosis of epilepsy are not dysmorphic. The *cardiovascular examination* can give early clues of congenital heart disease, which increases the risk of cerebral injury and subsequent seizures. In addition, cardiac defect may be associated with abnormalities of midline brain structures. Detection of hepatosplenomegaly on *abdominal examination* may be suggestive of a metabolic disorder such as a lysosomal storage disorder. The *skin*

Table 3 Key details of the history and physical

Maternal and neonatal history	Details to include
Prenatal history	Extent of prenatal care, details of diagnostic studies (fetal ultrasound, biophysical profile)
Maternal history	Prior miscarriages, preexisting or gestational diabetes, advanced maternal age, smoking and alcohol use, preeclampsia, medication use (i.e., SSRI), trauma, decreased fetal movement, abnormal fetal movements
Intrapartum history	Duration of labor, prolonged rupture of membranes, placental abruption, maternal fever, fetal distress
Postnatal course	APGAR scores, concerns for perinatal asphyxia, need for respiratory support, presence of meconium stained amniotic fluid or aspiration

SSRI selective serotonin reuptake inhibitor

examination may also give information regarding the likelihood of a neurocutaneous disorder such as Sturge–Weber syndrome.

The physical examination of a neonate must of course be tailored to the age of the child. The important aspects to examine are the tone, deep tendon reflexes and presence or absence of primitive reflexes. Occasionally, the baby may experience some seizures during the physical examination and that presents a good opportunity to note the semiology.

1.9.3 Initial Evaluation of Neonatal Seizures

When a seizure is suspected, a head ultrasound should be performed to assess for evidence of hemorrhage. Once completed, the history will guide the immediate next steps. A neonate with fever, and maternal risk factors for infection should undergo a lumbar puncture to evaluate for infection while being treated with broad spectrum antibiotics. An evaluation for electrolyte and metabolic abnormalities including hypoglycemia should be performed.

cvEEG is the gold standard in the diagnosis of NS and is essential to management as seizures in the neonate are commonly subclinical and electroclinical seizures once treated may become subclinical due to the phenomena of electroclinical dissociation or uncoupling. The ACNS suggests that cvEEG be continued for a minimum of 24 h to capture seizures [9]. In addition, cvEEG should be continued for 24 h after the last seizure is identified. The video is important as seizures in the neonatal period can be subtle and are often missed by bedside providers.

The use of aEEG has expanded in recent years. This technique relies on 1–2 channels (2–4 electrodes) placed over the central and parietal regions near watershed zones as opposed to a conventional EEG that uses several electrodes. The EEG signal is subsequently amplified, filtered, and compressed (6 cm/h). This technique allows one to assess general background trends. Seizures can be identified using aEEG; however, low amplitude and low frequency seizures may be missed. The sensitivity and specificity of this tool varies depending on the experience of the user and the ability to confirm seizures with raw EEG channels. Suspicious events on aEEG should be confirmed with cvEEG as mimics are common and include muscle and respiratory artifacts.

1.10 Differential Diagnosis of Neonatal Seizures [15]

There are several seizure mimics that pediatric providers must be aware of as misdiagnosis of an epileptic seizures may lead to unnecessary treatment with antiseizure medications (ASM): medications that may have adverse effects. Features that heighten the suspicion of seizure include associated fixed eye deviation, autonomic changes (i.e., tachycardia), and nonsuppressible movements (i.e., clonic jerking) (Table 4).

Table 4 Seizure mimics in neonates and infants

	Clinical features
Neonatal seizure mimic	
Benign neonatal sleep myoclonus	• Onset: first few days of life • Resolution by 4 months of age • Brief asynchronous or bilateral muscle contractions *only* during sleep and may be prolonged • Do not involve the face • Abate with arousal • EEG is normal
Jitteriness or neonatal tremor	• Onset: neonatal period • High frequency low amplitude movements • No associated unusual eye movements, fixed gaze, or autonomic disturbance • Stimulus sensitive • Suppressible with passive flexion • Etiologies: hypocalcemia, hypoglycemia, mediation withdrawal (i.e., maternal SSRI). • May be seen in the setting of HIE or intracranial hemorrhage
Apneic spells	• Onset: neonatal period • Often associated with bradycardia • More common in preterm • Apnea at term is more concerning and threshold is low for cvEEG to capture the spells • Temporal lobe seizures may manifest as apnea alone often with transient tachycardia • Consider sepsis, meningitis, gastroesophageal reflux
Infantile seizure mimics	
Benign myoclonus of infancy	• Onset: 1–12 months • Resolution by 3 years • Brief myoclonus, spasm like movements, head nodding, blinking, or shuddering
Shuddering attacks	• Onset: Infancy • Sudden head shaking and grimacing • No altered consciousness • EEG is normal
Spasmus nutans	• Onset: 4–12 months • Triad of ocular oscillations/pendular nystagmus, head nodding, torticollis • Resolves with time • Important to rule out intracranial lesion
Benign paroxysmal torticollis	• Onset: Early infancy and childhood • Attacks of torticollis lasting minutes to hours • Migraine variant (may go on to develop migraine) • Accompanied pallor and vomiting • Rare cases with CACNA1A gene mutation
Sandifer syndrome	• Onset: Infancy • Tonic or repetitive truncal extension due to gastroesophageal reflux • May be associated with feeding or positioning (lying flat)

Table 4 (continued)

	Clinical features
Benign paroxysmal tonic upgaze	• Onset: Early infancy • Prolonged intermittent upgaze • Duration: seconds to hours • Remits after a few years
Breath-holding	• Onset: Preschool children • After being upset breathing stops during expiratory phase • May lead to transient loss of consciousness and anoxic seizure with decerebrate posturing • Recovery of consciousness may be rapid • Some children sleep for hours after the event

cvEEG continuous video EEG, *SSRI* selective serotonin reuptake inhibitor, *HIE* hypoxic ischemic encephalopathy

1.10.1 Treatment of Neonatal Seizures

Once a NS is, identified treatment with antiseizure medication (ASM) should be considered, while noting that if NS are secondary to a metabolic disturbance (i.e., hypoglycemia) then correction of that underlying disturbance often times leads to cessation of NS. The first-line treatment for neonatal seizures is phenobarbital with the other first-line options being fosphenytoin. Painter et al. compared phenobarbital to fosphenytoin and found no difference in efficacy between the two drugs and noted that fewer than 50% of infants responded to either drug [16]. The use of levetiracetam has increased over the years due to its benign side effect profile and parenteral availability. A recent multicenter, randomized, blinded controlled trial of comparing first-line efficacy of levetiracetam (up to 60 mg/kg) versus phenobarbital (up to 40 mg/kg) revealed better efficacy for phenobarbital (80% seizure free for 24 h vs 28% for levetiracetam, $p < 0.001$) [17].

1.10.2 Mechanism of Action and Suggested Dosing

Phenobarbital enhances GABA transmission and cellular inhibition. The initial IV loading dose is 20 mg/kg. Care should be taken in patients with preexisting hepatic involvement as phenobarbital is metabolized by the liver. Increments of 5–10 mg/kg can be given up to a total of 40 mg/kg which includes the loading dose. The maintenance dose is 5 mg/kg/day divided BID. The half-life is long and in some studies, documented to be approximately 100 h. A 1–2-h postload level may be helpful. Common side effects include respiratory depression and hypotension.

Fosphenytoin blocks voltage-dependent sodium channels keeping the cell in a state of inhibition. The initial intravenous (IV) loading dose is 20 mg/kg and can be given at a maximum rate of 3 mg/kg/min. The loading dose may be followed by a maintenance dose of 5 mg/kg/day divided BID or TID. Additional 5 mg/kg IV boluses may be given based on a 1–2-h postload level. Common side effects include cardiac dysrhythmias and hypotension.

Levetiracetam may be loaded intravenously at 40 mg/kg although a dose of 60 mg/kg is not uncommon. Recommended maintenance dose varies but mostly it is suggested to be dosed at 40 mg/kg/day divided BID to TID. The side effect profile is benign and there are no appreciable interactions with other medications. Caution should be taken in neonates with renal failure as levetiracetam is cleared entirely by the kidneys.

1.10.3 Prognosis/Outcome

The direct impact that NS have on neurodevelopmental outcome has been and remains controversial with some studies showing worsening of underlying cerebral injury with seizures [18, 19]. The underlying etiology for NS is the most important factor associated with outcome. A recent study showed that high degrees of seizure burden have been associated with worse neurodevelopmental outcome in HIE independent of HIE severity or treatment with hypothermia [20].

1.10.4 When to Refer to a Tertiary Care Center

Neonates with suspected neonatal seizures need a complete evaluation including neuroimaging, and continuous EEG monitoring. If NS are refractory or if cvEEG monitoring is not available, referral should be made to a tertiary care center.

Key Points

- NS are common and often represent an acute disorder requiring immediate attention.
- Identification of NS by bedside providers is unreliable.
- Continuous electroencephalography is the gold standard for NS identification and is needed to guide therapy.
- NS are often subclinical or may become subclinical after treatment.

2 Infantile Seizures

2.1 Introduction

Onset of epilepsy in the first 2 years of life is more common than in later childhood. Epilepsy in infants may fit into a specific electroclinical syndrome, with recognizable electroclinical features, including specific seizure types, typical age at seizure onset, EEG characteristics, and distinctive comorbidities such as intellectual and psychiatric dysfunction [21]. Identifying a specific electroclinical syndrome is valuable although nearly half of infants with epilepsy have nonsyndromic presentations [22].

2.2 Epidemiology

The incidence of epilepsy in the infantile period is estimated to affect 70.1 per 100,000 children ≤2 years/year. There is a steep decrease in the incidence of newly diagnosed epilepsy in the second year compared to the first year of life. Infantile (epileptic) spasms constitute the largest single epilepsy subgroup, representing 13–45.5% of infantile population-based incidence studies. For other seizure types, there is limited data beyond case series (Class 3 and 4 studies) [23].

2.3 Etiology

International League Against Epilepsy (ILAE) has suggested six etiological subgroups [21].

1. Structural: refers to structural MRI abnormalities, acquired or genetic causes (brain malformations).
2. Genetic: results from a pathogenic genetic variant causing epilepsy. Genetic etiology does not equate with inherited as de novo mutations in the probands are increasingly recognized.
3. Infectious: should not be confused with acute symptomatic seizures in the setting of meningitis or encephalitis. Examples of infectious etiology include neurocysticercosis, tuberculosis, cerebral toxoplasmosis, and congenital infections such as Zika virus and cytomegalovirus. Postinfectious development of epilepsy, following viral encephalitis would be another example.
4. Metabolic: results from a known or presumed metabolic disorder. Some metabolic conditions, if identified early, can respond well to specific interventions such as glucose transporter 1 deficiency syndrome (GLUT1) deficiency treated with the ketogenic diet, and Pyridoxine-Dependent & Pyridox(am)ine 5′-Phosphate Deficiency (PNPO) dependent epilepsy will respond to pyridoxine, pyridoxal phosphate, folinic acid, and biotin.
5. Immune: results directly from an immune disorder mediating central nervous system inflammation (anti-N-methyl-D-aspartate receptor encephalitis).
6. Unknown etiology.

2.3.1 Electroclinical Syndromes

Epilepsy specialists will classify children into specific electroclinical syndromes using a combination of their seizure type and EEG patterns.

There are several benefits to doing so. These include.

(a) To understand the type of seizures present and inform the family about the possibility of other seizure types that can occur.

(b) Inform parents regarding the risks of comorbidities including learning difficulties, intellectual disability, autism spectrum disorder, and mortality risk such as sudden unexpected death in epilepsy (SUDEP).
(c) There has been licensing of syndrome specific anti- seizure medications following randomized controlled trials (e.g., Fenfluramine for Dravet's syndrome, Epidiolex for Dravet's, and Lennox–Gastaut syndrome) and development of precision, gene related therapies.
(d) Using common language allows epilepsy specialists to discuss a patient's case in greater detail and with precision.

2.4 Diagnostic Approach

The first stage in clinical management is to confirm that the abnormal movement or behavior is a seizure. Once confirmed, the type of seizure needs to be determined. The clinical history and EEG are essential to this process.

2.4.1 History

A detailed history of the paroxysmal events is key to differentiating an epileptic seizure from benign events. An inadequate history is the most common reason for misdiagnosis. Home videos taken by parents can be of considerable help. However, the differentiation of seizures from benign events based solely on video recording can be problematic. Well-synchronized clonic–tonic sequences involving all four limbs are extremely rare in infancy. On the other hand, unilateral hand or arm clonus (clonic seizure) with repetitive nonsuppressible jerking is a reliable sign for a focal motor seizure.

The following symptoms describe different types of epileptic seizures in an infant. These seizure types account for the majority of seizures observed during infancy [24]:

- Focal nonmotor seizure may have abrupt change in the typical behavior like behavioral arrest noticed by the caregiver. There can be other accompanying signs such as pallor or cyanosis.
- Atonic seizures have a sudden loss of posture (i.e., head drop or whole body drop).
- Epileptic spasms—Sudden jerk followed by stiffening, often recurring in a periodic fashion. Occurrence in daily clusters (typically 20–40 spasms per cluster, one spasm every 5–15 s), and jerks lasting a second to 2–3 s are typical.
- Myoclonic seizures—Brief muscle jerks on one or both sides of the body. Myoclonic seizures can be focal, confined to one region of the body, multifocal, or generalized.
- Tonic—Stiffening of a part or both sides of the body; when bilateral, this may be symmetric or asymmetric.

Once there is a reasonable suspicion for seizure based on the history, the next step is to determine if the seizures are provoked or unprovoked. Provoking factors include a variety of acute insults. The history should focus on eliciting such provoking factors such as presence of fever, infections (meningitis and encephalitis), trauma (including suspicion for nonaccidental injury), new motor weakness that may suggest acute stroke and risk factors for hypoglycemia, hypocalcemia, or other metabolic derangements.

Unprovoked seizures include epilepsies as a consequence of a known or suspected disorder of the central nervous system. Seizures that recur when the original provoking factor have been removed, such as a focal seizure in an infant with a history of stroke would be in this category.

The subsequent step is to identify the etiology by performing a detailed neurological history looking for risk factors. Enquire about premature birth, symptoms of hypoxic ischemic injury at birth, history of congenital infections (CMV, toxoplasmosis, herpes, etc.), startle reactions and hiccups (nonketotic hyperglycinemia), developmental delays, hypotonia, poor vision, hearing loss, and failure to thrive.

Family history is also important and should focus on sibling with seizures/similar presentation or sibling death.

2.4.2 Physical Examination

For provoked seizures, the *general physical examination* should focus on mental status, signs of infection, and other acute symptomatic causes.

For unprovoked seizures, evaluate for dysmorphic features, growth failure, macro or microcephaly, and organomegaly (lysosomal storage disorders). Cataracts and hearing loss may be seen with congenital infections and genetic disorders. Sparse, steely or "kinky" hair suggests Menkes disease, while jitteriness and dystonic movements are present with glutaric aciduria. The *skin examination* helps identify neurocutaneous disorders (Table 5).

The neurological examination should include assessment of higher mental functions, cranial nerves (to the extent possible), motor examination including gait and deep tendon reflexes. Assessment of developmental milestones is very important and should be followed closely on subsequent examinations as well.

Table 5 Neurocutaneous disorders and skin findings

Neurocutaneous disorder	Skin finding
Tuberous sclerosis	Hypopigmented lesions (Wood's lamp required)
Neurofibromatosis	Café-au-lait spots
Sturge–Weber syndrome	Facial angiomas (i.e., portwine stain)
Incontinentia Pigmenti	Hyperpigmented linear and whorled pattern lesions
PIK3CA-related overgrowth spectrum	Epidermal nevus, vascular malformation, lipomatous overgrowth

2.5 Differential Diagnosis

Many paroxysmal episodes can mimic epileptic seizures. Rates of misdiagnosis in epilepsy are high throughout the world [25–27]. When there is any doubt of the origin of the unusual movement, video-EEG monitoring to characterize the events is indicated Table 4. Please see chapter on "Unprovoked Seizures for a detailed differential diagnosis".

2.6 Evaluation

EEG (awake and sleep states) and magnetic resonance imaging (*MRI)* of the brain are fundamental when evaluating an infant with suspected seizure.

It is important to capture the suspected seizures as the ictal EEG (EEG recording during the ictus or event) is essential to characterize the seizure types. The EEG background can also give essential information.

Infantile onset epilepsy is commonly associated with structural brain abnormalities that may be congenital or acquired. Congenital abnormalities include brain malformations (focal cortical dysplasia, polymicrogyria, lissencephaly) or other diffuse brain disorders, acquired structural abnormalities include stroke, vascular malformation (Sturge–Weber syndrome) and infections [28]. MRI is recommended in all new-onset epilepsy before the age of 2 years. Children <2 years require special MRI sequences, as immature myelination affects the ability to identify cortical dysplasia. If MR imaging <2 years is normal, and seizures persist, then MRI may be repeated after age of 24–30 months when maturing myelination can reveal an otherwise unsuspected cortical dysplasia [29].

Metabolic testing includes glucose, hematologic screening, liver functions, ammonia, and lactate.

Urine analysis, arterial blood pH, arterial gases, serum electrolytes, serum amino acids, and urine organic acid [23] should be performed when MRI does not show structural abnormalities that are commonly reported in children with epilepsy.

Alpha amino adipic semialdehyde, pipecolic acid, and other specific metabolic testing may be dictated by the clinical condition.

Cerebrospinal fluid (CSF) testing for lactate and glucose (paired with blood glucose) for mitochondrial disorders and glucose transporter 1 deficiency syndrome is indicated in the appropriate situation.

Genetic Testing. In a study of early-life epilepsies, genetic testing provided a diagnosis in one-fourth of children whose cause would have otherwise remained unresolved [22]. Commercial gene panels allow for the sequencing of hundreds of genes using a single test via next-generation sequencing. Whole-exome sequencing involves sequencing of the exons, which encode proteins, but constitute only 1% of the genome. Next-generation sequencing tests have identified pathogenic or likely pathogenic variants in 18–37% of developmental and epileptic encephalopathy

(DEE) patients [30]. Sequencing tests are now considered a part of the initial evaluation of epilepsies with onset in early-life [22].

Specific epilepsy types that the pediatrician may encounter in this age group are described below.

Self-limited (Familial and Nonfamilial) Infantile Epilepsy [31–33]

- Accounts for 7–9% of all epilepsies beginning prior to 2 years of age.
- Age at onset ranges from 3 to 20 months with a peak of 6 months.
- In familial cases, inheritance is autosomal dominant with high penetrance. A genetic etiology can be identified in about 80% of the familial cases.
- Focal seizures with behavioral arrest, automatisms, head/eye version, and clonic movements which can progress to a bilateral tonic–clonic seizure, brief seizures with clustering (multiple seizures over 1–3 days) are common seizure types.
- EEG and MRI are normal. Ictal EEG shows seizure onset from posterior head regions.
- Genes implicated: PRRT2 (most common), others—SCN8A, SCN2A, KCNQ2, or KCNQ3.
- Differential diagnosis: needs to be differentiated from infantile seizures due to structural and metabolic causes and from other epilepsy syndromes in infancy.
- Treatment: responsive to antiseizure medications. Carbamazepine noted as possibly effective.
- Prognosis: Normal development and seizure resolution. Patients with PRRT2 and SCN8A pathogenic variants may develop paroxysmal kinesigenic dyskinesia/dystonia (brief episodes of choreoathetosis, dystonia, or a mixed pattern triggered by sudden movements, change in position, or change in movement velocity like getting up from a chair or getting out of a car frequently trigger attacks) beginning from childhood to adult life.

Myoclonic Epilepsy in Infancy [23, 34]

- 1.1% of all epilepsy with onset prior to 36 months of age.
- Age of onset between 4 months and 3 years with males more commonly affected.
- Normal perinatal, neonatal history, and development.
- Febrile seizures in up to one third and family history of febrile seizures in 10%.
- Myoclonic seizures involving the head and the upper arms occur multiple times per day, both in wakefulness and sleep. May be reflexive to sudden noise or touch.
- MRI and EEG background is normal. Interictally, generalized spike waves are seen.
- Ictal EEG shows brief bursts of generalized spike/polyspike-and-wave during episode of myoclonus.
- Differential diagnosis includes infantile spasms, Dravet syndrome, Myoclonic Atonic Epilepsy, Glucose Transporter Deficiency, and nonepileptic spells such as shuddering, benign myoclonus of infancy, and hyperekplexia.
- Valproic acid, topiramate, lamotrigine, and clonazepam are reported to be possibly effective.
- Myoclonic seizures remit in nearly all cases and children are able to come off antiseizure medications.

- Developmental outcome: normal in 63%–85% of cases. Others have intellectual disability, learning disability, and attentional difficulties.
- Around 10% develop other epilepsies in late childhood or adolescence, with generalized tonic–clonic seizures.

2.7 Syndromic DEE (Developmental Epileptic Encephalopathy)

West Syndrome [23, 35–37]

- Triad of epileptic (infantile) spasms, hypsarrhythmia and developmental stagnation or regression.
- Incidence is 30/100,000 liveborn infants.
- Epileptic spasms are mandatory for diagnosis; focal seizures may be seen. Typically, spasms are brief symmetrical contractures of the axial and appendicular muscles that occur in clusters as the child arouses from sleep. Spasms may be subtle including just a head nod.
- It is important to conduct a complete neurological and skin examination to rule out tuberous sclerosis (TS).
- EEG shows hypsarrhythmia which is an EEG pattern characterized by an extremely high voltage chaotic background activity with multifocal sharp waves. The background activity is not well organized (see Figs. 1 and 2).
- Brain MRI is abnormal in half to two-thirds of children with either acquired or congenital lesions.

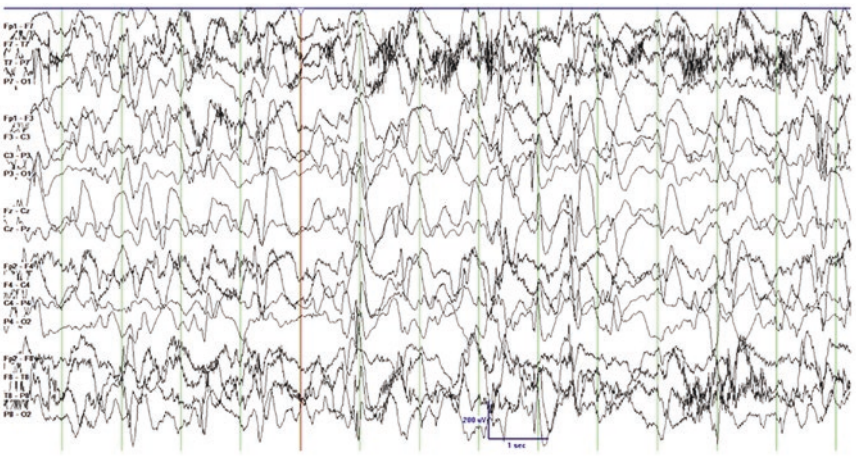

Fig. 1 EEG on a 9-month-old baby with infantile spasms. Hypsarrhythmia in awake state. EEG settings LFF 1 Hz, HFF 70 Hz, Sensitivity 70 μV/mm

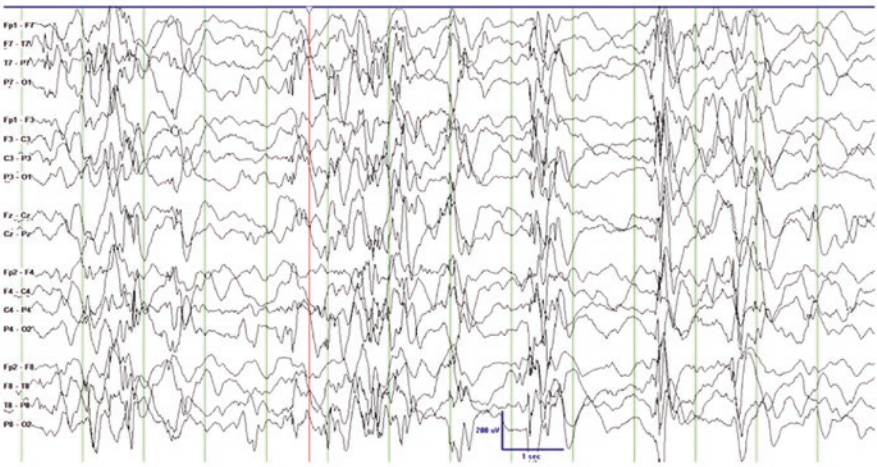

Fig. 2 Hypsarrhythmia in sleep state. EEG settings LFF 1 Hz, HFF 70 Hz, Sensitivity 70 μV/mm

- Genetic and metabolic studies should be considered if no etiology is found after initial evaluation. Trisomy 21, ARX, CDKL5, STXBP1, IQSEC2, TSC1, TSC2, and others are known to be associated with epileptic spasms.
- Differential diagnosis: EIEE and other myoclonic epilepsies.
- Rapid diagnosis of infantile spasms is essential as early treatment of spasms leads to improved outcomes.
- Standard first-line treatment for infantile spasms includes hormonal therapy (adrenocorticotropin hormone or high-dose steroids) or vigabatrin (first line in TS patients).
- Prior to hormonal therapy pediatric tuberculosis risk assessment needs to be completed. If any risk factor is identified, then PPD needs to be placed unless there is a previous documentation of positive TB test either positive PPD or interferon gamma release assay.
- In patients with current or prior history of cytomegalovirus infection, consult ID to determine if hormonal therapy can be safely given.

Treatment for infantile spasms is different from other epilepsy syndrome and spasms do not respond to standard antiepileptic drugs.

Treatment Guidelines for Infantile Spasms Recommended by Pediatric Epilepsy Research Consortium are discussed below [38].

(a) ACTH—adrenocorticotropic hormone; intramuscular injection
Days 1–14—75 U/m^2 IM twice daily
Days 15–17—30 U/m^2 IM in the morning
Days 18–20—15 U/m^2 IM in the morning
Days 21–23—10 U/m^2 IM in the morning
Days 24–29—10 U/m^2 IM every other morning (3 total doses)

(b) Prednisolone by mouth
Days 1–14—10 mg oral four times daily*
Days 15–19—10 mg oral three times daily
Days 20–24—10 mg oral two times daily
Days 25–29—10 mg oral daily
*If there is no clinical response after day 7 (i.e., no 24-h period free of infantile spasms), the dose can be increased to 20 mg three times daily. If done, the taper schedule from days 15–19 would be 10 mg four times daily, then proceeding as in the table beginning on day 20.

(c) Vigabatrin
Days 1–3—50 mg/kg/day divided two times daily
Days 4–6—100 mg/kg/day divided two times daily
>7 days—150 mg/kg/day divided two times daily
Side effects (e.g., sedation, hypotonia) may necessitate slower titration.
For all treatments—If no clinical response by day 14, consider alternative treatment.

Monitoring while on hormonal therapy (ACTH and oral prednisolone):

- Famotidine for gastrointestinal (GI) protection.
- The issue of vaccination following high-dose steroids should be discussed with an infectious disease expert.
- Child's blood pressure to be checked twice a week by either a visiting nurse or pediatrician's office. If the blood pressure is above 20% of the child's normal blood pressure (measured during the hospitalization before initiation of the hormonal therapy) on two separate occasions, then the child needs to be referred to a nephrologist to start antihypertensive medication.
- If the child's bowel movement are black or bloody testing for occult blood is needed. If positive, then increasing the famotidine or consultation with GI specialist.
- Urine for sugar (glucose) should be tested each morning using urine test strips. If it reads 2+ glucose, on 2 days back to back, blood glucose should be checked.
- Consider use of stress dose steroids during time of ACTH taper and/or prednisolone use when a child has a febrile illness of >101*F and vomiting. Any scheduled procedure that will require sedation may require additional use of steroids. Children with mild illness (URI, occasional emesis/diarrhea) will usually not require stress dose steroids unless they also exhibit signs of adrenal insufficiency.

In general, we consider the child as adrenal insufficient for 6 weeks following initiation of 4 weeks of steroid therapy. Medication choices for stress dose steroids (Prednisone or Hydrocortisone) and dosing parameters are available in Lexicomp. If child is on prolonged use of steroids of >4 weeks we recommend an appointment with the endocrine clinic.

Families should be educated regarding possible side effects of steroids and the following topics should be covered:

- Upset stomach

- Bloody or black stool
- Irritability, won't stop crying and difficulty sleeping
- Increased hunger, weight gain
- High blood sugar and/or sugar (glucose) in the urine
- Skin changes
- An increased chance of getting sick because of a weakened immune system

Prognosis: About one-third to half of the patients with West syndrome evolve to Lennox–Gastaut syndrome, a syndrome with developmental disability and drug resistant seizures. Others have drug-resistant focal/multifocal epilepsies. There are increased comorbidities of intellectual disability and autism. Long-term data looking at intelligence found that only 24% had normal or slight impairment in IQ (>68).

2.8 Treatment/Management [23, 37]

There is significant lack of evidence to support a standard of care for the management of most of the infantile epilepsies except infantile spasms. Please see each section for treatment of the specific syndromes.

2.8.1 Novel Treatments

Customized treatment based on the involved gene and the specific molecular alteration could make precision medicine part of standard clinical practice. Examples of treatment based on precision medicine include potassium channel openers (Retigabine and Ezogabine) for loss of function variants (LOF) in KCNQ2 gene, and potassium channel openers (Quinidine) for gain of function (GOF) variants in KCNT1 gene.

2.9 Prognosis/Outcomes

Self-limited epilepsies have better prognosis while DEE (syndromic or not) carry a high risk for drug-resistant seizures, developmental/cognitive disability and early mortality.

2.10 When to Refer/Admit

Infants with recurrent seizures or epileptic spasms warrant urgent assessment in a facility with pediatric epilepsy specialists.

2.11 Prevention

Primary prevention is through improvements in prenatal and perinatal care to reduce the incidence of hypoxic ischemic encephalopathy, hypoglycemia. The child's genetic and environmental background and the epileptogenic pathology may not be modifiable. Secondary prevention strategies aim to reduce the impact of the epileptogenic substrates on brain networks to limit epileptogenesis. In one trial, preventive treatment with vigabatrin reduced the risk and severity of epilepsy in Tuberous sclerosis [39]. Early effective therapy of seizures optimizes eventual cognitive functioning in DEE as ongoing seizures may cause permanent and progressive changes in brain structure and connectivity.

3 Clinical Pearls/Key Points

- Infantile epilepsies can be a self-limited electroclinical syndromes or DEE.
- Brain MRI, metabolic, and genetic testing are essential to determine etiology.
- Early diagnosis and treatment of infantile spasms are crucial to improve outcomes.
- DEE carry a high risk for drug-resistant seizures, developmental/cognitive disability and early mortality.
- Genetic discoveries will redefine electroclinical syndromes and enable precision medicine to be a part of standard clinical practice.

References

1. Pressler RM, Cilio MR, Mizrahi EM, Moshe SL, Nunes ML, Plouin P, 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):615–28.
2. Pisani F, Facini C, Bianchi E, Giussani G, Piccolo B, Beghi E. Incidence of neonatal seizures, perinatal risk factors for epilepsy and mortality after neonatal seizures in the province of Parma, Italy. Epilepsia. 2018;59(9):1764–73.
3. Glass HC, Shellhaas RA, Wusthoff CJ, Chang T, Abend NS, Chu CJ, et al. Contemporary profile of seizures in neonates: a prospective cohort study. J Pediatr. 2016;174:98–103.e1.
4. Vasudevan C, Levene M. Epidemiology and aetiology of neonatal seizures. Semin Fetal Neonatal Med. 2013;18(4):185–91.
5. Volpe JJ, Volpe JJ. Volpe's neurology of the newborn. 6th ed. Philadelphia: Elsevier; 2018. xv, 1224 pages. p. 203–244.
6. Nguyen T, Wusthoff CJ. Clinical manifestations of neonatal seizures. Pediatr Int. 2021;63(6):631–5.
7. Abend NS, Dlugos DJ, Clancy RR. A review of long-term EEG monitoring in critically ill children with hypoxic-ischemic encephalopathy, congenital heart disease, ECMO, and stroke. J Clin Neurophysiol. 2013;30(2):134–42.

8. Scher MS, Alvin J, Gaus L, Minnigh B, Painter MJ. Uncoupling of EEG-clinical neonatal seizures after antiepileptic drug use. Pediatr Neurol. 2003;28(4):277–80.
9. Shellhaas RA, Chang T, Tsuchida T, Scher MS, Riviello JJ, Abend NS, et al. The American Clinical Neurophysiology Society's guideline on continuous electroencephalography monitoring in neonates. J Clin Neurophysiol. 2011;28(6):611–7.
10. Glass HC, Wusthoff CJ, Shellhaas RA, Tsuchida TN, Bonifacio SL, Cordeiro M, et al. Risk factors for EEG seizures in neonates treated with hypothermia: a multicenter cohort study. Neurology. 2014;82(14):1239–44.
11. Sansevere AJ, Kapur K, Peters JM, Fernandez IS, Loddenkemper T, Soul JS. Seizure prediction models in the neonatal intensive care unit. J Clin Neurophysiol. 2019;36(3):186–94.
12. Lehman LL, Rivkin MJ. Perinatal arterial ischemic stroke: presentation, risk factors, evaluation, and outcome. Pediatr Neurol. 2014;51(6):760–8.
13. Axeen EJT, Olson HE. Neonatal epilepsy genetics. Semin Fetal Neonatal Med. 2018;23(3):197–203.
14. Pavone P, Spalice A, Polizzi A, Parisi P, Ruggieri M. Ohtahara syndrome with emphasis on recent genetic discovery. Brain Dev. 2012;34(6):459–68.
15. Cross JH. Differential diagnosis of epileptic seizures in infancy including the neonatal period. Semin Fetal Neonatal Med. 2013;18(4):192–5.
16. Painter MJ, Scher MS, Stein AD, Armatti S, Wang Z, Gardiner JC, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. N Engl J Med. 1999;341(7):485–9.
17. Sharpe C, Reiner GE, Davis SL, Nespeca M, Gold JJ, Rasmussen M, et al. Levetiracetam versus phenobarbital for neonatal seizures: a randomized controlled trial. Pediatrics. 2020;145(6):e20193182.
18. Boylan GB, Panerai RB, Rennie JM, Evans DH, Rabe-Hesketh S, Binnie CD. Cerebral blood flow velocity during neonatal seizures. Arch Dis Childhood Fetal Neonatal Ed. 1999;80(2):F105–10.
19. Miller SP, Weiss J, Barnwell A, Ferriero DM, Latal-Hajnal B, Ferrer-Rogers A, et al. Seizure-associated brain injury in term newborns with perinatal asphyxia. Neurology. 2002;58(4):542–8.
20. Kharoshankaya L, Stevenson NJ, Livingstone V, Murray DM, Murphy BP, Ahearne CE, et al. Seizure burden and neurodevelopmental outcome in neonates with hypoxic-ischemic encephalopathy. Dev Med Child Neurol. 2016;58(12):1242–8.
21. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512–21.
22. Berg AT, Coryell J, Saneto RP, Grinspan ZM, Alexander JJ, Kekis M, et al. Early-life epilepsies and the emerging role of genetic testing. JAMA Pediatr. 2017;171(9):863–71.
23. Wilmshurst JM, Gaillard WD, Vinayan KP, Tsuchida TN, Plouin P, Van Bogaert P, et al. Summary of recommendations for the management of infantile seizures: task force report for the ILAE Commission of Pediatrics. Epilepsia. 2015;56(8):1185–97.
24. Nordli DR Jr. Infantile seizures and epilepsy syndromes. Epilepsia. 2002;43(Suppl 3):11–6.
25. Uldall P, Alving J, Hansen LK, Kibaek M, Buchholt J. The misdiagnosis of epilepsy in children admitted to a tertiary epilepsy centre with paroxysmal events. Arch Dis Child. 2006;91(3):219–21.
26. Petkar S, Hamid T, Iddon P, Clifford A, Rice N, Claire R, et al. Prolonged implantable electrocardiographic monitoring indicates a high rate of misdiagnosis of epilepsy—REVISE study. Europace. 2012;14(11):1653–60.
27. Ferrie CD. Preventing misdiagnosis of epilepsy. Arch Dis Child. 2006;91(3):206–9.
28. Eltze CM, Chong WK, Cox T, Whitney A, Cortina-Borja M, Chin RF, et al. A population-based study of newly diagnosed epilepsy in infants. Epilepsia. 2013;54(3):437–45.
29. Gaillard WD, Chiron C, Cross JH, Harvey AS, Kuzniecky R, Hertz-Pannier L, et al. Guidelines for imaging infants and children with recent-onset epilepsy. Epilepsia. 2009;50(9):2147–53.

30. Willimsky EK, Munzig A, Mayer K, Biskup S, Abicht A, Hoertnagel K, et al. Next generation sequencing in pediatric epilepsy using customized panels: size matters. Neuropediatrics. 2021;52(2):92–7.
31. Vigevano F, Fusco L, Di Capua M, Ricci S, Sebastianelli R, Lucchini P. Benign infantile familial convulsions. Eur J Pediatr. 1992;151(8):608–12.
32. Caraballo RH, Cersósimo RO, Espeche A, Fejerman N. Benign familial and non-familial infantile seizures: a study of 64 patients. Epileptic Disord. 2003;5(1):45–9.
33. Schubert J, Paravidino R, Becker F, Berger A, Bebek N, Bianchi A, et al. PRRT2 mutations are the major cause of benign familial infantile seizures. Hum Mutat. 2012;33(10):1439–43.
34. Auvin S, Pandit F, De Bellecize J, Badinand N, Isnard H, Motte J, et al. Benign myoclonic epilepsy in infants: electroclinical features and long-term follow-up of 34 patients. Epilepsia. 2006;47(2):387–93.
35. Wirrell EC, Shellhaas RA, Joshi C, Keator C, Kumar S, Mitchell WG. How should children with West syndrome be efficiently and accurately investigated? Results from the National Infantile Spasms Consortium. Epilepsia. 2015;56(4):617–25.
36. Kelley SA, Knupp KG. Infantile spasms—have we made progress? Curr Neurol Neurosci Rep. 2018;18(5):27.
37. Grinspan ZM, Shellhaas RA, Coryell J, Sullivan JE, Wirrell EC, Mytinger JR, et al. Comparative effectiveness of levetiracetam vs phenobarbital for infantile epilepsy. JAMA Pediatr. 2018;172(4):352–60.
38. Knupp KG, Coryell J, Nickels KC, Ryan N, Leister E, Loddenkemper T, et al. Response to treatment in a prospective national infantile spasms cohort. Ann Neurol. 2016;79(3):475–84.
39. Kotulska K, Kwiatkowski DJ, Curatolo P, Weschke B, Riney K, Jansen F, et al. Prevention of epilepsy in infants with tuberous sclerosis complex in the EPISTOP trial. Ann Neurol. 2021;89(2):304–14.

Child with Febrile Seizures

Rajkumar Agarwal and Roshani Agarwal

1 Introduction

Febrile seizures are an age-dependent phenomenon and the most common type of seizures seen in children [1]. Febrile seizures are not considered a form of epilepsy; rather they are a manifestation of a distinct syndrome. In the past, it was believed that febrile seizures can lead to brain damage as well as epilepsy later in life. However, multiple studies have now established that febrile seizures generally have a favorable outcome and that epilepsy only develops in a small minority of children who had febrile seizures during childhood [2–6].

A febrile seizure is defined as a seizure that occurs in children between 6 months and 5 years of age, accompanied by fever (temperature ≥ 100.4 °F or 38 °C), and in the absence of a previous afebrile seizure or other provoking causes for seizures including central nervous system (CNS) infection, electrolyte abnormalities, drug withdrawal, trauma, or known epilepsy [7, 8]. The presence of an underlying neurological abnormality (other than epilepsy) is not relevant to the diagnosis of febrile seizures. The most common seizure type is a tonic–clonic seizure, but other seizure types may also occur. Most children experience a febrile seizure within 24 h of fever onset, although a fever does not have to be present at the time of the seizure [9]. In some instances, the fever may occur after the seizure.

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Febrile seizures can be classified into simple febrile seizures or complex febrile seizures. This classification is important for treatment as well as prognosis.

(a) Simple febrile seizure: The seizure is generalized in nature, lasts <15 min AND occurs only once in a 24-h period.
(b) Complex febrile seizure: The seizure is focal in nature, lasts ≥15 min, or occurs ≥2 times within 24 h.

The term febrile status epilepticus is used for febrile seizures that last ≥30 min [10].

2 Epidemiology

Febrile seizures are the most common convulsive events in children who are less than 5 years of age. The incidence of febrile seizures in children before the age of 5 years varies widely across different geographic regions; from 2 to 5% in Europe and North America, 6 to 9% in Japan, and up to 14% children in Guam [1, 8, 11–15]. The peak incidence of febrile seizures is at about 18 months of age, with >90% children having experienced their first febrile seizure prior to 3 years of age [13]. No gender predilection has been noted in large epidemiological studies [12, 13].

The most common form is a simple febrile seizure; about 18–35% children present with complex febrile seizures [12, 16]. About two-thirds of the children only have a single febrile seizure in their lifetime [13, 17, 18]. Multiple recurrences (three or more distinct episodes of febrile seizures) are seen in 5–10% children [18, 19]. Febrile status epilepticus accounts for 5% of febrile seizures; but is the most common cause of convulsive status epilepticus in this age group [20].

3 Etiology

Genetic predisposition is the most important risk factor for febrile seizures. Febrile seizures occur when a genetically susceptible child, in the appropriate age group, develops a febrile illness. A positive family history of febrile seizures is seen in 25–40% of children with febrile seizures; younger siblings of a child with febrile seizures have a 10–20% risk of having febrile seizures [21–23]. Several genetic loci have been reported including chromosome 8 (*FEB1*), chromosome 19 (*FEB2*), and chromosome 2 (*FEB3*) [23]. However, a known genetic abnormality can still be identified in only a small subset of children with febrile seizures. Variable modes of transmission including autosomal dominant, autosomal recessive as well as polygenic modes of inheritance have been described with febrile seizures.

The peak temperature during the febrile illness, rather than the rate of rise of temperature, is an important factor associated with febrile seizures [24]. The underlying trigger is often an infection such as human herpesvirus 6 (HHV-6) or

influenza which can lead to high fever. Other causes of fever including bacterial infections, immunizations especially DTwP (diphtheria, tetanus toxoid, and whole-cell pertussis) and MMR (measles, mumps, and rubella) can also lead to febrile seizures. Studies have noted association with attendance at daycare, low gestational age, and prenatal exposure to nicotine and iron deficiency, although the evidence for these is limited [24–27]. Gastroenteritis as the underlying illness appears to have a lower incidence of febrile seizures when compared with other childhood febrile illnesses [24].

4 Differential Diagnosis

There is no diagnostic test for febrile seizures. It is important to rule out other causes of seizures when an age-appropriate child presents with a seizure in the setting of a febrile illness. Some important differential diagnoses to consider include:

1. *Infection of the central nervous system (CNS)*: A major concern for any child presenting with a seizure in the setting of a febrile illness is CNS infection in the form of meningitis and/or encephalitis. The incidence of meningitis in children who present with an apparent febrile seizure is between 2 and 5% [11]. In most children, a careful history and physical examination may be sufficient to rule out a CNS infection. Look for other clinical features of CNS infection including alteration of mental status, excessive irritability, photophobia, bulging fontanelle, or presence of a petechial rash. Cerebrospinal fluid (CSF) examination may be considered in some situations (Fig. 1).

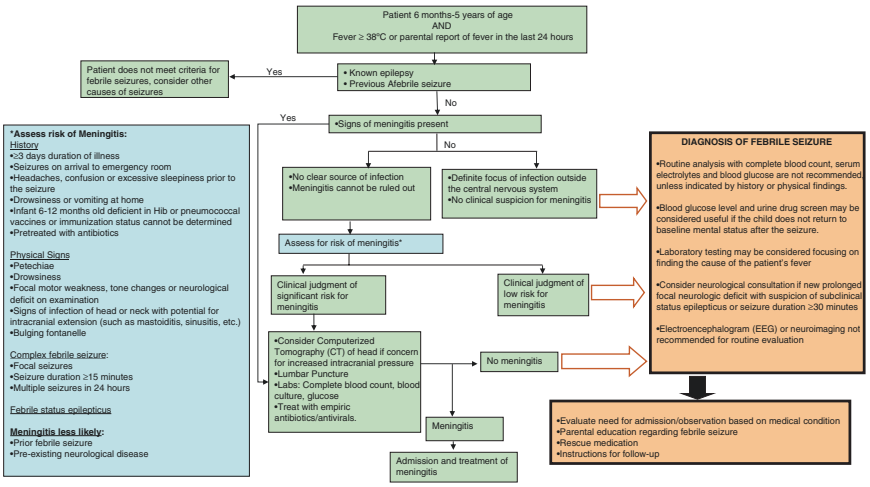

Fig. 1 Clinical approach to a child with suspected febrile seizure

2. *Epileptic seizure triggered by fever*: Children with epilepsy (due to any cause) often present with breakthrough seizures when they are sick, as fever decreases their seizure threshold. A fever-triggered seizure may sometimes be the *initial* presentation of epilepsy in some children and may be misdiagnosed as a febrile seizure.
3. *Epilepsy syndromes with propensity for febrile seizures*: In some children, febrile seizures could be an early manifestation of specific forms of genetic epilepsies like GEFS+ (generalized epilepsy with febrile seizures plus) and Dravet syndrome. Children with GEFS+ present with recurrent seizures provoked by fever, however, unlike febrile seizures, these children continue to have seizures triggered by fever much beyond the typical age of 5–6 years [28]. Children with Dravet syndrome (severe myoclonic epilepsy of childhood) may present with recurrent complex febrile seizures (often with febrile status epilepticus involving one half of the body—hemiconvulsions) in the first year of life. They then go on to develop afebrile seizures and experience developmental regression that progresses to medically refractory epilepsy. Many children with Dravet syndrome have mutations in the voltage-gated sodium channel (SCN1A) [29].
4. *Other causes of seizures*: It is important to consider other common causes of seizures including metabolic abnormalities like hypoglycemia or electrolyte disturbances like hyponatremia. This is especially true when the child has symptoms of gastroenteritis or poor feeding associated with febrile illness.
5. *Postictal fever*: A convulsive seizure can cause elevation in body temperature likely secondary to the excessive muscle activity during the seizure. This phenomenon has not been well studied; but is believed to be transient and resolves spontaneously [30].

5 Diagnostic Approach

It is important to remember that febrile seizure is a diagnosis of exclusion. Appropriate differential diagnoses including CNS infections, other neurological diseases and electrolyte imbalance should be excluded prior to making a diagnosis of a febrile seizure, especially after the first episode. Detailed history and physical examination are often enough to reach a definitive diagnosis of febrile seizure. In addition, a thorough evaluation for the underlying etiology for fever should be sought. The clinical approach is summarized in Fig. 1.

5.1 History

- It is important to get first-hand information from eyewitnesses as the seizure may be witnessed by a teacher, grandparent or another caregiver. A detailed description of the seizure semiology should include presence of focal symptoms or signs

during the seizure, duration of the seizure as well as presence of postictal focal neurological deficits (Todd's paralysis).
- Transient postictal drowsiness is not unusual after a febrile seizure. However, if the patient continues to have prolonged state of unresponsiveness after a seizure, an alternative etiology, like CNS infection, should be suspected.
- Presence of neurological symptoms like headaches, emesis, confusion or excessive sleepiness prior to the seizure would also point towards other CNS causes of seizures.
- Prolonged duration of fever prior to the seizure can also point toward a possible CNS infection.
- Ask about recent use of antibiotics as that could potentially mask clinical signs of meningitis.
- History should also be geared toward finding out the source of fever including but not limited to recent immunizations, sick contacts, and presence of respiratory or gastrointestinal symptoms, ear pain and rash.
- Ask about use of antipyretics as they could mask fever potentially leading to misdiagnosis.
- Ask about previous history of febrile or afebrile seizures in the child.
- A detailed family history of febrile seizures as well as of epilepsy is pertinent.
- Information about risk factors for epilepsy including perinatal trauma, developmental delay and head injury should be obtained.

5.2 Physical Examination

The physical examination should be focused on evaluating the cause of fever as well as eliminating other potential causes of seizures.

- General physical examination: This should focus on evaluation for the source of infection. Look for rash, signs of upper respiratory or ear infection and lymphadenopathy.
- Evaluate for signs of an underlying neurological disease including abnormal head circumference, presence of neurocutaneous markers, and abnormal muscle tone.
- Neurological Examination:
  - Assess for signs of meningeal inflammation (neck stiffness, Kernig's sign), although in young infants these could be absent despite presence of meningitis.
  - A bulging and nonpulsatile anterior fontanelle could indicate raised intracranial pressure and CNS infection in young children.
  - Look for any focal neurological deficits (unilateral weakness of the face or extremities) as those indicate a focal nature to the seizure, thereby, categorizing the seizure as a complex febrile seizure.
  - In a child with encephalopathy, evaluate for subtle signs of ongoing nonconvulsive seizure which may include forced eye deviation (lateral deviation of the eyes not overcome by oculocephalic maneuver), repetitive eye blinking and lip-smacking movements.

5.3 Evaluation (Laboratory Studies/Imaging)

Routine laboratory evaluation is not recommended in children with febrile seizures. Investigations should be pursued if history and/or physical examination are suggestive of other causes of seizures or for evaluation of fever as clinically necessary.

- If the patient has vomiting, diarrhea, or has signs of dehydration or lethargy, it may be reasonable to consider checking blood glucose, serum electrolytes, calcium, phosphorous, and/or magnesium.
- If there is concern for a systemic infection or meningitis, complete blood count and blood culture may be drawn.
- Blood glucose and drug screen should be considered in the presence of prolonged unexplained encephalopathy.
- The most important question faced by the clinician is whether a lumbar puncture (LP) should be performed to exclude meningitis. LP is unnecessary in most well-appearing children who have returned to a normal baseline after a febrile seizure. The risk factors for an underlying CNS infection include prolonged duration of fever prior to the seizure (>48–72 h), a visit for medical care within the previous 48 h (which is probably reflective of the prolonged duration of fever), seizures on arrival to the emergency room, complex febrile seizure, or suspicious findings on physical or neurologic examination (e.g., rash, cyanosis, respiratory distress, signs of meningeal inflammation, or increased tone) [31].

The American Academy of Pediatrics issued guidelines for the neurodiagnostic evaluation of a child with a simple febrile seizure between 6 months and 5 years of age [8]. The following is a summary of the guidelines pertaining to use of lumbar puncture:

1. A lumbar puncture should be performed if there are symptoms or signs of meningeal irritation or if there is clinical suspicion for intracranial infection.
2. Consider lumbar puncture in children between 6 and 12 months of age if they have not been immunized for *Haemophilus influenzae* type b (Hib) or *Streptococcus pneumoniae* or if their immunization status cannot be determined.
3. Consider lumbar puncture when the child is on antibiotics as there is a possibility of partially treated bacterial meningitis.

- Routine neuroimaging is not recommended in children with simple febrile seizures. Indications for neuroimaging in the acute setting include persistent focal neurological deficit, signs and symptoms of raised intracranial pressure, and febrile status epilepticus. While magnetic resonance imaging (MRI) is better for structural definition of the brain, a computerized tomography (CT) scan is often reasonable in the acute settings to rule out emergent pathologies. An outpatient brain MRI may be considered in children with focal or prolonged febrile seizures and in those with risk factors for epilepsy including children with neurodevelopmental impairment at baseline.

- Electroencephalogram (EEG) is not warranted for evaluation of children with simple febrile seizures. An outpatient EEG may be considered for children with focal febrile seizures or those considered to be at high risk for epilepsy. An EEG is typically not required in the acute settings, except for children with persistent encephalopathy when nonconvulsive status epilepticus is suspected.

6 Treatment

A febrile seizure is a frightening experience for parents and caregivers. Families may have several questions regarding the etiology, the risk of recurrence, likelihood of brain damage, possibility of epilepsy, and the impact of febrile seizures on their child's life. Many families are afraid that their child could have died. The treating physician plays a vital role in alleviating the families' anxiety by educating them about the benign nature of febrile seizures, providing reassurance about the prognosis and providing a contingency plan for management of recurrent seizures. In most cases, counseling and education will be the sole and the most important treatment. For subsequent episodes of febrile seizures—as long as the seizures are brief and associated with fever—it is not necessary for the family to seek care on an emergent basis for the seizure. The patient may need further evaluation in the office to determine the etiology of the fever.

6.1 Management of an Acute Seizure

- **Acute care setting**: In most instances, the seizure terminates spontaneously before the child is brought to medical attention. If the child is actively seizing for more than 5 min, a benzodiazepine should be administered. The various benzodiazepines and their doses are summarized in Table 1. If the seizure does not

Table 1 Management of febrile seizures at home

• Stay calm
• Do not hold the child down—allow the seizure to happen
• Move any sharp or heavy objects away to prevent injury
• Turn the child to his/her side to keep the airway clear
• Place something soft (e.g., a folded cloth) under the child's head or cup the child's head under your hand to prevent it from hitting the ground
• Loosen clothes around the neck
• Do not put anything in the child's mouth
• Time the duration of the seizure. Do not attempt to keep the child awake after the seizure has stopped

Table 2 Benzodiazepines for treatment of febrile seizures

	Drug	Route	Dose	Maximum dose
Acute care setting	Diazepam	Intravenous	0.1–0.2 mg/kg	10 mg
	Lorazepam	Intravenous	0.05–0.1 mg/kg	4 mg
	Midazolam	Intranasal	0.2–0.5 mg/kg	10 mg
		Buccal	0.2 mg/kg	10 mg
		Intramuscular	0.2 mg/kg	6 mg
Home setting	Diazepam	Rectal	2–5 years of age: 0.5 mg/kg (round to the nearest multiple of 2.5 mg)	20 mg
	Midazolam	Intranasal	0.2–0.3 mg/kg	10 mg

respond to an initial dose of benzodiazepine, a repeat dose of a benzodiazepine and/or additional antiseizure medications (phenytoin, fosphenytoin, phenobarbital, levetiracetam) should be administered intravenously and the child should be treated along the lines of status epilepticus.

- **Home setting**: Families should be provided education regarding identification of seizures and management of an acute seizure in the home setting (Table 1). In children with an initial prolonged febrile seizure and in those with high risk of recurrence, a rescue medication can be prescribed for use in the home/child-care settings. The most commonly used preparations are diazepam rectal gel and intranasal midazolam, typically administered by caregivers if the seizure lasts longer than 5 min (Table 2).

6.2 Use of Antipyretics

Antipyretics can be administered to decrease fever and make the child comfortable during the febrile illness. Antipyretics administered after the first febrile seizure may decrease the likelihood of another febrile seizure during the same illness but have not shown to reduce the occurrence of a subsequent febrile seizures [32–34]. Parents should be counseled regarding the limitations of using antipyretics to avoid creating unnecessary anxiety and feelings of guilt.

7 Prognosis

7.1 Recurrence of Febrile Seizures

Most children with febrile seizures experience only one seizure in their lifetime [13, 17, 18]. About one-third of children with febrile seizures may have recurrence of febrile seizure; with 5–10% children experiencing three or more febrile seizures

Table 3 Risk factors for recurrence of febrile seizures and risk factors for development of epilepsy

Risk factors for recurrent febrile seizures	Risk factors for epilepsy
Young age of onset	Complex febrile seizure
Lower peak temperature	Neurodevelopmental impairment at baseline
Brief duration of fever prior to the seizure	Brief duration of fever prior to the seizure
Family history of febrile seizures	Family history of epilepsy

[18, 19]. The risk factors for recurrence of febrile seizures are summarized in Table 3. The single strongest predictor of recurrent febrile seizures is age of onset (<12–18 months at initial presentation) [3, 9]. This is probably due to the fact that when febrile seizures start at a young age there is a relatively longer period of time during which the child can continue to have febrile seizures. Studies have also shown that occurrence of a febrile seizure at a lower body temperature seems to be associated with a higher risk of recurrence [18, 19]. In addition, shorter duration of fever prior to the seizure increases the likelihood of recurrent febrile seizures. The last two factors imply an overall lower threshold for seizures in affected children [18, 19]. Recurrence is also more likely in children who have a family history of febrile seizures in a first degree relative [9, 11]. Children with multiple risk factors tend to have the highest risk of recurrence. A child with two or more risk factors has a greater than 30% recurrence risk at 2 years whereas a child with three or more risk factors has a greater than 60% recurrence risk [18, 19].

A history of complex febrile seizure or presence of a neurodevelopmental abnormality in the child does not increase the risk of subsequent febrile seizures. If the initial seizure is a complex febrile seizure, the risk of a subsequent episode also being of complex nature is not high. If the initial seizure is prolonged, the recurrence risk of febrile seizure is not increased; however, if a recurrent febrile seizure does develop, it is more likely to be prolonged in nature.

7.2 Epilepsy and Febrile Seizures

Several risk factors have been identified that impact the development of epilepsy in children with febrile seizures. These risk factors are summarized in Table 2. In the absence of these risk factors, the rate of epilepsy in children with febrile seizures is essentially no different than for children without febrile seizures.

In children with simple febrile seizures, the long-term risk of epilepsy is about 1–2% which is comparable to the risk of epilepsy in the general population [35]. In contrast, the risk of epilepsy in children with complex febrile seizures is about 5–10% [16, 35]. While this is about 5–10 times the risk of epilepsy in the general population, it is worth noting that ≥90% children with complex febrile seizures *do not* develop epilepsy. The higher incidence of epilepsy in children with complex febrile seizures is likely related to an underlying genetic predisposition for epilepsy

rather than any neurological injury caused by febrile seizures. There has been an association between prolonged febrile seizures in childhood and development of hippocampal sclerosis in adults; however, a definite causal relationship has not been clearly established [36].

7.3 Neurologic Dysfunction

In the absence of another neurological disease, febrile seizures do not cause cognitive dysfunction or poor academic performance, regardless of the type, duration, or frequency of febrile seizures [37, 38].

8 When to Refer/Admit

Most children with simple febrile seizures do not require hospitalization and can be discharged home from the emergency department. Admission may be required in the following scenarios:

- Febrile status epilepticus
- Persistent encephalopathy or neurological deficit after the seizure has stopped
- Parental anxiety
- Severe underlying febrile illness necessitating hospitalization

Most children with simple febrile seizures can be managed by their primary care physician. Neurological consultation should be considered in the following situations:

- Multiple episodes of simple febrile seizures
- Complex febrile seizures
- Febrile status epilepticus
- Children considered to be at high risk for epilepsy

9 Prevention of Febrile Seizures

There is no evidence of benefit from prophylactic antiseizure medications in children with simple febrile seizures. The risks of sedation and other adverse effects of these drugs outweigh the benefits [11, 34]. Use of antiseizure medications do not reduce the risk of epilepsy later in life. As such, routine use of preventative therapy is not recommended by the American Academy of Pediatrics for children with one or more simple febrile seizures [34].

In children with recurrent complex febrile seizures, especially if they have prolonged febrile seizures, intermittent use of antiseizure medications may be considered *(Intermittent prophylaxis)*. Intermittent diazepam, phenobarbital, valproic acid, and clobazam have all been used in small studies with potential benefit [33, 39]. The antiseizure medication is usually started at the onset of fever and given for a total of 3–5 days during the febrile illness. In patients with recurrent prolonged febrile seizures where intermittent treatment with antiseizure medications fail or when parents are unable to promptly recognize the onset of fever, continuous antiseizure drug therapy has been suggested *(Continuous prophylaxis)*. However, this should be considered only in exceptional situations after weighing the risks of antiseizure medications with the potential benefit of preventing febrile seizures.

10 Clinical Pearls/Key Points

- Febrile seizures are a benign type of seizure disorder seen in children between 6 months and 5 years of age.
- Diagnosis is based on careful history and physical examination; most children do not require laboratory testing or neuroimaging.
- The most important step in management of febrile seizures is parental reassurance and identifying the cause for fever.
- Home use of benzodiazepines can be considered in some children with febrile seizures.

References

1. Hauser WA. The prevalence and incidence of convulsive disorders in children. Epilepsia. 1994;35:S1–6.
2. Vestergaard M, Pedersen CB, Sidenius P, Olsen J, Christensen J. The long-term risk of epilepsy after febrile seizures in susceptible subgroups. Am J Epidemiol. 2007;165(8):911–8.
3. Berg AT. Febrile seizures and epilepsy: the contributions of epidemiology. Paediatr Perinat Epidemiol. 1992;6(2):145–52.
4. Wolf SM, Forsythe A. Epilepsy and mental retardation following febrile seizures in childhood. Acta Paediatr. 1989;78(2):291–5.
5. Berg AT, Shinnar S. Unprovoked seizures in children with febrile seizures: short-term outcome. Neurology. 1996;47(2):562–8.
6. Annegers JF, Hauser WA, Shirts SB, Kurland LT. Factors prognostic of unprovoked seizures after febrile convulsions. N Engl J Med. 1987;316(9):493–8.
7. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Guidelines for epidemiologic studies on epilepsy. Epilepsia. 1993;34(4):592–6.
8. Subcommittee on Febrile Seizures. Febrile seizures: guideline for the neurodiagnostic evaluation of the child with a simple febrile seizure. Pediatrics. 2011;127(2):389–94.

9. Berg AT, Shinnar S, Hauser WA, Alemany M, Shapiro ED, Salomon ME, Crain EF. A prospective study of recurrent febrile seizures. N Engl J Med. 1992;327(16):1122–7.
10. Hesdorffer DC, Shinnar S, Lewis DV, Moshé SL, Nordli DR Jr, Pellock JM, MacFall J, Shinnar RC, Masur D, Frank LM, Epstein LG. Design and phenomenology of the FEBSTAT study. Epilepsia. 2012;53(9):1471–80.
11. Shinnar S, Glauser TA. Febrile seizures. J Child Neurol. 2002;17(1_suppl):S44–52.
12. van den Berg BJ, Yerushalmy J. Studies on convulsive disorders in young children: I. Incidence of febrile and nonfebrile convulsions by age and other factors. Pediatr Res. 1969;3(4):298–304.
13. Verity CM, Butler NR, Golding J. Febrile convulsions in a national cohort followed up from birth. I—Prevalence and recurrence in the first five years of life. Br Med J (Clin Res Ed). 1985;290(6478):1307–10.
14. Tsuboi T. Epidemiology of febrile and afebrile convulsions in children in Japan. Neurology. 1984;34(2):175–81.
15. Stanhope JM, Brody JA, Brink JA, Brink E, Morris CE. Convulsions among the Chamorro People of Guam, Mariana Islands: II. Febrile convulsions. Am J Epidemiol. 1972;95(3):299–304.
16. Berg AT, Shinnar S. Complex febrile seizures. Epilepsia. 1996;37(2):126–33.
17. Waruiru C, Appleton R. Febrile seizures: an update. Arch Dis Child. 2004;89(8):751–6.
18. Berg AT, Shinnar S, Darefsky AS, Holford TR, Shapiro ED, Salomon ME, Crain EF, Hauser AW. Predictors of recurrent febrile seizures: a prospective cohort study. Arch Pediatr Adolesc Med. 1997;151(4):371–8.
19. Offringa M, Bossuyt PM, Lubsen J, Ellenberg JH, Nelson KB, Knudsen FU, Annegers JF, El-Radhi AS, Habbema JD, Derksen-Lubsen G, Hauser WA. Risk factors for seizure recurrence in children with febrile seizures: a pooled analysis of individual patient data from five studies. J Pediatr. 1994;124(4):574–84.
20. Raspall-Chaure M, Chin RF, Neville BG, Bedford H, Scott RC. The epidemiology of convulsive status epilepticus in children: a critical review. Epilepsia. 2007;48(9):1652–63.
21. Hauser WA, Annegers JF, Anderson VE, Kurland LT. The risk of seizure disorders among relatives of children with febrile convulsions. Neurology. 1985;35(9):1268–73.
22. Corey LA, Berg K, Pellock JM, Solaas MH, Nance WE, DeLorenzo RJ. The occurrence of epilepsy and febrile seizures in Virginian and Norwegian twins. Neurology. 1991;41(9):1433–6.
23. Tsuboi T, Endo S. Genetic studies of febrile convulsions: analysis of twin and family data. Epilepsy Res Suppl. 1991;4:119–28.
24. Berg AT, Shinnar S, Shapiro ED, Salomon ME, Crain EF, Hauser WA. Risk factors for a first febrile seizure: a matched case-control study. Epilepsia. 1995;36(4):334–41.
25. Vestergaard M, Wisborg K, Henriksen TB, Secher NJ, Østergaard JR, Olsen J. Prenatal exposure to cigarettes, alcohol, and coffee and the risk for febrile seizures. Pediatrics. 2005;116(5):1089–94.
26. Vestergaard M, Basso O, Henriksen TB, Østergaard JR, Olsen J. Risk factors for febrile convulsions. Epidemiology. 2002;13(3):282–7.
27. Hartfield DS, Tan J, Yager JY, Rosychuk RJ, Spady D, Haines C, Craig WR. The association between iron deficiency and febrile seizures in childhood. Clin Pediatr. 2009;48(4):420–6.
28. Camfield P, Camfield C. Febrile seizures and genetic epilepsy with febrile seizures plus (GEFS+). Epileptic Disord. 2015;17(2):124–33.
29. Dravet C. The core Dravet syndrome phenotype. Epilepsia. 2011;52(Suppl 2):3–9.
30. Rossetti AO, Tosi C, Despland PA, Staedler C. Post-ictal fever: a rare symptom of partial seizures. Eur J Neurol. 2007;14(5):586–90.
31. Joffe A, McCormick M, DeAngelis C. Which children with febrile seizures need lumbar puncture?: a decision analysis approach. Am J Dis Child. 1983;137(12):1153–6.
32. Murata S, Okasora K, Tanabe T, Ogino M, Yamazaki S, Oba C, Syabana K, Nomura S, Shirasu A, Inoue K, Kashiwagi M. Acetaminophen and febrile seizure recurrences during the same fever episode. Pediatrics. 2018;142(5):e20181009.
33. Offringa M, Newton R, Cozijnsen MA, Nevitt SJ. Prophylactic drug management for febrile seizures in children. Cochrane Database Syst Rev. 2017;2(2):CD003031.

34. Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures. Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures. Pediatrics. 2008;121(6):1281–6.
35. Nelson KB, Ellenberg JH. Predictors of epilepsy in children who have experienced febrile seizures. N Engl J Med. 1976;295(19):1029–33.
36. Lewis DV, Shinnar S, Hesdorffer DC, Bagiella E, Bello JA, Chan S, Xu Y, MacFall J, Gomes WA, Moshé SL, Mathern GW. Hippocampal sclerosis after febrile status epilepticus: the FEBSTAT study. Ann Neurol. 2014;75(2):178–85.
37. Verity CM, Greenwood R, Golding J. Long-term intellectual and behavioral outcomes of children with febrile convulsions. N Engl J Med. 1998;338(24):1723–8.
38. Nørgaard M, Ehrenstein V, Mahon BE, Nielsen GL, Rothman KJ, Sørensen HT. Febrile seizures and cognitive function in young adult life: a prevalence study in Danish conscripts. J Pediatr. 2009;155(3):404–9.
39. Capovilla G, Mastrangelo M, Romeo A, Vigevano F. Recommendations for the management of "febrile seizures" ad hoc task force of LICE guidelines commission. Epilepsia. 2009;50:2–6.

Child with Epilepsy

Norimitsu Kuwabara and James W. Wheless

Epilepsy is one of the most common neurological conditions affecting children. It is estimated that 1.2% of the population in the United States (US) had epilepsy in 2015. This translates to 3.4 million people with epilepsy in the United States, including three million adults and 470,000 children [1]. With the frequent occurrence of epilepsy in children, it is essential for pediatricians to know how to approach common pediatric epilepsy syndromes.

Table 1 describes the common pediatric epilepsy syndromes that primary care physicians may encounter in their daily clinic settings. Childhood absence epilepsy (CAE), benign epilepsy of childhood with centrotemporal spikes (BECTS), and juvenile myoclonic epilepsy (JME) are common epilepsy syndromes seen in children and are the epilepsy syndromes discussed in detail in this chapter. However, they might be missed or unrecognized as unique epilepsy syndromes since they may not be accompanied by generalized tonic–clonic seizures in all instances, leading to delay in diagnosis, care, and inaccurate prognosis.

This chapter aims to describe three common pediatric epilepsy syndromes and in doing so, enhance the pediatrician's ability to make the diagnosis promptly allowing timely referral to a neurologist, proper treatment and counseling.

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Table 1 Common pediatric epilepsy syndromes encountered in primary care settings

Onset	Epilepsy syndrome	Type of seizures	Description of EEG	Prognosis
Neonatal period	Benign familial neonatal epilepsy (BFNE)	Focal clonic or secondary generalized tonic–clonic	Normal	Spontaneous recovery with favorable outcome
Infancy	Infantile spasms	Spasms	Hypsarrhythmia	Depends on underlying etiology, often poor outcome
Childhood	Childhood absence epilepsy (CAE)	Absences	3 Hz generalized spike-and-slow waves	Favorable
	Panayiotopoulos syndrome	Focal autonomic seizures, frequently with emesis	Occipital focal epileptiform discharges	Favorable
	Benign rolandic epilepsy with centrotemporal spikes (BECTS)	Nocturnal focal motor	Uni-or bi-lateral centrotemporal epileptiform discharges, increased during sleep	Favorable
	Lennox–Gastaut syndrome (LGS)	Tonic, atypical absences	2–2.5 Hz spike-and-slow wave, diffuse background slowing, generalized fast activity in sleep	Poor with developmental delay and mental impairment, ongoing seizures, behavior and sleep problems
Adolescence-adult	Juvenile absence epilepsy (JAE)	Absences	Normal, or generalized 3 Hz polyspike-and- slow waves	Potentially long-term treatment, seizures usually controlled
	Juvenile myoclonic epilepsy (JME)	Myoclonic	Normal, or generalized 3.5–5 Hz polyspike-and-slow waves	Potentially life-long treatment, seizures usually controlled

1 Childhood Absence Epilepsy (CAE)

Introduction: CAE is the most common generalized epilepsy in childhood. It accounts for 10–17% of all childhood epilepsies [2, 3].

Epidemiology & Etiology: The age of onset of CAE is 4–10 years, with peak onset at ages 6–7 years. The upper limit of onset is typically considered to be age 10 years [4].

Semiology: CAE is characterized by frequent absence seizures (often tens to hundred events per day) with an abrupt onset and offset. During the seizure, the child

has a sudden behavioral arrest and unresponsiveness often described by parents as staring off. The child may have chewing movements, subtle clonic motor movements (i.e., eyelid jerks or slight jerks in their arms) or eyelid fluttering. These are brief events, most lasting under 15 s.

Diagnostic Approach: Electroencephalogram (EEG) is the gold-standard diagnostic modality. Seizures are typically provoked by hyperventilation that is often performed during the recording of the EEG, but seizures may occur spontaneously during the initial EEG, as well (Fig. 1).

History: It may be challenging to differentiate CAE from normal daydreaming or an attention disorder. Patients with CAE typically do not respond immediately to auditory (i.e., calling their name) or sensory stimuli (light touch) during the seizure. One of the things that may help when taking the history is asking if the events occur when the child is active (playing a video game, walking around the house, playing sports, etc.) or only occur when sedentary (i.e., sitting in the classroom or at the dinner table). If the episodes occur only when sedentary, attention problems are a more likely cause for the child's symptoms and they do occur frequently in this age group.

Physical Examination: If CAE is suspected, hyperventilation should be performed in the outpatient setting, as this can trigger absence seizures. A pinwheel is the best method to ensure participation by the child. The examiner asks the children to blow a pinwheel repetitively for 3–5 min to provoke absence seizures. (This should only be done with simultaneous EEG monitoring. While hyperventilation can be performed in the office setting, the results are often confusing and the gold standard is EEG confirmation during hyperventilation.)

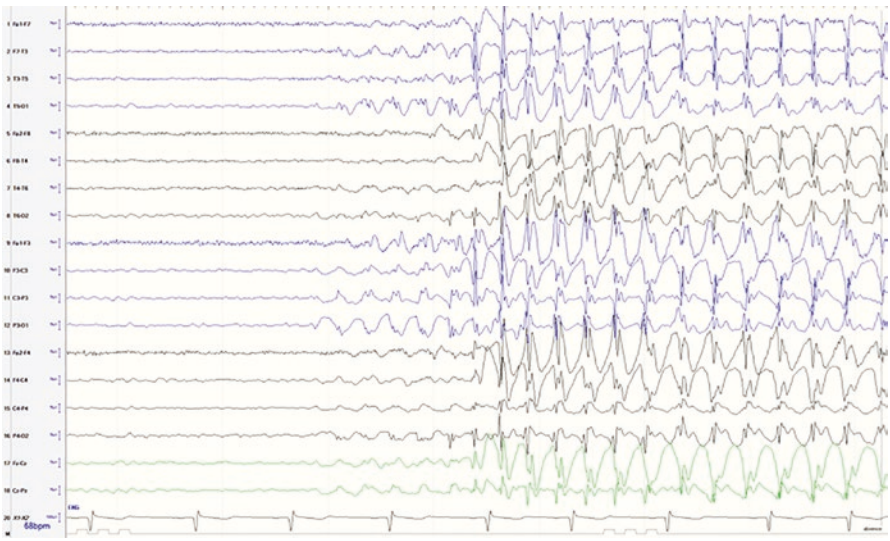

Fig. 1 CAE. The classic generalized 3 Hz spike and wave complexes in a 7-year-old girl

Evaluation (Laboratory Investigations/Imaging/EEG findings): The EEG abnormality seen is generalized 3 Hz spike and slow wave complexes, usually lasting from a few to 10 s in duration. The background EEG is otherwise normal (i.e., no diffuse or focal slowing, normal wake and sleep patterns). Background of the EEG refers to the pattern of brain waves that one can observe while the child is awake, quiet, and not experiencing a seizure. Laboratory studies (hematology, chemistries) or brain imaging are not usually indicated.

Differential Diagnosis: Patients with CAE can appear to be inattentive. Attention-deficit hyperactivity disorder (ADHD), hearing impairment, developmental and learning problems are included in the differential. Also, focal seizure with alternation of awareness (previously called complex partial seizures) can present with sudden alteration of consciousness and automatisms. (These are seemingly normal behaviors which the patient is performing, while unaware, during the seizure (i.e., picking at their clothes, swallowing movements, etc.) Focal seizures with altered awareness can be distinguished by their longer duration (typically 60–90 s), lack of response to hyperventilation, infrequent number (even untreated, usually less than one a week), and different EEG findings (normal EEG, or focal slowing or focal epileptiform discharges).

Of note, if children younger than 4 years of age present with absence seizures and features atypical for CAE such as a history of developmental delay, a movement disorder, additional seizure types, refractory epilepsy or have a first-degree relative with absence epilepsy, glucose transporter type 1 (GLUT1) deficiency should be considered [5, 6]. GLUT1 deficiency is caused by mutations in the Solute Carrier Family 2 Member 1 (*SLC2A1*) gene, which is responsible for familial GLUT1 deficiency. GLUT1 deficiency can cause a wide spectrum of neurological disorders including early-onset absence epilepsy (EOAE). The cut-off age between early-onset absences and typical CAE is arbitrarily set at 4 years. One out of 10 patients with EOAE has a mutation in the *SLC2A1* [5].

Treatment/Management/Prevention: CAE usually responds well to pharmacological treatment. The goal of treatment is to have no clinical or EEG seizures; therefore, a follow-up EEG is indicated after the family reports they are no longer seeing absence seizures. Treatment is usually continued until the child is seizure free for 4 years, and then a follow-up EEG is helpful. If the follow-up EEG is normal, consideration may be given to withdrawal of medication. First line medications for CAE are ethosuximide or valproate; however, the former is preferred (Table 2) [7]. Valproic acid and lamotrigine are also effective, but when compared to ethosuximide, valproic acid has more unfavorable side effects and lamotrigine is slightly less effective. It should be noted that ethosuximide is not efficacious for generalized tonic–clonic seizures (GTCs). If tonic–clonic seizures coexist with absence seizures, valproic acid or lamotrigine should be used initially, in an attempt to control both seizure types with one medication. The treatment for EOAE with a *SLC2A1* gene mutation is the ketogenic diet.

Prognosis/Outcomes: The prognosis of CAE is good. Approximately two-thirds of children with CAE will have resolution of epilepsy by mid-adolescence. The prognostic factors for lack of remission of CAE include a history of absence status

Table 2 Pharmaceutical options for childhood absence epilepsy (CAE)

Common medication for CAE	Suggested dose for children	Common adverse effect	Key drug interaction
Ethosuximide (ESM)	Start: 10 mg/kg/day, given twice daily with food Increase every week, by 5 mg/kg/day Initial goal: 15–20 mg/kg/day Serum levels: 40–100 mcg/mL	Gastrointestinal adverse effects are most common including abdominal discomfort, vomiting, diarrhea, and hiccups. These effects can be often alleviated by taking with food	Enzyme-inducing antiseizure drugs (e.g., phenytoin, phenobarbital, carbamazepine) increase ESM clearance, leading to lower plasma level There is no interaction between ethosuximide and oral contraceptives
Valproic acid (VPA)	Start: 5–10 mg/kg/day, given three times a day if liquid, sprinkles, or DR formulation. ER formulation can be given twice daily Increase every 7 days, by 5–10 mg/kg/day Initial goal: 15–25 mg/kg/day Serum levels: 50–100 mcg/mL	Weight gain, gastrointestinal symptoms (nausea, vomiting, diarrhea, and abdominal pain) are common Hair loss is also common and transient (Biotin 1 mg/day may prevent.) Acute hemorrhagic pancreatitis is a rare occurrence in younger patients. The symptom of severe abdominal pain should prompt measurement of lipase and amylase levels Thrombocytopenia and hepatotoxicity can occur There is higher risk of teratogenicity to the fetus, and polycystic ovarian syndrome can occur in women taking VPA	VPA is an enzyme-inhibiting drug that may inhibit the clearance of certain antiseizure drugs (e.g. phenobarbital, lamotrigine, carbamazepine) and psychotropic drugs (e.g. amitriptyline, nortriplytine, paroxetine) Of note, VPA can more than double the elimination half-life of lamotrigine (LTG), which could lead to its toxicity and adverse effects (These two are often an effective combination, however, they require a dose adjustment for LTG given this interaction.)
Lamotrigine (LTG)	[Monotherapy]* Start: 0.5 mg/kg/day, given twice daily Increase every 2 weeks, by 0.5–1 mg/kg/day Initial goal: 3–5 mg/kg/day Serum levels: 2–18 mcg/mL * If patient is taking other antiseizure drugs, especially valproic acid, a much slower titration should be observed (see LTG package insert)	Central nervous system-related side effects can be seen including dizziness, diplopia, headache, ataxia, blurred vision, nausea, vomiting, and somnolence Simple rashes can occur, however, careful assessment is required to ensure that serious and life-threatening rash (Stevens-Johnson syndrome) is not developing	LTG does not appear to significantly alter concentrations of other antiseizure drugs, however, the half-life of LTG is reduced when administered with enzyme-inducing drugs (e.g., phenytoin, phenobarbital, carbamazepine). Also the level of LTG should be closely monitored for patients taking VPA as described above

epilepticus (prolonged or continual periods of absence seizures), myoclonus or GTCs while on antiseizure medication, diffuse slowing of the wake background rhythms on the EEG (normal frequency of background waves on EEG when awake and quiet is 8–12 Hz in children of this age group), family history of GTCs in a first-degree relative, and cognitive difficulty at presentation [8]. Some children continue to have absence seizures beyond puberty. Also, it is important to note that CAE is associated with an increased risk of cognitive, behavioral, and psychiatric comorbidities. More than half of children with CAE are noted to have psychiatric diagnoses, particularly ADHD [9]. If psychiatric co-morbidities such as ADHD are present, they may be treated in the same manner as a child without absence epilepsy.

When to Refer/Admit: If the family cannot be certain if their child is responsive during their staring spells then an EEG is indicated. If they appear to be in absence status (ongoing absence seizures for over 30 min), referral to a local pediatric neurologist for urgent EEG is indicated. A child in absence status may appear confused/disoriented and slow to follow directions but will not have convulsive seizures. These symptoms may present a diagnostic challenge to the clinician and may be overlooked.

Clinical Pearls/Key Points

- The main pharmaceutical treatment options for CAE are ethosuximide, valproic acid, or lamotrigine.
- Absence seizures are not life threatening, but frequent recurrences can affect the cognitive ability of the child and potentially be associated with injury.
- The pediatrician should inquire into school performance, and if there are any concerns should refer early for psychoeducational assessment.

2 Benign Epilepsy of Childhood with Centrotemporal Spikes (BECTS)/Self-Limited Epilepsy with Centrotemporal Spikes (SeLECTS)

Introduction: Benign epilepsy of childhood with centrotemporal spikes (BECTS) is the most common focal epilepsy syndrome in childhood. It accounts for 15–25% of childhood epilepsy [10]. The seizure originates from the central (Rolandic) fissure, so it is also referred to as Rolandic epilepsy.

Epidemiology & Etiology: The age of onset of BECTS is age 3–10 years, with peak onset between 5 and 8 years of age [11].

Semiology: Most seizures of BECTS occur during sleep or during transition periods, i.e., during sleep onset or offset. Less than 10% of seizures in BECTS occur only during the wake state. Patients often present with gurgling sounds, “throaty” noises, hemifacial spasms with speech arrest and profuse salivation. Clonic seizure activity may progress from the face area to the ipsilateral upper limb, and less commonly to the lower limbs. Since seizures in BECTS are typically nocturnal, families may miss the initial partial phase of the seizure and only become aware of the

secondarily generalized tonic–clonic seizure [12]. Seizures of BECTS are brief, usually lasting no more than 2–3 min. More than half of patients with BECTS retain consciousness during the partial seizure.

Diagnostic Approach: An EEG is the gold standard to confirm the existence of centrotemporal spikes, the hallmark of BECTS (Fig. 2). These focal epileptiform discharges are dramatically increased in frequency during Non-REM (NREM) sleep. Therefore, the EEG should ideally include both awake and sleep recording, and ideally extra electrodes should be placed over the Rolandic regions (C5 & C6 electrodes).

History: Most of the seizures in BECTS occur at night (during sleep). Many families often report that they thought the child had a stroke due to the presence of hemifacial weakness and clonic jerking, and difficulty speaking during the seizure. The two most common scenarios are for the parents to be awakened by the child having a generalized seizure associated with profuse drooling; or the child awakening with an unusual sensation on one half of their face and tongue, which may progress to unilateral oropharyngeal motor activity. The child then walks to the parent's room, awakens them and points to his/her twitching face being unable to talk.

Physical Examination: Children with BECTS typically have a normal neurological examination, although some may have neurodevelopmental co-morbidities such as language, literacy, and attention impairments. Reading disability is a prominent comorbidity in BECTS. Approximately 30% of patients with BECTS will experience reading disabilities, while 50% will have language impairment [13]. The learning issues may not come to notice until high school.

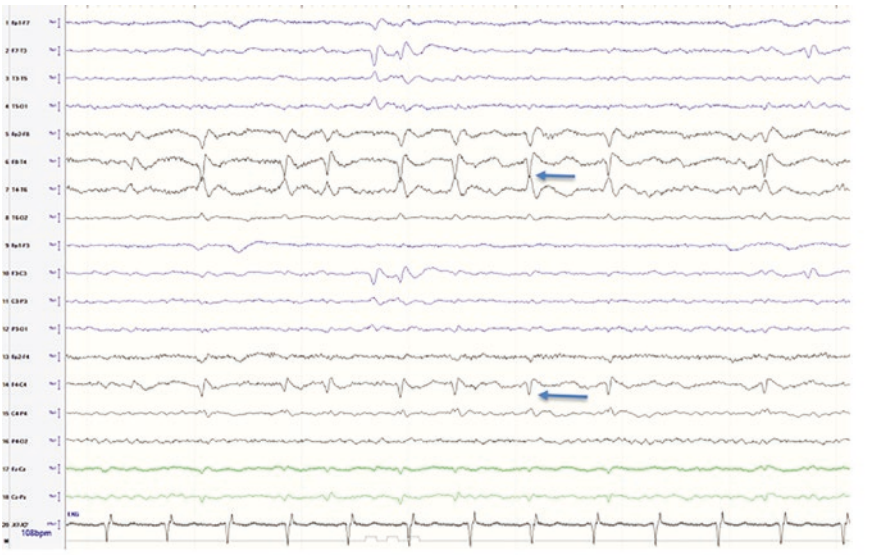

Fig. 2 BECTS. Right centrotemporal spikes predominantly in right hemisphere during NREM sleep in a 6-year-old boy

Evaluation (Laboratory Investigations/Imaging/EEG Findings): The EEG abnormality consists of centrotemporal spikes, seen either unilateral or bilateral (and if bilateral, they occur independently from each other) and the spikes increase dramatically in frequency during sleep. Additionally, the epileptiform discharges may be reactive to contralateral finger movements. As noted above, since the EEG must capture NREM sleep to establish a diagnosis of BECTS, a routine bedside EEG recording may not suffice. A longer EEG (lasting 24 h or overnight) can be helpful for some children. Laboratory studies (hematology, chemistries) or brain imaging are not indicated.

Differential Diagnosis: Any nocturnal seizure type or parasomnia can be in the differential diagnosis of BECTS. An EEG will be required to differentiate from other nocturnal seizures. Psychogenic events are typically not considered in the differential since psychogenic events usually occur during wakefulness. If there is any aspect that is not typical for BECTs, then obtaining an MRI scan of the brain is suggested to exclude a Rolandic structural abnormality (such as a brain malformation) or space occupying lesion.

Treatment/Management/Prevention: Seizures in BECTS are typically self-limited and majority of children have low seizure frequency. Treatment for BECTS has been controversial. Many experts choose to not treat after the first couple of seizures. However, discussion with the family should include the risk of seizure recurrence, costs of emergency room visits (should there be any), and social stigma. Medication treatment may be advisable if children with BECTS have recurrent seizures. In most cases, the seizures in BECTS respond well to conventional focal seizure medications (e.g., oxcarbazepine, lacosamide, levetiracetam, eslicarbazepine, or perampanel), often only requiring nighttime dosing of medication (Table 3). Seizure in BECTS can be triggered by sleep deprivation or sleep fragmentation. Knowing this, the family should exercise caution during long distance travel and during late night parties or sleepovers.

Prognosis/Outcomes: The long-term outcome of BECTS is excellent. Most children will have fewer than 10 seizures, and about 15% will only have a single seizure. More than 90% of patients show remission of seizures by the age of 12 or 13 years, and 99.8% of patients show remission by the age of 18 years [14]. However, about 25% will develop migraine headaches, some disabling enough to require preventive therapies [15].

When to Refer/Admit: School age children who present with nocturnal seizures at transition between sleep and wakefulness should be referred to a neurologist for further investigation, and have an EEG performed (capturing wake and sleep).

Clinical Pearls/Key Points

- BECTS is a common, self-limiting childhood epilepsy syndrome with an excellent remission rate.
- However, clinicians should be aware that learning difficulties may have more of an impact on the child's quality of life than the seizures.
- As a result, the child's school performance should be periodically evaluated, and if there are any concerns, referral for appropriate neuropsychological testing is important.

Table 3 Pharmaceutical options for benign epilepsy of childhood with centrotemporal spikes (BECTs)

Common medication for BECTS	Suggested dose for children	Common adverse effect	Key drug interaction
Lacosamide (LCS)	Start: 2 mg/kg/day, given twice daily Increase every week, by 2 mg/kg/day Initial goal: 8 mg/kg/day Serum levels: 2–12 mcg/mL	The most frequent adverse effects are dizziness, ataxia, nausea, vomiting, headache, diplopia, and vertigo, but LCS is generally well tolerated Cardiac conduction disturbances have been reported as rare incidents in adults. LCS should be used cautiously in patients with known conduction problems or significant cardiac disease	LCS does not appear to significantly alter concentrations of other antiseizure drugs. However, the typical adverse effects may be more frequent when LCS is used in conjunctions with other sodium channel-blocking antiseizure drugs (e.g., oxcarbazepine, lamotrigine)
Levetiracetam (LEV)	Start: 10–20 mg/kg/day, given twice daily Increase every 7 days, by 10 mg/kg/day Initial goal: 20–40 mg/kg/day Serum levels: 15–45 mcg/mL	Behavioral side effects (aggression, emotional labiality, oppositional behavior, and rarely psychosis) can occur especially in children with a history of behavioral and emotional problems	LEV has no known interactions with other antiseizure drugs LEV does not affect the efficacy of oral contraceptives
Oxcarbazepine (OXC)	Start: 5–10 mg/kg/day, given twice daily Increase every 5–7 days, by 5 mg/kg/day Initial goal: 15–20 mg/kg/day Serum levels: 15–35 mcg/mL	Dizziness, sedation, and fatigue can be seen and likely dose-related Hyponatremia may occur and be more common with children taking other medications that may affect sodium balance (e.g., diuretics, selective serotonin reuptake inhibitors (SSRIs))	OXC has mild hepatic enzyme induction OXC may reduce the efficacy of oral contraceptives

3 Juvenile Myoclonic Epilepsy (JME)

Introduction: Juvenile myoclonic epilepsy (JME) is one of the more common epilepsy syndromes, and accounts for 10–11% of all epilepsies [16, 17]. JME often begins in the teenage years with myoclonic seizures.

Epidemiology & Etiology: The typical age of onset of JME is age 8–26 years [18], with peak onset between ages 12 and 18 years [19]. There is female predominance with 65–75% of all affected individuals being girls [20, 21].

Semiology: Seizures typically present with early morning myoclonus in patients with JME. The myoclonus is often described as "shock-like" jerks predominantly seen in the shoulder and/or upper extremities, precipitated by fatigue, sleep deprivation, alcohol consumption, and menstruation. They may be asymmetric. Generalized tonic–clonic seizures (GTCs) occur in over 90% of patients with JME. Absence seizures can be also seen in approximately one-third of patients with JME [22].

Diagnostic Approach: A supportive history and the presence of characteristic interictal epileptiform discharges (e.g., generalized polyspike-and-slow wave complex, and a possible photoparoxysmal response (abnormal occurrence of epileptiform discharges on EEG in response to intermittent light stimulation) seen on the routine EEG would lead to the diagnosis of JME (Fig. 3).

History: JME is frequently unrecognized or misdiagnosed mainly because of inadequate history taking and misinterpretation of myoclonus. The patient or family may not mention the presence of early morning myoclonic seizures until specifically asked. Some patients may have predominantly unilateral jerks, which may be misinterpreted as focal seizure [23]. Inquiry about early morning jerks should be

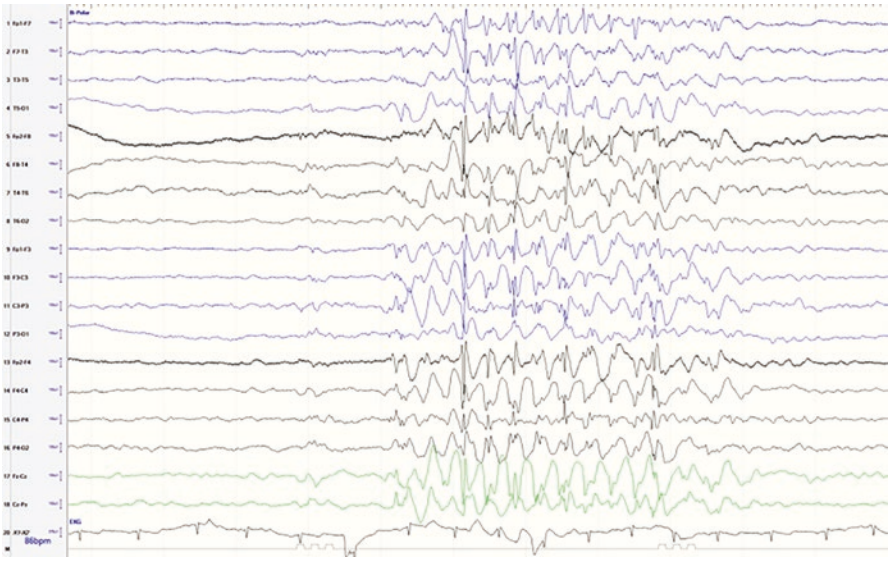

Fig. 3 Juvenile myoclonic epilepsy. The brief burst of the generalized polyspike and wave in a 16-year-old girl

performed in all teenagers with new onset GTC seizures. The clinicians can ask if they drop things or almost drop objects when getting ready in the bathroom in the morning or if they are "twitchy," and if this occurs intermittently.

Physical Examination: Adolescents with JME usually have a normal and nonfocal neurologic examination. Intelligence is typically preserved.

Evaluation (Laboratory Investigations/Imaging/EEG Findings): The interictal EEG shows normal wake and sleep background patterns. Interictal refers to the EEG pattern while the child is not experiencing active seizures. The interictal epileptiform abnormality, which is diagnostic, is an admixed 4–6 Hz frontally dominant generalized polyspike-and-slow wave complexes; however, 3–4 Hz generalized spike-and-slow-wave can also be seen [24]. Polyspike-and-wave discharges are typical EEG findings for JME, but it is not pathognomonic as they may be also seen in other genetic generalized epilepsies. Photoparoxysmal responses (Spike and wave pattern on EEG provoked by strobe lights that are utilized during the recording) with or without myoclonic jerks can be seen in 30% of patients [25]. Importantly, there may be asymmetry of the polyspike-and-slow wave discharges or focal spikes in the EEG of patients with JME, that may potentially mislead the clinician into making a diagnosis of focal seizure [26]. Laboratory studies (hematology, chemistries) or brain imaging are normal, and not usually indicated unless they have atypical EEG findings or refractory seizures.

Differential Diagnosis: Myoclonic seizure in JME can be mistaken for physiologic myoclonus, tics, tremors or clumsiness. Patients or family may consider the morning twitches unimportant or may not regard them as seizures. Also, myoclonic seizure could be misinterpreted as focal seizures since myoclonic jerks can be isolated to a single shoulder or upper extremity. Absence seizures may be mistaken for daydreaming or inattention. The pediatrician needs to ask about "jerks," "twitches," and "blank stares" in light of these characteristics of JME.

Treatment/Management/Prevention: Valproic acid has historically been the gold standard for treatment of JME, with complete seizure control in up to 86% of patients [27]. However, alternative antiseizure medications should be considered for female patients of reproductive age due to valproate's teratogenicity. Lamotrigine is highly effective with more than 80% of patients being seizure-free [28], although lamotrigine can rarely aggravate the myoclonic seizures. In addition, topiramate, levetiracetam, perampanel, lacosamide, and possibly brivaracetam are all effective for the generalized tonic–clonic seizures (Table 4). Paradoxical proconvulsant effects are occasionally seen with carbamazepine, oxcarbazepine, eslicarbazepine, and phenytoin and therefore should be avoided when of JME is suspected [2, 4, 5].

Prognosis/Outcomes: In most patients with JME, seizures can be completely controlled with appropriate antiseizure medications. The remission rate (or chances of coming off all antiseizure medications and continuing to be seizure-free) for JME varies among the different studies, but overall is very low [15]. In general, most patients with JME will require lifelong treatment due to a very high relapse rate after medication withdrawal.

When to Refer/Admit: Adolescents who presented with generalized tonic–clonic seizure should be referred to a neurologist for further investigations including

Table 4 Pharmaceutical options for juvenile myoclonic epilepsy

Common medication for JME	Maintenance does	Common adverse effect	Key drug interaction
Valproic acid	See Tables 2 and 3: Common treatments for CAE & BECTS		
Lamotrigine			
Levetiracetam			
Topiramate (TPM)	Start: 0.5–1 mg/kg/day, given twice daily Increase every 1–2 weeks, by 1–2 mg/kg/day Initial goal: 5 mg/kg/day Serum levels: 2–15 mcg/mL	Central nerve system-related side effects can be seen including ataxia, impaired concentration, confusion, dizziness, fatigue, paresthesias, somnolence, and abnormal thinking (Extended release formulation may minimize these side-effects.) Nephrolithiasis and dose-related weight loss are potential side-effects Oligohydrosis with hyperthermia has been reported, more common in young children, especially if prolonged exposure to hot climate	TPM can reduce the efficacy of oral contraceptives
Perampanel (PER)	Start: 2 mg at bedtime for 2–3 weeks, then increase to 4 mg at bedtime Increase every 2–3 weeks, by 2 mg as needed Initial goal: 4–6 mg at bedtime Serum levels: 150–500 ng/mL	Behavior changes (irritability, aggression) can occur, typically dose-related More common adverse effects are somnolence, dizziness, nausea, and ataxia	May lower the efficacy of oral contraceptives Enzyme inducing antiseizure drugs (e.g., phenytoin, phenobarbital, carbamazepine) lower serum perampanel levels

EEG. EEG and detailed clinical history including morning jerks will differentiate JME from other types of seizures.

Clinical Pearls/Key Points

- The hallmark of JME is myoclonic jerks in the morning, or a history of a generalized tonic–clonic seizure after sleep deprivation.
- If correctly diagnosed, patients with JME have a high probability of becoming seizure-free on a regimen of appropriate medication.
- However, life-long treatment may be necessary, unlike in other epilepsy syndromes of childhood.
- Counseling patients and family regarding the importance of sleep hygiene, alcohol restriction and medication compliance will also make a big impact in terms of achieving complete seizure control.

4 Lifestyle Modifications and Counseling

In general, our goal is for the child or adolescent with epilepsy to live as normal as a life as possible. "Don't let epilepsy define the child's life." This is an important message to relay to families. How successfully this can be done relates to the degree of seizure control. In principle, for the child whose seizures are controlled on medications, few modifications are needed; for those with ongoing seizures, modifications must be made based on the seizure type. As a general rule, these are "common sense" modifications, to prevent risk of injury or death if a seizure occurs during an activity. Discussing these lifestyle modifications with the family is a crucial part of seizure management. This is important for improving the child and family's quality of life; therefore, general pediatricians can provide some tips to share with patients and their family.

- Ensure that patients take medications as prescribed. The most common cause of nonadherence is forgetfulness. Patients and family may benefit from using mobile phone based medication adherence applications to alert and remind them to take the medications. If the child vomits immediately after a dose, repeat the dose.
- Get enough sleep every night with consistent schedule. Limit studying late at night and avoid use of cell phone in bed. If patients are toddlers who need a nap, avoid napping in the early evening as that can interfere with night-time sleeping habits.
- Monitor closely if patients become ill or develop a fever.
- If children need to take other medications, ask their pharmacists or doctor to be sure they will not aggravate seizures or interact with antiseizure medications.
- Always carry a medication list when going out of town.
- Find best ways to cope with stress and avoid extreme tiredness.
- If photosensitive, avoid flashing or flickering lights (e.g., disco, strobe lights). Such lights at particular frequencies may trigger a seizure for certain patients with epilepsy.
- Exercise improves overall health and can reduce seizures. The benefits of exercise outweigh the risks in the majority of patients. Ask doctors before starting a new sport or exercise to ensure the sport is safe.
- Wear a helmet during any sport or activity that could result in a head injury (e.g., riding a bike), or if patients have a seizure type that may lead to frequent falls.
- Children with epilepsy should be advised to shower instead of bathe. Swimming is not generally discouraged in children if epilepsy is well controlled. However, adequate supervision is essential, and possibly wearing a life jacket if the water is not clear.
- Patients with epilepsy should be fully immunized according to the routine schedule recommended for age.
- Alcohol and recreational drugs should be avoided.
- Record the date and the time, the duration, and the features of seizures in a seizure diary. Bring this to each doctor visit no primary or secondary prevention section?

References

1. Obeid T, Panayiotopoulos CP. Juvenile myoclonic epilepsy: a study in Saudi Arabia. Epilepsia. 1988;29:280–2.
2. Panayiotopoulos CP, Obeid T, Tahan AR. Juvenile myoclonic epilepsy: a 5-year- prospective study. Epilepsia. 1994;35:285–96.
3. Janz D. Die Epilepsien. Stuttgatt: Thime Verlag; 1969.
4. Delgado-Escueta AV, Enrile-Bacsal F. Juvenile myoclonic epilepsy of Janz. Neurology. 1984;34:285–94.
5. Asadi-Pooya AA, Emami M, Sperling MR. A clinical study of syndromes of idiopathic (genetic) generalized epilepsy. J Neurol Sci. 2013;324:113–7.
6. Camfield CS, Camfield PR. Juvenile myoclonic epilepsy 25 years after seizure onset: a population-based study. Neurology. 2009;73:1041–5.
7. Gardiner M. Genetics of idiopathic generalized epilepsies. Epilepsia. 2005;46:15–20.
8. Usui N, Kotagal P, Matsumoto R, Kellinghaus C, Lüders HO. Focal semiologic and electroencephalographic features in patients with juvenile myoclonic epilepsy. Epilepsia. 2005;46(10):1668–76.
9. Wheless JW, Kim HL. Adolescent seizures and epilepsy syndromes. Epilepsia. 2002;43(Suppl 3):33–52.
10. Janz D. Epilepsy with impulsive petit mal (juvenile myoclonic epilepsy). Acta Neurol Scand. 1985;72:449–59.
11. Shahnaz, Sher K, Abdul Sattar R. Clinical and EEG characteristics of juvenile myoclonic epilepsy. Pak J Med Sci. 2014;30(1):12–5.
12. Penry JK, Dean JC, Riela AR. Juvenile myoclonic epilepsy: long-term response to therapy. Epilepsia. 1989;30(Suppl 4):S19–23.
13. Machado RA, Garcia VF, Astencio AG, et al. Efficacy and tolerability of lamotrigine in juvenile myoclonic epilepsy in adults: a prospective, unblinded randomized controlled trial. Seizure. 2013;22:846–55.
14. Healy L, Moran M, Singhal S, et al. Relapse after treatment withdrawal of antiepileptic drugs for juvenile absence epilepsy and juvenile myoclonic epilepsy. Seizure. 2018;59:116–22.
15. Bouma P, Bovenkerk A, Westendorp R, et al. The course of benign partial epilepsy of childhood with centrotemporal spikes: a meta-analysis. Neurology. 1997;48:430–7.
16. CDC epilepsy data and statistics. https://www.cdc.gov/epilepsy/data/index.html.
17. Berg AT, Shinnar S, Levy SR, Testa FM, Smith-Rapaport S, Beckerman B. How well can epilepsy syndromes be identified at diagnosis? A reassessment 2 years after initial diagnosis. Epilepsia. 2000;41:1269–75.
18. Jallon P, Loiseau P, Loiseau J. Newly diagnosed unprovoked epileptic seizures: presentation at diagnosis in CAROLE study. Epilepsia. 2001;42:464–75.
19. Wolf P, Inoue Y. Therapeutic response of absence seizures in patients of an epilepsy clinic for adolescents and adults. J Neurol. 1984;231:225–9.
20. Suls A, Mullen SA, Weber YG, et al. Early-onset absence epilepsy caused by mutations in the glucose transporter GLUT1. Ann Neurol. 2009;66:415–9.
21. Soto-Insuga V, López RG, Losada-Del Pozo R, et al. Glut1 deficiency is a rare but treatable cause of childhood absence epilepsy with atypical features. Epilepsy Res. 2019;154:39–41.
22. Glauser TA, Cnaan A, Shinnar S, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. N Engl J Med. 2010;362:790–9.
23. Wirrell EC. Natural history of absence epilepsy in children. Can J Neurol Sci. 2003;30:184–8.
24. Caplan R, Siddarth P, Stahl L, et al. Childhood absence epilepsy: behavioral, cognitive, and linguistic comorbidities. Epilepsia. 2008;49(11):1838–46.
25. Shields DW, Carter SO. Benign epilepsy with centrotemporal spikes. Epilepsia. 2009;50:10–5.

26. Beaumanoir A, Ballis T, Varfis G, et al. Benign epilepsy of childhood with Rolandic spikes. Epilepsia. 1974;15:301–15.
27. Loiseau P, Beaussart M. The seizures of benign childhood epilepsy with Rolandic paroxysmal discharges. Epilepsia. 1973;14(4):381–9.
28. Smith A, Kavros PM, Clarke T, et al. A neurocognitive endophenotype associated with Rolandic epilepsy. Epilepsia. 2012;53(4):705–11.

Status Epilepticus

Cristina Rosado Coelho and Jun T. Park

Abbreviations

ADHD	Attention-deficit hyperactivity disorder
AEDs	Antiepileptic drugs
AES	American Epilepsy Society
cEEG	Continuous EEG
CNS	Central nervous system
CT	Computed tomography
EEG	Electroencephalograph
ES	Epileptic seziures
FIRES	Febrile infection-related epilepsy syndrome
ILAE	International League Against Epilepsy
MRI	Magnetic resonance imaging
NCSE	Nonconvulsive SE
NORSE	New-onset refractory status epilepticus
PNEE	Psychogenic nonepileptic events
RSE	Refractory status epilepticus

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SE Status epilepticus
SRSE Super-refractory status epilepticus

1 Introduction

Pediatric status epilepticus (SE) is a condition that requires urgent identification and treatment and can be associated with significant morbidity and mortality. Careful history taking, neurological examination, and tests such as lumbar puncture and electroencephalograph (EEG) may provide information about etiology and differential diagnosis.

This chapter provides an up-to-date, evidence-based approach to the acute management of children with SE. In order to better understand this condition, we will start by reviewing the definition of SE.

1.1 Definitions

The definition of *status epilepticus* has changed over the years. According to International League Against Epilepsy (ILAE) in 1981, the term was used "whenever a seizure persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur" [1]. Nevertheless, this definition did not specify the exact duration of seizures. Subsequently, a seizure duration of 60 min was proposed as a requirement for status epilepticus. Later, a shorter seizure duration of 30 min was proposed to reflect the deleterious effect of prolonged seizures on neurons [2]. Clinicians argued that the prognosis of SE was worse with increasing duration, reflecting the need for even earlier treatment. Lowenstein and associates then proposed that generalized, convulsive SE in adults and children older than 5 years should be defined as "…≥5 min of (a) continuous seizure or (b) two or more discrete seizures between which there is incomplete recovery of consciousness" [3]. Finally, in 2015, ILAE proposed a definition to encompass all types of SE and to reflect the aforementioned concepts: "SE is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point t1). It is a condition that can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures." This definition includes two operational dimensions: Time point t1 is the threshold after which the seizure is abnormally prolonged. This can lead to long-term consequences after time point t2. Time points for tonic–clonic SE (convulsive SE) are: Time (t1) = 5 min and Time (t2) = 30 min. Time points for focal SE with impaired consciousness are: Time (t1) = 10 min and Time (t2) > 60 min [4].

When SE continues for up to 2 h despite two appropriately selected and dosed antiepileptic drugs, including one benzodiazepine, this prolonged seizure is classified as refractory SE (RSE). However, if SE continues for 24 h or more after the onset of anesthetic therapy, including recurrences during the reduction or withdrawal of anesthetic agents, the term super-refractory SE (SRSE) is applied [5].

2 Epidemiology

Pediatric status epilepticus has an overall incidence of 3.86–38/100,000 per year worldwide [6–10]. The highest incidence of SE and RSE occurs in children under 2 years of age (and also in elderly), as observed in several population-based studies [6–8, 11]. A high incidence of SE in children may be partly due to the natural course of metabolic or genetic diseases, an increased susceptibility to seizures in the developing brain, and/or a higher rate of symptomatic etiologies [12]. It has been estimated that RSE occurs in 2.5–8/100,000 children per year, while SRSE occurs in about 1/100,000 children per year in the United States of America [12].

3 Etiology

Status epilepticus can occur as the first manifestation of epilepsy or other underlying medical conditions or may occur in the setting of pre-existing epilepsy. The ILAE has recently categorized the underlying causes of SE into two major categories: (a) known/symptomatic and (b) unknown/cryptogenic. The known etiologies can be further subdivided into acute, remote, and progressive[4] (Table 1).

The etiology of SE is often identified after initial investigations. However, this initial work-up may not be revealing in certain situations. As such, two clinical syndromes have been described in children recently: new-onset refractory status epilepticus (NORSE) and febrile infection-related epilepsy syndrome (FIRES).

Table 1 Categorization of etiologies in status epilepticus with examples. (Data from Trinka et al. [4])

Known (i.e., symptomatic)
Acute (e.g., stroke, intoxication, malaria, encephalitis, etc.)
Remote (e.g., posttraumatic, postencephalitic, poststroke, etc.)
Progressive (e.g., brain tumor, Lafora disease and other progressive myoclonic epilepsies, dementias)
SE in defined electroclinical syndromes
Unknown/cryptogenic

- New-onset RSE (NORSE) is a clinical presentation of new onset RSE in a patient without active epilepsy, and without a clear acute or active structural, toxic or metabolic cause. This condition is considered after initial diagnostic evaluation (investigating for causes such as acute strokes, brain masses, drug intoxication, and Herpes simplex virus type I - HSV1 encephalitis) is negative. However, NORSE includes cases with viral encephalitis (except HSV1 encephalitis) or autoimmune etiologies (found after a more thorough investigation). If no cause is found after extensive evaluation, the terms "*cryptogenic"* NORSE or NORSE of "*unknown etiology"* are used [13, 14].
- Febrile infection-related epilepsy syndrome (FIRES) is considered a subcategory of NORSE. FIRES is preceded by a febrile illness starting between 2 weeks and 24 h prior to the onset of RSE, with or without fever at the onset of SE. This condition can be diagnosed in all ages [13, 14]. SE associated with FIRES is particularly difficult to treat, and has an estimated incidence of 1/1,000,000 [15].

4 Differential Diagnosis

The recognition of status epilepticus is not always straightforward. While the diagnosis of SE after a generalized tonic–clonic seizure is easier to make, a diagnosis of nonconvulsive or subtle SE may be more challenging as the child may have no motor movements at all or movements that are not easily recognizable as seizures, e.g., lip-smacking, chewing, or eye deviation to one side. Importantly, psychogenic nonepileptic events (PNEE) must be ruled out as the clinical features may resemble epileptic seizures. Adding to the challenge of correctly diagnosing PNEE, epileptic seizures can occur in approximately 10% of patients with PNEE [16]. Thus, both types of paroxysmal events—true epilepsy and PNEE—must be clearly differentiated in a given patient so appropriate treatment of either or both entities may be instituted, thereby preventing iatrogenic complications.

Nonepileptic paroxysmal events can be divided into two major types of clinical manifestations based on presence or absence of prominent motor manifestations [17] (Table 2):

1. Episodes *with* prominent motor manifestations: rhythmic and vigorous motor activity (generalized or focal) [17]. Examples:
   (a) Convulsive syncope results from an abrupt cerebral hypoperfusion leading to brief extensor stiffening and nonsustained myoclonus or jerks. It is a *common imitator* of a generalized tonic–clonic seizure; however, it is usually of shorter duration and presents with fewer jerks [20].
   (b) Limb-shaking transient ischemic attack is a form of paroxysmal, involuntary, and jerky hypermotor activity affecting the contralateral arm, hand, or leg of the hypoperfused dorsolateral frontal and motor cortices. This has been associated with a high-grade stenosis or occlusion of the internal carotid artery, and is often accompanied by paresis and precipitated by rising or exercise [21, 22].

Table 2 Differential diagnosis for SE. (Data from Dworetzky and Bromfield [17], LaFrance Jr. et al. [18], Navarro et al. [19]. This is a nonexhaustive list (see text for more detailed information))

Prominent motor manifestations (generalized or focal type)
Vascular disorders: e.g., convulsive syncope, transient ischemic attack
PNEE
Structural lesions: e.g., decerebrate, decorticate posturing
Movement disorders: e.g., tremor, dystonia, chorea, myoclonus, tic disorder, hemifacial spasm
Sleep disorders: e.g., periodic limb movements of sleep, restless leg syndromes
Without prominent motor manifestations
Akinetic episodes: e.g., Locked-in state, akinetic mutism, catatonia
Atonic episodes: e.g., Periodic paralysis, cataplexy, vertebrobasilar insufficiency, syncope (cardiac, vagal, hypovolemic), postictal state
Cognitive-behavioral imitators: e.g., postictal state, encephalopathy, transient global amnesia, dementia, drug or alcohol intoxication, psychiatric and behavioral episodes, sleep disorders (confusional arousals, Kleine–Levin syndrome, nocturnal enuresis, sleep terrors)
Aura continua (without impairment of consciousness): e.g., migraine, psychiatric disorders (anxiety, panic attack, depression, psychosis), vestibular pathology
PNEE

PNEE psychogenic nonepileptic events, *SE* status epilepticus

(c) PNEE may present with features that provide clues to help differentiate from epileptic seizures. PNEE may have waxing and waning features with asynchronous movements, and are usually more prolonged than epileptic seizures. Side to side head (similar to "no-no") or body movements in "convulsive" events are also suggestive of PNEE. Table 3 summarizes the clinical characteristics and semiology that may help distinguish both conditions. These elements have higher diagnostic value when used *in combination*, and are less reliable *as individual elements* [18, 19, 23]. PNEEs are associated with psychologic causes, and the use of antiepileptic drugs (AEDs) is not indicated. Various stressors have been identified in children with PNEE, including difficulties in school, family discord, and interpersonal conflicts such as bullying and physical abuse. Sexual abuse was less frequently identified. Depression is frequently associated with PNEE in adolescents, while cognitive dysfunction and comorbid epilepsy are commonly associated with PNEE in prepubescent individuals [24].

(d) Different type of movement disorders can be mistaken for a generalized SE, particularly when there is a change in the state of consciousness. Clinical history, characteristics of movements, combined with EEG recording can help differentiate movement disorders from epileptic seizures [19].

2. Episodes *without* prominent motor manifestations: akinetic, atonic, cognitive-behavioral types, imitators of aura continua (without impairment of consciousness), and PNEE [17, 19]. Examples include:

(a) Akinetic episodes: locked-in state, catatonia [17];

Table 3 Clinical features of psychogenic nonepileptic events and epileptic seizures. (Data from Avbersek et al. [23], LaFrance Jr. et al. [18], and Navarro et al. [19])

Features	PNEE	Epileptic seizures
Occurrence during sleep	No	Yes
Occurrence during "pseudosleep"	Yes	No
Waxing and waning/ fluctuation	Yes	No
Duration	<1–150 min [23]	If convulsive seizure usually ≤ 2 min (when SE, longer duration) [18, 23]
Asynchronous movements	Usually present (44–96% of patients) [23]	Not usually present (5–7.4% of ES, with higher percentage in frontal lobe seizures) [23]
Side to side head or body movement in convulsive events	Yes	No
Closed eyes and/or jaw clenching during tonic phase	Yes	No
Ictal stuttering	Yes	No
Lateral tongue bites	No	Yes
Stertorous breathing	No	Yes
Postictal confusion	Not usually present (13–16% of patients) [23]	When present favors ES (61–100% of patients) [18, 23]

ES epileptic seizures, *min* minutes, *PNEE* psychogenic nonepileptic events, *SE* status epilepticus

(b) Atonic seizures typically occur in epileptic syndromes, such as Lennox–Gastaut syndrome and Doose syndrome. However, nonepileptic atonic events can manifest as sudden collapse, loss of tone, or prolonged weakness.

Hypokalemic or hyperkalemic periodic paralysis can be imitators. These are hereditary conditions characterized by episodes of muscle weakness, mostly associated with alteration in serum potassium levels.

Cataplexy (sudden loss of muscle tone, often following strong emotions), which can be prolonged, is usually associated with other symptoms that suggest the diagnosis of narcolepsy.

A sudden "drop attack" due to vertebrobasilar insufficiency or stroke can also mimic atonic seizure. However, associated brainstem symptoms and abnormalities on MRI will help differentiate epileptic versus nonepileptic atonia. An important caveat should be mentioned: patients may lie still in postictal phase of a tonic–clonic seizure. Therefore, if the beginning of the episode was not witnessed, epileptic disorder remains a possibility [17, 18].

(c) Cognitive-behavioral mimics: Encephalopathies of any cause (for instance, metabolic or toxic), characterized by changes in the state of consciousness with different degrees of severity, from mild somnolence to deep coma (sometimes associated with myoclonic manifestations), can be difficult to distinguish from nonconvulsive SE (NCSE). EEG may not always help distinguish the two conditions [17, 19].

Psychiatric and behavioral episodes may also mimic SE. Temper tantrums with a sudden behavioral change may be quite prolonged. If an episode of inattention is prolonged in a child with attention-deficit hyperactivity disorder (ADHD), it may also resemble SE. These children may also have epilepsy as a comorbidity.

Self-stimulation or stereotyped behaviors in young children and in children with intellectual disability can be associated with a dazed appearance, with rocking, swaying, or chewing movements.

Episodes of rage attacks and impulse control disorder can also be imitators of SE, although these behavioral episodes are typically more goal-oriented and distinguished by a specific "trigger" event [17].

(d) Epileptic aura continua (without impairment of consciousness) associated with persistent neurologic symptoms can be a manifestation of SE. An epileptic aura is considered a seizure without impairment of consciousness and involves subjective sensory or psychic phenomena [25]. However, *nonepileptic* aura continua can also be found in other conditions manifesting as the following symptoms:

- Paresthesias (in cervical spinal cord disease, peripheral neuropathy, or hyperventilation)
- Olfactory changes (in head trauma affecting orbitofrontal regions, in nasal pathology, migraine, side-effects of medications, etc.)
- Visual hallucinations (in migraine, toxic-metabolic states, drugs, or as a "release phenomenon" in occipital stroke or ocular disorders)
- Auditory hallucinations (in psychosis), vertigo (frequently seen in vestibular pathology)
- Prolonged emotional and psychic phenomena (in anxiety, panic attacks, depression) [17, 19].

(e) PNEE: "swoon," "catatonic," or "pseudosyncope" events lasting more than a minute should raise suspicion for PNEE. These patients may fall down and lie still, with eyes closed and exhibit unresponsiveness. Vasovagal or cardiac syncope is also a possible cause of this paroxysmal event [17, 18].

5 Diagnostic Approach

5.1 History

When a diagnosis of status epilepticus is considered, obtaining history should not delay initial evaluation, management, and treatment. Details obtained from a caregiver or parent may provide clues to the etiology of SE. The following information should be sought during interview of family members or caretakers:

- Preceding event, illness, fever, toxic exposure, or behavior of the child. Duration of SE, how it started (involvement of specific body parts, type of manifestations), postictal neurologic deficit, any prehospital treatment including use of rescue medications at home.
- Presence of prior epileptic seizures or family history of seizures.
- Presence of risk factors and relevant medical history: birth history and development delay, past central nervous system (CNS) infection or other CNS disease (for instance, neurocutaneous syndrome), severe metabolic disturbance, past (or present) traumatic brain injury, previous neurosurgical procedures, chronic and recent medication use, or change in dose or type of antiepileptic drug [26].

5.2 Physical Examination

When a child with SE presents to the emergency room, a brief and directed physical examination assessing respiratory and circulatory status is paramount. After clinical stabilization, a more thorough physical and neurologic examination should be performed, looking for fever, meningeal signs, presence of skin changes, petechiae or herpetic vesicles, evidence of increased intracranial pressure, weak pupillary response, and changes or asymmetry in neurological examination [26]. In addition, when the physician is able to observe a seizure, seizure semiology should be carefully noted. ILAE has recently proposed a new classification that considers the presence or absence of prominent motor manifestations, and the degree of impaired consciousness [4] (Table 4).

5.3 Evaluation (Laboratory Investigations/Imaging/ Other Tests)

The management of status epilepticus should proceed in parallel to (if not already done) evaluation and treatment of the underlying etiology and administration of AEDs should not be delayed in order to perform diagnostic testing. There are several types of diagnostic evaluations; some are indicated for all children, and others are guided by specific clinical scenarios and suspected etiology (Table 5). Laboratory studies that should be universally considered include bedside fingerstick blood glucose, serum glucose, complete blood count with differential, serum electrolytes, calcium, and magnesium [27]. Other extensive laboratory studies may be considered depending on clinical presentation (Table 5). If subclinical SE is suspected, an EEG should be performed without delay.

Computed tomography (CT) may be considered in the emergency department; however, magnetic resonance imaging (MRI) is superior in identifying the etiology of seizure [31].

Table 4 Classification of status epilepticus, according to ILAE. (Data from Trinka et al. [4])

With prominent motor manifestations	Without prominent motor manifestations (i.e., NCSE)
Convulsive SE (CSE, synonym: tonic–clonic SE)	**NCSE with coma (including so-called "subtle" SE)**
Generalized convulsive	**NCSE without coma**
Focal onset evolving into bilateral CSE	Generalized
Unknown whether focal or generalized	Typical absence status
Myoclonic SE (prominent epileptic myoclonic jerks)	Atypical absence status
With coma	Myoclonic absence status
Without coma	Focal
Focal motor	Without impairment of consciousness (aura continua with autonomic, sensory, visual, olfactory, gustatory, emotional/psychic/experiential, or auditory symptoms)
Repeated focal motor seizures (Jacksonian)	
Epilepsia partialis continua (EPC)	
Adversive status	
Oculoclonic status	Aphasic status
Ictal paresis (i.e., focal inhibitory SE)	With impaired consciousness
Tonic status	Unknown whether focal or generalized
Hyperkinetic SE	Autonomic SE

CSE convulsive status epilepticus, *EPC* Epilepsia partialis continua, *PNEE* psychogenic nonepileptic events, *NCSE* nonconvulsive status epilepticus, *SE* status epilepticus

A lumbar puncture should be considered when a CNS infection is suspected, particularly in children presenting with SE, who are less than 2 years old, immunosuppressed, or have received recent antibiotics [31].

If PNEE is suspected, continuous video-EEG can clarify the diagnosis [18]. Recording the events on video-EEG and finding normal awake background activity associated with the events will help support the diagnosis PNEE [18]. Reaching a correct diagnosis of PNEE helps avoid iatrogenic complications, which can result from unnecessary treatment with AEDs or pharmacologically induced comatose state. It should be noted that a patient who has had a generalized or focal SE may have abnormally slow background or epileptiform discharges, at least for a few hours after the event [18]. These abnormalities on EEG should not be mistaken as being indicative of active seizures. It may help to ask the neurologist interpreting the EEG whether the EEG discharges are indicative of active seizures or not, and whether there is a clinical correlate when motor movements are observed by the nursing staff or physicians. In other words, an abnormal EEG in the setting of altered level of consciousness may or may not be diagnostic of SE. Conversely, a child with certain forms of SE may have a normal EEG. For instance, in *epilepsia*

Table 5 Evaluation studies in children with status epilepticus. (Data from Brophy et al. [27], Yoong et al. [28], Wilfong [29] and Riviello et al. [30])

When a given study should be performed	Type of evaluation studies	Comments
In all patients	Complete blood count, fingerstick and serum glucose, serum electrolytes, serum calcium, and magnesium	–
	EEG	Helpful when PNEE or NCSE are suspected, to guide treatment
Children with epilepsy, already taking AEDs	Serum AEDs levels	An evidence based review showed that 32% of children with epilepsy presenting with SE, had subtherapeutic levels [30]
If SE is the first presentation of epilepsy or if recovery not following the expected course (e.g., RSE, or new/persisting neurological abnormalities) [28]	Brain imaging (CT or MRI)	Allows to exclude anatomical abnormalities, intracranial lesions, cerebral edema
Febrile children	Cultures and serology for bacterial, viral, or fungal infections	–
	Lumbar puncture	After excluding increased intracranial pressure (with brain imaging)
Children with suspected intoxication	Serum and urine toxicology screens (cocaine, amphetamines, tricyclic antidepressants, alcohol, etc.)	–
	Arterial blood gas and pH	
	ECG	
Infants and children at risk for inborn errors of metabolism	Arterial blood gas and pH	Consider discuss with a pediatric neurologist or geneticist to perform additional metabolic studies
	Liver function and coagulation tests	
	Serum ammonia, lactate, pyruvate, amino and urine organic acid levels	
RSE or SRSE	Consider all the above	–
	Autoimmune evaluation (complement levels, antinuclear antibodies, etc.)	
	Antibodies for immune-mediated encephalitis (paraneoplastic or not): neuronal and ion channels antibodies	
	Consider genetic testing	Consider discuss with a pediatric neurologist or geneticist to perform additional metabolic studies

AEDs antiepileptic drugs, *CT* computed tomography, *ECG* electrocardiogram, *EEG* electroencephalograph, *MRI* magnetic resonance imaging, *PNEE* psychogenic nonepileptic events, *RSE* refractory status epilepticus, *SE* status epilepticus, *SRSE* super-refractory status epilepticus

partialis continua, a low percentage of patients (up to 17%) may have normal EEG due to an activation of a small cortical area insufficient for scalp EEG to detect, or due to a dipole oriented or localized in a deeper structure [32–34].

Continuous EEG (cEEG) monitoring is indicated for patients who present with SE [35, 36]. Studies in critically ill children who undergo cEEG showed that 28–33% had electrographic seizures, often without clinical correlate, and frequently had electrographic status epilepticus. Previous diagnosis of epilepsy, younger age, clinical seizures prior to EEG monitoring, presence of an abnormal EEG background, or interictal epileptiform discharges were found to be risk factors for electrographic seizures in critically ill children [36–38]. EEG can help determine whether there are focal or generalized epileptiform abnormalities to guide evaluation and treatment [30].

6 Treatment/Management

The goals of treating status epilepticus are to identify and correct precipitating factors, stop seizures, while maintaining hemodynamic and respiratory stability. Convulsive status epilepticus (CSE) is considered life threatening and a medical emergency.

The American Epilepsy Society has developed important guidelines for the management and treatment of CSE [39]. This algorithm (Table 6) comprises three phases that should occur in specific points in time during treatment.

- Stabilization phase (0–5 min after seizure activity starts): During this phase an initial assessment and monitoring, along with first aid to control seizure activity, should be given.
- Initial therapy phase (5–20 min of seizure activity): If a convulsive seizure persists after 5 min, this is considered a convulsive SE, and it requires medical intervention. The initial therapy of choice is a benzodiazepine. Specifically, intramuscular (IM) midazolam, intravenous (IV) lorazepam, or IV diazepam. The choice can be guided by the presence or absence of IV access and availability of medication.
- Second-therapy phase (20–40 min of seizure activity): If seizure duration reaches 20 min, a nonbenzodiazepine AED should be given [39]. However, the Neurocritical Care Society has suggested even earlier treatment initiation, with administration of a benzodiazepine within 5 min of seizure onset followed by a swift escalation therapy to a second-line AED, if seizure persist for longer than 10 min (Table 6) [27]. The failure of initial treatment can manifest as ongoing convulsions or intermittent seizures, or not regaining consciousness between seizures. Different options are available, including intravenous fosphenytoin, valproic acid, and levetiracetam. There is no clear evidence that any one of these options is better than the others. Two studies compared levetiracetam versus phenytoin as a second-line treatment after benzodiazepine in pediatric CSE, and

Table 6 Proposed management algorithm for status epilepticus combining different guidelines and expert opinions. (Data from Glauser et al. [39], Brophy et al. [27], and Singh et al. [40])

Stabilization phase (0–5 min)
1. **Stabilize patient (airway, breathing, circulation, disability**—physical and neurological examination)
2. **Time seizure from its onset, brief history taking,** and **monitor vital signs**
3. **Assess oxygenation, give oxygen** (nasal cannula/mask)**, consider intubation if respiratory assistance needed**
4. **Initiate ECG monitoring**
5. **Fingerstick blood glucose.** If glucose <60 mg/dL, then 2 mL/kg D25W IV (if children ≥ 2 years) or 4 mL/kg D12.5 W (if children <2 years). Consider give thiamine before
6. **Attempt IV access and collect hematology, electrolytes,** and if appropriate **toxicology screen and AEDs levels**
Initial therapy phase (5–20 min) (or consider a benzodiazepine in <5 min)
Choose one of the following three equivalent first-line options:
(a) **IM Midazolam** (0.2 mg/kg, max 10 mg) **OR**
(b) **IV Lorazepam** (0.1 mg/kg, max 4 mg/dose, can repeat once) **OR**
(c) **IV Diazepam** (0.15–0.2 mg/kg, max 10 mg, can repeat once)
If none of the previous options are available, choose one of the following:
(a) **IV phenobarbital** (15–20 mg/kg) **OR**
(b) **Rectal Diazepam** (0.2–0.5 mg/kg, max 20 mg) **OR**
(c) **Intranasal midazolam** (0.2 mg/kg, max 10 mg)**, buccal midazolam** (0.2–0.5 mg/kg, max 10 mg)
Second-therapy phase (20–40 min) (or consider earlier, after 10 min of seizure activity)
Choose one of the following second line options, and give as a single dose:
(a) **IV Fosphenytoin** 15–20 mg PE/kg (max dose of 1500 mg, can repeat 5–10 mg PE/kg if needed) **OR**
(b) **IV Valproic acid** 20–40 mg/kg (max dose 3000 mg, can repeat 20 mg/kg if needed) **OR**
(c) **IV Levetiracetam** 20–60 mg/kg (max dose 4500 mg, can repeat 30 mg/kg if needed)
If none of the options above are available, choose IV phenobarbital 15–20 mg/kg (if not given already) (may repeat addition boluses of 5–10 mg/kg if needed)
(a) **IV Fosphenytoin** 15–20 mg/kg (max dose of 1500 mg) **OR**
Third-therapy phase (>40 min)
(a) **Repeat the second-therapy phase AED mentioned** (as indicated in brackets) **or give a different one if seizure continues AND/OR**
(b) **Anesthetic agents (ideally in association with cEEG):**
Midazolam (load with 0.2 mg/kg at 2 mg/min infusion, max 2 mg/kg/h) **OR**
Pentobarbital (load with 5 mg/kg at 50 mg/min, max 5 mg/kg/h) **OR**
Thiopental (load with 2–7 mg/kg at 50 mg/min, max 5 mg/kg/h) **OR**
Propofol (load with 1–2 mg/kg/h at 20 mcg/kg/min, caution with doses >65 mcg/kg/min and prolonged application due to propofol infusion syndrome) **OR**
Ketamine (load with 1–3 mg/kg, max 4.5 mg/kg, max 100 mcg/kg/min)

AEDs antiepileptic drugs, *ECG* electrocardiogram, *cEEG* continuous electroencephalograph, *IM* intramuscular, *IV* intravenous

none of them was found superior to the other [41, 42]. The ESETT (Established Status Epilepticus Treatment Trial) recently published their results. This trial randomized patients >2 years of age to fosphenytoin 20 mg PE/kg (maximum 1500 mg PE), valproate 40 mg/kg (maximum 3000 mg), and levetiracetam 60 mg/kg (maximum 4500 mg). They found no significant difference regarding efficacy, with similar responses to fosphenytoin, valproate, and levetiracetam. It was found that endotracheal intubation of children occurred more frequently in the fosphenytoin group [43]. IV phenobarbital is a reasonable second-therapy alternative when none of the previous recommended AEDs are available [39] (Table 7).

Table 7 First- and second-therapy phase, and other AEDs available to use in pediatric status epilepticus. (Data from Brophy et al. [27], Singh et al. [40], Glauser et al. [39], and Abend and Loddenkemper [44])

Drug	Dose	Serious adverse effects	Mechanism of action	Considerations
Diazepam	• 0.15 mg/kg, IV up to 10 mg/dose (may repeat in 5 min) • 2–5 years: 0.5 mg/kg, rectal • 6–11 years: 0.3 mg/kg, rectal • >12 years: 0.2 mg/kg, rectal (max dose of 20 mg)	• Hypotension • Respiratory depression • Sedation • Dizziness	• Positive allosteric modulator of $GABA_A$ receptor	• Fast penetration in BBB (rapid onset of action)
Lorazepam	• 0.1 mg/kg IV up to 4 mg/dose (may repeat once in 5–10 min)			• Slower onset of action and longer duration
Midazolam	• 0.2 mg/kg, IM (max dose of 10 mg) • 0.2 mg/kg, IN (max dose of 10 mg) • 0.2–0.5 mg/kg, buccal (max dose of 10 mg)			• Short half-life, after a single dose (>with infusion) • Renal elimination • Metabolized by CYT P450

(continued)

Table 7 (continued)

Drug	Dose	Serious adverse effects	Mechanism of action	Considerations
Levetiracetam	• 20–60 mg/kg, IV (max dose of 4500 mg) (may repeat 30 mg/kg if needed)	• Well tolerated	• Binding to SV2A (modulates synaptic neurotransmitter release)	• Minimal drug interactions • Not hepatic metabolized
Valproate	• 20–40 mg/kg, IV (max dose of 3000 mg) (pediatric dose 1.5–3 mg/kg/min, may repeat 20 mg/kg if needed)	• Hyperammonemia • Pancreatitis • Hepatotoxicity • Thrombocytopenia • Use with caution in patients with mitochondrial disease	• Sodium channel inactivation • Attenuates calcium mediated currents • Increases GABA	• CYT P450 inhibitor (several interactions)
Fosphenytoin	• 15–20 mg/kg IV (max dose of 1500 mg) (may give additional dose of 5–10 mg/kg 10 min after loading infusion) (up to 150 mg PE/min but pediatric dose up to 3 mg/kg/min)	• Hypotension • Arrhythmias • Bradycardia	• Blocks voltage gated sodium channels	• CYT P450 inducer (several interactions)
Phenytoin	• 15–20 mg/kg IV (max dose of 1500 mg) (may give additional dose of 5–10 mg/kg 10 min after loading infusion) (not to exceed 50 mg/min, but pediatric dose up to 1 mg/kg/min)	• Hypotension • Arrhythmias • Bradycardia • Purple-glove syndrome		• CYT P450 inducer (several interactions) • Cardiac and blood pressure monitoring needed

Table 7 (continued)

Drug	Dose	Serious adverse effects	Mechanism of action	Considerations
Phenobarbital	• 20 mg/kg IV (may give an additional 5–10 mg/kg 10 min after loading infusion) (50 mg/min IV)	• Hypotension • Respiratory depression	• Barbiturate that enhances GABA-mediated inhibition	• Strong enzyme inducer
Topiramate	• No pediatric dose is established • Start with 1 mg/kg/day divided twice a day • Case series described initial doses of 5–10 mg/kg/day that were escalated to doses of about 25 mg/kg/day	• Metabolic acidosis • Nephrolithiasis • Anhidrosis	• Enhances GABA-mediated inhibition • Inhibits sodium, potassium, calcium (L-type channels) • Decrease glutamatergic transmission • Inhibition of carbonic anhydrase	• No IV formulation • Caution when combining with valproic acid (>risk of hyperammonemic encephalopathy)
Lacosamide	• No pediatric dose is established • Typically dose of 2–4 mg/kg/day is used, and some studies used higher doses (up to 8–10 mg/kg/day)	• PR prolongation (caution in AV block, atrial fibrillation) • Hypotension	• Enhances slow inactivation of voltage-dependent sodium channels	• Cardiac monitoring is needed • Minimal drug interactions • Limited experience in SE treatment

AEDs antiepileptic drugs, *CYT* cytochrome, *IM* intramuscular, *IN* intranasal, *IV* intravenous, *NG* nasogastric, *PO* by mouth

- Third-therapy phase (>40 min of seizure activity): There is no clear evidence to guide this phase. One may consider repeating the same medications from second-therapy phase. Another alternative is to give anesthetic agents, such as thiopental, midazolam, pentobarbital, or propofol (ideally while the patient is being monitored on cEEG) [27, 39, 40] (Table 8).

While the previous algorithm provides guidance in the first minutes/hours of status epilepticus, other type of therapies may be considered if seizures continue.

1. Immunomodulatory therapies: During last few years, there has been an increasing interest in immune-mediated encephalitis with several recognized antineuronal antibodies. Due to the discovery of an inflammatory role in seizure generation and propagation, different immunotherapies have been used with some success and those may be considered in RSE, particularly in cases of NORSE or even

Table 8 Anesthetic agents used in third-phase therapy or in refractory or super refractory pediatric status epilepticus. (Data from Brophy et al. [27], Singh et al. [40], and Glauser et al. [39])

Drug	Loading dose (rate of administration) CI: maintenance dose and rate Breakthrough SE management	Serious adverse effects	Mechanism of action	Considerations
Midazolam	• Loading: 0.2 mg/kg (2 mg/min infusion) • CI: 0.05–2 mg/kg/h • Breakthrough SE: 0.1–0.2 mg/kg bolus, titrate rate with EEG in steps of 0.05–0.1 mg/kg/h in time intervals as clinically indicated (e.g., every 3–4 h)	• Hypotension • Respiratory depression (requires intubation)	• Positive allosteric modulator of $GABA_A$ receptor	• Tachyphylaxis with prolonged infusion may necessitate progressively higher doses • Active metabolite is renally eliminated • CYP 3A4 substrate
Pentobarbital	• Loading: 5 mg/kg (≤ 50 mg/min) • CI: 0.5–5 mg/kg/h • Breakthrough SE: 5 mg/kg bolus, titrate rate with EEG in steps of 0.5–1 mg/kg/h in time intervals as clinically indicated (e.g., every 12 h)	• Hypotension • Respiratory depression (requires intubation) • Paralytic ileus • Cardiac depression	• Activation of GABA receptors • Inhibition of NMDA receptors • Change in conductance of chloride, potassium, and calcium channels	• Drug accumulation with prolonged use • CYP 2A6 enzyme inducer • Can exacerbate porphyria • IV contains propylene glycol

Table 8 (continued)

Drug	Loading dose (rate of administration) CI: maintenance dose and rate Breakthrough SE management	Serious adverse effects	Mechanism of action	Considerations
Propofol	• Loading: 1–2 mg/kg (20 mcg/kg/min) • CI: 20–200 mcg/kg/min • Peds: caution with doses >65 mcg/kg/min, for >48 h, contraindicated in young children • Breakthrough SE: increase CI by 5–10 mcg/kg/min stepwise every 5 min or 1 mg/kg bolus plus CI titration	• Hypotension • Cardiac, respiratory depression • Reduces intracranial pressure • Rhabdomyolysis and metabolic acidosis • Renal failure with propofol infusion syndrome (associated with high mortality)	• Chloride channel conductance • Enhances $GABA_A$ receptor	• Relative contraindication in children and mitochondrial disorders or hypertriglyceridemia, as it may cause propofol infusion syndrome
Thiopental	• Loading: 2–7 mg/kg (≤ 50 mg/min) • CI: 0.5–5 mg/kg/h • Breakthrough SE: 1–2 mg/kg bolus, titrate rate with EEG in steps of 0.5–1 mg/kg/h in time intervals as clinically indicated (e.g., every 12 h)	• Hypotension • Respiratory depression (requires intubation) • Cardiac depression	• Same as pentobarbital	• Nonlinear metabolism • Long half-life (11–36 h) • Autoinduction of its metabolism • Several drug interactions
Ketamine	• Loading: 1–3 mg/kg every 3–5 min until seizures stop • CI: 10–100 mcg/kg/h • Breakthrough SE: 1–2 mg/kg bolus, with titration in steps of 5–10 mcg/kg/min with EEG as clinically indicated up to a maximum of 100 mcg/kg/min	• Sympathetic response leading to hypertension • Possible increased intracranial pressure • Agitation, confusion, psychosis after stopping ketamine	• Noncompetitive NMDA glutamate receptor antagonist	• Fast onset, extensive distribution • Elimination half-life 2–3 h • Metabolized by CYT P450 into norketamine (active metabolite)

CI continuous infusion, *CYT* cytochrome, *EEG* electroencephalograph

FIRES (listed below) [13, 14, 40]. Some experts suggest a trial of these treatments despite not having a documented immune-mediated etiology for RSE (negative antineuronal antibodies tested), particularly in cases of NORSE and when several treatments have already failed [13, 14].

(a) IV methylprednisolone (in children: 10–30 mg/kg per day, maximum dose of 1000 mg/day, for 3–5 days, sometimes followed by tapering dose of oral prednisone 1 mg/kg/day potentially over a period of 2 weeks
(b) IV Immunoglobulin (1.2–2 g/kg over 3–5 days or 0.4 g/kg per day for 5 days)
(c) Plasmapheresis (5 exchanges, in alternating days)
(d) Other therapies including rituximab, azathioprine, tacrolimus, or cyclophosphamide

2. Ketogenic diet is an established treatment for drug-resistant epilepsy. The diet is high-fat, low-carbohydrate, with adequate protein intake, mimicking fasting state, and induces ketosis. It also has a role in reducing inflammation. Different case series showed that SRSE resolved in a significant portion of patients (20–90%) within 7 days after diet initiation, allowing to later wean off anesthetic infusions. It is probably under-utilized [40, 45–48].
3. Therapeutic hypothermia: While animal studies have shown a neuroprotective and antiepileptic role of therapeutic hypothermia [49], a recent multicenter trial, HYBERNATUS, found the efficacy of therapeutic hypothermia to be no better than placebo for RSE/SRSE. This study assigned 270 patients with convulsive RSE receiving mechanical ventilation to hypothermia treatment (32°–34°C for 24 hours). The findings of the study raised concerns about its adverse effects, as there was higher rate of aspiration pneumonia in the hypothermia group than in the control group [50].

7 Prognosis/Outcomes

Status epilepticus can be fatal or have acute or long-term consequences. Short-term mortality associated with SE in children ranges from 2.7 to 5.2% of cases in high income countries [7, 51]. However, this percentage is higher in other regions, including sub-Saharan Africa (15%) [52]. Delayed initial treatment and symptomatic etiology are associated with higher mortality rates [7, 51, 52].

According to a systematic review of childhood convulsive status epilepticus (CSE), long-term mortality rate has been found to be 5.4–17% with 3% at 10 years' follow-up. However, a more recent study estimates that after the acute hospitalization, 8% will die over the next 8.5 years (excluding prolonged febrile seizures) [53]. The same study found that the presence of pre-existing clinically significant neurological impairments at the time of convulsive status epilepticus is the main risk factor for mortality within 8 years after the acute episode, supporting a role for the underlying condition in the determination of prognosis [53].

In addition, immediate complications of SE can be severe and include respiratory failure, tachycardia, hypo or hypertension, metabolic and/or respiratory acidemia, rhabdomyolysis, renal failure, electrolyte disturbances, and increased intracranial pressure. These complications can further interfere with oxygen and substrate supply, resulting in cerebral edema [12].

Outcomes regarding the time to treatment were recently studied in a prospective, observational cohort study of 218 children with refractory CSE. The cohort was divided into two groups: (1) patients who received the first-line benzodiazepine treatment in less than 10 min and (2) patients who received the first-line benzodiazepine treatment 10 or more minutes after seizure onset. The results showed that a first-line benzodiazepine treatment given after 10 min (instead of within 10 min) is independently associated with use of continuous infusions, longer convulsion duration, more frequent hypotension, and a higher frequency of death [54].

Neurologic disability after SE include focal motor deficits (paresis, imbalance, uncoordinated movements, gait or limb ataxia, nystagmus, chorea, dystonia) and cognitive-behavioral disorders. One study found that patients with symptomatic etiology had greater odds of having cognitive and behavioral problems compared with patients with unknown etiology [55]. An 8-year follow-up study in children after CSE identified 37% with behavioral problems and 28% with psychiatric disorder, including autism, attention deficit disorder, and developmental coordination disorder [56].

The estimated overall recurrence of CSE is 20% after 4 years [51]. Recurrence is almost three times more likely if the child had a previous neurological abnormality [7]. Etiology was the most important risk factor, particularly symptomatic etiologies (recurrence risk for SE: 67% for progressive, >44% for remote symptomatic, and >11% for acute symptomatic etiologies) [12].

The risk of subsequent epilepsy has been variably reported between studies, from 13 to 25 to 74% [51, 57]. Recent work showed a cumulative incidence, 9 years post-CSE, of 25% with 89% emerging within 18 months post-CSE. The cumulative incidence of epilepsy is lower in previously neurologically healthy children post-prolonged febrile illness (14%) and in survivors of acute symptomatic CSE (13%), than in children with remote symptomatic CSE (46%). Etiology is the main predictor of the risk of developing subsequent epilepsy, and this risk is not related to the duration of SE [57].

8 When to Refer or Admit

Consider referring to a hospital with pediatric ICU:

- When seizure activity cannot be controlled with first-line treatment using benzodiazepines
- After seizure is controlled in a child with a history of previous afebrile seizures [26]
- When inborn error of metabolism is suspected in a child with prolonged seizures

Always admit if:

- A child is in convulsive status epilepticus when you suspect nonconvulsive status epilepticus
- After an epileptic seizure, the child is unresponsive or did not return to his/her baseline [26]

9 Prevention

Small daily routines may help to prevent status epilepticus (SE), such as taking medicine(s) on time, not forgetting any doses, avoiding alcohol or drug abuse, keeping regular sleep schedule, and teaching caregivers to use rescue medicine, if necessary. Education of caregivers/parents/school personnel and friends who may be present in the vicinity, when the child has a seizure is important. The following information should be reviewed with them as to when immediate medical care should be sought: a seizure that lasts more than 5 min, having more than 1 seizure within a 5-min period, or not recovering consciousness between seizures.

More recently, closed loop seizure detection-treatment systems are being developed. The combination of seizure detection sensors based on EEG and extra-cerebral signals are being integrated into portable devices in order to facilitate seizure detection in ambulatory settings. Since these can provide active feedback, if a seizure is detected, the caregiver may be informed through an interface application. This may lead to an intervention or corrective response (abortive pharmacotherapy, neurostimulation, or even acute seizure care and transport to an emergency room, if needed).

10 Clinical Pearls/Key Points

- Status epilepticus is a neurologic emergency, requiring urgent recognition and treatment. It may be associated with significant morbidity and mortality.
- Operational dimensions of the definition of SE: Time point t1 indicates when treatment should be initiated, and time point t2 indicates when long-term consequences may appear. For tonic–clonic SE (convulsive SE), Time (t1) = 5 min, while Time (t2) = 30 min. For focal SE with impaired consciousness, Time (t1) = 10 min, while Time (t2) > 60 min.
- Electrographic seizures are common in pediatric intensive care unit, particularly in children with specific risk factors. Continuous video-EEG is indicated to optimize care.
- Management of SE involves three simultaneous components: identification and management of underlying precipitant causes; administration of antiepileptic drugs to terminate SE; and identification and management of systemic complications that could result in secondary brain injury.

- Having a predetermined status epilepticus management algorithm can expedite management.
- Education of the child (at appropriate level), parents, and/or caregivers can help prevent SE.

References

1. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia. 1981;22(4):489–501.
2. Treatment of convulsive status epilepticus. Recommendations of the Epilepsy Foundation of America's working group on status epilepticus. JAMA 1993;270(7):854–859.
3. Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. Epilepsia. 1999;40(1):120–2.
4. Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, et al. A definition and classification of status epilepticus—report of the ILAE task force on classification of status epilepticus. Epilepsia [Internet]. 2015;56(10):1515–23. https://doi.org/10.1111/epi.13121.
5. Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. Brain. 2011;134(Pt 10):2802–18.
6. Chin RFM, Neville BGR, Scott RC. A systematic review of the epidemiology of status epilepticus. Eur J Neurol. 2004;11(12):800–10.
7. Chin RFM, Neville BGR, Peckham C, Bedford H, Wade A, Scott RC. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. Lancet (London, England). 2006;368(9531):222–9.
8. DeLorenzo RJ, Hauser WA, Towne AR, Boggs JG, Pellock JM, Penberthy L, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. Neurology. 1996;46(4):1029–35.
9. Coeytaux A, Jallon P, Galobardes B, Morabia A. Incidence of status epilepticus in French-speaking Switzerland: (EPISTAR). Neurology. 2000;55(5):693–7.
10. Wu YW, Shek DW, Garcia PA, Zhao S, Johnston SC. Incidence and mortality of generalized convulsive status epilepticus in California. Neurology. 2002;58(7):1070–6.
11. Shinnar S, Pellock JM, Moshé SL, Maytal J, O'Dell C, Driscoll SM, et al. In whom does status epilepticus occur: age-related differences in children. Epilepsia [Internet]. 1997;38(8):907–914. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1528-1157.1997.tb01256.x.
12. Gurcharran K, Grinspan ZM. The burden of pediatric status epilepticus: epidemiology, morbidity, mortality, and costs. Seizure [Internet]. 2019;68:3–8. https://doi.org/10.1016/j.seizure.2018.08.021.
13. Gaspard N, Hirsch LJ, Sculier C, Loddenkemper T, van Baalen A, Lancrenon J, et al. New-onset refractory status epilepticus (NORSE) and febrile infection-related epilepsy syndrome (FIRES): state of the art and perspectives. Epilepsia. 2018;59(4):745–52.
14. Sculier C, Gaspard N. New onset refractory status epilepticus (NORSE). Seizure. 2019;68:72–8.
15. van Baalen A, Vezzani A, Häusler M, Kluger G. Febrile infection-related epilepsy syndrome: clinical review and hypotheses of epileptogenesis. Neuropediatrics. 2017;48(1):5–18.
16. Benbadis SR, Agrawal V, Tatum WO. How many patients with psychogenic nonepileptic seizures also have epilepsy? Neurology [Internet]. 2001;57(5):915–917. http://n.neurology.org/content/57/5/915.abstract.
17. Dworetzky BA, Bromfield EB. Differential diagnosis of status epilepticus. In: Drislane FW, editor. Status epilepticus: a clinical perspective [Internet]. Totowa: Humana Press; 2005. p. 33–54. https://doi.org/10.1385/1-59259-945-1:033.
18. LaFrance Jr. WC, Baker GA, Duncan R, Goldstein LH, Reuber M. Minimum requirements for the diagnosis of psychogenic nonepileptic seizures: a staged approach. Epilepsia [Internet]. 2013;54(11):2005–18. https://onlinelibrary.wiley.com/doi/abs/10.1111/epi.12356.

19. Navarro V, Fischer C, Convers P. [Differential diagnosis of status epilepticus]. Rev Neurol (Paris). 2009;165(4):321–327.
20. Shmuely S, Bauer PR, van Zwet EW, van Dijk JG, Thijs RD. Differentiating motor phenomena in tilt-induced syncope and convulsive seizures. Neurology [Internet]. 2018;90(15):e1339–e1346. http://n.neurology.org/content/90/15/e1339.abstract.
21. Persoon S, Kappelle LJ, Klijn CJM. Limb-shaking transient ischaemic attacks in patients with internal carotid artery occlusion: a case-control study. Brain. 2010;133(Pt 3):915–22.
22. Kassab A, Tremblay J, Poppe AY, Létourneau-Guillon L, Gallagher A, Nguyen DK. Cerebral hemodynamic changes during limb-shaking TIA: a near-infrared spectroscopy study. Neurology. 2016;86(12):1166–8.
23. Avbersek A, Sisodiya S. Does the primary literature provide support for clinical signs used to distinguish psychogenic nonepileptic seizures from epileptic seizures? J Neurol Neurosurg Psychiatry. 2010;81(7):719–25.
24. Patel H, Scott E, Dunn D, Garg B. Nonepileptic seizures in children. Epilepsia. 2007;48(11):2086–92.
25. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde BW, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE commission on classification and terminology, 2005-2009. Epilepsia. 2010;51(4):676–85.
26. Roddy SM, McBride MC. Status epilepticus. In: McInerny TK, Adam HM, Campbell DE, Dewitt TG, Foy JM, Kamat DM, editors. American Academy of Pediatrics textbook of pediatric care. American Academy of Pediatrics; 2008.
27. Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care. 2012;17(1):3–23.
28. Yoong M, Madari R, Martinos M, Clark C, Chong K, Neville B, et al. The role of magnetic resonance imaging in the follow-up of children with convulsive status epilepticus. Dev Med Child Neurol. 2012;54(4):328–33.
29. Wilfong A. Management of convulsive status epilepticus. UpToDate [Internet], accessed 20 Dec 2020.
30. Riviello JJJ, Ashwal S, Hirtz D, Glauser T, Ballaban-Gil K, Kelley K, et al. Practice parameter: diagnostic assessment of the child with status epilepticus (an evidence-based review): report of the quality standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2006;67(9):1542–50.
31. Abend NS, Loddenkemper T. Pediatric status epilepticus management. Curr Opin Pediatr. 2014;26(6):668–74.
32. Cockerell OC, Rothwell J, Thompson PD, Marsden CD, Shorvon SD. Clinical and physiological features of epilepsia partialis continua: cases ascertained in the UK. Brain [Internet]. 1996;119(2):393–407. https://doi.org/10.1093/brain/119.2.393.
33. Pandian JD, Thomas S V, Santoshkumar B, Radhakrishnan K, Sarma PS, Joseph S, et al. Epilepsia partialis continua—a clinical and electroencephalography study. Seizure [Internet]. 2002;11(7):437–41. https://www.sciencedirect.com/science/article/pii/S1059131101906466.
34. Thomas JE, Reagan TJ, Klass DW. Epilepsia partialis continua. A review of 32 cases. Arch Neurol. 1977;34(5):266–75.
35. Tay SKH, Hirsch LJ, Leary L, Jette N, Wittman J, Akman CI. Nonconvulsive status epilepticus in children: clinical and EEG characteristics. Epilepsia. 2006;47(9):1504–9.
36. Sánchez Fernández I, Abend NS, Arndt DH, Carpenter JL, Chapman KE, Cornett KM, et al. Electrographic seizures after convulsive status epilepticus in children and young adults: a retrospective multicenter study. J Pediatr. 2014;164(2):332–9.
37. Abend NS, Arndt DH, Carpenter JL, Chapman KE, Cornett KM, Gallentine WB, et al. Electrographic seizures in pediatric ICU patients: cohort study of risk factors and mortality. Neurology. 2013;81(4):383–91.
38. Fung FW, Jacobwitz M, Vala L, Parikh D, Donnelly M, Xiao R, et al. Electroencephalographic seizures in critically ill children: management and adverse events. Epilepsia. 2019;60(10):2095–104.
39. Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, 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.

40. Singh A, Stredny CM, Loddenkemper T. Pharmacotherapy for pediatric convulsive status epilepticus. CNS Drugs. 2020;34(1):47–63.
41. Lyttle MD, Rainford NEA, Gamble C, Messahel S, Humphreys A, Hickey H, et al. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. Lancet [Internet]. 2019;393(10186):2125–2134. https://doi.org/10.1016/S0140-6736(19)30724-X.
42. Dalziel SR, Borland ML, Furyk J, Bonisch M, Neutze J, Donath S, et al. Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial. Lancet (London, England). 2019;393(10186):2135–45.
43. Chamberlain JM, Kapur J, Shinnar S, Elm J, Holsti M, Babcock L, et al. Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial. Lancet [Internet]. 2020;395(10231):1217–1224. https://doi.org/10.1016/S0140-6736(20)30611-5.
44. Abend NS, Loddenkemper T. Management of pediatric status epilepticus. Curr Treat Options Neurol. 2014;16(7):301.
45. Arya R, Rotenberg A. Dietary, immunological, surgical, and other emerging treatments for pediatric refractory status epilepticus. Seizure. 2019;68:89–96.
46. Arya R, Pearlso K, Gaínza-Lein M, Harvey J, Bergin A, Brenton JN, et al. Efficacy and safety of ketogenic diet for treatment of pediatric convulsive refractory status epilepticus. Epilepsy Res [Internet]. 2018;144:1–6. http://www.sciencedirect.com/science/article/pii/S092012111830038X.
47. Appavu B, Vanatta L, Condie J, Kerrigan JF, Jarrar R. Ketogenic diet treatment for pediatric super-refractory status epilepticus. Seizure [Internet]. 2016;41:62–5. http://www.sciencedirect.com/science/article/pii/S1059131116300930.
48. Caraballo RH, Flesler S, Armeno M, Fortini S, Agustinho A, Mestre G, et al. Ketogenic diet in pediatric patients with refractory focal status epilepticus. Epilepsy Res [Internet]. 2014;108(10):1912–6. http://www.sciencedirect.com/science/article/pii/S0920121114002769.
49. Schmitt FC, Buchheim K, Meierkord H, Holtkamp M. Anticonvulsant properties of hypothermia in experimental status epilepticus. Neurobiol Dis [Internet]. 2006;23(3):689–96. http://www.sciencedirect.com/science/article/pii/S0969996106001367.
50. Legriel S, Lemiale V, Schenck M, Chelly J, Laurent V, Daviaud F, et al. Hypothermia for neuroprotection in convulsive status epilepticus. N Engl J Med [Internet]. 2016;375(25):2457–67. https://doi.org/10.1056/NEJMoa1608193.
51. Raspall-Chaure M, Chin RFM, Neville BG, Scott RC. Outcome of paediatric convulsive status epilepticus: a systematic review. Lancet Neurol. 2006;5(9):769–79.
52. Sadarangani M, Seaton C, Scott JAG, Ogutu B, Edwards T, Prins A, et al. Incidence and outcome of convulsive status epilepticus in Kenyan children: a cohort study. Lancet Neurol [Internet]. 2008;7(2):145–50. http://www.sciencedirect.com/science/article/pii/S1474442207703319.
53. Pujar SS, Neville BGR, Scott RC, Chin RFM, Network NLER. Death within 8 years after childhood convulsive status epilepticus: a population-based study. Brain [Internet]. 2011;134(10):2819–27. https://doi.org/10.1093/brain/awr239.
54. Gaínza-Lein M, Sánchez Fernández I, Jackson M, Abend NS, Arya R, Brenton JN, et al. Association of time to treatment with short-term outcomes for pediatric patients with refractory convulsive status epilepticus. JAMA Neurol. 2018;75(4):410–8.
55. Jafarpour S, Hodgeman RM, De Marchi CC, de Lima MTA, Kapur K, Tasker RC, et al. New-onset status epilepticus in pediatric patients: causes, characteristics, and outcomes. Pediatr Neurol. 2018;80:61–9.
56. Martinos MM, Pujar S, Gillberg C, Cortina-Borja M, Neville BGR, De Haan M, et al. Long-term behavioural outcomes after paediatric convulsive status epilepticus: a population-based cohort study. Dev Med Child Neurol. 2018;60(4):409–16.
57. Pujar SS, Martinos MM, Cortina-Borja M, Chong WKK, De Haan M, Gillberg C, et al. Long-term prognosis after childhood convulsive status epilepticus: a prospective cohort study. Lancet Child Adolesc Health [Internet]. 2018;2(2):103–11. http://www.sciencedirect.com/science/article/pii/S2352464217301748.

Child with Syncope

Diana M. Torpoco Rivera, Marjorie Gayanilo, and Sehgal Swati

1 Introduction

Syncope is defined as a sudden, self-limited loss of consciousness, and loss of postural tone resulting from transient global cerebral hypoperfusion. The recovery is complete, spontaneous and without any neurologic sequelae [1, 2]. In its most common form, it is typically preceded by a prodromal phase consisting of nonspecific symptoms such as nausea, blurry vision, dizziness, sweating, and pallor or cold skin lasting from few seconds to couple minutes [3]. Presyncope is another term commonly used in the context of syncope. This is usually defined as the feeling that one is about to pass out but the child remains conscious albeit a transient loss of postural tone [4]. Although pediatric syncope is usually due to non-life-threatening causes and requires minimal evaluation in the emergency department, most children with syncope, especially recurrent syncope will experience stress and anxiety and will be referred for cardiac and or neurologic evaluation. The primary objective of evaluation of a child with syncope is to determine the etiology and rule out life-threatening cardiac and neurological disorders. This can be accomplished in most situations by obtaining a detailed history and performing a thorough physical examination.

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2 Epidemiology

Syncope occurs in approximately 15–25% of children with predominance in girls [3, 5]. Despite being so commonly encountered in the first two decades of life, only a small percentage of children seek medical attention. Syncope accounts for in 1 in 2000 visits to the emergency department, i.e., approximately 1% of all pediatric ED visits. It occurs at any age, with different frequencies and different etiologies and accounts for 126/100,000 children seeking medical attention [6–8]. Fifteen percent of all children will experience at least one episode of syncope before the age of 18 years [9].

3 Etiology

Syncope is caused by transient global hypoperfusion of the brain. In adults, the most common cause of syncope is cardiac disease while in children the most frequent cause of syncope is neurocardiogenic, also known as vasovagal syncope. Vasovagal syncope accounts for 75% of all causes while cardiac disease accounts for 10% of causes of syncope in children. See Table 1 for the different forms of syncope that can be encountered in children. Seizure disorders and neurologic disorders are another category that can present as syncope in 5% of children. This section will focus on how to distinguish benign from life-threatening causes of syncope with

Table 1 Causes of pediatric syncope

1.	Neurally mediated syncope
	Neurocardiogenic or vasovagal syncope
	Orthostatic hypotensive syncope
	Postural orthostatic tachycardia syndrome (POTS)
	Breath holding spells
	Situational syncope (coughing, micturition, defecation, hair grooming)
2.	Cardiac syncope
	Hypertrophic cardiomyopathy
	Aortic stenosis
	Coronary anomalies
	Myocarditis or cardiomyopathy
	Arrhythmias
3.	Other causes of syncope
	Seizures
	Convulsive syncope
	Psychogenic syncope
	Metabolic (hypoglycemia, hypoxia, or electrolyte abnormalities)
	Drug-induced syncope

some pointers to distinguish syncope from seizures. Please see Table 1 in chapter "Child with Attention Deficit Disorder/Child with Attention Deficit Hyperactivity Disorder (ADHD)" where differential diagnosis of seizures is discussed.

4 Neurally Mediated Syncope

4.1 Orthostatic Intolerance Syndromes

Orthostasis refers to the upright position. The conditions listed below all share a common thread, i.e., the symptoms are brought on by change in posture and there is inability to tolerate the upright posture.

4.2 Orthostatic Intolerance and Orthostatic Hypotension

Orthostatic intolerance is a common disorder in children, and it is frequently seen in the outpatient setting. It is characterized by the presence of symptoms that start with a change to upright position and are relieved by lying down. If symptoms start in the supine position, then orthostatic intolerance is ruled out. The most frequently reported symptoms (also called orthostatic symptoms) include palpitations, lightheadedness, headache, fatigue, weakness, nausea, abdominal discomfort, pallor, and diaphoresis [10].

Orthostatic hypotension or postural hypotension is defined as a sustained decrease in systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg within 3 min of standing. Orthostatic hypotension is a sign and it is not always associated with symptoms. If the fall in blood pressure is prominent, cerebral blood perfusion is decreased and it can lead to syncope [11].

4.3 Neurocardiogenic Syncope (Vasovagal Syncope)

In vasovagal syncope, also referred to as "common faint," there is a series of events leading to loss of cerebral function. See Fig. 1 for pictorial depiction. Following certain triggers such as sudden or prolonged standing, hot shower, the sight of blood, any orthostatic stress, or venous pooling, there is decrease in ventricular preload. This results in initial hypotension followed by increased heart rate. Reflexive tachycardia is not able to compensate for the decrease in cardiac output leading to cardiovascular collapse with progressive hypotension, vasodilation, and bradycardia. This phase corresponds with symptoms of autonomic activation such as nausea and warmth with symptoms of cerebral hypoperfusion: blurry vision and

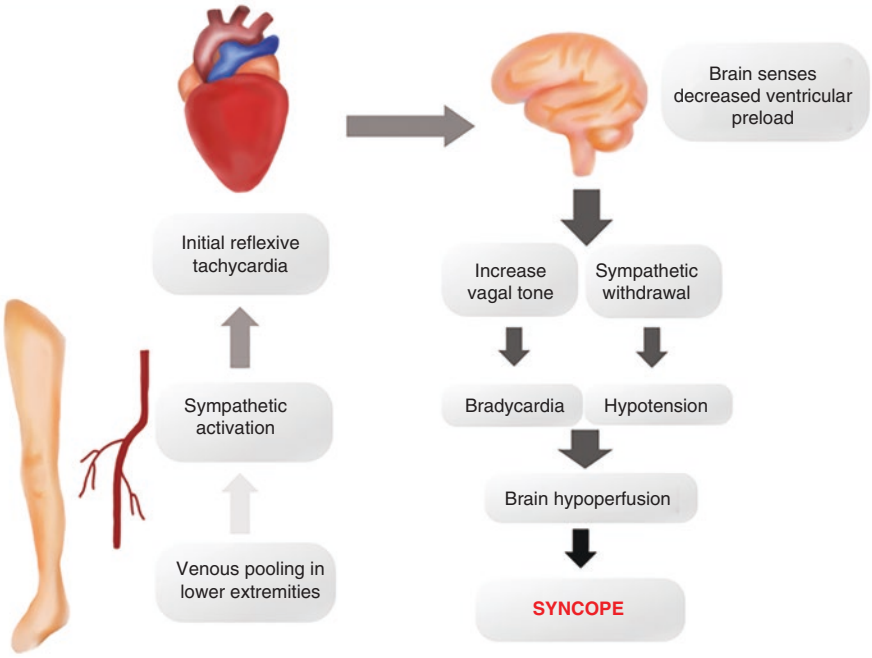

Fig. 1 Mechanism of vasovagal syncope

dizziness. Progressive decrease in blood pressure, systolic below 60 mmHg or mean arterial blood pressure of 30–40 mmHg results in loss of consciousness. Once the child is in the supine position, there is rapid increase in venous blood return to the heart, resulting in improved mean arterial pressure and improvement of symptoms which usually occurs within 30 seconds of being placed back in the horizontal position [12, 13].

4.4 Postural Orthostatic Tachycardia Syndrome (POTS)

POTS is a clinical syndrome characterized by symptoms of orthostatic intolerance with a change from supine position to an upright position. It is defined by an increase in heart rate of ≥30 beats/min, or a rate that exceeds 120 beats/min within 10 min of standing or head-up tilt, without orthostatic hypotension (a decrease in systolic blood pressure of 20 mmHg or more and/or decrease in diastolic blood pressure of 10 mmHg or more) [14]. This condition has a prevalence of 0.2% in the United States, is seen more frequently between ages of 15 and 25 years, and also has a female predominance. Symptoms experienced by patients with POTS include: light-headedness, palpitations, tremor, generalized weakness, blurred vision,

exercise intolerance, and fatigue. Many of these patients will faint although presyncope is seen more frequently. Patients with POTS will have chronic symptoms that can typically last for 6 months or longer and will often experience chronic fatigue with limitations to complete their daily activities [8, 14].

5 Cardiac Syncope

Cardiac syncope is the result of a sudden decrease in cardiac output, leading to decreased brain perfusion with subsequent loss of consciousness [5]. Although this group accounts for only 10% of all causes of syncope in children, it has the highest risk for sudden death compared to other causes of syncope [5]. History and physical examination serve as the main pillars in distinguishing cardiac causes of syncope from the more common vasovagal syncope. Several features that will be discussed in subsequent sections may serve as red flags for potentially life-threatening cardiac causes of syncope. In this review, we have divided the cardiac causes of syncope into two main categories: structural or anatomical and cardiac arrhythmias. The main cardiac diseases in the first category include: aortic stenosis, hypertrophic cardiomyopathy, and coronary abnormalities. Although myocarditis and other forms of cardiomyopathy are primarily disorders of myocardial function, they will be included in this category of cardiac syncope for practical purposes. Among arrhythmias presenting as syncope in children, the most common are: complete heart block and tachyarrhythmias including Long QT syndrome, Wolff–Parkinson–White syndrome, and Brugada syndrome [6, 7, 15]. Table 2 below presents an overview of common causes of cardiac syncope in children.

Table 2 Causes of cardiac syncope

1. Structural or anatomic	
Hypertrophic cardiomyopathy (HCM)	Syncope during exercise Family history of HCM or sudden death Systolic murmur that increases with Valsalva maneuvers Left ventricular hypertrophy on EKG
Aortic stenosis	Syncope during exercise Systolic murmur and ejection click Left ventricular hypertrophy on EKG
Myocarditis and/or cardiomyopathies	Symptoms of heart failure Abnormal vital signs: tachycardia and hypotension S3 or S4 gallop ST- T wave abnormalities on EKG
Coronary abnormalities	History of chest pain with exercise Abnormal EKG
Pulmonary hypertension	Loud P2 component or abnormal S2 splitting Right ventricular hypertrophy on EKG

(continued)

Table 2 (continued)

2. Arrhythmias	
Wolff–Parkinson–White syndrome	History of palpitations Ventricular pre-excitation or delta wave on EKG
Supraventricular tachycardia	History of palpitations of sudden onset and offset
Bradycardia	Abnormal heart rate for age Second-degree or third-degree heart block on EKG
Long QT syndrome	Syncope during exercise or startle Family history of sudden death or congenital deafness Prolonged QTc on EKG

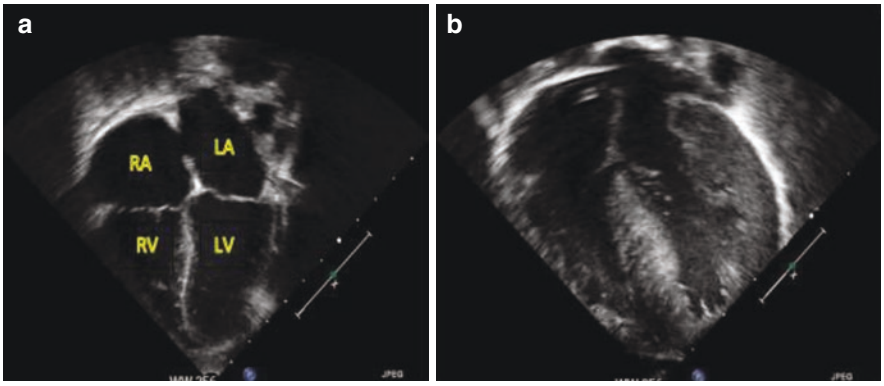

Fig. 2 Echocardiogram of a patient with normal heart (**a**) and a patient with hypertrophic cardiomyopathy (**b**). *RA* right atrium, *RV* right ventricle, *LA* left Atrium, *LV* left ventricle

5.1 Hypertrophic Obstructive Cardiomyopathy (HOCM)

Hypertrophic obstructive cardiomyopathy (HOCM) is a genetic disorder that is characterized by asymmetric septal hypertrophy, which produces a dynamic left ventricular outflow tract obstruction (LVOTO). The majority of patients have a benign course and are mostly asymptomatic. Palpitations, presyncope, and syncope in these patients might be caused by arrhythmia, usually ventricular tachycardia, or LVOTO. When arrhythmias and/or syncope are present they are considered a major risk factor for sudden cardiac death. A systolic ejection murmur at the mid and lower left sternal borders or at the apex, a left ventricular lift and a systolic thrill at the apex or along the lower left sternal border may be present. Electrocardiographic abnormalities include left ventricular hypertrophy, ST segment, T wave abnormalities, and abnormal deep Q waves. The treatment is aimed at providing symptomatic relief and decreasing the risk of sudden cardiac death. Since HOCM is the most common cause of sudden cardiac death in young competitive athletes, patients with HOCM need to be evaluated and cleared by a cardiologist before returning to sports [1, 6]. Figure 2 is an echocardiogram of a child with HOCM.

5.2 Aortic Stenosis

Aortic stenosis is the most common type of congenital left ventricular outflow tract obstruction, which causes decreased blood flow to the aorta and poor coronary perfusion. Abnormalities of the aortic valve can range from asymptomatic malformations (bicuspid aortic valve, which is the most common form of aortic valve disease) to severe ductal dependent lesions (critical aortic stenosis). On physical examination, an ejection click may be identified and if aortic stenosis is severe, there might be paradoxical splitting of S2. A harsh, mid-systolic ejection murmur might also be heard at the second right or left intercostal space. Most children with mild-to-moderate aortic stenosis are asymptomatic and they can present with occasional exercise intolerance, exertional chest pain, and easy fatigability. Children with severe obstruction can present with syncope; and even sudden cardiac death from ischemia in 1–2% of patients with severe aortic stenosis. Treatment options include balloon valvuloplasty or surgical relief of the obstruction [2, 7].

5.3 Congenital Coronary Artery Abnormalities

Congenital coronary anomalies are those in which there is an abnormal origin of the coronary arteries that lead to an increased risk for myocardial ischemia. Congenital coronary abnormalities are the second leading cause of sudden cardiac death in young athletes in the United States. Most affected children are asymptomatic and have a normal physical examination, and sudden cardiac death may be their first symptom. Therefore, when patients present with palpitations, exertional chest pain, or syncope, anomalous coronary artery must be considered under the differential diagnosis [1].

5.4 Pulmonary Hypertension

Pulmonary hypertension is a group of conditions with multiple etiologies and it is defined as mean pulmonary arterial (PA) pressure of 25 mm Hg or above in a resting individual at sea level. Regardless of its cause, pulmonary hypertension involves pulmonary arteriolar constriction which results in increased pulmonary vascular resistance. This increases the afterload of the right ventricle resulting in right ventricular hypertrophy and in severe/chronic cases, right ventricular dysfunction. Children with pulmonary hypertension can present with decreased cardiac output when there is volume and pressure overload of the right ventricle that leads to poor cardiac function and decreased coronary perfusion with left ventricular dysfunction. Similar to conditions described previously, patients with pulmonary hypertension will present with fatigue, dyspnea, exertional chest pain, or syncope. On physical

examination, a single S2, loud P2, and diastolic decrescendo murmur (due to pulmonary regurgitation) can be noted. Electrocardiogram, echocardiogram, and chest radiography will confirm the diagnosis if there is suspicion for pulmonary hypertension. Treatment will depend on the underlying cause of pulmonary hypertension [2, 7].

5.5 *Long QT Syndrome*

Long QT syndrome is a genetic disorder caused by mutations in genes that affect development of cardiac ion channels. EKG of a child with long QT syndrome is shown in Fig. 3. This syndrome is characterized by abnormal myocardial repolarization and prolonged QT interval on the electrocardiogram. Prolonged QT interval is defined as a corrected QT interval (QTc) longer than 440 ms in males and 460 ms in females [2, 7]. Symptoms can occur during exercise or be associated with emotional upheaval. It is important to identify activities that the child may have participated in prior to onset of syncope since long QT syndrome is associated with adrenergic arousal, intense emotion, and exercise (specifically swimming). Other associated triggers are auditory, such as alarm clocks, cellphones, or doorbells. Once prolonged QTc is identified, it is recommended that the child be referred to a pediatric cardiologist for further evaluation and management due to the high risk for arrhythmias and sudden cardiac death [6].

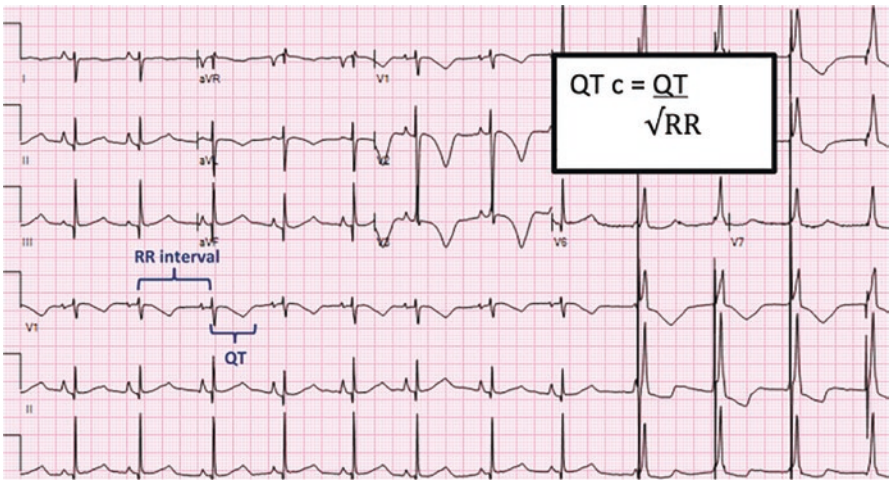

Fig. 3 Electrocardiogram in a patient with prolonged QT

5.6 *Other Dysrhythmias*

Wolff–Parkinson–White (WPW) syndrome is a condition characterized by a short PR interval associated with ventricular pre-excitation and a characteristic delta wave and wide QRS on electrocardiogram. Clinical presentation ranges from asymptomatic to paroxysmal episodes of supraventricular tachycardia with symptoms of palpitations, sudden cardiac arrest and rarely sudden cardiac death [2, 7].

Congenital complete atrioventricular block is a condition that has been strongly associated with exposure to maternal SSA/Ro and/or SSB/La autoantibodies and it is usually seen with structurally normal hearts. Clinical presentation and prognosis vary depending on time of diagnosis. It ranges from asymptomatic bradycardia to syncope, heart failure, or sudden death [6, 7].

EKGs of children with WPW syndrome and third degree atrioventricular blocks are depicted in Figs. 4 and 5, respectively.

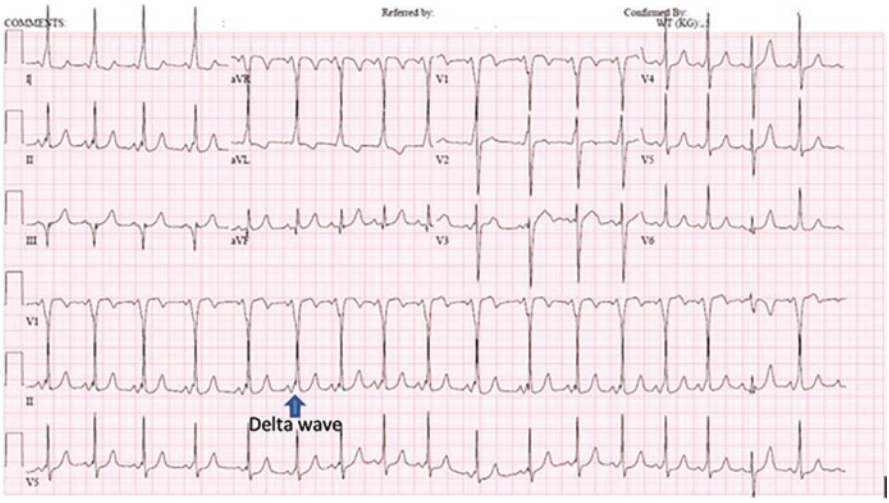

Fig. 4 Wolff–Parkinson–White syndrome or pre-excitation

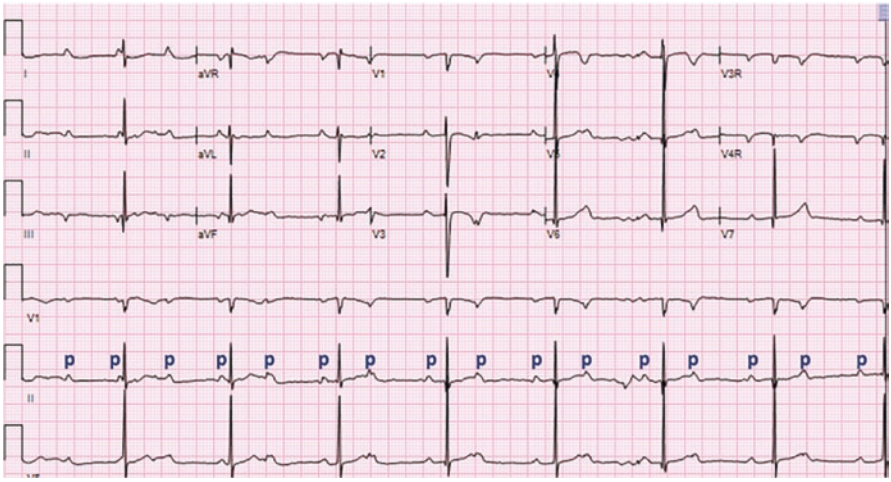

Fig. 5 Third-degree atrioventricular block. P waves marching out independently of QRS complexes

6 Differential Diagnosis

Syncope should be considered as a symptom of an underlying disorder. Although vasovagal syncope is the most common cause of syncope, this must be differentiated from life-threatening cardiac and neurological causes of syncope. Precipitating factors might help to distinguish these conditions. A family history of cardiomyopathy, pacemaker placement or internal cardiac defibrillator dependent conditions at a young age, history of sudden cardiac death, or congenital sensorineural hearing loss should raise suspicion for possible cardiac syncope. Similarly, presence of a pathological heart murmur and/or abnormal vital signs such as tachycardia or bradycardia, hypotension, or hypoxia will indicate a possible cardiac cause of syncope.

Other, not uncommon causes of syncope seen in infants are breath-holding spells which are a type of reflex or situational syncope. The key to the diagnosis of breath holding spells is the presence of a trigger: pain, fear, or any other emotional insult. The children can appear cyanotic or pale before losing consciousness. Breath-holding spells are generally benign and represent a variant of neurocardiogenic syncope. No treatment is required other than behavioral management [3].

Psychogenic or psychiatric causes of syncope should also be considered in older children. For patients presenting with unusual loss of consciousness, with multiple episodes per day, not associated or triggered by change in position, and usually lasting longer than 3–4 min, a diagnosis of conversion disorder should be considered. Likewise, a thorough clinical history including psychosocial triggers such as stressors or anxiety will aid in syncope evaluation [6].

Seizures may occasionally be confused with neurally mediated syncope. In atonic seizures, there may be sudden loss of tone when the child is standing causing the episode to resemble a syncopal spell. However, there are no prodromal symptoms or orthostatic symptoms such as pallor, diaphoresis or light-headedness before the onset of the event. Furthermore, atonic seizures may occur even when a child is sitting down unlike orthostatic symptoms that are typically brought on by change in posture. A child who is experiencing a convulsive seizure (also called a generalized tonic–clonic seizure) may fall before the actual seizure starts. Witnesses may note the typical sequence of events such as stiffening of limbs, clenching of teeth, lateral/upward deviation of eyes, followed by rhythmic jerking of limbs, and finally a period of altered consciousness when a child has a convulsive seizure.

7 Diagnostic Approach

7.1 History

A detailed history is the most important aspect to identify the cause of syncope and distinguish it from other conditions. The prodrome or premonitory factors such as warm or clammy sensation, nausea, light-headedness, or visual changes will suggest vasovagal syncope. Absence of these symptoms should raise suspicion for cardiac causes of syncope [16]. Circumstances surrounding the event such as prolonged standing, change in position, hot weather, poor hydration or hunger is usually seen in vasovagal syncope. If the child presents with syncope mid-exercise, that should raise concern for cardiac syncope [17]. In contrast, postexertional syncope, as is commonly seen in adolescents walking off the field after the game, often indicates vasovagal syncope. This phenomenon is secondary to peripheral vasodilation and hypotension [16]. Abrupt onset of syncope triggered by a loud noise or emotions like frightening or other startle events without any other prodromal symptoms should raise concern for ventricular arrhythmias secondary to long QT syndrome and requires urgent evaluation [18].

It is essential to ask questions about precipitating factors. Factors such as the sight of blood, hair grooming, micturition/defecation, injuries causing pain as well as hyperventilation secondary to emotional stress are usually seen with vasovagal syncope. Chest pain and palpitations during exercise or immediately before syncope should raise concern for cardiac syncope [19].

Similarly, a detailed family history is absolutely essential in differentiating cardiac from non-cardiac causes of syncope. Family history of sudden unexplained death at a young age, congenital deafness, cardiomyopathy, arrhythmia, placement of a pacemaker or defibrillator, or death from an unknown cause should raise suspicion for a cardiac cause for syncope. Family history of seizures, migraine, sleep or vestibular disorders as well as mental disorders in the family will help in identifying other possible causes of syncope.

Other diagnostic hallmarks of vasovagal syncope are the duration and recovery after the event. In general, the loss of consciousness is brief, lasting for few seconds to couple minutes with rapid and spontaneous recovery and no neurologic sequelae. Patients might have brief tonic–clonic seizure like activity during the episode and on rare occasions syncope is accompanied by urinary incontinence. Prolonged episodes, lasting over 5 min, may indicate neurologic or psychiatric causes of syncope (seizures, stroke, and somatization disorder). Another way to differentiate a seizure from vasovagal syncope is the postictal state. In seizures, the state of confusion can last from minutes to hours whereas after vasovagal syncope, the patient can be tired but there is no confusion [20].

Questions pertinent to seizures include inquiry regarding an aura. The aura of a seizure may take the form of an unpleasant smell/taste or a déjà vu phenomenon. An older child may be able to relay these symptoms but sometimes a directed history is important. Most children who experience a seizure, no matter their age, will have their eyes open unlike in syncope [21].

Uprolling of eyes can be present in both seizures and syncope and does not constitute a salient differentiating feature. Enuresis can occur both during syncope and seizure as well, as mentioned above. However, most children are confused or sleepy after a seizure for a variable length of time, whereas there is rapid return to baseline following syncope.

7.2 Physical Examination

In general, physical examination in patients with neurally mediated syncope will be normal. However, the presence of abnormal findings on physical examination will help tailor further evaluation.

7.3 General Examination

A careful evaluation for heart murmurs, distinguishing innocent murmurs from pathologic murmurs can raise or quell concerns for anatomical cardiac conditions like aortic stenosis and hypertrophic obstructive cardiomyopathy [22]. Assessment of vital signs with orthostatic changes are helpful in assessing hydration status and demonstrating dysautonomic responses to orthostatic stress. However, the absence of positive orthostatic vital signs does not rule out vasovagal syncope. Similarly, about 40% of euvolemic teenagers have positive orthostatic signs [23]. Therefore, vital signs should not be used in isolation to direct the evaluation of syncope.

7.4 Neurological Examination

Focal neurologic symptoms or persistent neurologic deficits: motor weakness, ataxia, altered mental status, or slurred speech should raise concern for neurologic conditions such as seizures, complex migraine or stroke [24].

Most children will present to the clinician's office several hours or days after a seizure and therefore will have a normal neurological examination. In the immediate aftermath of a seizure a child may be noted to be drowsy, confused, combative or irritable. In rare instances, Todd's paralysis (motor weakness of a limb or one-half of the body) may be present.

7.5 Evaluation (Laboratory Studies/Imaging)

Diagnostic evaluation is usually guided by history and physical examination. However, all patients with syncope should have an electrocardiogram (EKG) especially if syncope occurred during exercise. When EKG is integrated with a detailed medical history, family history, and physical examination, it has a sensitivity of up to 96% for ruling out cardiac syncope and is Class I recommendation per the 2017 American College of Cardiology/American Heart Association guidelines for evaluation of patients with syncope [23, 25]. If a patient presents with additional risk factors for cardiac cause of syncope, referral to a pediatric cardiologist should be prompt for comprehensive cardiac evaluation that includes but is not limited to echocardiogram, and 24-h or 30-day ambulatory rhythm monitor (Holter monitor or event monitor).

Routine use of blood tests is not usually recommended and has low diagnostic value in the evaluation of a patient with syncope. If necessary, laboratory evaluation should be directed by the history, physical examination and underlying medical condition [16].

Tilt-table test or head-up tilt table test is a non-invasive test frequently performed in adults but also used in children for diagnosis of dysautonomia. It has been safely used in children greater than 6 years of age but it can be used in younger children. The test is performed by positioning the patient upright at an angle of 60°–80° for 15–60 min on a tilt table. The test is concluded with reproduction of clinical symptoms, accompanied by hypotension and or bradycardia. Tilt table test is not helpful if the diagnosis of vasovagal syncope is clear by history and physical examination as it is fraught with a high rate of false positive test results. Neuroimaging studies and electroencephalography may be indicated if patients have specific neurologic findings, but otherwise they are not routinely recommended [26].

8 Treatment/Management and Prevention

The approach to management of patients with syncope should be guided by the underlying mechanism of syncope. See Fig. 6 for our diagnostic approach and referral patterns. For children with vasovagal syncope, the objective is to prevent the recurrence or reduce the frequency of syncopal episodes, to identify triggers and provide reassurance to the family. Most patients with vasovagal syncope do not require hospitalization and have few recurrences. In general, an increase in fluid intake, of at least 60–80 oz, is recommended and additional salt intake in the diet. Equally important is educating the family and patient about physical maneuvers to counteract the effects of gravity that decrease the pooling of venous blood into the lower limbs and abdomen. These maneuvers include elevation of the legs and lowering the head, leg crossing, and tensing of the abdominal muscles [27]. For prevention of vasovagal syncope, patients should be taught other physical techniques like crossing legs or buttocks-clenching while upright or squatting that have been proven to effective in adults and are safe to practice in children [28]. Parents should also be reassured that vasovagal syncope is not life threatening, provided patients learn how to protect themselves from trauma or injuries caused by sudden falls during syncope.

Pharmacologic therapy is not the first choice of treatment due to potential side effects and controversy regarding benefits of long-term prophylaxis. It should be considered if vasovagal syncope is refractory to at least 6 months of conservative management [14]. Among the pharmacologic agents: beta blockers,

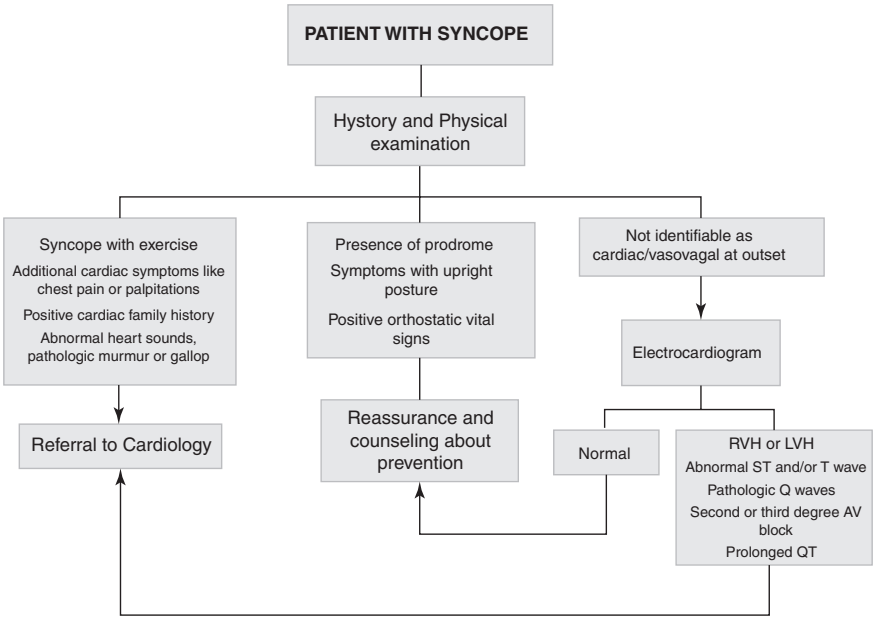

Fig. 6 Diagnostic approach to syncope

mineralocorticoids like fludrocortisone, an alpha-adrenergic receptor agonist like midodrine are the most commonly prescribed medications in children [29].

Beta blockers reduce cardiac inotropy and mechanoreceptor activation, and increase the peripheral arterial resistance. It might not be beneficial in patients that require sympathetic compensatory mechanisms such in postural tachycardia syndrome, highly competitive athletes and patients with asthma. Physicians should inform patients and their families about the side effects of beta-blockers that include headache, hypotension, irritability, depression, and suicide attempts. Only atenolol has been effective in the treatment of vasovagal syncope in children [30]. Fludrocortisone is a corticosteroid with mineralocorticoid activity and acts by enhancing central blood volume by increasing sodium and fluid retention. The dose is usually 0.1 mg once daily or twice daily, with maximum dose of 1 mg/day. At lower doses it is well tolerated with adverse effects usually seen with higher doses which include hypertension, hypokalemia, edema, depression, migraine, or acne. The benefit of fludrocortisone is weak as shown in a small randomized clinical trial, where symptoms and recurrence of syncope were better with placebo than with fludrocortisone [31]. Midodrine is a selective α-1 adrenergic agonist with peripheral effects only that increases peripheral vascular resistance and diminishes the venous pooling. It can be used alone or in combination with fludrocortisone. The dose of midodrine ranges from 2.5–10 mg three times per day with maximum dose of 40 mg/day. It needs to be administered every 6–8 h due to its short duration of action. Among the side effects, hypertension, headache, and edema are common. Low-dose midodrine is considered as first line therapy for vasovagal syncope and small randomized study has shown that midodrine prevents recurrence of vasovagal syncope when compared with placebo [14, 32].

9 Prognosis/Outcomes

Children with vasovagal syncope have an excellent prognosis. The majority of children will have resolution of symptoms within the first year of onset of syncope and 5–10% would continue to present with symptoms up to 5 years from diagnosis [33]. For patients with cardiac syncope, prognosis will depend on prompt recognition and treatment of the underlying cause. Although these patients are at increased risk for sudden death, the majority of children with cardiac syncope can be treated effectively following timely referral to a cardiology specialist.

10 When to Refer/Admit

Whereas most syncopal episodes of childhood are of benign etiology, there is small group of patients with syncope of cardiac origin who are at risk for life-threatening events. It is important to recognize the unusual characteristics that these patients

demonstrate in order to initiate a timely referral to a pediatric cardiologist. These include exertional syncope, absence of a prodrome/premonitory symptoms, syncope preceded by chest pain or palpitations, an event requiring cardiopulmonary resuscitation, neurologic sequelae, prior cardiac history, positive family history of cardiac disease or sudden cardiac death, an abnormal cardiac physical examination, and an abnormal EKG [33].

11 Clinical Pearls/Key Points

- Syncope is common in childhood, especially in adolescent girls.
- Vasovagal syncope is the most common cause of syncope in adolescents.
- Cardiac syncope is rare and can be differentiated from vasovagal syncope based on key elements on history and physical examination.
- Syncope with physical exercise is cardiac syncope until proven otherwise and should initiate a prompt referral to the pediatric cardiologist.

References

1. Gupta P, Humes R. Adolescent cardiac issues. Pediatr Clin N Am. 2014;61(1):xvii–xviii. https://doi.org/10.1016/j.pcl.2013.09.022.
2. Schunk PC, Ruttan T. Pediatric syncope: high-risk conditions and reasonable approach. Emerg Med Clin North Am. 2018;36(2):305–21. https://doi.org/10.1016/j.emc.2017.12.005.
3. Singhi P, Saini AG. Syncope in pediatric practice. Indian J Pediatr. 2018;85(8):636–40. https://doi.org/10.1007/s12098-017-2488-9.
4. Fischer JW, Cho CS. Pediatric syncope: cases from the emergency department. Emerg Med Clin North Am. 2010;28:501–16.
5. McHarg ML, Shinnar S, Rascoff H, Walsh CA. Syncope in childhood. Pediatr Cardiol. 1997;18(5):367–71. https://doi.org/10.1007/s002469900202.
6. Anderson JB, Willis M, Lancaster H, Leonard K, Thomas C. The evaluation and management of pediatric syncope. Pediatr Neurol. 2016;55:6–13. https://doi.org/10.1016/j.pediatrneurol.2015.10.018.
7. Kanjwal K, Calkins H. Syncope in children and adolescents. Cardiol Clin. 2015;33(3):397–409. https://doi.org/10.1016/j.ccl.2015.04.008.
8. Bayram AK, Pamukcu O, Per H. Current approaches to the clinical assessment of syncope in pediatric population. Childs Nerv Syst. 2016;32(3):427–36. https://doi.org/10.1007/s00381-015-2988-8.
9. Friedman NR, Ghosh D, Moodley M. Syncope and paroxysmal disorders other than epilepsy. In: Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors. Swaiman's pediatric neurology: principles and practice. 5th ed. China: Elsevier; 2012. p. 906–10.
10. Stewart JM. Common syndromes of orthostatic intolerance. Pediatrics. 2013;131(5):968–80. https://doi.org/10.1542/peds.2012-2610.
11. Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Auton Neurosci. 2011;161(1–2):46–8. https://doi.org/10.1016/j.autneu.2011.02.004.

12. Jardine DL, Wieling W, Brignole M, Lenders JWM, Sutton R, Stewart J. The pathophysiology of the vasovagal response. Heart Rhythm. 2018;15(6):921–9. https://doi.org/10.1016/j.hrthm.2017.12.013.
13. Stewart JM, Medow MS, Sutton R, Visintainer P, Jardine DL, Wieling W. Mechanisms of vasovagal syncope in the young: reduced systemic vascular resistance versus reduced cardiac output. J Am Heart Assoc. 2017;6(1):e004417. Published 2017 Jan 18. https://doi.org/10.1161/JAHA.116.004417.
14. Sheldon RS, Grubb BP 2nd, Olshansky B, et al. 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. Heart Rhythm. 2015;12(6):e41–63. https://doi.org/10.1016/j.hrthm.2015.03.029.
15. Moodley M. Clinical approach to syncope in children. Semin Pediatr Neurol. 2013;20(1):12–7. https://doi.org/10.1016/j.spen.2012.12.003.
16. Sanatani S, Chau V, Fournier A, Dixon A, Blondin R, Sheldon RS. Canadian Cardiovascular Society and Canadian Pediatric Cardiology Association position statement on the approach to syncope in the pediatric patient. Can J Cardiol. 2017;33(2):189–98. https://doi.org/10.1016/j.cjca.2016.09.006.
17. Colivicchi F, Ammirati F, Santini M. Epidemiology and prognostic implications of syncope in young competing athletes. Eur Heart J. 2004;25(19):1749–53. https://doi.org/10.1016/j.ehj.2004.07.011.
18. Vincent GM. The Long QT and Brugada syndromes: causes of unexpected syncope and sudden cardiac death in children and young adults. Semin Pediatr Neurol. 2005;12(1):15–24. https://doi.org/10.1016/j.spen.2004.11.008.
19. Hurst D, Hirsh DA, Oster ME, et al. Syncope in the Pediatric Emergency Department—can we predict cardiac disease based on history alone? J Emerg Med. 2015;49(1):1–7. https://doi.org/10.1016/j.jemermed.2014.12.068.
20. Chen L, Zhang Q, Ingrid S, Chen J, Qin J, Du J. Aetiologic and clinical characteristics of syncope in Chinese children. Acta Paediatr. 2007;96(10):1505–10. https://doi.org/10.1111/j.1651-2227.2007.00446.x.
21. Bauder F, Wohlrab G, Schmitt B. Neonatal seizures: eyes open or closed? Epilepsia. 2007;48(2):394–6. https://doi.org/10.1111/j.1528-1167.2006.00950.x.
22. Massin MM, Malekzadeh-Milani S, Benatar A. Cardiac syncope in pediatric patients. Clin Cardiol. 2007;30(2):81–5. https://doi.org/10.1002/clc.28.
23. Stewart JM. Transient orthostatic hypotension is common in adolescents. J Pediatr. 2002;140(4):418–24. https://doi.org/10.1067/mpd.2002.122643.
24. Massin MM, Bourguignont A, Coremans C, Comté L, Lepage P, Gérard P. Syncope in pediatric patients presenting to an emergency department. J Pediatr. 2004;145(2):223–8. https://doi.org/10.1016/j.jpeds.2004.01.048.
25. Ritter S, Tani LY, Etheridge SP, Williams RV, Craig JE, Minich LL. What is the yield of screening echocardiography in pediatric syncope? Pediatrics. 2000;105(5):E58. https://doi.org/10.1542/peds.105.5.e58.
26. Writing Committee Members, Shen WK, Sheldon RS, et al. 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with syncope: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Rhythm Society. Heart Rhythm. 2017;14(8):e155–217. https://doi.org/10.1016/j.hrthm.2017.03.004.
27. Yilmaz S, Gökben S, Levent E, Serdaroğlu G, Özyürek R. Syncope or seizure? The diagnostic value of synchronous tilt testing and video-EEG monitoring in children with transient loss of consciousness. Epilepsy Behav. 2012;24(1):93–6. https://doi.org/10.1016/j.yebeh.2012.02.006.
28. van Dijk N, Quartieri F, Blanc JJ, et al. Effectiveness of physical counterpressure maneuvers in preventing vasovagal syncope: the physical Counterpressure Manoeuvres Trial (PC-Trial). J Am Coll Cardiol. 2006;48(8):1652–7. https://doi.org/10.1016/j.jacc.2006.06.059.

29. Qingyou Z, Junbao D, Chaoshu T. The efficacy of midodrine hydrochloride in the treatment of children with vasovagal syncope. J Pediatr. 2006;149(6):777–80. https://doi.org/10.1016/j.jpeds.2006.07.031.
30. Massin M. Neurocardiogenic syncope in children: current concepts in diagnosis and management. Paediatr Drugs. 2003;5(5):327–34. https://doi.org/10.2165/00128072-200305050-00005.
31. Mahanonda N, Bhuripanyo K, Kangkagate C, et al. Randomized double-blind, placebo-controlled trial of oral atenolol in patients with unexplained syncope and positive upright tilt table test results. Am Heart J. 1995;130(6):1250–3. https://doi.org/10.1016/0002-8703(95)90150-7.
32. Salim MA, Di Sessa TG. Effectiveness of fludrocortisone and salt in preventing syncope recurrence in children: a double-blind, placebo-controlled, randomized trial. J Am Coll Cardiol. 2005;45(4):484–8. https://doi.org/10.1016/j.jacc.2004.11.033.
33. Stewart JM. Midodrine for the treatment of vasovagal syncope (simple faint). J Pediatr. 2006;149(6):740–2. https://doi.org/10.1016/j.jpeds.2006.08.026.

Child with Sleep Disturbances

Sanjeev V. Kothare and Ivan Pavkovic

Abbreviations

ADHD	Attention-deficit hyperactivity disorder
DLMO	Dim light melatonin onset
DSWPD	Delayed sleep wake phase disorder
FDA	Food and Drug Administration
ICSD-3	International Classification of Sleep Disorders
KLS	Kleine–Levin syndrome
MSLT	Multiple sleep latency test
NREM	Nonrapid eye movement sleep
NT 1	Narcolepsy type I
NT 2	Narcolepsy type II
ODD	Oppositional defiant disorder
OSA	Obstructive sleep apnea
PMLDS	Periodic limb movement disorder of sleep
PSG	Polysomnography
RBD	REM behavior disorder
REM	Rapid eye movement sleep
SCN	Suprachiasmatic nucleus

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SHE	Sleep-related hypermotor epilepsy
SLD	Sublaterodoral nucleus
SOREMP	Sleep onset REM period
vlPAG-LPT	Ventrolateral periaqueductal gray matter—lateral pontine tegmentum

1 Introduction

Sleep complaints are very common in infancy and childhood with the prevalence of sleep problems often cited at 80% [1, 2]. Sleep disorders are classified based on the International Classification of Sleep Disorders (ICSD-3). Diagnostic categories of sleep disorders include insomnias, parasomnias, hypersomnias, circadian rhythm disorders, sleep-related breathing disorders, and sleep-related movement disorders [3].

2 Insomnia

The chief complaint of "my child can't sleep" maps to the nosological category of insomnia. Although the purpose of sleep is still unknown, sleep is essential for wellness [4]. Transient and self-limited difficulties with initiation and maintenance of sleep in infants and children are almost universal [5, 6]. In order to meet the definition of chronic insomnia disorder, the sleep disturbance and daytime symptoms occur, at least, 3 days per week and have been present for 3 months [3]. Patient or caregiver may report the following: difficulty initiating sleep, difficulty maintain sleep, waking up earlier than desired, resistance to going to bed on appropriate schedule, difficulty sleeping without parent or caregiver intervention. Daytime symptoms include: fatigue or malaise; attention, concentration, or memory impairment; impaired social, family, occupational, or academic performance; mood disturbance or irritability; daytime sleepiness; behavioral problems such as hyperactivity, impulsivity and aggression; reduced motivation, energy or initiative; proneness for errors or accidents; and general concerns about or dissatisfaction regarding sleep [3, 7].

Epidemiology: 20–30% of young children resist bedtime and awaken frequently [8]. Among adolescents insomnia may be even more common with 20–26% taking more than 30 minutes to fall asleep [9]. There is lifetime prevalence of 10.7% among teens with 88% reporting persistent insomnia [10].

Etiology: Impaired regulation of the stress response and hyperarousal are neurobiological factors contributing to insomnia. Sleep reactivity refers to the propensity for individuals to experience sleep disturbance in response to stress. Sleep reactivity does predict the development of chronic insomnia [11]. Resting state functional MRI (magnetic resonance imaging) studies have demonstrated aberrant functional connectivity in the default mode network and salience network associated with

insomnia. The complex changes demonstrated in these networks result in hyperarousal and disturbed regulation of emotions and response to stress [12]. Individuals are likely to be genetically predisposed to insomnia with environmental factors such as adverse childhood experiences resulting in the full manifestation of the disorder. It appears that insomnia is more likely related to dysfunction in the brain circuits involved with regulation of emotion and arousal, rather than those circuits responsible for circadian and homeostatic regulation of sleep. It has been recently hypothesized that this may be related to hypersensitivity or overwhelming input to the locus coeruleus from the salience network even during REM (rapid eye movement) sleep [13].

Differential Diagnosis: The differential diagnosis for insomnia in childhood includes biological and behavioral causes. The biological causes, often identified as intrinsic factors, consist of medical conditions that can lead to sleeplessness such as pulmonary conditions inclusive of asthma and chronic cough, gastrointestinal disorders including gastroesophageal reflux and milk soy protein intolerance, dermatological processes resulting in pruritus such as atopic dermatitis, and almost any disorder resulting in pain [7, 14]. Neuropsychiatric disorders that are considered intrinsic factors for insomnia include anxiety, depression, post-traumatic stress disorder, and attention-deficit hyperactivity disorder (ADHD) [15]. Insomnia is very common in children on the autism spectrum [16]. Behavioral and environmental causes, also known as extrinsic factors, are almost certainly the leading causes for insomnia in childhood. "Screen time" which means the amount of time children are exposed to a lighted video screen such as a cell phone has a negative impact on physical and cognitive abilities in children leading to obesity, sleep disruption, anxiety, and depression [17]. Specifically with respect to sleep, exposure to a light source at bedtime suppresses melatonin release shifting the circadian sleep wake pattern resulting in delayed sleep onset and decreased morning alertness [18]. Behavioral issues that result in insomnia are related to caregiver or patient behaviors that inadvertently lead to impaired sleep. This type of insomnia is classified as behavioral insomnia of childhood. One subtype of behavioral insomnia is the limit-setting subtype characterized by bedtime struggles and stalling behaviors. The sleep onset association subtype is due to learned behaviors associating certain caregiver actions (simple presence, rocking or singing) or environmental cues (pacifier, blanket, stuffed animal) with falling asleep [19].

Diagnostic Approach—History: The evaluation for insomnia in childhood is based on a detailed sleep history. Formalized questionnaires such as the BEARS sleep screening tool and the Children's Sleep Habits Questionnaire (CSHQ), among others, can be useful [20–22]. The BEARS acronym outlines the basic elements of a sleep history inclusive of: B = Bedtime Issues, E = Excessive Daytime Sleepiness, A = Night Awakenings, R = Regularity and Duration of Sleep, and S = Snoring. If the parent answers in the affirmative to any of the screening questions then additional information should be elicited [23]. Sleep diaries provide essential information regarding a child's sleep patterns. The presence of significant and severe psychiatric comorbidities, including suicidality, makes screening for these disorders in children and teenagers with insomnia very appropriate [24, 25].

Diagnostic Approach—Physical Examination: Physical examination should be guided by the medical conditions that might contribute to insomnia or comorbid sleep disorders including obesity, craniofacial anomalies and pulmonary disease [26].

Diagnostic Approach—Evaluation: An actigraphy device can be worn in a relatively unobtrusive manner on the wrist or ankle to measure the acceleration or deceleration of body movements. These measures indirectly indicate the state of sleep or wakefulness. Actigraphy can provide more objective data regarding sleep patterns [27]. Although widely used, consumer sleep wearable devices are not yet validated for tracking sleep patterns [28, 29]. Polysomnography (PSG) is not required unless sleep history raises concerns of obstructive sleep apnea (OSA) or restless leg syndrome/periodic limb movement disorder of sleep [27].

Treatment/Management: The most effective treatment for pediatric insomnia based upon the preponderance of evidence is behavioral therapy. The key features of behavioral treatment for infants and young children include consistent bedtime routines, institution of appropriate sleep association and development of self-soothing skills, positive reinforcement of appropriate sleep behaviors and decreased caregiver attention for disruptive bedtime behaviors [30, 31]. Sleep training is the term often used to describe the behavioral interventions to address infant and toddler sleep problems. Sleep training includes strategies such as unmodified extinction, otherwise known as "cry it out," in which caregivers put child to bed and ignore the child until morning, monitoring for safety and illness concerns. A more palatable approach for parents involves graduated extinction in which the caregiver ignores crying or tantrums for progressively lengthening time intervals before checking on the child. This approach enables the child to develop self-soothing skills and promotes independent sleep [32]. While sleep training is often used to improve sleep for infants and younger children prior to the development of chronic insomnia, Cognitive Behavioral Treatment for Insomnia (CBT-I) is an evidence-based behavioral therapy that effectively treats insomnia for older children, adolescents and adults. Components of CBT-I include stimulus control to strengthen the association between the bed and sleep, sleep restriction to limit the time spend in bed not sleeping, cognitive therapy to identify and change beliefs that interfere with sleep, as well as relaxation techniques aimed at reducing anxiety related to sleep [33]. Sleep hygiene rules entail a consistent place to sleep (children should have their own bed, regular bedtimes, avoidance of lying in bed for too long while waiting to sleep, a sleep supporting environment (comfortable temperature, minimal light, quiet), reduction of light exposure prior to bedtime (no lighted screens for 30 min before sleep), reduction of stimulating activity before bed, adequate physical activity during the day with no napping permitted during the day [34]. Education in the principals of sleep hygiene is a core component of CBT-I which although necessary may not, in and of itself, be sufficient for treating insomnia [35, 36].

Pharmacotherapy for pediatric insomnia is not recommended as a first-line treatment. Medications should be used only when behavioral interventions are ineffective and should always be used in conjunction with behavioral treatment [37]. There

is growing consensus that treatment of pediatric insomnia with melatonin is safe and likely to be effective both for neurotypical children and those with neurodevelopmental disorders [38–42]. Recommended dosing is 1 mg in infants, 2.5–3 mg in older children, and 5 mg in adolescents [37]. There are guidelines for use of melatonin to treat insomnia in children on the autism spectrum [43]. Alpha-2 adrenergic agonists, clonidine and guanfacine, are also used for the treatment of insomnia both in neurotypical children and those with neurodevelopmental disorders based on limited data [44]. As both the extended-release preparations of clonidine and guanfacine are approved for use in treatment of ADHD in children, we have considerable data regarding their safety [45]. Doxepin is tricyclic antidepressant agent that is approved for the treatment of insomnia in adults at a low dosage due to preferential binding to H1 receptors at doses less than 10 mg [46]. An open-label observational study at a single center suggested that low dose doxepin is effective and well tolerated in children proposing an algorithm in which this agent is tried after failure of behavioral interventions and melatonin [47]. Agents approved for the treatment of insomnia in adults including benzodiazepines, nonbenzodiazepine receptor agonists, melatonin receptor agonist, and dual orexin receptor agonists all have very limited or no pediatric data upon which to base their use [37]. Although commonly recommended, diphenhydramine was found to be no more effective than placebo in a randomized controlled clinical trial [48]. Other sedating tricyclic antidepressant and atypical neuroleptic agents have been tried for the treatment of insomnia in children with neurodevelopmental disorders with very limited evidence [49].

Prognosis/Outcome: Concern has been expressed in the popular media that the type of sleep training used to address sleep problems in infants and young children may lead to emotional problems later in childhood, but the medical literature does not support this conclusion. In fact, there is evidence to support that sleep training may have a positive impact beyond improvements in children's sleep [19]. Poor sleep habits in adolescents can lead to chronic insomnia [33].

When to Refer: Children and adolescents with severe, persistent and disruptive insomnia that is not responding to simple behavioral measures should be referred to a behavioral health specialist for further evaluation and treatment [50].

Prevention: A online insomnia program has been demonstrated to prevent depressive episodes in individuals 18–64 years of age with insomnia who did not meet criteria for major depressive disorder [51].

Clinical Pearls/Key Points

- Insomnia is very common in children and adolescents.
- The most important aspect of the diagnostic approach is a detailed sleep history.
- Behavioral interventions are the preferred therapeutic approach.
- Melatonin is safe and likely to be effective.
- There is limited evidence to support pharmacotherapy which should be considered only after other treatments have failed.

3 Restless Leg Syndrome/Periodic Limb Movement Disorder of Sleep

Restless leg syndrome (RLS) and the closely related periodic limb movement disorder of sleep (PLMDS) are classified as sleep-related movement disorder in the ICSD-3. RLS is defined as "a sensorimotor disorder characterized by a complaint of a strong, nearly irresistible urge to move the limbs." Periodic limb movement disorder of sleep is defined by "periodic episodes of repetitive, highly stereotyped limb movements that occur during sleep (PLMDS), in conjunction with clinical sleep disturbance or fatigue that cannot be accounted for by another primary sleep disorder or other etiology" [3]. RLS makes it difficult to fall asleep leading to bedtime refusal and delayed sleep onset. PLMDS results in difficulty falling asleep and frequent awakenings result in daytime sleepiness and behavioral problems [52, 53]. Periodic limb movements of 5/h or greater are commonly associated with RLS in children. These movements occur in 70% of RLS cases on a single sleep study and up 90% if multiple polysomnographic studies are performed. Although very common in RLS, their presence is not considered to be pathognomonic [53–55].

Epidemiology: RLS occurs in childhood with a frequently cited prevalence of 2–4% [56]. Periodic limb movements of greater than 5/h are considered to be uncommon in typically developing children (0–5%) but much more common in those with ADHD (24–64%) [57–59].

Etiology: The familial nature of RLS is well established with greater than 90% of children having affected family members [60, 61]. Genome wide association studies point to allelic variations in six different genes that confer risk for RLS in nearly 80% of the population [62]. Polymorphisms in the BTBD9 gene were associated with low ferritin levels and periodic limb movements in adults with RLS [63]. The BTBD9 gene codes for a protein that is involved in multiple cellular functions including transcription, cytoskeletal arrangement, ion conductance, and protein ubiquitination. BTBD9 knockout mice demonstrated alterations in neuronal activity in the striatum, cerebellum, and primary sensory cortex [64–66]. In children with restless leg syndrome, polymorphisms were demonstrated in MEIS1 but not in BTBD9 [60]. The function of the protein coded for by this gene is still not completely understood but it does have a role in iron homeostasis in the brain and in dopaminergic neurons in the substantial nigra and red nucleus [67]. Both RLS and PMDS are related to an impairment in dopaminergic neurotransmission that is linked to brain iron status [68–70].

Differential Diagnosis: Secondary causes of RLS/PLMDS must be considered including peripheral neuropathy, iron deficiency anemia, and renal insufficiency [71]. There is considerable overlap between the symptoms of growing pains and those of RLS. Growing pains are distinguished from RLS by lack of urge to move. Growing pains are always painful, as the name implies, while RLS sensory symptoms are not always painful [72, 73]. A variety of medications and substances can also provoke or aggravate RLS including many drugs used to treat psychiatric disorders including selective serotonin reuptake inhibitors, tricyclic antidepressants,

venlafaxine, and mirtazapine. Substances that exacerbate RLS include nicotine, caffeine, and alcohol [52]. Other conditions that may mimic RLS include positional discomfort, sore leg muscles, ligament or tendon strains, arthritis, Osgood–Schlatter disease, chondromalacia patella, and dermatitis. Differential diagnosis of PLMDS includes hypnic jerks, fragmentary Non-Rapid Eye Movement (NREM) myoclonus, benign neonatal sleep myoclonus, and sleep-related hypermotor seizures. These other sleep-related movements do not exhibit the same degree of periodicity [53].

Diagnostic Approach—History: The diagnosis of RLS is based on history. The established diagnostic criteria are:

(a) An urge to move legs, usually accompanied by or thought to be caused by uncomfortable and unpleasant sensations in the legs. These symptoms must:
    1. Begin or worsen during periods of rest or inactivity such as lying down or sitting
    2. Be partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
    3. Occur exclusively or predominantly in the evening or night rather than during the day.

(b) The above features are not solely accounted from as symptoms of another medical or a behavioral condition (see differential diagnosis).
(c) The symptoms of RLS cause concern, distress, sleep disturbance, or impairment in mental, physical, social, educational, behavioral, or other important areas of functioning [3].

In pediatric patients, the ICSD-3 specifies that the description of RLS sensory symptoms and movements must be "in the child's own words" [3]. It is noted that children do not use the word "urge" to describe the sensation but rather use phrases like "need to," "have to," or "got to." Children use the word "kick" to describe the movement. This is a useful word to use when attempting to elicit a history of periodic limb movements in children. Children use words like "bugs crawling," "weird feelings," and "tingling" [74]. It should be noted that children express similar sensations in the upper extremities and during daytime when not moving [53]. Specific diagnostic criteria for pediatric patients were updated in 2013. Categories for probable and possible RLS were established. The probable RLS category includes all features except the occurrence in the evening or night. The criteria for possible RLS are based on behavioral observations rather than direct report of child [75].

There is a close association between RLS/PLMDS and various neuropsychiatric disorders including ADHD), ODD (oppositional defiant disorder), and depression. In one study, 64% of children with RLS exhibited one or more comorbid psychiatric disorders. The association with ADHD and RLS/PLMS is well established. Twenty-five percent of children with ADHD have RLS [76]. These disorders may share a common etiology related to disordered dopaminergic neurotransmission potentially related to low iron stores [77]. Sleep disruption due to RLS/PLMDS may contribute to daytime neurocognitive dysfunction including impaired attention [78]. Given

these association, screening for ADHD and other neurodevelopmental disorders is appropriate in children with disturbed sleep. Bedtime resistance in autism may be related to restless leg syndrome [79].

Diagnostic Approach—Physical Examination: Careful examination of the skin and musculoskeletal system is important to evaluate for RLS mimics. Neurological examination is aimed at identifying signs of peripheral neuropathy [26].

Diagnostic Approach—Evaluation: RLS is a clinical diagnosis for which polysomnography is not required. The diagnosis of PLMDS requires polysomnography [27]. The polysomnographic criteria are a frequency of >5 periodic limb movements/hour in children [80]. Periodic limb movements must cause significant sleep disturbance or impairment in daytime functioning [3]. Although not required for the diagnosis, a PSG with >5 periodic limb movements per hour is an important confirmatory finding for RLS given the relationship between these disorders [55]. Laboratory studies must include serum ferritin. Relatively low iron stores indicated by ferritin level less than 50 μg/L are associated with RLS/PLMS [70]. As ferritin is an acute phase reactant, this level alone may not be an accurate reflection of iron stores in a pro-inflammatory state (presence of infection, inflammatory disease, obesity). Performing additional iron studies including transferrin saturation and the nonspecific acute inflammation marker, CRP (C reactive protein), would be helpful at accurately determining iron status [81, 82].

Treatment/Management: The International Restless Leg Syndrome Study Group (IRLSSG) offered consensus guidelines with respect to use of iron in the treatment of RLS in 2018. This group concluded that there was insufficient evidence to conclude that iron was effective in the treatment of RLS in children [83]. Improvement of low serum ferritin levels with iron supplementation demonstrated modest improvement in restless sleep and RLS symptoms but did not reach statistical significance [84]. Dye et al. in a retrospective study found sustained improvement in the periodic limb movement index with iron therapy resulting in adequate ferritin levels for pediatric patients [85]. Despite the limited evidence, iron should be considered first line therapy for children the RLS/PLMDS when the serum ferritin level is less than 50 μg/L [86–88]. The recommended dosage is 3 mg of elemental iron/kg/day. Addition of Vitamin C may improve absorption. Calcium and daily products should be avoided within 2 h of administration as these may interfere with absorption. Adverse effects of iron supplementation may include nausea, abdominal pain, constipation and darkening of the stools. Liquid iron may cause staining of the teeth and should be taken with a straw if possible. Iron is contraindicated in hemolytic anemia or hemochromatosis. Intravenous iron can be administered if oral supplementation is not tolerated or ineffective [70, 88]. Nonpharmacological interventions should always be attempted in children. Appropriate sleep hygiene measures must be instituted. Dietary interventions would include avoidance of caffeine and chocolate (theobromine) in the afternoon. Regular physical exercise is helpful but strenuous exercise should be avoided within a few hours of bedtime. Stretching exercises prior to bedtime may help children fall asleep faster. Sensory stimulation such as

rubbing, massaging cool pads, or heating pads may be personalized for each child based on response. Medications known to exacerbate RLS should be avoided including selective serotonin reuptake inhibitors, tricyclic antidepressants, and antihistamines [86, 89]. Avoiding these agents may make the treatment of comorbid psychiatric disorders challenging [52]. There is insufficient evidence to support pharmacotherapy for RLS/PLMDS in children. Pharmacotherapy should be reserved for children who fail iron therapy and nonpharmacological interventions [52, 53, 86]. In adult patients, dopaminergic agents such as pramipexole and ropinirole are approved for treatment of RLS [63]. These agents are generally avoided in children due to concerns about adverse effects. Expert consensus relegates their use to the most severe and refractory cases of pediatric RLS [88]. The alpha-2-delta ligands gabapentin, pregabalin, and gabapentin encarbil have demonstrated efficacy in the treatment of RLS in adults [63, 90]. In pediatric RLS, gabapentin has emerged as the pharmacotherapy of choice despite the lack of clinical trials to support its use. As gabapentin is an approved drug for the treatment of refractory partial seizures in children older than 3 years of age, information about dosing and safety in children is available [88]. Side effects include somnolence and dizziness. Dosing for pediatric insomnia in one study was 5–15 mg/kg at bedtime [91]. A variety of other medications including levetiracetam, clonidine, and clonazepam have been tried in pediatric RLS [52, 53, 86, 88].

Prognosis/Outcome: In adults with early onset RLS, there is a slow progression with sometimes extended periods of stability. There are only a small percentage of cases in which remission occurs [92, 93]. A similar pattern is reported in children [94]. Emerging evidence indicates that RLS/PLMS has negative effects on cardiovascular health in adults [95]. Pregnancy often results in worsening of preexisting RLS and may be associated with new onset of symptoms [96].

When to Refer: Refractory cases that are not responding to first and/or second line treatments may be referred to a pediatric sleep specialist.

Prevention: There are no specific preventive measures recommended. Based upon the emerging understanding of the pathophysiology of RLS/PLMDS, reasonable considerations for prevention might include early identification and treatment of iron deficiency, regular exercise, avoidance of caffeine and nicotine, and appropriate sleep hygiene.

Clinical Pearls/Key Points

- RLS is a clinical diagnosis.
- PLMDS is closely associated with RLS and is diagnosed based on PSG criteria of >5 PLM's/h plus evidence of sleep disruption.
- Iron studies should be performed and treatment with iron instituted if serum ferritin is less than 50 μg/L.
- Pharmacotherapy may be instituted with gabapentin but only if iron supplementation and nonpharmacological interventions prove to be ineffective.

4 Delayed Sleep Wake Phase Disorder

Delayed sleep wake phase disorder (DSWPD) is classified in the ICSD-3 as a circadian rhythm sleep wake disorder. The essential feature of this disorder is "habitual sleep wake timing that is delayed, usually by more than two hours, relative to conventional or socially acceptable timing." Individuals with DSWPD find it very difficult to fall asleep and awaken at times that are acceptable to society. When allowed to sleep according to their preferred schedule, sleep is of normal duration and appropriately restful [3]. This disorder is prevalent in adolescents who have great difficulty awakening for school or work, a source of great frustration to their parents [97]. Adolescents will make up for insufficient sleep by napping during the day [50]. Motivated delayed sleep wake phase disorder is a subtype of DSWPD identified in adolescents who are not motivated to change sleep habits in order to achieve a normal lifestyle. This subtype is associated with autism spectrum disorder, anxiety, social phobia, and school avoidance [26, 50]. DSWPD, as is the case with other sleep disorder, is associated with significant impairment in daytime functioning and psychiatric comorbidities with 70% receiving a lifetime diagnosis of an Axis I disorder [98–100]. It has been posited that DSWPD may be a cause of late-onset ADHD in adolescents [101].

Epidemiology: Reports prevalence of DSWPD are highly variable but it is clear that the disorder is much more common in adolescents and young adults [102]. Prevalence in this age group ranges from 1 to 16% [103].

Etiology: The etiology of DSWPD is unknown but the high prevalence in adolescents and young adults points to a developmental change in sleep physiology. Sleep timing is derived from the interaction between the circadian system and the homeostatic sleep drive [26]. The mammalian circadian system is comprised of multiple cellular clocks located in cells, tissues, and organs. The circadian system exhibits a hierarchical organization with the suprachiasmatic nucleus (SCN) representing the "master clock" [104]. The SCN is synchronized by light through the retinohypothalamic tract with input from a specific subset of retinal light-sensing cells containing melanopsin [26]. SCN neurons project to the pineal gland for the circadian regulation of melatonin secretion. During the day, the SCN sends inhibitory signals which suppress melatonin secretion and during the night excitatory output from the SCN results in increased melatonin synthesis and secretion [102]. The homeostatic sleep drive is increased by the duration of wakefulness and cognitive activity resulting in activation of the sleep-promoting area of the hypothalamus and inhibition of the wake-promoting regions of the hypothalamus as well as wake-promoting basal forebrain.

Significant changes occur in both the circadian and homeostatic processes during adolescents which result in or, at least, predispose to the development DSWPD. Multiple studies have demonstrated reduction in sleep pressure and physiological phase delay in adolescents. The timing of melatonin secretion was progressively delayed based on pubertal stage. Hypersensitivity to evening light and

diminished response to morning light is reported in adolescents. The homeostatic sleep pressure slows at puberty, but the dissipation does not change until mature adolescence indicating the need for sleep is not reduced in the younger adolescents. A leading authority on the development of sleep, Dr. Carskadon, has called this the "perfect storm" referring to the biopsychosocial factors that are converging to interfere with adolescent sleep [105, 106]. Environmental factors contributing to DSWPD in adolescents have been well documented representing the psychosocial part of the "perfect storm" resulting in inadequate sleep for vast swaths of teenagers. The ubiquity of technological devices used by children and adolescents has contributed to an explosion in "screen time" with evening light stimulation disrupting the normal circadian patterns of melatonin secretion with resulting delay in sleep phase [26, 105].

Chronotype refers to a person's natural inclination with regard to the times of day when they prefer to sleep or when they are most alert or energetic. "Larks" exhibit a preference for early morning awakening and "owls" prefer to stay up late. Sixty percent of individuals have a neutral chronotype [105, 106]. Chronotypes are, in part, determined by genetic polymorphisms in circadian clock genes [102]. Twin studies have demonstrated a concordance of 40–50% supporting a genetic contribution to DSWPD. A mutation in the clock gene CRY-1 is associated with familial DSWPD inherited in an autosomal dominant fashion [107].

Differential Diagnosis: An evening circadian preference, "night owl," that does not disrupt daytime functioning is possible if the individual's school or work obligations can be delayed allowing adequate sleep. Differential diagnosis should also include inadequate sleep hygiene, use of stimulant drugs or substances, and chronic insomnia [102].

Diagnostic Approach—History: The diagnosis of DSWPD is based on history and review of sleep logs obtained over 7–14 days, preferably 14 days. The sleep log will demonstrate a consistent delay in the habitual sleep period for both work/school days and free days. Use of standardized chronotype questionnaires (e.g., Morningness-Eveningness Questionnaire) can be helpful to establish the chronotype [3, 26, 97].

Diagnostic Approach—Physical Examination: The general physical examination and neurological examination are usually unrevealing.

Diagnostic Approach—Evaluation: An actigraphy device can be worn in a relatively unobtrusive manner on the wrist, ankle or waist and acts to record the occurrence and degree of limb movements over time. Actigraphy may be obtained over 7–14 days (14 days is preferred) to objectively document a habitual delay in sleep phase [3, 108]. Dim light melatonin onset (DLMO) is a well-studied and accurate marker of circadian phase often considered to be the "gold standard" measurement due to its exceptional reliability. Melatonin levels typically rise about 2–3 h prior to sleep onset. DLMO can be determined based on noninvasive measurement on saliva and/or urine. Testing protocols have been established for both. The measurement of DLMO can confirm the delay in circadian phase [3, 102].

Treatment/Management: Circadian-based therapies for DSWPD are aimed at advancing the sleep phase and consist of light therapy upon awakening and/or strategically time melatonin administration. Based on the clinical practice guideline from the American Academy of Sleep Medicine (AASM) published in 2015, the evidence is only weakly supportive of these treatment approaches [109]. Timing of these therapies is considered to be important. Light administered before the nadir in core body temperature which typically occurs about 2 h prior to awakening advances the sleep phase. Light administered after the nadir in temperature delays the sleep phase. Dosing of light considered to be optimal is 10,000 lux for 30–45 min. Exposure to sunlight outdoors is effective, but if not possible, then relatively inexpensive light boxes can be purchased [26, 97, 102, 110]. Melatonin exhibits the most potent phase-advancing effect when given 3–5 h prior to the DLMO. If given 2–3 h after the DLMO, this effect is lost or reversed. Starting at a low dose of melatonin (0.2–0.5 mg) administered 3–4 h prior to the actual bedtime is suggested [26, 38].

Phase advancement combined with light therapy and/or melatonin is used when the difference between the current sleep onset and desired sleep onset is less than 3 h. Waketimes are shifted by 30–60 min each day or every other day. Light therapy is employed upon awakening. This schedule can be slowed if needed for patients with very chronic sleep phase delay. Sleep restriction is employed to augment homeostatic sleep drive resulting in readiness to fall asleep earlier. Chronotherapy or phase delay is utilized for more severely delayed sleep phase, that is, a delay of greater than 3 h. This approach involves delaying sleep onset and awakening by 2–3 h daily to every other day until the desired sleep wake schedule is achieved [50]. Considerable motivation is required for adherence to these treatments both from teenagers and their parents [50, 111].

Prognosis/Outcomes: There is evidence that circadian-based therapies do improve sleep parameters and cognitive outcomes in adolescents but relapse occurs in a substantial minority [112, 113].

When to Refer: Referral to a behavioral health specialist with expertise in sleep disorders is appropriate for chronotherapy [50].

Prevention: The American Academy of Sleep Medicine recommends delaying school start times to "ensure that every student arrives at school healthy, awake, alert, and ready to learn" [114].

Clinical Pearls/Key Points

- DSWPD is quite common in adolescents and young adults resulting in significant daytime social, emotional, occupational, and educational impairment.
- Genetic variations, developmental changes in sleep regulation, and psychosocial factors are predisposing or causative.
- Circadian-based therapeutic approaches include light therapy and/or appropriately timed melatonin administration.
- Adherence to therapeutic interventions requires considerable motivation by all concerned.

5 Parasomnias

Parasomnias are "undesirable physical events or experiences that occur during entry into sleep, within sleep or during arousal from sleep" [3]. Parasomnias may occur during NREM, REM sleep, or transitions to and from sleep [3]. Parasomnias that occur during NREM sleep are very common during childhood and are most often benign [26]. The REM sleep-related parasomnia known as REM sleep behavior disorder (RBD) is very rare in childhood and is manifested by dream enactment. In childhood, RBD occurs in association with narcolepsy and neurodevelopmental disorders [115]. NREM parasomnias are considered to be disorders of arousal. Three main subtypes with overlapping features are observed: confusional arousal, sleepwalking, and sleep terrors. During confusional arousals, patients exhibit confused mentation and behaviors but do not exhibit terror or ambulation outside the bed. Sleepwalking is characterized by variably complex behaviors that result in the patient leaving the bed sometimes simply standing at the bedside or walking about in an agitated state. Semi-purposeful behaviors such as eating or drinking can be associated [26, 116, 117]. Sleep terrors, also called night terrors or pavor nocturnus, result in extreme terror or panic associated with vocalizations, movements, and autonomic activity arising suddenly out of sleep. The affected child may exhibit fearful screaming vocalizations, inconsolable crying, and frantic motor activity as if trying to escape from an unseen danger. Autonomic hyperactivity consists of tachycardia, tachypnea, diaphoresis, mydriasis, tremulousness, and muscular rigidity. Recall for the event, if present at all, may include fragmentary dream images with threatening or fear-inducing content. Duration of the episodes is typically on the order of minutes but can last up to hours [26, 116–118].

Epidemiology: NREM parasomnias are common in children decreasing in prevalence with age [117]. Seventy-eight percent of all children had at least one childhood parasomnia [119]. The peak prevalence for sleep terrors was at 18 months of age (34.4%) and for sleep walking at 10 years of age (13.4%). One-third of children with sleep terrors developed sleep walking later in childhood [120]. All NREM parasomnias exhibit much lower prevalence figures in adults [117, 121].

Etiology: The pathophysiology of NREM parasomnias involves a genetic predisposition, sleep state instability, sleep inertia, and state dissociation. An HLA DQB1 allele was identified in 35% of sleepwalkers and only 13.3% of normal controls [122]. A positive family history is found in up to 80% of children with disorder of arousal [123]. Sleep state instability refers to the propensity for arousals during NREM sleep. The analysis of the cyclic alternating pattern, the periodic variation in cerebral electrical activity during NREM sleep, demonstrate that sleep walking and sleep terror patients exhibit instability of NREM sleep [124, 125]. The incomplete awakening or disengagement form sleep is known as sleep inertia. Functional neuroimaging and electrophysiological studies demonstrate that awakening is a gradual process which is exaggerated in NREM parasomnias [125–127]. Sleep states, although conceived as distinct, are on a continuum and it is possible to span two

states. This phenomenon is known as sleep state dissociation. Functional neuroimaging and electrophysiological studies have also confirmed the existence of sleep state dissociation in NREM parasomnias [125, 128–130]. The underlying NREM instability is exacerbated by precipitating factors such as sleep deprivation, sedating medications, alcohol, and comorbid sleep disorders such as OSA and RLS/PLMDS. There is also an association between NREM parasomnias and anxiety in children [119].

Differential Diagnosis: Physicians are often tasked with the project of distinguishing sleep-related hypermotor seizures, formerly called nocturnal frontal lobe epilepsy from NREM parasomnias. Dysfunction in the arousal system may represent a shared pathogenic mechanism for both sleep-related hypermotor epilepsy (SHE) and parasomnias [131]. Sleep-related hypermotor seizures tend to occur very frequently during sleep with 1–20 events per night. Paroxysmal arousals and minor motor events are characterized by very brief stereotyped movements lasting seconds. Sleep-related hypermotor seizures can exhibit bizarre clinical features that result in confusion with psychogenic nonepileptic events, but the latter should never arise from sleep [132]. The complex motor activity that occurs in both parasomnias and sleep-related hypermotor seizures likely represents activation of central pattern generators located in the midbrain, pons, and spinal cord. The clinical distinction between NREM parasomnias and SHE is very difficult due to these shared clinical features and comorbidity [132–135].

Diagnostic Approach—History: The diagnosis of NREM parasomnias is based upon history. A detailed inquiry must be conducted into the characteristics of the sleep-related behavior. This inquiry should include the timing, frequency, and duration of the events [134]. A video recording of the behavior in question is very helpful [117]. Historical features that support the diagnosis of NREM parasomnia include consistent occurrence in the first third of the night when slow wave sleep density is greatest [116, 117, 136]. Sleep-related hypermotor seizures tend to be very brief, almost always less than 2 min, and occur very frequently during the course of the night. Parasomnias are less frequent and of longer duration [134, 137]. Structured assessments have been developed to aid in the distinction of sleep-related hypermotor seizures from NREM parasomnias including the Structured Interview for Nocturnal Frontal Lobe Epilepsy and Frontal Lobe Epilepsy and Parasomnia Scale which demonstrate good diagnostic specificity [138, 139]. Screening questions for comorbid sleep disturbances such as OSA and RLS/PLMDS are important. Patients with very frequent NREM parasomnias, occurring 2–3 times per week, may have a comorbid sleep disorder that results in sleep disruption. OSA is more likely the cause than RLS/PLMDS [140, 141]. The clinical history should include queries about snoring (volume and frequency), mouth breathing, difficulty breathing (gasping, struggling to breath, heavy breathing), hyperextension of neck, sleeping in seated position, diaphoresis, and enuresis [26]. Children with OSA are much less likely to present with excessive daytime sleepiness [142] and far more likely to experience daytime behavioral and/or neurocognitive symptoms [143].

Diagnostic Approach—Physical Examination: There are no specific physical examination findings for NREM parasomnias in children but a careful physical

examination to assess the upper airway patency to evaluate for comorbid OSA is important [140]. Attention should be paid to body habitus, height, weight, body mass index, and neck size. In the past, OSA was associated with failure to thrive, but in the twenty-first century, obesity has emerged as a major risk factor for pediatric OSA [144]. The examination should include tonsillar size, nasal patency, integrity of palate, and position of mandible [26]. Assessment of oropharyngeal crowing can be scored using the Mallampati scale [145, 146]. Adenotonsillar hypertrophy is an important risk factor for pediatric OSA [147, 148].

Diagnostic Approach—Evaluation: Polysomnography is not required for the diagnosis of a NREM parasomnia when the clinical presentation is typical. PSG with expanded EEG monitoring is an option for atypical presentations or potentially injurious parasomnias and to differentiate a parasomnia from sleep-related hypermotor seizures [27]. Video EEG monitoring represents the "gold standard" for the diagnosis of sleep-related hypermotor seizures but the inaccessibility of much of the frontal lobe to scalp EEG and obscuring muscle artifact can represent significant challenges to confirming an epileptic basis for complex sleep-related behaviors [149–151]. The clinical history for OSA in children is not reliable, specifically history cannot distinguish between primary snoring and OSA [152–155]. For this reason in children with snoring and frequent NREM parasomnias, a PSG should be strongly considered to exclude comorbid OSA [140].

Treatment/Management: NREM parasomnias that occur infrequently in healthy children and adolescents are typically benign and do not require any specific treatment beyond reassurance [26, 116, 117, 140]. Attempts to interrupt the episode should be avoided as these may inadvertently result in increased confusion and may provoke a violent reaction [156, 157]. The episode should be allowed to resolve on its own and the child should be guided gently back to bed. Modifications of the environment may be required to ensure the safety to the child including locating bedroom on the ground floor, placing mattress on the floor and door alarms. Dangerous objects should be removed from the bedroom [116, 117, 158]. Scheduled awakenings can be effective in about 60% of cases. This technique involves anticipatory awakening about 15–20 min prior to the habitual parasomnia episode in order to shift the child into a lighter stage of sleep thereby preventing the episode from occurring. Repetition of this practice results in prompt extinction of the behavior [158, 159]. Hypnotherapy is a helpful psychotherapeutic intervention for NREM parasomnias [160, 161]. Pharmacotherapy for parasomnias is based upon anecdotal and retrospective data. There are no properly powered, randomized clinical trials to support the use of medications for NREM parasomnias. Fortunately, medications are rarely needed in children and adolescents. The indications for medication treatment would include persistence of frequent and severe episodes despite adequate nonpharmacological interventions especially if there exists a high risk of injury. The most commonly used medications are the intermediate and long activity benzodiazepines with clonazepam representing the agent most commonly employed. Antidepressant medications including both tricyclic and selective serotonin reuptake inhibitors have been tried [140, 156, 159, 162, 163]. There are some case reports that support the use of melatonin [164, 165].

A critical aspect of the treatment of NREM parasomnias in childhood is appropriately addressing comorbid sleep disorders that provoke episodes. The first-line treatment for OSA in children is adenotonsillectomy [166–169]. Positive airway pressure is indicated in obese children and those who respond incompletely to adenotonsillectomy, but significant challenges exits in administering this therapy to children [170]. Other treatments employed for OSA in childhood include medical treatment with anti-inflammatory agents such as nasal corticosteroids and montelukast [171], maxillary expansion and myofunctional therapy. Each of these approaches has only low-quality evidence to support their use [166]. Note that montelukast can result in nightmares and parasomnias as a side effect [172]. Adenotonsillectomy in children with OSA and NREM parasomnias does result in resolution of the parasomnia [141]. Treatment of comorbid RLS/PLMS with iron also has a favorable impact on NREM parasomnias [173].

Prognosis/Outcomes: NREM parasomnias during childhood are common but generally benign disorders declining in prevalence with age into adulthood due to decreased slow wave sleep density with aging [117].

When to Refer/Admit: The diagnostic evaluation of SHE and treatment, especially when medically refractory, requires referral to a pediatric epilepsy center [174].

Prevention: Attention to sleep hygiene is important to prevent sleep disruption [158]. Addressing deficiencies in the sleep environment, especially the number of co-sleeping members and dysfunctional beliefs regarding sleep, may help to prevent NREM parasomnias in children [175].

Clinical Pearls/Key Points

- NREM parasomnias are common in childhood and are generally benign.
- Distinction from SHE can be very difficult in certain cases given the shared clinical features and comorbidity requiring PSG combined with video EEG.
- Evaluation for comorbid sleep disorders such as OSA and RLS/PLMDS in children with frequent NREM parasomnias will likely require a PSG.
- Treatment of OSA and RLS/ PLMDS favorably impacts frequent NREM parasomnias.
- Treatment of infrequent NREM parasomnias is often not required and simple reassurance can be provided to concerned family members with appropriate attention to child safety.

6 Narcolepsy

Narcolepsy is a rare sleep disorder with the cardinal feature of excessive daytime sleepiness [3, 176, 177]. Excessive daytime sleepiness (EDS) is defined as the "inability to stay awake and alert during major waking episodes of the day resulting in periods of irrepressible need for sleep or unintended lapses into drowsiness and sleep" [3]. Narcolepsy is classified as Type I or Type II based on presence (Type I)

or absence (Type II) of cataplexy [3, 176, 177]. Cataplexy is defined as "more than one episode of generally brief (<2 min), usually bilaterally symmetrical loss of muscle tone with retained consciousness" [3]. Cataplexy is evoked by strong emotions with laughter, in particular, representing a frequent precipitant [3, 178, 179]. Deep tendon reflexes are absent during the cataplectic attack [178, 180, 181]. Complete attacks of cataplexy lead to collapse with loss of postural control resulting in falls. Partial attacks may be much more subtle with loss of facial tone and head nods [3, 178, 180, 182]. Children may exhibit "cataleptic facies" characterized by open mouth, tongue protrusion and drooping eyelids [183]. Cataplexy in children may develop after the onset of EDS leading to initial "misdiagnosis" of narcolepsy type II [184–187]. The clinical features of childhood cataplexy vary from those typically seen in adults in that episodes can be unprovoked and are more often associated with positive motor phenomena such as facial grimacing, eyebrow raising, tongue movements and "puppet-like behavior" [185, 186, 188]. EDS and cataplexy are specific to narcolepsy but other sleep symptoms are commonly associated including hypnagogic or hypnopompic hallucinations, sleep paralysis, and difficulty with maintenance of sleep [3, 176, 177]. The classic pentad of narcolepsy (EDS, cataplexy, hypnogogic/hypnopompic hallucinations, and fragmented sleep) does not develop simultaneously in children. The prevalence of hallucinations ranges from 39 to 50% in children. Sleep paralysis occurs in 25–74% of pediatric cases [185, 186]. Sleep is fragmented and nightmares are common in children [189].

Epidemiology: The most commonly cited prevalence figure for narcolepsy is 1 per 2000 individuals in the Caucasian population. The highest prevalence occurs in Japanese populations and lowest prevalence occurs in Semitic populations. Narcolepsy most often starts in adolescence with a second peak at 35 years of age. In 10–15% of patients, narcolepsy starts before the age of 10 years [176, 177, 190]. In Europe from 2000 to 2010, the pooled incidence of narcolepsy in children was 0.93 per 100,000 person years.

Etiology: Narcolepsy type I (NT1) is caused by loss of orexinergic neurons in the lateral hypothalamus. The pathogenesis of narcolepsy type II (NT2) is not as well understood; however, there is evidence that the orexin neurons are also affected but to a lesser degree [176, 177, 190]. Orexin A and Orexin B are neuropeptides that act through specific receptors in multiple brain networks to stabilize sleep states. The deterioration of orexinergic function in narcolepsy results in poor maintenance of wakefulness and impaired regulation of REM sleep. The atonia that occurs in cataplexy and sleep paralysis likely represents dysregulated function of the brainstem pathways that produce the physiological paralysis associated with REM sleep. The best way to characterize the pathogenesis of NT1 is the "multiple hit hypothesis" which posits an underlying genetic predisposition, environmental factors and triggering events which lead to immune-mediated destruction of the orexin-producing neurons in the lateral hypothalamus [176]. The association of narcolepsy with HLA class II antigens first discovered in the 1980s promptly directed attention to the immune system as a potential actor in the pathogenesis of narcolepsy. The HLA-DQB*06:02 is present in the majority of patients with NT1 and about half of those with NT2 but only very rarely in the general population [191]. There was marked

spike in the incidence of narcolepsy, especially in children, associated with the administration of a specific influenza vaccination in Europe and H1N1 outbreak in China in 2009.

Differential Diagnosis: Insufficient sleep is the leading cause of daytime sleepiness in adolescent patients [192, 193]. As discussed in the section of DSWPD, this is related to societal factors including widespread electronic use [105, 194, 195]. Idiopathic hypersomnolence (IH) begins in adolescence. IH is characterized by EDS but there are not sleep onset REM periods (SOREMP) on MSLT (multiple sleep latency test) and cataplexy is absent [3, 196]. Excessive sleepiness can be associated with psychiatric disorders including depression [197]. The use or abuse of prescription and recreational drugs must also be taken into account when evaluating an adolescent for EDS [193]. Episodes of hypersomnia raise the possible diagnosis of Kleine–Levin syndrome (KLS). KLS also exhibits onset in adolescence and is far more common in boys than girls. Episodes of hypersomnia last for weeks during which the affected individual will sleep from 12 to 20 h/day. Associated cognitive and behavioral disturbances include disturbed eating behaviors (anorexia or hyperphagia), cognitive impairment, and disinhibited behaviors (hypersexuality). Interictal behavior sleep patterns and behavior are normal [192, 198, 199]. There are very few disorders that must enter the differential diagnostic considerations for cataplexy including genetic and metabolic disorder such Niemann–Pick Type C, Prader–Willi syndrome, Norrie disease, Moebius syndrome, and Angelman syndrome [178, 200–202]. The stimulus induced drop attacks seen in patients with Coffin Lowry appear similar to cataplexy but are induced by unexpected tactile or auditory stimuli [203]. Cataplexy associated with ataxia should raise suspicion for a DNA methyltransferase mutation [204, 205]. Pseudocataplexy refers to episodes that clinically appear consistent with cataplexy but are likely psychogenic in etiology [178, 206]. As is the case with psychogenic nonepileptic events that occur in patients with epilepsy, pseudocataplexy can occur in patients with NT1 [207]. Based on video recordings of cataplexy, the facial atonia with abrupt termination of laughter and associated facial jerks prior to loss of postural control are characteristic of cataplexy aiding in the distinction from pseudocataplexy [180].

Diagnostic Approach—History: Differentiation of fatigue from excessive daytime sleepiness is important. Fatigue is characterized as lack of physical energy and feeling of muscular exhaustion [192]. Excessive daytime sleepiness refers to an inability to stay awake with unintended lapses into drowsiness or sleep [3]. A detailed sleep history should be obtained from parents, child and any relevant caretakers. Sleep logs or diaries are a very helpful adjunct to this history [208]. The sleep history should include bedtimes, wake times, and nap times during the school week and on weekends. The history should include the likelihood that the child will fall asleep in usual positions such as standing and during various activities such as riding in car, watching television, in classroom, or during meals [209]. The sleep questionnaires validated for adults are often also used in children to supplement the history and quantify the degree of sleepiness. The commonly used Epworth Sleepiness Scale has been modified for children but studies confirming validity are still lacking. Parents or caretakers are often called upon to answer questions for

younger children who may not fully understand the instrument leading to concerns about accuracy [210, 211]. Children with narcolepsy often experience academic underachievement despite normal intelligence. Children who are sleepy can be perceived as "lazy" or unmotivated. ADHD is a comorbidity and may also be associated with comorbid OSA. Review of the child's school performance is an important part of the initial evaluation for narcolepsy [158, 185, 212, 213]. The very common association of narcolepsy in children with emotional and behavioral problems merits screening for these comorbidities. A biopsychosocial approach to narcolepsy is appropriate [214–217]

Diagnostic Approach—Physical Examination: There are no physical examination findings that support the diagnosis of narcolepsy. Attention to body habitus, weight, body mass index, and upper airway patency are important as abnormalities may support comorbid OSA. This is particularly important given association between obesity and narcolepsy in children. Rapid weight gain is often noted in temporal proximity to onset of narcolepsy symptoms [186]. Obesity is noted in 25–75% of children with narcolepsy, more commonly in NT1 than in NT2. Physical examination should also include assessment of Tanner stage as narcolepsy has been associated with precocious puberty [185]. Dysmorphic features may support an identifiable genetic syndrome associated with cataplexy. Neurological examination should be normal in children with NT1 and NT2. Abnormal findings on neurological examination might support other causes of cataplexy such as Niemann–Pick Type C (supranuclear gaze palsy), Norrie Disease (retinopathy, deafness), Moebius syndrome (bilateral VI and VII nerve palsies), and Autosomal Dominant Cerebellar Ataxia with Deafness and Narcolepsy due to DNA methylase 1 mutation [200].

Diagnostic Approach—Evaluation: The objective documentation of excessive daytime sleepiness requires the Multiple Sleep Latency Test (MSLT). The recommendation is that the MSLT be conducted after 2 weeks of adequate sleep with actigraphy documentation. The study is performed following a PSG which is required to document adequate sleep and exclude other sleep disorders [3]. This test involves electrophysiological monitoring during a series of five naps lasting 20 min initiated every 2 h during the day. Sleep latency and occurrence of REM sleep are assessed. A sleep onset REM period (SOREMP) is the occurrence of REM sleep within 15 min of sleep onset [90]. In order to meet the established diagnostic criteria for narcolepsy, the mean sleep latency must be less than or equal to 8 min and there must be two or more SOREMPs [3]. The MSLT has been validated for the diagnosis of NT1 in children [218]. Genetic testing for HLA-DQB1*06:02 if positive adds little to the diagnosis but a negative result makes NT1 highly improbable. CSF orexin level represents the most sensitive and specific test for NT1. The CSF orexin is less than 110 pg/ml or undetectable in NT1. In patients without cataplexy and those who are HLA-DQB1*06:02 negative, the CSF orexin level is often normal [176, 177, 190]. Clinical scenarios in which CSF orexin testing might be considered include patients with nondiagnostic PSG/MSLT in a patient with cataplexy and EDS, or a nondiagnostic PSG/MLT in a patient who does not exhibit cataplexy but has EDS and is HLA-DQB1*06:02 positive. It may also be useful in a patient with suspected narcolepsy based on symptoms of EDS and cataplexy and

HLA-DQB1*06:02 positivity who cannot stop REM suppressing medications due to safety concerns. CSF orexin determination should be considered in very young children with EDS in whom cataplexy may be difficult to establish and PSG/MSLT may be nondiagnostic [219].

Treatment/Management: Nonpharmacological interventions for childhood narcolepsy include sleep hygiene education. Scheduled napping can be an effective measure to deal with daytime sleepiness. Given the association between narcolepsy and obesity, dietary education and implementation of an exercise program is important. Children with narcolepsy often exhibit academic underachievement so school services should be mobilized with a 504 plan and/or an Individualized Educational Program. Close attention to psychiatric comorbidities with prompt institution of psychotherapy and pharmacotherapy is appropriate. Cognitive behavioral therapy for narcolepsy focuses on maintaining good sleep hygiene practices and adhering to medication treatment. Social support can be provided by specific narcolepsy patient organizations. Education regarding safety including discussion of driving restrictions is critical [219–222]. Sodium oxybate is the only FDA-approved medication for the treatment of EDS in children and adolescents. All other medications are administered on an off-label basis [220, 221]. Sodium oxybate, a GABA B receptor agonist, is effective at treating both EDS and cataplexy [223]. This medication is distributed through a specialized central pharmacy with registration required in order to prescribe. Suggested dosing is from 2 to 8 g per night administered in divided doses just before bedtime and 2.5–3 h later. Modafinil and armodafinil are very commonly prescribed for children to treat EDS although the FDA approval is for individuals older than 16 years of age. The exact mechanism of action of these agents is unknown. Armodafinil is more potent and has a longer half-life than modafinil. Stevens Johnson syndrome is a rare potential side effect. The psychostimulant medications methylphenidate and mixed amphetamine salts are also commonly used to treat EDS in children. These medications are FDA approved for the treatment of ADHD in children and have demonstrated efficacy for EDS in adults. The relatively low cost and prescriber comfort due to widespread use for ADHD support their use as first-line agents [220, 221]. Pitolisant, a novel histaminergic alerting agent, is FDA approved for the treatment of EDS and cataplexy in adults. A small case series in adolescents demonstrated good tolerability and reduced EDS. A clinical trial to evaluate efficacy in children is ongoing [224]. As noted, sodium oxybate is the only FDA approved drug for the treatment of cataplexy in children. Tricyclic agents, selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors are used for cataplexy treatment off-label. Note that these agents carry a “black box” warning regarding suicidal ideation in adolescents and young adults [220, 221]. Although immune-mediated damage to orexin neurons is a very likely the cause for NT1, there is insufficient evidence to support immunomodulatory treatments at this time [225].

Prognosis/Outcomes: Narcolepsy is a lifelong condition that requires ongoing monitoring and treatment [177].

When to Refer/Admit: Referral to a behavioral health specialist for cognitive behavioral therapy is indicated. Referral to a child psychiatrist for management of comorbid psychiatric conditions may also be appropriate.

Prevention: There are no preventative strategies for narcolepsy [177]. The increased prevalence of narcolepsy in Northern Europe after vaccination with a specific adjuvanted vaccine has not been seen with other types of influenza vaccinations. The benefits of influenza immunization still far outweigh the risks [158, 226–228].

7 Clinical Pearls/Key Points

- The diagnosis of narcolepsy in childhood requires a high degree of clinical suspicion.
- A comprehensive sleep history is essential with objective documentation of EDS by MSLT.
- Evidence points to immune-mediated injury of orexin neurons as the cause for NT1, but there is insufficient evidence for immunomodulatory treatment at this time.
- Sodium oxybate is the only FDA-approved treatment for EDS and cataplexy in childhood.

8 Conclusion

Sleep disorders are very common in childhood. Diagnosis is typically based upon detailed sleep history. Ancillary testing including polysomnography and multiple sleep latency testing is helpful in certain situations. Treatment focuses on changing sleep behaviors with pharmacotherapy representing a second-line treatment option with exception of narcolepsy.

References

1. Sadeh A, Mindell J, Rivera L. “My child has a sleep problem”: a cross-cultural comparison of parental definitions. Sleep Med. 2011;12(5):478–82.
2. Sadeh A, Mindell JA, Owens J. Why care about sleep of infants and their parents? Sleep Med Rev. 2011;15(5):335–7.
3. American Academy of Sleep Medicine. International classification of sleep disorders. Darien: American Academy of Sleep Medicine; 2014.
4. Spruyt K. Neurocognitive effects of sleep disruption in children and adolescents. Child Adolesc Psychiatr Clin N Am. 2021;30(1):27–45.

5. Wake M. Prevalence, stability, and outcomes of Cry-Fuss and sleep problems in the first 2 years of life: prospective community-based study. Pediatrics. 2006;117(3):836–42.
6. Fricke-Oerkermann L, Plück J, Schredl M, Heinz K, Mitschke A, Wiater A, et al. Prevalence and course of sleep problems in childhood. Sleep. 2007;30(10):1371–7.
7. Medalie L, Gozal D. Pediatric insomnia: update and future directions. J Child Sci. 2018;8(1):e172–80.
8. Sadeh A, Mindell JA, Luedtke K, Wiegand B. Sleep and sleep ecology in the first 3 years: a web-based study. J Sleep Res. 2009;18(1):60–73.
9. Gradisar M, Gardner G, Dohnt H. Recent worldwide sleep patterns and problems during adolescence: a review and meta-analysis of age, region, and sleep. Sleep Med. 2011;12(2):110–8.
10. Johnson EO. Epidemiology of DSM-IV insomnia in adolescence: lifetime prevalence, chronicity, and an emergent gender difference. Pediatrics. 2006;117(2):e247–56.
11. Kalmbach D, Cuamatzi-Castelan A, Tonnu C, Tran KM, Anderson J, Roth T, et al. Hyperarousal and sleep reactivity in insomnia: current insights. Nat Sci Sleep. 2018;10:193–201.
12. Schiel JE, Holub F, Petri R, Leerssen J, Tamm S, Tahmasian M, et al. Affect and arousal in insomnia: through a lens of neuroimaging studies. Curr Psychiatry Rep. 2020;22(9):44.
13. Van Someren EJW. Brain mechanisms of insomnia: new perspectives on causes and consequences. Physiol Rev. 2021;101(3):995–1046. https://doi.org/10.1152/physrev.00046.2019.
14. Brown KM, Malow BA. Pediatric insomnia. Chest. 2016;149(5):1332–9.
15. Bourchtein E, Langberg JM, Eadeh H-M. A review of pediatric nonpharmacological sleep interventions: effects on sleep, secondary outcomes, and populations with co-occurring mental health conditions. Behav Ther. 2020;51(1):27–41.
16. Miano S, Ferri R. Epidemiology and management of insomnia in children with autistic spectrum disorders. Paediatr Drugs. 2010;12(2):75–84.
17. Domingues-Montanari S. Clinical and psychological effects of excessive screen time on children: effects of screen time on children. J Paediatr Child Health. 2017;53(4):333–8.
18. Snyder CK, Chang AM. Mobile technology, sleep, and circadian disruption. In: Sleep and health [Internet]. Elsevier; 2019 [cited 2020 Dec 20]. p. 159–70. https://linkinghub.elsevier.com/retrieve/pii/B9780128153734000137.
19. Owens JA, Moore M. Insomnia in infants and young children. Pediatr Ann. 2017;46(9):e321–6.
20. Owens JA, Dalzell V. Use of the 'BEARS' sleep screening tool in a pediatric residents' continuity clinic: a pilot study. Sleep Med. 2005;6(1):63–9.
21. Owens JA, Spirito A, McGuinn M. The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. Sleep. 2000;23(8):1–9.
22. Lewandowski AS, Toliver-Sokol M, Palermo TM. Evidence-based review of subjective pediatric sleep measures. J Pediatr Psychol. 2011;36(7):780–93.
23. Shahid A, editor. STOP, THAT and one hundred other sleep scales. New York: Springer; 2012. 421 p.
24. McGlinchey EL, Courtney-Seidler EA, German M, Miller AL. The role of sleep disturbance in suicidal and nonsuicidal self-injurious behavior among adolescents. Suicide Life Threat Behav. 2017;47(1):103–11.
25. Lopes M, Boronat AC, Wang Y, Fu-I L. Sleep complaints as risk factor for suicidal behavior in severely depressed children and adolescents. CNS Neurosci Ther. 2016;22(11):915–20.
26. Bruni O, Nevšímalová S, editors. Sleep disorders in children. 1st ed. Cham: Springer International Publishing: Imprint: Springer; 2017. 1 p.
27. Aurora RN, Lamm CI, Zak RS, Kristo DA, Bista SR, Rowley JA, et al. Practice parameters for the non-respiratory indications for polysomnography and multiple sleep latency testing for children. Sleep. 2012;35(11):1467–73.
28. Depner CM, Cheng PC, Devine JK, Khosla S, de Zambotti M, Robillard R, et al. Wearable technologies for developing sleep and circadian biomarkers: a summary of workshop discussions. Sleep. 2020;43(2):zsz254.
29. Lee XK, Chee NIYN, Ong JL, Teo TB, van Rijn E, Lo JC, et al. Validation of a consumer sleep wearable device with actigraphy and polysomnography in adolescents across sleep opportunity manipulations. J Clin Sleep Med. 2019;15(9):1337–46.

30. Zhou ES, Owens J. Behavioral treatments for pediatric insomnia. Curr Sleep Med Rep. 2016;2(3):127–35.
31. Lunsford-Avery JR, Bidopia T, Jackson L, Sloan JS. Behavioral treatment of insomnia and sleep disturbances in school-aged children and adolescents. Child Adolesc Psychiatr Clin N Am. 2021;30(1):101–16.
32. Liu A. Sleep training. Pediatr Ann. 2020;49(3):e101–5.
33. Himelfarb M, Shatkin JP. Pediatric insomnia. Child Adolesc Psychiatr Clin N Am. 2021;30(1):117–29.
34. Dewald-Kaufmann J, de Bruin E, Michael G. Cognitive Behavioral Therapy for Insomnia (CBT-I) in school-aged children and adolescents. Sleep Med Clin. 2019;14(2):155–65.
35. Hall WA, Nethery E. What does sleep hygiene have to offer children's sleep problems? Paediatr Respir Rev. 2019;31:64–74.
36. Stepanski EJ, Wyatt JK. Use of sleep hygiene in the treatment of insomnia. Sleep Med Rev. 2003;7(3):215–25.
37. Ekambaram V, Owens J. Medications used for pediatric insomnia. Child Adolesc Psychiatr Clin N Am. 2021;30(1):85–99.
38. Bruni O, Alonso-Alconada D, Besag F, Biran V, Braam W, Cortese S, et al. Current role of melatonin in pediatric neurology: clinical recommendations. Eur J Paediatr Neurol. 2015;19(2):122–33.
39. Abdelgadir IS, Gordon MA, Akobeng AK. Melatonin for the management of sleep problems in children with neurodevelopmental disorders: a systematic review and meta-analysis. Arch Dis Child. 2018;103(12):1155–62.
40. Smits MG, van Stel HF, van der Heijden K, Meijer AM, Coenen AML, Kerkhof GA. Melatonin improves health status and sleep in children with idiopathic chronic sleep-onset insomnia: a randomized placebo-controlled trial. J Am Acad Child Adolesc Psychiatry. 2003;42(11):1286–93.
41. van Geijlswijk IM, van der Heijden KB, Egberts ACG, Korzilius HPLM, Smits MG. Dose finding of melatonin for chronic idiopathic childhood sleep onset insomnia: an RCT. Psychopharmacology. 2010;212(3):379–91.
42. Weiss M, Wasdell M, Bomben M, Rea K, Freeman R. Sleep hygiene and melatonin treatment for children and adolescents with ADHD and initial insomnia: J Am Acad Child Adolesc Psychiatry [Internet]. 2006 [cited 2020 Dec 20];PAP. http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00004583-900000000-00011.
43. Williams Buckley A, Hirtz D, Oskoui M, Armstrong MJ, Batra A, Bridgemohan C, et al. Practice guideline: treatment for insomnia and disrupted sleep behavior in children and adolescents with autism spectrum disorder: report of the guideline development, dissemination, and implementation Subcommittee of the American Academy of Neurology. Neurology. 2020;94(9):392–404.
44. Nguyen M, Tharani S, Rahmani M, Shapiro M. A review of the use of clonidine as a sleep aid in the child and adolescent population. Clin Pediatr (Phila). 2014;53(3):211–6.
45. Mattes JA. Treating ADHD in prison: focus on alpha-2 agonists (clonidine and guanfacine). J Am Acad Psychiatr Law. 2016;44(2):7.
46. Katwala J, Kumar AK, Sejpal JJ, Terrence M, Mishra M. Therapeutic rationale for low dose doxepin in insomnia patients. Asian Pac J Trop Dis. 2013;3(4):331–6.
47. Shah YD, Stringel V, Pavkovic I, Kothare SV. Doxepin in children and adolescents with symptoms of insomnia: a single-center experience. J Clin Sleep Med. 2020;16(5):743–7.
48. Merenstein D, Diener-West M, Halbower AC, Krist A, Rubin HR. The trial of infant response to diphenhydramine: the TIRED study—a randomized, controlled, patient-oriented trial. Arch Pediatr Adolesc Med. 2006;160(7):707.
49. Bruni O, Angriman M, Calisti F, Comandini A, Esposito G, Cortese S, et al. Practitioner review: treatment of chronic insomnia in children and adolescents with neurodevelopmental disabilities. J Child Psychol Psychiatry. 2018;59(5):489–508.

50. Mindell JA, Owens JA. A clinical guide to pediatric sleep diagnosis and management of sleep problems [Internet]. Wolters Kluwer Health; 2015 [cited 2021 Jan 1]. http://search.ebscohost.com/login.aspx?direct=true&scope=site&db=nlebk&AN=1473049.
51. Christensen H, Batterham PJ, Gosling JA, Ritterband LM, Griffiths KM, Thorndike FP, et al. Effectiveness of an online insomnia program (SHUTi) for prevention of depressive episodes (the GoodNight Study): a randomised controlled trial. Lancet Psychiatry. 2016;3(4):333–41.
52. DelRosso LM, Mogavero MP, Baroni A, Bruni O, Ferri R. Restless legs syndrome in children and adolescents. Child Adolesc Psychiatr Clin N Am. 2021;30(1):143–57.
53. Sharon D, Walters AS, Simakajornboon N. Restless legs syndrome and periodic limb movement disorder in children. J Child Sci. 2019;9(1):e38–49.
54. Chervin RD, Hedger KM. Clinical prediction of periodic leg movements during sleep in children. Sleep Med. 2001;2(6):501–10.
55. Picchietti DL, Rajendran RR, Wilson MP, Picchietti MA. Pediatric restless legs syndrome and periodic limb movement disorder: parent–child pairs. Sleep Med. 2009;10(8):925–31.
56. Picchietti D, Allen RP, Walters AS, Davidson JE, Myers A, Ferini-Strambi L. Restless legs syndrome: prevalence and impact in children and adolescents the Peds REST study. Pediatrics. 2007;120(2):253–66.
57. Begum E, Goodday A, Spurr K, Rajda M, Corkum P. Periodic limb movements of sleep in children with attention-deficit/ hyperactivity disorder: baseline frequency and impact of psychostimulant medication. SM J Sleep Disord. 2018;4(1):1–11.
58. Picchietti DL, Underwood DJ, Farris WA, Walters AS, Shah MM, Dahl RE, et al. Further studies on periodic limb movement disorder and restless legs syndrome in children with attention-deficit hyperactivity disorder. Mov Disord. 1999;14(6):8.
59. Picchietti DL, England SJ, Walters AS, Willis K, Verrico T. Periodic limb movement disorder and restless legs syndrome in children with attention-deficit hyperactivity disorder. J Child Neurol. 1998;13(12):588–94.
60. Muhle H, Neumann A, Lohmann-Hedrich K, Lohnau T, Lu Y, Winkler S, et al. Childhood-onset restless legs syndrome: clinical and genetic features of 22 families. Mov Disord. 2008;23(8):1113–21.
61. Sander HH, Eckeli AL, Costa Passos AD, Azevedo L, Fernandes do Prado LB, França Fernandes RM. Prevalence and quality of life and sleep in children and adolescents with restless legs syndrome/Willis-Ekbom disease. Sleep Med. 2017;30:204–9.
62. Rye DB. The molecular genetics of restless legs syndrome. Sleep Med Clin. 2015;10(3):227–33.
63. Garcia-Malo C, Peralta SR, Garcia-Borreguero D. Restless legs syndrome and other common sleep-related movement disorders. Continuum. 2020;26(4):963–87.
64. Lyu S, Xing H, DeAndrade MP, Liu Y, Perez PD, Yokoi F, et al. The role of BTBD9 in striatum and restless legs syndrome. eNeuro. 2019;6(5):ENEURO.0277-19.2019.
65. Lyu S, Xing H, DeAndrade MP, Perez PD, Zhang K, Liu Y, et al. The role of BTBD9 in the cerebral cortex and the pathogenesis of restless legs syndrome. Exp Neurol. 2020;323:113111.
66. Lyu S, Xing H, DeAndrade MP, Perez PD, Yokoi F, Febo M, et al. The role of BTBD9 in the cerebellum, sleep-like behaviors and the restless legs syndrome. Neuroscience. 2020;440:85–96.
67. Sarayloo F, Dion PA, Rouleau GA. MEIS1 and restless legs syndrome: a comprehensive review. Front Neurol. 2019;10:935.
68. Connor JR, Patton SM, Oexle K, Allen RP. Iron and restless legs syndrome: treatment, genetics and pathophysiology. Sleep Med. 2017;31:61–70.
69. Khan FH, Ahlberg CD, Chow CA, Shah DR, Koo BB. Iron, dopamine, genetics, and hormones in the pathophysiology of restless legs syndrome. J Neurol. 2017;264(8):1634–41.
70. Munzer T, Felt B. The role of iron in pediatric restless legs syndrome and periodic limb movements in sleep. Semin Neurol. 2017;37(4):439–45.
71. Chokroverty S. Differential diagnoses of restless legs syndrome/Willis-Ekbom disease. Sleep Med Clin. 2015;10(3):249–62.

72. Walters AS, Gabelia D, Frauscher B. Restless legs syndrome (Willis–Ekbom disease) and growing pains: are they the same thing? A side-by-side comparison of the diagnostic criteria for both and recommendations for future research. Sleep Med. 2013;14(12):1247–52.
73. Kanta P, Gopinathan NR. Idiopathic growing pains in pediatric patients: review of literature. Clin Pediatr (Phila). 2019;58(1):5–9.
74. Picchietti DL, Arbuckle RA, Abetz L, Durmer JS, Ivanenko A, Owens JA, et al. Pediatric restless legs syndrome: analysis of symptom descriptions and drawings. J Child Neurol. 2011;26(11):1365–76.
75. Picchietti DL, Bruni O, de Weerd A, Durmer JS, Kotagal S, Owens JA, et al. Pediatric restless legs syndrome diagnostic criteria: an update by the International Restless Legs Syndrome Study Group. Sleep Med. 2013;14(12):1253–9.
76. Pullen SJ, Wall CA, Angstman ER, Munitz GE, Kotagal S. Psychiatric comorbidity in children and adolescents with restless legs syndrome: a retrospective study. J Clin Sleep Med. 2011;7(6):587–96.
77. Srifuengfung M, Bussaratid S, Ratta-apha W, Sanguanpanich N, Hosiri T. Restless legs syndrome in children and adolescents with attention-deficit/hyperactivity disorder: prevalence, mimic conditions, risk factors, and association with functional impairment. Sleep Med. 2020;73:117–24.
78. Furudate N, Komada Y, Kobayashi M, Nakajima S, Inoue Y. Daytime dysfunction in children with restless legs syndrome. J Neurol Sci. 2014;336(1–2):232–6.
79. Kanney ML, Durmer JS, Trotti LM, Leu R. Rethinking bedtime resistance in children with autism: is restless legs syndrome to blame? J Clin Sleep Med. 2020;16(12):2029–35.
80. Berry RB, Quaan SF, Abreu AR, et al. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Darien: American Academy of Sleep Medicine; 2020. (Version 2.6).
81. Mackie S, Winkelman JW. Normal ferritin in a patient with iron deficiency and RLS. J Clin Sleep Med. 2013;9(5):511–3.
82. Li J, Moore H, Lin L, Young T, Finn L, Peppard PE, et al. Association of low ferritin with PLM in the Wisconsin Sleep cohort. Sleep Med. 2015;16(11):1413–8.
83. Allen RP, Picchietti DL, Auerbach M, Cho YW, Connor JR, Earley CJ, et al. Evidence-based and consensus clinical practice guidelines for the iron treatment of restless legs syndrome/Willis-Ekbom disease in adults and children: an IRLSSG task force report. Sleep Med. 2018;41:27–44.
84. Rosen GM, Morrissette S, Larson A, Stading P, Barnes TL. Does improvement of low serum ferritin improve symptoms of restless legs syndrome in a cohort of pediatric patients? J Clin Sleep Med. 2019;15(8):1149–54.
85. Dye TJ, Jain SV, Simakajornboon N. Outcomes of long-term iron supplementation in pediatric restless legs syndrome/periodic limb movement disorder (RLS/PLMD). Sleep Med. 2017;32:213–9.
86. DelRosso L, Bruni O. Treatment of pediatric restless legs syndrome. In: Advances in pharmacology [Internet]. Elsevier; 2019 [cited 2020 Dec 21]. p. 237–53. https://linkinghub.elsevier.com/retrieve/pii/S1054358918300462.
87. Picchietti DL. Should oral iron be first-line therapy for pediatric restless legs syndrome and periodic limb movement disorder? Sleep Med. 2017;32:220–1.
88. Dye TJ, Gurbani N, Simakajornboon N. How does one choose the correct pharmacotherapy for a pediatric patient with restless legs syndrome and periodic limb movement disorder?: expert guidance. Expert Opin Pharmacother. 2019;20(13):1535–8.
89. Sharon D. Nonpharmacologic management of restless legs syndrome (Willis-Ekbom disease). Sleep Med Clin. 2015;10(3):263–78.
90. Chokroverty S, editor. Sleep disorders medicine: basic science, technical considerations and clinical aspects. 4th ed. New York: Springer: Imprint: Springer; 2017. 1 p.
91. Robinson AA, Malow BA. Gabapentin shows promise in treating refractory insomnia in children. J Child Neurol. 2013;28(12):1618–21.

92. Allen RP, Earley CJ. Defining the phenotype of the restless legs syndrome (RLS) using age-of-symptom-onset. Sleep Med. 2000;9:11–9.
93. Walters AS, Hickey K, Maltzman J, Verrico T, Joseph D, Hening W, et al. A questionnaire study of 138 patients with restless legs syndrome: the 'Night-Walkers' survey. Neurology. 1996;46(1):92–5.
94. Picchietti DL, Stevens HE. Early manifestations of restless legs syndrome in childhood and adolescence. Sleep Med. 2008;9(7):770–81.
95. Winkelman JW. Association of restless legs syndrome and cardiovascular disease in the Sleep Heart Health Study. Neurology. 2008;70(1):35–42.
96. Chen S-J, Shi L, Bao Y-P, Sun Y-K, Lin X, Que J-Y, et al. Prevalence of restless legs syndrome during pregnancy: a systematic review and meta-analysis. Sleep Med Rev. 2018;40:43–54.
97. Feder MA, Baroni A. Just let me sleep in. Child Adolesc Psychiatr Clin N Am. 2021;30(1):159–74.
98. Reid KJ, Jaksa AA, Eisengart JB, Baron KG, Lu B, Kane P, et al. Systematic evaluation of axis-I DSM diagnoses in delayed sleep phase disorder and evening-type circadian preference. Sleep Med. 2012;13(9):1171–7.
99. Prevalence of circadian misalignment and its association with depressive symptoms in delayed sleep phase disorder. Sleep [Internet]. 2017 [cited 2021 Jan 2]. https://academic.oup.com/sleep/article/doi/10.1093/sleep/zsw002/2957267/Prevalence-of-Circadian-Misalignment-and-Its.
100. Rajaratnam SMW, Licamele L, Birznieks G. Delayed sleep phase disorder risk is associated with absenteeism and impaired functioning. Sleep Health. 2015;1(2):121–7.
101. Lunsford-Avery JR, Kollins SH. Editorial perspective: delayed circadian rhythm phase: a cause of late-onset attention-deficit/hyperactivity disorder among adolescents? J Child Psychol Psychiatry. 2018;59(12):1248–51.
102. Auger RR, SpringerLink (Online service). Circadian rhythm sleep-wake disorders an evidence-based guide for clinicians and investigators. 2020.
103. Gradisar M, Crowley SJ. Delayed sleep phase disorder in youth. Curr Opin Psychiatry. 2013;26(6):580–5.
104. Dibner C, Schibler U, Albrecht U. The mammalian circadian timing system: organization and coordination of central and peripheral clocks. Annu Rev Physiol. 2010;72(1):517–49.
105. Carskadon MA. Sleep in adolescents: the perfect storm. Pediatr Clin North Am. 2011;58(3):637–47.
106. Crowley SJ, Wolfson AR, Tarokh L, Carskadon MA. An update on adolescent sleep: new evidence informing the perfect storm model. J Adolesc. 2018;67:55–65.
107. Patke A, Murphy PJ, Onat OE, Krieger AC, Özçelik T, Campbell SS, et al. Mutation of the human circadian clock gene CRY1 in familial delayed sleep phase disorder. Cell. 2017;169(2):203–215.e13.
108. Smith MT, McCrae CS, Cheung J, Martin JL, Harrod CG, Heald JL, et al. Use of actigraphy for the evaluation of sleep disorders and circadian rhythm sleep-wake disorders: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. J Clin Sleep Med. 2018;14(7):1209–30.
109. Auger RR, Burgess HJ, Emens JS, Deriy LV, Thomas SM, Sharkey KM. Clinical practice guideline for the treatment of intrinsic circadian rhythm sleep-wake disorders: advanced sleep-wake phase disorder (ASWPD), delayed sleep-wake phase disorder (DSWPD), non-24-hour sleep-wake rhythm disorder (N24SWD), and irregular sleep-wake rhythm disorder (ISWRD). An update for 2015: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2015;11(10):1199–236.
110. Bjorvatn B, Pallesen S. A practical approach to circadian rhythm sleep disorders. Sleep Med Rev. 2009;13(1):47–60.
111. Micic G, Richardson C, Cain N, Reynolds C, Bartel K, Maddock B, et al. Readiness to change and commitment as predictors of therapy compliance in adolescents with Delayed Sleep-Wake Phase Disorder. Sleep Med. 2019;55:48–55.

112. Richardson C, Cain N, Bartel K, Micic G, Maddock B, Gradisar M. A randomised controlled trial of bright light therapy and morning activity for adolescents and young adults with Delayed Sleep-Wake Phase Disorder. Sleep Med. 2018;45:114–23.
113. Richardson C, Micic G, Cain N, Bartel K, Maddock B, Gradisar M. Cognitive performance in adolescents with Delayed Sleep-Wake Phase Disorder: treatment effects and a comparison with good sleepers. J Adolesc. 2018;65:72–84.
114. Watson NF, Martin JL, Wise MS, Carden KA, Kirsch DB, Kristo DA, et al. Delaying middle school and high school start times promotes student health and performance: an American Academy of Sleep Medicine position statement. J Clin Sleep Med. 2017;13(4):623–5.
115. Lloyd R, Tippmann-Peikert M, Slocumb N, Kotagal S. Characteristics of REM sleep behavior disorder in childhood. J Clin Sleep Med. 2012;8(2):127–31.
116. Ekambaram V, Maski K. Non-rapid eye movement arousal parasomnias in children. Pediatr Ann. 2017;46(9):e327–31.
117. Bruni O, DelRosso LM, Melegari MG, Ferri R. The parasomnias. Child Adolesc Psychiatr Clin N Am. 2021;30(1):131–42.
118. Leung AKC, Leung AAM, Wong AHC, Hon KL. Sleep terrors: an updated review. Curr Pediatr Rev. 2020;16(3):176–82.
119. Laberge L, Tremblay RE, Vitaro F, Montplaisir J. Development of parasomnias from childhood to early adolescence. Pediatrics. 2000;106(1 Pt 1):67–74.
120. Petit D, Pennestri M-H, Paquet J, Desautels A, Zadra A, Vitaro F, et al. Childhood sleepwalking and sleep terrors: a longitudinal study of prevalence and familial aggregation. JAMA Pediatr. 2015;169(7):653.
121. Singh S, Kaur H, Singh S, Khawaja I. Parasomnias: a comprehensive review. Cureus [Internet]. 2018 31 [cited 2021 Jan 7]. https://www.cureus.com/articles/16963-parasomnias-a-comprehensive-review.
122. Lecendreux M, Bassetti C, Dauvilliers Y, Mayer G, Neidhart E, Tafti M. HLA and genetic susceptibility to sleepwalking. Mol Psychiatry. 2003;8(1):114–7.
123. Hublin C, Kaprio J. Genetic aspects and genetic epidemiology of parasomnias. Sleep Med Rev. 2003;7(5):413–21.
124. Zucconi M, Oldani A, Ferini-Strambi L, Smirne S. Arousal fluctuations in non-rapid eye movement parasomnias: the role of cyclic alternating pattern as a measure of sleep instability. J Clin Neurophysiol [Internet]. 1995;12(2). https://journals.lww.com/clinicalneurophys/Fulltext/1995/03000/Arousal_Fluctuations_in_Non_Rapid_Eye_Movement.5.aspx.
125. Rodriguez CL, Foldvary-Schaefer N. Clinical neurophysiology of NREM parasomnias. In: Handbook of clinical neurology [Internet]. Elsevier; 2019 [cited 2021 Jan 9]. p. 397–410. https://linkinghub.elsevier.com/retrieve/pii/B9780444641427000631.
126. Balkin TJ. The process of awakening: a PET study of regional brain activity patterns mediating the re-establishment of alertness and consciousness. Brain. 2002;125(10):2308–19.
127. Peter-Derex L, Magnin M, Bastuji H. Heterogeneity of arousals in human sleep: a stereo-electroencephalographic study. Neuroimage. 2015;123:229–44.
128. Gibbs SA, Proserpio P, Terzaghi M, Pigorini A, Sarasso S, Lo Russo G, et al. Sleep-related epileptic behaviors and non-REM-related parasomnias: insights from stereo-EEG. Sleep Med Rev. 2016;25:4–20.
129. Terzaghi M, Sartori I, Tassi L, Didato G, Rustioni V, LoRusso G, et al. Evidence of dissociated arousal states during NREM parasomnia from an intracerebral neurophysiological study. Sleep. 2009;32(3):4.
130. Castelnovo A, Lopez R, Proserpio P, Nobili L, Dauvilliers Y. NREM sleep parasomnias as disorders of sleep-state dissociation. Nat Rev Neurol. 2018;14(8):470–81.
131. Halász P, Kelemen A, Szűcs A. Physiopathogenetic Interrelationship between nocturnal frontal lobe epilepsy and NREM arousal parasomnias. Epilepsy Res Treat. 2012;2012:1–8.
132. Bisulli F, Vignatelli L, Provini F, Leta C, Lugaresi E, Tinuper P. Parasomnias and nocturnal frontal lobe epilepsy (NFLE): lights and shadows—Controversial points in the differential diagnosis. Sleep Med. 2011;12:S27–32.

133. Derry C. Nocturnal frontal lobe epilepsy vs parasomnias. Curr Treat Options Neurol. 2012;14(5):451–63.
134. Derry CP. Sleeping in fits and starts: a practical guide to distinguishing nocturnal epilepsy from sleep disorders. Pract Neurol. 2014;14(6):391–8.
135. Mutti C, Bernabè G, Barozzi N, Ciliento R, Trippi I, Pedrazzi G, et al. Commonalities and differences in NREM parasomnias and sleep-related epilepsy: is there a continuum between the two conditions? Front Neurol. 2020;11:600026.
136. Erickson J, Vaughn BV. Non-REM parasomnia. Sleep Med Clin. 2019;14(3):363–70.
137. Boursoulian LJ, Schenck CH, Mahowald MW, Lagrange AH. Differentiating parasomnias from nocturnal seizures. J Clin Sleep Med. 2012;8(1):108–12.
138. Bisulli F, Vignatelli L, Naldi I, Pittau F, Provini F, Plazzi G, et al. Diagnostic accuracy of a structured interview for nocturnal frontal lobe epilepsy (SINFLE): a proposal for developing diagnostic criteria. Sleep Med. 2012;13(1):81–7.
139. Manni R, Terzaghi M, Repetto A. The FLEP scale in diagnosing nocturnal frontal lobe epilepsy, NREM and REM parasomnias: data from a tertiary sleep and epilepsy unit. Epilepsia. 2008;49(9):1581–5.
140. Kothare SV, Ivanenko A, editors. Parasomnias: clinical characteristics and treatment. New York: Springer; 2013. 488 p.
141. Guilleminault C, Palombini L, Pelayo R, Chervin RD. Sleepwalking and sleep terrors in prepubertal children: what triggers them? Pediatrics. 2003;111(1):e17–25.
142. Gozal D, Wang M, Pope DW. Objective sleepiness measures in pediatric obstructive sleep apnea. Pediatrics. 2001;108(3):693–7.
143. da Silva Gusmão Cardoso T, Pompéia S, Miranda MC. Cognitive and behavioral effects of obstructive sleep apnea syndrome in children: a systematic literature review. Sleep Med. 2018;46:46–55.
144. Keefe KR, Patel PN, Levi JR. The shifting relationship between weight and pediatric obstructive sleep apnea: a historical review. Laryngoscope. 2019;129(10):2414–9.
145. Samsoon GLT, Young JR. Difficult tracheal intubation: a retrospective study. Anesthesia. 1987;42:487–90.
146. Kumar HVM, Schroeder JW, Gang Z, Sheldon SH. Mallampati score and pediatric obstructive sleep apnea. J Clin Sleep Med. 2014;10(9):985–90.
147. Hwang S-H, Guilleminault C, Park C-S, Kim T-W, Hong S-C. Usefulness of adenotonsillar size for prediction of severity of obstructive sleep apnea and flow limitation. Otolaryngol Head Neck Surg. 2013;149(2):326–34.
148. Yan X, Zhao Y, Wang J, Shen T, Yang W, Qiao Y, et al. Associations among sleep symptoms, physical examination, and polysomnographic findings in children with obstructive sleep apnea. Eur Arch Otorhinolaryngol. 2020;277(2):623–30.
149. Tinuper P, Bisulli F. From nocturnal frontal lobe epilepsy to sleep-related hypermotor epilepsy: a 35-year diagnostic challenge. Seizure. 2017;44:87–92.
150. Tinuper P, Bisulli F. Definition and diagnostic criteria of sleep-related hypermotor epilepsy. Neurology. 2016;86(19):1834–42.
151. Menghi V, Bisulli F, Tinuper P, Nobili L. Sleep-related hypermotor epilepsy: prevalence, impact and management strategies. Nat Sci Sleep. 2018;10:317–26.
152. Certal V, Catumbela E, Winck JC, Azevedo I, Teixeira-Pinto A, Costa-Pereira A. Clinical assessment of pediatric obstructive sleep apnea: a systematic review and meta-analysis. Laryngoscope. 2012;122(9):2105–14.
153. Carroll JL, McColley SA, Marcus CL, Curtis S, Loughlin GM. Inability of clinical history to distinguish primary snoring from obstructive sleep apnea syndrome in children. Chest. 1995;108(3):610–8.
154. Patel AP, Meghji S, Phillips JS. Accuracy of clinical scoring tools for the diagnosis of pediatric obstructive sleep apnea. Laryngoscope. 2020;130(4):1034–43.

155. Brietzke SE, Katz ES, Roberson DW. Can history and physical examination reliably diagnose pediatric obstructive sleep apnea/hypopnea syndrome? A systematic review of the literature. Otolaryngol Head Neck Surg. 2004;131(6):827–32.
156. Attarian H. Treatment options for parasomnias. Neurol Clin. 2010;28(4):1089–106.
157. Drakatos P, Leschziner G. Diagnosis and management of nonrapid eye movement-parasomnias. Curr Opin Pulmon Med. 2019;25(6):629–35.
158. Mindell JA, Owens JA. A clinical guide to pediatric sleep diagnosis and management of sleep problems [Internet]. Wolters Kluwer Health; 2015 [cited 2021 Jan 17]. http://search.ebscohost.com/login.aspx?direct=true&scope=site&db=nlebk&AN=1473049.
159. Kotagal S. Treatment of dyssomnias and parasomnias in childhood. Curr Treat Options Neurol. 2012;14(6):630–49.
160. Hauri PJ, Silber MH, Boeve BF. The treatment of parasomnias with hypnosis: a 5-year follow-up study. J Clin Sleep Med. 2007;03(04):369–73.
161. Kurz PJ, Kohler WC. Hypnosis in the management of sleep disorders. New York: Routledge; 2017.
162. Proserpio P, Terzaghi M, Manni R, Nobili L. Drugs used in parasomnia. Sleep Med Clin. 2020;15(2):289–300.
163. Drakatos P, Marples L, Muza R, Higgins S, Gildeh N, Macavei R, et al. NREM parasomnias: a treatment approach based upon a retrospective case series of 512 patients. Sleep Med. 2019;53:181–8.
164. Jan J, Freeman R, Wasdell M, Bomben M. A child with severe night terrors and sleepwalking responds to melatonin therapy. Dev Med Child Neurol [Internet]. 2004 [cited 2021 Jan 10];46(11). http://doi.wiley.com/10.1017/S0012162204231358.
165. Özcan Ö, Dönmez YE. Melatonin treatment for childhood sleep terror. J Child Adolesc Psychopharmacol. 2014;24(9):528–9.
166. Gozal D, Tan H-L, Kheirandish-Gozal L. Treatment of obstructive sleep apnea in children: handling the unknown with precision. J Clin Med. 2020;9(3):888.
167. Bitners AC, Arens R. Evaluation and management of children with obstructive sleep apnea syndrome. Lung. 2020;198(2):257–70.
168. Kaditis AG, Alonso Alvarez ML, Boudewyns A, Alexopoulos EI, Ersu R, Joosten K, et al. Obstructive sleep disordered breathing in 2- to 18-year-old children: diagnosis and management. Eur Respir J. 2016;47(1):69–94.
169. Salman SO. Modern management of obstructive sleep apnea [Internet]. Cham: Springer International Publishing; 2019 [cited 2021 Jan 17]. https://link.springer.com/book/10.1007/978-3-030-11443-5.
170. Parmar A, Baker A, Narang I. Positive airway pressure in pediatric obstructive sleep apnea. Paediatr Respir Rev. 2019;31:43–51.
171. Liming BJ, Ryan M, Mack D, Ahmad I, Camacho M. Montelukast and nasal corticosteroids to treat pediatric obstructive sleep apnea: a systematic review and meta-analysis. Otolaryngol Head Neck Surg. 2019;160(4):594–602.
172. Calapai G, Casciaro M, Miroddi M, Calapai F, Navarra M, Gangemi S. Montelukast-induced adverse drug reactions: a review of case reports in the literature. Pharmacology. 2014;94(1–2):60–70.
173. Gurbani N, Dye TJ, Dougherty K, Jain S, Horn PS, Simakajornboon N. Improvement of parasomnias after treatment of restless leg syndrome/periodic limb movement disorder in children. J Clin Sleep Med. 2019;15(5):743–8.
174. Ramantani G, Kadish NE, Mayer H, Anastasopoulos C, Wagner K, Reuner G, et al. Frontal lobe epilepsy surgery in childhood and adolescence: predictors of long-term seizure freedom, overall cognitive and adaptive functioning. Neurosurgery. 2018;83(1):93–103.
175. Lee J, Yeo S, Kim K, Chung S. Sleep environment and non-rapid eye movement-related parasomnia among children: 42 case series. Sleep Med Res. 2020;11(1):49–52.

176. Bassetti CLA, Adamantidis A, Burdakov D, Han F, Gay S, Kallweit U, et al. Narcolepsy—clinical spectrum, aetiopathophysiology, diagnosis and treatment. Nat Rev Neurol. 2019;15(9):519–39.
177. Kornum BR, Knudsen S, Ollila HM, Pizza F, Jennum PJ, Dauvilliers Y, et al. Narcolepsy. Nat Rev Dis Primers. 2017;3(1):16100.
178. Pillen S, Pizza F, Dhondt K, Scammell TE, Overeem S. Cataplexy and its mimics: clinical recognition and management. Curr Treat Options Neurol. 2017;19(6):23.
179. Schiappa C, Scarpelli S, D'Atri A, Gorgoni M, De Gennaro L. Narcolepsy and emotional experience: a review of the literature. Behav Brain Funct. 2018;14(1):19.
180. Pizza F, Antelmi E, Vandi S, Meletti S, Erro R, Baumann CR, et al. The distinguishing motor features of cataplexy: a study from video-recorded attacks. Sleep [Internet]. 2018 [cited 2021 Jan 17];41(5). https://academic.oup.com/sleep/article/doi/10.1093/sleep/zsy026/4841988.
181. Lammers GJ, Overeem S, Tijssen MAJ, van Dijk JG. Effects of startle and laughter in cataplectic subjects: a neurophysiological study between attacks. Clin Neurophysiol. 2000;111(7):1276–81.
182. Parmar A, Murray BJ, Narang I. Clinical characteristics of cataplectic attacks in type 1 narcolepsy. Curr Neurol Neurosci Rep. 2020;20(9):38.
183. Serra L, Montagna P, Mignot E, Lugaresi E, Plazzi G. Cataplexy features in childhood narcolepsy: cataplexy in childhood narcolepsy. Mov Disord. 2008;23(6):858–65.
184. Nevsimalova S, Pisko J, Buskova J, Kemlink D, Prihodova I, Sonka K, et al. Narcolepsy: clinical differences and association with other sleep disorders in different age groups. J Neurol. 2013;260(3):767–75.
185. Plazzi G, Clawges HM, Owens JA. Clinical characteristics and burden of illness in pediatric patients with narcolepsy. Pediatr Neurol. 2018;85:21–32.
186. Postiglione E, Antelmi E, Pizza F, Lecendreux M, Dauvilliers Y, Plazzi G. The clinical spectrum of childhood narcolepsy. Sleep Med Rev. 2018;38:70–85.
187. Com G, Einen MA, Jambhekar S. Narcolepsy with cataplexy: diagnostic challenge in children. Clin Pediatr (Phila). 2015;54(1):5–14.
188. Plazzi G, Pizza F, Palaia V, Franceschini C, Poli F, Moghadam KK, et al. Complex movement disorders at disease onset in childhood narcolepsy with cataplexy. Brain. 2011;134(12):3480–92.
189. Pisko J, Pastorek L, Buskova J, Sonka K, Nevsimalova S. Nightmares in narcolepsy: underinvestigated symptom? Sleep Med. 2014;15(8):967–72.
190. Scammell TE. Narcolepsy. Campion EW, editor. N Engl J Med. 2015;373(27):2654–62.
191. Ollila HM. Narcolepsy type 1: what have we learned from genetics? Sleep. 2020;43(11):99.
192. Merdad RA, Akil H, Wali SO. Sleepiness in adolescents. Sleep Med Clin. 2017;12(3):415–28.
193. Goswami M, Pandi-Perumal SR, Thorpy MJ, editors. Narcolepsy: a clinical guide. 2nd ed. Cham: Springer International Publishing: Imprint: Springer; 2016. 1 p.
194. Keyes KM, Maslowsky J, Hamilton A, Schulenberg J. The great sleep recession: changes in sleep duration among US adolescents, 1991-2012. Pediatrics. 2015;135(3):460–8.
195. Wheaton AG, Jones SE, Cooper AC, Croft JB. Short sleep duration among middle school and high school students—United States, 2015. MMWR Morb Mortal Wkly Rep. 2018;67(3):85–90.
196. Trotti LM. Idiopathic hypersomnia. 2018;20.
197. Chellappa SL, Schröder C, Cajochen C. Chronobiology, excessive daytime sleepiness and depression: is there a link? Sleep Med. 2009;10(5):505–14.
198. Al Suwayri SM, BaHammam AS. The "known unknowns" of Kleine-Levin syndrome. Sleep Med Clin. 2017;12(3):345–58.
199. Gadoth N, Oksenberg A. Kleine–Levin syndrome; An update and mini-review. Brain Dev. 2017;39(8):665–71.
200. Lima FCB, do Nascimento Junior EB, Teixeira SS, Coelho FM, da Paz Oliveira G. Thinking outside the box: cataplexy without narcolepsy. Sleep Med. 2019;61:118–21.

201. Smit LS, Lammers GJ, Catsman-Berrevoets CE. Cataplexy leading to the diagnosis of Niemann-Pick disease type C. Pediatr Neurol. 2006;35(1):82–4.
202. Sabaneeff L, Mendes Motta H, Castro J, Tufik S, Santos Coelho FM. Moebius syndrome and narcolepsy: a case dissertation. Sleep Sci. 2014;7(1):43–6.
203. Hahn JS, Hanauer A. Stimulus-induced drop episodes in Coffin–Lowry syndrome. Eur J Med Genet. 2012;55(5):335–7.
204. Postiglione E, Antelmi E, Pizza F, Vandi S, La Morgia C, Carelli V, et al. Cataplexy and ataxia: red flags for the diagnosis of DNA methyltransferase 1 mutation. J Clin Sleep Med. 2020;16(1):143–7.
205. Catania A, Peverelli L, Tabano S, Ghezzi D, Lamperti C. DNMT1-complex disorder caused by a novel mutation associated with an overlapping phenotype of autosomal-dominant cerebellar ataxia, deafness, and narcolepsy (ADCA-DN) and hereditary sensory neuropathy with dementia and hearing loss (HSN1E). Neurol Sci. 2019;40(9):1963–6.
206. Reading P. Cataplexy. Pract Neurol. 2019;19(1):21–7.
207. Meinen CN, Smith KM, Tillema J-M, Kotagal S. Pseudo status cataplecticus in narcolepsy type 1. J Clin Sleep Med. 2018;14(09):1625–7.
208. Fishbein A, Sheldon SH. Allergy and sleep basic principles and clinical practice [Internet]. 2019 [cited 2021 Jan 18]. https://doi.org/10.1007/978-3-030-14738-9
209. Malhotra RK, editor. Sleepy or sleepless: clinical approach to the sleep patient. 1st ed. 2015. Cham: Springer International Publishing: Imprint: Springer; 2015. 1 p.
210. Benmedjahed K, Wang YG, Lambert J, Evans C, Hwang S, Black J, et al. Assessing sleepiness and cataplexy in children and adolescents with narcolepsy: a review of current patient-reported measures. Sleep Med. 2017;32:143–9.
211. Kallweit U, Schmidt M, Bassetti CL. Patient-reported measures of narcolepsy: the need for better assessment. J Clin Sleep Med. 2017;13(5):737–44.
212. Kim J, Lee G-H, Sung SM, Jung DS, Pak K. Prevalence of attention deficit hyperactivity disorder symptoms in narcolepsy: a systematic review. Sleep Med. 2020;65:84–8.
213. Thieux M, Zhang M, Marcastel A, Herbillon V, Guignard-Perret A, Seugnet L, et al. Intellectual abilities of children with narcolepsy. J Clin Med. 2020;9(12):4075.
214. Ingram DG, Jesteadt L, Crisp C, Simon SL. Perceived challenges in pediatric narcolepsy: a survey of parents, youth, and sleep physicians. J Clin Sleep Med. 2021;17(1):13–22.
215. Graef DM, Byars KC, Simakajornboon N, Dye TJ. Topical review: a biopsychosocial framework for pediatric narcolepsy and idiopathic hypersomnia. J Pediatr Psychol. 2020;45(1):34–9.
216. Shelton AR, Malow B. Correlates to problem behaviors in pediatric narcolepsy: a pilot study. J Clin Sleep Med. 2017;13(12):1435–40.
217. Ludwig B, Smith S, Heussler H. Associations between neuropsychological, neurobehavioral and emotional functioning and either narcolepsy or idiopathic hypersomnia in children and adolescents. J Clin Sleep Med. 2018;14(4):14.
218. Pizza F, Barateau L, Jaussent I, Vandi S, Antelmi E, Mignot E, et al. Validation of multiple sleep latency test for the diagnosis of pediatric narcolepsy type 1. Neurology. 2019;93(11):e1034–44.
219. Morse AM. Narcolepsy in children and adults: a guide to improved recognition, diagnosis and management. Med Sci. 2019;7(12):106.
220. Kotagal S. Treatment of narcolepsy and other organic hypersomnias in children. Paediatr Respir Rev. 2018;25:19–24.
221. Franceschini C, Pizza F, Antelmi E, Folli MC, Plazzi G. Narcolepsy treatment: pharmacological and behavioral strategies in adults and children. Sleep Breath. 2020;24(2):615–27.
222. Bhattarai J, Sumerall S. Current and future treatment options for narcolepsy: a review. Sleep Sci [Internet]. 2017 [cited 2021 Jan 17];10(1). http://www.gnresearch.org/doi/10.5935/1984-0063.20170004.
223. Plazzi G, Ruoff C, Lecendreux M, Dauvilliers Y, Rosen CL, Black J, et al. Treatment of paediatric narcolepsy with sodium oxybate: a double-blind, placebo-controlled, randomised-

withdrawal multicentre study and open-label investigation. Lancet Child Adolesc Health. 2018;2(7):483–94.
224. de Biase S, Pellitteri G, Gigli GL, Valente M. Evaluating pitolisant as a narcolepsy treatment option. Expert Opin Pharmacother. 2021;22:155–62.
225. Giannoccaro MP, Sallemi G, Liguori R, Plazzi G, Pizza F. Immunotherapy in narcolepsy. Curr Treat Options Neurol. 2020;22:2.
226. Edwards K, Lambert P-H, Black S. Narcolepsy and pandemic influenza vaccination: what we need to know to be ready for the next pandemic. Pediatr Infect Dis J. 2019;38(8):873–6.
227. Zhang Z, Gool J, Fronczek R, Bassetti CL, Dauvilliers Y, Mayer G, et al. A new incidence peak of childhood narcolepsy type 1 in 2013: a new perspective on the role of influenza virus? [Internet]. Neurology. 2020 [cited 2021 Jan 5]. http://medrxiv.org/lookup/doi/10.1101/2019.12.31.19016246.
228. Edwards K, Hanquet G, Black S, Mignot E, Jankosky C, Shimabukuro T, et al. Meeting report narcolepsy and pandemic influenza vaccination: what we know and what we need to know before the next pandemic? A report from the 2nd IABS meeting. Biologicals. 2019;60:1–7.

Child with Unilateral or Bilateral Vision Loss

Amanda A. Ismail and Robert L. Tomsak

1 Introduction

Vision loss in childhood presents a unique diagnostic challenge. By nature, visual perception is subjective and so can be particularly difficult for young patients to describe. As a result, a directed history and targeted physical examination are essential when assessing this population. In this chapter, we will review the approach to evaluating children with unilateral or bilateral vision loss, discuss potential etiologies, and suggest appropriate diagnostic evaluations.

2 Epidemiology

Childhood blindness is a public health concern with significant emotional, social, and economic costs to the child and family. It is estimated that worldwide, approximately 1.4 million children suffer from blindness and 17.5 million from moderate–severe visual impairment [1, 2]. Unfortunately, in children less than 50% of causes are preventable or treatable [1]. Therefore, the prompt detection of low vision in a child is critical to ensuring that appropriate vision services are provided in a timely manner to children in whom such interventions are likely to be most beneficial.

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3 Etiology and Differential Diagnosis

Vision loss can be the result of abnormalities in the eye or visual pathways to the brain. The anterior visual pathway consists of the optic nerve and retina. Early damage to the anterior visual pathway can lead to congenital nystagmus. The optic nerves decussate in the chiasm, form the optic tracts and then the optic radiation before conveying visual signals to the occipital cortex. In this section, we will outline a few etiologies of vision loss in the pediatric population involving both the anterior and posterior pathways (Fig. 1). Disorders of the anterior pathway may be detected by examination of the eye, but disorders of the posterior pathway typically have no physical findings as pertain to the eye, as they are neurological disorders.

It is a standard practice to discuss conditions associated with vision loss by dividing them into two categories: disorders of the anterior and posterior vision pathways. Disorders of the anterior pathway include amblyopia due to refractive errors, strabismus, retinal disorders, cataracts, glaucoma, and conditions that affect the optic nerve. Commonly encountered conditions affecting the anterior pathway are detailed in Tables 1, 2, and 3. Posterior pathway disorders include conditions that affect the optic tracts, optic radiations and visual cortices such as hypoxic brain damage, stroke, and trauma to the brain parenchyma.

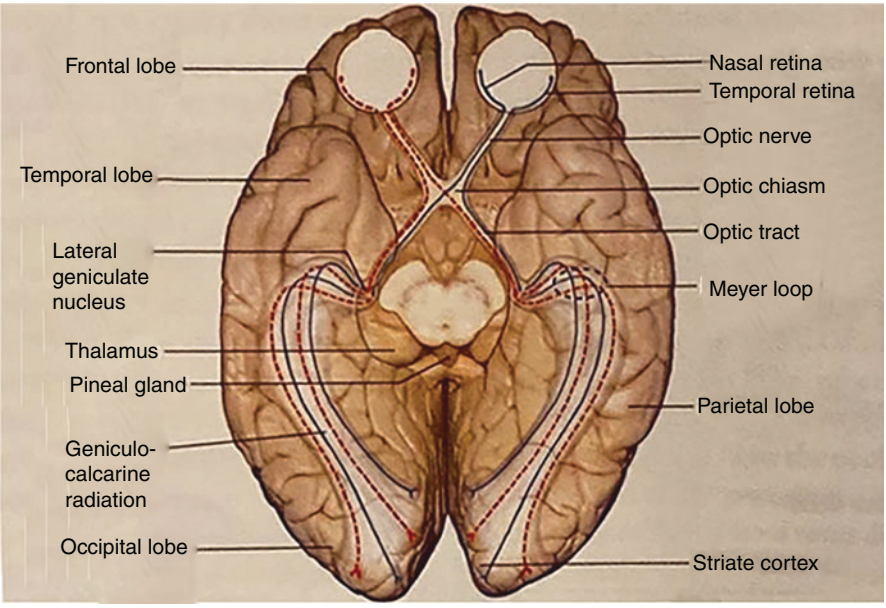

Fig. 1 Diagram of the anterior and posterior visual pathways [3]

3.1 Amblyopia and Strabismus

Amblyopia describes decreased vision in one or both eyes that cannot be directly attributed to a structural abnormality of the visual pathway. Amblyopia results from abnormal visual stimulation during infancy or childhood. This results in faulty development of the visual cortex during the "critical period" which occurs from ages 2–8 years in humans [4–7]. Amblyopia can be caused by uncorrected refractive error (see below), strabismus or deprivation of vision caused by cataracts or ptosis. Patients are often unaware of vision loss unless visual acuity is tested.

Strabismus describes a misalignment of the eyes. Patients may have horizontal deviations such as esotropia or exotropia (inward or outward drifting of eye) or vertical deviations such as hypertropia or hypotropia (upward or downward drifting of eye) [4, 8]. Regardless, if a deviation is intermittent or constant, it must always be evaluated by an ophthalmologist. Patients with strabismus are at risk of amblyopia as the brain utilizes cortical suppression to reduce the visual input from the strabismic eye in order to avoid diplopia [4–6, 8]. For more information regarding strabismus and disorders of eye movements please refer to chapter 15 by Saboo et al.

Treatment of amblyopia is driven by the cause. For example, cataracts or ptosis require early surgical repair and any refractive error must be corrected with glasses. If there is poor visual acuity even after treatment, then occlusion therapy with patching of the unaffected eye can be used to strengthen the vision of the amblyopic eye. Children less than 8 years of age have strong cortical suppression [5]. Cortical suppression describes the ability of the brain to inhibit visual information from one eye from reaching consciousness in order to avoid diplopia. Thus, amblyopia treatment must be started early in childhood in the hopes of improving vision. In addition, prognosis is dependent on when amblyopia treatment is started and compliance with therapy.

3.2 Refractive Errors

Uncorrected refractive errors are a common cause of amblyopia as well as decreased vision in the pediatric population [4, 7]. Myopia (nearsightedness) is where distant objects appear blurred. Images are focused in front of the retina and require a "minus power" lens for correction. Hyperopia (farsightedness) is where near objects appear blurred. Images are focused behind the retina and require a "plus power" lens for correction. Astigmatism describes abnormal corneal curvature resulting in images being focused at different points. This causes blurred vision at both distance and near. It requires cylindrical lenses for proper correction.

Vision screening in the primary care or school setting may detect refractive errors that can lead to vision loss. This can be performed by simply checking visual acuity or by photoscreening whereby the machine (called a photoscreener) estimates refractive error via the red reflex. Although accuracy varies, any abnormalities on the photoscreen should be referred.

High levels of hyperopia and myopia require correction as does significant astigmatism [4, 5]. In addition, a significant difference in the refractive error between the eyes, known as anisometropia, also requires correction [4, 6]. The degree of anisometropia considered significant depends on the age and type of refractive error (i.e., myopia, hyperopia, astigmatism) and ranges between 1.50 and 4.00 diopters [4, 5]. Otherwise, due to the plasticity of the young visual system, patients may fail to develop vision in one eye.

Note that not all refractive errors require correction with spectacles. The refractive state of the eye changes over time as the eye grows. It is typically hyperopic at birth, which increases until approximately age 6–7 years [4]. The eye then undergoes a myopic shift toward no refractive error or "emmetropia" into early adulthood [4]. Young patients can neutralize the hyperopic error by accommodation, or by changing the focusing power of the human lens, to provide a clear image on the retina, thus allowing for proper visual development in both eyes [4]. Therefore, although a refractive error may be measured, patients may still have good visual acuity and so are simply monitored. Nevertheless, as noted above, any refractive error detected on photoscreening should be referred to an ophthalmologist.

3.3 Cortical Visual Impairment (Disorders of the Posterior Pathway)

Cortical visual impairment (CVI) is one of the major causes of blindness in the developed world [2, 9]. It is the result of damage to the posterior visual pathway within the brain [9]. Most commonly, CVI is described as poor vision without nystagmus and normal pupillary light reflexes and eye examination. It is associated with neurologic or systemic diseases such as cerebral palsy, hydrocephalus, or seizure disorders [9]. Note that some developmentally delayed children may in fact exhibit visual inattention due to lack of interest rather than CVI.

The most common cause of CVI in children is hypoxic brain injury, resulting in reduced blood supply to the posterior visual pathway, especially the optic radiations [9]. This can occur perinatally, after respiratory or cardiac arrest or generalized hypotension. Other causes of CVI include cerebral malformations (Chiari malformations), neurometabolic disorders or trauma especially with associated intracranial findings such as fractures or hemorrhage [9]. Neuroimaging findings range from normal to significant abnormalities in the posterior visual pathway.

The visual prognosis is variable. Patients with ischemic or traumatic CVI are more likely to show improvement in vision than those with neurometabolic

disorders [9]. It is important to note that the severity of neuroimaging findings do not correlate with visual disability. Finally, there is no specific treatment for CVI.

3.4 Delayed Visual Maturation

Delayed visual maturation (DVM) describes a child who does not exhibit expected visual function for age but eventually reaches visual milestones at a later time. Visual function typically improves around 4–6 months of age, but it may take up to 1 year for normal vision to develop [9]. Both the eye examination and neuroimaging are normal. Patients may have delayed motor development or exhibit infantile spasms [9].

These children may initially be diagnosed with CVI given poor vision, normal pupillary response and the absence of nystagmus [9]. Note that while vision can improve in CVI, it never improves to a normal level as in DVM. In addition, CVI is associated with an underlying cerebral insult resulting in abnormal vision whereas the etiology of DVM is unknown.

3.4.1 Perinatal Infectious Exposure

With the advent of vaccination protocols and prenatal screening, vision loss as a result of exposure to infections in utero has declined [1, 4]. Table 1 includes common congenital infections that may result in vision loss; a few will be discussed below.

Rubella: Intrauterine infection with rubella during the first 20 weeks of pregnancy may lead to congenital rubella syndrome. Patients may have deafness,

Table 1 Common retinal disorders causing decreased visual acuity at birth

Disorder	Features
Leber congenital amaurosis	A dystrophy of both rods and cones resulting in severe vision loss with a normal appearing fundus early on
Achromatopsia	Absence or dysfunction of cones with very poor vision and color blindness with a normal appearing fundus early on
Albinism	An inherited condition with decreased or absent melanin affecting eyes and/or skin. Ocular features include decreased vision, photophobia, nystagmus, iris transillumination, and foveal hypoplasia
Aniridia	A congenital hypoplasia of the iris associated with cataract, glaucoma, optic nerve hypoplasia and foveal hypoplasia
Congenital infections	(Ocular manifestations): Toxoplasmosis, Rubella, Cytomegalovirus, Herpes simplex virus, Syphilis
Coloboma of the macula	Failure of the embryonic fissure to close resulting in defect in retina and choroid within the macula

cardiac malformations and ocular manifestations including pigmentary retinopathy, cataracts, microphthalmia, and/or glaucoma. Microphthalmia describes an abnormally small eye with anatomical malformations. Pigmentary retinopathy is the most common eye finding [10]. However, vision loss is typically secondary to cataracts and microphthalmia [4, 10]. Vaccination against rubella has helped reduce the infection rate and thus incidence of congenital rubella syndrome [1, 4, 11].

Toxoplasmosis: Congenital toxoplasmosis is transmitted from a newly infected mother to the fetus during pregnancy. The disease is most severe if transmission occurs during the third trimester of pregnancy [12]. Ophthalmic findings include chorioretinal scars, microphthalmia, cataract, optic atrophy, and later uveitis. Visual prognosis is dependent on the extent and severity of the ocular involvement [4, 10, 12]. Long-term patients may develop uveitis from reactivation of the parasite. Systemically, patients may have hydrocephalus, prematurity, or seizures. Mothers are counseled to avoid undercooked meat, unwashed vegetables, and exposure to cat feces during pregnancy to prevent exposure [12].

Ophthalmia Neonatorum: This describes conjunctivitis within the first month of life, often caused by exposure to gonorrhea or chlamydia while in the birth canal [4]. Infants have extensive ocular discharge and eye redness with possible corneal involvement. Treatment involves systemic and topical antibiotic therapy, and in some cases frequent ocular lavage to prevent further damage to the cornea [4, 11]. Proper prenatal care and prophylactic instillation of topical agents in infants at birth has reduced the incidence [4, 11].

3.4.2 Xerophthalmia

Xerophthalmia describes a spectrum of ocular disease secondary to vitamin A deficiency and is the leading cause of childhood blindness in the developing world [13]. The most common etiology is malnutrition although in the developed world other causes should be investigated [13]. These include malabsorption conditions such as cystic fibrosis or liver disorders resulting in poor vitamin metabolism.

Nyctalopia or night blindness is the earliest symptom of xerophthalmia followed by xerosis or “dryness” of the ocular surface. Later stages of the disease involve severe corneal involvement (ulceration or perforation), retinal changes, and optic atrophy. In addition to ophthalmic findings, patients with vitamin A deficiency are susceptible to severe infections resulting in a high mortality [13, 14]. Treatment involves ocular lubrication and vitamin A supplementation, and if started in early stages there is complete resolution of ophthalmic findings within 1–4 weeks [13, 14]. However, even if vitamin A levels are normalized in the later stages of disease, there can be permanent vision loss [13, 14].

Pediatric patients, especially those with cognitive delay or autism spectrum disorder, may be unable to articulate early symptoms of xerophthalmia. Therefore, such patients require detailed dietary histories and early screening for vitamin deficiencies to ensure they receive prompt treatment [15].

3.4.3 Hereditary Retinal Disorders

Children with hereditary retinal disorders may present with bilateral decreased vision, photophobia, and color deficiencies. On history, patients typically report impaired vision in either day or night settings and may exhibit the oculodigital reflex, which is the manual stimulation of the eyes with fingers or hands (discussed below) [9, 10]. Eliciting a family history of similar symptoms or blindness is helpful. Depending on the specific retinal condition, patients may or may not have significant retinal findings. Tables 1 and 2 list common retinal disorders causing vision loss at birth and in childhood. A select few are discussed in detail below.

Retinopathy of Prematurity (ROP): ROP is the result of abnormal development of blood vessels in the retina of premature infants. It is characterized by peripheral retinal neovascularization that in advanced stages can lead to retinal detachment and blindness. Risk factors include prematurity, low birth weight and oxygen therapy [4, 16]. At-risk patients who meet screening criteria are closely followed by an ophthalmologist.

In most cases, ROP resolves without causing damage but those who progress to certain stages require treatment to prevent retinal detachment [16]. Treatment includes laser photocoagulation to the immature retina or injection of a medication such as the anti-VEGF drug, bevacizumab, to stop abnormal blood vessel growth [4, 16].

Leber Congenital Amaurosis (LCA): LCA is a retinal dystrophy involving both rods and cones and is responsible for 10–18% of childhood blindness [9, 10]. There is severe though nonprogressive visual disability. Patients are typically blind at birth

Table 2 Common retinal disorders causing decreased visual acuity in childhood

Disorder	Features
Retinopathy of prematurity	Peripheral neovascularization and possible retinal detachment resulting from abnormal retinal blood vessel growth in a premature infant exposed to oxygen
Stargardt disease	An inherited macular dystrophy causing vision loss with pisciform flecks in the central retina
Juvenile X-linked retinoschisis	An inherited condition with splitting of the retina with petaloid appearance in fovea and gradually decreased vision
Best disease	An inherited dystrophy with mildly decreased vision within the first two decades of life and classic “egg-yolk” appearance of fovea
Retinitis pigmentosa	Progressive degeneration of the photoreceptors, especially rods, with symptoms of peripheral vision loss and night blindness. Classic findings include pigment clumping, retinal vessel attenuation and waxy pallor of the optic nerve
Cone-rod dystrophies	Dysfunction of photoreceptors, especially cones, resulting in significantly decreased vision, abnormal color vision and vision loss in bright light (hemeralopia)
Coats disease	Unilateral congenital retinal telangiectasia that progresses to exudative retinal detachment, typically affecting males by age 8

with poorly or nonreactive pupils and eventually nystagmus. There are a wide range of retinal findings typically normal at birth to eventual pigmentary changes and optic nerve pallor. Patients rarely report photophobia but do exhibit the oculodigital sign. Up to 25% of patients with LCA have associated neurologic or developmental abnormalities [10].

Vision is typically very poor ranging from 20/200 to light perception [4, 9, 10]. For qualifying patients, there is potential for improved visual prognosis with gene therapy [9]. It is approved for patients with a specific mutation on the RPE65 gene [4]. For patients without this mutation, treatment is supportive.

Note that LCA is a different entity than Leber hereditary optic neuropathy (LHON).

Stargardt Disease: This inherited macular dystrophy causes vision loss typically starting in adolescence. It is slowly progressive though eventually stabilizes. The final visual acuity ranges from normal to 20/100 [4, 9]. Stargardt disease is characterized by yellow-white flecks in the maculas caused by lipofuscin accumulation. The most common symptom is central vision loss [4, 16]. Treatment at this time is supportive with low vision aids as needed.

3.4.4 Optic Disc Anomalies

Anomalies of the optic disc are present at birth and result in various degrees of visual dysfunction. Management of visual disability related to optic disc anomalies is supportive. Frequently, congenital anomalies of the optic disc are accompanied by other neurologic and/or systemic abnormalities [9].

Optic Nerve Hypoplasia (ONH): ONH describes abnormally small optic nerves. The classic appearance is a small nerve surrounded by a yellow ring of the typical optic disc size. Findings may be unilateral or bilateral.

Visual function varies from only visual field defects to no light perception vision and nystagmus [9, 10]. Importantly, visual function does not correlate with optic nerve appearance. In other words, a severely hypoplastic nerve may have good visual acuity.

Many cases of ONH have associated anomalies of the central nervous system such as an absent septum pellucidum (DeMorsier's syndrome or septo-optic dysplasia) or pituitary ectopia [9, 10]. Patients may have hypopituitarism, especially insufficient production of growth hormone. Therefore, optic nerve hypoplasia, especially if bilateral, warrants neuroimaging, endocrinologic evaluation, referral to a neurologist and developmental evaluation [9, 10].

Optic Nerve Coloboma: Colobomas are the result of a failure of the embryonic fissure to close [9, 10, 17]. Many are considered idiopathic although when identified, the most common cause is genetic [17]. Colobomas can be associated with central nervous system defects, genetic syndromes, or chromosomal disorders [17]. Ocular colobomas may involve the iris, lens, retina, choroid, and/or optic nerve [10,

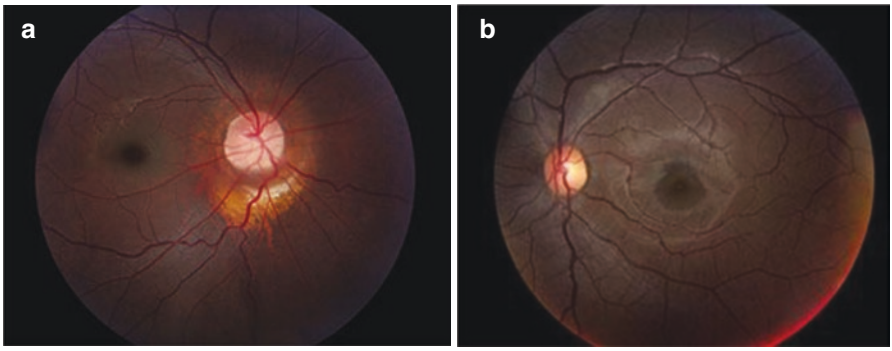

Fig. 2 (**a**) Optic nerve photo reveals a right retinochoroidal coloboma involving the optic disc. (**b**) Optic nerve photo of the patient's normal left optic nerve for comparison

17]. Optic nerve colobomas are typically an inferonasal segmental disc anomaly. The nerve appears to be an enlarged oval with abnormal vessel origin (Fig. 2). Often, patients with optic nerve colobomas have reduced acuity along with visual field defects associated with the location of coloboma [10].

3.4.5 Optic Atrophy

Optic atrophy is the result of damage to the anterior visual pathway leading to retinal ganglion cell axon loss [9]. The examination reveals optic nerve pallor in a diffuse or segmental pattern. Early-onset bilateral atrophy may be caused by suprasellar tumors or hydrocephalus such that this finding warrants emergent neuroimaging [9]. Unilateral optic atrophy requires neuroimaging to exclude a structural lesion, but frequently no cause is found [10].

Isolated Optic Atrophy: The most common form of isolated optic atrophy is dominantly inherited (dominant optic atrophy; DOA) and is the result of mutations in the OPA 1 class of genes [10]. Patients present with bilateral mild–moderate vision loss early in childhood. Vision is typically 20/200 or better with some progression over time [10]. Color vision is affected early and often patients have central scotomas. Examination reveals optic nerve pallor in a pattern involving a triangular portion of the temporal disc [9, 10]. In some cases, once the vision stabilizes patients may be able to function well in normal school classes and the workforce.

Associated Neurologic or Systemic Diseases: There are numerous inherited neurologic or systemic diseases that may have associated vision loss secondary to optic atrophy. Many have associated ataxia and speech abnormalities [9]. Others may have associated conditions including sensorineural deafness or diabetes [9]. As a result, systemic history and physical examination is critical when evaluating patients with optic atrophy.

3.4.6 Other Optic Neuropathies

Papilledema: Bilateral optic disc swelling due to elevated intracranial pressure is also known as papilledema. Examination reveals blurred disc margins, optic nerve elevation, obscuration of the vessels, and possible splinter hemorrhages or cotton–wool exudates on the optic disc. Patients report blackouts in vision lasting seconds (transient visual obscurations) but with normal visual acuity. Symptoms also include headaches and possibly diplopia if there is an associated cranial nerve six palsy.

Papilledema requires immediate neuroimaging to exclude a structural cause like brain tumor. Frequently no cause is found and, after further testing, the diagnosis of idiopathic intracranial hypertension (pseudotumor cerebri) is made, but this diagnosis is always one of exclusion [9, 10]. If the intracranial pressure is reduced in timely fashion permanent visual disability can be avoided. Patients can be managed medically with acetazolamide or surgically with lumbo-peritoneal shunts or optic nerve sheath fenestrations [10]. Papilledema per se does not cause visual loss but chronic optic nerve swelling can lead to optic atrophy with visual field loss and decreased visual acuity [9, 10].

Ophthalmic imaging with optical coherence tomography (OCT) provides high-resolution visualization of the optic nerve head and retina. On OCT, optic nerve edema results in increased retinal nerve fiber (RNFL) thickness in all quadrants compared to normal controls [18]. When permanent damage to the optic nerve occurs ganglion cell complex thinning is the first and most sensitive OCT finding and serial OCT is the preferred method for monitoring papilledema. Figure 3 illustrates an example of papilledema with corresponding OCT findings. In addition, findings such as optic nerve drusen, a common cause of pseudopapilledema in children, can be visualized with OCT [18].

Compressive or Traumatic Optic Neuropathies: Compression of the optic nerve can cause decreased visual acuity, visual field defects, color desaturation, or a relative afferent pupillary defect. Long-standing compression (usually by a tumor) can result in permanent damage to the optic nerve. Even mild closed-head injuries can lead to traumatic optic neuropathies [10]. Therefore, any trauma around the time of the vision changes should be noted.

Optic Neuritis: In children, optic neuritis is typically a bilateral, postinfectious condition associated with optic disc swelling. The vision loss is severe, but patients demonstrate excellent visual recovery within 6 months [9, 19]. Contrary to adults, optic neuritis in children is less likely to be associated with multiple sclerosis [9, 19]. In addition, children with optic neuritis have more severe vision loss than adults, experience better recovery, have more common optic nerve edema, and less orbital pain [19]. Treatment is typically with steroids; however, there are no controlled studies investigating the efficacy of treatment in the pediatric patients with optic neuritis [19].

Glaucoma: Glaucoma is an optic neuropathy typically resulting from elevated intraocular pressure (IOP). It initially results in peripheral vision loss but, if uncontrolled eventually, leads to irreversible blindness. In the pediatric population, glaucoma may be congenital or juvenile onset and requires ophthalmological examination for diagnosis and treatment [4, 20].

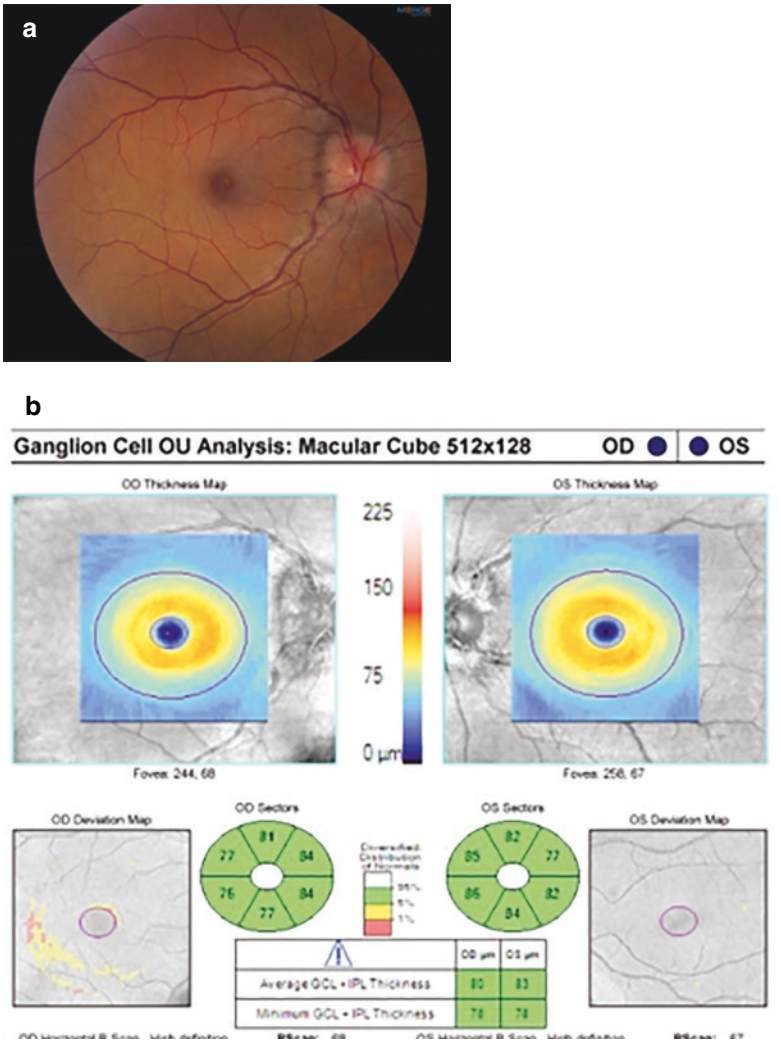

Fig. 3 (**a**) Optic nerve photos showing optic nerve edema. (**b**) Corresponding OCT images of the optic nerves showing elevation of both optic discs with corresponding thickening of the retinal nerve fiber layers (RNFL) (left). Normal ganglion cell complex maps indicate the absence of permanent damage to the optic nerves (right)

Table 3 Causes of secondary glaucoma

Axenfeld–Rieger syndrome
Aniridia
Sturge–Weber syndrome
Neurofibromatosis
Uveitis
Chronic steroid use
Trauma
Previous eye surgery (cataract removal as child)

Congenital glaucoma may be present at birth usually developing between ages 1 and 24 months [20]. It is the result of abnormal development of the aqueous drainage system resulting in elevated IOP. The common triad of symptoms includes excessive tearing, light sensitivity and large, cloudy corneas [4, 20]. Although the most common cause of excessive tearing in childhood is a nasolacrimal duct obstruction, any other symptoms require urgent referral to an ophthalmologist to rule out glaucoma. Congenital glaucoma requires surgical treatment aimed at opening the trabecular meshwork, a part of the aqueous drainage system.

Juvenile glaucoma resembles adult glaucoma but presents after age 3 years [4, 20]. Like adults, there are minimal if any symptoms as vision loss begin peripherally. Ophthalmic evaluation reveals elevated IOP along with optic disc enlargement. The initial treatment involves medical therapy with advanced cases requiring surgery.

Secondary glaucoma describes glaucoma associated with a specific condition. Examples of secondary glaucoma in childhood are listed in Table 3.

3.4.7 Tumors of Visual System

Retinoblastoma: This is the most common intraocular malignancy in children with most presenting within the first 3 years of life [4, 10]. There may be a family history in approximately 6% of cases [10]. Most patients present initially with leukocoria (white pupillary reflex) or strabismus rather than decreased vision [4, 10].

Management of retinoblastoma is dependent on the stage of the disease. Notably, management requires a multidisciplinary approach with specialists from ophthalmology, oncology, and genetics. Potential ocular treatment modalities include laser photocoagulation, cryotherapy, plaque radiation, and enucleation. Chemotherapy is often required as well. The visual prognosis is dependent on staging, which includes the location of the tumor(s). However, the overall cure rate has significantly improved to approximately 95% at present [4].

Optic Nerve Glioma: These low-grade astrocytomas of the optic nerve are typically unilateral and present within the first two decades of life. Most are sporadic but there is an association with neurofibromatosis type 1 (NF1) (see below). Patients present with decreased vision and orbital signs (proptosis, decreased vision, pain, and/or restricted eye movements). Fundoscopic examination may reveal optic nerve edema or atrophy. Orbital imaging reveals fusiform enlargement of the intradural optic nerve. Patients are observed unless there is declining vision and/or rapid growth. Chemotherapy is first-line treatment [21]. Newer molecularly targeted

therapies such as mitogen-activated protein kinase pathway inhibitors and bevacizumab have shown promise in refractory cases [21]. Given the high morbidity associated with surgical excision and radiotherapy, these treatment modalities are considered last resort [21]. The prognosis is dependent on the extent of the tumor and recurrence rate, which is higher in cases associated with NF1 [10].

Rhabdomyosarcoma: This is the most common primary orbital malignancy in children, typically occurring around age 7–8 years [4, 10]. It arises from undifferentiated mesenchymal cells and in some cases may originate from the adjacent sinuses. Rhabdomyosarcoma presents with rapid onset, painless unilateral proptosis, and eyelid edema and discoloration. Urgent imaging and biopsy are required. Treatment involves surgery (depending on size), radiation, and chemotherapy. Prognosis is dependent on location, histological appearance, and stage. The overall survival rate is 90% [4].

3.4.8 Phakomatoses

Phakomatoses are a group of neurocutaneous conditions with multiple organ involvement including skin, brain, eyes, and more [4, 9, 10]. In many cases, retinal lesions can lead to exudation of fluid with subsequent retinal detachments and vision loss [10]. Syndromes such as Neurofibromatosis Type 1 and Sturge–Weber are at risk of developing glaucoma, and so must be monitored by an ophthalmologist. Table 4 lists a select group of phakomatoses in which the eye manifestations may result in vision loss.

Table 4 Phakomatoses with risk of vision loss

Disorder	Systemic features	Ocular involvement
Neurofibromatosis type 1	– Cafe-au-lait macules – Neurofibromas – Axillary freckling – Osseous lesions	– Lisch nodules[a] – Optic nerve glioma – Plexiform neurofibroma[b]
Sturge–Weber syndrome	– Facial port-wine nevus – Leptomeningeal vascular malformations – Seizures – Intellectual disability	– Choroidal hemangioma – Glaucoma
Tuberous sclerosis	– Adenoma sebaceum – Ash-leaf spots – Shagreen patch – Cortical tubers – Subependymal nodules – Seizures – Intellectual disability	– Retinal astrocytoma
Von Hippel–Lindau syndrome	– Cerebellar hemangioblastoma – Renal cell carcinoma – Pheochromocytoma	– Retinal hemangioblastoma
Wyburn–Mason syndrome	– Facial vascular malformation – CNS vascular malformation	– Retinal arteriovenous malformation

[a]Ocular manifestation not associated with vision loss

[b]May cause ptosis that could affect vision. Presence is associated with a higher risk of developing glaucoma

3.4.9 Transient and Psychogenic Visual Loss

Migraine: The most common cause of episodic vision loss in childhood is a migraine [9]. Patients may describe visual hallucinations such as flashing lights or patterns. Note the typical throbbing headache is often not present in children. A family history of migraines is helpful to elicit. Treatment includes reassurance along with headache management as indicated.

Functional Vision Loss: Functional vision loss describes visual dysfunction with no organic cause. This may be conscious or unconscious (ocular conversion reaction). Note that conscious malingering behavior, for personal gain, is a rare occurrence in children [9, 10]. Most importantly functional vision loss is a diagnosis of exclusion. It typically presents in children around 11-years-old who will often describe blurry vision with a visual field abnormality [10]. Most patients improve with time and reassurance is the best management strategy. The history should include a family history of eye diseases and the possibility of abuse.

4 Diagnostic Approach

4.1 History

A targeted history is critical when assessing any complaint in the pediatric population. Visual behavior in children should be assessed by age as appropriate. Namely, how is the child functioning in the world around them. Younger children typically explore their environment, so reduced vision will limit this behavior. In addition, ask about appropriate developmental milestones such as developing a social smile, grasping for objects, recognizing faces, or crawling [4]. Although children may reach these milestones at a range of ages, patients may be delayed due to visual disability. Older children may have difficulty in school or with reading [4].

Patients may exhibit an oculodigital reflex in an attempt to mechanically stimulate retinal photoreceptors in order to produce a visual percept called phosphenes [4, 10, 16]. It is important to note when present as it is found in patients with bilateral, poor vision specifically from retinal disease.

While parents often provide the history in the pediatric population, verbal children should be asked to describe their symptoms given the subjective nature of the complaint. Important historical features include laterality of symptoms, time of onset, length of vision loss when episodic, and description of the vision loss. Associated symptoms to elicit include photophobia or headache. Note any history of trauma. Finally, a family history of any ophthalmic conditions is important.

4.2 Physical Examination

The physical examination in a child begins with observation, and in an uncooperative child that may be all the information that can be realistically obtained [4, 9, 10]. General examination should focus on neurocutaneous markers and measurement of head circumference.

Look for misalignments of the eyes, abnormal eyelid position such as ptosis or abnormal eye movements. Externally, note any excessive tearing, conjunctival injection, corneal opacities, or any obvious foreign body. If the patient has unilateral symptoms, comparison of the appearance between the eyes can be useful for any subtle findings. Finally, assess the child's overall responsiveness to the environment and interactions with both the examiner and caregiver [4, 10].

A proper ocular examination in children begins with an age appropriate visual acuity assessment. Vision should be checked by each eye individually or "monocularly," and in older children at distance and near. Children are notorious for attempting to "peek" past an occluder, thus it is recommended that the examiner occlude each eye to ensure vision is in fact tested monocularly [4]. In addition, a child who resists occlusion of an eye may suggest reduced vision in the other eye [4]. Tables 5 and 6 review a detailed approach to a complete ocular examination in a child reporting vision loss. Finally, when possible the physician should attempt to test for an afferent pupillary defect as noted in Fig. 4.

Table 5 Assessment of visual acuity in children

Infants	
Reaction to light	An eye with visual potential reflexively closes after a bright light is shined into it *"Eye Popping" sign*: eyes open wide when room lights turned off, indicates at least light perception vision
Fix and follow	An eye follows a target moved within its field, develops around age 2–3 months Failure to fix and follow may be due to reduced vision, poor attention or neurologic delay
Preferential looking	When presented a card with grating bars on one side, an infant chooses to look at the bars rather than uniform gray Grating bars become smaller until infant no longer demonstrates a preference Distance between bars provides rough visual acuity estimate
Preliterate children	
Letter matching	Present with one of four common images (LEA) or letters (HOTV), and elicit a verbal response or match to a reference card
Literate children	
Snellen acuity	Present letters singly or linearly Linear snellen acuity most accurate, attempt as early as possible
Low vision	
Count fingers	Patient reports how many fingers the examiner is holding up starting at 5 ft. away. The examiner moves closer until patient accurately counts fingers
Hand motion	Patient reports direction examiner's hand moving in front of eye
Light perception	Shine bright light into and out of eye, patient reports when light is turned "on or off"

Table 6 Ocular examination in children

Ocular motility	Observe for signs of strabismus, nystagmus, motility deficits *Doll's head maneuver*: for young patients with apparent abduction deficit, rotate head to each side to ensure full abduction via the vestibulo-ocular reflex *Hirschberg light reflex*: detects eye misalignment, shine light both eyes simultaneously, a normal reflex is centrally located on each cornea
Pupil exam	Shine a bright light into each eye comparing the quality (brisk vs. sluggish) and symmetry of reaction between the eyes "*Swinging flashlight test*" (Fig. 4): assess for a relative afferent pupillary defect (RAPD), which indicates unilateral or asymmetric disease
Fundus exam	Direct ophthalmoscopy to assess optic nerve appearance
Systemic exam	Pay particular attention to neurologic deficits

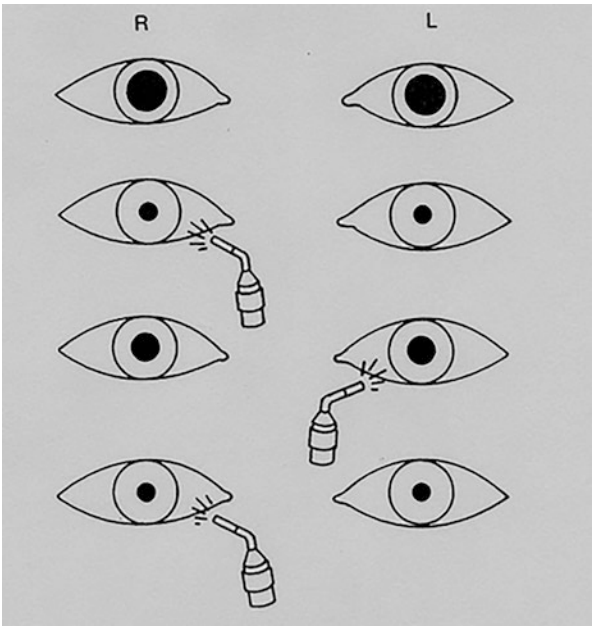

Fig. 4 Illustration of the "swinging light test" to detect a left relative afferent pupillary defect in a patient with a left optic neuropathy [22]. Normally, both pupils are equal in size and the direct and consensual light responses are equal. In a patient with unilateral left optic neuropathy, the direct response is less than on the right. This results in an attenuated consensual response of the right pupil as well. If one swings the light from right to left about once every 1–2 s, the left pupil dilates under direct illumination and the right pupil constricts when the light is swung back to illuminate it. The normal response is no change between pupil sizes when alternately illuminating each eye. (Courtesy of Robert L. Tomsak MD, PhD)

4.2.1 Nystagmus

Nystagmus can be a useful diagnostic clue, particularly in infancy and in conditions with minimal ocular signs. It is a rhythmic, involuntary oscillation of the eyes. Eye movement recordings are the only way to truly define and quantitate types of nystagmus, but unfortunately are almost never used clinically [23]. Infantile nystagmus, formerly called congenital nystagmus, is present prior to 6 months of age, and is bilateral and horizontal regardless of gaze position. Infantile nystagmus occurs most often in otherwise normal children about 50% of the time [23]. However, it may accompany abnormalities in the anterior visual pathways, especially albinism [23]. Infantile nystagmus from anterior visual pathway disease typically occurs when vision loss is acquired at less than 2 years of age [9].

Infantile nystagmus is most often horizontal and may be associated with a face turn to put the eyes in a position (the "null" position) where the nystagmus is lessened, or damped, thus maximizing visual acuity [9]. It is dampened by convergence and frequently remains horizontal in upgaze [9, 10]. Some patients with infantile nystagmus have associated head oscillations, but these do not have a salutary effect on the nystagmus or visual function [10].

Roving or drifting eye movements must be distinguished from nystagmus. Roving movements describe slow, unpatterned drifting of the eyes. Like nystagmus, they are typically due to ocular or anterior pathway lesions but imply worse visual function and an inability to fixate [9].

Since most of the visual pathway is located in the brain a detailed neurological examination, as appropriate for the age of the child, should be undertaken in every child with suspected vision loss. Examples of children who may have an abnormal neurological examination in conjunction with vision loss may include cerebral palsy, hydrocephalus and neurodegenerative disorders such as neuronal ceroid lipofuscinosis [9, 10].

5 Evaluation

Routine laboratory investigations are not typically warranted for vision loss without initial referral to an ophthalmologist. Therefore, the most critical decision for the provider evaluating a child with vision loss is when and how urgently to refer to ophthalmology with or without neuroimaging. This will be addressed in the section below.

A number of additional tests may be required for further evaluation following a proper evaluation by ophthalmology. These may include optical coherence tomography (OCT) or visual field testing depending on a patient's age and cooperation. Younger or poorly cooperative patients may undergo visual evoked potential (VEP) testing, which globally assesses the visual system [4]. This is an electrophysiological test that is typically performed in the office of a child neurologist. Electroretinography (ERG) evaluates electrical activity within the retina and may be performed when disorders of the retina are suspected.

Magnetic resonance imaging (MRI) is the best neuroimaging modality for evaluating the orbit and visual pathways of the brain. Findings such as papilledema or a cranial nerve deficit require immediate imaging. Children with small optic nerves also require imaging as noted above as other brain anomalies may be present.

6 Treatment and Management

The management of vision loss in the pediatric population is geared toward the particular etiology. In cases where specific treatment is not available, supportive therapy with low-vision services is offered to patients with poor visual acuity. The goal of low-vision therapy is to provide patients with the tools and techniques to best utilize the vision they have. Finally, children with decreased vision may qualify for additional services in school and/or at home. The sooner these patients attain these services, the better for their overall development.

7 Prognosis and Outcome

As discussed above, the prognosis of vision loss in the pediatric population is dependent on the particular etiology and early management.

8 When to Refer

- Following a thorough history or physical examination, additional evaluation can be performed by an ophthalmologist.
- Any patient with abnormal findings on physical examination warrants a referral to a specialist.
- These include findings such as optic nerve abnormalities, nystagmus, and/or a relative afferent pupillary defect (Fig. 4).
- However, patients with significant family history of vision loss or hereditary ophthalmic conditions may also require additional evaluation.
- Photoscreening can be performed by the primary care provider to screen for any refractive error or strabismus.
- Any patient with failed testing should be referred.
- When papilledema is suspected, the child should be sent to the emergency department for immediate evaluation by ophthalmologists and a pediatric neurologist.

9 Prevention

The prevention of vision loss in the pediatric population is dependent on etiology. For example, in cases of inherited conditions such as retinal dystrophies or optic nerve malformations there is no prevention. However, in-utero exposure to congenital infections can be prevented by proper prenatal screening, treatment, and vaccination. Similarly, adequate intake of vitamin A can prevent vision loss due to vitamin A deficiency.

10 Clinical Pearls/Key points

- Vision loss is a subjective complaint and therefore, history may be difficult to elicit, especially in the pediatric population.
- A directed physical examination is important when evaluating vision loss in children. Clues found on observation can be helpful.
- There are numerous potential etiologies for vision loss involving the anterior or posterior visual pathway.
- Any abnormalities noted on examination require referral to ophthalmology for a detailed evaluation.
- Although many causes of childhood vision loss are not preventable or treatable, there are numerous services and various forms of supportive care that may be available.

References

1. Wadhwani M, Vashist P, Singh SS, Gupta V, Gupta N, Saxena R. Prevalence and causes of childhood blindness in India: a systematic review. Indian J Ophthalmol. 2020;68(2):311–5.
2. Alagaratnam J, Sharma TK, Lim CS, Fleck BW. A survey of visual impairment in children attending the Royal Blind School, Edinburgh using the WHO childhood visual impairment database. London. 2002;16(5):557–61.
3. American Academy of Ophthalmology, Bhatti MT, et al. Basic and clinical science course (BCSC) section 5: neuro-ophthalmology. San Francisco: American Academy of Ophthalmology; 2017.
4. American Academy of Ophthalmology, Lueder GT, et al. Basic and clinical science course (BCSC) section 6: pediatric ophthalmology and strabismus. San Francisco: American Academy of Ophthalmology; 2017.
5. Wright KW, Strube NYJ. Color atlas of strabismus surgery: strategies and techniques. 4th ed. New York: Springer; 2015.
6. Bennetti Zagui RM. Amblyopia: types, diagnosis, treatment and new perspectives. American Academy of Ophthalmology [Internet]. 2019 [cited 2020 Dec]. https://www.aao.org/disease-review/amblyopia-types-diagnosis-treatment-new-perspectiv.

7. Von Noorden GK, Campos EC. Binocular vision and ocular motility: theory and management of strabismus. 6th ed. St. Louis: Mosby; 2002.
8. Kushner BJ. Strabismus. 1st ed. Madison: Springer; 2017.
9. Brodsky MC, Baker RS, Hamed LM, Flynn J. Pediatric neuro-ophthalmology. 1st ed. New York: Springer. p. 1996.
10. Tomsak RL. Pediatric neuro-ophthalmology. 1st ed. Newton: Butterworth-Heinemann; 1995.
11. Gogate P, Gilbert C, Zin A. Severe visual impairment and blindness in infants: causes and opportunities for control. Middle East Afr J Ophthalmol. 2011;18(2):109.
12. American Academy of Ophthalmology, Read RW, et al. Basic and clinical science course (BCSC) section 9: intraocular inflammation and uveitis. San Francisco: American Academy of Ophthalmology; 2017.
13. Chae T, Foroozan R. Vitamin A deficiency in patients with a remote history of intestinal surgery. Br J Ophthalmol. 2006;90:955–6.
14. Gilbert C. The eye signs of vitamin A deficiency. Commun Eye Health. 2013;26(84):66–7.
15. Duignan E, Kenna P, Watson R, Fitzsimon S, Brosnahan D. Ophthalmic manifestations of vitamin A and D deficiency in two autistic teenagers: case reports and review of the literature. Case Rep Ophthalmol. 2015;6, 24:–29.
16. American Academy of Ophthalmology, McCannel CA, et al. Basic and clinical science course (BCSC) section 12: retina and vitreous. San Francisco: American Academy of Ophthalmology; 2017.
17. ALSomiry AS, Gregory-Evans CY, Gregory-Evans K. An update on the genetics of ocular coloboma. Hum Genet. 2019;138(8–9):865–80.
18. Bassi ST, Mohana KP. Optical coherence tomography in papilledema and pseudopapilledema with and without optic nerve head drusen. Indian J Ophthalmol. 2014;62(12):1146.
19. Pineles SL, Repka MX, Liu GT, Waldman AT, Borchert MS, Khanna S, Heidary G, Graves JS, Shah VS, Kupersmith MJ, Kraker RT, Wallace DK, Cotter SA, Holmes JM. Assessment of pediatric optic neuritis visual acuity outcomes at 6 months. JAMA Ophthalmol. 2020;138(12):1253–61.
20. American Academy of Ophthalmology, Girkin CA, et al. Basic and clinical science course (BCSC) section 10: glaucoma. San Francisco: American Academy of Ophthalmology; 2017.
21. Farazdaghi MK, Katowitz WR, Avery RA. Current treatment of optic nerve gliomas. Curr Opin Ophthalmol. 2019;30(5):356–63.
22. Levatin P. Pupillary escape in disease of the retina or optic nerve. Arch Ophthalmol. 1959;62:768–79.
23. Leigh JR, Zee DS. The neurology of eye movements. 5th ed. New York: Oxford University Press; 2015.

Child with Diplopia

Homer Chiang, Martha P. Schatz, and Ujwala S. Saboo

1 My Child's Eyes Are Misaligned/My Child Complains of Double Vision

1.1 Introduction

Strabismus refers to ocular misalignment. The symptom of double vision is defined as diplopia. If the ocular misalignment is latent (only seen when binocular viewing is interrupted), then it is termed a heterophoria. Constant, or manifest, ocular misalignment is known as heterotropia. Childhood-onset nonparalytic strabismus usually has normal extraocular movements. The angle of deviation, or degree of misalignment, is the same in all positions of gazes and is termed comitant strabismus. Children with constant strabismus learn to suppress one eye to avoid diplopia. In such cases, the deviated eye may develop amblyopia. If the deviation is latent (phoria), it can occasionally become manifest during periods of stress and tiredness and can cause diplopia. Ocular misalignment that changes degree of misalignment with position of gaze is known as incomitant strabismus.

1.2 Epidemiology

Strabismus or ocular misalignment affects 2–4% of preschool children [1].

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1.3 Horizontal Deviation

1.3.1 Nonparalytic Horizontal Deviation

Esotropia

Inward deviation of the eye is known as esotropia.

Infantile Esotropia

If the onset of esotropia is before one year of age, then it is called infantile esotropia. This entity presents as a large angle constant esotropia (Fig. 1). It may alternate between both eyes, and occasionally children may have cross-fixation, which means they look to the left with the right eye and to the right with the left eye. Infantile esotropia can occur in children with neurologic and developmental problems, including cerebral palsy, hydrocephalus, and prematurity [2]. Children may fixate with only one eye while the fellow eye remains constantly deviated. In such cases, the deviated eye will lose vision due to the development of amblyopia. These children require a detailed eye examintion by an ophthalmologist. Treatment involves patching of the non-deviated eye to treat amblyopia, and eye muscle surgery is typically required.

Accommodative Esotropia

Another common cause of esotropia in children is accommodative esotropia. Children with this entity can present between 6 months and 7 years, averaging 2 1/2 years of age. The esotropia is usually intermittent at onset and slowly becomes constant. Occasionally children may complain of diplopia. On eye examination, these children have a hyperopic refractive error. Accommodative esotropia occurs when accommodation compensates for hyperopia. Because convergence accompanies accommodation, one eye turns inward. Accommodative esotropia is treated with appropriate hyperopic refractive correction with glasses or contact lenses, although surgical correction is required in approximately 30% of the cases [3].

Acquired Nonaccommodative Esotropia

This is a late-onset esotropia not associated with hyperopic refractive error. It may be acute in onset, and children may present with diplopia. A careful motility evaluation is essential to rule out a lateral rectus paretic component. The angle of

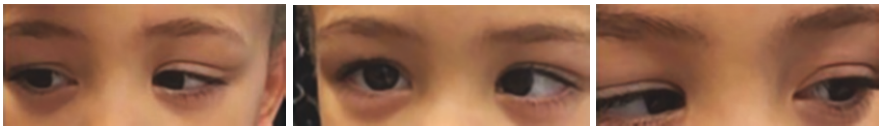

Fig. 1 Infantile esotropia: 1-year-old male with large angle constant inward deviation of the left eye first noted at age 6 months, with normal horizontal ocular motility

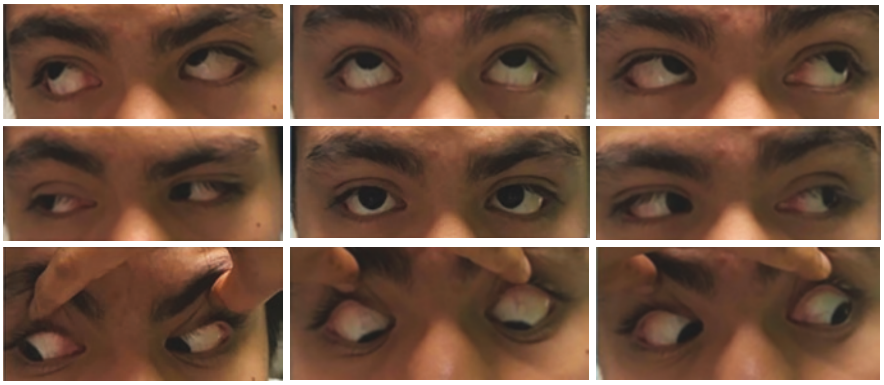

Fig. 2 Acute non accommodative esotropia: Nine gaze picture of a 15-year-old male with acute onset of diplopia and inward deviation of the left eye. Extraocular movements were normal with normal abduction. No refractive error, neuroimaging was normal

deviation is the same in all gazes (Fig. 2). Because the onset of nonaccommodative acute onset esotropia could be a sign of underlying neurological disorder, neurologic evaluation and neuroimaging are indicated if there are associated signs and symptoms of neurologic abnormality such as abduction deficit, incomitant strabismus, distance deviation greater than near deviation, associated headaches, abnormal head position, diplopia, or diurnal variations in case of myasthenia gravis. If neurological causes have been ruled out, the acquired nonaccommodative esotropia is usually treated with eye muscle surgery after appropriate prism adaptation.

Exotropia

Exotropia is an outward deviation of the eyes. It may be latent (exophoria) or manifest (exotropia). Manifest deviation could be intermittent; that is, the deviation manifests only sometimes of the day, especially when the child is tired or daydreaming, and constant deviation is present all the time.

Exophoria

Exophoria is an outward deviation that is controlled by fusion of images under normal viewing conditions. An exophoria is detected when binocular vision is interrupted during an alternate cover test. It is a common condition, and most of the time, children are asymptomatic. At times decompensation of this exophoria to transient exotropia may occur due to weakness, illness, or influence of sedatives and can cause transient diplopia. Treatment is not indicated unless it progresses to intermittent exotropia or causes asthenopia, eyes strain/ocular weakness.

Intermittent Exotropia

Usually presents before 5 years of age. Parents notice exodeviations, usually during periods of inattention, daydreaming, drowsiness, or first thing after waking up. The deviation is more noticed when the children are viewing a distant target. The extraocular movements are full. Untreated intermittent exodeviation may get worse and become constant over time. If the deviation is constant and more in one eye, the child may develop amblyopia in the deviated eye. A complete eye exam by an ophthalmologist and treatment with patching and possibly eye muscle surgery is needed.

The human eye is supported by seven extraocular muscles (EOMs). The extraocular muscles, their nerve supply, and their primary, secondary, and tertiary functions are shown in Table 1.

1.3.2 Paralytic Horizontal Deviations

Abducens (Cranial Nerve 6) Palsy

The sixth nerve innervates only the lateral rectus muscle, and the only action of the lateral rectus muscle is abduction. The clinical feature of an isolated sixth nerve palsy is limitation of abduction in the paretic eye. Children with an acute sixth nerve palsy present either with acute onset diplopia with complaints of seeing two images that are side by side, inability to move the paretic eye outwards, or an inward turning of the paretic eye (esotropia). Esotropia increases in the gaze toward the affected eye and decreases in the gaze away from the affected eye. Some children may present with a head turn towards the side of the lesion, which helps to minimize the diplopia. The exodeviation is usually greater in magnitude at distance fixation as compared to near fixation.

Table 1 Extraocular muscles actions and nerve supply

Muscle	Primary action	Secondary action	Tertiary action	Nerve supply
Medial rectus	Adduction			Lower division of the oculomotor nerve
Lateral rectus	Abduction			Abducens nerve
Inferior rectus	Depression	Extorsion	Adduction	Lower division of the oculomotor nerve
Superior rectus	Elevation	Intorsion	Adduction	Upper division of the oculomotor nerve
Inferior oblique	Extorsion	Elevation	Abduction	Lower division of the oculomotor nerve
Superior oblique	Intorsion	Depression	Abduction	Trochlear nerve
Levator palpebrae superioris	Elevation of the upper eyelid			Upper division of the oculomotor nerve

Congenital CN6 Palsy

Congenital CN6 palsy may be associated with conditions such as Moebius and Duane's retraction syndrome. These syndromes are associated with failure of development of cranial nerve nuclei or nerves during embryogenesis. Moebius syndrome features both abduction and adduction deficits with facial weakness, skeletal abnormalities, and developmental delay. Duane's retraction syndrome is a sporadic syndrome which is associated with varying degrees of hypoplasia or absence of the sixth cranial nerve and nucleus, with abnormal innervation of the lateral rectus muscle by cranial nerve 3 (CN3). This neural misdirection leads to co-contraction of the lateral rectus and the medial rectus muscle and a characteristic retraction of the globe on attempted adduction (Fig. 3). Large vertical deviations on adduction ("upshoots and down shoots") can be seen owing to slippage of the horizontal rectus muscles around the globe.

Isolated congenital CN6 palsies are rare. Most nonsyndromic congenital sixth nerve palsies are transient, probably arising as sequelae to perinatal cranial trauma. In some cases of congenital CN6 palsy, the abducens nerve is absent, and its nucleus is hypoplastic.

Acquired CN6 Palsy

The most common etiology of acquired CN6 palsy in children is neoplasm [4]. Other common causes of acquired sixth nerve palsy are trauma, demyelinating lesions, vascular malformations, infections, inflammation, elevated intracranial pressure, and stroke [4, 5]. Compared to adults, posterior fossa neoplasms are far more common in children, particularly those involving the pontocerebellar angle (acoustic neuroma or meningioma).

The intracranial portion of CN6 is especially vulnerable to elevated intracranial pressure (ICP). In children, causes of acquired CN6 palsy secondary to increased

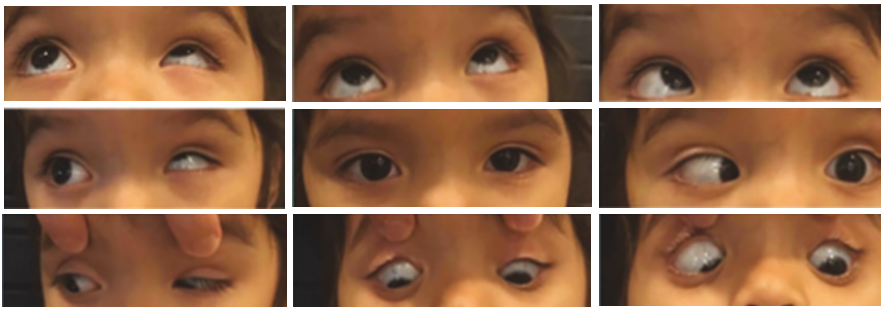

Fig. 3 Duane's retraction syndrome left eye: 3-year-old female with limited abduction in left eye seen on central panel left gaze picture. Retraction of left globe and upshoot of left eye seen on the central panel right gaze picture

ICP include hydrocephalus, meningitis, intracranial hemorrhage, craniosynostosis, idiopathic intracranial hypertension (IIH), space-occupying mass lesions, and infiltration [4–6]. The mechanism is thought to be downward traction on the nerve while tethered between the brainstem exit and Dorello's canal [6]. CN6 palsy due to elevated ICP is often bilateral. On examination, swelling of the optic nerve head (papilledema) may be seen due to raised ICP.

The "free-floating" cavernous portion of the CN6 lacks the mechanical support of the other cranial nerves that run along the lateral wall of the cavernous sinus and is, therefore, more susceptible to disruption by trauma or lesions of the cavernous sinus. Additionally, postganglionic sympathetic fibers briefly travel along with CN6 anteriorly within the cavernous sinus before entering the orbit. Thus, an ipsilateral Horner syndrome may also be seen along with sixth nerve palsy in lesions of the cavernous sinus. In children, an often isolated, self-limited CN6 palsy may be seen, typically lasting weeks to months. This may follow a febrile illness or vaccination, of which the underlying pathophysiology is poorly understood [7]. Benign CN6 palsy of childhood is a diagnosis of exclusion only after appropriate neuroimaging and lumbar puncture (LP) have been performed.

Differential Diagnosis

Differential diagnosis of CN6 palsy includes myasthenia gravis, spasm of near reflex—a condition characterized by transient spells of accommodation and convergence, medial orbital wall fracture with entrapment of the medial rectus muscle, acute onset comitant nonaccommodative esotropia.

Diagnostic Approach

A detailed ophthalmologic examination is warranted in patients with suspected cranial nerve six palsy to detect other causes of esotropia and diplopia. A detailed neurologic examination and neuroimaging should be performed with careful attention to the posterior fossa. If imaging is inconclusive, lumbar puncture should be performed to measure the opening pressure and cerebrospinal fluid analysis.

Treatment

Prevention of amblyopia is critical in children younger than 7–9 years of age. Patching the contralateral dominant eye for a few hours of the day prevents vision loss due to amblyopia. Botulinum toxin injection into the antagonist medial rectus muscle to prevent tightening of the unopposed medial rectus and allow binocular vision in the primary position is occasionally performed. The effect of botulinum toxin is transient and may ultimately need surgery for persistent esotropia. Children with stable deviations of 6–12 months duration may be candidates for strabismus surgery.

Oculomotor (Cranial Nerve 3) Palsy

The cranial nerve 3 (CN3) nucleus lies in the rostral midbrain just anterior to the cerebral aqueduct. The CN3 nucleus is actually a complex of subnuclei, with each individual muscle innervated by a specific subnucleus. The Edinger–Westphal subnucleus supplies preganglionic parasympathetic innervation to both pupil sphincters.

Classically, the diplopia caused by a CN3 palsy is horizontal, although a vertical or torsional component may also be present. Patients with severe ptosis may not complain of diplopia due to occlusion of one or both eyes. The examination will show varying degrees of ptosis, anisocoria, and limitations in upgaze, downgaze, adduction, and excyclotorsion (outward torsional rotation of the eye, or the 12 o'clock position rotated laterally) (Fig. 4).

A complete CN3 palsy involves the levator, superior rectus, medial rectus, inferior rectus, and inferior oblique. A partial or incomplete CN3 palsy only involves some of these structures. The classic complete CN3 palsy with pupil involvement is an exotropic and hypotropic ("down and out") eye with ptosis and mydriasis. The down and out position of the eye is due to the unopposed action of the lateral rectus and superior oblique muscle.

Congenital CN3 Palsy

Congenital CN3 palsies feature paresis of various combinations of muscles innervated by CN3. Pupillary involvement is common, as is aberrant regeneration and amblyopia [8]. Patients may not complain of diplopia due to ptosis, amblyopia, or

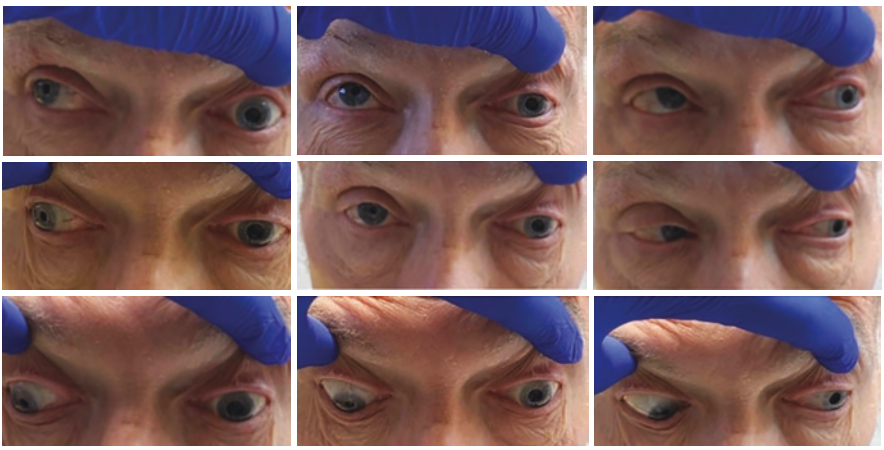

Fig. 4 Left third nerve palsy: 65-year-old male with left complete third nerve palsy due to CNS lymphoma showing left eye ptosis (the left eyelid is elevated by examiner to show the eye), 9 gaze picture showing limitation of left eye adduction, upgaze and down gaze. There is anisocoria with dilation of left pupil

suppression (ability of the brain to ignore the diplopic image), but may develop diplopia if the strabismus becomes acutely decompensated from infections or other stressors.

Patients with congenital CN3 palsies may also present with cyclic oculomotor spasms, characterized by intervals of paresis alternating with spasms of the extraocular and intraocular muscles innervated by CN3 [9, 10]. This condition is usually noticed during the first year of life and consists of partial or complete CN3 palsy. Every 1½ to 2 min, the paretic upper lid elevates, the pupil constricts, the eye adducts, and a myopic shift may occur in the refraction. The spastic phase may last for less than a minute.

Congenital palsies are thought to arise from developmental abnormalities or other insults in-utero or during the perinatal period, such as birth trauma [11, 12]. Combinations of cranial nerve palsies are common, as is developmental delay and other neurological symptoms and signs. Neuroimaging and careful neurologic examination are recommended for all children with congenital CN3 palsies to assess structural abnormality.

Acquired CN3 Palsy

Trauma is the most common cause of acquired CN3 palsy in children [13], typically following large blows to the head. Damage may be caused by coup-countercoup, shearing forces, acceleration, or traction at the skull base. Penetrating trauma may damage the nerve anywhere along its course. It is essential to assess for an orbital fracture to differentiate between paresis and extraocular muscle entrapment. An acquired palsy occurring after only light trauma should raise suspicion for an underlying intracranial lesion.

Differential diagnosis of acquired CN3 palsy in the pediatric population includes tumors, vascular malformations, stroke, infections, inflammations, trauma, and demyelinating lesions [13, 14].

Within the subarachnoid space, CN3 is especially vulnerable to compression. Classically, an expanding posterior communicating aneurysm causes a pupil-involving palsy owing to the unique location of pupillary fibers in the intracranial portion of the nerve. Although aneurysms are rare in the pediatric population than adults [8], noninvasive angiography must be obtained to rule out aneurysms, especially if “red flag” signs such as headache or altered consciousness are present. A CN3 palsy in the setting of altered mental status should raise suspicion for uncal herniation. The palsy may be caused by compression of the intracranial portion of the nerve, kinking of the nerve over the clivus, or direct compression of the nuclear complex.

Tumors may cause CN3 palsy anywhere along its course. A child with a brainstem glioma, cyst, or vascular malformation, for example, may present with other brainstem signs. A child presenting with proptosis should raise suspicion for rhabdomyosarcoma or other tumors of the orbit. A patient with neurofibromatosis should

raise suspicion for a schwannoma or meningioma. Ophthalmoplegic migraine discussed later can also lead to CN3 palsy and is a diagnosis of exclusion.

Differential Diagnosis

Differential diagnosis of CN3 palsy includes myasthenia gravis, which is a great mimicker, orbital blow out fracture, congenital fibrosis of extraocular muscles, Duane's syndrome type 2, and internuclear ophthalmoplegia (discussed below).

Diagnostic Approach

The general diagnostic approach for a child with acquired CN3 palsy should begin with a careful history to assess for underlying congenital palsy, recent illness or vaccinations, and trauma. Detailed neurology examination to assess for other associated neurological signs and symptoms is recommended. Neuroimaging of the brain and orbit with noninvasive angiography should be obtained. If imaging is unrevealing, LP should be considered to assess meningitis or other inflammatory conditions such as Guillain–Barré syndrome (Miller Fischer variant). In older children with unrevealing imaging and LP and high clinical suspicion for aneurysm, conventional angiography should be considered.

Treatment

Treatment is directed at the underlying cause. From an ocular standpoint, acutely, prisms may be used to alleviate diplopia. Botulinum toxin can be occasionally used to chemically denervate the unopposed lateral rectus muscle. In younger children, patching of the fellow eye is aimed at treating amblyopia. Children with ptosis are also at high risk of deprivation amblyopia on top of strabismic amblyopia. Persistent deviations after 6–12 months need strabismus surgery and ptosis correction. Among the three cranial nerve palsies involving the extraocular muscles, the CN 3 palsy is the most difficult to treat to achieve ocular alignment because of the multiple muscles involved. The aim is to achieve ocular alignment, at least in primary gaze and reading gaze. Eyelid ptosis surgery may be considered after strabismus surgery.

Internuclear Ophthalmoplegia (INO)

Internuclear ophthalmoplegia is an ocular movement disorder caused by a lesion of the medial longitudinal fasciculus. An "internuclear" lesion is one that disrupts the medial longitudinal fasciculus (MLF), a bundle of fibers that connects the CN VI nucleus on one side of the pons to the medial rectus subnucleus (of CN III) on the contralateral side of the midbrain. It is characterized by adduction deficiency in the ipsilateral eye and abducting nystagmus in the fellow eye. The adduction deficit may range from mild to total.

INO is rare in the pediatric population. Causes include arteriovenous malformations, tumors, Arnold–Chiari malformation, demyelinating disease, and trauma [15, 16].

1.4 Vertical Deviations

1.4.1 Paralytic Vertical Deviations

Trochlear (Cranial Nerve 4) Nerve Palsy

The cranial nerve 4 (CN4) nucleus lies caudal and inferior to the CN3 nucleus. CN4 has the longest intracranial course. Like the other cranial nerves, CN4 palsies can be congenital or acquired.

Congenital CN4 Palsy

In congenital cases, abnormal development in-utero may cause hypoplasia or aplasia of the CN4 nucleus [17]. The nerve may be injured during birth. Besides, the patient may have developmental abnormalities or fibrosis of the superior oblique muscle, tendon, or the trochlea [18, 19]. The palsy may be bilateral. Patients may have a longstanding head tilt, seen on review of old photos, or facial asymmetry on the external examination with upward slanting and posterior displacement of the mouth ipsilateral to the head tilt. The head is typically tilted towards the contralateral shoulder (Fig. 5a, b). Patients with congenital CN4 palsy may not complain of diplopia as they usually develop the ability to fuse larger angles of deviation unless they become decompensated.

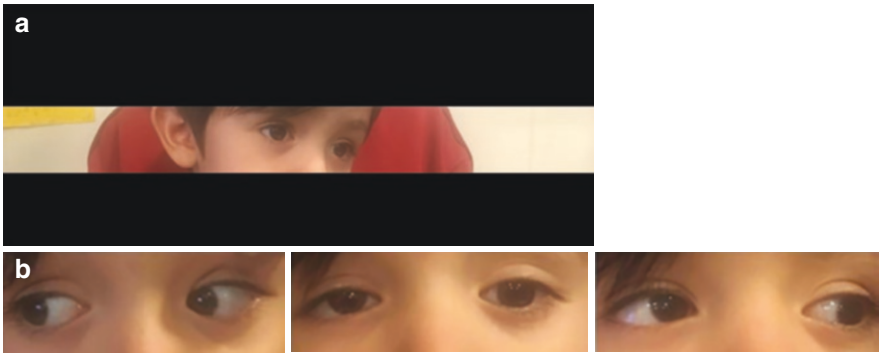

Fig. 5 (**a**) Right cranial nerve four palsy: 3-year-old male with left head tilt toward the left shoulder in patient with congenital right superior oblique palsy. (**b**) Right cranial nerve four palsy: Primary, right and left gaze picture of patient with right congenital superior oblique palsy which shows right hypertropia (upward deviation) in forced primary position

Acquired CN4 Palsy

Trauma is the most common cause of acquired CN4 palsy, likely owing to its long intracranial course. Other causes include neoplasms, infections, inflammation, and demyelinating lesions [20]. Patients complain of vertical diplopia, which may have an oblique or torsional component. They may have a compensatory head tilt toward the opposite shoulder. On examination, the affected eye is hypertropic. The hyperdeviation, and hence the diplopia, worsens with horizontal gaze to the contralateral side and with head tilt to the ipsilateral shoulder. Traumatic palsies may also be bilateral. Other causes of acquired CN4 palsy include synostosis, hydrocephalus, compressive lesions such as schwannoma, posterior fossa, and orbital tumors.

Differential Diagnosis

The differential diagnosis of CN4 palsy includes dissociated vertical divergence (DVD), synostotic plagiocephaly, double elevator palsy, and skew deviation.

Diagnostic Approach

History should be taken with attention to trauma and other neurological deficits. If the history is not suggestive of trauma or decompensated congenital CN4 palsy, imaging of the brain and orbits should be obtained. If the child exhibits signs and symptoms of meningitis, an LP should be obtained.

Treatment

Treatment is aimed at preserving single, binocular vision in primary gaze. Prisms can be used to alleviate vertical diplopia, although torsional diplopia may persist if present to a significant degree. Amblyopia should be treated accordingly. Traumatic cases typically resolve within 3 months. Persistent deviation beyond 3 months may need strabismus surgery.

1.4.2 Nonparalytic Vertical Deviations

Brown Syndrome

Brown syndrome is characterized by abnormalities of the superior oblique muscle, tendon, or trochlear pulley that results in restricted movement, hence also called superior oblique tendon sheath syndrome. Clinically, Browns syndrome presents with the inability to elevate the eye in adduction. Most of the Brown cases are congenital or traumatic, although the syndrome can also be seen from orbital tumors [21], adjacent sinusitis, inflammatory conditions [22], or postsurgically. Acquired

cases, in the absence of trauma, should therefore undergo orbit and sinus imaging. Brown syndrome may resolve with treatment of the underlying condition. Some cases of congenital Brown syndrome spontaneously resolve over many years [23].

Skew Deviation

Skew deviation is an acquired vertical misalignment of the eyes resulting from disruption of input from the otolithic organs (the utricle and saccule of the inner ear). It is typically a comitant hypertropia but can be incomitant. Patients present with vertical diplopia, binocular torsion, and perceived tilting of the visual field. Patients that develop skew deviation usually have damage to the brainstem, cerebellum, or vestibular structures [24, 25]. Skew deviation in children may be associated with various conditions such as tumors, Arnold–Chiari malformation [26], paroxysmal hemiparesis of childhood [27], and increased intracranial pressure [28]. The diagnosis of skew deviation is usually a diagnosis of exclusion. It is generally considered when ocular findings do not fit a cranial nerve insult (such as CN4 palsy) or when a brainstem or cerebellar injury is expected. If a skew deviation is suspected, evaluation to look for other neurological signs of the brainstem and cerebellar disease and MRI of brain with contrast should be obtained. Treatment depends on the etiology. Most skew deviation cases that are demyelinating or ischemic are transient and spontaneous recovery is common. Fresnel prisms to help with diplopia can be used. Persistent cases may need strabismus surgery.

1.5 Other Causes of Horizontal or Vertical Diplopia

1.5.1 Thyroid Eye Disease

Thyroid eye disease (TED) occurs in up to one-half of patients with pediatric Grave's disease or hyperthyroidism [29]. Antibodies binding to thyroid-stimulating hormone (TSH) receptor sites stimulate fibroblast proliferation and glycosaminoglycan (GAG) production within orbital fat and extraocular muscles, leading to swelling and inflammation. This leads to the constellation of signs, including axial proptosis, lid retraction ("scleral show," in which the lid margin rests outside of the corneal limbus), and varied gaze limitation. The most severe complication of TED is compressive optic neuropathy at the orbital apex. Patients may complain of diplopia and ocular surface irritation. Orbital pain is uncommon, and its presence should alert the examiner to other differential diagnoses, including orbital inflammation and orbital cellulitis. Localized injection of the conjunctiva over the muscle insertions may be seen. If optic neuropathy is present, the patient may exhibit decreased visual acuity, color vision, and/or a relative afferent pupillary defect.

Imaging classically shows enlargement of the extraocular muscle bellies while sparing the muscle tendons. The most involved extraocular muscle in TED is the inferior rectus, followed by the medial rectus and the superior and lateral rectus

muscles. Motility restriction, exposure of the sclera, and compressive optic neuropathy are uncommon in children with TED compared to adults [30]. If proptosis is severe, orbital fat decompression may help. The diplopia caused by the extraocular muscles' involvement can be treated with prisms, and longstanding stable deviations may need strabismus surgery.

1.5.2 Ophthalmoplegic Migraine

Ophthalmoplegic migraine, recently reclassified as recurrent painful oculomotor neuropathy, is a rare disorder affecting young children [31]. Patients typically exhibit classic migraine symptoms, including unilateral headache, nausea, vomiting, photophobia, and phonophobia. The ophthalmoplegia occurs days later and has features of CN3, CN4, or CN6 palsy. Enhancement of CN3 is typically seen on neuroimaging [32], leading some to believe that the disorder is one of recurrent inflammation [32, 33]. The enhancement and ophthalmoplegia will typically resolve over weeks [32]. Children may experience recurrent bouts separated by months or years, occasionally resulting in permanent strabismus.

Abortive therapies including steroids, beta-blockers, and ergotamines have been tried, but none have proven beneficial, as most cases resolve spontaneously. Ophthalmoplegic migraine is a diagnosis of exclusion once neuroimaging and LP have ruled out other etiologies.

1.6 History

Patients with acquired ocular misalignment or disorders of ocular motility will complain of diplopia (double vision). The amount of diplopia constitutes a continuous spectrum correlating with the amount of deviation between the visual axes. Patients with only a small degree of misalignment, for instance, may only report "blurry vision," while patients with higher degrees of misalignment will perceive two discrete images. Depending on the patient's motility deficit, they may be asymptomatic in primary gaze and only experience diplopia on attempted gaze in the direction of the paretic muscle.

The examiner should inquire about monocular vs. binocular diplopia. Binocular diplopia occurs only when both eyes are open and resolves with either eye is covered and suggests ocular misalignment. Monocular diplopia persists when the unaffected eye is covered and suggests an ocular etiology. Common causes for monocular diplopia in children are refractive error (i.e., astigmatism), lens disorders, opacity in the ocular media, or retinal disorders. It is crucial to check if diplopia is monocular or binocular as monocular diplopia is unlikely to be caused by neurological, ocular misalignment and can save a patient from unnecessary neurological investigations.

Patients should be asked about the relative positions of the two images. Horizontal diplopia—two images side by side—indicates the limitation of one or more

Table 2 History for evaluation of diplopia

Does the diplopia resolve when either eye is covered?
Is the diplopia horizontal, vertical, oblique, or torsional?
Is the diplopia the same in all directions of gaze or different?
When was the onset of diplopia?
Does the child have a history of eye misalignment, eye patching, or spectacle correction?
Is the diplopia constant, intermittent, or variable or history of variability throughout the day?
Is the diplopia worse when the child is fatigued or distressed?
Is there history of orbital trauma?
Is there history of eye surgery?
Does the child have any pain with eye movement?
Does the child have any fever?
Does the child have any weakness or numbness?
Does the child complain of headaches?
Has the child had any recent viral illness or vaccinations?

horizontal rectus muscles. Vertical diplopia—two images above or below one another—indicates the limitation of one or more vertical rectus muscles or oblique muscles.

Patients should also be asked about the directionality of their diplopia. Comitant diplopia, as noted above, refers to diplopia of similar magnitude in all directions of gaze. Incomitant diplopia varies in magnitude depending on the direction of gaze. In the case of incomitant deviations, diplopia generally worsens with gaze in the direction of the paretic muscle. In younger children, it will manifest as a face turn.

Additional questions can guide the examiner in determining the etiology of the motility dysfunction and aid in lesion localization. History of a closed head injury may suggest damage to the intracranial portion of an extraocular nerve. Blunt facial trauma should raise suspicion for an orbital fracture. A bulging red eye suggests an orbital infection or mass. Headaches or focal neurological symptoms should prompt a further evaluation for intracranial etiologies. Relevant questions are listed in Table 2.

1.7 Examination

The evaluation of the diplopic patient should begin with obtaining visual acuity. The patient is asked to cover one eye with either the palm of their hand or an occluder. Care should be taken to ensure no peeking, as children are often tempted to "cheat" to please the examiner. Various distance and near vision charts are available. Testing distance is guided by the chart manufacturer. Visual acuity should be tested with their refractive correction, if available.

Next, a careful examination of the pupils should be undertaken. A bright light should be directed at each pupil individually, noting the shape, diameter, and rate of contraction. Then the light should be "swung" from eye to eye, watching for dilation

signaling a relative afferent pupillary defect (RAPD). See Chap. 14 for more details regarding how to test for RAPD. An RAPD suggests a compromise of the optic nerve and the anterior visual pathway. The size of both the pupils in light and dark should be noted. The presence of anisocoria (asymmetry in the size of both pupils) should be noted. Care should be taken not to place the light directly in front of the pupil, which may trigger the accommodation reflex.

An external examination may reveal important clues to the nature of the diplopia. The examiner should note any craniofacial dysmorphism, exophthalmos (eye protruding out), or enophthalmos (eye sunken in). Any abnormal head posture such as a head tilt, head turn, or chin-up/chin-down position as occasionally children, may adopt such a posture to relieve the diplopia. In cases of paralytic strabismus, the head turn is most often in the direction of the paretic muscle. Eyelid swelling, conjunctival chemosis, or injection may accompany proptosis and strongly suggest orbital pathology.

Eye movements should be assessed in each eye individually (ductions) and with both eyes together (versions). The degree of misalignment should be measured in all directions of gaze. The deviation will worsen when looking in the direction of the paretic muscle.

If the ocular misalignment occurs at an early age, is constant, and of longer duration, then the child may not experience double vision. This is due to the suppression of one image to avoid diplopia.

1.8 Prognosis and Outcomes

Prognosis and outcomes depend on the etiology. Nonparalytic strabismus is easier to treat owing to full extraocular movement. Generally, strabismus surgery performed at a younger age is associated with better binocularity, improved treatment outcomes for amblyopia, improved eye contact, subjective appearance, interactions with others, and self-esteem, as compared to older children. Amblyopia is ideally treated before age 6, although modest gains can be made in children up to age 10. The outcomes of paralytic strabismus depend on the etiology. Complete or partial recovery of cranial nerve palsy is more likely in cases of traumatic, infectious, postviral, and inflammatory causes of cranial nerve palsies than those with intracranial space-occupying lesions. Persistent ocular misalignment after 6 months of onset will require definitive treatment with prisms, surgery, or botulinum toxin injections.

1.9 When to Refer/Admit

Referral to a pediatric ophthalmologist is indicated for all patients presenting with a new-onset ocular misalignment. Referral should also be made in children with known strabismus who experience new or worsening symptoms or a new deviation.

Immediate workup and urgent referral are recommended for all patients with acute onset of acquired strabismus and diplopia.

1.10 Prevention

Prevention is not relevant in nontraumatic childhood strabismus. Safety measures should be taken to avoid unnecessary head or facial trauma.

2 My Child's Eyes Are "Wiggling or Bouncing"

2.1 Introduction

Nystagmus describes rhythmic, often back-and-forth movement of the eyes. Jerk nystagmus is characterized by a slow drift followed by a fast corrective saccade. By convention, the nystagmus is described by the direction of the fast component. Pendular nystagmus exhibits equal velocity in both directions of the oscillation. Nystagmus with similar direction, equal amplitude, and equal frequency in both eyes is described as conjugate. Nystagmus, in which the amplitude is different between the two eyes, is described as dissociated. Nystagmus may be horizontal, vertical, or rotatory (torsional).

2.2 Epidemiology

The overall prevalence of nystagmus in children under 18 years of age is estimated to be 16.6 per 10,000 but varies greatly depending on subtype, as discussed in the subsequent sections.

2.3 Types of Nystagmus

2.3.1 Congenital Nystagmus

Congenital nystagmus can be divided into congenital motor nystagmus (CMN) and congenital sensory nystagmus (CSN) based on the degree of visual function [34]. Patients with CMN commonly have normal vision, while children with CSN typically have binocular abnormalities of the anterior visual system (typically worse than 20/200). Clinically, their waveforms are indistinguishable.

Congenital nystagmus is classically conjugate, binocular nystagmus that is most often horizontal. The waveform may be jerk, pendular, or a combination of both.

The intensity of nystagmus typically worsens on fixation and improves with convergence; thus, patients may develop an accompanying esotropia (nystagmus blockage syndrome). Patients typically have a null point, a position of gaze at which the intensity of nystagmus is minimal and foveation is greatest. This may lead the patient to develop a head turn. Patients with congenital nystagmus rarely complain of oscillopsia (visual disturbance in which objects in the visual field appear to oscillate). Patients with CMN may demonstrate a reversal of the optokinetic response [35]. For example, an optokinetic drum spinning to the patient's right will elicit a slow rightward drift followed by a rapid leftward saccade. In a patient with reversal of the optokinetic response, a drum spinning to the patient's right will elicit a leftward drift followed by a rightward saccade.

Careful evaluation of visual function can aid in differentiation between CMN and CSN. If the child is developmentally normal and has a normal ocular and neurological exam, no further evaluation is necessary. Decreased vision, paradoxical pupils (constriction in the dark rather than dilation), oculodigital reflex (excessive pressing on the eyes to stimulate light perception), abnormal red reflex, or photophobia may suggest a retinal disorder. Referral to a vision specialist for electroretinography (ERG) is beneficial for identifying retinal or optic nerve abnormalities, especially in preverbal children. If the nystagmus cannot be explained by the ocular exam, neuroimaging is warranted [36].

2.3.2 Latent Nystagmus

Latent nystagmus arises from disruption of normal binocular fusion. This may be secondary to strabismus, vision loss in one or both afferent pathways, hence the alternative name fusion maldevelopment nystagmus syndrome (FMN). Latent nystagmus is binocular jerk nystagmus that is manifested by occluding one eye. The uncovered eye will characteristically display a horizontal jerk nystagmus with the fast phase away from the covered eye. Thus, latent nystagmus can reverse direction depending on which eye is occluded. The intensity of nystagmus can vary depending on which eye is occluded. Therefore, when a standard occluder is used to measure visual acuity in patients with FMN, acuity is often degraded by the induced nystagmus. Partial optical blurring of one eye (with a high-plus lens or filter) may not induce FMN and, therefore, may permit better visual acuity measurement in the fellow eye. FMN occurs with any condition that disrupts binocular development in the initial 6 months of life, such as infantile esotropia, severe anisometropia, constant infantile exotropia, monocular cataract, corneal opacities, or retinal disorders.

2.3.3 Opsoclonus

Opsoclonus is a nystagmoid disorder characterized by rapid, multidirectional saccades (saccadomania). Children with acquired opsoclonus should be investigated for neuroblastoma, which is present in up to two thirds of cases of acquired

opsoclonus [37, 38]. A para- and postinfectious form can also be seen in children and is associated with presumed viral or other encephalitides [38, 39].

Evaluation for neuroblastoma should include pan-MRI, metaiodobenzylguanidine (MIBG) scan, urine vanillylmandelic acid (VMA), and homovanillic acid (HVA) levels, as well as CSF analysis.

2.3.4 Spasmus Nutans

Spasmus nutans is defined by the triad of nystagmus, head bobbing, and torticollis. The nystagmus exhibits a high frequency, low amplitude ("shimmering") waveform and is usually asymmetric or monocular. Spasmus nutans is typically benign but may be due to a sellar or hypothalamic tumor, the most common of which is a glioma [40, 41]. In the benign form, the onset is typically between 1 and 4 years old (therefore, it is an acquired condition) with a resolution at 5 years. Less frequently, spasmus nutans is associated with congenital retinal dystrophies [42]. Neuroimaging is recommended in all children with spasmus nutans to rule out a mass lesion. If neuroimaging is unrevealing, ERG may be obtained to assess for retinal disease. Refractive error, strabismus, and amblyopia are common and should be treated accordingly.

2.4 Differential Diagnosis

The differential diagnosis of nystagmus and nystagmoid movements include congenital or acquired motor nystagmus, nystagmus secondary to decreased vision, intracranial lesion, or paraneoplastic effect.

2.5 History

Evaluation of nystagmus should begin with a full ocular and medical history, including prenatal history. The examiner should inquire about intrauterine toxic exposures, infections, and prematurity. A developmental history is also useful in identifying events that may lead to maldevelopment of the visual system. Congenital or acquired ocular conditions, particularly those that reduce vision or normal binocular vision, of which many are familial, can lead to the development of nystagmus. Congenital motor nystagmus (CMN) is often sporadic, although familial inheritance can be seen.

The onset of CMN is typically within the first few months of life but need not be present at birth. The presence of oscillopsia (the sensation that the environment is spinning, like vertigo) can often help differentiate between congenital and acquired

nystagmus in children old enough to give subjective complaints. CMN rarely causes oscillopsia, while acquired nystagmus often causes oscillopsia.

For children 3 months or older who can support their head against gravity, one should inquire about head turns, head thrusts, and gaze preference. Those with CMN may preferentially hold their gaze at the null point, or the point at which the nystagmus exhibits the smallest amplitude, to increase foveation time and better vision.

2.6 Examination

As with any child with ocular complaints, visual acuity, intraocular pressure, pupils, and extraocular movements should be assessed. Significantly decreased visual acuity or asymmetry should be noted. A relative afferent pupillary defect or anisocoria suggests dysfunction of maldevelopment of the afferent or efferent visual systems. The external examination may reveal head turn, head bobbing, or head thrusting. Obvious ocular characteristics like albinism may be identified. The waveform, frequency, amplitude, and direction of nystagmus should be noted in all gaze positions.

Congenital motor nystagmus often worsens with fixation and improves when the gaze is shifted to the null point or with convergence. Monocular occlusion may reveal latent nystagmus. Dissociated nystagmus may occur with internuclear ophthalmoplegia. A slow vertical oscillation in one eye suggests severe vision loss in that eye (Heimann–Bielschowsky phenomenon).

Physiologic nystagmus may be seen with optokinetic nystagmus (OKN) or with the vestibulo-ocular reflex (VOR). OKN may be elicited by spinning an optokinetic drum in front of the patient's full field of vision. The eyes will demonstrate a slow pursuit, followed by a rapid refixating saccade. The VOR is characterized by a slow phase opposite the direction of a head turn followed by a refixating saccade in the same direction of the head turn.

The head impulse test is useful if a peripheral vestibular lesion is suspected. The patient is asked to fix on the examiner's nose while the examiner grips the patient's head and quickly turns it to one side. A normal response is one of smooth pursuit. An abnormal response is characterized by drifting of the eyes in the same direction as the head turn, followed by a refixating saccade.

2.7 When to Refer

Referral to a pediatric ophthalmologist for a complete eye examination is indicated for all children who present with new-onset nystagmus, or nystagmoid movements.

2.8 Treatment

If vision loss is present, the appropriate treatment should be initiated. Refractive errors, amblyopia, and strabismus should be treated. In CMN, treatment is aimed at reducing the intensity of nystagmus in primary gaze. Base out prism can be used to induce convergence. Alternatively, prisms can also be used to shift the null point to the primary gaze. Eye muscle surgery (Anderson–Kestenbaum procedure) can also be used to shift the null point to primary gaze and reduce head turn.

2.9 Prognosis/Outcomes

The prognosis for childhood nystagmus varies greatly depending on the underlying etiology and if ocular pathology is present. Spasmus nutans typically resolves spontaneously. Roughly 75% of patients undergoing the Anderson–Kestenbaum procedure experience a residual abnormal head turn less than 10°.

2.10 Prevention

Prevention is not relevant in childhood nystagmus.

3 My Child Has "Droopy Eyelids/Sleepy Eyes"

3.1 Ptosis

Blepharoptosis, commonly referred to as ptosis, can be congenital or acquired.

3.2 Etiology/Differential Diagnosis

It is essential to differentiate between congenital and acquired cases and, among acquired cases, into different etiological groups. Acquired ptosis in children may be neurogenic, myogenic, or mechanical, as shown in Table 3 due to their systemic implications. These are discussed in more detail in the following sections.

Table 3 Congenital and acquired causes of ptosis

Congenital	
Neurogenic	Congenital myasthenic syndromes
	Marcus–Gunn jaw wink
	Congenital third nerve palsy Blepharophimosis
Acquired	
Myogenic	Myasthenia gravis Chronic progressive external ophthalmoplegia
Neurogenic	Congenital Horner Third nerve palsy
Mechanical	Trauma Tumors

3.2.1 Congenital Ptosis

The most common form of congenital ptosis is myogenic secondary to dysgenesis of the levator muscle [43]. Two common syndromes associated with ptosis are discussed below.

Blepharophimosis-ptosis-epicanthus inversus syndrome (BPES), or simply blepharophimosis syndrome, is characterized by the tetrad of blepharophimosis (narrow horizontal and vertical palpebral fissure), ptosis, epicanthus inversus (lower eyelid fold overlying the medial canthus), and telecanthus (abnormally wide intercanthal distance). The syndrome may occur sporadically or inherited in an autosomal dominant fashion [44]. Female children should be counseled about premature ovarian failure.

Congenital fibrosis of the extraocular muscles (CFEOM) features bilateral ptosis and ophthalmoplegia. CFEOM is primarily neurogenic with aplasia of the cranial nerve nuclei resulting in secondary fibrosis. The eyes are typically fixed in slight downgaze, and patients adopt a chin-up position. CFEOM is differentiated from chronic progressive external ophthalmoplegia (CPEO) by its nonprogressive natural history. A stepwise approach to treatment begins with strabismus surgery to align the eyes in primary position, followed by ptosis repair.

3.2.2 Acquired Ptosis

Various causes of acquired ptosis in children include myasthenia gravis, CPEO, trauma, eyelid tumors, and Horner syndrome.

Myasthenia gravis is rare in children. Myasthenia gravis is a neuromuscular disorder characterized by fatiguability and variable muscular weakness, with a predilection for the extraocular muscles. The congenital myasthenic syndromes are distinguishable from myasthenia gravis by pre- or postsynaptic defects at the neuromuscular junction, in contrast to antibodies against motor endplate acetylcholine receptors. These syndromes can be inherited in an autosomal dominant or recessive

fashion. Children with congenital myasthenic syndromes demonstrate varying amounts of fatigable ptosis, ophthalmoplegia, or extremity weakness. The ice pack test is performed by holding a piece of ice against the eyelid for 1 min. Improvement in ptosis indicates a positive test. Edrophonium testing can be done in children but has many false positives and false negatives. Electromyography can be done if the edrophonium or ice pack tests are unrevealing or cannot be performed.

Nearly 25–50% of children with ocular myasthenia develop generalized myasthenia [45, 46], and up to 50% are seropositive. A transient perinatal myasthenic syndrome may result from the transplacental crossing of maternal antiacetylcholine receptor antibodies. All children with myasthenia gravis should have imaging to look for thymoma.

Chronic progressive external ophthalmoplegia is a maternally inherited disorder of mitochondrial DNA. As the name suggests, the ptosis and ophthalmoplegia are progressive, eventually leading to a locked-in appearance. Because the ophthalmoplegia is slowly progressive and symmetric, diplopia is uncommon. Muscle biopsy shows characteristic of ragged red fibers.

The Kearns–Sayre variant features pigmentary retinopathy and cardiac conduction defects or cardiomyopathy, leading to sudden cardiac death [47]. The onset of Kearns–Sayre is before age of 20 years. Thus, all patients suspected of having CPEO should undergo careful cardiac evaluation.

Trauma can cause disinsertion of the upper lid retractors leading to ptosis. Orbital roof fractures may occur after severe blows to the forehead or brow and can uncommonly cause entrapment of the superior rectus levator complex.

Eyelid tumors of the upper eyelid and orbit can cause mechanical ptosis. These can include large capillary hemangiomas, epidermoid and dermoid cysts, squamous papillomas, and nevi. Plexiform neurofibromas can be seen in children with neurofibromatosis.

Horner syndrome is characterized by the classic triad of ptosis, miosis, and anhidrosis of the affected side (Fig. 6). Congenital cases also feature iris heterochromia, with the lighter pigmented iris on the side where the sympathetic pathways are affected. In infants, there may be a lack of skin flushing on the affected side when crying.

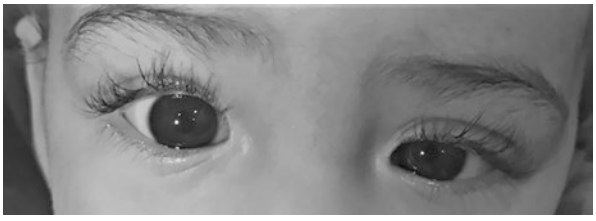

Fig. 6 Left Horner syndrome: 1-year-old female with mild left upper eyelid ptosis and anisocoria with left pupil smaller than right pupil. The anisocoria was more in the dark with inability of the left pupil to dilate completely. Neck imaging revealed a neuroblastoma at T1–T2 level

Most cases of congenital Horner syndrome are idiopathic, thought to be secondary to a congenital malformation, or other insults along the sympathetic pathway [48]. However, the most identifiable cause is neuroblastoma. Therefore, all children with congenital or acquired Horner syndrome should be carefully evaluated with urine VMA/HVA testing and MRI of the head, neck, and chest. Palpation of the neck and chest may suggest the presence of a mass.

In acquired Horner syndrome, a history of trauma, particularly if neck pain or cerebral signs are present, suggests a carotid artery dissection or an orbital fracture.

The ptosis associated with congenital Horner syndrome is unique in that the Mueller muscle, rather than the levator, is de-innervated. Hence, the ptosis in Horner syndrome is minimal up to 2 mm ptosis. Thus, surgical correction of ptosis in Horner syndrome typically involves Mueller muscle resection.

3.3 History

A thorough prenatal and maternal past medical history, including family history or ptosis, should be obtained. The examiner should inquire about intrauterine toxic exposures and birth trauma. Childhood photographs are often helpful when evaluating for ptosis.

3.4 Examination

On examination, the ptosis may be unilateral, bilateral, or asymmetric. Children with bilateral ptosis may adopt a chin-up head position. The examiner should assess the degree of ptosis by measuring the lid margin reflex distance (MRD1), the distance between the upper lid margin, and the corneal light reflex when the eye is in primary gaze. Levator function is assessed by asking the patient to look down, then up, and measuring the distance traveled by the eyelid margin. Gentle pressure is applied on the brow to prevent recruitment of the frontalis muscle. Any lagophthalmos (incomplete closure of the eyelids) should be noted, as well as the degree of Bell's reflex (upward rolling of the eyes with eyelid closure) should be noted. Ptosis that is covering the visual axis can cause vision deprivation amblyopia in young children.

3.5 When to Refer

All children with ptosis need a complete ophthalmic examination by an ophthalmologist. Ptosis that is covering the visual axis needs sooner referral and subsequent treatment to prevent vision deprivation amblyopia. If the ptosis is variable,

acquired, associated with ophthalmoplegia or pupil abnormalities, then these signs are red flags. These patients need urgent referral to ophthalmology, and a detailed neurology evaluation to rule out the possibility of myasthenia gravies, third nerve palsy, and Horner syndrome.

3.6 Treatment

Treatment is indicated if severe ptosis threatens deprivation amblyopia in infants or if cosmetically unacceptable in older children. Treatment is primarily surgical, and options include levator resection or frontalis sling.

3.7 Prognosis/Outcomes

Of children who undergo ptosis surgery, 30% require a second procedure. Postoperative lagophthalmos is not uncommon, but children rarely develop symptomatic dry eye.

3.8 Prevention

Common-sense safety measures should be taken to avoid unnecessary head or facial trauma.

4 Other Eye Movement Disorders of Childhood

The horizontal and vertical gaze palsies describe a heterogeneous group of eye movement disorders characterized by bilateral conjugate gaze deficits, typically involving supranuclear structures rather than a specific cranial nerve nucleus or extra-axial cranial nerve. Gaze palsy is a symmetric limitation of the movements of both eyes in the same direction.

4.1 Horizontal Gaze Palsy

Horizontal gaze palsy is a conjugate, bilateral, limitation of eye movements horizontally to the right and/or left. Damage to the frontal eye fields produces saccadic deficits, while damage to the occipito-temporal-parietal junction or supplemental eye fields produces smooth pursuit deficits. Pontine lesions involving the PPRF or

CN6 nucleus produce a horizontal gaze palsy to the affected side (see section One-and-a-half Syndrome). Midbrain lesions damaging descending fibers subserving the PPRF may also produce a horizontal gaze deficit [49]. Cerebellar and medullary lesions more often cause over- and undershoot rather than true gaze paresis. A rare familial syndrome of horizontal gaze palsy and progressive scoliosis has been described. Patients with this syndrome often have hypoplasia of the pons and cerebellar peduncles, as well as lesions of the pons and medulla [50] with a classic "butterfly" appearance on MRI.

4.2 Vertical Gaze Palsy

A vertical gaze palsy (VGP) is a conjugate, bilateral, limitation of the eye movements in upgaze and/or downgaze. Lesions of the rostral part of the MLF may cause vertical gaze palsies. The rostral MLF resides in the midbrain. Lesions of this area result in the pretectal syndrome, also known as Parinaud or dorsal midbrain syndrome. Both upgaze and downgaze are affected, but upgaze paresis is more common. Other features of the syndrome include pupillary light-near dissociation (pupils more reactive to near fixation than to light stimulus), upper eyelid retraction, and convergence retraction nystagmus. Convergence retraction nystagmus is characterized by adduction and retraction of the globe into the orbit with attempted upgaze. This type of nystagmus is highly localizing to the pretectal area. In children, the pretectal syndrome may be caused by hydrocephalus, infections, demyelinating disease, and a wide range of tumors and cysts of the pineal region.

Neimann–Pick disease causes a characteristic vertical saccadic paresis in two-thirds of affected children [51]. Paresis of downward saccades is typically the first manifestation, followed by paresis of upward saccades. Vertical pursuits and horizontal eye movements are typically spared.

4.3 History

A thorough prenatal and birth history should be obtained. History of the onset of eye movement disorders, birth history, prematurity, history of trauma, developmental delays, any lysosomal storage disorders, hydrocephalus must be elicited.

4.4 Examination

A detailed complete eye examination is recommended to note the type of gaze palsy, associated features such as vision abnormalities, pupil abnormalities, lid retraction, nystagmus. Gaze palsy is a limitation of eye movement seen in both eyes when the eyes move in any particular direction either horizontal or vertical. In

individual cranial nerve palsy the limitation of the eye movement is only the direction of the action the muscle supplied by the paretic nerve.

4.5 When to Refer

All patients with gaze palsies need to be referred to an ophthalmologist and neurologist for a detailed eye and neurological examination. New-onset symptoms need an urgent referral.

4.6 Treatment

Amblyopia, if noted, is treated with patching. Horizontal gaze palsy associated with progressive scoliosis is almost always bilateral and symmetric; patients do not develop diplopia and do not need treatment for ocular motility disturbances.

4.7 Prognosis Outcome

Patients with gaze palsies adapt by using head movements to look to the sides.

4.8 Prevention

No prevention methods are available.

5 Clinical Pearls/Key Points

- The most common cause of an acquired 6th nerve palsy is a tumor. Therefore, a child with new onset lateral rectus weakness should be investigated for raised ICP/space occupying lesion.
- The young child with 4th nerve palsy may present with head tilt towards the opposite shoulder, to minimize the discomfort caused by the vertical diplopia.
- Thyroid eye disease can present with lid retraction, proptosis and various forms of gaze limitation due to fatty infiltration of the extraocular muscles.
- Opsoclonus refers to chaotic eye movements and may be the presenting manifestation of neuroblastoma in children.
- Acquired Horner syndrome can be the result of dissection of the carotid artery and in cases of new onset a vascular etiology needs to be investigated.

References

1. Repka MX, Lum F, Burugapalli B. Strabismus, strabismus surgery, and reoperation rate in the United States: analysis from the IRIS registry. Ophthalmology. 2018;125(10):1646–53.
2. Calis F, Atilla H, Bingol Kiziltunc P, Alay C. Brain abnormalities in infantile esotropia as predictor for consecutive exotropia. Strabismus. 2019;27(4):199–204.
3. Lembo A, Serafino M, Strologo MD, Saunders RA, Trivedi RH, Villani E, Nucci P. Accommodative esotropia: the state of the art. Int Ophthalmol. 2019;39(2):497–505.
4. Merino P, Gómez de Liaño P, Villalobo JM, Franco G, Gómez de Liaño R. Etiology and treatment of pediatric sixth nerve palsy. J AAPOS. 2010;14(6):502–5.
5. Lee MS, Galetta SL, Volpe NJ, Liu GT. Sixth nerve palsies in children. Pediatr Neurol. 1999;20(1):49–52.
6. Reid JE, Reem RE, Aylward SC, Rogers DL. Sixth nerve palsy in paediatric intracranial hypertension. Neuroophthalmology. 2016;40(1):23–7.
7. Woo EJ, Winiecki SK, Ou AC. Motor palsies of cranial nerves (excluding VII) after vaccination: reports to the US vaccine adverse event reporting system. Hum Vaccin Immunother. 2014;10(2):301–5.
8. Miller NR. Solitary oculomotor nerve palsy in childhood. Am J Ophthalmol. 1977;83(1):106–11.
9. Loewenfeld IE, Thompson HS. Oculomotor paresis with cyclic spasms. A critical review of the literature and a new case. Surv Ophthalmol. 1975;20(2):81–124.
10. Susac JO, Smith JL. Cyclic oculomotor paralysis. Neurology. 1974;24(1):24–7.
11. Victor DI. The diagnosis of congenital unilateral third-nerve palsy. Brain. 1976;99(4):711–8.
12. Tsaloumas MD, Willshaw HE. Congenital oculomotor palsy associated neurological and ophthalmological findings. Eye. 1997;11:500–3.
13. Schumacher-Feero LA, Yoo KW, Solari FM, Biglan AW. Third cranial nerve palsy in children. Am J Ophthalmol. 1999;128(2):216–21.
14. Ing EB, Sullivan TJ, Clarke MP, Buncic JR. Oculomotor nerve palsies in children. J Pediatr Ophthalmol Strabismus. 1992;29(6):331–6.
15. Keane JR. Internuclear ophthalmoplegia: unusual causes in 114 of 410 patients. Arch Neurol. 2005;62(5):714–7.
16. Rizzo JL, Lloyd M, O'Hara MA. Pediatric internuclear ophthalmoplegia. J Neuroophthalmol. 2013;33(2):134–6.
17. Mansour AM, Reinecke RD. Central trochlear palsy. Surv Ophthalmol. 1986;30(5):279–97.
18. Plager DA. Tendon laxity in superior oblique palsy. Ophthalmology. 1992;99(7):1032–8.
19. Helveston EM, Krach D, Plager DA, Ellis FD. A new classification of superior oblique palsy based on congenital variations in the tendon. Ophthalmology. 1992;99(10):1609–15.
20. Kodsi SR, Younge BR. Acquired oculomotor, trochlear, and abducent cranial nerve palsies in pediatric patients. Am J Ophthalmol. 1992;114(5):568–74.
21. Thorne JE, Volpe NJ, Liu GT. Magnetic resonance imaging of acquired Brown syndrome in a patient with psoriasis. Am J Ophthalmol. 1999;127:233–4.
22. Talebnejad MR, Lankaranian D, Warrian K, Attarzadeh AJ, Kumar PV, Farvardin M. Osteochondroma of the trochlea presenting as acquired Brown syndrome: a case report. J AAPOS. 2007;11(3):305–6.
23. Dawson E, Barry J, Lee J. Spontaneous resolution in patients with congenital Brown syndrome. J AAPOS. 2009;13(2):116–8.
24. Brandt T, Dieterich M. Skew deviation with ocular torsion: a vestibular brainstem sign of topographic diagnostic value. Ann Neurol. 1993;33(5):528–34.
25. Wong AM, Sharpe JA. Cerebellar skew deviation and the torsional vestibuloocular reflex. Neurology. 2005;65(3):412–9.
26. Cogan DG, Barrows LJ. Platybasia and the Arnold-Chiari malformation. AMA Arch Ophthalmol. 1954;52(1):13–29.
27. Dittrich J, Havlová M, Nevsímalová S. Paroxysmal hemipareses in childhood. Dev Med Child Neurol. 1979;21(6):800–7.

28. Baker RS, Buncic JR. Vertical ocular motility disturbance in pseudotumor cerebri. J Clin Neuroophthalmol. 1985;5(1):41–4.
29. Jevalikar G, Solis J, Zacharin M. Long-term outcomes of pediatric Graves' disease. J Pediatr Endocrinol Metab. 2014;27(11–12):1131–6.
30. Liu GT, Heher KL, Katowitz JA, Kazim M, Moazami G, Moshang T, Teener JW, Sladky J, Volpe NJ, Galetta SL. Prominent proptosis in childhood thyroid eye disease. Ophthalmology. 1996;103(5):779–84.
31. Förderreuther S, Ruscheweyh R. From ophthalmoplegic migraine to cranial neuropathy. Curr Pain Headache Rep. 2015;19(6):21.
32. Bharucha DX, Campbell TB, Valencia I, Hardison HH, Kothare SV. MRI findings in pediatric ophthalmoplegic migraine: a case report and literature review. Pediatr Neurol. 2007;37(1):59–63.
33. Carlow TJ. Oculomotor ophthalmoplegic migraine: is it really migraine? J Neuroophthalmol. 2002;22(3):215–21.
34. Kupersmith MJ. Practical classification of nystagmus in the clinic [letter]. Arch Ophthalmol. 2008;126:871–2.
35. Halmagyi GM, Gresty MA, Leech J. Reversed optokinetic nystagmus (OKN): mechanism and clinical significance. Ann Neurol. 1980;7:429–35.
36. Gottlob I, Proudlock FA. Aetiology of infantile nystagmus. Curr Opin Neurol. 2014;27:83–91.
37. Krug P, Schleiermacher G, Michon J, Valteau-Couanet D, Brisse H, Peuchmaur M, Sarnacki S, Martelli H, Desguerre I, Tardieu M. Opsoclonus-myoclonus in children associated or not with neuroblastoma. Eur J Paediatr Neurol. 2010;14(5):400–9.
38. Pranzatelli MR, Tate ED, McGee NR. Multifactorial analysis of opsoclonus-myoclonus syndrome etiology ("Tumor" vs. "No tumor") in a cohort of 356 US children. Pediatr Blood Cancer. 2018;65(8):e27097.
39. Hoyt CS, Mousel DK, Weber AA. Transient supranuclear disturbances of gaze in healthy neonates. Am J Ophthalmol. 1980;89(5):708–13.
40. Lavery MA, O'Neill JF, Chu FC, Martyn LJ. Acquired nystagmus in early childhood: a presenting sign of intracranial tumor. Ophthalmology. 1984;91(5):425–53.
41. Koenig SB, Naidich TP, Zaparackas Z. Optic glioma masquerading as spasmus nutans. J Pediatr Ophthalmol Strabismus. 1982;19(1):20–4.
42. Khan AO, Alrashed M, Alkuraya FS. 'Cone dystrophy with supranormal rod response' in children. Br J Ophthalmol. 2012;96(3):422–6.
43. Clark BJ, Kemp EG, Behan WM, Lee WR. Abnormal extracellular material in the levator palpebrae superioris complex in congenital ptosis. Arch Ophthalmol. 1995;113(11):1414–9.
44. Allen CE, Rubin PA. Blepharophimosis-ptosis-epicanthus inversus syndrome (BPES): clinical manifestation and treatment. Int Ophthalmol Clin. 2008;48(2):15–23.
45. Pineles SL, Avery RA, Moss HE, Finkel R, Blinman T, Kaiser L, Liu GT. Visual and systemic outcomes in pediatric ocular myasthenia gravis. Am J Ophthalmol. 2010;150(4):453–459.e3.
46. Afifi AK, Bell WE. Tests for juvenile myasthenia gravis: comparative diagnostic yield and prediction of outcome. J Child Neurol. 1993;8:403–11.
47. Khambatta S, Nguyen DL, Beckman TJ, Wittich CM. Kearns-Sayre syndrome: a case series of 35 adults and children. Int J Genet Med. 2014;7:325–32.
48. Weinstein JM, Zweifel TJ, Thompson HS. Congenital Horner's syndrome. Arch Ophthalmol. 1980;98:1074–8.
49. Chen CM, Wei JC, Huang TY. Mesencephalic bilateral horizontal gaze palsies. Neurology. 2008;71(13):1039.
50. Bosley TM, Salih MA, Jen JC, Lin DD, Oystreck D, Abu-Amero KK, MacDonald DB, al Zayed Z, al Dhalaan H, Kansu T, Stigsby B, Baloh RW. Neurologic features of horizontal gaze palsy and progressive scoliosis with mutations in ROBO3. Neurology. 2005;64(7):1196–203.
51. van de Vlasakker CJ, Gabreëls FJ, Wijburg HC, Wevers RA. Clinical features of Niemann-Pick disease type C. An example of the delayed onset, slowly progressive phenotype and an overview of recent literature. Clin Neurol Neurosurg. 1994;96(2):119–23.

Child with Facial Weakness

Danielle Nolan and Daniel Arndt

1 Epidemiology

The prevalence of childhood facial weakness is widely dependent upon the etiology. The incidence of acquired childhood peripheral facial nerve palsy is estimated at 2.7 per 100,000 per year in children younger than 10 years and 10.1 per 100,000 per year in children between 10 and 20 years old [1]. Most common age ranges are between 1–3 years and 8–12 years. There appears to be no gender predominance. Most cases of childhood peripheral facial nerve paralysis are labeled Bell's palsy (previously categorized as idiopathic), ranging from 40 to 70% of cases. Indeed, Bell's palsy has been estimated as affecting approximately 20 per 100,000 people per year [2]. This is followed by other infectious (13–36%) and traumatic etiologies (19–21%), congenital disorders (8–14%), and lastly neoplastic causes (2–3%) [1, 3]. The incidence of centrally mediated childhood facial weakness is harder to quantify, ranging from pediatric ischemic and hemorrhagic stroke with an incidence of 1.2–13 cases per 100,000 children [4], congenital myotonic dystrophy with an incidence of 4.76 per 100,000 children [5], to diffuse intrinsic pontine glioma which has an incidence of 1–2 cases per 100,000 children [6].

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2 Etiology

Etiologies of childhood facial weakness can be divided into the following categories: idiopathic, infectious, congenital, traumatic, and neoplastic. Further categorization into peripheral and central nervous system localization is important. While peripherally mediated facial nerve lesions (also called lower motor neuron facial nerve weakness) often present with diffuse (involving upper and lower half) facial weakness, central causes (or upper motor neuron type) of childhood weakness are most easily identified due to "forehead sparing" or ability to wrinkle the forehead when eyebrows are raised. This is due to the fact that nerve fibers innervating the forehead receive bilateral input via the corticobulbar tracts. A cortical lesion may lead to hemiparesis of the contralateral facial muscles while a brainstem lesion can be associated with unilateral facial weakness as well as ipsilateral abducens nerve palsy. Identification of a central etiology shifts the diagnostic focus to a group of conditions that may be different from those causing peripheral facial nerve weakness.

Overall, infectious etiologies are the most common cause of childhood facial weakness. They are more likely to cause peripheral facial nerve weakness. The most common peripheral cause is Bell's palsy, previously synonymous with acute idiopathic peripheral facial nerve weakness. Although broadly categorized as idiopathic, it is now often attributed to infectious or post-infectious causes. Peripheral facial nerve weakness related to infection typically occurs due to axonal spread and multiplication of a reactivated neurotropic virus leading to inflammation, demyelination, and dysfunction [2]. Before the use of antibiotics, otitis media was one of the most common causes of acute childhood facial nerve paralysis; however, it currently is thought to represent only about 0.005% of cases (decreased from previous 0.7%) [1]. Lyme disease now tops this list, notably accounting for up to 50% of cases in endemic areas [1]. Lyme disease can lead to unilateral or bilateral peripheral facial weakness, typically of a short duration (less than 2 months) with subacute onset and gradual resolution. Varicella infection can lead to a peripheral facial weakness during either the initial infection or with viral reactivation. This etiology has been found in up to 37% of pediatric facial weakness cases [7]. Notable but less common pediatric infectious etiologies include the coxsackievirus, adenovirus, influenza, neuroborellosis, CMV, EBV, HHV6, HIV, and Rickettsia [2, 8, 9]. Postinfectious autoimmune disorders, such as Guillain–Barre syndrome, may also evolve to bilateral facial weakness, although often subacute in presentation and associated with broader neurologic signs and symptoms [10].

Infectious etiologies of central facial weakness are due to structural changes that affect the primary motor cortex or facial nucleus in the brainstem. Infections may cause lesions such as abscess, empyemas, or cysts that would lead to unilateral facial weakness of the central variety. Autoimmune or postinfectious neurologic disorders may also be included in this category and can lead to peripheral or central childhood facial weakness. Notable implicated syndromes include myasthenia gravis, multiple sclerosis, and Miller Fisher syndrome.

Traumatic causes of peripheral nerve facial weakness or paralysis are often categorized based on age of presentation. Traumatic births, for which risk factors include birth weight >35,000 g, forceps-assisted delivery, and prematurity, are common etiologies of neonatal unilateral facial weakness [2]. Facial nerve injury and resulting weakness can occur in childhood head trauma, especially in cases involving a longitudinal fracture of the temporal bone (90%) [3]. Potential for iatrogenic trauma resulting in facial weakness or injury is also noted, such as during a parotidectomy [11].

Pediatric stroke may be considered an important cause of centrally mediated facial weakness. Perinatal stroke is categorized as occurring between 20 weeks gestational age and 28 days postnatal age. Perinatal stroke more frequency presents with encephalopathy and seizures, although unilateral facial weakness may be a sequela. Childhood stroke is a multifactorial disease with risk factors that include recent infection (especially varicella zoster), autoimmune disease, vascular malformations, and rare genetic etiologies (such as ACTA2-related disorder) [12]. Acute severe systemic hypertension in childhood can also rarely lead to unilateral focal deficits, such as facial weakness, in conjunction with more systemic symptoms such as headache, vomiting, convulsion, and altered consciousness [3].

Congenital disorders can present with bilateral or unilateral neonatal/childhood peripheral facial nerve palsy [1]. Moebius syndrome demonstrates bilateral facial nerve palsy as well as abducens nerve palsy and club foot. Goldenhaar syndrome presents with facial nerve palsy in addition to malar and maxillary hypoplasia, and hemifacial macrosomia. Melkersson–Rosenthal syndrome notably demonstrates recurrent attacks of intermittent facial nerve palsy with facial swelling and the presence of a fissured tongue. Congenital unilateral lower lip palsy is a common congenital mimicker of facial nerve palsy. As opposed to a true facial nerve palsy, this syndrome is due to congenital hypoplasia of the depressor angularis oris muscle and is also referred to as asymmetric crying facies [13]. Newborns with this disorder can demonstrate lip pursing, symmetric eye closure, and symmetric nasolabial folds but reveal asymmetric mouth activation. This is most frequently noted during crying. Although this can be an isolated finding, associated systemic abnormalities may include heart and/or renal congenital abnormalities.

Congenital or genetic childhood syndromes may also be associated with childhood facial weakness—though technically speaking, these conditions do not involve the facial nerve per se. They are characterized by involvement of the muscles that are supplied by the facial nerve. This category is broad and includes childhood neuromuscular disorders such as metabolic myopathies [14] and myotonia dystrophy [15] or disorders involving the neuromuscular junction such as congenital myasthenia gravis.

Lastly, neoplasms are a rare but important etiology of peripheral and central childhood facial weakness. Facial nerve paralysis occurs when a tumor, such as schwannoma or astrocytoma, invades the facial nerve. This often progresses gradually and may present sub acutely over 3 weeks without return of function after 6 months [1]. Cholesteatomas, a benign and slow-growing growth, have also been

described to cause a gradual onset of childhood unilateral facial weakness [2]. Cortical-located neoplasms of the primary motor cortex or facial nucleus in the brainstem may cause central facial weakness and include leukemia, meningeal carcinoma, neurofibromatosis, or brainstem glioma.

3 Differential Diagnosis

Onset and duration of facial weakness are helpful factors to further narrow the differential diagnosis. Acute onset (1–2 days), unilateral or bilateral, of upper and lower facial weakness most commonly represents peripheral etiologies such as idiopathic facial nerve palsy (Bell's palsy) or traumatic etiologies. Typical symptoms include the sudden onset of inability to close the eye, disappearance of nasolabial fold, and asymmetric smile along with a notable absence of forehead wrinkling, the hallmark indicator of peripheral facial weakness. Other symptoms seen in Bell's palsy include decreased tearing, hyperacusis, and/or loss of taste sensation on the anterior two-thirds of the tongue [16]. The diagnosis of Bell's (idiopathic) facial nerve palsy requires the following criteria: diffuse involvement of the muscles supplied by the facial nerve (with involvement of the forehead), acute onset with some degree of recovery within 6 months, and may also involve an associated prodrome, ear pain, and/or loss of taste [16].

4 Diagnostic Approach

4.1 History

If the symptom has been present since birth, a detailed birth history, including nature of delivery, history of prematurity, and birth weight, is important to elicit. One must inquire regarding other neurological symptoms such as limb weakness or delay in motor milestones (in a younger child) to investigate if the facial weakness is an isolated symptom or associated with other symptoms suggestive of perinatal stroke. In an older child, a history of recent otitis media, head injury, and recent systemic illnesses should be elicited. One must also inquire regarding symptoms such as headache, weight loss, night sweats, rash, and history of camping in tick-infested areas. The presence of erythema migrans lesion, typically located in the head and/or neck region is a key finding in Lyme disease. Ramsey–Hunt syndrome is when Bell's palsy presents along with a painful vesicular rash within the external auditory canal due to Varicella infection. The historian must also review all symptoms that might indicate involvement of other cranial nerves even if the child or parent does not bring it up.

The history may help to differentiate a peripheral facial nerve weakness from a central facial nerve weakness as the latter is rarely isolated. When a child has a central facial nerve weakness there are associated symptoms suggestive of involvement of the brain stem or the cerebral hemispheres such as limb weakness or weakness of other cranial nerves. When facial weakness that persist >3 weeks or without improvement >3 months are more suggestive of central etiologies such as neoplastic or congenital cause [3].

4.2 Physical Examination

4.2.1 General Examination

Asymmetry of the face may indicate a long-standing lesion of the facial nerve. Facial edema and a fissured tongue may be present in Melkersson–Rosenthal syndrome. General muscle bulk should be noted. A thorough cardiac examination is important when the symptom is noted in a baby (see asymmetric crying facies above). Lymphadenopathy or parotid swellings should be looked for as they can indicate underlying malignancy.

4.3 Neurological Examination

A complete neurological examination should be performed on every child presenting with facial weakness. This includes testing of higher mental functions, all cranial nerves, motor strength, gait, coordination, and deep tendon reflexes. Of course, examination of individual facial muscles is of greatest importance. The muscles that can easily be tested at the bedside include the frontalis (wrinkling of forehead), orbicularis oculi (forceful closure of the eyelids), orbicularis oris (wide smile), buccinator (puffing of cheeks), and occasionally the platysma (stretching of skin of the neck that occurs when the corner of the mouth is drawn inferiorly as in fright).

Peripheral etiologies of facial nerve palsy generally result in complete unilateral facial weakness including upper facial or forehead muscles. Conversely, central etiologies result in unilateral, lower facial weakness. Supranuclear lesions (occurring in central structures innervating the CN VII nucleus) result in asymmetric, contralateral, lower facial weakness including the perioral muscles used facial expression, lower periocular muscles used in eye closure (rarely upper), and asymmetric nasolabial fold (due to unilateral CN VII innervation of these muscles), with sparing of the upper facial, eye closure, or forehead muscles (receive bilateral CN VII innervation). Infranuclear lesions (occurring in the CN VII axon) generally result in ipsilateral, unilateral, complete facial weakness including forehead and upper periocular

muscles resulting in the inability to wrinkle forehead and close eyes (Bell's phenomena is noted, i.e., eyes roll up when lids are closed). Patients can rarely have bilateral facial weakness which obviates the examiner's ability to decipher central versus peripheral weakness localization by neurologic examination using the aforementioned paradigm, as the patient loses the bilateral central innervation effect on upper facial or forehead muscles observed in central supranuclear or nuclear lesions.

5 Diagnostic Investigations

Once the factors are met for a diagnosis of Bell's palsy, diagnostic studies are typically not necessary. However, atypical presentations require a closer look and diagnostic studies including neuroimaging, electrodiagnostic studies, serology testing, and/or CSF investigations via lumbar puncture may be indicated to help guide treatment and determine prognosis [2, 3]. Electrodiagnostic studies, such as motor nerve conduction studies, help different between peripheral (e.g., traumatic) versus central etiologies when it is unclear based on the examination and can also aid in prognostication. If a central etiology is suspected based on physical findings, neuroimaging may identify a structural lesion such an abscess, temporal bone trauma, or neoplasm. Common imaging studies include magnetic resonance imaging of the brain (MRI) (including brain, brainstem, temporal bone, and parotid gland) and/or head CT. Whereas peripheral facial weakness has an acute onset, central face weakness may be more subacute related to gradual development of worsening cerebral lesion and neuroimaging is indicated.

Serological testing is often broad but can be tailored based on clues found in the preceding history. For instance, Lyme disease testing is strongly indicated for all children with acute-onset facial palsy when there is any possibility of exposure (Lyme-endemic areas during spring-autumn seasons). CSF findings in Lyme disease-related facial paralysis may include lymphocytic pleocytosis (55%) and specifically free *B.* burgdorferi antibodies (82%) [1]. If there is a clinical suspicion for meningitis, lumbar puncture is recommended and may revealed elevated WBC count or protein concentration. A slight increase in monocytes and lymphocytes is compatible with Bell's palsy but does not definitively diagnose the condition nor exclude an inflammatory process [2]. Systemic findings may also guide infectious work-up; for example, external ear vesicle or scabbing rash seen in Ramsay–Hunt syndrome.

6 Treatment/Management

The treatment of childhood facial weakness is directed based on the etiology and severity of the condition. A mainstay of symptomatic treatment is protection of the cornea, which is left vulnerable to injury due to incomplete eye closure. Artificial

tears during the day maintain lubrication while patching at night helps to avoid accidental corneal abrasions. Attention must be paid to any symptoms of poor mastication that may lead to dysphagia and related complications.

For treatment of idiopathic peripheral facial nerve palsy (i.e., Bell's palsy), early glucocorticoids treatment within 3 days of symptom onset is currently recommended (AAN citation, [17]. A suggested regimen is prednisone 2 mg/kg daily (up to 60–80 mg) for 5 days, followed by a 5-day taper [2]. Some studies have suggested the concurrent use of steroids and valacyclovir. However, the most recent Cochrane review reported that corticosteroids alone were probably more effective than antivirals alone and that the combination of antivirals and corticosteroids probably reduced the late sequelae of Bell's palsy compared with corticosteroids alone in all populations [18]. Botulinum toxin injections are considered for long-term sequelae such as synkinesis, facial spasm, hyperlacrimation, and cosmetic appearance [19]. Childhood facial paralysis due to other underlying infection, whether it be central or peripheral, require infection-specific treatment. However, it should be noted that other infection-related treatment, such as doxycycline use in Lyme disease, is primarily recommended to prevent complications of disseminated disease as antibiotics therapy may not have a major impact on the outcome of the facial palsy [20]. Overall, irrespective of specific treatment, infection related childhood peripheral facial nerve palsy, has a high rate of spontaneous recovery over a range of week–months.

Treatment options for congenital or certain forms of acquired peripheral lesions such as traumatic etiologies are often surgical, including muscle transfers and nerve grafts. Further studies are required regarding the benefit and risk of these procedures in children [2]. Congenital unilateral lower lip palsy can be cosmetically treated with botulinum injections to the unaffected side [2]. Peripheral neoplasms, such as cholesteatoma, often require resection.

Congenital centrally mediated facial weakness is more often bilateral. Neonatal myasthenia gravis frequently demonstrated facial diplegia. Once the results from neostigmine challenge confirm neonatal myasthenia gravis, neostigmine treatment should be initiated. With prompt recognition and management, symptomatic improvement can occur within weeks [21]. Congenital myotonic dystrophy unfortunately has no disease-modifying therapy available and often require respiratory and nutrition support [22].

Management of pediatric stroke and autoimmune disorders is an evolving topic and dependent upon age of presentation. Perinatal ischemic stroke treatment is largely supportive with antiplatelet or anticoagulants being rarely used [23]. Acute reperfusion therapies with IV thrombolysis and/or mechanical thrombectomy may be considered in select childhood arterial ischemic stroke. Consideration of the etiology may guide specific management for pediatric stroke, for example, Moya Moya disease may require surgery, whereas a child with sickle cell disease may need a regular regime of exchange transfusions.

7 Prognosis/Outcome

The prognosis and outcome of facial weakness is variable and dependent upon the etiology. The majority of children with Bell's palsy demonstrate recovery between 3 weeks and 3 months irrespective of treatment [3] [24]. However, treatment with corticosteroids with or without antivirals may lead to a faster rate of recovery or decreased long-term sequela. Conversely, if no degree of recovery is seen during that time, the underlying diagnosis should be re-explored with additional evaluation for an alternative etiology. Recurrence of childhood Bell's palsy is rare, occurring in <10% of cases, and should also prompt investigation for alternative etiologies, such as Melkersson–Rosenthal syndrome [2]. The prognosis for functional recovery with Melkersson–Rosenthal syndrome is poorer and may require surgical facial nerve decompression.

Numerous studies of acquired peripheral facial nerve palsy in children demonstrate excellent recovery rates, greater than 95%, irrespective of etiology [2]. This has been found to hold true even in the setting of severe facial nerve trauma. While adults with grade I–VI facial nerve trauma have an overall poor prognosis for recovery, children consistently outperformed their adult counterparts in term of recovery [2, 25]. Indeed, when facial paralysis occurs due to trauma in the perinatal period, all patients have at least some degree of improvement [2]. As noted above, electrodiagnostic study with motor nerve conduction evaluation can help guide prognostication in these events. A compound muscle actin potential (CMAP) greater than 30–50% of normal has a greater change of partial-complete function recovery [2].

Unfortunately, congenital facial paralysis has a much poorer prognosis. Recovery of function is limited due maldevelopment of the facial nerve.

8 When to Refer/Admit

While facial weakness that fits criteria for Bell's palsy can be managed effectively by the primary physician, certain factors indicate need for referral and/or escalation of care. If the facial weakness is accompanied by subacute systemic factors, when there are bilateral facial symptoms, or facial weakness becomes recurrent, referral should be considered. Specialists that may be considered, depending on the clinical presentation, include Pediatric Neurology, Neurosurgery, ENT, Infectious Disease, and/or Oncology. Red flag symptoms such as concurrent vomiting, fever, extremity weakness or other focal neurologic deficits should prompt immediate Emergency Room evaluation for investigation of potential central etiology.

9 Clinical Pearls/Key Points

- Important infectious etiologies that can lead to peripheral type of facial nerve weakness include Lyme disease, herpes simplex viral infection, otitis media, adenovirus, enterovirus, and HIV infection.
- Recurrent childhood Bell's palsy is rare and should prompt investigation for alternative etiologies.
- Acquired childhood peripheral facial nerve palsy has overall recovery rates of up to 95%.
- Symptoms concerning for a central etiology, such as other focal neurologic deficits, should prompt immediate evaluation in an emergency department.

References

1. Lorch M, Teach SJ. Facial nerve palsy: etiology and approach to diagnosis and treatment. Pediatr Emerg Care. 2010;26:763–72.
2. Zaidman C. Facial nerve palsy in children. UpToDate. [Online]. 2020. https://www.uptodate.com/contents/facial-nerve-palsy-in-children?search=child%20facial%20weakness&source=search_result&selectedTitle=1~116&usage_type=default&display_rank=1.
3. Malik V, Joshi V, Green KMJ, Bruce IA. 15 minute consultation: a structured approach to the management of facial paralysis in a child. Arch Dis Child Educ Pract Ed. 2012;97:82–5.
4. Tsze DS, Valente JH. Pediatric stroke: a review. Emerg Med Int. 2011;2011:734506.
5. Johnson NE, et al. Population-based prevalence of myotonic dystrophy type 1 using genetic analysis of statewide blood screening program. Neurology. 2021;96:e1045–53.
6. Pellot JE, De Jesus O. Diffuse intrinsic pontine glioma. StatPearls. [Online]. 2021. https://www.ncbi.nlm.gov/books/NBK560640.
7. Furuta Y, et al. Varicella-zoster virus reactivation is an important cause of acute peripheral facial paralysis in children. Pediatr Infect Dis J. 2005;24:97–101.
8. Morgan M, Nathwani D. Facial palsy and infection: the unfolding story. Clin Infect Dis. 1992;14:263–71.
9. Papan C, et al. Pediatr Infect Dis J. 2020;39:326–9.
10. Estrade S, et al. Prognostic factors for the sequelae and severity of Guillain-Barre syndrome in children. Muscle Nerve. 2019;60:716–23.
11. El Sayed Ahmad Y, Winters R. Parotidectomy. StatPearls. [Online]. 2020. https://www.ncbi.nlm.nih.gov/books/NBK557651/.
12. Rajani NK, et al. Pediatric stroke: current diagnostic and management challenges. Quant Imaging Med Surg. 2018;8:984–91.
13. Kobayashi T. Congenital unilateral lower lip palsy. Acta Otolaryngol. 1979;88:303–9.
14. Finsterer J. Update review about metabolic myopathies. Life (Basel). 2020;10:43.
15. Echenne B, Bassez G. Congenital and infantile myotonic dystrophy. Handb Clin Neurol. 2013;113:1387–93.
16. Shargorodsky J, Lin HW, Gopen Q. Facial nerve paley in the pediatric population. Clin Pediatr. 2010;49:411–7.
17. Vishnu MB, et al. Corticosteroids for Bell's palsy (idiopathic facial paralysis). Cochrane Database Syst Rev. 2016;7:CD001942.

18. Gagyor I, et al. Antiviral treatment for Bell's palsy (idiopathic facial paralysis). Cochrane Database Syst Rev. 2019;9:CD001869.
19. Eviston TJ, et al. Bell's palsy: aetiology, clinical features and multidisciplinary care. J Neurol Neurosurg Psychiatry. 2015;86:1356–61.
20. Clark JR, et al. Facial paralysis in Lyme disease. Laryngoscope. 1985;95:1341–5.
21. Papazian O. Transient neonatal myasthenia gravis. J Child Neurol. 1992;7:135–41.
22. Darras BT. Myotonic dystrophy: treatment and prognosis. UpToDate. [Online]. 2021. https://www.uptodate.com/contents/myotonic-dystrophy-treatment-and-prognosis?search=congenital%20myotonic%20dystrophy%20treatment&sectionRank=1&usage_type=default&anchor=H2624714493&source=machineLearning&selectedTitle=1~81&display_rank=1#H2624714493.
23. Ferriero DM, et al. Management of stroke in neonates and children: a scientific statement from the American Heart Association/American Stroke Association. Stroke. 2019;50:51–96.
24. Peitersen E. Bell's palsy: the spontaneous course of 2500 peripheral facial nerve palsies of different etiologies. Acta Otolaryngol Suppl. 2002;549:4–30.
25. Hanci F, et al. Childhood facial palsy: etiologic factors and clinical findings, an observational retrospective study. J Child Neurol. 2019;34:907–12.

Hearing Loss in Children

Sonal Saraiya and Catherine Mae Geller

1 Introduction

Blindness separates people from things; deafness separates people from people. — Helen Keller

Hearing loss in children constitutes a major public health and economic problem. Congenital handicapping hearing loss affects as many as 1.7 per 1000 live births making it the most common neurologic birth defect in the United States [1]. Hearing loss has significant impact on communication skills, psychosocial development, and educational progress, with early detection of hearing loss crucial for language, academic, and socio-emotional advancement [2, 3].

2 Epidemiology

Population-based studies in Europe and North America demonstrate a consistent prevalence where 0.1% of children have hearing loss greater than 40 decibels (dB). The estimated prevalence of permanent bilateral hearing loss is 1.33 per 1000 live births in developed countries. In children of primary school age, the prevalence increases to 2.83 per 1000 children, with a further increase to 3.5 per 1000 in adolescents [4]. Genetic causes are responsible for up to 50–70% of hearing loss with the remaining 30% from environmental causes including birth complications and congenital infections. The most common developmental disabilities associated with hearing loss are intellectual disability (23%), cerebral palsy (10%), autism spectrum

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disorder (7%), and/or vision impairment (5%) [5]. Children may lose hearing from multiple etiologies as they age. Therefore, they may require reevaluation when symptoms develop despite previously passed hearing screenings. Congenital genetic hearing loss may be delayed in onset (not be present at birth) or progressive; unilateral losses may be missed in hearing screening due to the normal hearing abilities of the contralateral ear. Children may acquire hearing loss later in life due to temporal bone fractures, head trauma or infection, especially bacterial meningitis. The prevalence of hearing loss in children by age 18 years has been estimated to be as high as 18% [6].

According to the National Center on Birth Defects and Developmental Disabilities approximately 40% of young adults with hearing loss identified during childhood reported experiencing at least one limitation in daily functioning [7]. It is expected that the lifetime costs for all people with hearing loss who were born in 2000 will total $2.1 billion (in 2003 dollars) in direct medical and nonmedical expenses, and indirect costs such as lost wages. However, 71% of young adults with hearing loss without other related conditions (such as intellectual disability, cerebral palsy, epilepsy, or vision loss) were employed [8].

3 Pathophysiology

Human hearing is normally in the range of 20–20,000 Hz. Any pathology that arises along the complex course of the acoustic pathway to the auditory cortex may result in a hearing loss. As sound enters the auricle, the acoustic energy is collected and funneled through the external auditory canal to the tympanic membrane (Fig. 1).

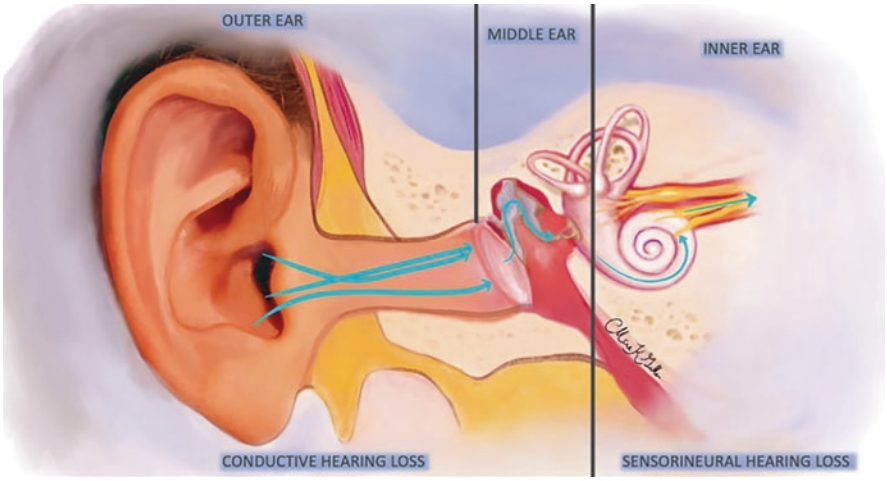

Fig. 1 The ear: Acoustical energy is collected and funneled by the auricle and delivered to the tympanic membrane. The middle ear space converts acoustics to mechanical and then hydraulic energy where it enters the cochlea. The inner ear converts these sound waves to neuroelectric stimulus which is transmitted to the brain. Pathology of the outer and middle ear produce conductive hearing loss while the inner ear results in sensorineural hearing loss. (Printed with permission)

The three ossicles (malleus, incus and stapes) then function jointly as levers, converting, amplifying and concentrating the acoustic energy applied to the tympanic membrane into mechanical energy and subsequently into a hydraulic force that is transmitted through the piston-like action of the stapes at the oval window. These sound waves then propagate along the cochlear scala causing movement of the cochlear hair cells of the Organ of Corti where mechanical and chemical energy are converted to electrical energy with stimulation of the cochlear nerve endings. This electrical signal is transmitted from the cochlear nerve to the auditory cortex. From the cochlea to the auditory cortex, there are multiple crossovers of the auditory nerve fibers in subcortical pathways through nuclei of the auditory brainstem and midbrain (cochlear nucleus, superior olivary nuclei, lateral lemniscus, inferior colliculus, and medial geniculate nuclei). Ultimately the auditory signals have binaural representation in each cortex, i.e., each auditory cortex, located in the temporal lobe obtains information from both ears.

In order to understand meaningful sounds in everyday listening conditions, the auditory system must extract spectral, temporal, and spatial information from the acoustic signals. Hermann von Helmholtz in the 1850s described the cochlea as an inverse piano, with individual tones of incoming sound being separated and represented at different locations along the cochlea (Fig. 2). Each of the 16,000 hair cells that line the cochlea is a receptor that is programmed to respond to a specific frequency. Integration and filtration of this information through the subcortical pathways ultimately forms the sound perceived by the cortex. For adequate auditory processing, all levels of the central auditory system receive information from both the ipsilateral and contralateral sides, with predominant information being transmitted to the auditory cortex from the contralateral side. There is a left hemispheric dominance in higher level speech processing in all patients due to the location of the Broca and Wernicke areas. Right ear stimuli are transmitted to the left hemispheric

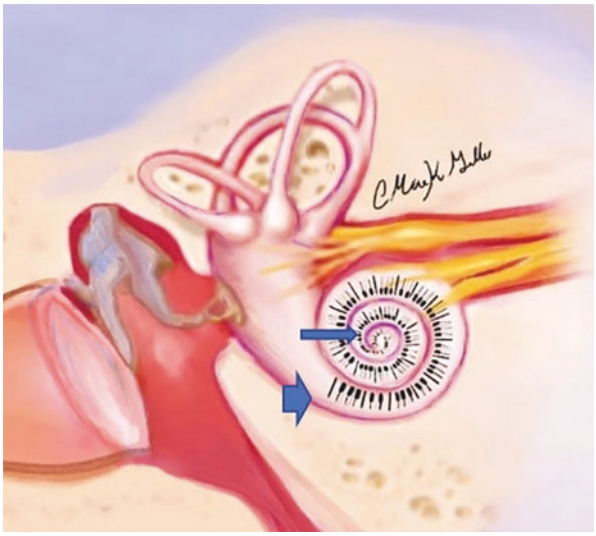

Fig. 2 Cochlea depicting inverse piano representation where high frequencies are processed at the base of the cochlea and low frequencies at the apex. Thin arrow—Apex, thick arrow—Base of the cochlea. (Printed with permission)

speech perception areas directly; however, the left ear stimuli first transmit to the right hemisphere and then through the corpus callosum, to the left hemispheric speech perception areas. This results in the right ear advantage. Knowing this is crucial for rehabilitation for right-sided hearing loss, or for choosing laterality for unilateral cochlear implant.

Multiple pathways exist for modulation and amplification of sound as well as integration of sound into the vestibular reflexes. Hearing impairment can occur despite normal ear function, suggesting a contribution from abnormal central processing disorders. The auditory pathway completely matures by 4 years of age [9]. Stimulating the auditory cortex by 12 months of age is crucial for well-formed tracts and prevents significant delays in development of linguistic and intellectual capabilities of the child.

Any dysfunction of the above pathway may result in hearing impairment in day-to-day surroundings. In general, lesions in the auricle, external auditory canal, or middle ear (peripheral structures) result in a conductive hearing loss (CHL) while a loss of cochlear hair cell function, cochlear nerve or intracranial pathology leads to a sensorineural hearing loss (SNHL) (Fig. 1). Mixed hearing loss (MHL) is the presence of both conductive and sensorineural components.

4 Genetic Hearing Loss

4.1 Conductive Hearing Loss

The tympanic membrane and middle ear ossicles are responsible for the collection of sound waves and transmission of sound to the cochlea; disruption to this system can result in a conductive hearing loss [10]. Congenital causes of conductive hearing loss may be readily apparent on physical examination such as in cases of microtia and aural atresia. Twenty to sixty percent of patients with microtia and atresia have syndromic causes or associated anomalies [11]. More subtle congenital causes of conductive hearing loss, such as ossicular malformations, sclerosis or fixation, can coexist with canal atresia or occur independently. Conductive hearing loss related to eustachian tube dysfunction is commonly encountered in children with Down syndrome, Pierre Robin Sequence (with or without corresponding syndrome), Treacher Collins, FGFR mutations (Apert, Crouzon, and Pfeiffer), Branchio-oto-renal, Goldenhar, and Turner syndromes.

4.2 Sensorineural Hearing Loss

The etiology of sensorineural hearing loss is heterogeneous: it is believed that about 50% of cases of prelingual onset sensorineural hearing loss are due to genetic causes and up to 30% environmental causes (Fig. 3).

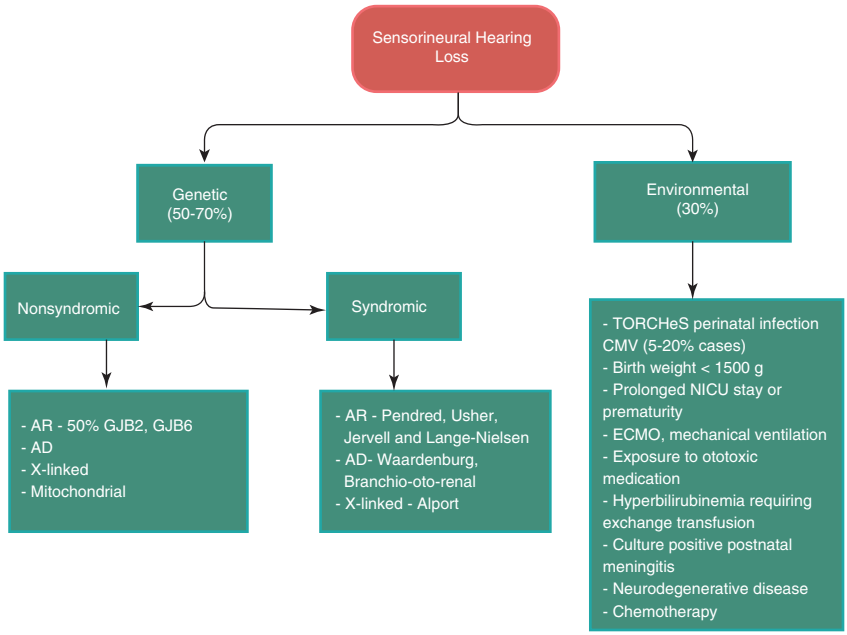

Fig. 3 Etiologic causes of prelingual sensorineural hearing loss. *AR* autosomal recessive, *AD* autosomal dominant, *CMV* cytomegalovirus, *ECMO* extracorporeal membranous oxygenation, *NICU* neonatal intensive care unit

4.2.1 Nonsyndromic Hearing Loss

Nonsyndromic hearing loss due to single-gene mutation may be transmitted as an autosomal recessive (>65%), autosomal dominant (35%), or X-linked trait (<1%). At least 123 different genes have been identified for nonsyndromic hearing loss [12]. The DFN loci (nonsyndromic deafness gene) with genes GJB2, GJB6 coding for the gap junction proteins connexin 26 and 30 are responsible for up to 50% of the autosomal recessive hearing loss.

4.2.2 Syndromic Hearing Loss

Syndromic sensorineural hearing loss comprises 30% of genetic hearing loss. More than 300 syndromes with an associated hearing loss have been described [4]. Knowledge of characteristic patterns of syndromes and variations of congenital malformations on imaging aid in the identification and screening of patients for other comorbid and possibly life-threatening conditions (Table 1). Syndromic hearing loss may be progressive and cannot be excluded by normal hearing screens at birth. Syndromes may present with a long-standing family history in autosomal dominant, recessive, X-linked or mitochondrial patterns. They also may present

Table 1 Syndromic hearing loss: associated clinical features and management [13]

Syndrome	Inheritance	Associated clinical features	Audiologic and radiologic findings	Additional testing
Waardenburg	Most common AD AD/AR: I-PAX3, II-MITF, III-PAX3, IV-EDNRB	Dystopia canthorum (I, III), pigmentary abnormalities, white forelock, heterochromia iridis, limb abnormalities (III), Hirschprung's disease (IV)	Bilateral low to mid frequency SNHL: Type 1—60%, Type 2—90% Imaging: inner ear anomalies, especially of posterior semicircular canal (26%)	
Usher	AR: USH1/USH2 50% deaf-blind population in US	Retinitis pigmentosa (RP); Type 1 childhood onset with vestibular dysfunction; Type 2 progressive adolescent onset RP; Type 3 onset variable + progressive	SNHL: Type 1 severe/profound at birth, vestibular imbalance at birth; Type 2 mild/moderate at birth, progressive, no vestibular imbalance; Type 3 progressive, late onset vestibular imbalance	Fundoscopic examination, Electroretinography, Vestibular testing
Pendred	Most common SNHL AR: SLC26A4	Euthyroid goiter in older children	Mild to moderate, fluctuating, often asymmetric SNHL Imaging: inner ear anomaly (100%), enlarged vestibular aqueduct (80%)	Thyroid ultrasound, Thyroid function
Jervell and Lange–Nielsen	AR: KVLQT1, KCNE1	"Seizures"/syncope or sudden death	Severe to profound bilateral SNHL	EKG: prolonged QTc
Alport	X-linked: COL4A	Glomerulonephritis, ocular abnormalities i.e. retinopathy	Progressive SNHL	Renal function tests, Renal biopsy

Stickler	AD: COL2A1, COL11A1, COL11A2	Pierre Robin sequence (micrognathia, glossoptosis, possible cleft palate), myopia, cataracts, retinal detachment in 80%, joint hypermobility, premature arthropathy	Mild to progressive SNHL in 80%, Significant SNHL or Mixed in 15% CHL due to eustachian tube dysfunction ± ossicular anomalies	Fundoscopy, vision testing, airway evaluation
Branchio-oto-renal	AD: EYA6, SIX1, SIX5	Branchial remnants, External ear (atresia/microtia), middle ear (ossicular) and inner ear anomalies, Renal anatomic or functional anomalies	CHL, MHL or SNHL	Renal function tests, Renal ultrasound
CHARGE association	AD: CHD7	Coloboma, Cardiac anomalies, Choanal atresia, Growth retardation, Genital hypoplasia, Ear defects (outer, middle, or inner ear), hearing loss	CHL, MHL, SNHL	Ophthalmology, Cardiology, Endocrinology, Neurology, Vestibular
Craniosynostosis	AD: Apert FGFR2, Crouzon FGFR2/FGFR3, Pfeiffer FGFR1/FGFR2	Craniosynostosis, hypoplastic maxilla Apert: syndactyly, frontal prominence, hypertelorism, saddle nose Crouzon: first branchial arch abnormalities, exophthalmos, beak nose, strabismus, mandibular prognathism Pfeiffer: tower skull	CHL, SNHL—eustachian tube dysfunction Imaging: ossicular and inner ear abnormalities	Craniofacial/Plastic Surgery, Neurosurgery
Microtia/atresia	Syndromic/Nonsyndromic	Treacher Collins, Nager, CHARGE, Miller	CHL, MHL; Imaging: external and middle ear abnormalities	Renal ultrasound

CHL conductive hearing loss, *SNHL* sensorineural hearing loss, *MHL* mixed hearing loss

with de novo mutations, as chromosomal abnormalities or as the result of an intrauterine insult to the developing fetus. The origin of hearing loss is diverse but most often relates to malformation or incomplete partition of the cochlea.

5 Environmental Causes for Hearing Loss

Hearing loss in a young child can be caused by a variety of etiologies from dry occluding ear wax or a conveniently stored foreign body to life-threatening infections or trauma [14]. Of the preventable causes of childhood hearing loss, the World Health Organization attributes 31% to infections, 17% to postnatal birth complications, 4% to use of ototoxic medications such as aminoglycosides by pregnant mothers and infants, and 8% to other causes [15]. Hearing loss occurs in 1.2–7.5% of infants in neonatal intensive care units (NICUs) [8, 16]. The Joint Committee on Infant Hearing (JCIH) enumerates the high-risk criteria for hearing loss in newborns and provides recommendations for management (Table 2).

5.1 Congenital Cytomegalovirus Infection

Congenital CMV (cCMV) infection is the most common cause of progressive nonhereditary congenital hearing loss. It is estimated that cCMV infection accounts for about 13–22% of all cases of neonatal sensorineural or mixed hearing loss [17–19].

Table 2 Environmental risk factors associated with neonatal hearing loss [8]

• Family history of childhood congenital hearing loss
• Congenital infections—TORCHeS (Toxoplasmosis, Rubella, Cytomegalovirus, Herpes and Syphilis), Zika virus
• Craniofacial anomalies, including morphological abnormalities of the pinna, ear canal, nose, and throat
• Birth weight less than 1500 g
• Prolonged NICU stay or prematurity
– ECMO
– Mechanical ventilation >5 days
– Exposure to ototoxic medications (aminoglycosides or loop diuretics)
– Hyperbilirubinemia requiring exchange transfusion
• Culture positive postnatal meningitis including viral or bacterial meningitis
• APGAR scores of 0–4 at 1 min or 0–6 at 5 min
• Neurodegenerative disease or sensorimotor neuropathies
• Chemotherapy

Whether it is primary or reinfection maternal CMV, first trimester infections are associated with SNHL. Though 90% of those infected congenitally are asymptomatic at birth, 22–65% of symptomatic children and 6–23% of asymptomatic children will have hearing loss following cCMV infection, with more than half the patients born with normal hearing developing late onset hearing loss. Hearing loss can present as bilateral or unilateral, progressive or fluctuating and range from mild to profound, often resulting in missed diagnosis at newborn hearing screen. Delayed diagnosis in early educational years often results from reliance on school testing. High index of suspicion is warranted in patients with normal hearing with history of cCMV infection and early referral to an audiologist for screening audiograms should be considered.

5.2 Childhood Infections

Otitis media is the most common cause of hearing loss in the developed nations [20–22]. Eustachian tube dysfunction and recurrent acute or chronic otitis media with effusion (OME) are common causes of temporary conductive hearing loss in children which can progress to permanent damage [23]. By 5 years of age, 50–90% of children have developed at least one episode of OME with 2.2 million children diagnosed annually in the United States [21, 22, 24, 25]. Otitis media consists of a spectrum of disorders ranging from simple uncomplicated effusion to suppurative otitis media with a perforated tympanic membrane which can progress to retraction pocket, ossicular erosion, or cholesteatoma. The risk of developing sensorineural hearing loss in adulthood is particularly high in children with chronic otitis media with cholesteatoma secondary to labyrinthitis, or erosion into the cochlea or the semicircular canals. Untreated otitis media, particularly with cholesteatoma, in childhood can result in long term development of hearing loss or dizziness in adulthood - which are thought to be the residual effects of inflammatory mediators [26–29].

Bacterial meningitis predisposes a child to progressive sensorineural hearing loss, especially if caused by *Streptococcus pneumoniae*. In these patients, hearing rehabilitation in the form of cochlear implantation is considered an emergency as the infection often results in labyrinthitis ossificans (ossification of the cochlear vestibular apparatus). This can occur within a few weeks of the initial infection and prognosis for hearing is poor if the patient does not expeditiously receive cochlear implantation.

Irritation to the external ear canal via trauma, attempts at removal of a foreign body or skin conditions like eczema and psoriasis can predispose a child to episodes of otitis externa or “swimmer’s ear” from bacterial and fungal pathogens. This may cause a temporary conductive hearing loss from inflammation of the canal wall and presence of debris.

5.3 Trauma

Trauma can result in conductive, mixed, or sensorineural hearing loss depending on location and type of injury to the temporal bone. Direct trauma to the ear, such as from cotton tipped applicators, results in over 12,000 visits to the emergency room annually in the United States and remains the highest cause of traumatic tympanic membrane perforation [30]. Direct injury to the middle ear can cause ossicular discontinuity or subsequent fixation with scarring. Tympanic membrane perforations can also result from barotrauma, thermal injuries from slag or lightning, or iatrogenic causes (following removal of pressure equalizing tubes).

More significant mechanisms of injury may lead to temporal bone fractures and can damage the cochlea, injure the cochlear nerve, or cause a perilymphatic fistula, which often results in severe to profound sensorineural hearing loss [31]. Concussive injuries to the temporal bone without fracture may also result in temporary or permanent sensorineural hearing loss [32]. Trauma to the cochlea can also be in the form of noise exposure, damaging the outer hair cells resulting in permanent loss [33]. Hearing loss either presents at the time of injury or may be delayed.

5.4 Ototoxins

Ototoxic medications include loop diuretics, antineoplastic agents (particularly cisplatin), and aminoglycosides. Various mitochondrial variants confer increased susceptibility to aminoglycoside ototoxic effects [34]. Salicylates and macrolides, including azithromycin, can cause reversible hearing loss.

5.5 Auditory Neuropathy Spectrum Disorders

Auditory neuropathy spectrum disorder (ANSD) refers to a group of disorders with retained otoacoustic emissions or cochlear microphonics with an abnormal or absent brainstem response (ABR). Due to the lack of synchronous transmission of sound by the nerve, there will be normal hearing on standard audiometry testing, however, speech perception remains poor, with resultant difficulties in language and speech comprehension. In newborns, there will be presence of otoacoustic emissions (OAEs); however, there will be hearing loss on ABR. Initially thought to be rare, it accounts for 10–15% of children with severe-to-profound sensorineural hearing loss [35]. ANSD is postulated to be from dyssynchronous neural discharges of the inner hair cells and the auditory nerve fibers, as well as a dysfunction of these structures themselves, hence the term auditory neuropathy or auditory dyssynchrony.

High risk neonates (Table 2) are most prone to ANSD and require close monitoring of speech and language skills even if they have good pure tone thresholds as they may still have very poor speech perception [8]. The suspected etiology is varied from environmental (i.e., auditory trauma) to congenital absence or hypoplasia of the auditory nerve, cerebellopontine angle lesion or multiple sclerosis [36, 37].

Hereditary neurodegenerative diseases such as Friedreich's Ataxia and Charcot–Marie-tooth disease can cause ANSD and 40–50% of patients have a genetic basis. ANSD is also associated with autosomal recessive inheritance mutations of the otoferlin gene which is essential for normal inner hair cell function.

5.6 Autoimmune-Related Hearing Loss

Autoimmune-related progressive hearing loss can be due to primary immune dysfunction localized to the inner ear, genetic (NLRP3 gene) or systemic autoimmune disorders such as Cogan syndrome (interstitial keratitis, progressive hearing loss, and vestibular dysfunction) [38, 39]. Autoinflammatory genes, such as the *NLRP3* may also be associated with syndromic and nonsyndromic hearing loss [39].

5.7 Neoplasms

Tumors of the external and middle ear spaces are rare, and include congenital vascular and lymphatic malformations, congenital cholesteatoma, Langerhans Cell Histiocytosis, nerve sheath tumors, and rhabdomyosarcoma.

6 Diagnostic Approach

6.1 History

A thorough history taking, physical examination and audiometric evaluation can assist in distinguishing conductive from sensorineural and mixed hearing losses and can aid in investigation of the etiology of the hearing loss [8, 40].

Of special attention is the perinatal history, family history and social history (Table 2). Over 12% of patients with hearing loss will identify a family history of hearing loss. Any suggestion of cardiac symptoms or renal symptoms necessitates prompt evaluation. History and frequency of ear infections and associated symptoms, meningitis or trauma should be elicited (Fig. 4).

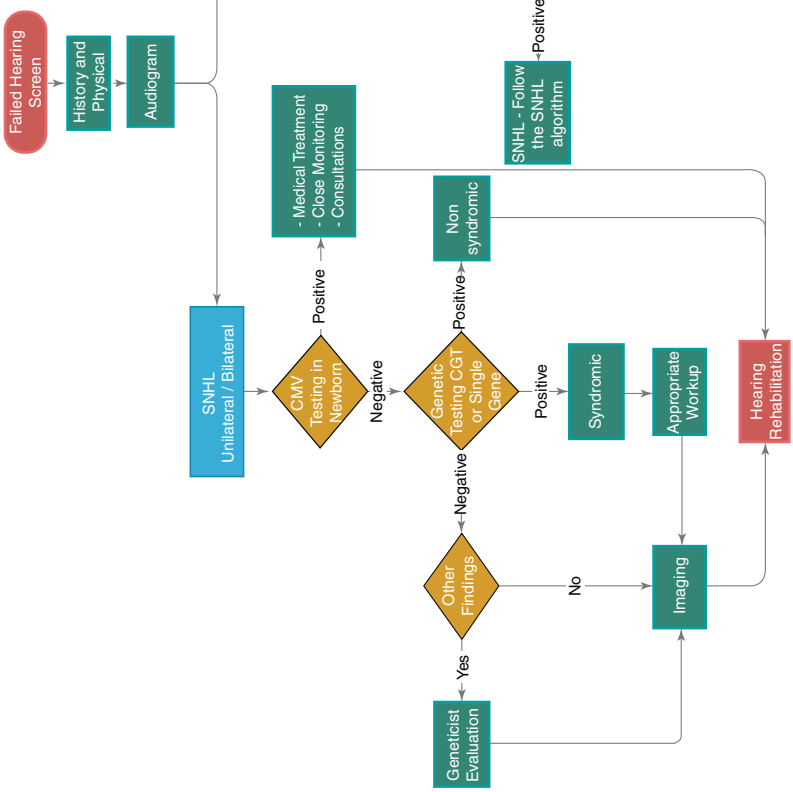

Fig. 4 Approach to failed hearing screen. *SNHL* sensorineural hearing loss, *CHL* conductive hearing loss, *CMV* cytomegalovirus, *CGT* comprehensive genetic testing

6.2 Physical Examination

6.2.1 General Examination

Physical examination should include a comprehensive head and neck examination with particular attention to any facial or structural asymmetry or abnormalities including thorough external ear and otoscopic, neck, and thyroid examination. Identification of other co-existent abnormalities such as visual issues, cognitive issues or developmental delays, or dysmorphic features assists in identifying syndromes that may be associated with hearing loss and directs further work-up and genetic testing (Table 1).

6.2.2 Neurologic Examination

In addition to a complete history, a comprehensive examination must include cranial nerves evaluation with extraocular muscle movements, tuning fork examination for hearing, facial examination for asymmetry, and an examination for vestibular dysfunction as tolerated by the age of the patient. The tuning fork examination can provide insight into the presence of a conductive and/or a sensorineural hearing loss as well as the magnitude of the loss. Rinne test is performed with 512 Hz steel tuning fork, where the vibrating tuning fork is placed on the mastoid bone posteriorly and when the sound is no longer heard, it is placed in front of the external auditory canal. It is considered positive if the air conduction is better than the bone conduction. Weber test is performed with a vibrating 512 Hz tuning fork placed on the forehead to identify the ear the sound lateralizes to. Both should be used in conjunction to rule out false negative Rinne's test (Table 3). While Rinne can be performed with 256 Hz and 1024 Hz for quantifying hearing loss, it does not correlate with audiometry, and hence is not routinely used.

6.2.3 Evaluation

In the pediatric population, additional testing is often necessary when evaluating hearing loss. All patients must undergo audiometry. Once a hearing loss is established additional testing such as genetic testing, imaging, ophthalmologic

Table 3 Interpretation of tuning fork tests

Hearing loss	Rinne test (Conduction)	Weber test (Lateralization)
Normal	AC>BC	Equal on both sides
Sensorineural hearing loss	AC>BC	Opposite side
Conductive hearing loss	BC >AC	Same side

AC air conduction, *BC* bone conduction

examination, laboratory tests, and electrocardiography may be indicated (Table 1). This, in turn, is vital to comprehensive patient evaluation and treatment.

6.2.4 Audiologic Evaluation

Comprehensive audiometric evaluation is accomplished through various tests dependent on a patient's age and cognitive ability. It can be challenging to obtain reliable ear specific data in young children. Otoacoustic emissions (OAE) are used to assess the health and functionality of the cochlear outer hair cells and are often used as a newborn hearing screen. Tympanometry investigates the compliance of the tympanic membrane to pressure and provides information on the middle ear space (Fig. 5a).

Behavioral audiometric evaluation methods to assess the degree of hearing loss exist based on a patient's age and cognition. Visual reinforcement audiometry (VRA) is used for children from 6 months to 3 years. For children older than 2 years, conditioned play audiometry (CPA) may be considered. However, since they provide limited ear specific data, auditory brainstem response (ABR) or auditory steady state response (ASSR), are used in these younger patients. Conventional pure tone audiometry (PTA) is used in older patients to obtain ear specific data and to assess the degree of hearing loss (Fig. 5b).

For universal NBHS, both OAEs and automated ABRs can be used, but the latter are preferred [8]. OAEs reflect the status of the peripheral auditory system extending to the cochlear outer hair cells. In contrast, ABR measurements are obtained from surface electrodes that record neural activity generated in the cochlea, auditory nerve, and brainstem in response to acoustic stimuli delivered via an earphone and

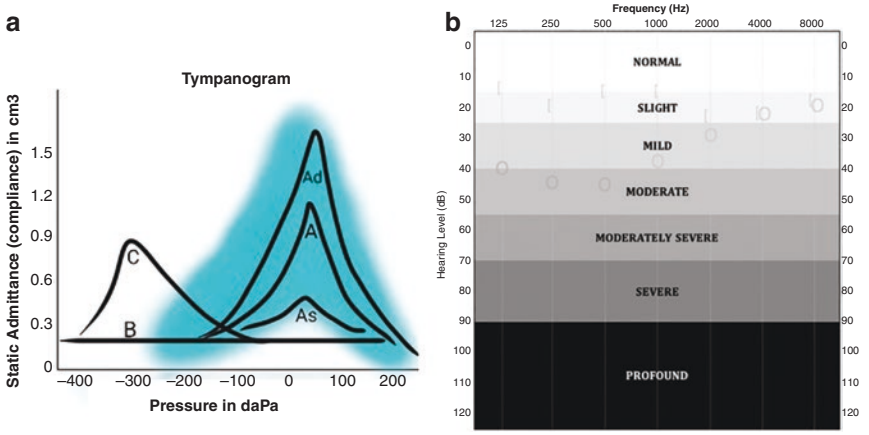

Fig. 5 (**a**) Tympanometry. Type A—normal (As with reduced compliance/ossicular fixation, Ad with high compliance possibly from ossicular discontinuity), Type B—flat in otitis media (low volume) or perforation (large volume), Type C—restrictive negative pressure. (**b**) Audiogram can provide insight into the type (conductive, sensorineural or mixed) and degree of hearing loss

provide ear-specific data. Automated ABR measurements reflect the status of the peripheral auditory system, the eighth nerve, and the brainstem auditory pathway.

Comprehensive vestibular testing is warranted in patients with hearing loss suspected due to Usher's syndrome, CHARGE association, or cCMV infection.

6.2.5 Laboratory Testing

Neonates who fail universal hearing screen at birth should undergo urine and salivary PCR for CMV within the first 3 weeks of life [41, 42]. Salivary studies show both high sensitivity and specificity. Retrospective diagnosis of cCMV can be made through CMV PCR studies on a newborn dried blood spot card if available. While this has a low sensitivity (up to 10%) it can avoid further workup of hearing loss and enable prompt treatment if positive [17–19].

Comprehensive genetic testing (CGT) is high yield for diagnosis in children with SNHL, and some instances of conductive and mixed hearing loss. The diagnostic rate is approximately 40–65% and is best served by referral to a pediatric geneticist. The utility is for prognosis, identifying associated symptoms, family planning and treatment planning. Single gene testing for GJB2 and GJB6 can be considered if CGT and geneticist are not available.

CGT includes nonsyndromic and syndromic mutations. Next-generation sequencing (NGS) combines targeted genomic enrichment and massively parallel sequencing (MPS) to capture and sequence all exons of all genes implicated in nonsyndromic hearing loss with less effort and at lower cost than previous genetic testing. Sensitivity is 100% and specificity is 99.9%.

6.2.6 Imaging Studies

Computed tomography (CT) and magnetic resonance imaging (MRI) are both implemented in the evaluation of unilateral or bilateral hearing loss [43, 44]. CT temporal bone provides bony anatomy, insight into middle and inner ear anomalies and surgical planning. It is low cost and often can be performed without anesthesia. Limitations include exposure to ionizing radiation and limited evaluation of cochlear nerve deficiencies [45]. The most common inner ear malformation seen in children with nonsyndromic hearing loss is vestibular aqueduct enlargement (10–15%) [46].

MRI of the brain evaluates for the presence of cochlear nerve, inner ear anomalies and growths in the cerebellopontine angle. Limitations include need for general anesthesia in younger patients. Microcephaly or intracranial calcification in patients with isolated hearing loss may suggest a diagnosis of cCMV and is associated with poor neurological outcome and risk of progressive SNHL [47–49]. In patients who are candidates for cochlear implants, the preoperative MRI can be crucial due to the artifacts from the implant in all future imaging studies of the brain.

Syndromic hearing loss often have specific findings on imaging studies (Table 1) [50, 51]. Dual-modality imaging technique with high-resolution CT and MRI

identifies a substantially larger number of abnormalities in children being evaluated for cochlear implantation than either technique alone, however, at additional cost with debatable additional benefits [44]. While MRI is the preferred imaging study for SNHL and CT temporal bone is preferred to evaluate conductive loss, the ideal imaging modality for hearing loss is both controversial and case specific and early referral to the otolaryngologist is preferred for decision-making.

6.2.7 Additional Testing

Renal ultrasound, thyroid ultrasound, thyroid function tests, EKG, urine, and blood tests can be considered in select cases based on suspected etiology for hearing loss (Table 1).

6.2.8 Consultations

Comprehensive ophthalmologic evaluation is warranted for all children with SNHL with to a 2–3-fold increase in ocular abnormalities ranging from refractive and non-refractive errors to retinitis pigmentosa. Early identification of auditory and visual disability aids in management since hearing impaired children depend on visual cues for social interactions and communication [52–59].

7 Treatment/Management

7.1 Conductive Hearing Loss and Mixed Hearing Loss

The removal of wax or foreign bodies from the external canal should be performed by an experienced provider to minimize risks of trauma to both the canal and tympanic membrane which may result in bleeding, infection, tympanic membrane perforation, or ossicular disruption with potential need for further surgical intervention [14].

Otitis externa should be treated with ototopical antibiotic with placement of a wick. Some infections including fungal will require repeated debridement by an otolaryngologist.

Otitis media treatment is dependent on the age of a child, speech development, and severity of the symptoms. Uncomplicated bilateral effusions can be observed for 3 months. Recurrent infections with fever, purulence and persistent effusions beyond 3–6 months warrant surgical placement of ventilating tubes. Patients deemed to be at higher risk for eustachian tube dysfunction and hence OME (those with craniofacial anomalies including Down syndrome and cleft palate), as well as for permanent hearing loss, speech and language impairment, blindness or

developmental delays should be promptly referred to an otolaryngologist for further management [21, 22]. Middle ear exploration and surgical intervention is recommended for tympanic membrane perforation, cholesteatoma, and for biopsy to guide further treatment of external and middle ear tumors.

Aural atresia (unilateral or bilateral) requires multidisciplinary management with surgical hearing rehabilitation using bone conduction hearing device or atresioplasty as indicated [60, 61].

7.1.1 Mixed Hearing Loss

After diagnosis and treatment of a conductive loss, the audiogram should be repeated to rule out persisting conductive or co-existing sensorineural hearing loss. Careful monitoring of otitis media is warranted in patients with known mixed or SNHL, craniofacial anomalies, syndromes or developmental delays as hearing loss may present suddenly in adolescence or be slowly progressive and go unnoticed. Prompt treatment with definitive resolution of OME would avoid delaying the fitting of an amplification device.

7.2 Sensorineural Hearing Loss

A multidisciplinary approach is important in the evaluation and treatment of children with SNHL to ensure that their medical, educational, and social needs are met. The team consists of an otolaryngologist, audiologist, speech language pathologist or auditory verbal therapist and, if available, neuropsychologist and social worker.

With Universal Newborn Hearing Screening, all newborns who failed screens must be referred by 1 month of age for comprehensive audiologic testing, must ideally obtain a definitive diagnosis by 3 months of age, and initiate rehabilitative services by 6 months of age, known as the 1-3-6 as benchmarked by Joint Commission on Infant Hearing (JCIH) with the new goals being 1-2-3 [8]. Infants may vocalize up to 6–8 months of age in spite of hearing loss which can falsely reassure parents in light of a failed hearing screen. Appropriate parent counseling is necessary to ensure timely follow up for repeat testing.

Early identification of hearing loss allows for prompt initiation of parent-child programs such as Early Childhood Intervention providing hearing rehabilitation and intensive speech-language therapy allowing for mainstream schooling. Frequency-modulated (FM) systems are often used in classroom settings in older children, along with preferential seating.

Hearing rehabilitation should always involve binaural hearing and listening as this is associated with improved communication skills and school performance. Patients with good speech perception, with up to a moderate hearing loss can have good hearing benefit with a conventional hearing aid or bone anchored hearing device. For patients with poor speech perception or worse magnitude of hearing

loss, either bimodal (hearing aid with cochlear implant) or bilateral cochlear implants (CI) are recommended. CI can be placed safely in infants as young as 9 months [62]. Early device placement shows improved spoken language and academic performance [63]. To obtain maximum benefit from the CI, the patients need consistent and prolonged habilitation speech and language therapy by a trained therapist.

Hearing loss that is identified early, in patients with cCMV infection, can be medically treated to prevent progression of hearing deterioration. For this reason, asymptomatic and symptomatic patients with CMV infection should be closely followed with audiologic assessment every 3–6 months for the first year, every 6 months until 3 years and then annually until 6 years of age, regardless of the absence or severity of the initial loss to monitor the hearing status for deterioration [64].

Ganciclovir therapy begun in the neonatal period in neonates with cCMV infection halts hearing deterioration; however, treatment is currently indicated only for symptomatic cCMV infection with central nervous system involvement to improve hearing and neurodevelopmental outcomes [65]. Treatment with valganciclovir may improve hearing outcomes in children with asymptomatic cCMV infection, where hearing loss is the only symptom, but this is not the standard of care at present [66, 67].

Auditory Neuropathy, a heterogeneous spectrum of disorders, poses challenges to hearing rehabilitation with unpredictable outcomes. Synchronous electric stimulation by cochlear implants is postulated to overcome the dyssynchrony of ANSD where conventional amplification by hearing aids fails. The current recommendation is a trial of hearing aids with close monitoring and consider candidacy for cochlear implantation if there is no benefit with hearing aids. The results are not as encouraging in patients with severe cognitive disability, CNS pathology or absent cochlear nerves on MRI.

While spoken language is always the preferred mode for habilitation, a thorough informative discussion and parent involved decision-making should be pursued when sign language is offered as the communication modality.

8 Prognosis/Outcomes

Infants and children with mild to profound permanent hearing loss identified in the first 6 months of life and provided with prompt appropriate intervention have significantly better outcomes in language and social-emotional development compared to infants and children with delayed identification of hearing loss [8]. Children enrolled in early intervention programs within the first year of life are shown to develop language that is within the normal range by 5 years of age [68, 69].

The combination of newborn hearing screening programs, advances in cochlear implant and hearing aid technology, and legislative policy changes allow more than 75% of children with hearing loss to attend public schools and be mainstreamed with normal-hearing students.

Otitis media may be associated with hearing loss, speech and language disorders, balance disorders, academic struggles with poor performance and socio-behavioral dysfunction with poor quality of life [70]. Damage to the tympanic membrane or ossicles or progression to cholesteatoma results in need for surgical intervention and auditory rehabilitation. Progression to permanent hearing loss can occur in 2–35 people in 10,000 patients [22, 71]. Prompt intervention for otitis media, especially in patients at risk for poor language development or future hearing or sensory deficits, with placement of ventilation tubes results in improvement in speech and language skills [72, 73]. The effect of otitis media with effusion (OME) is greater for infants with sensorineural hearing loss than for those with normal cochlear function. Interim conductive hearing loss due to otitis media with effusion exacerbates pre-existing hearing loss. Though transient, long duration otitis media with effusion requires readjusting hearing aid amplifications with loss of auditory cues.

Thirty to forty percent of children with confirmed permanent hearing loss demonstrate other developmental delays, especially those with cCMV infection. Such children often require modifications of therapy and interventions with slow progress or inability to reach all auditory-oral communication goals. Early intervention results in higher language skills. Even in patients with good language skills, a high index of suspicion and close monitoring for working memory, executive functions, academic struggles and other such developmental delays should be maintained.

Early cochlear implantation is an appropriate treatment option in children with qualifying syndromic hearing loss [74–76]. Two main factors are often considered critical for better language and speech development—(1) Early hearing rehabilitation with implantation before 18 months of age, (2) Enriching parental involvement along with specialized therapists early in life. In syndromes with a component of cognitive delay, neuropsychological evaluation helps to differentiate hearing loss from cognitive impairment. Developmental delays impact hearing and hence speech and language outcomes. Cochlear implantation in patients with auditory neuropathy spectrum disorder show variable results depending on etiology of the disorder (anoxia, genetic mutations, and cochlear nerve deficiencies) [35, 77–79].

Half of children with cochlear implants, and 17–48% of children with unilateral hearing loss have impaired vestibular function hindering participation in normal childhood activities [80, 81]. While unilateral hearing loss was not rehabilitated in the past, binaural hearing has been consistently shown to be beneficial over unilateral hearing [82, 83]. Loss of higher function processing of sound in the brain with unilateral hearing has been associated with poor academic and school performance [84]. Unilateral hearing loss is associated with worse speech-language scores in children with a known right ear advantage of improved mental tasks when information is presented to the right ear [60, 85–87]. Right ear advantage refers to the inherent asymmetry that is noted during audiology testing with preferential use of the right ear during conversational language.

Gene therapy, with adeno-associated vectors for OTOF (otoferlin), though in the preclinical trial, has shown promising results in murine models [88]. The difficulty

in accessing the inner ear due to the bony cochlea, with risk of damage to the hair cells poses a translational barrier.

9 When to Refer

The initiation of early intervention services through an otolaryngologist, audiologist and auditory verbal or speech language pathologist should begin as soon as possible after diagnosis of a hearing loss in patients of all ages. Even when the hearing status is not determined to be the primary disability, the family and child should have access to counseling and intervention from the multidisciplinary team [89].

Urgent Referrals to ENT Specialists

- All neonates or children with failed hearing screen, especially children with suspected severe to profound hearing loss
  - Saliva and urine for PCR testing for CMV is mandatory prior to 3 weeks of age
- *Streptococcus pneumoniae* Meningitis
- Facial nerve or vestibular dysfunction

Routine Referrals to ENT Specialists

- Neonates with high risk features regardless of newborn hearing screen results
- Delayed onset unilateral or bilateral hearing loss of all types and degrees, regardless of suspected etiology
- Speech and language delay
- Recurrent Otitis externa, recurrent Otitis media, suspected cholesteatoma
- Otitic trauma including perforations, foreign body or temporal bone trauma
- Children with known syndrome causing craniofacial anomaly or hearing loss
- Children undergoing genetic evaluation for comorbidities known to be associated with hearing loss

10 Clinical Pearls/Key Points

- Newborn hearing screen should include automated auditory brainstem response with or without otoacoustic emissions to avoid missing auditory neuropathy.
- All newborns with failed hearing screens must be referred to an audiologist and otolaryngologist for definitive hearing test and diagnosis by 1–3 months of age, and for early intervention by 3–6 months of age.
- Children with severe to profound hearing loss should be referred to the cochlear implant team by 6 months of age, to discuss options including cochlear implantation before the neurobiological window of opportunity for language development closes.

- Congenital cytomegalovirus infection is a preventable risk factor for hearing loss among children. All newborns with failed hearing screen should get a saliva CMV PCR within the first 3 weeks of life.
- Half of all newborns with hearing loss have a genetic cause and 70% are the result of nonsyndromic genetic mutations. Next generation sequencing is a low cost test with high yield.
- High risk newborns should be monitored for progressive hearing loss or speech and language delay through referral to an otolaryngologist and audiologist.
- Ideal imaging study is controversial and chosen modality should be tailored based on the type of hearing loss and anticipated intervention.
- Early identification of permanent hearing loss, and appropriate interventions including hearing rehabilitation with hearing aid or cochlear implants, along with early auditory verbal therapy is the key to achieving good language and socio-emotional outcomes.
- Binaural hearing is necessary for long-term intellectual, speech and language, social, and communicative skills of the growing child.

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References

1. CDC. Summary of 2018 National CDC EHDI data: CDC; 2018. https://www.cdc.gov/ncbddd/hearingloss/2018-data/documents/01_2018-HSFS-Data-Summary.pdf.
2. Korver AM, Konings S, Dekker FW, Beers M, Wever CC, Frijns JH, et al. Newborn hearing screening vs later hearing screening and developmental outcomes in children with permanent childhood hearing impairment. JAMA. 2010;304(15):1701–8.
3. Carney AE, Moeller MP. Treatment efficacy: hearing loss in children. J Speech Lang Hear Res. 1998;41(1):S61–84.
4. Morton CC, Nance WE. Newborn hearing screening—a silent revolution. N Engl J Med. 2006;354(20):2151–64.
5. Van Naarden BK, Christensen D, Doernberg N, Schieve L, Rice C, Wiggins L, et al. Trends in the prevalence of autism spectrum disorder, cerebral palsy, hearing Loss, intellectual disability, and vision impairment, Metropolitan Atlanta, 1991–2010. PLoS One. 2015;10(4):e0124120.
6. Wang J, Sung V, Carew P, Burt RA, Liu M, Wang Y, et al. Prevalence of childhood hearing loss and secular trends: a systematic review and meta-analysis. Acad Pediatr. 2019;19(5):504–14.
7. Van Naarden BK, Yeargin-Allsopp M, Lollar D. Activity limitations among young adults with developmental disabilities: a population-based follow-up study. Res Dev Disabil. 2009;30(1):179–91.
8. Year 2007 position statement: principles and guidelines for early hearing detection and intervention programs. Pediatrics. 2007;120(4):898–921.
9. Inagaki M, Tomita Y, Takashima S, Ohtani K, Andoh G, Takeshita K. Functional and morphometrical maturation of the brainstem auditory pathway. Brain Dev. 1987;9(6):597–601.

10. Chang EW, Cheng JT, Röösli C, Kobler JB, Rosowski JJ, Yun SH. Simultaneous 3D imaging of sound-induced motions of the tympanic membrane and middle ear ossicles. Hear Res. 2013;304:49–56.
11. Luquetti DV, Heike CL, Hing AV, Cunningham ML, Cox TC. Microtia: epidemiology and genetics. Am J Med Genet A. 2012;158A(1):124–39.
12. Loss HH. Hereditary hearing loss homepage 2021. https://hereditaryhearingloss.org/.
13. Koenig JL, Amoils M, Grade MM, Chang KW, Truong MT. Renal ultrasound abnormalities in children with syndromic and non-syndromic microtia. Int J Pediatr Otorhinolaryngol. 2018;113:173–6.
14. Schwartz SR, Magit AE, Rosenfeld RM, Ballachanda BB, Hackell JM, Krouse HJ, et al. Clinical practice guideline (update): earwax (Cerumen impaction). Otolaryngol Head Neck Surg. 2017;156(1_suppl):S1–S29.
15. World Health Organization. Childhood hearing loss: strategies for prevention and care; 2016. https://www.who.int/docs/default-source/imported2/childhood-hearing-loss%2D%2Dstrategies-for-prevention-and-care.pdf?sfvrsn=cbbbb3cc_0.
16. Korver AM, Smith RJ, Van Camp G, Schleiss MR, Bitner-Glindzicz MA, Lustig LR, et al. Congenital hearing loss. Nat Rev Dis Primers. 2017;3:16094.
17. Fowler KB, Boppana SB. Congenital cytomegalovirus (CMV) infection and hearing deficit. J Clin Virol. 2006;35(2):226–31.
18. Fowler KB, Dahle AJ, Boppana SB, Pass RF. Newborn hearing screening: will children with hearing loss caused by congenital cytomegalovirus infection be missed? J Pediatr. 1999;135(1):60–4.
19. Fowler KB, McCollister FP, Dahle AJ, Boppana S, Britt WJ, Pass RF. Progressive and fluctuating sensorineural hearing loss in children with asymptomatic congenital cytomegalovirus infection. J Pediatr. 1997;130(4):624–30.
20. Qureishi A, Lee Y, Belfield K, Birchall JP, Daniel M. Update on otitis media—prevention and treatment. Infect Drug Resist. 2014;7:15–24.
21. Rosenfeld RM, Culpepper L, Doyle KJ, Grundfast KM, Hoberman A, Kenna MA, et al. Clinical practice guideline: otitis media with effusion. Otolaryngol Head Neck Surg. 2004;130(5 Suppl):S95–118.
22. Rosenfeld RM, Shin JJ, Schwartz SR, Coggins R, Gagnon L, Hackell JM, et al. Clinical practice guideline: otitis media with effusion (update). Otolaryngol Head Neck Surg. 2016;154(1 Suppl):S1–S41.
23. Jung TT, Alper CM, Hellstrom SO, Hunter LL, Casselbrant ML, Groth A, et al. Panel 8: complications and sequelae. Otolaryngol Head Neck Surg. 2013;148(4 Suppl):E122–43.
24. Casselbrant ML, Brostoff LM, Cantekin EI, Flaherty MR, Doyle WJ, Bluestone CD, et al. Otitis media with effusion in preschool children. Laryngoscope. 1985;95(4):428–36.
25. Zielhuis GA, Rach GH, van den Broek P. Screening for otitis media with effusion in preschool children. Lancet. 1989;1(8633):311–4.
26. Aarhus L, Tambs K, Hoffman HJ, Engdahl B. Childhood otitis media is associated with dizziness in adulthood: the HUNT cohort study. Eur Arch Otorhinolaryngol. 2016;273(8):2047–54.
27. Aarhus L, Tambs K, Kvestad E, Engdahl B. Childhood otitis media: a cohort study with 30-year follow-up of hearing (the HUNT study). Ear Hear. 2015;36(3):302–8.
28. Yehudai N, Most T, Luntz M. Risk factors for sensorineural hearing loss in pediatric chronic otitis media. Int J Pediatr Otorhinolaryngol. 2015;79(1):26–30.
29. Soman TB, Krishnamoorthy KS. Paroxysmal non-epileptic events resembling seizures in children with otitis media. Clin Pediatr (Phila). 2005;44(5):437–41.
30. Carniol ET, Bresler A, Shaigany K, Svider P, Baredes S, Eloy JA, et al. Traumatic tympanic membrane perforations diagnosed in emergency departments. JAMA Otolaryngol Head Neck Surg. 2018;144(2):136–9.
31. Kenna MA. Acquired hearing loss in children. Otolaryngol Clin North Am. 2015;48(6):933–53.
32. Ishman SL, Friedland DR. Temporal bone fractures: traditional classification and clinical relevance. Laryngoscope. 2004;114(10):1734–41.

33. Chen JX, Lindeborg M, Herman SD, Ishai R, Knoll RM, Remenschneider A, et al. Systematic review of hearing loss after traumatic brain injury without associated temporal bone fracture. Am J Otolaryngol. 2018;39(3):338–44.
34. Nguyen T, Jeyakumar A. Genetic susceptibility to aminoglycoside ototoxicity. Int J Pediatr Otorhinolaryngol. 2019;120:15–9.
35. Walton J, Gibson WP, Sanli H, Prelog K. Predicting cochlear implant outcomes in children with auditory neuropathy. Otol Neurotol. 2008;29(3):302–9.
36. Manchaiah VK, Zhao F, Danesh AA, Duprey R. The genetic basis of auditory neuropathy spectrum disorder (ANSD). Int J Pediatr Otorhinolaryngol. 2011;75(2):151–8.
37. Sawada S, Mori N, Mount RJ, Harrison RV. Differential vulnerability of inner and outer hair cell systems to chronic mild hypoxia and glutamate ototoxicity: insights into the cause of auditory neuropathy. J Otolaryngol. 2001;30(2):106–14.
38. Maiolino L, Cocuzza S, Conti A, Licciardello L, Serra A, Gallina S. Autoimmune ear disease: clinical and diagnostic relevance in Cogan's Syndrome. Audiol Res. 2017;7(1):162.
39. Nakanishi H, Prakash P, Ito T, Kim HJ, Brewer CC, Harrow D, et al. Genetic hearing loss associated with autoinflammation. Front Neurol. 2020;11:141.
40. Deklerck AN, Acke FR, Janssens S, De Leenheer EM. Etiological approach in patients with unidentified hearing loss. Int J Pediatr Otorhinolaryngol. 2015;79(2):216–22.
41. Greinwald JH Jr, Hartnick CJ. The evaluation of children with sensorineural hearing loss. Arch Otolaryngol Head Neck Surg. 2002;128(1):84–7.
42. Preciado DA, Lim LH, Cohen AP, Madden C, Myer D, Ngo C, et al. A diagnostic paradigm for childhood idiopathic sensorineural hearing loss. Otolaryngol Head Neck Surg. 2004;131(6):804–9.
43. Clemmens CS, Guidi J, Caroff A, Cohn SJ, Brant JA, Laury AM, et al. Unilateral cochlear nerve deficiency in children. Otolaryngol Head Neck Surg. 2013;149(2):318–25.
44. Trimble K, Blaser S, James AL, Papsin BC. Computed tomography and/or magnetic resonance imaging before pediatric cochlear implantation? Developing an investigative strategy. Otol Neurotol. 2007;28(3):317–24.
45. Adunka OF, Jewells V, Buchman CA. Value of computed tomography in the evaluation of children with cochlear nerve deficiency. Otol Neurotol. 2007;28(5):597–604.
46. Arcand P, Desrosiers M, Dubé J, Abela A. The large vestibular aqueduct syndrome and sensorineural hearing loss in the pediatric population. J Otolaryngol. 1991;20(4):247–50.
47. Adunka OF, Roush PA, Teagle HF, Brown CJ, Zdanski CJ, Jewells V, et al. Internal auditory canal morphology in children with cochlear nerve deficiency. Otol Neurotol. 2006;27(6):793–801.
48. Davidson HC. Imaging evaluation of sensorineural hearing loss. Semin Ultrasound CT MR. 2001;22(3):229–49.
49. Parry DA, Booth T, Roland PS. Advantages of magnetic resonance imaging over computed tomography in preoperative evaluation of pediatric cochlear implant candidates. Otol Neurotol. 2005;26(5):976–82.
50. Huang BY, Zdanski C, Castillo M. Pediatric sensorineural hearing loss, part 1: practical aspects for neuroradiologists. AJNR Am J Neuroradiol. 2012;33(2):211–7.
51. Huang BY, Zdanski C, Castillo M. Pediatric sensorineural hearing loss, part 2: syndromic and acquired causes. AJNR Am J Neuroradiol. 2012;33(3):399–406.
52. Armitage IM, Burke JP, Buffin JT. Visual impairment in severe and profound sensorineural deafness. Arch Dis Child. 1995;73(1):53–6.
53. Guy R, Nicholson J, Pannu SS, Holden R. A clinical evaluation of ophthalmic assessment in children with sensori-neural deafness. Child Care Health Dev. 2003;29(5):377–84.
54. Leguire LE, Fillman RD, Fishman DR, Bremer DL, Rogers GL. A prospective study of ocular abnormalities in hearing impaired and deaf students. Ear Nose Throat J. 1992;71(12):643–6, 651.
55. Mafong DD, Pletcher SD, Hoyt C, Lalwani AK. Ocular findings in children with congenital sensorineural hearing loss. Arch Otolaryngol Head Neck Surg. 2002;128(11):1303–6.
56. Nikolopoulos TP, Lioumi D, Stamataki S, O'Donoghue GM. Evidence-based overview of ophthalmic disorders in deaf children: a literature update. Otol Neurotol. 2006;27(2 Suppl 1):S1–24, discussion S0.

57. Regenbogen L, Godel V. Ocular deficiencies in deaf children. J Pediatr Ophthalmol Strabismus. 1985;22(6):231–3.
58. Sharma A, Ruscetta MN, Chi DH. Ophthalmologic findings in children with sensorineural hearing loss. Arch Otolaryngol Head Neck Surg. 2009;135(2):119–23.
59. Siatkowski RM, Flynn JT, Hodges AV, Balkany TJ. Ophthalmologic abnormalities in the pediatric cochlear implant population. Am J Ophthalmol. 1994;118(1):70–6.
60. Jensen DR, Grames LM, Lieu JE. Effects of aural atresia on speech development and learning: retrospective analysis from a multidisciplinary craniofacial clinic. JAMA Otolaryngol Head Neck Surg. 2013;139(8):797–802.
61. Kesser BW, Krook K, Gray LC. Impact of unilateral conductive hearing loss due to aural atresia on academic performance in children. Laryngoscope. 2013;123(9):2270–5.
62. Cosetti M, Roland JT Jr. Cochlear implantation in the very young child: issues unique to the under-1 population. Trends Amplif. 2010;14(1):46–57.
63. Lieu JEC, Kenna M, Anne S, Davidson L. Hearing loss in children: a review. JAMA. 2020;324(21):2195–205.
64. Society NDCs. Congenital cytomegalovirus and deafness. 2015. https://www.ndcs.org.uk/documents-and-resources/congenital-cytomegalovirus-cmv-and-deafness/.
65. Kimberlin DW, Lin CY, Sánchez PJ, Demmler GJ, Dankner W, Shelton M, et al. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. J Pediatr. 2003;143(1):16–25.
66. Chiopris G, Veronese P, Cusenza F, Procaccianti M, Perrone S, Daccò V, et al. Congenital cytomegalovirus infection: update on diagnosis and treatment. Microorganisms. 2020;8(10):1516.
67. Kadambari S, Williams EJ, Luck S, Griffiths PD, Sharland M. Evidence based management guidelines for the detection and treatment of congenital CMV. Early Hum Dev. 2011;87(11):723–8.
68. Calderon R, Naidu S. Further support of the benefits of early identification and intervention with children with hearing loss. Volta Review. 1999;100(5):53–84.
69. Moeller MP. Early intervention and language development in children who are deaf and hard of hearing. Pediatrics. 2000;106(3):E43.
70. Rosenfeld RM, Schwartz SR, Pynnonen MA, Tunkel DE, Hussey HM, Fichera JS, et al. Clinical practice guideline: tympanostomy tubes in children. Otolaryngol Head Neck Surg. 2013;149(1 Suppl):S1–S35.
71. Monasta L, Ronfani L, Marchetti F, Montico M, Vecchi Brumatti L, Bavcar A, et al. Burden of disease caused by otitis media: systematic review and global estimates. PLoS One. 2012;7(4):e36226.
72. Paradise JL, Feldman HM, Campbell TF, Dollaghan CA, Colborn DK, Bernard BS, et al. Effect of early or delayed insertion of tympanostomy tubes for persistent otitis media on developmental outcomes at the age of three years. N Engl J Med. 2001;344(16):1179–87.
73. Rosenfeld RM, Jang DW, Tarashansky K. Tympanostomy tube outcomes in children at-risk and not at-risk for developmental delays. Int J Pediatr Otorhinolaryngol. 2011;75(2):190–5.
74. Alzhrani F, Alhussini R, Hudeib R, Alkaff T, Islam T, Alsanosi A. The outcome of cochlear implantation among children with genetic syndromes. Eur Arch Otorhinolaryngol. 2018;275(2):365–9.
75. Hoshino AC, Echegoyen A, Goffi-Gomez MV, Tsuji RK, Bento RF. Outcomes of late implantation in Usher syndrome patients. Int Arch Otorhinolaryngol. 2017;21(2):140–3.
76. Koyama H, Kashio A, Sakata A, Tsutsumiuchi K, Matsumoto Y, Karino S, et al. The hearing outcomes of Cochlear implantation in Waardenburg syndrome. Biomed Res Int. 2016;2016:2854736.
77. McMahon CM, Patuzzi RB, Gibson WP, Sanli H. Frequency-specific electrocochleography indicates that presynaptic and postsynaptic mechanisms of auditory neuropathy exist. Ear Hear. 2008;29(3):314–25.

78. Rodríguez-Ballesteros M, del Castillo FJ, Martín Y, Moreno-Pelayo MA, Morera C, Prieto F, et al. Auditory neuropathy in patients carrying mutations in the otoferlin gene (OTOF). Hum Mutat. 2003;22(6):451–6.
79. Teagle HF, Roush PA, Woodard JS, Hatch DR, Zdanski CJ, Buss E, et al. Cochlear implantation in children with auditory neuropathy spectrum disorder. Ear Hear. 2010;31(3):325–35.
80. Cushing SL, Papsin BC. Cochlear implants and children with vestibular impairments. Semin Hear. 2018;39(3):305–20.
81. Idstad M, Tambs K, Aarhus L, Engdahl BL. Childhood sensorineural hearing loss and adult mental health up to 43 years later: results from the HUNT study. BMC Public Health. 2019;19(1):168.
82. Arsenault MD, Punch JL. Nonsense-syllable recognition in noise using monaural and binaural listening strategies. J Acoust Soc Am. 1999;105(3):1821–30.
83. Bronkhorst AW, Plomp R. The effect of head-induced interaural time and level differences on speech intelligibility in noise. J Acoust Soc Am. 1988;83(4):1508–16.
84. Fischer C, Lieu J. Unilateral hearing loss is associated with a negative effect on language scores in adolescents. Int J Pediatr Otorhinolaryngol. 2014;78(10):1611–7.
85. Henkin Y, Taitelbaum-Swead R, Hildesheimer M, Migirov L, Kronenberg J, Kishon-Rabin L. Is there a right cochlear implant advantage? Otol Neurotol. 2008;29(4):489–94.
86. Kimura D. Cerebral dominance and the perception of verbal stimuli. Can J Psychol. 1961;15(3):166–71.
87. Lieu JE, Tye-Murray N, Karzon RK, Piccirillo JF. Unilateral hearing loss is associated with worse speech-language scores in children. Pediatrics. 2010;125(6):e1348–55.
88. Thorpe RK, Smith RJH. Future directions of screening and treatment in congenital hearing loss. Precis Clin Med. 2020;3(3):175–86.
89. Kennedy C, McCann D, Campbell MJ, Kimm L, Thornton R. Universal newborn screening for permanent childhood hearing impairment: an 8-year follow-up of a controlled trial. Lancet. 2005;366(9486):660–2.

Worst Headache of Their Life

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1 Introduction

The "worst headache of my life" is a complaint that is more likely to be encountered in the emergency department (ED) than in an ambulatory clinic. This phrase has been interchangeably used to connote a thunderclap headache that is frequently associated with an aneurysmal subarachnoid hemorrhage. Thunderclap headache was first described by Day and Raskin in 1986 as a sentinel headache that occurred prior to a rupture of a cerebral aneurysm [1]. The unexpected development of the intense head pain is likened to a "clap of thunder."

Thunderclap headache is defined as a sudden, extremely excruciating headache that reaches maximum intensity within one minute or less [2]. It can last minutes to days, and there is no specific location or headache characteristic that will differentiate from other headache disorders, except for the hyperacute onset. Frequency can be a single attack but may also be recurrent for days. Thunderclap headache has not been well studied in the pediatric age group, and available literature consists mostly of case reports and series. In fact, the most common causes of thunderclap headache in adults, aneurysmal subarachnoid hemorrhage and reversible cerebral vasoconstriction syndrome, are uncommon in children and adolescents. However, the associated high rates of morbidity and mortality from vascular causes of thunderclap headache warrant awareness among clinicians of the uncommon severe acute-onset headaches in pediatric patients.

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2 Etiology

While clinicians have been traditionally taught that a thunderclap headache is pathognomonic for subarachnoid hemorrhage, multiple studies have identified other etiologies. The causes of thunderclap headache vary from vascular to nonvascular etiologies; as well occasional benign causes (Table 1). Despite this, subarachnoid hemorrhage remains the most frequent etiology [3]. In this chapter, we highlight certain causes of thunderclap headache that are important to recognize in the pediatric population.

2.1 Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) is the most common and one of the most serious causes of thunderclap headache. In adult literature, it accounts for 25% of patients with thunderclap headache, and 50% of patients with SAH present with isolated thunderclap headache [4, 5]. In nontraumatic subarachnoid hemorrhage, 85% of cases are due to ruptured cerebral aneurysm. Other causes of subarachnoid hemorrhage include arteriovenous malformation, moya-moya syndrome, and coagulopathies [6–8].

Table 1 Causes of thunderclap headache

Vascular
• Subarachnoid hemorrhage[a]
• Reversible cerebral vasoconstriction syndrome[a]
• Cerebral venous sinus thrombosis
• Cervical arterial dissection
• Intracerebral hemorrhage
Nonvascular
• Pituitary apoplexy
• Third ventricle colloid cyst
• Spontaneous intracranial hypotension
• Brain tumor
• Posterior reversible encephalopathy syndrome
• Crash migraine[b]
• Primary exercise headache[b]
• Primary thunderclap headache[b]

[a] Identified as the most common causes of thunderclap headache

[b] Diagnosis of exclusion and after an extensive evaluation for secondary causes has been completed

2.1.1 Clinical Presentation

The classic presentation of SAH is a sudden-onset, severe, thunderclap headache. The headache of SAH is typically occipital in location but can also be generalized. There are no other distinct headache features to differentiate SAH headache from other causes of thunderclap headache. Headache can be the only presenting symptom of SAH; however, commonly associated symptoms are impairment of consciousness, neck stiffness or pain, vomiting or meningismus manifesting as lower back pain [9–11]. If seizures occur, it is rare and predicts poor outcome [12]. Neurologic examination can be normal in 40% of patients with SAH [13]. If focal findings are present, it is dependent on the location of the hemorrhage with third nerve palsy as the most cited finding of SAH. Complications can occur and include rebleeding, hydrocephalus, cerebral edema and vasospasm that can lead to stroke.

Sentinel headache, a thunderclap headache that can occur within days or weeks prior to the SAH, has been reported in up to 43% of patients with aneurysmal SAH. It is thought to represent a "warning leak" or partial rupture from the weakened walls of the aneurysm before a major rupture [14]. Despite limitations in its true incidence, it is wise for clinicians to recognize this warning headache.

2.1.2 Diagnosis/Evaluation

A noncontrast head CT is the first step in the evaluation of SAH. The sensitivity of head CT is time dependent due to the physiologic brisk flow of the CSF. In other words, the continuous turnover of cerebrospinal fluid may render it difficult to view the blood on imaging, since the blood may be "diluted" out by the spinal fluid. CT is most sensitive in the first 6 h after SAH; although the sensitivity is reduced over time or in low volume bleeds. If head CT is negative, a lumbar puncture (LP) should be done to evaluate for opening pressure, routine CSF analysis, cell count and xanthochromia [15]. Xanthochromia is a unique distinguishing feature in SAH that represents hemoglobin degradation products. It can be visually inspected by comparing a tube of xanthochromic CSF with a tube of plain water against a white background. If both head CT and LP are done within 2 weeks of presenting symptoms and if both tests are negative, the diagnosis of SAH is less likely. However, in cases presenting after 2 weeks of initial headache onset, CT angiography (CTA), or magnetic resonance angiography (MRA) are necessary.

2.1.3 Management and Prognosis

Manage all SAH patients in an intensive care unit with focus on continuous neurologic monitoring, airway management as well as blood pressure and pain control. Urgent neurosurgical consultation is required for surgical or endovascular

procedures for ruptured cerebral aneurysm; and to manage SAH-related hydrocephalus. Essential support also includes prevention and management of re-bleeding, vasospasm, and hypo/hypernatremia. Prophylactic anticonvulsants must be considered in the immediate post-hemorrhagic period [15]. Early identification of SAH is crucial as approximately 30% of patients ultimately have poor outcomes, resulting in significant morbidity and mortality [16].

2.2 Reversible Cerebral Vasoconstriction Syndrome

Reversible cerebral vasoconstriction syndrome (RCVS) is a clinico-radiologic syndrome characterized by reversible segmental and multifocal narrowing of cerebral arteries and severe onset headaches with or without focal neurologic deficits or seizures [17]. It is a well-recognized cause of thunderclap headache in adults, and multiple pediatric cases have been reported in the literature. In pediatric cases, it is more common in males as opposed to female predominance in adults. Otherwise, the clinical and radiologic features are similar in pediatric and adult cases [18].

2.2.1 Clinical Presentation

RCVS typically presents as a dramatic sudden severe thunderclap headache similar to aneurysmal subarachnoid hemorrhage. However, the pathognomonic feature in RCVS is the pattern of multiple thunderclap headaches that recur every day or so for a span of days to weeks [19, 20]. Other distinguishing features of RCVS are presence of precipitating factors such as postpartum state, exposure to vasoactive, immunosuppressive and recreational drugs (particularly cannabis), exposure to cold or heat, sexual activity, trauma, or exercise [18–20]. Occasionally, the headache has migrainous features consisting of nausea, vomiting, photophobia, and phonophobia; and can be accompanied by surges of blood pressure [21]. Some patients with RCVS can have seizures, transient focal neurologic deficits (such as motor weakness) and ischemic and hemorrhagic strokes with permanent deficits [19, 20].

The pathophysiology of RCVS remains elusive. However, one hypothesis is that it is a disorder of cerebral arterial tone with sympathetic overactivity in susceptible patients [19].

2.2.2 Diagnosis/Evaluation

The diagnosis of RCVS requires the presence of diffuse, segmental constriction of cerebral arteries on MRA, CTA, or direct catheter angiography (the former 2 imaging modalities are more frequently used in practice). Angiography can be initially normal, and it is prudent to repeat neurovascular imaging as cerebral vasoconstriction can manifest several days later [19]. Other diagnostic criteria to fulfill

to clinch the diagnosis are absence of aneurysmal SAH, normal or near normal CSF analysis (protein <1 g/L, WBC counts <15/mL and normal glucose) and complete or marked normalization of arteries on follow-up indirect or direct angiography within 12 weeks of clinical onset [13, 19].

2.2.3 Management and Prognosis

There is no established treatment for RCVS. Triggers, if identified, must be eliminated when possible or avoided. Standard management must be instituted if RCVS is associated with stroke or hemorrhage. Technically, the diagnosis of RCVS cannot be definitively made until the follow-up angiography; nonetheless, when vasoconstriction is identified, presumptive treatment of vasospasm must be started. Calcium channel blockers are widely used, particularly Nimodipine and Verapamil [19, 21]. Duration of treatment with calcium channel blockers is still not established. Outcome is generally good, however some children with RCVS and associated stroke may have permanent neurologic deficits [20, 22].

2.3 Cervical Arterial Dissection

Cervical arterial dissection (CAD) is a well-recognized cause of stroke; however, the exact incidence in the pediatric population is unknown. Arterial dissection occurs when blood extravasates into the arterial wall from either secondary to an intimal tear or rupture of vasa vasorum, resulting in an intramural clot. In children and adolescents, male predominance is observed [23, 24]. In 50% of cases, the dissection is related to a head and/or neck trauma, which can be mild or trivial in nature [23–25]. Among those with spontaneous cervical arterial dissection, connective tissue disorders such as Ehlers–Danlos syndrome, vascular abnormalities such as cervical artery tortuosity and genetic predisposition were identified as risks factors [24].

2.3.1 Clinical Presentation

Headache and neck pain are the most common presenting symptoms of CAD [26]. Pain may occur as the only symptom in 15–20% of cases; however, the headache is usually associated with neurologic deficits due to ischemic stroke [27]. Neck pain appears to be more predominant with vertebral artery dissection than with carotid artery dissection [28].

The head pain in CAD is typically acute, severe and continuous or a thunderclap headache. It is usually ipsilateral to the dissection; localizes to the temporal area in cases of carotid dissection; and to the occipital region with vertebral artery dissection. Horner syndrome can be a manifestation of internal carotid artery dissection, and is usually partial, involving only miosis and ptosis [29]. Other presenting

symptoms and signs of CADs include pulsatile tinnitus, cranial neuropathies for carotid artery dissection; and dizziness/vertigo for vertebral artery dissection.

2.3.2 Diagnosis/Evaluation

Clinicians must have a high index of suspicion for CAD in patients presenting with acute or subacute headache and/or neck pain particularly in the setting of trauma, history of connective tissue disorder and symptoms suggestive of stroke. The headache of CAD can mimic primary headache disorders such as migraine and cluster headache. Thorough history to look for any change in the pre-existing headache pattern is important. Neurologic examination must look for subtle findings such as a Horner syndrome, cranial nerve palsies and posterior fossa signs such as gait ataxia, vertigo, limb incoordination, dysarthria, or dysphonia. Confirmation of the diagnosis can be made by obtaining urgent brain MRI and MRA of the head and neck; or CTA of the head and neck. The former is the preferred imaging modality by the authors due to radiation exposure from CTA. In cases when MRA or CTA are nondiagnostic and suspicion for CAD remains high, conventional angiography can be considered. Typical angiographic findings include stenosis (string sign), occlusion, luminal irregularity, aneurysmal dilatation, and intimal flap [25].

2.3.3 Management and Prognosis

Management approach to patients with CAD presenting with or without stroke symptoms must include cardiac monitoring, blood pressure control, fluid administration, and avoidance of hyperthermia, or hyperglycemia. Antiplatelet and/or anticoagulation therapy are often used for secondary prevention of ischemic symptoms. In the adult population, the use of either anti-platelet therapy (e.g., Aspirin) or anticoagulation therapy (e.g., low molecular weight heparin) is generally recommended. However, expert's consensus on optimal treatment has not been reached. In pediatrics, anticoagulation is still the advocated treatment due to thromboembolism being the likely mechanism of stroke in arterial dissection. With the collaboration of an experienced hematologist, the commonly practiced recommendations for dissection is 3–6 months of anticoagulation followed by antiplatelet therapy. Anticoagulation is not recommended for children with an intracranial dissection or those with SAH resulting from CAD [25, 30].

Risk of recurrence of stroke or TIA in pediatric series with CAD ranges from 12.5 to 15% [23, 25, 31]. Approximately 60% of pediatric cases of CAD showed resolution or improvement of the affected artery after anticoagulation; and those with arterial occlusion compared to those with stenosis, pseudoaneurysm or intimal flap on initial neuroimaging, had worst outcome for recanalization [25, 31]. Functional prognosis is variable with complete recovery in up to 70% of cases [23, 25, 31].

2.4 Cerebral Venous Sinus Thrombosis

The venous sinuses exist between the layers of dura mater covering the brain and serve to collect and drain venous blood from the brain. These sinuses contain no valves. When a blood clot forms in a venous sinus, it prevents the draining venous blood from exiting the head. This can lead to an increase in intracranial pressure (ICP) or hemorrhage and venous infarction.

2.4.1 Clinical Presentation

Symptom onset can be acute (most common), subacute, or even chronic [32, 33]. The most frequent presenting symptoms include headache, nausea and vomiting, visual field defects, and seizures. The headache is often subacute in onset; however, up to 5% of patients present with thunderclap headache [34–36]. Other focal neurologic deficits and encephalopathy or coma are less common presentations of cerebral venous sinus thrombosis (CVST).

In contrast to arterial ischemic stroke, CVST is less frequent and less commonly presents as an identifiable stroke syndrome (with specific localizing signs and symptoms). It tends to affect younger patients than arterial ischemic stroke, and there is a female predominance.

Risk factors for CVST include underlying genetic prothrombotic disorders and hypercoagulable states such as pregnancy, malignancy, dehydration, and infection. Estrogen-containing oral contraceptives and tobacco use also increase one's risk for clot formation.

2.4.2 Diagnosis/Evaluation

High index of suspicion is essential to make the diagnosis. A thorough medical history with attention to risk factors is important. Clinicians must remember that CVST should be part of the differential diagnosis for any pregnant or recently postpartum woman presenting with new onset severe headache. As intracranial hypertension is a known presentation of CVST, it is vital to query the patient on aggravating factors to the new onset headache such as laying supine or by activities that raise the intrathoracic and intra-abdominal pressure (e.g., bearing down or straining during a bowel movement, Valsalva maneuver). Other symptoms of raised intracranial pressure include vision changes such as blurred vision, diplopia or transient visual obscurations (TVOs), as well as so-called "whooshing" or pulsatile tinnitus. The neurologic examination should include fundoscopy looking for papilledema and bedside visual field testing.

Diagnosis is confirmed by neuroimaging. A noncontrast head CT can identify deep venous thrombosis and a contrast-enhanced head CT may show the "empty delta" sign, a triangular filling defect that represents a thrombus. Pediatric stroke

guidelines recommend CT venography (CTV) and brain MRI and magnetic resonance venography (MRV) as preferred methods for evaluating CVST [30].

2.4.3 Management and Prognosis

Treatment is usually initiated in the inpatient hospital setting. Anticoagulation is the mainstay of treatment, and typically this is started as either intravenous unfractionated heparin or subcutaneous low molecular weight heparin. The duration of anticoagulation has not been established; however, 3–6 months is the typical duration of therapy in clinical practice [30]. Hematology consultation is recommended both for ongoing management and for evaluation of potential prothrombotic state(s).

Aside from anticoagulation, treatment is symptom-directed. Patients with seizures should be treated with anti-seizure medication. In the absence of acute symptomatic seizures, there is no evidence to support prophylaxis with antiseizure medication [37]. Headaches can be managed with analgesic medications. For patients with evidence of intracranial hypertension (e.g., papilledema), pharmacologic therapies aimed at lowering intracranial pressure such as acetazolamide or furosemide can be used concurrently with anticoagulation. These patients should ideally have a baseline evaluation by an ophthalmologist as well. Other supportive measures include hydration, antimicrobial therapy for suspected bacterial infection, discontinuation of oral contraceptive pills to reduce risk of recurrence, and monitoring of intracranial pressure [30].

The mortality rate for acute cerebral sinus venous thrombosis is low, less than 2%. Most patients who receive anticoagulation exhibit venous recanalization within a few months to a year [38]. Favorable functional outcome is achieved in most patients, irrespective of whether the vein anatomically recanalizes or not.

2.5 Pituitary Apoplexy

A rare endocrinologic emergency, pituitary apoplexy refers to acute ischemic infarction or hemorrhage of the pituitary gland [39]. It most often occurs in the setting of a pituitary adenoma but can also occur in a normal pituitary gland especially during pregnancy.

2.5.1 Clinical Presentation

Pituitary apoplexy most commonly presents with sudden onset, one-time, severe thunderclap headache that is located in the retro-orbital or frontal region or is holocranial [40–42]. Due the location of the pituitary gland along the optic pathway and adjacent to the cavernous sinuses, other presenting symptoms include visual

abnormalities such as decreased visual acuity, visual field defect or ophthalmoplegia (weakness of the extraocular muscles); and cranial nerve palsies. It may also present with nausea and vomiting. Patients may exhibit signs of meningeal irritation secondary to SAH as blood from the hemorrhagic pituitary gland may seep into the subarachnoid space. Altered mental status, particularly decreased level of consciousness, can occur and should prompt one to consider the possibility of elevated ICP from pituitary enlargement.

Adrenal insufficiency can occur, with resultant hemodynamic instability and hypoglycemia. Hypothalamic dysfunction can occur as well, with impairment in temperature regulation presenting as pyrexia/fever. In majority of patients, at least one anterior pituitary hormone will be deficient at time of presentation [39, 42].

2.5.2 Diagnosis/Evaluation

While CT is rapidly available in the emergency setting, it can miss pituitary hemorrhage in many cases. MRI identifies pituitary hemorrhage in majority of cases and hence is the preferred imaging study for definitive diagnosis. A thorough neurologic examination with emphasis on looking for deficits of cranial nerves III, IV and V is essential (since these cranial nerves lay in proximity to the pituitary gland). Risk factors for pituitary apoplexy such as systemic hypertension, coagulopathies or anticoagulation therapy, estrogen therapy, pregnancy or postpartum state, and prior radiation therapy or pituitary surgery must be assessed. The presentation of pituitary apoplexy may most closely mimic that of a ruptured cerebral aneurysm, especially if SAH is present.

2.5.3 Management and Prognosis

Initial medical management should focus on hemodynamic stabilization of the patient and replacement of corticosteroids for adrenal insufficiency. Trans-sphenoidal surgical resection may be considered, particularly in cases of significant visual deficit or deteriorating level of consciousness. Alternatively, a conservative watchful waiting approach may consist of close monitoring with serial neuroimaging and laboratory evaluations of pituitary function. Care team members must include neurosurgical and endocrinology consultants. Serial eye exams (visual acuity, extraocular movements, visual fields) and assessments of pituitary function for residual endocrine deficiency are most important to monitor long-term sequelae [39, 42].

2.6 Third Ventricle Colloid Cyst

Colloid cysts are rare, accounting for less than 2% of primary brain tumors, and typically diagnosed in adulthood. They are histologically benign growths that are lined with columnar epithelium and are filled with material that is often described as mucous-like or gelatinous in quality. These cysts most commonly arise at the anterior aspect of the third ventricle, at or near the foramen of Monro.

2.6.1 Clinical Presentation

Most colloid cysts are identified as an incidental finding on neuroimaging [43]. The majority of third ventricle colloid cysts are asymptomatic, but it is important to note that they can enlarge in size causing symptom progression. Symptoms include those seen with hydrocephalus, such as headache, nausea, vomiting, blurred vision, diplopia, dizziness, ataxic gait, cognitive decline, and syncope or drop attacks (attacks wherein the child suddenly drops to the ground with no premonitory symptoms).

A significant proportion of patients who are symptomatic at the time of initial presentation present with obstructive hydrocephalus due to blockage of cerebrospinal fluid (CSF) flow from the lateral ventricle to the third ventricle via the foramen of Monro. Patients presenting with acute obstructive hydrocephalus are at risk for sudden neurologic deterioration including sudden death from brain herniation.

2.6.2 Diagnosis/Evaluation

The focus of the clinician should be on timely diagnosis through neuroimaging when children present with symptoms suggestive of possible third ventricle colloid cyst. Attention to the mental status, extra-ocular movements and fundoscopy portions of the neurologic exam is recommended, as these can reveal signs of hydrocephalus: somnolence, restriction of upward gaze and papilledema, respectively. Unsteady gait and hyper-reflexia are additional neurologic exam findings that may be seen in cases of obstructive hydrocephalus.

In the ED setting, once the patient is stabilized, an urgent CT of the head is enough to identify obstructive hydrocephalus. On head CT, the cyst itself is a hyperdense mass [44]. For patients who present in the outpatient setting with stable symptoms, MRI is the preferred imaging modality. MRI done both with and without intravenous gadolinium contrast is recommended in order to differentiate between various types of neoplasm—colloid cysts should not enhance following administration of contrast material during MRI.

2.6.3 Management and Prognosis

Neurosurgical consultation is recommended. For patients presenting with acute obstructive hydrocephalus, stabilization of airway, breathing, and circulation is of course paramount. CSF-diverting procedures such as external ventricular drain (EVD) placement to relieve hydrocephalus may be necessary in the acute, emergency setting. There are multiple surgical options for removal of symptomatic colloid cysts.

Asymptomatic colloid cysts do not necessitate surgical resection at time of diagnosis. However, referral to a neurosurgeon is recommended for asymptomatic patients as well to monitor for increase in size of the cyst.

2.7 Primary Exercise Headache

Previously termed primary exertional headache or benign exertional headache, primary exercise headache is as its name suggests a primary headache disorder. The precise pathophysiology of primary exercise headaches remains unknown and there is no underlying organic or structural etiology to explain the symptoms. It has been hypothesized that vascular distension induced by physical activity may be the potential underlying mechanism for the pain of primary exercise headache [2]. Causes of secondary/symptomatic headache should be excluded before settling upon this diagnosis.

2.7.1 Clinical Presentation

Primary exercise headache occurs exclusively during or after physical activity, usually sustained strenuous exercise, and particularly in hot weather or at high altitudes. Compared to other primary headache disorders, primary exercise headache is relatively rare [45]. However, it is important to note that primary exercise headache is often comorbid with other primary headache disorders, particularly migraine [46].

The pain of primary exercise headache is most commonly described as bilateral in location and pulsating or throbbing in quality, with a duration typically lasting minutes to hours. There may or may not be associated symptoms such as light or sound sensitivity, nausea or vomiting (the latter being rare). Epidemiological studies suggest that this disorder is seen most commonly in younger more than middle-aged adults with at least a slight female predominance.

2.7.2 Diagnosis/Evaluation

The diagnosis of primary exercise headache is clinical, based upon meeting the diagnostic criteria outlined in the International Classification of Headache Disorders (ICHD-3). The diagnosis requires at least two separate attacks of headache or episodes with each attack lasting less than 48 h. The head pain should be triggered by strenuous physical exercise but may occur during or after the activity [2].

At time of initial presentation, it is necessary to exclude possible underlying secondary causes including SAH and arterial dissection. In addition to a thorough headache history and neurologic examination, neuroimaging including vascular imaging is recommended [47]. Patients with cardiovascular risk factors or cardiac symptoms warrant evaluation for underlying heart disease as an etiology for their exercise-induced headaches, so termed cardiac cephalalgia.

2.7.3 Management and Prognosis

Primary exercise headache is often self-limited, though reports on the period during which attacks are expected to resolve vary on the order of months to years. Patients should be counseled to avoid, if possible, activities that provoke their headaches or up until secondary causes have been excluded. For those with frequent or prolonged symptoms or for whom trigger avoidance is not feasible, prophylactic treatment should be considered. Primary exercise headache is an Indomethacin-responsive headache disorder. As a first-line short-term treatment, indomethacin can be taken 30–60 min before planned strenuous physical activity, specifically before known exertional triggers [48]. Indomethacin has alternatively been proposed as daily scheduled prophylaxis. If Indomethacin is not tolerated, it is reasonable to start prophylactic treatment using beta-blockers [47].

2.8 Primary Thunderclap Headache

Primary thunderclap headache is a diagnosis that is made following a negative comprehensive evaluation for thunderclap headache has been done. It is previously termed benign thunderclap headache. Literature available on this type of headache is limited to case reports and series. Its exact mechanism is not known.

2.8.1 Clinical Presentation

Primary thunderclap headache presents with a highly intense pain of abrupt onset and mimics the headache of a ruptured cerebral aneurysm. In a study of 11 adult cases, the thunderclap headache occurred almost daily, and duration was 1–8 h. The headache may occur spontaneously even when at rest. In up to half of cases the

headache was triggered by Valsalva or minor exertion such as defecating, coughing, bathing, and laughing. The physical and neurological examinations are normal. Blood pressure is normal except during the headache attack when it becomes elevated [49]. A thunderclap headache can also be an initial presentation of new daily persistent headache [50].

2.8.2 Diagnosis/Evaluation

The diagnosis of primary thunderclap headache is based on the ICHD-3 criteria and requires all of the following to be fulfilled: (a) severe head pain; (b) abrupt onset, reaching maximum intensity in <1 min; (c) lasting more than or equal to 5 min; (d) not better accounted for by another ICHD-3 diagnosis [2]. It is imperative that this diagnosis be made only after all possible underlying secondary causes of thunderclap headache have been ruled out. As such, the diagnosis also requires normal brain and vascular imaging and normal CSF findings.

2.8.3 Management and Prognosis

Treatment of primary thunderclap headache is focused on pain relief. In cases when analgesics are ineffective, calcium channel blockers specifically nimodipine can be effective [49, 50]. Improvement of headache has also been reported with gabapentin [51]. Significant disability and impairment of social functioning have been reported in patients with recurrent primary thunderclap headache [52]. Overall, the long-term outcome is good.

3 Diagnostic Approach to a Worst-Ever Headache

3.1 History

The initial step in evaluating a patient with a worst-ever headache is to identify the temporal pattern of the headache. A very severe headache that begins suddenly and peaks instantaneously (usually within minute or less of onset) is the distinguishing feature of thunderclap headache from other acutely severe headaches. As patients have the tendency to perceive their headache as explosive or sudden and severe, it is essential not just to ask if it is the worse headache of their life but also to ask “how long did it take for your headache to reach its maximum intensity?” This question may be challenging for some children who may not have a concept of time or for those who have pre-existing neurologic conditions such as autism and who are unable to communicate well. Therefore, clinicians must query parents and caregivers regarding patient’s activity prior to the headache and patient’s response and

behavior at the onset of the headache. For example, was the child happily playing and abruptly screamed and cried in pain? Or did the child stop playing and lay down on the bed for several minutes before the headache worsened? As there are no distinct clinical features that can consistently identify a specific cause of thunderclap headache, assessing for associated symptoms and circumstances preceding the onset can provide clues to a possible etiology. For example, neck pain or stiffness can be due to SAH or CAD; or a recurrent thunderclap headache following exposure to cannabis can be from RCVS.

3.2 Physical Examination

General Examination: Assessments of vital signs is important as some children with a thunderclap headache may require emergent measures to maintain their airway or deal with increased intracranial pressure. A bruit may be audible over the carotid arteries in cases of cervical dissection. Check for meningismus that may occur when there is irritation of the meninges due to SAH.

Neurological Examination: Neurological examination with emphasis on assessing level of consciousness, pupillary reaction, visual field deficits, ptosis and cerebellar function can augment clues to the diagnosis. Take into consideration that a normal neurologic examination does not decrease the probability of a serious intracranial etiology. Therefore, all patients presenting with thunderclap headache must be evaluated as a medical emergency.

3.3 Investigations (Laboratory Investigations/Imaging)

Routine laboratory investigations are rarely helpful in the setting of a thunderclap headache.

Following history and neurologic examination, a noncontrast head CT must be urgently obtained to primarily rule out SAH. When head CT is suggestive of SAH, specific evaluation for aneurysm such as CTA or MRA will be required. If head CT is nondiagnostic, LP is recommended as the next diagnostic step to further evaluate for SAH [3, 5, 15]. This is to assess for xanthochromia, a unique CSF finding in SAH. Examining the CSF for cell count and opening pressure can also provide hints for other causes of thunderclap headache such as meningitis and spontaneous intracranial hypotension. If LP is also nondiagnostic and neurological examination is normal, additional work-up with MRI of the brain, MRA, and MRV can be considered depending on the suspected condition, i.e., cerebral venous sinus thrombosis, dissection, or pituitary apoplexy.

The above sequence of tests is in concordance with most expert's opinion as well as guidelines for management of aneurysmal SAH. Recognizing that not all thunderclap headaches are due to SAH and with easier access to MRI, MRA, and MRV

that can provide more information regarding other potential etiologies, alternative diagnostic strategies have been proposed by other experts. In a patient with thunderclap headache who has a normal neurological examination and normal head CT obtained within 6 h from headache onset, advanced neuroimaging is recommended as the next step before performing a LP [13, 53, 54]. Some of the arguments for this diagnostic sequence include: (1) xanthochromia (breakdown of hemoglobin that starts between 6 and 12 h) cannot be visually detected if LP is done early; (2) a traumatic LP can confound the finding of xanthochromia; (3) Brain MRI is sensitive to detect SAH or other types of intracranial bleeds; (4) MRI, MRA, and MRV can detect other potential causes of thunderclap headache such as RCVS, CVST, CAD, pituitary apoplexy, and cerebral aneurysm. In pediatric cases, a unique challenge to the traditional evaluation is the need for sedation when performing either a LP or MRI. To avoid sedating patients more than once, it is common practice to proceed with brain MRI and/or MRA and MRV after a nondiagnostic head CT. If further neuroimaging remains nondiagnostic and suspicion for SAH, CNS infection or intracranial hypotension is high, LP is performed.

4 When to Admit or Refer

A patient presenting with the worst headache of their life or thunderclap headache requires urgent evaluation for its underlying cause; hence clinicians must always refer a patient with thunderclap to the ED as soon as possible. If first-line investigation, head CT, is nondiagnostic, early neurology consultation is recommended to coordinate next diagnostic tests, especially for pediatric patients who will need sedation for LP or other neuroimaging studies. As patients with isolated thunderclap headache with normal neurologic examination, normal head CT, and CSF analysis can still have a serious underlying condition, it is prudent to admit the patient for observation for other evolving symptoms and for further evaluation.

5 Clinical Pearls/Key Points

- A worst-ever headache or thunderclap headache refers to a very severe headache that starts abruptly and peaks in intensity within 1 min or less.
- Thunderclap headache must be considered a medical emergency due to its association with serious neurovascular disorders.
- Subarachnoid hemorrhage commonly presents with thunderclap headache and must be the first condition to be ruled out.
- Reversible cerebral vasoconstriction syndrome is another common cause of thunderclap headache that typically presents with recurrent thunderclap headaches over days. High index of suspicion and repeat vascular imaging are required for this diagnosis.

- Initial evaluation of thunderclap headache should include head CT followed by lumbar puncture if head CT is nondiagnostic. If both are negative, patients must be further evaluated with contrast-enhanced brain MRI and noninvasive vascular imaging of the head and neck. The sequence of tests following a negative head CT can be tailored based on the need for procedural sedation in pediatric patients.
- Benign cause of thunderclap headache can be considered only when all potential underlying secondary causes have been excluded.

References

1. Day JW, Raskin NH. Thunderclap headache: symptom of an unruptured cerebral aneurysm. Lancet. 1986;2:1247–8.
2. Headache Classification Committee of the International Headache Society. The international classification of headache disorders, 3rd edition. Cephalalgia. 2018;38(1):1–211.
3. Schwedtt TJ. Thunderclap headache. Continuum (Minneap Minn). 2015;21:1058–71.
4. Linn FH, Wijdicks EF, van der Graaf Y, Weedesteynvan Vliet FA, Bartelds AI, van Gijn J. Prospective study of sentinel headache in aneurysmal subarachnoid hemorrhage. Lancet. 1994;344:590–3.
5. Ducros A, Bousser MG. Thunderclap headache. BMJ. 2013;346:e8557. https://doi.org/10.1136/bmj.e8557.
6. Hourihan MD, Gates PC, McAllister VC. Subarachnoid hemorrhage in childhood and adolescence. J Neurosurg. 1984;60:1163–6.
7. Rinkel GJ, van Gijn J, Wijdicks EF. Subarachnoid hemorrhage without detectable aneurysm. A review of the causes. Stroke. 1993;24:1403–9.
8. van Gijn J, Rinkel GJE. Subarachnoid haemorrhage: diagnosis, causes and management. Brain. 2001;124:249–78.
9. Landtblom AM, Fridriksson S, Boivie J, Hillman J, Johansson G, Johansson I. Sudden onset headache: a prospective study of features, incidence and causes. Cephalalgia. 2002;22:354–60.
10. Linn FH, Rinkel GJ, Algra A, van Gijn J. Headache characteristics in subarachnoid hemorrhage and benign thunderclap headache. J Neurol Neurosurg Psychiatry. 1998;65:791–3.
11. Mac Grory B, Vu L, Cutting S, Marcolini E, Gottschalk C, Greer D. Distinguishing characteristics of headache in nontraumatic subarachnoid hemorrhage. Headache. 2018;58:364–70.
12. Butzkueven H, Evans AH, Pitman A, Leopold C, Jolley DJ, Kaye AH, Kilpatrick CJ, Davis SM. Onset seizures independently predict poor outcome after subarachnoid hemorrhage. Neurology. 2000;55:1315–20.
13. Edlow JA. Managing patients with nontraumatic, severe, rapid-onset headache. Ann Emerg Med. 2018;71:400–8.
14. Polmear A. Sentinel headaches in aneurysmal subarachnoid hemorrhage: what is the true incidence? A systematic review. Cephalalgia. 2003;23:935–41.
15. Connolly ES Jr, Rabinstein AA, Carhuapuoma JR, Derdeyn CP, Dion J, Higashida RT, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2012;43:1711–37.
16. Wijdicks EF, Kallmes DF, Manno EM, Fulgham JR, Piepgras DG. Subarachnoid hemorrhage: neurointensive care and aneurysm repair. Mayo Clin Proc. 2005;80:550–9.
17. Calabrese LH, Dodick DW, Schwedt TJ, Singhal AB. Narrative review: reversible cerebral vasoconstriction syndromes. Ann Intern Med. 2007;146:34–44.
18. Coffino SW, Fryer RH. Reversible cerebral vasoconstriction syndrome in pediatrics: a case series and review. J Child Neurol. 2017;31:614–23.

19. Ducros A. Reversible cerebral vasoconstriction syndromes. Lancet Neurol. 2012;11:906–17.
20. Singhal AB, Hajj-Ali RA, Topcuoglu MA, Fok J, Bena J, Yang D, Calabrese LH. Reversible vasoconstriction syndromes analysis of 139 cases. Arch Neurol. 2011;68:1005–12.
21. Ghosh PS, Rothner AD, Zahka KG, Friedman NR. Reversible cerebral vasoconstriction syndrome: a rare entity in children presenting with thunderclap headache. J Child Neurol. 2011;26:1580–4.
22. Ducros A, Fiedler U, Porcher R, Boukobza M, Stapf C, Bousser MG. Hemorrhagic manifestations of reversible cerebral vasoconstriction syndrome: frequency, features, and risk factors. Stroke. 2010;41:2505–11.
23. Simonnet H, Deiva K, Bellesme C, Cabasson S, Husson B, Toulgoat F, et al. Extracranial vertebral artery dissection in children: natural history and management. Neuroradiology. 2015;57:729–38.
24. Nash M, Rafay MF. Craniocervical arterial dissection in children: pathophysiology and management. Pediatr Neurol. 2019;95:9–18.
25. Rafay MF, Armstrong D, deVeber G, Domi T, Chan A, MacGregor DL. Craniocervical arterial dissection in children: clinical and radiographic presentation and outcome. J Child Neurol. 2006;21:8–16.
26. Gallerini S, Marsili L, Bartalucci M, Marotti C, Chiti A, Marconi R. Headache secondary to cervical artery dissections: practice pointers. Neurol Sci. 2019;40:613–5.
27. Engelter ST, Traenka S, Lyrer P. Dissection of cervical and cerebral arteries. Curr Neurol Neurosci Rep. 2017;8:59.
28. Debette S, Grond-Ginsbach C, Bodenant M, Kloss M, Engelter S, Metso T, Pezzini A, et al. Differential features of carotid and vertebral artery dissections: the CADISP study. Neurology. 2011;77:1174–81.
29. Diamanti S, Longoni M, Agostini EC. Leading symptoms in cerebrovascular diseases: what about headache? Neurol Sci. 2019;40:147–52.
30. Roach ES, Golomb MR, Adams R, Biller J, Daniels S, deVeber G, et al. Management of stroke in infants and children: a scientific statement from a special writing group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young. Stroke. 2008;39:2644–91.
31. Fullerton HJ, Johnston SC, Smith WS. Arterial dissection and stroke in children. Neurology. 2001;57:1155–60.
32. Ferro JM, de Sousa DA. Cerebral venous thrombosis: an update. Curr Neurol Neurosci Rep. 2019;19:74.
33. Duman T, Uluduz D, Midi I, Bektas H, Kablan Y, Goksel BK, et al. A multicenter study of 1144 patients with cerebral venous thrombosis: the VENOST study. J Stroke Cerebrovasc Dis. 2017;26:1848–57.
34. De Bruijn SF, Stam J, Kappelle LJ. Thunderclap headache as first symptom of cerebral venous sinus thrombosis. Lancet. 1996;348:1623–5.
35. Cumurciuc R, Crassard I, Sarov M, Valade D, Bousser MG. Headache as the only neurological sign of cerebral venous thrombosis: a series of 17 cases. J Neurol Neurosurg Psychiatry. 2005;76:1084–7.
36. Wasay M, Kojan S, Dai AI, Bobustuc G, Sheikh S. Headache in cerebral venous thrombosis: incidence, pattern and location in 200 consecutive patients. J Headache Pain. 2010;11:137–9.
37. Lindgren E, Silvis SM, Hiltunen S, Heldner MR, Serrano F, de Scisco M, et al. Acute symptomatic seizures in cerebral venous thrombosis. Neurology. 2020;95:1706–15.
38. de Sousa DA, Lucas Neto L, Canhão P, Ferro JM. Recanalization in cerebral venous thrombosis. Stroke. 2018;49:1828–35.
39. Ranabir S, Baruah MP. Pituitary apoplexy. Indian J Endocrinol Metab. 2011;15:S188–96.
40. Randeva HS, Schoebel J, Byrne J, Esiri M, Adams CB, Wass JA. Classical pituitary apoplexy: clinical features, management and outcome. Clin Endocrinol. 1999;51:181–8.
41. Siegel S, Carneiro RW, Buchfelder M, Kleist B, Grzywotz A, Buslei R, et al. Presence of headache and headache types in patients with tumors of the sellar region—can surgery solve the problem? Results of a prospective single center study. Endocrine. 2017;56:325–35.

42. Singh TD, Valizadeh N, Meyer FB, Atkinson JLD, Erikson D, Rabinstein AA. Management and outcomes of pituitary apoplexy. J Neurosurg. 2015;122:1450–7.
43. Beaumont TL, Limbrick DD, Rich KM, Wippold FJ, Dacey RG. Natural history of colloid cysts of the third ventricle. J Neurosurg. 2016;125:1420–30.
44. Tenny S, Thorell W. Colloid brain cyst. [Updated 2020 Jun 30]. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2020. https://www.ncbi.nlm.nih.gov/books/NBK470314/.
45. Upadhyaya P, Nandyala A, Ailani J. Primary exercise headache. Curr Neurol Neurosci Rep. 2020;20:9.
46. Bahra A. Other primary headaches—thunderclap-, cough-, exertional-, and sexual headache. J Neurol. 2020;267:1554–66.
47. Halker RB, Vargas BB. Primary exertional headache: updates in the literature. Curr Pain Headache Rep. 2013;17:337.
48. Trotta K, Hyde J. Exercise-induced headaches: prevention, management, and treatment. US Pharm. 2017;42:33–6.
49. Lu SR, Liao YC, Fuh JL, Lirng JF, Wang SJ. Nimodipine for treatment of primary thunderclap headache. Neurology. 2004;62:1414–6.
50. Rozen TD, Beams JL. New daily persistent headache with a thunderclap headache onset and complete response to nimodipine (a new distinct subtype of NDPH). J Headache Pain. 2013;14:100.
51. Garza I, Black DF. Persistent primary thunderclap headache responsive to gabapentin. J Headache Pain. 2006;7:419–21.
52. Linn FHH, Rinkel GJE, Algra A, van Gijn J. Follow-up of idiopathic thunderclap headache in general practice. J Neurol. 1999;246:946–8.
53. Long D, Koyfman A, Long B. The thunderclap headache: approach and management in the emergency department. J Emerg Med. 2019;56:633–41.
54. Ravishankar K. Looking at “thunderclap headache” differently? Circa 2016. Ann Indian Acad Neurol. 2016;19:295–301.

Child with Chronic Headache

Naznin Mahmood and Lalitha Sivaswamy

1 Introduction

The child with a chronic headache is a classic example of a neurological condition that requires the expertise of both the pediatrician and neurologist and longitudinal follow-up by both. While the symptom can cause anxiety in the parents and the child, in most instances a directed history and detailed physical examination can reasonably rule out serious or life-threatening neurological conditions. In one study of children with chronic headache, up to 47% of mothers and 60% of children expressed that their purpose in seeking medical attention was to be reassured by the doctor that a serious illness was not present, and 62% of mothers' desired to find out the cause for their child's headaches [1].

2 Epidemiology

The overall prevalence of chronic headache in children is estimated to be 3.5% [2]. The prevalence of each etiological category is highly variable, with chronic migraine accounting for most cases of chronic headache in children who present to a physician, but chronic tension-type headache being most prevalent in population- based studies. The prevalence of chronic tension-type headache is 0.9–1.5%. Idiopathic

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intracranial hypertension (IIH) previously known as Pseudotumor cerebri, another cause of chronic headache, has a prevalence of 0.7 per 100,000 and primary brain tumors have a prevalence of 13 per 100,000 in children below the age of 19 years [3–5]. A female preponderance has been noted in many forms of chronic headaches such as migraine and pseudotumor cerebri.

3 Etiology

As noted above, the etiological basis for chronic headache in children can range from benign causes such a tension-type headache to disorders that result in raised intracranial pressure. Table 1 outlines causes as pertinent to children. As can be

Table 1 Etiology and time line of chronic headache disorders of childhood

Chronic intermittent headache	Chronic unremitting headache
Primary headache disorders	
Chronic migraine	New daily persistent headache
	Hemicrania continua
Chronic cluster/PH	Chronic TTH
	Occipital neuralgia
Secondary headache disorders	
(a) Vascular	Cerebral venous sinus thrombosis
	Headache attributed to unruptured vascular malformations
(b) Related to changes in intracranial pressure	Pseudotumor cerebri (IIH)
	Space occupying lesion
	Chiari malformation/syrinx
	Spontaneous low CSF pressure
(c) Inflammatory disorders	Aseptic meningitis (noninfectious)
(d) Infectious disorders	Brain abscess
(e) Following trauma	Chronic posttraumatic headache
	Chronic headache following whiplash injury
(f) Medication overuse headache	Withdrawal of simple analgesics
(g) Rare genetic disorders/neurocutaneous syndromes	MELAS
	CADASIL
	Sturge–Weber syndrome
(h) Psychiatric co-morbidity	Anxiety
	Somatization
Questionable associations	
• Hypertension	
• Eye strain/sinusitis	
• Temporo-mandibular joint disease	

TTH tension type headache, *IIH* idiopathic intracranial hypertension, *MELAS* mitochondrial encephalopathy with lactic acidosis and stroke like episodes, *CADASIL* cerebral autosomal dominant arteriopathy with subacute leukoencephalopathy, *PH* Paroxysmal Hemicrania
Any disorder listed under intermittent may transform to unremitting over time

seen, some chronic headaches start as repeated bouts of short-lasting pain that progress to daily or unremitting headaches over time. Others cannot be strictly classified as intermittent or continuous at onset, and can be highly variable in their presentation. In this section, we will briefly highlight important clinical aspects of each of these conditions, in order of prevalence in a typical pediatric practice.

(a) **Chronic Migraine (CM)**: is one of the most common identifiable causes for chronic headache in children [6]. Most children with CM start having acute migraine attacks and progress to chronicity over time [7]. The International Classification of Headache Disorders (ICHD-3) defines CM as occurring at least 15 days per month with at least half of those headache fulfilling criteria for migraine, i.e., pounding in nature, moderate to severe in intensity, associated with both nausea/vomiting and photophobia/phonophobia [8]. A family history of migraine may be elicited in over half of cases [9]. While most postpubertal children with migraine are girls with a 3:1 ratio, in the prepubertal group the prevalence may be slightly higher in boys [10]. Physical examination rarely yields findings of note and the history is what guides the clinician to the right diagnosis. Depression and anxiety occur in about 50% of all individuals with underlying migraine, more so in those with CM, and the two can occur concurrently [11]. CM is associated with significant impairment in day-to-day functioning, impaired health-related quality of life, increased social anxiety, and school phobia. Children with infantile colic are predisposed to CM in later life.

(b) **Chronic Tension-Type Headache** (TTH): This type of headache is often misinterpreted by both parents and physicians as being secondary to the "tensions" of day-to-day life or the pressures of academic performance. However, no such predisposing factor or association is necessary to fulfill the criteria for this common type of headache. In young children, the differentiation from migraine can be difficult due to certain overlapping symptoms and indeed the two often co-exist in children and children may not meet strict criteria for either [2, 12]. There is usually not a family history, or associated condition such as history of colic/motion sickness or marked impairment of day-to-day activities. These children do not miss school or social activities and while they admit to frequent headaches, they are not disabled by the presence of the pain. Physical examination is reassuring in all instances and imaging is not indicated. Per ICHD-3 chronic TTH is characterized by dull bilateral pain that is low to moderate in intensity and can be associated with photophobia or phonophobia and mild nausea but no vomiting.

(c) **Idiopathic Intracranial Hypertension (IIH)**: This very important subacute-chronic headache disorder can masquerade as chronic TTH or CM but requires prompt attention to avoid permanent vision loss. While the term "benign intracranial hypertension" has fortunately been abandoned, as the disorder can be far from benign, it can be difficult to recognize, especially in younger children. Girls with a high body mass index (BMI) comprise most cases in the postpubertal age group, though girls and boys are equally susceptible in the prepubertal period [13]. Importantly, one-third of children are asymptomatic and may only be diagnosed following a routine visit to an optometrist [14]. Physical examination must focus on detecting papilledema or sixth nerve palsy and more importantly excluding other neurological findings. While imaging might be helpful in

veering the clinician towards the diagnosis and excluding other causes of raised intracranial pressure, a conclusive diagnosis can only be made by measuring the opening pressure of cerebrospinal fluid (CSF). CSF opening pressure of greater than 20 cm of H_2O in nonobese children and over 25 cm of H_2O in obese children are the established norms to diagnose IIH in children [15]. The procedure is best performed in the lateral decubitus position, though with children who have very high BMI, one may consider performing the spinal tap under fluoroscopic guidance for technical ease. In cases of diagnostic uncertainty, intraventricular pressure monitoring may be required as a single measurement of CSF may not be reliable.

(d) **Intracranial Hypotension**: Intracranial hypotension which may be spontaneous or follow a traumatic tear to the dura is less frequently recognized than intracranial hypertension. The headache is characterized by postural variation (better when laying down) and may be associated with interscapular pain, neck pain, vomiting and hearing disturbances, e.g., feeling of being under water [16]. Spontaneous intracranial hypotension can follow strenuous activity or be the result of a congenital weakness in the dura that predisposes to tears. Disorders of the connective tissue matrix, such as Ehlers Danlos and Marfan syndrome, or pre-existing areas of dural weakness may lead to a spontaneous tear [17]. A rent or tear in the dura leads to leakage of CSF, causing sagging of the structures in the posterior fossa, traction on the meninges and resultant pain [18].

(e) **New Daily Persistent Headache** (NDPH): This is an enigmatic and highly refractory chronic headache disorder that often begins abruptly with no provoking factor that the patient can recall, and tends to persist continuously from that point on for several months or even years [19]. While considered rare in the adult population, a prevalence of 21–28% has been noted in children who have chronic headache [6]. Many individuals can recall the exact date and time when the headache started. A smaller subgroup may note that the headache followed a flu-like illness or stressful life event [20]. The headache itself has no pathognomonic features and can resemble migraine, including the presence of photophobia, phonophobia, nausea, and vomiting [21]. The impact on day-to-day functioning can be severe and associated anxiety and depression have been reported in more than 50% of adults with this condition [22, 23].

(f) **Chiari Malformation**: Chiari malformation type 1 is a fairly common incidental finding and may be radiologically noted in 1–3% of children [24]. By definition, there is descent of the tonsils of the cerebellum to at least 5 mm below the foramen magnum, due to crowding of the posterior fossa of the brain. As a result of the downward displacement of the tonsils, there is obstruction to flow of cerebrospinal fluid and compression of the brain stem. Cavitation of the spinal cord (syringomyelia) may occur in 30% of children with Chiari type 1 malformation [25]. About a third to half of children with Chiari malformation remain asymptomatic and do not come to the attention of a physician [26]. When symptomatic, headache in the occipital region with radiation to the neck is noted. Associated symptoms may include dysphagia, dysphonia (change in quality of the voice), new onset sleep apnea, sensory disturbances in a cape-like

distribution around the shoulders, gait disturbances, or rapidly progressive scoliosis. The presence of these symptoms is suggestive of brain stem compression or marked increase in size of the syrinx.

(g) **Primary Tumors of the Brain**: Brain tumors and other space occupying lesions are the most dreaded secondary cause of chronic pediatric headaches and often (one of) the main reasons a family may seek medical advice when their child has a chronic headache. Primary tumors of the brain are typically classified by location as supratentorial or infratentorial, i.e., originating above the tentorium cerebelli (or the "tent) or below this structure which separates the cerebellum and brain stem from the rest of the brain parenchyma. There are shifting patterns of brain tumor presentation with regards to location and children aged 0–3 years will present more often with supratentorial tumors, while children 4–10 years old present mostly with infratentorial tumors. As children mature from age 10 to early adulthood, the incidence of both of these distributions is equalized [27]. Tumors in the supratentorial location tend to present with seizures, change in personality, or declining ability to concentrate and process information. Infratentorial tumors may come to the attention of the family earlier as they often impinge on the brainstem or block CSF outflow and are most often associated with ataxia, hearing problems, facial weakness, diplopia, focal cranial nerve palsies, dysphagia, and balance problems. Since posterior fossa tumors are more common in children and more likely to obstruct CSF outflow pathways, papilledema is reliably seen in brain tumors in the pediatric population [28]. Gliomas, especially astrocytomas, are the most commonly encountered supratentorial tumors. Other tumors in this location may include ependymomas, oligodendrogliomas and choroid plexus tumors. The latter are unique, as they are congenital and tend to present in the first few months of life. Primitive neuroectodermal tumors, tumors of the pineal gland and subependymal giant cell astrocytomas (SEGA) are less prevalent tumors in the supratentorial location. Common infratentorial tumors include medulloblastomas and pilocytic astrocytomas. The clinician must have a high index of suspicion in certain populations, such as children with underlying neurocutaneous syndromes, as they are predisposed to tumors of the central nervous system. Despite the low prevalence, malignancies of the brain are the single most common solid tumors in children and are the leading cause of death among all childhood cancers.

(h) **Venous Sinus Thrombosis** (VST): Thrombosis in the venous drainage system of the brain can create increased intracranial pressure resulting in a dangerous source of headaches. VST can lead to venous infarction of brain tissue with or without hemorrhage, in cortical or thalamic locations, or it can cause intraventricular hemorrhage. In cohort studies of pediatric patients with increased intracranial pressure, 11% are found to have venous sinus thrombosis as the underlying etiology [29]. Risk factors for VST are noted to be present in at least 60% of children. These include dehydration (25%), genetic coagulopathies (32%), infections of the head and neck, head trauma, as well as certain medications [29, 30]. Oral contraceptive pills have been shown to convey seven times

higher risk for VST [31]. Other risk factors include chronic systemic diseases like systemic lupus erythematosus, inflammatory bowel disease, anemia, and conditions like nephrotic syndrome, diabetic ketoacidosis and thyrotoxicosis.

(i) **Functional Somatic Symptoms**: Anxiety and depression may predispose to physical complaints in children. A bi-directional relationship between psychological disorders and headache has been noted. Anxiety may alter the pathophysiology of the disease process by altering cytokine levels and fostering maladaptive behaviors such as inadequate sleep or nonadherence to treatment regimens [32]. On the other hand, chronic medical illnesses are known to predispose to and be associated with anxiety in children. This relationship has been well studied in children with migraine.

4 Differential Diagnosis

When evaluating a child with chronic headache it is important to consider if it is a "primary" headache, i.e., a de novo disorder not associated with an underlying structural lesion or disease state, or whether it is a "secondary" phenomenon in which the headache is a manifestation of an underlying entity. CM, chronic TTH, and headaches associated with functional somatic disorders are examples of primary headaches, while Chiari malformation, venous sinus thrombosis and tumors are classic examples of secondary headaches in children. As can be seen above, the differential diagnosis is broad but a thorough history and physical examination can often eliminate need for unnecessary investigations and imaging.

5 Diagnostic Approach

5.1 History

An accurate and detailed history is key to arriving at a diagnosis in a child with chronic headache. In the majority of cases, the physical examination tends to be normal. Therefore, a meticulous history can guide the clinician towards performing further investigations or reassuring the family, as appropriate. The history must be directed towards assigning the headache to primary or secondary category. It must be noted that response to an analgesic does not rule out a secondary cause for headache.

Certain disorders have a predictable pattern of headache and the clinician can reach a reliable diagnosis by the end of the history taking process. Therefore, one should aim to elicit these pathognomonic features (outlined below). However, the

historical aspects must be placed in context of the physical examination, and significant overlap between characteristics of headache may occur.

The headache of migraine is easily recognized in most instances, as it is pounding in nature, associated with photophobia, phonophobia/osmophobia (sensitivity to odors) and nausea/vomiting. Other symptoms such as light-headedness, pallor, feeling of warmth and epistaxis are common in children and need not prompt a search for another etiology in most instances when an underlying diagnosis of migraine is being considered. Unlike in adults, most children have bilateral head pain during an attack of migraine. On the other hand, visual aura and food as a migraine trigger are relatively uncommon in children. Early morning headaches are not uncommon in children with migraine. However, as noted below, certain secondary headache types can mimic a migraine headache.

TTH, on the other hand, are usually associated with a band-like dull pain that is mild to moderate in intensity. Mild photo and phonophobia may be present as well, but never vomiting. Other primary headache disorders such as the autonomic cephalgias (e.g., cluster headache) are strictly unilateral and associated with injection of the eye, tearing, and ipsilateral nasal congestion. They can be diagnosed by obtaining a photograph of the child during a typical attack. They are very rare in children and therefore should be diagnosed with caution and only after appropriate imaging of the brain. The most striking headache pattern is noted in children with NDPH wherein the pain starts abruptly and is unremitting from that point on. The headache may mimic the pain of migraine or TTH and does not have any distinguishing features per se.

Headache associated with conditions that cause raised intracranial pressure (ICP) may have some overlapping features. The most recognizable feature is the postural variation of the headache (worse while laying down) and exacerbation with exertion/Valsalva maneuver. Typically, a chronic, progressive pattern of headache would be expected with a gradual rise in intracranial pressure. However, occasional acute patterns of presentation can happen with rapidly growing tumors, with hemorrhage into a tumor site or rapid progression of venous thrombosis. While headache associated with raised ICP is typically moderate to severe in intensity, the frequency can be intermittent rather than daily and persistent- thereby misleading to the clinician. Vomiting, double vision (due to impingement on the sixth cranial nerve), seizures, altered mental status, hemiparesis, or ataxia may accompany the headache and lead the clinician to search for an underlying etiology.

With regards to pediatric brain tumors the headache patterns can be highly variable and range from tension-type headache pattern to autonomic cephalgias and worsening of pre-existing headaches. Even migraine headaches with aura and exertional headaches have been associated with brain tumors [33, 34]. The quality of the pain can be dull pressure, throbbing, or shooting or any combinations of these. In children ages 4 years old and above with brain tumors, morning onset and nocturnal headaches are more common (79%) as are nausea and vomiting (72–86%) [35]. Notably, associated neurologic findings are usually noted in brain tumor related

headaches and can correlate broadly with the location of the tumor. In children with supratentorial tumors affecting the cerebrum, seizures are a common occurrence and are noted in 22% of those under 14 years age and in 68% of older teenagers [36]. In these children, declining academic performance or an abnormality of personality, speech, walking, or sensation are also more likely to be present although such symptoms could also be present without headache in children with brain tumors. Infratentorial tumors tend to present with imbalance of gait and symptoms of cranial nerve involvement such as difficulty with articulation, change in quality of voice, choking on food/liquids and difficulty swallowing.

Some conditions causing raised ICP can be associated with systemic symptoms. Presence of fever for instance, is commonly noted with VST. In children with pseudotumor cerebri, in addition to headache, which may not have any defining features, the presence of transient visual obscurations (vision that fades in and out over a period of seconds) and pulsatile tinnitus (described as a "whooshing" sound in the ears) are fairly prevalent and should routinely be asked for in any child with chronic headache.

Psychological co-morbidities are common in children with chronic headache disorders [37]. Therefore, screening for anxiety and depression constitutes an important aspect of obtaining the history, especially if a primary headache disorder is suspected. Another important historical feature that is often overlooked is the quantity and quality of sleep. Children with concomitant sleep disturbances have higher levels of functional disability, anxiety and depression than those with chronic headache alone. These aspects of the history are often overlooked as the family may not be aware of the association and be reluctant to discuss these aspects unless questioned directly.

Last, but not least, a family history of migraine or coagulation disorders such as those causing pulmonary embolism, venous sinus thrombosis or recurrent strokes at a young age may help the clinician narrow the differential diagnosis. See Table 2 for important pointers regarding history.

5.2 Physical Examination

5.2.1 General Physical Examination

General aspects that can provide a clue to arriving at a diagnosis are the body mass index (increased in children with pseudotumor cerebri, decreased in children with certain tumors that affect the hypothalamus), blood pressure elevation, signs of systemic disease such as precocious puberty, hair loss or joint swelling (latter suggestive of disorders such as lupus). A thorough examination of the skin is important in any child with a suspected neurological disorder and chronic headache is no exception. Children with facial nevi, café-au-lait or hypopigmented macules, or telangiectasia on their conjunctiva or flexural aspects of the elbow may have a

Table 2 Important pointers regarding history in children with chronic headache

History in child less than 5 years of age (preschool)
• Vomiting
• Abdominal pain
• Pallor/flushing/diaphoresis/light-headedness
• Vertigo, clumsy gait
• Visual disturbances -flashes of light, transient loss of vision, double vision, tunnel vision
• Pounding sensation in the ears or "whooshing" sound
• Withdraws to a dark room or quiet space, asks for volume of TV or music to be reduced
• Motion sickness
• Colic as a baby
• Preceding trauma
• Recent gastroenteritis or systemic illness associated with vomiting/diarrhea
• Reduced appetite
• Change in social circumstances, death of a family member
• Family history of migraine, brain tumors
• Recent change in personality
History in child older than 5 years of age (school-age)- in addition to the historical aspects mentioned above
• Visual disturbances -flashes of light, transient loss of vision, double vision, tunnel vision
• Pounding sensation in the ears or "whooshing" sound (tinnitus)
• Location of the headache-especially ask regarding occipital location, confined to one side only, pain between shoulder blades
• Numbness, tingling in an extremity or in a cape like distribution over shoulders
• Difficulty chewing, swallowing, voice change, hearing loss or difficulty drinking liquids
• Injection, tearing from one eye, rhinorrhea from same side nostril, ptosis on affected side
• Personal history of depression, anxiety, other functional disorders

neurocutaneous syndrome which can be associated with tumors of the central nervous system. Neck stiffness may indicate disorders such as Chiari malformation, intracranial hypotension or cervicogenic headache. The latter are headaches that originate in the cervical spine but may radiate to the head. While disc pathology and root compression are predominantly disorders of adults, one must not forget to examine the upper spine in cases of predominantly occipital headache.

5.3 Neurological Examination

Higher mental functions and affect can be useful indicators of associated or underlying disease states. A child with depressed affect may have migraine, whereas a child with change in mood or personality that is out or character for him/her, might have raised intracranial pressure.

Swollen optic nerves (papilledema), sixth nerve palsy as indicated by weakness of abduction in one or both eyes, or failure to gaze upwards, may be indicative of raised ICP. On the other hand, a nasal tone to the voice, failure of the palate to elevate and dysarthria may indicate involvement of the "lower cranial nerves" and is suggestive of a Chiari malformation or tumor affecting the posterior fossa. Focal motor weakness may be noted in a child with a stroke secondary to venous sinus thrombosis. Gait examination may reveal an ataxic gait in a child with raised ICP. Finally, children with raised ICP may have brisk deep tendon reflexes with a positive Babinski sign.

6 Evaluation (Laboratory Investigations/Imaging)

Routine hematological and biochemical profiles are of little benefit in most children with primary headache disorders. An important facet of evaluating for chronic headache is the decision to order imaging of the brain. Imaging is unlikely to yield findings of note in the presence of a normal neurological examination [38]. Incidental findings may be present in up to 16% of pediatric imaging studies and require follow-up in less than 1% of cases [39]. Magnetic Resonance Imaging (MRI) of the brain without contrast is the preferred preliminary modality of imaging in most instances. Computed tomography (CT) may detect tumors that present with mass effect and hemorrhage, but MRI has a higher sensitivity and specificity for neoplasms of the posterior fossa [40]. Figures 1 and 2 provide examples of utility of MRI in certain situations.

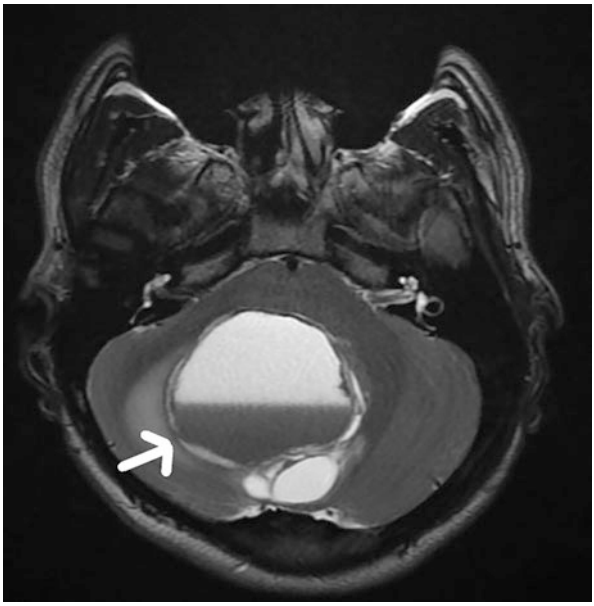

Fig. 1 Axial T2 weighted MRI of a child with chronic headache noting a large tumor in the posterior fossa (white arrow)

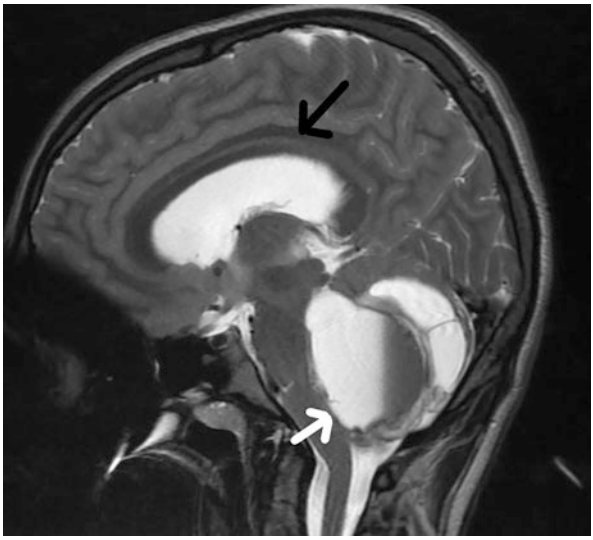

Fig. 2 Sagittal T2 weighted MRI of the same child noting significant hydrocephalus (black arrow) and mass in the posterior fossa that is compressing the brain stem and fourth ventrile (white arrow)

Other types of imaging such as magnetic resonance venography and angiography (MRV, MRA) may be performed in unique situations. For instance, MRV with time of flight technique (TOF) is the most sensitive imaging modality to detect venous sinus thrombosis [41].

7 Treatment/Management

- **Chronic Migraine:** Children with chronic migraine are best treated by a gradual taper of over the counter analgesics (if they are being overused), addressing sleep, hydration, concurrent psychological conditions, lifestyle habits and commencing prophylactic agents. The choice of prophylaxis is dependent on the co-morbidities. There are no Food and Drug Administration (FDA)-approved prophylactic agents in children, and only consensus guidelines are available. The CHAMP study, conducted in teenagers with chronic migraine, has noted the non-inferiority of placebo such as riboflavin over prescription drugs such as topiramate or amitryptiline [42]. It is reasonable therefore in most children with chronic migraine to start with a single supplement or combination of natural supplements, e.g., riboflavin and magnesium oxide. The dosages and common side effects for prescription drugs that are found to be effective are listed in Table 3.
- Onabotulinumtoxin A (BOTOX ^{R}) is approved by the FDA for prophylaxis of migraine in adults and has shown to be efficacious in children [43]. A new class of drugs called CGRP blockers (Calcitonin Gene Related Peptide blockers) has been found to be efficacious for adults with migraine but there is not enough evidence of efficacy in the pediatric age group [44]. All children with chronic migraine must also have a treatment plan for acute attacks of migraine and that may include use of a nonsteroidal anti-inflammatory agent with a serotonin ago-

nist (sumatriptan, rizatriptan, zolmitriptan have been studied in the pediatric age group). Please see Chap. 20 for management of acute attacks of migraine. As a general rule of thumb, it is best to start "low and slow" with prophylactic drugs, counsel families that it may take a minimum of 8–12 weeks before efficacy is noted and monitor for side-effects. Regular follow-up with implementation of headache diaries are important aspects of long-term care. Some children may benefit from acupuncture, biofeedback and relaxation techniques in addition to the pharmacological measures discussed above.

- **Chronic TTH:** A connection seems possible between TTH, anxiety, mood disorders, and psychosocial stress. Therefore, addressing these aspects is important to ensure a good outcome in this cohort of children. A combination of nonpharmacological measures such as cognitive behavior therapy (CBT), relaxation techniques and pharmacological agents such as amitryptiline, topiramate or gabapentin may be helpful. Use of any of these drugs is off-label. Amitryptiline is usually the first-line prophylactic agent in children. For dosage please refer to Table 3.
- **Idiopathic Intracranial Hypertension**: most children with IIH can be managed by medication alone along with a weight loss regimen. Acetazolamide which reduces production of CSF is the first line of treatment [45]. It is started at a dose of 15–25 mg/k/day divided twice a day and may need to be titrated upward, depending on symptomatology and degree of papilledema to a maximum of 3000–4000 mg/day in older children. A small percentage of children may require optic nerve sheath fenestration or placement of a ventriculoperitoneal or lumboperitoneal shunt to in the face of impending vision loss [46].
- **Intracranial Hypotension**: may require specific intervention such as an epidural blood patch if symptomatic measures such as hydration and bed rest are not effective.
- **New Daily Persistent Headache**: The pathophysiology remains speculative and while several treatment options have been studied in small case series, no unifying recommendations can be made. Steroids, melatonin, tetracycline derivatives, nerve blocks, and Onabotulinumtoxin A have been studied with varying results [19].
- **Chiari Malformation**: Surgical decompression is the only curative treatment option available for symptomatic children. The decision to undergo surgery is typically made when there are symptoms and signs of brain stem compression or progressive increase in size of the syrinx and not for headache alone. In fact, the headache may not resolve after decompressive surgery. Furthermore, children with Chiari 1 may also have concomitant migraine or TTH and one must clearly differentiate the different headache patterns, so as not to miss a treatable cause for headache in this population [47]. Spontaneous resolution of childhood Chiari 1 has been described in some instances.
- **Raised Intracranial Pressure**: Treatment should be directed towards the causative disorder.

  (a) Primary treatment of venous sinus thrombosis is aimed at recanalization of the occluded vein with anticoagulation for 3–6 months, although in some patients with an underlying prothrombotic condition, long-term anticoagulation may be needed.

(b) Treatment of primary brain tumors is dependent on the staging and the WHO classification. Surgical resection, followed by chemotherapy and/or radiation, is common treatment options. However, urgent referral to a neurosurgeon is important so that a decision regarding placement of a shunt or use of steroids to reduce vasogenic edema can be made.

Table 3 Dosages and common side effects of pharmacological therapies for chronic migraine

Drug name	Dosage	Common side effects
Riboflavin	100–400 mg/day once a day or divided BID	Urine becomes bright yellow
Magnesium (oxide, citrate, or glycinate most commonly used)	200–400 mg; Maximum daily dose 500 mg	Diarrhea and gastrointestinal discomfort
Topiramate	<12 yo: 1–2 mg/kg/day divided bid >12 yo: initial dose 25 mg nightly, weekly increase of 25 mg up to max of 100 mg/day either nightly or divided bid	Transient paresthesias, exacerbation of anorexia, cognitive slowing, decreased sweating, kidney stones, closed angle glaucoma, metabolic acidodosis, rare mood changes/suicidality In teens/pregnancy: decreased effectiveness of estrogen birth control, increased risk of cleft palate
Amitryptiline	Target dose 10–75 mg qhs (best) or divided BID; (0.25–0.5 mg/kg/day) <12 yo initial dose of 5–10 mg >12 yo, initial dose 10 mg Similar increments of weekly increase as starting dose; Max. dose typically 1 mg/kg/day	Sedation, dry mouth, constipation, blurry vision, narrow angle glaucoma, QT prolongation, urinary retention, hematologic effects, orthostatic hypotension, increased risk of serotonin syndrome, mood changes/suicidal ideation (black box warning)
Cyproheptadine	Off label usage 2 mg at night Maximum dosage 8–10 mg at night	Sedation; therefore, best used at night Increased appetite
Valproic acid	250 mg/day to 1000 mg/day divided BID	Increased appetite, hair loss, weight gain, tremors, requires monitoring of liver function, requires monitoring of white cell count and platelet counts, teratogenic effect on fetus
Lamotrigine	Off label usage Start at 0.5–1 mg/kg per day divided BID Maximum dose of 100 mg per day divided BID	If dose is increased rapidly can cause Stevens-Johnson syndrome. Requires gradual and supervised titration
Propranolol	Start at 20 mg bid Maximum dose of 120 mg per day	Lowers heart rate, may cause light-headedness and pre-syncope, can exacerbate poorly controlled asthma and blunts body's response to hypoglycemia, can cause depression
Verapamil	Off label usage	Constipation At higher dose may need EKG to monitor for heart block Avoid use with grapefruit juice

As noted in the section on "history," addressing associated psychological comorbidities are vital in children who are suspected of having a primary headache disorder and to some extent in children with secondary forms of headache. Psychotherapeutic approaches such as CBT and pharmacotherapy are the mainstay of treatment for depression and anxiety. Selective serotonin reuptake inhibitors (SSRIs) have proven efficacy in children and are considered first line pharmacotherapy options for treatment of anxiety [48]. Finally, in all children with primary chronic headache disorders, addressing sleep hygiene practices, ensuring adequate quantity of sleep, and identifying obstructive sleep apnea is of importance.

8 Prognosis/Outcomes

The prognosis is dependent on the underlying etiology.

Many children with CM will continue to experience them into adulthood. Children with VST have mortality less than 10% but neurologic sequelae may range from 17 to 79% [30] and can manifest in lifelong neurologic and developmental deficits. While Chiari malformation can be addressed by surgical decompression the headache may not necessarily resolve. Addressing the underlying etiology (when present) can lead to resolution of the headache. The prognosis of brain tumors is dependent on the type of and staging of the malignancy. Good prognosis can be expected for astrocytomas and medulloblastomas while the prognosis for choroid plexus carcinoma is dependent on the extent to which the primary tumor can be surgically resected.

9 When to Refer/Admit

- In general, a change in the quality of headaches, increasing frequency, and refractoriness are good indicators to consider referral to a neurologist or obtain imaging.
- Be cautious when any individual symptom, or combination of these symptoms is present: postural variation in headache, transient loss of vision, tinnitus, headache that is grid locked to one side since onset or consistently occipital in location, unilateral injection of the eye with tearing or unilateral rhinorrhea during the headache and intractable vomiting.
- When neurological symptoms persist between attacks early referral should be considered. These include ataxia, limb weakness, sensory symptoms, hoarseness of voice, or dysarthria.

- Swelling of the optic nerve is difficult to detect unless one is familiar with the technique in children and more importantly, may not always be present in the setting of raised ICP. However, when noted, the child should be evaluated by the neurologist on an emergent basis or be referred to the emergency department for immediate evaluation and possible admission.
- Referral to a counselor or psychologist may be beneficial in children with associated psychological co-morbidities.

10 Prevention

Prevention of most conditions that lead to chronic headache is not feasible, as a genetic basis is responsible for primary forms such as chronic migraine, and no clear-cut etiology has been discerned for most forms of secondary headache. However, certain lifestyle modifications such as regular exercise, adequate hydration, addressing sleep apnea, avoiding frequent use of opiates or over the counter analgesics and maintaining appropriate BMI for age can prevent transformation of certain forms of acute headache to chronic forms and reduce risk for PTC and venous sinus thrombosis. Female gender, lower socioeconomic status, depression, anxiety, and head injury constitute risk factors for transformation of episodic to chronic migraine in adult populations. Whether the same risk factors hold true across the pediatric age group is unclear. The pros and cons of oral contraceptives must be weighed prior to prescribing them and might best be avoided in children with a family history of coagulation disorders.

11 Clinical Pearls/Key Points

- Headaches that are predominantly occipital in location, have postural variation, are increased by cough or exertion should be assessed promptly.
- Associated symptoms such as gait disturbances, recent onset clumsiness, decline in academic performance, complaints of double vision, change in voice or slurred speech should be actively sought and if present call for early referral and potential imaging.
- Physical examination should focus on the optic disc in older cooperative children and extra-ocular movements, lower cranial nerves, and gait in younger children.
- MRI brain without contrast is the preferred first line imaging modality if available and technically feasible.
- In children with CM avoid frequent use of over the counter analgesics and consider early prophylaxis.

References

1. Raieli V, Compagno A, Pandolfi E, La Vecchia M, Puma D, La Franca G, Ragusa D. Headache: what do children and mothers expect from pediatricians? Headache. 2010;50(2):290–300. https://doi.org/10.1111/j.1526-4610.2009.01583.x.
2. Lipton RB, Manack A, Ricci JA, Chee E, Turkel CC, Winner P. Prevalence and burden of chronic migraine in adolescents: results of the chronic daily headache in adolescents study (C-dAS). Headache. 2011;51(5):693–706. https://doi.org/10.1111/j.1526-4610.2011.01885.x.
3. Cleves-Bayon C. Idiopathic intracranial hypertension in children and adolescents: an update. Headache. 2018;58(3):485–93. https://doi.org/10.1111/head.13236.
4. Anttila P. Tension-type headache in children and adolescents. Curr Pain Headache Rep. 2004;8(6):500–4.
5. Patel S, Bhatnagar A, Wear C, Osiro S, Gabriel A, Kimball D, et al. Are pediatric brain tumors on the rise in the USA? Significant incidence and survival findings from the SEER database analysis. Childs Nerv Syst. 2014;30(1):147–54. https://doi.org/10.1007/s00381-013-2307-1.
6. Bigal ME, Lipton RB, Tepper SJ, Rapoport AM, Sheftell FD. Primary chronic daily headache and its subtypes in adolescents and adults. Neurology. 2004;63(5):843–7. https://doi.org/10.1212/01.wnl.0000137039.08724.18.
7. Manack AN, Buse DC, Lipton RB. Curr Pain Headache Rep. 2011;15(1):70–8. https://doi.org/10.1007/s11916-010-0157-z.
8. ICHD-3.
9. Family history of migraine.
10. Bille B. A 40-year follow-up of school children with migraine. Cephalalgia. 1997;17:488–91. https://doi.org/10.1046/j.1468-2982.1997.1704488.x.
11. Minen MT, Dhaem OBD, Diest AKV, Powers S, Schwedt TJ, Lipton R, Silbersweig D. Migraine and its psychiatric comorbidities. J Neurol Neurosurg Psychiatry. 2016; https://doi.org/10.1136/jnnp-2015-312233.
12. Abu-Arafeh I. Chronic tension-type headache in children and adolescents. Cephalalgia. 2001;21(8):830836. https://doi.org/10.1046/j.0333-1024.2001.00275.x.
13. Phillips PH, Sheldon CA. Pediatric Pseudotumor cerebri syndrome. J Neurooncol. 2017;37(Suppl 1):S33–40. https://doi.org/10.1097/WNO.0000000000000548.
14. Balcer LJ, Liu GT, Forman S, Pun K, Volpe NJ, Galetta SL, Maguire MG. Idiopathic intracranial hypertension: relation of age and obesity in children. Neurology. 1999;52(4):870–2. https://doi.org/10.1212/wnl.52.4.870.
15. Shelden CA, Paley GL, Beres SJ, MCormack SE, Liu GT. Semin Pediatr Neurol. 2017;24(2):110–5. https://doi.org/10.1016/j.spen.2017.04.002.
16. Amorim JA, Gomes de Barros MV, Valença MM. Post-dural (postlumbar) puncture headache: risk factors and clinical features. Cephalalgia. 2012;32(12):916–23. https://doi.org/10.1177/0333102412453951.
17. Mokri B. Spontaneous intracranial hypotension. Continuum. 2015;21(4 Headache):1086–8. https://doi.org/10.1212/CON.0000000000000193.
18. Ozge A, Bolay H. Intracranial hypotension and hypertension in children and adolescents. Curr Pain Headache Rep. 2014;18(7):430. https://doi.org/10.1007/s11916-014-0430-7.
19. Yamani N, Olesen J. New daily persistent headache: a systematic review on an enigmatic disorder. J Headache Pain. 2019;20(1):80. https://doi.org/10.1186/s10194-019-1022-z.
20. Rozen TD. Triggering events and new daily persistent headache: age and gender differences and insights on pathogenesis—a clinic-based study. Headache. 2016;56(1):164–73. https://doi.org/10.1111/head.12707.
21. Kung E, Tepper SJ, Rappaport AM, Sheftell FD, Bigal ME. Cephalalgia. 2009;29(1):17–22. https://doi.org/10.1111/j.1468-2982.2008.01647.x.
22. Reidy BL, Riddle EJ, Powers SW, Slater SK, Kacperski J, Kabbouche MA, Hershey AD. Clinic-based characterization of continuous headache in children and adolescents: com-

paring youth with chronic migraine to those with new daily persistent headache. Cephalalgia. 2020;40(10):1063–9. https://doi.org/10.1177/0333102420920644.
23. Uniyal R, Paliwal VK, Tripathi A. Psychiatric comorbidity in new daily persistent headache: a cross-sectional study. Eur J Pain. 2017;21(6):1031–8. https://doi.org/10.1002/ejp.1000.
24. Abu-Arafeh I, Campbell E. Headache, Chiari malformation type 1 and treatment options. Arch Dis Child. 2017;102(3):210–1. https://doi.org/10.1136/archdischild-2016-312137.
25. Burina A, Smajlovic D, Sinanovic O, Vidovic M, Ibrahimagic OC. Arnold-Chiari malformation and syringomyelia. Acta Med Sal. 2009;38:44–6.
26. Wu YW, Chin CT, Chan KM, Barkovich AJ, Ferriero DM. Pediatric Chiari I malformations: do clinical and radiologic features correlate? Neurology. 1999;53(6):1271–6.
27. Udaka YT, Packer RJ. Pediatric brain tumors. Neurol Clin. 2018;36(3):533–56. https://doi.org/10.1016/j.ncl.2018.04.009.
28. Rigi M, Almarzouqi SJ, Morgan ML, Lee AG. Papilledema: epidemiology, etiology, and clinical management. Eye Brain. 2015;7:47–57. https://doi.org/10.2147/EB.S69174. eCollection 2015.
29. Dsouza S, Aylward BS, Rogers DL, Aylward SC. Presenting symptomatology and risk factors in pediatric secondary intracranial hypertension due to venous sinus thrombosis. Pediatr Neurol. 2019;101:53–6. https://doi.org/10.1016/j.pediatrneurol.2019.04.016.
30. Dlamini N, Billinghurst L, Kirkham F. Cerebral venous sinus (sinovenous) thrombosis in children. Neurosurg Clin N Am. 2010;21(3):511–27. https://doi.org/10.1016/j.nec.2010.03.006.
31. Amoozegar F, Ronksley PE, Suave R, Menon BK. Hormonal contraceptives and cerebral venous thrombosis risk: a systematic review and meta-analysis. Front Neurol. 2015;6:7. https://doi.org/10.3389/fneur.2015.00007.
32. Ramsawh H, Chavira D, Stein M. The burden of anxiety disorders in pediatric medical settings: prevalence, phenomenology and a research agenda. Arch Pediatr Adolesc Med. 2010;164:965–72. https://doi.org/10.1001/archpediatrics.2010.170.
33. Schlake HP, Grotmeyer KH, Husstedt IW, Schuierer G, Brune GG. "Symptomatic migraine": intracranial lesions mimicking migrainous headache—a report of three cases. Headache. 1991;31(10):661–5. https://doi.org/10.1111/j.1526-4610.1991.hed3110661.x.
34. Symonds C. Cough headache. Brain. 1956;79(4):557–68. https://doi.org/10.1093/brain/79.4.557.
35. Rossi LN, Vassella F. Headache in children with brain tumors. Childs Nerv Syst. 1989;5(5):307–9. https://doi.org/10.1007/BF00274519.
36. Gilles FH, Sobel E, Leviton A, Hedley-Whyte ET, Tavare CJ, Adelman LS, Sobel RA. Epidemiology of seizures in children with brain tumors. The Childhood Brain Tumor Consortium. J Neurooncol. 1992;12(1):53–68. https://doi.org/10.1007/BF00172457.
37. Gandhi B, Cheek S, Campo JV. Anxiety in the pediatric medical setting. Child Adolesc Psychiatr Clin N Am. 2012;21(3):643–53. https://doi.org/10.1016/j.chc.2012.05.013.
38. Lewis DW, Dorbad D. The utility of neuroimaging in the evaluation of children with migraine or chronic daily headache who have normal neurological examinations. Headache. 2000;40(8):629–32. https://doi.org/10.1046/j.1526-4610.2000.040008629.x.
39. Dangalouff-Ros V, Roux C-J, Boulouis G, Levy R, Nicolas N, Lozach C, Grevent D, Brunelle F, Boddaert N, Naggara O. Incidental brain MRI findings in children: a systematic review and meta-analysis. AJNR Am J Neuradiol. 2019;40(11):1818–23. https://doi.org/10.3174/ajnr.A6281.
40. Lay CL, Sun-Edelstein C. Brain tumor headache. In: Eichler A, editor. UpToDate. https://www.uptodate.com/contents/BrainTumorHeadache. Accessed 25 July 2020.
41. Jalli R, Zarei F, Farahangiz S, Khaleghi F, Petramfar P, Borhani-Haghighi A, Yadollahikhales G. The sensitivity, specificity, and accuracy of contrast-enhanced T1-weighted image, T2*-weighted image, and magnetic resonance venography in diagnosis of cerebral venous sinus thrombosis. J Stroke Cerebrovasc Dis. 2016;25(8):2083–6.
42. Hershey AD, Powers SW, Coffee CS, Eklund DD, Chamberlin LA, Korbee LL, CHAMP Study Group. Childhood and Adolescent Migraine Prevention (CHAMP) study: a double-blinded,

placebo-controlled, comparative effectiveness study of amitriptyline, topiramate, and placebo in the prevention of childhood and adolescent migraine. Headache. 2013;5(53):799–816. https://doi.org/10.1111/head.12105.
43. Shah S, Calderon MD, Wu WD, Grant J, Reinhart J. Onabotulinumtoxin A (BOTOX®) for ProphylaCTIC treatment of pediatric migraine: a retrospective longitudinal analysis. J Child Neurol. 2018;33(9):580–6. https://doi.org/10.1177/0883073818776142.
44. Papetti L, Ursitti F, Moavero R, Ferilli MAN, Sforza G, Tarantino F, Vigevano S, Valeriani M. Prophylactic treatment of pediatric migraine: is there anything new in the last decade? Front Neurol. 2019;10:771. https://doi.org/10.3389/fneur.2019.00771.
45. Melby JM, Miner LC, Reed DJ. Effect of acetazolamide and furosemide on the production and composition of cerebrospinal fluid from the cat choroid plexus. Can J Physiol Pharmacol. 1982;60(3):405–9. https://doi.org/10.1139/y82-059.
46. Chen H, Zhang Q, Tan S, Fu H, Farris B, Yang Z. Update on the application of optic nerve sheath fenestration. Restor Neurol Neurosci. 2017;35(3):275–86. https://doi.org/10.3233/rnn-160693.
47. Aitken LA, Lindan CE, Sidney S, Gupta N, Barkovich AJ, Sorel M, Wu YW. Chiari type I malformation in a pediatric population. Pediatr Neurol. 2009;40(6):449–54. https://doi.org/10.1016/j.pediatrneurol.2009.01.003.
48. Rynn M, Regan J. Anxiety disorders. In: Findling R, editor. Clinical manual of child and adolescent psychopharmacology. Washington, DC: American Psychiatric Publishing; 2008. p. 143–88.

Child with New Onset Headache

Riddhiben Patel

1 Introduction

Headache is a common complaint in the pediatric population and a frequent chief complaint in office settings. Almost all children experience a headache at some point during their childhood and it ranks among the top 5 health problems of childhood [1, 2]. This symptom can cause significant anxiety and distress for a child and their family. However, the impact of headaches is often underestimated by parents, teachers, and primary care providers and they fail to recognize it as a significant problem, resulting in marked disability and poor quality of life for the child. The majority of pediatric headaches are primary headache disorders, such as migraine and tension-type headaches (TTH), or due to a benign secondary etiology but in a small proportion, they can be secondary to serious life-threatening conditions. It is essential for clinicians to obtain a detailed history and perform a thorough neurologic examination, which will allow the provider to distinguish between primary and secondary headache disorders. Recognition of "red flags" for secondary headaches is important as it will help to pursue appropriate diagnostic testing and guide management.

In this chapter, we will discuss the recognition and management of common primary headache disorders such as migraine and TTH, how to differentiate between primary and secondary headaches and a systematic approach to the evaluation and management of new onset headaches in children.

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2 Epidemiology

Headaches are a major health problem in the pediatric population. The prevalence of headaches increases with age, ranging from 37% to 51% in 7-year-olds, to 57% to 82% by 15 years of age, and as many as 40% of school children have at least one episode of headache weekly [3, 4]. Primary headaches result from a complex interaction between genes and environment and are not a symptom of an underlying disease or condition. Migraine and TTH are the most common primary headache disorders.

Migraine is the leading cause of neurological disability in children and adolescents worldwide [5, 6]. The reported prevalence for migraine headache increases from 3% in preschool years to 4%–11% by the elementary school years and up to 8%–23% during high-school years. The mean age at onset is 7.2 years for boys and 10.9 years for girls [7, 8]. In prepubertal children, boys tend to be more affected than girls, whereas females are more frequently affected than boys after the onset of puberty [3].

Tension-type headache (TTH) is also a common primary headache disorder among children with an estimated prevalence of 10%–30% and similar to migraine the prevalence of TTH increases with age, especially in girls [9, 10].

It appears that the economic impact of migraine on the child, family, and society far exceeds that of other headache disorders [11, 12].

3 Etiology/Pathophysiology

The pathophysiology of migraine and TTH is not fully clear; however, recent advances in basic science and clinical research have increased our understanding of the mechanisms of these headaches.

Migraine is a complex neurological disorder with a genetic basis. The previously held theory of isolated vasoconstriction-triggered pain has been replaced by a neurovascular theory. This entails a complex cascade of events such as activation of a trigeminal nucleus in the brainstem and cortical spreading depression due to disturbances in cortical and brainstem excitability in response to a variety of internal and external stressors. These sequence of events activate the trigeminovascular system, followed by the release of neuropeptides such as substance P, calcitonin gene-related peptide (CGRP) and neurokinin A which leads to inflammation, vasodilation, and a clinical migraine episode.

The pathophysiology of migraine can be divided into the biological processes that occur during the migraine attack and the underlying reason for the risk of having migraine.

The risk of developing migraine depends on the balance between genetic inheritance and environmental triggers (i.e., weather changes, hormones, changes in sleep pattern, bright light, odors, skipping meals being classic examples) to start a cascade of biological process. Each member of a family cohort with migraines may have a different clinical presentation. Furthermore, each episode of migraine may manifest differently for a given individual, which explains the clinical complexity of the condition. Mutations in individual genes such as the calcium channel gene (CACNA1A), a sodium/potassium pump (ATP1A2) gene, and a sodium channel (SCN1A) gene can result in rare subtypes of migraine such as hemiplegic migraine [13]. These associations highlight the importance of ion channels in migraine pathophysiology. There are likely to be other hitherto unrevealed genetic variances that can alter neuronal or glial function, and lead to the clinical syndrome of migraine.

As a result of several recent studies, we have a better comprehension of the underlying pathophysiology of different phases of migraine: premonitory, aura, headache, and postdrome phases.

The premonitory phase starts hours to a couple of days before the actual pain of a migraine attack and involvement of the hypothalamus and brainstem dopaminergic neurons have been identified [14]. Cortical spreading depression (CSD) has been well studied and a leading theory to explain the aura. CSD is a spreading wave of depolarization that occurs across the cortex, at approximately 3 mm/min and often begins in the occipital lobe [15]. CSD temporarily disrupts ion homeostasis, results in neuronal dysfunction and transient regional hyperemia followed by oligemia [15]. The headache phase involves activation of the trigeminovascular pathway which conveys sensory (pain processing) information from the meninges (periphery) to the central areas of the brain with signal transmission through the thalamus to the cortex [16]. A variety of inflammatory chemicals, most notably neuropeptide, pituitary adenylate cyclase-activating polypeptide, and calcitonin gene-related peptide (CGRP) are implicated in trigeminal neurovascular activation and it seems to be a vital step in migraine pain processing [17]. Owing to this novel observation of the pathophysiology of migraine, CGRP antagonists and antibodies have been recently approved by the FDA for the treatment of migraine in adults.

Identification of this complex pain network and its connection with different areas of the brain helps to explain the clinical symptoms that characterize a migraine attack such as cognitive (memory and attention deficit), affective (mood changes and irritability), and autonomic (lacrimation, conjunctival injection, rhinorrhea, and facial swelling) involvement in a patient with migraine.

The exact etiology of TTH also remains elusive. Currently available data suggest that nociceptive input from pericranial myofascial components triggers these headaches initially, and if these noxious stimuli are sustained, central sensitization (meaning increased responsiveness of pain-processing neurons in the central nervous system to their normal or subthreshold afferent inputs) can occur and it seems to be responsible for the conversion of episodic to chronic TTH [18].

4 Differential Diagnosis of New Onset Headache

As mentioned above, when approaching a child with a new onset headache, the clinician can categorize into primary headache disorder seconor dary headaches. Secondary headaches are associated with an identifiable underlying disease process that results in head pain and may be due to altered intracranial pressure, brain abscess, meningitis, intracranial tumor, trauma, CNS inflammation, cerebral venous sinus thrombosis, intracranial hemorrhage, aneurysmal rupture, or acute febrile illness.

4.1 Primary Headache Disorders

4.1.1 Migraine

Migraine is the most common primary headache disorder seen in children. Typical characteristics of migraine pain are: unilateral location (can be bilateral in children especially bi-frontal or bi-temporal), pulsating quality, moderate to severe intensity, aggravation by routine physical activity, and associated with nausea and/or vomiting, or photophobia and phonophobia [19]. Duration of migraine in children can be shorter compared to adults (2 hours in children versus 4 hours in adults) especially in children younger than 7 years of age [20]. Children tend to experience prominent gastrointestinal symptoms such as abdominal pain, anorexia, nausea, and vomiting. Other symptoms that may be associated with a migraine attack include dizziness, blurry vision, difficulty focusing, facial flushing, sweating, pallor, and dark circles around the eyes. Autonomic symptoms such as nasal congestion, tearing or itchy eyes, or ear pressure can occur and it should not be misdiagnosed as sinus headache [21]. Children may have difficulty describing the pain or associated symptoms; asking the child to draw his or her headache can help to diagnose the condition [22]. In younger children, behavioral observations during migraine episodes can be helpful, for example, they may appear ill or pale, irritable, crying, stop their activity, and tend to seek a dark room for sleeping [23].

Children with migraines can experience premonitory symptoms and postdrome symptoms in addition to the headache phase symptoms of migraine and aura [24]. Premonitory symptoms may precede the headache phase by an hour to days and are seen in approximately two-thirds of children and adolescents. They may include symptoms such as, irritability/mood change, food cravings, fatigue, photophobia/phonophobia, and increased yawning [25]. Postdrome symptoms follow the headache phase and include fatigue, a “washed out” feeling, and brain fog [25].

Migraine can be diagnosed by history and physical examination without neuroimaging. ICHD-3 (The International Classification of Headache Disorders third edition) criteria for the diagnosis of migraine without aura and with aura are outlined in Table 1.

Table 1 The ICHD-3 criteria for the diagnosis of migraine are as follows

A. At least 5 attacks fulfilling criteria B through D
B. Headache attack duration of 2–72 hours for children younger than 18 years (untreated or unsuccessfully treated)
C. Headache has at least 2 of the following 4 characteristics:
(1) Unilateral or bilateral location in children younger than 18 years and often frontal, (2) pulsating quality, (3) moderate or severe pain intensity, and (4) aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least 1 of the following occurs: (1) nausea and/or vomiting and (2) photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis
The ICHD-3 criteria for the diagnosis of migraine with aura are as follows:
A. At least 2 attacks fulfilling criteria B and C
B. One or more of the following 6 fully reversible aura symptoms: Visual, sensory, speech and/or language, motor, brainstem, and retinal
C. At least 3 of the following 6 characteristics: (1) at least 1 aura symptom spreads gradually over 5 min or more, (2) 2 or more symptoms occur in succession, (3) each individual aura symptom lasts 5–60 min, (4) at least 1 aura symptom is unilateral, (5) at least 1 aura symptom is positive, and (6) the aura is accompanied, or followed within 60 min, by headache

Migraine with aura:

The aura is the transient complex neurological symptoms that occur usually before the headache phase, but it may begin after the headache phase has started or continue into the headache phase. Aura for most migraineurs lasts from 5 to 60 min, consists of fully reversible symptoms, gradually spreads over minutes and is usually followed by headache and associated migraine symptoms [19].

Approximately 20% of migraines can be preceded by an aura. Typical aura can be visual (area of impaired or decrease vision within the visual field, zig-zag lines, or flashing lights), sensory (numbness or tingling) or involving speech (dysarthria). Other uncommon/atypical auras include those arising from brainstem involvement (dysarthria, vertigo, tinnitus, hyperacusis, diplopia, ataxia), affecting retina (monocular visual symptoms) or motor symptoms (hemiplegic migraine characterized as hemiplegia, aphasia). When aura symptoms are multiple, they usually follow one another in sequence (i.e., visual then sensory then speech; but the reverse and other orders have been reported) [19].

4.1.2 Tension-Type Headache

Tension-type headache (TTH) is another common type of primary headache disorder in children. Tension headaches are less likely to present to emergency departments or primary care physicians due to their mild intensity and low impact on daily life. TTH is typically defined as bilateral head pain of pressing, tightening, or a band-like quality, which is mild-to-moderate in intensity, lasting from 30 min to 7 days, and is not exacerbated by physical activity. It may be associated with either

Table 2 The ICHD-3 diagnostic criteria for episodic TTH are as follows

A. At least 10 episodes of headache occurring on fewer than 15 day per month and fulfilling criteria B through D
B. Lasting from 30 min to 7 days
C. At least 2 of the following 4 characteristics: (1) bilateral location, (2) pressing or tightening (nonpulsating) quality, (3) mild or moderate intensity, and (4) not aggravated by routine physical activity such as walking or climbing stairs
D. both of the following: No nausea or vomiting and no more than 1 of photophobia or phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

light sensitivity or sound sensitivity, but there is an absence of nausea or vomiting. Episodic TTHs can be divided into infrequent (<1/month) or frequent (1–14 times/month). Tension headaches appear to be more common when individuals are under significant stress due to emotional orschool-related distress, poor sleep, or missed meals [26].

Patients with TTH should have a normal neurological exam aside from some pericranial tenderness over the forehead, neck, and shoulder muscles. ICHD-3 criteria for the diagnosis of TTH are outlined in Table 2.

4.1.3 Other Primary Headache Syndromes

Trigeminal autonomic cephalalgias (TACs) are rare in children but common treatment modalities that are effective for migraine or tension headaches may not be helpful for TACs, so recognition of these headaches is very important. This diagnostic group includes cluster headaches, paroxysmal hemicranias, short-lasting unilateral neuralgiform headaches, and hemicrania continua. These headaches are characterized by frequent short-lasting attacks of unilateral pain usually in the orbital, supraorbital, or temporal region that typically last minutes and are accompanied by ipsilateral autonomic symptoms, such as ipsilateral eye redness, tearing, nasal congestion, rhinorrhea, eyelid swelling, forehead or facial sweating, miosis, or ptosis [19]. ICHD-3 criteria for TACs are outlined in Table 3.

Another rare headache that is important to recognize is the primary stabbing headache. These patients have stabbing pain in the orbital, temporal, and parietal area that lasts for a few seconds and recurs in an irregular pattern.

Given that secondary causes of TACs and stabbing headaches have been reported in the pediatric population, the clinician should keep a higher degree of suspicion for secondary pathology (pituitary and cavernous sinus abnormality) when children with stabbing headache are evaluated [27].

Table 3 The ICHD-3 diagnostic criteria for TACs are as follows

Diagnostic criteria for cluster headache:
A. At least 5 attacks fulfilling criteria B–D
B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes (when untreated)
C. Either or both of the following:
1. At least one of the following symptoms or signs, ipsilateral to the headache:
– conjunctival injection and/or lacrimation
– nasal congestion and/or rhinorrhea
– eyelid edema
– forehead and facial sweating
– miosis and/or ptosis
2. A sense of restlessness or agitation
D. Occurring with a frequency between one every other day and 8 per day
E. Not better accounted for by another ICHD-3 diagnosis.
Diagnostic criteria for paroxysmal hemicrania:
A. At least 20 attacks fulfilling criteria B–E
B. Severe unilateral orbital, supraorbital and/or temporal pain lasting 2–30 min
C. Either or both of the following:
1. at least one of the following symptoms or signs, ipsilateral to the headache:
– conjunctival injection and/or lacrimation
– nasal congestion and/or rhinorrhea
– eyelid edema
– forehead and facial sweating
– miosis and/or ptosis
2. a sense of restlessness or agitation
D. Occurring with a frequency of >5 per day
E. Prevented absolutely by therapeutic doses of indomethacin
F. Not better accounted for by another ICHD-3 diagnosis.
Diagnostic criteria for short-lasting unilateral neuralgiform headache attacks:
A. At least 20 attacks fulfilling criteria B–D
B. Moderate or severe unilateral head pain, with orbital, supraorbital, temporal and/or other trigeminal distribution, lasting for 1–600 s and occurring as single stabs, series of stabs or in a saw-tooth pattern
C. At least one of the following cranial autonomic symptoms or signs, ipsilateral to the pain:
– Conjunctival injection and/or lacrimation
– Nasal congestion and/or rhinorrhea
– Eyelid edema
– Forehead and facial sweating
– Forehead and facial flushing
– Sensation of fullness in the ear
– Miosis and/or ptosis
D. Occurring with a frequency of at least one a day
E. Not better accounted for by another ICHD-3 diagnosis.

4.2 Secondary Headaches

4.2.1 Headaches Attributed to Abnormal Intracranial Pressures

Altered intracranial pressure (ICP) is an uncommon but important cause of new onset headache in the pediatric population and has various causes.

Hydrocephalus is an important cause of raised ICP. Hydrocephalus is characterized by excessive accumulation of cerebrospinal fluid (CSF) leading to ventricular enlargement and increased intracranial pressure. Hydrocephalus can be due to space-occupying lesions, blockage of CSF flow (due to aqueductal stenosis, colloid cyst, or mass), or impaired CSF absorption. Another potential cause for raised ICP can be increased volume of tissue or fluids in the cranial vault (e.g., inflammation, mass lesions, hemorrhage). Headaches are the most common presenting symptom of raised ICP. Typically, these headaches are progressive, worsen with the Valsalva maneuver or exertion, and can be associated with other signs or symptoms suggestive of raised ICP (e.g., papilledema, cranial nerve palsies, pupillary and eye movement abnormalities, increasing head circumference, nighttime awakening, persistent vomiting, seizures, focal neurologic deficits, lethargy, or personality change) [28].

Headaches may also occur with low ICP. Intracranial hypotension should be considered if there is a risk for CSF leak (e.g., a recent history of lumbar puncture or spinal surgery, trauma, connective tissue disease). Headaches caused by intracranial hypotension worsen within minutes of a patient obtaining an upright posture (sitting and standing) and improve when the patient is supine, with or without additional symptoms such as photophobia, nausea, tinnitus, difficulty with thinking, fatigue, or neck pain. Meningeal enhancement on brain magnetic resonance imaging (MRI) may be seen with intracranial hypotension [29].

Idiopathic Intracranial Hypertension (IIH), brain tumors and Chiari malformations can lead to increased ICP and often present with headaches. See Chap. 19 for details regarding these conditions.

4.2.2 Headache Attributed to Vascular Intracranial Disorder

Vascular disorders including intracerebral and subarachnoid hemorrhage, ischemia, aneurysms, vascular malformations, pituitary apoplexy, dissections, or vasculitis are rare causes of headache in children and discussed Chap. 18. The temporal pattern of the headache is usually that of a “thunderclap” or “worst headache of life,” with a sudden, acute onset that may also be associated with focal neurologic deficits, seizures, or altered mental status.

Cerebral venous sinus thrombosis (CVST) is another uncommon cause of secondary headaches in children. The most common presenting symptoms of CVST in children are headache, focal neurologic signs, seizures, decreased level of consciousness, and papilledema. The vast majority have some risk factor for CVST, including head or neck infection, chronic systemic disease, dehydration, pregnancy, or other prothrombotic states.

4.2.3 Headache Attributed to Head Trauma (Post-Traumatic)

Headache is one of the most common symptoms following mild traumatic brain injury in children. Headache typically develops within 1 week of head trauma, concussion, or whiplash. These headaches may have qualities of migraine or tension headaches and often are associated with other postconcussive symptoms such as sleep disturbance, dizziness, balance abnormalities, cognitive changes, and mood changes. The vast majority of post-traumatic headaches resolve within 2 weeks [30]. Please see Chap. 30 on "Child with Closed Head injury" for details of this type of headache.

4.2.4 Headache Attributed to Infection

Headaches may occur secondary to a variety of childhood infectious processes; in fact, acute viral illness with fever is a very common cause of pediatric headache. Typically, these children will have an acute onset of headache, and the headache resolves as the other viral symptoms get better. Many other infections can be associated with headaches, including streptococcal pharyngitis, acute otitis media, dental caries, and sepsis but rarely is a headache the only symptom.

Although sinusitis may cause or trigger headaches in some children, the majority of patients diagnosed as having "sinus headaches" have some form of primary headache syndrome. Sinus-related pain generally is pressure-like and dull periorbital pain, worse in the morning, associated with nasal congestion, nasal purulence, and lasts for days at a time. It is usually not associated with nausea, visual changes, phonophobia, or photophobia. The presence of a positive Mueller sign (ask the patient to pinch their nose shut, blows their nose hard, and then cough—they will feel localized pain over sinus area while performing this maneuver) on physical examination may also help to further confirm the diagnosis of sinusitis [31].

Headaches due to meningitis or encephalitis are often associated with photophobia, nausea, vomiting, and pain with eye movements. These patients typically have concurrent symptoms such as fever, altered mental status, and nuchal rigidity.

5 Diagnostic Approach

5.1 History

The approach to the child with headache begins with a detailed history. Both the child and the parents should be included in this discussion to provide clarification and supporting details as indicated. The key to appropriate workup, counseling, and treatment of headache is to make an accurate diagnosis so clinicians need to define whether the headache is primary or secondary and what "red flags" in the history or examination should warrant further work-up.

5.1.1 Headache Onset and Pattern

The onset and temporal pattern of the headache can help to guide differential diagnoses, like episodic/recurrent and chronic nonprogressive headaches are generally associated with primary headache disorders, whereas acute or chronic progressive headaches may suggest a secondary etiology.

5.1.2 Headache Characteristics

The clinician should ask about headache location, whether the pain is unilateral or bilateral, and whether it radiates. Inquire regarding the quality of the pain and obtain details regarding severity and duration. In younger children, these details may be difficult to elicit so asking them to draw what they feel like during a headache can be helpful. Occasionally, directed questions may need to be asked, e.g., providing adjectives to describe the pain may help the child choose one that better describes their headache. Occipital location and strictly unilateral headache warrant careful consideration for secondary etiology (e.g., posterior fossa tumor and structural lesions). Duration of headache is equally important as migraine or tension-type headache last for a couple of hour as compared to TACs which are short-lasting (minutes).

5.1.3 Associated Symptoms

Every headache history should include a comprehensive review regarding associated symptoms. The clinician should focus not just on the classic symptoms of migraine but also ask about other symptoms such as prodromal changes in appetite, sleep, or mood, presence of aura, gastrointestinal symptoms, and any comorbid autonomic symptoms, focal neurological symptoms such as hemiparesis and orthostatic symptoms. Patients with primary headaches usually return to their baseline between episodes of pain, but ongoing progressive symptoms (such as

forgetfulness, confusion, or localizing neurological symptoms) may suggest a secondary etiology.

One should also focus on exacerbating and alleviating factors. When discussing these, remember to address potential associations with menses, positionality, any specific time of the day, and worsening with Valsalva or exertional activity. Some children with migraines have consistent triggers for their headache such as certain foods, strong smells, light, loud noises, smells, lack of sleep, hunger, stress, or weather changes. Additionally, patients may have discovered alleviating factors for their headache such as, lying down or sleeping in a dark and quiet room (migraine), sitting upright (increase intracranial pressure), avoiding neck movement (meningitis).

Questions about daily lifestyle such as patient's daily caffeine intake, sleep schedule, nutrition, physical activity, and hydration status are also very important while obtaining a headache history.

It is important to understand how pain impacts their daily life. Validated scales such as the Pediatric Migraine Disability Score (PedMIDAS) are simple to administer and give a rapid assessment of disability [32]. These questions aim to determine how the headaches impact the child's performance in both the school/home settings and during social events.

Review of other symptoms, including questions about recent head or neck trauma, fever, rash, systemic illnesses, and other symptoms suggestive of a systemic disease, is essential to screen for possible secondary causes of headache (e.g., a malar rash suggestive of systemic lupus erythematosus, fever suggestive of infection/meningitis or encephalitis).

Along with a detailed headache history, a child's general medical history including past medical history, family history, and social history is very important. Ask about other comorbid medical conditions (i.e., chronic diseases, malignancy, hypercoagulability states, and neurocutaneous disorders). It is important to ask about family history of any type of headaches—not just migraines because often family members have not received a formal diagnosis of "migraine." They may say that they have a sinus headache, stress headache, or menstrual-related headache while "migraine" is denied. Self-diagnosed sinus headache is nearly always a migraine [33].

Exploring the social history in the pediatric and adolescent populations including a HEADSS (Home, Education/employment, peer group Activities, Drug use and abuse, Sexuality, and Suicide/depression) assessment is important [34], as social and life stressors can be significant contributors to headaches and often need to be addressed before there is clinical improvement. A dysfunctional family situation, regular consumption of alcohol, caffeine ingestion, smoking, a low level of physical activity and, bullying by peers are social risk factors for chronification of headache in children and adolescents [4].

All medications that the patient is taking, including over-the-counter medications, supplements, any failed abortive or prophylactic headache medications and the frequency of abortive medication should be discussed.

5.2 Physical Examination

Thorough general and neurological examination should be performed on all headache patients. Aspects of the general examination include careful attention to the vital signs (temperature, heart rate, and blood pressure), cranial bruits, the Müller sign to assess for sinus infection, assessing for meningeal signs, allodynia (abnormal pain sensation with a light touch, often associated with a migraine), and inspection of the skin for neurocutaneous stigmata. The neurological examination should assess for abnormalities in mental status, cranial nerves, strength, sensation, and reflexes. Gait examination should be performed along with assessment for ataxia, balance, and coordination. The examination is not considered complete without a funduscopic examination as the presence or absence of optic nerve edema is very important in determining whether the patient's headaches have a secondary etiology.

5.3 Evaluation (Laboratory Investigations/Imaging)

By performing the above history and physical examination, any "red flags" suggesting a secondary etiology for headaches may be uncovered. Red flags for secondary headaches are mentioned in detail in Table 4. The diagnosis of a primary headache

Table 4 Red flags for secondary headaches are as follow

1. Less than 6-month duration
2. Headache associated with confusion, mental status changes, or focal neurological complaints
3. Atypical presentation of the headache: Vertigo, intractable vomiting, and headache waking the child from sleep
4. Lack of family history of migraine
5. Progressive course
6. Acute, severe onset (first or worse ever)
7. Change in the headache characteristics or severity
8. Abnormal neurologic exam
9. Consistently worse in the morning
10. Worsening with Valsalva
11. Positional headaches
12. Comorbid seizures or fever
13. Symptoms of systemic illness
14. High-risk population (patients with sickle cell anemia, malignancy, recent head trauma, ventricular-peritoneal shunt, others)
15. Increased head circumference
16. Occipital location of the headache
17. Child younger than 5 years of age

Adapted from [41, 42]. A positive answer to any of the above should make providers question the diagnosis of primary headache disorder and may warrant further workup

disorder is a clinical diagnosis and the American Academy of Neurology (AAN) practice parameter advises against routine laboratory studies, lumbar puncture, EEG, and neuroimaging in patients without red flags and a normal neurologic examination in children with recurrent headaches [3].

If the presence of a secondary headache is likely, further investigation including laboratory evaluation, EEG, neuroimaging, or lumbar puncture may be warranted. Brain MRI is the modality of choice to investigate potential structural abnormalities, infection, inflammation, and ischemia; however, a computed tomography scan is preferred if there is a concern for hemorrhage or fracture. If there is a suspicion for elevated ICP and the neuroimaging results are normal, lumbar puncture with measurement of opening pressure and measurement of CSF indices is appropriate.

5.4 Treatment

Once a diagnosis of migraine or tension headache has been established and serious secondary causes of headache have been excluded, headache education and management can begin.

Education about primary headaches, confident reassurance about the absence of serious underlying neurologic disease, outlining treatment strategies, and establishing realistic goals for the child and their family are essential.

Treatment of migraines in children consists of a multifaceted approach including (A) lifestyle modification; (B) acute headache management; (C) complementary therapies; and (D) preventive treatment.

Goals of migraine or TTH treatment include reduction of headache frequency, severity, duration, and resultant disability.

1. Lifestyle Modification:

   Healthy lifestyle habits should be an important focus in the treatment plan. These include adequate hydration, avoidance of potential triggers including caffeinated beverages and missed meals, regular sleep patterns, removing electronics from the bedroom at night, and regular exercise. Optimizing these factors can improve the chances of successful treatment. For those with anxiety, depression, or significant stressors, management should be addressed by stress management techniques, psychological therapy, or psychiatry referral when needed.
2. Acute Management in the Outpatient Setting:

   All patients with migraines should be given instructions on the appropriate use of abortive medications. The patient should be instructed to treat the headache as quickly as possible, use appropriate dosage, and have them available at all times (especially at school) to be effective. A combination of rest and hydration along with the medicine are important first steps and children will often naturally seek out dark, quiet spaces when they have a migraine and such accommodations may need to be made at school.

A physician should counsel patients and families that a series of medications may need to be used to find the most beneficial treatments for the patient. Usually start with oral analgesic, ibuprofen (most preferable), acetaminophen, or naproxen as an initial treatment option. If nonsteroidal anti-inflammatory drugs (NSAIDs) are not effective, consider using "triptans" (migraine-specific treatment) in appropriate circumstances. The "triptans" refer to a class of drugs that end in the words triptan eg. sumatriptan or rizatriptan. The mechanism of action of such drugs is through activation of 5-HT1B/1D receptors within cerebral and dural vessel walls causing vasoconstriction and inhibition of trigeminal perivascular nerve terminals. Activation of these receptors prevents the release of vasoactive neuropeptides and blocks depolarization of trigeminal axons, ultimately blocking the transmission of pain [35]. There are seven triptans available in the market but only four are approved by the FDA in the pediatric population [36]. Name and dosage are listed in Table 5. If one triptan fails to provide pain relief, a physician should offer an alternate triptan, to find the most effective agent to reduce pain [37]. One should prescribe a nonoral route when headache peaks in severity quickly, is accompanied by nausea and/or vomiting, or if oral formulations fail to provide pain relief.

Given the distinct mechanisms of action between medications in the triptan class and the NSAID class, the addition of an NSAID to a triptan may improve the rate of response to pain [37], so in adolescents whose migraine is incompletely responsive to a triptan, clinicians should offer ibuprofen or naproxen in addition to a triptan to improve migraine pain.

Triptans must not be prescribed to those with a history of ischemic vascular disease or accessory conduction pathway disorders of the heart. The side effects are relatively common but typically well tolerated and include tightness of the chest, tingling hands and feet, and nausea.

Antiemetic medications (Compazine, Phenergan, Zofran) can be useful adjuncts to the NSAIDs and triptans when patients have significant nausea and vomiting with their migraines. A detailed description of antiemetics is listed in Table 5.

Tension-type headache is most commonly self-treated with over-the-counter analgesics such as NSAIDs and acetaminophen. Treatment goals for children with episodic tension-type headache should include:

(a) Recommending effective analgesic agents, rest, and adequate hydration.
(b) Discovering and ameliorating any circumstances that may be triggering the headaches.
(c) Avoid using combination therapies containing either butalbital or opioids because of the risk of tolerance, dependency, toxicity, and the development of medication overuse headache.

Patients should not use acute treatments more than 2–3 days per week (<15 days per month for NSAIDs and <10 days per month for triptans) to avoid developing medication overuse headaches. Opiates (tramadol, percocet, oxycodone, and hydrocodone) and barbiturates combinations like fioricet are not indi-

Table 5 Common abortive medications used in pediatric migraine

Medication	Dosage range		Adverse effects; warning	Forms used in children	Notes
Analgesics					
Ibuprofen	7.5–10 mg/kg—Max 800 mg Q6h		GI upset, bleeding, kidney dysfunction	Syrup: 100 mg per 5 mL Chewable tablets: 100 mg Tablets: 200, 400, 500, 600, 800 mg	First line
Naproxen	5–10 mg/kg—Max 500 mg Q12h		GI upset, bleeding, kidney dysfunction	Tablets: 220,[a] 250, 375, 500 mg Liquid 125 mg/5 mL	First line, longer period of action
Acetaminophen	10–15 mg/kg—Max 1000 mg Q8h or 3000 mg total/day		Liver dysfunction	Chewable tablets: 160 mg Tablets: 325, 500 mg Elixir: 160 mg per 5 mL	First line, especially in patients with Contraindication or sensitivity to NSAIDs
Triptans					
Medication	*Available dosage(mg)*	*<40 kg*	*>40 kg*	*Notes*	
Rizatriptan (tablet or MLT)	5, 10	5 mg	10 mg	MLT and tablet both are FDA labeled for ages 6–17 years	
Almotriptan (tablet)	6.25, 12.5	6.25 mg	12.5 mg	FDA labeled for ages 12–17 years	
Zolmitriptan (tablet or MLT or NS)	2.5, 5	2.5 mg	5 mg	Nasal spray is FDA labeled for ages 12–17 years	
Sumatriptan (tablet)	25,50, 100	12.5–25 mg	50–100 mg	Combined sumatriptan/naproxen is labeled by the US FDA for ages 12–17 years: 10 mg/60 mg to 85 mg/500 mg	
Sumatriptan (NS)	5,20	5 mg	10–20 mg		
Sumatriptan (SQ)	3,6	0.1 mg/kg	4–6 mg		
Eletriptan (tablet)	20,40,80	20 mg	40–80 mg	Not specifically studied in children	
Longer-acting triptans					
Naratriptan (tablet)	1, 2.5	1 mg	2.5 mg		

(continued)

Table 5 (continued)

Medication	Dosage range		Adverse effects; warning	Forms used in children	Notes
Frovatriptan (tablet)	2.5	1.25 mg	2.5 mg	Not specifically studied in children	
Antiemetic					
Medication		Dosage		Forms used in children	
Prochlorperazine (Compazine)[a]		0.125–0.25 mg/kg every 4–6 h		Tablets: 5, 10, mg Syrup: 5 mg per 5 mL Suppositories: 2.5, 5 mg	
Promethazine (Phenergan)[a]		0.25–0.5 mg/kg every 6–8 h		Tablets: 12.5, 25, 50 mg Syrup: 6.25, 25 mg per 5 mL Suppositories: 12.5, 25, 50 mg	
Metoclopramide (Reglan)[a]		1–2 mg per kg (<10 mg)) every 4 h		Tablets: 5, 10 mg Syrup: 5 mg per 5 mL	
Hydroxyzine (Vistaril)		10–25 mg every 8–12 h		Syrup: 10 mg per 5 mL Tablets: 10, 25, 50 mg	
Ondansetron (Zofran)		0.15 mg/kg every 4 to 6 h		Orally disintegrating tabs 4, 8 mg	

MLT dissolving tablet (melt), *NS* nasal spray, *SQ* subcutaneous injection, *GI* gastrointestinal, *FDA* food and drug administration

[a]Coadministration of diphenhydramine with these medications can be effective in preventing or minimizing extrapyramidal side effects and dopamine antagonists carry a risk of prolongation of the QT interval so consider doing an electrocardiogram before the use [43]

cated for the treatment of primary pediatric headache disorders. Opiates may alter the pain response, increasing the risk of chronification of pain, and both compounds can lead to overuse headaches and addiction.

3. Common complementary therapies include vitamin supplementation (riboflavin, magnesium, melatonin, CoQ10), herbals (petadolex, feverfew), psychological therapies (biofeedback, cognitive behavioral therapy, relaxation therapy), and physical therapies (acupuncture and massage therapy), which can all be important tools for the treatment of migraine and tension-type headaches.
4. Preventive therapies are discussed in detail in Chap. 19 "Child with Chronic Headache"

6 Prognosis/Outcome

The prognosis and natural history of childhood headaches have not been well defined. The clinical picture of migraine may change with age in some patients. However, we still lack sufficient data to assess whether these changes are hereditary and whether early abortive and prophylactic treatments play a role in the clinical shifts or improvements of the temporal pattern.

It is important to advise children with headaches that the long term goal of management is to control rather than cure the headaches because approximately 70% will continue to experience headaches 30 years after diagnosis [38]. Encouraging children to identify the cause/triggers of their headaches and to subsequently manage the headaches with medicine or complementary therapies and precipitant avoidance appears to have long-term benefits.

Studies show that childhood headache persists into adolescence and adulthood, although the diagnoses changed over time [39]. Approximately one in four migraine patients had their diagnosis switched to TTH [39]. Headache prevalence increases with advancing age, especially in females, and stress factors are the most important determinants. However, male gender is associated with remission [38–40].

TTH is more likely than migraine to improve in the transition from childhood/adolescence to young adulthood. A switch to migraine was observed in 25% of patients. As in migraine, male gender was found to be associated with remission and early developmental disorders to be associated with persistence [39].

A better understanding of diagnostic criteria, early diagnosis, and comprehensive acute and preventive therapy for children and adolescents is key to curtailing progression and improving long-term outcomes - which in turn may influence the prevalence of headaches in adults.

7 When to Refer/Admit

Referral for neurologic consultation depends on the clinician's experience and comfort.

Children younger than 3 years of age experience primary headache syndromes infrequently, and a complete neurologic examination, including visualization of the fundus, though necessary, can be difficult. These younger patients should be referred.

Patients with a new severe headache of acute onset, headache with focal neurologic deficits, or papilledema should be referred to the emergency department for urgent neuroimaging.

Presence of "red flags" suggesting a secondary etiology for headaches may need a referral.

Most pediatric patients with migraine can be successfully managed by the primary care physician but if recurrent headache that has been present for at least 6 months and is not responsive to standard medical treatment including lifestyle modification and acute abortive treatment, they should be referred to a child neurologist or headache specialist.

Headache that results in missed school days, worsening of school participation (declining grades, extracurricular activity limitation), and limits the child's ability to lead a fulfilling life should be referred.

8 Prevention

Since migraine has a complex genetic, environmental, and psychosocial basis, prevention is not possible in most instances. Primary headaches especially migraine headaches remain underdiagnosed and undertreated in the pediatric population. Appropriate recognition is essential so that effective therapies can be employed to mitigate the negative impact of migraine on social and personal functioning while reducing the possibility of transformation to chronic migraine.

Similar to migraine, tension-type headache prevention is difficult but with treatment and stress management, will probably have them less often and milder in nature.

9 Clinical Pearls/Key Points

- Headache is a common complaint in the pediatric population and many times can cause significant anxiety for the family and the clinicians.
- Although most pediatric headaches are due to primary headache disorder or a secondary benign etiology, a stepwise approach is essential to avoid missing serious causes of headache.
- The examination is not considered complete without a funduscopic examination as the presence or absence of optic nerve edema is of foremost importance in determining whether the patient's headaches have a serious secondary etiology.
- Neuroimaging is not routinely indicated in children with normal neurologic examination findings who have recurrent headaches.
- If "red flags" for secondary headache are noted, further investigations including laboratory evaluation, EEG, neuroimaging, or lumbar puncture may be warranted.
- Migraine is the most common acute and recurrent headache affecting children. Symptoms of migraine in children may differ as compared to those in adults, and certain features may be inferred through behavioral observations.
- Educating the child and family about migraine is an important aspect of care.
- Treatment of headaches and migraines in children consists of a multifaceted approach including lifestyle modifications, abortive agents, preventive agents, and complementary therapies.

References

1. Hershey AD, Winner PK. Pediatric migraine: recognition and treatment. J Am Osteopath Assoc. 2005;105(4 Suppl 2):2S–8S.
2. Krogh AB, Larsson B, Linde M. Prevalence and disability of headache among Norwegian adolescents: a cross-sectional school-based study. Cephalalgia. 2015;35(13):1181–91.
3. Lewis DW, Ashwal S, Dahl G, Dorbad D, Hirtz D, Prensky A, et al. Practice parameter: evaluation of children and adolescents with recurrent headaches: report of the quality standards

Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2002;59(4):490–8.
4. Straube A, Heinen F, Ebinger F, von Kries R. Headache in school children: prevalence and risk factors. Dtsch Arztebl Int. 2013;110(48):811–8.
5. Collaborators GBDH. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018;17(11):954–76.
6. Group GBDNDC. Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Neurol. 2017;16(11):877–97.
7. Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States. Relation to age, income, race, and other sociodemographic factors. JAMA. 1992;267(1):64–9.
8. Stewart WF, Linet MS, Celentano DD, Van Natta M, Ziegler D. Age- and sex-specific incidence rates of migraine with and without visual aura. Am J Epidemiol. 1991;134(10):1111–20.
9. Anttila P. Tension-type headache in childhood and adolescence. Lancet Neurol. 2006;5(3):268–74.
10. Stovner L, Hagen K, Jensen R, Katsarava Z, Lipton R, Scher A, et al. The global burden of headache: a documentation of headache prevalence and disability worldwide. Cephalalgia. 2007;27(3):193–210.
11. Goldberg LD. The cost of migraine and its treatment. Am J Manag Care. 2005;11(2 Suppl):S62–7.
12. Lanteri-Minet M. Economic burden and costs of chronic migraine. Curr Pain Headache Rep. 2014;18(1):385.
13. Charles A. The pathophysiology of migraine: implications for clinical management. Lancet Neurol. 2018;17(2):174–82.
14. Maniyar FH, Sprenger T, Monteith T, Schankin C, Goadsby PJ. Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. Brain. 2014;137(Pt 1):232–41.
15. Hadjikhani N, Sanchez Del Rio M, Wu O, Schwartz D, Bakker D, Fischl B, et al. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. Proc Natl Acad Sci U S A. 2001;98(8):4687–92.
16. Bartsch T, Goadsby PJ. The trigeminocervical complex and migraine: current concepts and synthesis. Curr Pain Headache Rep. 2003;7(5):371–6.
17. Messlinger K, Fischer MJ, Lennerz JK. Neuropeptide effects in the trigeminal system: pathophysiology and clinical relevance in migraine. Keio J Med. 2011;60(3):82–9.
18. Ashina S, Bendtsen L, Ashina M. Pathophysiology of tension-type headache. Curr Pain Headache Rep. 2005;9(6):415–22.
19. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1–211.
20. Raieli V, Pitino R, Giordano G, Spitalieri C, Consolo F, Puma D, et al. Migraine in a pediatric population: a clinical study in children younger than 7 years of age. Dev Med Child Neurol. 2015;57(6):585–8.
21. Gelfand AA, Reider AC, Goadsby PJ. Cranial autonomic symptoms in pediatric migraine are the rule, not the exception. Neurology. 2013;81(5):431–6.
22. Stafstrom CE, Goldenholz SR, Dulli DA. Serial headache drawings by children with migraine: correlation with clinical headache status. J Child Neurol. 2005;20(10):809–13.
23. Youssef PE, Mack KJ. Episodic and chronic migraine in children. Dev Med Child Neurol. 2020;62(1):34–41.
24. Cuvellier JC, Mars A, Vallee L. The prevalence of premonitory symptoms in paediatric migraine: a questionnaire study in 103 children and adolescents. Cephalalgia. 2009;29(11):1197–201.
25. Karsan N, Bose P, Goadsby PJ. The migraine premonitory phase. Continuum (Minneap Minn). 2018;24(4, Headache):996–1008.

26. Kroner-Herwig B, Gassmann J. Headache disorders in children and adolescents: their association with psychological, behavioral, and socio-environmental factors. Headache. 2012;52(9):1387–401.
27. Mack KJ, Goadsby P. Trigeminal autonomic cephalalgias in children and adolescents: cluster headache and related conditions. Semin Pediatr Neurol. 2016;23(1):23–6.
28. Kahle KT, Kulkarni AV, Limbrick DD Jr, Warf BC. Hydrocephalus in children. Lancet. 2016;387(10020):788–99.
29. Spears RC. Low-pressure/spinal fluid leak headache. Curr Pain Headache Rep. 2014;18(6):425.
30. Choe MC, Blume HK. Pediatric posttraumatic headache: a review. J Child Neurol. 2016;31(1):76–85.
31. Hershey AD. Chapter 14: sinus headache and nasal disease. Pediatric headaches in clinical practice. West Sussex, UK: Wiley-Blackwell; 2014. p. 172–9.
32. D'Amico D, Grazzi L, Usai S, Andrasik F, Leone M, Rigamonti A, et al. Use of the migraine disability assessment questionnaire in children and adolescents with headache: an Italian pilot study. Headache. 2003;43(7):767–73.
33. Patel ZM, Kennedy DW, Setzen M, Poetker DM, DelGaudio JM. "Sinus headache": rhinogenic headache or migraine? An evidence-based guide to diagnosis and treatment. Int Forum Allergy Rhinol. 2013;3(3):221–30.
34. Cohen E, Mackenzie RG, Yates GL. HEADSS, a psychosocial risk assessment instrument: implications for designing effective intervention programs for runaway youth. J Adolesc Health. 1991;12(7):539–44.
35. Kroger IL, May A. Triptan-induced disruption of trigemino-cortical connectivity. Neurology. 2015;84(21):2124–31.
36. Oskoui M, Pringsheim T, Holler-Managan Y, Potrebic S, Billinghurst L, Gloss D, et al. Practice guideline update summary: acute treatment of migraine in children and adolescents: report of the guideline development, dissemination, and implementation Subcommittee of the American Academy of neurology and the American headache society. Neurology. 2019;93(11):487–99.
37. Practice guideline update summary. Acute treatment of migraine in children and adolescents: report of the guideline development, dissemination, and implementation Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2020;94(1):50.
38. Dooley JM, Augustine HF, Brna PM, Digby AM. The prognosis of pediatric headaches—a 30-year follow-up study. Pediatr Neurol. 2014;51(1):85–7.
39. Antonaci F, Voiticovschi-Iosob C, Di Stefano AL, Galli F, Ozge A, Balottin U. The evolution of headache from childhood to adulthood: a review of the literature. J Headache Pain. 2014;15:15.
40. Brna P, Dooley J, Gordon K, Dewan T. The prognosis of childhood headache: a 20-year follow-up. Arch Pediatr Adolesc Med. 2005;159(12):1157–60.
41. Raucci U, Della Vecchia N, Ossella C, Paolino MC, Villa MP, Reale A, et al. Management of childhood headache in the emergency department. Review of the literature. Front Neurol. 2019;10:886.
42. Kabbouche MA. Chapter 3: diagnostic testing and concerning variants. Pediatric headaches in clinical practice. West Sussex, UK: Wiley-Blackwell; 2009. p. 24–5.
43. Greene K, Irwin SL, Gelfand AA. Pediatric migraine: an update. Neurol Clin. 2019;37(4):815–33.

Child with New Onset Paraparesis

Erin E. Neil Knierbein

1 Introduction

Acute or subacute onset of bilateral leg weakness must be viewed as a medical emergency. Paraparesis is defined as weakness affecting both lower extremities whereas paraplegia describes complete paralysis. The precise differentiation between partial and complete loss of leg movement is less important than recognition of new onset bilateral leg weakness. In young children, particularly those who are not yet walking independently, or only beginning to walk, clinical assessment of leg weakness if often particularly challenging. A relatively common error in clinical assessment of young children with new onset leg weakness is the assumption that preservation of some residual spontaneous or stimulus-evoked movement argues against the need for urgent evaluation of paraparesis. Most etiological conditions that cause paraparesis can also cause paraplegia.

Acute onset of bilateral leg weakness is most likely attributable to an injury or disease in the spinal cord. Acute leg weakness requires immediate evaluation because neural tissue in the spinal cord is highly vulnerable to irreversible injury, and in some cases, rapid intervention can significantly mitigate on-going injury and restore function.

An understanding of spinal cord anatomy clarifies the clinical features that emerge with distinct types of spinal cord injury or disease.

The spinal cord is an integral element of the central nervous system and this neural structure extends from the brainstem to around the level of the first or second lumbar vertebrae and ends in the conus medullaris and then the cauda equina, which contains spinal nerves. The spinal cord is contained within the vertebral column, and has four divisions: cervical, thoracic, lumbar and sacral [1]. Constituents of the

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spinal cord include intrinsic neurons, and axons, that convey signals from the brain to the rest of the body to regulate movement and others that provide sensory input from the body to the brain. The third major group of axons regulates autonomic activity. An injury of the spinal cord disrupts motor and/or sensory function, as well as autonomic function, below the level of injury. Function of the lower extremities is controlled by nerves which originate between the mid-thoracic and lumbar spinal cord levels. Therefore, the acute onset of bilateral lower extremity paraparesis or paraplegia localizes to disruption of function in the thoracic or lumbar spinal cord. Injury to the lower thoracic or upper lumbar cord can also impair leg sensation as well as bladder and bowel function. The severity and distribution of deficits is dependent on the precise anatomic locus of injury.

The anatomy of the spinal cord influences the signs and symptoms caused by injuries or disruptions of the lateral, dorsal, or ventral/anterior portions. The lateral portions of the spinal cord contain the descending lateral corticospinal tract and rubrospinal tract, both of which control movement of the extremities. There are also descending pathways in the lateral cord which control urinary sphincter function. The lateral and anterior/ventral cord contains the corticospinal tracts which, when acutely injured, cause flaccid weakness and hyporeflexia. The dorsal cord contains the autonomic tracts for bladder control. The ventral/medial/anterior portion of the cord generally carries motor (descending) information from the brain to the extremities and sends pain and temperature information from the extremities to the brain (ascending) [2].

This chapter will focus primarily on the evaluation and treatment of acute/subacute onset of leg weakness in previously healthy children.

Both extrinsic injury (compressing spinal cord structures) and intrinsic abnormalities (i.e., arising within spinal cord) can result in acute paraparesis. Urgent evaluation may reveal an opportunity for surgical decompression that can enable restoration and preservation of strength, sensation, and autonomic function. However, given the high risk for rapid onset of irreversible damage to nerves and tracts in the spinal cord, the time window for effective surgical intervention is quite brief.

2 Epidemiology and Etiology

Acute onset of paraparesis or paraplegia is less common in children than adults. Children are at high risk for delayed diagnosis of potentially treatable spinal cord compression, in view of lack of familiarity with these clinical syndromes [3]. It is important for pediatricians and other primary care providers to be aware of clinical symptoms or presentations that necessitate urgent assessment.

There are many possible etiologies for new onset paraparesis in children. In some cases, deficits may have had an indolent onset, and it is only in retrospect that the duration of progressive leg weakness becomes apparent (e.g., with compressive lesions), whereas in other cases there is a very rapid onset of paraplegia (e.g., with traumatic lesions or strokes affecting the spinal cord).

A practical approach to thinking about the etiology of paraparesis is to consider intrinsic (within the spinal cord) and extrinsic (outside the spinal cord) mechanisms separately.

3 Intrinsic Lesions

Intrinsic causes refer to etiologies affecting the spinal cord itself, whether arising from within the cord or from a more systemic process which results in involvement of spinal cord function.

3.1 Inflammatory, Para-Infectious, and Postinfectious Causes

Transverse myelitis is a well-defined clinical syndrome in children. It typically presents with leg weakness, of variable degree, often accompanied by pain or paresthesias, and sphincter dysfunction, i.e., constipation and urinary retention [4, 5]. Transverse myelitis can be idiopathic, i.e., without an identified cause, can follow a provocative systemic illness (such as measles, varicella, influenza, or adenovirus) or immunization, or be a manifestation of a systemic autoimmune disorder. Neuromyelitis Optica (NMO) is a well-defined central nervous system demyelinating disease that occurs both in children and adults, and characteristically affects the optic nerves and spinal cord and is associated with the NMO antibody [4]. In children, as in adults, multiple sclerosis may also affect the spinal cord in addition to the brain. More recently, transverse myelitis has been described in the setting of COVID-19 infection [5].

Guillain–Barré syndrome, which often occurs after a viral, sometimes gastrointestinal, illness, causes inflammation of nerves in the peripheral and central nervous system. It classically presents as ascending weakness which can progress quickly from mild weakness to flaccid paralysis, involving first the lower extremities and eventually upper extremities and even the diaphragm (which threatens breathing) [4]. These patients can experience pain and paresthesias [4, 6]. Often, children have low back or leg pain, which may cause initial confusion about the true diagnosis [7].

A distinctive pediatric syndrome that has garnered attention in recent years is acute flaccid myelitis. The temporal clusters of cases in late summer and early autumn and association with specific enterovirus serotypes have implicated both para- and postinfectious mechanisms of spinal cord pathology; no single infection has been implicated in all cases. Some studies suggest that the underlying mechanism of acute weakness is direct infection of spinal cord motor neurons, analogous with poliomyelitis; however, an autoimmune response to infection has not been fully excluded [8, 9].

3.2 Ischemia

In an otherwise healthy child, spinal cord ischemic injury resulting in acute paraparesis is exceedingly rare. However, in children who have undergone recent major cardiovascular surgery, embolic or hypoperfusion mechanisms could result in spinal cord ischemia. Another scenario which can result in acute ischemic spinal injury after minor trauma is extrusion of vertebral disk material into a spinal artery, resulting in a fibrocartilaginous embolism [10] that compromises blood flow to the spinal cord. A characteristic feature of this syndrome is a hyperacute onset and rapid progression to maximum disability—often within 4 h [4]. Vascular malformations can bleed spontaneously or after minor trauma and the resulting hemorrhage within or compressing the spinal cord can lead to paraparesis; these congenital malformations are rarely diagnosed prior to a catastrophic bleed.

3.3 Tumors

Only about 25% of all pediatric spinal cord tumors are intrinsic or intramedullary [4] and only 1%–10% of all pediatric central nervous system (CNS) tumors arise within the spinal cord [3, 11]. These include astrocytomas, ependymomas, or hemangioblastomas. The presentation may not be acute and often the first complaint is of back pain and then stiffness of paraspinal muscles caused by pressure from expansion of the spinal cord and thecal sac. While outside the scope of this article, an intramedullary tumor of the cervical spine can present with torticollis or symptoms of cranial nerve palsies (dysphagia, dysphonia, or dyspnea), in addition to paraparesis [4]. While these tumors are usually low-grade, their location within the spinal cord often renders them inoperable or not completely resectable.

4 Extrinsic Lesions

4.1 Infectious

The vertebral disk, a highly vascular structure between the vertebral bodies, can be a site of infection; microabscesses that arise within a disk can spread to compress the spinal cord from the ventral surface. This type of progression often occurs over a 2–4-week period and results in gradual onset of leg weakness. Children may exhibit refusal to walk, back pain, fever, irritability or even abdominal pain. Most commonly staphylococci or streptococci are the causative organisms [12].

Although uncommon in healthy children, abscesses can develop in the epidural space and compress the spinal cord. Typically, this results in dorsal compression with signs and symptoms that reflect pressure on the posterior columns. The dorsal/posterior spinal cord primarily relays sensory symptoms. If this is the etiology of lower extremity paraparesis, typically the child would usually

have additional risk factors such as congenital heart disease, immune system disorder, or dermal sinuses [4, 13].

Tuberculosis, which is now unusual in children in well-resourced settings but continues to be an important cause of infection in low- and middle-income countries, can cause paraparesis as a result of paraspinous abscesses that result in spinal cord compression.

4.2 Trauma

Trauma to the spinal cord most often results in damage to the cervical spinal cord, because of the relatively bigger size of the head to the body in children as compared to adults. Cervical cord trauma results in weakness of both the arms and legs, which while technically not paraparesis, is also a medical emergency. Falls, commonly the cause of trauma in the pediatric population, can result in trauma to other areas of the spine. In an illustrative case, trauma causing a L1 vertebral fracture and spinal cord injury resulted in saddle (perineal) anesthesia and urinary retention in an adolescent who fell out of a tree; Fig. 1 provides a representative sagittal MRI image. Children with Down syndrome and those who have hereditary disorders of connective tissue are susceptible to atlanto-axial subluxation.

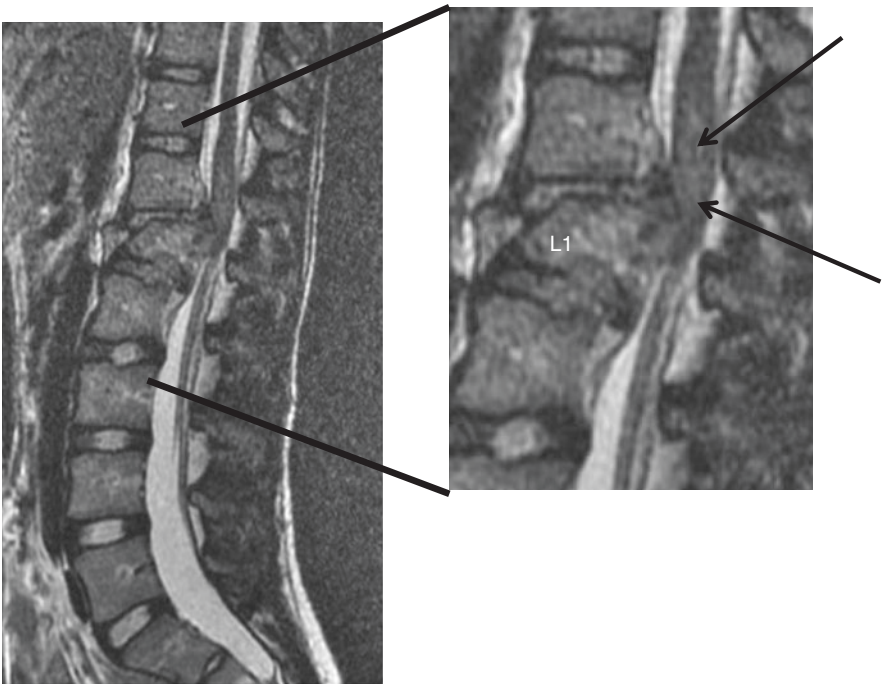

Fig. 1 Sagittal T2-weighted spinal MRI spine of a 15-year-old adolescent who fell out of a tree. The MRI demonstrates a vertebral compression fracture and edema of the conus medullaris (bold arrows). The patient experienced saddle anesthesia and urinary retention

4.3 Tumor

In children, 75% of spinal tumors are of extradural (exterior to the duramater, that encases the spinal cord) or intradural-extramedullary (within the duramater but outside of the substance of the spinal cord) origin. Neuroblastoma is the most common extradural tumor in children. Other extradural tumors include bone tumors and extra-spinal tumors that invade into the spine [4]. As an example of a bone tumor arising from the vertebrae, the MR imaging from an infant who had reduced leg movement due to Langerhans cell histiocytosis which caused collapse of the T1 vertebrae and invasion of the spinal cord is presented in Fig. 2. Bone tumors often present with pain because of the destruction of the bone and subsequent collapse of vertebrae and compression of the spinal cord.

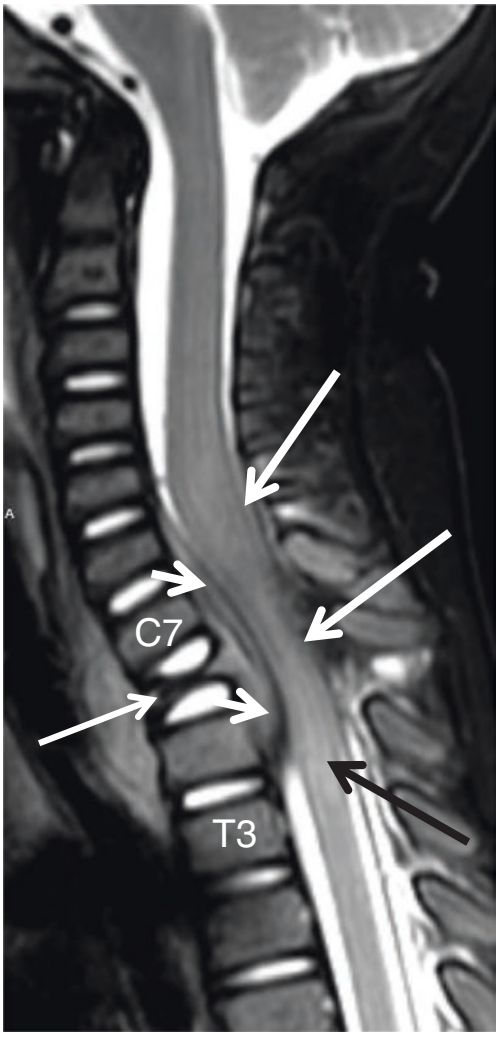

Fig. 2 Sagittal T2-weighted MRI from an infant with reduced leg movement. The child was found to have Langerhans Cell Histiocytosis with collapse of the T1 vertebral body (white arrow), invasion of spinal canal (white arrowheads) and spinal cord compression with edema (three bold black arrows)

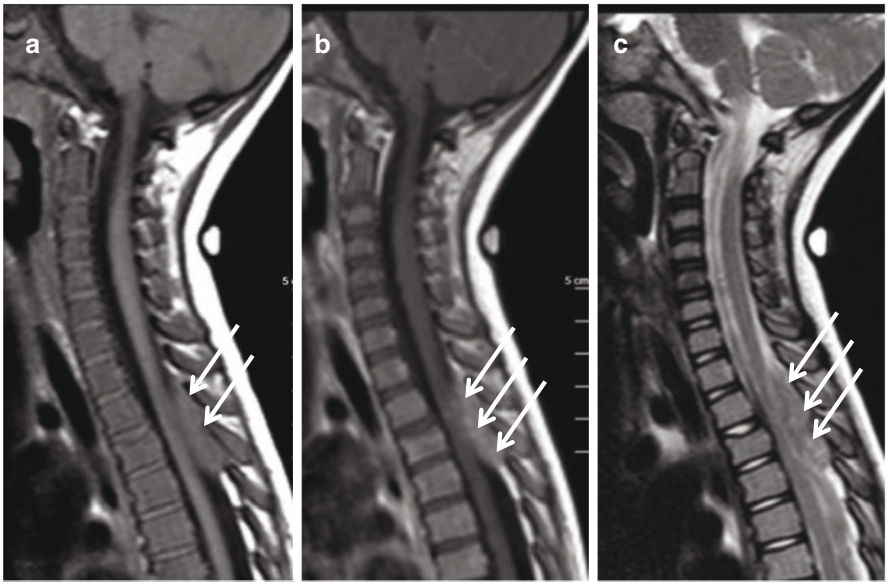

Fig. 3 Sagittal spine MRI of metastatic neuroblastoma in a 3-year-old child. The metastasis are highlighted by white bold arrows. The tumor at levels T1–T3, caused compression of spinal cord. The patient had upper extremity sensory changes and was also found to have a palpable abdominal mass. (**a**) T1-weighted sequence, (**b**) Postcontrast T1-weighted, (**c**) T2-weighted

A classic pediatric spinal cord tumor is the compressive neuroblastoma. Neuroblastoma can be metastatic in very young children, and in this case may present with abdominal masses as well as compression of the spinal cord. The child whose MR images are presented in Fig. 3 had changes in arm sensation as a result of upper thoracic spinal cord compression due to metastatic neuroblastoma. Both the spinal cord and spinal roots can be compressed, often in the paravertebral area. These tumors can be quite large and result in bilateral or asymmetric leg weakness.

Intradural-extramedullary tumors are not within the spinal cord but still within the meninges covering the cord; [4] these are the least common spinal cord tumor type in children and include neurofibromas and Schwannomas. Such tumors cause pain and symptoms of cord compression, including leg weakness.

4.4 Differential Diagnosis

Transverse myelitis, Guillain–Barré syndrome or acute flaccid myelitis are all in the differential in a child with recent viral illness who has acute bilateral leg weakness. Onset of weakness in these conditions is relatively rapid, on the order of hours to days. Infections, abscesses or direct infection of the spinal cord with tuberculosis, more often evolve over days to weeks, and are more common in an immunocompromised child. Presence of fever or back pain would suggest consideration of an

infection. Indolent changes in gait or bowel or bladder function should prompt consideration of a tumor or mass in the spinal cord as the cause for a slow progression of leg weakness. Trauma would be expected to have the most acute presentation of paraparesis and could affect any level of the spinal cord.

5 Diagnostic Approach

The clinician must concurrently think about the neuroanatomic localization of new onset leg weakness and identify the underlying cause. Some of the above etiologies for paraparesis have similar presenting symptoms but may differ in the cadence of onset of symptoms. The history, physical examination, and essential urgent neurodiagnostic evaluation all play important roles. In some cases, even when the likelihood of spinal cord pathology as a cause of leg weakness is quite low, consideration of myelopathy takes precedence in the evaluation to ensure that opportunities for treatment are not missed.

5.1 History

Historical aspects regarding the speed and order of onset of symptoms (e.g., whether the child first developed pain, weakness, or bowel or bladder dysfunction) can provide clues regarding the underlying cause. Additionally, symmetric versus asymmetric weakness points to different etiologies.

It can be particularly challenging to recognize and evaluate new lower extremity weakness accurately in young children. A young child may stop walking but the range of underlying mechanisms and causes is broad and includes weakness, pain, ataxia, and systemic illness. Additionally, recognition of concurrent changes in bowel and bladder function can be more difficult to recognize in a child not yet toilet trained. A nonverbal or young child with limited speech may struggle to express what they are or are not feeling during a sensory examination.

Obtaining a history from the patient or family regarding recent febrile, upper respiratory or gastrointestinal illnesses; exposures to immunosuppressant medications or to people who are at higher risk of being infected with tuberculosis is helpful. Information regarding recent procedures, especially those involving prolonged anesthesia and risk of systemic hypoperfusion as well as spinal surgery; trauma; or other systemic medical conditions may help direct the evaluation. It is also relevant to ask about recent onset of other neurological or systemic symptoms, or known underlying systemic disorders (e.g., lupus).

Children who have recently undergone major surgery, especially cardiac surgery, could have an ischemic cause of acute onset of bilateral leg weakness. A child who has sustained major trauma would be expected to present via ambulance but minor trauma may be less obvious and therefore should be a consideration in any child with acute onset of lower extremity weakness.

5.2 Physical Examination

5.2.1 General Examination

Evaluation of vital signs, including presence of fever, possibly indicating infectious cause, and reduced blood pressure or reduced heart rate, may point toward spinal shock. Spinal shock refers to the acute period after a spinal cord injury, during which muscle tone is flaccid, deep tendon reflexes are absent, and input from the sympathetic nervous system is interrupted. The parasympathetic nervous system provides more input, causing decreased blood pressure [2, 14]. A patient with a paravertebral abscess will often have a fever and may have pain to palpation of the spinal processes and back.

5.2.2 Neurological Examination

Mental status and cranial nerves are not expected to be affected if the child has isolated paraparesis; however, pain may interfere with a child's ability to communicate effectively. The Miller Fisher subtype of Guillain–Barré is an exception and involves ophthalmoplegia (weakness of muscles that control eye movements), lack of deep tendon reflexes and ascending weakness. A toddler with erratic and irregular eye movements in numerous directions (i.e., opsoclonus), in the setting of lower extremity weakness and/or bowel and bladder control abnormalities, should be evaluated for neuroblastoma [15].

Strength and power are assessed in several ways. It is important to observe spontaneous movements, and discrepancies between reported leg weakness and normal movement and strength while recumbent would raise concerns about a functional etiology of reported leg weakness, particularly in an older child or adolescent. Formal measurement of strength may be challenging in the emergency setting but could be particularly useful for evaluation of the progression of weakness over the initial period of evaluation.

Strength evaluation encompasses measuring effort against gravity and the examiner's resistance. Upper extremities would be expected to be spared in most children with paraparesis, at least initially. Lower extremity strength is conventionally measured using a standardized motor grading scale (Medical Research Council) where 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. However, scoring differences may emerge among examiners, particularly individuals who do not frequently perform this type of testing. This evaluation should be complemented with descriptions of observed spontaneous movement.

Assessment of tone is completed by manipulating the legs to flexion and extension of the joints (hips, knees, and ankles) and assessing the amount of resistance provided (low-hypotonic, normal, or increased-hypertonic or spastic). Deep tendon reflexes are measured with a scale of 0 absent, 1+ slight but present response, 2+ brisk response, 3+ very brisk response, 4+ a tap elicits clonus. Reflexes are

classically increased (3+ or 4+, clonus) in upper motor neuron lesions, as would result from an established spinal cord injury. It is important to be aware that contrary to expected evidence of hyper-reflexia with spinal cord lesions, reflexes may be decreased (1+) or absent and accompanied by flaccid tone in the setting of acute spinal cord injuries ("spinal shock"). Therefore, difficult to elicit deep tendon reflexes do not eliminate diagnostic consideration of a spinal cord lesion. Similarly, initially, following a spinal cord injury or lesion, plantar stimulation may not elicit the expected Babinski response (i.e., upgoing great toes).

Evaluation of sensation is dependent, at least in part, on the patient's report, and this can be challenging in young children, particularly for modalities other than pinprick (which is more likely to elicit a behavioral response). The degree of sensory impairment and the modalities affected are dependent on the anatomical extent of spinal cord injury. The priority in the sensory examination in the setting of possible spinal cord injury is to determine if there is a specific level below which sensation is impaired.

Since the spinal nerve roots leave the spinal cord and provide sensory innervation to relatively consistent areas of skin, the level at which an injury has occurred can be assessed by testing sensation to light touch and pin prick. To assess for a sensory level, the examiner should evaluate both the loss of sensation when testing from head to foot and the level above which sensation appears when testing upward from the feet toward the face. Delineation of a specific level may not be precise, but even in infants a change in awareness of sensation (e.g., to pinprick) can often be inferred. Importantly the sensory level can be different from the spinal cord level at which motor function is affected (e.g., if there is more extensive anterior vs. posterior cord injury).

Other important elements of the examination include evaluation for bladder distension, and rectal tone via a digital rectal examination. Identification of urinary retention in particular, should accelerate evaluation for spinal cord pathology.

Elements in the physical examination contribute to distinguishing acute flaccid myelitis, transverse myelitis, and Guillain–Barré syndrome (highlighted in Table 1). Weakness in transverse myelitis is usually symmetric and children often complain of pain and on examination may have a distinct sensory level; early urinary

Table 1 Differences and similarities between transverse myelitis, acute flaccid myelitis, and Guillain–Barré syndrome

Condition	Motor	Sensory	Bowel/Bladder
Transverse myelitis	Leg weakness. Most often symmetric	Numbness/sensory loss usually present, often also with pain/paresthesias	Sphincter dysfunction, constipation, urinary retention
Acute flaccid myelitis	Weakness of any combination of extremities, often asymmetric	Typically no sensory loss but can have pain and paresthesias	Less often have bowel or bladder changes
Guillain-Barré syndrome	Ascending weakness, can also affect respiratory diaphragm and breathing	May have pain or paresthesias	Can have urinary retention and constipation, though uncommon

dysfunction is common. Acute flaccid myelitis most often has asymmetric weakness, which may involve upper and lower extremities, and usually does not manifest changes in bowel or bladder function. In Guillain–Barré syndrome, weakness can be symmetric or asymmetric, and typically ascends proximally quite rapidly; deep tendon reflexes are often lost early, and eye movement abnormalities (e.g., sixth nerve palsies) and asymmetric facial weakness may be evident quite early in the course [12]. Pain or paresthesias are often reported early in Guillain–Barré syndrome (and may precede weakness); up to 40% of patients will have some sensory involvement [12]. However, transverse myelitis and acute flaccid myelitis may also be accompanied by paresthesias or hyperesthesia (increased sensitivity to tactile stimulation), perceived as discomfort [8].

Spinal cord tumors can result in a slower, indolent change to a child's gait with symmetric or asymmetric weakness, sometimes with changes in bowel and bladder function and other systemic symptoms, such as back pain or changes in balance. Increased deep-tendon reflexes in the lower limbs, hypertonicity, and positive plantar responses point to more long-standing spinal cord lesions.

6 Evaluation (Laboratory Tests and Imaging)

For children with acute paraparesis, a plain X-ray of the abdomen and spine may provide initial information [16], but the most important study is typically magnetic resonance imaging (MRI) with and without contrast of the thoracic, lumbar and sacral spine. Depending on the MRI results, as well as the level of concern for Guillain–Barré syndrome, a lumbar puncture may be indicated. Cerebrospinal fluid in Guillain–Barré syndrome will demonstrate elevated protein but normal cell counts, also described as albuminocytologic dissociation. The MRI must be performed and reviewed prior to the lumbar puncture to exclude any mass or infection which could change the safety of the procedure. If Guillain–Barré syndrome is a consideration, the MRI must be completed with contrast in order to evaluate for contrast enhancement of the anterior roots of the cauda equina [4]. In the rare case of a vascular cause of acute paraparesis, angiography of the spine vasculature could be considered. If there is suspicion for infection, laboratory evaluation including complete blood count (CBC) with differential count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and viral polymerase chain reaction (PCR) in CSF along with blood and CSF cultures may be helpful.

When multiple sclerosis, acute disseminated encephalomyelitis, or other rarer demyelinating disorders such as neuromyelitis optica syndrome are diagnostic considerations, MRI of both spine and brain should be performed. Unexpected (and possibly asymptomatic) patchy MRI abnormalities in the brain and/or cervical spinal cord can guide further diagnostic and treatment plans.

Spinal MRI in idiopathic transverse myelitis may be normal, especially early on, but can also show an expanded, hyperintense spinal cord (as illustrated in Fig. 4). The imaging abnormality in transverse myelitis should span more than 3–4

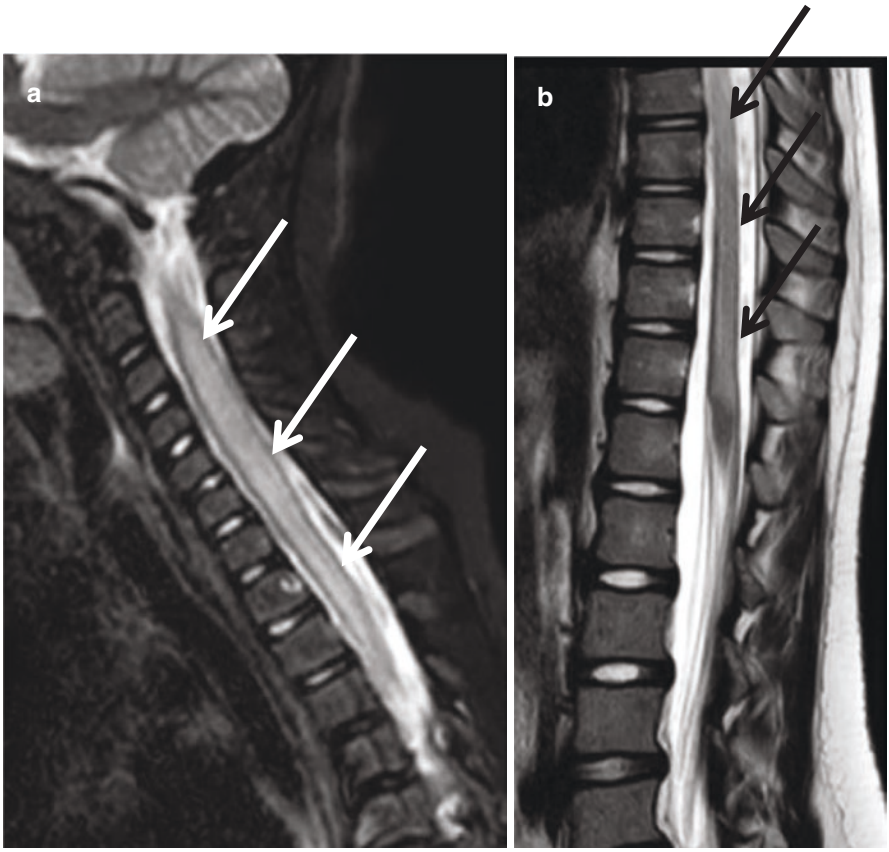

Fig. 4 Sagittal T2 MRI of young child with transverse myelitis. MRIs demonstrate holo-cord expansion and swelling at multiple levels. This patient presented with rapid onset of lower extremity weakness with inability to bear weight or to stand independently. Acute changes in breathing occurred in the emergency room, leading to pediatric intensive care unit admission. (**a**) Cervical and upper thoracic spinal cord involvement, white arrows. (**b**) Lower spinal cord at conus medullaris involvement, black arrows

vertebral levels and involve more than two-third of the cross-sectional area of the cord [3]. The spine abnormalities and lesions involve white matter or both gray and white matter of the spinal cord [8].

The spinal lesions in acute flaccid myelitis typically are isolated to the gray matter [8]. The MRI images in vertebral discitis or an intraspinal abscess will show enhancement with gadolinium. Blood work, including CBC with differential, ESR and CRP should also be ordered if infection is suspected. When a tumor is suspected, an MRI with and without contrast should be completed as the post contrast images will typically show enhancement, indicating disruption of the barrier between the blood and the central nervous system, of which the spinal cord is an important part.

7 Treatment/Management

The initial treatment and management involves stabilization of the patient while monitoring for spinal shock and vital sign instability. Often admission to a pediatric intensive care unit is needed to provide close evaluation and frequent assessments for progression of neurologic signs or symptoms. Evaluation and monitoring for progression of weakness to involve upper extremities and the respiratory diaphragm is essential as this requires rapid intervention. Testing respiratory function at a regular schedule may be possible in an ICU with a cooperative child. The use of methylprednisolone in acute spinal cord injury is controversial, both in adults and children. There have not been any randomized controlled trials in pediatric populations and although there may be slight short-term improvements in motor scores if administered within 8 h of the injury, there do not seem to be any long-term differences in function and increased risk of side effects [17–19]. While there are no Food and Drug administration (FDA)-approved drugs for the treatment of children with acute transverse myelitis, retrospective analysis and open-label studies seem to indicate that empiric treatment with intravenous methylprednisolone at a dose of 30 mg/k/g/day for 3–5 days may be beneficial [6].

The recommended treatment of Guillain–Barre syndrome is either 2 gm/kg over 2 days of intravenous immunoglobulin (IVIG) or 5 plasma exchange (PE) treatments over 2 weeks [20]. There is no evidence that using both IVIG and PE is better than either individually. Acute flaccid myelitis treatment is less straightforward. IVIG is widely used given its proposed mechanism of containing antibodies to enterovirus strains, but there are not randomized trials to support this [21]. Additionally, there is not clear data supporting the use of steroids, plasma exchange, fluoxetine or anti-viral drugs [21, 22]. High-dose IV corticosteroids, typically methylprednisolone, 30 mg/kg/dose, once daily for 3–5 days are used in the treatment of pediatric transverse myelitis [6]. Plasma exchange as well as IVIG are also used but with less definitive recommendations. Plasma exchange may also be helpful in children with myelitis in the setting of NMO.

Depending on the etiology, emergent neurosurgical consultation may be needed, for example, if imaging demonstrates a tumor or abscess or hematoma requiring drainage or relief of pressure. An infectious disease specialist can assist in choice of antibiotics to treat infection. If tumor or mass is discovered, an oncologist is needed to provide expertise and recommend the best way to obtain tissue for diagnosis, and most effective treatments for each tumor type. Although not initially indicated, for long term management of changes in function, physical medicine and rehabilitation specialists are key to planning return to school, home, and the community. Similarly, physical and occupational therapy are helpful after the acute period has elapsed.

8 Prognosis/Outcomes

Prognosis and outcomes after paraparesis are highly dependent on the etiology as well as the timing and extent of any interventions. A detailed discussion of this is outside the scope of this chapter.

Patients with Guillain–Barré syndrome, transverse myelitis, and acute flaccid myelitis may have variable degrees of recovery of motor function and may take up to several years to reach a new baseline. Oncologic etiologies for paraparesis also vary in outcomes depending whether the tumor can be removed, treated with radiation therapy or chemotherapy. The prognosis after infections of the spinal cord or epidural space rely on how early in the process the infection is recognized and treatment initiated.

9 When to Refer/Admit

Examination findings of new onset bilateral or asymmetric weakness in a pediatric patient almost always justify emergent evaluation and usually subsequent hospitalization. The initial examination and assessment may be difficult to interpret and symptoms can evolve rapidly. Weakness can progress from the legs to involve upper extremities or respiratory muscles—rapid intervention is required if declining respiratory function is detected. For this reason, admission to an intensive care unit with frequent respiratory function monitoring may be indicated. A multidisciplinary inpatient pediatric team may provide the best approach to diagnosis and treatment. Patients with malignancy may be eligible and benefit from radiation therapy which is often time sensitive.

10 Clinical Pearls/Key Points

- A plain X-ray of the chest and abdomen may identify a paraspinal mass which provides timely information to guide next steps but normal X-rays may not rule out significant pathology.
- If compression of the spinal cord is suspected, early consultation with neurosurgery can be essential for diagnosis and preservation of motor function through rapid treatment initiation.
- In the setting of acute spinal shock or injury, tone will initially be flaccid and deep tendon reflexes decreased. Spasticity and hyper-reflexia are often absent in an acute cord lesion (hours to days) but become apparent when the lesion is chronic (weeks to months).

References

1. Kirshblum SC, Burns SP, Biering-Sorensen F, Donovan W, Graves DE, Jha A, et al. International standards for neurological classification of spinal cord injury (revised 2011). J Spinal Cord Med. 2011;34(6):535–46.
2. Blumenfeld H. Neuroanatomy through clinical cases. 2nd ed. Sinauer Associates; 2010.
3. Hsu W, Jallo GI. Chapter 100—Pediatric spinal tumors. AND Thompson DNP. Chapter 103—Acute myelopathy: tumoral or traumatic spinal cord compression. In: Dulac O, Lassonde M, Sarnat HB, editors. Handb clin Neurol. Pediatric neurology part II. Amsterdam, Netherlands: Elsevier; 2013. p. 959–65. and 993-997.
4. Rossi A, Martinetti C, Morana G, Severino M, Tortora D. Diagnostic approach to pediatric spine disorders. Magn Reson Imaging Clin N Am. 2016;24(3):621–44. New 5 –.
5. Roman GC, Gracia F, Torres A, Palacios A, Gracia K, Harris D. Acute transverse myelitis: clinical review of 43 patients with COVID-19 associated ATM and 3 post-vaccination ATM serious adverse events with the ChadOx 1 nCov-19 vaccine (AZD 1222). Front Immunol. 2021;12:653786. https://doi.org/10.3389/fimmu.2021.653786. eCollection 2021.
6. Absoud M, Greenberg BM, Lim M, Lotze T, Thomas T, Deiva K. Pediatric transverse myelitis. Neurology. 2016;87(9 Suppl 2):S46–52.
7. Nguyen DK, Agenarioti-Belanger S, Vanasse M. Pain and the Guillain-Barre syndrome in children under 6 years old. J Pediatr. 1999;134(6):773–6.
8. Theroux LM, Brenton JN. Acute transverse and flaccid myelitis in children. Curr Treat Options Neurol. 2019;32(12):64.
9. Messacar K, Schreiner TL, Van Haren K, Yang M, Glaser CA, Tyler KL, et al. Acute flaccid myelitis: a clinical review of US cases 2012-2015. Ann Neurol. 2016;80(3):326–38.
10. Palasis S, Hayes LL. Acquired pathology of the pediatric spine and spinal cord. Pediatr Radiol. 2015;45(Suppl 3):S420–32.
11. Wilson PE, Oleszek JL, Clayton GH. Pediatric spinal cord tumors and masses. J Spinal Cord Med. 2007;30(Suppl 1):S15–20.
12. Rossi A. Pediatric spinal infection and inflammation. Neuroimaging Clin N Am. 2015;25(2):173–91.
13. Tyagi R. Spinal infections in children: a review. J Orthop. 2016;13(4):254–8.
14. Popa C, Popa F, Grigorean VT, Onose G, Sandu AM, Popescu M, et al. Vascular dysfunctions following spinal cord injury. J Med Life. 2010;3(3):275–85.
15. Fisher JPH, Tweddle DA. Neonatal neuroblastoma. Semin Fetal Neonatal Med. 2012;17(4):207–15.
16. Lemley K, Bauer. Pediatric spinal cord injury: recognition of injury and initial resuscitation, in hospital management, and coordination of care. J Pediatr Intensive Care. 2015;4(1):27–34.
17. Caruso MC, Daugherty MC, Moody SM, Falcone RA, Bierbrauer KS, Geis GL. Lessons learned from administration of high-dose methylprednisolone sodium succinate for acute pediatric spinal cord injuries. J Neurosurg Pediatr. 2017;20(6):567–74.
18. Pettiford JN, Bikhchandani J, Ostlie DJ, St Peter SD, Sharp RJ, Juang D. A review: the role of high dose methylprednisolone in spinal cord trauma in children. Pediatr Surg Int. 2012;28(3):287–94.
19. Evaniew N, Belley-Cote EP, Fallah N, Noonan VK, Rivers CS, Dvorak MF. Methylprednisolone for the treatment of patients with acute spinal cord injuries: a systematic review and meta-analysis. J Neurotrauma. 2016;33(5):468–81.
20. Esposito S, Longo MR. Guillain-Barre syndrome. Autoimmun Rev. 2017;16(1):96–101.
21. Hopkins SE, Elrick MJ, Messacar K. Acute flaccid myelitis—keys to diagnosis, questions about treatment, and future directions. JAMA Pediatr. 2019;173(2):117–8.
22. Morens DM, Folkers GK, Fauci AS. Acute flaccid myelitis: something old and something new. MBio. 2019;10(2):e00521–19.

Child with New Onset Hemiparesis

Melissa G. Chung

1 Introduction

Acute hemiparesis, i.e., weakness affecting one half of the body is a complaint that practitioners may encounter in both the inpatient and outpatient settings. Regardless of setting, new onset hemiparesis in a child presents a challenging diagnostic question—is this an acute neurological emergency such as acute stroke or a more benign mimic? The differential diagnosis for new onset hemiparesis is broad and this chapter focuses upon the diagnosis and management of pediatric stroke, especially arterial ischemic stroke (AIS) in children. Other conditions such as hemiplegic migraine, acute disseminated encephalomyelitis, neoplasms, and new onset seizures that can cause hemiparesis are described in detail in other chapters of this book. It must be noted that hemiparesis can be the result of disorders affecting the brain or the spinal cord.

2 Epidemiology

The most common presenting feature of acute cerebrovascular disease in children is hemiparesis. Focal weakness occurs in 67%–90% of children with acute stroke [1–3]. In a prospective study of 280 children with stroke mimics and 102 children with stroke, arm weakness was the neurological symptom that was most strongly associated with stroke (OR 8.66) though a wide confidence interval of 2.5–30.02 suggests poor specificity [4].

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Overall, ischemic and hemorrhagic stroke occur in 3–25 per 100,000 children per year [5]. Risk is highest during the perinatal period with an incidence of neonatal stroke of about 1 in 4000 live births [6]. Neonates that are diagnosed with an acute stroke more often present with seizures and encephalopathy rather than with focal weakness. Many neonatal cases are diagnosed in a delayed fashion during infancy as part of the workup for an early hand preference or new onset focal seizures rather than diagnosed in the acute perinatal period. The incidence of AIS after the neonatal period has been estimated to be about 1–2 per 100,000 children per year [1, 7, 8]. In one study, 61% of children with AIS in the Canadian Stroke registry presented with focal deficits; more specifically 490 of the 915 children with AIS had motor deficits/hemiparesis [8]. In general, though, acute hemiparesis is less likely to be a presenting feature of stroke in children under the age of one than in older children [9].

The incidence of hemorrhagic stroke is estimated to be 0.5–5.1 per 100,000 children per year. The incidence of cerebral sinovenous thrombosis (CSVT) is approximately 0.67 per 100,000 children per year [10].

3 Etiology/Differential Diagnosis

While acute hemiparesis is the most common presenting feature of stroke in older children, the diagnosis of stroke cannot be based upon this symptom alone. About 20%–30% of children that present with acute hemiparesis will have an alternative diagnosis or a "stroke mimic" [11]. The numbers of stroke mimics are even higher in studies of pediatric stroke pathways with the caveat that these pathways may be triggered by concerns other than acute hemiparesis. These hospital-based pediatric stroke pathways are designed to try identify acute strokes in children in a rapid fashion to allow for possible hyperacute stroke therapies; thus, the stroke pathways can be triggered by complaints such as change in vision, abnormal gait, vertigo, etc. to optimize the sensitivity of the pathway [4].

The most common stroke mimics in children include encephalitis/meningitis, intracranial neoplasm, Bell's palsy, functional neurologic disorders, migraines, and seizures [4, 12–14]. The differential diagnosis for acute hemiparesis is broad in children but certain features of the history and examination may guide the practitioner to an alternate diagnosis (Table 1). Unfortunately, ruling in or out stroke as the cause of acute hemiparesis in a child can be challenging based upon history alone in most cases.

Traditionally, acute stroke is thought to present with an abrupt onset of symptoms. However, in children, stroke can present with stuttering symptoms including fluctuating weakness [15]. The reason for this difference in presentation is that almost 45% of strokes in children are due to arteriopathy. Thus, a child's symptoms may fluctuate with vacillations of cerebral perfusion through the abnormal cerebral vessel(s). Children with moyamoya disease and syndrome exemplify this phenomenon; their cerebral perfusion often is significantly affected by hydration status, mild changes in blood pressure or carbon dioxide (e.g., with hyperventilation) and can therefore present with fluctuation of symptoms.

Table 1 Differential diagnosis for acute hemiparesis in children

Diagnosis	Potential distinguishing features	Diagnostic evaluation
Arterial ischemic stroke (AIS)	• Symptoms that suggest a vascular distribution, such as aphasia with right hemiparesis • May have acute and abrupt onset of symptoms but with arteriopathy, may have a stuttering presentation • Known risk factors for arterial ischemic stroke, such as congenital heart disease, Trisomy 21, sickle cell disease, etc.	• MRI brain with diffusion weighted imaging and susceptibility weighted imaging with vascular imaging as indicated • CT of the head to rule out hemorrhage first if unstable patient and/or unable to do emergent MRI • Further discussed in text
Cerebral sinovenous thrombosis (CSVT) +/− venous infarct	• May have insidious onset of symptoms with more abrupt development of hemiparesis/focal symptoms if associated with venous infarction • Often associated with encephalopathy or seizures in neonates • May be associated with signs and symptoms of increased intracranial pressure • Presence of known risk factors for CSVT, such as head and neck infection, nephrotic syndrome, inflammatory bowel disease, etc.	• Neuroimaging including venous imaging
Hemorrhagic stroke	• Signs and symptoms of increased intracranial pressure • Known bleeding diathesis	• Neuroimaging with vascular imaging if indicated
Transient ischemic attack	• See above regarding AIS	• See above regarding AIS
Vasospasm including post-traumatic or Reversible vasoconstriction syndrome	• Known traumatic brain injury especially with subarachnoid blood • Known aneurysmal subarachnoid hemorrhage • Severe “thunderclap” headache • Physical examination localizes to ischemia in multiple vascular distributions • History of exposure to vasoactive medication	• Neuroimaging including vascular imaging

(continued)

Table 1 (continued)

Diagnosis	Potential distinguishing features	Diagnostic evaluation
Mass occupying lesion, e.g., neoplasm	• Signs and symptoms of increased intracranial pressure • Subacute symptoms with more recent acute decline	• Neuroimaging
Migraine, especially hemiplegic migraine	• Family history of migraine, especially hemiplegic migraine • Associated headache with classic migraine features (photophobia, phonophobia, nausea/vomiting) *Caution—Headache may be a symptom in childhood AIS as well*	• Neuroimaging usually is recommended with first episode of hemiparesis with migraine as complex migraine is a diagnosis of exclusion • Consider genetic testing
Focal seizure	• Transient altered awareness • Clinical description of movements consistent with seizure, such as repeated jerking *Caution—New onset focal seizure can be a presenting symptom in pediatric AIS, esp. in young children*	• Detailed history • Neuroimaging • Electroencephalogram • Electrolytes and glucose if clinically indicated
Postictal phenomenon (i.e., Todd's paralysis)	• Preceding history of seizure • Transient postictal state • Rapidly improving weakness	• See above regarding evaluation for focal seizure
Functional neurological disorder	• Non-neurologic distribution of complaints • Recent psychological stressors	• Detailed history and examination • Diagnosis of exclusion. Evaluation for other etiologies should be considered
Dystonic episode	• Characteristic twisting motion of movements • Resolves with sleep, increases with agitation and pain	• Clinical diagnosis • Neuroimaging may be indicated because stroke may cause dystonia
Subdural or epidural empyema	• Signs and symptoms of infection such as fever	• Neuroimaging
Encephalitis, including infectious or autoimmune	• Encephalopathy • Neurological examination with findings not limited to single vascular distribution • Subacute onset • Signs and symptom of infection • Systemic autoimmune/rheumatologic disease	• Neuroimaging • Lumbar puncture • Infectious and autoimmune studies as clinically indicated

Table 1 (continued)

Diagnosis	Potential distinguishing features	Diagnostic evaluation
Demyelinating disorder including acute disseminated encephalomyelitis (ADEM)	• History and examination with findings not limited to a single vascular distribution • Vision loss suggesting optic neuritis • May have subacute onset • Encephalopathy with ADEM	• Neuroimaging • Further studies depending upon pattern seen on neuroimaging
Methotrexate toxic leukoencephalopathy	• History of recent exposure to methotrexate, especially intrathecal, within the preceding 2–14 days	• Neuroimaging
Posterior reversible encephalopathy syndrome (PRES)	• Hypertension • Complaints and examination may not be confined to a single neurological distribution • Encephalopathy • Known exposure to agents with high risk of PRES, such as tacrolimus	• Neuroimaging
Alternating hemiplegia of childhood	• Episodes of temporary hemiparesis, potentially migrating sides • May have associated dystonia, choreoathetosis • Resolution of hemiparesis with sleeping (but potential recurrence upon awakening) • Developmental delay/ cognitive problems	• Consider genetic testing
Musculoskeletal injury	• History of recent trauma • Pain with movement/ palpation of limb • Local findings of trauma, such as bruising or deformity • Examination is not consistent with neurological distribution	• Plain X-ray films if indicated
Focal neuropathy	• Complaints and examination are consistent with neuropathy	• Clinical examination • If consistent with plexopathy then may require MR of the plexus • Consider EMG/NCV

(continued)

Table 1 (continued)

Diagnosis	Potential distinguishing features	Diagnostic evaluation
Hypoglycemia	• Predisposing factors such as preceding vomiting/poor intake • Known history of hypoglycemia • Associated diaphoresis, encephalopathy, fatigue	• Blood glucose level
Toxic/drug ingestion	• History of drug exposure • Other signs/symptoms and exam findings indicative of a toxidrome	• Drug screen • Consider toxicology consult
Spinal cord lesion	• Sparing of the face • Bowel/bladder symptoms • Sensory level • Neck/back pain	• Neuroimaging
Acute hydrocephalus	• Signs/symptoms of increased intracranial pressure including subacute preceding symptoms	• Neuroimaging
Metabolic stroke, such as with mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS)	• Nonvascular distribution of complaints/examination findings • History of developmental delay, failure to thrive, multisystemic disease • Known personal or family history of metabolic/mitochondrial disorder	• Neuroimaging • Serum and CSF lactate • Serum amino acids, urine organic acids • Dedicated genetic testing
Headache and Transient Neurological Deficits with cerebrospinal Lymphocytosis (HaNDL syndrome)	• Recurrent episodes • Significant migraine-like headache • Possible fever	• Neuroimaging • Ophthalmologic examination • Lumbar puncture to evaluate for lymphocytosis • Neuroimaging, including contrast

The diagnosis of the cause of acute hemiparesis is made even more challenging by the fact that there is significant overlap between symptoms of conditions that mimic a stroke and an acute stroke in children. For instance, complex migraines are one of the most frequent pediatric stroke mimics. However, the presence of headache alone does not indicate a diagnosis of migraine as headaches occur frequently in children with hemorrhagic stroke or cerebral venous sinus thrombosis (CSVT). Less commonly recognized is the fact that headache is a common complaint in pediatric AIS as well, unlike in adults. In the International Pediatric Stroke Study, headache was a presenting symptom in more than 50% of children with AIS that affect the "posterior circulation" i.e., brain stem or cerebellum; while less common in "anterior circulation" stroke (affecting the areas of the brain supplied by the carotid arteries), headache still occurred in about one-third of the children [16].

Another common cause of new onset hemiparesis in a child is seizures especially when followed by Todd's paralysis. However, stroke in children, especially infants,

may present with a new onset focal seizure. Seizures at stroke onset occur in up to a quarter of children [1–3]. Thus, an acute stroke needs to be considered as the possible cause for new onset seizure with acute hemiparesis in children with significant stroke risk factors such as a critical congenital heart disease, genetic disease with high risk for vasculopathy like Trisomy 21, etc. Lack of rapid improvement in weakness also should trigger the practitioner to consider stroke as an underlying cause for the new onset focal seizure as well.

4 Diagnostic Approach

4.1 History

A detailed history should include the timing and progression of neurological symptoms. The last known time when the child was well, is a particularly important piece of information. Information should be obtained about any recent infectious symptoms (including minor illness within the last 2 weeks), history of trauma, recent medication/drug use, cardiac history and general medical history, especially of any history of sickle cell disease, cardiac, or inflammatory diseases. A careful review of symptoms also is important as many systemic diseases, such as inflammatory bowel disease and rheumatologic disorders, are associated with increased risk of stroke in children.

Handedness (right or left-handed) should be documented. Most individuals are right–handed, i.e., left brain dominant. Handedness is normally established around the age of 2–3 years. Early handedness may be indicative of a perinatal stroke.

For neonates, a thorough maternal history also is useful and may reveal risk factors associated with perinatal AIS including chorioamnionitis, vacuum extraction, emergency Cesarian section, preeclampsia, oligohydramnios, etc.

The review of family history should include an evaluation for clues to an alternative diagnoses (such as family history of hemiplegic migraines) or for potential genetics/inherited causes of stroke such as mitochondrial or metabolic disorders, connective tissue disorders, etc. Specifically, the practitioner should ask if there is a family history of stroke or heart attack before the age of 50 years, multiple miscarriages or clots including leg or lung clots to screen for prothrombotic conditions.

4.2 Physical Examination

4.2.1 General Examination

A thorough general physical examination is imperative in the workup for possible pediatric stroke as it may reveal clues to the cause of the stroke (Table 2). Vital signs should be noted. Severe hypertension can cause stroke or worsen it (especially in the case of hemorrhagic strokes) or may be a physiological response to stroke to optimize cerebral perfusion. Hypotension or hypoxemia may worsen injury after an

Table 2 Common risk factors for stroke in older children

Risk factors for AIS	Diagnosis	Comments
– Genetic	Neurofibromatosis	
	Trisomy 21	
	Sickle cell disease	
	COL4A1 and 2	
	DADA mutation	
	Moyamoya disease	Including RNF213 gene mutation
	Aicardi–Goutieres syndrome (SAHMD1 mutation)	
	Alagille syndrome	
	ACTA2 mutation	
	Noonan syndrome	
	Seckel syndrome	
	Fabry disease	
	Microcephalic osteodysplastic primordial dwarfism	
	Ehler's Danos type IV	
	Marfan's syndrome	
	Loeys–Dietz syndrome	
	Mitochondrial disorders	Metabolic stroke rather than true arterial ischemic stroke
	PHACE syndrome	
– Rheumatologic	Lupus	
	Behcet's syndrome	
	Polyarteritis nodosa	
	Primary angiitis of the central nervous system	
– Cardiac	Congenital heart disease with shunting lesion, especially single ventricle heart disease	
	Extracorporeal life support, especially veno-arterial	
	Left ventricular assist device	
	Endocarditis, left sided	
	Atrial myxoma	
– Thrombophilia	Prothrombin gene mutation *PTG20210*	
	Factor V Leiden *G1691A*	
	Protein C or S deficiency	
	Elevated homocysteine	
	Elevated lipoprotein A	
	Antiphospholipid syndrome	

Table 2 (continued)

Risk factors for AIS	Diagnosis	Comments
– Other	Fibromuscular dysplasia	
	Dynamic vertebral artery compression (Bowhunter's syndrome)	
	Thoracic outlet syndrome	
	Recent upper respiratory illness	
	Estrogen containing birth control pills	
	Central nervous system infection	
Risk factors for CSVT	Diagnosis	Comments
– Thrombophilia	See above re risk factors for AIS	
	Antithrombin deficiency	
– Trauma		
– Protein losing conditions	Enteropathy	
	Nephrotic syndrome	
– Inflammatory conditions	Inflammatory bowel disease	
	Central nervous system or head and neck infections	
	Rheumatologic diseases, such as lupus	
– Medications	Steroid use	
	Estrogen containing birth control pills	
	PEG-Asparginase	
– Other	Iron deficiency anemia	
	Dehydration	
	Obesity	
Risk factors for hemorrhagic stroke	Diagnosis	Comments
– Hematologic	Hemophilia	
	Von Willebrand disease	
	Factor VII deficiency	
	Vitamin K-dependent clotting factor deficiency	Including with liver failure
	Severe thrombocytopenia	Including with idiopathic thrombocytopenic purpura
	Factor II deficiency	
	Factor XIII deficiency	
– Trauma		
– Structural	Arterial venous malformation/fistula	
	Aneurysm	
	Cavernous malformation	
	Tumor	

(continued)

Table 2 (continued)

Risk factors for AIS	Diagnosis	Comments
– Genetic	Hereditary Hemorrhagic Telangiectasia	ENG and ACRL1 mutations
	COL4A1 and 2	
	RASA-1 mutation	

AIS arterial ischemic stroke, *CSVT* cerebral sinus venous thrombosis

acute stroke. An irregular heart rate may indicate a cardiac etiology for an acute stroke. Any dysmorphic features should be noted (as certain syndromes such as Down syndrome and Marfan syndrome predispose to stroke). The practitioner should evaluate for signs of infection on head and neck exam, such as a red/inflamed mastoid bone, dental abscess, and for meningimus. A careful cardiac examination should include listening for murmurs and/or arrhythmias. The respiratory examination should note any signs of hypoxemia, respiratory distress, and/or difficulty with airway protection. Rashes, unusual bruising/bleeding, and birthmarks should be noted on skin examination. For example, children with Sturge–Weber syndrome may have a portwine stain on their face and are predisposed to strokes in the hemisphere ipsilateral to the facial nevus. Joints should be evaluated for evidence of arthritis. Joint or bony deformities or pain with palpation/range of motion may signify a musculoskeletal rather than neurological cause for acute hemiparesis. Hypermobility should be noted, preferably with calculation of the Beighton Score if present (to evaluate for Ehlers–Danlos syndrome). If spinal cord injury is on the differential based upon the patient's history, then rectal tone should be assessed.

4.2.2 Neurological Examination

For the neurological examination, use of the Pediatric National Institutes of Health Stroke Scale (PedsNIHSS) is encouraged for the initial evaluation, especially in a time sensitive situation [17]. Ultimately, a complete neurological examination should be performed to help with localization of lesion and differentiation of a true stroke from a stroke mimic. Level of alertness should be noted. Fundoscopic examination may provide clues to potential causes of stroke (such as a systemic vasculitis) but is also needed to evaluate for elevated intracranial pressure as in children who have venous sinus thrombosis or a space occupying lesion in the brain. On motor examination, pattern of weakness should be observed as one would expect a pyramidal pattern on weakness in a patient with an intracranial cause for acute hemiparesis (particularly stroke). A pyramidal pattern of weakness presents as greater weakness in the extensor than flexor muscles in the upper extremities and greater weakness in the extensor muscles than flexor muscles in the lower extremities; for this reason, pronator drift in the arms and leg raise are useful screening tools for pyramidal weakness. Assessment of gait is particularly important. In conversion disorders for instance, patients may exhibit unusual gait patterns (astasia-abasia)

which cannot be explained by an organic disease process. If the neurological examination improves over the course of minutes to hours one may suspect disorders such as Todd's paralysis or transient ischemic attack.

4.3 Evaluation (Laboratory Studies/Imaging)

In some situations, a diagnosis other than stroke may be favored after a detailed history and physical examination. Table 1 lists a brief general approach to some of these alternative etiologies for new onset hemiparesis in a child. In many cases, though, acute stroke will remain on the differential diagnosis after initial history and physical examination. In these cases, urgent evaluation is needed.

Standard management in adult medicine for patients with suspected stroke is to evaluate with a noncontrast head computerized tomography (CT). This approach relies on the fact that strokes are more common than stroke mimics in adults [18]. Since the reverse is true in pediatrics, confirmation of diagnosis of acute stroke in a child is recommended before proceeding with targeted management.

The risk of delaying the diagnosis of a stroke in a child must be balanced with the risk of inappropriate treatment in an unconfirmed stroke given the greater incidence of stroke mimics than true strokes in children. To expedite diagnosis, many pediatric centers have instituted acute stroke or "brain attack" pathways over the last decade. After activation of the stroke protocol that sends alerts to many providers including the on-call neurologist, radiologist, MRI technician and anesthesiologist, intravenous access, acute stroke labs (complete blood count, coagulation studies including fibrinogen, type and screen, serum chemistry including glucose, beta human chorionic gonadotropin if applicable) and an electrocardiogram (EKG) are obtained. Drug screen may be considered. The primary common element to these pathways is emergent neuroimaging, preferably a short stroke protocol magnetic resonance imaging (MRI) of the brain that includes a very limited number of sequences, such as diffusion-weighted imaging (DWI and ADC), to evaluate for acute cytotoxic injury, and susceptibility weighted imaging to evaluate for hemorrhage. These limited sequences allow for rapid evaluation for "cannot miss" acute neurological diagnoses that need timely intervention, including but not limited to stroke. In the majority of cases, the short duration of these limited MRI sequences also eliminates the need for sedation that would delay imaging and/or cloud the examination. In studies of pediatric acute stroke pathways, up to 40% of patients are found to have time sensitive neurological diagnoses [4, 14, 19] such as tumors and demyelinating disorders.

If the child presents to an outpatient setting and stroke is a concern after history and examination, then they should be sent urgently to the emergency department. If the child presents at a center without a rapid pediatric stroke pathway and/or one without pediatric stroke expertise, then the above laboratory tests and EKG should be obtained. A rapid MR can be completed if easily obtained. If this is not feasible

then a head CT may be considered to rule out a hemorrhage or mass lesion but should not be considered sufficient to rule out acute stroke. However, if the patient presents in a hyperacute fashion, then we recommend early discussion of potential transfer with the closest pediatric tertiary care center; depending upon distance and time since symptoms onset, it may be preferable to first transfer the patient and then obtain the MR expeditiously after arrival to prevent delays in treatment if the child does have a stroke. Clinical practice varies widely but some adult stroke centers also may be comfortable with evaluation and management of potential stroke in adolescents.

If the diagnosis is not evident from the rapid sequence MRI head, then the patient ultimately may need a full brain MRI. Further vascular imaging also may be necessary if stroke/transient ischemic attack and/or vasculopathy remain on the differential for presentation based upon history and examination. Imaging should be done with and without contrast if an inflammatory/infections etiology is on the differential. If full neuroimaging is negative, then consider workup for alternative diagnoses (Table 1).

If the diagnosis of acute hemorrhagic stroke is made, then more detailed neurovascular imaging may be indicated depending upon the distribution of the hemorrhage. CBC and coagulation studies should be done if not already completed. Hematology consultation for a bleeding workup should be considered in cases of spontaneous hemorrhage without an obvious etiology.

If the diagnosis of CSVT with or without venous infarction is made, then one should ensure that coagulation studies were performed. Further laboratory investigations for hypercoaguable testing can be considered in conjunction with pediatric hematology specialists. Frequently sent hypercoaguable studies include antithrombin, protein C and S activity, lupus anticoagulation, anticardiolipin antibody, anti-B2 glycoprotein antibody and testing for Factor V Leiden mutation and prothrombin G20210A mutation.

If the diagnosis of AIS is made, then the child needs detailed vascular imaging; MR angiogram is sufficient in some cases but other patients may need to proceed to CT angiogram of the head/neck and/or conventional cerebral angiogram depending upon the clinical scenario and vascular distribution of the stroke. Patients with sickle cell disease should have a type and cross and hemoglobin electrophoresis done urgently. In most cases, an echocardiogram with bubble study should be done to evaluate for a right to left shunt. A fasting lipid panel especially in older patients without clear etiology can be considered. Hypercoaguable labs can be done, preferably in consultation with hematology. If there are signs/symptoms of an underlying genetic or systemic etiology for the stroke, then further workup is tailored to the individual patient. A useful reference for more specific workup is the American Heart Association (AHA) guidelines on the management of stroke in neonates and children [5].

As a brief aside, while neonatal stroke is unlikely to present acutely with new onset hemiparesis—it is worth noting that the workup and management of neonatal stroke differs from that in older infants and children. Hypercoaguable workup has a

low yield and little clinical impact so no longer is routinely recommended [5, 20, 21]. Evaluation of the placenta may yield some insight into etiology. Also, depending upon maternal history, testing of the mother for lupus anticoagulant/antiphospholipid antibodies may be warranted.

4.4 Treatment/Management

4.4.1 General Stroke Management

Initial management focuses on general neuroprotective measures including maintenance of cardiorespiratory stability in patients, especially since hypoxia and hypotension may contribute to secondary neurological injury in patients with acute stroke [5]. Supplemental oxygen should be provided to maintain oxygen saturation greater than 92%. Patients with severe encephalopathy, especially if there are concerns for increased intracranial pressure and/or inability to protect their airway, may require early definitive airway management. Hypotension should be avoided. Blood pressure goals are normotension to mild permissive hypertension. Patients with fever should be aggressively treated to avoid increasing cerebral metabolic demand. Antiepileptics should be given for suspected seizure activity. For patients with encephalopathy, monitoring with electroencephalogram (EEG) should be considered to monitor for subclinical or subtle clinical seizures. Very young patients and those with hemorrhagic stroke are at particularly high risk for acute symptomatic seizures. Isotonic fluids should be provided to correct and avoid dehydration. Goal glucose is 140–180 mg/dL. All patients warrant serial neurological examination. Neurosurgical and critical care consultation may be needed for ongoing management of patients with signs/symptoms of increased intracranial pressure or those with high risk for developing increased pressure, e.g., patients with intracranial hemorrhage, large territory middle cerebral artery infarctions and/or significant posterior fossa infarctions. Decompressive craniectomy may be warranted in some patients. Offending agents for the stroke, such as estrogen containing oral contraceptives, should be discontinued if possible. If infection is the provoking factor for stroke, then approximate antimicrobial treatment should be initiated. Anemia should be corrected.

In the subacute phase of treatment, most children benefit from consultation for rehabilitation therapies. A swallow evaluation by occupational or speech therapy should be strongly considered if the child has facial weakness because of the high risk of silent aspiration. Depending upon the severity of deficits and the age of the child, physical medicine and rehabilitation consultation or neuropsychology involvement may be warranted as well. In the long term, constraint-induced movement therapy (CIMT) has shown promise for rehabilitation of hemiparesis after stroke in children [22–24]. Transcranial magnetic stimulation also has shown promise [25–28].

4.4.2 Hemorrhagic Stroke

Neurosurgical consult is recommended for patients with hemorrhagic stroke. Depending upon the size and distribution of the hemorrhage, patients may require acute management of increased intracranial pressure including potentially decompressive surgery and/or evacuation of the hemorrhage. Coagulation abnormalities should be corrected. Long-term treatment of the underlying etiology for the hemorrhage is beyond the scope of this chapter.

4.4.3 CSVT

In patients with a head or neck infection associated CSVT, antibiotic therapy/definitive management of the infection is the primary treatment. Otherwise, anticoagulation is recommended in most children with CSVT unless there is significant intracranial hemorrhage or other contraindications to anticoagulation [5, 29]. If the child is unable to start anticoagulation, then repeat imaging is recommended within 3–7 days to monitor for extension of the thrombus. Generally, neonates are treated with anticoagulation for 6 weeks to 3 months (with repeat imaging used to guide duration of therapy). In older children, anticoagulation is continued for 3–6 months of therapy. If not already done, then a detailed ophthalmologic examination is needed to evaluate for papilledema and assess visual fields. If papilledema is present, then children may need treatment with medications such as acetazolamide. If the papilledema is severe, then a lumbar puncture is performed sometimes to acutely lower intracranial pressure. However, the benefit of the lumbar puncture needs to be weighed against the risk of delaying definitive treatment with anticoagulation. In patients with CSVT, it is especially important to avoid dehydration and some specialists advocate for initial use of intravenous fluids at 1.5 times the maintenance especially while anticoagulation is not therapeutic.

4.4.4 Arterial Ischemic Stroke

Currently, high-quality studies on hyperacute AIS management in children including use of tissue plasminogen activator (tPA) and endovascular intervention/thrombectomy (hyperacute therapies) are lacking. However, hyperacute therapies are being increasingly used among pediatric patients based upon adult data [30, 31]. Many tertiary care pediatric centers are now capable of hyperacute management of stroke in children in the appropriate scenario [31, 32]. Children that present within 4.5 h of an acute arterial ischemic stroke may be eligible for systemic treatment with tPA. Select children with AIS and proximal large vessel occlusion (LVO) may be candidates for mechanical thrombectomy within 6–24 h after symptom onset. However, hyperacute therapies remain controversial in pediatrics, though, given complicating factors including lack of pediatric specific data, differences in stroke etiology and technical challenges in children with smaller craniocervical vessels.

The current AHA guidelines for management of stroke in neonates and children recommend that hyperacute therapies be limited to a select children including specifically those with persistent and significant deficits (such as peds NIHSS of at least 6) and that ultimately the decision to proceed is made in collaboration with a neurologist with pediatric stroke expertise [5].

Beyond hyperacute therapies, most pediatric patients with AIS warrant antithrombotic therapy. Anticoagulation is recommended for patients with cardioembolic stroke. Data for craniocervical dissection is mixed but some pediatric stroke experts still prefer use of anticoagulation over antiplatelet therapy for extracranial dissections, specifically with posterior circulation due the higher risk of recurrence. Patients that do not receive anticoagulation usually are started on antiplatelet therapy, such as aspirin 3–5 mg per kilogram per day for 2–5 years.

Neonatal stroke is managed differently than AIS in older infants and children. Risk of recurrence is generally only approximately 1% after neonatal stroke with the exception being children with significant cardiac disease [21, 33]. Thus, antithrombotic therapy generally is not recommended in these children. Hyperacute stroke therapies such as thrombolysis or thrombectomy also are not recommended in neonates.

Another subgroup of patients with AIS that deserves special mention are children with sickle cell disease. In these patients, primary stroke management consists of exchange transfusion to decrease hemoglobin S percentage to below 15% and raise hemoglobin to about 10 g/deciliter [5, 34]. One retrospective study found that patients were five times less likely to have recurrent stroke if they had an exchange transfusion compared to if they had a simple transfusion [35]. However, if exchange transfusion is not feasible and/or delayed, then simple blood transfusion might be considered to bring hemoglobin up to no more than 11 grams per deciliter.

5 Prognosis/Outcomes

Despite the mantra that pediatric patients do better than adults, stroke causes significant morbidity and mortality in children. Stroke is one of the leading causes of death in childhood. Mortality from AIS and underlying conditions is estimated to be 7%–28% and from hemorrhagic stroke, 6%–54% [16, 36, 37]. A study by Fullerton et al. reported that the annual mortality between 1979 and 1998 was estimated to be 0.09 per 100,000 person years for AIS in children and 0.14 per 100,000 person years for hemorrhagic stroke in children [38].

Approximately 70% of children have some degree of neurologic deficit after AIS, though only 10% of these can be classified as severe deficits [8]. Deficits may occur in multiple domains including motor, cognitive and behavior. Long-term outcome, especially cognitive, often is difficult to tease out until years after the stroke, especially in very young children. Approximately 10% of children develop epilepsy by 1 year poststroke with increased risk particularly in children with a history of neonatal seizures and prolonged and/or recurrence acute symptomatic seizures

[39–43]. Studies suggest that predictors of poor outcome after AIS include acute symptomatic seizures, infarct size, combined cortical and subcortical involvement, multifocal infarcts, and involvement of the basal ganglia and/or posterior limb of the internal capsule [8, 39, 44, 45].

In children with CSVT, outcome can be variable but children are more likely to do poorly if they have associated hemorrhage or venous infarction [46]. One study found that up to 15% of children will develop epilepsy after CSVT [47].

In children with hemorrhagic stroke, hemorrhage volume, infratentorial involvement, early altered mental status, hematologic disorder, and age <3 years are predictive of poor outcome [36, 48]. Approximately 13% of children ultimately develop epilepsy by 1 year after diagnosis [49].

Mood disorders also are another potential consequence after stroke and attention should be made to screen for them during follow-up and treat/refer accordingly [45].

6 When to Refer/Admit

Any patient with acute onset of hemiparesis requires urgent neurological evaluation unless there is a clear cause identified on history and/or examination, such as a hypoglycemia or a musculoskeletal injury. If arterial ischemic stroke is on the differential, then rapid triage is paramount. Given the limited number of physicians with experience in management of hyperacute stroke in children, transfer to a tertiary care center with a pediatric neurovascular team is recommended.

Even if the patient is not eligible for hyperacute treatment pediatric patients with acute stroke or suspected transient ischemic attack should be hospitalized for ongoing monitoring for clinical worsening due to secondary injury and/or additional ischemia, especially with patients with vasculopathy or posterior circulation strokes, and also for workup of the underlying etiology. Most children with acute stroke warrant initial monitoring in a critical care setting [50]. In particular, patients with large hemispheric stroke are at high risk for developing malignant middle cerebral artery syndrome and associated increased intracranial pressure; patients with posterior fossa ischemia also are at higher risk for increased intracranial pressure and cardiorespiratory deterioration. Admission also allows for evaluation for therapies and determination of whether the child might benefit from intensive rehabilitation after medical stabilization.

7 Prevention

As previously mentioned, recurrence risk is quite low in cases of neonatal stroke and therefore ongoing antithrombotic therapy is not warranted for secondary stroke prevention. However, in the case of neonatal CSVT, anticoagulation may be provided for 6 weeks to 3 months.

Risk of recurrent stroke, specifically AIS, is higher in children outside of the neonatal period with about a 1 in 10 risk of recurrence within the first year after their stroke [33]. Risk is highest in children with arteriopathies. Children with posterior circulation strokes also seemed to be at significantly increased risk for recurrence with one study reporting recurrence in 19% of children after 3 years versus in only 4% of children with anterior circulation strokes [51]. In general, the mainstay of secondary prevention in children like adults is antithrombotic therapy. However, standardized trials are lacking in pediatrics regarding the efficacy of specific antiplatelet agents or anticoagulation or duration of treatment for secondary prevention. Children with cardioembolic disease, recurrent thrombosis, and/or a known hypercoagulable disorder usually are placed on anticoagulation for at least 3–6 months (AHA guidelines). Otherwise, most children are kept on aspirin (3–5 mg per kilogram per day) as noted in the treatment section for at least 2 years when risk of recurrence is highest [5].

An exception to the above discussion on antithrombotic therapy are children with sickle cell disease. Mainstay of therapy for these children instead is indefinite chronic blood transfusions though bone marrow transplantation and perhaps eventually gene therapy may obviate long-term need for ongoing transfusion therapy [52, 53]. In cases where chronic blood transfusion is not feasible then treatment with hydroxyurea is superior to no treatment for secondary stroke prevention [34].

Another subset of patients that require unique management are children with moyamoya disease or syndrome. These patients are at particularly high risk for stroke recurrence, up to 66%–90% at 5 years [54–59]. Maximal medical management includes avoidance of factors that can lead to cerebral hypoperfusion including avoiding dehydration, hypotension, hyperventilation (including with activity or uncontrolled pain/agitation). Surgical revascularization may significantly decreased risk of recurrence and should be considered in most patients in conjunction with an experienced pediatric stroke neurologist and neurosurgeon [55, 58, 60, 61].

8 Clinical Pearls/Key Points

- Acute stroke should be considered as a cause for acute onset of hemiparesis in a child and warrants urgent evaluation
- The most common mimics of stroke in children include migraines, seizures, Bell's palsy, and functional neurological disorders
- Headaches and seizures especially if accompanied by acute hemiparesis may be presenting symptoms of acute stroke in a child
- Pediatric patients with acute stroke may benefit from transfer to a center with pediatric stroke expertise for management, including potential hyperacute therapies
- Up to 70% of children will have long term deficits after stroke

References

1. Steinlin M, Pfister I, Pavlovic J, Everts R, Boltshauser E, Capone Mori A, et al. The first three years of the Swiss Neuropaediatric Stroke Registry (SNPSR): a population-based study of incidence, symptoms and risk factors. Neuropediatrics. 2005;36(2):90–7.
2. Mallick AA, Ganesan V, Kirkham FJ, Fallon P, Hedderly T, McShane T, et al. Childhood arterial ischaemic stroke incidence, presenting features, and risk factors: a prospective population-based study. Lancet Neurol. 2014;13(1):35–43.
3. Christerson S, Strömberg B. Childhood stroke in Sweden I: incidence, symptoms, risk factors and short-term outcome. Acta Paediatr. 2010;99(11):1641–9.
4. Mackay MT, Yock-Corrales A, Churilov L, Monagle P, Donnan GA, Babl FE. Differentiating childhood stroke from mimics in the emergency department. Stroke. 2016;47(10):2476–81.
5. Ferriero DM, Fullerton HJ, Bernard TJ, Billinghurst L, Daniels SR, DeBaun MR, et al. Management of stroke in neonates and children: a scientific statement from the American Heart Association/American Stroke Association. Stroke. 2019;50(3):e51–96.
6. Agrawal N, Johnston SC, Wu YW, Sidney S, Fullerton HJ. Imaging data reveal a higher pediatric stroke incidence than prior US estimates. Stroke. 2009;40(11):3415–21.
7. Fullerton HJ, Wu YW, Zhao S, Johnston SC. Risk of stroke in children: ethnic and gender disparities. Neurology. 2003;61(2):189–94.
8. deVeber GA, Kirton A, Booth FA, Yager JY, Wirrell EC, Wood E, et al. Epidemiology and outcomes of arterial ischemic stroke in children: the Canadian Pediatric Ischemic Stroke Registry. Pediatr Neurol. 2017;69:58–70.
9. Zimmer JA, Garg BP, Williams LS, Golomb MR. Age-related variation in presenting signs of childhood arterial ischemic stroke. Pediatr Neurol. 2007;37(3):171–5.
10. deVeber G, Andrew M, Adams C, Bjornson B, Booth F, Buckley DJ, et al. Cerebral sinovenous thrombosis in children. N Engl J Med. 2001;345(6):417–23.
11. Shellhaas RA, Smith SE, O'Tool E, Licht DJ, Ichord RN. Mimics of childhood stroke: characteristics of a prospective cohort. Pediatrics. 2006;118(2):704–9.
12. DeLaroche AM, Sivaswamy L, Farooqi A, Kannikeswaran N. Pediatric stroke and its mimics: limitations of a Pediatric stroke clinical pathway. Pediatr Neurol. 2018;80:35–41.
13. De Jong G, Kannikeswaran N, DeLaroche A, Farooqi A, Sivaswamy L. Rapid sequence MRI protocol in the evaluation of Pediatric brain attacks. Pediatr Neurol. 2020;107:77–83.
14. Ladner TR, Mahdi J, Gindville MC, Gordon A, Harris ZL, Crossman K, et al. Pediatric acute stroke protocol activation in a Children's hospital emergency department. Stroke. 2015;46(8):2328–31.
15. Braun KP, Rafay MF, Uiterwaal CS, Pontigon AM, DeVeber G. Mode of onset predicts etiological diagnosis of arterial ischemic stroke in children. Stroke. 2007;38(2):298–302.
16. Goeggel Simonetti B, Rafay MF, Chung M, Lo WD, Beslow LA, Billinghurst LL, et al. Comparative study of posterior and anterior circulation stroke in childhood: results from the International Pediatric Stroke Study. Neurology. 2020;94(4):e337–e44.
17. Ichord RN, Bastian R, Abraham L, Askalan R, Benedict S, Bernard TJ, et al. Interrater reliability of the Pediatric National Institutes of Health Stroke Scale (PedNIHSS) in a multicenter study. Stroke. 2011;42(3):613–7.
18. Long B, Koyfman A. Clinical mimics: an emergency medicine-focused review of stroke mimics. J Emerg Med. 2017;52(2):176–83.
19. Harrar DB, Salussolia CL, Kapur K, Danehy A, Kleinman ME, Mannix R, et al. A stroke alert protocol decreases the time to diagnosis of brain attack symptoms in a Pediatric Emergency Department. J Pediatr. 2020;216:136–41.e6.
20. Curtis C, Mineyko A, Massicotte P, Leaker M, Jiang XY, Floer A, et al. Thrombophilia risk is not increased in children after perinatal stroke. Blood. 2017;129(20):2793–800.

21. Lehman LL, Beaute J, Kapur K, Danehy AR, Bernson-Leung ME, Malkin H, et al. Workup for perinatal stroke does not predict recurrence. Stroke. 2017;48(8):2078–83.
22. Gordon AM, Hung YC, Brandao M, Ferre CL, Kuo HC, Friel K, et al. Bimanual training and constraint-induced movement therapy in children with hemiplegic cerebral palsy: a randomized trial. Neurorehabil Neural Repair. 2011;25(8):692–702.
23. Gordon AM, Charles J, Wolf SL. Efficacy of constraint-induced movement therapy on involved upper-extremity use in children with hemiplegic cerebral palsy is not age-dependent. Pediatrics. 2006;117(3):e363–73.
24. Hebert D, Lindsay MP, McIntyre A, Kirton A, Rumney PG, Bagg S, et al. Canadian stroke best practice recommendations: stroke rehabilitation practice guidelines, update 2015. Int J Stroke. 2016;11(4):459–84.
25. Kirton A, Ciechanski P, Zewdie E, Andersen J, Nettel-Aguirre A, Carlson H, et al. Transcranial direct current stimulation for children with perinatal stroke and hemiparesis. Neurology. 2017;88(3):259–67.
26. Kirton A, Deveber G, Gunraj C, Chen R. Cortical excitability and interhemispheric inhibition after subcortical pediatric stroke: plastic organization and effects of rTMS. Clin Neurophysiol. 2010;121(11):1922–9.
27. Kirton A, Chen R, Friefeld S, Gunraj C, Pontigon AM, Deveber G. Contralesional repetitive transcranial magnetic stimulation for chronic hemiparesis in subcortical paediatric stroke: a randomised trial. Lancet Neurol. 2008;7(6):507–13.
28. Gillick BT, Krach LE, Feyma T, Rich TL, Moberg K, Menk J, et al. Safety of primed repetitive transcranial magnetic stimulation and modified constraint-induced movement therapy in a randomized controlled trial in pediatric hemiparesis. Arch Phys Med Rehabil. 2015;96(4 Suppl):S104–13.
29. Monagle P, Chan AKC, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Göttl U, et al. Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e737S–801S.
30. Sporns PB, Sträter R, Minnerup J, Wiendl H, Hanning U, Chapot R, et al. Feasibility, safety, and outcome of endovascular recanalization in childhood stroke: the save ChildS study. JAMA Neurol. 2020;77(1):25–34.
31. Rivkin MJ, Bernard TJ, Dowling MM, Amlie-Lefond C. Guidelines for urgent management of stroke in children. Pediatr Neurol. 2016;56:8–17.
32. Bernard TJ, Friedman NR, Stence NV, Jones W, Ichord R, Amlie-Lefond C, et al. Preparing for a "Pediatric Stroke Alert". Pediatr Neurol. 2016;56:18–24.
33. Fullerton HJ, Wu YW, Sidney S, Johnston SC. Risk of recurrent childhood arterial ischemic stroke in a population-based cohort: the importance of cerebrovascular imaging. Pediatrics. 2007;119(3):495–501.
34. Kassim AA, Galadanci NA, Pruthi S, DeBaun MR. How I treat and manage strokes in sickle cell disease. Blood. 2015;125(22):3401–10.
35. Hulbert ML, Scothorn DJ, Panepinto JA, Scott JP, Buchanan GR, Sarnaik S, et al. Exchange blood transfusion compared with simple transfusion for first overt stroke is associated with a lower risk of subsequent stroke: a retrospective cohort study of 137 children with sickle cell anemia. J Pediatr. 2006;149(5):710–2.
36. Blom I, De Schryver EL, Kappelle LJ, Rinkel GJ, Jennekens-Schinkel A, Peters AC. Prognosis of haemorrhagic stroke in childhood: a long-term follow-up study. Dev Med Child Neurol. 2003;45(4):233–9.
37. Mallick AA, Ganesan V, O'Callaghan FJ. Mortality from childhood stroke in England and Wales, 1921-2000. Arch Dis Child. 2010;95(1):12–9.
38. Fullerton HJ, Chetkovich DM, Wu YW, Smith WS, Johnston SC. Deaths from stroke in US children, 1979 to 1998. Neurology. 2002;59(1):34–9.

39. Fox CK, Jordan LC, Beslow LA, Armstrong J, Mackay MT, deVeber G. Children with post-stroke epilepsy have poorer outcomes one year after stroke. Int J Stroke. 2018;13(8):820–3.
40. Fox CK, Mackay MT, Dowling MM, Pergami P, Titomanlio L, Deveber G, et al. Prolonged or recurrent acute seizures after pediatric arterial ischemic stroke are associated with increasing epilepsy risk. Dev Med Child Neurol. 2017;59(1):38–44.
41. Fox CK, Glass HC, Sidney S, Smith SE, Fullerton HJ. Neonatal seizures triple the risk of a remote seizure after perinatal ischemic stroke. Neurology. 2016;86(23):2179–86.
42. Fox CK, Glass HC, Sidney S, Lowenstein DH, Fullerton HJ. Acute seizures predict epilepsy after childhood stroke. Ann Neurol. 2013;74(2):249–56.
43. Billinghurst LL, Beslow LA, Abend NS, Uohara M, Jastrzab L, Licht DJ, et al. Incidence and predictors of epilepsy after pediatric arterial ischemic stroke. Neurology. 2017;88(7):630–7.
44. Goldenberg NA, Bernard TJ, Fullerton HJ, Gordon A, deVeber G, Group IPSS. Antithrombotic treatments, outcomes, and prognostic factors in acute childhood-onset arterial ischaemic stroke: a multicentre, observational, cohort study. Lancet Neurol. 2009;8(12):1120–7.
45. Elbers J, deVeber G, Pontigon AM, Moharir M. Long-term outcomes of pediatric ischemic stroke in adulthood. J Child Neurol. 2014;29(6):782–8.
46. Moharir MD, Shroff M, Stephens D, Pontigon AM, Chan A, MacGregor D, et al. Anticoagulants in pediatric cerebral sinovenous thrombosis: a safety and outcome study. Ann Neurol. 2010;67(5):590–9.
47. Mineyko A, Kirton A, Billinghurst L, Tatishvili NN, Wintermark M, deVeber G, et al. Seizures and outcome one year after neonatal and childhood cerebral sinovenous thrombosis. Pediatr Neurol. 2020;105:21–6.
48. Adil MM, Qureshi AI, Beslow LA, Malik AA, Jordan LC. Factors associated with increased in-hospital mortality among children with intracerebral Hemorrhage. J Child Neurol. 2015;30(8):1024–8.
49. Beslow LA, Abend NS, Gindville MC, Bastian RA, Licht DJ, Smith SE, et al. Pediatric intracerebral hemorrhage: acute symptomatic seizures and epilepsy. JAMA Neurol. 2013;70(4):448–54.
50. Fox CK, Johnston SC, Sidney S, Fullerton HJ. High critical care usage due to pediatric stroke: results of a population-based study. Neurology. 2012;79(5):420–7.
51. Uohara MY, Beslow LA, Billinghurst L, Jones BM, Kessler SK, Licht DJ, et al. Incidence of recurrence in posterior circulation childhood arterial ischemic stroke. JAMA Neurol. 2017;74(3):316–23.
52. Ware RE, Helms RW, Investigators S. Stroke with transfusions changing to hydroxyurea (SWiTCH). Blood. 2012;119(17):3925–32.
53. Hulbert ML, McKinstry RC, Lacey JL, Moran CJ, Panepinto JA, Thompson AA, et al. Silent cerebral infarcts occur despite regular blood transfusion therapy after first strokes in children with sickle cell disease. Blood. 2011;117(3):772–9.
54. Zhao M, Zhang D, Wang S, Zhang Y, Wang R, Zhao J. Transient ischemic attack in pediatric patients with moyamoya disease: clinical features, natural history, and predictors of stroke. Pediatr Neurol. 2017;75:48–54.
55. Zhao M, Deng X, Gao F, Zhang D, Wang S, Zhang Y, et al. Ischemic stroke in young adults with moyamoya disease: prognostic factors for stroke recurrence and functional outcome after revascularization. World Neurosurg. 2017;103:161–7.
56. Lee S, Rivkin MJ, Kirton A, deVeber G, Elbers J, Study IPS. Moyamoya disease in children: results from the international Pediatric stroke study. J Child Neurol. 2017;32(11):924–9.
57. Kuroda S, Hashimoto N, Yoshimoto T, Iwasaki Y, Japan RCoMDi. Radiological findings, clinical course, and outcome in asymptomatic moyamoya disease: results of multicenter survey in Japan. Stroke. 2007;38(5):1430–5.
58. Ikezaki K. Rational approach to treatment of moyamoya disease in childhood. J Child Neurol. 2000;15(5):350–6.

59. Gatti JR, Torriente AG, Sun LR. Clinical presentation and stroke incidence differ by Moyamoya etiology. J Child Neurol. 2020;883073820967160
60. Scott RM, Smith JL, Robertson RL, Madsen JR, Soriano SG, Rockoff MA. Long-term outcome in children with moyamoya syndrome after cranial revascularization by pial synangiosis. J Neurosurg. 2004;100(2 Suppl Pediatrics):142–9.
61. Mukawa M, Nariai T, Matsushima Y, Tanaka Y, Inaji M, Maehara T, et al. Long-term follow-up of surgically treated juvenile patients with moyamoya disease. J Neurosurg Pediatr. 2012;10(5):451–6.

Child with Tics and Other Common Movement Disorders

Keisuke Ueda and Kevin J. Black

1 Introduction/Definition

Movement disorders are central nervous system disorders that cause abnormal, unwanted movements and are usually unrelated to weakness, or spasticity. Dysfunction of the basal ganglia and frontal cortex plays an important role in most movement disorders in children [1].

Conventionally, movement disorders are divided into two categories. The first category is hyperkinetic movement disorders, associated with an excess of movement (e.g., excessive, unnatural, and involuntary movement). These include tics, stereotypies, chorea, myoclonus, dystonia, and tremor [2]. The second group is hypokinetic movement disorders, where there is a paucity of movement (e.g., decreased amplitude, decreased speed, or loss of movement), including bradykinesia, akinesia, and rigidity. Unlike hypokinetic movement disorders, hyperkinetic movement disorders, especially tic disorders, are relatively common in the pediatric population.

The most common movement disorders in the pediatric population are tic disorders, including Tourette syndrome (TS). In 1825, Jean-Marc Gaspard Itard reported

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the case of a French noblewoman who exhibited involuntary body movements and vocalizations such as barking sounds and uttering obscene language [2]. Subsequently, George Gilles de la Tourette referred to this case and reported nine patients with tic disorders [2]. Notably, these reports described the essential clinical features of tic disorders, such as onset at an early age, waxing and waning course, echolalia (repetition of sentences), coprolalia (inexplicable utterances of obscene words), and echopraxia (mimicking gestures of others). For some time, a tic was regarded as a symptom of functional disorders such as hysteria, neurosis, or narcissism. In 1968, the first case was reported of a patient whose tics improved with neuroleptics [3]. Since then, tic disorders have been discussed primarily in a neurobiological context.

Tics are defined as sudden, rapid, recurrent, nonrhythmic motor movement (motor tics) or vocalization (vocal or phonic tics) [4]. Both motor and vocal tics are classified as simple or complex, although differentiating a simple tic from a complex tic is not always straightforward. Simple motor tics are brief, abrupt, repetitive, and seemingly nonpurposeful movements and involve only one muscle group or body part (e.g., face, neck, or limbs) [2]. Examples of motor tics include blinking, eye rolling, wide opening of the eyes or mouth, tilting the neck, raising the shoulders, and hand-movements. Based on the characteristics of the movements, simple motor tics are subdivided into three groups: clonic, dystonic, and tonic tics [5]. Clonic tics are abrupt, rapid, brief jerking movements (e.g., blinking, facial grimacing, head jerking). Dystonic tics are slower, resulting in briefly, sustained abnormal postures (e.g., a prolonged involuntary upward deviation of the eyes, eye closure, bruxism, mouth opening, or torticollis). Tonic tics are isometric contractions (e.g., tensing of abdominal and limb muscles). Some tics may result in transient interruption of ongoing motor activities or speech without loss of consciousness. Such tics are often referred to as blocking tics [6]. By contrast, complex motor tics are caused by several muscle groups and sometimes appear to be purposeful, coordinated, or orchestrated patterns of movement. Examples include touching, tapping, waving, kicking, jumping, echopraxia, and copropraxia (performing obscene or forbidden gestures or inappropriate touching).

Simple vocal tics are meaningless sounds made by moving air through the nose, mouth, or throat. Vocal tics are often referred to as "phonic tics," because the sound may be produced not only by contraction of the vocal cords but also by contraction of the nasal, oral, laryngeal, pharyngeal, and respiratory muscles. Examples include coughing, throat clearing, grunting, mimicking animal noises, and tongue clicking. Complex vocal tics involve several muscle groups and are characterized by words, phrases, or sentences. Examples include shouting and yelling, echolalia, and coprolalia.

The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), defines five tic disorders: Provisional Tic Disorder, Persistent (chronic) Motor or Vocal Tic Disorder, Tourette's Disorder (also known as Tourette syndrome), Other Specified Tic Disorder, and Unspecified Tic Disorder [4]. The first three tic disorders require that the onset be before age 18 years and the symptoms not be caused by other medical illnesses such as Huntington's disease, substance

abuse, or medication side effects. Provisional Tic Disorder is considered when tics (motor or vocal or both) have been present for less than 1 year since tic onset. Both TS and Persistent (chronic) Motor or Vocal Tic Disorder indicate the presence of tics for longer than 1 year (though intervening tic-free periods are allowed). Persistent (chronic) Motor or Vocal Tic Disorder is diagnosed when individuals have exhibited either motor or vocal tics (but not both) at some time during the illness. When both motor and vocal tics occur during the course of the disease, though not necessarily concurrently, TS is diagnosed. Patients with TS tend to have a higher severity of tics, greater prevalence of complex motor tics (e.g., copropraxia and echopraxia), and more comorbid symptoms than patients with Persistent Motor Tic Disorder [7]. The final two DSM-5 tic disorders are used for patients whose presentation does not fit the first three. Importantly, the diagnostic criteria of tic disorders do not mention tic severity.

2 Epidemiology

It is difficult to estimate the true prevalence of tic disorders [8]. The reported prevalence of tics in children varies considerably [9]. Tics are more likely to affect boys than girls by a ratio of 2–4:1 [9, 10]. The overall cross-sectional prevalence of tics during childhood was approximately 19%–24% [10–12]. The prevalence of TS is estimated at around 0.8%–4% in regular school students [9, 12]. Furthermore, the prevalence of chronic tic disorders in children with autistic spectrum disorder and children receiving special education is higher at 22% and 7%, respectively [12, 13].

Tics usually begin between 3 and 8 years of age. Conventionally, most tics are believed to go away on their own within a few months. A clinical follow-up study, however, found that all the children still experienced tics 1 year after onset, although the ticks occur less frequently or milder [14]. If tics persist for more than 1 year, the severity usually peaks around 8–12 years of age. Most patients with tics experience significant improvement or complete resolution by early adulthood [15].

3 Etiology

The pathophysiology of tic disorders involves impaired function of cortical-striatal-thalamic-cortical circuits with aberrant associated neurotransmitter function [16]. The primary neurotransmitters involved in causation of tic disorders are dopamine, serotonin, and gamma-aminobutyric acid (GABA). The higher prevalence in children suggests atypical functional brain connectivity related to an immature nervous system [17]. The etiology of tic disorders is complicated and multifactorial, including genetic and non-genetic factors such as environmental factors and immune-mediated mechanisms, contributing to the heterogeneous clinical phenotypes [18].

3.1 Environmental Factors

The environmental influence on the phenotype of tic disorders has remained elusive. Various studies have investigated prenatal and perinatal epigenetic factors including maternal stressors during pregnancy, prenatal history (e.g., smoking, use of alcohol, cannabis), parental psychiatric disorders, gestational age, complications of delivery, the Apgar score, or birth weight, but these studies had limitations such as selection bias and restrospective study data. Children from nuclear families with poor parental relationships were at more risk of developing TS [19]. However, the onset of tics was not associated with stressful life events [20].

3.2 Genetic Etiology

In 1885, Georges Gilles de la Tourette pointed out possible genetic factors of tic disorders [21]. Currently, tic disorders are considered to be polygenic inherited disorders involving a large number of different genes. Segregation analyses demonstrated autosomal dominant transmission patterns [21]. Studies of monozygotic (MZ) and dizygotic (DZ) twins showed concordance rates for tics of 77%–94% and 23% for MZ and DZ pairs respectively, and for TS of 53%–56% and 8% for MZ and DZ pairs respectively, which indicates genetic etiology with high penetrance [22, 23]. In a population-based cohort study using the Genome-wide Complex Trait Analysis program, the heritability estimate of tic disorders was given as 0.77 and the risk of developing tic disorders for first-degree relatives of probands with tic disorders was significantly higher than that for second and third-degree relatives [24]. Full siblings of individuals with tic disorders have a significantly higher risk of developing tic disorders than maternal half-siblings, regardless of similar environmental exposure, suggesting that environmental factors are less important in causing tic disorders [24].

3.3 Immunologic Mechanisms

Abnormal immune responses have been proposed as underlying causes of tics, and such proposals have prompted investigation with different approaches, including animal studies, postmortem studies, and laboratory studies. These studies have revealed some evidence for immune-mediated mechanisms involving humoral and cellular immunity. An autoimmune process caused by the cross-reaction of streptococcal bacterial antigens to brain antineuronal antibodies, similar to the process of Sydenham's chorea, was suggested as a pathophysiological mechanism of TS, called pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). However, multiple concerns about the diagnosis and treatment of PANDAS have been raised [25, 26].

4 Diagnostic Approach

4.1 History

In clinical practice, the diagnosis of tics is usually straightforward and can be made by reference to the patient's clinical history. Understanding the natural course of tics is therefore essential. On average, tics usually begin at 3–8 years old, peak around 8–12 years, and improve substantially by early adulthood. Several characteristics are useful in identifying tics. Tics usually follow a waxing and waning pattern in severity and frequency, with a mixture of old and new tics. Although the onset of TS does not seem to be associated with life events, tics may be temporarily exacerbated by psychological strains (e.g., stress, anxiety, excitement, anger), physical strains (e.g., fatigue, sleep deprivation, infections), and environmental changes. Individuals with tics often experience an unpleasant sensation preceding the tics, referred to as a premonitory urge, which is temporarily relieved by the execution of the tics [16]. Unlike other movement disorders, tics may be voluntarily suppressed for variable periods [27, 28].

Tourette syndrome is frequently comorbid with other psychiatric symptoms, such as attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), depression, anxiety disorder, sleep disorders, and migraine [29]. About 85% of patients with TS have at least one psychiatric comorbidity that usually appears between the ages of 4 and 10 years [30]. The most common comorbidities are ADHD and OCD.

4.1.1 Attention-Deficit Hyperactivity Disorder

The average prevalence of ADHD in patients with TS is about 50%–60% with male dominance. The onset of ADHD symptoms usually precedes the onset of motor and vocal tics by an average of 2.4 years [30, 31]. Compared to pure TS, patients with TS and ADHD experience more deficits in planning, working memory, inhibitory function, and visual attention [32]. The Brainstorm Consortium genome-wide association studies of TS suggested modest shared etiological overlap between ADHD and TS [33].

In the past, the use of stimulants for patients with tics was not recommended. Many clinicians still worry that using stimulants for the treatment of ADHD in patients with tics may make their tics worse. However, substantial evidence has dispelled the idea that stimulants are contraindicated in children with tics [34]. A large randomized control trial involving children with TS and ADHD demonstrated a small but significant improvement of tics with methylphenidate [35]. Thus, clinicians treating patients with tics and ADHD can use stimulants for the treatment of ADHD symptoms.

4.1.2 Obsessive-Compulsive Disorder

Obsessions are intrusive and unwanted images or thoughts that occur repetitively, and compulsions are behaviors that are performed to reduce the obsession or relieve obsession-related anxiety. Lifetime prevalence rates of OCD in patients with TS are estimated to be 30%–50%), with OCD symptoms usually beginning within a few years after the onset of tics [30]. As TS and OCD can occur in clusters in families, a shared genetic architecture has been suggested, but a possible different underlying genetic susceptibility for TS and OCD compared with OCD alone has also been suggested [36].

Obsessive-compulsive disorder and TS have some common characteristics, such as a chronic waxing and waning course, premonitory phenomena preceding movement, and repetitive behavior [37]. Interestingly, obsessive-compulsive behaviors of TS differ somewhat from those of pure OCD. Contamination fears and negative thoughts (e.g., something going wrong, worry regarding becoming sick, or something "bad" happening) are more prevalent in patients with pure OCD than in patients with TS and OCD [38]. In contrast, patients with TS tend to have compulsions such as counting, checking, ordering, arranging, touching, and hoarding as well as aggressive, sexual, religious, and symmetry obsessions [38]. Moreover, "just right" perception, where patients need to perform the same action repeatedly until they feel "just right," is characteristic of TS with OCD [39]. The "just right" sensation relates to a mental phenomenon (a want), distinguishing it from other premonitory urges that involve a bodily sensation (e.g., an itch) [39].

Trichotillomania is characterized by recurrent pulling out of hair and can be seen in both TS and OCD. Due to its repetitive nature, trichotillomania is generally considered part of the OCD spectrum, but has some common features with TS. Trichotillomania is typically preceded by urges but not obsessions, and can be treated similarly to tics (e.g., antipsychotics and habit-reversal training) [40]. Similarly, skin picking is diagnosed separately in DSM-5, but also has long been considered a complex tic [41].

4.1.3 Anxiety and Depression

Anxiety and depression each occur in about 30% of patients with TS [30]. The high-risk age period begins around 4 years for anxiety disorders and around 7 years for mood disorders [30]. Comorbid depression positively correlates with tic severity and a positive family history of depression [42]. About 10% of youth with tic disorders experience suicidal thoughts and attempts, which often occur in the context of anger and frustration [43]. Although there is no correlation between suicidal ideation and tic severity, the presence of anxiety and depression increases the risk of suicidality in patients with tic disorders [44]. It is therefore important to assess depression and anxiety symptoms, especially in patients with a positive family history of depression. In clinics, brief screening questions about anxiety and depression should be performed and the comorbid symptoms should be addressed appropriately.

4.1.4 Other Neuropsychological Symptoms

Eating disorders such as anorexia nervosa and bulimia nervosa are present in 2% of patients with TS, with female predominance and onset in adolescence (15–19 years old) [30]. Retching and vomiting may be symptomatic of tics if they occur alongside other tics and are accompanied by signs of tics such as suppressibility and premonitory urges [45]. However, medications for the treatment of TS symptoms, such as selective serotonin reuptake inhibitors and alpha-2 adrenergic agonists, can cause retching and vomiting.

Disruptive behaviors and rage episodes including explosive anger, temper outbursts, irritability, and aggressiveness are reported in 25%–70% of TS patients [46]. Oppositional defiant disorder is reported in approximately 11%–54% of TS patients and conduct disorder in approximately 6%–20% [47].

Children with tics are at higher risk of being bullied and experiencing difficulties in socializing due to the social stigma [48]. Difficulties in school often lead to discrimination, which may lower self-esteem [48]. Poor self-perception and self-esteem are also related to the presence of comorbidity such as OCD, ADHD, and anxiety [49]. The quality of life of patients with tic disorders is tied to their self-perception, so clinical treatment should address their self-concept and self-esteem [49]. Although patients with TS occasionally exhibit socially unacceptable behaviors, they rarely commit criminal acts [50].

4.1.5 Sleep Disorders

Sleep disorders such as difficulty with sleep initiation and sleep maintenance, parasomnia, abnormal arousal, and excessive daytime sleepiness occur in 64% of patients with TS [51]. A polysomnography study demonstrated that both motor and vocal tics are observable during all stages of sleep [52]. The likelihood of sleep disturbance is higher when ADHD or OCD is present [53, 54]. Moreover, sleep disturbances themselves can aggravate tic symptoms in the daytime [53]. Treatment of sleep problems in patients with tics may therefore reduce the severity of tics as well as improve the sleep disorders themselves.

4.1.6 Headache

Headache is a common symptom in TS. A prospective questionnaire interview study showed that about 55% of children and adolescents with TS experience headache symptoms [55]. Migraine has been reported in about 17%–25% of patients with TS, commonly around age 14–15 years [55, 56]. Tension-type headache is also commonly seen in patients with tics.

4.1.7 Learning Disability

It is widely accepted that tic disorders do not affect intelligence. However, tic severity, use of medication for tics, executive dysfunction, and coexisting ADHD, OCD, or other illnesses can affect performance in school [57]. Patients with TS and tic disorders who seek treatment are more likely to underachieve academically across all educational levels, even after accounting for various confounders and comorbidities [58]. Detecting and addressing their difficulties at school (e.g., providing extra time to finish tasks, establishing a private space to release tics) is warranted to support their educational needs and enable them to reach their academic potential [58].

4.2 Physical Examination

The neurological examination is normal in children with a tic disorder, except for the tics themselves. A normal examination is important for ruling out secondary causes of tics (such as Huntington's disease). Patients with tics may subconsciously suppress their tics in the clinic [59], so one may need to ask their guardians to video record their tics at home to understand their characteristics and severity.

5 Evaluation (Laboratory Evaluation/Imaging)

Tic disorders are clinical diagnoses and no diagnostic laboratory or neuroimaging tests exist. If unusual historical or examination features suggest secondary tic disorders, evaluations with blood, neuroimaging, or electrophysiological testing are warranted.

6 Treatment and Management

Treatment and management of tic disorders begin with an assessment of tic frequency and severity and the presence of comorbid symptoms. To assess the frequency and severity of tic symptoms, the Yale Global Tic Severity Scale (YGTSS), a semi-structured clinical rating instrument for the assessment of tic severity, is often used in clinics [41]. Unless tics are bothersome to patients, supportive care, reassurance, and education of the patient, family, and school are usually sufficient. It is also important to debunk myths and misconceptions promulgated by stereotyped social media images. For example, many guardians and patients believe that TS is caused by stress or neglect; that tics will always progress to nonstop motor tics

and socially inappropriate behaviors such as cursing; and that individuals with tics are intellectually impaired and cannot lead normal lives. In the United States, the Tourette Association of America, a nonprofit voluntary organization, and the Centers for Diseases Control and Prevention provide comprehensive materials to guardians and patients about TS and tic disorders in a variety of languages.

Pharmacological tic-suppressing treatment and behavioral therapy should be considered when tics cause physical, emotional, or social impairment (e.g., musculoskeletal injury, peer relation difficulty such as bullying, disruptive tic behaviors, low self-esteem, and difficulty in conducting physical or academic activities). The goal of the treatment is to lessen the severity of the tics to improve the patient's quality of life.

6.1 Behavioral Therapy

The American Academy of Neurology practice guideline recommendations recommend a form of behavioral therapy as the first-line treatment for tics [60]. Tic-suppression-based behavioral interventions include exposure and response prevention and habit-reversal therapy (or its descendant comprehensive behavioral interventions for tics, CBIT) (Table 1). The therapies can be effective for both motor and vocal tics. In clinical practice, patients and therapists first determine a tic hierarchy from most to least distressing and then first address the most distressing tic [61]. With practice, patients can participate more effectively and efficiently. Although these therapies can eventually diminish the urges and decrease tic frequency and severity, finding a trained therapist can be difficult. Recently, internet-based training programs have been made available to solve this issue. For example, "TicHelper" (https://www.tichelper.com) is an interactive, self-administered online CBIT program for school-age children [62]. Internet-based behavioral therapy gives patients and guardians more access to evidence-based therapies and may be effective in the long run [63].

Table 1 Tic suppressing behavior therapies

Behavioral therapy	Description
Exposure and response prevention	Repeated, prolonged exposure to stimuli that tend to induce tics, and practice to resist tic behavior
Habit-reversal therapy	Consists of awareness training and competing-response training to encourage tic suppression for long periods of time
Awareness training	Self-monitoring tics and identifying early signs or warning signs, such as the premonitory urge
Competing-response training	Engagement in an active voluntary response that is incompatible with tics, such as tensing muscles antagonistic to tic-related muscles

6.2 Other Nonpharmacological Treatments

Various complementary and alternative medicines have been used for the treatment of tics, including prayer, vitamins, massage, dietary or nutritional supplements (e.g., the B vitamins, vitamins C, D, and E, calcium, magnesium, Coenzyme Q10, fish oil), chiropractic manipulations, meditation, diet, yoga, acupuncture, hypnosis, homeopathy, and biofeedback [64]. Patients find some of these helpful, but there have been no randomized control studies to establish dosing, safety, and efficacy [64].

6.3 Pharmacological Treatment Options

Pharmacological treatment should be considered when behavioral interventions fail or are not available, or when patients exhibit severe, violent tics that need immediate treatment. Before starting patients on a course of medication, clinicians must explain the purpose and set a realistic goal—that is, to reduce the severity and frequency of tics to the extent that they no longer bother the patients or cause significant problems.

Various therapeutic algorithms have helped clinicians choose medicines for the treatment of tics. In general, there are two tiers of medicines, based on tic severity. The first-tier medicines are for mild tics, and the second-tier medicines are for severe tics or tics that are resistant to the first-tier medicines (Table 2). As a rule, the

Table 2 Tic-suppressing medications

Categories	Medicines	Potential mechanisms for tic suppression	Dosage	Side effects
First line medication	Clonidine	Alpha-2-adrenergic agonist	Starting dose: 0.025–0.05 mg/day; titrated up to 0.1–0.3 mg/day	Sedation, drowsiness, lightheadedness, tiredness, irritability, dry mouth, bradycardia, and hypotension
	Guanfacine	Alpha-2-adrenergic agonist	Starting dose: 0.5–1.0 mg/day; titrated up to 1.0–4.0 mg/day	Fatigue, drowsiness, dry mouth, headache, and irritability
	Topiramate	GABA A receptor agonist and AMPA/kainate glutamate receptor agonist	Starting dose: 25 mg/day; titrated up to 50–200 mg/day	Diarrhea, abdominal pain, drowsiness, cognitive slowing, and kidney stones
	Levetiracetam	Atypical GABAergic effect	Starting dose: 20 mg/kg/day; titrated up to 30–40 mg/kg/day	Irritability and somnolence

Table 2 (continued)

Categories	Medicines	Potential mechanisms for tic suppression	Dosage	Side effects
	Clonazepam	GABA A receptor agonist	Starting dose: 0.01–0.03 mg/kg/day; titrated up to 0.5–10 mg/day	Drowsiness, sedation, and dependence
	Baclofen	GABA B receptor agonist	Starting dose: 10 mg/day; titrated up to 80 mg/day	Sedation and drowsiness
Second line medication	Haloperidol	D2 receptor antagonist	Starting dose: 0.5 mg/day; titrated up to 2–10 mg/day	Lethargy and extrapyramidal side effects (e.g., acute dystonic reactions, parkinsonism, and akathisia)
	Pimozide	Dopamine receptor antagonist	Starting dose: 0.05 mg/kg/day: Titrated up to 0.2 mg/kg or 10 mg/day.	Arrhythmias, hypotension, and extrapyramidal symptoms (e.g., acute dystonic reactions, parkinsonism, and akathisia)
			In poor CYP2D6 metabolizers, the maximum dose should not exceed 0.05 mg/kg/day. Titration should be no sooner than every 14 days	
	Aripiprazole	Dopamine-serotonin partial agonist	Starting dose: 1.25–2.5 mg/day; titrated up to 2.5–20 mg/day	Drowsiness, nausea, vomiting, weight gain, headache, and insomnia
	Risperidone	D2 and 5-HT2 receptor antagonist	Starting dose: 0.25 mg/day; titrated up to 0.25–4.0 mg/day	Drowsiness, extrapyramidal symptoms, orthostatic hypotension, gynecomastia hyperprolactinemia, and weight gain
	Olanzapine	Dopamine, serotonin, histamine, and muscarinic receptor antagonist	Starting dose: 2.5–5.0 mg/day; titrated up to 30 mg/day	Weight gain, sedation, and drowsiness
	Ziprasidone	D2 and 5-HT2 receptor antagonist	Starting dose: 5–10 mg/day; titrated up to 40 mg/day	Dose-dependent QTc interval prolongation

medicines should be started on a low dose with gradual titration until they become effective. Once the symptoms subside to such a degree that the tics are no longer bothersome, physicians should discuss weaning off the medicines with patients and caregivers. The trial of weaning off the medicines should be undertaken only when the patient is mentally and physically healthy and does not anticipate any especially stressful situations or events.

6.3.1 First-Line Medications

Medicines in this category are nondopaminergic agents that are mildly to moderately effective in tic suppression and do not have severe adverse effects. The typical medicines in this category are alpha-2-adrenergic agonists such as clonidine and guanfacine. Both tics and ADHD symptoms may improve with the alpha-2-adrenergic agonists. Although electrocardiogram monitoring is not necessary [65], close monitoring of blood pressure and heart rate is essential. Guanfacine has a longer half-life and less severe adverse effects such as sedation and dizziness [66]. Thus, guanfacine is often more favored than clonidine. However, a randomized double-blind study of the extended-release formulation of guanfacine in children with moderate-to-severe chronic tic disorder did not show a clinically meaningful effect for tic suppression [67].

GABAergic medications such as antiepileptic drugs such as topiramate, levetiracetam, and clonazepam, and baclofen have been used for the treatment of tics. Evidence of the efficacy of these medicines is not as robust as that of alpha-2 adrenergic agonists, but these medicines can be used as a monotherapy or as add-on therapy in the treatment for tics.

6.3.2 Second-Line Medications

Medicines in this category are dopamine receptor blocking agents (DRBA) (e.g., typical and atypical neuroleptics). D2 receptor blocking agents reduce tic severity by about 70% [68]. The medications approved by the US Food and Drug Administration (FDA) for the treatment of tics are haloperidol, pimozide, and aripiprazole. They are more effective in tic suppression than the first-line medicines but cause more adverse effects such as sedation, metabolic syndrome (e.g., obesity, insulin resistance, hypertension, and dyslipidemia), cardiovascular adverse effects (e.g., torsades de pointes, QTc prolongation, myocarditis, and cardiomyopathy) [69], akathisia, dystonia, rigidity-bradykinesia [70], or antipsychotic-induced tardive dyskinesia (TD). Haloperidol is not regarded as a preferred treatment for tic suppression due to its side effects but instead is recommended for patients who have not responded to other tic-suppressing medicines [71]. Because coadministration of potent cytochrome P450 (CYP) 2D6 inhibitor (e.g., sertraline) could increase

pimozide concentration and the arrhythmogenic side-effects of pimozide are concentration-dependent, the FDA recommends CYP2D6 genotyping [72].

Ecopipam is a selective D1 receptor agonist and has drawn attention as a treatment for tics. A randomized, placebo-controlled crossover study of children and adolescents with TS showed that ecopipam reduced tics significantly and was well tolerated [73]. Dopamine-depleting agents that deplete presynaptic dopamine by blocking the vesicular monoamine transporter type 2 are safer with little or no risk of TD and have been used in the treatment of movement disorders such as chorea, TD, and tics [74]. Tetrabenazine is usually reserved for patients with severe tics who did not respond to or cannot tolerate other tic medicines. Importantly, tetrabenazine carries a black box warning regarding possible deterioration of an already present depression and should be used cautiously. Unfortunately, initial trials of two tetrabenazine derivatives in TS failed to show efficacy (the results are not published but the information is available from: https://neurocrine.gcs-web.com/news-releases/news-release-details/neurocrine-biosciences-announces-topline-data-phase-iib-t-force; https://clinicaltrials.gov/ct2/show/results/NCT03452943).

6.4 Other Treatment Options

Aside from oral pharmacological treatment, botulinum toxin injections have been used in the treatment of spasticity and movement disorders [75]. An injection of botulinum toxin into muscles that cause tic movements improves tic symptoms but also reduces the premonitory urge [75]. Similarly, the injection into the vocal cords also improves vocal tics and the premonitory urge [75]. Treatment with botulinum toxin should be considered in patients with severe self-injurious motor tics (e.g., repetitive cervical extension) to prevent the progression of disabling myelopathy.

Deep brain stimulation (DBS) is a neurosurgical procedure to implant a device called a neurostimulator to deliver electrical stimulation to a targeted brain region and may be a promising treatment for patients with tics [76]. Further studies are needed to identify the optimum target, the benefits and risks, indications, timing for the procedure, and stimulation parameters [77].

7 Prognosis and Outcomes

Most patients with TS follow a similar clinical course with a reduction of tic severity over time [15]. Tic symptoms usually reach their highest severity around age 10 years and improve during adolescence [78]. Although tics are still present on direct examination in 88%–100% of adults with a TS diagnosis in childhood or adolescence, about 33%–47% of patients with TS report being completely tic free,

less than 50% have mild tics, and less than 25% have moderate or severe tics in adulthood [15, 78, 79]. In other words, most patients with TS are no longer bothered by tics in adulthood. Various studies including genetic studies, neuropsychological testing studies, and neuroimaging studies have revealed only a few predictive factors of future tic disorders [80].

Adults with TS reported good psychosocial functioning, attainment of social milestones such as graduating from school, securing a job, and getting married, and high quality of life [81]. As many people still have misconceptions about tic disorders (e.g., tics are due to psychological issues, or individuals with tics cannot lead normal lives), providing anticipatory guidance at the time of the diagnosis of TS can reassure patients and their families [81].

Even when tic symptoms do not impair social, behavioral, or emotional functioning, the comorbidities and non-tic-related symptoms can negatively affect patients' quality of life more than tics do [82]. Keeping in mind the comorbidities and their adverse consequences is important, and continuous assessment for them is warranted.

8 When to Refer and Admit

Given the benign outcome and prognosis of tics, patients usually do not need to be referred to specialists. If tics are severe and bothersome enough to affect quality of life, activities, and self-esteem and cause significant social, emotional, and physical impairments, it is appropriate to refer the patient to specialists including pediatric neurologists, psychologists, psychiatrists, and behavioral therapists who have had training in CBIT, depending on what problems most bother the patient.

Although hospital admission due to tics is very rare, hospital admission will be required for the rare patient with life-threatening tics, known as "malignant TS" (e.g., violent hyperextension of the neck) [83]. Treatment for malignant TS is challenging. The first-line and second-line tic medicines are used, but may not be effective. Behavioral therapy or CBIT may be used with some benefit. For cases refractory to behavior therapy and medication, DBS may be an option [83]. Abrupt withdrawal of neuroleptics or clonazepam may lead to severe, disabling, and continuous tics, referred to as "tic status." Tic status may interfere with activities and sleep, can be refractory to tic-suppression medicines, and often requires sedation with propofol and midazolam [84].

9 Prevention

There are no preventive measures for the development or progression of tics.

10 Differential Diagnosis

Various movements may resemble tics, from the common (e.g., habits, stereotypies, and mannerisms) to the abnormal (e.g., compulsion, chorea, dystonia, and myoclonus). To distinguish such movements from tics, one can confirm the presence of the premonitory urge, suppressibility, and suggestibility, as well as the phenomenology and timing of the movements.

Habits (or body-focused repetitive behaviors) are movements elicited by environmental stimuli or contexts and not performed to obtain future outcomes (e.g., nail biting, picking, thumb sucking, and hair twirling) [85]. Stereotypies are described as repetitive, patterned, nonpurposeful movements (e.g., body rocking, tapping, hand flapping, arm waving) that stop with distraction or calling the child's name, are frequently seen in early childhood and may persist until adolescence with gradual reduction in frequency and duration [86]. They can occur in otherwise healthy children and in children with ADHD, OCD, anxiety, and autistic spectrum disorder [87]. Tics and stereotypies may coexist and may be differentiated by certain features. Stereotypies usually begin before the age of 3 years, which is earlier than the onset of tics, and they tend to improve during childhood [88]. Compared to tics, stereotypies are longer in duration and less variable in type and location [88]. The premonitory urge is not seen in patients with stereotypies. Stereotypies often provide a comforting, enjoyable, and pleasing experience for children, in contrast to the discomfort and distress of tics [87]. Reassurance and psychoeducation are usually appropriate for stereotypies. In severe cases, behavioral therapies such as habit-reversal training or response interruption and redirection might reduce the severity and frequency of stereotypies, but pharmacotherapy is usually not effective [89]. The use of an instructional DVD as a home-based, parent-administered behavioral therapy has been shown to reduce stereotypies by 15%–24% [90].

Mannerisms are repetitive and unusual habits or gestures unique to the individual that may seem stereotypical at times [91]. Mannerisms can be seen not only in healthy individuals but also in patients with schizophrenia with delusions [92]. Unlike tics, mannerisms may be goal-directed (e.g., performing a ritualistic action for luck) [92]. Mannerisms do not require treatment.

Compulsions are repetitive behaviors (e.g., hand washing) or mental acts (e.g., praying, counting) that are performed in response to an obsession or to prevent distress [4]. Some complex motor tics such as touching, tapping, and knocking resemble compulsions. Clinically, compulsions are associated with specific, sometimes ritualistic rules, or are performed in response to an obsession to reduce anxiety, distress, or discomfort [93]. Unlike patients with tics, those with compulsions do not experience premonitory sensations. Compulsions improve with treatments for OCD, such as behavior therapy or serotonin reuptake inhibitors.

Chorea is characterized by brief, abrupt, irregular, unpredictable, purposeless, non-stereotyped movements flowing randomly from one part of the body to another [94]. Damage or dysfunction of the interconnection between the motor

cortical areas and the basal ganglia leads to chorea [95]. The etiologies of acute chorea include autoimmune disease, infection, vascular disease, mitochondrial disease, toxins, and functional disease and those of chronic chorea include genetic, metabolic, and vascular diseases [94]. To differentiate between chorea and tics, it is essential to obtain a detailed history of the disease onset, progression, and associated symptoms. Chorea may be voluntarily suppressible [27], but unlike tics, patients with chorea do not have premonitory urges and never perceive the movements as voluntary. Compared to chorea, tic movements are usually more patterned and are repeated in a predictable and stereotypical manner.

Dystonia is a movement disorder characterized by involuntary sustained muscle contractions that produce abnormal postures or repetitive movements [96]. The etiology of dystonia is not fully understood, but structural abnormalities in the basal ganglia, cerebellum, cortex, brainstem, and thalamus, as well as neurotransmitter diseases that can affect dopaminergic dysfunction, have been suggested [97]. The most distinctive features of dystonia are sustained twisting movements, a sensory phenomenon called sensory trick (e.g., touching the affected body part may ameliorate the dystonia), task specificity, and directionality (e.g., alternates between quick jerking movements in one direction and slower movements in the opposite direction) [96, 98]. Unlike tics, dystonia is not preceded by premonitory urges.

Myoclonus is a movement disorder characterized by brief, sudden, involuntary muscle jerks. It arises from all levels of the nervous system, including the cortical and subcortical areas, brainstem, spinal cord, and peripheral areas and causes muscle contractions (positive myoclonus) or brief inhibition during sustained posture (negative myoclonus) [99]. Tics and myoclonus can be visibly indistinguishable, but some clinical features are useful to distinguish them. Myoclonus is very brief (traditionally <200 ms on EMG), is usually nonsuppressible and is not associated with a premonitory urge [100].

Tardive dyskinesia (TD) is characterized by involuntary, repetitive hyperkinetic movement around the mouth (e.g., chewing, protrusion of the tongue, jaw movements, lip smacking, or puckering) [101]. TD is commonly seen in patients receiving neuroleptics and emerges insidiously, usually after long-term use of neuroleptics [102]. However, TD is apparently quite rare in TS. TD can be distinguished from tics by the time course and by several other features, including that TD is usually rhythmic at 0.5–2 Hz, does not include premonitory phenomena, and is perceived by the patient as truly involuntary. A rapid reduction or sudden discontinuation of the medicine may lead to transient worsening of dyskinesia, known as withdrawal dyskinesia [103]. Slow and gradual tapering of the offending medication is recommended for patients who develop TD. Although many patients with TD showed some improvement within the first year of discontinuation of neuroleptic, the chance of complete remission has been reported to be low [104].

11 Clinical Pearls and Key Points

- Tics are the most common movement disorder in the pediatric population.
- Most tics seem to diminish within 1 year.
- Tics of Tourette syndrome usually improve over time after adolescence.
- The presence of a premonitory urge, suppressibility, and suggestibility can distinguish tics from other movement disorders.
- It is important to address comorbidities such as ADHD, OCD, mood disorders, sleep disorders, and migraines.
- Treatment for tics should be considered when the tics are bothersome to patients. The first-line treatment is comprehensive behavioral therapy. If the therapy is not available or the tics are severe, pharmacological treatment should be considered.

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References

1. Mink JW. The basal ganglia and involuntary movements: impaired inhibition of competing motor patterns. Arch Neurol. 2003;60:1365–8. https://doi.org/10.1001/archneur.60.10.1365.
2. Fahn S, Jankovic J, Hallett M. Tics and Tourette syndrome. In: Principles and practice of movement disorders E-book. Elsevier Health Sciences; 2011. p. 350–79.
3. Shapiro AK, Shapiro E. Treatment of Gilles de la Tourette's syndrome with haloperidol. Br J Psychiatry. 1968;114:345–50. https://doi.org/10.1192/bjp.114.508.345.
4. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub; 2013.
5. Jankovic J. Tourette's syndrome. N Engl J Med. 2001;345:1184–92. https://doi.org/10.1056/NEJMra010032.
6. Jankovic J, Kurlan R. Tourette syndrome: evolving concepts. Mov Disord. 2011;26:1149–56. https://doi.org/10.1002/mds.23618.
7. Müller-Vahl KR, Sambrani T, Jakubovski E. Tic disorders revisited: introduction of the term "tic spectrum disorders". Eur Child Adolesc Psychiatry. 2019;28:1129–35. https://doi.org/10.1007/s00787-018-01272-7.
8. Cubo E. Review of prevalence studies of tic disorders: methodological caveats. Tremor Other Hyperkinet Mov (N Y). 2012;2:tre-02-61-349-1. https://doi.org/10.7916/D8445K68.
9. Knight T, Steeves T, Day L, Lowerison M, Jette N, Pringsheim T. Prevalence of tic disorders: a systematic review and meta-analysis. Pediatr Neurol. 2012;47:77–90. https://doi.org/10.1016/j.pediatrneurol.2012.05.002.
10. Snider LA, Seligman LD, Ketchen BR, Levitt SJ, Bates LR, Garvey MA, et al. Tics and problem behaviors in schoolchildren: prevalence, characterization, and associations. Pediatrics. 2002;110:331–6. https://doi.org/10.1542/peds.110.2.331.
11. Black KJ, Black ER, Greene DJ, Schlaggar BL. Provisional tic disorder: what to tell parents when their child first starts ticcing. F1000Res. 2016;5:696. https://doi.org/10.12688/f1000research.8428.1.

12. Kurlan R, McDermott MP, Deeley C, Como PG, Brower C, Eapen S, et al. Prevalence of tics in schoolchildren and association with placement in special education. Neurology. 2001;57:1383–8. https://doi.org/10.1212/wnl.57.8.1383.
13. Canitano R, Vivanti G. Tics and Tourette syndrome in autism spectrum disorders. Autism. 2007;11:19–28. https://doi.org/10.1177/1362361307070992.
14. Kim S, Greene DJ, Bihun EC, Koller JM, Hampton JM, Acevedo H, et al. Provisional tic disorder is not so transient. Sci Rep. 2019;9:3951. https://doi.org/10.1038/s41598-019-40133-4.
15. Leckman JF, Zhang H, Vitale A, Lahnin F, Lynch K, Bondi C, et al. Course of tic severity in Tourette syndrome: the first two decades. Pediatrics. 1998;102:14–9. https://doi.org/10.1542/peds.102.1.14.
16. Leckman JF. Tourette's syndrome. Lancet. 2002;360:1577–86. https://doi.org/10.1016/S0140-6736(02)11526-1.
17. Nielsen AN, Gratton C, Church JA, Dosenbach NUF, Black KJ, Petersen SE, et al. Atypical functional connectivity in Tourette syndrome differs between children and adults. Biol Psychiatry. 2020;87:164–73. https://doi.org/10.1016/j.biopsych.2019.06.021.
18. Robertson MM, Eapen V, Singer HS, Martino D, Scharf JM, Paschou P, et al. Gilles de la Tourette syndrome. Nat Rev Dis Primers. 2017;3:16097. https://doi.org/10.1038/nrdp.2016.97.
19. Zhu P, Wu M, Huang P, Zhao X, Ji X. Children from nuclear families with bad parental relationship could develop tic symptoms. Mol Genet Genomic Med. 2020;8:e1286. https://doi.org/10.1002/mgg3.1286.
20. Horesh N, Zimmerman S, Steinberg T, Yagan H, Apter A. Is onset of Tourette syndrome influenced by life events? J Neural Transm (Vienna). 2008;115:787–93. https://doi.org/10.1007/s00702-007-0014-3.
21. Pauls DL, Leckman JF. The inheritance of Gilles de la Tourette's syndrome and associated behaviors. Evidence for autosomal dominant transmission. N Engl J Med. 1986;315:993–7. https://doi.org/10.1056/NEJM198610163151604.
22. Price RA, Kidd KK, Cohen DJ, Pauls DL, Leckman JF. A twin study of Tourette syndrome. Arch Gen Psychiatry. 1985;42:815–20. https://doi.org/10.1001/archpsyc.1985.01790310077011.
23. Hyde TM, Aaronson BA, Randolph C, Rickler KC, Weinberger DR. Relationship of birth weight to the phenotypic expression of Gilles de la Tourette's syndrome in monozygotic twins. Neurology. 1992;42(3 Pt 1):652–8. https://doi.org/10.1212/wnl.42.3.652. PMID: 1549232.
24. Mataix-Cols D, Isomura K, Pérez-Vigil A, Chang Z, Rück C, Larsson KJ, et al. Familial risks of Tourette syndrome and chronic tic disorders. A population-based cohort study. JAMA Psychiatry. 2015;72:787–93. https://doi.org/10.1001/jamapsychiatry.2015.0627.
25. Gilbert DL. Inflammation in tic disorders and obsessive-compulsive disorder: are PANS and PANDAS a path forward? J Child Neurol. 2019;34:598–611. https://doi.org/10.1177/0883073819848635.
26. Martino D, Schrag A, Anastasiou Z, Apter A, Benaroya-Milstein N, Buttiglione M, et al. Association of Group A Streptococcus Exposure and Exacerbations of chronic tic disorders: a multinational prospective cohort study. Neurology. 2021; https://doi.org/10.1212/WNL.0000000000011610.
27. Koller WC, Biary NM. Volitional control of involuntary movements. Mov Disord. 1989;4:153–6. https://doi.org/10.1002/mds.870040207.
28. Ueda K, Kim S, Greene DJ, Black KJ. Correlates and clinical implications of tic suppressibility; 2020. OSF Preprints: https://osf.io/5sg2d/
29. Robertson MM. A personal 35 year perspective on Gilles de la Tourette syndrome: prevalence, phenomenology, comorbidities, and coexistent psychopathologies. Lancet Psychiatry. 2015;2:68–87. https://doi.org/10.1016/S2215-0366(14)00132-1.
30. Hirschtritt ME, Lee PC, Pauls DL, Dion Y, Grados MA, Illmann C, et al. Lifetime prevalence, age of risk, and genetic relationships of comorbid psychiatric disorders in Tourette syndrome. JAMA Psychiat. 2015;72:325–33. https://doi.org/10.1001/jamapsychiatry.2014.2650.

31. Comings DE, Comings BG. A controlled study of Tourette syndrome. I. Attention-deficit disorder, learning disorders, and school problems. Am J Hum Genet. 1987;41:701–41.
32. Termine C, Luoni C, Fontolan S, Selvini C, Perego L, Pavone F, et al. Impact of comorbid attention-deficit and hyperactivity disorder on cognitive function in male children with Tourette syndrome: a controlled study. Psychiatry Res. 2016;243:263–7. https://doi.org/10.1016/j.psychres.2016.06.048.
33. Brainstorm Consortium. Analysis of shared heritability in common disorders of the brain. Science. 2018;360:eaap8757. https://doi.org/10.1126/science.aap8757.
34. Kurlan R. Methylphenidate to treat ADHD is not contraindicated in children with tics. Mov Disord. 2002;17:5–6. https://doi.org/10.1002/mds.10094.
35. Tourette's Syndrome Study Group. Treatment of ADHD in children with tics: a randomized controlled trial. Neurology. 2002;58:527–36. https://doi.org/10.1212/wnl.58.4.527.
36. Yu D, Mathews CA, Scharf JM, Neale BM, Davis LK, Gamazon ER, et al. Cross-disorder genome-wide analyses suggest a complex genetic relationship between Tourette's syndrome and OCD. Am J Psychiatry. 2015;172:82–93. https://doi.org/10.1176/appi.ajp.2014.13101306.
37. Worbe Y, Mallet L, Golmard JL, Béhar C, Durif F, Jalenques I, et al. Repetitive behaviours in patients with Gilles de la Tourette syndrome: tics, compulsions, or both? PLoS One. 2010;5:e12959. https://doi.org/10.1371/journal.pone.0012959.
38. Eapen V, Robertson MM, Alsobrook JP 2nd, Pauls DL. Obsessive compulsive symptoms in Gilles de la Tourette syndrome and obsessive compulsive disorder: differences by diagnosis and family history. Am J Med Genet. 1997;74:432–8. https://doi.org/10.1002/(sici)1096-8628(19970725)74:4<432::aid-ajmg15>3.0.co;2-j.
39. Leckman JF, Walker DE, Goodman WK, Pauls DL, Cohen DJ. "just right" perceptions associated with compulsive behavior in Tourette's syndrome. Am J Psychiatry. 1994;151:675–80. https://doi.org/10.1176/ajp.151.5.675.
40. Lamothe H, Baleyte JM, Mallet L, Pelissolo A. Trichotillomania is more related to Tourette disorder than to obsessive-compulsive disorder. Braz J Psychiatry. 2020;42:87–104. https://doi.org/10.1590/1516-4446-2019-0471.
41. Leckman JF, Riddle MA, Hardin MT, Ort SI, Swartz KL, Stevenson J, et al. The Yale global tic severity scale: initial testing of a clinician-rated scale of tic severity. J Am Acad Child Adolesc Psychiatry. 1989;28:566–73. https://doi.org/10.1097/00004583-198907000-00015.
42. Rizzo R, Gulisano M, Martino D, Robertson MM. Gilles de la Tourette syndrome, depression, depressive illness, and correlates in a child and adolescent population. J Child Adolesc Psychopharmacol. 2017;27:243–9. https://doi.org/10.1089/cap.2016.0120.
43. Storch EA, Hanks CE, Mink JW, McGuire JF, Adams HR, Augustine EF, et al. Suicidal thoughts and BEHAVIORS in children and adolescents with chronic tic disorders. Depress Anxiety. 2015;32:744–53. https://doi.org/10.1002/da.22357.
44. Johnco C, McGuire JF, McBride NM, Murphy TK, Lewin AB, Storch EA. Suicidal ideation in youth with tic disorders. J Affect Disord. 2016;200:204–11. https://doi.org/10.1016/j.jad.2016.04.027.
45. Rickards H, Robertson MM. Vomiting and retching in Gilles de la Tourette syndrome: a report of ten cases and a review of the literature. Mov Disord. 1997;12:531–5. https://doi.org/10.1002/mds.870120409.
46. Budman CL, Rockmore L, Stokes J, Sossin M. Clinical phenomenology of episodic rage in children with Tourette syndrome. J Psychosom Res. 2003;55:59–65. https://doi.org/10.1016/s0022-3999(02)00584-6.
47. Eapen V, Robertson MM. Clinical correlates of tourette's disorder across cultures: a comparative study between the United Arab Emirates and the United Kingdom. Prim Care Companion J Clin Psychiatry. 2008;10:103–7. https://doi.org/10.4088/pcc.v10n0203.
48. Cox JH, Nahar A, Termine C, Agosti M, Balottin U, Seri S, et al. Social stigma and self-perception in adolescents with tourette syndrome. Adolesc Health Med Ther. 2019;10:75–82. https://doi.org/10.2147/AHMT.S175765.

49. Silvestri PR, Baglioni V, Cardona F, Cavanna AE. Self-concept and self-esteem in patients with chronic tic disorders: a systematic literature review. Eur J Paediatr Neurol. 2018;22:749–56. https://doi.org/10.1016/j.ejpn.2018.05.008.
50. Jankovic J, Kwak C, Frankoff R. Tourette's syndrome and the law. J Neuropsychiatry Clin Neurosci. 2006;18:86–95. https://doi.org/10.1176/jnp.18.1.86.
51. Ghosh D, Rajan PV, Das D, Datta P, Rothner AD, Erenberg G. Sleep disorders in children with Tourette syndrome. Pediatr Neurol. 2014;51:31–5. https://doi.org/10.1016/j.pediatrneurol.2014.03.017.
52. Jankovic J, Rohaidy H. Motor, behavioral and pharmacologic findings in Tourette's syndrome. Can J Neurol Sci. 1987;14(3 Suppl):541–6. https://doi.org/10.1017/s0317167100038087.
53. Kirov R, Kinkelbur J, Banaschewski T, Rothenberger A. Sleep patterns in children with attention-deficit/hyperactivity disorder, tic disorder, and comorbidity. J Child Psychol Psychiatry. 2007;48:561–70. https://doi.org/10.1111/j.1469-7610.2007.01729.x.
54. Mol Debes NM, Hjalgrim H, Skov L. Validation of the presence of comorbidities in a Danish clinical cohort of children with Tourette syndrome. J Child Neurol. 2008;23:1017–27. https://doi.org/10.1177/0883073808316370.
55. Ghosh D, Rajan PV, Das D, Datta P, Rothner AD, Erenberg G. Headache in children with Tourette syndrome. J Pediatr. 2012;161:303–7. https://doi.org/10.1016/j.jpeds.2012.01.072.
56. Kwak C, Vuong KD, Jankovic J. Migraine headache in patients with Tourette syndrome. Arch Neurol. 2003;60:1595–8. https://doi.org/10.1001/archneur.60.11.1595.
57. Singer HS, Schuerholz LJ, Denckla MB. Learning difficulties in children with Tourette syndrome. J Child Neurol. 1995;10(Suppl 1):58–61. https://doi.org/10.1177/08830738950100S112.
58. Pérez-Vigil A, Fernández de la Cruz L, Brander G, Isomura K, Jangmo A, Kuja-Halkola R, et al. Association of Tourette syndrome and chronic tic disorders with objective indicators of educational attainment: a population-based sibling comparison study. JAMA Neurol. 2018;75:1098–105. https://doi.org/10.1001/jamaneurol.2018.1194.
59. Goetz CG, Leurgans S, Chmura TA. Home alone: methods to maximize tic expression for objective videotape assessments in Gilles de la Tourette syndrome. Mov Disord. 2001;16:693–7. https://doi.org/10.1002/mds.1159.
60. Pringsheim T, Okun MS, Müller-Vahl K, Martino D, Jankovic J, Cavanna AE, et al. Practice guideline recommendations summary: treatment of tics in people with Tourette syndrome and chronic tic disorders. Neurology. 2019;92:896–906. https://doi.org/10.1212/WNL.0000000000007466.
61. Piacentini J, Woods DW, Scahill L, Wilhelm S, Peterson AL, Chang S, et al. Behavior therapy for children with Tourette disorder: a randomized controlled trial. JAMA. 2010;303:1929–37. https://doi.org/10.1001/jama.2010.607.
62. Conelea CA, Wellen BCM. Tic treatment goes tech: a review of TicHelper.com. Cogn Behav Pract. 2017;24:374–81. https://doi.org/10.1016/j.cbpra.2017.01.003.
63. Andrén P, Aspvall K, Fernández de la Cruz L, Wiktor P, Romano S, Andersson E, et al. Therapist-guided and parent-guided internet-delivered behaviour therapy for paediatric Tourette's disorder: a pilot randomised controlled trial with long-term follow-up. BMJ Open. 2019;9:e024685. https://doi.org/10.1136/bmjopen-2018-024685.
64. Kumar A, Duda L, Mainali G, Asghar S, Byler D. A comprehensive review of Tourette syndrome and complementary alternative medicine. Curr Dev Disord Rep. 2018;5:95–100. https://doi.org/10.1007/s40474-018-0137-2.
65. Gutgesell H, Atkins D, Barst R, Buck M, Franklin W, Humes R, et al. Cardiovascular monitoring of children and adolescents receiving psychotropic drugs: a statement for healthcare professionals from the committee on congenital cardiac defects, council on cardiovascular disease in the young. Am Heart Assoc Circul. 1999;99:979–82. https://doi.org/10.1161/01.cir.99.7.979.

66. Sharma A, Couture J. A review of the pathophysiology, etiology, and treatment of attention-deficit hyperactivity disorder (ADHD). Ann Pharmacother. 2014;48:209–25. https://doi.org/10.1177/1060028013510699.
67. Murphy TK, Fernandez TV, Coffey BJ, Rahman O, Gavaletz A, Hanks CE, et al. Extended-release guanfacine does not show a large effect on tic severity in children with chronic tic disorders. J Child Adolesc Psychopharmacol. 2017;27:762–70. https://doi.org/10.1089/cap.2017.0024.
68. Roessner V, Plessen KJ, Rothenberger A, Ludolph AG, Rizzo R, Skov L, et al. European clinical guidelines for Tourette syndrome and other tic disorders. Part II: pharmacological treatment. Eur Child Adolesc Psychiatry. 2011;20:173–96. https://doi.org/10.1007/s00787-011-0163-7.
69. Stoner SC. Management of serious cardiac adverse effects of antipsychotic medications. Ment Health Clin. 2018;7:246–54. https://doi.org/10.9740/mhc.2017.11.246.
70. Stroup TS, Gray N. Management of common adverse effects of antipsychotic medications. World Psychiatry. 2018;17:341–56. https://doi.org/10.1002/wps.20567.
71. Budman CL. The role of atypical antipsychotics for treatment of Tourette's syndrome: an overview. Drugs. 2014;74:1177–93. https://doi.org/10.1007/s40265-014-0254-0.
72. Rogers HL, Bhattaram A, Zineh I, Gobburu J, Mathis M, Laughren TP, et al. CYP2D6 genotype information to guide pimozide treatment in adult and pediatric patients: basis for the U.S. Food and Drug Administration's new dosing recommendations. J Clin Psychiatry. 2012;73:1187–90. https://doi.org/10.4088/JCP.11m07572.
73. Gilbert DL, Murphy TK, Jankovic J, Budman CL, Black KJ, Kurlan RM, et al. Ecopipam, a D1 receptor antagonist, for treatment of tourette syndrome in children: a randomized, placebo-controlled crossover study. Mov Disord. 2018;33:1272–80. https://doi.org/10.1002/mds.27457.
74. Jankovic J. Dopamine depleters in the treatment of hyperkinetic movement disorders. Expert Opin Pharmacother. 2016;17:2461–70. https://doi.org/10.1080/14656566.2016.1258063.
75. Jankovic J. Botulinum toxin in clinical practice. J Neurol Neurosurg Psychiatry. 2004;75:951–7. https://doi.org/10.1136/jnnp.2003.034702.
76. Martinez-Ramirez D, Jimenez-Shahed J, Leckman JF, Porta M, Servello D, Meng FG, et al. Efficacy and safety of deep brain stimulation in Tourette syndrome: the international Tourette syndrome deep brain stimulation public database and registry. JAMA Neurol. 2018;75:353–9. https://doi.org/10.1001/jamaneurol.2017.4317.
77. Coulombe MA, Elkaim LM, Alotaibi NM, Gorman DA, Weil AG, Fallah A, et al. Deep brain stimulation for Gilles de la Tourette syndrome in children and youth: a meta-analysis with individual participant data. J Neurosurg Pediatr. 2018;23:236–46. https://doi.org/10.3171/2018.7.PEDS18300.
78. Bloch MH, Leckman JF. Clinical course of Tourette syndrome. J Psychosom Res. 2009;67:497–501. https://doi.org/10.1016/j.jpsychores.2009.09.002.
79. Black KJ, Kim S, Yang NY, Greene DJ. Course of tic disorders over the lifespan. 2020. Preprint.; https://doi.org/10.31219/osf.io/vehjr.
80. Bloch MH, Peterson BS, Scahill L, Otka J, Katsovich L, Zhang H, et al. Adulthood outcome of tic and obsessive-compulsive symptom severity in children with Tourette syndrome. Arch Pediatr Adolesc Med. 2006;160:65–9. https://doi.org/10.1001/archpedi.160.1.65.
81. Lowe TL, Capriotti MR, McBurnett K. Long-term follow-up of patients with Tourette's syndrome. Mov Disord Clin Pract. 2018;6:40–5. https://doi.org/10.1002/mdc3.12696.
82. Eddy CM, Rizzo R, Gulisano M, Agodi A, Barchitta M, Calì P, et al. Quality of life in young people with Tourette syndrome: a controlled study. J Neurol. 2011;258:291–301. https://doi.org/10.1007/s00415-010-5754-6.
83. Cheung MY, Shahed J, Jankovic J. Malignant Tourette syndrome. Mov Disord. 2007;22:1743–50. https://doi.org/10.1002/mds.21599.
84. Kovacs N, Herold R, Janszky J, Komoly S, Nagy F. Tics status: a movement disorder emergency: observations. J Neurol. 2011;258:143–5. https://doi.org/10.1007/s00415-010-5680-7.

85. Robbins TW, Costa RM. Habits. Curr Biol. 2017;27:R1200–6. https://doi.org/10.1016/j.cub.2017.09.060.
86. Oakley C, Mahone EM, Morris-Berry C, Kline T, Singer HS. Primary complex motor stereotypies in older children and adolescents: clinical features and longitudinal follow-up. Pediatr Neurol. 2015;52:398–403. https://doi.org/10.1016/j.pediatrneurol.2014.11.002.
87. Martino D, Hedderly T. Tics and stereotypies: a comparative clinical review. Parkinsonism Relat Disord. 2019;59:117–24. https://doi.org/10.1016/j.parkreldis.2019.02.005.
88. Freeman RD, Soltanifar A, Baer S. Stereotypic movement disorder: easily missed. Dev Med Child Neurol. 2010;52:733–8. https://doi.org/10.1111/j.1469-8749.2010.03627.x.
89. Katherine M. Stereotypic movement disorders. Semin Pediatr Neurol. 2018;25:19–24. https://doi.org/10.1016/j.spen.2017.12.004.
90. Specht MW, Mahone EM, Kline T, Waranch R, Brabson L, Thompson CB, et al. Efficacy of parent-delivered behavioral therapy for primary complex motor stereotypies. Dev Med Child Neurol. 2017;59:168–73. https://doi.org/10.1111/dmcn.13164.
91. Mulligan HF, Anderson TJ, Jones RD, Williams MJ, Donaldson IM. Tics and developmental stuttering. Parkinsonism Relat Disord. 2003;9:281–9. https://doi.org/10.1016/s1353-8020(03)00002-6.
92. Kaufmann C, Agalawatta N, Malhi GS. Catatonia: stereotypies, mannerisms and perseverations. Aust N Z J Psychiatry. 2018;52:391–3. https://doi.org/10.1177/0004867418765669.
93. Palumbo D, Kurlan R. Complex obsessive compulsive and impulsive symptoms in Tourette's syndrome. Neuropsychiatr Dis Treat. 2007;3:687–93.
94. Gilbert DL. Acute and chronic chorea in childhood. Semin Pediatr Neurol. 2009;16:71–6. https://doi.org/10.1016/j.spen.2009.03.009.
95. Cardoso F, Seppi K, Mair KJ, Wenning GK, Poewe W. Seminar on choreas. Lancet Neurol. 2006;5:589–602. https://doi.org/10.1016/S1474-4422(06)70494-X.
96. Geyer HL, Bressman SB. The diagnosis of dystonia. Lancet Neurol. 2006;5:780–90. https://doi.org/10.1016/S1474-4422(06)70547-6.
97. Ribot B, Aupy J, Vidailhet M, Mazère J, Pisani A, Bezard E, et al. Dystonia and dopamine: from phenomenology to pathophysiology. Prog Neurobiol. 2019;182:101678. https://doi.org/10.1016/j.pneurobio.2019.101678.
98. Mink JW. Basal ganglia mechanisms in action selection, plasticity, and dystonia. Eur J Paediatr Neurol. 2018;22:225–9. https://doi.org/10.1016/j.ejpn.2018.01.005.
99. Mills K, Mari Z. An update and review of the treatment of myoclonus. Curr Neurol Neurosci Rep. 2015;15:512. https://doi.org/10.1007/s11910-014-0512-2.
100. Faught E. Clinical presentations and phenomenology of myoclonus. Epilepsia. 2003;44(Suppl 11):7–12. https://doi.org/10.1046/j.1528-1157.44.s11.3.x.
101. Schooler NR, Kane JM. Research diagnoses for tardive dyskinesia. Arch Gen Psychiatry. 1982;39:486–7. https://doi.org/10.1001/archpsyc.1982.04290040080014.
102. Waln O, Jankovic J. An update on tardive dyskinesia: from phenomenology to treatment. Tremor Other Hyperkinet Mov (N Y). 2013;3:tre-03-161-4138-1. https://doi.org/10.7916/D88P5Z71.
103. Widschwendter CG, Hofer A. Antipsychotic-induced tardive dyskinesia: update on epidemiology and management. Curr Opin Psychiatry. 2019;32:179–84. https://doi.org/10.1097/YCO.0000000000000491.
104. Glazer WM, Morgenstern H, Schooler N, Berkman CS, Moore DC. Predictors of improvement in tardive dyskinesia following discontinuation of neuroleptic medication. Br J Psychiatry. 1990;157:585–92. https://doi.org/10.1192/bjp.157.4.585.
105. Ueda K, Black KJ. A Comprehensive Review of Tic Disorders in Children. J Clin Med. 2021;10(11):2479. https://doi.org/10.3390/jcm10112479. PMID: 34204991; PMCID: PMC8199885.

Child with Congenital and Acquired Torticollis

Barbara Sargent and Young Ah Lee

Child with Torticollis

Torticollis is characterized by a head tilt or postural preference. The term "torticollis" is derived from two Latin terms, tortum collum, meaning twisted neck. Torticollis is categorized as congenital torticollis, which includes congenital muscular torticollis (CMT), and acquired torticollis. The first part of this chapter focuses on the child with CMT and the second part on acquired torticollis.

1 Part 1: Infant with Congenital Muscular Torticollis (CMT)

1.1 Introduction

This portion of the chapter on CMT aligns with the Academy of Pediatric Physical Therapy 2018 CMT Evidence-based Clinical Practice Guideline [1, 2] and the Congress of Neurological Surgeons 2016 Positional Plagiocephaly Evidence-based Guideline [3].

CMT is a common postural deformity identified at birth or in early infancy (<6 months of age) and accounts for more than 80% of pediatric torticollis cases [4]. It is characterized by a head preference into ipsilateral cervical lateral flexion and contralateral cervical rotation due to unilateral shortening of the involved sternocleidomastoid (SCM) muscle, with or without an SCM mass. CMT is named

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for the side of the involved SCM; for example, a tight right SCM with head positioned in right cervical lateral flexion and left cervical rotation is diagnosed as right CMT.

CMT is classified into three types: postural, muscular, and SCM mass. Postural CMT is the mildest form and presents as a positional preference of the head and neck without passive cervical range of motion limitations [5, 6]. Muscular CMT presents as a unilateral tightness of the SCM with passive range limitations into cervical rotation and/or lateral flexion. SCM mass is the most severe form and presents as a palpable nodule [7] or fibrous bands [8] in the SCM and passive range limitations into cervical rotation and/or lateral flexion [9].

Up to 90% of infants with CMT exhibit cranial deformation [10] due to deformational plagiocephaly which increases the risk of facial [11], ear [11], and mandibular asymmetry [12]. Deformational plagiocephaly is characterized by ipsilateral occipital flattening that can progress to a parallelogram-shaped deformation of the skull without fusion of the cranial sutures. As the severity of the deformity increases, it may result in ear asymmetry with the ear ipsilateral to the posterior flattening displaced anteriorly, inferiorly, or both; protrusion of the frontal bone ipsilateral to the posterior flattening (frontal bossing); facial asymmetry with deviation of the nose and mandible; and atypical vertical growth of the posterior skull [11, 13]. The plagiocephaly is named for the side of the flattened occiput, and is typically contralateral to the tight SCM; for example, right CMT is associated with left deformational plagiocephaly.

Infants with CMT who are diagnosed early and initiate comprehensive physical therapy intervention before 3 months of age have the best prognosis for full resolution of asymmetries with shorter durations of physical therapy [14–17]. If untreated or treated after early infancy, the prognosis for full resolution decreases even with extensive physical therapy and the risk for secondary impairments increases, such as craniofacial deformities [18], cervical spine dysmorphism [19, 20], painful limited cervical motion, and the need for invasive interventions such as botulinum toxin injections [21] and surgery [17, 22, 23].

1.2 Epidemiology

CMT is a common postural deformity that affects 3.9% [24, 25] to 16% [26] of infants. Factors associated with increased risk of CMT identified within 24–72 h of birth include: presence of facial asymmetry or plagiocephaly, first-born, perineal trauma during delivery, and longer body length at birth [24]. In addition, infants with a history of neonatal abstinence syndrome (NAS) requiring postnatal medication have a higher incidence of torticollis and associated plagiocephaly than infants without NAS [27].

1.3 Etiology

The etiology of CMT is unclear. It has been attributed to mal-development of the fetal SCM [28, 29], prenatal or perinatal compartment syndrome [30], and birth trauma.

1.4 Differential Diagnosis

The differential diagnosis of CMT includes congenital torticollis originating from a nonmuscular cause and acquired torticollis.

Nonmuscular causes of congenital torticollis include musculoskeletal anomalies (e.g., congenital vertebral malformation, congenital scoliosis, unilateral absence of the SCM), ocular anomalies (e.g., congenital paralytic squint, congenital nystagmus), neurological anomalies (e.g., congenital brain anomalies, agenesis of the right cerebellar hemisphere), ligamentous laxity (e.g., Down syndrome, achondroplasia, osteogenesis imperfecta) [4, 31]. These etiologies are discussed in the portion of the chapter on acquired torticollis.

Acquired torticollis can present at any age, but typically has an acute or delayed onset (≥6 months of age) [31].

1.5 Diagnostic Approach

1.5.1 History

A thorough history is important for determining the onset of the torticollis, whether the condition is acute or chronic, and associated signs and symptoms.

The clinical presentation of CMT is typically an infant with head preference from birth and probable craniofacial asymmetry. The clinical presentation of acquired torticollis is typically an infant or child with a delayed onset of torticollis noted after 6 months of age or an acute onset of torticollis following a traumatic injury or in association with infections [31].

Important aspects of the history include:

1. Head posture/preference [5, 31] and asymmetries of the head/face [32]. Congenital torticollis may be associated with craniofacial asymmetries, but acquired causes of torticollis generally are not.

2. Type and age of onset of symptoms. CMT is evident soon or after birth [31]. In children with an acute onset or delayed onset (≥6 months of age) of head preference, other types of congenital torticollis or acquired causes of torticollis must be considered [31].
3. Screening for nonmuscular causes of asymmetry.
   (a) Trauma: history of suspected trauma, cervical spine injury, surgery to the head or neck, clavicular fracture [4, 31]. Cervical pain and range limitations are common in acquired torticollis due to trauma.
   (b) Neurological: history of neurological symptoms including headaches, ataxia, brachial plexus palsy [4, 31].
   (c) Visual: history of vision concerns, such as strabismus and diplopia [4, 31].
   (d) Gastrointestinal: history of gastroesophageal reflux as infants may arch the trunk and flex the neck to the right following feeding [31, 33].
   (e) Cardiorespiratory: history of respiratory distress [31, 34].
   (f) General health: history of fever, infection, vomiting, headache [31].
   (g) Medications: history of medication use as some medications may induce dystonic reactions (e.g., phenothiazines, carbamazepine).
   (h) Genetic: family history of torticollis or other congenital or developmental conditions that have been associated with torticollis [35, 36].
   (i) Other known or suspected medical conditions [4, 31].
4. Screening for conditions associated with CMT
   (a) Delayed developmental milestones [37–39].
   (b) Preferential feeding from one side [5].
   (c) Cranial deformation with or without facial asymmetry [10].
   (d) Other positional deformities, such as developmental dysplasia of the hip, metatarsus adductus, and clubfoot [10, 31].
5. Caregiving routines, including positioning of the infant during sleep, time spent in the prone position while awake, and time spent in infant positioning equipment to identify caregiving routines that may perpetuate the head preference [1]. Caregiving routines that may perpetuate the head preference include consistently feeding or providing environmental stimulation from one side, especially when the infant is supine or semi-reclined in a sitting position in infant positioning equipment.

1.5.2 Physical Examination

General Examination

Examination findings of unilateral CMT include:

1. Head preference with the head laterally flexed towards the involved SCM and rotated to the opposite side [5, 31].

2. Reduced passive cervical range of motion into lateral flexion and/or cervical rotation corresponding to the involved SCM. Assess for full passive cervical range of motion in both directions for cervical lateral flexion (ear approximates the shoulder) and cervical rotation (chin turns past shoulder to 100°). For right CMT, passive cervical range of motion will be limited into left lateral flexion and right rotation.
3. Palpable tightness or mass of the involved SCM. The mass is typically located in the inferior portion of the involved SCM but can extend to the middle or entire SCM, is 1–3 cm in diameter, and is smooth, firm, nondiscolored, nontender, and nonfluctuant [40].
4. Absence of findings associated with nonmuscular causes of head preference [31].

Assess for nonmuscular causes of head preference

1. Visual Examination. Evaluation of ocular alignment using the corneal light reflex test and the cover/uncover test, checking extraocular movements, and looking for nystagmus.
2. Orthopedic Examination. Evaluation of the cranium, spine, scapula and associated musculature including tenderness, cervical range of motion, and palpation of the SCM. In children with possible cervical spine injury or instability, the exam should be done gently and carefully.
3. Neurologic Examination. Evaluation of tone, developmental and deep tendon reflexes, integrity of the cranial nerves, sensation, and active movement as appropriate for the age of the child.

Assess for conditions associated with CMT

1. Cranial deformation with or without facial asymmetry, including ruling out craniosynostosis. Assess for head shape asymmetries by observing the symmetry of the skull from the front, top and sides, noting symmetry of the ears, eyes and midline alignment of the chin and nose relative to the perimeter of the face [32]. Mild deformational plagiocephaly is defined as ipsilateral occipital flatness only, whereas moderate to severe plagiocephaly adds asymmetrical facial features, including anterior or inferior displacement of the ipsilateral ear, ipsilateral protrusion or bossing of the frontal bone, and atypical vertical growth of the posterior skull [11].

   Deformational plagiocephaly and lambdoid synostosis, closure of one of the lambdoid sutures, can be difficult to differentiate. Both conditions present with ipsilateral occipital flatness, but with lambdoid synostosis there is contralateral frontal bossing, versus ipsilateral frontal bossing in deformational plagiocephaly, contralateral parietal bossing, and a reduction in ipsilateral posterior skull height; the positioning of the ear canals is not a reliable diagnostic tool [41].
2. Developmental dysplasia of the hip and foot deformities, such as metatarsus adductus and clubfoot [31].

1.5.3 Evaluation (Laboratory Testing/Imaging)

Cervical spine radiographs are not indicated for CMT unless there are findings suggestive of a cervical spine abnormality [42]. Examples include infants with medical conditions associated with atlantoaxial instability (e.g., Down syndrome), infants with cervical rotation toward the involved SCM, infants without obvious tightness of the SCM, or infants with a short neck and low posterior hair line.

Ultrasonography of the SCM is not indicated for CMT unless the SCM mass does not appear to be muscular in origin [43]. Examples include if an SCM mass is not firm or well circumscribed.

1.6 Treatment/Management

Parent education to prevent or minimize deformational plagiocephaly. Parent education to prevent and minimize deformational plagiocephaly includes repositioning to decrease pressure on the flattened area of the skull both when positioned semi-reclined in infant positioning devices and when sleeping in supine, encouraging supervised prone play for 30–60 min a day, and limiting time in infant positioning devices (e.g., car safety seats, infant swings, strollers) [3, 44–46].

Physical therapy intervention for CMT. CMT is not expected to resolve spontaneously. Infants with CMT require immediate referral for a pediatric physical therapy evaluation to provide a comprehensive management program. Evidence strongly supports that early physical therapy intervention is associated with improved clinical outcomes [14], shorter durations of physical therapy [14, 47], and reduced need for invasive interventions, such as botulinum toxin injections and surgery [17, 21, 48]. A comprehensive physical therapy intervention program includes cervical stretching, cervical and trunk strengthening, activities to promote symmetrical movement, environmental adaptations to counteract the head preference, and ongoing parent/caregiver education [1]. Ongoing parent/caregiver education is critical to support the parents/caregivers to implement and progress the daily home management program necessary to resolve CMT [1].

In the past, it was common for pediatricians to provide advice on positioning as well as passive stretching of neck muscles and monitor the condition for a few months before referral to physical therapy [49], but it is now recognized that this only delays the initiation of the comprehensive physical therapy management program needed to resolve the CMT.

Botulinum toxin injections for recalcitrant CMT. Botulinum toxin type A (BTX) is used off label for infants with recalcitrant CMT to reduce the need for surgical correction when the CMT has not resolved as expected with physical therapy intervention [21]. BTX is a neurotoxin that inhibits acetylcholine release resulting in muscle paralysis. It is injected into the involved SCM and other tight neck muscles to allow for easier stretching [21]. In a recent meta-analysis, the overall effectiveness rate of BTX combined with physical therapy intervention was 84%

(95% CI, 67%–96%), the conversion rate to surgical intervention was 9% (95% CI 4%–22%), and the adverse reaction rate was 1% (95% CI, 0%–3%) [21]. The most common adverse reactions included bruising, fever of unknown origin, neck pain, neck weakness, and transient dysphagia [21]. No consensus has been reached on when to initiate the BTX injections, injection dose, location of injection sites, number of injected points, and injection intervals [21].

Surgical intervention for recalcitrant CMT. Surgical intervention is rare, but referral to a pediatric orthopedic surgeon is indicated for infants with CMT who received physical therapy intervention yet continue to have persistent residual tightness of >15° or craniofacial asymmetry over 1 year of age [50], or progressing passive cervical range limitations over 9 months of age [51]. The goal of surgical intervention is to normalize cervical range of motion and minimize craniofacial asymmetry through lengthening the SCM. Outcomes are best for young children [52], however, older children and untreated adults can also benefit from surgical intervention [53].

1.7 Prognosis/Outcomes

Infants with CMT have excellent clinical outcomes when physical therapy is initiated early [47]. If initiated before 1 month of age, 98% of infants with CMT achieve normal cervical range of motion within 1.5 months [14]. Waiting until after 1 month of age prolongs the duration of physical therapy to 6 months and waiting until after 6 months of age prolongs the duration of physical therapy to 9–10 months, with fewer infants achieving normal cervical range of motion [14].

For infants with moderate-to-severe deformational plagiocephaly, evidence strongly supports that cranial remolding therapy using a soft helmet is effective in reducing cranial asymmetry when implemented by 6 months of age and parents/caregivers follow the prescribed wearing schedule [44, 54].

1.8 When to Refer

Refer immediately to a pediatric physical therapist for CMT.

Refer to a craniofacial team or cranial orthotist to assess if cranial remolding therapy is indicated if the infant is 4–6 months of age or older with continued moderate-to-severe plagiocephaly after a course of repositioning and/or physical therapy [3, 55].

Refer to a pediatric orthopedic surgeon if an infant with CMT is not progressing as anticipated, is not progressing after 6 months of physical therapy intervention, or when the child is diagnosed with CMT at 12 months of age or older [1]. Also, refer to an orthopedist for musculoskeletal conditions, such as unilateral absence of SCM, clavicle fracture, developmental dysplasia of the hip, foot deformities, and

vertebral anomalies, including Klippel–Feil syndrome, congenital scoliosis, atlantoaxial rotary subluxation, and hemivertebrae [4, 31].

Refer to an ophthalmologist for visual conditions, such as refractive errors, spasmus nutans, fourth cranial nerve (trochlear) palsy, Brown syndrome, congenital fibrosis of the extraocular muscles, Duane syndrome, and visual field defects [4, 31].

Refer to a neurologist or neurosurgeon for neurological conditions, such as Arnold–Chiari malformation, posterior fossa tumors, cerebral palsy, brachial plexus palsy, and brain tumors [4, 31].

Refer immediately to a neurosurgeon or craniofacial team for craniosynostosis [3].

Refer to the appropriate specialist if the head preference is suspected to be due to a condition other than CMT [31].

1.9 Prevention

Evidence strongly supports that early identification of CMT results in improved clinical outcomes with shorter durations of physical therapy [14, 47]. Therefore, it is recommended that all expectant parents and parents of newborns be educated on the importance of supervised prone/tummy play when awake for 3 or more times daily, full active movement in all developmental positions, prevention of postural preferences, and the role of a pediatric physical therapist if asymmetries or motor delays are concerns [1]. Pediatricians can provide this education by distributing and reviewing the Academy of Pediatric Physical Therapy 2018 CMT Clinical Practice Guideline [1] resources with parents of newborns https://pediatricapta.org/clinical-practice-guidelines/Congenital-Muscular-Torticollis.cfm

The goal of this education is to prevent postural and craniofacial asymmetries from developing and empower parents to report asymmetries to their pediatrician immediately so that early physical therapy intervention is initiated in a timely manner. The importance of daily supervised ‘tummy time while awake’ cannot be overemphasized. Many parents do not regularly place awake infants on their stomach during play [56], yet time in prone encourages activation of the cervical muscles, minimizes the potential for cranial deformation, and promotes motor development [57, 58].

Clinical Pearls/Key Points

- To prevent or identify CMT and cranial deformation early, all expectant parents and parents of newborns should be educated on the importance of supervised prone/tummy play when awake for three or more times daily, full active movement in all developmental positions, prevention of postural preferences, and the role of a pediatric physical therapist if asymmetries or motor delays are concerns [1].

- Infants with head preference require a thorough evaluation to confirm the diagnosis of CMT since up to 18% will have a nonmuscular cause of the head preference [4, 31].
- Infants with CMT require a prompt referral to a pediatric physical therapist to provide a comprehensive assessment and intervention program to improve clinical outcomes, reduce time to resolution, and negate the need for invasive interventions [1].

2 Part 2: Child with Acquired Torticollis

2.1 Introduction

Torticollis is a symptom that can be associated with several underlying disorders. Acquired torticollis usually presents between 5 and 12 years of age but can appear at any age [34, 59]. A majority of patients with acquired torticollis are diagnosed later in life, but when symptoms develop in neonates or infants, differentiating congenital from acquired torticollis can be challenging. Relatively low incidence and a large number of associated underlying disorders may make it difficult to categorize acquired torticollis in children on the basis of etiology [60–62]. Furthermore, a variety of classification schemes exist, such as muscular vs nonmuscular and paroxysmal (dynamic) vs nonparoxysmal (nondynamic) [63]. There is no consensus in terms of clearly demarcating acquired torticollis from congenital or genetic disorders with an indolent clinical course. For example, a patient with unilateral atlantooccipital fusion, which is a congenital anomaly, may present with torticollis in preschool years. Therefore, in addition to identifying timing of onset, a thorough diagnostic evaluation for underlying conditions is a critical step in the management of patients with acquired torticollis.

2.2 Epidemiology

The following two studies have evaluated the relative prevalence of acquired torticollis in children. Of 288 children diagnosed with torticollis at the Texas Scottish Rite Hospital for Children, 53 (18.4%) children were found to have nonmuscular torticollis, while the rest had congenital muscular torticollis [4]. Among the 53 patients with nonmuscular torticollis, 16 patients had Klippel–Feil syndrome or congenital scoliosis, indicating that purely acquired torticollis (implying no congenital factors) is fairly uncommon in children. In another study by Armstrong et al., in which 271 children with torticollis evaluated at Duke University Medical Center were analyzed, 92 patients were found to have presented with torticollis in

their infancy and childhood [64]. Among the 92 patients, 13 (14.1%) patients had associated abnormalities. Based on the data, acquired torticollis cases made up for less than 20% of torticollis cases in children, and a majority of the patients were children over the age of 7 years.

2.3 Etiology

There are various causes for acquired torticollis. The most important etiological categories in children are listed below:

1. Trauma: Torticollis can follow bone fractures (most commonly second cervical vertebra) or can be the result of injuries to the sternocleidomastoid following trauma [65, 66]. In post-traumatic torticollis, cervical dystonia usually begins a few days after traumatic incidents. Compared to congenital torticollis, there is significant limitation of range of motion. In contrast to primary cervical dystonia, geste antagonistique (temporary reduction of severity of dystonic posture by voluntary maneuver) is not observed in acquired torticollis secondary to trauma. Unlike in situations where the torticollis is congenital, pain and spasms in the paracervical muscles are prominent features in the forms associated with trauma.
2. Infections: Most common infectious conditions of the head and neck associated with acquired torticollis include pharyngitis, lymphadenitis, retropharyngeal abscess, otitis media, and osteomyelitis [67–69]. Tonsillitis and cervical lymphadenitis can irritate neck muscles and induce spasm of the sternocleidomastoids. Meningitis can also present with torticollis.
3. Atlantoaxial rotary subluxation/fixation (AARF): The atlas (C1 vertebra) and the axis (C2 vertebra) are mainly stabilized by the transverse ligament. AARF is a problem of the atlantoaxial joint that causes limitation of rotation or possibly fixation of the neck. Fielding and Hawkins originally grouped AARF into four types. Type 1 AARF is the most commonly encountered form. In this type, there is a rotary fixation of movement between the atlas and axis within the normal range without subluxation. There is no displacement of the atlas. Type 2 AARF consists of rotary fixation with an anterior shift of the atlas by 5 mm or less. Type 3 AARF is rotary fixation with anterior shift of the atlas by more than 5 mm. Type 4 AARF is rotary fixation with posterior displacement of the atlas and is the most uncommon type. Type 5 AARF, proposed later on by Roche, is combined with atlanto-occipital rotary subluxation or fixation [70, 71]. The condition may be idiopathic, follow trauma, or occur in association with other conditions such as Down syndrome and Marfan syndrome [72, 73]. Grisel syndrome is a type of AARF associated with head and neck infections such as mastoiditis and retropharyngeal abscess [74].
4. Juvenile idiopathic arthritis (JIA) may affect the joints of the cervical spine. JIA, formerly known as juvenile rheumatoid arthritis (JRA), occurs in approximately

1 in 1000 children. Monoarticular upper cervical spine involvement occurs in children with JIA and can result in torticollis [75, 76].

5. Neoplasms: Central nervous system tumors and bone tumors are rare causes of acquired torticollis. Posterior fossa tumors and tumors of the spinal cord are central nervous system tumors that cause acquired torticollis [77]. Among benign bone tumors, osteochondroma, osteoid osteoma, and osteoblastoma may affect the cervical spine [78, 79]. Malignant tumors such as Langerhans cell histiocytosis, Ewing sarcoma, and metastatic tumors, may also rarely present with torticollis [80].
6. Genetic disorders: Down syndrome is associated with laxity of ligaments, and therefore children with Down syndrome may present with either acquired or congenital torticollis depending on the age of onset [81]. In children with Down syndrome, laxity of the ligaments in the cervical spine leads to atlantoaxial instability, as type VI collagen gene is located on chromosome 21 [82]. It is thought that overproduction of collagen VI due to extra-copy of the genes *COL6A1* and *COL6A2* plays a role. Excessive collagen VI helices affect tensile properties of the ligament.
7. Ocular torticollis: Children with diplopia or nystagmus may tilt their heads for adjustment of the visual image.
8. Dystonic reactions: Drugs such as phenothiazines and carbamazepine may induce dystonic reactions.
9. Benign paroxysmal torticollis: Benign paroxysmal torticollis is believed to be a variant of migraine that primarily affects infants. The child may present with spells of torticollis, vomiting, and irritability that resolve spontaneously. The mechanism of benign paroxysmal torticollis remains unknown, and duration of a spell typically varies from hours to days [83, 84].

In addition, a report of 10 rare cases of acquired torticollis by Per et al. described acute disseminated encephalomyelitis, spinal epidural hematoma in a boy with hemophilia, posterior fossa arachnoid cyst, aneurysm of the anterior communicating artery, pontine glioma, and psychogenic torticollis [61].

2.4 Differential Diagnosis

The primary differential diagnosis of acquired torticollis is congenital torticollis, which is the most common type of torticollis in children. Acquired torticollis can be diagnosed at the age of 4–6 months but usually presents between 5 and 12 years of age.

Torticollis in older children is a nonspecific sign that mandates a meticulous evaluation to identify underlying causative lesions. Therefore, for appropriate management of children who develop acquired torticollis, differential diagnosis of associated conditions is important. Potential causes are listed under Etiology above.

2.5 Diagnostic Approach

2.5.1 History

Clinical presentation of acquired torticollis can be acute following traumatic injury or in association with infections. Chronic cases can persist for several months. A detailed history is important to determine whether the condition is acute or chronic. History of suspected trauma and other diseases needs to be confirmed. Pain and limitation of motion of the neck are common complaints in traumatic torticollis. Whether the injury accounts for the symptoms should be ascertained.

One should obtain a history suggestive of tumors of the posterior fossa of the brain including headache, projectile emesis, new onset of strabismus, diplopia, ataxia, and dysphagia. Presence of common symptoms of infection such as fever, sore throat, and dysphagia that may have preceded the onset of torticollis needs to be inquired. History of recent or remote medications needs to be recorded. Some medications may induce dystonic reactions (e.g., phenothiazines, carbamazepine, metoclopramide). A family history of migraine may point the clinician towards a diagnosis of paroxysmal torticollis. Finally, note must be made of previous surgery to the head and neck region.

2.5.2 Physical Examination

Physical examination of children with torticollis should be systematic and address vital signs, the head, eyes, neck, throat, and respiratory and central nervous systems.

Head and Neck

In children with possible cervical spine injury or instability, examinations should be performed gently and carefully. Range of motions will need to be checked (flexion, extension, rotation, and lateral bending).

1. Tenderness and spasm in the sternocleidomastoid which are frequent symptoms in traumatic torticollis can be assessed by palpation of the affected muscles. Focal tenderness is often associated with fractures.
2. Fever, drooling, and dysphagia are common symptoms of retropharyngeal abscess. Painful cervical lymph node enlargement may indicate cervical lymphadenitis.

Neurological Examination

Cranial nerves, motor and sensory functions, and deep tendon reflex should be examined. Special attention should be paid to extraocular movements. Children with posterior fossa tumors may have signs associated with increased intracranial

pressure such as papilledema. Spinal cord tumors can occasionally cause torticollis, and therefore one must assess for neurological findings such as motor weakness of the limbs, loss of deep tendon reflexes, sensory level, and rectal tone. Gait disturbances, truncal ataxia, or limb ataxia may indicate presence of brain tumors.

2.5.3 Evaluation (Laboratory Testing and Imaging)

History and physical examination can guide further evaluation. Routine laboratory investigations are not helpful in most instances. When infectious etiology or JIA is suspected as an underlying cause, complete blood count, erythrocyte sedimentation rate, C-reactive protein, creatine kinase, antinuclear antibody profile, throat culture, rapid strep antigen, infectious mononucleosis, and purified protein derivative (PPD) testing can be helpful.

Trauma and Injuries

1. Cervical radiographs (anteroposterior, lateral, and open mouth odontoid) need to be obtained, and CT scans (both static and dynamic) are very helpful for documentation of cervical vertebrae fracture/dislocation and extent of AARF [85–87].
2. Relationship between C1 and C2 cervical vertebrae can be assessed based on open mouth odontoid view radiographs. In cases with spinal tenderness and pain persisting more than 1 week or with risk of atlantoaxial instability (Down syndrome, Morquio syndrome, and Marfan syndrome), cervical spine radiographs should be taken [85, 87].
3. Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) are obtained in cases with suspected injuries of cervical ligaments, spinal cord, or vertebral vessels. MRI of the cervical spine and brain is mandatory when neoplasms are suspected. CT is helpful for evaluation of skull and upper cervical vertebral bodies, and dynamic CT with 3D reconstruction is used for the diagnosis and classification of AARF [87].

Infections and Inflammation

Cervical spinal radiographs and CT scans are helpful for urgent evaluation of infections or inflammatory conditions [86]. Ultrasound examination is used to assess the presence of cervical masses including enlarged lymph nodes [87]. MRI is helpful for diagnosis of osteomyelitis and discitis.

2.6 Treatment and Management

Treatment of acquired torticollis depends on the underlying etiology.

1. Nonsteroidal anti-inflammatory drugs (NSAIDs) and cervical collars are common modalities for pain relief. Antibiotics are used to treat pharyngitis, cervical lymphadenitis, or other infectious conditions.
2. Traumatic atlantoaxial rotary displacement is treated with pain medications, muscle relaxants, and soft collars. If symptoms persist for more than a week, cervical traction may be needed. Cervical orthosis is necessary to maintain head position for 4–6 weeks after reduction. Cervical fusion is indicated in cases with recurrent torticollis or in situations where there is secondary instability of the atlantoaxial vertebral segment.
3. Drainage of abscess is necessary in Grisel syndrome. Antibiotics, pain medications, anti-inflammatory medications, muscle relaxants, and soft collars are additional therapeutic measures required for managing Grisel syndrome. If subluxation does not reduce within 7–10 days, then admission will be necessary for traction.
4. Anticholinergic, antihistamine, or benzodiazepine is used to treat dystonic reactions to medications.

2.7 Prognosis and Outcomes

Conditions ranging from trivial to life-threatening lead to acquired torticollis. Treatment of underlying etiology is key for successful outcome. Overall, prognosis of acquired torticollis is good when the underlying etiology is addressed.

2.8 When to Refer or Admit

When necessary, consultation with other specialists (neurology, orthopedics, otolaryngology, ophthalmology, and neurosurgery) is helpful and essential for management of children with acquired torticollis.

1. Orthopedics: Children with acute onset of torticollis and severe neck pain, stiffness, and spasms after traumatic injury are immobilized in cervical collars. Timely referral to orthopedic surgeons is critical.
2. Otolaryngology: Retropharyngeal abscess should be drained by otolaryngologists.
3. Ophthalmology: Basic and detailed ocular examinations should be done by ophthalmologists if possible.
4. Neurosurgery: Patients with brain or spinal cord tumors are best managed by pediatric neurosurgeons.

3 Clinical Pearls and Key Points

- Acquired torticollis may be associated with several underlying disorders/syndromes that range from benign to life threatening.
- Directed history and meticulous physical examinations are important for determining the etiology of acquired torticollis and distinguishing this condition from congenital torticollis.
- CT and MRI are useful for assessing trauma, neck infections, vertebral anomalies, and tumors in older children. Decision regarding specific imaging modality should be discussed with the radiologist.
- Treatment of acquired torticollis depends on the etiology.

References

1. Kaplan SL, Coulter C, Sargent B. Physical therapy management of congenital muscular torticollis: a 2018 evidence-based clinical practice guideline from the APTA Academy of Pediatric Physical Therapy. Pediatr Phys Ther. 2018;30(4):240–90.
2. Sargent B, Kaplan S, Coulter C, Baker C. Congenital muscular torticollis, bridging the gap between research and clinical practice. Pediatrics. 2019;144(2):e20190582.
3. Flannery A, Tamber M, Mazzola C, et al. Congress of Neurological Surgeons systematic review and evidence-based guidelines for the management of patients with positional plagiocephaly: executive summary. Neurosurgery. 2016;79(5):623–4.
4. Ballock RT, Song KM. The prevalence of nonmuscular causes of torticollis in children. J Pediatr Orthop. 1996;16:500–4.
5. Boere-Boonekamp MM, van der Linden-Kuiper LT. Positional preference: prevalence in infants and follow-up after two years. Pediatrics. 2001;107:339–43.
6. Sönmez K, Turkyilmaz Z, Demirogullari B, et al. Congenital muscular torticollis in children. ORL J Otorhinolaryngol Relat Spec. 2005;67(6):344–7.
7. Freed SS, Coulter-O'Berry C. Identification and treatment of congenital muscular torticollis in infants. J Prosthet Orthot. 2004;16:S18–23.
8. Lee Y-T, Yoon K, Kim Y-B, et al. Clinical features and outcome of physiotherapy in early presenting congenital muscular torticollis with severe fibrosis on ultrasonography: a prospective study. J Pediatr Surg. 2011;46(8):1526–31.
9. Nucci P, Kushner BJ, Serafino M, Orzalesi N. A multi-disciplinary study of the ocular, orthopedic, and neurologic causes of abnormal head postures in children. Am J Ophthalmol. 2005;140(1):65–8.
10. Cheng JC, Tang SP, Chen TM, Wong MW, Wong EM. The clinical presentation and outcome of treatment of congenital muscular torticollis in infants—a study of 1,086 cases. J Pediatr Surg. 2000;35(7):1091–6.
11. Argenta L. Clinical classification of positional plagiocephaly. J Craniofac Surg. 2004;15(3):368–72.
12. St John D, Mulliken JB, Kaban LB, Padwa BL. Anthropometric analysis of mandibular asymmetry in infants with deformational posterior plagiocephaly. J Oral Maxillofac Surg. 2002;60(8):873–7.
13. Moon I, Lim S, Oh K. Analysis of facial asymmetry in deformational plagiocephaly using three-dimensional computed tomographic review. Arch Craniofac Surg. 2014;15(3):109–16.
14. Petronic I, Brdar R, Cirovic D, et al. Congenital muscular torticollis in children: distribution, treatment duration and outcome. Eur J Phys Rehabil Med. 2010;45(2):153–8.

15. Emery C. The determinants of treatment duration for congenital muscular torticollis. Phys Ther. 1994;74(10):921–9.
16. Cheng JCY, Wong MWN, Tang SP, Chen TM, Shum SL, Wong EM. Clinical determinants of the outcome of manual stretching in the treatment of congenital muscular torticollis in infants: a prospective study of eight hundred and twenty-one cases. JBJS. 2001;83(5):679–87.
17. Demirbilek S, Atayurt HF. Congenital muscular torticollis and sternomastoid tumor: results of nonoperative treatment. J Pediatr Surg. 1999;34(4):549–51.
18. Seo SJ, Kim JH, Joh YH, et al. Change of facial asymmetry in patients with congenital muscular torticollis after surgical release. J Craniofac Surg. 2016;27(1):64–9.
19. Hussein MA, Yun IS, Lee DW, Park H, Oock KY. Cervical spine dysmorphism in congenital muscular torticollis. J Craniofac Surg. 2018;29(4):925–9.
20. Hussein MA, Yun IS, Park H, Kim YO. Cervical spine deformity in long-standing, untreated congenital muscular torticollis. J Craniofac Surg. 2017;28(1):46–50.
21. Qiu X, Cui Z, Tang G, et al. The effectiveness and safety of botulinum toxin injections for the treatment of congenital muscular torticollis. J Craniofac Surg. 2020;31(8):2160–6.
22. Hung NN, Anh LT. A comparison of outcome of age at time surgery between younger and older than 8 years old in children with congenital muscular torticollis. OALibJ. 2017;04(11):1–12.
23. Lee GS, Lee MK, Kim WJ, Kim HS, Kim JH, Kim YS. Adult patients with congenital muscular torticollis treated with bipolar release: report of 31 cases. J Korean Neurosurg Soc. 2017;60(1):82–8.
24. Chen M, Chang H, Hsieh C, Yen M, Chen T. Predictive model for congenital muscular torticollis: analysis of 1021 infants with sonography. Arch Phys Med Rehabil. 2005;86(11):2199–203.
25. Aarnivala HEI, Valkama AM, Pirttiniemi PM. Cranial shape, size and cervical motion in normal newborns. Early Hum Dev. 2014;90(8):425–30.
26. Stellwagen LM, Hubbard E, Chambers C, Jones KL. Torticollis, facial asymmetry and plagiocephaly in normal newborns. Arch Dis Child. 2008;93(10):827–31.
27. McAllister J, Hall E, Ger H, Merhar S, Pl U, Wexelblatt S. Torticollis in infants with a history of neonatal abstinence syndrome. J Pediatr. 2018;196:305–8.
28. Hardgrib N, Rahbek O, Moller-Madsen B, Maimburg RD. Do obstetric risk factors truly influence the etiopathogenesis of congenital muscular torticollis? J Orthop Traumatol. 2017;18(4):359–64.
29. Chen HX, Tang SP, Gao FT, et al. Fibrosis, adipogenesis, and muscle atrophy in congenital muscular torticollis. Medicine (Baltimore). 2014;93(23):e138.
30. Davids JR, Wenger DR, Mubarak SJ. Congenital muscular torticollis: sequela of intrauterine or perinatal compartment syndrome. J Pediatr Orthop. 1993;13(2):141–7.
31. Nuysink J, van Haastert IC, Takken T, Helders PJM. Symptomatic asymmetry in the first six months of life: differential diagnosis. Eur J Pediatr. 2008;167(6):613–9.
32. Cunningham ML, Heike CL. Evaluation of the infant with an abnormal skull shape. Curr Opin Pediatr. 2007;19:645–51.
33. Deskin R. Sandifer syndrome: a cause of torticollis in infancy. Int J Pediatr Otorhinolaryngol. 1995;32:183–5.
34. Tomczak KK, Rosman NP. Torticollis. J Child Neurol. 2013;28(3):365–78.
35. Thompson F, McManus S, Colville J. Familial congenital muscular torticollis: case report and review of the literature. Clin Orthop Relat Res. 1986;202:193–6.
36. Sönmez K, Turkyilmaz Z, Demirogullari B, et al. Congenital muscular torticollis in children. J Oto-Rhino-Laryngology. 2005;67(6):344–7.
37. Tessmer A, Mooney P, Pelland L. A developmental perspective on congenital muscular torticollis: a critical appraisal of the evidence. Pediatr Phys Ther. 2010;22(4):378–83.
38. Schertz M, Zuk L, Zin S, Nadam L, Schwartz D, Bienkowski RS. Motor and cognitive development at one-year follow-up in infants with torticollis. Early Hum Dev. 2008;84(1):9–14.
39. Öhman A, Nilsson S, Lagerkvist A, Beckung E. Are infants with torticollis at risk of a delay in early motor milestones compared with a control group of healthy infants? Dev Med Child Neurol. 2009;51:545–50.

40. Cheng JC-Y, Metreweli C, Chen TM-K, Tang S-P. Correlation of ultrasonographic imaging of congenital muscular torticollis with clinical assessment in infants. Ultrasound Med Biol. 2000;26(8):1237–41.
41. Fearon J. Evidence-based medicine: craniosynostosis. Plast Reconstr Surg. 2014;133:1261–75.
42. Boyko N, Eppinger MA, Straka-DeMarco D, Mazzola CA. Imaging of congenital torticollis in infants: a retrospective study of an institutional protocol. J Neurosurg Pediatr. 2017;20(2):191–5.
43. Haque S, Shafi BBB, Kaleem M. Imaging of torticollis in children. Radiographics. 2012;32:557–71.
44. Flannery ABK, Looman WS, Kemper K. Evidence-based care of the child with deformational plagiocephaly, part II: management. J Pediatr Health Care. 2012;26(5):320–31.
45. Aarnivala H, Vuollo V, Harila V, Heikkinen T. Preventing deformational plagiocephaly through parent guidance: a randomized, controlled trial. Eur J Pediatr. 2015;174:1197–208.
46. Laughlin J, Luerssen TG, Dias MS. Prevention and management of positional skull deformities in infants. Pediatrics. 2011;128(6):1236–41.
47. Lee KS, Chung EJ, Lee BH. A comparison of outcomes of asymmetry in infants with congenital muscular torticollis according to age upon starting treatment. J Phys Ther Sci. 2017;29:543–7.
48. Cameron BH, Langer JC, Cameron GS. Success of nonoperative treatment for congenital muscular torticollis is dependent on early therapy. J Pediatr Surg. 1994;9:391–3.
49. Fradette J, Gagnon I, Kennedy E, Snider L, Majnemer A. Clinical decision making regarding intervention needs of infants with torticollis. Pediatr Phys Ther. 2011;23(3):249–56.
50. Burstein FD. Long-term experience with endoscopic surgical treatment for congenital muscular torticollis in infants and children: a review of 85 cases. Plastic Reconstr Surg. 2004;114(2):491–3.
51. van Vlimmeren LA, Helders PJM, van Adrichem LNA, Engelbert RHH. Torticollis and plagiocephaly in infancy: therapeutic strategies. Pediatr Rehabil. 2006;9:40–6.
52. Burstein FD, Cohen SR. Endoscopic surgical treatment for congenital muscular torticollis. Plastic Reconstr Surg. 1998;101(1):20–4.
53. Kim HJ, Ahn HS, Yim SY. Effectiveness of surgical treatment for neglected congenital muscular torticollis: a systematic review and meta-analysis. Plast Reconstr Surg. 2015;136(1):67e–77e.
54. Goh JL, Bauer DF, Durham SR, Stotland MA. Orthotic (helmet) therapy in the treatment of plagiocephaly. Neurosurg Focus. 2013;35(4):1–6.
55. Tamber M, Nikas D, Beler A, et al. Congress of neurological surgeons systematic review and evidence-based guideline on the role of cranial modeling orthosis (helmet) therapy for patients with positional plagiocephaly. Neurosurgery. 2016;79:E632–3.
56. Koren A, Reece SM, Kahn-D'angelo L, Medeiros D. Parental information and behaviors and provider practices related to tummy time and back to sleep. J Pediatr Health Care. 2003;24(4):222–30.
57. van Vlimmeren LA, van der Graaf Y, Boere-Boonekamp MM, L'Hoir MP, Helders PJM, Engelbert RHH. Risk factors for deformational plagiocephaly at birth and at 7 weeks of age: a prospective cohort study. Pediatrics. 2007;119:e408–18.
58. Hewitt L, Kerr E, Stanley RM, Okely A. Tummy time and infant health outcomes: a systematic review. Pediatrics. 2020;145(6):c20192168.
59. Eran A, Ilivitzki A. Torticollis in children—differential diagnosis approach. Poster presented at: European Congress of Radiology; March 4–8, 2015; Vienna, Austria.
60. Herman MJ. Torticollis in infants and children: common and unusual causes. Instr Course Lect. 2006;55:647–53.
61. Per H, Canpolat M, Tumturk A, et al. Different etiologies of acquired torticollis in childhood. Childs Nerv Syst. 2014;30(3):431–40.
62. Tumturk A, Kaya Ozcora G, Kacar Bayram A, et al. Torticollis in children: an alert symptom not to be turned away. Childs Nerv Syst. 2015;31(9):1461–70.
63. Do TT. Congenital muscular torticollis: current concepts and review of treatment. Curr Opin Pediatr. 2006;18(1):26–9.

64. Armstrong D, Pickrell K, Fetter B, Pitts W. Torticollis: an analysis of 271 cases. Plast Reconstr Surg. 1965;35:14–25.
65. Schuyler-Hacker H, Green R, Wingate L, Sklar J. Acute torticollis secondary to rupture of the sternocleidomastoid. Arch Phys Med Rehabil. 1989;70(12):851–3.
66. Helenius I. Pediatric orthopedic cervical spine problems. Duodecim. 2016;132(11):1025–32.
67. Bredenkamp JK, Maceri DR. Inflammatory torticollis in children. Arch Otolaryngol Head Neck Surg. 1990;116(3):310–3.
68. Harries PG. Retropharyngeal abscess and acute torticollis. J Laryngol Otol. 1997;111(12):1183–5.
69. Peyrou P, Moulies D. Torticollis in children: diagnostic approach. Arch Pediatr. 2007;14(10):1264–70.
70. Fielding JW, Hawkins RJ. Atlanto-axial rotatory fixation. (Fixed rotatory subluxation of the atlanto-axial joint). J Bone Joint Surg Am. 1977;59(1):37–44.
71. Roche CJ, O'Malley M, Dorgan JC, Carty HM. A pictorial review of atlanto-axial rotatory fixation: key points for the radiologist. Clin Radiol. 2001;56(12):947–58.
72. Pueschel SM, Scola FH, Perry CD, Pezzullo JC. Atlanto-axial instability in children with down syndrome. Pediatr Radiol. 1981;10(3):129–32.
73. Levander B, Mellstrom A, Grepe A. Atlantoaxial instability in Marfan's syndrome. Diagnosis and treatment. A case report. Neuroradiology. 1981;21(1):43–6.
74. Fernandez Cornejo VJ, Martinez-Lage JF, Piqueras C, Gelabert A, Poza M. Inflammatory atlanto-axial subluxation (Grisel's syndrome) in children: clinical diagnosis and management. Childs Nerv Syst. 2003;19(5–6):342–7.
75. Uziel Y, Rathaus V, Pomeranz A, Solan H, Wolach B. Torticollis as the sole initial presenting sign of systemic onset juvenile rheumatoid arthritis. J Rheumatol. 1998;25(1):166–8.
76. Seaman SC, Hong S, Dlouhy BJ, Menezes AH. Current management of juvenile idiopathic arthritis affecting the craniovertebral junction. Childs Nerv Syst. 2020;36(7):1529–38.
77. Kumandas S, Per H, Gumus H, et al. Torticollis secondary to posterior fossa and cervical spinal cord tumors: report of five cases and literature review. Neurosurg Rev. 2006;29(4):333–8. discussion 338
78. Raskas DS, Graziano GP, Herzenberg JE, Heidelberger KP, Hensinger RN. Osteoid osteoma and osteoblastoma of the spine. J Spinal Disord. 1992;5(2):204–11.
79. Amirjamshidi A, Roozbeh H, Sharifi G, Abdoli A, Abbassioun K. Osteoid osteoma of the first 2 cervical vertebrae. Report of 4 cases. J Neurosurg Spine. 2010;13(6):707–14.
80. Menezes AH, Ahmed R. Primary atlantoaxial bone tumors in children: management strategies and long-term follow-up. J Neurosurg Pediatr. 2014;13(3):260–72.
81. Taggard DA, Menezes AH, Ryken TC. Treatment of down syndrome-associated craniovertebral junction abnormalities. J Neurosurg. 2000;93(2 Suppl):205–13.
82. Karousou E, Stachtea X, Moretto P, et al. New insights into the pathobiology of Down syndrome—hyaluronan synthase-2 overexpression is regulated by collagen VI alpha2 chain. FEBS J. 2013;280(10):2418–30.
83. Danielsson A, Anderlid BM, Stodberg T, Lagerstedt-Robinson K, Klackenberg Arrhenius E, Tedroff K. Benign paroxysmal torticollis of infancy does not lead to neurological sequelae. Dev Med Child Neurol. 2018;60(12):1251–5.
84. Moavero R, Papetti L, Bernucci MC, et al. Cyclic vomiting syndrome and benign paroxysmal torticollis are associated with a high risk of developing primary headache: a longitudinal study. Cephalalgia. 2019;39(10):1236–40.
85. Lustrin ES, Karakas SP, Ortiz AO, et al. Pediatric cervical spine: normal anatomy, variants, and trauma. Radiographics. 2003;23(3):539–60.
86. Pharisa C, Lutz N, Roback MG, Gehri M. Neck complaints in the pediatric emergency department: a consecutive case series of 170 children. Pediatr Emerg Care. 2009;25(12):823–6.
87. Haque S, Bilal Shafi BB, Kaleem M. Imaging of torticollis in children. Radiographics. 2012;32(2):557–71.

Child with Microcephaly or Macrocephaly

Ishani Kumar and Nancy McNamara

1 Introduction

A basic but essential portion of the examination of an infant and toddler is measurement of head circumference, also known as occipitofrontal circumference (OFC). It can help to guide the evaluation of a child with neurological symptoms and is arguably the most easily performed part of the evaluation. And though seemingly rudimentary, its utility should not be minimized. When combined with the child's history, growth chart and previous head circumferences, the OFC measurement can be diagnostic in some situations, as we will discuss in this chapter. In a full-term infant, OFC ranges from 32 to 37 cm at birth. It increases by 0.4 cm per week for the first couple of months and then by 1 cm per month in the first year. A child will experience the greatest brain growth in the first 2 years of life [1].

There are three factors that contribute to head size in infancy: brain, cerebrospinal fluid (CSF), and blood. If one of these factors is increased or decreased, the other two factors will compensate to maintain intracranial pressure and volume within the cranium. If compensatory mechanisms fail, the head circumference will change and either increase or decrease. Until the closure of the sutures (finalized at 12 months), an infant's head circumference can expand or contract depending on pressure. Thickness of skull as well as rate of fusion of cranial sutures can also contribute to head size and shape [2].

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2 Epidemiology

Macrocephaly is defined as head size larger than 2 standard deviations (SD) from the mean. By this definition, 2% of the population will have macrocephaly[1] .A common problem associated with macrocephaly is hydrocephalus. Hydrocephalus itself has a prevalence of around 1 in 1000 births [3].

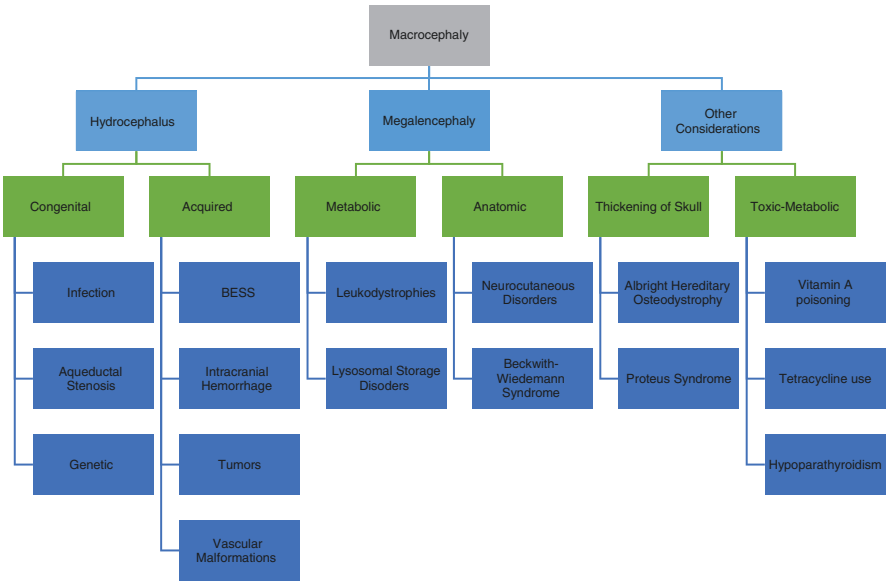
Similarly, microcephaly is defined as head circumference more than two standard deviations below the mean for sex and age. Many experts use stricter criteria, with a cut off of more than three standard deviations below the mean [1]. Many patients with a head circumference between 2 and 3 SDs have normal development. The incidence of severe microcephaly (more than −3 SD) is 1:10,000 [4]. About 15% of children referred for developmental delay to pediatric neurologists have microcephaly [1].

3 Etiology

3.1 Macrocephaly

A key feature in the evaluation of a child with macrocephaly is determining if it is congenital versus acquired, and thus previous OFC measurements are vital. Figure 1 shows the difference between congenital (A) and acquired (B) macrocephaly. A head may be large due excessive intracranial CSF volume (hydrocephalus), enlargement of the brain (megalencephaly), thickening of the skull, or hemorrhage into subdural or epidural areas [2]. Algorithm 1 shows the breakdown of macrocephaly into various etiologies and then subcategories to aid clinicians in diagnosis.

Algorithm 1



BESS: Benign enlargement of the subarachnoid space

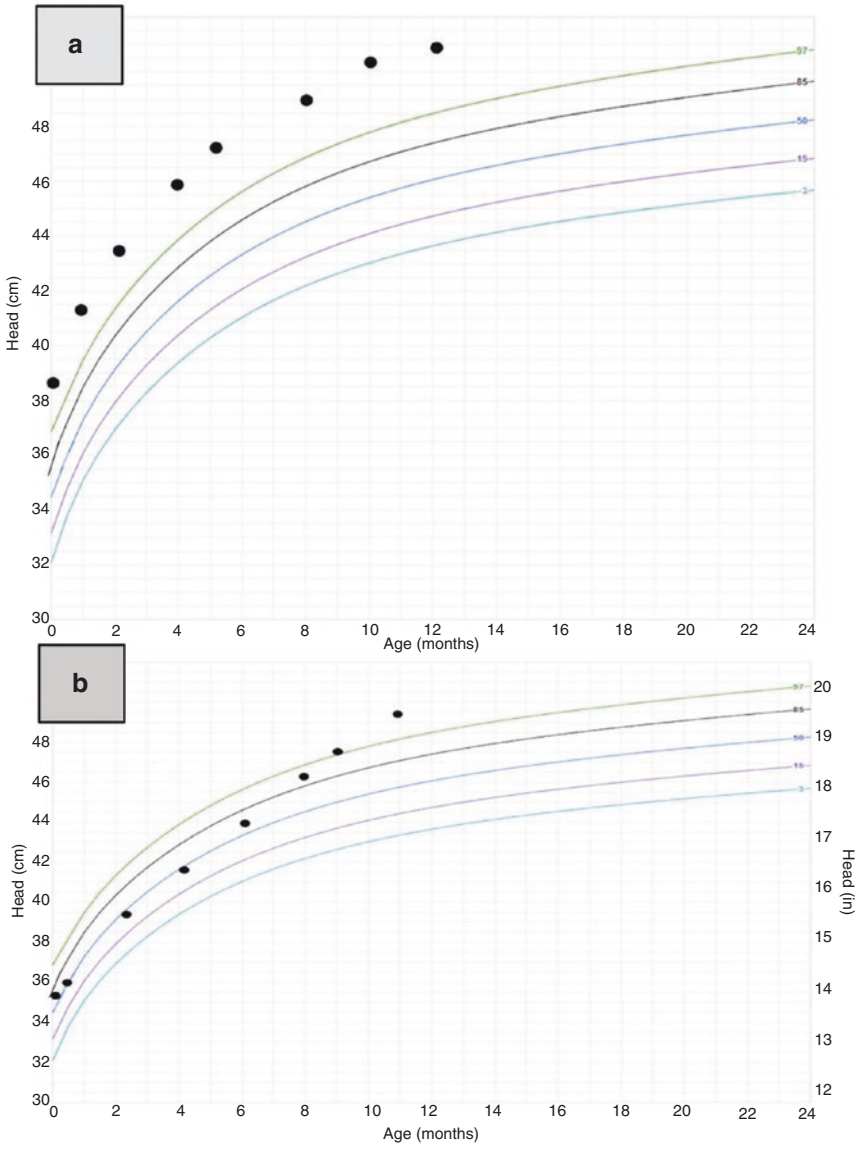


Fig. 1 (**a**) OFC measurements from time of birth until 12 months of age. The green line shows the 97th percentile. This head circumference graph shows congenital macrocephaly because this patient's head circumference has been large since birth. (**b**) An example of acquired macrocephaly: OFC measurements from birth to about 6 months of age are following the growth curve at 50thpercentile. However, after 6 months of age, OFC measurements are crossing percentiles and after 11 months of age, OFC >97th percentile

Algorithm for macrocephaly divided into hydrocephalus, megalencephaly, and other etiologies. Each category is discussed in further detail with more examples provided in the chapter.

3.1.1 Hydrocephalus

Hydrocephalus is defined as excess CSF within cerebral ventricles and/or subarachnoid spaces. Excess CSF causes dilation of ventricles and may even lead to increased intracranial pressure (ICP) [2]. Hydrocephalus can be congenital or acquired. It is often difficult to clearly characterize the type of hydrocephalus because there can be prenatal insults, such as infection or intrauterine hemorrhage, that can cause congenital hydrocephalus, but due to the etiology may be considered acquired. Hydrocephalus should be suspected in infants with congenital macrocephaly who are symptomatic or when head circumference is crossing percentiles on growth curves with serial measurements. Some risk factors for congenital hydrocephalus are male sex, prematurity (usually before 28 weeks), and either low birth weight or high birth weight (<tenth percentile or >90th percentile, respectively) [5]. Figure 2 shows an example of congenital hydrocephalus. Specific causes of hydrocephalus are described in detail below.

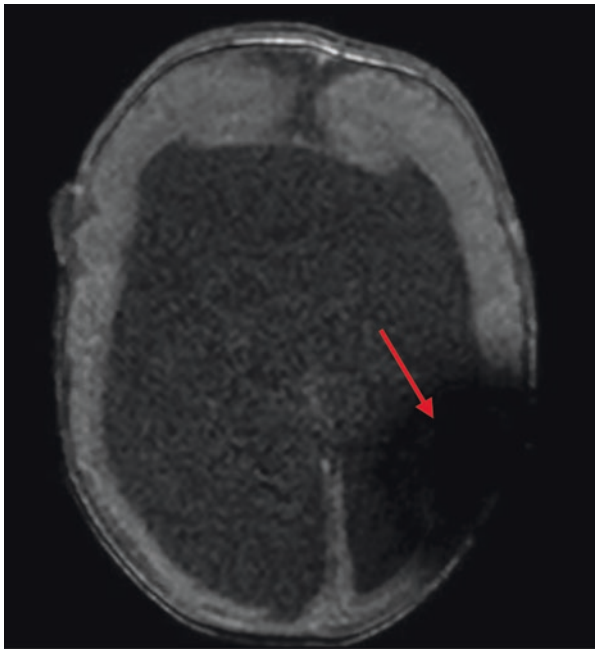


Fig. 2 MRI image of a 4-week-old with congenital hydrocephalus due to obstruction at cerebral aqueduct. The red arrow shows the shadow on left side of brain, which is artifact from VP shunt

3.1.2 Megalencephaly

Megalencephaly is defined as a large brain which may be a cause of macrocephaly and is diagnosed by neuroimaging. Signs and symptoms of megalencephaly are nonspecific but can be associated with various neurodevelopmental disorders such as intellectual disability, autism spectrum disorder, and epilepsy [1]. Megalencephaly is divided into either an anatomic or metabolic. With anatomic disorders, patients are macrocephalic at birth. In contrast, patients with metabolic megalencephaly are often normocephalic at birth and develop macrocephaly during neonatal period due to cerebral edema. There is often a period of normal development followed by developmental regression [2].

3.1.3 Other Considerations

There are other causes of macrocephaly that will be briefly discussed in this section. Increased thickness of the skull, such as seen in Albright hereditary osteodystrophy, can cause macrocephaly in infancy but is usually absent at birth or the neonatal period. Trauma can also cause macrocephaly most likely due to a subdural hematoma. Toxic-metabolic/endocrine disorders such as vitamin A poisoning or hypoparathyroidism can also cause macrocephaly by causing brain edema [6].

3.2 Microcephaly

A small head at birth is indicative of a prenatal cause. Prenatal causes of microcephaly can be divided into primary (congenital) and secondary (acquired) causes. Figure 3 shows head growth velocity between the two types of microcephaly. Primary causes develop before 32 weeks of gestation versus secondary causes that occur after 32 weeks gestation [7]. Primary causes are usually due to disruption in neurogenesis, such as seen in genetic syndromes. Secondary causes are acquired as the brain was developing normally until an insult occurred. Examples of secondary causes of microcephaly are infections, vascular insults and toxic exposures. Usually, in children with secondary microcephaly head circumference is normal at birth but with time the head does not grow at an adequate rate, thus dropping percentiles. It must be noted that factors that cause secondary microcephaly can also cause primary microcephaly if they occur early enough in gestation. Algorithm 2 breaks down on how to approach microcephaly.

Comorbidities often seen with microcephaly are similar to those seen with macrocephaly such as epilepsy, developmental delay, or autism (note that autism can be associated with a large head as well as mentioned in the section above) [1]. Such

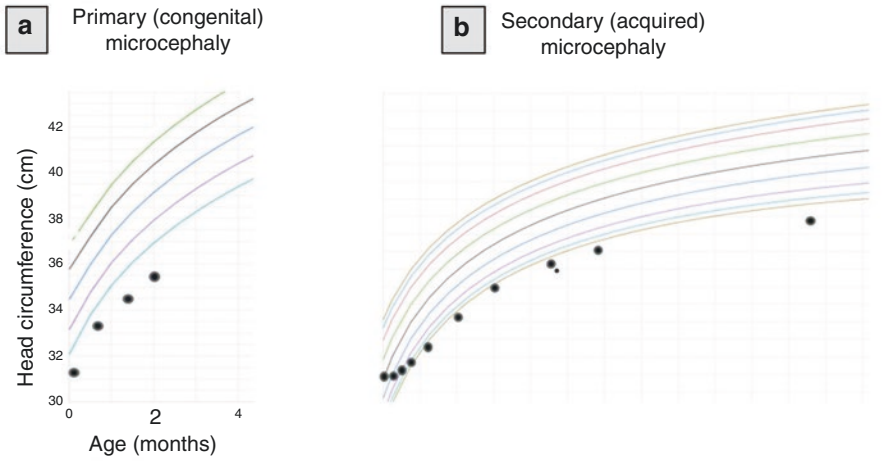
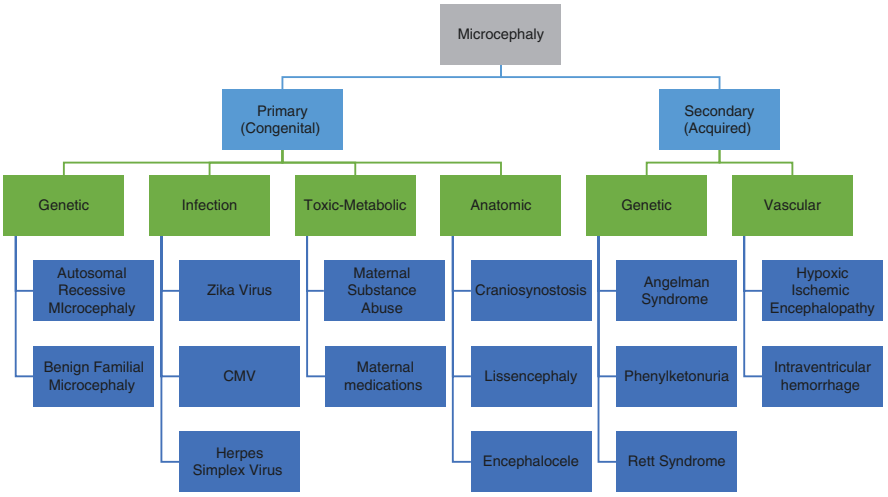


Fig. 3 (**a**) This graph shows congenital or primary microcephaly because head size remained microcephalic since birth. Graph (**b**) demonstrates secondary (acquired) microcephaly as head size was within normal range at birth and then over time, the head growth velocity decreased

findings are most common in children with genetic syndromes with concomitant cerebral abnormalities such as corpus callosal abnormalities, simplified gyral pattern, or delayed myelination patterns [8]. A small head size often means a small brain and can be isolated or be in conjunction with low weight and short length.

Algorithm 2



Algorithm for microcephaly divided into primary (congenital) and secondary (acquired) microcephaly. These categories are further divided into common causes

within each section. Each category is discussed in further detail with more examples given in the chapter.

4 Differential Diagnosis

4.1 Macrocephaly

4.1.1 Hydrocephalus

Hydrocephalus is the most common problem addressed by pediatric neurosurgeons and costs the health care system about $2 billion a year in the United States [3]. Below, the differential diagnosis for both congenital and acquired hydrocephalus are discussed in detail. The most common causes of hydrocephalus are listed in Table 1.

Acquired Hydrocephalus

Structural

A relatively common diagnosis made in children with macrocephaly is that of benign external hydrocephalus, also known as benign enlargement of the subarachnoid space (BESS). This diagnosis is often made without any imaging in clinic when a developmentally normal child is found to have macrocephaly and as does one of her/his parents. BESS can be seen in anywhere from 58% to 75% of cases of macrocephaly [9]. These patients have normal neurological examinations and normal development. Even though they are macrocephalic starting around 3–6 months of age and stabilizing by 18 months of age, their head growth will parallel a normal curve. It is hypothesized that the condition is due to immature arachnoid villi unable to fully absorb CSF, which usually will mature by 18 months of age [10]. Motor development may be marginally slower due to these infants needing more time to

Table 1 These are some of the most common causes of acquired and congenital hydrocephalus. Of note, the causes listed for acquired hydrocephalus can be present at birth and may be mistaken for congenital hydrocephalus. However, given that the hydrocephalus occurred due to secondary insult, it is considered acquired [3]

Acquired hydrocephalus	Congenital hydrocephalus
• Subarachnoid hemorrhage • Intraventricular hemorrhage • Tumors • Vascular malformation (vein of Galen or AV malformation) • Venous sinus thrombosis • Benign enlargement of the subarachnoid space • Inflammation	• Congenital aqueductal stenosis • Neural tube defects • Dandy–Walker complex • Genetic causes (L1CAM, Walker–Warburg syndrome, neurofibromatosis type 1) • In utero infection

control their large heads, but otherwise their neurodevelopment is normal [8]. On neuroimaging such as cranial US or MRI, they will have normal ventricular size but show large frontal subarachnoid space and widening of Sylvian fissures and other sulci [11, 2]. Figure 4 shows a cartoon figure of BESS.

The enlarged spaces typically resolve by 2–3 years old. There is an increased risk of subdural hematoma formation due to the stretching of bridging veins in the enlarged subarachnoid spaces [2, 8]. Continuing to plot head circumference monthly for 6 months after diagnosis is typically recommended. Further evaluation is necessary if the child's head growth deviates from a normal curve, if their neurologic examination becomes abnormal, or if social/language development is delayed. Rarely, a follow-up MRI is done around 2–3 years of age to confirm resolution of BESS [9].

Inflammation

Hydrocephalus due to a CNS infection or hemorrhage (subarachnoid or intraventricular) is usually due to impaired absorption of CSF. These processes affect the arachnoid villi either by infiltration or by inflammation [2]. Intraventricular hemorrhage of prematurity is a common cause of macrocephaly in neonates. An abnormal neurological examination is often seen and thus warrant prompt evaluation including MRI, which may show increased ventricular size. Serial head circumferences are obtained to help follow the need for shunting, if not done immediately after the insult [3]. Figure 5 shows neuroimaging of a patient with hydrocephalus secondary to intraventricular hemorrhage.

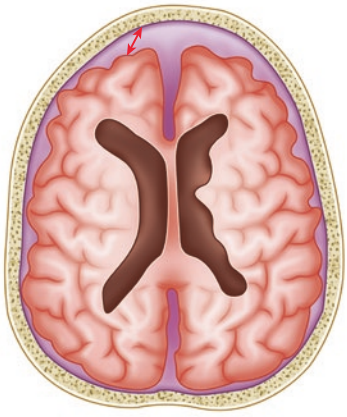


Fig. 4 This cartoon drawing shows BESS. The ventricular system is of normal caliber; however, there are enlarged, frontal extra-axial spaces as noted by the arrow

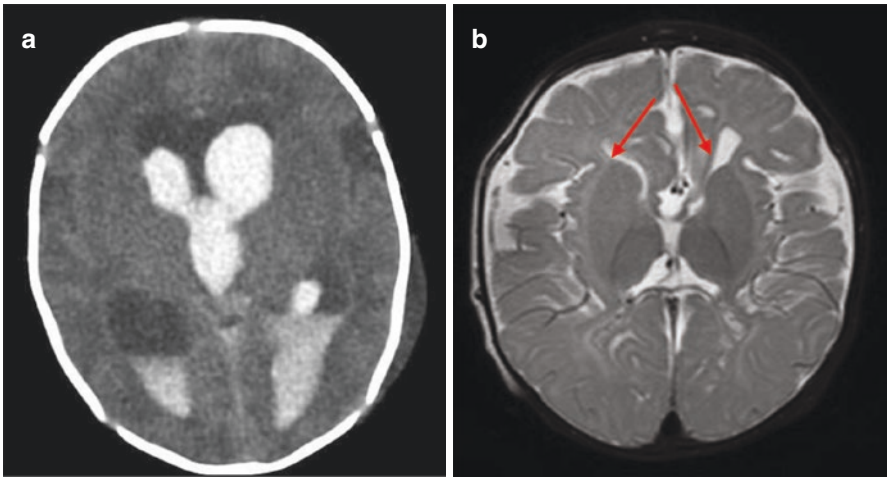


Fig. 5 Both brain scans are from the same patient. Image (**a**) is a CT scan of the patient at 3 weeks of age with significant intraventricular hemorrhage (white fluid in the ventricles is blood) and hydrocephalus of the lateral ventricles. Image (**b**) is an MRI, T2 sequence, at 9 months of age after VP shunt was placed. The image shows marked reduction in ventricular size (red arrows)

Table 2 Most common brain tumors in infancy. Any kind of mass lesion in the brain can cause hydrocephalus and leading to macrocephaly [2, 5]

Common brain tumors during infancy
• Astrocytoma
• Atypical teratoid or rhabdoid tumor
• Medulloblastoma
• Choroid plexus papilloma
• Primitive neuroectodermal tumor (PNET)

Neoplasms

Brain tumors are another cause of hydrocephalus. These can develop at any time in childhood and can also be congenital, which are most frequently supratentorial and midline. Many pediatric brain tumors, such as pontine gliomas and medulloblastoma, are notorious for obstructing the fourth ventricle and subsequently causing hydrocephalus. Table 2 lists the most common brain tumors in infancy.

Newborns may develop hydrocephalus in utero or shortly after birth typically due to obstruction at the cerebral aqueduct. Features include enlarging head size, loss of developmental milestones, and symptoms of raised ICP as noted in Table 9. Of note, medulloblastomas are located in the posterior fossa and not only can these obstruct the fourth ventricle and cause hydrocephalus, but they can also cause cerebellar and brainstem symptoms such as apnea, setting-sun sign, nystagmus, and opisthotonos [2]. Seizures may also occur with any form of brain tumor. Fetal ultrasound (US) can identify tumors but MRI should be obtained after birth given better sensitivity than cranial ultrasound.

Vascular

Vascular malformations can cause ventricular obstruction or decreased venous compliance. For example, a vein of Galen malformation is associated with hydrocephalus in the neonatal period. This is due to persistence of the median prosencephalic vein of Markowsky as a result of which the vein of Galen never develops, leading to dilation of the vein of Markowsky [2]. There can be multiple arteriovenous fistulas associated with it as well. Most patients with these types of vascular malformation are male, for unclear reasons. Initial features are a rapidly growing head size due to hydrocephalus from compression of aqueduct or high output cardiac failure due to the large amounts of blood shunted from the arterial to venous system. Often, a cranial bruit is heard [6]. Other signs include feeding intolerance, vomiting, lethargy, and full fontanelle. Figure 6 shows an example of vein of Galen malformation.

Congenital Hydrocephalus

Congenital Hydrocephalus

Structural

Aqueductal stenosis is the most common cause of congenital hydrocephalus without other cerebral malformations [2]. The cerebral aqueduct is prone to deleterious effects due to its small size easily affected by infection, hemorrhage or compression from a tumor causing acquired hydrocephalus or congenital stenosis/atresia [3]. These patients often have macrocephaly at birth and have dilated scalp veins, forehead bowing, and greatly separated skull sutures. They may also have eyes deviated downwards (setting-sun sign) as well as cranial nerve six palsy causing impairment

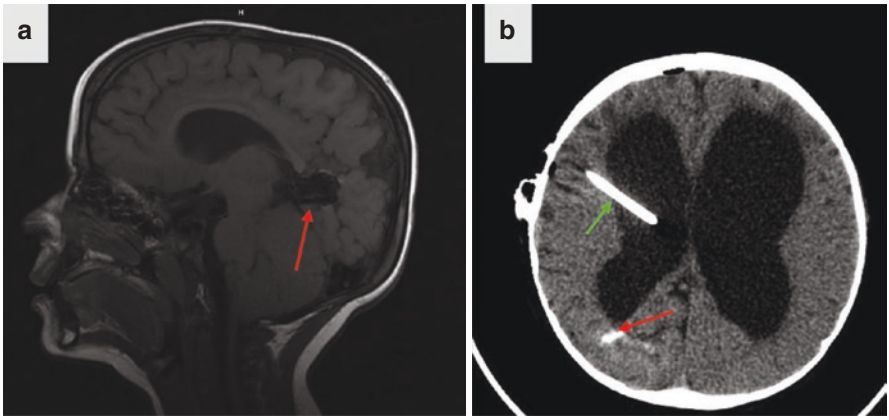


Fig. 6 (**a**) Red arrow shows a vein of Galen malformation on a sagittal sequence an MRI image. (**b**) This is the same patient's CT scan almost 1 year later who went on to develop hydrocephalus due to the vein of Galen malformation. The red arrow shows a coil that was used to treat the malformation. The green arrow shows the VP shunt

of abduction of the eyes. Diagnosis is often made by fetal ultrasound after 20 weeks of gestation [2]. At birth, cranial ultrasound can help make a postpartum diagnosis of aqueductal stenosis.

Various neural tube defects such as myelomeningocele or Chiari II malformation can cause congenital hydrocephalus [3]. A Chiari II malformation is where part of the cerebellum and brain stem extends down into the spinal canal through the foramen magnum. This condition is frequently associated with lumbosacral myelomeningocele. Hydrocephalus develops due to third and fourth ventricle outlet obstruction. These conditions are often detected by prenatal ultrasound and they frequently require shunting to aid in resolution.

Genetic

Macrocephaly secondary to hydrocephalus has been identified in more than 200 genetic syndromes. We will discuss some of the most common genetic syndromes associated with hydrocephalus below.

Genetic causes of obstructive hydrocephalus include Dandy-Walker malformation which is defined as hypoplasia of the cerebellar vermis, cystic enlargement of fourth ventricle leading to an enlarged posterior fossa. Usually macrocephaly is the initial feature. Bulging of the skull is seen which is more prominent in the occipital than frontal area. Due to compression of structures in the posterior fossa which houses the brainstem and cerebellum, neurologic dysfunction such as cranial nerve palsies, ataxia, apneic spells, and nystagmus can be seen [2]. Dandy–Walker malformation can be caused by a chromosomal deletion in *ZIC1* or *ZIC4* genes or seen in a variety of genetic syndromes such as PHACES syndrome (cardiac, skeletal, dermatologic, and Dandy–Walker malformation) [12].

Another genetic disorder causing hydrocephalus is L1CAM syndrome which is inherited in an X-linked manner [3]. These male patients have hydrocephalus, increased tone (most commonly in the legs), developmental delay, and adducted thumbs [2]. Severity is dependent on the mutation and diagnosis is made via genetic testing.

Klippel–Feil syndrome is a congenital malformation of the cranial and cervical skeleton which has been associated with genetic and nongenetic causes. It is caused by fusion of at least two cervical vertebrae. In this condition, hydrocephalus is caused by obstruction of flow from the fourth ventricle causing neurologic symptoms similar to those seen in Dandy-Walker malformation given posterior fossa compression. Scoliosis is seen in about 50% of cases. X-ray of the spine shows cervical fusion and MRI shows hydrocephalus or possibly a Chiari malformation [2].

In Utero Insults

Intrauterine infections can lead to hydrocephalus in a neonate. Some infections causing hydrocephalus are enterovirus 71 and lymphocytic choriomeningitis [6]. Other maternal factors such as alcohol-use, illicit drug use, maternal diabetes, preeclampsia, low socioeconomic status, and obesity have an increased risk of congenital hydrocephalus [6].

4.1.2 Megalencephaly

Anatomic Megalencephaly

Anatomic megalencephaly is the most common type of megalencephaly and can be characterized by many types of cellular defects causing increased cell size or increased cell count [2]. These cellular defects may be due to various brain malformations such as heterotopia, cortical abnormalities, or hamartomas. Many anatomic megalencephaly syndromes are due to single gene mutations which arise de novo [1]. Table 3 shows some of the most common types of anatomic megalencephaly.

Neurocutaneous Disorders

Neurocutaneous disorders can lead to macrocephaly either by megalencephaly or secondary to hydrocephalus. Examples of these include neurofibromatosis 1, tuberous sclerosis and Sturge Weber, all of which typically have signs of these disorders in infancy and childhood manifesting unique skin findings. In neurofibromatosis type 1 (NF1), 45% of patients have macrocephaly; on skin examination, there are typically café-au-lait spots [11]. In Sturge–Weber syndrome, another neurocutaneous disorder associated with megalancephaly, a port wine stain is seen usually following the V1 distribution [6]. Figure 7 shows a port wine stain on a patient as well as MRI findings. These patients may have learning disabilities or refractory epilepsy. In tuberous sclerosis, which is caused by overgrowth and lack of control of the mTOR pathway, children have hypomelanoic macules (ash leaf spots), shagreen patches and facial angiofibromas; intracranially, they have noncancerous tubers which grow overtime and can cause overt megalencephaly, hemimegalencephaly, or obstructive hydrocephalus.

At times, there may be hemihypertrophy or hypertrophy of a single limb in association with neurocutaneous disorders and megalencephaly such as in Hypomelanosis of Ito. Additionally, just one half of the brain may demonstrate abnormal enlargement, which is then called hemimegalencephaly.

Table 3 The table above shows some common syndromes of anatomic megalencephaly [11]

Anatomic megalencephaly
• Achondroplasia
• Sotos syndrome
• Neurocutaneous disorders (neurofibromatosis type 1 & 2, Sturge–weber syndrome, tuberous sclerosis)
• Beckwith–Wiedemann syndrome

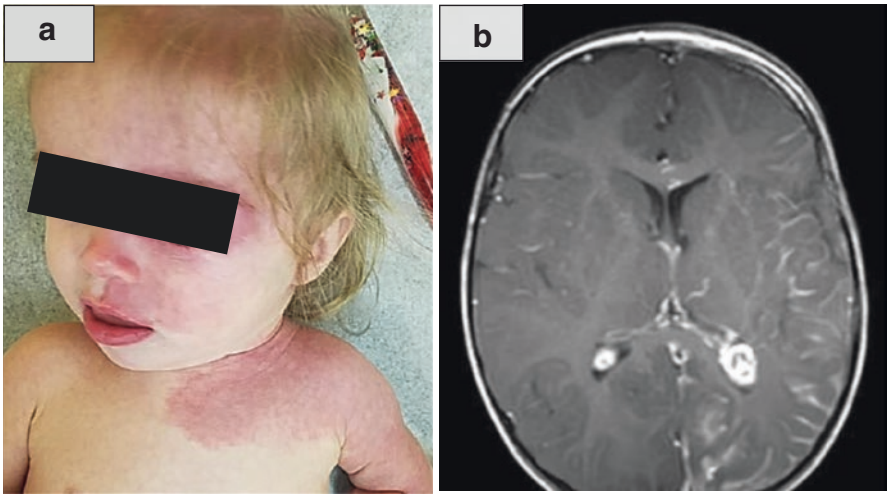


Fig. 7 (**a**) Port wine stain noted in V1 and V2 distribution on the trigeminal nerve as well as on her upper left chest and left arm. (**b**) Her MRI findings show extensive left hemispheric leptomemingeal angiomatosis; a finding seen with Sturge–Weber Syndrome. She has resultant right-sided weakness and intractable focal epilepsy and ultimately underwent a functional hemispherectomy

Metabolic Causes for Megalencephaly

Metabolic megalencephaly is caused by broad range of diseases where accumulation of abnormal substrates causes neuronal hypertrophy rather than cellular hyperplasia [2, 6]. Several inborn errors of metabolism can cause metabolic megalencephaly. Often the initial feature may be developmental regression, sometimes after a mild head trauma, or seizures. There may be other features on examination such as low tone, spasticity, or deficits in vision. MRI of the brain often shows white matter abnormalities. Table 4 lists some common causes of metabolic megalencephaly.

4.1.3 Other Considerations

There are several cranio-skeletal dysplastic conditions that cause macrocephaly such as Albright hereditary osteodystrophy, Proteus syndrome, and Gorlin syndrome. Also important to consider are toxic-metabolic etiologies, for example, steroid use, lead poisoning, tetracyclines use, iron-deficiency anemia, hypoparathyroidism, and hypoadrenocorticism [6].

Table 4 Most common causes for metabolic megalencephaly. Many of these syndromes have overlapping features and often require genetic testing to confirm diagnosis [2, 3]

Metabolic causes of megalencephaly
• Leukodystrophies – Canavan disease – Alexander disease – Megalencephalic leukoencephalopathy with subcortical cysts (MLC) • Glutaric aciduria type 1 • Lysosomal storage disorders – Hunter syndrome – Tay–Sachs disease – Gaucher disease – Niemann–pick disease • Menkes syndrome

4.2 Microcephaly

4.2.1 Genetic Syndromes

There are over 800 syndromes with an association with microcephaly. Often the mutations associated with microcephaly target cell cycle progression leading to premature apoptosis thus causing neuronal cell death or abnormal neuronal development [8]. Microcephaly in a small percentage of patients with genetic cause may be due to mitochondrial disorders or inborn errors of metabolism. There are also potentially treatable metabolic disorders such as phenylketonuria where microcephaly is an associated sign of the disorder. Table 5 lists some common genetic causes of microcephaly.

An isolated, genetic cause of primary microcephaly is autosomal recessive primary microcephaly, in which the child has isolated microcephaly with normal neuroimaging and no other abnormal findings on examination [8].

There is also benign familial microcephaly where the infant's head is microcephalic as is the parent's head and there are no other concerning neurologic symptoms.

There are also some genetic conditions that can cause *acquired* microcephaly including Angelman syndrome, Rett syndrome as well as inborn errors of metabolism such as phenylketonuria or *GLUT1* deficiency [13]. These children have normal head circumference at birth but fall off the growth chart over time.

4.2.2 Perinatal/Postnatal Causes

Infectious

Infections causing microcephaly are more common in developing countries due to lack of access to healthcare. Examples of organisms causing intrauterine infections leading to microcephaly include Zika virus, *Toxoplasma gondii,* Cytomegalovirus (CMV), and herpes simplex virus [4]. Table 6 lists some infections that can cause

Table 5 Common genetic causes of microcephaly [13]

Common genetics causes of congenital microcephaly	
Isolated causes	Syndromes
• Autosomal recessive microcephaly • X-linked microcephaly • Autosomal dominant microcephaly • Benign familial microcephaly	• Trisomy 13, 18, 21 • Williams syndrome • Cornelia de Lange syndrome • Wolf–Hirschhorn syndrome

Table 6 Some common infectious causes of microcephaly [4]

Intrauterine infections causing microcephaly
• Cytomegalovirus • Herpes simplex virus • Rubella virus • Zika virus • *Toxoplasma gondii* • Varicella • Syphilis • Parvovirus B-19 • Acquired immunodeficiency syndrome

microcephaly. It should also be noted that intrauterine infections that affect the brain may not always result in microcephaly. Seizures are a common clinical feature of congenital infection with associated microcephaly. Neuroimaging may show calcifications.

The Zika outbreak of 2015–2016 brought worldwide attention to viral infections causing severe microcephaly and neurologic impairment in neonates and infants.

Vascular

Hypoxic-ischemic encephalopathy (HIE) is a known cause of acquired microcephaly due to neurons undergoing apoptosis after an insult. Full-term newborns with HIE initially have a normal head circumference, then over the first year of life the rate of head growth slows leading to eventual microcephaly as seen in Fig. 3b. Not all infants with HIE will go on to develop microcephaly. Obtaining an MRI of brain shortly after birth has prognostic significance because there may be white matter lesions which may be predictive of impairment in head growth velocity [14]. White matter forms the largest part of the brain thus severe injury will have a higher likelihood of developing microcephaly. Moreover, infants with HIE have a higher rate than the general population of developing epilepsy, cerebral palsy, and other neurological sequelae [15].

Another neurovascular cause of acquired microcephaly is intraventricular hemorrhage (IVH) with similar disease course as HIE. However, a subset of children with IVH, most notably grades 3 and 4, may develop a secondary hydrocephalus with rapid onset macrocephaly and require a shunt placement.

Finally, placental insufficiency is associated with microcephaly [16]. Depending on the timing this insufficiency, the child may have onset of microcephaly early versus later in the gestation and may have short stature as well.

Toxic-Metabolic

Intrauterine exposure to alcohol, cocaine, radiation, and medications such as hydantoin derivatives (e.g., fosphenytoin) or valproic acid, as well as maternal malnutrition have been linked with microcephaly [4]. There has also been association with protein-energy malnutrition in infants that can lead to severe microcephaly [17]. Figure 8 shows an example of a toxic-metabolic etiology to microcephaly.

Anatomic

There are many anatomic abnormalities that may be associated with microcephaly. For example, neural tube defects can be associated with abnormal brain development leading to microcephaly. An example of a neural tube defect would be an

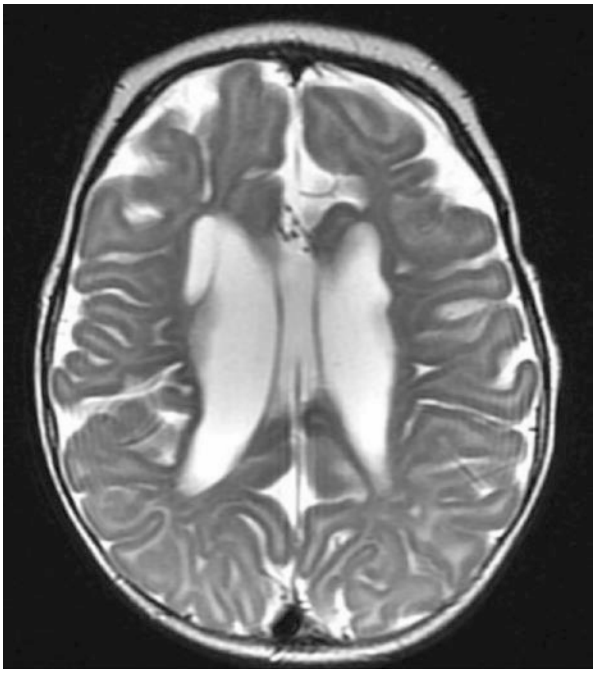


Fig. 8 This patient was 5 months of age at the time of MRI scan, T2 image. Note global cerebral volume loss and extensive white matter abnormality. There was a history of maternal diabetic ketoacidosis at 20 weeks of gestation. Head circumference was below 2 SD at time of birth. This patient went on to develop infantile spasms and spastic quadriplegic cerebral palsy

encephalocele, which is a protrusion of the cerebral cortex through a skull defect. Another cause includes lissencephaly where the cortex does not develop properly and there are fewer sulci than expected. All patients with lissencephaly will develop microcephaly by the first year of life [18]. Figure 9 shows a cartoon drawing of lissencephaly. Holoprosencephaly occurs when there is lack of full septation of the midline structures of the central nervous system. There may be associated midline abnormalities including close-set eyes and nasal and oral malformations or clefts. Table 7 lists a variety of neuroanatomic abnormalities.

Craniosynostosis can be associated with microcephaly. Cranial sutures may fuse prematurely if the brain is underdeveloped and the head remains microcephalic. Also, primary craniosynostosis itself may lead to microcephaly [19].

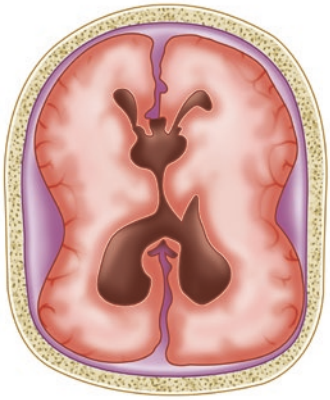


Fig. 9 This cartoon shows an axial cut of a brain with lissencephaly. In lissencephaly, there is diminished cerebral folds causing the appearance of a smooth brain

Table 7 A variety of structural abnormalities related to microcephaly [19]

Anatomic abnormalities associated with microcephaly
• Encephalocele
• Pachygyria: Decreased sulci
• Schizencephaly: In-folding of gray matter of cortex forming a brain cleft
• Polymicrogyria: Overabundance of gyri
• Atelencephaly: Lack of cerebrum
• Holoprosencephaly: Defect in septation of midline CNS structures
• Hydranencephaly: Fluid-filled cavities after a vascular injury
• Lissencephaly: Smooth gyri due to decreased sulci

5 Diagnostic Approach

5.1 History

It is important to obtain a detailed history regarding pregnancy and delivery because there are certain in utero insults whether it be maternal infection, toxic exposure, or maternal comorbidities that affect neurodevelopment. Also, check the results of newborn screening tests as certain disorders that are screened for can cause microcephaly or macrocephaly and can be treated. Other important information one need to obtain is if the child is progressing appropriately developmentally or if the development is plateaued or if there is regression in development. A family history might reveal large head sizes, and often it is helpful to measure parents' head sizes and plot them on adult charts. Keep in mind that female and male head circumferences differ and should be plotted on gender specific charts. Family history may also reveal certain genetic disorders such as neurofibromatosis in which patients often have macrocephaly.

5.2 Physical Examination

5.2.1 General Examination

Physical examination plays a key role in determining possible etiologies of macrocephaly. A tight or bulging fontanelle or widely separated sutures raises concern for increased intracranial pressure (ICP). A cranial bruit may be indicative of a vein of Galen malformation. It is important to closely evaluate the skin for any abnormalities. For example, café-au-lait spots are seen with neurofibromatosis and hypopigmented areas such as ash leaf spots may be seen with tuberous sclerosis. If there is organomegaly, this may be a sign of a metabolic disorder. Any dysmorphic features may be related to a genetic syndrome associated with macrocephaly or microcephaly. If infection is suspected to be a cause of microcephaly, it is important to evaluate the child for rash, jaundice, arrhythmias, and organomegaly.

Routine plotting of head circumference is part of a general pediatric examination starting at birth. It is also imperative to obtain height and weight at each encounter. This will help to determine if head size is growing in parallel with the rest of the body or if abnormality in head size is an isolated finding.

Measuring the head size accurately is important as improper measurements can lead to erroneous diagnosis of microcephaly or macrocephaly. The most accurate way to measure OFC is to wrap the measuring tap right above the eyebrow and ear all the way to the occiput, demonstrated in Fig. 10. A simple way to remember head circumference velocity in an infant, is to learn the rules of 3's and 5's as seen in

Table 8. Average head circumference is 35 cm at birth, at 3 months 40 cm, at 9 months 45 cm, at 3 years 50 cm, and at 18 years of age (adult) 55 cm.

Head circumference can be influenced by head shape and fluid beneath the scalp. For example, after a difficult delivery, blood and edema can thicken scalp or a neonate may develop cephalohematoma and it will falsely increase head circumference [2]. Infants who do not get "tummy time" and who almost exclusively lay in the supine position may develop flat occiputs. Premature infants whose heads are resting on one side will have flattening causing a large occipitofrontal diameter causing dolichocephaly.

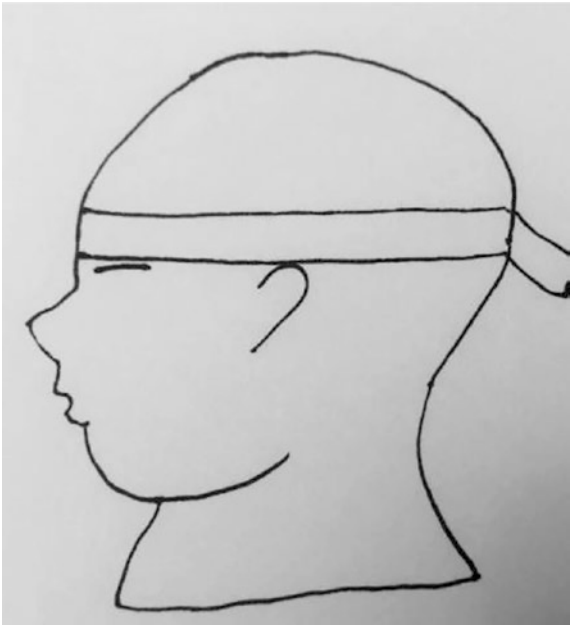


Fig. 10 Measure right above eyebrow and ear, which will give greatest occipitofrontal circumference, which is the most accurate OFC

Table 8 Average OFC based on age range. This is the rule of 3's and 5's. At age 3 months, 9 months, 3 years, and 18 years (adult), the head circumference increases on average by 5 cm [11]

Age	OFC
Birth (0 months)	35 cm
3 months old	40 cm
9 months old	45 cm
3 years old	50 cm
Adult	55 cm

5.2.2 Neurological Examination

A thorough neurological examination is warranted in all children with micro and macrocephaly. Examination of the cranial nerves to assess for increased intracranial pressure (sixth cranial nerve in particular), assessment of tone, deep tendon reflexes and gait are important. The child's developmental milestones should be carefully assessed and followed serially.

5.3 Evaluation (Laboratory Testing/Imaging)

Based on history and physical examination, evaluation should be tailored to identify and confirm the etiology for abnormal head size. An MRI scan of head is the most useful neuroimaging study to evaluate for macrocephaly or microcephaly. If an MRI scanner is not available, a cranial ultrasound in an infant with open anterior fontanelle or a CT head may be useful. However, CT scan carries risk of exposure to radiation. If there is concern for a genetic cause specific genetic studies as well as complete blood count (CBC), basic metabolic panel, urine and blood screen for amino acids, organic acids and reducing substances are recommended Chromosomal microarray or Fragile X testing may be performed as a first line screen when genetic basis is suspected. For microcephaly, screening for toxic substances such as lead levels or vitamin A levels may be useful.

6 Treatment/Management

Depending on the etiology of macrocephaly or microcephaly there are various management options. For example, if MRI shows concern for hydrocephalus, a referral to neurosurgery is recommended for consideration of ventriculo-peritoneal shunt placement. Patients with hydrocephalus may have developmental delay or regression and placement of a shunt may help in reaching developmental milestones. A shunt may also be recommended if there are signs of increased ICP as noted in Table 9. A child with Dandy-Walker malformation may require decompression of the cyst for immediate relief of symptoms such as inconsolability, vomiting, or abnormal eye movements. Certain vascular malformations such as vein of Galen

Table 9 Symptoms that may present in an infant with signs of increased intracranial pressure [6]

Symptoms suggestive of increased intracranial pressure in an infant
• Inconsolability
• Persistent vomiting
• Abnormal eye movements
• Lethargy
• Weakness

malformation require embolization procedure to prevent hydrocephalus. Management of brain tumors includes resection of tumor, radiation, and chemotherapy [5]. Patients with *GLUT-1* deficiency require life-long therapy with ketogenic diet.

For patients with craniosynostosis, often reconstructive surgery is needed to ensure proper brain development. In situations where microcephaly caused by certain TORCH infections such as cytomegalovirus (CMV), children may benefit from postnatal antiviral treatment. Other toxic-metabolic etiologies may require correction such as iron supplementation in iron deficiency anemia, phenylalanine/protein restricted diet in phenylketonuria.

7 Prognosis/Outcomes

The severity of neurologic manifestations in patients with micro or macrocephaly varies greatly and it can be challenging to prognosticate based on the severity of the intracranial malformations. It has been noted that if the degree of macrocephaly or microcephaly stays stable over time, patients fare better neurologically than patients who have acceleration or deceleration of head growth either starting prenatally or postnatally [7]. As described above, some patients have a benign course with milder forms of microcephaly or macrocephaly without neurologic symptoms or developmental delays.

8 When to Refer/Admit

If a child is microcephalic or macrocephalic without any other concerning signs or symptoms, then a referral to neurology may not be needed though the child should continue to be monitored closely by the PCP for head growth. As a clinician, if there is decelerated or accelerated head growth and regression in developmental milestones, consider neurology and genetics referral for further evaluation.

Another indication for referral to other specialists is when microcephaly is due to an infection. Ophthalmology and audiology evaluations are recommended to assess for cataracts, vision abnormalities, and hearing loss which can be seen with TORCH infections.

For craniosynostosis or other skeletal dysplasias, a referral to neurosurgery or plastic surgery may be helpful as there are often surgical options to address craniosynostosis.

If an infant has any signs or symptoms of raised ICP, it constitutes an emergency and should be referred to the closest emergency department immediately. These patients may need neurosurgical evaluation for a VP shunt. Tables 9 and 10 list symptoms and signs in patients with increased ICP, respectively.

Table 10 This table shows important physical examination findings in patients with raise ICP [3]

Physical examination findings suggestive of increased intracranial pressure in an infant
• Macrocephaly • Bulging Fontanelle • Frontal bossing • Dilated scalp veins • Abnormal extraocular movements: CN III, IV palsy or setting sun sign (impaired upgaze and eyes stay deviated downward) • Papilledema

9 Prevention

Most etiologies of macrocephaly and microcephaly are not preventable. Clinicians should educate expecting mothers to abstain from substance use such as recreational drugs, alcohol, and tobacco products. Certain medications have a teratogenic effect during pregnancy including abnormal head size and thus medications taken during the pregnancy should be reviewed.

10 Clinical Pearls and Key Points

- Pediatricians will encounter patients with macrocephaly and microcephaly relatively frequently.
- In conjunction with a history, evaluation of development, and pertinent examination findings including an accurate measurement of occipitofrontal circumference may greatly influence the appropriate diagnostic evaluation.
- Plotting out the head circumference and observing the trajectory is of value when one is suspecting variations of head size. Obtaining previous measurements is key to this process.
- First step in determining the etiology of micro or macrocephaly is to determine if the abnormality in size of the head is congenital or acquired in origin.
- At times, obtaining neuroimaging can be sufficient for diagnosis. However, often a referral to pediatric neurology, neurosurgery, and/or genetics may be needed for further evaluation and management.

References

1. Pirozzi F, Nelson B, Mirzaa G. From microcephaly to Megalencephaly: determinants of brain size. Dialogues Clin Neurosci. 2018;20:267–81.
2. Eric P-G. Disorders of cranial volume and shape. In: Clinical pediatric neurology. 7th ed. Elsevier; 2013. p. 348–65.
3. Kahle K, Kulkarni A, Limbrick D, Warf B. Hydrocephalus in children. Lancet. 2016;387:788–99.

4. Devakumar D, Bamford A, Ferreira MU, et al. Infectious causes of microcephaly: epidemiology, pathogenesis, diagnosis, and management. Lancet Infect Dis. 2018;18
5. Kalyvas A, Kalamatianos T, Pantazi M, et al. Maternal environmental risk factors for congenital hydrocephalus: a systematic review. Neurosurg Focus. 2016; https://doi.org/10.3171/2016.8.FOCUS16280.
6. Garg BP, Walsh L. Clinical approach to the child with a large head. Indian J Pediatr. 2001;68:867–71.
7. Boonsawat P, Joset P, Steindl K. Elucidation of the phenotypic spectrum and genetic landscape in primary and secondary microcephaly. Genet Med. 2019; https://doi.org/10.1038/s41436-019-0464-7.
8. Hanzlik E, Gigante J. Microcephaly. Children. 2017; https://doi.org/10.3390/children4060047.
9. Tucker J, Choudhary A, Piatt J. Macrocephaly in infancy: benign enlargement of the subarachnoid spaces and subdural collections. J Neurosurg Pediatr. 2016:16–20.
10. Tan AP, Mankad K, Guimaraes Goncalves F, Talenti G, Alexia E. Macrocephaly: solving the diagnostic dilemma. Top Magn Reson Imaging. 2018:197–217.
11. Fujimura M, Seryu JI. Velocity of head growth during the perinatal period. Arch Dis Child. 1977:105–10.
12. Grinberg I, Northrup H, Ardinger H, et al. Heterozygous deletion of the linked genes ZIC1 and ZIC4 is involved in Dandy-Walker malformation. Nat Genet. 2004;36:1053–5.
13. Baxter PS, Rigby AS, Rotsaert MH, Wright I. Acquired microcephaly: causes, patterns, motor and IQ effects, and associated growth changes. Pediatrics. 2009;124:590–5.
14. Mercuri E, Ricci D, Cowan F, et al. Head growth in infants with hypoxic–ischemic encephalopathy: correlation with neonatal magnetic resonance imaging. Pediatrics. 2000; https://doi.org/10.1542/peds.106.2.235.
15. Cordes I, Roland EH, Lupton BA, Hill A. Early prediction of the development of microcephaly after hypoxic-ischemic encephalopathy in the full-term newborn. Pediatrics. 1994;93:703–7.
16. Gelber SE, Grossman T, Grunebaum A. 274: Microcephaly: a misnomer for small head circumference. Am J Obstet Gynecol. 2017; https://doi.org/10.1016/j.ajog.2016.11.180.
17. Tiwari K, Goyal S, Malvia S, Sanadhya A, Suman RL, Jain R. Impact of malnutrition on head size and development quotient. Int J Res Med Sci. 2017;5:3003.
18. Leroy JG, Frías JL. Nonsyndromic microcephaly: an overview. Adv Pediatr. 2005;52:261–93. https://doi.org/10.1016/j.yapd.2005.04.003.
19. Sawh-Martinez R, Steinbacher DM. Syndromic craniosynostosis. Clin Plast Surg. 2019;46:141–55. https://doi.org/10.1016/j.cps.2018.11.009.

Child with Ataxia

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1 Introduction and Definition

Ataxia is a common sign encountered by pediatricians and neurologists in the emergency department, and occasionally in the office setting. The word ataxia, from the Greek root "lacking in taxis," implies lack of order. The neurological sign, ataxia, is characterized by lack of coordination in gait, speech, limb or head movements. While ataxia is usually due to a disturbance in the cerebellum, it can be caused by other nervous system abnormalities such as posterior spinal cord lesions or sensory nerve abnormalities. Careful history taking and physical examination can help localize the causes of ataxia and build a differential diagnosis which further helps with ordering appropriate diagnostic studies. Additionally, children can present with a gait abnormality due to a non-neurological cause such as limping due to limb trauma or inflammatory causes such as transient synovitis. An astute clinician should be able to assess the gait for the possibility of a non-neurological etiology, recognize and localize the cause of a neurological ataxia and guide diagnostic evaluation. The approach to evaluation of ataxia should first aim to rule out potentially serious causes and then focus on identifying and addressing treatable causes. Ensuring the child's safety and supporting the family is of essence and should happen simultaneously as the evaluation is being sequentially performed. This chapter

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will focus on the practical approach to a child with ataxia in the pediatric primary care setting with an emphasis on acute ataxia. Recurrent and chronic ataxias often need subspecialist referral for further evaluation and management.

2 Etiology/Epidemiology

The most common etiology of acute ataxia in children is a postinfectious condition referred to as acute cerebellar ataxia [1], followed by drug intoxication, and opsoclonus myoclonus ataxia syndrome. Other commonly encountered causes in the acute setting include acute cerebellitis, cerebellar stroke, acute disseminated encephalomyelitis (ADEM), meningitis, cerebral vein thrombosis, Miller Fisher syndrome, first episode of Episodic Ataxia (often genetic in origin) and mitochondrial disease. For recurrent and chronic ataxia, metabolic and genetic causes should be considered.

3 Diagnostic Approach

3.1 History

A detailed history is key to the evaluation of ataxia [2]. Key initial elements should include onset and timing. Is the ataxia acute, recurrent, or chronic? Acute ataxia is defined as ataxia with an onset less than 72 h in an otherwise developmentally appropriate child [2]. The most common cause of acute ataxia in children continues to be acute postinfectious cerebellar ataxia, which is usually self-limited and benign [1–6]. But serious causes like an infection of the central nervous system, posterior fossa lesions, posterior circulation ischemia or toxic ingestion, should be considered in the differential of acute onset ataxia.

A history of precipitating events should be explored—Is there a history of trauma (neck trauma can lead to vertebral artery dissection), any recent toxic or medication exposures (many antiseizure medication toxicities can cause ataxia), any current or preceding illnesses (postinfectious cerebellar ataxia, cerebellitis and ADEM can follow a viral illness).

A history of early morning headache or vomiting can be a symptom of raised intracranial pressure. Associated changes in mental status (drowsiness, irritability), behavior, or sleep patterns can be seen in infectious and postinfectious etiologies like ADEM, toxic ingestion or in conditions wherein there is brain stem involvement. Eye movement abnormalities could be a clue for opsoclonus myoclonus ataxia syndrome that usually presents with ataxia in children and would point towards the need to evaluate for an underlying neuroblastoma. Double vision can be a clue to a posterior fossa tumor and any loss of vision may be a symptom of optic

neuritis which can be a presenting symptom of ADEM. Speech abnormalities and nystagmus can occur in various disorders of the cerebellum. Hence, a systematic history of associated symptoms and a complete review of systems must be explored.

Is this episode the first or has the child had self-resolving similar episodes in the past? Recurrent episodes in an otherwise developmentally appropriate child would bring benign paroxysmal vertigo or migraine into the differential. Recurrent episodes in association with developmental concern would suggests the possibility of metabolic disorders or genetic forms of episodic ataxias [7].

Lastly, ataxia can present as a chronic symptom of developmental delay especially with gross and fine motor skills disorders. Therefore, a detailed history of birth and delivery, developmental milestones and family history are important. Understanding the clinical progression would be important in classifying chronic ataxia into static or progressive. Evaluation for regression and any loss of skills is vital to identify neurodegenerative disorders that could present with ataxia [7].

3.2 General Physical Examination

The physical examination starts with reviewing the vital signs. A fever would point towards an infectious/inflammatory etiology. Bradycardia or hypopnea needs laboratory evaluation for toxic ingestions or may indicate an acute brain stem compression in a child with altered mental status. An elevated blood pressure should initiate an urgent evaluation for raised intracranial pressure. Autonomic dysfunction with vital sign lability might point toward Guillain–Barrè syndrome (GBS).

The growth chart in children may reveal useful information as it may indicate failure to thrive which can be a sign of malabsorption syndrome with impaired absorption of vitamin E resulting in ataxia. Rapid onset macrocephaly raises concern for hydrocephalus, whereas microcephaly can be seen in brain malformations causing chronic ataxia.

Careful observation may reveal useful clues. Is the child's mental status altered? Is the child ill appearing or awake and interactive? Is there a hesitancy to move or a tendency to lean or fall to one side? Does the child appear to be in pain and thus have an abnormal gait secondary to discomfort?

Any dysmorphic features especially cranio-facial abnormalities like hyper or hypotelorism (wide set or narrow set eyes), nasal bridge abnormalities, low set ears which could suggest an underlying genetic etiology, should be noted. Certain skin findings can also provide clues such as a pellagra like rash seen in Hartnup disease or ichthyosis that can be associated with Refsum disease [8]. Neurocutaneous markers could point to neurofibromatosis, ataxia telangiectasia, or tuberous sclerosis.

Examination of the ear and the mastoid is important to rule out otitis media or mastoiditis that can cause vertiginous symptoms [9]. A comprehensive general physical examination may reveal hip or spine issues that cause a painful gait and thus masquerade as ataxia.

3.3 Neurological Examination:

A thorough neurological examination is crucial to determining the cause of ataxia. The comfort level of the child is critical to the neurological examination. Evaluation by observation with the child in the parent's lap or in a position of ease with toys of interest is likely to yield a more reliable examination.

Mental Status: Examination of mental status should assess the level of alertness, orientation to surroundings and attention span. An alteration in mental status is common in toxic ingestions whereas altered mental status in conjunction with cranial nerve abnormalities or abnormal fundus examination are clues to increased intracranial pressure/brain stem compression. In chronic ataxia, cognitive impairment may be seen.

Cranial Nerve Examination: Cranial nerve examination should include evaluation of the eyes, face and speech. Pertinent eye examination findings include funduscopic examination for papilledema and visual acuity testing individually for each eye, particularly if symptom of visual loss is reported. The examiner should evaluate for abnormalities of eye movements such as nystagmus or cranial nerve palsies (abduction palsy can be a sign of raised intracranial pressure). Opsoclonus is characterized by irregular and chaotic conjugate eye movements. In selected cases, a referral to an ophthalmologist is helpful to diagnose telangiectasias (salient feature of ataxia telangiectasia), optic nerve abnormalities (such as optic atrophy or optic neuritis) or retinitis pigmentosa (Refsum disease, abetalipoproteinemia). Assessment of facial symmetry, sensation of the limbs and face, taste and speech would help evaluate for brain stem involvement. Speech abnormalities such as slow, scanning or slurred speech can also point to a disorder of the cerebellum.

Motor Examination and Reflexes: Evaluation of a child's resting tone, strength and reflexes can help localize the lesion that is the cause of ataxia. Disturbances of the vermis of the cerebellum (midline structures) manifests as a lack of truncal control such as swaying in sitting position and titubation (head bobbing). Assessment of muscle strength should be performed to detect any weakness. A hypotonic child can have an abnormal ataxic gait and the weakness can masquerade as tremor and dysmetria. An absence of deep tendon reflexes would raise the suspicion for conditions such as Miller Fisher variant of GBS and neuropathies. Exaggerated deep tendon reflexes are seen in upper motor neuron lesions such as compressive lesions of the spinal cord or spino-cerebellar ataxias.

Sensory Examination: Romberg test is performed by asking the child to stand with feet close together with eyes closed and is positive (swaying observed) in sensory ataxia. It should be noted that a positive Romberg test is not indicative of disorders of the cerebellum. Sensory ataxia due to disturbances of posterior column of spinal cord (that convey sensation from the floor) or proprioceptive sensory nerves

can present with high steppage gait. Proprioception refers to the ability to locate the different parts of the body in relationship to each other, and then to the ground. Disturbances of proprioception lead to uncoordinated movement in patients with sensory ataxia and this instability tends to worsen on further sensory deprivation (eye closure in Romberg's sign).

Examination of the Cerebellum: Lesions of the cerebellum can present with an abnormality in coordinated hand movements or abnormalities in gait. Upper extremity coordination can be tested by asking the child to point to the examiner's finger and then to his/her nose (a finger puppet or a stuffed animal can often be useful) and leg coordination can be tested by heel-knee-shin test. Past pointing, over shooting or undershooting is a sign of ataxia. Intention tremor (tremor which occurs when the child stretches out her finger to touch an object and worsens as the finger gets close to the target) is an important sign that should be elicited. Dysdiadochokinesia can be tested by having the child perform rapid alternating hand movements such as patting their own thigh with first the palm and then the dorsum of their hand. A child with disorders of the cerebellum may appear clumsy during this portion of the examination.

Gait Examination: Younger children may refuse to walk but may be willing to take a few steps towards their parent standing at the opposite end of the examination room. Tandem gait assessment (heel-to-toe walking in a straight line) can be performed in children 8 years and older. Cerebellar abnormalities can present with a broad-based gait. Hemispheric disturbances of the cerebellum can present as falling to the ipsilateral side. Sensory ataxia as noted above can present with a high steppage gait. The term astasia-abasia gait is often used to describe the gait disturbance seen in conversion disorder, where patients are unable to maintain a standing posture or walk steadily despite having normal strength and coordination.

A normal neurological examination is a significant pertinent negative and should lead to an evaluation for possible non-neurological abnormalities or conversion disorder [2].

4 Etiology and Differential Diagnosis of Acute, Subacute, and Recurrent Ataxia

The differential diagnoses of acute and recurrent ataxia along with the salient clinical features are discussed in the Table 1 [2, 10, 11]. A brief discussion of a few causes follows thereafter.

Table 1 Differential diagnosis of acute and recurrent ataxia in children

	Examples	Salient clinical features	Pertinent investigations	Treatment
Acute				
Toxic ingestions	Benzodiazepines, antiseizure medications, antihistamines, alcohol	Mental status changes are common.	Urine and/or serum toxicology screen may detect unsuspected ingestions.	Supportive management and specific treatment depend on the toxin.
Postinfectious/ inflammatory	Postinfectious cerebellar ataxia	Gait impairment and other signs of ataxia in a well appearing child without fever or other neurological signs or symptoms.		Supportive care
Trauma/ vascular	Posterior circulation stroke, vertebrobasilar dissection, venous thrombosis, posterior fossa hemorrhage, postconcussion syndrome	History of head/ neck trauma, hypercoagulable risk factors. Deficit is maximal at onset.	Emergent neuroimaging is indicated	Patients often require intensive care unit monitoring and treatment in conjunction with a neurologist and/or neurosurgeon
Conversion disorder		Suggestible[a], distractible neurological examination, astasia-abasia gait.		Behavioral health involvement with functional neurorehabilitation
Subacute				
Postinfectious/ inflammatory	GBS including Miller Fisher variant	Preceding illness, in particular diarrheal illness. Features of Miller Fisher variant are oculomotor palsy (restriction in eye movements), diplopia, bulbar weakness (difficulty with speech or swallowing, respiratory abnormalities), areflexia. Need monitoring for respiratory failure and autonomic dysfunction.	Cyto-albuminoid dissociation in CSF analysis.	IVIG Plasma exchange Supportive care Patient may require monitoring in an intensive care unit

Table 1 (continued)

	Examples	Salient clinical features	Pertinent investigations	Treatment
Postinfectious/ inflammatory	ADEM	Mental status changes, multifocal neurological deficits.	Brain MRI shows multiple disseminated gray and white matter lesions in brain and spinal cord.	IV high dose steroids IVIG Plasma Exchange
Paraneoplastic/ idiopathic	Opsoclonus myoclonus syndrome	Triad of opsoclonus, myoclonus and ataxia, often associated with irritability. Paraneoplastic work up is indicated, though postinfectious etiology is common as well.	Urine HVA, VMA, Pan imaging, MIBG scan	If found, tumor resection and management under oncology. ACTH protocol IV steroids IVIG Other immunomodulatory agents such as Rituximab may be needed for long-term treatment
Mass lesions	Posterior fossa malignancies	Headaches, vomiting, cranial nerve palsies, papilledema	MRI brain with and without contrast	Neurosurgical intervention
Recurrent				
Migraine	Basilar migraine, benign paroxysmal vertigo	Episodic ataxia, vertigo, nystagmus, vomiting, headache. Child is normal in between attacks.	At initial presentation, imaging is necessary to rule out other causes.	Symptomatic
Metabolic	Disorders of amino acid metabolism mitochondrial disease	Can be triggered by intercurrent illnesses	Serum amino acids, urine organic acids, lactate genetic testing	Depends on etiology. Dietary leucine restriction in maple syrup urine disease. Thiamine supplementation with carbohydrate restriction in pyruvate dehydrogenase deficiency.

(continued)

Table 1 (continued)

	Examples	Salient clinical features	Pertinent investigations	Treatment
Episodic ataxias [7, 11]	Episodic ataxia Type 1–8	Brief or longer attacks of dysarthria, ataxia often triggered by movement, emotion, exercise, or fever.	Genetic testing	Acetazolamide in EA 1 and EA2.

IVIG intravenous immunoglobulins, *ACTH* adrenocorticotropic hormone, *IV* intravenous, *ADEM* acute disseminated encephalomyelitis, *MRI* magnetic resonance imaging, *HVA* homovallinic acid, *VMA* vanillylmandelic acid, *MIBG* metidobenzylguanidine; *CSF* cerebrospinal fluid; *EA 1* Episodic ataxia type 1; *EA 2* Episodic ataxia type 2

[a]Suggestible: symptoms can be induced and are responsive to verbal suggestions

Adapted from [12]

4.1 Postinfectious Cerebellar Ataxia and Cerebellitis

Postinfectious cerebellar ataxia is the most common pediatric cause of ataxia in a previously healthy child [1, 13]. Although there is scarcity of data on incidence of acute ataxia, a recent large multicenter study conducted in Italy showed that acute ataxia represents 0.02% of all pediatric emergency department attendances, a third of which were due to postinfectious ataxia [4]. This condition is most commonly seen in children who are between 2 and 5 years of age, commonly presents as a gait disturbance without other systemic or neurological symptoms [1, 6, 13, 14]. Antecedent viral illness is commonly reported about a week before presentation [1, 14]. While varicella was the most common illness associated with this condition in the pre-vaccination era, a recent large single center study showed no cases were attributed to varicella [1, 6]. It is important to note that postvaccination cerebellar ataxia is rare [1]. Brain MRI is usually normal [15]. Cerebrospinal fluid (CSF) studies are not necessary if presentation is classic but can show pleocytosis in about 50% of children [1, 6, 14]. Most children recover completely within days to a few weeks of presentation [5, 6, 13, 14]. No specific treatment is indicated, since the condition typically self-resolving [1].

A more severe form known as acute cerebellitis can present with signs of raised intracranial pressure, abnormal MRI with signs of inflammation in the cerebellum, with or without hydrocephalus and CSF pleocytosis [1, 16]. Prognosis is variable but this condition can result in long term neurological sequelae and rarely even death [16].

4.2 Opsoclonus Myoclonus Syndrome (OMS)

OMS also known as opsoclonus myoclonus ataxia syndrome (OMAS), is characterized by opsoclonus (multidirectional, chaotic, conjugate eye movements), myoclonus (myoclonic jerks), ataxia and encephalopathy. Typical age of presentation is around 18 months [17] and children usually also have behavioral irritability with or without sleep disturbance and often a loss of developmental skills [18, 19]. Due to the rarity of this condition and difficulty in detecting opsoclonus and/or myoclonus, it can be easily missed and confused with postinfectious cerebellar ataxia [20]. Hence, a diagnosis of OMS should be considered, in a child with presumed postinfectious cerebellar ataxia, who is not improving or has features of encephalopathy or irritability [20]. Paraneoplastic (associated with neuroblastoma) causes account for about 40% of the cases and the remainder are usually postinfectious [17, 19]. Neuroblastoma associated with OMS may be occult and need more than one and often repeated diagnostic evaluation. Investigations for neuroblastoma include evaluation of urine for catecholamine metabolites such as vanillylmandelic acid (VMA) and homovanillic acid (HVA), imaging studies such as CT or MRI of neck, chest, abdomen and pelvis, and nuclear scintigraphy studies using radioiodinated metaiodobenzylguanidine (MIBG) [17, 18]. It is important to note the low sensitivity of catecholamine metabolites and MIBG scan in detection of neuroblastoma which is reflective of the metabolically inactive nature of the tumors associated with OMS [18]. Treatment consists of surgical resection of tumor and immune therapies for treatment of OMS. Different protocols with corticosteroids, ACTH, IVIG and a variety of immunomodulatory agents such as cyclophosphamide, mycophenolate and rituximab have been used [17, 18]. Unfortunately, this is usually a chronic condition and long-term sequelae are common in spite of treatment [17, 19, 21].

4.3 Chronic Ataxias

Chronic ataxias can be progressive or nonprogressive. For nonprogressive ataxias, structural causes like posterior fossa or cerebellar malformations, prenatal insults, intrauterine vascular events etc. should be considered. Neuroimaging would help delineate these lesions. The progressive ataxias include genetic and metabolic causes [7]. The differential of chronic ataxia is broad and a few important causes are listed in Table 2.

Table 2 Differential diagnosis of chronic ataxia in children

Chronic ataxias
1. Nonprogressive ataxias: • Cerebellar malformations or hypoplasia. • Dandy–Walker malformation • Chiari malformations • Joubert syndrome • Perinatal strokes • Genetic causes
2. Progressive ataxias: • Autosomal dominant: Spinocerebellar ataxias, episodic ataxias. • Autosomal recessive [22]: Friedreich ataxia, ataxia telangiectasia, ataxia with oculomotor apraxias, ataxia with vitamin E deficiency • Mitochondrial: mitochondrial encephalopathy, lactic acidosis, stroke-like episodes (MELAS), neuropathy, ataxia and retinitis pigmentosa (NARP), myoclonic episodes with ragged red fibers (MERRF), etc. • X linked: Fragile X tremor-ataxia syndrome (FXTAS), MECP2-related syndromes • Leukodystrophies like adrenoleukodystrophy (ALD), Alexander disease, metachromatic leukodystrophy (MLD).
Causes of ataxia wherein disease modifying therapies are available [23, 24]
1. Ataxia with vitamin E deficiency
2. Cobalamin deficiency
3. Thiamine responsive encephalopathy
4. Glucose transporter 1 (GLUT1) deficiency
5. Abetalipoproteinemia
6. Cerebrotendinous xanthomatosis
7. Neimann–Pick type C
8. Refsum's disease
9. Maple syrup urine disease
10. Pyruvate dehydrogenase deficiency

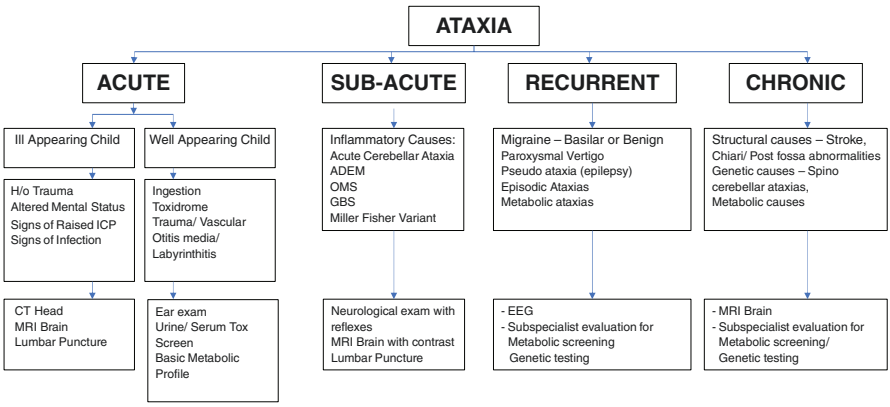
MECP2 methyl CpG binding protein 2

5 Approach to the Evaluation

A detailed history and physical examination are the most important steps in the evaluation of a child with ataxia.

The evaluation of acute ataxia in an otherwise developmentally appropriate, well appearing child should start with urine toxicology and a basic metabolic panel [5, 25].

Algorithm 1
Approach to Ataxia in Children [10].



Neuroimaging: If there are focal signs on the neurological examination or an alteration in mental status, urgent neuroimaging is indicated after the patient is stabilized. The decision regarding the type of neuroimaging depends on the general presentation of the child and the precipitating factors. A history of trauma or a child who presents with an acute alteration in consciousness, once stabilized would benefit from a CT scan of the head. On the other hand, in a child with normal mentation and isolated ataxia, an MRI of the brain would be more beneficial and reduce exposure to radiation. A concern for underlying infectious, inflammatory, or neoplastic etiology would indicate the need for MRI brain with contrast.

Laboratory Investigations: A lumbar puncture would need to be considered for the evaluation of infectious causes or postinfectious etiology like GBS where one may note elevated protein level but no pleocytosis. GLUT1 deficiency would be suggested by isolated low CSF glucose in the presence of a normal serum glucose level.

Evaluation of recurrent ataxia would need to include evaluation for genetic and metabolic etiologies. Occasionally, seizures can mimic recurrent ataxia in a child who has transient alteration of consciousness with seizures. In such cases, an EEG to assess for epileptiform discharges is warranted [26].

Chronic ataxia in children is usually a sign of underlying structural, genetic or metabolic causes. Neuroimaging with an MRI of the brain is essential in children with chronic ataxias. If neuroimaging is unrevealing, referral for subspecialist evaluation and screening for treatable causes should be considered. An initial screen for treatable causes (Table 3) can be initiated in circumstances where referral to a subspecialist is delayed [22–24].

Table 3 Initial screening of chronic ataxia in children

Initial screening
1. Ophthalmologic exam
2. Brain MRI
3. Complete blood count and serum electrolytes
4. Ammonia, liver function tests
5. CPK (elevated in mitochondrial disease)
6. Serum amino acids
7. Urine organic acids
8. Plasma homocysteine
9. Thyroid function test
10. Vitamin E, B1, and B12 levels
11. Lysosomal storage panel
12. Urine oligosaccharides/urine glycosaminoglycans
13. Alpha fetoprotein (elevated in ataxia telangiectasia)
14. Lumbar puncture for glucose

When to Refer for Emergency Care
- Ill appearing child with fever or altered mental status
- Signs of brain stem involvement
- Absent reflexes

When to Refer for Subspecialist Evaluation
- Chronic ataxia
- Recurrent ataxia with neurological symptoms
- Persistent symptoms after 2–4 weeks of follow-up after acute ataxia
- Family history of chronic ataxia
- Regression of neurological milestones

6 Management and Outcomes

The management of children with ataxia is based on the underlying etiology.

Children who present with an acute alteration in consciousness with changes in their vital signs will need stabilization first. Posterior fossa lesions, neoplastic and hemorrhagic causes might need acute neurosurgical intervention. Children suspected to have an underlying infection will need empiric coverage with antibiotics while awaiting cultures and characterization of the infection. The most common acute ataxia, postinfectious cerebellar ataxia is usually self-resolving. Acute ataxias due to inflammatory or postinfectious etiology like ADEM or GBS, could require immuno-modifying therapy. OMS often requires a combination of immune modulating therapies and coordinated care by neurologists and oncologists.

A follow-up examination within 2–4 weeks for children who present with acute ataxia is indicated to ensure no residual abnormalities and signs and symptoms suggestive of recurrence are present.

Management of a child with chronic ataxia would be directed based on the underlying diagnosis. In children, where treatable causes have been excluded, supportive care is essential [22–24]. Persistent disability with ataxia would need rehabilitative care services including physical and occupational therapy. Coordination of care for adaptive medical devices is often necessary and vital.

7 Conclusions

While childhood ataxia has a broad differential diagnosis, most commonly it is due to postinfectious cerebellar ataxia. When approaching a child with acute onset ataxia, the pediatrician must first ensure that acute life threatening, and serious causes are identified and managed. This should be followed by a careful history and examination focused on identifying potentially treatable causes of ataxia [22–24]. A select group of children may require referral to a neurologist or geneticist for further evaluation. Counseling and supportive care of the child and family during this process is paramount.

8 Clinical Pearls/Key Points

- While ataxia is usually due to a disturbance of the cerebellum, it can be caused by a lesion anywhere in the nervous system including spinal cord. Sensory and vestibular causes of ataxia need to be considered.
- Postinfectious cerebellar ataxia is the most common cause of acute ataxia and is usually self-limited.
- Serious causes of ataxia including meningitis, posterior fossa lesions, inflammatory, and vascular causes will need to be ruled out.
- Consider genetic and metabolic etiology for recurrent and chronic ataxias. An initial screen should focus on identifying treatable causes.
- Symptomatic care to ensure safety is crucial in the management of children with ataxia.
- Specific treatment depends on underlying etiology for ataxia.

References

1. Thakkar K, Maricich SM, Alper G. Acute ataxia in childhood: 11-year experience at a major pediatric neurology referral center. J Child Neurol. 2016;31(9):1156–60.
2. Overby P, Kapklein M, Jacobson RI. Acute ataxia in children. Pediatr Rev. 2019;40(7):332–43.
3. Caffarelli M, Kimia AA, Torres AR. Acute ataxia in children: a review of the differential diagnosis and evaluation in the emergency department. Pediatr Neurol. 2016;65:14–30.

4. Garone G, Reale A, Vanacore N, Parisi P, Bondone C, Suppiej A, et al. Acute ataxia in paediatric emergency departments: a multicentre Italian study. Arch Dis Childhood. 2019;104(8):768–74.
5. Segal E, Schif A, Kasis I, Ravid S. Acute ataxia in children: Common causes and yield of diagnostic work-up in the era of varicella vaccination. J Clin Neurosci. 2019;68:146–50.
6. Connolly AM, Dodson WE, Prensky AL, Rust RS. Course and outcome of acute cerebellar ataxia. Ann Neurol. 1994;35(6):673–9.
7. TD B. Hereditary ataxia overview. 1998 Oct 28 [Updated 2019 Jul 25]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2020. https://www.ncbi.nlm.nih.gov/books/NBK1138/. Accessed 2 Nov 2020.
8. Winchester S, Singh PK, Mikati MA. Ataxia. Handb Clin Neurol. 2013;112:1213–7.
9. Pellegrini S, Gonzalez Macchi ME, Sommerfleck PA, Bernáldez PC. Intratemporal complications from acute otitis media in children: 17 cases in two years. Acta Otorrinolaringol Esp. 2012;63(1):21–5.
10. Pavone P, Praticò AD, Pavone V, Lubrano R, Falsaperla R, Rizzo R, et al. Ataxia in children: early recognition and clinical evaluation. Ital J Pediatr. 2017;43(1):6.
11. Garone G, Capuano A, Travaglini L, Graziola F, Stregapede F, Zanni G, et al. Clinical and genetic overview of paroxysmal movement disorders and episodic ataxias. Int J Mol Sci. 2020;21(10)
12. Singer SHMJ, Gilbert DL, Jankovic J. Ataxia. Movement disorders in childhood. 2nd ed. Philadelpia: Butterworth-Heinemann; 2015.
13. Gieron-Korthals MA, Westberry KR, Emmanuel PJ. Acute childhood ataxia: 10-year experience. J Child Neurol. 1994;9(4):381–4.
14. Nussinovitch M, Prais D, Volovitz B, Shapiro R, Amir J. Post-infectious acute cerebellar ataxia in children. Clin Pediatr. 2003;42(7):581–4.
15. Luetje M, Kannikeswaran N, Arora R, Wang B, Farooqi A, Sivaswamy L. Utility of neuroimaging in children presenting to a pediatric emergency department with ataxia. Pediatr Emergency Care. 2019;35(5):335–40.
16. Emelifeonwu JA, Shetty J, Kaliaperumal C, Gallo P, Sokol D, Soleiman H, et al. Acute cerebellitis in children: a variable clinical entity. J Child Neurol. 2018;33(10):675–84.
17. Brunklaus A, Pohl K, Zuberi SM, de Sousa C. Outcome and prognostic features in opsoclonus-myoclonus syndrome from infancy to adult life. Pediatrics. 2011;128(2):e388–94.
18. Pang KK, de Sousa C, Lang B, Pike MG. A prospective study of the presentation and management of dancing eye syndrome/opsoclonus-myoclonus syndrome in the United Kingdom. Eur J Paediatr Neurol. 2010;14(2):156–61.
19. Tate ED, Allison TJ, Pranzatelli MR, Verhulst SJ. Neuroepidemiologic trends in 105 US cases of pediatric opsoclonus-myoclonus syndrome. J Pediatr Oncol Nurs. 2005;22(1):8–19.
20. Desai J, Mitchell WG. Acute cerebellar ataxia, acute cerebellitis, and opsoclonus-myoclonus syndrome. J Child Neurol. 2012;27(11):1482–8.
21. Mitchell WG, Wooten AA, O'Neil SH, Rodriguez JG, Cruz RE, Wittern R. Effect of increased immunosuppression on developmental outcome of opsoclonus myoclonus syndrome (OMS). J Child Neurol. 2015;30(8):976–82.
22. Synofzik M, Puccio H, Mochel F, Schöls L. Autosomal recessive cerebellar ataxias: paving the way toward targeted molecular therapies. Neuron. 2019;101(4):560–83.
23. van Karnebeek CD, Houben RF, Lafek M, Giannasi W, Stockler S. The treatable intellectual disability APP https://www.treatable-id.org: a digital tool to enhance diagnosis & care for rare diseases. Orphanet J Rare Dis. 2012;7:47.
24. Ramirez-Zamora A, Zeigler W, Desai N, Biller J. Treatable causes of cerebellar ataxia. Movement Disord. 2015;30(5):614–23.
25. Whelan HT, Verma S, Guo Y, Thabet F, Bozarth X, Nwosu M, et al. Evaluation of the child with acute ataxia: a systematic review. Pediatr Neurol. 2013;49(1):15–24.
26. Poretti A, Benson JE, Huisman TA, Boltshauser E. Acute ataxia in children: approach to clinical presentation and role of additional investigations. Neuropediatrics. 2013;44(3):127–41.

Child with Gait Disturbances

Meghan Harper-Shankie and Heather Little

1 Introduction

This review will summarize the features of normal gait, typical development of gait and variations of normal gait, the differential diagnosis of gait abnormalities, and diagnostic approach and management of such disorders. Specific patterns of gait disorders will be addressed, along with their differential diagnosis and treatment plan.

1.1 Epidemiology

One study identified the prevalence of children presenting to an emergency department with a traumatic limp at 1.8 per 1000 children, 80% of whom complained of pain. These children were all less than 14 years-old with a median age of 4.4 years [1].

1.2 Analysis of Normal Gait

To identify an abnormal gait, one must first understand the mechanics of normal gait and the typical progression of development in children. Gait is divided into two phases, the stance and swing phases [2]. During the stance phase, the heel strikes the ground and rolls forward until the foot flattens and bears weight, then pushes off the

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metatarsal heads. In the swing phase, the foot leaves the ground and accelerates in the air prior to deceleration just before heel strike again. This phase is associated with swinging of the limbs, with the opposite arm and leg swinging simultaneously. The stance phase occupies the majority (60%) of walking time and therefore most gait disorders predominantly affect the stance phase, particularly due to the impact of weight bearing [2].

Normal development of gait in children reflects the cephalocaudal development of the nervous system [3]. When children first begin walking, at approximately 10–15 months-old, their gait is wide based and unsteady. They frequently walk with arms flexed and outward for balance, along with hyperflexion of the knees [2]. Cadence is fast but the velocity of walking is slow. By 15–18 months-old, children begin to develop reciprocal arm movements, gait remains wide albeit narrower, velocity is faster and they have greater heel strike [3]. Over the toddler years, the gait becomes progressively more efficient and smooth, with lengthening of the stride and increased velocity. By age 7, most children demonstrate a gait pattern similar to that of adults [3]. Some in-toeing and out-toeing of the feet can be normal in this early period [4]. In-toeing is typically related to either tibial torsion, where the patella faces forward and toes point inward, or femoral anteversion, where the patella and feet both point inward. Tibial torsion is common at 1 to 3 years of age and femoral anteversion occurs between 3 and 8 years-of age [4]. Genu varum or "bow-leggedness" is common in the first 2 years of life, is often associated with out-toeing, and typically resolves by 18 months-old. Genu valgus or "knock knees" is frequently associated with in-toeing and typically resolves by 7 years of age [3].

2 Diagnostic Approach

Disorders of gait can be related to neurological, orthopedic, infectious, neoplastic or psychologic causes. The majority of etiologies localize to the peripheral nervous system, i.e., muscles/nerves or the musculoskeletal system, i.e., joints, or bones of the hip, knee, ankle or foot [2–5]. The cause can also be related to the central nervous system, either the brain or spinal cord [6]. A thorough history and physical examination can guide the clinician towards the most likely etiology, to be confirmed with ancillary testing.

2.1 History

A thorough history is a critical component in narrowing the differential diagnosis for abnormalities of gait. Understanding the acuity of symptoms can help determine both the etiology and urgency of evaluation. The family and child should be asked when the symptoms were first noted and how they were noted, as well as whether the symptoms have been worsening, improving or stable since onset [2, 5]. A recent

and abrupt onset of gait disturbance increases the likelihood of a traumatic, infectious, or postinfectious etiology, whereas chronic slowly progressive issues typically implicate an orthopedic, cerebral, spinal, or musculoskeletal cause [7]. Whether the symptoms are episodic or constant should also be ascertained, along with whether there are provoking or palliative factors.

The presence of pain or absence of pain along with location of pain are helpful features for localization of the problem. Older children can typically describe the location and quality of pain, whereas younger children may only limp or refuse to walk. Particularly in this scenario, the diurnal pattern and provoking and palliative factors can help narrow differential. For example, pain upon awakening in the morning is common in juvenile rheumatoid arthritis and transient synovitis of the hip, whereas pain that progresses throughout the day and with activity is more common in orthopedic and neurological pathologies [7]. Pain that awakens a child at night is always cause for concern as it can implicate a neoplastic cause. The quality of the pain is also helpful. For example, cramping is common in both neurogenic and myopathic causes whereas a dull pain may implicate bone pathology [5, 8].

Other associated symptoms can further help in narrowing the differential [5]. Fever can indicate infectious, inflammatory or, less commonly, neoplastic disorders. Systemic symptoms such as anorexia, weight loss and fatigue could also implicate a neoplastic etiology. Difficulties with bowel or bladder control likely suggest a neurological entity, especially an intraspinal one. Delays in development, altered mental status, or seizures typically localize to the cerebral hemispheres. Motor weakness is typical of disorders of the muscle or neuromuscular junction. Care should be taken to differentiate true muscle weakness from generalized fatigue, which patients may describe as “feeling weak.”

Complaints of weakness in other areas of the body, such as the shoulder girdle, face or eyes, can aide in developing the differential diagnosis, particularly if there is suspicion of neuromuscular disorders. With rare exception, weakness that is most prominent in the proximal muscle groups is suggestive of disorders of the muscle, whereas motor weakness that is predominantly distal (affecting the fingers or feet) implicates a disease of the peripheral nerves. Difficulty with breathing, dysphagia, frequent respiratory infections, and symptoms of facial weakness, such as difficulty chewing, drinking from a straw, blowing bubbles or whistling, can occur in myopathies or disorders of the neuromuscular junction [9]. Children with neuromuscular junction disorders such as myasthenia gravis and congenital myasthenia may also have complaints about their vision (such as diplopia) in addition to shoulder girdle and facial weakness [9].

Functional limitations help determine not only etiology, but also safety concerns which guide management. In particular, difficulty walking upstairs can indicate hamstring weakness, whereas difficulty walking downstairs implies weakness of the quadriceps [5]. Difficulty rising from the floor or a low seat is consistent with hip girdle weakness. Tripping frequently is often associated with distal leg weakness, especially the foot dorsiflexors. Issues with opening bottles, handwriting, and buttoning imply finger and distal arm weakness [2, 3, 5, 8]. Taken together, the distal extremity weakness can be suggestive of peripheral neuropathies, such as

Charcot–Marie–Tooth disease (CMT), or certain forms of distal muscular dystrophy, such as myotonic dystrophy [8, 9].

As with most pediatric complaints, an assessment of birth and developmental history can significantly impact your differential diagnosis [2, 3, 5]. A history of prematurity, perinatal distress or neonatal encephalopathy increases the likelihood of cerebral palsy [10]. A history of gross motor delay suggests a disorder of the motor unit, and a history of developmental regression nearly always suggests a neurological cause whether due to disorder of the central nervous system, as in neurodegenerative disorders, or peripheral nervous system, as in dystrophinopathies [8]. Family history is quite helpful as many neuromuscular disorders are heritable [9].

2.2 Physical Examination

General physical examination should note the presence of fever, skin rashes, and measurement of head circumference. The cardiac myocytes are a target of many muscular dystrophies, eventually resulting in heart failure. However, early in the disease course, the cardiac evaluation is typically normal. The same is true for pulmonary evaluation. Hepatosplenomegaly, if identified on abdominal examination, could indicate the presence of a hematologic disorder, malignancy, or storage disorder [11, 12]. Occasionally, intra-abdominal mass or infection, as with appendicitis, can manifest with a limp due to direct irritation of the psoas muscle and referred pain [1]. For the musculoskeletal evaluation, the child should be examined with legs exposed so that the thighs, knees, ankles and feet are all able to be visualized during assessment. A standardized scale may be helpful to ensure thoroughness in the musculoskeletal evaluation of the lower limbs and pelvis. The pGALS (pediatric Gait, Arms, Legs, Spine) assessment is a standardized musculoskeletal examination to evaluate joint and musculoskeletal concerns and is freely available online [13]. The assessment is a head-to-toe screening measure which has been validated in detection of pediatric rheumatological disorders, particularly Juvenile idiopathic arthritis (JIA), in school-aged children and takes approximately 2 min to complete [13]. Scales such as this can provide a useful guide for both novice and experienced examiner, reminding the physician to “look, feel, move” [13]. Visualization of the extremities can identify asymmetry, muscle atrophy or hypertrophy, leg length discrepancies, and alignment issues. Muscle atrophy can indicate the presence of peripheral neuropathy, muscular dystrophy or inflammatory condition such as JIA [8, 9]. Swelling or redness over joints may be present in infectious and rheumatological disorders [13]. Palpation should evaluate for any localized bony or muscle tenderness, which can indicate fracture, malignancy, or osteomyelitis, as well as for restrictions in range of motion or excessive mobility of joints. If present, the examiner should note whether the abnormalities above are symmetric or not.

2.3 Neurological Examination

A systematic neurological examination including testing of higher mental functions, cranial nerves, and motor examination should be performed. The neurological examination includes testing of strength of individual muscle groups if possible, appreciation of sensation to touch, pinprick, and vibration as well as deep tendon reflexes (DTRs). Children with neuropathies often have weakness in proportion to the degree of muscle atrophy and decreased DTRs, whereas children with myopathies often have weakness which is much greater than that expected for their appearance, and DTRs are variably affected although typically correlate with degree of weakness [5, 10]. Increased tone and spasticity in the legs, along with increased DTRs and upgoing plantar response, indicate upper motor neuron dysfunction and therefore localize to the brain or spinal cord. The most common reason for this finding is a remote insult, as seen in cerebral palsy. However, if new or progressive, neurodegenerative disorders such as X-linked adrenoleukodystrophy or neoplasm need to be considered. Diminished sensation to vibration, proprioception and decreased DTRs should raise suspicion for vitamin deficiencies or a genetic ataxia syndrome, such as episodic ataxia or Friedrich's ataxia [5].

The child's stance should be observed from the front, side, and back to evaluate for symmetry of the legs, angulation of the knees and distal lower extremities, and for spinal curvature [2, 13]. Lordosis is a common compensatory measure in children with hip girdle weakness and is therefore often seen in most muscular dystrophies and myopathies [8].

Assessment of the gait itself should be done while observing the child walking down a hallway, both toward and away from the examiner, and also while running if feasible [2]. Observations regarding cadence, fluidity of gait, heel strike and arm swing should be compared to developmentally appropriate milestones as discussed earlier [2, 3, 5, 14]. The examiner should also note any angulation, such as in-toeing or out-toeing. Inspection and palpation of the extremities should be performed in both the supine and prone positions [4, 13]. In particular, inspection should note any leg length discrepancies and abnormal angulation which can occur with orthopedic conditions such as legg-calve perthes disease, tibial torsion, or hip torsion.

Finally, specialized maneuvers may be necessary for further clarification. One of the most widely practiced of these is the Gower's maneuver, in which the child is asked to sit on the floor and rise without the use of hands. In a child with hip girdle weakness, they are unable to do so and first must place hands on the floor to help propel their hips and trunk upward, then use their hands to walk up their legs [5]. Percussion of the tongue or thenar eminence of the hand can precipitate percussion myotonia in those with myotonic dystrophy [8, 10]. In cooperative patients with suspected myasthenia, sustained upgaze for more than 60s will lead to ptosis and lateral gaze for more than 60s will lead to horizontal diplopia [8, 10].

3 Specific Patterns of Gait Abnormalities\Differential Diagnosis

Observing specific features of a child's gait can help delineate the location and cause of the symptoms. Common patterns of abnormal gait include:

The Antalgic Gait occurs due to pain. The stance phase is shortened on affected side due to discomfort with bearing weight on it, often resulting in a limp [2, 3, 7]. Common causes include trauma resulting in fractures, sprains or other injuries as well as infection or inflammation, as occurs with a septic joint, synovitis or arthritis. Bone pain secondary to malignancy should also be considered.

Limping not associated with pain results in an equal stance phase [3]. The limp occurs as a result of the child shifting their center of gravity over a single extremity to remain balanced, typically due to muscle weakness or joint instability. The differential diagnosis of a limping child is broad and there are multiple papers dedicated solely to the evaluation of a limp, with the differential diagnosis varying significantly by age [3, 15].

Circumduction Gait, where the affected leg has excessive hip abduction and swings outward in a semicircle rather than forward during the swing phase [4], and can occur for multiple reasons. Patients with hemiplegic cerebral palsy can demonstrate circumduction on the affected side due to the increased extensor tone in the leg and limited dorsiflexion in the foot. It is often associated with decreased arm swing on the affected side, sometimes with the arm held in a flexed and adducted position, as well as upper motor neuron (UMN) signs on examination [16]. The child may also demonstrate choreo-athetoid or dystonic movements on the affected side with running [3]. A leg-length discrepancy can produce an asymmetric stance phase where there is depression of the pelvis on the shorter leg and the longer leg circumducts in the swing phase [2]. Circumduction gait can also occur when there is pain in the knee or ankle resulting in insufficient flexion of the knee or limited range of motion at the ankle [2].

The Trendelenburg Gait occurs secondary to weakness of the hip girdle and in particular the hip abductors including the gluteus medius [2, 5]. When functioning well, the hip abductors work to stabilize the pelvis and keep it level while walking. During the stance phase, if one hip abductor is weak the corresponding hip is unable to abduct and therefore the contralateral pelvis appears to drop [2, 5]. If bilateral hip abductor weakness, this process alternates with each step, resulting in a waddling appearance. If the weakness is mild, the gait abnormality may only be present with running. The Trendelenburg gait most commonly occurs bilaterally, is reflective of proximal weakness, and is a common manifestation of muscular dystrophy [8]. In Duchenne muscular dystrophy (DMD), patients typically have associated gluteus maximus weakness, and they often must hyperextend the pelvis and trunk to maintain their balance [8, 10]. If a unilateral Trendelenburg gait pattern is seen, a focal neuropathy should be considered in the appropriate clinical context, including L5 radiculopathy or superior gluteal nerve injury [2].

The Steppage Gait involves an abnormality during the swing phase. Due to weakness of the foot dorsiflexors, patients have foot drop. In order to avoid tripping, they lift their knee higher to clear the floor and then the foot slaps down [2, 5]. This

is a common manifestation of peripheral neuropathies, especially the most common subtypes of CMT, as well as distal myopathies [4, 8].

Toe-walking can occur for a variety of reasons, both benign and pathological. Most commonly, toe-walking is idiopathic and is often seen intermittently in children without neurodevelopmental issues until 3 years-old [4]. These children can walk flat-footed with appropriate heel-strike when reminded and have full passive range of motion in the Achilles tendon when assessed. Prolonged toe-walking, regardless of cause, results in shortening of the Achilles tendon and tightness of the heel cords on examination [2]. If there are UMN signs on examination including lower limb spasticity, hyperreflexia, clonus or an upgoing plantar response then cerebral or spinal cord pathology should be considered [7]. This is often seen in spastic diplegic cerebral palsy; if severe, children also demonstrate a stiff, "scissor-like" walk. Spinal pathology can include tethered cord or malignancy. Due to the forward thrusting of the pelvis and relative strength of the gastrocnemius muscles to the peroneal muscles, patients with DMD preferentially walk on their toes. This can be differentiated from CP by the depressed deep tendon reflexes on examination in boys with DMD [5].

The Ataxic Gait is characterized by a wide-based, unsteady appearance where the patient has no apparent control over posture [3]. Ataxic gait can occur due to a lesion anywhere along the proprioceptive-cerebellar pathways and localization can be determined by associated symptoms and signs [5]. A sensory cause from peripheral nerve and/or dorsal column dysfunction is typically associated with a positive Romberg sign as well as decreased sensation of proprioception and vibration, and diminished Achilles reflexes. Patients often complain of worsening balance in the dark and with eye closure. Lesions of the vermis can be associated with head titubation and lesions of the cerebellar hemispheres can result in veering off to the affected side, as well as the presence of cerebellar signs on examination, including tremor and dysmetria [5]. In children, acute onset of ataxia is most commonly secondary to drug ingestion followed by postinfectious cerebellitis. Less commonly, abrupt onset of vertigo and ataxia can be associated with a migraine variant [5]. Posterior fossa tumors as well as genetic conditions such as the episodic ataxias, ataxia telangiectasia and Friedrich ataxia can cause ataxic gait.

Functional Gait Disorders, formerly called "psychogenic gait disorders" can be of the ataxic, spastic, dystonic, hemiparetic or generally weak subtypes [17]. A common diagnosis is "astasia abasia" which is literally defined as inability to stand and walk but is often applied to circumstances where the patient claims to be unable to stand or walk, yet the neurological examination and gait assessment confirms normal strength, sensation, reflexes, and balance. It is often noted that the exaggerated movements during the gait assessment take a high level of balance and coordination to maintain and are therefore inconsistent with the patient's complaints regarding weakness or balance. The hallmarks of functional disorders are inconsistency and incongruence [17]. Inconsistency in the severity of the gait abnormality with different tasks or in different situations is suggestive of a functional disorder. The presence of intact quadriceps strength is incongruent with an organic etiology for a "buckling" gait. Features that suggest that an abnormal gait may be functional

include abnormalities relieved with mental or conversational distractions, large variability in sway and movement, and marked fluctuation in occurrence of gait abnormalities. Patients with functional gait disorders rarely fall or sustain injury, and often demonstrate remarkable balance and strength in their attempts not to fall. It is not uncommon for true organic gait disorders to occur in tandem with functional gait disorders and therefore caution must be exercised before labeling a patient with a functional gait or movement disorder. Additionally, rarely such movements have been associated with cortical strokes in the deep gray matter, or frontal lobe tumors [17].

4 Evaluations

Additional evaluation will likely be warranted based on history and examination findings discussed above, with the type and extent of testing depending on the specific presentation.

Laboratory investigations are indicated when there is suspicion for an infectious, inflammatory or neoplastic process and should include a complete blood count (CBC) with manual differential, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and blood cultures [10]. Antinuclear antibody (ANA) and rheumatoid factor (RF) should be added if evaluating for an inflammatory etiology such as JIA [13]. If a neuromuscular etiology is suspected, in addition to CBC, ESR, CRP, RF and ANA, a creatine kinase (CK level), thyroid stimulating hormone (TSH) with T4, basic metabolic panel (BMP), and vitamin D level should be checked.

Routine radiographs of the affected extremity should be done if there is concern for trauma or injury. Hip radiographs should be included if leg length discrepancy, hip dysplasia, or subluxation are being considered as a diagnostic possibility [7].

If UMN signs are noted, particularly if in the setting of spasticity or focal weakness, neuroimaging studies, including MRI brain and spinal cord, should be ordered [5].

Further studies, including neurophysiological testing with nerve conduction studies and electromyography (NCS/EMG), muscle imaging and/or biopsy, and genetic testing may be required and is best facilitated by local neuromuscular expert [8].

5 When to Refer/Admit

If symptoms are acute, and in particular if associated with high fever, refusal to walk, new focal deficit or new UMN signs, further evaluation is needed emergently, and the child should be referred to the emergency department for expedited evaluation [10].

Gait alterations which should prompt orthopedic referral include persistent in-toeing or out-toeing beyond the expected ages, as well as concern for leg-length discrepancy and hip dysplasia [3, 4]. Referral to a rheumatologist should be considered in children with acute or chronic joint pain or swelling and particularly if there are associated constitutional symptoms such as low-grade fevers, fatigue, and weight loss [13].

Referral to a neurologist is recommended when the patient has objective signs of weakness on examination, developmental regression, spasticity, decreased or increased DTRs, abnormal motor movements, concerns for seizures, or altered mental status.

6 Treatment

Treatment is highly dependent on the underlying etiology of the gait abnormality. Most chronic gait abnormalities will benefit from a trial of physical therapy, particularly if there are deficits of strength, range of motion or function. Prolonged toe-walking may require serial casting and use of ankle foot orthosis (AFO), and if severe, botulinum toxin injections, or Achilles tendon tenotomy. Several neuromuscular disorders have ongoing trials or approved therapies for disease-specific interventions, such as gene therapy [8]. Rheumatological disorders may require immunosuppressants such as steroids. Of course, any infectious etiology is likely to require antibiotics and aspiration of the joint if septic joint is suspected [2, 3].

7 Prognosis

Prognosis depends on the cause of gait abnormality. Many orthopedic etiologies have good prognosis for near complete resolution, either spontaneously or with the assistance of bracing or surgical intervention. The prognosis of rheumatological and neuromuscular conditions is highly variable depending on the underlying etiology.

8 Clinical Pearls/Key Points

- Gait disorders are frequent in children and can be due to neurological, orthopedic, infectious, postinfectious, neoplastic, or psychiatric disorders.
- History is critical in creating the differential diagnosis, with important differentiating features being:
  - Acute versus chronic onset
  - Episodic versus constant symptoms

  - Provoking and palliative factors
  - Weakness in other areas of body
  - Functional limitations
  - Birth and developmental history

- Understanding mechanics of gait and identifying location of pathology via a thorough history and physical examination can help narrow the differential diagnosis.
- Important aspects of the physical examination in a child with gait disturbance include:

  - Careful examination of the legs, hips, knees, ankles, feet and spine
  - Careful observation of gait
  - Thorough neurological examination including assessment of strength, muscle tone, muscle bulk, deep tendon reflexes, and sensation

- Red flag signs or symptoms which should prompt immediate referral to the ED include acute gait changes particularly if associated with high fever, refusal to walk, new focal neurological deficit or new upper motor neuron signs.
- Depending on symptoms and signs, further testing may be warranted such as laboratory tests, imaging studies including radiographs, MRI of the brain and/or spinal cord, NCS/EMG, muscle biopsy, or genetic testing to establish the diagnosis.
- Treatment and prognosis of gait disturbance are highly variable and dependent on underlying etiology of gait dysfunction.

References

1. Sawyer J, Kapoor M. The limping child: a systemic approach to diagnosis. Am Fam Physician. 2009;79(3):215–24.
2. Zitelli B, McIntire S, Nowalk A. Atlas of pediatric physical diagnosis. 6th ed. Philadelpha, PA: Saunders Elsevier; 2012.
3. Kliegman RM, Behrman RE, Jenson HB, Stanton BF. Nelson textbook of pediatrics. 18th ed. Philadelphia, PA: Saunders Elsevier; 2007.
4. Foster H, Drummond P, Jandial S. Assessment of gait disorders in children. BMJ Best Practice. BMJ Publishing Group Ltd (BMJ). https://bestpractice.bmj.com/topics/en-gb/709. Reviewed April 16, 2021. Accessed April 28, 2021.
5. Fenichel DGM. Clinical pediatric neurology: a signs and symptoms approach. 7th ed. Philadelphia, PA: Saunders Elsevier; 2013.
6. Yeshokumar A. Gait disturbance as the presenting symptom in young children with anti-NMDA receptor encephalitis. Pediatrics. 2016;138(3):e20160901. Epub 2016 Aug 16
7. Griffin LY. Essentials of musculoskeletal care. 3rd ed. Rosemont, IL: The American Academy of Orthopedic Surgeons; 2005.
8. Menkes J, Sarnat H, Maria B. Child neurology. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.
9. Darras B, Jones R, Ryan M, Devivo D. Neuromuscular disorders of infancy, childhood and adolescence: a clinician's approach. 2nd ed. San Diego, CA: Academic Press; 2015.

10. Willacy H. Gait abnormalities in children. https://patient.info/doctor/gait-abnormalities-in-children#ref-1. Edited September 3, 2019. Accessed April 28, 2021.
11. Garbash M, et al. An unusual cause of limp. *BMJ Case Reports*. 2012. Published online April 4, 2012.
12. Stirnemann J, et al. A review of Gaucher disease pathophysiology, clinical presentation and treatments. Int J Mol Sci. 2017;18(2):441.
13. Foster HE, Jandial S. pGALS—paediatric gait arms legs and spine: a simple examination of the musculoskeletal system. Pediatr Rheumatol. 2013;11:44. https://doi.org/10.1186/1546-0096-11-44.
14. Kennedy R, Carroll K, McGinley J, Paterson K. Walking and weakness in children: a narrative review of gait and functional ambulation in paediatric neuromuscular disease. J Foot Ankle Res. 2020;13(10)
15. Shah A, Indra S, Kannikeshwaran N, et al. Diagnostic approach to limp in children. Pediatr Ann. 2015;44(12):548–50, 552–554, 556.
16. Rethlefsen S, Blumstein G, Kay R, Dorey F, Wren T. Prevalence of specific gait abnormalities in children with cerebral palsy revisited: influence of age, prior surgery, and gross motor function classification system level. Dev Med Child Neurol. 2017;59:79–88.
17. Nonnekes J, et al. Functional gait disorders: a sign based approach. Neurology. 2020;94:1093–9.

Child with Dizziness

Ross J. O'Shea and Jacob R. Brodsky

1 Introduction

Dizziness can cause much distress and reduced quality of life. Fortunately, most causes of dizziness in children are straightforward to diagnose and are effectively treatable. Thus, all physicians caring for children should gain a basic appreciation of the diagnosis and treatment of the most common causes of dizziness in children. Dizziness is a lay term that may refer to subjective sensations of imbalance, spinning of objects around oneself, spinning of self, rocking, or light headedness.

2 Etiology

Common causes of dizziness in children can be broadly classified into six categories: (1) Migraine, (2) Autonomic/cardiovascular, (3) Neurological, (4) Otological, (5) Ophthalmological, and/or (6) Psychological/developmental. The general prevalence of each category can be seen in (Fig. 1), while specific diagnoses within each category are individually discussed later in this chapter. Notably, a large proportion of children with dizziness may have multiple, inter-related causes of their symptoms [1].

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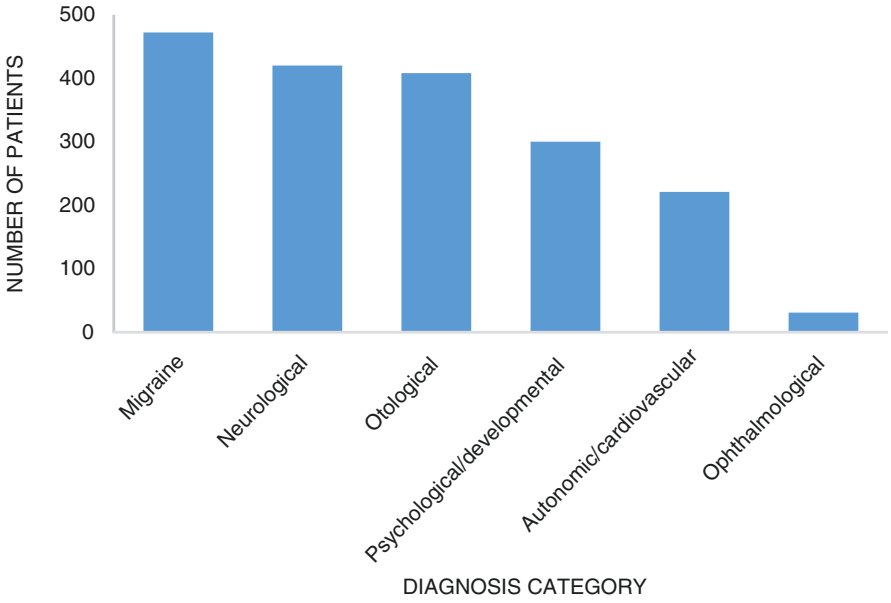

Fig. 1 Number of patients assigned diagnoses within each system category from retrospective study of 1021 pediatric patients seen at a pediatric vestibular program over a 7-year period for symptoms of dizziness and/or imbalance [1]. Note that total number of diagnoses assigned is greater than total number of patients, because more than half of patients were assigned more than one concurrent, inter-related diagnosis

3 Epidemiology

Dizziness and/or imbalance affect approximately 5.6% of the pediatric population in the United States, based on data from the 2016 National Health Interview Survey (NIHS) [2]. Balance concerns typically present in toddlers in the setting of gross motor delay, while the incidence of dizziness peaks in adolescents [1, 2].

4 Anatomy of the Vestibular System

Providers evaluating and treating dizziness should have a general understanding of the anatomy and physiology of the vestibular system, since many causes of pediatric dizziness are vestibular in origin. The vestibular system senses head motion to maintain stable vision and posture as the head moves through space. The sensory

component primarily consists of the vestibular organs in the inner ear (peripheral vestibular system) while processing, sensory integration, and output occur mostly in the brain (central vestibular system). The peripheral vestibular system consists of two otolith organs that detect linear movement—the utricle and saccule—and three semicircular canals (SCC) that detect angular movement—the anterior (aka, superior), lateral (aka, horizontal, and posterior (aka, inferior) canals [3, 4]. Each SCC is nearly perpendicular to the other two ipsilateral canals and is directly parallel to an opposite, paired canal of the contralateral labyrinth. Specifically, the left anterior canal is parallel to the right posterior canal (LARP plane), the right anterior canal is parallel to the left posterior canal (RALP plane), and the right and left lateral canals are parallel to each other. The vestibular nerves have a resting "tone" of depolarization in the absence of head movement. Head movement in a given canal plane (RALP, LARP, or lateral) triggers an excitatory response from the ipsilateral canal and an inhibitory response from the paired contralateral canal in that plane. This redundant pairing, i.e., excitatory response on one side coupled with an inhibitory response in the complementary canal, allows for compensation and recovery followed an acute, unilateral vestibular loss (VL). This push–pull phenomenon is also the primary source of many of the oculomotor phenomena that occur from unilateral VL, such as nystagmus and corrective saccades, as well as abnormalities on many vestibular tests, including calorics, rotary chair, and video head impulse testing.

The utricle and saccule contain small calcium carbonate crystals (otoliths) embedded in a gelatinous substance that covers the maculae [3, 4]. These otolith particles give the maculae a higher specific weight than the endolymph and its surrounding substance, allowing the otolith organs to primarily respond to gravitational movements of the head (primarily vertical for the saccule and horizontal for the utricle).

Afferent fibers from the utricle, superior, and lateral SCC's converge in the superior vestibular nerve, while fibers from the saccule and posterior canal converge in the inferior vestibular nerve. Primary afferent vestibular nerve fibers terminate in the vestibular nuclei in the floor of the fourth ventricle [3]. The vestibular nuclei also receive afferents from the cerebellum, spinal cord, superior colliculus and the cerebral cortex. Efferent connections from the vestibular nuclei result in a number of important vestibular reflexes: (1) The vestibulo-ocular reflex (VOR) stabilizes images on the retina during head movement by causing the eyes to move in the opposite direction as the head; (2) The vestibulo-spinal reflexes play a key role in maintaining upright posture by causing contraction of limb muscles; and (3) The vestibulo-colic reflexes support maintenance of upright head position, by acting on the neck muscles.

See Fig. 2 for important connections of the vestibular pathway.

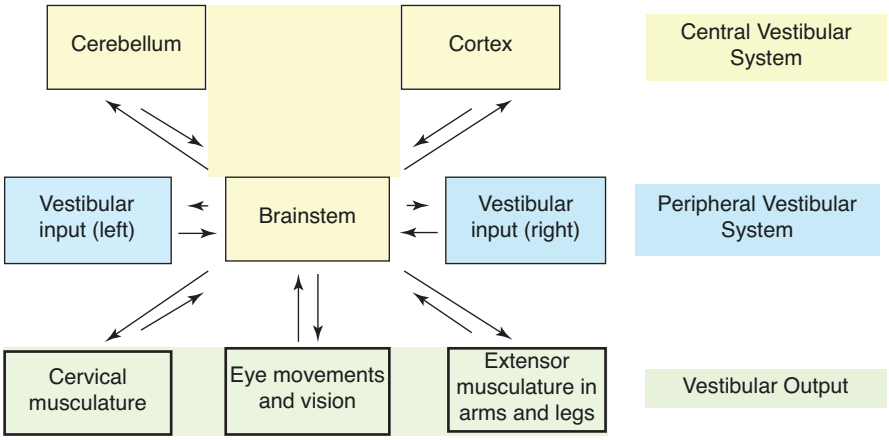

Fig. 2 Overview of the general components of the vestibular system

Table 1 Relative proportion of patients with most common diagnoses out of 1021 pediatric patients seen at a pediatric vestibular program over a 7-year period for symptoms of dizziness and/or imbalance [1]. Note that many patients had multiple, concurrent causative diagnoses, so percentages total to >100%. Percentages represent the proportion of patients out of the entire cohort with that diagnosis

Diagnosis	%
(**a**) Patients without preceding history of concussion (n = 757)	
Vestibular migraine	31.0%
Benign paroxysmal positional vertigo	19.9%
Primary dysautonomia	14.0%
Persistent postural perceptual dizziness	12.7%
Anxiety disorder	11.6%
Benign paroxysmal vertigo of childhood	7.7%
Vestibular neuritis	6.5%
Middle ear disease	5.5%
Global developmental delay	5.4%
(**b**) Patients with preceding history of concussion (n = 264)	
Vestibular migraine	46.2%
Benign paroxysmal positional vertigo	26.5%
Primary dysautonomia	20.5%
Anxiety disorder	18.9%
Persistent postural perceptual dizziness	6.8%

5 Differential Diagnosis

The relative prevalence of the most common individual causes of pediatric dizziness are shown in Table 1a, b based on a recent study of >1000 patients seen at the senior author's pediatric vestibular program [1]. Descriptions of the most common

disorders divided into general body systems is provided below. These diagnoses are not mutually exclusive, and many patients may have multiple, concurrent, interrelated, causative diagnoses. This list is not exhaustive, and other conditions may also need to be considered in some cases.

5.1 Migraine Variants

5.1.1 Vestibular Migraine (VM)

Multiple studies have shown vestibular migraine (VM) to be the most common cause of vertigo in children, accounting for 25%–31% of all pediatric cases of dizziness/imbalance [1, 5, 6]. The diagnostic criteria for VM from the International Classification of Headache Disorders, third Edition (ICHD-3) are summarized in (Table 2) [7]. Notably, concurrent headaches are not necessary for the diagnosis if other migrainous features (e.g., visual aura, photo/phonophobia, etc.) occur with the dizziness episodes. Current evidence suggests that VM is physiologically similar to other types of migraine, but includes stimulation of the central and/or peripheral vestibular system during episodes, primarily via the trigemino-vascular pathway [8]. Thus, patients with VM can develop interictal vestibular symptoms from concurrent peripheral VL, benign paroxysmal positional vertigo (BPPV), and/or persistent postural perceptual dizziness (PPPD), which are all described in subsequent sections.

VM can often be managed with lifestyle modifications that elevate a patient's threshold for triggering migraine flares and may include optimizing consistency and adequacy of sleep, hydration, diet, physical activity, and stress management. Identification and avoidance of food triggers can be high yield. Abortive pharmacological therapy for VM is mostly limited to the triptan medications [9]. A number of preventative medications have been studied in adult VM, though pediatric studies are limited. Those that have shown the highest rates of efficacy include

Table 2 Vestibular migraine—Diagnostic criteria (International Classification of Headache Disorders, third edition) [7]

1.	At least five episodes fulfilling criteria C and D
2.	A current or past history of migraine without aura or migraine with aura
3.	Vestibular symptoms of moderate or severe intensity, lasting between 5 minutes and 72 hours
4.	At least half of episodes are associated with at least one of the following three migrainous features: (a) Headache with at least two of the following four characteristics: • Unilateral location • Pulsating quality • Moderate or severe intensity • Aggravation by routine physical activity (b) Photophobia and phonophobia (c) Visual aura
5.	Not better accounted for by another ICHD-3 diagnosis or by another vestibular disorder.

amitriptyline, topiramate, propranolol, and verapamil [9, 10]. Cyproheptadine has been reported to be effective for nonvestibular migraine in children, though it has not been well studied in VM [11]. Doses of medications used for migraine variants are listed in the chapter on chronic headaches.

5.1.2 Benign Paroxysmal Vertigo of Childhood (BPVC)

BPVC causes periodic attacks of spinning vertigo without warning that resolve spontaneously [7]. Typical onset is between 4 and 8 years of age and episodes usually last only a few minutes [11]. The diagnostic criteria are outlined in (Table 3). Resolution is usually about 2 years after onset. Children with BPVC have an increased risk of developing migraine in adolescence or adulthood. Most patients do not require treatment, but cyproheptadine may be helpful in patients whose episodes are frequent or prolonged [11].

5.1.3 Benign Paroxysmal Torticollis of Childhood and Infancy (BPTI)

BPTI is characterized by recurrent episodes of head tilting. The diagnostic criteria are summarized in (Table 4) [7]. Episodes occur spontaneously and can last hours to days. Episodes typically start during the first year of life and resolve by 3–5 years of age [11]. All children with paroxysmal torticollis should undergo audiometry, since paroxysmal torticollis can also occur in children with enlarged vestibular aqueducts (EVA), which is a congenital condition associated with sensorineural hearing loss (SNHL) and vestibular dysfunction [12]. Treatment for BPTI is usually not needed, but cyproheptadine may be helpful when episodes are frequent or prolonged [11].

Table 3 Benign paroxysmal vertigo of childhood—Diagnostic criteria (International Classification of Headache Disorders, 3rd edition) [7]

1.	At least five attacks fulfilling criteria B and C
2.	Vertigo occurring without warning, maximal at onset and resolving spontaneously after minutes to hours without loss of consciousness
3.	At least one of the following five associated symptoms or signs: (a) Nystagmus (b) Ataxia (c) Vomiting (d) Pallor (e) Fearfulness
4.	Normal neurological examination and audiometric and vestibular functions between attacks
5.	Not attributed to another disorder.

Table 4 Benign paroxysmal torticollis of infancy—Diagnostic criteria (International Classification of Headache Disorders, 3rd edition) [7]

1.	Recurrent attacks in a young child, fulfilling criteria B and C
2.	Tilt of the head to either side, with or without slight rotation, remitting spontaneously after minutes to days
3.	At least one of the following five associated symptoms or signs: (a) Pallor (a) Irritability (a) Malaise (a) Vomiting (a) Ataxia
4.	Normal neurological examination between attacks
5.	Not attributed to another disorder

Table 5 Hemodynamic orthostatic dizziness—Diagnostic criteria [13]

A.	Five or more episodes of dizziness, unsteadiness or vertigo triggered by arising (change of body posture from lying to sitting/standing or sitting to standing), or present during upright position, which subsides by sitting or lying down
B.	Orthostatic hypotension, postural orthostatic tachycardia syndrome, or syncope documented on standing or during head-up tilt table test[a]
C.	Not better accounted for by another disease or disorder

[a]A diagnosis of "probable" hemodynamic orthostatic dizziness/vertigo should be made if criteria B is not met, but the patient meets criteria A and C while also reporting at least one of the following accompanying symptoms: generalized weakness/tiredness, difficulty thinking/concentrating, blurred vision, tachycardia/palpitations

5.2 Dysautonomia/Orthostatic Dizziness

Dysautonomia symptoms are episodic and typically presyncopal in character, including light-headed dizziness, tunnel vision, tachycardia, tinnitus, and/or cognitive changes. Hemodynamic orthostatic dizziness occurs when arising to sitting or standing (Table 5) [13]. It is particularly common in adolescents. Dysautonomia can also occur from many systemic conditions, including dehydration, malnutrition, infection, sleep deprivation, etc. Panic attacks should also be considered when autonomic episodes are not specifically triggered by position changes. Treatment of hemodynamic orthostatic dizziness includes optimizing hydration and increasing salt/electrolyte intake. Occasionally, medical management with fludrocortisone, midodrine, or beta blockers is warranted when conservative measures fail, though consultation with a cardiologist is recommended in those cases. Management of panic attacks may include cognitive behavioral therapy (CBT), biofeedback (BFB), and/or anxiolytics.

5.3 Neurological

5.3.1 Traumatic Brain Injury (TBI)/Concussion

Dizziness after concussion or after major TBI can occur from the impact of the injury on the brain itself and/or other conditions triggered by the head injury. An algorithm for the evaluation and management of post-concussive dizziness is pictured in (Fig. 3) and details on the specific causes outlined in the algorithm are summarized in other sections of this chapter [14].

5.3.2 Episodic Ataxia

The inherited ataxias are discussed in detail in a separate chapter in this book (Chap. 26). However, the episodic ataxias deserve special mention here since they can present in childhood or adolescence and cause dizziness and imbalance. The most common is Episodic ataxia, type 2 (EA-2), which causes episodes of ataxia, vertigo, and headache that can last from hours to days, making it difficult to differentiate from VM [15]. EA-2 is typically associated with mutations in the CACNA1A gene that can be identified on genetic testing [16]. Patients with EA-2, typically have interictal nystagmus (usually downbeating) and other central abnormalities on vestibular testing. Acetazolamide and 4-amino-pyridine are typically effective in reducing or eliminating EA-2 flares [17].

5.3.3 Posterior Fossa Anomalies

Posterior fossa lesions are fortunately a very rare cause of vertigo symptoms in children [1, 4, 6]. Chiari malformations are an incidental finding on as many as 2% of routine brain MRIs, but are rarely symptomatic. Imbalance is more common than vertigo with posterior fossa lesions, and additional neurological manifestations are ubiquitous, such as gaze palsies, motor weakness, papilledema, respiratory compromise, and/or vertical nystagmus. Symptomatic and/or malignant posterior fossa lesions typically warrant surgical excision, but conservative management is often warranted for benign lesions when symptoms are mild. A stroke in the vertebral/basilar artery territory can present with dizziness, in addition to other focal neurological deficits.

5.4 Otological

5.4.1 Middle-Ear Dysfunction

Chronic or recurrent otitis media (OM) is a common cause of balance impairment in young children, though the mechanism is unknown. Symptoms typically improve with tympanostomy tube placement [18], though vestibular rehabilitation (VR) may also be warranted when deficits persist.

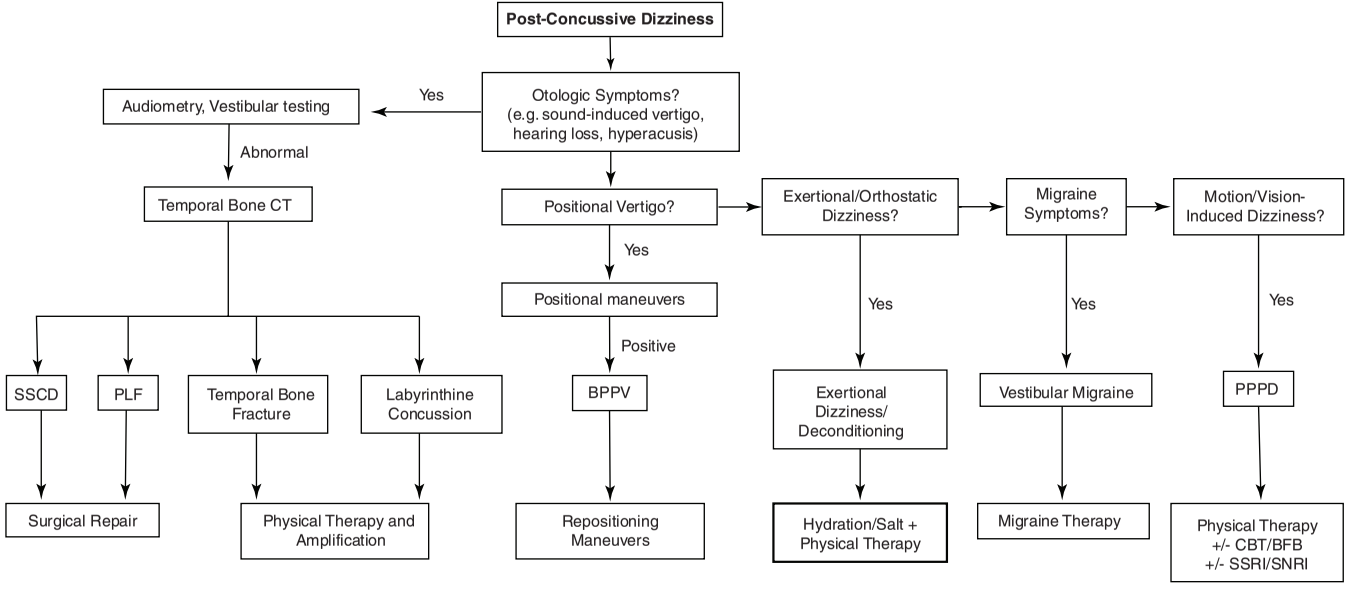

Fig. 3 Postconcussion dizziness algorithm—Adapted from Brodsky et al. 2018 [14]
Note that diagnoses are not mutually exclusive and more than one can be present concurrently in a single patient
CT computed tomography, *SSCD* superior semicircular canal dehiscence, *PLF* perilymphatic fistula, *BPPV* benign paroxysmal positional vertigo, *PPPD* persistent postural perceptual dizziness, *CBT* cognitive behavioral therapy, *BFB* biofeedback, *SSRI* serotonin reuptake inhibitor, *SNRI* serotonin norepinephrine reuptake inhibitor

5.4.2 Vestibular Neuritis/Labyrinthitis

Vestibular neuritis causes sudden, severe, room-spinning vertigo accompanied by ataxia and nausea/vomiting. The acute phase resolves after approximately a week followed by a recovery phase where central compensation takes place, characterized by milder disequilibrium and imbalance. Many patients also develop secondary BPPV and/or Persistent postural-perceptual dizziness (PPPD) (see sections below). Adolescents have a higher risk of prolonged recovery and residual symptoms relative to younger children [19]. The most well-accepted mechanism is a herpes simplex virus infection of the vestibular nerve(s) [20]. "Acute vestibulopathy" or "acute vestibular syndrome" are now the preferred terms for this phenomenon, given the still unclear etiology and the potential for an initial episode of VM or Ménière's disease to present similarly [21].

Acute labyrinthitis presents in a similar fashion, but also causes hearing loss (HL) that is often severe and permanent. Acute labyrinthitis can be serous/inflammatory or suppurative/infectious. It usually occurs as a complication of acute or chronic OM in children.

Early steroid administration has demonstrated benefit in adults with vestibular neuritis [22], and may be helpful in labyrinthitis, though studies in children are lacking. Urgent tympanostomy tube placement should be considered when labyrinthitis is related to OM. VR with a physical therapist is important to facilitate central compensation and symptomatic recovery in all patients with acute vestibular syndrome.

5.4.3 Cochleo-Vestibulopathy/Sensorineural Hearing Loss (SNHL)

Children with sensorineural hearing loss (SNHL) have a high prevalence of gross motor delay, imbalance, and vestibular dysfunction [23, 24]. Certain etiologies of congenital SNHL have higher rates of vestibular impairment, including meningitis, CHARGE syndrome, Usher syndrome, congenital cytomegalovirus (CMV) infection, enlarged vestibular aqueducts (EVA), Pendred, and Waardenberg syndrome [23]. Many of these conditions also impact vision, which further impairs balance. Many children with severe SNHL will undergo cochlear implantation, which can further impact vestibular function [25], though vestibular preservation after cochlear implantation is improving with current surgical approaches [26]. VR is recommended for all children with balance impairment in the setting of SNHL [24].

5.4.4 Benign Paroxysmal Positional Vertigo

BPPV is caused by the displacement of utricular otoconia into one or more of the SCCs. Benign paroxysmal positional vertigo (BPPV) may be present in as many as 1 in 5 pediatric dizziness patients without concussion and 1 in 4 with concussion [1,

14, 27]. Approximately 80% of pediatric BPPV occurs secondary to other inciting events (e.g., concussion, VM, etc.) [14, 27]. Diagnostic positional maneuvers are used to confirm the diagnosis (Figs. 4, 5, 6). Treatment of BPPV consists of canalith repositioning maneuvers of the head, which can be done in an office setting and vary depending on which canal(s) are involved, though details of these treatments are beyond the scope of this chapter.

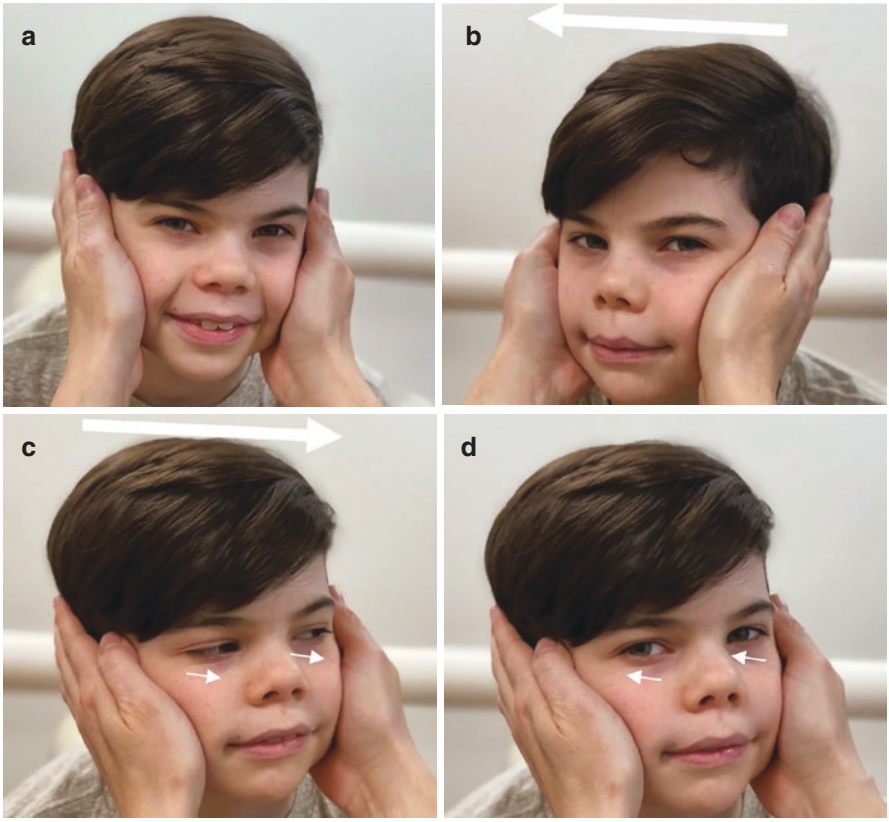

Fig. 4 The head impulse test: (**a**) The examiner holds the child's head with the chin tilted downward approximately 20 degrees below the horizontal plane. The patient is instructed to fix their gaze on the examiner's nose. For younger children a lighted toy or smartphone can be held by an assistant in front of the patient's face to attract their gaze. (**b**) The head is briskly rotated approximately 30 degrees to the right. The eyes remain fixed on the target indicating an intact lateral canal vestibulo-ocular reflex on that side (right). (**c**) The head is then briskly rotated approximately 30 degrees to the left. Movement of the eyes toward the side of head rotation followed by (**d**) a quick corrective saccade back to the target indicates an impaired lateral canal vestibulo-ocular reflex on that side (left)

Fig. 5 Dix–Hallpike maneuver: (**a**) Right-sided maneuver, first position—Patient is sitting with head turned 45 degrees to the right side; (**b**) Right-sided maneuver, second position—Patient is briskly brought into a position where the head is hanging approximately 45 degrees below the horizontal plane with the head still rotated approximately 45 degrees to the right side; (**c**) Left-sided maneuver, first position—Patient is sitting with head turned 45 degrees to the left side; (**d**) Left-sided maneuver, second position—Patient is briskly brought into a position where the head is hanging approximately 45 degrees below the horizontal plane with the head still rotated approximately 45 degrees to the left side

5.4.5 Superior Semicircular Canal Dehiscence (SSCD)

Superior semicircular canal dehiscence syndrome (SSCD) results from thinning of the bone between the superior SCC and the middle cranial fossa dura [28]. The proposed mechanism is a "third-window" effect, where the dehiscence creates a third entry point into the inner ear, in addition to the oval and round windows. In this situation, the SCC in the affected ear may be stimulated by sound (Tullio phenomenon) or pressure (Hennebert sign) causing vertigo and nystagmus around the axis of the affected superior SCC (ipsiversive, downbeat, torsional). This also amplifies

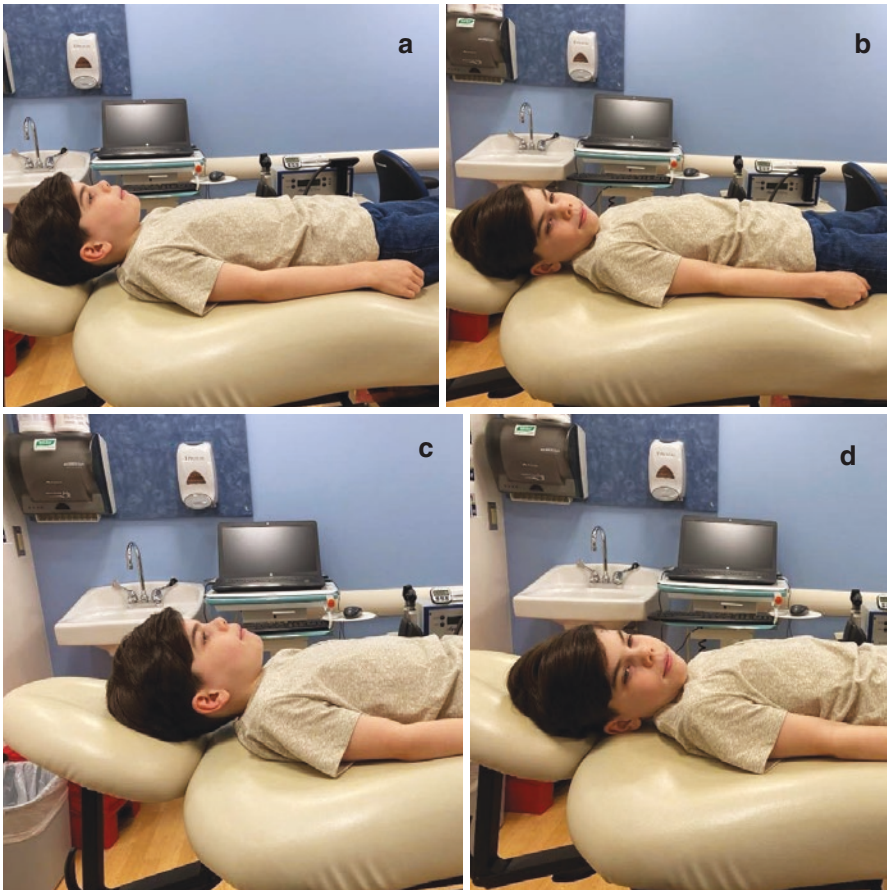

Fig. 6 Supine head-roll maneuver: (**a**) Right-sided maneuver, first position—Patient is lying supine with head elevated approximately 30 degrees above the horizontal plane; (**b**) Right-sided maneuver, second position—The head is rotated toward the right side; (**c**) Left-sided maneuver, first position—Patient is lying supine with head elevated approximately 30 degrees above the horizontal plane; (**d**) Left-sided maneuver, second position—The head is rotated toward the left side

perception of internal sounds (e.g., eye blinks, footsteps, etc.), which is called conductive hyperacusis. Diagnosis is confirmed by high-resolution, thin-cut temporal bone computed tomography (CT) with oblique reformats through the plane of the superior SCCs, as well as a low threshold and high amplitude ("third window") response pattern on cervical and/or ocular vestibular-evoked myogenic potential (VEMP) testing. Surgical management has a high success rate, though the optimal approach remains controversial [29].

6 Inner Ear Trauma

(i) Perilymphatic Fistula (PLF)

Leakage of perilymph can result from stapes footplate fracture, rupture of the round window membrane and/or disruption of the stapes annular ligament, usually from direct ear trauma. Hearing loss is typically seen (conductive, sensorineural, or mixed), but is not ubiquitous. Third window symptoms and VEMP findings similar to those seen with SSCD (see above section) are common [29]. Temporal bone CT can be helpful, but definitive diagnosis can only be made with surgical middle ear exploration. Most cases resolve spontaneously, but some require surgical repair.

(ii) Temporal Bone Fracture

Temporal bone fractures which involve the otic capsule can cause VL and HL. Diagnosis is made via temporal bone CT. The VL is managed with VR, and the HL is managed with amplification with hearing aids or cochlear implantation.

(iii) Labyrinthine Concussion

Labyrinthine concussion causes unilateral peripheral VL and SNHL following a head injury without visible fracture on temporal bone CT or evidence of perilymph fistula [14]. The mechanism is unknown. The VL and HL may be permanent, but can improve gradually over the weeks following the injury in some cases. Treatments are the same as described above for temporal bone fractures (VR, amplification).

7 Ophthalmological

Approximately 5% of children with vestibular symptoms have an associated optometric disorder [30]. Binocular vision disorders, such as convergence insufficiency and accommodative dysfunction, are especially common with concussion [31]. Ophthalmological disorders are also one of the most common causes of balance impairment in young children, and many causes of congenital SNHL and VL are also associated with ophthalmologic conditions [4]. Any child with balance impairment of unclear etiology should be evaluated by an ophthalmologist/optometrist. Treatments may include prescription lenses, prism lenses, and/or vision therapy.

8 Functional/Psychological

Chronic/recurrent dizziness raises baseline sympathetic tone triggering anxiety symptoms in most patients, even in the absence of a preexisting anxiety disorder. Thus, dizziness should not be attributed entirely to anxiety without an adequate work-up. Conversely, treatment of chronic dizziness without addressing the concurrent anxiety symptoms will rarely be successful.

8.1 Persistent Postural-Perceptual Dizziness

Persistent postural-perceptual dizziness is a functional neurological disorder (FND) causing chronic and recurrent dizziness with perceived unsteadiness/imbalance [32]. Approximately 1 in 10 pediatric patients with vestibular symptoms have PPPD [1]. PPPD is a recently developed umbrella term encapsulating multiple vestibular FND's that previously went by other names, including chronic subjective dizziness, phobic postural vertigo, space motion discomfort, and visual vertigo. The diagnostic criteria are summarized in (Table 6). Dizziness is either described as constant or present for >50% of the time along with frequent flares. Symptoms are typically provoked by standing, visual flow, loud noises, crowds, and large, open spaces. Patients typically feel like they are going to fall, but rarely do. The condition is triggered by an initial dizziness episode of vestibular, neurological or psychiatric origin, which evolves into continued involuntary over-utilization of reflexive postural control strategies and a disproportionate overdependence on visual stimuli to maintain balance, even when visual cues are unreliable. These are exacerbated by maladaptive cognitive processes. Premorbid anxiety and high neuroticism personality types are risk factors for developing the condition. An inciting vestibular condition may still be present concurrently at the time of diagnosis (e.g., BPPV, VM, etc.). Treatment includes VR, CBT, and selective serotonin reuptake inhibitor (SSRI) therapy [32]. Recovery is typically gradual over several months with treatment.

Table 6 Persistent postural perceptual dizziness—Diagnostic criteria [47]

1.	One or more symptoms of dizziness, unsteadiness, or non-spinning vertigo are present on most days for 3 months or more. (a) Symptoms last for prolonged (hours long) periods of time, but may wax and wane in severity. (b) Symptoms need not be present continuously throughout the entire day.
2.	Persistent symptoms occur without specific provocation, but are exacerbated by three factors: (a) Upright posture (b) Active or passive motion without regard to direction or position (c) Exposure to moving visual stimuli or complex visual patterns
3.	The disorder is precipitated by conditions that cause vertigo, unsteadiness, dizziness, or problems with balance including acute, episodic, or chronic vestibular syndromes, other neurologic or medical illnesses, or psychological distress. (a) When the precipitant is an acute or episodic condition, symptoms settle into the pattern of criterion A as the precipitant resolves, but they may occur intermittently at first, and then consolidate into a persistent course. (b) When the precipitant is a chronic syndrome, symptoms may develop slowly at first and worsen gradually.
4.	Symptoms cause significant distress or functional impairment.
5.	Symptoms are not better accounted for by another disease or disorder.

8.2 Panic Disorder

Panic attacks cause lightheaded dizziness and/or true vertigo, typically with tunnel vision, tinnitus, tachypnea, tachycardia, paresthesias, and an impending sense of doom. A tendency toward recurrent panic attacks is classified as panic disorder [33]. Other causes of vertigo can trigger panic attacks, so the presence of panic attacks does not rule out a concurrent vestibular condition. Treatment may include CBT/BFB, SSRIs, beta blockers, and/or benzodiazepines.

9 Diagnostic Approach

A thorough, systematic history and physical examination may be challenging in young children, but they are paramount to reaching an accurate diagnosis and effective treatment plan. An intake questionnaire and the aid of an assistant are often helpful.

10 History

A distinction should be made between dizziness and imbalance, as these symptoms do not necessarily occur concurrently in the pediatric population [2]. In young children with imbalance, the medical history should focus on any otologic, ophthalmologic, or neurologic issues, as well as a careful assessment of motor milestones.

Dizziness should be characterized by asking the patient to describe the sensation without the word "dizziness," when age appropriate, along with recounting any associated symptoms. Lightheadedness, particularly if accompanied by tunnel vision, tinnitus, confusion, and/or paresthesias, suggests dysautonomia, orthostatic dizziness, or panic attacks. Room-spinning vertigo suggests a migraine disorder, BPPV, or acute vestibular syndrome (vestibular neuritis/labyrinthitis). Dysequilibrium, rocking/swaying, and/or motion sensitivity are typical of PPPD and VM. Associated symptoms of headache, photophobia, phonophobia, and/or visual aura suggest migraine.

Episode duration and triggers are also important clues. Episodes lasting seconds to minutes that are triggered by position changes suggest dysautonomia/orthostasis or BPPV. Episodes lasting hours suggest VM, particularly if triggered by stress, weather changes, poor sleep, or particular foods. Episodes lasting for days suggest acute vestibular syndrome. Chronic symptoms with flares triggered by standing and visual flow suggest PPPD.

11 Physical Examination

Young children's behavior, gait, and coordination can be observed while obtaining the history. Otoscopy and a full neurological exam should be conducted. Specialized vestibular assessments are tailored to age and cooperation. In addition to the Romberg test, the single leg stance with eyes closed is a particularly high yield evaluation of balance impairment, particularly in children with SNHL [34]. The head impulse test (Fig. 4) is a highly sensitive and specific bedside test to evaluate for peripheral VL [35]. Spontaneous nystagmus should be assessed. Gaze-evoked nystagmus should be evaluated with gaze only about 30 degrees in each direction to prevent confusion from the normal few beats of nystagmus that can often be seen with extreme gaze deviation. Frenzel lenses magnify the eyes and suppress the patient's vision, which aids in visualization of nystagmus, particularly when peripheral in origin. Nystagmus direction is named by its fast phase. Peripheral nystagmus is typically unidirectional, often torsional, suppressed by visual fixation, and enhanced with gaze toward the side of the fast phase. Central nystagmus is often vertical, switches direction with gaze, and is present with and without visual fixation.

Positional diagnostic maneuvers are used for diagnosing BPPV and involve moving the head briskly through the plane of each individual SCC and maintaining the head/body in the gravity-dependent position of each canal for 30–60 s. The diagnostic positional maneuvers are summarized in Table 7. All positional maneuvers should be included in the examination of pediatric patients with dizziness, as children and adolescents are more prone than adults to involvement of the lateral and superior SCCs and of multiple canals, simultaneously. If vertigo and characteristic nystagmus (Table 7) are detected with a particular maneuver, then that indicates BPPV affecting that SCC. See Figs. 5, 6, and 7 for pictorial depiction of these maneuvers.

Table 7 Diagnostic positional maneuvers and characteristic nystagmus patterns for benign paroxysmal positional vertigo of each semicircular canal

Semicircular canal	Posterior canal	Lateral canal	Superior canal
Maneuver(s)	Dix–Hallpike	Supine head roll	Dix–Hallpike and/or midline head hang
Vertical component	Upbeating	None	Downbeating
Horizontal component[a]	Geotropic	Geotropic or apogeotropic	Geotropic or apogeotropic
Torsion[b]	Present	Absent	Sometimes present
Other features	Latency of 10–30 s before onset; fatigues after 1–2 min	May have dizziness and nystagmus with head roll to both sides	Increased dizziness when returning to sitting position

[a]Geotropic nystagmus refers to the fast phase moving toward the downward ear/ground. Apogeotropic nystagmus refers to the fast phase moving toward the upward ear/ceiling
[b]Torsion refers to a twisting motion of the eye around the axis of the stimulated semicircular canal

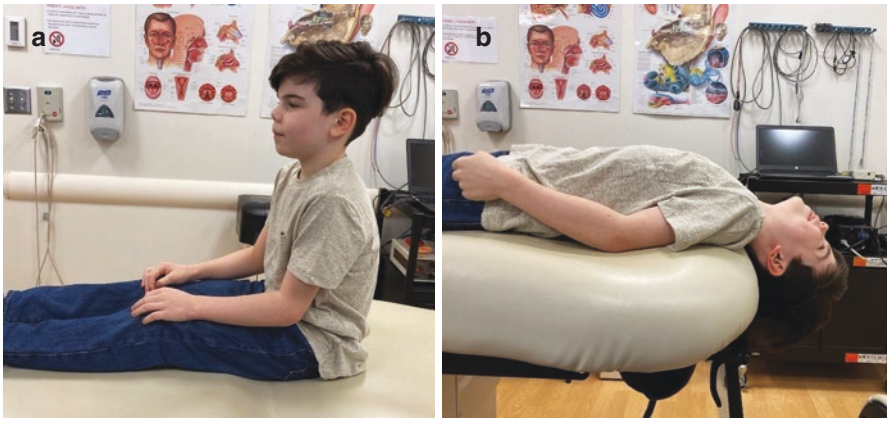

Fig. 7 Midline head-hang maneuver: (**a**) First position—Patient is seated upright with head facing forward; (**b**) Second position—Patient is brought briskly into the supine position with head extended to approximately 90 degrees below the horizontal plane

Table 8 Summary of vestibular tests, organs/functions tested, and appropriate ages for each test. Listed age ranges for each test are those used at the senior author's pediatric testing center, but are likely to vary widely between different testing centers. Note that adult vestibular centers may not be willing or able to test young children

Test	Organ/function tested	Age
Videonystagmography (VNG)	Oculomotor function, nystagmus, BPPV	>6 months
Calorics	Lateral semicircular canal function	>10 years
Rotary chair	Lateral semicircular canal function	>6 months
Video head impulse test (VHIT)	Lateral, posterior, and superior semicircular canal function	>4 years[a]
Vestibular-evoked myogenic potential (VEMP)	Saccule and inferior vestibular nerve (cervical VEMP) Utricle and superior vestibular nerve (ocular VEMP)	Any age[b]
Subjective visual vertical (SVV)	Utricle	>6 years
Computerized dynamic posturography (CDP)	Balance	>4 years

BPPV benign paroxysmal positional vertigo
[a]Posterior and superior canals often cannot be reliably tested until at least 7 years old
[b]Cervical VEMP can be reliably tested in infants, but ocular VEMP cannot be reliably performed until about 3 years of age

12 Testing

Some children will require specialized vestibular testing to confirm a suspected diagnosis (Table 8). Some adult vestibular centers will test adolescents and older children, but very young children may need to be evaluated at a dedicated pediatric vestibular program.

12.1 Audiometry

Audiometry should be obtained in all children with balance impairment, due to its frequent association with OM or congenital SNHL. However, dizziness in older children is rarely associated with hearing loss, so audiometry may not be needed unless specific otologic symptoms are present.

12.2 Videonystagmography (VNG)

Videonystagmography (VNG) goggles (Fig. 8) include infrared cameras that track and record eye movements with and without visual fixation via high-resolution video images and computer-generated tracings of eye movements over time. The VNG test battery includes evaluation of spontaneous and gaze-evoked nystagmus (with and without fixation), smooth pursuits, saccades, and optokinetic nystagmus. Positional testing for BPPV is also frequently included. Caloric testing is included in adults, but is avoided in children when possible, as it is difficult to tolerate. Bithermal, binaural caloric testing involves the successive administration of warm and then cold water to each ear canal inducing characteristic nystagmus patterns with each irrigation that are recorded with VNG to determine if there is a unilateral weakness "reduced vestibular response" of the lateral SCC on either side (score >20 or >25%, depending on the lab) [36].

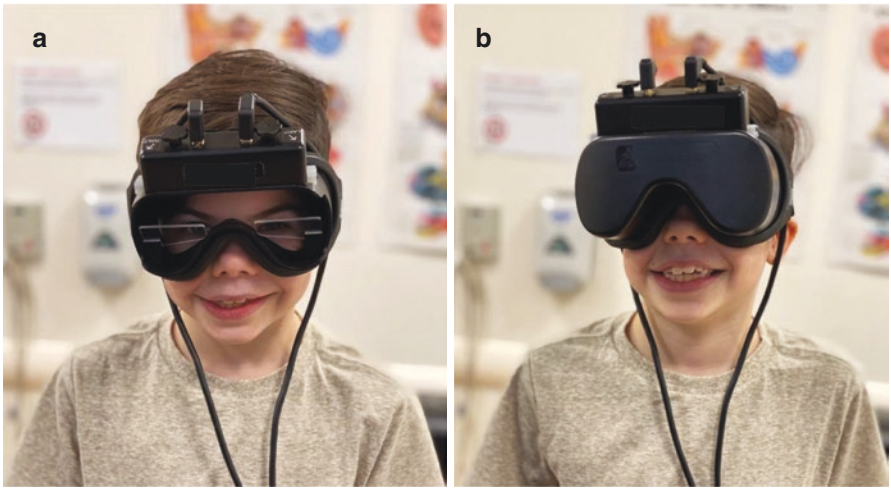

Fig. 8 Videonystagmography (VNG) goggles: (**a**) With cover removed; (**b**) With cover in place

12.3 Rotatory Chair

Rotatory chair evaluates the VOR response of the lateral SCC by applying stimuli of angular acceleration with the patient secured in a rotational chair in a dark room or cylindrical enclosure (Fig. 9). VOR characteristics (gain, phase lead, time constant, asymmetry) are assessed with VNG goggles and compared to age-adjusted normative values. A chair-mounted high-resolution, infrared camera can be used in children who are too small for VNG goggles, and young children can be tested in their parent's lap. Rotatory chair testing also assesses only the lateral SCC but has the advantages over caloric testing of effectively diagnosing bilateral vestibular loss, assessing a broader range of frequencies, and being better tolerated in children.

12.4 Video Head Impulse Test (VHIT)

The video head impulse test (VHIT) uses lightweight VNG goggles with an accelerometer to quantify VOR gain and corrective saccades [37]. It has the advantages over calorics and rotary chair of evaluating all six semi-circular canals individually, testing the VOR at more natural head velocities, and being much better tolerated in children. However, it has a low sensitivity for milder or well-compensated VL [38].

Fig. 9 Rotary chair (enclosure type)

12.5 Vestibular-Evoked Myogenic Potentials (VEMP)

Vestibular-evoked myogenic potential (VEMP) testing uses electromyography to detect a reflexive response at either the sternocleidomastoid muscle (cervical or cVEMP) or the inferior oblique muscle (ocular or oVEMP) following otolithic end-organ stimulation via air or bone conducted sound stimuli administered via a probe in the ipsilateral ear. cVEMPs are predominantly conducted via the saccule and inferior vestibular nerve and oVEMPs are predominantly conducted via the utricle and superior vestibular nerve [39, 40]. VEMP is also helpful in diagnosing third window conditions, such as SSCD (see above section).

12.6 Subjective Visual Vertical (SVV)

Subjective visual vertical (SVV) testing requires the patient to reposition a line in darkness to what they perceive to be the true vertical. Deviation of the perceived vertical >2 degrees toward one side of the true vertical is considered to be indicative of ipsilateral utricular impairment [41]. The test can be conducted with a hemispheric dome, a rotary chair enclosure, or a smartphone [41, 42].

12.7 Computerized Dynamic Posturography

This test evaluates balance in multiple conditions using a force plate to sense positional sway compared to age-specific norms. The sensory organization test includes an analysis of the relative contributions of vestibular, visual, and somatosensory inputs to maintaining balance.

13 Treatment/Management

A general summary of each treatment category is outlined below, while specific treatments for particular conditions are described under each respective disorder in the differential diagnosis section above. A multimodal treatment approach is often necessary.

13.1 Vestibular Rehabilitation (VR)

VR is administered by a specially trained physical or occupational therapist. The cornerstone of VR is to facilitate central compensation for VL, though many other approaches are also frequently employed (Table 9), depending on the condition(s)

Table 9 Common vestibular rehabilitation approaches. This list is not exhaustive and many more approaches exist, but these are general categories of those most commonly used for patients with vestibular disorders. A combination of these techniques is often employed for a single patient and should be tailored to their specific condition(s) and deficit(s)

Technique	Indications	Description
Adaptive/ compensatory	Peripheral vestibular loss (e.g., acute vestibular syndrome, vestibular migraine, congenital hearing loss, etc.)	Facilitates central compensation for unilateral peripheral vestibular loss and strengthens weakened existing vestibular reflexes
Habituative	PPPD	Gradually and systematically increases tolerance to triggers (movements, positions, visual flow)
Substitutive	Bilateral, severe peripheral vestibular loss	Strengthens reliance on non-vestibular cues (vision, proprioception) to maintain balance
Reconditioning	Postconcussive dizziness; PPPD	Increases strength/endurance and tolerance of physical activity
Repositioning maneuvers	BPPV	Repositions displaces canalith particles
Vision therapy	Binocular vision disorders (e.g., convergence insufficiency; accommodative dysfunction)	Retrains eyes to coordinate together more effectively

PPPD persistent postural perceptual dizziness, *BPPV* benign paroxysmal positional vertigo

being treated, and the approach should be tailored to the specific patient's condition(s) and level of functioning.

13.2 Medication

Vestibular suppressant and antinausea medications (e.g., meclizine, hydroxyzine, scopolamine, odansetron, metoclopramide, promethazine, benzodiazepines, etc.) can be used for acute vertigo, but should be minimized in patients with acute vestibular syndrome once nausea/vomiting has resolved, as they may inhibit compensation [43]. Medications are a core component of VM management in many patients, as described in further detail in the VM section earlier in this chapter.

13.3 Surgery

The need for surgical intervention for pediatric vestibular disorders is rare. Vestibular conditions in children that may benefit from surgical intervention are chronic/recurrent OM, traumatic PLF, SSCD, Chiari malformations, posterior fossa lesions, and treatment-resistant BPPV, as described in the relevant sections above.

13.4 Cognitive Behavioral Therapy (CBT)/Biofeedback

CBT is a form of talk therapy administered by a specially trained mental health provider involving multiple approaches to modifying a patient's maladaptive thought and behavior patterns that impact the way that the brain and body respond to stressful stimuli (both emotional and physical). CBT is often a key component of treatment for PPPD and panic disorder [44], and is also often effective in the management of migraine disorders [45]. Biofeedback uses specialized equipment to train the patient to directly modulate their physical responses to stress (e.g., heart rate, breathing, carbon dioxide level, etc.) using CBT techniques. Biofeedback may enhance the treatment of PPPD and VM, though further study is needed.

13.5 Alternative Therapies

Trigger avoidance and "migraine hygiene" are important strategies for VM prevention. Many alternative and complementary therapies are used for vestibular disorders, though further study of their efficacy is needed, particularly in children. These include supplements (e.g., magnesium, riboflavin, etc.), acupuncture, craniosacral therapy, massage therapy, chiropractic treatments, and others.

14 Prognosis/Outcomes

14.1 Recovery with Age

BPTI and BPVC typically resolve by 3 and 7 years of age, respectively, though both are associated with an increased risk of migraine in later life. OM often resolves by about 2–3 years of age, unless other factors are present (e.g., adenoid hypertrophy, allergic rhinitis, etc.). Orthostatic dizziness often resolves after adolescence.

14.2 Recovery with Compensation/Rehabilitation

Symptoms of acute vestibular syndrome will typically resolve within a few weeks, especially with effective VR, though associated hearing loss may not fully recover, and secondary conditions such as BPPV and PPPD can develop. The majority of patients with concussion will fully recover within <3 weeks, but approximately 12%–30% of patients will have a prolonged recovery [14], which results from multiple interrelated factors that vary between patients and warrant a multimodal treatment approach.

14.3 Recovery with Treatment

The symptoms of SSCD and PLF typically resolve after surgical intervention [29], though SNHL from PLF can be permanent. BPPV typically resolves entirely after effective treatment maneuvers, though many patients will have recurrences [27].

14.4 Chronic Conditions

VM is considered to be a chronic condition in adults, though VM in childhood or adolescence may improve or resolve in adulthood in many patients. Bilateral vestibulopathy (e.g., Usher, CMV, meningitis, aminoglycoside toxicity, etc.) can have significant impacts on children that can be lifelong, including impaired balance, limited gross motor skills, and oscillopsia, usually in conjunction with bilateral hearing loss. Recovery from PPPD varies widely and symptoms can last anywhere from weeks to years, even after initiating treatment [32]. Further study is direly needed to develop more effective treatment strategies and prognostic indicators in this challenging condition.

15 When to Refer/Admit

Referral to a vestibular specialist should be considered based on the managing provider's comfort level with determining an appropriate diagnosis and treatment plan for a child with vestibular symptoms. Referrals to specialized providers may be necessary to initiate treatments beyond medications, including VR, CBT/BFB, or surgery. A useful resource for finding vestibular specialists in North America is the provider search engine on the website for the Vestibular Disorder Association (VEDA: www.vestibular.org). Worrisome signs that should prompt an urgent work-up and/or hospital admission in a patient with dizziness or imbalance, include sudden HL, speech changes, unilateral muscle weakness, seizures, or severe nausea/vomiting resulting in dehydration.

16 Prevention

Migraine hygiene and trigger avoidance can be effective for preventing VM flares. Orthostatic dizziness can be minimized by consistent hydration and a moderate increase in salt/electrolyte intake. Vitamin D supplementation can be helpful in preventing BPPV recurrence [46]. Sports-related concussions can be avoided by use of appropriate protective equipment, minimizing high-risk sports activities in younger

children (particularly tackling in American football and heading the ball in soccer), and even from avoiding contact sports, altogether. Prevention of PPPD has not yet been well studied, but earlier initiation of effective VR and appropriate counseling/education for patients with dizziness may help to minimize the development of this condition.

17 Clinical Pearls/Key Points

- The vestibular system senses motion via the peripheral vestibular organs in the inner ears to maintain stable vision and posture during movements of the head and body.
- Multiple causes of dizziness can occur concurrently in one patient.
- Vestibular migraine disorders are the most common cause of dizziness in the pediatric age group.
- Acute vestibulopathy causes sudden, severe vertigo for several days followed by weeks of disequilibrium.
- BPPV is a common cause of pediatric vertigo that usually resolves with office-based repositioning maneuvers, but is frequently overlooked.
- Congenital SNHL is often associated with vestibular dysfunction and imbalance.
- Vestibular testing is feasible and sometimes helpful in evaluating dizziness in children, though most causes are determined by a careful history and physical examination.
- Urgent referral/admission should be considered if dizziness or imbalance are accompanied by sudden HL, speech changes, unilateral muscle weakness, seizures, or severe nausea/vomiting resulting in dehydration.

References

1. Wang A, Zhou G, Lipson S, Kawai K, Corcoran M, Brodsky JR. Multifactorial characteristics of pediatric dizziness and imbalance. Laryngoscope. 2020; https://doi.org/10.1002/lary.29024.
2. Brodsky JR, Lipson S, Bhattacharyya N. Prevalence of pediatric dizziness and imbalance in the United States. Otolaryngol Head Neck Surg. 2020;162(2):241–7. https://doi.org/10.1177/0194599819887375.
3. Cummings CW. Cummings otolaryngology head & neck surgery. 4th ed. Philadelphia, PA: Elsevier Mosby; 2005.
4. O'Reilly R, Morlet T, Brodsky JR, Cushing SL. Manual of pediatric balance disorders. 2nd ed. San Diego, CA: Plural Publishing, Inc.; 2020.
5. O'Reilly RC, Greywoode J, Morlet T, Miller F, Henley J, Church C, et al. Comprehensive vestibular and balance testing in the dizzy pediatric population. Otolaryngol Head Neck Surg. 2011;144(2):142–8. https://doi.org/10.1177/0194599810393679.
6. Wiener-Vacher SR. Vestibular disorders in children. Int J Audiol. 2008;47(9):578–83. https://doi.org/10.1080/14992020802334358.

7. Headache classification Committee of the International Headache Society (IHS) the international classification of headache disorders, 3rd edition. Cephalalgia. 2018;38(1):1–211. https://doi.org/10.1177/0333102417738202.
8. Lempert T, von Brevern M. Vestibular migraine. Neurol Clin. 2019;37(4):695–706. https://doi.org/10.1016/j.ncl.2019.06.003.
9. Brodsky JR, Cusick BA, Zhou G. Evaluation and management of vestibular migraine in children: experience from a pediatric vestibular clinic. Eur J Paediatr Neurol. 2016;20(1):85–92. https://doi.org/10.1016/j.ejpn.2015.09.011.
10. Byun YJ, Levy DA, Nguyen SA, Brennan E, Rizk HG. Treatment of vestibular migraine: a systematic review and meta-analysis. Laryngoscope. 2021;131(1):186–94. https://doi.org/10.1002/lary.28546.
11. Brodsky J, Kaur K, Shoshany T, Lipson S, Zhou G. Benign paroxysmal migraine variants of infancy and childhood: transitions and clinical features. Eur J Paediatr Neurol. 2018;22(4):667–73. https://doi.org/10.1016/j.ejpn.2018.03.008.
12. Brodsky JR, Kaur K, Shoshany T, Manganella J, Barrett D, Kawai K, et al. Torticollis in children with enlarged vestibular aqueducts. Int J Pediatr Otorhinolaryngol. 2020;131:109862. https://doi.org/10.1016/j.ijporl.2020.109862.
13. Kim HA, Bisdorff A, Bronstein AM, Lempert T, Rossi-Izquierdo M, Staab JP, et al. Hemodynamic orthostatic dizziness/vertigo: diagnostic criteria. J Vestib Res. 2019;29(2–3):45–56. https://doi.org/10.3233/VES-190655.
14. Brodsky JR, Shoshany TN, Lipson S, Zhou G. Peripheral vestibular disorders in children and adolescents with concussion. Otolaryngol Head Neck Surg. 2018;159(2):365–70. https://doi.org/10.1177/0194599818770618.
15. Beh SC. Vestibular migraine: how to Sort it out and what to do about it. J Neuroophthalmol. 2019;39(2):208–19. https://doi.org/10.1097/wno.0000000000000791.
16. Choi KD, Choi JH. Episodic ataxias: clinical and genetic features. J Mov Disord. 2016;9(3):129–35. https://doi.org/10.14802/jmd.16028.
17. Zwergal A, Strupp M, Brandt T. Advances in pharmacotherapy of vestibular and ocular motor disorders. Expert Opin Pharmacother. 2019;20(10):1267–76. https://doi.org/10.1080/14656566.2019.1610386.
18. Cohen MS, Mandel EM, Furman JM, Sparto PJ, Casselbrant ML. Tympanostomy tube placement and vestibular function in children. Otolaryngol Head Neck Surg. 2011;145(4):666–72. https://doi.org/10.1177/0194599811412038.
19. Brodsky JR, Cusick BA, Zhou G. Vestibular neuritis in children and adolescents: clinical features and recovery. Int J Pediatr Otorhinolaryngol. 2016;83:104–8. https://doi.org/10.1016/j.ijporl.2016.01.027.
20. Le TN, Westerberg BD, Lea J. Vestibular neuritis: recent advances in etiology, diagnostic evaluation, and treatment. Adv Otorhinolaryngol. 2019;82:87–92. https://doi.org/10.1159/000490275.
21. Kerber KA. Acute vestibular syndrome. Semin Neurol. 2020;40(1):59–66. https://doi.org/10.1055/s-0039-3402739.
22. Karlberg ML, Magnusson M. Treatment of acute vestibular neuronitis with glucocorticoids. Otol Neurotol. 2011;32(7):1140–3. https://doi.org/10.1097/MAO.0b013e3182267e24.
23. Cushing SL, Gordon KA, Rutka JA, James AL, Papsin BC. Vestibular end-organ dysfunction in children with sensorineural hearing loss and cochlear implants: an expanded cohort and etiologic assessment. Otol Neurotol. 2013;34(3):422–8. https://doi.org/10.1097/MAO.0b013e31827b4ba0.
24. Rine RM, Braswell J, Fisher D, Joyce K, Kalar K, Shaffer M. Improvement of motor development and postural control following intervention in children with sensorineural hearing loss and vestibular impairment. Int J Pediatr Otorhinolaryngol. 2004;68(9):1141–8. https://doi.org/10.1016/j.ijporl.2004.04.007.
25. De Kegel A, Maes L, Van Waelvelde H, Dhooge I. Examining the impact of cochlear implantation on the early gross motor development of children with a hearing loss. Ear Hear. 2015;36(3):e113–21. https://doi.org/10.1097/AUD.0000000000000133.

26. Jang JH, Kim H, Choo OS, Park HY, Choung YH. Changes in vestibular symptoms and function after cochlear implantation: relevant factors and correlations with residual hearing. Clin Exp Otorhinolaryngol. 2020; https://doi.org/10.21053/ceo.2019.01851.
27. Brodsky JR, Lipson S, Wilber J, Zhou G. Benign paroxysmal positional vertigo (BPPV) in children and adolescents: clinical features and response to therapy in 110 Pediatric patients. Otol Neurotol. 2018;39(3):344–50. https://doi.org/10.1097/MAO.0000000000001673.
28. Minor LB, Solomon D, Zinreich JS, Zee DS. Sound- and/or pressure-induced vertigo due to bone dehiscence of the superior semicircular canal. Arch Otolaryngol Head Neck Surg. 1998;124(3):249–58. https://doi.org/10.1001/archotol.124.3.249.
29. Weinreich HM, Carey JP. Perilymphatic fistulas and superior semi-circular canal dehiscence syndrome. Adv Otorhinolaryngol. 2019;82:93–100. https://doi.org/10.1159/000490276.
30. Anoh-Tanon MJ, Bremond-Gignac D, Wiener-Vacher SR. Vertigo is an underestimated symptom of ocular disorders: dizzy children do not always need MRI. Pediatr Neurol. 2000;23(1):49–53. https://doi.org/10.1016/s0887-8994(00)00140-5.
31. Raghuram A, Cotter SA, Gowrisankaran S, Kanji J, Howell DR, Meehan WP 3rd, et al. Postconcussion: receded near point of convergence is not diagnostic of convergence insufficiency. Am J Ophthalmol. 2019;206:235–44. https://doi.org/10.1016/j.ajo.2019.04.008.
32. Popkirov S, Staab JP, Stone J. Persistent postural-perceptual dizziness (PPPD): a common, characteristic and treatable cause of chronic dizziness. Pract Neurol. 2018;18(1):5–13. https://doi.org/10.1136/practneurol-2017-001809.
33. Locke AB, Kirst N, Shultz CG. Diagnosis and management of generalized anxiety disorder and panic disorder in adults. Am Fam Physician. 2015;91(9):617–24.
34. Oyewumi M, Wolter NE, Heon E, Gordon KA, Papsin BC, Cushing SL. Using balance function to screen for vestibular impairment in children with sensorineural hearing loss and cochlear implants. Otol Neurotol. 2016;37(7):926–32. https://doi.org/10.1097/MAO.0000000000001046.
35. Lehnen N, Aw ST, Todd MJ, Halmagyi GM. Head impulse test reveals residual semicircular canal function after vestibular neurectomy. Neurology. 2004;62(12):2294–6. https://doi.org/10.1212/wnl.62.12.2294.
36. Jongkees LB. Caloric examination of the balance organ. Ned Tijdschr Geneeskd. 1948;92(10):742–5.
37. Hamilton SS, Zhou G, Brodsky JR. Video head impulse testing (VHIT) in the pediatric population. Int J Pediatr Otorhinolaryngol. 2015;79(8):1283–7. https://doi.org/10.1016/j.ijporl.2015.05.033.
38. Altunay ZO, Ozkarakas H. Comparison of the efficacy of video head impulse and bithermal caloric tests in vertigo. Ear Nose Throat J. 2020:145561320962597. https://doi.org/10.1177/0145561320962597.
39. Govender S, Dennis DL, Colebatch JG. Vestibular evoked myogenic potentials (VEMPs) evoked by air- and bone-conducted stimuli in vestibular neuritis. Clin Neurophysiol. 2015;126(10):2004–13. https://doi.org/10.1016/j.clinph.2014.12.029.
40. Zhou G, Dargie J, Dornan B, Whittemore K. Clinical uses of cervical vestibular-evoked myogenic potential testing in pediatric patients. Medicine (Baltimore). 2014;93(4):e37. https://doi.org/10.1097/MD.0000000000000037.
41. Brodsky JR, Cusick BA, Kenna MA, Zhou G. Subjective visual vertical testing in children and adolescents. Laryngoscope. 2016;126(3):727–31. https://doi.org/10.1002/lary.25389.
42. Brodsky JR, Cusick BA, Kawai K, Kenna M, Zhou G. Peripheral vestibular loss detected in pediatric patients using a smartphone-based test of the subjective visual vertical. Int J Pediatr Otorhinolaryngol. 2015;79(12):2094–8. https://doi.org/10.1016/j.ijporl.2015.09.020.
43. Walker MF. Treatment of vestibular neuritis. Curr Treat Options Neurol. 2009;11(1):41–5. https://doi.org/10.1007/s11940-009-0006-8.
44. Freidl EK, Stroeh OM, Elkins RM, Steinberg E, Albano AM, Rynn M. Assessment and treatment of anxiety among children and adolescents. Focus (Am Psychiatr Publ). 2017;15(2):144–56. https://doi.org/10.1176/appi.focus.20160047.

45. Nahman-Averbuch H, Schneider VJ 2nd, Chamberlin LA, Kroon Van Diest AM, Peugh JL, Lee GR, et al. Identification of neural and psychophysical predictors of headache reduction after cognitive behavioral therapy in adolescents with migraine. Pain. 2020; https://doi.org/10.1097/j.pain.0000000000002029.
46. Jeong SH, Lee SU, Kim JS. Prevention of recurrent benign paroxysmal positional vertigo with vitamin D supplementation: a meta-analysis. J Neurol. 2020; https://doi.org/10.1007/s00415-020-09952-8.
47. Staab JP, Eckhardt-Henn A, Horii A, Jacob R, Strupp M, Brandt T, et al. Diagnostic criteria for persistent postural-perceptual dizziness (PPPD): consensus document of the committee for the classification of vestibular disorders of the Bárány society. J Vestib Res. 2017;27(4):191–208. https://doi.org/10.3233/ves-170622.

Cerebral Palsy

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1 Introduction

Cerebral palsy (CP) is the most common motor disability in childhood, representing a broad clinical spectrum with diverse etiologies. Although often pictured as a severe disability, in fact, most children (56%) with CP will walk independently and have normal cognitive functions [1]. While genetic etiologies are increasingly being discovered, a CP diagnosis is as important as ever, connecting affected children to invaluable resources, allowing families of children with CP to find a community of other families, and empowering providers to appropriately treat children with similar clinical needs. CP is defined as:

> "A *group of permanent disorders of the development of movement and posture, causing limitation of activity, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior, by epilepsy, and by secondary musculoskeletal problems*." [2]

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Notes about the definition:

1. *Cerebral palsy is a clinical description and not an etiology.* CP is a diagnosis that describes the observed phenotype, independent of etiology. Furthermore, a child diagnosed with CP deserves additional investigation for the underlying etiology.
2. *Cerebral palsy is a permanent disability.* A child with a motor disability that resolves later in life or a child whose motor abnormalities do not impair function does not have cerebral palsy.
3. *Cerebral palsy is due to a non-progressive brain process; however, the physical manifestations are not static.* Progressive orthopedic complications occur in children with CP and spasticity and dystonia can worsen at times of illness, stress, or growth. Furthermore, one-third of people with cerebral palsy will lose some motor function in their adulthood with peak mobility typically occurring in their late teens [3].

1.1 Classification

The severity of CP is commonly classified in children aged 2 years and older using the Gross Motor Function Classification System (GMFCS), grouping children into one of five levels of severity [4, 5]:

Level I: Walks independently without limitations
Level II: Walks independently with limitations
Level III: Walks using a handheld mobility device (a walker)
Level IV: Self-mobility with limitations; may use powered mobility
Level V: Fully dependent for all mobility

Establishing the GMFCS level helps guide interventions, screening, and referrals. The GMFCS level should not significantly change during childhood.

CP is further classified by the predominant motor type as spastic (85%), dyskinetic (including dystonia and chorea), and ataxic [6], with spasticity classified by distribution, i.e., unilateral (hemiplegia) and bilateral including diplegia (in which the legs are more involved than the arms) and quadriplegia. However, children with CP rarely present with a pure motor phenotype, with dystonia present in up to 75% of children classified as the predominant spastic-type [7].

1.2 Comorbid Conditions

Comorbidities of CP may include epilepsy (35%), orthopedic complications, intellectual disability (49%), autism, disordered sleep (23%), behavioral problems (26%), psychiatric disorders, scoliosis, pain (75%), feeding disorders (50%),

communication disorders (80%; 23% no spoken words), sialorrhea (22%), vision impairment (11% blind), hearing loss (4% severe), and bowel and bladder dysfunction (24%) [8–11]. Pain and sleep problems are often underrecognized in individuals with CP but have a significant impact on their quality of life.

2 Epidemiology and Economic Impact

CP affects an estimated 2–3/1000 live births in the United States and 1–5/1000 live births worldwide [12–14]. The most important risk factor for CP is prematurity, with the risk markedly increasing among those with birth weight <1500 g or gestational age <32 weeks [15]. The prevalence of CP in children with a birth weight of 1000 g or less is 56.6/1000, whereas the prevalence is 1.3/1000 in those with a birth weight of more than 2500 g [15]. Furthermore, the prevalence of CP in babies born before 28 weeks of gestational age is 82/1000, whereas the prevalence is 1.4/1000 in babies born after 36 weeks of gestational age [15, 16]. Historically, there appears to be a declining incidence in CP over time, and this may be attributable to a decreasing incidence among those born prematurely [16]. Boys, those belonging to a lower socioeconomic status, and Black children are at higher risk of CP [17, 18]. As the leading cause of motor disabilities in children, CP bears a marked and increasing economic impact. The medical costs for children with CP are 10 times higher than those for children without CP [19], with estimated costs approaching one million per person with CP in their lifetime [20]. Caring for children with cerebral palsy also has direct financial and emotional impacts on families [21–24].

3 Etiology

Cerebral palsy is due to a disturbance in the developing fetal or infant brain. It is unclear when the brain stops developing, though many practitioners set 2 years as the age beyond which a brain insult does not result in a cerebral palsy diagnosis. The abnormality may be acquired through infection, trauma, hypoxic-ischemic encephalopathy (HIE), intraparenchymal hemorrhage, or stroke. Hypoxic-ischemic encephalopathy is the etiology of only about 5–10% of CP cases. Perinatal stroke represents the most common cause of hemiplegic CP, and prematurity is the most common risk factor for the development of CP overall. However, only half of the children with CP have known risk factors [25]. The etiology of CP is genetic in 14–35% of individuals [26, 27]. Therefore, an underlying genetic etiology does not preclude a diagnosis of CP. Please see the section below for examples of genetic conditions that include CP as a phenotypic feature.

4 Differential Diagnosis

When considering whether a child with disordered motor development has cerebral palsy, the following diagnostic categories should be distinguished (Fig. 1):

- *Cerebral palsy with a genetic etiology*: An example of this would be a person with non-progressive spastic quadriplegia and seizures due to diffuse pachygyria and subcortical band heterotopias from a pathological *KIF2A* mutation.
- *Progressive motor disability with a genetic etiology*: Examples of this include disorders such as Rett syndrome and leukodystrophies. The term "cerebral palsy mimic" is a disorder that may initially meet the clinical criteria for cerebral palsy but subsequently declares itself as a progressive condition.
- *Motor disabilities not of cerebral origin*: Motor disabilities due to spinal cord injuries, neuromuscular disorders, or musculoskeletal abnormalities fall under this category.

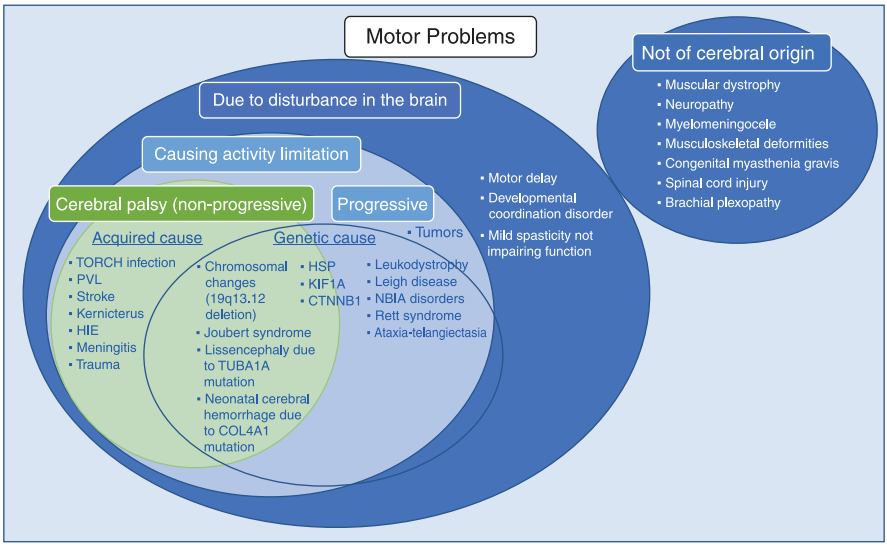

Fig. 1 Cerebral palsy causes, mimics, and differential diagnosis. Cerebral palsy falls under the broad umbrella of motor problems, specifically due to a non-progressive brain disturbance, and is associated with activity limitation. Examples are provided of motor disorders that are not of cerebral origin, do not cause activity limitation, or have a progressive clinical course. Furthermore, genetic conditions may meet the criteria for cerebral palsy if they do not prove to be progressive. Classifying the motor phenotype of some genetic conditions as progressive or non-progressive may be controversial (e.g., HSP, KIF1A, CTNNB1). *CTNNB* catenin (cadherin-associated protein), beta 1, *HIE* hypoxic-ischemic encephalopathy, *HSP* hereditary spastic paraplegia, *K1F1A* kinesin family member 1A, *NBIA* neurodegeneration with brain iron accumulation, *PVL* periventricular leukomalacia

5 Diagnostic Approach

It is important to make a diagnosis of cerebral palsy as early as possible. Historically, a delayed diagnosis of cerebral palsy was common and even believed to be necessary for accuracy. However, a landmark meta-analysis by Novak et al. demonstrated that specialized examination tools (the Prechtl General Movements Assessment or the Hammersmith Infant Neurological Examination) combined with brain magnetic resonance imaging (MRI) abnormalities allow for a diagnosis of cerebral palsy or "high-risk cerebral palsy" in early infancy before 6 months of age [28, 29]. An early and accurate diagnosis of CP enables access to targeted therapy services, which are believed to be disease-modifying, resulting in improved outcomes [28]. Furthermore, caregivers prefer that the diagnosis be made as early as possible [30]. A diagnosis of cerebral palsy provides access to a large community of people who share this diagnosis and can provide emotional and experiential support [28].

Cerebral palsy is a clinical diagnosis based on history and physical examination, which are used to establish the presence of a persistent, non-progressive motor disability of cerebral origin. If the child is old enough, then the cerebral palsy is classified by motor phenotype, distribution, and function (e.g., GMFCS). The child is then assessed for common comorbidities. Once the "what" question has been answered, the "why" question remains, and an evaluation of the etiology is planned (see "Diagnostics"). The diagnosis must be compassionately and accurately conveyed to the patient/family. The practitioner must be prepared to answer questions about the prognosis and resources, refer for therapies and subspecialty care if needed, or refer to a provider with expertise in the evaluation and care of children with cerebral palsy.

6 History

6.1 The Young Child with a Motor Problem

In a child presenting with a motor problem, the clinician aims to establish whether risk factors or clear etiology are evident from history and to clarify the severity, trajectory, and phenotype of the motor problem.

6.1.1 Pregnancy and Birth

Information should be ascertained about complications or maternal illnesses during pregnancy, gestational age, and complications at delivery. Characterization of the neonatal intensive care unit course should include results of brain imaging, need for respiratory support, or other complications.

6.1.2 Developmental History

In general, a child exhibiting developmental skills at less than 50% of what is generally expected at a specified age (for example, an 8-month-old who is not yet rolling or a 12-month-old who is not yet sitting) has a motor disorder, not a delay. However, some children with cerebral palsy have mild delays or may even be meeting motor milestones. For example, a child with unilateral cerebral palsy may not have motor delays, but early symmetry may be noted. Historical factors inconsistent with cerebral palsy would be a period of early normal development followed by a lack of developmental progress, or regression, or significant fluctuation in symptoms (see Sect. 9.6.2). The developmental history also helps establish a GMFCS level, which guides interventions, screening, and referrals and shapes discussions regarding motor prognosis.

6.1.3 Characteristics of the Motor Abnormalities

Parents may note difficulty with head control in a child with more severe cerebral palsy or an early (under 18 months) hand preference suggesting hemiplegic cerebral palsy. In older infants or toddlers, hypertonicity becomes more apparent and parents may note that the child is "always tight," arches frequently, tends to push their feet down, or stand on their toes. Parents may detect behaviors indicative of retained primitive reflexes, observing that the child continues to startle easily. Caregivers may observe characteristics of dystonia: increased tone triggered with movement or stress, or the disappearance of high tone when the child sleeps.

6.1.4 Other Historical Clues

An infant with more severe cerebral palsy will typically also have other medical and developmental concerns such as poor feeding/failure to thrive, constipation, reflux, irritability, poor sleep, cognitive/language delay, and strabismus or concerns about visual behavior.

6.1.5 Family History

A family history of cerebral palsy or other neurodevelopmental disorders could suggest a genetic etiology or a motor disorder other than cerebral palsy.

7 Physical Examination

7.1 General Examination

General examination may provide helpful information. Dysmorphic features may suggest a genetic etiology. The head circumference is an important clue. As brain growth drives skull growth, children with cerebral palsy due to an acquired injury tend to have microcephaly that is stable. Positional plagiocephaly may be significant due to axial hypotonia, lack of mobility, and retained primitive reflexes (asymmetric tonic neck reflex). Macrocephaly may suggest hydrocephalus or a genetic cause. Birth marks may indicate a neurocutaneous condition (e.g., incontinentia pigmenti).

7.2 Neuromotor Examination

7.2.1 Unilateral CP

The most common cause of hemiplegic cerebral palsy is neonatal stroke, and all children with a complete middle cerebral artery (MCA) territory infarction will develop hemiplegic cerebral palsy [31]. Neonates with stroke commonly present with seizures (though many go unrecognized in the neonatal period and such children may present later with hemiplegia or epilepsy) but may otherwise look perfectly well, which may result in false optimism about motor outcome. This occurs because the cortical spinal tract, which allows volitional motor movements, is not yet active, and movements are governed by deeper brain structures. At 4–6 months of age when volitional movements begin, a hand preference becomes apparent. The infant will reach preferentially with one hand even when reaching for objects on the opposite side of the body. On observation, the child will often show decreased spontaneous movements and fisting of the hand on the affected side. There may be subtle increases in tone as well, though this can be difficult to assess in an infant. The practitioner may utilize emergence of postural reflexes to assess for asymmetry: asymmetric lateral propping reflex and parachute reflexes are particularly helpful. Supportive evidence may come from demonstration of a visual field deficit (bringing an object into the periphery of vision and noting decreased responsiveness on the affected side) or neglect (zero or minimal attempt to use the affected side due to being "unaware" of that side). Clonus and brisk deep tendon reflexes are likely to be noted on the affected side.

7.2.2 Bilateral CP

Axial hypotonia is a common early finding in young infants with CP and tends to persist in later infancy as appendicular hypertonicity and/or movement abnormalities become more apparent. Spasticity may be more obvious after 1 year of age.

Spasticity is evaluated by moving a limb slowly, then quickly, and finding increased resistance, often in the form of a "catch" with fast movement. Children with CP have decreased selective motor control, with less dexterity in hand movements, such as grasping and releasing, and sometimes patterned/stereotyped leg movements. Early dystonic features may include increases in tone with activities such as reaching, involuntary mouth opening, persistence of primitive reflexes (e.g., asymmetric tonic reflex present after 4–6 months), persistent torticollis, or the presence of opisthotonos. In general, persistent primitive reflexes and/or delayed emergence of postural reflexes are important clues supporting a diagnosis of CP.

8 Diagnostics

Cerebral palsy is a clinical diagnosis that does not require any diagnostic evaluation for confirmation. An MRI is recommended as the first step to evaluate the etiology of cerebral palsy [32]. The timing of imaging depends on the child. If the child cannot stay still for an MRI but has a clear history suggestive of an acquired injury that matches the child's clinical phenotype, then one might delay obtaining the MRI until that child is old enough to tolerate it without sedation, and the quality of imaging is better (anatomical details are better seen on an MRI performed after 2 years of age when myelination is more mature). Further diagnostic evaluations beyond a brain MRI, will include genetic and metabolic evaluations and, in some cases, cerebrospinal fluid analysis. Therefore, if there is any mismatch between the child's perinatal history, pattern of brain injury, and clinical phenotype, then that child should be referred to a specialist for further diagnostic workup and for evaluation of the etiology of cerebral palsy (see Sect. 9.6.2).

9 Treatment/Management

The primary care physician plays a critical role in medical homes for children with cerebral palsy. This involves working with the family to establish and re-evaluate goals, make appropriate referrals for subspecialists and rehabilitation supports, advocate for appropriate educational needs in coordination with schools, and transition planning. The primary care physician should routinely screen for common comorbid conditions such as feeding and communication disorders, seizures, and hearing and vision impairment, with careful attention to sleep and pain, which are often underassessed in people with cerebral palsy and can have significant effects on their behavior and quality of life. It may be helpful for the primary care physician to anticipate the need for longer visits with more complex patients with cerebral palsy and to maintain a form or checklist of needs and associated medical problems, which is updated at each visit [33]. Table 1 summarizes the broad categories of care of children with cerebral palsy by age.

Table 1 Summary of care of children with cerebral palsy by age

	0–1 Years	1–2 Years	2–5 Years	5–10 Years	10–20 Years
Orthopedic	Parental education, anticipatory guidance	Ankle foot orthotic use Stander/gait trainer if non-ambulatory	Begin hip surveillance	Hip surveillance Monitor contractures, scoliosis Orthopedic surgery needed for some	Monitor contractures, scoliosis Orthopedic surgery needed for some
Motor function and therapy	Therapies focused on parents' education CIMT if unilateral	Developing mobility, fine motor function CIMT if unilateral	Developing mobility, fine motor function CIMT if unilateral	Self-care, maintain mobility	Independence, maintain mobility
Spasticity and dystonia	Parental education	Consider baclofen if severe	Medications, botulinum toxin injection[a]	Medications, botulinum toxin injection[a] Consider baclofen pump for severe spasticity, SDR for diplegia, DBS for dystonia	
Vision/hearing	Complete ophthalmology and audiology evaluations	Repeat audiology and ophthalmology evaluations as indicated by the initial screening			
Feeding and nutrition	Assess dysphagia, monitor weight, intervene as needed				
Sleep	Regularly assess. Consider sleep study if snoring or frequent awakenings				
Pain	Regularly assess, evaluate etiology				
Fracture prevention	Vitamin D supplementation, weight-bearing activities (e.g., regular standing/gait training)				
Communication	Parental education	Begin speech therapy, introduce AAC	Heavy focus on communication, AAC systems explored	Consistency of communication supports school/home	Maintain communication supports

(continued)

Table 1 (continued)

	0–1 Years	1–2 Years	2–5 Years	5–10 Years	10–20 Years
School	Home-based supports	Home-based supports	Cognitive evaluation, establish IEP goal of least restrictive environment	Continue IEP Goal of least restrictive environment	Continue IEP Post-high school planning
Mental health	Monitor, treat irritability	Monitor, treat irritability	Screen/address behavioral concerns	Screen for and treat psychiatric problems with attention to anxiety and depression	
Transition					Transition planning[b] Consider conservatorship

AAC augmentative and alternative communication, *CIMT* constraint-induced movement therapy, *DBS* deep brain stimulation, *IEP* individualized education plan, *SDR* selective dorsal rhizotomy

[a]Treat only if interfering with comfort or function

[b]Begin discussion at age 12–14 years

Table 2 Framework for approach to treatment of cerebral palsy

WHO's International Classification of Functioning, Disability and Health	The "F-words" in childhood disability	Interpretation
Body structure and function	Fitness	How children stay physically active
Activity	Function	What people do—Job, task, school, or play
Participation	Friends	Social interactions
Environmental factors	Family	The essential environment
Personal factors	Fun	Enjoyable activities
	Future	Expectations for the future

As a framework for the management of disability, the WHO Classification of Functioning, Disability and Health summarizes the "F-words" in childhood disability.

Treatment of CP should be understood using the World Health Organization (WHO)'s International Classification of Functioning, Disability and Health (ICF) framework, which highlights the importance of an individual's function in their environment [34]. This concept is encapsulated by the "F-words" in childhood disability, which can be used to communicate with families, highlight strengths, and personalize interventions (Table 2) [35].

The practitioner should always consider a patient's goals when customizing treatment approach. For example, a child with cerebral palsy who does no weight-bearing activities will not improve their function and participation by undergoing a surgical procedure to correct contracture at their ankle. Similarly, a child with cervical dystonia might undergo botulinum toxin injections if the dystonia is uncomfortable or specifically impairs their ability to use their head switch for communication. Children with more severe motor disabilities often have multiple associated problems and warrant multidisciplinary team care.

9.1 Motor Development and Function

There is a limited window of time for children to achieve motor skills, as children with cerebral palsy achieve 90–95% of their gross motor skills before 5–6 years of age. To optimize outcomes, cerebral palsy-specific early intervention is critical and should be initiated as soon as a child is identified as being at risk for cerebral palsy [28]. Orthotics/bracing may be used to improve arm function or gait kinematics. Children with hemiplegic (unilateral) cerebral palsy should be referred for constraint-induced movement therapy (CIMT), in which the unaffected limb is constrained for periods of time to improve the function of the affected limb [36]. There is continued benefit from therapy services throughout adolescence and adulthood to help maintain function and prevent orthopedic complications and pain.

9.2 Orthopedic Complications and Management

Children with cerebral palsy are at risk for orthopedic complications that require surveillance. In general, the higher the GMFCS level, the greater is the risk of orthopedic complications.

Hip displacement and dislocation: Spasticity drives a gradual displacement of the femoral head outside of the acetabulum in some children with cerebral palsy, especially those who are non-ambulatory. This may be clinically occult when amenable to surgical correction and, then later, is painful in about 50% of cases, at a time when surgical intervention may be more challenging. Hip surveillance starts by the age of 2 years with examination and measurement of the migration index on hip X-rays [37–39].

Contracture/torsional deformity: Formation of contractures is common and can occur at any joint that has not established a sufficient range of motion. Contractures may be prevented by bracing, such as with ankle foot orthoses (AFOs), and a mobility program. Once a contracture has developed, casting may treat a distal joint with a mild contracture, but, for proximal joints or more severe contractures, orthopedic surgery may be considered. Bony rotational abnormalities can also develop over time. Multilevel orthopedic surgery is sometimes pursued to address these issues within the same surgery [40]. In ambulatory children, gait analysis can additionally help identify the gait kinematic features that contribute the most to functional impairment.

Scoliosis: Fixed spine curvature may develop later in childhood or in adolescence, typically in children with GMFCS IV or V cerebral palsy and can severely impact mobility and motor functions. Surgical intervention is undertaken in children with large curves (40–50°) and/or curves impacting their health and quality of life, with careful considerations of the risks for the particular patient.

Fractures: Children with cerebral palsy are at a risk for low bone density and fractures. Risk factors include non-ambulatory status, dysphagia, vitamin D deficiency, low weight, and epilepsy. Practitioners should ensure that children with cerebral palsy have adequate vitamin D and calcium intake, which often requires supplementation. Emphasis should also be placed on a mobility program with daily weight-bearing activities such as using a standing frame. In children who have had a low-impact fracture, it is reasonable to refer to an endocrinologist for consideration of bisphosphonate therapy [41].

9.3 Tone and Movement Abnormalities

In general, tone and movement abnormalities may be treated if bothersome, such as interfering with function, causing discomfort, impacting hygiene, or making it difficult to care for the child. Children often have multiple abnormalities in tone and/or movement, which may add complexity to treatment. Furthermore, treatment

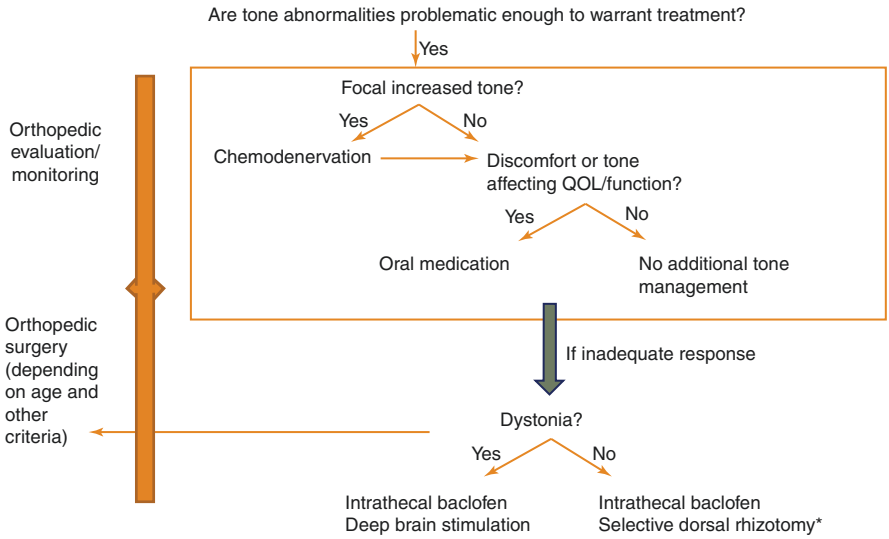

Fig. 2 Approach to management of muscle tone. An approach to the management of increased muscle tone in children with cerebral palsy. Tone should be treated if problematic, and the type of treatment depends on whether the tone abnormality is focal or generalized. Orthopedic care should be integrated. *QOL* quality of life

success is variable and is associated with some risks. A child with more complex movement abnormalities warrants subspecialty care with neurology or physiatry. Figure 2 outlines a treatment approach to spasticity and dystonia.

Spasticity: Spasticity causing discomfort can be treated with oral medications such as baclofen. Other medication options include tizanidine, benzodiazepines, or dantrolene. Oral medications are infrequently needed under the age of 2. Focal spasticity may be treated with botulinum toxin injections, which are Food and Drug Administration (FDA)-approved for children 2 years and older [42]. Children of adequate size who have not responded to more conservative measures may be treated with surgical options such as intrathecal baclofen therapy, via use of an implanted baclofen pump, or selective dorsal rhizotomy (SDR), a surgical procedure indicated for children with GMFCS I–III spastic diplegic cerebral palsy [43] and as a palliative measure for some non-ambulatory patients [44, 45].

Dystonia: If dystonia is problematic, then oral medications (baclofen, benzodiazepines, clonidine, gabapentin) or botulinum toxin injections may be tried, though data are lacking [46]. In more severe cases, intrathecal baclofen therapy with catheter placement at the cervical level may be considered off-label [47]. Finally, deep brain stimulation (DBS) typically targeting the globus pallidus is growing in use, though data are limited [48]. The American Academy for Cerebral Palsy and Developmental Medicine (AACPDM) provides a useful care pathway [49].

Tone/movement exacerbation and status dystonicus: Children with hypertonicity or hyperkinetic movements, particularly those with dystonia, may experience exacerbations during periods of rapid growth or provoked by illness, pain, stress, medical factors such as constipation, or mood changes such as anxiety, sometimes requiring admission. These children should be evaluated for triggers such as infection, medication side effects, occult fracture or dislocation, gastrointestinal process (constipation), or other sources of pain (menstruation, headache, irritation from feeding tube). Serum creatine kinase (CK) should be checked to monitor for associated rhabdomyolysis, and children may need inpatient management with benzodiazepines, clonidine, gabapentin, and intravenous sedation [49, 50].

Chorea: Chorea can be challenging to treat, and data are limited. Retrospective data support the efficacy and tolerability of tetrabenazine in children with chorea [51, 52]. Other treatment options may include antiepileptic medications (valproic acid, carbamazepine) and D2 receptor blockers [53].

9.3.1 Experimental/Alternative Therapies

There are a variety of novel, experimental, and alternative approaches to the treatment of cerebral palsy. Some approaches such as hippotherapy have some evidence of benefits and little downside other than cost [54]. Others, such as hyperbaric oxygen therapy, are proven to be no better than placebo and are costly and potentially dangerous [55]. Physicians should help families navigate interventions based on the current data.

Stem cells: Limited data indicate modest improvement in gross motor function in children with cerebral palsy who receive stem cells from umbilical cord blood [56], though this treatment is not available for most children and long-term effects are not clear. Families should be steered away from practitioners marketing stem cell treatments outside of an experienced medical center.

Cannabis: Although cannabidiol (CBD) has efficacy data for severe epilepsies [57] and cannabis products containing CBD and tetrahydrocannabinol (THC) have limited data for spasticity treatment in the setting of multiple sclerosis [58], no high-quality studies are available for assessment of medical cannabis in CP [46]. As many families choose to administer cannabis products to their children, physicians should inquire about this and have open discussions with the family about the risks, benefits, and interactions with other medications.

9.4 Treatment of Associated Problems

9.4.1 Communication

Children should be evaluated early for communication difficulties. Given that hearing impairment is prevalent and can be a treatable contributor to communication difficulties, children should receive comprehensive audiology evaluations. As some

children (e.g., children with dyskinetic cerebral palsy) have preserved intelligence but profound motor impairment, augmentative and alternative communication (AAC) is crucial to their ability to interact with others and their environment. Introduction to AAC may start in infancy, though an evaluation can be sought at any age. Methods may include using "switches" (buttons) activated by a child's hand, foot, or head, picture cards, electronic tablets, or eye gaze technologies. If a trial with an AAC device is unsuccessful, then a repeat evaluation may still be warranted at an older age.

9.4.2 Vision

Children with cerebral palsy are at a high risk of vision impairments. A pediatric ophthalmologist should assess for ophthalmologic abnormalities as well as cortical visual impairment, which affect 60–70% children with cerebral palsy. Affected children may benefit from specific therapeutic approaches [59].

9.4.3 Feeding and Nutrition

Feeding disorders are more common in children with more extensive motor involvement (e.g., GMFCS IV and V). As aspiration is one of the main causes of morbidity and mortality in children with CP, attention to feeding problems cannot be overstated. Children should undergo screening for dysphagia and weight should be monitored regularly. The presence of prolonged or stressful feeding, poor weight gain, congestion with meals, chronic cough, or frequent respiratory illness should prompt a consultation with a feeding specialist [60]. A gastrostomy tube should be considered for children who are unable to safely feed by mouth, sustain adequate weight gain/nutrition, maintain feeding and hydration at times due to illness, or for whom oral feeding is overly time-consuming and/or distressing.

9.4.4 Other Gastroenterological Complications

Gastroesophageal reflux and constipation are especially common in children with CP and can significantly impact their health and quality of life. A gastroenterologist may need to be involved in more complicated cases.

9.4.5 Sialorrhea

Treatment may be considered if drooling leads to aspiration, skin breakdown, or interference with function or social interactions. Medications such as benzodiazepines and baclofen may worsen sialorrhea. Treatments may include optimizing positioning, behavioral approaches, medications, botulinum toxin injections, or salivary gland surgery. Ophthalmologic atropine drops have been used sublingually

with a low risk of systemic effect [61]. Glycopyrrolate or scopolamine can be effective, although they can have anticholinergic side effects. The American Academy for Cerebral Palsy and Developmental Medicine (AACPDM) has provided a care pathway regarding the evaluation and management of sialorrhea [62].

9.4.6 Pain

The most common sources of pain are hip subluxation, dystonia, and gastrointestinal causes, with significant impact on quality of life [63]. Practitioners should inquire about and investigate the sources of pain and administer treatment to the source. They should also ask about irritability and poor sleep as these can also be indicators of pain. If spasticity or dystonia is causing pain, then the treatment should be directed at the tone. Gabapentin has data for treating painful dystonia [46, 64] as well as unexplained irritability in infants and children with neurological disabilities [65–67]. A trial of gabapentin may be considered for severe pain/irritability even if a source cannot be found. Dosing may start at 5–15 mg/kg/day divided three times daily and uptitrated up to 60 mg/kg/day. The most common side effect is sedation, though mood changes and edema of the lower extremities can also occur [66, 67].

9.4.7 Sleep

Children with cerebral palsy are much more likely to have sleep disorders than are typically developing children. Practitioners should inquire about sleep disturbances and offer recommendations around sleep hygiene and sleep safety. A sleep study should be considered for disrupted sleep or snoring. Although there are no FDA-approved medications for treatment of insomnia in children, melatonin (start with 0.5–3 mg, titrate to a maximum of 10 mg) is often used. If sleep is disrupted by hypertonicity, then clonidine (initial: 25–50 μg at bedtime; start with 2–3 μg/kg up to 25–50 μg, titrate by 25 μg increments to 5–10 μg/kg, do not exceed 10 μg/kg or 300 μg), gabapentin (3–5 mg/kg, titrate to a maximum of 15 mg/kg), or baclofen (<7 years: start with 2–5 mg, titrate to a maximum of 15–20 mg; >7 years: start with 5–10 mg, uptitrate to a maximum of 20–30 mg) may address the underlying tone and provide a mild hypnotic effect. Embarking on these treatment courses should include careful consideration of the risks involved [68–70].

9.4.8 Mood

Children with cerebral palsy are at an increased risk of mood disorders. Although screening for mood disorders should take place across all ages, adolescence is a particularly difficult time for children with disabilities, and, thus, careful screening of adolescent patients is imperative. Frustration with impairments, recognition of differences from peers, disordered sleep and nutrition, pain, and other factors may

contribute to the development of a mood disorder. For children with CP, a mood disorder may manifest as agitation, irritability, undesirable behaviors, or an increase in dystonia or spasticity. Furthermore, mood disorders directly impact a child's function, e.g., decreasing compliance with physical/occupational therapy in the setting of depression. Children with CP manifesting symptoms of suspected mood disorders should be treated with appropriate therapy and/or medication management [9]. Primary care physicians should consider initiating selective serotonin reuptake inhibitor (SSRI) therapy for children with cerebral palsy who have moderate to severe anxiety or depression [71, 72].

9.4.9 Transition

Transition planning should start in early adolescence (before the age of 14) [73]. It may be challenging to find adult providers for individuals with cerebral palsy. A specialist or clinic designed for transition may be useful. Early identification and discussion of school-based and community resources with the patient and family can offer additional education and job skill support.

9.5 Prognosis/Outcomes

9.5.1 Walking

Gross motor developmental trajectories are predictable based on early milestones and CP distribution [74]. Sitting by the age of 2 years is the most consistent predictor but is not a guarantee of future ambulation [75]. Observational data indicate that 50% of children who sit independently but do not pull to a stand at age 2 will walk with or without support by age 7, as compared to only 7% of children not sitting or rolling by 2 years of age [76]. Practitioners should be optimistic about ambulation for children with unilateral CP including neonates with unilateral stroke, as around 90% of these children will walk indepedently [77].

9.5.2 Mortality

About 50% of deaths in children with cerebral palsy are attributable to respiratory causes [78]. As such, factors that increase the risk of aspiration (feeding ability and gross motor function) are the most important predictors of mortality [79]. Dyskinetic type of CP, quadriplegia, epilepsy, and lower cognitive functions are additional risk factors [78]. One can reassure the parents of a child with GMFCS I or II cerebral palsy, who eats independently by mouth, that their child's life expectancy is similar to that of a child without cerebral palsy. In contrast, a 4-year-old child, who is gastrostomy tube-fed and cannot lift their head when prone, has a 58% chance of

surviving until 15 years of age [79]. Particularly, for these higher-risk children who may have frequent medical complications and hospitalizations, involvement of palliative care specialists may be appropriate.

9.6 When to Refer/Admit

9.6.1 The Young Child with a Motor Concern

General practitioners who suspect that their patients have CP based on parental concern, history, motor delay, and/or abnormal neuromotor examination should refer without delay to a pediatric neurologist or other specialists with expertise in motor disorders and initiate therapies. Specific signs of motor delay should prompt referral to a specialist for an evaluation of cerebral palsy [80]:

- Early handedness at less than 12 months of age
- Stiffness or tightness in the legs between 6 and 12 months of age
- Persistent fisting of the hands at greater than 4 months of age
- Persistent head lag at greater than 4 months of age
- Inability to sit without support at greater than 9 months of age
- Asymmetry in posture or movement at any age

9.6.2 The Child with Cerebral Palsy of Unknown Etiology

A child with an established CP diagnosis but an uncertain etiology may need further subspecialty evaluations. Further diagnostic evaluations may be necessary if there is a mismatch between the child's (1) perinatal history, (2) pattern of brain injury, and (3) clinical phenotype, for example, a child born prematurely with mild periventricular leukomalacia on MRI but severe generalized dystonia without significant spasticity on examination. Practitioners should be aware of the "red flags" that may indicate a genetic etiology or CP mimic [81, 82]:

- Normal brain MRI
- Severe symptoms in the absence of a history of acquired injury
- Family history of the disorder or consanguinity
- Neurodevelopmental regression or progressively worsening symptomatology
- Rigidity (as opposed to spasticity)
- Isolated dystonia, chorea, ataxia, or hypotonia
- Leg involvement without arm involvement (suggests spinal cord injuries or hereditary spastic paraplegia)
- Oculogyric crises (episodic, sustained, involuntary eye movements, suggestive of a neurotransmitter disorder)
- Paroxysmal motor symptoms
- Hyporeflexia/areflexia

9.6.3 Referrals for Management of Symptoms

Children with cerebral palsy usually benefit from rehabilitation such as physical therapy starting in infancy, which may be provided through state- or county-based programs. Most children with cerebral palsy are referred to an orthopedist by the age of 2 years for monitoring. If spasticity or dystonia is bothersome and not adequately treated with oral medications, then referral to a specialist in tone/movement disorder management is indicated. The medical complications of cerebral palsy often require subspecialty involvement and sometimes hospital admission.

9.7 Prevention

As prematurity is the most important single risk factor for CP, the varied efforts to preventing premature delivery and its complications such as antenatal magnesium sulfate and corticosteroids decrease the incidence of CP [83]. Therapeutic hypothermia for neonatal hypoxic-ischemic encephalopathy (HIE) has also decreased the incidence of cerebral palsy [84]. However, half of the individuals who develop cerebral palsy did not have any identifiable risk factors, which poses a challenge to prevention. Understanding the genetic underpinnings of CP may pave the way for better treatment and prevention.

Children with cerebral palsy require lifelong interdisciplinary care to address their unique needs across all stages of development, with the goal of helping each child live to their fullest potential.

10 Clinical Pearls/Key Points

- Diagnosis of cerebral palsy and specific interventions should be pursued early (ideally in infancy).
- Cerebral palsy is a clinical diagnosis, though an etiology should always be sought initially with a brain magnetic resonance imaging (MRI) study; spine MRI should be considered in any child with isolated leg involvement.
- Management of cerebral palsy often requires multiple disciplines.
- The primary care physician should regularly assess for associated conditions and be aware of screening recommendations available through professional organizations including the American Academy for Cerebral Palsy and Developmental Medicine.
- Identification and treatment of non-motor impairment (pain, mood disorders, communication, vision, hearing, etc.) significantly impacts the quality of life of children with cerebral palsy and their families.

References

1. Kirby RS, Wingate MS, Van Naarden BK, Doernberg NS, Arneson CL, Benedict RE, Mulvihill B, Durkin MS, Fitzgerald RT, Maenner MJ, Patz JA, Yeargin-Allsopp M. Prevalence and functioning of children with cerebral palsy in four areas of the United States in 2006: a report from the autism and developmental disabilities monitoring network. Res Dev Disabil. 2011;32:462–9.
2. Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, Dan B, Jacobsson B. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl. 2007;109:8–14.
3. Smith SE, Gannotti M, Hurvitz EA, Jensen FE, Krach LE, Kruer MC, Msall ME, Noritz G, Rajan DS, Aravamuthan BR. Adults with cerebral palsy require ongoing neurologic care: a systematic review. Ann Neurol. 2021;89:860–71.
4. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol. 1997;39:214–23.
5. Palisano R, Rosenbaum P, Bartlett D, Livingston M. GMFCS – E & R. Gross motor function classification system expanded and revised. https://www.canchild.ca/system/tenon/assets/attachments/000/000/058/original/GMFCS-ER_English.pdf. Accessed 11 May 2021.
6. Prevalence and characteristics of children with cerebral palsy in Europe. Dev Med Child Neurol. 2002;44:633–40.
7. Rice J, Skuza P, Baker F, Russo R, Fehlings D. Identification and measurement of dystonia in cerebral palsy. Dev Med Child Neurol. 2017;59:1249–55.
8. Odding E, Roebroeck ME, Stam HJ. The epidemiology of cerebral palsy: incidence, impairments and risk factors. Disabil Rehabil. 2006;28:183–91.
9. Downs J, Blackmore AM, Epstein A, Skoss R, Langdon K, Jacoby P, Whitehouse AJO, Leonard H, Rowe PW, Glasson EJ. The prevalence of mental health disorders and symptoms in children and adolescents with cerebral palsy: a systematic review and meta-analysis. Dev Med Child Neurol. 2018;60:30–8.
10. Parkinson KN, Dickinson HO, Arnaud C, Lyons A, Colver A. Pain in young people aged 13 to 17 years with cerebral palsy: cross-sectional, multicentre European study. Arch Dis Child. 2013;98:434–40.
11. Novak I, Hines M, Goldsmith S, Barclay R. Clinical prognostic messages from a systematic review on cerebral palsy. Pediatrics. 2012;130:e1285–312.
12. Dolk H, Pattenden S, Johnson A. Cerebral palsy, low birthweight and socio-economic deprivation: inequalities in a major cause of childhood disability. Paediatr Perinat Epidemiol. 2001;15:359–63.
13. Vincer MJ, Allen AC, Joseph KS, Stinson DA, Scott H, Wood E. Increasing prevalence of cerebral palsy among very preterm infants: a population-based study. Pediatrics. 2006;118:e1621–6.
14. Stanley FJ, Blair E, Alberman E. Cerebral palsies: epidemiology and causal pathways. Holborn, London: Mac Keith Press; 2000.
15. Oskoui M, Coutinho F, Dykeman J, Jetté N, Pringsheim T. An update on the prevalence of cerebral palsy: a systematic review and meta-analysis. Dev Med Child Neurol. 2013;55:509–19.
16. Durkin MS, Benedict RE, Christensen D, Dubois LA, Fitzgerald RT, Kirby RS, Maenner MJ, Van Naarden BK, Wingate MS, Yeargin-Allsopp M. Prevalence of cerebral palsy among 8-year-old children in 2010 and preliminary evidence of trends in its relationship to low birthweight. Paediatr Perinat Epidemiol. 2016;30:496–510.
17. Durkin MS, Maenner MJ, Benedict RE, Van Naarden BK, Christensen D, Kirby RS, Wingate M, Yeargin-Allsopp M. The role of socio-economic status and perinatal factors in racial disparities in the risk of cerebral palsy. Dev Med Child Neurol. 2015;57:835–43.
18. McGuire DO, Tian LH, Yeargin-Allsopp M, Dowling NF, Christensen DL. Prevalence of cerebral palsy, intellectual disability, hearing loss, and blindness, National Health Interview Survey, 2009-2016. Disabil Health J. 2019;12:443–51.

19. Kancherla V, Amendah DD, Grosse SD, Yeargin-Allsopp M, Van Naarden BK. Medical expenditures attributable to cerebral palsy and intellectual disability among Medicaid-enrolled children. Res Dev Disabil. 2012;33:832–40.
20. Economic costs associated with mental retardation, cerebral palsy, hearing loss, and vision impairment—United States, 2003. MMWR Morb Mortal Wkly Rep. 2004;53:57–9.
21. Bourke-Taylor H, Cotter C, Stephan R. Young children with cerebral palsy: families self-reported equipment needs and out-of-pocket expenditure. Child Care Health Dev. 2014;40:654–62.
22. Majnemer A, Shevell M, Law M, Poulin C, Rosenbaum P. Indicators of distress in families of children with cerebral palsy. Disabil Rehabil. 2012;34:1202–7.
23. Guyard A, Michelsen SI, Arnaud C, Fauconnier J. Family adaptation to cerebral palsy in adolescents: a European multicenter study. Res Dev Disabil. 2017;61:138–50.
24. Lowes L, Clark TS, Noritz G. Factors associated with caregiver experience in families with a child with cerebral palsy. J Pediatr Rehabil Med. 2016;9:65–72.
25. McIntyre S, Morgan C, Walker K, Novak I. Cerebral palsy—don't delay. Dev Disabil Res Rev. 2011;17:114–29.
26. Jin SC, Lewis SA, Bakhtiari S, Zeng X, Sierant MC, Shetty S, Nordlie SM, Elie A, Corbett MA, Norton BY, van Eyk CL, Haider S, Guida BS, Magee H, Liu J, Pastore S, Vincent JB, Brunstrom-Hernandez J, Papavasileiou A, Fahey MC, Berry JG, Harper K, Zhou C, Zhang J, Li B, Zhao H, Heim J, Webber DL, Frank MSB, Xia L, Xu Y, Zhu D, Zhang B, Sheth AH, Knight JR, Castaldi C, Tikhonova IR, López-Giráldez F, Keren B, Whalen S, Buratti J, Doummar D, Cho M, Retterer K, Millan F, Wang Y, Waugh JL, Rodan L, Cohen JS, Fatemi A, Lin AE, Phillips JP, Feyma T, MacLennan SC, Vaughan S, Crompton KE, Reid SM, Reddihough DS, Shang Q, Gao C, Novak I, Badawi N, Wilson YA, McIntyre SJ, Mane SM, Wang X, Amor DJ, Zarnescu DC, Lu Q, Xing Q, Zhu C, Bilguvar K, Padilla-Lopez S, Lifton RP, Gecz J, MacLennan AH, Kruer MC. Mutations disrupting neuritogenesis genes confer risk for cerebral palsy. Nat Genet. 2020;52:1046–56.
27. Moreno-De-Luca A, Millan F, Pesacreta DR, Elloumi HZ, Oetjens MT, Teigen C, Wain KE, Scuffins J, Myers SM, Torene RI, Gainullin VG, Arvai K, Kirchner HL, Ledbetter DH, Retterer K, Martin CL. Molecular diagnostic yield of exome sequencing in patients with cerebral palsy. JAMA. 2021;325:467–75.
28. Novak I, Morgan C, Adde L, Blackman J, Boyd RN, Brunstrom-Hernandez J, Cioni G, Damiano D, Darrah J, Eliasson AC, de Vries LS, Einspieler C, Fahey M, Fehlings D, Ferriero DM, Fetters L, Fiori S, Forssberg H, Gordon AM, Greaves S, Guzzetta A, Hadders-Algra M, Harbourne R, Kakooza-Mwesige A, Karlsson P, Krumlinde-Sundholm L, Latal B, Loughran-Fowlds A, Maitre N, McIntyre S, Noritz G, Pennington L, Romeo DM, Shepherd R, Spittle AJ, Thornton M, Valentine J, Walker K, White R, Badawi N. Early, accurate diagnosis and early intervention in cerebral palsy: advances in diagnosis and treatment. JAMA Pediatr. 2017;171:897–907.
29. Novak I, Morgan C, Adde L, Badawi N, Blackman J, Boyd RN, Brunstrom-Hernandez J, Cioni G, Damiano D, Darrah J, Eliasson A, de Vries L, Einspieler C, Fahey M, Fehlings D, Ferriero D, Fetters L, Fiori S, Forssberg H, Gordon A, Greaves S, Guzzetta A, Hadders-Algra M, Harbourne R, Kakooza-Mwesige A, Karlsson P, Krumlinde-Sundholm L, Latal B, Loughran-Fowlds A, Maitre N, McIntyre S, Noritz G, Pennington L, Romeo D, Shepherd R, Spittle A, Thornton M, Valentine J, Walker K, White R. American Academy of Cerebral Palsy and Deelopmental Medicine: Care Pathway for Early Detection of Cerebral Palsy; 2020.
30. Byrne R, Duncan A, Pickar T, Burkhardt S, Boyd RN, Neel ML, Maitre NL. Comparing parent and provider priorities in discussions of early detection and intervention for infants with and at risk of cerebral palsy. Child Care Health Dev. 2019;45:799–807.
31. Wagenaar N, Martinez-Biarge M, van der Aa NE, van Haastert IC, Groenendaal F, Benders M, Cowan FM, de Vries LS. Neurodevelopment after perinatal arterial ischemic stroke. Pediatrics. 2018;142

32. Ashwal S, Russman BS, Blasco PA, Miller G, Sandler A, Shevell M, Stevenson R. Practice parameter: diagnostic assessment of the child with cerebral palsy: report of the quality standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2004;62:851–63.
33. Liptak GS, Murphy NA. Providing a primary care medical home for children and youth with cerebral palsy. Pediatrics. 2011;128:e1321–9.
34. International Classification of Functioning. Disability and health (ICF). Geneva: World Health Organization; 2001.
35. Rosenbaum P, Gorter JW. The 'F-words' in childhood disability: I swear this is how we should think! Child Care Health Dev. 2012;38:457–63.
36. Eliasson AC, Holmefur M. The influence of early modified constraint-induced movement therapy training on the longitudinal development of hand function in children with unilateral cerebral palsy. Dev Med Child Neurol. 2015;57:89–94.
37. The American Academy of Cerebral Palsy and Developmental Medicine: Hip surveillance care pathways. https://www.aacpdm.org/publications/care-pathways/hip-surveillance. Accessed 20 March 2021.
38. Australian Academy of Cerebral Palsy and Developmental Medicine: Australian Hip Surveillance Guidelines. https://www.ausacpdm.org.au/resources/australian-hip-surveillance-guidelines/. Accessed 20 March 2021.
39. Shore BJ, Mulpuri K, Shrader W. Radiographic hip screening in cerebral palsy: developing POSNA-wide consensus. J Pediatr Orthop Soc N Am. 2021;3
40. Dreher T, Thomason P, Švehlík M, Döderlein L, Wolf SI, Putz C, Uehlein O, Chia K, Steinwender G, Sangeux M, Graham HK. Long-term development of gait after multilevel surgery in children with cerebral palsy: a multicentre cohort study. Dev Med Child Neurol. 2018;60:88–93.
41. National Guideline A. National Institute for Health and Care Excellence: clinical guidelines. Cerebral palsy in under 25s: assessment and management. London: National Institute for Health and Care Excellence (UK) Copyright National Institute for Health and Care Excellence 2017; 2017.
42. Delgado MR, Hirtz D, Aisen M, Ashwal S, Fehlings DL, McLaughlin J, Morrison LA, Shrader MW, Tilton A, Vargus-Adams J. Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review): report of the quality standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2010;74:336–43.
43. Tu A, Steinbok P. Long term outcome of selective dorsal rhizotomy for the management of childhood spasticity-functional improvement and complications. Childs Nerv Syst. 2020;36:1985–94.
44. D'Aquino D, Moussa AA, Ammar A, Ingale H, Vloeberghs M. Selective dorsal rhizotomy for the treatment of severe spastic cerebral palsy: efficacy and therapeutic durability in GMFCS grade IV and V children. Acta Neurochir. 2018;160:811–21.
45. Ingale H, Ughratdar I, Muquit S, Moussa AA, Vloeberghs MH. Selective dorsal rhizotomy as an alternative to intrathecal baclofen pump replacement in GMFCS grades 4 and 5 children. Child Nerv Syst. 2016;32:321–5.
46. Bohn E, Goren K, Switzer L, Falck-Ytter Y, Fehlings D. Pharmacological and neurosurgical interventions for individuals with cerebral palsy and dystonia: a systematic review update and meta-analysis. Dev Med Child Neurol. 2021;
47. Bonouvrié LA, Becher JG, Vles JSH, Vermeulen RJ, Buizer AI. The effect of intrathecal baclofen in dyskinetic cerebral palsy: the IDYS trial. Ann Neurol. 2019;86:79–90.
48. Elia AE, Bagella CF, Ferré F, Zorzi G, Calandrella D, Romito LM. Deep brain stimulation for dystonia due to cerebral palsy: a review. Eur J Paediatr Neurol. 2018;22:308–15.
49. Fehlings D, Brown L, Harvey A, Himmelmann K, Lin J, MacIntosh A, Mink J, Monbaliu E, Rice J, Silver J, Switzer L, Walter I. American Acadamy of Cerebaral Palsy and Developmental

Medicine: dystonia in cerebral palsy care pathway. https://www.aacpdm.org/publications/care-pathways/dystonia. Accessed 27 March 2021.
50. Allen NM, Lin JP, Lynch T, King MD. Status dystonicus: a practice guide. Dev Med Child Neurol. 2014;56:105–12.
51. Chatterjee A, Frucht SJ. Tetrabenazine in the treatment of severe pediatric chorea. Mov Disord. 2003;18:703–6.
52. Jain S, Greene PE, Frucht SJ. Tetrabenazine therapy of pediatric hyperkinetic movement disorders. Mov Disord. 2006;21:1966–72.
53. Yilmaz S, Mink JW. Treatment of chorea in childhood. Pediatr Neurol. 2020;102:10–9.
54. Martín-Valero R, Vega-Ballón J, Perez-Cabezas V. Benefits of hippotherapy in children with cerebral palsy: a narrative review. Eur J Paediatr Neurol. 2018;22:1150–60.
55. Lacey DJ, Stolfi A, Pilati LE. Effects of hyperbaric oxygen on motor function in children with cerebral palsy. Ann Neurol. 2012;72:695–703.
56. Novak I, Walker K, Hunt RW, Wallace EM, Fahey M, Badawi N. Concise review: stem cell interventions for people with cerebral palsy: systematic review with meta-analysis. Stem Cells Transl Med. 2016;5:1014–25.
57. de Carvalho RR, Almeida KJ, da Silva LL, de Melo Mendes CM, Bor-Seng-Shu E. Efficacy and adverse event profile of cannabidiol and medicinal cannabis for treatment-resistant epilepsy: systematic review and meta-analysis. Epilepsy Behav. 2020;102:106635.
58. Nielsen S, Germanos R, Weier M, Pollard J, Degenhardt L, Hall W, Buckley N, Farrell M. The use of cannabis and cannabinoids in treating symptoms of multiple sclerosis: a systematic review of reviews. Curr Neurol Neurosci Rep. 2018;18:8.
59. Fazzi E, Signorini SG, Piana RLA, Bertone C, Misefari W, Galli J, Balottin U, Bianchi PE. Neuro-ophthalmological disorders in cerebral palsy: ophthalmological, oculomotor, and visual aspects. Dev Med Child Neurol. 2012;54:730–6.
60. Arvedson JC. Feeding children with cerebral palsy and swallowing difficulties. Eur J Clin Nutr. 2013;67(Suppl 2):S9–12.
61. Dias BLS, Fernandes AR, Maia HSF. Treatment of drooling with sublingual atropine sulfate in children and adolescents with cerebral palsy. Arq Neuropsiquiatr. 2017;75:282–7.
62. American Academy of Cerebral Palsy and Developmental Medicine Care Pathways: Sialorrhea in Cerebral Palsy. https://www.aacpdm.org/publications/care-pathways/sialorrhea. Accessed 21 March 2021.
63. Fairhurst C, Shortland A, Chandler S, Will E, Scrutton D, Simonoff E, Baird G. Factors associated with pain in adolescents with bilateral cerebral palsy. Dev Med Child Neurol. 2019;61:929–36.
64. Liow NY, Gimeno H, Lumsden DE, Marianczak J, Kaminska M, Tomlin S, Lin JP. Gabapentin can significantly improve dystonia severity and quality of life in children. Eur J Paediatr Neurol. 2016;20:100–7.
65. Burnsed JC, Heinan K, Letzkus L, Zanelli S. Gabapentin for pain, movement disorders, and irritability in neonates and infants. Dev Med Child Neurol. 2020;62:386–9.
66. Collins A, Mannion R, Broderick A, Hussey S, Devins M, Bourke B. Gabapentin for the treatment of pain manifestations in children with severe neurological impairment: a single-Centre retrospective review. BMJ Paediatr Open. 2019;3:e000467.
67. Hauer JM, Wical BS, Charnas L. Gabapentin successfully manages chronic unexplained irritability in children with severe neurologic impairment. Pediatrics. 2007;119:e519–22.
68. Bruni O, Angriman M, Calisti F, Comandini A, Esposito G, Cortese S, Ferri R. Practitioner review: treatment of chronic insomnia in children and adolescents with neurodevelopmental disabilities. J Child Psychol Psychiatry. 2018;59:489–508.
69. Tanner K, Noritz G, Ayala L, Byrne R, Fehlings D, Gehred A, Letzkus L, Novak I, Rosenberg N, Vargus-Adams J, Winter S, Maitre NL. Assessments and interventions for sleep disorders in infants with or at high risk for cerebral palsy: a systematic review. Pediatr Neurol. 2020;
70. Blackmer AB, Feinstein JA. Management of sleep disorders in children with neurodevelopmental disorders: a review. Pharmacotherapy. 2016;36:84–98.

71. Cheung AH, Zuckerbrot RA, Jensen PS, Laraque D, Stein REK. Guidelines for adolescent depression in primary care (GLAD-PC): part II. Treatment and ongoing management. Pediatrics. 2018:141.
72. Walter HJ, Bukstein OG, Abright AR, Keable H, Ramtekkar U, Ripperger-Suhler J, Rockhill C. Clinical practice guideline for the assessment and treatment of children and adolescents with anxiety disorders. J Am Acad Child Adolesc Psychiatry. 2020;59:1107–24.
73. Brown LW, Camfield P, Capers M, Cascino G, Ciccarelli M, de Gusmao CM, Downs SM, Majnemer A, Miller AB, SanInocencio C, Schultz R, Tilton A, Winokur A, Zupanc M. The neurologist's role in supporting transition to adult health care: a consensus statement. Neurology. 2016;87:835–40.
74. Rosenbaum PL, Walter SD, Hanna SE, Palisano RJ, Russell DJ, Raina P, Wood E, Bartlett DJ, Galuppi BE. Prognosis for gross motor function in cerebral palsy: creation of motor development curves. JAMA. 2002;288:1357–63.
75. Keeratisiroj O, Thawinchai N, Siritaratiwat W, Buntragulpoontawee M, Pratoomsoot C. Prognostic predictors for ambulation in children with cerebral palsy: a systematic review and meta-analysis of observational studies. Disabil Rehabil. 2018;40:135–43.
76. Wu YW, Day SM, Strauss DJ, Shavelle RM. Prognosis for ambulation in cerebral palsy: a population-based study. Pediatrics. 2004;114:1264–71.
77. Beckung E, Hagberg G, Uldall P, Cans C. Probability of walking in children with cerebral palsy in Europe. Pediatrics. 2008;121:e187–92.
78. Himmelmann K, Sundh V. Survival with cerebral palsy over five decades in western Sweden. Dev Med Child Neurol. 2015;57:762–7.
79. Brooks JC, Strauss DJ, Shavelle RM, Tran LM, Rosenbloom L, Wu YW. Recent trends in cerebral palsy survival. Part II: individual survival prognosis. Dev Med Child Neurol. 2014;56:1065–71.
80. Boychuck Z, Andersen J, Bussières A, Fehlings D, Kirton A, Li P, Oskoui M, Rodriguez C, Shevell M, Snider L, Majnemer A. Use of consensus methods to determine the early clinical signs of cerebral palsy. Paediatr Child Health. 2020;25:300–7.
81. Lee RW, Poretti A, Cohen JS, Levey E, Gwynn H, Johnston MV, Hoon AH, Fatemi A. A diagnostic approach for cerebral palsy in the genomic era. NeuroMolecular Med. 2014;16:821–44.
82. Pearson TS, Pons R, Ghaoui R, Sue CM. Genetic mimics of cerebral palsy. Mov Disord. 2019;34:625–36.
83. Shepherd E, Salam RA, Middleton P, Makrides M, McIntyre S, Badawi N, Crowther CA. Antenatal and intrapartum interventions for preventing cerebral palsy: an overview of Cochrane systematic reviews. Cochrane Database Syst Rev. 2017;8:Cd012077.
84. Shepherd E, Salam RA, Middleton P, Han S, Makrides M, McIntyre S, Badawi N, Crowther CA. Neonatal interventions for preventing cerebral palsy: an overview of Cochrane Systematic Reviews. Cochrane Database Syst Rev. 2018;6:Cd012409.

Child with Closed Head Injury

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1 Introduction

Concussions in children and adolescents remain a significant public health concern in the United States (US), with all 50 states passing legislation to manage concussions in children playing sports [1]. Recent data have also suggested that a substantial proportion of concussions or mild traumatic brain injuries (TBIs) are seen in primary care settings, and, so, it has become paramount that primary care clinicians are comfortable with diagnosing and managing concussions [2]. Clinicians must also be aware of the increased emphasis on return-to-play, return-to-learn, parental education, and longer-term follow-up of pediatric patients diagnosed with a concussion.

The diagnosis and management of concussions in the pediatric population has been challenging and is often controversial, given the broad spectrum of symptoms that may follow a concussion. Concussions are also believed to affect children differently than adults because of their significant cognitive, developmental, and physiological differences. Historically, a concussion was characterized as a homogeneous injury. We now have a better understanding of the diverse, complex nature of a

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concussion, broadly defined as functional impairment due to neurometabolic and neuropathologic changes that occur in the brain after a biomechanical trauma [3]. These changes may result in signs and symptoms that can include somatic complaints, cognitive dysfunction, behavioral changes, visual abnormalities, balance impairment, autonomic dysfunction, or sleep irregularities [4–6]. As knowledge about concussions has substantially increased over the last 10 years, our treatment approach has also evolved to include a more individualized symptomatic approach to concussion management.

When there is suspicion of a concussion, it is always best to be cautious and remove the individual from play immediately and evaluate them with serial reassessments. Concussed individuals should be seen within 72 hours of injury by a health-care professional with expertise in concussion care to ensure proper management, avoid delay in recovery, and prevent a premature return to sport or school-based activities. Some pediatric patients may underreport their symptoms, thus complicating the evaluation [7, 8].

2 Epidemiology

According to the Centers for Disease Control and Prevention (CDC), between 1.6 and 3.8 million concussions (including both children and adults) occur annually in the United States from sports participation or recreational activities, with nearly 30% treated in emergency departments [2]. The overall incidence of concussions in children and adolescents has continued to increase [3, 4]. Between one-quarter and one-half million emergency department visits among children and adolescents between 0 and 19 years of age are due to traumatic brain injuries (TBIs) [9, 10]. The CDC reported that almost half of the pediatric TBI-related emergency department visits were caused by falls and one-quarter by the patient being struck by or against an object [11]. The number one cause of TBI-related hospitalizations among adolescents remains motor vehicle crashes [11]. A recent study has found that among boys' high school sports in 2018–2019, the highest overall number of concussions occurring during competitions were in American football, soccer, lacrosse, wrestling, ice hockey, basketball, and baseball [12]. However, boys' high school sports with the highest proportion of concussions with respect to competition injuries were ice hockey (31.4%), lacrosse (28.8%), soccer (20.9%), American football (20.4%), wrestling (15.9%), basketball (12.6%), and baseball (8.8%). Among girls' high school sports in 2018–2019, the highest overall number of concussions occurring during competitions were in soccer, basketball, lacrosse, field hockey, volleyball, and softball. However, the highest proportion of concussions among girls with respect to competition injuries occurred in girls' lacrosse (35%), soccer (24.5%), field hockey (22.7%), basketball (21.7%), volleyball (15.1%), and softball (12.8%) [12].

3 Diagnostic Approach

3.1 A Symptom-Based Approach to Clinical History

Clinical history is vital to make a diagnosis of concussion. Depending on when the evaluation occurs, clinicians should inquire about symptoms that presented at the time of injury and any new symptoms that may have developed. Attention should be paid to the timing of symptom occurrence and progression. With pediatric patients who may be unaware of their symptoms or reluctant to report them, it is vital to ask directed questions about the symptoms [8, 13]. With most concussions, the signs and symptoms are immediate, although some symptoms may develop and evolve, particularly within the first few hours following injury [3]. Alternative diagnostic explanations should be sought for symptoms developing more than 24 h following the injury. Although there are many available objective screening tools for use in the initial assessment of a patient with a suspected concussion, these tools should only be used by trained personnel within a specific time from the injury because most tools have been developed for sideline usage (Table 1) and have limitations in the pediatric population. Importantly, these screening tools should only be used to augment in-office history and examination.

A concussion can result in various non-specific symptoms that often overlap with preexisting medical conditions, such as migraine, mood disorders, or learning disabilities, thus making the diagnosis difficult. During evaluation, clinicians should not only inquire about the history of prior concussions but also ask about previous headache/migraine history and information regarding past mental health or cognitive issues such as depression, anxiety, attention-deficit disorder (ADD), attention-deficit hyperactivity disorder (ADHD), or learning disabilities. A free-to-use concussion symptom evaluation checklist can detect individual symptoms and their severity and can be used at the initial evaluation and subsequent visits to monitor progression and recovery [14, 15]. Notably, many individuals may report certain symptoms found on the checklists at the pre-injurious or baseline state, and, so, it is essential to ask about this as well. Additional information regarding the family history of migraine, mental health issues, or neurological comorbidities can help in concussion diagnosis and management.

To aid in the diagnosis, clinicians should obtain pertinent information regarding the mechanism of injury, signs, and symptoms at the time of injury including loss of consciousness (LOC), memory impairment, headache, dizziness, and cognitive or behavioral issues. Information regarding the characteristics of the associated factors, such as object of collision, height of fall, speed of impact, and safety devices used, can assist in assessment [13]. Clinicians must ask whether the patient continued to play or practice after the injury since this may affect the duration of symptoms. Clinicians should attempt to quantify the force of injury with available footage or through reported history if the event was witnessed. These data, coupled with a

Table 1 Screening tools for the assessment of a pediatric patient with a suspected concussion

Screening tools in the initial assessment of a pediatric patient with suspected concussion

Potential Symptom Barrier to Recovery	Screening & Exam Tool Examples	Treatment Category
Neck Pain	• Joint Mobility • Tenderness topalpation, • Muscle strength & extensibility.	Cervical physical therapy Intervention Examples • Manual therapy, • Range of motion exercises • Cervical prorioceptive training.
Dizziness **Balance** **Motion Sensitivity** **Lightheadedness**	• Vestibular Ocular Motor Screen • Dix-Halpike test • Orthostatics	Increased water and salt intake Sub-symptom exercise Vestibular therapy Intervention Examples • Gaze stability training • Postural stability training, • Habituation exercises
Vision-Related Problems	• Vestibular Ocular Motor Screen • Accommodative amplitude and accommodative facility testing • Vergence testing	Vision Therapy Intervention Examples • Brock string exercises • Exercises for saccades • Visual motion desensitization training. • Accommodative exercises (i.e. near-far)
Sleep Difficulties	• Sleep History	Sleep hygiene techniques Pharmacotherapy Intervention Examples • Nap restriction • Maintain sleep schedule • Avoid electronics before bed • Low dose melatonin
Mental Health Symptoms	• Mental Health Screen	Cognitive behavioral therapy Individual psychotherapy Intervention Examples • Mindfulness techniques • Breathing exercises

thorough history of previous injuries with duration of symptoms, are important for making return-to-play or retirement decisions in cases where the injury may be a recurrent concussion [13].

Clinicians should acquire details of each relevant symptom, and, in some instances, a directed history is important. It is important to follow up on each symptom during the recovery stages. Notably, the medical provider should gather information regarding the onset of headache, the precise characteristic and location of the headache, and the clinical course to identify specific triggers since the causes of head pain can also be multifaceted with contributions from the spinal musculoskeletal system and visual and vestibular pathways. In its acute phase, a headache is often initially characterized by constant pain with a transition to pain-free periods. Like many symptoms of a concussion, a headache typically worsens with cognitive and physical activities. Headaches, secondary to musculoskeletal pathology, may be localized to the suboccipital, paraspinal, anterior neck, or shoulder regions.

Clinicians must also ask about neck pain. Like other muscle strains, it is common for musculoskeletal symptoms (including neck pain) to be present and worsen 1–2 days after an injury. Some children may develop cervicogenic headaches (headaches where the primary pathology is in the cervical spine or the muscles of the neck). These headaches are worse in the morning and improve as the day goes on. As noted above, patients may have a concomitant headache from both a concussion and a neck injury.

Dizziness is one of the most common and disabling concussion symptoms in the acute symptomatic and recovery phases. Dizziness can be difficult for pediatric patients to describe. In general, dizziness can be characterized by a spinning sensation, visual motion sensitivity, lightheadedness, or imbalance. Using a detailed history, clinicians should seek to determine the cause of vestibular impairment because symptoms can have multiple etiologies, such as peripheral or central vestibular dysfunction, migraine, or cervicogenic or psychiatric causes. Dizziness can be continuously experienced, especially in the first few hours and days following injury, but often becomes episodic and provoked. The duration of the episodes can vary from seconds to hours. The episodes are generally longer in duration closer to the injury, and, in the recovery phase, they gradually become shorter, less frequent, and require more stimulus to provoke. Dizziness can occur independently, be present solely with a headache, or occur with and without a headache. When dizziness is more severe, it can also be accompanied by nausea. Dizziness is not typically associated with phono- or photophobia. Patients who describe symptoms that include a headache, nausea, or eye fatigue presenting with dizziness are commonly triggered by specific activities such as reading, riding in a car, or walking in a busy environment.

Many patients report difficulty in concentration, memory deficits, confusion, or feeling slowed down or mentally foggy after a concussion. These symptoms may not appear immediately after the injury and may only be reported once the pediatric

patient returns to the academic environment. Some children may describe difficulty in falling and/or staying asleep in addition to poor sleep quality. Patients may report the need for increased sleep or sleeping more than usual but with ongoing daytime fatigue and drowsiness.

Finally, the provider must also ask about the symptoms related to vision such as blurry vision, eye strain, or difficulty focusing on objects that are located close by (convergence insufficiency (CI)).

3.2 A Symptom-Based Approach to Physical Examination

3.2.1 General Physical Examination

An examination should include orthostatic vitals (heart rate and blood pressure measurements in the lying, sitting, and standing positions) because of the prevalence of autonomic dysfunction following concussion. A detailed head, eye, ear, nose, and throat (HEENT) examination should be conducted to look for lacerations, abrasions, or bruising in the head and neck regions as well as otorrhea or rhinorrhea. Tenderness over the scalp, orbits, and mastoid regions should be observed as well. Evaluation of the neck should include evaluations of the range of motion, generalized or point tenderness with assessment for palpable bony step-off along the cervical spine, muscle tenderness, or spasm flexibility and strength assessment of the neck muscles.(22–24].

3.2.2 Neurological Examination

A detailed neurological examination should be conducted, including cranial nerve (CN) testing. A cranial nerve evaluation includes an assessment of the pupils and fundoscopic evaluation (CN II and III), extraocular movement (CN III, IV, and VI), allodynia (heightened sensitivity to touch) or facial sensory loss (CN V), facial weakness (CN VII), hearing loss or vertigo (CN VIII), gag reflex/swallow (CN IX, X, and XII), and shoulder elevation (CN XI). Notably, CN I, which can be challenging to assess routinely, could be checked by letting the patient smell coffee or an alcohol pad but only if the patient raises specific concerns.

A physical examination should also include specialized testing of the visual–vestibular system. The vestibular ocular motor screen (VOMS) is an easy, quick assessment tool that can be administered in approximately 5 min by the clinician and should be part of the initial screen, especially if history suggests vestibular ocular impairment [16]. VOMS testing will query the pre-test level of symptoms for headache, dizziness, nausea, and fogginess. Subsequently, the provider assesses symptom exacerbation and/or observed deficits associated with visual tracking (i.e., smooth pursuits), horizontal and vertical movement of the eyes between two fixed points (i.e., horizontal and vertical saccades), and/or vestibular ocular reflex (VOR).

Clinicians should look for subtle observed findings such as hypometria (undershooting the visual target) or hypermetria (overshooting the visual target) with horizontal or vertical eye movements. One should also assess for saccadic intrusions (irregular episodic occurrences of a series of two or more fast eye movements while the eye tries to track a moving object) with smooth pursuit, nystagmus, difficulty in performing near point convergence and accommodation (looking at an object at a close range), or corrective saccades during vestibular ocular reflex testing with the head impulse test. Clinical head impulse testing assesses the vestibular ocular reflex (VOR) by identifying compensatory eye movements during rapid head movements. The presence of catch-up saccades during head impulse testing is useful for identifying the peripheral vestibular deficits. Catch-up or corrective saccades are small extra movements that the eyes must make to maintain gaze on the visual target. When they are of sufficient amplitude, they can be detected by the clinician. Any of these findings in association with reports of dizziness, headache, nausea, or fogginess not only aid in the diagnosis of a concussion but also guide individualized treatment options such as vestibular or vision therapy (Table 1) [17].

A motor and sensory screen, including assessment of deep tendon reflexes, should then be conducted, and a more serious injury should be considered if abnormalities are found. A neurological examination can be conducted with an assessment of coordination, balance, and gait. When looking for evidence of difficulty in balance in the pediatric athlete population, dynamic balance tests such as timed tandem (in which the athlete walks 3 m along a straight line using an alternate heel-to-toe gait, turns, and returns to the starting position as quickly as possible in <14 s (+2 standard deviation (SD)) can be applied [18].

A concussion evaluation should also include an assessment of cognition. A mental status evaluation should be conducted, and this starts with obtaining details of the patient's history. The patient should try to provide as many details of the injury as well as symptoms associated with activities such as school, work, or physical activity. Many practitioners use the Standardized Assessment of Concussion (SAC), a validated sideline tool. However, this tool was created as a sideline cognitive assessment tool to be used at the time of injury and loses sensitivity and specificity 72 hours post-injury [19]. During an in-office examination, a well-validated mental status examination can be conducted, including the Mini-Mental Status Examination, Montreal Cognitive Assessment, Kokmen Short Test of Mental Status, or Cognitive Log, with the latter measure being specifically developed for cognitive screening after a traumatic brain injury.

3.2.3 Evaluation (Laboratory Investigations/Imaging)

A concussion is diagnosed clinically. There is currently no test, biomarker, or imaging study that can diagnose a concussion [9]. A thorough assessment based on clinical findings and deficits is vital to properly manage a concussion. No laboratory investigations are indicated in most instances. Imaging is also not required in most situations. If motor weakness, numbness, or loss of sensation is reported and

observed in a limb or limbs, then advanced imaging (e.g., magnetic resonance imaging—MRI) should be considered, especially if there was possible trauma to the neck or forceful extension or flexion. Similarly, clinicians should ask about the red-flag symptoms associated with post-concussion headaches, which may include an altered level of consciousness during episodes of the headache, positional components of the headache, focal neurological symptoms of the headache such as motor weakness that progressively worsens in severity over time, or intractable vomiting associated with the headache. If red flags are present, then structural abnormalities should be considered and a neuroimaging of the brain and/or the cervical spine is warranted.

3.3 A Symptom-Based Approach to Concussion Management

A symptom-based approach can be applied so that a concussion is characterized by symptom profiles corresponding to targeted rehabilitation strategies [7]. Clinical evaluation can identify particular symptom presentations and examination findings, which can then guide individualized treatment strategies associated with specific clinical presentations [7].

Head Pain/Headache: A headache is the most commonly reported symptom after a concussion [13, 20, 21]. Generally, pain originates from the area of impact, but it can also be located at a site distinct from the area of impact or can encompass the entire head. Pain quality can range from sharp, to dull and achy, to throbbing or pressure-like [22]. Photophobia, phonophobia, nausea, and dizziness (migraine-like features) can all occur relatively constantly in the first few days following an injury and can worsen with more severe head pain. Clinicians should seek factors contributing to the headache, such as vestibular and musculoskeletal involvement, and initiate treatment plans for them. An acute post-concussion headache can be treated with over-the-counter analgesics. Evidence supporting the use of daily preventative medications, typically used to treat migraine, is lacking and should be avoided in managing acute concussion.

Neck (Cervicogenic) Pain: Musculoskeletal neck pain, directly resulting from the mechanism of injury, frequently accompanies concussion. Initial severe neck pain represents a medical emergency and requires immediate stabilization and medical evaluations. Musculoskeletal neck symptoms can be minor and can gradually resolve on their own over days but can also be prominent, worsen over the first few days following injury, and be a persistent factor in prolonged symptoms [23]. Because neck pain can cause symptoms that closely resemble concussion symptoms and are treatable, clinicians must identify and treat the cause of these musculoskeletal symptoms [24]. These musculoskeletal symptoms can be a significant contributor to or the sole cause of the headache with referred neck pain presenting as head pain, i.e., a cervicogenic headache. Musculoskeletal symptoms are not typically associated with photophobia or photophobia but can be associated with nausea and dizziness. Focused treatment plans usually include formal spine physical therapy

and a home exercise program with soft tissue mobilization, manual cervical and thoracic mobilization, range of motion (ROM) exercises, posture re-education, and biofeedback modalities [24]. Additional pharmacological interventions including anti-inflammatories, analgesics, and muscle relaxants can be used. Other treatment options, such as trigger point injections or nerve blocks, can be considered.

Vestibular and Ocular Motor Symptoms: Research shows that vestibular impairment is a common symptom following a concussion and can occur in up to 90% of individuals with concussions [25, 26]. Symptoms of vestibular impairment can include dizziness, motion sensitivity, and imbalance. Imbalance is more prominent at the time of injury and is reported to resolve in most within 3–5 days of injury [27]. These patient-reported symptoms indicate that vestibular ocular motor dysfunction is present. The clinician should focus on asking questions about the types of activities that trigger symptoms, such as walking in a busy store or hallway, riding in a car, reading on a screen, etc. The VOMS can help identify patients that need formal evaluation and treatment by a trained physical therapist to mitigate the effects of untreated vestibular and ocular motor-related symptoms on recovery [17].

Vision problems are frequently reported immediately following a concussion and gradually improve, but, if unrecognized and untreated, these can be a cause of prolonged symptoms. Blurred vision, eye strain, and difficulty in using the eyes for tasks such as reading or screen time that provoke headaches and dizziness are common. Consequently, the concussed patient may also experience difficulty in reading, which can manifest in difficulty in school and concomitant poor academic or work performance. If not identified or treated correctly, vestibular and ocular motor system impairment recovery will be delayed and may have negative psychological ramifications [28]. Vision problems can be associated with headaches, dizziness, nausea, and cognitive symptoms. Vision-related symptoms can be a significant barrier to successfully returning to school and work. Generally, patients have co-impairment of the vestibular and ocular motor systems, which results in difficulties associated with alignment, convergence (bringing the eyes in to look at a nearby object), version (conjugate movements of the eyes in the same direction, e.g., moving both the eyes to the right), and accommodation (a mechanism by which the eyes make changes to look from a distant to a near image), leading to vision-related symptoms [29]. Convergence insufficiency (CI) is frequently reported following a pediatric concussion seen in as many as ~40% patients [30]. CI is a condition in which the eyes are unable to work synchronously to view a nearby image or object. One eye may fail to turn inward, causing blurry vision. CI is associated with difficulty in reading and provocation of headaches and can be treated with specific exercises and/or therapy.

Importantly, clinicians should not universally restrict the use of electronic devices or exposures to screens. Restricting email and social media can lead to social isolation and worsening of concussion-like symptoms. The judicious use of electronic devices and social media during recovery from a concussion may be undertaken to avoid the potential complications of boredom and social isolation as long as it does not significantly worsen the symptoms.

Lightheadedness: Lightheadedness is typically experienced with position change from lying or sitting to standing or with physical activity and exercise and may be mediated by the autonomic nervous system's dysfunction compared to dizziness caused by pathology in the vestibular system. During changes in posture, increases in heart rate may be noted without significant changes in blood pressure. Within the uninjured pediatric population, lightheadedness with standing is common, so it is crucial to distinguish lightheadedness that is new and that resolves through recovery [31]. Lightheadedness is typically transient, lasting seconds to minutes, and can be alleviated by sitting or lying. It is not commonly associated with other symptoms but, occasionally, can also be associated with nausea. In the recovery phase, lightheadedness gradually abates or returns to pre-injury levels. Hydration and mild limitations of physical activities can help alleviate these symptoms.

Cognitive Symptoms: Cognitive symptoms, such as confusion and memory problems, frequently occur in the pediatric population after a concussion. Acutely, confusions regarding time and place are common. Loss of consciousness (LOC), although dramatic, occurs in only ~5–10% of patients with a concussion [19]. In the minutes to hours following a concussion, the individual who has suffered the concussion may appear to be interacting with their environment naturally or may appear to be mildly impaired but may later report having no memory of events following the injury (~20%) (anterograde amnesia) and may report loss of memories before the event (~7%) (retrograde amnesia) [19]. Typically, this period is relatively short, lasting seconds to several minutes, but can extend for several hours before or after the injury. A particularly striking example of cognitive dysfunction soon after an injury is a presentation similar to transient global amnesia. In this presentation, the patient loses the ability to form new memories and, as a result, will ask the same questions repeatedly. Neither the presence of LOC or amnesia has been consistently demonstrated to be associated with adverse outcomes [32]. Cognitive testing after a concussion has consistently demonstrated that cognitive problems following a concussion are short-lived, with cognitive abilities returning to their pre-injury state within a week from injury [33]. However, some cognitive symptoms can persist past the first week well into the recovery phase [34]. Cognitive symptoms that persist longer than expected are generally related to symptom burden and resolve as other symptoms lessen or abate. Academic accommodations are vital to optimize recovery, and the individual should be encouraged to return to school. Clinicians should work with the school athletic trainer and school counselors to facilitate the accommodations necessary for a smooth transition back. Importantly, clinicians must decipher somatic issues that may be the sole cause of these complaints since pain or discomfort can impede the patient's ability to concentrate and process information, which can then negatively affect the patient's memory. A formal neurocognitive evaluation may be warranted in individuals who no longer report issues with sleep or have somatic complaints or mood changes but continue to report cognitive deficits.

Sleep Symptoms: Disturbances in sleep are commonly seen after a concussion [21, 35]. Sleep disturbance may contribute to and worsen other symptoms and recovery. Adequate high-quality sleep is essential for pediatric patients recovering

from a concussion. Head pain, dizziness, neck pain, and nausea can all lead to sleep-onset insomnia (difficulties going to sleep). Sleep maintenance insomnia (difficulty staying asleep) can also result in disrupted, low-quality sleep [36]. Often, physical activities during the day and sleep hygiene can improve sleep disturbances, but, occasionally, melatonin may be needed for sleep and can be started at a dose of 1–3 mg before bedtime for pediatric patients. Individuals with headaches or neck pain symptoms may often report sleep issues due to discomfort and a sensation of fogginess from the headache itself or sleep abnormalities. Sleep may be managed differently in these cases since neck pain is the leading cause of sleep disruption.

Mental Health: Immediately following a pediatric concussion, uncontrolled laughter or, more commonly, uncontrolled crying can occur. Irritability is commonly reported during the acute phase as well. During the recovery phase, new or worsened anxiety or depression can also develop. Mental health symptoms may be directly related to a concussion but are also influenced by downstream factors. Removal from school and activities that are key to developing self-identity, especially in the adolescent population, frequently lead to anxiety and depression. Concussion symptoms reduce the ability to engage in school work. Without academic accommodations, falling behind and reduced performance can lead to anxiety and, if not correctly managed, could lead to an altered academic trajectory and unfulfilled goals. If not identified and addressed, mental health issues can become more severe as recovery is prolonged and can become a major symptom generator for the pediatric patient with concussion. Identifying these issues early on and providing resources such as individualized therapy or cognitive behavioral therapy with a trained social worker, psychologist, or school counselor can help optimize recovery from concussion.

4 Symptoms Throughout the Acute Symptomatic and Recovery Phases

Recovery from a concussion can be divided into three phases: (1) acute symptomatic phase, (2) symptomatic recovery phase, and (3) recovery phase. The time spent in each phase is influenced by many modifiable factors and has individual variation. The key milestones in the recovery process are return-to-learn, return to school, return to exercise, and return to sport. These milestones are gradually achieved from limited activity, with some symptom worsening, to full participation without symptom provocation [29]. The acute symptomatic phase is defined as the time from injury through maximum symptom burden to the beginning of symptom resolution. Typically, this phase lasts less than 3 days. During the acute symptomatic phase, near-complete rest is essential, but, as soon as symptoms allow, returning to activities of daily living and light cognitive and physical activities should be undertaken. Common symptoms during the acute symptomatic phase include cognitive issues, head pain, spinal musculoskeletal pain, dizziness, visual problems, and mental

health issues. Although the symptom burden during the acute symptomatic phase may be quite limiting, it is important to return to light cognitive and physical activities as soon as possible. Complete restriction from normal activities of daily living for more than 1–3 days (aka cocoon therapy) can lead to prolonged recovery [37]. After a 1–2-day period of rest, gradually increasing cognitive and physical activities should be encouraged. The symptomatic recovery phase is characterized by a lessening symptom burden, the ability to perform more intense thinking and physical activities without significant symptom worsening, and a gradual return to the pre-injury state. During this phase, it is expected that symptoms may worsen with more taxing cognitive and physical activities but that the overall symptom burden gradually improves to the point of being asymptomatic at rest, with thinking activities, and then with physical exertion.

5 Symptom-Based Anticipatory Guidance

Symptom Based Return to Learning: Symptoms such as attention difficulties, memory problems, headaches, dizziness, and difficulties with vision can impede return to learning and school. Guidelines have been developed that can be used as a framework to facilitate return to learning, but recommendations should be individualized [38]. It is not expected that the student will be symptom-free during the return-to-learn process. The gradual transition to pre-injury performance can start with beginning school work at home in short 10–15-min intervals. Once the patient is able to engage in symptom-free periods of school work, they can undertake a gradual transition to the academic environment. Return-to-learn plans should be developed in collaboration with school personnel, physicians, and associated medical teams. The return-to-school environment can be eased by returning part-time with the use of breaks to alleviate symptoms. Students should not be expected to make up all the missed work during the recovery process. A plan for meeting the minimal requirements for missed work while performing essential work should be developed. Examinations should not be taken while being symptomatic from a concussion. The goal of these accommodations is to maintain the pace in classroom activities and to provide a smooth transition to full academic activities. The inability to maintain academic progress is a common source of psychiatric symptoms, and the development of a return-to-learn plan is critical to avoid this complication and prolong symptom burden. Successful return to school must occur before full return to sport [6].

Symptom-Based Return to Exercise and Play: Studies looking at the role of exercise in concussion recovery have determined that both too little and too much exercise may prolong recovery [39]. Optimal timing, duration, type, and intensity of exercise during the recovery phase are all areas of active research. Evidence suggests that after a short period of rest during the acute symptomatic phase, returning to activity and exercise that does not significantly worsen symptoms, i.e., subsymptom threshold exercise, facilitates recovery [40, 41]. As soon as symptoms allow,

returning to activities of daily living and light cognitive and physical activities should be undertaken. Examples of light thinking activities include watching television, pleasure reading (if tolerated), listening to music, and short periods of school work. Examples of light physical activities include light activities around the house and short walks. With commonly available exercise and monitoring equipment, determining the subsymptom exercise threshold is relatively straightforward and incorporated into outpatient concussion care [41]. In general, this consists of exercising on a stationary exercise machine, gradually increasing exertion. During the graded exertion, symptoms, heart rate, and relative perceived exertion are serially monitored. While being symptomatic from a concussion, it is expected that exercises will provoke symptoms in patients. The level of exercise that provokes symptoms is considered the "symptom exercise threshold." After the symptom threshold is determined, parameters can be set to perform exercises at an intensity below this level (subsymptom exercises). Because motion sensitivity and dizziness are frequent in the recovery phase, a stationary bike is preferred as the initial exercise equipment. At-home exercises generally consist of a 5-min warm-up, gradually building up the heart rate to achieve the subsymptom exercise heart rate goal, then maintaining the exercise intensity at approximately the subsymptom exercise heart rate goal for the duration of the exercise session, and then cooling down for 5 min. The recommended initial exercise duration is 15 min, and this can be lengthened to 30–45 min per day gradually and as tolerated. As recovery proceeds, the duration and intensity of exercises that are tolerated increase. At subsequent office visits, a new subsymptom threshold can be determined and new parameters for at-home exercises are recommended. During the recovery phase, beginning and then gradually advancing subsymptom threshold exercises should be undertaken to speed up recovery.

Return-to-play decisions can be complex; therefore, it is essential to understand the sport in question and its risks [42]. The progression should be overseen by a health-care provider trained in the evaluation and management of concussion. The return-to-play process begins with a subsymptom threshold exercise and then gradually proceeds through a stepwise progression by increasing exercise intensity, duration, and complexity (Table 2). The goal of the return-to-play process is to safely test for symptom provocation in a stepwise progression of increasing risk. If symptoms develop during or after the activity at an individual stage, then the following day, the same stage can be attempted again and the athlete does not progress. When asymptomatic at a given stage, the subsequent stage may be undertaken the following day. A slower progression may be used for children or as clinically warranted [21, 43].

Exercises performed while being symptomatic from a concussion should not be considered as part of the return-to-play protocol but as part of concussion treatment. Once a patient is asymptomatic at rest and is progressing with the subsymptom threshold exercise, the level of exercise that has been tolerated during the recovery phase can be used as a guide to understand where to begin the return-to-play protocol. For example, if jogging has not precipitated symptoms during the recovery

Table 2 Graduated return-to-play protocol

Stage of Activity	Activity	Stage Objective
Relative rest	Symptom-limited activities of daily living; light walking	Gradual reintroduction of activities involved with daily living and school/work.
Cardiovascular activity	Light to moderate aerobic exercise without resistance training on stationary bike or walking	Increase cerebral blood flow and heart rate.
Sport-specific non-contact exercise	Progressive aerobic exercise with sports-specific activity (drills) without head impact. May start progressive resistance training.	Interval training by adding fluctuations in heart rate and adding cognitive activity while increasing movement.
Non-contact training practice	Complex training drills, conditioning drills [can add limited controlled contact drills (e.g. pushing or hitting sleds or dummies)].	Increase cognitive demand and assess processing speed and coordination. Assess for recurrence of symptoms after adding limited controlled magnitude of force.
Unrestricted training	Participation in training activity only after medical clearance.	Assess for recurrence of symptoms. Assess functional skills by coaching staff. Ensure self-confidence and readiness to play.
Full return-to-play	Participation in full activity without restrictions	Full game day participation.

phase, then more intense running, such as sprints, can be initiated as the next stage in the return-to-play protocol in conjunction with non-contact training practice.

Determination of recovery from a concussion is challenging. A patient's report of symptom recovery may not accurately reflect the resolution of concussion pathophysiology [44]. A study of physiological markers suggests that they may be useful in return-to-play management [45, 46]. One approach utilizes the response to a high-intensity exercise with a cardiovascular load of a 90–100 maximum heart rate and incorporation of sport-specific agility. In this method, an asymptomatic athlete with a 90–100 maximum heart rate and high-intensity sport-specific agility is considered to have likely recovered from the concussion. Not until this is clinically observed can the patient be cleared to participate in higher-risk sport activities such as contact practice. The athlete can then progress to a full-contact practice and, if asymptomatic, can be cleared for full participation in sport.

6 Potential Long-Term Symptoms of Repetitive Mild Brain Trauma

There is concern that concussions or repetitive head impacts that not severe enough to cause concussions (subconcussive blows) may cause or be a risk factor for the development of symptoms later in life [47]. It is clear, primarily from studies of

retired boxers, that some individuals appear to have developed neurological and psychiatric problems secondary to repetitive mild head trauma in their athletic careers [48]. Researchers subsequently discovered microscopic brain changes, chronic traumatic encephalopathy (CTE), in individuals exposed to repetitive mild head trauma [47]. CTE is a pathological diagnosis, and the consequences of CTE pathology in life are unknown. The important issue of the risks of long-term consequences in children who participate in contact and collision sports has been addressed in epidemiological studies that did not identify long-term neurological or psychiatric consequences, but further studies are needed for children having moderate and severe traumatic brain injuries [49, 50].

7 Clinical Pearls/Key Points

- The treatment approach to concussions has evolved to include a more individualized symptomatic approach to concussion management.
- A concussion can result in various non-specific symptoms that often overlap with preexisting medical conditions, such as migraine, mood disorders, or learning disabilities. It is essential to differentiate whether the symptoms are new or long-standing and also whether the long-standing symptoms are worse after the concussion.
- Identifying symptoms, including headache, neck pain, vestibular, oculomotor, cognitive, sleep, and mental health symptoms, as well as examination findings can be used to guide individualized treatment strategies.
- Evidence supporting the use of daily preventative medications, typically used to treat migraine, is lacking and should be avoided in managing acute concussion.
- Clinicians must be aware of the increased emphasis on the return-to-play, return-to-learn, parental education, and longer-term follow-up of pediatric patients diagnosed with a concussion.

References

1. Centers for Disease Control and Prevention. Report to congress: the management of traumatic brain injury in children. Atlanta, GA: National Center for Injury Prevention and Control; Division of Unintentional Injury Prevention; 2018.
2. Arbogast KB, Curry AE, Pfeiffer MR, Zonfrillo MR, Haarbauer-Krupa J, Breiding MJ, et al. Point of health care entry for youth with concussion within a large pediatric care network. JAMA Pediatr. 2016;170(7):e160294.
3. McCrory P, Meeuwisse W, Aubry M, Cantu B, Dvorak J, Echemendia RJ, et al. Consensus statement on concussion in sport—the 4th international conference on concussion in sport held in Zurich, November 2012. Clin J Sport Med. 2013;23(2):89.

4. Dobson JL, Yarbrough MB, Perez J, Evans K, Buckley T. Sport-related concussion induces transient cardiovascular autonomic dysfunction. Am J Physiol-Regul Integr Comp Physiol. 2017;312(4):R575–R84.
5. Master CL, Scheiman M, Gallaway M, Goodman A, Robinson RL, Master SR, et al. Vision diagnoses are common after concussion in adolescents. Clin Pediatr. 2015;55(3):260–7.
6. McCrory P, Meeuwisse W, Dvorak J, Aubry M, Bailes J, Broglio S, et al. Consensus statement on concussion in sport-the 5th international conference on concussion in sport held in Berlin, October 2016. Br J Sports Med. 2017;51(11):838.
7. Charek DB, Collins M, Kontos A. Office-based concussion evaluation, diagnosis, and management: adult, vol. 158. Netherlands: Elsevier Health Sciences; 2018. p. 91–105.
8. McCrea M, Hammeke T, Olsen G, Leo P, Guskiewicz K. Unreported concussion in high school football players: implications for prevention. Clin J Sport Med. 14(1):13–7.
9. Schutzman S, Mannix R. Injury: head. In: Shaw K, Bachur R, editors. Fleisher and Ludwig's textbook of pediatric emergency medicine. 7th ed. Philadelphia: Wolters Kluwer; 2016. p. 247–53.
10. Sarmiento K, Thomas KE, Daugherty J, Waltzman D, Haarbauer-Krupa JK, Peterson AB, et al. Emergency department visits for sports- and recreation-related traumatic brain injuries among children—United States, 2010-2016. MMWR Morb Mortal Wkly Rep. 2019;68(10):237–42.
11. Centers for Disease Control and Prevention: Traumatic brain injury and concussion 2019 [cited 2021 February 6]. https://www.cdc.gov/traumaticbraininjury/get_the_facts.html.
12. Pierpoint LA, Collins C. Epidemiology of sport-related concussion. Clin Sports Med. 2021;40(1):1–18.
13. Paquin H, Taylor A, Meehan WP 3rd. Office-based concussion evaluation, diagnosis, and management: pediatric. Handb Clin Neurol. 2018;158:107–17.
14. Sport concussion assessment tool, 5th ed. Br J Sports Med; 2017. https://bjsm.bmj.com/content/bjsports/early/2017/04/26/bjsports-2017-097506SCAT5.full.pdf.
15. Echemendia RJ, Meeuwisse W, McCrory P, Davis GA, Putukian M, Leddy J, et al. The sport concussion assessment tool 5th edition (SCAT5): background and rationale. Br J Sports Med. 2017;51(11):848–50.
16. Mucha A, Collins MW, Elbin RJ, Furman JM, Troutman-Enseki C, DeWolf RM, et al. A brief vestibular/ocular motor screening (VOMS) assessment to evaluate concussions. Am J Sports Med. 2014;42(10):2479.
17. Alsalaheen B, Carender W, Grzesiak M, Munday C, Almeida A, Lorincz M, et al. Changes in vestibular/ocular-motor screen scores in adolescents treated with vestibular therapy after concussion. Pediatr Phys Ther. 2020;32(4):331–7.
18. Howell DR, Osternig LR, Chou LS. Single-task and dual-task tandem gait test performance after concussion. J Sci Med Sport. 2017;20(7):622–6.
19. McCrea M, Guskiewicz KM, Marshall SW, Barr W, Randolph C, Cantu RC, et al. Acute effects and recovery time following concussion in collegiate football players: the NCAA Concussion Study. JAMA. 2003;290(19):2556–63.
20. Doperak JDO, Anderson KDO, Collins MP, Emami KP. Sport-related concussion evaluation and management. Clin Sport Med. 2019;38(4):497–511.
21. Harmon KG, Drezner J, Gammons M, Guskiewicz K, Halstead M, Herring S, et al. American Medical Society for sports medicine position statement: concussion in sport. Clin J Sport Med. 2013;23(1):1.
22. Lucas S, Hoffman JM, Bell KR, Dikmen S. A prospective study of prevalence and characterization of headache following mild traumatic brain injury. Cephalalgia. 34(2):93–102.
23. Kennedy E, Quinn D, Chapple C, Tumilty S. Can the neck contribute to persistent symptoms post concussion? A prospective descriptive case series. J Orthop Sports Phys Ther. 2019;49(11):845–54.
24. Quatman-Yates CC, Hunter-Giordano A, Shimamura KK, Landel R, Alsalaheen BA, Hanke TA, et al. Physical therapy evaluation and treatment after concussion/mild traumatic brain injury. J Orthop Sports Phys Ther. 2020;50(4):Cpg1–cpg73.

25. Ellis MJ, Cordingley D, Vis S, Reimer K, Leiter J, Russell K. Vestibulo-ocular dysfunction in pediatric sports-related concussion. J Neurosurg Pediatr. 2015;16(3):248–55.
26. Corwin DJ, Wiebe DJ, Zonfrillo MR, Grady MF, Robinson RL, Goodman AM, et al. Vestibular deficits following youth concussion. J Pediatr. 2015;166(5):1221–5.
27. Guskiewicz KMPATC. Balance assessment in the management of sport-related concussion. Clin Sport Med. 2011;30(1):89–102.
28. Anzalone AJ, Blueitt D, Case T, McGuffin T, Pollard K, Garrison JC, et al. A positive vestibular/ocular motor screening (VOMS) is associated with increased recovery time after sports-related concussion in youth and adolescent athletes. Am J Sports Med. 2017;45(2):474–9.
29. Ciuffreda KJ, Kapoor N, Rutner D, Suchoff IB, Han ME, Craig S. Occurrence of oculomotor dysfunctions in acquired brain injury: a retrospective analysis. Optometry (Saint Louis, MO). 78(4):155–61.
30. Pearce KL, Sufrinko A, Lau BC, Henry L, Collins MW, Kontos AP. Near point of convergence after a sport-related concussion : measurement reliability and relationship to neurocognitive impairment and symptoms. Am J Sports Med. 2015;43(12):3055–61.
31. Skinner JE, Driscoll SW, Porter C-BJ, Brands CK, Pianosi PT, Kuntz NL, et al. Orthostatic heart rate and blood pressure in adolescents: reference ranges. J Child Neurol. 25(10):1210–5.
32. Iverson GL, Gardner AJ, Terry DP, Ponsford JL, Sills AK, Broshek DK, et al. Predictors of clinical recovery from concussion: a systematic review. Br J Sports Med. 2017;51(12):941.
33. Rohling ML, Binder LM, Demakis GJ, Larrabee GJ, Ploetz DM, Langhinrichsen-Rohling J. A meta-analysis of neuropsychological outcome after mild traumatic brain injury: re-analyses and reconsiderations of Binder et al. (1997), Frencham et al. (2005), and Pertab et al. (2009). Clin Neuropsychol. 2011;25(4):608–23.
34. Alsalaheen B, Stockdale K, Pechumer D, Broglio SP, Marchetti GF. A comparative meta-analysis of the effects of concussion on a computerized neurocognitive test and self-reported symptoms. J Athl Train. 2017;52(9):834–46.
35. Phillips S, Woessner D. Sports-related traumatic brain injury. Prim Care. 2015;42(2):243–8.
36. Murdaugh DL, Ono KE, Reisner A, Burns TG. Assessment of sleep quantity and sleep disturbances during recovery from sports-related concussion in youth athletes. Arch Phys Med Rehabil. 99(5):960–6.
37. Schneider KJ, Leddy JJ, Guskiewicz KM, Seifert T, McCrea M, Silverberg ND, et al. Rest and treatment/rehabilitation following sport-related concussion: a systematic review. Br J Sports Med. 2017;51(12):930.
38. O'Neill JA, Cox MK, Clay OJ, Johnston JM Jr, Novack TA, Schwebel DC, et al. A review of the literature on pediatric concussions and return-to-learn (RTL): implications for RTL policy, research, and practice. Rehabil Psychol. 2017;62(3):300–23.
39. Grool AM, Aglipay M, Momoli F, Meehan WP, Freedman SB, Yeates KO, et al. Association between early participation in physical activity following acute concussion and persistent postconcussive symptoms in children and adolescents. JAMA. 316(23):2504–14.
40. Leddy JJ, Haider MN, Ellis MJ, Mannix R, Darling SR, Freitas MS, et al. Early subthreshold aerobic exercise for sport-related concussion: a randomized clinical trial. JAMA Pediatr. 2019;173(4):319–25.
41. Popovich M, Almeida A, Freeman J, Eckner JT, Alsalaheen B, Lorincz MT, et al. Use of supervised exercise during recovery following sports-related concussion. Neurology 2018;91(23 Supplement 1):S15-S.
42. Almeida A, Kutcher J. In: Daroff RB, Jankovic J, Mazziotta JC, Pomeroy S, editors. Neurology in clinical practice. 7th ed. Philadelphia, PA: Elsevier; 2014.
43. Guay JL, Lebretore BM, Main JM, DeFrangesco KE, Taylor JL, Amedoro SM. The era of sport concussion: evolution of knowledge, practice, and the role of psychology. Am Psychol. 2016;71(9):875.
44. Kamins J, Bigler E, Covassin T, Henry L, Kemp S, Leddy JJ, et al. What is the physiological time to recovery after concussion? A systematic review. Br J Sports Med. 51(12):935–40.

45. Haider MN, Leddy JJ, Pavlesen S, Kluczynski M, Baker JG, Miecznikowski JC, et al. A systematic review of criteria used to define recovery from sport-related concussion in youth athletes. Br J Sports Med. 2018;52(18):1179–90.
46. Marshall CM, Chan N, Tran P, DeMatteo C. The use of an intensive physical exertion test as a final return to play measure in concussed athletes: a prospective cohort. Phys Sportsmed. 2019;47(2):158–66.
47. Manley GT, Gardner AJ, Schneider KJ, Guskiewicz KM, Bailes J, Cantu RC, et al. A systematic review of potential long-term effects of sport-related concussion. NewsRX LLC; 2017. p. 271.
48. Roberts AH. Brain damage in boxers: a study of the prevalence of traumatic encephalopathy among ex-professional boxers. London: Pitman Medical & Scientific Publishing Co, Ltd; 1969, 132 p. p.
49. Deshpande SK, Hasegawa RB, Rabinowitz AR, Whyte J, Roan CL, Tabatabaei A, et al. Association of playing high school football with cognition and mental health later in life. JAMA Neurol. 2017;74(8):909.
50. Janssen PHH, Mandrekar J, Mielke MM, Ahlskog JE, Boeve BF, Josephs K, et al. High school football and late-life risk of neurodegenerative syndromes, 1956-1970. Mayo Clin Proc. 2017;92(1):66.

Child with Neurocutaneous Syndrome

James H. Tonsgard and Nikolas Mata-Machado

1 Neurocutaneous Disorders

1.1 Introduction

1.1.1 Activation of the Mechanistic Target of Rapamycin (mTOR) Pathway

Neurocutaneous disorders are a heterogeneous group of diseases that share skin and brain involvement. Most neurocutaneous disorders involve activation of signaling components, both upstream and downstream of the protein kinase mammalian target of rapamycin (mTOR). Upstream of mTOR, the key signaling molecules are p21 Ras guanosine triphosphate (GTP)ase, Raf, Mek, Erk, the lipid kinase phosphoinositide 3-kinase (PI3K), the Akt kinase, tuberous sclerosis complex (TSC)1/TSC2, and the GTPase Rheb. Downstream pathways regulate angiogenesis, protein translation, gene amplification, and cell cycling. Defects in these signaling molecules and pathways form the molecular basis for tuberous sclerosis complex (TSC), neurofibromatosis type 1 (NF-1), Proteus syndrome, Cowden syndrome, Lhermitte–Duclos disease, Sturge–Weber disease, and Von Hippel–Lindau disease [1]. The mTOR signaling pathway is depicted in Fig. 1.

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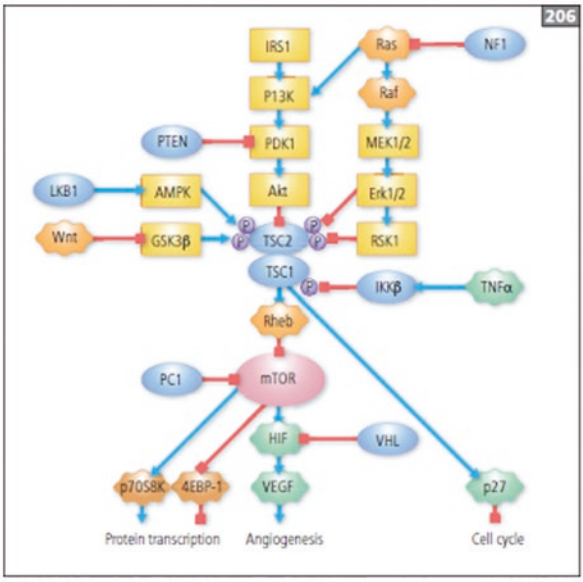

Fig. 1 The mammalian rapamycin target (mTOR) signaling pathway, showing key signaling molecules upstream and downstream of mTOR. Mutations in the mTOR component genes, *TSC1*, *TSC2*, *LKB1*, *PTEN*, *VHL*, *NF1*, *PKD1* (*PC1*), and *IKK*, result in the development of tuberous sclerosis complex (TSC1 and TSC2), Peutz–Jeghers syndrome, Cowden syndrome, Bannayan–Riley–Ruvalcaba syndrome, Lhermitte–Duclos disease, Proteus syndrome, Von Hippel–Lindau disease (VHL), neurofibromatosis type 1 (NF-1), polycystic kidney disease, and incontinentia pigmenti. Activation of the PI3K–Akt pathway and increased vascular endothelial growth factor (VEGF) receptors are implicated in neurofibromatosis type 2 (NF-2). *HIF* hypoxia-inducible factor, *TNF* tumor necrosis factor, *VEGF* vascular endothelial growth factor

2 Neurofibromatosis Type 1 (NF-1)

2.1 Introduction and Epidemiology

NF-1 is a common autosomal dominant disorder, presenting with hyperpigmented macules of the skin (café au lait spots). There is multisystemic involvement including learning problems, bony abnormalities, eye abnormalities (optic gliomas and Lisch nodules in the iris), and an increased risk of certain forms of cancer. Tumors of the peripheral nerves (cutaneous or dermal neurofibromas) and tumors of the nerve trunks and roots (plexiform neurofibromas) may occur.

The incidence of NF-1 is 1 in 2500– 3000 live births. NF-1 affects males and females equally [2]. NF-1 occurs in all racial and ethnic groups. Manifestations of NF-1 are often apparent at birth and are more evident within the first years of life. One-half of all cases are spontaneous mutations.

2.2 Etiology and Pathogenesis

NF-1 occurs due to a gene defect on chromosome 17q that encodes the protein neurofibromin, a Ras guanosine triphosphate (GTP)ase-activating protein (Ras GAP). Neurofibromin is ubiquitous, with the highest expression in the nervous system. Neurofibromin stimulates the hydrolysis of GTP bound to p21 Ras, converting it to the inactive state. Active Ras stimulates cell growth and proliferation and is part of the mTOR signaling pathway. NF-1 results from dysregulation of cell growth and proliferation due to excessive Ras activation [3]. It is inherited in an autosomal dominant manner.

2.3 Differential Diagnosis

The differential diagnosis for NF-1 includes:

(a) Legius syndrome, an autosomal dominant condition caused by mutation of the *SPRED 1* gene. Like NF-1, it is characterized by café au lait spots, learning disabilities, and pulmonic stenosis but lacks neurofibromas. It is distinguished by genetic testing.
(b) Mosaic NF-1: Patients who have isolated features of NF-1 such as plexiform neurofibromas or café au lait spots localized to one side of the body, or to one quadrant, have mosaicisms, with one segment of the body having the *NF1* gene mutation and the rest of the body having a normal *NF1* gene. Similarly, there are patients with mild features of NF-1 who have whole-body mosaicisms.
(c) Schwannomatosis is a condition in which there are multiple nerve tumors, including the tumors of the spinal roots. This disease lacks café au lait spots, skin tumors, and intracranial features of NF.

2.4 Diagnostic Approach

2.4.1 History

Half of patients have a family history of NF-1, café au lait spots, or skin tumors. Patients often have developmental delay, learning problems, macrocephaly, or hypotonia in infancy.

2.4.2 Physical Examination

General Examination

An examination should focus on blood pressure, the skin, head, eyes, spine, and long bones.

(a) Hypertension occurs in a small percentage of young children and is usually indicative of renal artery stenosis.
(b) Skin: Café au lait spots are defined as hyperpigmented macules >0.5 cm in children and >1.5 cm in adults. They are often present at birth. Another clinical hallmark is axillary and inguinal freckling. Freckles tend to occur later than café au lait spots, around 3–10 years of age. The cardinal feature of NF-1 is a "neurofibroma," which is a tumor of the nerve consisting of a proliferation of Schwann cells, fibroblasts, mast cells, blood vessels, and extracellular matrix with nerve fibers running through the tumor mass. Neurofibromas can occur along small nerve fibers, spinal roots, plexi, nerve trunks, and autonomic nerves. Dermal neurofibromas are well-circumscribed tumors in the skin. Plexiform neurofibromas are similar but contain more extracellular matrix and sometimes appear in grape-like clusters distorting large nerves. The skin overlying plexiform neurofibromas is often thick and hyperpigmented. Plexiform neurofibromas may be well-circumscribed or highly invasive and infiltrative. Cutaneous neurofibromas occur in most NF patients, usually developing in the late teens or in young adults. They start as small, raised, soft papules or sometimes as purplish depressible macules along small nerve fibers and can enlarge over time to become pedunculated or even pendular. See Fig. 2 for examples of café au lait lesions and neurofibromas. Some neufibromas may be difficult to diagnose at the bedside. Figure 3 illustrates a neurofibroma on the flank of an individual with NF1.
(c) Head: Macrocephaly is a common feature in young children. Serial measurement of the head circumference is important during early childhood.
(d) A fundoscopic examination may reveal optic disc pallor (suggestive of an optic glioma), and the iris may show Lisch nodules (Fig. 4) which are typically not present until teenage years. A small percentage of patients have hypoplasia of the sphenoid wing, resulting in one eye being lower than the other and slightly proptotic, and, so, the orbits must be assessed for symmetry.

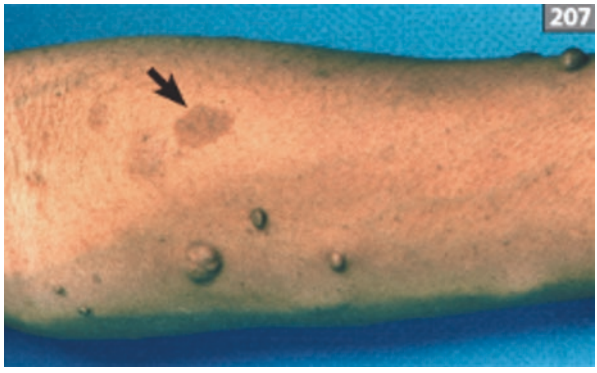

Fig. 2 A café au lait spot (arrow) and several pedunculated dermal neurofibromas on the forearm of a patient with NF-1

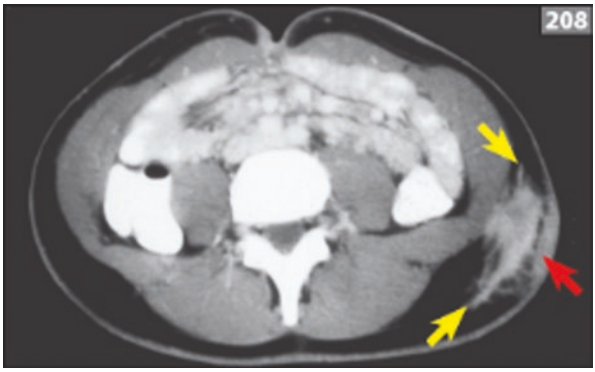

Fig. 3 A superficial plexiform neurofibroma. A CT scan of the abdomen showing an area of increased signaling on the left side of the patient's flank in the subcutaneous fat with some thickening of the skin (red arrow). The plexiform neurofibroma has thin "fingers" that extend to the limit of the abdominal musculature (yellow arrows)

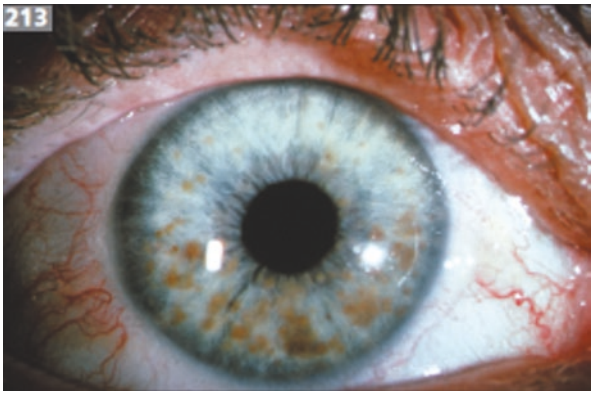

Fig. 4 Lisch nodules. A photograph of the eye of a patient with NF-1, showing a large number of reddish-brown spots predominantly in the lower pole of the iris

(e) Skeletal: A skeletal examination may reveal scoliosis and tibial bowing, in infants, suggestive of dysplasia (Fig. 5). It is important to look at the symmetry of limbs. Hypertrophy of one extremity may suggest an underlying plexiform neurofibroma.

Neurological Examination

Neurological examination often shows hypotonia in infancy. Cognitive assessment may show mild developmental delay, hyperactivity, a short attention span, and poor articulation; however, profound intellectual disability is atypical.

Gait should be examined. Tibial torsion and gait problems are common. Hyperactive or asymmetric tendon reflexes can be associated with paraspinal tumors and cord compression. This would be an unusual finding in children but is not uncommon in young adults.

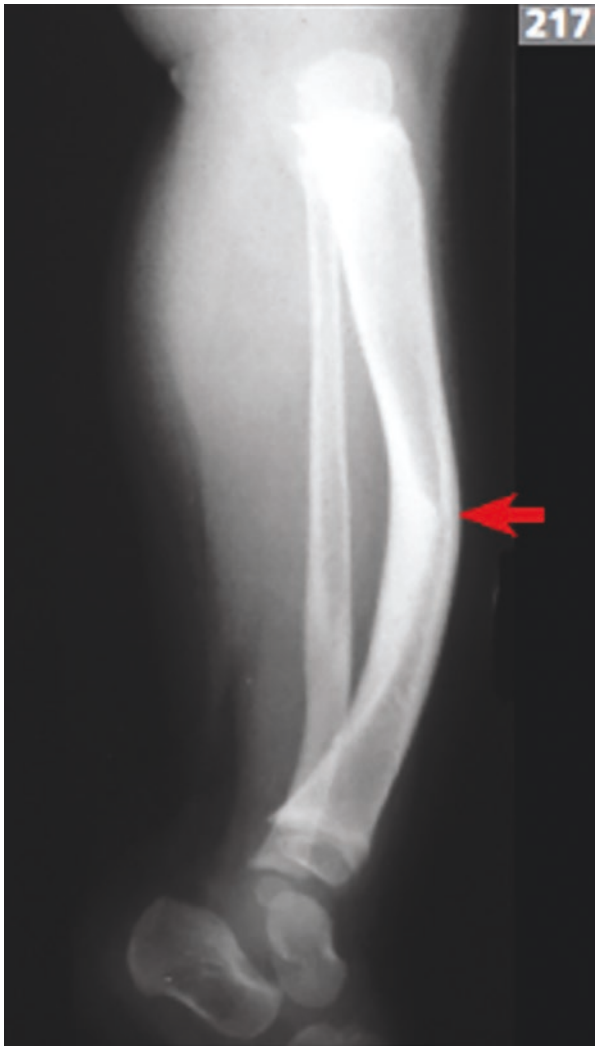

Fig. 5 Lateral view X-ray of the tibia and fibula, showing anterior bowing and narrowing of the intramedullary canal (red arrow)

2.4.3 Evaluations

The diagnosis of NF-1 can be usually made clinically and frequently at birth. Since café au lait spots and freckling may increase or appear over time, the diagnosis is sometimes delayed until 5–6 years of age. The diagnosis of NF-1 requires at least two of the following:

- Six or more café au lait spots that are >0.5 cm in diameter in pre-pubertal patients or >1.5 cm in diameter in post-pubertal patients
- Axillary or groin freckling
- Two or more cutaneous neurofibromas

- One plexiform neurofibroma
- Two or more iris Lisch nodules
- An optic glioma
- Characteristic bony lesions: sphenoid wing hypoplasia, dystrophic scoliosis, or pseudarthrosis
- A first-degree relative with NF-1

Genetic testing has >95% accuracy and can also identify patients with mosaicisms, large deletions, and some mutations that can help predict the clinical course. Genetic testing to confirm the diagnosis is therefore strongly recommended.

Routine imaging for screening purposes is not currently recommended because many lesions remain asymptomatic, and an incidental discovery of an asymptomatic abnormality would not significantly change management. Nevertheless, a whole-body magnetic resonance imaging (MRI) is used by some groups to assess tumor burden. Since recent studies have shown that mitogen-activated protein kinase (MEK) inhibitors can shrink plexiform neurofibromas in some patients, this may be a rationale in the future for surveillance of tumor burden including asymptomatic tumors.

Radiologic examination may show a variety of classic features:

2.4.4 Brain

- White matter hyperintensities (WMHs), previously called unidentified bright objects (UBOs), are seen on MRI in the basal ganglia, thalamus, pons, and cerebellum (Fig. 6). WMHs are prominent in some children and tend to disappear in adult years.

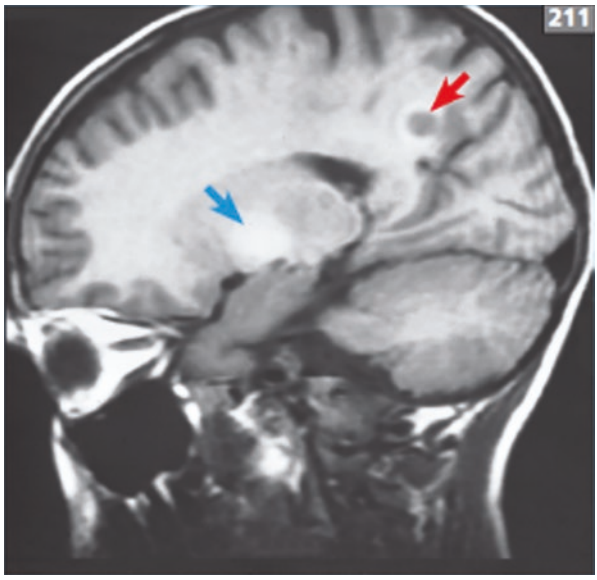

Fig. 6 Grade I glioma and WMHs in NF-1. A sagittal T1-weighted MRI of the brain, showing a target-like grade I glioma (red arrow) and an WMH in the basal ganglia (blue arrow)

- Grade I astrocytomas in the cortex, white matter, optic tracts, hypothalamus, and brainstem are found in 3–15% of patients and may regress over time. They are often asymptomatic. Figure 7 illustrates optic gliomas in a young child.
- Grades III and IV gliomas are uncommon and primarily seen in adults. The most common location is in the cerebellum.

2.4.5 Skeletal Changes in the Skull and Vertebral Bodies

Hypoplasia of the sphenoid wing is characteristic of NF 1 (Fig. 8). Scoliosis is found in up to 50% of patient with at least 3% having a severe dystrophic scoliosis (Fig. 9).

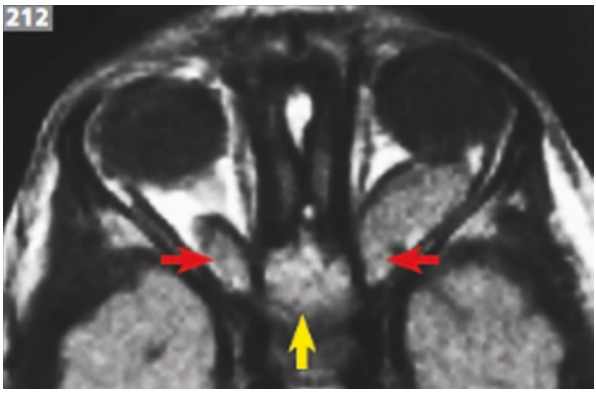

Fig. 7 An optic glioma. An axial T1-weighted MRI of the brain through the orbits, showing markedly enlarged optic nerves bilaterally (red arrows) as well as an enlarged optic chiasm (yellow arrow)

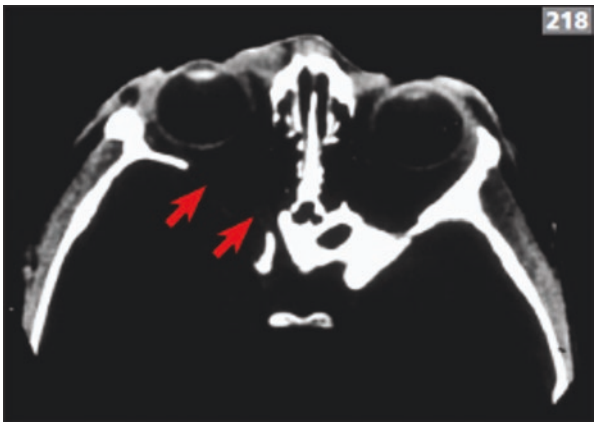

Fig. 8 Bone windows of a CT scan of the orbits, showing the absence of a portion of the back of the orbit on the right (arrows) due to hypoplasia of the sphenoid wing

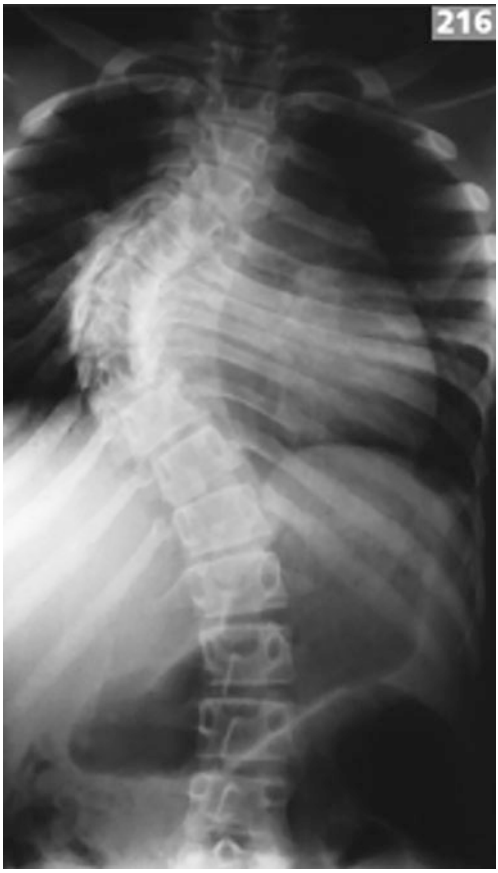

Fig. 9 An anterior–posterior chest X-ray, showing a marked scoliosis characteristic of the dystrophic scoliosis seen in neurofibromatosis type 1

2.4.6 Spinal Cord

A spine MRI can reveal paraspinal tumors, which can potentially compress the cord. These are more commonly identified in young adults and adults. MRIs of the spine or extremities may show plexiform neurofibromas that can appear as grape-like clusters on the nerves or nerve trunks (Fig. 10).

2.5 Treatment/Management

Treatment of NF1 is symptomatic at the present time. However, it is important to institute a regular regime of annual examinations to detect complications. Since the complications are age-specific, it is possible to focus on different problems at different ages:

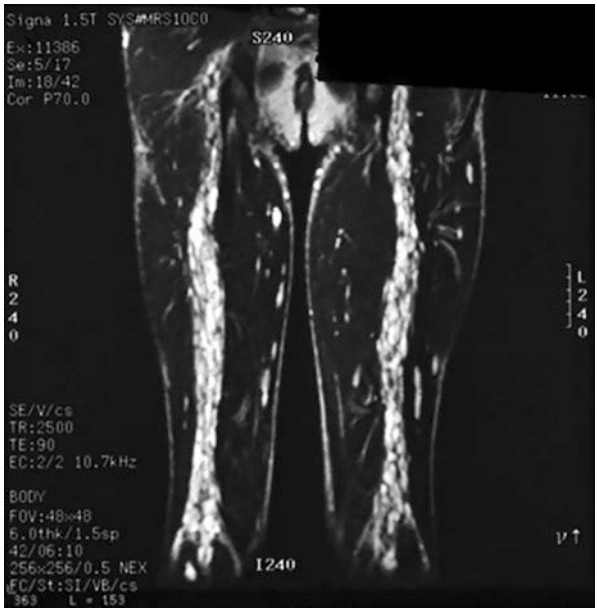

Fig. 10 An MRI of the proximal legs, showing nodular clusters of plexiform neurofibromas along the length of both sciatic nerves, with a number of isolated intramuscular and cutaneous neurofibromas that are visualized by increased signal intensity

- Birth and infancy:
  - Check the long bones.
  - Look for externally visible plexiform neurofibromas.
  - Monitor developmental milestones.
- Early childhood:
  - Monitor language and developmental milestones.
  - Check the spine for scoliosis.
  - Conduct an annual eye examination.
  - Check blood pressure.
- Childhood:
  - Monitor learning, attention span, and socialization.
  - Conduct an annual eye examination.
  - Check the spine for scoliosis.
- Teenage years:
  - Monitor learning and socialization.
  - Check for cutaneous neurofibromas.
- Adults:
  - Check for hypertension.
  - Check for cutaneous neurofibromas.
  - Investigate any cause of pain.

Genetic Counseling/Family Planning is Important in Management: Parents of patients should be carefully examined, and genetic testing should be considered for those who have features suspicious of NF-1. Recent studies have shown that a number of patients with NF-1 have parents who are mosaics with only minor features such as a few café au lait spots.

Surgical removal of visible and stigmatizing cutaneous tumors is appropriate. Careful debulking or even complete removal of plexiform neurofibromas is possible in some patients.

Additional organ-specific investigations may be indicated:

2.5.1 Brain

The intellectual development of patients with NF-1 should be carefully monitored. Formal developmental or neuropsychological testing is initiated if there is developmental delay or school problems. Tutoring is helpful for kids with learning disabilities. Speech therapy and physical therapy can be helpful adjuncts. Counseling is often indicated, especially in teenage years to help deal with the emotional burden of a chronic disease.

Imaging of the brain is not recommended unless patients are symptomatic. Seizures can sometimes be subtle. If there are staring episodes or sleep disturbances, then a 24-h electroencephalogram (EEG) is recommended, particularly in children with NF-1 with autism, cognitive developmental delay, or significant behavioral problems because the incidence of seizures in that group is significantly increased.

2.5.2 Eyes

Annual eye examinations to measure acuity and the appearance of the optic nerve are recommended for all patients between the ages of 18 months and 10 years. Significant deterioration in acuity needs to be assessed by an MRI. However, it is important to understand that less than half of optic gliomas impair vision and neither location of the optic nerve tumors nor contrast enhancement can predict deterioration in vision.

2.5.3 Cardiovascular

Hypertension in children requires a computed tomography (CT) angiogram of the kidneys. Since patients with renal artery stenosis may also have cerebral vascular disease, a brain MR angiogram (MRA) may also be warranted.

2.5.4 Skeletal/Orthopedic

If there is bowing of the long bones, particularly the tibia, within the first year of life, plain X-rays will reveal dysplasia. Tibial dysplasia can fracture and may be difficult to heal, so early identification is important. Any evidence of spinal curvature should also be investigated by X-rays and potentially followed up with an MRI. Muscle or skeletal pain is an unusual complaint and should be investigated, preferably with an MRI. Disturbances in gait or paresthesias may indicate spinal cord compression and should be evaluated by a spine MRI.

2.5.5 Prognosis

The majority of patients can lead normal and productive lives. NF-1 is associated with a mildly shortened life span because of the higher incidence of malignancy. Large numbers of cutaneous neurofibromas or large visible plexiform neurofibromas may seriously affect function and socialization in a small percentage of patients. Large plexiform neurofibromas can produce pain. A larger problem is recognizing and effectively treating learning disabilities. Owing to our understanding of the pathogenesis of NF, management and outcome are changing. Recent clinical trials of MEK inhibitors have shown considerable success in the treatment of plexiform neurofibromas as well as low-grade gliomas. The identification of chemotherapeutic approaches offers considerable hope.

2.5.6 When to Refer

Patients with NF-1 are best followed in multidisciplinary clinics in major medical centers with extensive experience with NF-1. Some of the complications of NF-1 are best observed, but this requires experience and judgment because some complications can be rapidly progressive, causing significant morbidity or mortality.

Key Points

- Half of all cases of NF-1 are familial. It is important to examine parents to look for features of NF and provide genetic counseling if the parents are affected.
- NF-1 is progressive, meaning that certain features can change or worsen with time and that different complications can occur at different ages.
- Genetic testing is accurate in 95% of cases and can provide confirmation of diagnosis as well as identify mosaicisms and specific mutations, which have a different prognosis. Genetic testing will also be helpful in the future for family planning.
- Regular examinations are important to identify new complications.
- Learning should be carefully monitored and, if needed, evaluated because of the high incidence of learning problems.
- Considerable advances have been made in understanding and treating NF-1.

3 Neurofibromatosis Type 2 (NF-2)

3.1 Introduction and Epidemiology

NF-2 is a genetic disorder characterized by multiple tumors of the central nervous system (CNS). The hallmark is a vestibular schwannoma, usually bilateral. Tumors of the spinal roots, spinal cord, and brainstem as well as meningeal-derived tumors are frequent. Although classically placed under the category of neurocutaneous syndromes it is different from other disorders in this category as there are no cutaneous findings.

The incidence is 1 in 25,000 live births. NF-2 is an autosomal dominant disorder that affects males and females equally [2]. It occurs in all racial and ethnic groups. One-half of all cases are spontaneous mutations, and almost two-thirds of nonfamilial cases are due to somatic mosaicisms. The mean age of onset/detection is 19 years, so it is predominantly a disease of young adults but pediatric cases certainly occur.

3.2 Etiology and Pathogenesis

NF-2 occurs due to a defect in chromosome 22q encoding the protein merlin. The signaling pathways linked to merlin include receptor tyrosine kinase (RTK), cell adhesion, small GTPases, mTOR, PI3K/Akt, and hippo pathways. Merlin acts as a tumor suppressor and regulator of Schwann and meningeal cells, with the highest level of expression in Schwann cells, meningeal cells, peripheral nerves, and the lens. Loss of merlin causes cell proliferation and tumor formation. The exact mechanism is unknown, but activation of the P13kinase–Akt and hippo pathways is clearly implicated.

3.2.1 Differential Diagnosis

The differential diagnosis includes:

1. Isolated CNS tumors. Since NF-2, like all the neurocutaneous disorders, is progressive, it is not unusual to see a child present with an isolated feature, such as a meningioma, a cataract, or a cranial nerve (CN) schwannoma, who will eventually develop more features of NF-2 during young adult years. The diagnosis may be difficult because more than half of all sporadic cases of NF-2 are mosaics, so genetic testing for NF-2 is often negative.
2. NF-2 must sometimes be distinguished from schwannomatosis. The latter is characterized by the presence of multiple nerve sheath tumors that are schwannomas. There are no other tumor types or vestibular schwannomas in

schwannomatosis. Recent studies have shown that a substantial percentage of patients with familial schwannomatosis and a small percentage of patients with sporadic schwannomatosis actually have NF-2. Distinguishing these two diseases requires genetic testing of the blood as well as of tumor samples. Schwannomatosis is often characterized by severe nerve pain and tends to be a disease of adulthood, although it can present in teenage years.

3.2.2 Diagnostic Approach

History

The history of children with NF-2 often reveals the presence of a cataract or strabismus due to a schwannoma of CN III (the oculomotor nerve) or CN VI (the abducens nerve). Seizures can also be a presenting feature with an MRI showing the presence of a cortical meningioma. Sometimes a child will present with unilateral facial weakness that does not resolve, and an MRI will show a schwannoma of the cranial nerve. Rarely is a skin tumor noticed, which, on a pathological review, is found to be a plexiform schwannoma. Unilateral hearing loss is usually an adult complication.

Physical Examination

When examining children, limitation of eye movements may be suggestive of a cranial nerve schwannoma. Rarely are skin tumors seen. Otherwise, the physical examination tends to be unremarkable.

Evaluations

An MRI of the brain with internal auditory canal views with and without contrast and an MRI of the entire spine with and without contrast are essential tests and are usually diagnostic. Contrast is an essential feature because both meningiomas and schwannomas enhance with administration of contrast material. In childhood, vestibular schwannomas can be small and easily missed, especially if the examination does not include views of the internal auditory canal and contrast. See the images below (Figs. 11 and 12):

A diagnosis can be made clinically if there is:

- A bilateral vestibular schwannoma or
- A first-degree relative with NF-2 and a unilateral vestibular schwannoma or any two of a meningioma, schwannoma, or glioma, or
- A unilateral vestibular schwannoma and any two of a meningioma, schwannoma, glioma, neurofibroma, or posterior subcapsular cataract, or

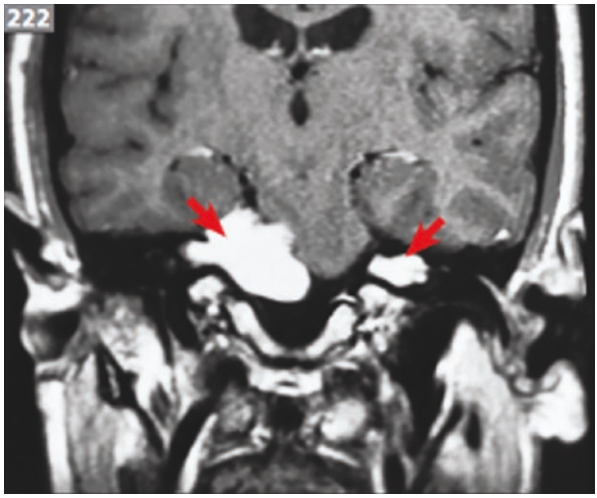

Fig. 11 Bilateral vestibular schwannomas. A coronal T1-weighted MRI with gadolinium enhancement in a patient with neurofibromatosis type 2, showing bilateral enhanced vestibular nerve tumors (arrows) compressing and displacing the pons

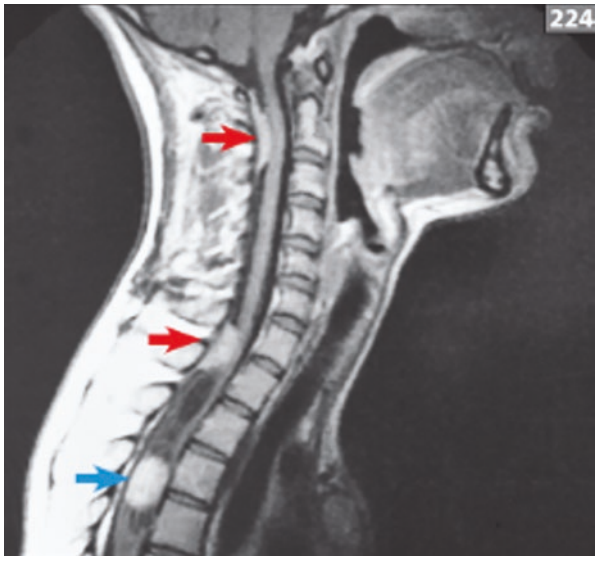

Fig. 12 Spinal cord lesions in neurofibromatosis type 2. A sagittal T1-weighted MRI of the cervical and thoracic spinal cord with gadolinium enhancement, showing two enhanced extramedullary tumors, which are meningiomas (red arrows), and an enhanced intramedullary cervical cord astrocytoma (blue arrow) with a syrinx (beginning at T1)

- Multiple meningiomas (two or more) and a unilateral schwannoma or any two of a schwannoma, glioma, neurofibroma, or cataract

Genetic Testing: Genetic testing is accurate in at least 90% of patients with germline mutations and typical NF-2. However, because almost 70% of patients with no family history have somatic mosaicisms, it is considerably more difficult to diagnose these patients using conventional genetic testing of blood. In these cases, genetic testing of the tumor is essential. A careful analysis of a large cohort of NF-2 patients has shown that molecular characterization of patients provides important

information that can guide clinical management. A variety of mutations have been demonstrated, including missense mutations, nonsense mutations, large deletions, splice-site mutations, point mutations, and small deletions. Missense mutations are associated with longer survival than are nonsense and frameshift mutations. Patients with mosaicisms may have a milder course and a lower risk of having offspring with NF-2. It is anticipated that treatment of NF-2 could ultimately be dictated by the genetic information.

4 Treatment/Management

Treatment is largely symptomatic and not without controversy, although advances in chemotherapy may ultimately significantly impact NF-2. Physicians must remember that intervention has potential consequences/complications. Aggressive prophylactic surgical intervention has not shown benefit compared to intervention dictated by clinical symptoms.

4.1 Vestibular Tumors

Resection of vestibular tumors in NF-2 is often more difficult than is treatment of sporadic vestibular schwannomas because the tumors can be multifocal and recur. Resection of vestibular tumors can be complicated by hearing loss and facial weakness. The treatment approach is to some extent dictated by the size of the vestibular schwannomas. Fractionated radiotherapy is used in some centers. It is not without long-term complications. Chemotherapy directed at VEGF expression may significantly reduce the size of large inoperable vestibular tumors and improve hearing. Additional chemotherapy approaches are undergoing evaluation.

4.2 Meningiomas

Although meningiomas are benign tumors, it is difficult to completely resect them. Often, the best course is to observe them by serial neurological examinations and imaging and operate only when symptomatic. The development of appropriate chemotherapy offers the best long-term hope.

4.3 Ependymomas

These are usually indolent intradural spinal cord tumors in NF-2. They almost never show evidence of malignancy and can often be observed without surgical intervention. Chemotherapy directed at VEGF receptors can reduce the cysts in ependymomas and reduce clinical symptoms.

4.4 Cataracts and Eyes

Cataracts usually do not require removal. Poor eyelid closure due to VIIth nerve injury can be surgically facilitated. Frequent eye drops help with dryness. No treatment is currently available for retinal hamartomas.

4.5 Hearing Loss

Cochlear implantation has shown some benefit in NF-2 patients and may influence the surgical approach to vestibular tumors. Signing is an important skill for patients and families to develop because of inevitable hearing loss. Because hearing loss can be due to an inflammatory process in the semicircular canals, steroids and other anti-inflammatory agents may be helpful.

4.6 Genetic Counseling

The risk of NF-2 for each pregnancy is 50%. The risk is less in mosaics. Assessment of children of patients is important because many patients with NF-2 are diagnosed after they have already had children.

4.7 Prognosis/Outcome

NF-2 is a severe progressive disorder that results in a shortened life span. However, the spectrum of severity can be quite wide and the tumors in NF-2 are often quite indolent. The age of onset and the number of tumors are helpful predictors of outcome: early onset and multiple brain and spinal tumors are associated with a poorer prognosis. Genetic testing also provides guidance on severity. As molecular understanding of this disease improves, chemotherapeutic approaches are likely to provide substantial help.

4.8 When to Refer

All NF-2 patients should be managed by multidisciplinary clinics devoted to NF-2. Many patients are best managed by careful observations. Decisions about surgery are often complicated and best handled by an experienced team familiar with NF-2.

Key Points

- The Manchester (modified National Institutes of Health (NIH)) diagnostic criteria for NF-2 are the most reliable.
- More than half of all spontaneous cases of NF-2 are mosaics, making genetic testing more complicated.
- Early aggressive surgery of asymptomatic lesions has not proven to improve prognosis. Tumors in NF-2 can be indolent and can remain static for prolonged periods, justifying a careful observation.
- Parents of patients with NF-2 should be evaluated with brain imaging because mosaicisms with mild features are common.
- Children with an isolated meningioma or schwannoma should be carefully evaluated for NF-2.

5 Tuberous Sclerosis Complex (TSC)

5.1 Introduction

TSC is a progressive disease characterized by hypopigmented macules of the skin, migrational errors of the brain, seizures, and cognitive impairment and hamartomas of multiple organ systems, including the skin, kidneys, brain, lungs, and heart.

5.2 Epidemiology

The prevalence is 1 in 6800–17,300 children. The age of onset is usually infancy. TSC is an autosomal dominant disorder with males and females being equally affected [2]. There is a high spontaneous mutation rate with only 40% cases being familial in nature.

5.3 Etiology and Pathogenesis

TSC occurs due to inactivation of either the *TSC1* gene on chromosome 9q or the *TSC2* gene on chromosome 16p, encoding the proteins hamartin and tuberin, respectively. These proteins are abundantly expressed in the brain, as well as in other tissues, and function as a heterodimeric signaling complex. Expression is

prominent in the embryo and is important for brain development and cellular organization. Hamartin may interact with the ezrin, radixin, and moesin (ERM) proteins (see NF-2) and regulate cytoskeleton-mediated processes, whereas tuberin appears to be GTPase-activating (GAP protein, see NF-1). The hamartin/tuberin complex is an important negative regulator of mTOR. TSC is believed to be associated with a relative GABAergic deficiency.

5.4 Differential Diagnosis

The differential diagnosis includes:

1. Genetic malformations of the brain and genetic epileptic syndromes.
2. Polycystic kidney disease

5.5 Diagnostic Approach

5.5.1 History

Intractable epilepsy, especially infantile spasms, can be a feature of TSC. A familial or personal history of epilepsy, autism, or polycystic kidney disease would be suggestive of TSC in patients with hypopigmented macules.

5.5.2 Physical Examination

A physical examination of patients with TSC reveals hypopigmented macules in 61–97% of cases. These are round or oval (ash-leaf spots). Some patients have small scattered hypopigmented spots (confetti lesions). Both ash-leaf spots and confetti lesions are best seen in a darkened room using an ultraviolet lamp. Children may also have small, raised areas of thickened skin on the back resembling the skin of an orange (shagreen patch). In late childhood years, patients develop flat, topped, brownish-red papules of the face in a butterfly distribution (adenoma sebaceum), which is sometimes confused with acne, or flat raised plaques on the forehead (fibrous plaques). Figure 13 depicts adenoma sebaceum on the face of a child with TSC. Older teenagers and young adults may have lesions growing from the bed of the fingernails or toenails (Fig. 14). A neurocognitive examination often reveals developmental or cognitive delay.

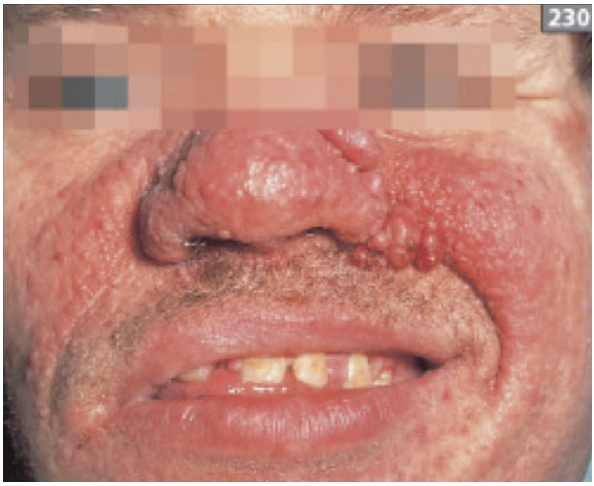

Fig. 13 Adenoma sebaceum. A photograph of the face of a patient with TSC, showing diffuse severe angiofibromas of the cheeks, chin, forehead, and nasolabial folds

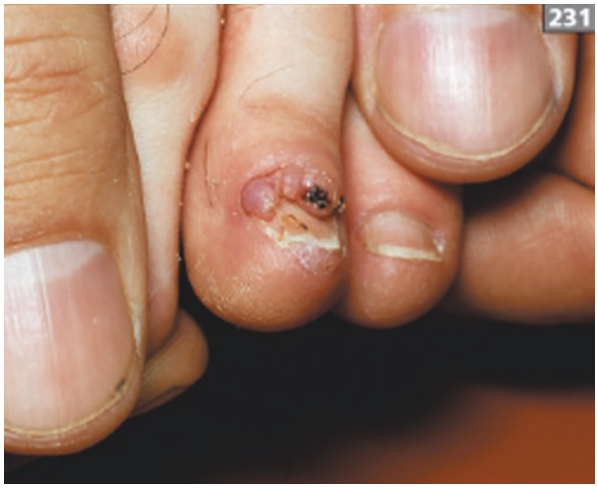

Fig. 14 Ungual fibromas. A photograph of the toes of a patient with tuberous sclerosis, showing multiple angiofibromas growing out of the nail bed, with a small superficial hemorrhage

5.5.3 Evaluations

A fetal ultrasound often detects TSC on the basis of intracardiac tumors or subependymal brain lesions in utero. After birth, an MRI of the brain with and without contrast is essential for evaluating the features of TSC. An MRI will reveal cortical tubers, subependymal nodules, and white matter lesions in most patients. A CT scan of the brain can show calcified subependymal nodules. Echocardiogram, CT, and MRI of the heart and kidneys can reveal intraventricular tumors and kidney cysts. An EEG is essential for the characterization and treatment of seizures. An EEG is strongly recommended for all infants with TSC within the first year of life even in the absence of seizures to look for any abnormal or potentially epileptogenic activity.

Genetic testing can identify mutations in 85–90% of patients. It is strongly recommended for all patients and should be considered in parents as well because of the potential for mosaicism in them. Knowing the genetic mutation can impact management.

A diagnosis can be usually made clinically by the presence of two major or one major and two minor criteria but should be confirmed by genetic testing:

- Major criteria: facial angiofibroma, ungual fibroma, shagreen patch, hypopigmented spots, cortical tuber, subependymal nodule, subependymal giant cell astrocytoma (SEGA), retinal hamartoma, cardiac rhabdomyoma, renal angiomyolipoma, lymphangiomyomatosis
- Minor criteria: dental enamel pits, hamartomatous rectal polyps, gingival fibroma, confetti skin lesions, multiple renal cysts

The radiologic findings of each organ system are listed below:

5.5.4 Brain

An MRI of the brain shows areas of broadening of the gyri on the surface referred to as cortical tubers (Fig. 15). The number of tubers varies in different patients. The tubers are composed of interlacing rows of fibrous astrocytes. The normal layered

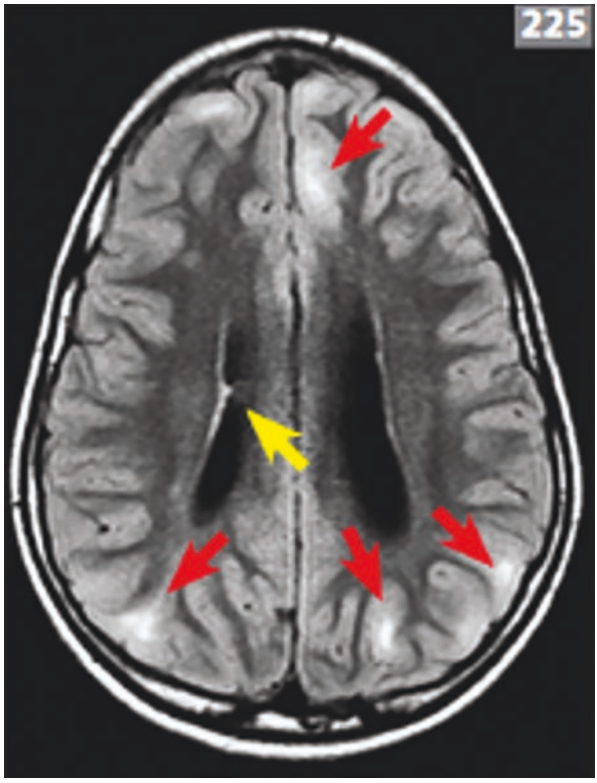

Fig. 15 Cortical tubers. An axial fluid-attenuated inversion recovery (FLAIR) MRI of the brain, showing areas of increased signaling within the cortex (red arrows) as well as slight swelling of the gyri. There are also subependymal nodules (yellow arrow) on the ventricular surface

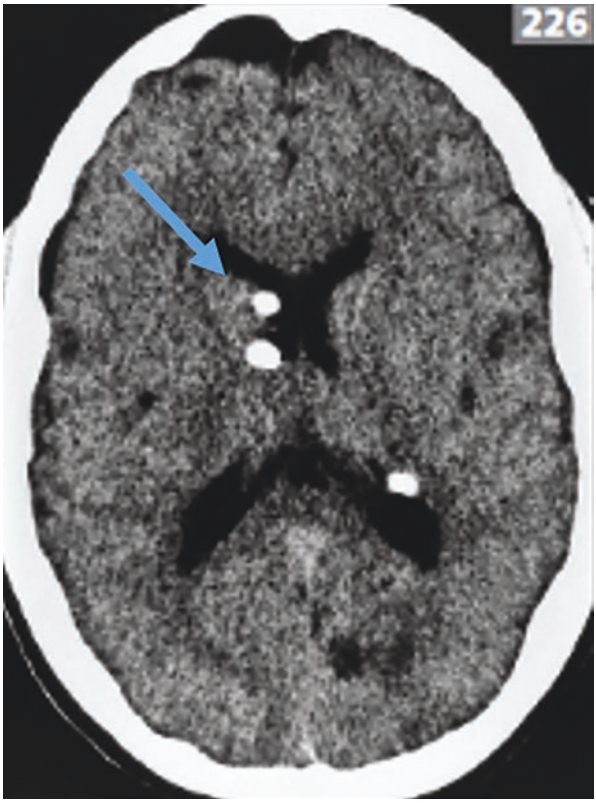

Fig. 16 A CT non-contrast scan of the brain, showing bright, calcified subependymal nodules bilaterally on the ventricular surface in tuberous sclerosis

architecture of the cerebral cortex is diffusely disturbed in the tubers, with increased glial cells, atypical large neurons, and giant glial cells.

The surface of the lateral ventricles may be encrusted with subependymal nodules made of glial cells, blood vessels, and abnormal neurons, which tend to calcify (Fig. 16). Some subependymal nodules have the potential to increase in size, transforming into SEGAs (subependymal giant cell astrocytomas), which can obstruct the foramen of Monro, causing hydrocephalus in 10% of patients (Fig. 17).

5.5.5 Kidneys

Imaging of the kidneys may reveal tumors and cysts. Angiomyolipomas (AMLs), found in 80% of patients, are tumor-like masses in the kidneys, consisting of sheets of disorganized smooth muscles, fat, foam cells, and large thick-walled blood vessels. They vary in size, measuring as much as 20 cm (8 in) in diameter. They are typically multiple and bilateral, bulging from the surface of the kidneys or

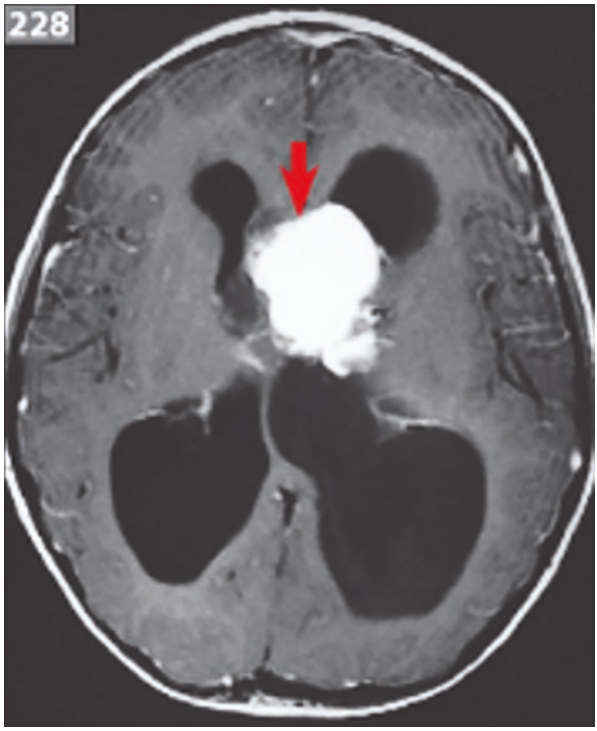

Fig. 17 An axial T1-weighted MRI with gadolinium enhancement, showing an enhanced subependymal giant cell astrocytoma (SEGA) at the foramen of Monro (arrow), with obstruction of the foramen and resulting enlarged lateral ventricles (hydrocephalus)

compressing and distorting the renal pelvis. They may be subtle in young children, enlarging in adulthood. Renal cysts are another feature of TSC and occur throughout the parenchyma in at least 20% of patients. The cysts are lined with the hyperplastic epithelium. Cysts, in some patients, are related to contiguous deletions affecting the polycystic kidney disease gene (*PKD1*) on chromosome 16. Like AMLs, renal cysts may be small in young children, enlarging with time, although a small percentage of young children have severe polycystic disease.

5.5.6 Heart

Rhabdomyomas are found in 50% of children and represent hamartomas of myocytes. They vary in size from millimeters to several centimeters and are most commonly found in the ventricles. They may be entirely intramural or protrude from the cardiac surface. They may obstruct valvular function or impinge on the cardiac conduction system in the first few months of life. After that, the tumors tend to involute.

5.5.7 Lungs

Lymphangiomyomatosis (LAM) occurs in 24–49% of adult female patients and resembles emphysematous changes. This is not seen in children.

5.5.8 Treatment/Management

TSC is a highly variable condition even within the same pedigree. Patients may range from having severe cognitive developmental delay with intractable seizures to mild, unnoticed disease. In the past, the diagnosis was made in infancy due to the appearance of seizures or developmental delay; mild cases often escaped notice. With the practice of ultrasounds to follow pregnancies, more and more children are being diagnosed in utero on the basis of rhabdomyomas of the heart and subependymal nodules in the brain. Mutations in the *TSC1* gene are associated with a milder phenotype. The complications of TSC, like the other neurocutaneous disorders, are age-specific.

Treatment is essentially symptomatic, and much of the treatment focuses on neurological complications. However, management is changing. The discovery that mTOR inhibitors (rapalogs) could shrink SEGAs in TSC has led to their application with considerable success. Animal models of TSC demonstrate improvement or even normalization of abnormalities with early exposure to rapalogs so that the emphasis is now on early identification of complications and extremely early intervention. In addition, because seizures in TSC often respond to vigabatrin, a gamma aminobutyric acid (GABA) agonist, it is postulated that patients with TSC have a relative deficiency of GABA in the brain. Early use of vigabatrin can reduce seizures.

Seizures and TSC-associated neuropsychiatric disorders (TANDs) are major complications of TSC and need to be identified early so that an intervention can be implemented. Seizures occur in 92% of patients, usually starting in infancy, with 90% occurring by the age of 3 years. Virtually all seizure types occur. Infantile spasms are the presenting sign in 70% of children. TSC is the cause of 25% of all cases with infantile spasms. Traditionally, seizures in TSC were often difficult to control and required consideration of more invasive treatments such as a vagal nerve stimulator and epilepsy surgery. However, a recent clinical trial of early intervention with vigabatrin before 1 year of age has suggested that seizures can be reduced in severity and number. Data from animal models demonstrating improvement with extremely early use of vigabatrin and mTOR inhibitors suggest that an extremely early treatment (within the first 6 weeks of life) with one or both medicines could substantially improve outcome. An early identification of autism with an appropriate behavioral intervention can also be helpful. Medication may be required to control behavior in some patients. Attention to appropriate support for learning in patients is essential.

Hydrocephalus caused by SEGAs obstructing cerebrospinal fluid (CSF) outflow from the lateral ventricles can be a major problem. Traditionally, SEGAs causing obstruction were treated surgically; however, trials of mTOR inhibitors indicate that as many as 77% of patients demonstrate a response of 30% or more tumor shrinkage. Regular brain imaging is important to identify growth of SEGAs and then treat patients with mTOR inhibitors.

Cardiac manifestations rarely require intervention and should be managed conservatively. Kidney lesions are monitored closely, and ablation of enlarged angiomyolipomas needs to be discussed. mTOR inhibitors can shrink angiomyolipomas and kidney cysts in many patients, so regular imaging of the kidneys is an important part of management. Adults, particularly women, need to undergo CT scans of the chest to look for any evidence of lymphangioleiomyomatosis (LAM).

Facial angiofibromas worsen with exposure to the sun, so sunscreen is important. Facial angiofibromas respond to both oral and topical rapalogs.

5.5.9 Prognosis

TSC is a progressive disorder with a shortened life span. However, because of the marked variability of expression, a significant percentage of patients may lead normal lives. With a greater understanding of the molecular basis of TSC, the use of medications, such as mTOR inhibitors, is already having a considerable impact on the disease and offers considerable hope.

5.5.10 When to Refer

Patients with TSC require a multispecialty approach to monitor all the aspects of TSC so that early intervention can be implemented. Since the management of TSC is changing with our understanding of the molecular biology, all of these patients should be referred to specialized clinics.

Key Points

- TSC has a wide spectrum of disease severity including some mildly affected individuals.
- TSC is a progressive multisystem disease. Seizures and cognitive development tend to capture early attention, but it is important to recognize that other organ systems can be affected, especially later.
- Inhibitors of mTOR have been extremely effective in treating complications.
- Early identification and intervention in TSC can have dramatically positive benefits.
- TSC appears to have a relative deficiency of GABA so that the antiepileptic vigabatrin can be extremely helpful.

6 Sturge–Weber Syndrome (SWS)

6.1 Introduction and Epidemiology

SWS is a neurocutaneous disorder characterized by a clinical triad of:

- A facial capillary cutaneous angioma (port-wine stain) that is usually unilateral but can occasionally be bilateral
- Abnormal blood vessels of the meninges (leptomeningeal angioma), usually ipsilateral to the skin lesion
- Abnormal blood vessels in the eye, leading to glaucoma

However, the syndrome is defined by a leptomeningeal angioma. Not all patients have other features. The incidence of SWS is 1 in 20,000–50,000 live births. It is a sporadic condition that affects both genders equally.

6.2 Etiology and Pathogenesis

SWS occurs ‘dueto a somatic mutation in the *GNAQ* gene in the skin and meninges. *GNAQ* encodes Ga_q, a member of the G-protein alpha subunits that mediate signals between G-protein-coupled receptors and downstream effectors. The mutation results in a reduction in GTPase activity, leading to increased signaling activity. It is postulated that dysregulation through G-protein-coupled receptors such as that for endothelin may result in malformed, progressively dilated blood vessels. A developmental abnormality of the embryonic vascular plexus in the cephalic mesenchyme adjacent to the telencephalic vesicle is postulated, which produces tortuous abnormal blood vessels in the leptomeninges, with sluggish blood flow that results in progressive ischemia to the underlying cortex.

Leptomeninges appear to be thickened and discolored by the angioma. Calcification of the meningeal arteries and cortical and subcortical veins underlying the angioma is present, as is laminar necrosis of the cortex. Neuronal loss and gliosis occur, with progression of the condition and recurrent thrombi due to venous stasis. There is progressive ischemia and atrophy of the underlying cortex.

6.3 Differential Diagnosis

The differential diagnosis is between an isolated congenital facial angioma and SWS. The risk of SWS in children with a facial angioma is 6% and increases to 26% when the port-wine stain is located in the distribution of the ophthalmic division of the trigeminal nerve.

6.3.1 Diagnostic Approach

History

Seizures, either partial or generalized, occur in 75–90% of cases, usually begin in infancy or early childhood, and are the first neurological symptom. Seizures can be intractable in 50% of cases. Recurrent transient focal deficits occur, usually hemiparesis or visual deficits, which last for hours or days. Headaches may be prominent and occur in 30–45% of cases. Developmental delay is commonly appreciated after normal milestones, initially, in two-thirds of patients.

Physical Examination

Skin: A cutaneous angioma on one side of the face and scalp is present, usually involving the first (ophthalmic) division of the trigeminal nerve (Fig. 18). The angioma has a deep red color (port-wine stain) that is present at birth and may be flat or slightly raised.

Eyes: Glaucoma occurs in 30–70% of patients. The affected eye may have a hazy cornea, may be injected, and may be larger than the contralateral eye. Most children develop glaucoma in infancy, and the remainder develop it in childhood or adult years.

Neurological Examination: Hemiparesis and hemiatrophy of the contralateral extremities are present in the majority of patients. Developmental delay or cognitive impairment may be apparent. Cognitive developmental delay is present in 50%. Hemianopsia may be present due to involvement of the occipital lobe.

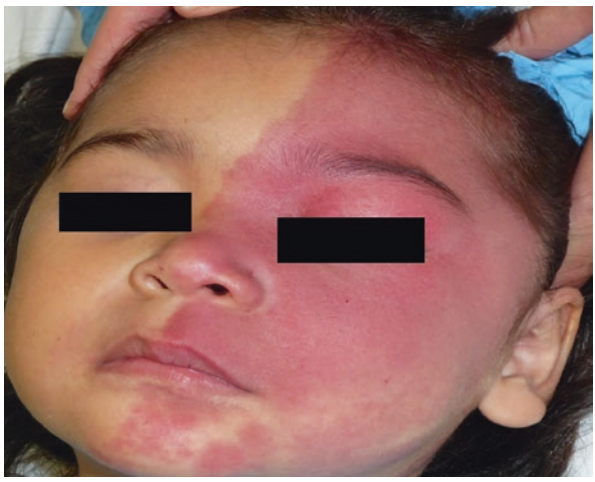

Fig. 18 A patient with a reddish cutaneous capillary angioma on one side of the face, involving all divisions of the trigeminal nerve

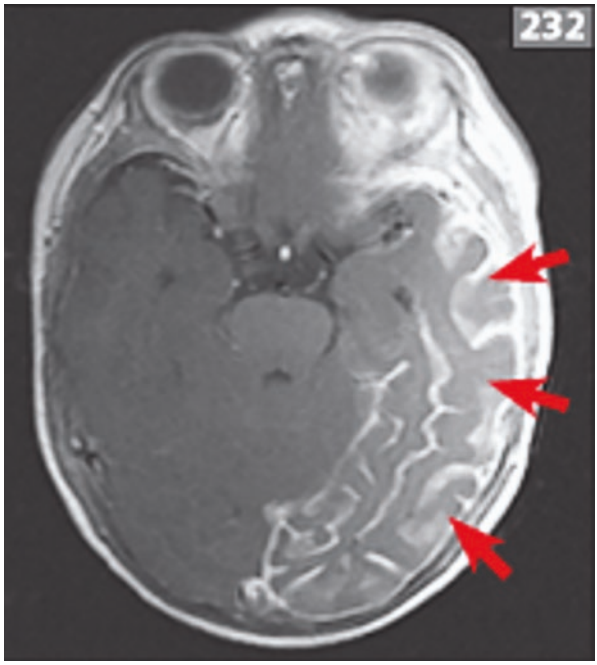

Fig. 19 A Sturge–Weber meningeal angioma. A post-contrast axial MRI of the brain, showing enhancement of the temporal, parietal, and occipital gyri (arrows) in the left hemisphere, with some left cortical atrophy

6.3.2 Evaluations

An MRI/MRV (magnetic resonance venography) of the brain is essential (Fig. 19). However, a CT scan can demonstrate calcification of the underlying cortex relatively early, usually within the first 2 years of life.

The diagnosis is usually straightforward in patients with all three characteristic features: a facial angioma, a leptomeningeal angioma, and the presence of glaucoma. However, in the first few months of life, the leptomeningeal angioma may be hard to detect and glaucoma can have a later onset. Additionally, not all patients have all three features. Some may only have a leptomeningeal angioma, so a repeat imaging of patients with recurrent focal seizures in infancy is important.

An EEG, particularly prolonged recordings, is essential for characterizing seizures and detecting subtle subclinical activity.

Positron emission tomography (PET) imaging may be useful in demonstrating decreased metabolism in the affected areas.

6.4 Treatment/Management

Aggressive control of seizures is essential. Radiologic studies suggest that seizures are associated with ischemic injury to the cortex underlying the leptomeningeal angioma because of abnormal regulation of blood flow in these vessels. This leads to laminar necrosis.

The goal is to minimize seizures. Epilepsy surgery should be discussed in some patients with intractable seizures. This is controversial because of the variable clinical course. It is also important to realize that epilepsy can be intractable in the first or second year of life, but seizures are often less frequent thereafter. Teenagers and adults can be seizure-free, even without seizure medicine.

Early antithrombotic therapy (i.e., daily aspirin) is important. This reduces cortical ischemia. Glaucoma should be treated with topical eye drops (beta blockers or carbonic anhydrase inhibitors) or surgical intervention, e.g., trabeculectomy. Educational assessment is important to identify learning difficulties and provide appropriate support. The most severely affected patients are those with bilateral disease who are not good surgical candidates. Laser treatment of the face is effective in eliminating a facial angioma and usually begins in the second to third year of life.

6.5 Prognosis

Prognosis varies widely because the extent of a leptomeningeal angioma can vary. The pace of the clinical course of SWS seems to be faster in early childhood and often stabilizes thereafter. SWS can present difficult problems and devastating complications in some patients; however, in others, the course is much milder.

Patients with seizure disorders can be seizure-free for many years with minimal deficits. In some patients, however, intractable seizures can also be quite mild and relatively infrequent. Half of patients graduate from secondary/high school and a significant percentage live independently.

7 Hereditary Hemorrhagic Telangiectasia (HHT)(Osler–Rendu–Weber Syndrome)

7.1 Definition and Epidemiology

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder characterized by multiple telangiectasias involving the skin, mucous membranes, viscera (particularly the gastrointestinal tract (GI) (liver and gut), nose, lungs, and genitourinary tracts), and, occasionally, the nervous system. HHT is often complicated by arteriovenous malformations (AVMs) in the brain, lungs, GI, and liver.

The prevalence of HHT is variable: 1 in 1331 in The Netherlands Antilles to 1 in 39,000 in northern England. A worldwide prevalence of 1 in 5000 is postulated. Although telangiectasias appear in childhood, the manifestations are primarily in adults. Both genders are equally affected.

7.2 Etiology and Pathophysiology

HHT has an autosomal dominant inheritance. A linkage analysis indicates at least five genes, four of which have been identified. The genes for HHT are located in the transforming growth factor-beta (TGF-ß) signaling pathway. Mutations in endoglin or *ENG*, activin receptor-like kinase or *ALK1/ACVRL*, and Smad 4 can cause the combined juvenile polyposis HHT syndrome. Endoglin and ACVRL1 mutations are seen in roughly 85% of cases and Smad4 mutations occur in less than 2%. Mutations in the bone morphogenetic 9 protein (*BMP9 – GDF2* gene) have been reported in some patients. Approximately 15% of patients who appear to have HHT clinically do not have identifiable mutations.

The genes for HHT encode proteins that modulate transforming growth factor (TGF)-ß superfamily signaling in vascular endothelial cells. Mutations lead to the development of fragile telangiectatic vessels and AVMs. TGF-ß modulates several processes of endothelial cells.

The fundamental lesion is a dysplasia of the vessel wall. Bleeding is due to the mechanical fragility of the vessel. Pulmonary and hepatic AVMs create a right-to-left shunt that may lead to cerebral hypoxia and polycythemia and may allow the passage of emboli (thrombotic, septic) from the systemic venous circulation or the right heart to the brain, causing stroke and cerebral abscess.

Telangiectasias range from small, focal dilatations of the post-capillary venules to large, markedly dilated and convoluted venules, which extend through the entire dermis, have excessive layers of smooth muscle without elastic fibers, and often connect directly to the dilated arterioles. Telangiectasias are commonly found in the skin, face, tongue, oral mucosa, conjunctiva, trunk, and gastrointestinal (GI) tract.

7.2.1 Differential Diagnosis

The differential diagnosis includes isolated vascular malformations and coagulation disorders.

7.2.2 Diagnostic Approach

History

Spontaneous and recurrent severe nosebleeds are the most common and earliest manifestation, often in early childhood. This is really the only feature in children. There is a rare form of HHT linked to a defect in the *SMAD4* gene that is associated with juvenile polyposis. Because this is an autosomal dominant disorder, there is often a family history of severe nosebleeds as well as pulmonary and brain AVMs and recurrent GI bleeding.

7.2.3 Physical Examination

General Examination

A skin examination reveals telangiectasias, which are bright red or violaceous, ranging in size from that of a pinhead to >3 mm. They blanch under pressure and have a tendency to bleed. They are widely distributed, apparent on the face, tongue, oral mucosa, and trunk (Fig. 20). Telangiectasias first appear during childhood, enlarge during adolescence, and may assume spidery forms, resembling the cutaneous telangiectasias seen with liver cirrhosis, in late adult life. They are found in at least 80% of patients in the skin, lips, and mouth.

Neurological Examination

A neurological examination in childhood is normal.

Evaluations

Blood tests:

- A full blood count will show severe anemia with iron deficiency.
- Genetic testing: If the phenotype is classic, then target genetic testing for mutations in ENG and ACVRL1 is appropriate, followed by testing SMAD4 if negative.

Additional testing in adults would include brain imaging to look for AVMs; however, screening is controversial because most cerebral AVMs never bleed. In adults, a CT scan of the chest as well as echocardiography are useful to look for pulmonary

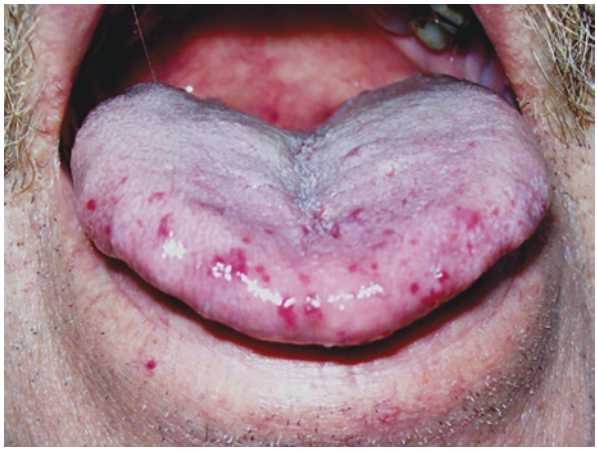

Fig. 20 A photograph of a patient with hereditary hemorrhagic telangiectasia, showing multiple small telangiectasias of the tongue and lower lips

AVMs and endoscopy and GI angiography can reveal GI AVMs and other vascular lesions.

Clinical diagnosis is based on the presence of three criteria; however, any two of the following are suspicions for HHT:

- Spontaneous, recurrent, and severe epistaxis
- Multiple telangiectasias at characteristic sites (the lips, oral cavity, fingers, nose)
- Visceral involvement:
  - Gastrointestinal telangiectasias with or without bleeding
  - Pulmonary AVM
  - Hepatic AVM
  - Cerebral AVM
  - Spinal AVM
- A first-degree relative with HHT. All offspring of an individual with HHT are at risk of the disease since it may not manifest until later in life.

Coagulation disorders should be excluded.

7.3 Treatment/Management

7.3.1 Telangiectasias

- Nasal:
- Humidification and packing of the nose is best carried out with lubricated, deflatable packing. Topical application to the nasal mucosa of the VEGF inhibitor, Avastin, can be helpful.
- Septal dermoplasty and laser ablation have been used.
  - Cautery eradicates a bleeding lesion, but satellite ones tend to form. The success of different treatments appears to correlate with the type of lesion causing the bleeding. Laser treatments may work best with isolated lesions, whereas dermoplasty may be better for more diffuse lesions.
- Skin telangiectasias
- Topical agents: oxidized cellulose applied to the lesion can be useful as well as laser ablation.

The risks of hemorrhage during pregnancy should be discussed.

7.4 Prognosis

Prognostic variability is marked in HHT. Older studies have indicated that the mortality in early adulthood approaches 50%. However, with genetic testing, it has become apparent that the spectrum of severity is wide, with some patients only having recurrent nosebleeds. Early diagnosis, detection of lesions (screening for lung AVMs), and monitoring have significantly improved the outlook.

7.4.1 When to Refer

In childhood, these patients do not require specialized management. Adults present with complicated problems that require expertise in management of aneurysms.

Key Points

- HHT should be considered in children with severe recurrent nosebleeds once coagulopathies have been ruled out.
- There is a family history of aneurysms, severe bleeding, or HHT in 50% of cases.
- HHT is linked to at least five genes. Not all of the genetic causes of HHT have been identified.

8 Incontinentia Pigmenti (IP)

8.1 Definition and Epidemiology.

Incontinentia pigmenti is a rare X-linked disorder primarily affecting the skin, brain, and eyes. It is characterized by a swirled pattern of hyperpigmentation with a history of preceding vesicles in the newborn. It is primarily noted in Caucasians and is believed to be lethal in utero in males. At least one-half of cases are familial. IP has four clinical phases: (1) vesicle formation with eosinophilia, (2) epidermal hyperplasia and hyperkeratosis, (3) melanin deposition in the dermis, leading to the concept that the epidermis is incontinent of melanin, and (4) atrophic skin changes.

8.2 Etiology and Pathogenesis

Incontinentia pigmenti is believed to be due to mutations in the *NEMO/IKKg* gene on chromosome Xq28. This gene encodes a transcription factor that regulates the expression of multiple genes. A deficiency of this transcription factor facilitates

apoptosis induced by the tumor necrosis factor (TNF) and other cytokines. The disease seems to involve a complicated process of cell death and increases in multiple cytokines that produce an inflammatory response in the epidermis associated with both systemic and local eosinophilia.

8.2.1 Differential Diagnosis

The differential diagnosis includes herpes zoster. However, unlike herpes, there are multiple stages of the disease. Hypomelanosis of Ito (HI) is also in the differential, but that disease is not associated with a history of vesicles or plaques in infancy. Hypomelanosis of Ito is characterized by hypopigmentation, whereas IP is associated with hyperpigmented lesions. Both disorders can have a swirled pigmentary pattern to the skin lesions and involvement of the CNS.

8.2.2 Diagnostic Approach

History

There is a history of evolving skin lesions. First, vesicles are noted on the skin of the trunk or extremities within the first 2 weeks of age in 90% of cases (Fig. 21). Following this early stage, dry papules or plaques appear. Later streaks of brown hyperpigmentation occur on the trunk and extremities and persist for several years or decades (Figs. 22 and 23). There may also be a history of seizures, learning

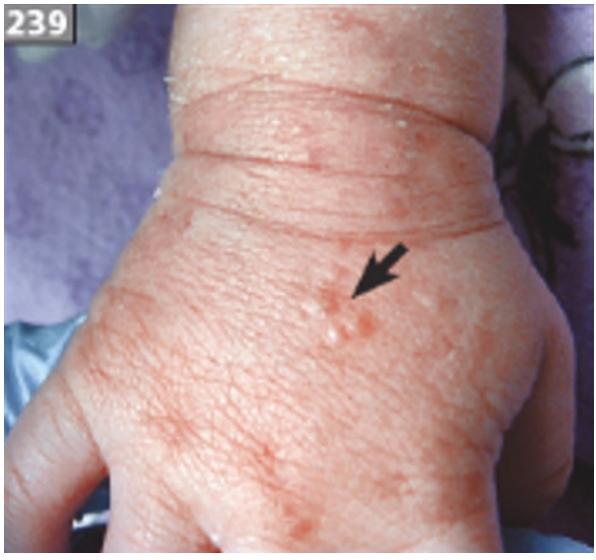

Fig. 21 Incontinentia pigmenti. A photograph of the hand of a newborn, showing vesicles (arrow) with an erythematous base

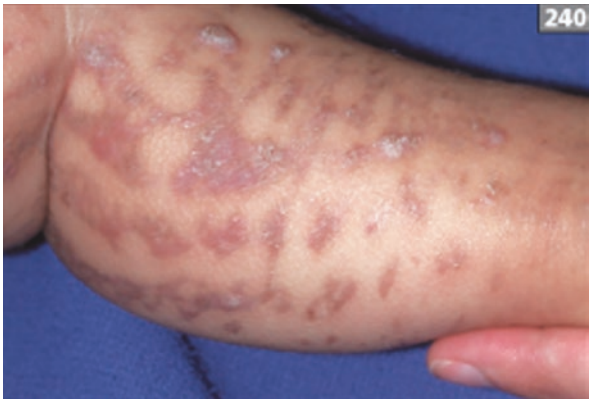

Fig. 22 Incontinentia pigmenti. The inner aspect of the leg of a 7-week-old baby, demonstrating crusted nodules of the early verrucous stage and hyperpigmented streaks

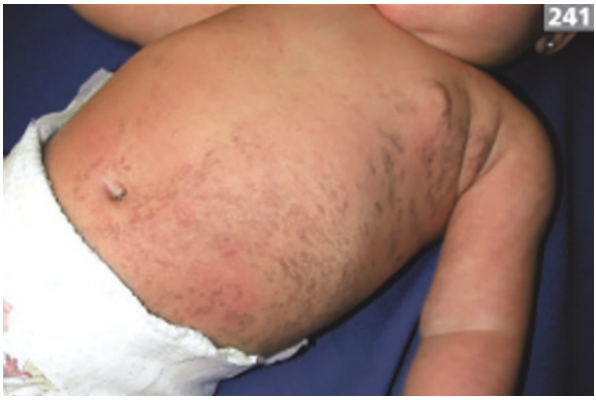

Fig. 23 The abdomen of a 9-month-old child, showing the third stage of incontinentia pigmenti, with whorls and streaks of grayish-brown hyperpigmentation

problems, developmental delay, motor problems, dental abnormalities, and nail dystrophy. There is often a history of multiple male miscarriages.

8.2.3 Physical Examination

Examination of the skin may show vesicles/plaques/streaks depending on the stage of the disease. Microcephaly is noted in 5% and strabismus occurs in 18% of children. Optic atrophy and retinal lesions are found in a small percentage. Dental abnormalities and nail dystrophy are common. A cognitive examination may show developmental delay, learning disabilities, or cognitive impairment. A neurological examination may show evidence of spasticity in 10% of children.

Evaluations

A skin biopsy is the mainstay of establishing a diagnosis and is essential for demonstrating inflammation and eosinophilia in the lesions.

Genetic testing for *NEMO/IKKg* gene mutations can be performed.

A peripheral white blood cell count shows leukocytosis and eosinophilia and can provide supportive evidence of the diagnosis.

The eyes should be examined to rule out retinal lesions.

Neurocognitive testing is helpful when academic problems are suspected.

8.2.4 Treatment/Management

Treatment of incontinentia pigmenti is largely symptomatic. The skin lesions usually do not cause major problems. The vesicular stage may need to be treated with sterile dressings. Genetic counseling can be offered.

8.3 Prognosis

The prognosis is generally good, although there is a group of patients with seizures, motor impairment, and cognitive developmental delay.

8.3.1 When to Refer

IP patients can be managed by experienced dermatologists with consultation of a pediatric neurologist for learning and cognitive issues.

Key Points

- IP presents a history of evolving skin lesions starting in the newborn period.
- IP is often associated with neurological symptoms such as seizures or learning problems.

9 Hypomelanosis of ITO

9.1 Introduction and Epidemiology

Hypomelanosis of Ito (HI), also known as pigmentary mosaicism of Ito, is a mosaic cutaneous disorder characterized by large areas of hypopigmentation in irregular streaks or whorls on the trunk and extremities, following the lines of Blaschko and appearing within the first year of life.

Rare familial cases have been reported, but, in general, it is sporadic. The reported incidence varies from rare to 1 in 10,000 children [3]. It is more easily detected in patients with increased skin pigmentation (Japanese, Hispanic, African American), but it is unclear whether this represents a racial predilection. It is more frequent in females (2:1 female to male) and is apparent within the first year of life. There are patients with an isolated skin disorder, and there are those with a complex malformation syndrome with skin findings as well as extracutaneous manifestations (particularly in the brain and musculoskeletal systems). Most investigators prefer to reserve the designation HI for the skin disorder associated with extracutaneous manifestations. HI is defined by large irregular streaks or whorls of pigmentation in at least two body areas. The trunk and limbs are the most common sites. It can be bilateral or unilateral.

9.2 Etiology and Pathogenesis

Hypomelanosis of Ito is believed to be due to a somatic cell mosaicism involving pigmentary genes. However, a variety of mosaic chromosomal abnormalities have also been reported including trisomy 18, triploidy, and tetrasomy 12p and mutations in the X chromosome. It is hypothesized that the chromosomal anomalies disrupt the expression or function of pigmentary genes, which control a variety of processes, including melanoblast migration from the neural crest in fetal life. It is suggested that the pigmentary pattern that follows Blaschko's lines is the result of the migration of two different clones of cells during embryogenesis. The complex malformation of HI is postulated to be due to somatic genetic changes early in development, whereas patients with isolated skin manifestations are believed to be due to somatic changes in the skin alone later in development. Mutations in the PI3K–AkT3–mTOR pathway have been seen in some patients.

Histopathology shows abnormal melanocytes that are also reduced in number, with absent or reduced dendrites. The absence of inflammatory cells is an important negative factor.

9.3 Differential Diagnosis

The clinician must differentiate incontinentia pigmenti from HI. The former is associated with vesicles of the skin in the newborn period, followed by hyperpigmented plaques and then persistent hyperpigmentation. In IP, there is evidence of inflammation and eosinophilia.

9.4 Diagnostic Approach

9.4.1 History

The history reveals pigmentary changes present since the first year of life with no history of vesicles in the newborn period. There is often a history of seizures, cognitive developmental delay, hyperactivity, or autism.

9.4.2 Physical Examination

The skin of the extremities and trunk shows extensive areas of irregular streaks or whorls or lacy patterns of hypopigmentation that follow the lines of Blaschko (Fig. 24). Alopecia and hair fragility are present in 20% of cases. The eyes show retinal hypopigmentation in 25%. A musculoskeletal examination may show kyphoscoliosis, hemihypertrophy, or finger abnormalities. A neurocognitive examination

Fig. 24 Hypomelanosis of Ito. A photograph of the arm, showing extensive lacy and whorl-like depigmentation

frequently shows mild-to-moderate cognitive deficits in 60%. Autistic features are seen in 10%. A neurological examination may show hypotonia or spasticity with hemiplegia in a small percentage of patients.

9.4.3 Evaluations

Skin biopsy and chromosomal studies are recommended because some patients have chromosomal anomalies that could be potentially familial or inheritable.

An MRI of the brain is indicated in patients with cognitive developmental delay or seizures or any focal findings (there are a small percentage with hemimegalencephaly). Spine films may be indicated if there is a suggestion of scoliosis.

An eye examination should be performed to look for retinal hypopigmentation.

A diagnosis of hypomelanosis of Ito is based on skin findings and a history that the skin findings appeared within the first year of life and were not preceded by either vesicles or warty lesions or scarring. The skin findings must be accompanied by either one major criterion or two minor criteria. The major criterion is nervous system involvement or musculoskeletal involvement. The minor criteria are retinal lesions, high arched palate, abnormal teeth, or kidney abnormalities.

9.5 Treatment/Management

Skin lesions dos not require treatment. Treatment of the associated condition is based on symptoms. Genetic counseling is indicated for patients with chromosomal anomalies.

9.6 Prognosis

The high frequency of cognitive developmental delay and seizures indicates a high risk of disability. However, this condition is generally not perceived as being life-limiting.

9.7 When to Refer

Patients with HI can be managed by general pediatricians or pediatric neurologists and do not require specialized clinics.

Key Points

- HI is associated with significant neurological problems, which can include brain malformations, cognitive impairment, and seizures.
- HI does not appear to be familial.

10 When To Refer

- When a newborn is noted to have a port-wine stain on the forehead and the upper lid in a unilateral distribution.
- A large number of café au lait lesions noted at birth, or if they appear to be increasing in number and size during early life.
- Child with cognitive impairment with suspicious skin lesions on the face, trunk, or extremities.
- Lesions on the extremities of a newborn that change pattern in the first few years of infancy.
- A family history of neurocutaneous syndromes should prompt early referral to genetics and neurology.

11 Prevention

Several of these disorders are inherited in an autosomal dominant manner. Therefore, genetic counselling is important when identified in one family member. These syndromes cannot be prevented.

12 Clinical Pearls/Key Points

- Children with Sturge-Weber syndrome have an easily identifiable nevus in the V1 distribution of the trigeminal nerve. Most have epilepsy and cognitive challenges.
- NF1 is easily identified by the café au lait lesions, neurofibromas and bony lesions. MRI of the brain and monitoring on a regular basis is important to detect lesions of the brain and other organ systems.
- NF2 is traditionally included in the category of neurocutaneous syndromes, but skin lesions are rare.
- TSC and NF1 are multisystem disorders and children need to be monitored by several specialists or in a multidisciplinary clinic.
- Some neurocutaneous syndromes can be identified by the evolution of the skin lesions, e.g., IP
- Several of these disorders are inherited in a Mendelian fashion, therefore a detailed family history can narrow the diagnosis.

Disclosures None

References

1. Rosner M, Hanneder M, Siegel N, Valli A, Fuchs C, Hengstschlager M. The mTOR pathway and its role in human genetics. Mutat Res. 2008;659:284–92.
2. Kresak JL, Walsh M. Neurofibromatosis: a review of NF1, NF2, and schwannomatosis. J Pediatr Genet. 2016;5(2):98–104. https://doi.org/10.1055/s-0036-1579766.
3. Barbel P, Brown S, Peterson K. Identification of hypomelanosis of ito in pediatric primary care. J Pediatr Health Care. 2015;29(6):551–4.

Child with Suspected Autoimmune Encephalitis

Jenny Joseph and J. Nicholas Brenton

1 Introduction

Encephalitis denotes an inflammatory disease process affecting the brain, resulting in alterations of consciousness (encephalopathy) in addition to other focal or multifocal neurological abnormalities (e.g., seizures, movement disorders, motor weakness, sensory alterations, autonomic dysfunction). Encephalitis, by way of autoimmunity, is not a new concept—in fact, the earliest cases of acute disseminated encephalomyelitis (ADEM) have been traced back to the 1700s [1]. However, since the 1990s and early 2000s, our understanding of autoimmune encephalitis (AIE) has undergone exponential growth—in terms of both our ability to clinically recognize/diagnose and our ability to understand the pathobiological mechanisms behind these disorders. We now recognize that autoimmune encephalitis is one of the most common causes of encephalitis in children—rivaling that of individual viral etiologies [2]. Furthermore, the treatment paradigm and prognostic counseling of a child with an AIE is quite distinct from that of other encephalitis causes—making a rapid, but correct, diagnosis of AIE all the more important for the patient and their family. A growing number of neuronal antibodies have been linked to AIEs in adults; however, many of these are quite rare in childhood. The most common causes of AIE in children include anti-NMDA-receptor (NMDAR) encephalitis and ADEM (with or without myelin oligodendrocyte glycoprotein (MOG) antibodies) [4].

This chapter will focus, in a general sense, on our current understanding of the epidemiology of pediatric AIEs in addition to the common clinical signs/symptoms

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noted at presentation and throughout the disease course. We will provide a discussion of the typical evaluation (including biomarker testing and neuroimaging), differential diagnoses, treatment approaches, and neurocognitive outcomes of pediatric AIEs. Importantly, though a number of individual antibody-mediated AIEs have been described, for the purpose of simplicity, we will focus on the two most common types of AIEs in childhood: anti-NMDAR encephalitis and ADEM.

2 Epidemiology

There are many types of autoimmune encephalitides; however, children most commonly experience anti-NMDAR encephalitis and ADEM, including those cases associated with myelin oligodendrocyte glycoprotein (MOG) antibodies. As the clinical recognition of AIE increases and our diagnostic capabilities improve, early detection of cases is expected to rise. Estimates from within the United States showed a combined (adults and children) AIE incidence of 0.8 per 100,000 person years and a prevalence of 13.7 per 100,000 in 2014 [3]. In The Netherlands, the mean reported incidence of AIE (excluding ADEM cases) was 1.54 children per million from 2015 to 2018. From the same study, the mean incidence of ADEM (including both MOG antibody-positive and antibody-negative cases) was 2.49 children per million [4]. Specifically, the incidence of MOG antibody-related disorders (including those with a non-encephalitic presentation) was higher in children (0.31/100,000) compared to those in adults (0.13/100,000). More than half of the children with MOG antibody disorders exhibited an ADEM or encephalitis phenotype [5].

From 2007 to 2011, more than 700 cases of encephalitis with an unclear etiology in individuals aged ≤ 30 years were reviewed in the California Encephalitis Project. This study demonstrated that in those cases with an identified etiology (n = 79), anti-NMDAR encephalitis was the most common entity—significantly more frequent than cases of viral etiology (including herpes simplex virus-1 (HSV-1), West Nile virus (WNV), enterovirus, and varicella-zoster virus (VZV)) [2]. This research underscores the importance of always considering an autoimmune etiology in the differential diagnosis of any child with encephalitis of unknown origin.

3 History and Physical Examination

Although the signs and symptoms of pediatric AIE may be varied, a shared clinical manifestation across all AIE subtypes is encephalopathy. Encephalopathy denotes an alteration in consciousness and/or behavior. In addition to encephalopathy, many children also present with neurological and/or psychiatric symptoms. Common

associated neurological abnormalities include seizures, movement disorders (e.g., dyskinesia, chorea), cognitive or developmental regression, focal neurological deficits (e.g., motor weakness, aphasia, sensory changes), and dysautonomia (alterations in the heart rate, blood pressure, and temperature) [6]. Typical psychiatric symptoms may include hallucinations, delusions, agitation, and insomnia.

One of the first and best-described AIEs is anti-NMDAR encephalitis [7]. There is a distinct female predominance in teenagers and adults. However, the gender predilection is less pronounced in children younger than 12 years of age [8]. Patients may develop a prodrome of fever, malaise, and headache, days to weeks prior to the clinical onset of anti-NMDAR encephalitis. This prodrome is followed by encephalopathy with a constellation of neuropsychiatric symptoms—such as behavioral changes, seizures, and movement disorders, specifically orolingual dyskinesias (abnormal involuntary movements that are not seizures). Although a majority of patients experience the full range of neurological and psychiatric signs/symptoms, the order in which these symptoms manifest may vary based on the age at presentation. To this end, adolescents typically present with abnormal behavior, whereas younger children often present first with abnormal movements or seizures [8]. Focal or generalized seizures are common in pediatric anti-NMDAR encephalitis, affecting up to 80% of children [8, 9]. Herpes simplex encephalitis can trigger a subsequent AIE attack (most commonly anti-NMDAR encephalitis), typically occurring a few months following the primary HSV infection. Thus, an AIE may initially be mistaken for reactivation of HSV; however, cases of AIE show evidence of specific autoantibodies (such as NMDAR antibodies) in the cerebrospinal fluid (CSF) and tests for HSV DNA in the CSF are negative [10].

Acute disseminated encephalomyelitis (ADEM) is an acquired demyelinating syndrome that manifests with acute/subacute encephalopathy that is unexplained by a fever or postictal state. Encephalopathy often manifests as confusion, sleepiness, delirium, depressed level of consciousness, or change in behavior. In addition, the child often exhibits a wide spectrum of neurological symptoms or signs that may indicate involvement of various parts of the central nervous system (CNS) (hence the term "disseminated"). The vast majority (>80%) of ADEM cases occurs in young children with a median age of onset of 5–8 years [11]. Many parents report an infectious prodrome days or weeks prior to the clinical onset of ADEM. There is no evidence to support a causative relationship between vaccination and pediatric ADEM. Beyond encephalopathy, children may experience a variety of neurological symptoms, based on the extent and distribution of CNS demyelination. Neurological manifestations may include optic neuritis (with associated optic disc edema, dyschromatopsia, i.e., alteration in color perception, diminished visual acuity, orbital pain on eye movements), myelitis (with the associated sensory level, weakness, or bowel/bladder dysfunction), cerebellar findings (ataxia, dysmetria), and cranial neuropathies (most commonly impacting the cranial nerves II, III, VI, and VII). Seizures are less commonly seen when compared to anti-NMDAR encephalitis but can be seen in up to 35% of cases [12].

More than half of children with ADEM have evidence of MOG antibodies in their serum [13, 14]. The MOG protein is exclusively expressed in the central nervous system (CNS) on the surface of myelin sheaths and oligodendrocytes. Antibodies against MOG are found in association with pediatric acquired demyelinating syndromes—most commonly ADEM (~50% of cases) in addition to optic neuritis (~30% cases) and transverse myelitis (~10% of cases) [15]. MOG-positive ADEM patients are clinically and radiologically indistinguishable from MOG-negative cases [14].

Beyond encephalitis associated with pediatric ADEM, MOG antibodies have also been associated with non-ADEM encephalitis. In a cohort of 296 Spanish children with definite or possible encephalitis (excluding ADEM), approximately 7% (n = 22) were found to have evidence of MOG antibodies in their serum [16], thus widening the spectrum of MOG antibody-associated disorders to include non-ADEM encephalitis.

Table 1 reviews, in brief, the clinical presentation and common neuroimaging findings associated with other, less common antibody-mediated AIEs of childhood. Many of the antibodies listed below can be tested via individual or, more commonly, commercial autoimmune encephalitis antibody panels.

Table 1 Antibody-mediated autoimmune encephalitides in childhood. Limbic encephalitis includes symptoms of confusion, mood alteration, memory deficits, and seizures [6, 25, 29, 30]

Antibody	Clinical presentation	Findings on MRI (magnetic resonance imaging) of the brain
AMPA [17]	– Limbic encephalitis – Memory loss – Seizures, status epilepticus	Unilateral or bilateral medial temporal T2-weighted/fluid-attenuated inversion recovery (T2/FLAIR) hyperintense lesions
Caspr2 [18, 19]	– Limbic encephalitis – Seizures – Neuromyotonia, neuropathic pain, muscle cramps, and fasciculation – Autonomic dysfunction	– T2/FLAIR hyperintensities in the medial temporal lobes – Hippocampal atrophy, mesial temporal, and/or hippocampal sclerosis
D2R [20]	– Lethargy – Seizures – Psychiatric symptoms – Abnormal movements (dystonia, parkinsonism, chorea, or ataxia)	T2/FLAIR hyperintensities within the basal ganglia
$GABA_AR$ [21]	– Seizures, status epilepticus – Cognitive dysfunction	Multifocal, widespread cortical–subcortical T2/FLAIR hyperintensities
$GABA_BR$ [22]	– Limbic encephalitis – Seizures, status epilepticus	T2/FLAIR hyperintensities in the medial temporal lobe
GAD [23]	– Focal epilepsy, with seizures arising from the temporal lobe – Cerebellar ataxia – Stiff-person syndrome	T2/FLAIR hyperintensities in the medial temporal lobe(s)

Table 1 (continued)

Antibody	Clinical presentation	Findings on MRI (magnetic resonance imaging) of the brain
GFAP [24, 25]	– Meningoencephalitis, including headache, stiff neck, seizures, and/or vomiting – Psychiatric symptoms – Myelopathy (numbness, paresthesias, weakness) – Ataxia	– Diffuse, periventricular T2/FLAIR hyperintensities – Leptomeningeal enhancement – Linear perivascular enhancement extending radially from the ventricles
GlyR [26]	– Progressive encephalomyelitis with rigidity and myoclonus (PERM) – Seizures	Normal
GQ1B [27]	– Ophthalmoplegia – Ataxia – Alteration of the mental status	Non-specific, transient FLAIR/T2 hyperintensities within the basal ganglia and brainstem
LGI1 [19]	– Limbic encephalitis – Seizures – Muscle cramps, neuropathic pain	FLAIR/T2 hyperintensities in the medial temporal lobe or brainstem
mGluR [28]	– Encephalopathy – Memory loss – Psychiatric symptoms	Diffusion or FLAIR cerebellar hyperintensities
MOG [15]	– Encephalopathy (ADEM or non-ADEM phenotype) – Seizures – Optic neuritis (reduction in visual acuity, scotoma, dyschromatopsia, pain with eye movements) – Transverse myelitis (weakness, numbness, paresthesias, bowel/bladder symptoms)	– Large, ill-defined FLAIR/T2 hyperintense white matter lesions that can involve deep gray matter – Spinal cord or optic nerve T2/FLAIR-hyperintense lesion(s) – Cortical T2/FLAIR hyperintensities with swelling and leptomeningeal enhancement
NMDA [6]	– Encephalopathy – Seizures, focal neurologic signs/symptoms – Psychiatric symptoms – Orolingual dyskinesias	– Nonspecific cortical, subcortical, basal ganglia, infratentorial FLAIR/T2-hyperintensities with or without transient meningeal enhancement – Cases with demyelinating features on MRI are often dually positive for MOG antibodies

Abbreviations: *T2/FLAIR* T-2 weighted/Fluid Attenuated Inversion Recovery; *FLAIR* Fluid Attenuated Inversion Recovery, *ADEM* Acute Disseminated Encephalomyelitis

4 Evaluation and Diagnosis

Autoimmune encephalitis should always be considered in the differential diagnosis of any child presenting with acute or subacute encephalopathy—particularly if there are concurrent neuropsychiatric signs and symptoms. The differential diagnosis for a child presenting with encephalopathy is quite broad but can often be significantly narrowed with a detailed history and physical examination. If concerns persist for an AIE, then one should proceed with further evaluations, which typically include neuroimaging, serological and CSF studies, and, often, an electroencephalogram (EEG) [31].

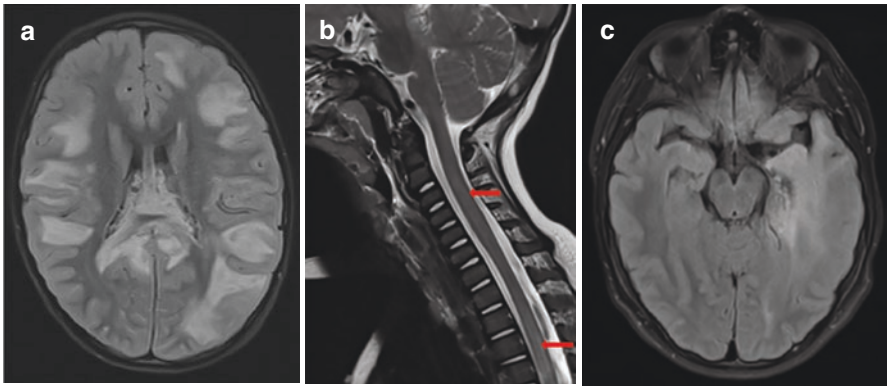

Fig. 1 MRI Findings in Pediatric AIE. (**a**) Axial FLAIR imaging of a 5-year-old boy with acute disseminated encephalomyelitis demonstrating numerous, large, ill-defined hyperintensities within the white matter of the brain and (**b**) sagittal T2-weighted imaging of the cervical spine in the same patient showing patchy hyperintensities throughout the spinal cord (red arrows). (**c**) Axial FLAIR imaging of a 13-year-old boy with limbic encephalitis associated with LGI-1 antibodies demonstrating hyperintensities within the left medial temporal lobe

With the exception of confirmatory autoantibody testing, the evaluations and procedures outlined below are not sufficient to make a definitive diagnosis of an AIE; however, these studies are immensely helpful in excluding alternative causes and guiding the differential diagnoses. The preferred neuroimaging modality of choice is magnetic resonance imaging (MRI) of the brain, which should include the use of gadolinium contrast. In cases of pediatric ADEM, large, ill-defined inflammatory lesions of the brain and/or spinal cord are essential for the diagnosis (Fig. 1a, b). However, in cases of pediatric anti-NMDAR encephalitis, the brain may be normal in more than half of cases [8, 9]. In less common causes of AIEs (e.g., leucine-rich glioma-inactivated 1 (LGI1), Caspr2), inflammatory lesions within the limbic and temporal lobe structures are noted (Fig. 1c). It is important to remember that a normal MRI does not exclude the possibility of an AIE in children. Imaging to identify an underlying tumor such as an ovarian teratoma may be necessary in certain circumstances.

In general, a cerebrospinal fluid (CSF) analysis should always be performed in children presenting with concern for an AIE. Evaluation should include cell count with differential, protein, glucose, lactic acid, oligoclonal bands, and an immunoglobulin G (IgG) index [32]. Testing for infectious causes should be pursued based on clinical suspicion and regional epidemiology. In children with an AIE, a CSF pleocytosis with or without an elevated protein level may be noted; however, a normal or "bland" CSF profile is not uncommon. The presence of intrathecal, unique oligoclonal bands or an elevated IgG index may also raise suspicion for an inflammatory/autoimmune process. Here, it is important to note that antibody testing should always be concurrently conducted in both the blood and CSF. Certain antibodies (e.g., NMDA antibodies) have a higher sensitivity in CSF compared to that in the serum [33]. Therefore, a subset of cases may only have these antibodies

detectable in the CSF. In contrast, other autoantibodies (e.g., MOG, LGI1) appear to have a higher sensitivity in the serum [34, 35].

EEG monitoring is often utilized in pediatric AIE patients who present with seizures or spells concerning for seizures. This testing may also be used in children who present with unexplained movements or mood/behavioral changes. EEG is most helpful in distinguishing seizures from non-epileptic spells; however, some AIEs exhibit unique EEG findings (e.g., "extreme" delta brush—a pattern often noted in anti-NMDAR encephalitis) that can support a clinical suspicion for an AIE [36].

There are guidelines to assist in suspected cases of autoimmune encephalitis classified into "possible" and "probable" categories. Of course, a definite diagnosis would depend on identifying the corresponding antibody via serum or CSF studies. Given that many commercial autoantibody panel results may not be available for weeks, proposed criteria are available to assist in the diagnosis of a possible AIE. These criteria can be quite helpful when deciding if and when to treat a patient for a suspected AIE, while confirmatory studies are pending. A patient with a suspected autoimmune encephalitis may be diagnosed with "possible" AIE if the patient meets the criteria shown in Table 2 [37].

Some children may have an AIE that is caused by an antibody that has yet to be identified. These patients, despite a clinical and paraclinical profile supportive of an AIE, will test negative for common, commercially available autoantibodies. A child with a suspected antibody-negative AIE may be considered a "probable" AIE when the criteria outlined in Table 2 are met [37].

Table 2 The diagnostic criteria for autoimmune encephalitides in childhood [37, 39]

"Possible" autoimmune encephalitis	The child must meet all of the following criteria: 1. Subacute onset of memory changes, altered mental status, or psychiatric symptoms 2. At least one of the following: (a) A new focal neurological finding localized to the central nervous system (b) New-onset seizures (c) CSF pleocytosis (white blood cell (WBC) count >5 mm^3) (d) MRI findings compatible with an AIE 3. Reasonable exclusion of alternative causes
Autoantibody-negative but "probable" autoimmune encephalitis	The child must meet all of the following criteria: 1. The absence of well-defined autoantibodies in the serum and CSF 2. Less than 3 months' onset of memory deficits, altered mental status, or psychiatric symptoms 3. Exclusion of well-defined AIE syndromes (e.g., ADEM) 4. At least two of the following: (a) MRI abnormalities suggestive of an AIE (b) An inflammatory CSF profile (i.e., CSF pleocytosis, intrathecal-unique oligoclonal bands, elevated IgG index) (c) Brain biopsy consistent with an autoimmune/inflammatory process 5. Reasonable exclusion of other causes

(continued)

Table 2 (continued)

Anti-NMDAR encephalitis[a]	The child must meet all of the following criteria: 1. Less than 3 months of at least four of six symptoms: (a) Behavioral or cognitive dysfunction (b) Speech dysfunction (c) Seizures (d) Movement disorder (e.g., dyskinesia) (e) Decreased level of consciousness (f) Autonomic dysfunction or central hypoventilation 2. At least one of the following study findings: (a) Abnormal EEG (extreme delta brush, background slowing, epileptiform discharges) (b) An inflammatory CSF profile (pleocytosis or intrathecal oligoclonal bands) 3. Reasonable exclusion of alternative causes
Acute disseminated encephalomyelitis (ADEM)	The child must meet all of the following criteria: 1. First polyfocal, clinical CNS event of presumed inflammatory demyelination 2. Encephalopathy that is not explained by fever, illness, or postictal symptoms 3. An abnormal brain MRI including: (a) Diffuse, ill-defined, large (>1–2 cm) lesions predominately involving the cerebral white matter (b) Deep gray matter lesions may be seen (c) T1 hypointense lesions on MRI are absent 4. The absence of new clinical or MRI findings that manifest >3 months after the clinical onset 5. Reasonable exclusion of alternative causes

[a]A definite diagnosis of anti-NMDAR encephalitis is made in the presence of at least one of the six major groups of symptoms and in the presence of anti-NMDAR IgG antibodies Abbreviations: *MRI* Magnetic Resonance Imaging, *CSF* Cerebrospinal Fluid; *ADEM* Acute Disseminated Encephalomyelitis; *AIE* Autoimmune encephalitis; *CNS* Central Nervous System

The current diagnostic criteria for ADEM are based on guidelines from the International Pediatric Multiple Sclerosis Study Group and require clinical encephalopathy in addition to neuroimaging abnormalities to make a diagnosis (Table 2). Although MOG antibodies are not part of the current ADEM diagnostic criteria, these antibodies are important to check in the serum of any child with a suspicion for ADEM, as they bode a typical ADEM course and strongly argue against a future diagnosis of multiple sclerosis (MS) [38].

5 Treatment

The current recommendations for acute and chronic treatments of autoimmune encephalitides are largely supported by retrospective case series. Clinical trials are needed; however, the relative rarity of the individual AIEs in the pediatric population poses obvious challenges to this type of research.

5.1 Acute Treatment of Autoimmune Encephalitides

The approach to acute treatment of AIE in childhood includes both effectively-dosed immunotherapy and the removal of the associated tumor, if identified. While most pediatric AIEs are not paraneoplastic, screening should be conducted in those who have a condition known to be associated with a neoplasm. For example, an ovarian teratoma can be seen in up to 30% of females with pediatric anti-NMDAR encephalitis, and, thus, a dedicated pelvic imaging should be conducted for every female diagnosed with anti-NMDAR encephalitis. Importantly, early treatment is a predictor of good outcomes (as measured by the Modified Rankin Scale score of 2 or lower) [8]—and thus appropriately-dosed immunotherapy should be started once a patient meets the criteria for a possible AIE and important AIE mimics (e.g., infectious, neoplastic) are excluded.

The acute, first-line treatment of AIE generally consists of intravenous (IV) methylprednisolone, intravenous immunoglobulin (IVIg), and/or plasma exchange as monotherapy or in various combinations. We recommend dosing IV methylprednisolone at 20–30 mg/kg (up to a maximum of 1 g) daily for 3–5 days. This may be followed by 2–4 weeks of an oral prednisone taper, starting at 1–2 mg/kg/day, which may prove helpful—particularly in MOG antibody-associated encephalitis. IVIg is dosed at 2 g/kg per course, and is divided over 2–5 days. Plasma exchange entails one plasma volume exchange every other day for 5–7 exchanges.

Although the majority of ADEM patients respond to treatment with first-line therapies, a subset of children with anti-NMDAR encephalitis (25% or more) have an incomplete response to first-line acute treatment [8, 9]. These patients typically require second-line immunotherapies—such as rituximab and/or cyclophosphamide [40].

5.2 Chronic Treatment of Autoimmune Encephalitides

Currently, there is a paucity of evidence supporting the use of chronic immunotherapy in AIE. In the majority of AIE cases (including anti-NMDAR encephalitis), the chances of a monophasic course are greater than the chances of relapse. The propensity for relapse is largely undefined for most antibody-mediated AIEs in childhood; however, anti-NMDAR encephalitis exhibits a relapse rate of 12–25% in children [8, 9]. Given this, some pediatric neurologists employ chronic immunotherapy (e.g., mycophenolate mofetil, rituximab, azathioprine, IVIg) for 1–2 years, following the initial anti-NMDAR encephalitis attack in an attempt to reduce the risk of relapse; however, long-term prospective data are lacking to support the utility of this approach [40].

A majority of pediatric ADEM patients (~90%) experience a monophasic course [11] and do not require long-term immunotherapy. Less commonly, ADEM can be followed by inflammatory attacks in future (e.g., multiphasic ADEM, ADEM

followed by optic neuritis). These relapsing conditions can be noted in MOG antibody-associated disorders. In situations in which further inflammatory attacks occur after a defined ADEM attack, the use of chronic immunotherapy (e.g., IVIg, rituximab, mycophenolate mofetil, azathioprine) for a defined period (e.g., 1–3 years) of time is appropriate [15].

6 Neurological Outcomes and Risk of Relapse

Factors that influence the neurological outcomes of pediatric AIE include (1) the associated antibody mediating the disease, (2) the time to treatment, which includes immunotherapy and removal of the associated tumor, if present, and (3) the need for intensive care unit-level care (a surrogate measure for the severity of symptoms). Neurological recovery from anti-NMDAR is good (i.e., a Modified Rankin Scale score of 2 or less) in more than 80% of pediatric patients [8]. The early literature suggests that in the years following an AIE, pediatric anti-NMDAR encephalitis patients report more problems with concentration, memory deficits, and adaptive functioning when compared to adult anti-NMDAR encephalitis patients [41]. Although other antibody-mediated AIEs are not as well-described in the pediatric population, good neurological outcomes are reported in pediatric patients with LGI1, Caspr2 [19], and glial fibrillary acidic protein (GFAP) astrocytopathy [24]. It is noteworthy that an AIE that follows a preceding herpes simplex encephalitis often bodes a worsened neurological outcome compared to classical AIEs (without preceding HSV encephalitis)—particularly in younger children [10]. The majority of patients with MOG antibody-associated disorders exhibit good recovery; however, there is a rare subset of MOG + non-ADEM encephalitis patients that exhibit severe encephalopathy, profound neurological impairments, extensive cortical inflammation, and severely increased intracranial pressure. These patients may be refractory to aggressive immunotherapy and often have a poor prognosis [16].

The vast majority of pediatric ADEM patients (with or without MOG antibodies) experience a good (if not full) neurological recovery. A subset of patients may experience long-term residual deficits that include visual impairments, bowel/bladder dysfunction, limb weakness, or persistent sensory alterations. Recovery is often gradual over weeks to months, and symptoms from ADEM can often wax and wane during this time. Even in patients who exhibit an apparent "full" neurological recovery, neuropsychological impairments—including attention, behavior, executive function, and visuomotor skills—may be evident on detailed testing [42, 43].

In general, the majority of the pediatric AIEs are monophasic disorders. There is a subset of children who may experience a relapsing disease course; however, the risk of relapse is dependent upon the antibody identified. Given that a majority of the individual AIEs are rare in children (with the exception of anti-NMDAR encephalitis and ADEM), the relapse rates for these less common entities remain largely unknown. In anti-NMDAR encephalitis, clinical relapses can occur in less than one-quarter of cases [8, 9]. Anti-NDMAR encephalitis relapses typically manifest within

the first 2 years from the initial attack. In children with ADEM, less than 10% will experience a second attack [11], which, by current definition, must occur more than 3 months after a first ADEM attack [39]. Future attacks may include a second ADEM event (termed "multiphasic ADEM") or optic neuritis (termed "ADEM-ON"), and many of these patients are often positive for MOG antibodies. Much less commonly, children who are initially diagnosed with ADEM that experience recurrent neurological attacks "without" the associated encephalopathy may go on to meet the criteria for a chronic, relapsing, demyelinating disease, such as MS or neuromyelitis optica spectrum disorder (NMOSD) [44].

7 When to Refer to Pediatric Neurology

Given the nature of the acute/subacute presenting signs/symptoms (e.g., behavioral changes, seizures, movement abnormalities), many children with a possible AIE encounter a pediatric neurologist via an emergency room or inpatient consultation. However, some AIE cases may have a more insidious, though still subacute, onset, which prompts a referral to a pediatric neurology outpatient clinic.

Outside of the obvious reasons for a referral to a pediatric neurologist (e.g., new-onset seizures), a referral for an evaluation of a possible AIE should be made for any child who exhibits evidence of new and unexplained personality or behavioral changes in a subacute manner (i.e., over the course of 3 months or less). New-onset psychiatric signs and symptoms are much more likely to have a neuroimmunological basis if the patient has concurrent neurological signs/symptoms (e.g., focal neurological examination findings, seizures, dysautonomia, etc.). In younger children, a subacute onset of symptoms such as developmental regression, temper tantrums, and self-mutilatory behaviors may also prompt a referral for evaluation [45]. Young children are also more likely to present with movement disorders—particularly choreiform movements—which may also prompt a referral.

8 Conclusions

Autoimmune encephalitis accounts for a sizeable subset of all pediatric encephalitis cases. Advances in research over the last several years have identified new antibody-mediated AIE syndromes, which have further improved our diagnostic capabilities. As a medical community, we have become more adept at recognizing these cases, thereby allowing us to implement appropriate treatments earlier in the disease course. To this end, AIE should always be included in the differential of a child with an unknown cause of acute/subacute onset of encephalopathy. In these cases, serological and CSF evaluations should be performed early, as it often takes days-to-weeks to get results. Neuroimaging with MRI frequently provides important clues toward a diagnosis, though it is important to recognize that normal

neuroimaging does not exclude AIE as a possibility. Once a patient meets the criteria for possible AIE and important mimics (e.g., infection, neoplastic disease) are ruled out, immunotherapy should be commenced promptly.

It is accepted that early treatment with highly effective first-line immunotherapy (i.e., a high dose IV steroids, IVIg, and/or plasma exchange) and, if needed, second-line therapy (i.e., cyclophosphamide, rituximab) is essential for a good neurological outcome. Robust clinical trials are needed to better define the best chronic treatment approach to AIEs with a predisposition for relapsing disease.

Primary care physicians should have a low threshold to refer pediatric patients for a neurological evaluation of AIE in the setting of subacute encephalopathy with focal neurological and/or psychiatric signs and symptoms.

9 Clinical Pearls and Key Points

- ADEM and anti-NMDAR encephalitis are two of the most common AIE in the pediatric age group.
- The presence of encephalopathy i.e. confusion, sleepiness or delirium is a key symptom of ADEM. More than half of all children with ADEM will demonstrate MOG antibodies in serum.
- In addition to encephalopathy, children with Anti-NMDAR encephalitis also manifest psychiatric symptoms and abnormal movements of the mouth and tongue.
- Immunotherapy is the cornerstone of treatment of AIE.

References

1. Clifton F. Dissertatio Medica Inauguralis: De Distinctis et Confluentibus Variolis. Leiden: apud Henricum Mulhovium; 1724.
2. Gable MS, Sheriff H, Dalmau J, Tilley DH, Glaser CA. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. Clin Infect Dis. 2012;54(7):899–904.
3. Dubey D, Pittock SJ, Kelly CR, McKeon A, Lopez-Chiriboga AS, Lennon VA, et al. Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. Ann Neurol. 2018;83(1):166–77.
4. de Bruijn M, Bruijstens AL, Bastiaansen AEM, van Sonderen A, Schreurs MWJ, Sillevis Smitt PAE, et al. Pediatric autoimmune encephalitis: recognition and diagnosis. Neurol Neuroimmunol Neuroinflamm. 2020;7(3)
5. de Mol CL, Wong Y, van Pelt ED, Wokke B, Siepman T, Neuteboom RF, et al. The clinical spectrum and incidence of anti-MOG-associated acquired demyelinating syndromes in children and adults. Mult Scler. 2020;26(7):806–14.
6. Brenton JN, Goodkin HP. Antibody-mediated autoimmune encephalitis in childhood. Pediatr Neurol. 2016;60:13–23.
7. Dalmau J, Tuzun E, Wu HY, Masjuan J, Rossi JE, Voloschin A, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol. 2007;61(1):25–36.

8. Titulaer MJ, McCracken L, Gabilondo I, Armangue T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013;12(2):157–65.
9. Florance NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol. 2009;66(1):11–8.
10. Armangue T, Spatola M, Vlagea A, Mattozzi S, Cárceles-Cordon M, Martinez-Heras E, et al. Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. Lancet Neurol. 2018;17(9):760–72.
11. Tenembaum S, Chamoles N, Fejerman N. Acute disseminated encephalomyelitis: a long-term follow-up study of 84 pediatric patients. Neurology. 2002;59(8):1224–31.
12. Pohl D, Alper G, Van Haren K, Kornberg AJ, Lucchinetti CF, Tenembaum S, et al. Acute disseminated encephalomyelitis: updates on an inflammatory CNS syndrome. Neurology. 2016;87(9 Suppl 2):S38–45.
13. Brilot F, Dale RC, Selter RC, Grummel V, Kalluri SR, Aslam M, et al. Antibodies to native myelin oligodendrocyte glycoprotein in children with inflammatory demyelinating central nervous system disease. Ann Neurol. 2009;66(6):833–42.
14. Waters P, Fadda G, Woodhall M, O'Mahony J, Brown RA, Castro DA, et al. Serial anti-myelin oligodendrocyte glycoprotein antibody analyses and outcomes in children with demyelinating syndromes. JAMA Neurol. 2019;77(1)
15. Hacohen Y, Banwell B. Treatment approaches for MOG-ab-associated demyelination in children. Curr Treat Options Neurol. 2019;21(1):2.
16. Armangue T, Olive-Cirera G, Martinez-Hernandez E, Sepulveda M, Ruiz-Garcia R, Munoz-Batista M, et al. Associations of paediatric demyelinating and encephalitic syndromes with myelin oligodendrocyte glycoprotein antibodies: a multicentre observational study. Lancet Neurol. 2020;19:234–46.
17. Gleichman AJ, Panzer JA, Baumann BH, Dalmau J, Lynch DR. Antigenic and mechanistic characterization of anti-AMPA receptor encephalitis. Ann Clin Transl Neurol. 2014;1(3):180–9.
18. Boyko M, Au KLK, Casault C, de Robles P, Pfeffer G. Systematic review of the clinical spectrum of CASPR2 antibody syndrome. J Neurol. 2020;267(4):1137–46.
19. López-Chiriboga AS, Klein C, Zekeridou A, McKeon A, Dubey D, Flanagan EP, et al. LGI1 and CASPR2 neurological autoimmunity in children. Ann Neurol. 2018;84(3):473–80.
20. Dale RC, Merheb V, Pillai S, Wang D, Cantrill L, Murphy TK, et al. Antibodies to surface dopamine-2 receptor in autoimmune movement and psychiatric disorders. Brain. 2012;135(Pt 11):3453–68.
21. Pettingill P, Kramer HB, Coebergh JA, Pettingill R, Maxwell S, Nibber A, et al. Antibodies to GABAA receptor alpha1 and gamma2 subunits: clinical and serologic characterization. Neurology. 2015;84(12):1233–41.
22. Zhu F, Shan W, Lv R, Li Z, Wang Q. Clinical characteristics of anti-GABA-B receptor encephalitis. Front Neurol. 2020;11:403.
23. Graus F, Saiz A, Dalmau J. GAD antibodies in neurological disorders—insights and challenges. Nat Rev Neurol. 2020;16(7):353–65.
24. Theroux LM, Goodkin HP, Heinan KC, Quigg M, Brenton JN. Extreme delta brush and distinctive imaging in a pediatric patient with autoimmune GFAP astrocytopathy. Mult Scler Relat Disord. 2018;26:121–3.
25. Kunchok A, Zekeridou A, McKeon A. Autoimmune glial fibrillary acidic protein astrocytopathy. Curr Opin Neurol. 2019;32(3):452–8.
26. Carvajal-Gonzalez A, Leite MI, Waters P, Woodhall M, Coutinho E, Balint B, et al. Glycine receptor antibodies in PERM and related syndromes: characteristics, clinical features and outcomes. Brain. 2014;137(Pt 8):2178–92.
27. Santoro JD, Lazzareschi DV, Campen CJ, Van Haren KP. Pediatric Bickerstaff brainstem encephalitis: a systematic review of literature and case series. J Neurol. 2018;265(1):141–50.

28. Marignier R, Chenevier F, Rogemond V, Sillevis Smitt P, Renoux C, Cavillon G, et al. Metabotropic glutamate receptor type 1 autoantibody-associated cerebellitis: a primary autoimmune disease? Arch Neurol. 2010;67(5):627–30.
29. Joubert B, Kerschen P, Zekeridou A, Desestret V, Rogemond V, Chaffois MO, et al. Clinical Spectrum of encephalitis associated with antibodies against the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor: case series and review of the literature. JAMA Neurol. 2015;72(10):1163–9.
30. van Sonderen A, Ariño H, Petit-Pedrol M, Leypoldt F, Körtvélyessy P, Wandinger KP, et al. The clinical spectrum of Caspr2 antibody-associated disease. Neurology. 2016;87(5):521–8.
31. Barbagallo M, Vitaliti G, Pavone P, Romano C, Lubrano R, Falsaperla R. Pediatric autoimmune encephalitis. J Pediatr Neurosci. 2017;12(2):130–4.
32. Cellucci T, Van Mater H, Graus F, Muscal E, Gallentine W, Klein-Gitelman MS, et al. Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. Neurol Neuroimmunol Neuroinflamm. 2020;7(2)
33. Gresa-Arribas N, Titulaer MJ, Torrents A, Aguilar E, McCracken L, Leypoldt F, et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. Lancet Neurol. 2014;13(2):167–77.
34. Malter MP, Frisch C, Schoene-Bake JC, Helmstaedter C, Wandinger KP, Stoecker W, et al. Outcome of limbic encephalitis with VGKC-complex antibodies: relation to antigenic specificity. J Neurol. 2014;261(9):1695–705.
35. Jarius S, Ruprecht K, Kleiter I, Borisow N, Asgari N, Pitarokoili K, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 1: frequency, syndrome specificity, influence of disease activity, long-term course, association with AQP4-IgG, and origin. J Neuroinflammation. 2016;13(1):279.
36. Armangue T, Titulaer MJ, Malaga I, Bataller L, Gabilondo I, Graus F, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. J Pediatr. 2013;162(4):850–6.e2.
37. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016;15(4):391–404.
38. Baumann M, Grams A, Djurdjevic T, Wendel EM, Lechner C, Behring B, et al. MRI of the first event in pediatric acquired demyelinating syndromes with antibodies to myelin oligodendrocyte glycoprotein. J Neurol. 2018;265(4):845–55.
39. Krupp LB, Tardieu M, Amato MP, Banwell B, Chitnis T, Dale RC, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. Mult Scler. 2013;19(10):1261–7.
40. Brenton JN, Kim J, Schwartz RH. Approach to the management of pediatric-onset anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis: a case series. J Child Neurol. 2016;
41. Gordon-Lipkin E, Yeshokumar AK, Saylor D, Arenivas A, Probasco JC. Comparative outcomes in children and adults with anti- N-methyl-D-aspartate (anti-NMDA) receptor encephalitis. J Child Neurol. 2017;32(11):930–5.
42. Hahn CD, Miles BS, MacGregor DL, Blaser SI, Banwell BL, Hetherington CR. Neurocognitive outcome after acute disseminated encephalomyelitis. Pediatr Neurol. 2003;29(2):117–23.
43. Suppiej A, Cainelli E, Casara G, Cappellari A, Nosadini M, Sartori S. Long-term neurocognitive outcome and quality of life in pediatric acute disseminated encephalomyelitis. Pediatr Neurol. 2014;50(4):363–7.
44. Brenton JN, Banwell BL. Therapeutic approach to the management of pediatric demyelinating disease: multiple sclerosis and acute disseminated encephalomyelitis. Neurotherapeutics. 2016;13(1):84–95.
45. Goldberg EM, Titulaer M, de Blank PM, Sievert A, Ryan N. Anti-N-methyl-D-aspartate receptor-mediated encephalitis in infants and toddlers: case report and review of the literature. Pediatr Neurol. 2014;50(2):181–4.

Child with Suspected Metabolic Disorder

Kara Pappas, Noelle Andrea V. Fabie, and Gerald L. Feldman

1 Introduction

Inborn errors of metabolism (IEMs) are genetic disorders that often affect the brain or nervous system, and, thus, many of them are also called neurometabolic diseases. Their effect on the brain and nervous system can begin immediately after birth or sometimes even prenatally and can continue throughout life if not properly treated. In some disorders, even with prompt and appropriate treatment, neurological deficits can persist. These disorders are caused by pathogenic variants in genes involved in many different intermediary metabolic pathways, including amino acids, fatty acids, organic acids, carbohydrates, and electron transport. Many of these enzymes require cofactors (usually vitamins), and pathogenic variants in genes controlling these processes can also impact these same pathways. An enzymatic defect

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essentially results in three different effects: (1) accumulation of the substrate, (2) deficiency of the product, and (3) production of alternate (often toxic) products.

The presentation of neurometabolic disorders varies from disorder to disorder but can often be grouped together into various subgroups. Some groups of disorders present with seizures or epilepsy, whereas others present with neurocognitive deficits, progressive neurological features, neuromuscular features, or neurodegeneration. Many disorders can present with a wide variety of neurological presentations. Most of these disorders are inherited as autosomal recessive conditions, meaning that each parent is typically a carrier of a pathogenic variant in the same gene. Some disorders are inherited as X-linked conditions and will be identified as such in this chapter. In an X-linked disorder, the mother is usually an asymptomatic carrier of a pathogenic variant, but de novo mutations can also occur.

This chapter will address the evaluation of patients with a suspected inborn error of metabolism that can present with neurological abnormalities, including the presenting laboratory abnormalities that suggest an IEM (such as hypoglycemia, metabolic acidosis, and hyperammonemia) and neurometabolic clinical features (such as developmental delay, regression, hypotonia, seizures, ataxia, movement disorders, and stroke) along with extra-neurological features of each disorder. IEM diagnostic confirmatory tests (including amino acid analysis, acylcarnitine testing, enzymatic analysis, and molecular genetic testing) and treatments (including dietary restrictions, enzyme substitution or replacement, bone marrow or stem cell transplantation, vitamin cofactor supplementation, and others) will also be discussed. This chapter will not focus on the intricacies of enzymatic and molecular testing for each disorder (or a group of disorders), as they are often complicated and require the expertise of a biochemical geneticist. In general, while the diagnosis of the disorders discussed in this chapter can often be strongly suggested by the laboratory tests mentioned above, confirmatory testing requires specific enzymatic and/or molecular testing. In addition to confirming deficient enzyme activity or pathogenic genetic variants, the results can often be helpful in determining disease severity and long-term prognosis (i.e., a genotype–phenotype correlation). Enzyme testing requires specific blood or tissue samples (i.e., skin fibroblasts, liver, or muscle biopsy), specific laboratories, and specific shipping conditions. Molecular testing, most often performed on a peripheral blood sample, can be ordered for a single gene (i.e., the phenylalanine hydroxylase gene for classic phenylketonuria) or for a panel of genes (using next-generation sequencing) that cause a similar disease phenotype (i.e., lysosomal storage diseases or epilepsy). Ordering the right test is critical to making a correct diagnosis in a timely and cost-efficient manner.

Newborn screening (NBS) is a public health program that consists of screening infants shortly after birth for conditions that are treatable but are often not clinically evident in the newborn period. The goal is to identify infants at risk for these conditions early enough to confirm the diagnosis and provide interventions that will alter the clinical course of the disease and prevent or ameliorate the clinical manifestations. Newborn screening in the United States consists of point-of-care tests (for hearing loss and congenital heart disease) as well as screening using dried blood

spots for a variety of other disorders, including amino acid disorders, organic acid disorders, fatty acid oxidation disorders (FAODs), urea cycle disorders (UCDs), endocrine disorders, hematological disorders, carbohydrate disorders, lysosomal storage disorders (LSDs), spinal muscular atrophy, and X-linked adrenoleukodystrophy. Newborn screening is performed in each US state. While each individual state in the United States determines which disorders are to be screened for in that state, the Department of Health and Human Services maintains the Recommended Uniform Screening Panel (RUSP). Currently, 35 primary disorders and 26 secondary disorders are included in that panel [1]. The majority of these disorders have associated neurological consequences if untreated, and some disorders, even with treatment implemented shortly after birth, can still have major neurological consequences. It is important to note that the presentation of these disorders has changed rapidly, since early diagnosis and management often prevents the historical classic presentations of many of these disorders [2].

Although many of the disorders discussed below are included in newborn screening, false negatives do occur, especially in mild, late-onset, or intermittent forms. Therefore, it is important that primary care physicians include these conditions in their differential diagnosis of patients with neurological abnormalities [3].

2 Amino Acid Metabolism Disorders

- Potential neurological signs/symptoms: acute encephalopathy, seizures, developmental delays, intellectual disability, psychiatric and behavioral problems, involuntary movements, ataxia, tremors
- Other signs/symptoms:
  - Acute: poor feeding, irritability, lethargy/coma, acute liver failure, thromboembolism
  - Chronic: abnormal body odor, skin pigmentation and texture abnormalities, renal tubular acidosis
- Laboratory abnormalities: transaminitis, electrolyte abnormalities
- Diagnostic tests: plasma amino acids, analyte-specific assays (e.g., succinylacetone in the plasma or urine), molecular (DNA) analysis

Amino acids are organic compounds that serve as the primary backbone of proteins. A deficiency in the breakdown (or catabolism) of specific amino acids may lead to an accumulation of corresponding amino acids or their by-products. Some amino acid disorders may also lead to the generation of abnormal organic acids (see Sect. 3 for further details). These disorders are primarily autosomal recessive conditions.

Common amino acid disorders include phenylketonuria (PKU), tyrosinemia, maple syrup urine disease (MSUD), and homocystinuria. The common neurological features of these disorders include a broad range of developmental delays,

neuropsychiatric difficulties, and seizures. These may present in an episodic manner or as a chronic progressive decline in the neurological status. Acute encephalopathy, which is a hallmark of some inborn errors of metabolism, occurs in certain diagnoses (i.e., MSUD), in which markedly elevated levels of leucine lead to cerebral edema. Other acute presentations include thromboembolism and stroke in homocystinuria. Brain magnetic resonance imaging (MRI) abnormalities, which are mostly signal abnormalities involving the white matter, are also seen, with some diagnoses having structural brain abnormalities [4].

Extra-neurological symptoms include unusual body odor, skin pigmentation and texture differences, liver dysfunction, and renal tubular acidosis. Many amino acid disorders are screened for during newborn screening, but mild or intermittent forms can occur, which present later in life or in an episodic manner. Plasma amino acid and urine organic acid studies may provide a biochemical diagnosis. A molecular confirmation is established by conducting gene-specific DNA studies.

The treatment for amino acid disorders is often a life-long restriction of the offending amino acid in the diet. Special formulas are also given to ensure that adequate amounts of other essential amino acids are supplied in the diet. Some disorders have adjunct medications that either enhance the remaining enzyme function (e.g., sapropterin dihydrochloride in PKU) or provide alternate metabolic routes (nitisinone in tyrosinemia type 1).

3 Organic Acidemias (OAs)

- Potential neurological signs/symptoms: acute encephalopathy, seizures, developmental delays, intellectual disability, psychiatric and behavioral problems, involuntary movements, ataxia
- Other signs/symptoms:
  - Acute: poor feeding, vomiting, irritability, lethargy/coma
  - Chronic: recurrent pancreatitis, chronic kidney disease, optic atrophy, cardiomyopathy, infections due to cytopenias, abnormal body odor
- Laboratory abnormalities: hypoglycemia, anion gap metabolic acidosis, ketosis, lactic acidosis, hyperammonemia, cytopenias
- Diagnostic tests: urine organic acids, acylcarnitine profile, plasma amino acids, enzymatic testing, molecular (DNA) analysis

Organic acidemias (OAs) are a group of conditions that result in the production of abnormal organic acids, which can be detected in the blood and urine. They are typically caused by defects in the breakdown of specific amino acids and occasionally due to deficient cofactors. Examples of organic acidemias include methylmalonic acidemia and propionic acidemia, which are due to defects in the metabolism of the amino acids isoleucine, valine, threonine, and methionine. These are inherited as autosomal recessive conditions.

The most typical presentation of an organic acidemia is a previously healthy baby who develops concerning symptoms in the first week of life. These symptoms might include poor feeding, vomiting, abnormal movements, seizures, and lethargy and may progress to coma. Laboratory investigations may reveal hypoglycemia, anion gap metabolic acidosis, ketosis, lactic acidosis, hyperammonemia, and cytopenias. The diagnosis is confirmed by the presence of abnormal urine organic acids in the urine organic acid profile. Acylcarnitine profile and plasma amino acids may help refine the diagnosis. Further confirmation of the diagnosis can be done via specific enzyme studies or molecular (DNA) studies. Many organic acidemias are screened for during newborn screening.

Organic acidemias have a variety of long-term neurological consequences, even if treated from an early age. Developmental delays and intellectual disability are common. Seizures can occur chronically or only during exacerbations. Some children develop movement disorders and present a cerebral palsy-type phenotype [5].

Some forms of organic acidemias may be mild or intermittent in nature. These may not present until a later age. These patients may present with similar laboratory results as noted above only when sick or fasting. They may develop neurological symptoms including developmental issues and seizures.

Biotinidase deficiency is a condition in which the body cannot recycle biotin (vitamin B7), which is an essential cofactor in the breakdown pathway of multiple amino acids. For this reason, untreated patients with biotinidase deficiency can present with a variety of neurological deficits as well as hearing loss, optic atrophy, and skin rashes [6]. Glutaric acidemia type 1 (GA-1) is an organic acidemia that typically solely presents with neurological features. If untreated, children with GA-1 undergo acute brain injury, following a stressor such as a febrile infection or gastroenteritis. This can lead to changes in tone, extrapyramidal movements, and intellectual disability [7].

The treatment for organic acidemia typically involves protein-restricted diets (including specific restrictions of the offending amino acids) and supplemental amino acid formulas. A variety of medications are used depending on the disorder. These commonly include carnitine, which binds excess organic acids and facilitates the breakdown of fats. A specific cofactor supplementation is often used as well, such as vitamin B12 in some forms of methylmalonic aciduria. A liver transplant is considered in some severe forms of organic acidemias [8].

4 Urea Cycle Disorders

- Potential neurological signs/symptoms: acute encephalopathy, changes in tone, spasticity, abnormal movements, an altered mental status, developmental delays, behavioral and psychiatric changes, seizures
- Other signs/symptoms:
  - Acute: lethargy/coma, poor feeding, vomiting, irritability
  - Chronic: liver dysfunction, trichorrhexis nodosa (brittle hair, seen in arginase deficiency)

- Laboratory abnormalities: respiratory alkalosis, hyperammonemia, transaminitis
- Diagnostic tests: plasma amino acids, urine orotic acid, enzymatic testing, molecular (DNA) analysis

Urea cycle disorders (UCDs) are a group of disorders resulting from a deficiency in the urea cycle that causes problems with removal of nitrogen waste from the body in the urine. This typically leads to a buildup of ammonia, which has a variety of consequences on the neurological system. Ornithine transcarbamylase (OTC) deficiency is the most common UCD and is an X-linked disorder that often affects males more severely than it does females. Other UCDs include citrullinemia, argininemia, argininosuccinate synthetase deficiency, argininosuccinate lyase deficiency, and more, which are all inherited as autosomal recessive disorders.

UCDs often present in the neonatal period, much like organic acidemias. A previously healthy baby will present, during early infancy, with poor feeding, lethargy, vomiting, abnormal movements, seizures, and even coma. Respiratory alkalosis and hyperammonemia are found on blood work. Hyperammonemia can lead to cerebral edema and a variety of neurotoxic reactions. Depending on the severity of the hyperammonemia, there may be long-lasting neurological consequences including developmental delays, epilepsy, spasticity, and more. Only some of the UCDs are screened for during newborn screening.

Mild and intermittent forms of UCDs can present later in life, at any age. These typically present with either recurrent or chronic encephalopathy. Symptoms of acute decompensations can include lethargy, headaches, ataxia, an altered mental status, behavioral changes, and/or vomiting. These symptoms are often precipitated by a major stressor, such as a severe illness or childbirth. Sometimes the ingestion of a large protein load can precipitate these symptoms as well. The chronic form may present with developmental delays and behavioral abnormalities.

Argininemia is a UCD that if untreated can present with spasticity and a cerebral palsy-type phenotype in early childhood [5].

The diagnosis of a UCD is confirmed with plasma amino acids, with certain patterns corresponding to certain disorders (for example, high citrulline in citrullinemia). Other abnormal metabolites may be detected in the blood or urine (e.g., orotic acid in some UCDs). Further confirmation of the diagnosis can be done via enzyme studies or molecular (DNA) studies.

The treatment for UCDs includes a protein-restricted diet and supplemental amino acid formula. Nitrogen scavenger medications are used (such as sodium benzoate) to help remove nitrogenous waste through alternative excretion pathways. Amino acid supplements such as citrulline and arginine are used in some disorders to help re-prime the urea cycle. In some cases of severe hyperammonemia, hemodialysis is needed. A liver transplantation for difficult-to-treat disorders or patients may be considered in some cases [9].

5 Fatty Acid Oxidation Disorders

- Potential neurological signs/symptoms: seizures, coma, peripheral neuropathy
- Other signs/symptoms: liver dysfunction, cardiomyopathy, cardiac arrhythmias, retinopathy
- Laboratory abnormalities: hypoglycemia, lactic acidosis, hyperammonemia, abnormal liver function
- Diagnostic tests: an acylcarnitine profile, plasma and urine carnitine levels, urine organic acids, urine acylglycine profile, enzymatic testing, molecular (DNA) analysis

Fatty acid oxidation disorders (FAODs) are conditions in which the patient cannot properly breakdown specific fatty acids. Fatty acids come in various "lengths"; therefore, there can be defects in metabolizing medium-chain, long-chain, very-long-chain, or all fatty acids. Carnitine is a molecule that helps shuttle long-chain fatty acids across the mitochondria in order to be metabolized; therefore, defects in the carnitine transport system and carnitine deficiency can also cause defective long-chain fatty acid metabolism. These are inherited as autosomal recessive conditions.

Hypoglycemia is a common presenting feature of FAODs. It typically occurs after a long fast or during an illness (due to a higher metabolic demand for energy). Hypoglycemia can lead to seizures, coma, permanent neurological damage, or death in its untreated state.

Long-chain fatty acid oxidation disorders can also present with cardiomyopathy, cardiac arrhythmias, liver dysfunction, and rhabdomyolysis. Lactic acidosis and hyperammonemia can occur during decompensation. Some can develop a chronic retinopathy and peripheral neuropathy, even when treated. Severe forms of some FAODs can present in the neonatal period with congenital anomalies including neuronal migration defects [5].

FAODs can be suspected in a patient with hypoglycemia, typically non-ketotic, after a long fast or during illness. Accompanying rhabdomyolysis, lactic acidosis, or hyperammonemia may point toward a long-chain defect. The diagnosis is confirmed by an acylcarnitine profile, plasma and urine carnitine levels, urine organic acids, and urine acylglycine profile. Enzymatic studies and molecular (DNA) studies can be conducted for further confirmation. FAODs are included during newborn screening.

The treatment for fatty acid oxidation disorders primarily includes avoidance of fasting and careful management, with the primary goal of maintaining normal glucose levels when sick. For patients with long-chain FAODs, long-chain fats are generally restricted in their diet. Medium-chain triglyceride supplementation is given as an alternate source of energy, as these patients can metabolize medium-chain fats normally [10].

6 Mitochondrial Disorders

- Potential neurological signs/symptoms: changes in muscle tone, myopathy, developmental delays or regression, seizures, ataxia, peripheral neuropathy, stroke-like episodes
- Other signs/symptoms: cardiomyopathy, cardiac arrhythmias, liver dysfunction, renal dysfunction, gastrointestinal dysfunction, endocrine abnormalities, hearing loss, ophthalmologic abnormalities
- Laboratory abnormalities: lactic acidosis, an elevated lactate:pyruvate ratio, elevated creatine kinase, abnormal liver function, hypoglycemia, hormone deficiencies, abnormal kidney function, tubulopathies
- Diagnostic tests: tissue (skin, muscle or liver) biopsy, enzymatic studies, molecular (DNA) analysis of nuclear or mitochondrial genes

Mitochondrial disorders are a diverse set of disorders related to the function of the mitochondria. The mitochondria, through oxidative phosphorylation via the respiratory chain, generate adenosine triphosphate (ATP), the main energy source for the body. A variety of other reactions take place inside the mitochondria as well, including fatty acid oxidation. Some examples of mitochondrial disorders include MELAS syndrome (Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-like episodes) and MERFF syndrome (Myoclonic Epilepsy, Ragged Red Fibers). Inheritance is either autosomal recessive (for nuclear genes) or maternal (for genes encoded in the mitochondrial genome).

Many mitochondrial disorders present with neurological symptoms. These symptoms can be extremely variable. Hypotonia, spasticity, myopathy, developmental delays, developmental regression, seizures, ataxia, and peripheral neuropathy are some of the more common presentations. “Stroke-like” episodes can also occur, in which patients develop hemiparesis, cortical blindness, or other symptoms of strokes with brain MRI changes in non-vascular territories. A variety of other brain MRI changes can be seen in mitochondrial disorders. A common pattern is abnormal signal intensities in the brain stem. A lactate peak may be seen on magnetic resonance spectroscopy (MRS).

Mitochondrial disorders can also affect almost every organ system. Cardiomyopathy, cardiac arrhythmias, liver dysfunction, abnormalities of the gastrointestinal system, hearing loss, renal dysfunction, and endocrine abnormalities can occur. Ophthalmologic abnormalities are common including ophthalmoplegia, ptosis, and retinopathies [5]. “Any symptom, in any system” is the mantra of mitochondrial specialists.

Laboratory abnormalities seen in mitochondrial disorders often include lactic acidosis and an elevated lactate:pyruvate ratio. A variety of other laboratory abnormalities may occur based on other organ system involvement, as noted above. Plasma amino acids may show elevation of alanine. Urine organic acids may show some non-specific abnormalities. Muscle biopsy will often show a specific finding called “ragged red fibers.” A confirmatory diagnosis typically depends on enzymatic studies (often in the muscle) or molecular (DNA) studies. The mitochondria

have their own genome, but many proteins are also encoded by nuclear DNA. Therefore, molecular studies should be conducted on both the genes in the nuclear DNA and the genes in the mitochondrial genome.

The treatment of mitochondrial disorders often involves the use of cofactors and supplements. Often, a so-called "mitochondrial cocktail" of these drugs is prescribed and may include carnitine, coenzyme Q10, B vitamins, vitamin C, and vitamin E, among others. The effectiveness of many of these treatments is controversial. Arginine has been shown to be helpful in MELAS syndrome during acute strokes. Otherwise, symptom-specific treatment is prescribed [11].

7 Lysosomal Storage Disorders

- Potential neurological signs/symptoms: hypotonia, developmental delays and regression, seizures, movement disorders, abnormal brain imaging
- Other signs/symptoms: visceromegaly, eye findings (corneal clouding, optic atrophy, retinal dystrophy), hearing loss, coarse facial features, skeletal abnormalities (contractures, bone pain, dysostosis), short stature, renal failure, cardiomyopathy
- Laboratory abnormalities: transaminitis, laboratory profile consistent with renal failure, pancytopenia
- Diagnostic tests: analysis of a disease-specific biochemical marker, enzyme-specific assays, electron microscopy, molecular (DNA) analysis

Lysosomes are organelles in the cell that perform a variety of functions, including the breakdown of many complex molecules. Lysosomal storage disorders (LSDs) are a broad group of disorders in which there is a generalized accumulation of complex molecules due to a deficiency of a specific lysosomal enzyme. The classification of LSDs is based on the type of complex molecule, with the major groups being mucopolysaccharidoses (MPS), oligosaccharidosis, mucolipidoses, sphingolipidoses, and neuronal ceroid lipofuscinoses. Certain disorders that are caused by the defects in the synthesis or trafficking of these complex molecules may also manifest with symptoms similar to LSDs (e.g., Niemann–Pick disease type C). A majority of these disorders are inherited in an autosomal recessive manner, with the exception of MPS II (Hunter syndrome) and Fabry disease, which are both X-linked.

The hallmark of LSD is the progressive appearance of dysmorphic and neurological features. Often, it is a combination of neurological deficits with the presence of multisystemic symptoms, which raises the possibility of an LSD as an underlying etiology.

Early neurological manifestations include hypotonia and developmental regression with loss of acquired milestones; both are frequently seen in sphingolipidoses such as the neurological form of Gaucher disease and acid sphingomyelinase-deficient Niemann–Pick disease (type A/B). Irritability and hyperesthesia are seen in infantile Krabbe disease. Secondary neurological symptoms such as

hydrocephalus or spinal cord compression may arise from skeletal issues such as spinal stenosis and spinal cord compression in MPS types I, II, IV, and VI. In older children, progressive cognitive impairment may be the presenting feature (MPS III). Seizures with variable ages of onset are common in neuronal ceroid lipofuscinoses. Development of late-onset neurological abnormalities including gait abnormalities, spasticity, neuropathy, and involuntary movements is also seen.

Symptoms involving other organ systems are also common and may also be the presenting symptom. Visceromegaly may be prominent in some LSDs (MPS I, II, Gaucher disease, Niemann–Pick disease). The characteristic skeletal abnormalities identified on imaging may suggest a diagnosis of a potential LSD (dysostosis multiplex). Other manifestations include cardiac abnormalities, specifically cardiomyopathy and electrocardiogram (EKG) abnormalities. In Pompe disease, cardiomegaly and cardiomyopathy may be the presenting features.

The diagnosis is established via a combination of biochemical tests and molecular testing. Assays measuring enzyme activities are available for some disorders. Measurement of urine analytes such as glycosaminoglycans, oligosaccharides, and other glycoproteins may provide patterns that suggest that a specific disorder may be helpful. Previously, the gold standard for establishing certain LSDs was the identification of characteristic cells in a tissue biopsy sample. Electron microscopy in leukocytes and skin fibroblasts may also demonstrate accumulation of abnormal storage material. Molecular genetic testing for these disorders is readily available and has decreased the need for these invasive procedures.

Multiple avenues for LSD treatment have emerged in the past few years. Enzyme replacement therapy (ERT) is widely available for some LSDs. ERT involves the infusion of the deficient lysosomal enzyme. The goal of the treatment is to slow down disease progression and even reverse some of the complications like cardiomyopathy. One of the challenges of ERT is its lack of effect on the progression of neurological symptoms due to the inability of these medications to cross the blood–brain barrier. Substrate reduction therapy is also available for some LSDs, such as miglustat in Gaucher disease. The goal of this treatment, as the name implies, is to limit the substrate that is fed into the broken enzymatic process to decrease accumulation of the unwanted waste or by-product. Bone marrow transplantation is also performed in disorders such as MPS I.

Because of the multiple opportunities for early treatment, newborn screening for certain LSDs, including Pompe disease, Fabry, MPS I, Gaucher disease, and Niemann–Pick A/B, has been introduced in some states and countries.

8 Peroxisomal Disorders

- Potential neurological signs/symptoms: ataxia, developmental delays, hypotonia, neuropathy, seizures, behavior difficulties
- Other signs/symptoms: adrenal insufficiency, hearing and vision loss, anosmia, skeletal abnormalities, facial dysmorphism

- Laboratory abnormalities: electrolyte abnormalities secondary to adrenal insufficiency, transaminitis, abnormal cholesterol and bilirubin levels
- Diagnostic tests: very-long-chain fatty acid profile, phytanic acid, pristanic acid, plasmalogens in red blood cells (RBCs), bile acids, molecular (DNA) analysis

Peroxisomes are enzyme-containing organelles that play an important role in the metabolism of various oxidation reactions and bile acid, lipid, and plasmalogen syntheses. Impairment in one or more of these peroxisomal functions gives rise to peroxisomal disorders, which are subdivided into peroxisomal biogenesis disorders (PBDs), single-protein deficiencies, and single peroxisomal substrate transport deficiencies [12].

Peroxisomal biogenesis disorders include Zellweger syndrome (ZS), neonatal adrenoleukodystrophy, and infantile Refsum disease (IRD), collectively known as the Zellweger spectrum disorders. These disorders are usually due to an underlying disease-causing variant in one of the *PEX* genes. Severe presentations include developmental delay, early-onset seizures, hypotonia, hepatomegaly, liver dysfunction, and coagulopathy with failure to thrive. Abnormalities on brain imaging such as neuronal migration defects and myelination with white matter abnormalities may be seen. Ocular anomalies and hearing loss are also common. Craniofacial and skeletal anomalies (chondrodysplasia punctate) may be present. A more pronounced leukodystrophy and adrenal insufficiency may be the presenting feature in the late-onset forms of the disease. All are inherited in an autosomal recessive manner.

Adult Refsum disease is the hallmark disorder for single-protein deficiencies. This is a disorder of fatty acid alpha-oxidation due to a deficiency of the phytanoyl-coenzyme A (CoA) hydroxylase. This disorder presents with late childhood-onset retinitis pigmentosa with anosmia. The development of deafness, sensory motor neuropathy, ataxia, ichthyosis, and cardiac arrhythmias may occur.

Finally, peroxisomal transport deficiency is represented by X-linked adrenoleukodystrophy (X-ALD). In this disorder, the transport of very-long-chain fatty acids is impaired due to the absence of a functional peroxisomal transport (ALD protein), which is encoded by the *ABCD1* gene. Affected males may present with subtle neurodevelopmental changes such as behavioral differences in mid-childhood. This progresses and may lead to the development of hearing and vision loss, ataxia, seizures, and motor decline. Brain imaging shows characteristic white matter changes involving the parieto-occipital region. Adrenal insufficiency may occur and may present with vomiting, weakness, and increased skin pigmentation. Females, on the other hand, may have milder features that may appear later in life.

Obtaining plasma very-long-chain fatty acid levels with measurement of phytanic and pristanic acids and plasmalogens in erythrocytes provides patterns that suggest a specific peroxisomal disorder. Molecular testing is available to confirm the diagnosis.

A definitive treatment is not available for most of the peroxisomal disorders, except for X-ALD. Hematopoietic stem cell transplantation is performed for symptomatic X-ALD patients. Because of this, X-ALD has also been included as one of the core conditions for newborn screening in some states and countries.

9 Glycogen Storage Disorders

- Potential neurological signs/symptoms: myopathy, exercise intolerance, muscle weakness and atrophy, neuropathy, hypotonia, seizures, developmental delays, neuroregression
- Other signs/symptoms: hepatosplenomegaly, cirrhosis, cardiomyopathy, arrhythmia
- Laboratory abnormalities: hypoglycemia, ketosis, lactic acidosis, abnormal liver enzymes, hyperlipidemia, hypertriglyceridemia, rhabdomyolysis, myoglobinuria, neutropenia
- Diagnostic tests: enzyme-specific assays and microscopy or muscle or hepatic tissue, muscle provocation testing (e.g., forearm ischemic test), molecular (DNA) testing

Glycogen is the storage form of sugar for the body, to be used later when needed for energy. Glycogen storage disorders (GSDs) or glycogenoses are conditions in which the body is not able to synthesize glycogen or break down glycogen (glycogenolysis) or glucose to pyruvate to generate energy (glycolysis). There are several subtypes for this group of IEMs based on the primary organ affected—hepatic, muscle, combined hepatic and muscle, and, rarely, brain glycogenoses [5]. The majority of the subtypes is inherited in an autosomal recessive manner, with rarer subtypes passed in an X-linked or dominant pattern [13].

The hepatic type includes GSD 0a, GSD 1, GSD VI, and GSD IX. These disorders are due to the body not being able to break down glycogen, leading to hypoglycemia. They also manifest with liver disease and may have severe transaminitis with hepatomegaly and eventual cirrhosis. Mild types, specifically GSD 0, may only have fasting ketotic hypoglycemia. However, the more severe types, such as GSD 1, may present with severe lactic acidosis, hyperuricemia, hyperlipidemia, and hypertriglyceridemia, and various hematological abnormalities including anemia, bleeding abnormalities, and neutropenia with neutrophil dysfunction, leading to recurrent infection, renal disease (hypertension, decreased glomerular function, nephrocalcinosis), osteopenia/osteoporosis, and increased risk of the development of hepatocellular adenomas. Severely affected individuals may have a unique facial appearance with doll-like faces, thin extremities, short stature, and a protuberant abdomen. Growth retardation may be present.

Combined hepatic and myopathic types, such as GSD II, III, and IV, may present with liver disease, often early on or with progressive muscle weakness and hypotonia. Cardiac muscle involvement may lead to hypertrophic or dilated cardiomyopathy and arrhythmia. Respiratory failure may be secondary to progressive myopathy.

The primary myopathic types, GSD V and VII, present with muscle intolerance and fatigue. Individuals may have muscle pain and stiffness. Rhabdomyolysis with creatine kinase elevation is common and may lead to myoglobinuria.

In the brain, deficiency of glycogenolytic enzymes in neurons present with a progressive, neurodegenerative/epileptic phenotype. An example of this is Lafora disease, which presents in adolescence with progressive myoclonic epilepsy. Other

GSDs may present with neuropathy, developmental delay, or cognitive impairment. These neurocognitive features are associated with the deposition of abnormal glycogen by-products within cells including neurons.

Screening for hypoglycemia, liver dysfunction, ketosis, lactic acidosis, elevations of creatinine kinase, uric acid, triglycerides, and cholesterol is often performed if there is suspicion of a GSD. Obtaining an echocardiogram +/− an electrocardiogram and liver imaging may be helpful. Prior to molecular testing, a tissue biopsy (often muscle) will be able to show the accumulation of abnormal glycogen. Electromyography can show non-specific myopathy findings. Measurement of specific enzymes is rarely performed as the liver tissue, muscle, or skin fibroblasts may be needed. Molecular (DNA) testing is more readily available.

For GSDs with hepatic symptoms, the treatment involves correction of metabolic abnormalities—prevention of hypoglycemia and ketosis, correction of lactic acidosis, hypertriglyceridemia, hypercholesterolemia, and hyperuricemia. Screening for extra-hepatic (cardiac, renal) involvement is recommended.

For myopathic forms, having a good exercise program with an optimal diet may be helpful.

10 Other IEMs

There are a variety of other rare inborn errors of metabolism that can present with neurological symptoms. Describing these conditions in detail is beyond the scope of this chapter. These include disorders of neurotransmission, disorders of metal metabolism, disorders of sterol metabolism, disorders of creatine metabolism, congenital disorders of glycosylation, and more. a Referral to a geneticist is recommended for a workup of these conditions if suspected.

11 Clinical Pearls and Key Points

- Newborn screening is an important tool to detect several common inborn errors of metabolism. Nonetheless, some disorders may present later in life and false negative results may occur. The physician should be alert to both these possibilities.
- Several IEMs are inherited in an autosomal recessive manner. Therefore, a family history may be lacking.
- Common clinical symptoms of IEM include seizures, hypotonia, developmental regression and developmental delay. It may be difficult to distinguish them entirely on the basis of history and physical examination. Specific laboratory investigations are required in most instances.
- Targeted treatment options are now available for certain disorders and therefore early recognition is important.

References

1. Advisory Committee on Heritable Disorders in Newborns and Children, Recommended Uniform Screening Panel. https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html. Accessed 30 Dec 2020.
2. Fabie NAV, Pappas KB, Feldman GL. The current state of newborn screening in the United States. Pediatr Clin N Am. 2019;66(2):369–86.
3. Saudubray JM, Garcia-Cazorla A. An overview of inborn errors of metabolism affecting the brain: from neurodevelopment to neurodegenerative disorders. Dialogues Clin Neurosci. 2018;20(4):301–25.
4. Reddy N, Calloni SF, Vernon HJ, Boltshauser E, Huisman TAGM, Soares BP. Neuroimaging findings of organic acidemias and aminoacidopathies. Radiographics. 2018;38(3):912–31.
5. Saudubray J-M, van den Berghe G, Walter JH. Inborn metabolic diseases: diagnosis and treatment. 5th ed. New York: Springer-Verlag Berlin Heidelberg; 2012.
6. Biotinidase WB. Deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993–2020. 2000 Mar 24 [Updated 2016 Jun 9]. https://www-ncbi-nlm-nih-gov.proxy.lib.wayne.edu/books/NBK1322/.
7. Larson A, Goodman S. Glutaric acidemia type 1. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2020. 2019 Sep 19. https://www-ncbi-nlm-nih-gov.proxy.lib.wayne.edu/books/NBK546575/.
8. Baumgartner MR, Hörster F, Dionisi-Vici C, Haliloglu G, Karall D, Chapman KA, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. Orphanet J Rare Dis. 2014;9:130.
9. Häberle J, Burlina A, Chakrapani A, Dixon M, Karall D, Lindner M, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders: first revision. J Inherit Metab Dis. 2019;42(6):1192–230.
10. Spiekerkoetter U, Lindner M, Santer R, Grotzke M, Baumgartner MR, Boehles H, et al. Management and outcome in 75 individuals with long-chain fatty acid oxidation defects: results from a workshop. J Inherit Metab Dis. 2009;32(4):488–97.
11. Parikh S, Goldstein A, Koenig MK, Scaglia F, Enns GM, Saneto R, et al. Diagnosis and management of mitochondrial disease: a consensus statement from the mitochondrial medicine society. Genet Med. 2015;17(9):689–701.
12. Aubourg P, Wanders R. Peroxisomal disorders. Handb Clin Neurol. 2013;113:1593–609.
13. Kanungo S, Wells K, Tribett T, El-Gharbawy A. Glycogen metabolism and glycogen storage disorders. Ann Transl Med. 2018;6(24):474.

Further Readings

Aliu E, Kanungo S, Arnold GL. Amino acid disorders. Ann Transl Med. 2018;6(24):471.

Aubourg P, Wanders R. Peroxisomal disorders. Handb Clin Neurol. 2013;113:1593–609.

Campistol J, Plecko B. Treatable newborn and infant seizures due to inborn errors of metabolism. Epileptic Disord. 2015;17(3):229–42.

Ebrahimi-Fakhari D, Van Karnebeek C, Münchau A. Movement disorders in treatable inborn errors of metabolism. Mov Disord. 2019;34(5):598–613.

Kanungo S, Wells K, Tribett T, El-Gharbawy A. Glycogen metabolism and glycogen storage disorders. Ann Transl Med. 2018;6(24):474.

Valayannopoulos V, Poll-The BT. Diagnostic work-up in acute conditions of inborn errors of metabolism and storage diseases. Handb Clin Neurol. 2013;113:1553–62.

van Karnebeek CD, Shevell M, Zschocke J, Moeschler JB, Stockler S. The metabolic evaluation of the child with an intellectual developmental disorder: diagnostic algorithm for identification of treatable causes and new digital resource. Mol Genet Metab. 2014;111(4):428–38.

Myasthenia Gravis

Kelsey Christoffel and Duygu Selcen

1 Introduction

Case: *A 12-year-old previously healthy girl presents to her pediatrician with new complaints of double vision, slurred speech, and difficulty in swallowing, which have been getting progressively worse over the last several weeks. She has felt fatigued and has had to take several breaks and sit on the sidelines at her basketball games recently and is easily becoming short of breath. Her vitals are notable at a respiratory rate of 28, although her oxygen saturations and the remainder of her vitals are normal. On examination, her breathing is shallow, but her lungs are clear at auscultation. She is noted to have slight bilateral ptosis at rest that worsens with sustained upgaze, and she endorses diplopia on horizontal gaze. Her speech has a breathy, nasal quality, and she has trouble counting beyond 10 in one breath. Her strength during finger extension, shoulder abduction, and with squatting gets worse with repeated attempts. You suspect that this child has myasthenia gravis and are concerned about a possible impending myasthenic crisis. What should you do next?*

Myasthenia gravis is a well-described neurological condition that can affect children of any age, from the newborn period to adolescence. When autoimmune myasthenia gravis has its onset in childhood, it is termed "juvenile myasthenia gravis." Pediatricians may find themselves caring for these patients in their general practice for primary care and are often the first providers to encounter children presenting with the initial symptoms of this disease. A basic understanding of the pathophysiology of myasthenia gravis and a prompt recognition of its signs and symptoms are crucial, as both supportive and disease-specific treatments exist and can prevent

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further exacerbation and deterioration. Timely recognition is especially important during an acute exacerbation as these spells, referred to as a myasthenic crisis, can impair the respiratory or swallowing function. This chapter will focus on information regarding juvenile myasthenia gravis, including the epidemiology and etiology of the condition, differential diagnosis for children presenting with motor weakness, diagnostic approach to suspected myasthenia gravis, management and prevention of acute exacerbations and crises, and prognosis of juvenile myasthenia gravis.

2 Epidemiology

Epidemiological data for juvenile myasthenia gravis are sparse, and there is variability amongst the available literature. The estimated incidence of juvenile myasthenia gravis in a recent population-based study in Olmsted County has been 1.2 per one million [1]. Myasthenia gravis is reported to have its onset in childhood or adolescence in 10–15% of all cases [2], although there is variability across geographic and ethnic regions. Asian populations tend to have a much higher incidence of juvenile myasthenia gravis compared to that of Caucasians. About half of all cases of myasthenia gravis in Asian populations occur in children [3], with most children presenting with isolated ocular manifestations [4]. Thymomas, which are typically benign tumors and have been implicated in myasthenia gravis, are quite rare in children compared to adults. In adults with myasthenia gravis, 10–15% are found to have a thymoma, whereas it has been reported to be present in less than 5% of children. Prior to puberty, girls and boys tend to be affected at similar rates, but, after puberty, girls tend to be affected more often than boys with a ratio of about 3:2 [5]. Girls after the age of 11 years are also more likely than boys to have a seropositive disease [6].

3 Etiology

Myasthenia gravis is a disorder of signal transmission at the neuromuscular junction. To understand the pathophysiology of myasthenia gravis, it is helpful to understand the normal physiology of signal transmission at the neuromuscular junction. The neuromuscular junction is the site at which there are synapses between the peripheral motor nerve ending and the surface of the muscle fiber, allowing for signal transmission to be activated and contract the muscle. The main neurotransmitter involved in muscle contraction is acetylcholine and is stored in vesicles at the end of the presynaptic nerve terminal. Normally, when an action potential from the presynaptic motor nerve reaches and depolarizes the nerve terminal, an influx of calcium ions into the motor terminal promotes the release of acetylcholine into the neuromuscular junction. The synapse is flooded with acetylcholine, which then binds to acetylcholine receptors (AChRs) on the postsynaptic muscle fiber

membrane. This results in depolarization at the muscle membrane and generation of an action potential that results in muscle contraction. The acetylcholine is then quickly removed from the synapse by acetylcholine esterase and diffusion.

In myasthenia gravis, this normal process of signal transmission is disrupted. In most instances, myasthenia gravis is autoimmune process involving immunoglobulin G (IgG) antibodies that target postsynaptic acetylcholine receptors. This process involves not only direct blockage of the receptors by the antibodies but also immune-mediated destruction and internalization of the acetylcholine receptors [7]. This impairment of the acetylcholine receptors essentially prevents the neurotransmitter from being able to generate a sufficient postsynaptic muscle action potential, and, therefore, the muscle does not contract. Antibodies to the acetylcholine receptor are detected in approximately 80% of adult cases, but antibodies can also target other proteins of the neuromuscular junction, resulting in clinically indistinguishable presentations of weakness. Antibodies to the muscle-specific kinase (MuSK) protein may be found in 5–10% of overall cases [8], and antibodies to the more recently discovered lipoprotein receptor-related protein 4 (LRP4) have been found in a minority of cases [9]. MuSK is another protein essential for the formation and maintenance of neuromuscular synapses. The mode of action of the anti-MuSK antibody differs from those of anti-AChR antibodies. Instead of direct binding and damage of the acetylcholine receptor, the anti-MuSK antibody blocks the binding sites of the MuSK protein to other proteins including LRP4, agrin, and ColQ, hence blocking the MuSK function [10]. Antibodies to other striated muscle proteins may be present as well but are more likely to be associated with the presence of an underlying thymoma [11] and are therefore infrequently encountered in children. Children are more likely than adults to be MuSK antibody-negative [12].

The precise pathways behind the development of autoimmune myasthenia gravis remain unclear, but the thymus gland appears to be implicated in several instances. The thymus gland plays an important role in the development of the immune system in children; its function is to produce T cells. It is theorized that the thymus may be the instigator of the autoimmune pathology of myasthenia gravis, but the mechanism is not clearly understood. In patients with myasthenia gravis who have their thymus removed, it was commonly observed that the thymus was enlarged and had lymphoid hyperplasia. In addition, benign tumors of the thymus known as thymomas are sometimes noted in these patients.

4 Differential Diagnosis

Children presenting with motor weakness of any kind require a thoughtful history and examination, as the differential diagnosis of motor weakness can be quite broad and varied. A thorough neurological examination can help distinguish weakness caused by an upper motor neuron cause (the brain and spinal cord) from weakness due to a lower motor neuron etiology (the peripheral nerves and neuromuscular junction). An upper motor neuron pattern of weakness typically presents with

increased tone in the muscles, hyperreflexia, and often pathological reflexes such as positive Babinski signs (an upgoing big toe with fanning of the rest of the toes with plantar stimulation). Other potential signs localizing to a central nervous system etiology include findings such as aphasia, encephalopathy, or seizures. Lower motor neuron weakness is often accompanied by low tone and decreased deep tendon reflexes. This constellation of findings narrows the differential considerably.

The differential diagnosis for progressive generalized weakness in a lower motor neuron pattern would include acute or chronic inflammatory demyelinating polyneuropathy, autoimmune myasthenia gravis, Lambert–Eaton myasthenic syndrome (LEMS), toxin or drug-mediated neuromuscular junction disorders, and myopathies.

Acute inflammatory demyelinating polyneuropathy (Guillain–Barre the word Barre has a line on top of the e syndrome) typically presents with gradual ascending weakness in the lower extremities, which can progress to involve the facial and respiratory muscles. The weakness tends to be a profound, more or less bilateral, flaccid paralysis rather than a fatigable weakness as seen in early myasthenia gravis. History may reveal a gastrointestinal or respiratory illness in the weeks preceding the onset of symptoms. Acute flaccid myelitis is a condition involving injury to the anterior horn cells of the spinal cord, resulting in a lower motor neuron pattern of weakness as well. It classically presents with flaccid weakness and could include facial or bulbar weakness but can be differentiated by the acute onset in an asymmetric pattern.

The weakness seen in LEMS can cause physical examination findings that are similar to those of myasthenia gravis and may have a predilection to affect the bulbar muscles and extraocular movements as well as the proximal muscles. However, the key feature that distinguishes LEMS from myasthenia gravis is that the motor weakness in LEMS is more prominent at the beginning of the day (as opposed to myasthenia gravis, which causes more weakness toward the end of the day) and improves rather than worsens with repetition and exercise. Botulism is a toxin-mediated disorder of the neuromuscular junction that often presents in infancy and may present with prominent oculobulbar symptoms. However, the progression of the symptoms from the onset to nadir is much more rapid in botulinum poisoning (compared to that in myasthenia gravis) and is often associated with the history of having ingested contaminated food products. Pupillary paralysis (no pupillary response to light) may be present in botulism but is not a feature of myasthenia gravis and can be a useful pointer to differentiate the two. The differential diagnosis for patients presenting only with isolated ocular or bulbar symptoms may be more challenging but could include cranial nerve palsies, brainstem pathology, multiple sclerosis, stroke, tumor, or neurodegenerative conditions.

Juvenile myasthenia gravis most commonly occurs after the age of 10 years and is uncommon in infancy. When infants demonstrate findings of neuromuscular junction disorders, transient neonatal myasthenia gravis and congenital myasthenia gravis should be considered. Neonatal myasthenia gravis can occur in neonates who are born to mothers affected by myasthenia gravis and is caused by the maternal to fetal passage of antibodies in utero. This may lead to transient disruption of neonatal neuromuscular transmission and manifest with symptoms such as weak

sucking or crying, difficulty in feeding, dysphagia, ptosis, hypotonia, or respiratory distress. Symptoms are typically transient and mild, present within the first few hours to days of life, and, for most neonates, the symptoms will resolve within a few weeks to a month. A known maternal history of myasthenia gravis and the transient nature of the symptoms help distinguish it from genetic syndromes like spinal muscular atrophy. The severity of maternal myasthenia gravis does not seem to strongly influence the likelihood of developing neonatal myasthenia gravis, but having a history of an older sibling affected by neonatal myasthenia gravis is a known risk factor. Congenital myasthenic syndromes are a group of disorders of the neuromuscular junction that may have their onset in the neonatal period but have a genetic rather than an autoimmune etiology that results in defects in the structure and function of proteins of the neuromuscular junction. Congenital myasthenia gravis typically presents in infancy or early childhood. These syndromes should be suspected if symptoms such as motor weakness start at birth or infancy, if there is a family history of myasthenic syndrome, if the patient shows no improvement with anticholinesterase drugs, or if testing does not identify antibodies in the serum.

5 Diagnostic Approach

5.1 History

Myasthenia gravis is classically associated with diffuse weakness and fatigability, but initial symptoms are often restricted to the ocular or bulbar muscles. Common presenting complaints include ptosis (drooping eyelids) and diplopia (double vision). If symptoms are restricted to the eye muscles, then the term "ocular myasthenia gravis" is sometimes used. Bulbar symptoms are also common and refer to symptoms such as dysphagia (difficulty in swallowing), dysarthria (difficulty in producing clear speech), dysphonia (changes in voice), or dyspnea (shortness of breath). Patients may also report weakness or fatigue of the jaw while chewing food in addition to dysphagia. The skeletal muscles tend to be weaker in the axial (trunk and neck) distribution, and the proximal muscles tend to be weaker than the distal muscles in the limbs. However, what patients observe may vary depending on their individual activity type and level. For example, a patient who is sedentary but types on the computer all day may observe their hands fatiguing as a more prominent feature than a patient who is active in sports and observes that they cannot run as far without needing a break. Age may also affect how symptoms are communicated. Therefore, skilled history taking is important to elucidate the characteristic symptoms. A younger child may not be able to express that they are weak or seeing double, for example. As a result, they may seem more irritable and perhaps refuse to walk or play, which parents could conceivably perceive as pain or discomfort, and this can delay diagnosis.

A salient feature of myasthenia gravis is that the weakness is fatigable with repetitive or sustained movements and improves after a period of rest. As such, symptoms tend to worsen with exertion or repetitive tasks and can also be worsened by illness or stress. Weakness may be minimal in the morning and is worse toward the end of the day. Patients may endorse noticeable changes in vision (due to diplopia/ptosis), ability to eat, or to keep their head upright toward the evening. Family members may note a change in the patient's speech or the quality of their voice, or they may appreciate more pronounced ptosis later in the day.

When the symptoms progress to involve the respiratory muscles, resulting in respiratory distress, and the bulbar muscles, impairing safe handling of secretions, it is classified as a myasthenic crisis. It is often triggered in patients with myasthenia gravis by an illness or stress but can also occur if the symptoms are inadequately treated. As such, any patient with myasthenia gravis who is admitted to the hospital for an illness, injury, labor and delivery, or major surgeries should be examined closely and serially for any signs of worsening symptoms or an impending crisis. Although less common, patients with undiagnosed myasthenia gravis may present to their pediatrician or to the emergency department with signs of respiratory distress for evaluation. Signs of respiratory muscle weakness are often subtle and could include orthopnea, poor quality of sleep, daytime sleepiness, and positional dyspnea. These symptoms may develop gradually and slowly build up over the course of several days to weeks and may be followed by a relatively rapid deterioration to respiratory failure. Bulbar dysfunction can also progress to respiratory failure due to airway compromise from poorly handled secretions. Particularly worrying signs of bulbar dysfunction include weak cough, dysphagia, pooling of secretions, and hypernasal speech. A myasthenic crisis is a medical emergency and may necessitate intubation and mechanical ventilation.

5.2 Physical Examination

5.2.1 General Examination

As with any patient encounter, a basic assessment of the airway and breathing is necessary for patients with known or suspected myasthenia gravis and should not be overlooked. Patients should be screened for any respiratory symptoms even if not part of their presenting complaints. Respiratory distress may be due to any of the following: diaphragmatic weakness, intercostal muscle weakness, and airway obstruction due to bulbar dysfunction. Identification of the signs of an impending neuromuscular respiratory failure is crucial for the pediatricians and frontline providers who often encounter these patients initially. Tachypnea at rest and shortness of breath, even when mild, are concerning signs of respiratory muscle weakness and could portend respiratory failure without intervention. Relying on pulse oximetry as a measure of the respiratory status can be extremely misleading in children with myasthenia gravis.

5.2.2 Neurological Examination

A neurological examination can reveal clues essential for diagnosing myasthenia gravis. A common finding in myasthenia gravis is eyelid ptosis, which may be unilateral or bilateral. Having the patient fix their eyes in sustained vertical upgaze can elicit, or worsen, eyelid ptosis. Placing a cold ice pack onto an eyelid with ptosis for at least 2 min may transiently improve neuromuscular transmission and therefore briefly improve ptosis. Examination of extraocular movements may reveal dysconjugate (failure of eyes to move together) eye movements that result in diplopia. Cogan's lid twitch is a finding that may occur in myasthenia gravis. When the eyes return to their primary gaze position after a sustained downward gaze, a few twitches of the upper lid may be noted before it settles down into the right position. This is referred to as Cogan's lid twitch.

Muscle strength should be assessed throughout, including the facial and oropharyngeal muscles, which may often be overlooked. Orbicularis oculi can be tested by trying to pry open the eyelids of a child who is asked to close them tightly. Lower facial muscles can be assessed by having the patient hold air in cheeks against resistance. The muscles of the tongue can be tested by asking the patient to push the tongue laterally against the inside of each cheek and holding it firmly in place while the examiner applies force against it from the outside of the cheek. A patient who has highly breathy, nasal sounding speech displays signs of a flaccid dysarthria. Having the patient count to as high a number as possible after taking a single breath can provide a good assessment of respiratory and bulbar muscle functioning. Strength in neck flexors and extensors as well as the proximal and distal muscles of the extremities should be assessed. Weakness in the extremities should be fairly symmetric and is often more prominent proximally. Repeated strength testing is performed to elicit fatigable weakness. This can also be used to serially monitor the disease status. For example, counting the number of times a patient can stand up from a chair in 1 min or horizontal arm elevation can be compared before and after treatment, as a clinical way to assess treatment efficacy.

5.3 Evaluation

An edrophonium (Tensilon) test is one possible diagnostic test for myasthenia gravis. Edrophonium is an acetylcholine esterase inhibitor and therefore increases the concentration of acetylcholine at the synapse and improves signal transmission at the neuromuscular junction. However, due to technical challenges such as requiring intravenous (IV) access, and strict monitoring requirements, this test is not routinely used. Edrophonium is typically administered intravenously, and a specific examination finding should be clearly identified before the test and that finding should be monitored for improvement. This test should be performed in a hospital or a closely monitored setting, as side effects such as bronchospasm and bradycardia can occur

on rare occasions. Atropine should be available when conducting the edrophonium test. More common side effects include muscle fasciculations, nausea, tearing, salivation, and sweating, and these are more likely to occur in children than in adults. Neostigmine is used for the same purpose as edrophonium and is often preferred in younger children as it can be administered once intramuscularly and the patient can observed over 15–30 min for improvement rather than requiring multiple intravenous aliquots.

Electrophysiological testing is an extremely useful tool in the diagnosis of myasthenia gravis. Repetitive nerve stimulation and single-fiber electromyography (EMG) are the two classic electrophysiological modalities used for this purpose. Repetitive nerve stimulation is a type of nerve conduction study and is best assessed in muscles that are known to be weak. It involves repetitive electric stimulation of a motor nerve at a high frequency. This results in the motor nerve releasing acetylcholine at the neuromuscular junction, which binds acetylcholine receptors in the muscle fiber and causes depolarization and muscle contraction. In a child with myasthenia gravis, with successive repetitive stimulation, the amount of acetylcholine that is available at the neuromuscular junction becomes successively lower, quickly falling below the threshold required to trigger muscle fiber contraction. This phenomenon is called a decremental response and is indicative of neuromuscular junction impairment. Single-fiber EMG is an even more sensitive test in which a small electrode is inserted into the muscle to isolate a single motor unit. It looks closely at action potentials generated in the muscle fibers within the same motor unit. There is variation in the time at which the action potential reaches the muscle. This variation can be measured, and, if above the range of what is defined as normal, then it is highly suggestive of myasthenia gravis. In young children, single-fiber EMG is typically performed under sedation.

Serum should be tested for acetylcholine receptor antibodies in any child suspected of having myasthenia gravis. Assays for antibodies should be performed early, and, if positive in a patient with a history consistent with myasthenia gravis, then they could preclude the need for electrodiagnostic studies. If symptoms are severe or progressive, then clinicians should not await the results of antibody assays to perform additional diagnostic studies or begin treatment. If acetylcholine receptor antibodies are not present, it does not rule out a diagnosis of myasthenia gravis. Seronegative disease is more common in children, in patients with isolated ocular symptoms or mild disease, and is more likely to be associated with spontaneous remission [13]. If acetylcholine receptor antibodies are negative, then testing anti-MuSK antibodies should be routinely performed as the next step. Other antibodies against the striated muscle have been identified, but these are more commonly associated with thymomas. Although thymomas are relatively rare in children, all patients with a diagnosis of myasthenia gravis require imaging of the chest to exclude a thymic mass, the presence of which would be a clear indication for thymectomy. A chest computed tomography (CT) scan or magnetic resonance imaging (MRI) is recommended, as a chest radiograph may miss about a quarter of thymomas [14].

6 Treatment/Management

Initial management in a patient who presents with a suspected myasthenic exacerbation or crisis requires prompt attention to the respiratory status. The patient's ability to maintain a patent airway should be assessed in the presence of significant secretions and bulbar weakness. Diaphragmatic and intercostal muscle weakness can cause rapid and shallow breathing, and fatiguability of those muscles can cause a fairly rapid respiratory decline. Respiratory mechanics, including forced vital capacity, should be obtained at presentation and monitored daily at a minimum, with more frequent assessments as needed. Respiratory rate and oxygenation should be monitored and blood gas periodically obtained. Oxygenation is often normal until later stages of respiratory failure, but a blood gas can reveal whether there is carbon dioxide retention or respiratory acidosis, suggestive of poor ventilation. In any scenario where the respiratory function is impaired or worsening, observation in a closely monitored setting is indicated. This usually means hospitalization and, in severe or rapidly progressing cases, admission to the intensive care unit. If there is a decline in measures of the respiratory status, then proactive steps must be taken to prevent complications of respiratory failure. Bilevel positive airway pressure (BiPAP) is an appropriate intervention if there is concern for hypoventilation due to respiratory muscle weakness, but the airway is not compromised. If the secretion burden is heavy due to bulbar dysfunction, then intubation is the safer choice to maintain the airway and prevent aspiration while assisting with ventilation [15].

Pyridostigmine, an acetylcholinesterase inhibitor, is the first-line maintenance therapy in both children and adults. During an exacerbation, pyridostigmine can be titrated to symptom control, with a maximum dosage of 7 mg/kg per day or 300 mg/day divided into up to five to six doses. If no respiratory or bulbar dysfunction is noted but other symptoms have worsened, then it is appropriate to optimize the treatment with pyridostigmine as the first step. Side effects may limit doses of pyridostigmine as well, particularly gastrointestinal symptoms like cramping and diarrhea. During an acute myasthenic crisis, titration of pyridostigmine is unlikely to be helpful in a timely manner. Furthermore, patients may no longer be able to take pyridostigmine orally due to bulbar dysfunction or necessary respiratory equipment. An intravenous form of pyridostigmine is available, but it should be noted that dosing differs from the oral form: 1 mg of IV pyridostigmine is equivalent to approximately 30 mg of oral pyridostigmine. Pyridostigmine is often held if the patient is already on a high dose of pyridostigmine when other more aggressive treatments like intravenous immunoglobulin (IVIG) and plasmapheresis are required, as there is a possibility of a cholinergic crisis that precipitates the worsening of the symptoms and myasthenic crises. It can be resumed when swallowing is deemed safe and at a lower dose and with slow titration.

Corticosteroids are often a first-line agent used to treat exacerbations of myasthenia gravis. For mild-to-moderate symptoms, if there is no response after

optimization of pyridostigmine, then oral prednisone can be administered as a daily medication and then tapered off over several months. Oftentimes, a gradual improvement in symptoms is seen within weeks. For patients with a higher symptom burden or rapid progression of symptoms, high-dose corticosteroids may be warranted [16]. Providers should exercise caution, however, because some patients experience a temporary, paradoxical worsening of their symptoms with the initiation of high-dose steroids, even progressing to respiratory failure and requiring intubation in some cases. For that reason, patients receiving high-dose corticosteroids should be observed in a closely monitored environment.

Acute management of a myasthenic crisis may include plasmapheresis or IVIG. Intravenous immunoglobulin (IVIG) is often used for myasthenic exacerbations, especially in children, and has advantages over plasmapheresis, in that it does not require a central line, is generally less cumbersome to administer, and has fewer side effects in children. As such, it is often preferred to plasmapheresis and is often used in conjunction with corticosteroids. A total dose of 2 g/kg is typically administered over 2–5 days and can be repeated every other week or monthly depending on the severity of the child's symptoms. Improvement may not be as rapid as with plasma exchange [17], but effectiveness at 2 weeks post-treatment is believed to be comparable [18].

Plasmapheresis removes the circulating acetylcholine receptor antibodies and may result in a more rapid improvement over the course of several days. A typical course would be composed of 4–6 rounds of plasma exchange every other day, depending on the patient's response to the treatment. There are risks associated with plasmapheresis and it requires a central line, so it is usually reserved for severe cases. These risks include hypotension, bleeding due to anticoagulant therapy, and risks associated with central lines like infection, pneumothorax, and thrombosis [19].

Other immune-modulating therapies may be used as maintenance therapies for myasthenia gravis when symptoms are not well-controlled, or are refractory to pyridostigmine; but these will not be discussed in detail in this chapter. These medications may include azathioprine, rituximab, mycophenolate mofetil, cyclosporine, cyclophosphamide, and tacrolimus. These medications typically need to be taken for months to notice a significant improvement and are not helpful in an acute setting. Each of these medications has a side effect profile that should be weighed carefully, and decisions regarding which agent is the most suitable for a given patient should be made after discussing with a neuromuscular specialist.

Given the potential role of the thymus gland in the pathogenesis of myasthenia gravis, a complete surgical removal of the thymus gland is common in both children and adults. Compared to adult-onset myasthenia gravis, it is known that juvenile myasthenia gravis is less likely to be associated with thymomas or with pre-existing autoimmune disorders [20]. Nevertheless, thymectomy is generally believed to be beneficial for children with myasthenia gravis with anti-AChR antibody positivity, regardless of the presence or absence of a thymic mass. Thymectomies are usually an adjunct measure, in addition to medical therapy, and, for that reason, data on the

outcomes of thymectomies are challenging to interpret. However, it has been reported that children are more likely to achieve remission when thymectomy occurs within 2 years of symptom onset [21], and it is usually strongly considered particularly in older children with generalized rather than ocular myasthenia gravis.

7 Prognosis

Juvenile myasthenia gravis is associated with a good prognosis when diagnosed and treated appropriately. Over time, there has been a drastic reduction in the mortality rate [22], with an overall mortality rate in the 1940s and 1950s at around 31% and the current mortality rate reported to be at around 3–4%. Fortunately, most patients diagnosed with myasthenia gravis today have an essentially normal life expectancy. This is believed to be due to improvement in respiratory care available to patients with a myasthenic crisis as well as the advances seen with the introduction of corticosteroids. Risk factors for mortality include age more than 40 years, a rapidly progressive disease, and the presence of a thymoma [23]. Specific mortality rates for juvenile myasthenia gravis have not been well-established, but the overall course of juvenile myasthenia gravis tends to be more benign than the adult-onset form. Juvenile myasthenia gravis is more likely to remit than is adult-onset myasthenia gravis. In one longitudinal study of 149 patients with juvenile myasthenia gravis, a spontaneous remission rate of 22.4 per 1000 person years was reported [24]. The prognosis differs slightly by the age of onset; children with a prepubertal onset more commonly present with isolated ocular findings, less frequently progress from ocular to generalized myasthenia gravis, and are more likely to achieve either spontaneous or medical remission [25].

8 Prevention

Myasthenic crises can be precipitated by numerous triggers, most commonly a significant biological stressor like a surgery or an infection. Symptoms may worsen with medication non-compliance or inadequate treatment. Additionally, several common medications are known to exacerbate myasthenia gravis, classically, non-depolarizing neuromuscular blocking agents, which are paralytics frequently used during medical procedures and surgeries. Neuromuscular blocking agents should be sparingly used in children with myasthenia gravis and, if needed, in the smallest effective doses. Several common antibiotics that can potentially interfere with transmission of a signal across the neuromuscular junction include aminoglycosides, erythromycin, tetracycline, penicillin, sulfonamides, fluoroquinolones, telithromycin, azithromycin, and clindamycin. Phenytoin, magnesium, beta blockers, procainamide, chloroquine, and d-penicillamine are just a few of the medications that may

also exacerbate myasthenic symptoms. Interestingly, patients without myasthenia gravis who are treated with d-penicillamine may develop a myasthenic syndrome due to induction of acetylcholine receptor antibodies, which may last several months after the drug is discontinued.

9 When to Refer/Admit

All children with suspected myasthenia gravis should be urgently referred to see a pediatric neurologist with expertise in treating this condition. Patients with orthopnea, tachypnea, and positional dyspnea may need to be admitted to the hospital for concern of a relatively rapid deterioration to respiratory failure. Patients with bulbar dysfunction who present with symptoms of weak cough, dysphagia, pooling of secretions, and hypernasal speech can also progress to respiratory failure and should be admitted to the hospital.

10 Clinical Pearls/Key Points

- Myasthenia gravis is caused by an antibody-mediated process that affects the acetylcholine receptors at the neuromuscular junction.
- Ptosis, diplopia, and proximal muscle weakness that worsen with repetitive or sustained activation of the muscles are the common presenting features of myasthenia gravis.
- Respiratory distress or bulbar symptoms that impair the ability of the child to handle oral secretions are signs of a myasthenic crisis.
- Patients should be regularly screened at routine visits for increased fatigue, difficulty in sleeping, orthopnea, dyspnea, dysphagia, and increased oral secretions, as these can portend a myasthenic crisis.
- Spirometry, blood gases to look for carbon dioxide retention, and oxygenation should be monitored closely at baseline and serially during a myasthenic crisis.
- A myasthenic crisis can result in the need for BiPAP or intubation with mechanical ventilation.
- Corticosteroids, IVIG, and plasmapheresis are some of the treatment options for acute myasthenia gravis exacerbations or crises.

References

1. Mansukhani SA, Bothun ED, Diehl NN, Mohney BG. Incidence and ocular features of pediatric myasthenias. Am J Ophthalmol. 2019;200:242–9. https://doi.org/10.1016/j.ajo.2019.01.004. Epub 2019 Jan 14.

2. Evoli A, Batocchi AP, Bartoccioni E, Lino MM, Minisci C, Tonali P. Juvenile myasthenia gravis with prepubertal onset. Neuromuscul Disord. 1998;8(8):561–7.
3. Zhang X, Yang M, Xu J, et al. Clinical and serological study of myasthenia gravis in HuBei Province, China. J Neurol Neurosurg Psychiatry. 2007;78(4):386–90.
4. Chiu HC, Vincent A, Newsom-Davis J, Hsieh KH, Hung T. Myasthenia gravis: population differences in disease expression and acetylcholine receptor antibody titers between Chinese and Caucasians Neurology. 1987;37(12):1854–7.
5. Andrews PI, Massey JM, Howard JF Jr, Sanders DB. Race, sex, and puberty influence onset, severity, and outcome in juvenile myasthenia gravis. Neurology. 1994 Jul;44(7):1208–14. https://doi.org/10.1212/wnl.44.7.1208.
6. Anlar B, Ozdirim E, Renda Y, Yalaz K, Aysun S, Topçu M, Topaloğlu H. Myasthenia gravis in childhood. Acta Paediatr. 1996;85(7):838–42. https://doi.org/10.1111/j.1651-2227.1996.tb14162.x.
7. Pevzner A, Schoser B, Peters K, Cosma NC, Karakatsani A, Schalke B, Melms A, Kröger S. Anti-LRP4 autoantibodies in AChR- and MuSK-antibody-negative myasthenia gravis. J Neurol. 2012;259(3):427–35. https://doi.org/10.1007/s00415-011-6194-7. Epub 2011 Aug 5
8. Zhang B, Tzartos JS, Belimezi M, Ragheb S, Bealmear B, Lewis RA, Xiong WC, Lisak RP, Tzartos SJ, Mei L. Autoantibodies to lipoprotein-related protein 4 in patients with double-seronegative myasthenia gravis. Arch Neurol. 2012;69(4):445–51. https://doi.org/10.1001/archneurol.2011.2393. Epub 2011 Dec 12
9. Hughes BW, Moro De Casillas ML, Kaminski HJ. Pathophysiology of myasthenia gravis. Semin Neurol. 2004;24(1):21–30. https://doi.org/10.1055/s-2004-829585.
10. Huijbers MG, et al. MuSK myasthenia gravis. Proc Natl Acad Sci. 2013;110(51):20,783–8. https://doi.org/10.1073/pnas.1313944110.
11. Limburg PC, The TH, Hummel-Tappel E, Oosterhuis HJ. Anti-acetylcholine receptor antibodies in myasthenia gravis. Part 1. Relation to clinical parameters in 250 patients. J Neurol Sci. 1983;58(3):357–70. https://doi.org/10.1016/0022-510x(83)90095-3.
12. Andrews PI. Autoimmune myasthenia gravis in childhood. Semin Neurol. 2004;24(1):101–10. https://doi.org/10.1055/s-2004-829591.
13. Afifi AK, Bell WE. Tests for juvenile myasthenia gravis: comparative diagnostic yield and prediction of outcome. J Child Neurol. 1993;8(4):403–11. https://doi.org/10.1177/088307389300800422.
14. Batra P, Herrmann C Jr, Mulder D. Mediastinal imaging in myasthenia gravis: correlation of chest radiography, CT, MR, and surgical findings. AJR Am J Roentgenol. 1987;148(3):515–9. https://doi.org/10.2214/ajr.148.3.515.
15. Pfeffer G, Povitz M. Respiratory management of patients with neuromuscular disease: current perspectives. Degener Neurol Neuromuscul Dis. 2016;6:111–8. Published 2016 Nov 18. https://doi.org/10.2147/DNND.S87323.
16. Rønager J, Ravnborg M, Hermansen I, Vorstrup S. Immunoglobulin treatment versus plasma exchange in patients with chronic moderate to severe myasthenia gravis. Artif Organs. 2001;25(12):967–73. https://doi.org/10.1046/j.1525-1594.2001.06717.x.
17. Barth D, Nabavi Nouri M, Ng E, Nwe P, Bril V. Comparison of IVIg and PLEX in patients with myasthenia gravis. Neurology. 2011;76(23):2017–23. https://doi.org/10.1212/WNL.0b013e31821e5505.
18. Misanovic V, Pokrajac D, Zubcevic S, et al. Plasmapheresis in Pediatric intensive care unit. Med Arch. 2016;70(5):332–5. https://doi.org/10.5455/medarh.2016.70.332-335.
19. Peragallo JH. Pediatric myasthenia gravis. Semin Pediatr Neurol. 2017;24(2):116–21. https://doi.org/10.1016/j.spen.2017.04.003. Epub 2017 Apr 7.
20. Ashraf VV, Taly AB, Veerendrakumar M, Rao S. Myasthenia gravis in children: a longitudinal study. Acta Neurol Scand. 2006;114(2):119–23. https://doi.org/10.1111/j.1600-0404.2006.00646.x.
21. Seybold ME. Thymectomy in childhood myasthenia gravis. Ann N Y Acad Sci. 1998;841:731–41. https://doi.org/10.1111/j.1749-6632.1998.tb11010.x.

22. Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. Muscle Nerve. 2008;37(2):141–9.
23. Mantegazza R, Baggi F, Antozzi C, Confalonieri P, Morandi L, Bernasconi P, Andreetta F, Simoncini O, Campanella A, Beghi E, Cornelio F. Myasthenia gravis (MG): epidemiological data and prognostic factors. Ann N Y Acad Sci. 2003;998:413–23. https://doi.org/10.1196/annals.1254.054.
24. Rodriguez M, Gomez MR, Howard FM Jr, Taylor WF. Myasthenia gravis in children: long-term follow-up. Ann Neurol. 1983;13(5):504–10. https://doi.org/10.1002/ana.410130506.
25. Finnis MF, Jayawant S. Juvenile myasthenia gravis: a paediatric perspective. Autoimmune Dis. 2011;2011:404101. https://doi.org/10.4061/2011/404101.

Approach to an Infant with Hypotonia

Gyula Acsadi and William D. Graf

1 Introduction

Hypotonia is a physical finding characterized by reduced muscle tension and decreased resistance to passive range of motion along with varying degrees of weakness. Hypotonia in neonates and infants can be noted as an isolated nonspecific examination finding or in association with other physical findings—but it is a physical sign that requires further evaluation for an etiological diagnosis. Hundreds of diverse neurodevelopmental and neurological disorders can cause hypotonia, and its evaluation is a clinical challenge that goes well beyond recognition and description. Etiologically, the evolving standard of diagnosis improves with specific knowledge and understanding of molecular and cellular pathophysiology. Without basic knowledge, any targeted biological treatment for hypotonia is unlikely to be effective. Consequently, the evaluation of a neonate or infant with hypotonia should involve a highly organized, step-by-step approach that is always mindful of the potentially treatable conditions.

1.1 Epidemiology

The incidence of infantile muscle hypotonia is difficult to determine because of the diversity of causes and lack of uniform reporting; however, it is one the most common abnormal neurological signs in a developing child. Some studies suggest that 60–80% of hypotonia cases are caused by disorders of the central nervous system

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(CNS) and the remainder are caused by peripheral nervous system (PNS) disorders, though definitive data are lacking.

1.2 Developmental Chronology

Hypotonia may be recognized prenatally (e.g., by decreased fetal movements), congenitally (i.e., by a physical examination), or postnatally (e.g., due to an acquired loss of tone). Determinants of muscle tone, such as the corticospinal and corticobulbar tracts, are still immature at birth before myelination, and axonal outgrowth and synaptic contacts fully develop over the first few years of life. Normal physical changes in muscle tone evolve chronologically along with anticipated neurodevelopmental maturation of the nervous system, and the presence of muscle hypotonia represents a deviation from the expected development.

1.3 Anatomical Localization (Fig. 1)

Neonatal and infant hypotonia can be caused by disorders primarily affecting the CNS (the brain and spinal cord), the PNS (the motor unit and the sensory loop), their transitional regions (such as the anterior horn of the gray matter of the spinal cord), the neuromuscular junction (NMJ), muscle, or cellular metabolism. "Central"

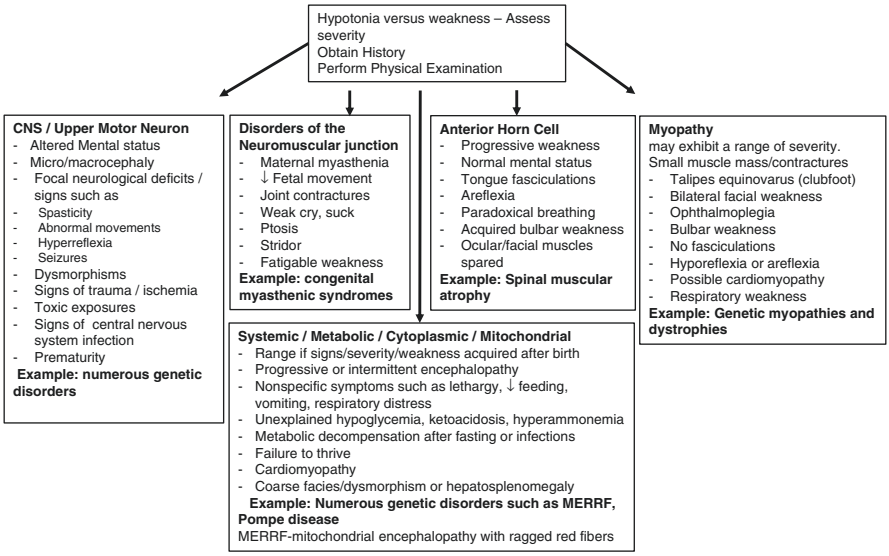

Fig. 1 Algorithm for the initial diagnostic evaluation of hypotonia in infants—LOCALIZATION

hypotonia indicates an "upper motor neuron" (UMN) localization above the "peripheral" level of the "lower motor neuron" (LMN). Such categorization, i.e., central versus peripheral hypotonia, is a basic but reliable clinical starting point in diagnostic algorithms and localization strategies. **Neonatal central hypotonia** is often considered within the spectrum of **neonatal encephalopathies** (including perinatal hypoxic-ischemic encephalopathy) with altered arousal, head growth and seizures. Hypotonia without significant weakness is more likely to arise from CNS disorders including acute, subacute, and chronic metabolic, nutritional, and endocrine disorders as well as mild, non-progressive, idiopathic (or "benign") hypotonia. Central hypotonia is typically associated with axial (truncal) hypotonia with normal or hyperactive myotatic (tendon stretch) reflexes. Neonates and infants with LMN disorders typically have a normal mental status and hypotonia with neuromuscular weakness. Beyond these general considerations, a wide range of genetic, metabolic, and neuroanatomical disorders can explain hypotonia in most cases. Diagnostic localization of hypotonia can be further assessed based on additional historical and physical clues summarized in Fig. 1.

2 The Anatomical Basis of Muscle Tone and its Regulation

2.1 The Motor Neuroaxis

Hypotonia reflects abnormal neuronal signal generation, transmission, or modulation at any level along the motor neuroaxis, which includes the cerebral cortex, subcortical white matter, basal ganglia, thalami, cerebellum, brainstem, and spinal cord leading to the peripheral nerves, neuromuscular junction, and muscle. Low muscle tone is a decrease in passive resistance against the stretching caused by a change at one or more levels along this neuroaxis.

2.2 Upper Motor Determinants of Muscle Tone

Posture, muscle tone, and strength are overlapping physical findings in neonates and infants. An abnormal posture implies a central imbalance between flexor and extensor muscle tone independent of strength. Central muscle tone regulation is dominated by two major pyramidal tracts, namely, the corticobulbar and the corticospinal tracts (Table 1). These pyramidal tracts, from the motor cortex through the brainstem and spinal cord, regulate either voluntary and involuntary facilitation or inhibition of muscle contraction. Some descending pathways from the brainstem (vestibulospinal, olivospinal, rubrospinal, and reticulospinal tracts) and from the cerebellum (cerebellospinal tracts) provide involuntary regulation of movements,

Table 1 The major pyramidal pathways in upper motor neuron regulation of muscle tone

Pyramidal tract	Anatomical tracts	Physiological mechanisms
Corticobulbar	Connects the primary frontal lobe motor cortex to the medulla oblongata "pyramids"	Serves lower (non-oculomotor) cranial nerves (CN V, VII, IX, and XII) and contributes to CN X (nucleus ambiguous), controlling the soft palate, pharynx, larynx, and upper esophagus
Corticospinal	Connects the cerebral cortex to the interneurons in the spinal cord	Controls voluntary movements of the limbs and trunk; clinically, decreased inhibition from the corticospinal tract leads to exaggerated myotatic (tendon stretch) reflexes, hand "fisting," sustained clonus, increased tone, or even opisthotonus

coordination, and balance. Tract maturation includes the arborization of terminal axonal contacts, synaptogenesis, and myelination as well as the maturation of the long axons responsible for the synthesis and transport of neurosecretory chemical transmitters. Functionally, the medial subcorticospinal and corticospinal pathways are antagonistic: the medial subcorticospinal neurons allow proximal extension and distal flexion, whereas the corticospinal tract promotes proximal flexion and distal extension. However, the corticospinal tract is predominantly an inhibitory pathway that determines muscle tone and posture by selectively suppressing massive excitation.

2.3 Lower Motor Determinants of Muscle Tone

A fully relaxed muscle has a certain tension due to the elastic parameters of the tissue in addition to contraction of some muscle fibers. At the muscle tissue level, thin and thick sarcomere filaments are evoked by depolarization of the neuromuscular junction, following acetylcholine release from the motor nerve endings. Intrafusal muscle spindles provide the sensory detection of muscle stretch and loops to the spinal cord functioning as a monosynaptic myotatic (tendon stretch) reflex. To regulate the muscle tension or stretch, the sensory loop is interconnected with the motor neurons to set appropriate and dynamic control on muscle contraction. See Table 2 for lower motor neuron determinants of muscle tone. Figure 2 is a pictorial representation of these pathways.

Table 2 The major mechanisms of lower motor neuron and muscle fiber determinants of muscle tone

Level	Anatomy	Physiological mechanisms
1. Anterior horn.	The motor neuron soma is in the ventral (anterior) horn of the spinal cord's gray matter; its axon passes through a ventral root to the peripheral nerves	Innervation of the arm and leg muscles through different segments of the spinal cord
2. Peripheral motor nerve.	Cranial, plexus, and somatic nerves and the ganglia outside the brain and spinal cord	Transmission of somatic signals from the spinal cord to the muscle
3. Neuromuscular junction.	Synaptic connection between the terminal end of a motor nerve and the muscle	Transmission of action potential from the nerve to the muscle
4. Skeletal muscle.	Thick and thin sarcomere filaments; intrafusal muscle spindles	The skeletal muscle is an "end organ" primarily controlling movement and posture

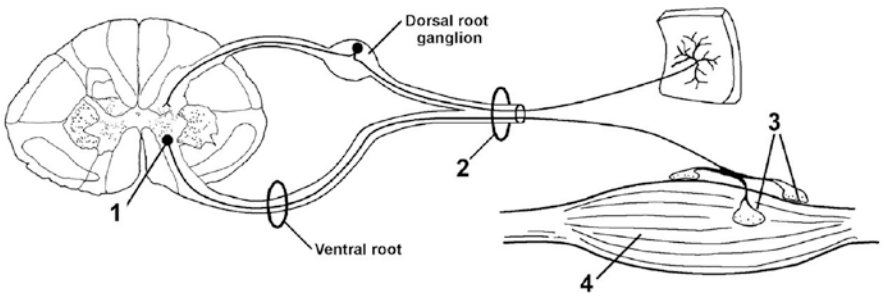

Fig. 2 Schematic diagram of anatomical "levels" of lower motor neuron determinants of muscle tone: (1) anterior horn; (2) peripheral motor nerve; (3) neuromuscular junction; and (4) skeletal muscle (see Table 2 for anatomical and physiological details)

3 Diagnostic Evaluations

3.1 Prenatal History

Maternal health and pregnancy histories may be relevant to neonatal or infant hypotonia. Maternal accounts of decreased intrauterine fetal movement or breech presentation may be signs of prenatal-onset hypotonia or neuromuscular weakness. A maternal history of infections or teratogen exposures during pregnancy is associated with a higher risk of cerebral malformation and central hypotonia. Polyhydramnios, oligohydramnios, a maternal history of previous miscarriages, and an advanced maternal age are factors associated with an increased risk of chromosomal disorders.

3.2 Perinatal History

A history of prematurity, delivery complications, low APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) scores (i.e., evidence of hypoxia–ischemia), sucking/swallowing difficulties, and poor respiratory effort are consistent with neonatal encephalopathy, but persistent unexplained weakness may prompt reconsideration of an overlooked neuromuscular disorder.

3.3 Neonatal and Early Postnatal History

Non-specific metabolic and endocrine abnormalities (e.g., hypoglycemia, metabolic acidosis, hyperammonemia, hypothyroidism) must be treated urgently even if the specific underlying metabolic disorder is not yet known. An attentive review of all organ systems may help expand the differential diagnosis in some infants whose signs of hypotonia are unexplained.

3.4 Family and Social History

The most pertinent family history relates to first- and second-degree family members who might have either a known genetic diagnosis or signs and symptoms of undiagnosed neuromuscular disorder. Consanguineous unions increase the risk of monogenetic autosomal recessive disorders as well as the frequency of large non-specific homozygous genomic segments and identity by descent shared between family members.

3.5 Chronology

In addition to the age of onset, changes over time should suggest a paroxysmal, progressive, stable (“static”), or improving chronological course. Formal neurodevelopmental assessments in older infants allow standardized measures (e.g., Bayley scales) of the attainment of developmental milestones over time.

4 Physical Examination

4.1 General Examination

Physical growth, the appearance of dysmorphic facial features, or the presence of associated non-neurological malformations may suggest a recognizable genetic syndrome or other patterns of human malformation. The shape and size of the head, and its rate of growth, should always be noted.

4.2 Neurological Examination of Muscle Tone

Neonatal or infant neurological examination starts with a simple observation of an undressed child in both supine and prone positions to note the degree of flexion of the elbows, hips, and knees along with spontaneous movements, followed by a passive range of motion of the arms and legs. A decreased movement of the limbs suggests weakness. A lack of flexion in the legs may exhibit the so-called "frog-legged" appearance. In the prone position, the arms stay parallel to the torso and flexed at the elbow when hypotonic. Muscle tone can be further assessed using four basic maneuvers, which include vertical and horizontal suspension, the "scarf sign," and "pull to sit." Vertical suspension is performed by holding the infant under the arms in the upright position. A healthy mature newborn held under the arms should be able to hold its head up for a few seconds, whereas a hypotonic infant may "slip through" and cannot hold the head—requiring caution and greater neck support by the caregiver in the vertical and horizontal positions. The horizontal suspension test is performed by lifting the infant in a prone position with a hand under the chest and abdomen. A healthy and awake term infant has some flexion of the arms and legs along with the ability to hold a sustained straight posture with the head above the horizontal plane for a few seconds. Infants with moderate-to-severe hypotonia form a so-called "inverted-U" posture. The grading of muscle hypotonia as mild, moderate, or severe is relative and subjective, but it is important to estimate the extent of inability compared to healthy infants with normal tone. The "scarf sign" is performed by pulling the hand across the chest to the point of mild resistance. The healthy term infant typically shows resistance when the elbow reaches the midline, whereas the hypotonic infant lacks resistance. The "pull-to-sit" test is performed by pulling a supine infant to the sitting position while noting the degree of head lag. Although head lag is expected in newborns, neutral neck strength is anticipated by about 2 months of age. This maneuver is a good indicator of tone in both the axial and appendicular muscles.

4.3 Neurological Examination of Strength

The determination of muscle strength in an infant is challenging and may require serial examinations. Decreased strength may be evident by weak crying and sucking, diminished facial expressions, absent antigravity movements, poor respiratory effort, diaphragmatic breathing, intercostal retractions, or stridor. Muscle atrophy, lack of myotatic reflexes, and muscle or tongue fasciculation strongly suggest neuromuscular weakness more than hypotonia.

4.4 Associated Physical and Neurological Observations

Signs of developmental encephalopathy (decreased alertness, lack of visual tracking, and delayed acquisition of a social smile) and increased myotatic reflexes are strongly suggestive of a brain neurodevelopmental disorder rather than neuromuscular. Slow feeding and dysphagia can be associated with either UMN or LMN disorders. The distinction between a "central" and "peripheral" or "combined" etiology of muscle hypotonia is not always straightforward. For example, there are various genetic muscular dystrophies and peripheral neuropathies, which also involve brain abnormalities. Similarly, predominant CNS disorders and diseases, particularly those with a metabolic basis (such as certain mitochondrial disorders and leukodystrophies), may also cause motor neuron loss or neuropathy. Electrophysiologic testing (nerve conduction, repetitive stimulation and electromyography) has some role in the differential diagnosis of hypotonia caused by neuromuscular diseases.

5 Laboratory Screening

5.1 Beyond Newborn Screening

There are no "cookbook" approaches to complex conditions such as neonatal or infant hypotonia. General guidelines for a basic metabolic screening will never be the same as a focused evaluation of an individual patient. A standard newborn screening allows for the detection of more than 60 genetic diseases from a single heel stick filter paper blood sample shortly after birth, and decisions about whether to pursue additional metabolic or genetic testing in the evaluation of hypotonia depend upon multiple factors such as the nature, severity, and chronology of the clinical findings, the experience of the physician, the perceived diagnostic yield of specific tests, or consideration of their cost/benefit ratio. Numerous disorders of hormones and small-molecule metabolism presenting with hypotonia along with

protein (feeding) intolerance, failure to thrive, lactic acidosis, hypoglycemia, or hyperammonemia need to be urgently diagnosed and appropriately treated. A **"basic panel" of diagnostic screening** tests should be strongly considered and include serum glucose with urine ketones, serum creatine kinase, ammonia, lactate, acylcarnitines, and thyroid hormone/thyroid-stimulating hormone, especially when resources are limited. If spinal muscular atrophy (SMA) is in the differential diagnosis (progressive muscle weakness and atrophy), then genetic testing for *SMN1* and *SMN2* copy number and mutation analysis should be performed. If Pompe disease (glycogen storage disease, type II) is in the differential diagnosis (hypotonia with cardiomegaly plus respiratory distress), then acid alpha-glucosidase (GAA) enzyme activity or gene sequencing should be performed. If Prader–Willi syndrome (PWS) is considered (severe hypotonia, weak crying with poor sucking, almond-shaped eyes, small hands), then a DNA methylation analysis, which detects >99% of PWS cases, including all of the major genetic subtypes of PWS (deletion, uniparental disomy, or imprinting mutation), must be conducted.

5.2 Genetic Testing

Advances in genetic testing technologies and greater knowledge of the human genome are resulting in significant changes in the diagnosis, classification, and treatments of early-onset pediatric disorders including many that initially present with hypotonia. Many hypotonia disorders will be recognized earlier or treated differently because of these changes. It is especially important for primary care physicians to recognize the clinical signs of progressive hypotonia and weakness and to know when to pursue advanced laboratory testing or referral to a pediatric subspecialty center.

5.3 Chromosomal Microarray

Rapid access to genetic testing has led to higher expectations and standards in clinical practice. Clinical recognition of hypotonia phenotypes along with a series of "first-line" and "second-line" metabolic and genetic tests provide a new approach to diagnosis. Chromosomal microarray analysis (including both microarray-based comparative genomic hybridization and single-nucleotide polymorphism microarray) is often a first-line genetic test in the etiological evaluation of hypotonia, especially when a syndrome is suspected and other organ systems are involved. The widespread use and high diagnostic yield of a microarray provide awareness of the unpredictability of human genomic gains and losses as a major cause of all neurodevelopmental disorders including those with hypotonia and multiple congenital anomalies. It is anticipated that most metabolic tests and microarrays will be

replaced by rapid next-generation sequencing (NGS) technologies over the next decade, allowing even earlier diagnoses of rare disorders at birth or in early infancy.

5.4 Gene "Panel" Testing

Next-generation sequencing-based genetic/genomic tests include disorder/disease-targeted gene panels (NGS panels), exome sequencing, or genome sequencing. Both NGS panels and exome sequencing require an enrichment step of the desired genomic regions before NGS can be performed, but this step is not necessary for genome sequencing. Genome sequencing techniques uncover virtually all variants within an individual's genome simultaneously, whereas exome sequencing typically evaluates all known genes, and multigene panel testing targets a group of selected genes (from several to hundreds) related to certain diseases or disorders for which both allelic and locus heterogeneities are substantial. Both hospital-based and commercial genetic testing laboratories provide a range of options for single gene and panel testing to diagnose infants with suspected primary (genetic) causes of hypotonia. Central hypotonia, which accounts for 60–80% of congenital hypotonia, can be assessed through sequencing of more than 1400 genes associated with congenital hypotonia. Numerous laboratories sequence more than two dozen genes associated with congenital myasthenic syndromes, a heterogeneous group of neuromuscular conditions characterized by fatigable weakness of the skeletal muscles (e.g., *AGRN*, *ALG14*, *ALG2*, *CHAT*, *CHRNA1*, *CHRNB1*, *CHRND*, *CHRNE*, *CHRNG*, *COL13A1*, *COLQ*, *DOK7*, *DPAGT1*, *GFPT1*, *GMPPB*, *LAMB2*, *LRP4*, *MUSK*, *MYO9A*, *PLEC*, *PREPL*, *RAPSN*, *SCN4A*, *SLC25A1*, *SLC5A7*, *SNAP25*, *STIM1*, *SYT2*). For infants whose phenotype suggests neuromuscular diagnoses, gene panels targeted at known causes of congenital myopathy and muscular dystrophy are readily available. In most cases, DNA can be extracted from whole blood, buccal swabs, saliva, oral rinse, fresh and frozen tissues, bone marrow, and dried blood spots.

5.5 Exome and Genome Sequencing

Different from conventional "targeted and specific" genetic testing strategies and NGS panels, which mostly target only known disease genes for diagnostic purposes, exome and genome sequencing are a process of scanning the exome/genome for both discovery and diagnostic purposes. In many cases, research discoveries may be directly translated into clinical diagnoses when compelling evidence for establishing causal relationships between novel variants and unique phenotypes exists. With wide application of NGS methods, genes related to many causes of infancy-onset hypotonia have been identified and more discoveries are anticipated. Variability in diagnostic rates depends on the differences in the types of patients included in different studies. However, the specificity and efficacy of NGS testing technology

might facilitate a "genotype-first" screening approach ahead of the traditional "phenotype-first" patient examination approach, but a pre-testing patient selection is essential to exclude patients who are **not** likely to have a genetic condition. New discoveries in medical science create new ethical issues for physicians and patients. The expansion of diagnostic testing in pre-symptomatic, at-risk individuals, especially where effective therapy is lacking, raises concerns about the suitability of some diagnostic processes. It must be noted that triplet repeat expansions such as in myotonic dystrophy will not be picked up by exome sequencing. These dilemmas about when to limit or expand the diagnostic evaluation will continue for practicing physicians even with contemporary guidelines derived from evidence-based medicine, advances from Internet-based consumer education resources, and appropriate patient counseling before, during, and after testing.

6 Hypotonia Disorders with Established or Emerging Treatments

6.1 Diagnostic Urgency

Progress in the treatment of neurological diseases is notable. Thus, the urgent diagnosis of hypotonia is particularly important for those diseases with available disease-modifying treatments. Many of these diseases may initially manifest subtle signs of hypotonia and other physical findings and may avoid detection even by experienced clinicians. Many treatable disorders and diseases are now included in standard neonatal screening platforms in almost all states. The American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics and Genomics (ACMG) have classified expanded carrier screening as an acceptable pre-pregnancy and prenatal screening strategy for all parents. An expanded screening refers to concurrently screening for as many as several hundred conditions, including both "inborn errors of metabolism" (IEMs) and non-IEMs.

6.2 Spinal Muscular Atrophy

As mentioned earlier, the neuromuscular system consists of the elements of the motor unit: motor neuron, peripheral nerve, neuromuscular junction, and the muscle—and all of these elements can be part of a disease process presenting with hypotonia. The most prevalent (incidence: 1: 6000–10,000 births) motor neuron disease in children is spinal muscular atrophy (SMA) caused by primary degeneration of large anterior horn cells in the spinal cord and brainstem; however, the cortical motor neurons are not affected. SMA disease manifestation includes proximal muscle weakness, atrophy, low muscle tone, decrease or lack of myotatic reflex, and

muscle fasciculation [1]. SMA represents a clinical spectrum of severity between the most severe infantile onset and less severe onset in older infants and children or adults. The severe infantile form (SMA type 1) is the most prevalent and causes "floppy infant syndrome" ranging from shortly after birth to the first few months of life. The striking clinical features include muscle hypotonia, weakness (worse in the legs compared to the arms), areflexia, tongue fasciculations, and paradoxical breathing. Without treatment, respiratory weakness is progressive. Autosomal recessive SMA is caused by pathogenic variants in the *SMN1* gene with a homozygous loss of exon 8 in approximately 95% of individuals with SMA. In about 5% of SMN1-related SMA (not detected by a neonatal screening), there is a pathogenic sequencing-based change on one allele and loss of exon 8 on the other allele. The presence of a "back-up" gene, the *SMN2* gene, in various copies provides a low level of SMN protein production and correlates with the phenotype severity of SMA. Severe SMA patients may have only one or two copies of SMN2, whereas less severe patients with a later onset may have three to five copies. Two approved treatments are designed to increase the SMN protein production from the *SMN2* genes by promoting full-length RNA and protein production. The first approved by the Food and Drug Administration (FDA) in 2016 is a synthetic oligonucleotide called nusinersen (Spinraza™), which has to be administered intrathecally every 4 months. Another is Risdiplam (Evrysdi™), a "small molecule" designed to have a similar mechanism of action on the *SMN2* gene, but it is bioavailable to motor neurons by daily oral administration [2]. Both medications have been approved by the US FDA for all types of SMAs for all ages. Gene therapy, using an adeno-associated virus (AAV) carrier to introduce the full-length SMN1-coding sequence into motor neurons, requires a single intravenous administration. Onasemnogene abeparvovec-xioi (Zolgensma™) was approved in May 2019 [3]. All three treatments have shown to be able to halt the progression of SMA or even promote motor development. Based on clinical trial data and now from "real-world" experience, all three treatments are the most effective when used before clinical onset of the disease. The differential diagnosis of SMA includes mitochondrial depletion syndromes and some variants of SMA with early respiratory distress (spinal muscular atrophy with respiratory distress, SMARD), which are genetically distinct forms.

6.3 Glycogen Storage Disease Type 2 (Pompe Disease)

Probably, the most important muscle disease requiring an early diagnosis is the glycogen storage disease type 2 myopathy caused by deficiency of acid alpha-glucosidase (GAA or acid maltase), also known as Pompe disease. The infantile form has an incidence of 1 in 100,000. Similar to SMA, it has a large clinical severity spectrum ranging from a severe early infancy-onset form to a milder adult-onset form [4]. The early infancy-onset form of GAA deficiency typically manifests before 3 months of age with initial symptoms most often related to heart and respiratory failure (cardiomegaly and tachypnea, respectively). The chest X-ray shows

an enlarged heart silhouette, and the typical echocardiogram demonstrates an enlarged left ventricular or septal wall without outflow obstruction. Without treatment, infants with GAA deficiency die from cardiorespiratory failure within a few months. The less severe "late-infancy-onset" form of Pompe disease generally causes progressive weakness without cardiomyopathy. The adult-onset variant has a presentation similar to limb-girdle muscular dystrophy. Enzyme replacement treatment with alglucosidase-alfa (Myozyme™; Lumizyme™) is an approved and effective treatment; however, the best outcomes are observed in patients who receive early treatment [5].

6.4 Congenital Myopathies and Infancy-Onset Myotonic Dystrophy

The so-called congenital myopathies (incidence: 1: 26,000) and dystrophies are genetic muscle diseases that should be considered in the differential diagnosis of hypotonia in infancy, and some forms may have specific therapies available, such as gene therapy for X-linked myotubular myopathy. Early-onset myotonic dystrophy (incidence: 1: 50,000) presents with severe hypotonia, weakness, and encephalopathy. It can be recognized by dysmorphic features ("fish mouth," temporal muscle wasting), and the family history should be helpful for this dominantly inherited disease. Examination of the parents for myotonia is a good clinical practice. Genetic testing should be specific to the triplet expansion of CTG repeats in the DM1 locus (the non-coding region of the *DMPK* gene) showing more than 1000 repeats in most cases (normal: below 49 repeats).

6.5 Disorders of the Neuromuscular Junction

Disorders and diseases involving the neuromuscular junction (NMJ) with the finding of hypotonia can be primary (genetic) or secondary (acquired). Infant botulism (incidence is variable: ~ 2: 100,000) is caused by the ingestion of the toxin produced by *Clostridium botulinum* (an anaerobic Gram-positive bacterium). The source can be found in soil, water, or even air in lethal minute amounts (mcg). The most prominent clinical symptom in a previously healthy infant is hypotonia in addition to constipation, weakness, ophthalmoplegia, sluggish pupils, poor feeding, emesis, and distended abdomen [6, 7]. The diagnosis can be confirmed by the detection of toxins or bacterial spores in feces. About half of all affected infants require ventilatory support. The treatment is largely supportive; however, Human Botulism Immune Globulin is an orphan intravenous drug that consists of human-derived anti-botulism toxin antibodies for the treatment of infant botulism types A and B. Aminoglycosides, including gentamicin, may exacerbate the symptoms of

botulism by competitive inhibition of the presynaptic portion of the neuromuscular junction and by decreasing acetylcholine release from nerve terminals.

Myasthenia gravis in infants can be caused by maternal transmission of acetylcholine receptor (AChR) antibodies through the placenta and blocking the neuromuscular transmission in the neonate, leading to diffuse weakness and respiratory insufficiency [8, 9]. It occurs in 10–20% of seropositive mothers with myasthenia gravis. The treatment of neonatal transient myasthenia gravis may include blood exchange, but supportive care by providing appropriate nutrition and respiratory support will lead to resolution of the weakness in few weeks and a full recovery is expected. Congenital myasthenic syndromes (estimated prevalence: 1–9 in one million) are caused by genetic variants coding various presynaptic or postsynaptic components of the neuromuscular junction. Congenital myasthenic syndromes are not uncommon, but they are commonly overlooked. At least 30 genetically distinct congenital myasthenic syndromes have been recognized including molecular defects in AChR subunits, rapsyn, *ColQ*, *Dok7*, and *ChAT* genes [10]. Variable clinical signs include generalized hypotonia associated with variable weakness and spells of apnea triggered by fever, stridor, ptosis, and delayed pupillary response. The diagnosis can be supported by electrophysiological studies of neuromuscular transmission, but, currently, it is largely based on genetic testing such as panel testing (see Sect. 5.4 in this chapter) or exome sequencing. There are various medications available to treat congenital myasthenic syndromes, but the treatment has to be tailored based on the pathophysiology caused by the genetic variant. For example, pyridostigmine improves the postsynaptic forms of congenital myasthenic syndromes, whereas fluoxetine, albuterol, and 3,4-diaminopyridine may be used for other types of these disorders.

7 When to Refer or Admit?

A request for an inpatient child neurology consultation or referral to a child neurology clinic for an infant or child with hypotonia depends on numerous factorss such as the age of onset, severity, and clinical course. Infants with signs of progressive hypotonia need an urgent referral. Other reasons for child neurology consultation are related to diagnostic considerations, therapeutic potential, and follow-up management. The availability of pediatric neurology services varies largely depending on the country or geographic region. Therefore, the general practitioner should have the tools available to make a diagnosis of the conditions that require immediate treatments. Although it is anticipated that exome and genome sequencing will become the standard diagnostic techniques in the future, such testing is not available in some countries or through some health-care systems. When next-generation DNA sequencing (NGS) is available, obtaining such genetic testing may require a formal consultation from a child neurologist or clinical geneticist and administrative prior approval from the health-care insurance provider. Additional concerns about genetic testing pertain to the adequacy of informed consent and pre-test

counseling, the balance between potential benefits and inadvertent harms, and the potential effects on future reproductive choices.

Many infants and children with hypotonia, with or without a biologically defined diagnosis, will have neurodevelopmental or neuromuscular disabilities that require supportive care services, medication management, orthopedic and rehabilitation consultation, special school services, respite care, and advocacy. Follow-up care with a child neurologist or an interdisciplinary care team may be necessary. For some diagnoses with unfavorable prognoses, pediatric neuropalliative care consultation benefits families striving to maximize the quality of their child's remaining life and allows parents or guardians to declare their preferences regarding advanced directives for their child. Finally, many issues with complex neurological and neurodevelopmental disorders have ethical, legal, and social considerations. Strategies to provide the best screening, testing, counseling, and long-term care for many severe and complex disorders are in continuous evolution in every society, especially with the growing understanding of these disorders and disease mechanisms that allow the active explorations of new therapeutic targets. Muscle hypotonia with severe weakness is often associated with cardiorespiratory compromise and/or feeding difficulty, requiring hospitalization and possibly intensive care.

8 Clinical Pearls/Key Points

- Muscle hypotonia refers to reduced resistance during passive movements, and it is dependent on the developmental stage of the infant.
- Lower-than-expected muscle tone is one of the most frequent abnormal neurological findings and has a long list of potential etiologies. However, 60–80% of the cases are caused by central nervous system diseases.
- The presence of upper motor neuron signs and encephalopathy suggest a central cause, whereas a lack of deep tendon reflexes indicates a neuromuscular cause.
- Diagnosing hypothyroidism, Pompe disease, and spinal muscular atrophy is a medical "emergency" because of the availability of effective therapies.

9 Conclusions

Muscle hypotonia is a frequent neurological finding in young children as a manifestation of many central or peripheral nervous system diseases [11]. A careful neurological examination that follows an anatomical localization will aid in the diagnosis. The minimal initial diagnostic test should include basic measurements of the thyroid function tests, creatine kinase levels, chromosomal microarray, acid alpha-glucosidase, DNA methylation test (for Prader–Willi syndrome), and genetic test for SMA. These would diagnose the most prevalent diseases associated with hypotonia for which effective therapy is now available. However, these disease-modifying

treatments are most effective when started early. New treatments are constantly evolving to include more and more diseases; therefore, early identification is crucial in order to achieve the best response to therapy.

References

1. Nicolau S, Waldrop MA, Connolly AM, Mendell JR. Spinal muscular atrophy. Semin Pediatr Neurol. 2021;37:100878.
2. Wadman RI, van der Pol WL, Bosboom WM, Asselman FL, van den Berg LH, Iannaccone ST, Vrancken AF. Drug treatment for spinal muscular atrophy type I. Cochrane Database Syst Rev. 2019;12(12)
3. Mendell JR, Al-Zaidy SA, Rodino-Klapac LR, Goodspeed K, Gray SJ, Kay CN, Boye SL, Boye SE, George LA, Salabarria S, Corti M, Byrne BJ, Tremblay JP. Current Clinical Applications of In Vivo Gene Therapy with AAVs. Mol Ther. 2021;29(2):464–88.
4. Gupta N, Kazi ZB, Nampoothiri S, Jagdeesh S, Kabra M, Puri RD, Muranjan M, Kalaivani M, Rehder C, Bali D, Verma IC, Kishnani PS. Clinical and molecular disease spectrum and outcomes in patients with infantile-onset Pompe disease. J Pediatr. 2020;216:44–50.e5.
5. Kronn DF, Day-Salvatore D, Hwu WL, Jones SA, Nakamura K, Okuyama T, Swoboda KJ, Kishnani PS. Pompe disease newborn screening working group. Pediatrics. 2017;140(Suppl 1):S24–45.
6. Rosow LK, Strober JB. Infant botulism: review and clinical update. Pediatr Neurol. 2015;52(5):487–92.
7. Chalk CH, Benstead TJ, Pound JD, Keezer MR. Medical treatment for botulism. Cochrane Database Syst Rev. 2019;4(4)
8. Kaler J, Hussain A, Patel S, Majhi S. Neuromuscular junction disorders and floppy infant syndrome: a comprehensive review. Cureus. 2020;12(2):e6922.
9. Ciafaloni E. Myasthenia gravis and congenital myasthenic syndromes. Continuum (Minneap Minn). 2019;25(6):1767–84.
10. Engel AG, Shen XM, Selcen D, Sine SM. Congenital myasthenic syndromes: pathogenesis, diagnosis, and treatment. Lancet Neurol. 2015;14(4):420–34.
11. AlBanji MH, AlSaad AN, AlAnazi RF, Aleisa ZA, Alam DS, Alhashim AH. Utility of hypotonia diagnostic investigations: a 12-year Center study. Mol Genet Metab Rep. 2020;25:100665. https://doi.org/10.1016/j.ymgmr.2020.100665. PMID: 33101984

Child with Acute Limb Weakness

John Brandsema and Ryan Cappa

1 Introduction

Neurological lesions or dysfunction leading to acute limb weakness can result from a lesion anywhere along the neuroaxis. Weakness is defined as the inability to perform a desired movement with normal force because of a reduction in muscle power. Clinicians are often presented with confounders such as musculoskeletal etiologies, endocrine disorders, conversion disorders, or malaise, to name a few. This chapter will focus on neurological etiologies that cause isolated or generalized limb weakness with a symptom onset of days or less than a week. The key features of the history and physical examination related to anatomical localization will be reviewed, followed by specific pathological processes grouped by location in the nervous system. The goal of this systematic process is to aid the clinician presented with a case of acute limb weakness to formulate an informed and pertinent diagnostic workup and ultimately institute appropriate management.

2 Etiology/Localization

Localizing a lesion along the neuroaxis is a key component of any neurological evaluation. The first major delineation is whether the weakness is of a central versus peripheral nervous system etiology. Classically, central nervous system (CNS)

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Table 1 Central vs. peripheral nervous system examination findings

	Central	Peripheral
Mental status	Encephalopathy Seizures Neglect Aphasia	Usually normal Can be secondarily affected (i.e., hypercapnic encephalopathy from respiratory failure)
Cranial nerves	Forehead-sparing facial palsy Brainstem syndromes	Upper and lower facial palsy Extraocular muscle involvement Ptosis Bulbar weakness
Motor	Bulk—Normal Tone—Increased (spastic)[a] Reflexes—Increased[a] Distribution—Hemibody weakness	Bulk—Reduced Tone—Decreased Reflexes—Decreased Distribution—Focal vs. length-dependent vs. proximal (limb-girdle)/distal
Sensory	Hemibody deficits Cape-like distribution Perineum Sensory/sweat level	Dermatome Nerve distribution Length-dependent

[a]Can be initially reduced in some cases, for example, an acute spinal injury can have a spinal shock initially before eventually progressing to classic UMN signs over days to weeks

etiologies are those of the cortex, deep gray matter structures, brainstem, and spinal cord. Differential diagnosis of peripheral nervous system (PNS) etiologies can be broken down by anatomy and include the anterior horn cell/motor neuron, which is located in the spinal cord but is the first structure in the peripheral nervous system, radiculopathy (disorders of the roots that exit from the anterior horn cells of the spinal cord)/neuropathy (disorders of the peripheral nerve), neuromuscular junction, and muscle.

CNS dysfunction is associated with key historical and examination findings (Table 1). Cortical signs and symptoms such as an altered mental status, seizures, or neglect (inability to "recognize" one-half of the body) strongly suggest a pathology of the CNS. Cranial nerve involvement such as facial nerve palsies sparing the forehead or brainstem syndromes, in which there is a combination of hemiparesis and cranial nerve dysfunction, points away from the PNS. On motor examination, upper motor neuron (UMN) signs such as normal muscle bulk, spastic hypertonia, and brisk deep tendon reflexes as well as weakness involving limbs on one side can be seen in CNS disorders. Sensory findings in specific patterns such as hemisensory loss, a cape-like distribution over the shoulders, the perineum, and a sensory or sweat level (a clear dermatomal level below which the child cannot feel certain sensations or does not sweat) are also more suggestive of a central etiology.

Peripheral nervous system dysfunction can be differentiated from a CNS lesion by examination and history, as can the different anatomical sites affected in the PNS. Common PNS findings are also summarized in Table 1. Table 2 lists common disorders of the PNS that can present with limb weakness.

Table 2 Peripheral nervous system localization

Anterior horn cell **Examples:** Acute flaccid myelitis Poliomyelitis	Weak Can be associated with a high arched palate if there is bulbar involvement Respiratory dysfunction Reduced muscle bulk Fasciculations present (especially the tongue) Reflexes absent
Neuropathy **Examples:** Guillain–Barré syndrome Trauma Compressive neuropathy Brachial neuritis Porphyria	Weak Reflexes absent or reduced Fasciculations (rare) Sensory deficits Autonomic dysfunction Radiculopathy: Sensory symptoms with a normal sensory examination
Neuromuscular junction **Examples:** Myasthenia gravis Botulism Cholinergic toxidrome Snake or spider toxins	Weakness = fatigability and fluctuation Muscle bulk—Normal Extraocular, bulbar, respiratory muscle involvement
Muscle **Examples:** Periodic paralysis Myositis	Weak Reduced muscle bulk (patterns can be helpful) Pseudohypertrophy Contractures Proximal >distal (in most cases) Extraocular, bulbar, respiratory muscle involvement

3 Diagnostic Approach

3.1 History

Disorders of the anterior horn cell or motor neurons are typically painless. Radiculopathies include myotomal symptoms (pertaining to the affected muscles such as motor weakness) and dermatomal symptoms (sensory symptoms) with classic radiating pain from the spine out to the associated nerve level. Neuropathies can cause sensory, motor, and autonomic symptoms alone or in combination. When neuropathies are acquired, sensory symptoms tend to be "positive" and are often endorsed by patients as painful (electric shock, burning, throbbing, etc.) or painless (tingling, swelling, bunched-up socks, wrapped, etc.). Positive sensory symptoms are less common in inherited neuropathies, such as Charcot–Marie–Tooth, or those that can present with acute flares, such as hereditary neuropathy with liability to pressure palsies. Autonomic neuropathic dysfunction should be considered when

symptoms such as orthostasis, early satiety, constipation, dysuria, sexual dysfunction in adolescents, or Adie's pupil are present. These symptoms may require a directed history as patients or parents may not be aware of their association with limb weakness.

Pathologies of the neuromuscular junction are to be suspected when there is history of fluctuating weakness (fluctuating from morning to evening or even day to day) and can present with ocular or generalized patterns of distribution. Muscle disease is commonly associated with negative symptoms including weakness and fatigue/exercise intolerance. Less frequently reported, but still pertinent, muscle disease can have positive symptoms such as myalgias and myoglobinuria in acute disorders and myotonia, hypertrophy/pseudohypertrophy and contractures out of keeping with weakness in more chronic myopathies. Table 2 summarizes the clinical distinctions of the different localization sites in the PNS.

3.2 Physical Examination

3.2.1 General Examination

Vital signs should be assessed, especially to look for signs of orthostasis that can occur in disorders affecting the autonomic nervous system. Evidence of trauma to the affected limb must be sought, and one must look for other etiologies that may implicate the musculoskeletal system. A skeletal survey, for scoliosis of the spine or assessment of high arches and hammered toes at the feet, can provide additional diagnostic cues. Examination of the skin and hair for a tick may be important in the appropriate situation.

3.2.2 Neurological Examination

In addition to performing a general neurological examination including mental status and cranial nerve examination, the clinician must pay special attention to the different aspects of the PNS. The important components include testing for muscle strength, looking at muscle bulk and tone of the limb/limbs, and assessing for sensory loss or sensory level with both light touch and, if possible, a pin prick (in older children). Finally, one must assess the deep tendon reflexes and gait.

Motor neuron diseases, such as acute flaccid myelitis, present with flaccid hypotonia, weakness, areflexia, response to sensory stimuli, and, typically, normal cognition. Radiculopathies can present with both muscle weakness and sensory symptoms in the affected dermatomes as noted in the history. Distribution of neuropathic symptoms can also suggest specific etiologies, with distal symmetric length-dependent polyneuropathies often caused by metabolic/toxic, idiopathic, or inherited causes and asymmetric non-length-dependent neuropathies more commonly seen in immune-mediated or infectious causes. Length-dependent refers to the fact

that the longest nerves are affected first, i.e., the feet first and rising to about knee level before the hands become involved. Sensory symptoms are often not reproducible on sensory examination in pure radiculopathy.

3.3 Laboratory Evaluation/Imaging

The clinical and historical components are of course further corroborated by the results of appropriate testing. Serum studies, imaging, electrodiagnostics, and pathology may contribute further information, depending on the clinical context, to rule in and out the components of the differential. Each test carries its own benefits and limits and in general are summarized in Table 3. To expand on localization in the PNS, we will use a series of cases to highlight the helpful details that can narrow the clinician's differential and lead to a more targeted hypothesis testing.

Table 3 Diagnostic testing related to the peripheral nervous system

Test	Benefits	Limitations
CK: Serum	• Elevation indicates muscle membrane disruption • Quick turnaround • Minimally invasive	• Can be normal in some muscle diseases such as congenital myopathies and mildly elevated in neurogenic etiologies such as motor neuron disease • Found in tissues other than the muscle, e.g., cardiac
AchR/MUSK antibodies: Serum	• Highly specific for autoimmune myasthenia gravis • Minimally invasive • AchR antibodies are positive in 60–70% of children with myasthenia gravis • MUSK antibodies are positive in 10–40% of children with generalized myasthenia gravis	• Decreased sensitivity in ocular phenotypes • May require repeat testing if initially negative • Congenital/genetic myasthenia gravis can also present throughout the life span and is not autoimmune
EMG/NCS	• Helps early in differential if the clinical picture is clouded between the muscle or nerve etiology • Can indicate localization, severity, and chronicity • Results are immediately available • No long-term risks • Repetitive nerve stimulation can help suggest pre- or post-synaptic neuromuscular junction defects • Single-fiber EMG is the most sensitive test for myasthenia gravis	• Some discomfort associated with testing • Younger age groups may require child life services or low levels of sedation

(continued)

Table 3 (continued)

Test	Benefits	Limitations
MRI arm/leg (muscle)	• Non-invasive • Standardized • Can be used to help in diagnosis or to help guide additional more specific testing such as ideal location for biopsy	• May require sedation in young age groups • Can be expensive • Not specific • Rarely needed in acute weakness presentation
Muscle ultrasound	• Non-invasive • Results are immediately available • Easy-to-assess the upper and lower extremities as well as paraspinals • Can suggest severity • Can reveal myopathic and neuropathic findings • Some specific disease patterns can be appreciated	• Non-standardized, can be variable between technicians/providers • Can be falsely negative early in the disease course • Rarely needed in acute weakness presentation
Biopsy: Muscle or nerve	• Can help differentiate between myopathic and neuropathic processes • Highly specific stains are available	• Invasive • Interpretation is dependent on the expertise of the surgeon and pathologist • Interpretation is dependent on the sample of the muscle selected and can be falsely negative in patchy pathological processes • Rarely needed in acute weakness presentation
Genetics: Single gene or panel	• Targeted and highly specific • Some panels can perform both sequencing and deletion/duplication analysis • Minimally invasive—Serum or buccal swab	• Limited genomic evaluation • Can be expensive • Turnaround can take weeks but is rapidly improving • Interpretation of uncertain variants can be challenging
Exome sequencing	• More comprehensive • Minimally invasive—Serum or buccal swab	• Expensive • Turnaround typically takes months but is rapidly improving • Report strength is dependent on the clarity of symptoms provided • Should be performed with a genetic counselor available • Does not discover trinucleotide repeats or some duplications/deletions • Possible incidental findings outside of the system of interest • Interpretation of uncertain variants can be challenging • Interpretation of strength requires a trio of proband and parents

CK (or CPK) creatine kinase (or creatine phosphokinase), *AchR* acetylcholine receptor, *MUSK* muscle-specific tyrosine kinase, *EMG/NCS* electromyography/nerve conduction study, *MRI* magnetic resonance imaging

Case 1

History:

A 16-year-old otherwise healthy young man experienced a significant traumatic force during a tackle in his role as his high school's football team running back. He immediately experienced a sharp pain shooting from his neck down his right arm and was told that it was just a "stinger." The pain persisted intermittently including some tingling in the upper arm, and, a week later, he noticed difficulty in raising his right arm and bending his elbow. He presents to your clinic for evaluation. Your examination corroborates his history, with intact reflexes and no atrophy or sensory deficits. You refer him to a neurologist who decides to perform electrophysiological studies.

Clinical reasoning:

Radiating dermatomal pain with associated myotomal weakness is the hallmark for the clinical presentation of a radiculopathy; mononeuropathies usually also have associated sensory signs unless a pure motor nerve has been affected. The C5 nerve root innervates both the deltoid and biceps and is likely to be the explanation in this case, though polyradiculopathies are also possible; brachial plexopathy typically also leads to sensory deficits. The electrophysiological studies rule out the other structural differentials such as proximal neuropathy, plexopathy, or distal entrapment neuropathy.

Discussion:

Radiculopathy

While radiculopathies are more common in the adult patient population due to the prevalence of degenerative disc disease, radiculopathies are caused by a variety of etiologies, many of which are pertinent to the pediatrician. Clinically, paresthesias distributed over a dermatome, sometimes accompanied by weakness of muscles in the associated myotome, depending on severity, is the classic presentation. Given the overlap in sensory coverage by adjacent dermatomes, frank numbness is not commonly reported, and a dense absence of sensation should raise suspicion for a peripheral sensory nerve lesion rather than that of the nerve root. Similarly, muscles obtain innervation from multiple root levels, so a monoradiculopathy rarely causes a full paralysis of the affected muscles.

The causes of nerve root pathology are broad. Structural impingement is the most common, either from degeneration (uncommon in pediatrics) or from trauma, as was seen in Case 1. Other structural causes can include epidural abscesses or tumors. Infections such as Lyme disease, acute flaccid myelitis such as from enterovirus, and viruses of the herpes family as well as rarer causes such as acquired demyelinating conditions or neuroinflammation from rheumatologic disorders such as Sjögren's syndrome can also affect the nerve root in the absence of a direct mass effect.

Evaluation frequently involves electrophysiological studies such as electromyography and nerve conduction (EMG/NCS), imaging, and targeted serum or cerebrospinal fluid (CSF) studies as indicated based on the systemic symptoms and history relating to the etiologies mentioned above. Contrast-enhanced magnetic resonance imaging (MRI) of the suspected spinal levels should be included if an

infectious, autoimmune, or neoplastic process is a reasonable consideration. Electromyography, coupled with nerve conduction studies, is often the most helpful tool for localization of an injury as it serves as a sensitive and objective extension of a physical examination. Additionally, EMG/NCS can also provide helpful information regarding the chronicity and severity of the underlying process and assist in prognostication of recovery [1]. A fundamental understanding of the natural electrophysiological progression of an axonal injury can be extremely useful to the ordering practitioner, as the timing of the injury relative to EMG can have a critical effect on study interpretation (see Table 4). As the table suggests, nerve conduction studies performed too acutely timed to the injury can be normal, especially if the nerve injury has been proximal. There can also be an overlap of findings at varying chronicities, so the expertise and skills of the electromyographer are also quite important. Prognostication is more accurate at least 10 days to 2 weeks after a nerve injury as by that time point it is clearer whether the injury has been primarily axonal, demyelinating, or a combination of both.

Therapeutic interventions vary depending on the etiology and severity of disease. In radicular pathology related to disc herniation, observation in mild-moderate cases is appropriate, coupled with symptomatic treatment as needed. In severe cases, a surgical referral is indicated. Outcomes also vary depending on the severity, with some level of recovery being the rule as long as there is evidence of nerve continuity to the affected muscles.

Table 4 Evolution of electrophysiological findings on electromyography and nerve conduction studies in nerve injury

	Nerve conduction studies	Spontaneous activity	Motor unit morphology	Recruitment pattern
Acute (0–10 days)	Normal	Normal	Normal	Normal or reduced
Subacute (1–6 weeks)	Normal	Fibrillations and PSWs – Earlier for proximal muscles. – Later for distal muscles.	Normal +/− polyphasic	Reduced
Early chronic (month(s))	Normal	+/− fibrillations and PSWs +/− CRDs	– Polyphasic. – Increased amplitude and duration.	Reduced
Late chronic (months to years)	Normal	+/− CRDs	– Polyphasic. – Increased amplitude and duration.	Reduced

PSWs positive sharp waves, *CRDs* complex repetitive discharges

Case 2

History:

A 9-year-old girl presents with 13 days of hand, and then foot, tingling and numbness that was followed by progressive limb weakness. She was found to have heart rate fluctuations on electrocardiogram (EKG) as well as blood pressure variability. An MRI of her lumbar spine revealed nerve root enhancement. A CSF analysis showed an elevated protein level of 70 mg/dl with a normal white blood cell (WBC) count of 1.

Clinical reasoning:

In this case of symmetric ascending weakness, the top differentials include Guillain–Barré Syndrome (GBS) and intoxication, with tick paralysis or porphyria being much less likely. The time course and sensory/autonomic symptoms raise suspicion for GBS. The girl's age is prime for outdoor adventures, which could make tick paralysis possible, so additional historical components such as time of year or location in an endemic area would be useful as well as a careful physical examination for an attached parasite. Ultimately, the high CSF protein level and normal WBC count, i.e., cytoalbuminologic dissociation, in this clinical context help cement the diagnosis of GBS, further supported by the nerve root enhancement on the available imaging.

Discussion:

Guillain–Barré Syndrome.

Guillain–Barré syndrome has an incidence of ~1 in 100,000. The demyelinating form, acute inflammatory demyelinating polyneuropathy (AIDP), is the most common presentation, but axonal and mixed forms are also possible and can carry different prognostic outcomes, with the demyelinating form typically having the best recovery [2]. The clinical vignette above is the most typical, with ascending, essentially symmetric (although asymmetries can occur), weakness and sensory abnormalities, often with autonomic instability. Painful neuropathic symptoms are atypical, though poorly localized neck, back, or extremity pain is a common feature. Areflexia is an important component of the examination. A little more than half of cases include prodromal gastroenteritis or respiratory illness 2–4 weeks prior to symptom onset, leading to the molecular mimicry mechanism of an immune attack on the peripheral nerve epitopes that overlap with the prior infectious agent.

The differentials include intoxication, porphyria, infections (e.g., Lyme, West Nile, diphtheria), snake or spider bite, and tick paralysis. Laboratory abnormalities suggestive of the diagnosis of GBS include cytoalbuminologic dissociation in the CSF with a protein level >45 mg/dL and a normal WBC count, enhancing the nerve roots on a contrasted spinal MRI and abnormal F waves seen soon after symptom onset on electrophysiological studies.

Treatment is with intravenous immunoglobulin (IVIG) or plasma exchange (PLEX) in those who cannot receive IVIG. Unlike with other immune-mediated diseases, the use of immune modulation with systemic steroids has not been found to be beneficial in the acute management of AIDP [3]. The clinical course typically finds its nadir by 4–6 weeks from symptom onset, with some studies finding most children (~80%) reaching their clinical nadir by 2 weeks. This is important for the

managing clinician to be aware of as short-term improvement early on and an overly enthusiastic hospital discharge can potentially place patients at the risk of a return due to clinical decline in the home setting. In general, children have a shorter clinical course and more complete recovery as compared to adults with GBS, with >90% of children having full recovery.

Tick Paralysis

This typically affects children from 1 to 5 years of age, likely reflecting a protection provided by increased size in older children and adults. Overall, it is a rather rare cause of flaccid paralysis, but clinicians must be vigilant given its ease in reversibility. The adult female tick of certain species is the culprit of toxin production, and these are most prevalent in the spring and summer months. There is typically a delay of days from tick attachment to paralysis, and it is more common in girls, possibly due to an easier environment with which to hide in the setting of longer hair [4]. The mechanism of the toxin's pathology is not entirely clear but is believed to affect the NMJ either pre-synaptically by reducing calcium availability or by interrupting sodium flux across the axonal membrane, leading to failed action potentials.

Clinically, the paralysis can be an ascending, symmetric weakness with areflexia but with a slower course compared to that of GBS. However, bulbar (i.e., the lower cranial nerves, which when affected can lead to dysphagia, difficulty chewing, slurred speech, etc.) and facial weakness as well as cases of focal weakness have also been reported. The most important component of the physical examination is a comprehensive skin examination in search for the culprit arachnid.

Treatment is satisfyingly simple: tick removal. The North American variants of ticks that cause paralysis can have symptom improvement within an hour of tick removal and recover completely in days. In contrast, the Australian species can require a couple of days before the reversal of the toxin's effect manifests as clinical improvement.

Porphyria

Porphyria refers to a heterogynous group of inherited disorders, leading to enzymatic deficits in heme production.

Clinically, hereditary hepatic porphyrias (HHPs) present as acute episodes of neurovisceral attacks of abdominal pain, nausea, vomiting, constipation, behavioral changes, and convulsions with a progressive, generalized, axonal, motor neuropathy. Photosensitivity leading to a cutaneous manifestation is only present in variegate porphyria and hereditary coproporphyria and not in acute intermittent porphyria, which can be a key distinguishing feature. Although HHPs are a rare form of inherited neuropathy, the acute clinician maintains awareness of them and is quick to add them to the differential for patients with episodes consisting of gastrointestinal and neurological symptoms.

A diagnosis is made in the correct clinical context and is further supported by elevated urine or serum porphobilinogen (PBG) during an episode. It is important that sample collection including protection from light be correctly carried out to minimize false negatives. Interictal levels can be normal. HHPs can be delineated by subtype with additional enzymatic or genetic testing.

The treatment starts with preventing the attacks by avoiding known triggers such as light exposure, alcohol, or cytochrome P450 inducers. During an attack, the provision of hematin can help downregulate heme's synthetic pathway as well as glucose intake to reduce aminolevulinic acid (ALA) synthase activity.

Case 3

History:

A 7-month-old baby girl presents with poor feeding for the past 2 days. She seems to fatigue when feeding. She has constipation that is a new symptom. On examination, she has a weak cry, excessive drooling, and her pupils are sluggish, poorly reactive, and ptosis is noted. Her strength is barely antigravity in all extremities and tone is significantly reduced, as are her deep tendon reflexes. She responds to light touch in all limbs.

Clinical reasoning:

This weak infant with poor feeding and bulbar symptoms has had a quick clinical onset of descending weakness without a clear sensory involvement. Possible differentials could include botulism or intoxication; a CNS infection is less likely as there is clear cranial nerve involvement without encephalopathy. A metabolic disorder could also be considered if there was a change in diet, although, again, mental status is typically impaired. The associated constipation, sluggish pupils, and areflexia make botulism the most likely cause. Thus, additional history should be obtained such as raw honey consumption or proximity to a construction site in an endemic region.

Discussion:

Botulism:

Infantile botulism is caused by ingestion of *Clostridium botulinum* spores and is the most common form of botulism. Toxins produced by the bacterium once activated by an anaerobic environment are pathological at the pre-synaptic level by inhibiting exocytosis of vesicles in motor neurons originating in the brainstem and spinal cord.

Clinical suspicion is raised when a descending, symmetric paralysis is preceded by painless constipation in an otherwise healthy infant. There are roughly 70–100 cases of infantile botulism annually in the United States. Diagnosis is of course initially clinical, with confirmation from stool samples via a bioassay for toxins. Additional diagnostic evaluation via electromyography and nerve conduction study (EMG/NCS) can also aid in rapid diagnosis when facilitation by high-frequency repetitive nerve stimulation is present.

Therapy is conducted with human botulism immune globulin (Baby-BIG) as well as supportive care. The addition of Baby-BIG has led to reduction in morbidity, length of hospital stay, and time intubated [5]. Given the importance of rapid treatment, Baby-BIG can be administered when the diagnosis is made clinically while the treating team is waiting for the confirmatory laboratory results. Treatment with respiratory and nutritional support typically takes weeks to months, with recovery of symptoms usually in the reverse order of their onset [6]. The child typically experiences complete recovery, with no relapse after return to baseline.

Case 4

History:

A 9-year-old boy who has previously been healthy woke up, unable to move his arms or legs. He feels mild tingling throughout his limbs but no pain. He has had no cognitive symptoms as well as normal bowel and bladder function. On your examination, his systemic, mental status, and cranial nerve examinations are all found to be normal. His strength is barely antigravity throughout and the deep tendon reflexes are 1+ at all sites. A baseline laboratory assessment shows a normal creatine kinase (CK) level but with a low potassium at 2.4 mEq/L.

Clinical reasoning:

Few disorders can cause a child to go to bed asymptomatic and wake up with such severe weakness/paralysis. Given the generality of his weakness, his intact mental status, lack of bowel/bladder symptoms or dyspnea, and age, differentials of the PNS such as periodic paralysis or possibly myasthenia gravis (MG) or myositis are much more likely than a CNS pathology such as a stroke or a cervical spinal lesion. This distinction is further supported by the lower motor neuron findings on examination. The hyperacute presentation within hours of normal is less likely for myasthenia gravis or myositis, which are typically subacute or chronic, although myasthenia gravis can rapidly flare up in the context of a triggering event such as a medication that impairs neuromuscular junction function. Presentation of symptoms in the morning rather than worsening throughout the day also lowers suspicion for myasthenia gravis, and additional historical components looking for fatigability should be elucidated. Myositis is also usually associated with elevated CK. The hypokalemia in his current clinical setting, especially if a previous level was normal during an asymptomatic period, suggests a periodic paralysis.

Discussion:

Periodic Paralysis:

Periodic paralyses, named after their relationship with potassium levels at the time of attacks, are pathologies of ion channel dysfunction that lead to muscle weakness. While initially the attacks are episodes of flaccid muscle weakness, either localized or general, over the years, permanent weakness may be sustained, especially in the hypokalemic form [7]. Onset is usually prior to 20 years of age, and episodes can be triggered by certain foods such as carbohydrates, potassium-rich foods, or rest after exercise.

Hyperkalemic periodic paralysis (hyperPP) is typically associated with frequent attacks, up to several per day, with each attack lasting a short duration, from minutes to hours. Hypokalemic periodic paralysis (hypoPP) is distinguished by infrequent attacks, usually a few per year, with longer durations, lasting hours to days. There can be a high degree of overlap clinically. Although the nomenclature suggests that the basic metabolic panel can provide the needed distinction, in reality, the ictal potassium level is not always outside the bounds of the upper or lower limits of normal.

Pathogenesis most commonly relates to genetic variants of the sodium (*SCN4A*) and calcium (*CACNA1S*) channels. The *SCN4A* gene is an interestingly complex example of allelic heterogeneity as, depending on the location of the variation in the

gene, there can be one of many phenotypes such as hypoPP, hyperPP, congenital myasthenic syndrome, or myotonia congenita to name a few. The diagnosis is confirmed if the appropriate dyskalemia is found during a weakness episode, with interictal normalization. Genetic testing as a single gene or incorporated in panels is also available.

The treatment starts with avoidance of triggers such as potassium-rich foods for hyperPP and carbohydrate-dense meals or heavy bodily work for hypoPP. Carbonic anhydrase inhibitors such as acetazolamide or dichlorphenamide can be used to help decrease the frequency and severity of the paralytic episodes. Potassium-sparing diuretics can also be considered in hypokalemic forms. Acutely, hypoPP attacks should be treated with potassium and hyperPP attacks with glucose or rarely with insulin if severe enough. Table 5 summarizes the genetic and clinical features as well as the treatments provided.

Myasthenia Gravis:

Autoimmune myasthenia gravis (MG), while more common in adults, presents roughly 10% of the time in people under 18 years of age [8]. Although the mean age of presentation in the pediatric age group is from 7 to 14 years, cases of autoimmune MG can present as early as prenatally in the case of passive maternal antibody transfer. The disease is caused by an inappropriate immune reaction to components of the neuromuscular junction, with antibodies against the post-synaptic acetylcholine receptors (AChRs) the most common. Muscle-specific tyrosine kinase (MUSK), which serves to aggregate acetylcholine receptors at the NMJ, can also be a target. The majority of children, 60–70%, is antibody-positive.

Classically, there are two patterns of weakness. An ocular distribution with ptosis and ophthalmoparesis is more prevalent, especially in children of Asian descent. A generalized distribution of limb weakness, bulbar symptoms, and respiratory difficulties can be the second presenting pattern. Ocular phenotypes can progress to a generalized phenotype, typically within 2 years of symptom onset. Symptoms fluctuate throughout the day, and fatigability is a crucial historical component to solidify from the child or family. Symptoms seem to correlate with triggers such as stress, warm temperatures, systemic illness, missed medications, infection, overexertion, pregnancy, consumption of alcohol, and certain medications.

Table 5 Comparison of hypokalemic with hyperkalemic periodic paralysis

	Hypokalemic periodic paralysis	Hyperkalemic periodic paralysis
Gene	*SCN4A*, *CACNA1S*	*SCN4A*
Clinical features	Episodic weakness lasting hours to days; infrequent attacks, e.g., semiannual	Episodic weakness lasting minutes to hours, can have myotonia; frequent attacks, e.g., multiple attacks per day
Triggers	Carbohydrates, rest after exercise	Potassium, rest after exercise
Treatment	Acute: Potassium Chronic: Acetazolamide, dichlorphenamide, potassium-sparing diuretic	Acute: Glucose Chronic: Acetazolamide, dichlorphenamide

Diagnostics start with clinical features. Examination findings such as worsening ptosis or ophthalmoparesis with a prolonged upgaze are simple to perform in a cooperative child. Ptosis can be symmetric or asymmetric. Pathological fatiguing with repetitive deep squats, prolonged shoulder or neck flexion, counting (re dysarthria), or single breath count (re dyspnea) can be assessed for generalized involvement. The ice pack test consists of cooling a child's ptosis for 2 min and is considered positive if there is improvement of ptosis by at least 2 mm. Serum antibody testing for binding, modulating, and blocking AchR as well as MUSK antibodies is commercially available. In the case of serum-negative cases, in which there is a high clinical suspicion, EMG/NCS can be performed by a reliable electrophysiologist, although a need for sedation can complicate this in younger or cognitively impaired patients. An electrodecrement of at least 10% of the compound motor action potential's amplitude with low-frequency repetitive nerve stimulation is suggestive of post-synaptic NMJ dysfunction. Single-fiber EMG is highly sensitive to MG but not entirely specific and can be highly challenging in children. Given the nature of the test's requirement for long periods of slight muscle contraction, it cannot be performed under sedation unless done with a stimulating electrode and thus is rarely used in the pediatric population, essentially reserved for the adolescent age group if needed.

Clinical distinction between a myasthenic crisis and a cholinergic crisis is important. This situation is commonly encountered in the child with a known diagnosis of MG who is being managed with an acetylcholinesterase inhibitor. There is overlap in the presentation of a myasthenic crisis with that of the side effects from overmedication. Both crises can have weakness; a flare-up of MG is caused by a worsening of its underlying symptoms, whereas cholinergic weakness is more consistent and less fluctuating. It is self-evident that improvement with a dose of the acetylcholine esterase inhibitor directs the practitioner to be concerned about a myasthenic flare-up, whereas a history of a recent medication dose increase suggests an iatrogenic etiology. An onset with a disease trigger also points to myasthenia gravis as the culprit. Fever, tachycardia, tachypnea, and evidence for infection are seen in a myasthenic crisis, whereas bradycardia, hypotension, and increased oral secretions are seen in a cholinergic crisis. Table 6 summarizes the two presentations.

The treatment of myasthenia gravis entails two stratagems, ideally used in synchrony. The first is to increase the available acetylcholine at the NMJ to overcome the clinical symptoms caused by the lack of receptor activation. Pyridostigmine, an acetylcholinesterase inhibitor, is the most commonly used, and its dosage is timed throughout the day when symptom management is needed (i.e., not at bedtime or during sleep when weakness is not affecting the quality of life). While the increase of the acetylcholine level at the NMJ provides immediate clinical benefit in most cases, it is not targeting the underlying pathology. Monotherapy of an acetylcholinesterase inhibitor can be concerning for the development of chronic destruction of the NMJ in the setting of an immunologically destructive milieu, leading to permanent irreversible symptoms over time. As such, it is standard practice to initiate

Table 6 Distinguishing a myasthenic crisis from a cholinergic crisis

Myasthenic crisis	Cholinergic crisis
Worsening myasthenia gravis symptoms with fluctuating severity	Weakness with less fluctuation
Rapid return of symptoms between previously adequate doses of the acetylcholinesterase inhibitor	Recent acetylcholinesterase inhibitor dose increase
Intercurrent illness, particularly febrile, or another stressor such as a new medication that is known to worsen myasthenia gravis	No obvious other precipitants
Fever, tachycardia, tachypnea, evidence of infection	Bradycardia, hypotension, increased salvation and tearing, abdominal pain, diarrhea, urinary urgency, and frequency
Treatment Follow pulmonary testing (NIF, FVC) PLEX, IVIG +/− pulse steroids (steroids can transiently worsen weakness before improvement begins)	Treatment: Hold the acetylcholinesterase inhibitor Atropine (0.05 mg/kg IV—Maximum 2 mg/dose)

NIF negative inspiratory force, *FVC* forced vital capacity, *PLEX* plasma exchange, *IVIG* intravenous immunoglobulin

early immunosuppressive therapies, the second arm of treatment. Myasthenia gravis is associated with thymic hyperplasia in 70% of cases and with thymoma in 10%, though less frequently in juvenile onset. Thymectomy has been shown to be therapeutic for both adult and pediatric MG, though with some raising concerns for immunological maturation if performed at too early an age. The risks and benefits can be discussed with the family, and thymectomy should be strongly considered in the generalized form of the disease, especially in cases that are pharmaceutically refractory. First-line immunomodulating therapy is typically an oral daily steroid, with cautious and gradual initiation of utmost importance as rapid dosing can trigger a paradoxical myasthenic flare. Intravenous immunoglobulin (IVIG), plasma exchange (PLEX), and steroid-sparing agents such as azathioprine, cyclosporine, methotrexate, cyclophosphamide, rituximab, and mycophenolate mofetil are used alone or in combination as needed for maintenance treatment.

In one study, remission rates including data from children and adults were found to be 22% after 1 year. Typically, juvenile onset has slightly higher remission rates, particularly in ocular types and also in generalized patients' status post thymectomy.

4 Conclusion

The assessment of acute limb weakness in infants, children, and adolescents can be quickly narrowed to a manageable differential with the application of localization techniques after a careful history and physical examination. Targeted laboratory,

imaging, and electrophysiological studies help confirm the suspected hypothesis. This chapter provides an approach to acute weakness and reviews a series of cases, reinforcing the peripheral nervous system's neurological causes for acute limb weakness in the pediatric population.

5 Clinical Pearls and Key Points

- The child with limb weakness can have a disorder of the central or peripheral nervous system. Features such as alteration in mental status, cranial nerve deficits and increased tendon reflexes/spasticity (when long standing) can distinguish between upper motor neuron and lower motor neuron pathology.
- Disorders of the peripheral nervous system may involve the anterior horn cell, spinal roots, neuromuscular junction, peripheral nerve or muscle. Physical examination findings may help localize the disease to each of these locations.
- Guillian-Barré syndrome is an important cause of bilateral lower limb weakness in children. Ataxia, areflexia and elevated protein in CSF are classic findings.
- Myasthenia gravis is a disorder of the neuromuscular junction that affects the face and bulbar muscles at initial presentation. The latter conditions may progress to respiratory muscle weakness and therefore early recognition is important.

References

1. Preston DC, Shapiro BE. Electromyography and neuromuscular disorders. Elsevier Health Sciences; 2012.
2. Yuki N, Hartung H-P. Guillain-Barré syndrome. N Engl J Med. 2012;366(24):2294–304.
3. Verboon C, van Doorn PA, Jacobs BC. Treatment dilemmas in Guillain-Barré syndrome. J Neurol Neurosurg Psychiatry. 2017;88(4):346–52.
4. Darras BT, Jones HR Jr, Ryan MM, Mathews KD, De Vivo DC, editors. Neuromuscular disorders of infancy, childhood, and adolescence: a clinician's approach. 2nd ed. San Diego, CA: Academic Press; 2014.
5. Arnon SS, Schechter R, Maslanka SE, Jewell NP, Hatheway CL. Human botulism immune globulin for the treatment of infant botulism. N Engl J Med. 2006;354(5):462–71.
6. Rosow LK, Strober JB. Infant botulism: review and clinical update. Pediatr Neurol. 2015;52(5):487–92.
7. Statland JM, Barohn RJ. Muscle channelopathies: the nondystrophic myotonias and periodic paralyses. Continuum (Minneap Minn). 2013;19(6 Muscle Disease):1598–614.
8. Chiang LM, Darras BT, Kang PB. Juvenile myasthenia gravis. Muscle Nerve. 2009;39(4):423–31.

Functional Neurological Disorder in Children and Adolescents

Kasia Kozlowska and Shekeeb Mohammad

Functional neurological (conversion) disorder (FND) in children (including adolescents) is a neuropsychiatric disorder involving complex interactions between brain, mind, body, and context—the lived experience of the child and the family. The last two decades have seen important advances in our understanding, diagnosis, assessment, and treatment of FND in children. Of note in this context are the emergence of new research technologies, a resurgence of research interest in FND, a growing understanding of the biological embedding of stress and of the role of psychological processes on sensory and motor function, new therapeutic approaches, and efforts to address and overcome past stigma. In this chapter we highlight key areas of knowledge, discuss recent advances in the field, and set out current best practices. Throughout the manuscript we use the pronoun she because in the civilian pediatric setting, more girls than boys present with FND. During wartime or in the context of the military action, the situation is reversed [1].

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1 Types of Functional Neurological Symptoms Seen in Children and Adolescents

Children with FND present with a broad range of functional neurological symptoms: motor symptoms that affect the limbs (weakness or loss of function, tics, tremors, unusual gaits, dystonia); functional seizures (including syncope-like events); loss of sensory function (loss of touch sensation, hearing, or vision); dizziness and balance difficulties; motor symptoms affecting the voice (aphonia or dysphonia), digestive tract (difficulty swallowing or rumination), or bladder (urinary retention); and changes in cognitive function or consciousness. Although motor symptoms and functional seizures are the most common presentations, it is also common for children to experience multiple symptoms—in various combinations and sometimes changing over the course of the presentation or across presentations [2, 3]. Occasionally, children may present with a mixture of symptoms that are difficult to bracket into discrete categories. For example, a hand tremor may progress, on some occasions, to an arm tremor (one or both arms) and, on other occasions, to whole-body shaking accompanied by a change in consciousness.

2 Epidemiology

As far back as 1859, Briquet reported that one-fifth of all FND cases developed in children before the age of 12 years and that 5% of child patients were male [4]. His findings challenged the prevailing view that FND—then termed "hysteria" (Greek for womb), a disorder of the "wandering womb"—was a disorder exclusively of adolescent and adult women. More recently, two epidemiological studies have reported a childhood incidence of 1.3–2.3/100000 and a female-to-male ratio of approximately 3:1 [2, 3]. Presentations are more common in the second decade of life, though younger children can also present with FND symptoms, with some studies describing children as young as 3 or 4 years old [2, 3, 5].

FND in children accounts for a substantial proportion of health-care expenditures in hospital settings [5]. Because the onset is typically acute and functionally disabling, children most commonly present via the emergency department or via a referral from the general medical (family) practice and general pediatricians to a specialist pediatric practice. A study from Australia found that children with functional somatic symptoms—of which FND is a subset—represented 1% of all hospital admissions during an 18-month study period [6]. Studies from the United States and the United Kingdom showed that 61% of emergency room presentations for FND resulted in inpatient admissions and that hospital stays for

children with FND were longer than those for children with other psychiatric diagnoses [5, 7]. Children with functional seizures can account for 5%–23% of presentations for clinicians working in specialist epilepsy clinics [8–10].

The current diagnostic criteria for FND—The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and International Classification of Diseases 11th Revision (ICD-11) [11, 12]—do not require the presence of an antecedent stressor. The diagnosis is made on the basis of a neurological examination (see section below). Notwithstanding, most children and families (73%–100%) report antecedent stressors when a comprehensive (biopsychosocial) assessment is undertaken [5, 13]. Stressors can be physical (a viral illness, a minor injury, or a medical procedure) or emotional (family conflict, difficulties with peers, or stress at school) and are often cumulative over time. Maltreatment—for example, physical, emotional, or sexual abuse—and traumatic events are important [14], but less common. Here, we emphasize that it is important to highlight that clinicians need to listen to the history as told by the child and family to avoid unwarranted assumptions. For example, the erroneous belief—based on the early work of Sigmund Freud—that FND is invariably associated with, and triggered by, sexual abuse has, in the past, led to much distress and iatrogenic stigma for children and their families [15, 16].

Comorbid "neurological/medical" diagnoses vary between cohorts and can be found in up to 35% of children [5, 17]. By contrast, comorbid "functional" symptoms—pain, fatigue, dizziness, nausea, other functional gut symptoms, and postural orthostatic intolerance—are common, presenting in approximately two-thirds of children [2, 3, 5, 17]. Here, it is important to highlight that because a majority of children presenting with FND have previously been well—and are often high-functioning (in sports or academically)—the sudden shift from wellness to illness (and substantial functional impairment) can be extremely distressing to the child and family.

Comorbid "psychiatric" diagnoses are present in a proportion of children (22%–84%), with anxiety being the most common [3, 5, 13, 18]. Even in the absence of a formal diagnosis of anxiety, psychological processes that contribute to symptom amplification—attention to symptoms (by the child or family), perfectionism, catastrophizing and rumination, negative expectations, and maladaptive illness beliefs—are common [15, 16, 19]. Modeling of FND symptoms in family members, peers, and online forums may play a role in some cases [5, 20]. For example, Han et al. hypothesize that an online forum—TikTok—has contributed to the recent spike of functional tic-like movements in teenage girls during the coronavirus disease-19 (COVID-19) pandemic [20]. Along the same lines, while FND support groups aim at providing support to patients and their family, online contact between newly diagnosed patients and patients with chronic symptoms may actually contribute to illness-promoting modeling. The problem is that the focus of patients with a longer-term engagement with such groups has

often shifted from the hope of getting well to the reality of long-term disability and chronic illness. As an example, some of our adolescent patients developed new FND symptoms (which they had never had before) after making contact with adolescents with chronic FND and viewing their personal websites (which displayed the given symptoms).

Fortunately, when FND in children is diagnosed early and treated promptly—by services with an established expertise—outcomes are excellent. The majority of children (63–95%) recover fully [18, 21–23]. A smaller proportion of children have a relapsing pattern of illness but are generally well. An even smaller proportion of children go on to have ongoing mental health concerns, chronic FND, or both [22, 24]. The key problem worldwide is that FND—and other functional somatic symptoms—have not been seen as an area of service priority and that adequate, evidence-based services have not been established. The expansion of services is of the highest priority because of the enormous long-term costs—in relation to health-care expenditures, socioeconomic consequences, and human impact on patients, families, and other caregivers—of poorly treated FND, which is then more likely to become chronic [24, 25].

3 Etiology

As a complex neuropsychiatric disorder, FND is best conceptualized using a developmental and systems (biopsychosocial) framework. This developmental framework emphasizes the dynamic relation between the child and her context and involves the identification of factors that influence the child's ability to organize and regulate experience—on the molecular, neurophysiological, cognitive, emotional, and interpersonal system levels—and, consequently, the child's level of adaptive functioning [26, 27]. Importantly, these factors interact with one another in nonlinear ways to shape the child's developmental pathway and patterns of adaptation and maladaptation (including the emergence of FND). Some of the key etiological factors—the focus of the current research—are listed in Box 1. In Fig. 1, we depict the current thinking about etiology using a visual metaphor.

Box 1 The Key Interacting Factors that Contribute to the Etiology of FND

- Predisposing genetic/epigenetic factors [28]
- Adverse childhood experiences (ACEs) are biologically embedded via epigenetics, stress system activation and reprogramming, and experience-dependent plasticity processes [15, 29]
- Increased arousal and increased salience of negative information play a key role in stress system activation, information processing, implicit learning, illness-promoting psychological processes, and (aberrant) patterns of neural network activation—all core feature of FND [30–36]
- The impact of misdirected attention, expectation, and self-agency [15, 19] because attention to FND symptoms by the child or family amplifies them
- Precipitating (triggering) factors can be physical (a minor illness, an injury, or a medical procedure), emotional, or both [15]
- Maintaining factors include late diagnosis and treatment (iatrogenic contribution), illness-promoting psychological processes (including attention to symptoms, catastrophizing, and illness beliefs), and illness-promoting changes in family organization [15]

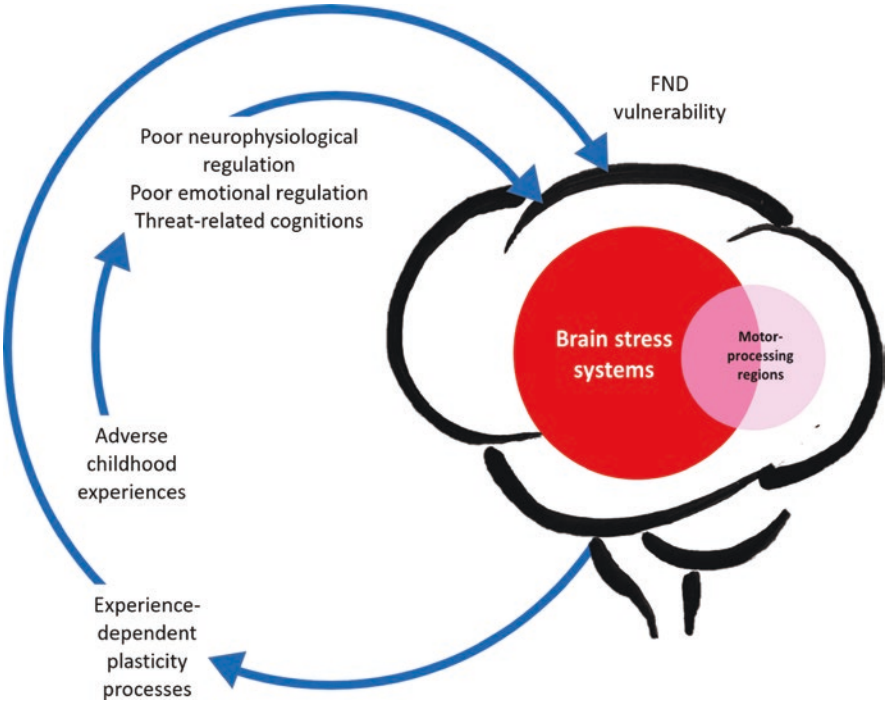

Fig. 1 A depiction of the hypothesized interactions between adverse childhood experiences, the embedding of these experiences in the child's neurobiology, and the resulting experience-dependent changes in the brain function, which are associated with a vulnerability to FND. © Kasia Kozlowska 2021

4 The Medical Assessment: The First Step in the Assessment and Treatment Process

In a well-conducted medical assessment for FND, the doctor—often a neurologist or pediatrician—establishes a good therapeutic alliance, makes a positive diagnosis of FND, provides a clear explanation, and directs the child onto the appropriate outpatient or inpatient treatment pathway. It is the first step in managing FND. When the process goes well, the child and family feel relieved and validated to receive a diagnosis; the anxiety felt by the child and family—that the child may be suffering from a terrible illness—settles; and the child and family are ready to accept referrals to appropriate clinicians or to a multidisciplinary team that treats functional somatic symptoms. In this manner, the doctor has created a "secure base" from which the child, family, and mental health clinician feel safe enough to move forward onto the path to health and well-being [15]. In the sections below, we provide more details about the key aspects pertaining to the medical assessment process.

4.1 History

There are two aspects to obtaining a history when evaluating a child with suspected FND. The first aspect, the history of the presenting symptoms, is an integral part of the medical assessment and is used by the doctor to arrive at a diagnosis. The second aspect of history taking is a comprehensive biopsychosocial assessment that provides detailed information about the child's developmental history and also information about the predisposing, precipitating, and perpetuating factors, which may be arising at multiple system levels (the individual child, the family, the school context, and so on). This detailed information is used to co-construct a biopsychosocial formulation and to guide the treatment intervention. While any clinician with the appropriate skills can undertake the biopsychosocial assessment, in many clinical settings, this element of history taking is undertaken by clinicians working in psychological services—in particular, clinicians who will be assuming the long-term responsibility of implementing the treatment intervention (see subsequent sections).

Regarding the first aspect of collecting history, some clues that lend support to a potential diagnosis of FND—and that indicate a need to include FND in the differential diagnosis—are listed in Box 2.

Box 2 Clinical Features—Elicited in History Taking—That Are Commonly Found (Yet Are Nonspecific) in Childhood Motor and Sensory FND

- A dramatic, sudden onset of symptoms, occurring spontaneously or in the context of identifiable physical (e.g., a physical injury or exertion) or emotional (e.g., falling out with a friend at school) factors that are not consistent with the severity of the symptoms. A typical example is the sudden onset of bilateral leg weakness and confusion after the child sustains a minor hit to the head with a ball.
- An extremely quick progression of symptoms from the initial onset to peak symptom severity. For example, tic-like behaviors might progress from small movements to explosive, large, violent movements (vocalizations) in a matter of days or weeks.
- Mixed neurological signs that are not clinically congruent in their origin. For example, jerky movements might change to a presentation with paralysis or ataxia and then revert back to jerky movements.
- A history of complete, sudden remission of symptoms, as in the case of sudden loss of vision that resolves spontaneously.
- Parent reports that the symptoms vary with distractibility (e.g., when the child is engaged on the mobile phone) and that the symptoms return on attention or suggestion (e.g., when the child's attention is no longer distracted away from the symptoms).
- In fixed dystonia, a history of pain accompanying the sudden onset of symptoms.
- A previous history of FND or other functional somatic symptoms, such as stress-related headaches, functional abdominal pain, other functional disorders of the brain–gut axis, or symptoms of autonomic dysregulation.
- The sudden onset of FND after a clear antecedent stressor—physical or emotional—identified by the child and family, as in the onset of symptoms in the context of a parental illness and hospitalization.
- The sudden onset of FND after a clear antecedent stressor—physical or emotional—in the context of a history of cumulative stress (e.g., bulling over the years, undiagnosed learning difficulties over the years, or chronic family stress over the years).
- The presence of comorbid anxiety or depression.

4.2 Neurological Examination

The diagnosis of FND—with the exception of functional seizures—is a clinical one based on rule-in (positive) physical signs elicited during a neurological examination [37] (see Table 1). Misdiagnoses are rare, ranging from 4% to <1% of cases [38]. A

Table 1 Common positive (rule-in) neurological signs found on physical examination in children with FND[a]

Neurological symptoms	Features that can support a diagnosis of FND
Motor FND	
Gait difficulty	• Apparent loss of balance (e.g., swaying from side to side) while walking with a narrow base gait • Effortful steps (e.g., a "magnetic" gait when each step lands with effort and the child lifts the limb with demonstrated effort before the next step) • Gait difficulty is "not" noted when the child turns around during the walking task; this is in contrast to ataxic disorders, where turning around without support is often compromised and results in a loss of stability
Weakness (generalized or partial)	• Variability in strength of the affected body part/side during examination, particularly when the child is distracted or asked to perform contralateral movements • Discordance between strength and functional ability of the child's affected body part, including weaker or absent movements on formal examination but partial or complete movements on reflex tasks (e.g., collapsing weakness, Hoover's sign (see Stone and Sharpe (2001) for details of clinical examination skills), or motor inconsistency) • Weakness not conforming to anatomically possible distribution (e.g., arm and leg weakness on opposite sides of the body)
Tremors[b]	• Variable distribution or frequency of the child's tremor when examined at different times • The child's tremor changes with contralateral body movements (entrainment) • The tremor decreases with distraction when the child is asked to perform mental tasks such as subtracting serial 7s or complex fine-motor tasks such as fractionated finger movements (touching the thumb to each finger) • The tremor increases when the child's attention is directed toward the affected body part
Tic-like movements	• Onset of the child's FND symptoms in the second decade of life (rather than the earlier onset typically seen in tic disorders) • No reported "urge" prior to the tic-like movements or vocalizations • No variability in distribution of movements • Predominant or isolated coprolalia • Axial jerky movements without any upper body, neck, or facial movements • Complete absence of voluntary suppressibility of jerky movements • Tic-like behaviors that cause injury to self or others • Concurrent mental health issues (self-harm, suicidal ideation, or comorbid anxiety or depression)
Myoclonus	• Presence of axial jerky movements only • Entrainment of the child's myoclonus or full suppressibility • Variability in duration or distribution of jerks or in latency of jerks
Chorea and ballism	• Predictable pattern of fluid movements rather than the unpredictable and semi-purposeful nature of chorea • Peculiar gait (e.g., salutation movements or marching-like gait) • Absence of motor impersistence (inability to sustain simple voluntary acts such as keeping the eyes closed or arms lifted and extended)

Table 1 (continued)

Neurological symptoms	Features that can support a diagnosis of FND
Dystonia	• Sudden onset of a fixed posture, often with pain • Strong resistance to passive manipulation • Co-contraction of muscles mediating opposing movements
Sensory FND	
Sensory symptoms (pain excluded)	• Sensory symptoms not conforming to a dermatomal distribution • Hemisensory loss of entire body with a sharp midline distribution
Visual loss	• Tunnel vision • Preserved response to a "menace reflex" (the rapid approach of an object) • Uniocular diplopia • The child is still able to maneuver around objects despite the subjective vision loss • The child reports being unable to read or write but is still able to text friends on the cell phone • A formal ophthalmology review is typically extremely helpful
Hearing loss	• The child responds to soft voice but not to normal or loud voice • The child takes a disproportionately long time to respond to questions • Audiometry can be helpful

[a] The table has been compiled from references number [20, 39–47]

[b] Tremors of varying frequencies in different muscle groups and tremors faster than 11 Hz in frequency are unlikely to indicate a functional tremor

positive diagnosis reflects a recent shift in clinical practice. Previously, the diagnosis of FND was a diagnosis of exclusion. Typically, the doctor provided the child and family with an FND diagnosis—if at all—only after all the medical investigations had been completed. The diagnosis of exclusion was unhelpful with regard to the child and family's perception and acceptance of the FND diagnosis and often led to substantial delays in diagnosis and treatment—including multiple medical visits (often to multiple doctors) coupled with a multitude of investigations (often unnecessary or associated with iatrogenic harm). In this context, the current emphasis on a positive FND diagnosis as the best practice reflects an important advance in clinical practice.

A neurological examination of a child with suspected FND is broadly similar to that used in examining patients with any other suspected organic disease process—with one additional component. Throughout the examination, the clinician pays particular attention to and utilizes bedside clinical tests that are likely to elicit the positive rule-in signs that typify FND: symptom variability over time/context; symptom variability with distraction; incongruence with organic patterns of presentation; and so on. Below, we offer some suggestions that support both the therapeutic and the information-gathering aspects of a neurological examination.

Suggestions that support the therapeutic aspects of a neurological assessment are as follows:

- The clinician's knowledge about FND should be sufficiently up-to-date to ensure that he or she does not bring outdated and stigmatizing attitudes, beliefs, and language to the interaction with the child and family [16].

- During the physical examination, the clinician should make use of his/her therapeutic skills—tone or voice, facial expression, use of respectful language—to establish a therapeutic relationship.
- The clinician can explain what is happening during the physical examination to put the child and family more at ease. A running commentary of the clinical findings—as often done in adult practice [48, 49]—can likewise be useful for adolescent patients and parents of younger children.

Suggestions that support the information-gathering aspects of a neurological examination:

- Observe the child—and her functional capacity—outside of the neurological examination when the child is not under direct observation (e.g., observations outside the room, observations in the waiting room, and observations reported by nurses on the ward or by teachers in the hospital school).
- Obtain video recordings from the family: extreme variability of neurological symptoms between different video recordings (and on the examination itself) is a useful clue in favor of an FND diagnosis.
- Consider examining the child at different times: extreme variability of neurological symptoms between different examinations (and on different home video recordings) may be a useful clue in favor of an FND diagnosis.
- Assess the distractibility of symptoms by asking the child to undertake either mental tasks or a particular movement with a different body part (e.g., touching the thumb to each finger on the hand ("fractionated finger movements").
- Observe the child for her ability to accomplish certain tasks such as dressing/undressing, taking off or putting on shoes, writing or texting despite the presence of symptoms (dramatic movements, motor loss, or visual loss) before and during the task.
- Attempt to elicit the positive neurological signs that are typically present in FND (see Table 1).

It is important to highlight that some presentations of FND can be more difficult to evaluate and may require assessment by a specialist or a second opinion from a colleague. Functional seizures (including syncope-like episodes) are best assessed by neurologists who have clinical expertise in functional seizures—on clinical history, witnessed descriptions, and home videos [50]—and who, in the best of circumstances, have access to a video electroencephalogram (vEEG), which constitutes the gold standard for establishing this diagnosis. Syncope-like events may require cardiac monitoring in a subgroup of children (and the opinion of a pediatric cardiologist). Research suggests that physicians who are not neurologists find the task of differentiating between epileptic and functional seizures difficult [51]. Dystonia is challenging in the best of circumstances [45, 52] because of symptom variability, task-related changes in dystonia, and sudden onset and can be a feature of both organic and functional dystonia. Dizziness and balance issues in children are also difficult to assess because they can be the clinical manifestations of various underlying processes, including poor motor head control (a symptom of motor FND), hyperventilation (which can cause dizziness or even syncope), and postural orthostatic tachycardia syndrome (POTS, an autonomic dysregulation that manifests as dizziness on standing) [15, 17, 31, 53, 54].

Rule-in (positive) signs may be more difficult to elicit for a small subset of FND symptoms and can make the distinction between a functional and organic diagnosis more challenging. Examples include urinary retention, rumination/vomiting, voice and swallowing difficulties, symptoms that occur when the patient may be in light sleep or drowsiness, and changes in cognitive function. Any of these presentations may require a second opinion from a urologist, a sleep physician, a gastroenterologist, a speech pathologist, or a neuropsychologist [55, 56].

4.3 Providing a Positive Diagnosis

In the majority of cases, the clinician will have made a positive diagnosis of FND based on the rule-in (positive) signs elicited during the neurological assessment. The next important step is to communicate the diagnosis to the child and family. The key elements of providing a positive diagnosis—in temporal order—are listed below:

- The clinician can explain that the physical examination—and the associated positive neurological signs—are consistent with an FND diagnosis and that he or she expects all the investigations (if they are not yet back) to be normal.
- The clinician tells the child and family that FND is a common diagnosis of childhood and that neurologists see FND all the time (which normalizes the diagnosis by communicating that it is common and part of daily neurological practice).
- The clinician explains what the diagnosis means—for example, that the structure of the nervous system is intact but its function has been disrupted.
- The clinician acknowledges the family's distress and the impact of the illness on function, but again, he or she emphasizes that FND is a common presentation in neurological practice and that, with treatment, the majority of children recover and return to health and well-being (thereby setting up positive expectations about the outcomes with treatment).
- The clinician emphasizes that FND needs prompt treatment. He or she outlines the treatment components that are likely to be needed, including physiotherapy, psychological work to help with regulation, and work with the family to help them support the child in getting better. Once again, the clinician sets up positive expectations about the child's probable outcome by informing the child and family that treatment outcomes in children are excellent.
- The clinician initiates the referral process to begin treatment as soon as possible.

4.4 Medical Investigations

In the case of functional seizures, a vEEG, which shows that the functional seizure events are not accompanied by a spike-and-wave pattern (the signature pattern of epileptic seizures), is the gold standard assessment. Other biomarkers specific to childhood functional seizures are a current topic of investigation [57]. Investigation of syncope-like events (a subtype of functional seizures) requires an

electrocardiogram (ECG)—and sometimes cardiac monitoring, in addition to a vEEG. For the common clinical features of functional seizures, see Ali et al. (2011) [58]. When a video EEG is not available a routine EEG and review of home videos by a pediatric neurologist may be sufficient to yield the diagnosis of functional seizures.

For other subtypes of FND, the inclusion of a blood panel and imaging (e.g., a head magnetic resonance imaging (MRI)) can be helpful in allaying the anxiety of the child, family, and treating team [59]. A critical point regarding medical investigations is the manner in which the clinician sets up appropriate expectations—that is, prepares the child and the family for a likely negative (normal) outcome of those investigations. Studies in adult patients with functional dyspepsia, headache, and noncardiac chest pain show that prior counseling—to establish appropriate expectations—improved both the acceptance of the diagnosis and the treatment outcomes [60, 61]. Occasionally, neurologists may utilize some specialist investigations—for example, polymyography and Bereitschaftspotential (a slow wave originating from the supplementary motor cortex and premotor cortex that precedes voluntary movements (derived from back-averaged EEG))—in difficult-to-diagnose movement disorders [62, 63], but these investigations are limited by their lesser availability and lesser applicability to younger children.

For children with comorbid anxiety and depression, blood panels to screen for common conditions that can contribute to such symptoms—for example, low iron, low B12, low vitamin D, thyroid issues, metabolic problems (abnormal fasting glucose)—should be obtained.

Finally, certain adjunct tests are extremely helpful in eliciting positive (rule-in) signs of stress system dysregulation—which are a core feature of FND in children [17, 31, 33, 57, 64]—because they identify specific areas of dysfunction that require targeted treatment.

- As a group, children with FND have elevated heart rates (and decreased heart rate variability)—a clinical marker of increased autonomic arousal [31, 54, 65]. To interpret clinical data, it is helpful to remember that the sinoatrial node (the body's inherent pacemaker) generates a heart rate of approximately 100 beats per minute. Reduced heart rates (<100 beats per minute) mark the activation of restorative parasympathetic activity (that functions to slow the heart), and heart rates >100 beats per minute mark a withdrawal of restorative parasympathetic activity (that functions to increase the heart rate) coupled with sympathetic activation (that functions to increase the heart rate even more) [15]. In children whose heart rates are consistently extremely high [66, 67], the clinician can use heart rate as a marker of autonomic arousal during the medical examination [15, 31, 54]. An important point here is that attention to functional symptoms amplifies them. In this context, the use of wearable heart rate monitors is contraindicated in children with FND: the child will typically obsessively focus on her heart rate and the symptoms will get worse. For a review of the contemporary understanding of the autonomic nervous system, see Chap. 6 in Kozlowska et al. (2020) [15].

- Biofeedback devices can be used to investigate the child's capacity to activate the restorative (calming) parasympathetic component of the autonomic nervous system—that is, to increase heart rate variability—via slow breathing. Interventions that aim at improving autonomic system regulation are an important component of treatment [15, 54].
- High respiratory rates provide a good marker of hyperventilation, the consequence of activating the respiratory motor system alongside autonomic arousal; hyperventilation is present in a sizable subgroup of children with FND [15, 17, 54]. About 50% of children with functional seizures trigger their seizure events by hyperventilation because it increases brain arousal. Identification, and, if necessary, treatment of hyperventilation and is therefore an important component of the treatment intervention for this subset of children with functional seizures [57, 64, 68]. For children ≥6 years of age, respiratory rates >25 breaths/ minute are in the ≥97.5th centile and respiratory rates >30 breaths/minute are in the ≥99.9th centile [66, 67].
- In specialist settings, hyperventilation (see above) can be formally assessed by measuring arterial CO_2 via a percutaneous monitor during the hyperventilation component of the EEG [15, 64].
- The standing test for postural orthostatic tachycardia syndrome (POTS)—a common comorbid presentation—is a simple way of documenting autonomic dysregulation. Heart rate and blood pressure are documented at 1-min intervals over ten minutes first thing in the morning when the child gets up from a lying to a standing position. A heart rate increase of 40 beats per minute—with no substantial change in blood pressure—yields a positive test. POTS "expresses itself via physical symptoms of dizziness, giddiness, palpitations, lightheadedness, near-fainting, and fainting on standing up from a reclined or sitting position. It involves too little restorative parasympathetic (vagal) activity (allowing the heart rate to increase), too much sympathetic activity (through which the heart rate increases even more), and no change in blood pressure" (pp. 131–132) [15, 69, 70]. The treatment of comorbid POTS can be an important component of treating children with FND [15, 69, 70].

4.5 Differential Diagnosis

FND is a clinical diagnosis with a high diagnostic accuracy, but there are some neurological presentations that the clinician should keep in mind—as part of the differential diagnosis—while formulating a clinical opinion (see Box 3).

Box 3 The Differential Diagnosis (for Exclusion)

- **Unusual epilepsy types**: Hyperkinetic frontal lobe seizures characterized by florid hyperkinetic movements, or temporal lobe/occipital lobe epilepsy with unusual psychiatric manifestations, can mislead the clinicians to consider a functional diagnosis. A video EEG clarifies the diagnosis in the majority of cases when events are captured during the recording, though it is possible that rare epileptic seizures originating from deep-seated brain structures may not show an EEG correlate.
- **Prodromal phase of autoimmune syndromes**: Sydenham chorea or anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis when behavioral symptoms may be present in isolation.
- **Paroxysmal dyskinesia**: Episodes can be short-lasting with bizarre, dyskinetic movements.
- **Intense imagery movements:** Complex stereotypical movements that occur when the child is engaged in conscious acts of imagery or imagination [71, 72].
- **Fixed dystonia**: Organic and functional dystonias can be difficult to differentiate [45, 52]. In some organic dystonias, the dystonia will emerge during certain tasks but not during others (e.g., the dystonia can be brought out by asking the child to walk normally, but it disappears on running or on walking backward).
- **Rapid-onset dystonia parkinsonism due to underlying genetic vulnerability** can sometimes be misdiagnosed as FND (functional dystonia) because of the crescendo onset of symptoms.
- **Tics:** Tic disorders and functional tics can be difficult to differentiate. Distraction strategies (physical or mental) integrated with a neurological examination coupled with historical features can be used to help make this distinction [20].
- **Anti-contactin-associated protein-like 2 (CASPR2) and anti-Lgi1 antibody-associated pain, bowel, bladder, or autonomic symptoms** can manifest over weeks to months.
- **Factitious disorders:** Factitious disorders are uncommon but may occasionally need to be part of the differential diagnosis [73]. Factitious disorders involve a conscious (deceitful) production of physical symptoms via mimicry, self-harm, or other actions that function to induce the symptoms. In contrast, FND involves aberrant neural network patterns that are not under conscious control [74].

5 The Biopsychosocial Assessment: The Second Step in the Assessment and Treatment Process

5.1 The Biopsychosocial Assessment

The second step in the assessment and treatment process is the comprehensive biopsychosocial assessment and co-construction of a formulation by the clinician(s) and the child and family. The biopsychosocial assessment elicits detailed information about the child's developmental history—including the child's lived experience and the child's adaptation to that experience—and also information about the predisposing, precipitating, and perpetuating factors pertaining to multiple system levels (the individual child, the family, the school context, and so on). The formulation is a synthesis or coherent summary of the relevant factors that contribute to the child's presentation [75–77]. The clinician uses the formulation to plan a treatment intervention that addresses the specific needs of the given child and family [75].

For the interested reader, detailed descriptions of the biopsychosocial assessment in childhood FND are available in case studies by Kozlowska et al. (2020, 2013) [15, 78], Khachane et al. (2019) [52], and Chandra et al. (2017) [79].

5.2 Explaining the FND Diagnosis from the Biopsychosocial Perspective

The co-construction of a formulation with the child and family provides the clinician(s) with a second opportunity to explain the FND diagnosis from a biopsychosocial perspective. In this manner, the two therapeutic processes, the construction of the formulation and the explanation concerning the FND itself, are woven together into a coherent whole. Because children enjoy looking at pictures, the use of visual metaphors facilitates this process (see Figs. 2 and 3).

Along the same lines, because many of the comorbid functional symptoms—nausea, functional gut symptoms, postural orthostatic intolerance—reflect activation and dysregulation of the autonomic nervous system, visual metaphors of the autonomic nervous system can be used to provide an understanding of these symptoms [15].

For visual metaphors pertaining to sensory functional symptoms or to comorbid complex chronic pain, see Kozlowska et al. (2020) [15]. Simple explanations for functional seizures—drawing from data about brain–body arousal or behavioral/psychological function—have also been developed [15, 21, 23, 80].

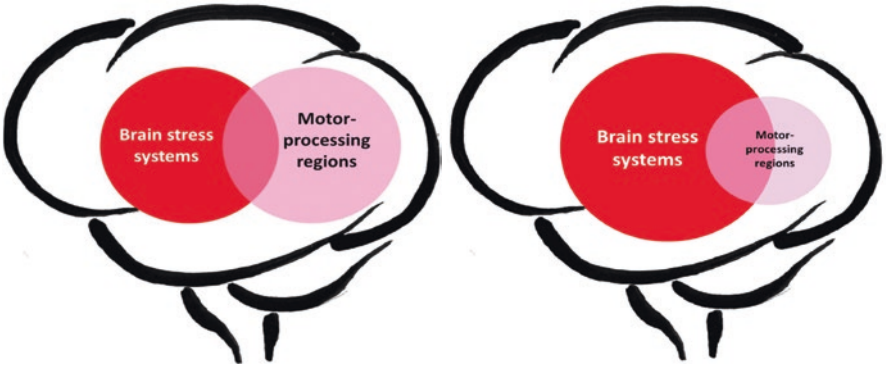

Fig. 2 The red ball represents the "brain stress systems." The pink ball represents the "motor-processing regions" (see left hand picture). When the "brain stress systems" are activated by an infection, illness, injury, or emotional stress, they become overactive and over-dominant and they disrupt motor function, causing functional motor symptoms (see right hand picture). © Kasia Kozlowska 2017

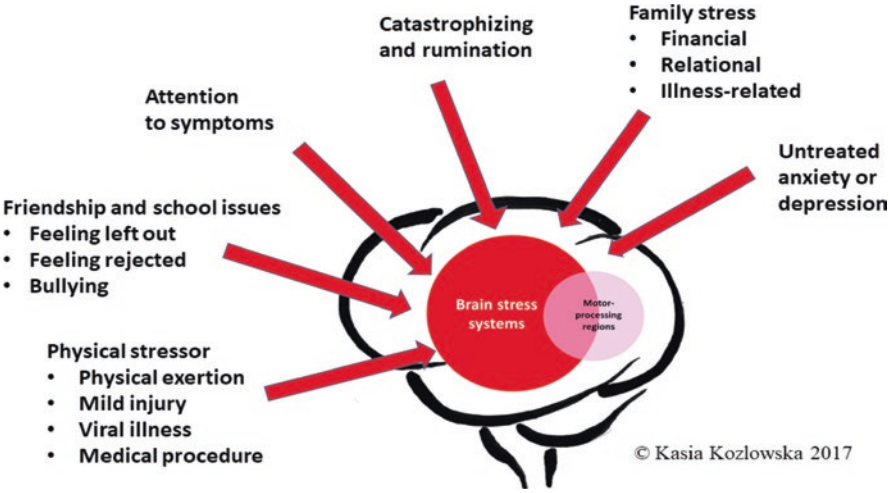

Fig. 3 A visual depiction of the formulation co-constructed by the clinician(s), the child, and the family. The clinician includes any predisposing, precipitating, or perpetuating factor, that has been elicited during the biopsychosocial assessment

6 The Treatment Intervention: The Third Step in the Assessment and Treatment Process

6.1 Using the Biopsychosocial Formulation to Plan the Treatment Intervention

The biopsychosocial formulation is used to develop the treatment intervention. In effect, the formulation (see Fig. 3) provides a rationale for multidisciplinary treatment that includes, but is not limited to, the following: physiotherapy to address motor dysfunction; psychological work to facilitate neurophysiological, emotional, and cognitive regulation; family work to address attentional processes, parental conflict, and other family issues; work with the school to address friendship, learning, or bullying issues at school; and pharmacotherapy as required. The overarching rationale is that the identified factors—in combination—function to maintain activation of the brain stress systems—hence the FND symptoms (see Fig. 2). The goal of the treatment is to settle the stress system (the red ball in Fig. 2) and to normalize motor function (the pink ball in Fig. 2), with the consequence that the FND symptoms resolve.

6.2 Implementing the Treatment Intervention(s)

The next step is to implement the treatment intervention(s)—in the inpatient or outpatient setting—to facilitate the child's return to health and well-being. The level and complexity of the intervention—informed by the biopsychosocial formulation—typically follow a stepped-care approach [18, 21, 81]. For transient FND symptoms, a good explanation coupled with a suggestion that the child and family avail themselves of commonly available therapeutic options—for example, a school- or group-based anxiety/stress management intervention—might be sufficient. For children whose symptoms persist but whose functional impairment is mild-to-moderate—for example, they are still able to attend school—more targeted interventions may be required and the clinician will need to make the necessary referrals (e.g., to a psychologist, a physiotherapist, or a speech therapist). Health providers not familiar with the treatment of FND are often grateful if the referring clinician provides FND-related resources in tandem with the referral (e.g., information about FND-informed physiotherapy [15, 82–84] or the broad range of mind–body interventions that can be utilized in psychological work [15]). Similarly, an intervention with the school (by the psychologist) can ensure that the children maintain their school attendance—a key goal of any treatment intervention—and are not sent home because of functional symptoms. For children with extremely disabling symptoms, specialist multidisciplinary teams located in inpatient settings—if available—are typically able to provide the needed interventions via an inpatient admission [21, 85, 86].

7 Prevention and Preemption

7.1 Taking the Intervention Home

The final step of the treatment intervention is to prevent relapse. The best intervention in this context is for the child and family to take ownership of the treatment program and to take it home. In this scenario, various elements of the treatment program (e.g., strategies to reduce arousal; recognition and communication about stress) become integrated with family routines, family communication, and ongoing engagement with professional services (for as long as they are needed).

7.2 Preventing Chronicity

In order to prevent acute FND from becoming chronic FND, the initial intervention needs to be appropriate to the level of functional impairment and then, in turn, effectively implemented. In most children with significant impairment, a prompt diagnosis, a good explanation, and a referral to multidisciplinary treatment facilitate a quick resolution of FND symptoms (with appropriate follow-up at home, as described above). Failure to follow these steps sustains or leads to high levels of anxiety for the child and family as well as visits to multiple doctors, unnecessary (and sometimes invasive) investigations, and functional somatic symptoms that increase in number and severity and that become chronic. Chronic FND symptoms are more difficult to treat presumably because set points in the stress system are altered (allostasis), aberrant neural network patterns become established, and it becomes harder to shift them back to healthier patterns.

7.3 Other Preventive Interventions

In a subset of children and adolescents with FND, their functional neurological symptoms emerge in the wake of other functional somatic symptoms—headaches, stomach pains, disrupted sleep, nausea, fatigue, symptoms associated with hyperventilation, and so on (see vignette of Mona below). The FND symptoms have been activated because health professions have failed to identify and treat the antecedent symptoms as symptoms of stress system activation. Moreover, when this activation continues unabated, functional neurological symptoms can eventually be triggered (see Fig. 2). To prevent the emergence of FND in this setting, functional somatic symptoms need to be identified as markers of stress system activation and then promptly treated.

8 The Vignette of Mona: Applying FND-Informed Care in Clinical Practice

The following vignette of Mona illustrates how the assessment and treatment processes discussed in this chapter are applied in daily clinical practice.

Mona was a 13-year-old girl who lived with her mother (a teacher), father (an electrician), and older sister (15-years-old). When Mona was in kindergarten, her sister developed a severe anxiety disorder, causing high stress levels at home and leaving Mona with less parental support and attention. In Year 4 of primary school, Mona's friendship with her best friend broke down. She sat alone on the playground and remembered feeling sad and rejected. In Year 5, Mona was bullied and actively rejected by some classmates. In parallel, her sister's mental health deteriorated: she was depressed and suicidal. The illness and death of Mona's grandmother during this period also contributed to the stress levels at home (rated as 9/10 by Mona). In Year 6, Mona became anxious about the upcoming transition to high school but was able, with therapeutic support, to manage the transition well and successfully establish a new peer group.

In the latter part of Year 7, during school holidays, Mona—exhausted by a long bushwalk and suffering from blisters and leach bites—tripped and was lagging behind. Alongside her physical exhaustion, intense feelings of exclusion and fear of being alone were triggered. Later that day, after the evening meal at home, Mona developed abdominal pain, joint pains, chest pains, and dizziness, and felt like she was unable to breath (symptoms of physical exhaustion coupled with a panic attack). Over the next few weeks, her sleep became fragmented: she found it difficult to get to sleep and woke many times at night (sympathetic arousals (autonomic nervous system activation) at night). She recurrently presented with the above-described symptoms to the emergency department. When Mona developed bilateral weakness in the legs and episodic twitching in her right hand, she was admitted to the hospital. The pediatric neurologist and her team completed a medical assessment (see previous sections), gave Mona a diagnosis of FND, and referred her for a biopsychosocial assessment with the psychological medicine team.

The biopsychosocial assessment yielded the above history. During the process of co-constructing the formulation, Mona's symptoms of episodic dizziness, chest pain (hyperventilation induced), and breathlessness were conceptualized as panic attacks (see Fig. 4). Everyone—Mona, her parents, and the clinicians—agreed that the panic attacks had been triggered by the physical and emotional stress experienced during the bushwalk. The clinicians also highlighted that Mona's story indicated that she had experienced chronic stress—repeated activations of her stress system—over many years in the context of her sister's illness. Not surprisingly, Mona's stress system had been sensitized (primed) and now responded to relatively minor stress in an overly vigorous, maladaptive manner. The clinicians explained the neurobiology of motor FND (see Fig. 2). They also

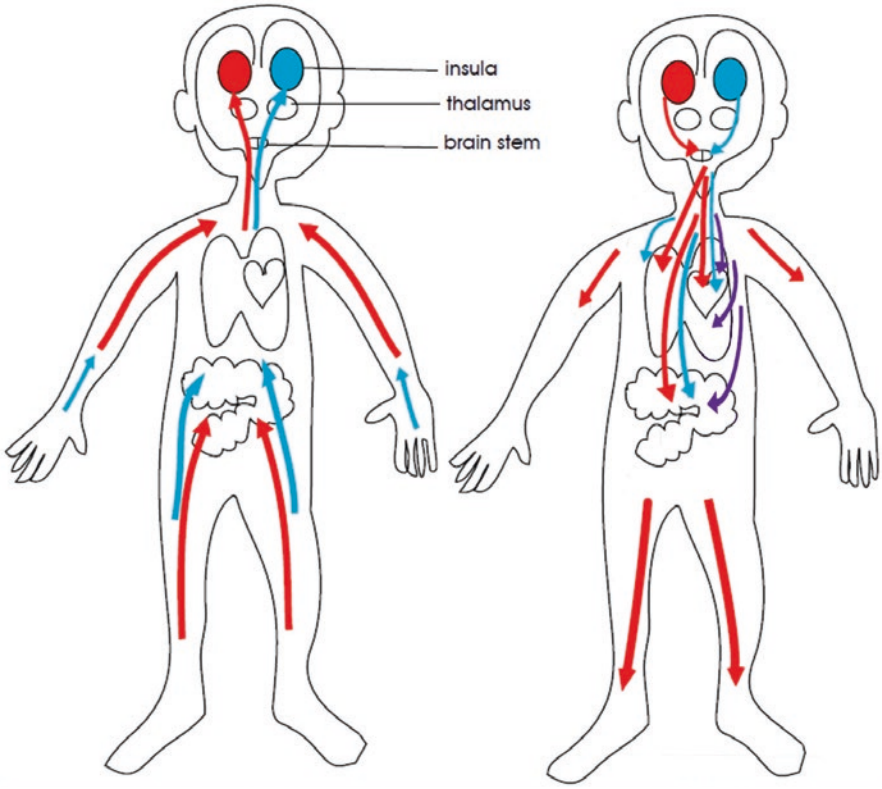

Fig. 4 A simplified functional visual representation of the autonomic nervous system. Afferent signals from the body to the brain provide the brain with interoceptive information about the state of the body (figure on the left). Efferent signals from the brain to the body—involving both the "sympathetic" (depicted in red) and "restorative parasympathetic" (depicted in blue) systems—provide second-by-second fine-tuning of the body state (figure on the right). Under conditions of safety and low stress, activation of the restorative parasympathetic system "downs" body arousal (e.g., by decreasing the heart rate), supports a mind–body state that facilitates a close emotional connection with significant others, and provides a physiological and subjective state of calm and well-being. The restorative parasympathetic system also supports a broad range of restorative life processes—heart rate variability (a marker of stress resilience), digestion, energy conservation, and tissue regeneration and repair. Under conditions of stress or in response to signals of danger, the restorative parasympathetic system is withdrawn, and activation of the sympathetic system "ups" body arousal (e.g., by increasing the heart rate, activating the sweat glands to cause sweating, activating the secretion of adrenalin (from the adrenal glands), and adjusting vascular tone). The motor respiratory system that drives hyperventilation can be activated alongside the autonomic nervous system. The "defensive parasympathetic" system (depicted in purple) works alongside the sympathetic system in response to threats by activating defensive programs in the gut (causing nausea, vomiting, and diarrhea), bladder (causing urination), and heart (causing threat-related fainting). In children with FND—who present with a state of high brain and body arousal—one expects to see "withdrawal" of the restorative parasympathetic system, "activation" of the sympathetic system, and "activation" of the defensive parasympathetic system, yielding a broad range of comorbid functional somatic symptoms. © Kasia Kozlowska 2013

highlighted that several factors contributed to the activation of Mona's stress system (see Fig. 3): her attention to her symptoms; her negative cognitions (catastrophizing and rumination); and her ongoing depression (Mona rated her mood as 3/10). Mona's abdominal and migrating limb pain were conceptualized as complex pain that commonly accompanies FND.

The intervention for Mona (see Box 4) exemplifies how a treatment intervention is tailored to the needs of each individual patient. Mona's treatment was begun in a hospital—a 10-day admission—and was continued in the community.

Box 4 The Treatment Program Implemented with a Hypothetical Child Mona and her Family

Physiotherapy: Daily physical therapy was provided in the hospital [82, 83]. On discharge, Mona was given an exercise program that set her up for graded return to her normal sporting activities (netball and swimming) over a period of 6 weeks.

Psychotherapy: The intervention began with implementation of regulation strategies—slow-breathing biofeedback, relaxation exercises using imaginal scripts, and hypnosis—that Mona used to downregulate her stress system (see Figs. 2, 3, and 4). Mona had also documented warning signs of an impending panic attack—faster breathing, thumping heart, and starting to get sweaty—on a body map [15] and used the slow-breathing intervention to avert the panic attacks (see Fig. 4). Subsequent interventions focused on diverting attention away from symptoms of stress system activation and toward her regulation strategies and on managing rumination and the catastrophizing thoughts that amplified the symptoms. On discharge, she was referred to a therapist for emotion regulation work and for cognitive behavioral therapy to help her become more adept at managing ongoing life stress.

Family work: Psychoeducation helped Mona's parents understand her symptoms and, in particular, the role of attention (from Mona or from family members) in amplifying the symptoms. Mona's parents also found the idea of a "family thermometer" useful—as a way of keeping tabs on the levels of family stress. They also planned to ensure that Mona's needs were not buried by those of her sister's. The team took steps to ensure that Mona's sister was receiving the help that she needed.

Pharmacotherapy: Mona was started on melatonin 3 mg at night to help regulate her sleep and a selective serotonin reuptake inhibitor for the treatment of her depression (now present for >6 months).

School intervention: Handover to the school counselor was completed to ensure that Mona received support at school and that the counselor checked in on her progress and ongoing health and well-being.

Following the admission, Mona and her family took the program home (relapse prevention). It included the following: maintaining a regular pleasurable exercise; ongoing psychotherapy to address the multiple issues identified; treatment with an antidepressant for a 2-year period while Mona's capacity to manage stress was bolstered; and management of family stress levels—including the sister's mental health issues—by Mona's parents and the family as a whole.

9 Clinical Pearls/Key Points

- Functional neurological (conversion) disorder (FND) is a common neuropsychiatric disorder seen in pediatric clinical practice.
- FND has characteristic neurological features: symptom variability over time/context; symptom variability with attention and distraction; and incongruence with organic patterns of presentation.
- The diagnosis of FND—except for functional seizures—is a clinical one based on rule-in (positive) physical signs elicited during a neurological examination.
- The clinical diagnosis of functional seizures is best performed by a neurologist—on clinical history, witnesses' accounts and descriptions, and home videos—with video electroencephalogram (vEEG) as the gold standard of assessment.
- Provision of a positive FND diagnosis, explanation of the diagnosis, and use of respectful language devoid of outdated preconceptions support the therapeutic process and the acceptance of the diagnosis by the child and the family.
- Treatment of FND is multidisciplinary and typically includes physiotherapy, psychological therapy with the child and family, and intervention with the school. Outcomes are excellent.
- As the stress of life in contemporary society increases for children and adolescents—with, for example, mounting academic, social (including social media), environmental (climate change), and political pressures—the incidence of FND (and other functional disorders) is likely to increase.

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References

1. Shephard B. A war of nerves: soldiers and psychiatrists in the twentieth century. Cambridge, Mass: Harvard University Press; 2001.
2. Ani C, Reading R, Lynn R, Forlee S, Garralda E. Incidence and 12-month outcome of non-transient childhood conversion disorder in the UK and Ireland. Br J Psychiatry. 2013;202:413–8.
3. Kozlowska K, Nunn KP, Rose D, Morris A, Ouvrier RA, Varghese J. Conversion disorder in Australian pediatric practice. J Am Acad Child Adolesc Psychiatry. 2007;46(1):68–75.
4. Briquet P. Traité clinique et thérapeutique de l'hystérie [Clinical and therapeutic treatise on hysteria]. Paris: J-B Baillière et Fils; 1859.

5. Watson C, Sivaswamy L, Agarwal R, Du W, Agarwal R. Functional neurologic symptom disorder in children: clinical features, diagnostic investigations, and outcomes at a tertiary care children's hospital. J Child Neurol. 2019;34(6):325–31.
6. Wiggins A, Court A, Sawyer SM. Somatic symptom and related disorders in a tertiary paediatric hospital: prevalence, reach and complexity. Eur J Pediatr. 2021;180(4):1267–75.
7. Rinaldi M, Ilzarbe D, Kyriakopoulos M. Hospital admission for severe Pediatric dissociative disorder. J Nerv Ment Dis. 2019;207(5):406–9.
8. Szabo L, Siegler Z, Zubek L, Liptai Z, Korhegyi I, Bansagi B, et al. A detailed semiologic analysis of childhood psychogenic nonepileptic seizures. Epilepsia. 2012;53(3):565–70.
9. Dhiman V, Sinha S, Rawat VS, Vijaysagar KJ, Thippeswamy H, Srinath S, et al. Children with psychogenic non-epileptic seizures (PNES): a detailed semiologic analysis and modified new classification. Brain and Development. 2014;36(4):287–93.
10. Kutluay E, Selwa L, Minecan D, Edwards J, Beydoun A. Nonepileptic paroxysmal events in a pediatric population. Epilepsy Behav. 2010;17(2):272–5.
11. American Psychiatric Association. Diagnostic and statistical manual of mental disorders : DSM-5. 4th ed. Washington, DC: American Psychiatric Association; 2013.
12. World Health Organization. International statistical classification of diseases and related health problems, 11th revision (ICD-11). Geneva: World Health Organization; 2018. https://icd.who.int/en.
13. Kozlowska K, Scher S, Williams LM. Patterns of emotional-cognitive functioning in pediatric conversion patients: implications for the conceptualization of conversion disorders. Psychosom Med. 2011;73(9):775–88.
14. Yang T, et al. "Childhood trauma in patients with epileptic versus non-epileptic seizures." MedRxiv. 2022.
15. Kozlowska K, Scher S, Helgeland H. Functional somatic symptoms in children and adolescents: the stress-system approach to assessment and treatment. London: Palgrave Macmillan; 2020.
16. Kozlowska K, Sawchuk T, Waugh JL, Helgeland H, Baker J, Scher S, et al. Changing the culture of care for children and adolescents with functional neurological disorder. Epilepsy Behav Rep. 2021;16:1004486.
17. Kozlowska K, Rampersad R, Cruz C, Shah U, Chudleigh C, Soe S, et al. The respiratory control of carbon dioxide in children and adolescents referred for treatment of psychogenic non-epileptic seizures. Eur Child Adolesc Psychiatry. 2017;26(10):1207–17.
18. Vassilopoulos A, Mohammad S, Dure L, Kozlowska K, Fobian AD. Treatment approaches for functional neurological disorders in children. Curr Treat Options Neurol. 2022;24:77–97.
19. Edwards MJ, Adams RA, Brown H, Parees I, Friston KJ. A Bayesian account of 'hysteria'. Brain. 2012;135(Pt 11):3495–512.
20. Han VX, Kozlowska K, Kothur K, Lorentzos M, Wong WK, Mohabmmad SS, et al. Rapid onset functional tic- like behaviours in children and adolescents during COVID-19: clinical features, assessment, and biopsychosocial treatment approach. J Paediatr Child Health. under review.
21. Sawchuk T, Buchhalter J, Senft B. Psychogenic nonepileptic seizures in children-prospective validation of a clinical care pathway & risk factors for treatment outcome. Epilepsy Behav. 2020;105:106971.
22. Kozlowska K, Gray N, Scher S, Savage B. Psychologically informed physiotherapy as part of a multidisciplinary rehabilitation program for children and adolescents with functional neurological disorder: physical and mental health outcomes. J Paediatr Child Health. 2020;
23. Fobian AD, Long DM, Szaflarski JP. Retraining and control therapy for pediatric psychogenic non-epileptic seizures. Ann Clin Transl Neurol. 2020;
24. Asadi-Pooya AA, Brigo F, Kozlowska K, Perez DL, Pretorius C, Sawchuk T, et al. Social aspects of life in patients with functional seizures: closing the gap in the biopsychosocial formulation. Epilepsy Behav. 2021;117:107903.
25. Stephen CD, Fung V, Lungu CI, Espay AJ. Assessment of emergency department and inpatient use and costs in adult and Pediatric functional neurological disorders. JAMA Neurol. 2021;78(1):88–101.

26. Engel GL. The need for a new medical model: a challenge for biomedicine. Science. 1977;196(4286):129–36.
27. Sameroff AJ. A dialectic integration of development for the study of psychopathology. Boston, MA: Springer US; 2014. p. 25–43.
28. Spagnolo PA, Norato G, Maurer CW, Goldman D, Hodgkinson C, Horovitz S, et al. Effects of TPH2 gene variation and childhood trauma on the clinical and circuit-level phenotype of functional movement disorders. J Neurol Neurosurg Psychiatry. 2020;91(8):814–21.
29. Diez I, Larson AG, Nakhate V, Dunn EC, Fricchione GL, Nicholson TR, et al. Early-life trauma endophenotypes and brain circuit-gene expression relationships in functional neurological (conversion) disorder. Mol Psychiatry. 2020;
30. Voon V, Brezing C, Gallea C, Hallett M. Aberrant supplementary motor complex and limbic activity during motor preparation in motor conversion disorder. Mov Disord. 2011;26(13):2396–403.
31. Kozlowska K, Palmer DM, Brown KJ, McLean L, Scher S, Gevirtz R, et al. Reduction of autonomic regulation in children and adolescents with conversion disorders. Psychosom Med. 2015;77(4):356–70.
32. Kozlowska K. A stress-system model for functional neurological symptoms. J Neurol Sci. 2017;383:151–2.
33. Radmanesh M, Jalili M, Kozlowska K. Activation of functional brain networks in children and adolescents with psychogenic non-epileptic seizures. Front Hum Neurosci. 2020;14:339.
34. Baek K, Donamayor N, Morris LS, Strelchuk D, Mitchell S, Mikheenko Y, et al. Impaired awareness of motor intention in functional neurological disorder: implications for voluntary and functional movement. Psychol Med. 2017;47(9):1624–36.
35. Lin D, Castro P, Edwards A, Sekar A, Edwards MJ, Coebergh J, et al. Dissociated motor learning and de-adaptation in patients with functional gait disorders. Brain. 2020;143(8):2594–606.
36. Voon V, Gallea C, Hattori N, Bruno M, Ekanayake V, Hallett M. The involuntary nature of conversion disorder. Neurology. 2010;74(3):223–8.
37. Perez DL, Edwards MJ, Nielsen G, Kozlowska K, Hallett M, LaFrance WC Jr. Decade of progress in motor functional neurological disorder: continuing the momentum. J Neurol Neurosurg Psychiatry. 2021;16:668–77.
38. Stone J, Smyth R, Carson A, Lewis S, Prescott R, Warlow C, et al. Systematic review of misdiagnosis of conversion symptoms and "hysteria". BMJ. 2005;331(7523):989.
39. Hallett M, Stone J, Carson A. Functional neurologic disorders. Cambridge, MA: Elsevier Ch .Aminoff MJ, Boller F, Swaab DF, editors. Netherlands: Elsevier Health Sciences; 2016.
40. Perez DL, Aybek S, Popkirov S, Kozlowska K, Stephen CD, Anderson J, et al. A review and expert opinion on the neuropsychiatric assessment of motor functional neurological disorders. J Neuropsychiatry Clin Neurosci. 2021;33(1):14–26.
41. Peris A, Telarovic S. On differences between Gilles de la Tourette syndrome and psychogenic/functional tics: A narrative review. Psychiatr Danub. 2019;31(Suppl 5):732–6.
42. Espay AJ, Aybek S, Carson A, Edwards MJ, Goldstein LH, Hallett M, et al. Current concepts in diagnosis and treatment of functional neurological disorders. JAMA Neurol. 2018;75(9):1132–41.
43. Gimenez-Roldan S, Aubert G. Hysterical chorea: report of an outbreak and movie documentation by Arthur van Gehuchten (1861-1914). Mov Disord. 2007;22(8):1071–6.
44. Schrag A, Trimble M, Quinn N, Bhatia K. The syndrome of fixed dystonia: an evaluation of 103 patients. Brain. 2004;127(Pt 10):2360–72.
45. Frucht L, Perez DL, Callahan J, MacLean J, Song PC, Sharma N, et al. Functional dystonia: differentiation from primary dystonia and multidisciplinary treatments. Front Neurol. 2020;11:605262.
46. Parodi M, Rouillon I, Rebours C, Denoyelle F, Loundon N. Childhood psychogenic hearing loss: identification and diagnosis. Eur Ann Otorhinolaryngol Head Neck Dis. 2017;134(6):415–8.
47. Stone J, Sharpe M. Hoover's sign. Pract Neurol. https://www.pnbmjcom/content/practneurol/1/1/50fullpdf. 2001;
48. Carson A, Lehn A, Ludwig L, Stone J. Explaining functional disorders in the neurology clinic: a photo story. Pract Neurol. 2015;16:56–61.

49. Stone J. Functional neurological disorders: the neurological assessment as treatment. Neurophysiol Clin. 2014;44(4):363–73.
50. Ricci L, Boscarino M, Assenza G, Tombini M, Lanzone J, Di Lazzaro V, et al. Clinical utility of home videos for diagnosing epileptic seizures: a systematic review and practical recommendations for optimal and safe recording. Neurol Sci. 2021;42(4):1301–9.
51. MacDonald T, Hill A, Phan T, Fitzgerald P, Seneviratne U. Psychiatry versus general physicians: who is better at differentiating epileptic from psychogenic non-epileptic seizures? Australas Psychiatry. 2012;20(5):379–83.
52. Khachane Y, Kozlowska K, Savage B, McClure G, Butler G, Gray N, et al. Twisted in pain: the multidisciplinary treatment approach to functional dystonia. Harv Rev Psychiatry. 2019;27(6):359–81.
53. Lehnen N, Schroder L, Henningsen P, Glasauer S, Ramaioli C. Deficient head motor control in functional dizziness: experimental evidence of central sensory-motor dysfunction in persistent physical symptoms. Prog Brain Res. 2019;249:385–400.
54. Chudleigh C, Savage B, Cruz C, Lim M, McClure G, Palmer DM, et al. Use of respiratory rates and heart rate variability in the assessment and treatment of children and adolescents with functional somatic symptoms. Clin Child Psychol Psychiatry. 2019;24(1):29–39.
55. Baker J, Barnett C, Cavalli L, Dietrich M, Dixon L, Duffy JR, et al. Management of functional communication, swallowing, cough and related disorders: consensus recommendations for speech and language therapy. J Neurol Neurosurg Psychiatry. 2021;
56. Alluri PR, Solit J, Leveroni CL, Goldberg K, Vehar JV, Pollak LE, et al. Cognitive complaints in motor functional neurological (conversion) disorders: a focused review and clinical perspective. Cogn Behav Neurol. 2020;33(2):77–89.
57. Braun M, Sawchuk T, Simpkins A, Heer N, Johnson J, Esser M, et al. Quantitative EEG during hyperventilation as a biomarker for Pediatric psychogenic non-epileptic seizures (PNES). Poster session presented at the annual meeting of the American Epilepsy Society, Chicago; 2021.
58. Ali S, Jabeen S, Arain A, Wassef T, Ibrahim A. How to use your clinical judgment to screen for and diagnose psychogenic nonepileptic seizures without video electroencephalogram. Innov Clin Neurosci. 2011;8:36–42.
59. LaFaver K, Lang AE, Stone J, Morgante F, Edwards M, Lidstone S, et al. Opinions and clinical practices related to diagnosing and managing functional (psychogenic) movement disorders: changes in the last decade. Eur J Neurol. 2020;27(6):975–84.
60. Howard L, Wessely S, Leese M, Page L, McCrone P, Husain K, et al. Are investigations anxiolytic or anxiogenic? A randomised controlled trial of neuroimaging to provide reassurance in chronic daily headache. J Neurol Neurosurg Psychiatry. 2005;76(11):1558–64.
61. Petrie KJ, Muller JT, Schirmbeck F, Donkin L, Broadbent E, Ellis CJ, et al. Effect of providing information about normal test results on patients' reassurance: randomised controlled trial. BMJ. 2007;334(7589):352.
62. Canavese C, Ciano C, Zibordi F, Zorzi G, Cavallera V, Nardocci N. Phenomenology of psychogenic movement disorders in children. Mov Disord. 2012;27(9):1153–7.
63. Canavese C, Ciano C, Zorzi G, Zibordi F, Costa C, Nardocci N. Polymyography in the diagnosis of childhood onset movement disorders. Eur J Paediatr Neurol. 2008;12(6):480–3.
64. Sawchuk T, Buchhalter J, Senft B. Psychogenic non-epileptic seizures in children—psychophysiology & dissociative characteristics. Psychiatry Res. 2020;294:113544.
65. Paredes-Echeverri S, Maggio J, Begue I, Pick S, Nicholson TR, Perez DL. Autonomic, endocrine, and inflammation profiles in functional neurological disorder: A Systematic Review and Meta-Analysis. J Neuropsychiatry Clin Neurosci. 2022;34:30–43.
66. Fleming S, Thompson M, Stevens R, Heneghan C, Pluddemann A, Maconochie I, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet. 2011;377(9770):1011–8.
67. Wallis LA, Healy M, Undy MB, Maconochie I. Age related reference ranges for respiration rate and heart rate from 4 to 16 years. Arch Dis Child. 2005;90(11):1117–21.

68. Kozlowska K, Chudleigh C, Cruz C, Lim M, McClure G, Savage B, et al. Psychogenic non-epileptic seizures in children and adolescents: part II—explanations to families, treatment, and group outcomes. Clin Child Psychol Psychiatry. 2018;23(1):160–76.
69. Wells R, Spurrier AJ, Linz D, Gallagher C, Mahajan R, Sanders P, et al. Postural tachycardia syndrome: current perspectives. Vasc Health Risk Manag. 2018;14:1–11.
70. Stewart JM. Update on the theory and management of orthostatic intolerance and related syndromes in adolescents and children. Expert Rev Cardiovasc Ther. 2012;10(11):1387–99.
71. Robinson S, Woods M, Cardona F, Baglioni V, Hedderly T. Intense imagery movements: a common and distinct paediatric subgroup of motor stereotypies. Dev Med Child Neurol. 2014;56(12):1212–8.
72. Robinson S, Woods M, Cardona F, Hedderly T. Intense imagery movements (IIM): more to motor stereotypies than meets the eye. Eur J Paediatr Neurol. 2016;20(1):61–8.
73. Bass C, Halligan P. Factitious disorders and malingering: challenges for clinical assessment and management. Lancet. 2014;383(9926):1422–32.
74. Rai S, Foster S, Griffiths KR, Breukelaar IA, Kozlowska K, Korgaonkar MS. Altered resting-state neural networks in children and adolescents with functional neurological disorder. Neuroimage Clin. 2022;35:103110.
75. Gordon C, Riess H, Waldinger RJ. The formulation as a collaborative conversation. Harv Rev Psychiatry. 2005;13(2):112–23.
76. Winters NC, Hanson G, Stoyanova V. The case formulation in child and adolescent psychiatry. Child Adolesc Psychiatr Clin N Am. 2007;16(1):111–32, ix.
77. Henderson S, Martin A. Case formulation and integration of information in child and adolescent mental health. In: Rey JM, editor. IACAPAP e-textbook of child and adolescent mental health. Geneva: International Association for Child and Adolescent Psychiatry and Allied Professions; 2014. https://iacapap.org/content/uploads/A.10-CASE-FORMULATION-2014.pdf.
78. Kozlowska K, English M, Savage B. Connecting body and mind: The first interview with somatizing patients and their families. Clin Child Psychol Psychiatry. 2013;18(2):223–45.
79. Chandra P, Kozlowska K, Cruz C, Baslet GC, Perez DL, Garralda ME. Hyperventilation-induced non-epileptic seizures in an adolescent boy with Pediatric medical traumatic stress. Harv Rev Psychiatry. 2017;25(4):180–90.
80. Savage B, Chudleigh C, Hawkes C, Scher S, Kozlowska K. Treatment of functional seizures in children and adolescents: A mind-body manual for health professionals: Australian Academic Press; in press.
81. Garralda ME, Rask CU. Somatoform and related disorders. In: Thapar A, Pine DS, Leckman JF, Scott S, Snowling MJ, Taylor E, editors. Rutter's child and adolescent psychiatry. 6th ed. Chichester, West Sussex; Ames: Wiley: John Wiley & Sons; 2015. p. 1035–54. https://onlinelibrary-wiley-com.ezp-prod1.hul.harvard.edu/doi/pdf/10.02/9781118381953.ch72.
82. Gray N, Savage B, Scher S, Kozlowska K. Psychologically informed physical therapy for children and adolescents with functional neurological symptoms: the wellness approach. J Neuropsychiatry Clin Neurosci. 2020;32(4):389–95.
83. Kim Y-N, Gray N, Jones A, Scher S, Kozlowska K. The role of physiotherapy in the management of functional neurological disorder in children and adolescents. Semin Pediatr Neurol. 2021:100947.
84. Kozlowska K. Management considerations for pediatric FMD. In: LaFaver K, Maurer C, Perez DL, Nicholson TRJ, editors. Functional movement disorders: an interdisciplinary case-based approach. Springer; forthcoming 2020:433–50.
85. Butz C, Iske C, Truba N, Trott K. Treatment of functional gait abnormality in a rehabilitation setting: emphasizing the physical interventions for treating the whole child. Innov Clin Neurosci (ICNS). 2019;16(7–8):18–21.
86. Kozlowska K, English M, Savage B, Chudleigh C. Multimodal rehabilitation: a mind-body, family-based intervention for children and adolescents impaired by medically unexplained symptoms. Part 1: the program. Am J Fam Ther. 2012;40(5):399–419.

Neurodiagnostic Studies in Children

Kallol K. Set and Deepak M. Kamat

1 Introduction

Several pediatric neurological disorders can be diagnosed at the end of gathering a thorough medical history along with careful physical examination. However, there are some situations wherein laboratory and imaging studies are necessary to establish a specific diagnosis and implement an appropriate therapeutic strategy. Over the last few decades, significant advancement has occurred in the field of neurodiagnostic studies. Commonly available neurodiagnostic investigations include cerebrospinal fluid (CSF) analysis, antibody tests, ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), electro-encephalogram (EEG), evoked potentials (EPs), nerve conduction studies (NCSs), and electro-myography (EMG). Specifically, over the last few years, antibody tests are widely used to diagnose autoimmune conditions affecting the nervous system. Sometime it becomes difficult to decide which test(s) to order in a particular situation. In this chapter, we will discuss each of the studies mentioned above with respect to their indications, contraindications, and interpretation, which might help the pediatrician choose the appropriate investigation for children with neurological symptoms.

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2 Analysis of CSF

In this section, we will review the indications and contraindications for lumbar puncture (LP), and the fundamentals of CSF analysis in the evaluation of neurological disorders.

CSF is secreted by the richly vascularized choroid plexus, which appear as villous invaginations in the walls of the lateral, third, and fourth ventricles. The total CSF volume ranges from 50 mL in term neonates to 150 mL in adults and undergoes complete replacement 3–4 times each day. From the lateral ventricles, CSF passes through the foramen of Monro into the third ventricle and, subsequently, through the aqueduct of Sylvius into the fourth ventricle. Through the lateral foramina of Luschka and the medial foramen of Magendie, CSF leaves the ventricular system. It flows downward posterior to the spinal cord, and then upward anterior to the cord, to reach the brain convexity to be absorbed into venous sinuses across the arachnoid villi. In the normal state, CSF absorption is equal to its production.

2.1 Indications for CSF Analysis

CSF analysis is indicated in suspected intracranial hypertension as in idiopathic intracranial hypertension (IIH). Other indications include infections of the central nervous system (CNS) such as meningitis and encephalitis. Subarachnoid hemorrhage, leptomeningeal carcinomatosis, neurometabolic disorders, pediatric neurotransmitter diseases, Guillain–Barré syndrome, and demyelinating disorders of the CNS such as acute disseminated encephalomyelitis (ADEM) are other conditions in which spinal fluid analysis is critical.

2.2 Contraindications to CSF Sampling

1. Cellulitis of the lower back
2. Clinical signs of raised intracranial pressure with progressive deterioration in the Glasgow Coma Scale (GCS) and other focal neurological signs such as unilateral pupillary dilatation, impaired upward gaze, respiratory irregularity, and fluctuations in blood pressure and pulse rate. These symptoms may place the child at increased risk of cerebral herniation following the lumbar puncture.
3. The following abnormalities on imaging studies:
   (a) Mass lesion
   (b) Lateral shift of midline structures
   (c) Loss of the suprachiasmatic or basal cisterns

(d) Obliteration of the fourth ventricle or quadrigeminal cistern
(e) Sinus venous thrombosis

4. Children with cyanotic congenital heart disease who are suspected to have meningitis. They will require neuroimaging prior to LP due to the possibility of a cerebral abscess. Even after normal imaging, herniation has been reported in rare instances [1]. When meningitis is suspected, especially in the setting of meningococcal infection, antibiotic administration should not be delayed to obtain imaging studies [2]. If an LP is contraindicated, then blood culture and polymerase chain reaction (PCR) tests should be performed and antibiotics should be started empirically.
5. Children who have a low platelet count and coagulation disorders. In order to proceed with a lumbar puncture, ideally, the platelet count should be greater than 10,000/mm^3 and the international normalized ratio (INR) should be less than 1.5. In addition, anticoagulation therapy should probably be delayed for at least 2 h after an LP [3].

2.3 Procedure

Younger children may require moderate or deep sedation, but anxiolytics and local anesthesia may be sufficient for older children [4]. Imaging guided LP may be needed for individuals with lumbar spine defect such as spina bifida and scoliosis. Placing the patient at a proper height with the patient's back lying close to the edge of the bed and proper positioning of the clinician is important to successfully perform the procedure. A curled-up position of the patient increases the size of the intervertebral space [4].

The L3–4 interspace is used to avoid damage to the conus and is found at the level of the superior iliac crests in the lateral recumbent position. Careful palpation of the space and marking of landmarks with a marker pen are important. Using eutectic mixture of local anesthetics (EMLA), which is a 5% emulsion of lidocaine and prilocaine, 20–30 min before the procedure or injection of 1% solution of lidocaine is helpful to reduce the discomfort associated with the procedure.

After cleaning the area with 10% povidone-iodine solution, drying and draping, a 2.5 or 5 cm long, 20- or 22-gauge spinal needle fitted with a stylet is introduced. The needle is slowly advanced through the ligamentum flavum and dura, with the beveled end facing up, into the subarachnoid space. The stylet is then withdrawan to allow CSF to flow. If there is no flow, then the needle is rotated a quarter turn and/or advanced a few millimeters more. If there is still no CSF, then reintroduce the stylet, slowly withdraw, and redirect the needle in the same space or the space above [5].

A stopcock and manometer is used to measure the opening pressure with the child relaxed and in the lateral decubitus position. Opening pressures from 120 to

200 mm of water are normal. In older children, CSF pressure of 250 mm of water may be considered normal as in obese adults [6]. In adults, <60 mm of water CSF opening pressure is considered to be intracranial hypotension. In a young child who is in the lateral recumbent position, normal CSF pressures range from 50 to 200 mm of water when the neck and legs are extended but can rise to 100–280 mm of water when the neck and legs are flexed. Normal pressures in newborns vary between 90 and 120 mm of water [7]. Opening pressures >280 mm of water in children and adolescents without sedation and > 250 mm of water in children who are sedated and obese are diagnostic of IIH [8]. First three tubes require 1–2 mL each for Gram stain, bacterial culture, cell count and differential, and glucose and protein concentrations. Two mL should be collected in a fourth tube to aid in the identification of subarachnoid hemorrhage or special microbiological, immunological, or metabolic tests. Additional tubes or another 5 ml of CSF may be useful for testing of suspected autoimmune encephalitis or demyelinating diseases. The tubes of CSF should be sent to the laboratory quickly to prevent lysis of white blood cells (WBCs) at room temperature. The stylet should be reintroduced before withdrawing the needle to prevent CSF leakage and post-spinal headache, which are the most common sequelae [9]. Treatment options for post-spinal headache include bed rest, fluid intake, an epidural blood patch or fibrin glue or surgical repair of the leakage [10].

Other rare complications include infection (meningitis, epidural abscess, and osteomyelitis) and hematoma (subarachnoid, subdural, epidural) of the spinal cord and/or brain.

2.4 CSF Analysis

Normal CSF is clear and colorless. Xanthochromia, a yellowish discoloration of CSF, results from the presence of oxyhemoglobin, bilirubin, and methemoglobin produced from red blood cells (RBCs). A small number of RBCs can be found in the fluid of normal older children, and higher numbers (a mean of 120/mm^3) can be found in normal newborns. Extremely high numbers of RBCs are seen in a subarachnoid hemorrhage or in a traumatic LP. In a traumatic LP, a formula commonly used for the correction of the WBC count is that there should not be more than 1 white blood cell/mm^3 (CSF) for every 700 red blood cells/mm^3 (CSF).

Normally, white blood cells (WBCs) in the CSF contain lymphocytes (70%) and monocytes (30%). An elevated WBC count or more than a few polymorphonuclear (PMN) cells in CSF may indicate an inflammation or infection. The presence of neoplastic cells, plasma cells, stem cells, and eosinophils in CSF is abnormal. The normal count of WBCs in the CSF varies according to age. In neonates, the normal count ranges between 0–10, gradually decreasing to 0–5 at 1 year of age, and, in older children, it varies from 0 to 4 [11, 12].

Normal CSF glucose concentrations range between 45 and 80 mg/dL or approximately two-thirds of the plasma glucose concentration. A CSF glucose concentration below 40 mg/dL (i.e., hypoglycorrhachia) or less than two-thirds of the plasma glucose level is considered abnormal.

The normal total protein content of CSF varies with age. It is the highest at birth (60–100 mg/dL) and gradually decreases over the first year of life to reach 14–20 mg/dL at the age of 1 year. The value gradually increases up to 24 mg/dL at 13 years of age to reach its adult value [13].

2.4.1 Abnormal CSF (Table 1)

Acute Bacterial Meningitis

Bacterial meningitis is suspected when there are high opening and closing pressures, a cloudy or turbid appearance of CSF, and pleocytosis with polymorphonuclear leukocytosis, diminished glucose concentration, and elevated protein and lactate levels. The pathogenic organism is identified by a polymerase chain reaction (PCR) test, a rapid antigen detection test, or culture of CSF. Gram stain and acid-fast stain should be performed on all samples. Blood cultures performed at the time of admission are positive in 80–90% of cases of bacterial meningitis [14]. A serum procalcitonin level greater than 0.5 ng/mL may be a sensitive and specific predictor of bacterial meningitis [15].

Chronic Bacterial Meningitis

Chronic bacterial meningitis includes tuberculosis, Lyme borreliosis, neurosyphilis, and leptospirosis. The CSF opening pressure is usually elevated with a WBC count of more than 500 cells/mm^3 with a predominance of lymphocytes. The protein content is elevated, and glucose concentration is usually diminished. Growth of *Mycobacterium tuberculosis* in culture and detection of the *M. tuberculosis* genome

Table 1 CSF characteristics in different CNS infections

	Viral	Bacterial	Mycobacterial	Fungal
Cell count	Normal to high	High to very high	High to very high	Normal to very high
Cell type	Lymphocytosis	Polymorphonuclear leukocytosis	Lymphocytosis	Mixed
Protein	Normal to high	High to very high	Normal to very high	Normal to very high
Glucose	Normal to high	Low to very low	Normal to low	Normal to low

in CSF confirm the diagnosis of tuberculous meningitis [16]. Increased cell counts (mostly mononuclear cells), elevated protein, and a positive Venereal Disease Research Laboratory (VDRL) test on CSF are indicative of syphilis. CSF lymphocytic pleocytosis, increased protein, increased immunoglobulin (Ig)M, IgG, and IgA, direct demonstration of spirochetes in CSF, and a PCR test may help diagnose Lyme disease.

Encephalitis

Acute Viral Encephalitis

Approximately 100 species of viruses have been found to be directly or indirectly associated with neurological disorders (Table 2) [17]. Several viruses can cause encephalitis in children, which may present with seizures and altered sensorium, ranging from excessive sleepiness to coma. The CSF in viral meningitis or encephalitis shows lymphocytic pleocytosis (5–500 cells/mL), mild increase in protein concentration (usually 50–200 mg/dL), and a normal or low glucose content. Many children with herpes simplex virus (HSV)-associated encephalitis (5–15%) may initially have normal results on a CSF examination [18, 19]. Therefore, if there is clinical or radiographic suspicion that the child has HSV encephalitis, then it is preferable to continue empirical treatment and repeat CSF studies in a few days.

Table 2 Viruses causing meningoencephalitis and their transmission

Virus causing meningitis/encephalitis	Transmission
Herpes simplex virus types 1 and 2	Skin and soft tissue contact, vertical
Rabies	Infected mammal contact/blood transfusion
West Nile	Mosquito, blood transfusion
Powassan	Tick
Eastern and western equine encephalitis viruses	Mosquito
St. Louis encephalitis virus	Mosquito
Lymphocytic choriomeningitis virus	Infected rodent, blood transfusion, organ transplant
Zika	Mosquito, sexual, vertical
Enterovirus	Fecal/oral
Measles, mumps, rubella	Aerosolized droplets
Cytomegalovirus	Blood, vertical, aerosol, direct contact
Varicella zoster virus	Skin and soft tissue contact
Corona (SARS-Cov-2)	Aerosolized droplets, skin contact

Immunological Disorders

Many infectious, inflammatory, and neoplastic conditions of the CNS may have increased levels of immunoglobulins, particularly IgG, in CSF. This indicates disruption of the blood–CSF barrier and an increased entry of proteins, including albumin, into the CSF. The presence of IgG in CSF is qualitatively demonstrated by oligoclonal banding and quantitatively shown using the IgG index. In normal subjects, IgG forms a monoclonal band [20]. An active humoral immune response produces more than two clonal bands. The presence of oligoclonal bands in the CSF but not in the plasma suggests an intrathecal origin of IgG. The IgG index is calculated by dividing the ratio of the CSF and plasma IgG concentrations by the ratio of the CSF and plasma albumin concentrations. CSF oligoclonal bands are found in 85% of children with multiple sclerosis (MS), and an elevated IgG index is present in 70% of patients with MS. CSF oligoclonal bands can also be seen in post-infectious encephalomyelitis such as acute disseminated encephalomyelitis (ADEM), subacute sclerosing panencephalitis (SSPE), progressive multifocal leukoencephalopathy (PML), human immunodeficiency virus encephalitis, and Lyme disease [21]. Therefore, CSF oligoclonal bands are a sensitive but not specific marker for MS.

According to the 2017 McDonald criteria for the diagnosis of multiple sclerosis (MS), CSF-specific oligoclonal bands are an independent predictor and the presence of two or more oligoclonal bands may be considered diagnostic, in the absence of MRI findings. The presence of oligoclonal bands enables the clinician to diagnose MS early on in the disease process, even during the first clinical episode [22].

The CSF WBC count is <50/mm^3 (lymphocytic predominance) in MS but may be variable in neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein (MOG-IgG) disease. Oligoclonal bands are seen in 30% of patients with NMOSD and in <15% of those with MOG-IgG disease [21].

CSF pleocytosis and/or a high protein level and/or oligoclonal bands along with specific antineuronal antibodies are found in patients with paraneoplastic autoimmune disorders. A normal CSF profile is also common in certain autoantibody (leucine-rich glioma-inactivated 1 (LGI1), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA))-related encephalitis.

Neurometabolic Disorders

Several neurometabolic disorders such as glucose transporter type 1 (GLUT1) deficiency, serine deficiency syndromes, glycine encephalopathy, cerebral folate deficiency, pyridoxine-dependent epileptic encephalopathies, and disorders of monoamine metabolism and gamma-aminobutyric acid (GABA) metabolism are diagnosed by CSF examination [23]. CSF studies include measurement of

lactate, pyruvate, 5-methyltetrahydrofolate, and amino acid for unexplained encephalopathy. Organic acid analysis of CSF is indicated when a child presents with clinical manifestations suggestive of an organic aciduria [5]. Elevated CSF interferon-alpha levels and lymphocytosis are found in a rare genetic leukoencephalopathy called Aicardi–Goutières syndrome.

3 Antibody Tests

Immune-mediated neurological disorders are an expanding group of disorders. Many of them are mediated by autoantibodies. Early recognition and institution of immunotherapy has been shown to improve the prognosis in children affected by autoimmune neurological disorders [24]. Therefore, antibody testing plays an important role in immune-mediated neurological disorders such as autoimmune encephalitis (AIE), myasthenia gravis (MG), and demyelinating diseases.

3.1 Antibody Tests for Autoimmune Encephalitis (AIE)

Antibody tests in the serum and cerebrospinal fluid (CSF) are indicated when AIE is considered in the differential diagnoses of a child presenting with acute or subacute encephalopathy. There are no contraindications to performing these studies other than contraindications to performing an LP itself, as noted earlier.

Patients with AIE express antibodies against both extracellular and intracellular antigens. Antibodies against extracellular antigens are usually pathogenic, whereas those against intracellular antigens serve as a biomarker of the disease. In children with AIE, antibodies against the *N*-methyl-D-aspartate receptor (NMDAR), myelin oligodendrocyte glycoprotein (MOG), glutamic acid decarboxylase 65 (GAD65), gamma-aminobutyric acid type A receptor (GABA AR), and gamma-aminobutyric acid type B receptor (GABA BR) 5–12 are the most tested [25]. Antibodies that are uncommonly tested are those that react with metabotropic glutamate receptor 5, dopamine-2 receptor, and glycine receptor. Some patients with typical clinical manifestations suggestive of AIE may not have any identifiable autoantibodies [25].

Even though each antibody is associated with characteristic clinical manifestations, there is significant overlap with clinical manifestations between different disorders, and, therefore, instead of ordering a single antibody test, it is recommended to order a panel of antibody tests. Some antibodies such as anti-NMDAR have higher sensitivity in CSF as compared to that in the serum, whereas the anti-MOG antibody has more sensitivity in the serum [26, 27]. Therefore, it is recommended to check these antibodies both in the serum and CSF. A definitive diagnosis of AIE can be made if CSF is positive for anti-NMDAR and anti-GAD65 antibodies, even in the absence of evidence of brain inflammation such as leukocytosis and/or the

presence of oligoclonal bands in CSF or signs of inflammation on brain MRI. In contrast, if antibodies are present only in the serum, then there should also be evidence of inflammation on CSF studies or on brain MRI to establish a diagnosis of AIE [25].

3.2 Antibody Tests in Myasthenia Gravis

Antibody studies for myasthenia gravis (MG) are indicated in any child who presents with fatigable weakness. The serum is tested for two groups of antibodies in patients with suspected MG: (1) antibodies against nicotinic acetylcholine-binding receptors (AChRs) and (2) antibodies against the muscle-specific tyrosine kinase (MuSK) and low-density lipoprotein receptor-related protein 4 (LRP4) [28]. These antibodies are directed against the antigens on the post-synaptic membrane receptor of the neuromuscular junction. AChR antibodies are positive in approximately 85% of patients with myasthenia gravis, whereas MuSK antibodies are positive in about half of the remaining, and LRP4 in a few patients with clinical features suggestive of MG [29].

3.3 Antibody Tests in Autoimmune Demyelinating Diseases

The anti-aquaporin 4 antibody (AQP4) or anti-NMO antibody may be positive in neuromyelitis optica. Myelin oligodendrocyte glycoprotein (MOG) is well-known for being the causative protein of a recently described disorder referred to as MOG-associated demyelinating disease. Antiganglioside antibodies (GM1, GD 3, GD1A, etc.) show the highest association with certain forms of Guillain–Barré syndrome and their presence is diagnostic in some situations.

4 Neuroimaging

Ultrasonography (US), two- and three-dimensional computed tomography (CT), and magnetic resonance imaging (MRI) are the mainstay of pediatric neuroimaging. Advanced techniques including diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI), diffusion tensor imaging (DTI), spectroscopy, and susceptibility-weighted imaging (SWI) can be applied while obtaining an MRI. Other modalities of imaging such as single-photon emission computed tomography (SPECT), positron emission tomography (PET), and blood oxygen level-dependent functional MRI (fMRI) are available in certain centers.

An MRI in children may require sedation or general anesthesia. An MRI of the brain is extremely useful in the evaluation of developmental anomalies, seizures,

hypoxic-ischemic injury, white matter abnormalities, sub-acute and chronic hemorrhages, tumors, and demyelinating lesions.

4.1 Cranial Ultrasound

Real-time gray-scale ultrasound is an extremely useful, portable, fast, and multiplanar imaging modality. A transducer is used to produce 3.5–10 Hz frequency pulses of non-ionizing ultrasound. A reflected sound wave or echo from an organ and tissue is represented as a dot. The gray shade of the dot depends on the depth and character of the structure. Color Doppler ultrasonography shows color-coded vascular flow and is used to detect the direction and velocity of blood flow. Prenatal and neonatal ultrasound along with CT and MRI are helpful in diagnosing developmental anomalies, intraventricular hemorrhage (IVH), and hydrocephalus [30]. Prenatal US may help detect ventriculomegaly and brain malformations. Even in the first trimester, transabdominal and endovaginal ultrasound can be used. Holoprosencephaly, schizencephaly, lissencephaly, hydrocephaly, encephalocele, Dandy–Walker malformation, spina bifida, and fetal seizures can be detected in the intrauterine period [31].

Open anterior fontanel in newborns is used for a head ultrasound, and sedation is not required. A normal brain has uniform echogenicity, and sonolucent structures in real-time sonography represent CSF and cysts. On real-time sonography, the choroid plexus, hemorrhage, tumors, and inflamed cerebrum appear bright. To evaluate intraventricular hemorrhage in premature infants who are less than 30 weeks of gestation, a head US screening is performed once between 7 and 14 days of age and is repeated between 36 and 40 weeks of post-menstrual age [32]. Ultrasound can also identify periventricular leukomalacia, encephalomalacia, ventriculomegaly, and intrauterine infections [33]. A spinal ultrasound can be used to detect myelodysplasia, spinal dysraphism, and tethering in neonates and infants [31].

4.2 Computed Tomography (CT)

A CT scan is quick, widely available for emergencies, and can be easily used in medically unstable patients for the evaluation/diagnosis of head and spine injuries, ventricular shunt malfunction, stroke, identifying the etiology of new-onset seizures, and raised intracranial pressure. A CT scan is particularly useful in detecting blood clots or bone injuries.

A few studies have suggested that the low-dose radiation used in CT scans may increase the risk of cancer in young children. Therefore, to reduce exposure to radiation, CT should be used judiciously and ultrasonography or MRI should be considered for imaging studies in children. Hypodense lesions in a CT scan represent edema, infarction, inflammation, necrosis, neoplasms, leukodystrophies, and cysts. A hypoxic-ischemic injury or a demyelinating process causes brain edema

and leads to loss of gray–white differentiation. Hyperdense lesions in a CT scan can be due to hemorrhage, calcification, or hypercellular tumors. Intracranial calcifications may be present in congenital infections, neurocysticercosis, tumors, hypoparathyroidism, tuberous sclerosis, Sturge–Weber syndrome, neurofibromatosis, Cockayne syndrome, encephalomalacia, arteriovenous malformations, vein of Galen malformations, or perinatal asphyxia [34]. A CT scan without contrast is useful for evaluation of the skull, orbits, sinuses, bones, and spine for fractures, or hemorrhages within the brain parenchyma. Subdural hemorrhage over the cerebral convexities, interhemispheric subdural space hemorrhage, hygroma with intracranial hemorrhage, and intracranial hemorrhage with the absence of a skull fracture may suggest a non-accidental trauma [35]. CT myelography and cisternography are performed by introduction of contrast material into the subarachnoid space. CT with contrast is helpful in detecting abscesses, empyema, vascular malformations, and tumors. A contrast-only CT scan may be helpful in detecting metastasis or seeding of neoplasms, especially when MRI is contraindicated in children who have implantable devices or a metallic foreign body.

4.3 Magnetic Resonance Imaging (MRI)

An MRI with multiplanar imaging and excellent resolution is the most powerful modality of neuroimaging. It has no ionizing radiation. Metallic objects produce distortion artifacts or signal void. The presence of non-MR-safe aneurysm clips, pacemakers, and implanted defibrillators are contraindications for an MRI study.

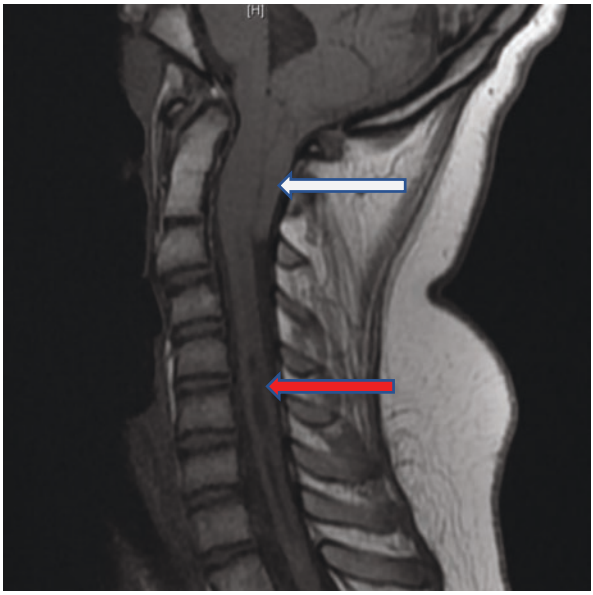

Fig. 1 11-year-old boy with Chiari 1 malformation (white arrow) and syringomyelia (red arrow) noted on Sagittal T1 sequence of the brain and spinal cord

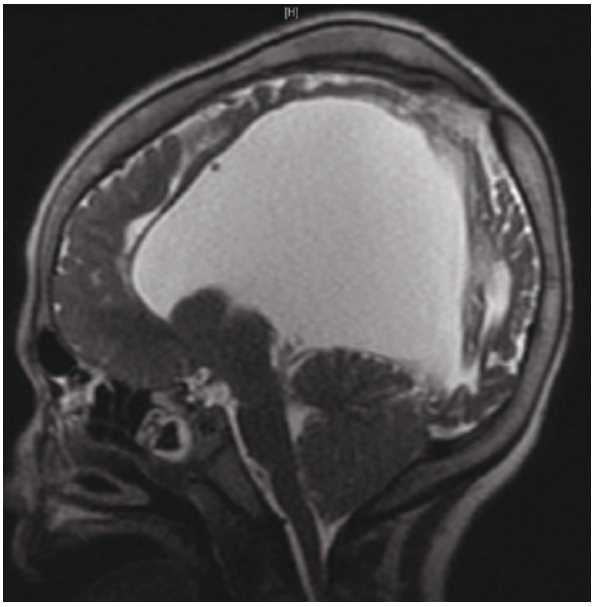

Fig. 2 Congenital hydrocephalus: Sagittal T2 sequence of the brain

Most young children require sedation or general anesthesia to prevent movement artifacts. An MRI of the brain is extremely useful in the evaluation of developmental anomalies, seizures, hypoxic-ischemic injury, white matter abnormalities, sub-acute and chronic hemorrhages, tumors, structural anomalies including malformations of the brain, post-traumatic pathology, and demyelinating lesions (Figs. 1 and 2).

An MRI is also useful in diagnosing rare diseases such as Wilson's disease (Panda sign), juvenile Huntington's disease (atrophy of the caudate), and pantothenate kinase deficiency (eye of the tiger sign). Large subdural hematomas with rapidly progressive atrophy are seen in Menkes disease [28]. Certain metabolic disorders like ethylmalonyl aciduria/encephalopathy can cause rapidly progressive brain atrophy (Fig. 9). Various leukodystrophies have specific MRI findings.

MR images are produced by sending radiofrequency pulses into an external magnetic field. Various signals are produced by unsettling hydrogen nuclei or protons.

Standard recommendations are to have diffusion-weighted imaging (DWI)/apparent diffusion coefficient (ADC), T1-weighted (gray matter gray, white matter bright, CSF dark), T2-weighted (gray matter bright, white matter dark, CSF bright), and fluid-attenuated inversion recovery (FLAIR) sequences (CSF dark). Other options include short-tau inversion recovery (STIR), gradient echo (GRE)/susceptibility-weighted imaging (SWI), and T1-weighted gadolinium sequences.

T1 and T2 are time constant. T1 is the time required for protons in a particular tissue to move back into equilibrium. T2 is the time required for transverse relaxation. T1-weighted images show anatomy and are the primary sequence used for comparison of pre- and post-contrast enhancement. T2-weighted sequences are used to show inflammation, edema, and fluid accumulation. FLAIR is a sequence

with inversion recovery, which helps nullify fluids. It can be used in brain imaging to suppress CSF effects on the image and to clearly visualize the periventricular hyperintense lesions, as in multiple sclerosis (MS).

STIR is useful for highlighting fluid or edema, while suppressing fat, and is used in imaging the spine. DWI and ADC sequences provide unique information based on the microscopic motion of water. Restricted diffusion is demonstrated when lesions are bright on DWI and dark on diffusion coefficient maps. DWI demonstrates restricted diffusion after an acute stroke, and this lasts for up to 10–14 days.

GRE or SWI sequences emphasize magnetic susceptibility and produce T2 hypointensity in microhemorrhages, calcifications, myeloid depositions, metastasis, or cavernomas.

While reviewing MRIs, a systematic approach is to first view DWI/ADC, then T2/FLAIR, and, finally, T1-weighted sequences with and without contrast. The remaining sequences are subsequently analyzed depending on the suspected pathology [36]. Some common characteristics are outlined here (although variations are common):

1. Tumors: Gadolinium-enhanced T1-weighted images may reveal interaxial or extra-axial, space-occupying lesions with or without a midline shift. T2 and FLAIR hyperintensities surrounding the lesions suggest peritumoral edema. Dark signals on SWI suggest hemorrhage or calcification. Low-grade tumors may be isointense without contrast enhancement [37] (Figs. 3, 4)
2. Acute vascular pathology, e.g., an acute ischemic stroke, demonstrates increased DWI signals with ADC reduction. If both DWI and ADC are hyperintense, then it is referred to as "T2 shine-through" and indicates chronic or subacute ischemic lesions. Hyperintense DWI but no FLAIR changes imply stroke, which has occurred less than 4.5 h earlier. GRE/SWI changes are indicative of a hemorrhage [38] (Fig. 5)
3. Hypoxic-ischemic injury, leukomalacia: MR images reveal increased DWI signals and T2 and FLAIR hyperintensities (Fig. 6)

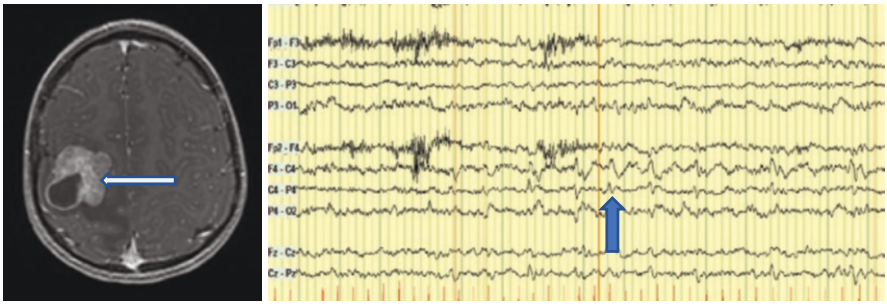

Fig. 3 3-year-old girl with solid/cystic contrast enhancing right frontal-parietal astroblastoma (white arrow on MRI image) noted on Axial T2 sequence with contrast enhancement. EEG showing rhythmic spike and slow waves (blue arrow) suggestive of focal seizure from right central-parietal region clinically characterized by left arm clonic jerking

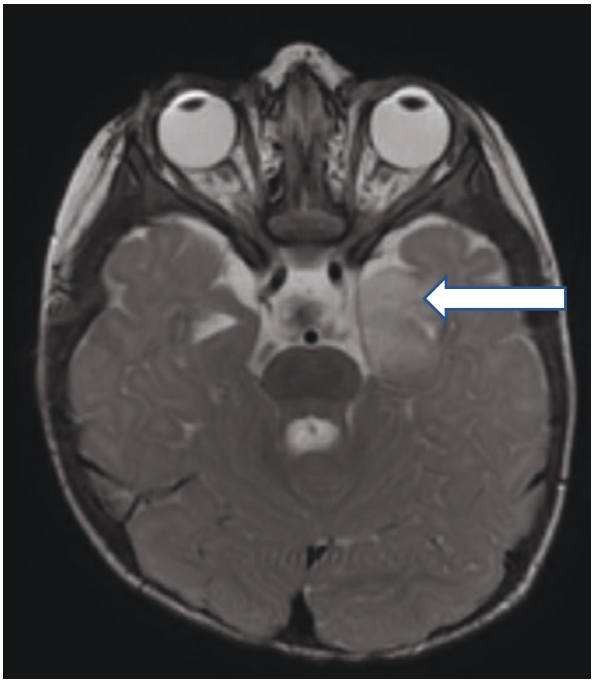

Fig. 4 MRI axial T2 sequence of a 9-month-old with new onset of left mid temporal low-grade astrocytoma (white arrow) with T2 hyperintensity without contrast enhancement

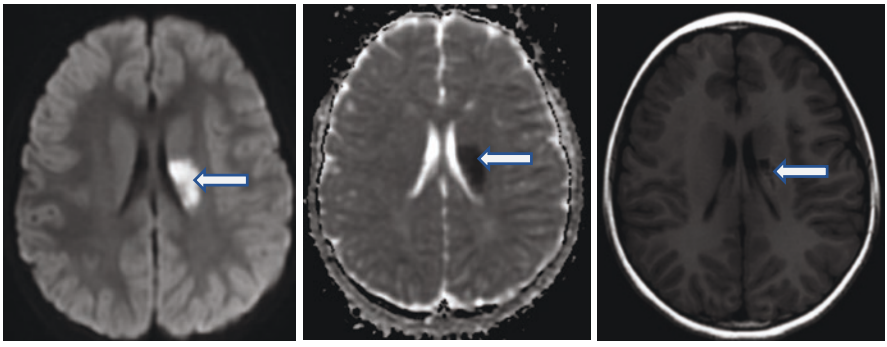

Fig. 5 Acute DWI hyperintensity and ADC hypointensity in left basal ganglia region, suggesting acute stroke in a 5-year-old girl. The lesion later turned into an area of encephalomalacia

4. Infections: swelling of the sulci and meningeal enhancement may be noted on T1 images with contrast.
5. Seizures: On a 3-Tesla MRI, areas of focal hyperintense T2 and/or FLAIR may suggest cortical dysplasia. T1 images should be analyzed to identify structural or developmental abnormalities [39]
6. Demyelinating diseases: An 1.5- or 3-Tesla MRI may show hyperintensity in DWI, T2-weighted, and/or FLAIR in the acute setting along with contrast enhancement for up to 3 weeks (not always associated with contrast enhance-

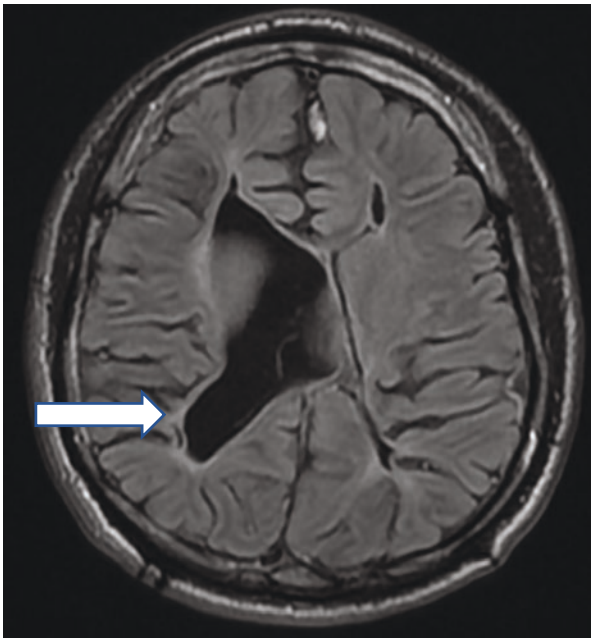

Fig. 6 Axial T1 weighted Image: Shunted right ventricular hydrocephalus with periventricular leukomalacia (white arrow) in a 15 year-old child born with extreme prematurity

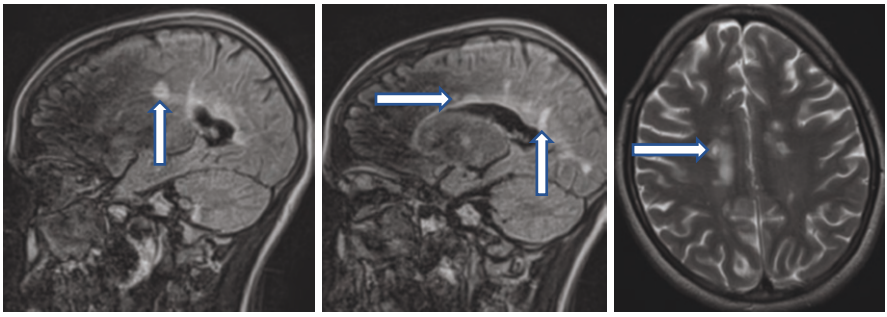

Fig. 7 T2 FLAIR hyperintensity (white arrow) in a 14-year-old girl with Multiple sclerosis. Panels 1 and 2 demonstrating lesion on sagittal images and panel 3 demonstrating lesion on axial T2 sequence. The lesions in panel 1 and 2 are classically referred to as "Dawson's fingers"

ment initially up to 2 months during which linear enhancement of the central vein alone or periventricular hyperintense signals on T2 FLAIR or T2 images are seen). T1-weighted images show hypointensity in chronic lesions [40] (Figs. 7, 8)

7. Degenerative diseases: may show focal or generalized atrophy (Fig. 9)
8. Posterior reversible encephalopathy syndrome (PRES): DWI shows hyperintensity, suggestive of a vasogenic edema [41]

The mainstay of a spinal cord image is a T2-weighted MRI. Fat-suppressed short-tau inversion recovery (STIR) images improve visualization of edemas,

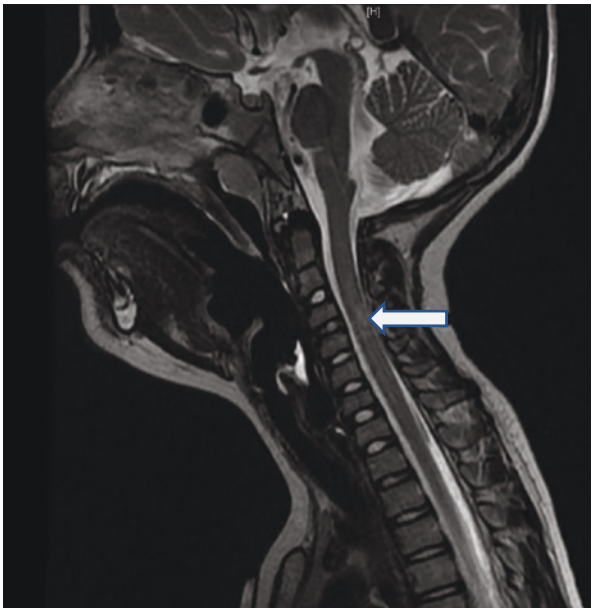

Fig. 8 Sagittal T2 sequence of the brain and spinal cord on a 5 year-old girl with T2 hyperintense (white arrow) lesion at C2-C3 level suggestive of acute cervical transverse myelitis

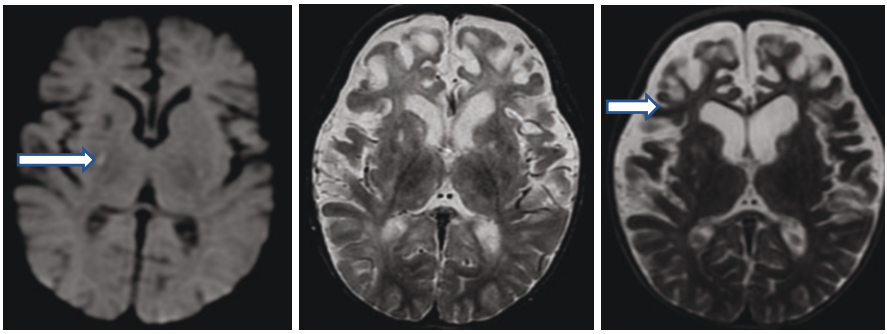

Fig. 9 Axial brain MRI at ages 3, 9, and 13 months showing multiple infarct (DWI with white arrow) and rapidly progressive atrophy in a case of metabolic disorder involving mitochondria

hemorrhages, and other pathologies. DWI images are used to check for edemas, abscesses, and tumors. DWI, T2, FLAIR, and contrast images of the spinal cord may be used to identify demyelinating diseases involving the spinal cord and nerve roots.

4.4 Magnetic Resonance Spectroscopy (MRS)

MRS (proton MRS) is a tool used to identify the biochemical state of the nervous system. It has been a useful adjunct to diagnose disorders such as neoplasms, hypoxia–ischemia, inherited metabolic diseases, traumatic brain injury, and demyelinating disorders. MRS shows peaks of neuronal metabolites such as *N*-acetyl aspartate (NAA), the glial metabolite myoinositol (mIns), choline (from the cell membrane), creatine (from neurons and glial cells), and neurotransmitters like glutamine, γ-aminobutyric acid, etc. An elevated NAA may be seen in mitochondrial disorders and Canavan disease. Gliosis produces an mIns peak. Elevated choline may be a marker of tumor and inflammation. Succinate and acetate are elevated in abscesses. A prominent lactate peak is indicative of anaerobic glycolysis and is a biomarker of several abnormalities including Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome, pyruvate dehydrogenase deficiency, and X-linked adrenoleukodystrophy.

4.5 Diffusion Tensor Imaging (DTI)

DTI derives information regarding the direction of neuronal tracts in the brain – a process called tractography. DTI is now widely used to evaluate normal brain development, response to injuries, and to detect a wide variety of neonatal and pediatric neurological conditions [42]. It is helpful in preoperative planning for resection of brain tumors and temporal lobectomy in cases of intractable epilepsy. Eloquent white matter tracts related to tumors, such as the pyramidal tracts and optic radiations, can be assessed before surgery, thereby reducing post-surgical neurological deficits [43].

Traumatic, inflammatory, and neoplastic lesions of the spinal cord may show displacement and distortion of the white matter tracts at the level of the lesions when DTI methodology is applied [44]. Diffuse axonal injury of the corticospinal tract at the subcortical level may be detected by DTI [45].

4.6 Perfusion-Weighted Imaging (PWI)

PWI, like DWI, can help in evaluating acute ischemic injury and direct precise thrombolytic therapy. Combined with spectroscopy, it may help in differentiating various types of tumors. PWI may be helpful in assessing areas of hyperperfusion, hypoperfusion, or venous congestion adjacent to arteriovenous malformations and other angiopathies [46].

4.7 Susceptibility-Weighted Imaging (SWI)

SWI is extremely useful in detecting small hemorrhagic lesions associated with diffuse axonal injury. This blood-sensitive sequence is also helpful in detecting hemorrhages related to venous thrombosis, stroke, accidental or non-accidental trauma, vascular malformation, and tumors.

4.8 Functional Magnetic Resonance Imaging (fMRI)

Functional MRI (fMRI) is used to assess brain activity or tissue perfusion in response to visual, sensorimotor, auditory, and cognitive stimulations like speech, language, and reading. It is used in preoperative assessment for epilepsy surgery or tumor resection, to lateralize language and motor functions.

4.9 Magnetoencephalography (MEG)

Magnetic fields generated by electrical currents in the cortex produce EEG and MEG signals. MEG helps localize interictal epileptic abnormality pre-surgically, when an MRI or scalp EEG are not conclusive. It can also localize the language, motor, somatosensory, visual, and auditory areas of the cortex, which is useful for planning surgical resection for epileptic foci, tumors, or other lesions.

4.10 Positron Emission Tomography (PET)

PET measures metabolic activity of cells by detecting radiation emitted from radioactive substances. 2-Deoxy-2-fluoro-D-glucose or FDG is a glucose analogue that tends to concentrate in metabolically active regions, such as tumors, infections, or areas of inflammation. FDG-PET is useful in detecting focal cortical dysplasia, identifying tubers that are epileptogenic in children with tuberous sclerosis, providing assistance in tumor grading, and estimating the extent of post-radiation necrosis.

4.11 Single-Photon Emission Computed Tomography (SPECT)

SPECT identifies increased cerebral blood flow, which may help to localize seizure foci. Usually, Tc-99 is administered during a seizure to localize the epileptogenic focus/foci.

4.12 Angiography

Cerebral angiography is one of the oldest techniques utilized to visualize lesions of blood vessels including atherosclerotic plaques, vessel narrowing, aneurysms, and arteriovenous malformations. Angiography is an invasive procedure, in which a catheter is inserted usually through the femoral artery and is pushed up to the aorta under fluoroscopy. Radiopaque iodine is injected through the catheter into the carotid and vertebral arteries on both sides, and images are captured during and after the injection. The arteries are visualized early in the study, whereas the veins are visualized later.

The availability of non-invasive procedures like Doppler ultrasound, magnetic resonance angiography (MRA), and CT angiography (CTA) has reduced the use of traditional angiography.

MRA without contrast captures the movement of protons to and out of the region. The direction and speed of flow can be detected via a computer. Sometimes gadolinium injections are used to improve contrast. Large vessels, but not the smaller and distal branches, can be seen by MRA. MRA is used to diagnose the potential sites of narrowing, thrombosis, aneurysm, dissection, or anomaly of the carotid and vertebral arteries in the head, neck, or even as they arise from the aortic arch.

Magnetic resonance venography (MRV) is used to diagnose venous sinus thrombosis.

CT angiography (CTA) reconstructed in a three-dimensional (3D) format is useful to obtain images of the blood vessels by rapid injections of intravenous contrast together with a helical CT scan. CTA can be used in those patients in whom MRI is contraindicated. It may be used to detect carotid stenosis, dissections, aneurysms, or vascular malformations.

5 Neurophysiologic Studies

Electrical activity in the brain can be spontaneous or evoked. Electro-encephalogram (EEG), evoked potentials (EPs), polysomnography, and computerized neurophysiological analyses are four neurophysiological studies that are widely used in children.

5.1 Electro-encephalogram (EEG)

According to the International 10–20 system of electrode placement, 22 silver–silver chloride electrodes are placed on the scalp. Electropotential differences between two electrode points or summated excitatory post-synaptic potentials are measured. The main sources of electrical activity that can be recorded on an EEG are derived from the cerebral cortex. Approximately 108 neurons and their

synaptic connections in a cortical area of 6 cm^2 (which may be up to 20 cm^2) are necessary to create a visible EEG [47]. An EEG cannot record activity from the base of the brain or from the sulcal depths. Therefore it can detect activity from only a small part of the brain surface. In normal conditions, both dorsal thalamic

Table 3 EEG findings in select childhood neurological conditions

Neurological condition	Common EEG patterns
1. Neonatal seizures.	Focal/diffuse rhythmic spikes and waves, lateralized periodic epileptiform discharges
2. Neonatal encephalopathy	Low voltage, burst suppression, discontinuous, lateralized, or generalized periodic epileptiform discharges
3. Focal epilepsy	Interictal lateralized focal spikes, sharps, spikes or sharp waves, ictal evolution of background frequency, amplitude, synchronization, rhythmic spikes and waves
4. Generalized epilepsy	Generalized spikes and waves, polyspikes and waves (myoclonic epilepsy), 3-Hz generalized spikes and waves (absence epilepsy), electrodecremental response (tonic seizure)
5. Epileptic spasms	Interictal hypsarrhythmia, electrodecremental response with superimposed beta (during spasm)
6. Febrile status epilepticus	Postictal focal slowing
7. Anoxic or hypoxic injury	Focal or multifocal spikes, seizures
8. Neurocutaneous syndrome	Focal or multifocal spikes or slowing, seizures
9. Acquired aphasia of childhood	Temporal or centrotemporal spikes and waves, seizures
10. Coma	Monotonous EEG pattern, burst suppression pattern
11. Brain death	Electrocortical silence
12. Tumor, abscess	Focal spikes or sharps and slow waves, seizures
13. Migraine and hemiplegia	Focal delta slowing
14. Acute measles, mumps, rubella, scarlet fever	Diffuse slowing
15. Herpes simplex encephalitis	Temporal spikes, lateralized periodic epileptiform discharges, seizures
16. Subacute sclerosing panencephalitis (SSPE)	High-voltage bilaterally symmetric periodic and synchronous bursts of polyphasic delta waves
17. Rasmussen's encephalitis	Corresponding hemispheric epileptiform discharges
18. Subdural effusion, meningitis, cerebritis	Focal slowing
19. Neuronal ceroid lipofuscinosis	High-amplitude polyspikes over the posterior head region in response to slow rates of photic stimulation
20. GM1 gangliosidosis and glycine encephalopathy	Stimulus-sensitive myoclonus with periodic or multifocal sharp waves
21. Angelman syndrome	Frontal 2–3-Hz high-amplitude rhythmic activity
22. Rett syndrome	Spikes in the central and centrotemporal regions
23. Lennox–Gastaut syndrome	Continuous slow spike and wave at 1–2.5 Hz
24. Hepatic or renal metabolic encephalopathy	Triphasic waves

and cortical regions interact to produce cortical post-synaptic potentials during wakefulness and sleep.

5.1.1 Abnormal EEG (Table 3)

Epileptiform discharges can be found in combination with slowing as an indication of a structural abnormality. Focal discharges during a seizure have better localizing value than do interictal spikes. In general, slow-growing neoplasms, such as oligodendrogliomas or astrocytomas, produce more epileptiform activity than do rapidly growing tumors [48].

Local suppression or the absence of background rhythmic activity is a strong indication of brain dysfunction, irrespective of age or location in the brain. Complete absence of activity usually implies cortical necrosis in regions that are close to the surface. The presence of symmetric suppression of frontal beta activity, central rhythms, dominant alpha activity, or sleep spindles in association with polymorphic delta waves strongly indicates a destructive process in the brain underlying those electrodes. Polymorphic delta waves commonly appear immediately after a seizure of focal onset and with reversible conditions, such as migraine [49].

In preterm neonates, asymmetric patterns, burst suppression (bursts of spikes in between suppressed background) patterns (Fig. 10), spikes, sharps, and seizures are observed depending on the age and underlying condition. Congenital or acquired brain lesions may produce neonatal seizures and lateralized brain EEG abnormality. Conventional long-term EEG or amplitude-integrated EEG (aEEG) in neonates has been used for diagnosis and prognosis. Neonates may have seizures that are not

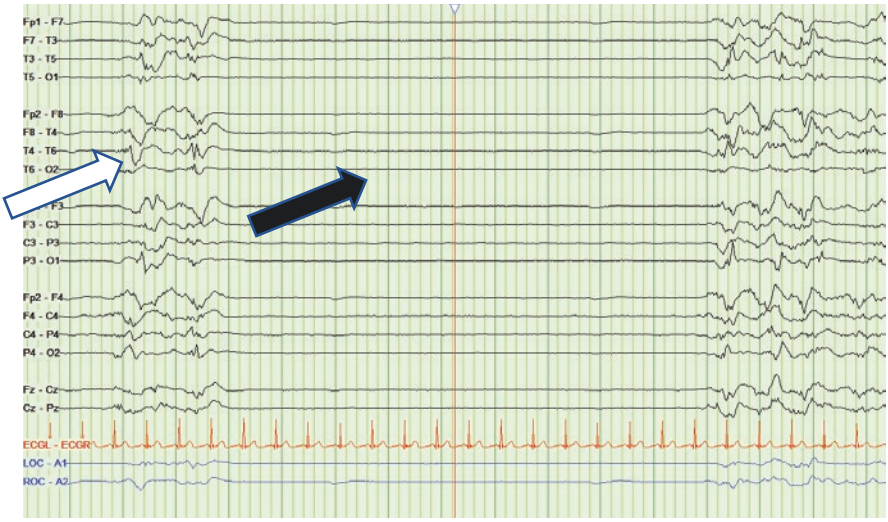

Fig. 10 Burst (white arrow) suppression (black arrow) pattern in a comatose 5-year-old child recorded on bipolar montage

detected unless an EEG is performed. The incidence of clinical seizures is 1–1.2% and that of electrographic seizures is 0.2% of live births [50].

Seizures are recognized on an EEG, by evolution of discharges in the location, amplitude, frequency waveform, or distribution for at least 10 s. There are five categories of clinical neonatal seizures: subtle, focal clonic, multifocal clonic, tonic, and myoclonic. An EEG with isoelectric, paroxysmal, and multifocal spikes or slow background patterns suggests a poor prognosis (Fig. 3).

An EEG remains the main investigation for children with epilepsy. Although interictal EEG recordings performed as early as possible after a seizure are helpful, approximately 50% of the first-routine interictal EEG may be normal. Repeated EEG recordings may increase the diagnostic yield. Epileptiform waveforms are spikes (20–70 ms), sharp waves (70–200 ms), spikes and waves, sharp and waves, and polyspikes.

During the awake state, 2.7% of normal children can exhibit epileptiform EEG activity, which may increase to 8.7% during sleep [51]. In some forms of genetic epilepsies, abnormal EEG discharges may be found in asymptomatic individuals [6]. Conversely, patients with well-documented seizures may have a normal EEG.

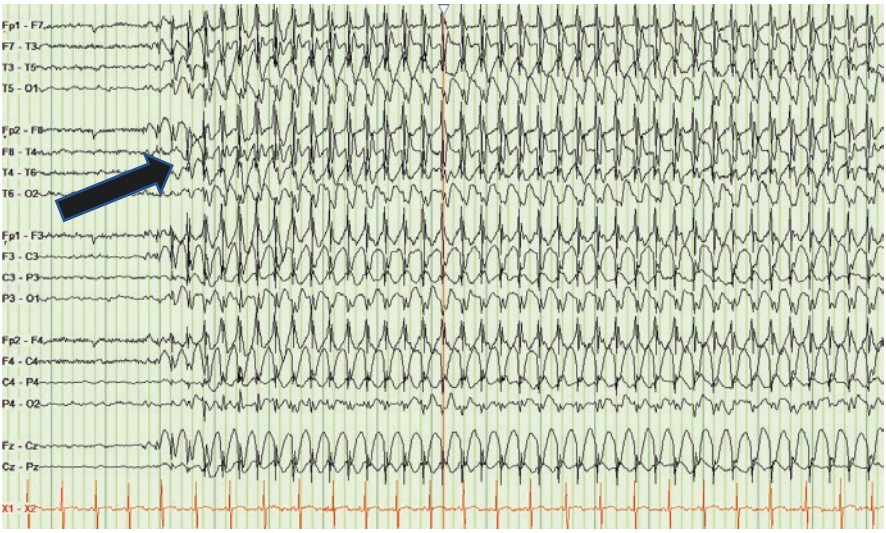

Fig. 11 3-Year-old boy with childhood absence epilepsy. EEG recording demonstrates generalized 3 Hz/s spike and wave pattern lasting more than 10 s

5.1.2 Generalized Epileptiform Discharges

Bilaterally synchronous, single, or polyspike discharges followed by slow waves are seen in generalized seizure disorders. Generalized, 3-Hz, spike-and-wave discharges are seen in the absence of epilepsy and may be induced by hyperventilation (Fig. 11). Up to 50% of adolescents with the 3-Hz, spike-and-slow-wave pattern develop generalized motor seizures. Patients can "outgrow" these discharges. A photoparoxysmal response is a spike-and-wave discharge induced by photic stimulation, which can be seen in certain generalized epilepsies and rare focal epilepsies

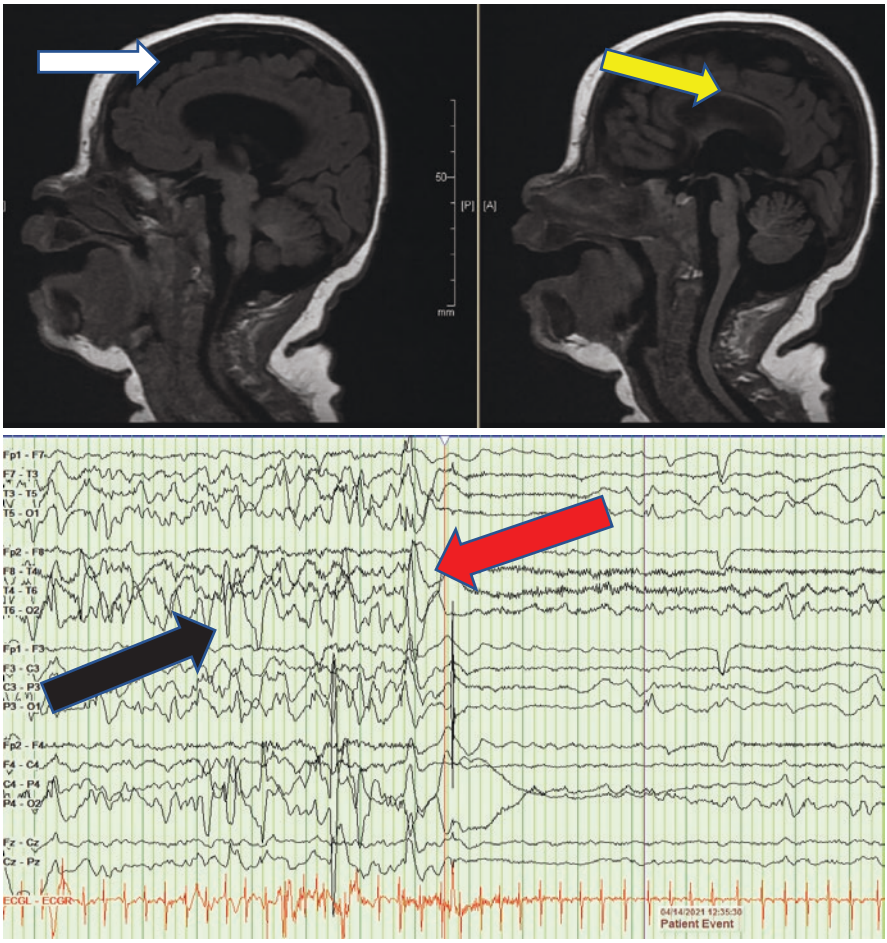

Fig. 12 9-Month-old boy with microcephaly (white arrow on MRI image), ventriculomegaly, dysgenesis of corpus callosum (yellow arrow on MRI image). EEG showed hypsarrythmia (black arrow) and captured an infantile spasm with electrodecremental (red arrow) response

[52]. Normal children and patients with electrolyte disturbances, patients on dialysis, those receiving barbiturates, or individuals with alcohol withdrawal may have photoparoxysmal responses. Structural lesions can cause suppression of photic driving responses.

Sharp- and slow-wave complexes are seen in tonic seizures. Lennox–Gastaut syndrome is characterized by sharp-wave and slow-wave complexes [53].

Hypsarrhythmia is the most common interictal EEG pattern associated with infantile spasms, which is an EEG pattern characterized by chaotic mixture of high-amplitude slow waves, multifocal spikes, and interhemispheric asynchrony. During a spasm, an electrodecremental response interrupts the slowing of high amplitude by a sudden diminution of all activities with a duration of 1 s to 1 min (Fig. 12).

5.1.3 Focal Epileptiform Pattern

Focal-spike discharges in symptomatic patients should be correlated with the clinical context, as they can be seen in normal children and in children with cerebral palsy in the absence of clinical seizures. Temporal, rolandic, and occipital spikes indicate focal epilepsy. Spike discharges in at least three non-contiguous electrode positions are considered multifocal spikes. Perinatal insults, CNS infections, genetic conditions, neurocutaneous syndromes, degenerative diseases, trauma, and anoxia can produce multifocal spikes. Periodic lateralized epileptiform discharges are suggestive of acute encephalopathy or seizures in herpes encephalitis.

5.1.4 Non-Epileptic Conditions with EEG Abnormalities

Spikes are seen in acquired aphasia of childhood, motor dysfunction, and visual perceptual difficulties. Landau Kleffner syndrome, also called acquired aphasia of childhood (3–8 years of age), is characterized by temporal or centroparietal spike-and-wave patterns. The aphasia can precede the onset of seizures [54]. Some children with central spikes may have motor difficulties, and those with occipital spikes may have visual perceptual and oculomotor abnormalities. Besides the diagnosis of epilepsy and focal cerebral disease, an EEG can be used to evaluate patients with neuronal dysfunction. Slow background or suppression of all EEG activities suggests diffuse neuronal dysfunction. The slower the frequency, the more severe is the abnormality.

An EEG may have a prognostic role in children with a severe head injury. Comatose patients with a slow monotonous EEG pattern are known to have a poor prognosis and long-term intellectual disability, whereas reactive patterns are predictive of recovery and a better prognosis [55]. Patients with hemiplegic migraine may have focal delta waves [56]. Electrocortical silence may be suggestive of brain death in an appropriate clinical setting. EEGs and evoked potentials can aid in the diagnosis and determining prognosis in coma and brain death.

In general, an EEG is abnormal in children with viral encephalitis. Measles, mumps, rubella, and scarlet fever may produce excessive slow activity even without CNS involvement. Subacute sclerosing panencephalitis (SSPE) can produce high-voltage, bilaterally symmetric periodic and synchronous bursts of polyphasic delta waves [57]. Rasmussen's encephalitis is a hemispheric progressive dysfunction of the brain, causing seizures, hemiparesis, and dementia due to atrophy. Serial EEG studies show interictal epileptiform patterns in the affected hemisphere. In meningitis, subdural effusion, empyema, or cerebritis EEG may show focal changes. High-amplitude polyspikes over the posterior head region in response to slow rates of photic stimulation may suggest neuronal ceroid lipofuscinosis [58]. Stimulus-sensitive myoclonus with periodic or multifocal sharp waves are seen in various inherited metabolic diseases such as GM1 gangliosidosis and glycine encephalopathy. In Angelman syndrome, a frontal high amplitude of 2–3 Hz rhythmic activity may be present [59]. Central or centrotemporal spikes may be seen in Rett syndrome.

A video EEG is useful to diagnose behavioral staring, psychogenic seizures, and migraine equivalents. Both conventional EEGs and amplitude-integrated EEG (aEEGs) have been utilized in specific clinical situations to offer efficient and accurate monitoring within the intensive care unit setting.

5.2 Evoked Potentials

Evoked potentials (EPs) are a quantitative method to assess the functional integrity of the somatosensory, motor, auditory, and visual pathways.

Somatosensory evoked potentials (SSEPs) assess the functional integrity of the proprioceptive pathway including the posterior column, medial lemniscus, and sensory cortex. SSEPs are recorded after an electrical stimulation of the mixed sensorimotor nerves (tibial, median, and ulnar nerves) in the periphery. Cortical, subcortical, spinal and peripheral waveforms/peaks are recorded. Peak latencies and amplitudes at several points of the peripheral and central proprioceptive pathways are measured and compared with age-matched values, which help in the localization of the lesion. An increase in latency and decrease in amplitude at a certain level may suggest acute insult. SSEPs are useful in intraoperative neurophysiologic monitoring of patients during spinal, brain and epilepsy surgeries and for prognostication of coma.

Brainstem auditory evoked potentials (BAERs) may be used as a functional assessment of the brainstem and central auditory pathway. They can be helpful during intraoperative monitoring of surgeries involving acoustic neuromas and lesions of the posterior fossa. Five reproducible waveforms (I-V) are elicited, and measurement or changes in the absolute and interpeak latencies helps to detect and localize the lesion.

Visual evoked potentials (VEPs) are useful in diagnosis of suspected multiple sclerosis or neuromyelitis optica, with abnormalities detected in pre-chiasmatic

optic nerve lesions. The VEP waveform is reported as a P100 waveform and is absent in ocular blindness.

5.3 Nerve Conduction Study and Electro-myography (NCS/EMG)

The motor and sensory NCS measures the functional integrity of the of the peripheral nerves and helps differentiate demyelination, axonopathy, and radiculopathy. In motor NCS, the recording electrode, which records the compound motor action potential (CMAP) is placed over the middle of the muscle, where motor endplate is situated. In sensory NCS, sensory nerve action potential (SNAP) is recorded over the nerve. Amplitude, distal latency, and conduction velocity are measured in NCS. Demyelination is suspected when there is 20% decrease in the CMAP amplitude (a conduction block), and a >30% increase in the duration of the CMAP (a temporal dispersion). A decrease in amplitude and normal conduction velocity usually suggests an axonal pathology.

F waves and H reflex represents the proximal segments of the nerve. In the early phase of Guillaine-Barré syndrome F-waves may be absent.

Cranial nerve conduction study: Assessment of the trigeminal nerve, it's connections within the brainstem, and the facial nerve is detected by trigeminal blink reflex.

Repetitive nerve conduction studies: Repetitive nerve stimulation ("Rep Stim") may be useful to diagnose myasthenia gravis (MG) and Lambert–Eaton myasthenic syndrome (LEMS). Normally, each stimulus produces a similar Compound Muscle Action Potential (CMAP) with a similar amplitude. In disorders of neuromuscular junction, with each successive stimulus, the CMAP amplitude decreases (decrements). After brief exercise for 10 seconds, neuromuscular junctional transmission improves transiently due to calcium-mediated exocytosis of acetylcholine vesicles. This Ach release may recover the decrement or increase (increment) in the CMAP amplitude, which is known as facilitation. The degree of facilitation can be helpful distinguishing a presynaptic disorder such as Lambert–Eaton myasthenic syndrome (LEMS) from a post-synaptic disorder such as myasthenia gravis. Increment of >100% is diagnostic of LEMS, while progressively weaker response is suggestive of MG.

A **Needle EMG** elicits electrical activity of the muscle fibers and helps distinguish neurogenic, myogenic, anterior horn cell, and motor root problems. Spontaneous activity is assessed with the muscles at rest. Fibrillation potential, fasciculation potentials, and positive sharp waves are abnormal spontaneous activities seen in neurogenic disorders. The myopathic disorder produces fibrillation potential and fasciculation potentials, which are also produced by disorders of anterior horn cells, motor roots, and motor nerves spontaneously. Myotonic discharges

(spontaneous discharges with waxing and waning of both amplitude and frequency, producing a characteristic audio profile often equivalent to a "dive bomber") are seen in myotonia and several channelopathies. Myokymic potentials (flickering of muscles producing regular or irregular discharge of groups of motor units) are seen in radiation neuropathy, demyelinating neuropathies, and mononeuropathies. Neuromyotonic discharges are seen in Isaacs' syndrome and Morvan's syndrome.

6 Conclusions

There are a large number of neurodiagnostic tools available to a clinician. Prompt and strategic use of these tools will not only lead to better clinical outcomes but also streamline expenses in the long run. Therefore, it is important to be familiar with the indications, contraindications, and interpretation of these neurodiagnostic studies.

7 Clinical Pearls/Key Points

- A variety of neurodiagnostic studies including newer MRI imaging modalities, functional imaging studies, and neurophysiological studies are available to a clinician to help diagnose neurological disorders in children.
- Over the last decade, a number of antibodies against several components of nervous system have been identified and they have aided in characterizing neurological conditions previously labeled "idiopathic."
- It is necessary to be familiar with the indications and contraindications of a particular study, in order to utilize them appropriately.
- It is equally important to develop knowledge and skills in interpreting test results so that a diagnosis can be established in a timely manner and communication with neurologist can be facilitated.

References

1. Oliver WJ, Shope TC, Kuhns LR. Fatal lumbar puncture: fact versus fiction—an approach to a clinical dilemma. Pediatrics. 2003 Sep;112(3 Pt 1):e174-e176. https://doi.org/10.1542/peds.112.3.e174.
2. Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, Whitley RJ. Practice guidelines for the management of bacterial meningitis. Clinical Infect Dis. 2004;39(9):1267–84.
3. Howard SC, Gajjar A, Ribeiro RC, Rivera GK, Rubnitz JE, Sandlund JT, Pui CH. Safety of lumbar puncture for children with acute lymphoblastic leukemia and thrombocytopenia. JAMA. 2000;284(17):2222–4.
4. Vandam LD. On the origins of intrathecal anesthesia. Reg Anesth Pain Med. 1998;23(4):335.

5. Michelson, D. J. (2017). Spinal fluid examination. Swaiman's pediatric neurology e-book: principles practice, 1(2), 160.
6. Corbett JJ, Mehta MP. Cerebrospinal fluid pressure in normal obese subjects and patients with pseudotumor cerebri. Neurology. 1983;33(10):1386–8.
7. Volpe JJ. Neurology of the newborn. ed. ed. Philadelphia, PA. London: Saunders; 2008.
8. Friedman DI. Headaches due to low and high intracranial pressure. Continuum (Minneapolis, Minn.). 2018 Aug;24(4, Headache):1066-1091. https://doi.org/10.1212/con.0000000000000623.
9. Strupp M, Brandt T, Müller A. Incidence of post-lumbar puncture syndrome reduced by reinserting the stylet: a randomized prospective study of 600 patients. J Neurol. 1998 Sep;245(9):589-592. https://doi.org/10.1007/s004150050250
10. Cousins MJ, Brazier D, Cook R. Intracranial hypotension caused by cervical cerebrospinal fluid leak: treatment with epidural blood patch. Anesth Analg. 2004 Jun;98(6):1794–1797, table of contents. https://doi.org/10.1213/01.ane.0000117225.31416.36
11. Nascimento-Carvalho CM, Moreno-Carvalho OA. Normal cerebrospinal fluid values in full-term gestation and premature neonates. Arq Neuropsiquiatr. 1998 Sep;56(3A):375–380. https://doi.org/10.1590/s0004-282x1998000300005.
12. Dyken PR, Mulina JL. The normal cellular population of the cerebrospinal fluid by sedimentation-flocculation techniques at various ages. Proc Child Neurol Soc. 1973;2:26.
13. Widell S. On the cerebrospinal fluid in normal children and in patients with acute abacterial meningo-encephalitis. Acta Paediatrica. 1958;47(6):711–3.
14. Feigin RD, McCracken Jr GH, Klein JO. Diagnosis and management of meningitis. Pediatr Infect Dis J. 1992;11(9):785.
15. Dubos F, Korczowski B, Aygun DA, Martinot A, Prat C, Galetto-Lacour A, et al. Serum procalcitonin level and other biological markers to distinguish between bacterial and aseptic meningitis in children: a European multicenter case cohort study. Arch Pediatr Adolesc Med. 2008;162(12):1157–63.
16. Farinha NJ, Razali KA, Holzel H, Morgan G, Novelli VM. Tuberculosis of the central nervous system in children: a 20-year survey. J Infect. 2000;41(1):61–8.
17. Johnson RT. Viral infections of the nervous system, vol. 1. New York: Raven; 1982. p. 433.
18. Whitley RJ, Soong SJ, Linneman C, Liu C, Pazin G, Alford CA. Herpes simplex encephalitis: clinical assessment. Jama. 1982;247(3):317–20.
19. Thusang K, Set KK, Jiang H. Premature termination of treatment in neonatal herpes simplex virus encephalitis. Pediatr Neurol. 2018;79:72–3.
20. Olsson T. Multiple sclerosis:cerebrospinal fluid. Ann Neurol. 1994;36(Suppl):S100–2. https://doi.org/10.1002/ana.410360723.
21. Flanagan EP. Neuromyelitis optica spectrum disorder and other non–multiple sclerosis central nervous system inflammatory diseases. Continuum. 2019;25(3):815–44.
22. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162–73.
23. Haliloğlu G, Vezir E, Baydar L, Onol S, Sivri S, Coşkun T, Topçu M. When do we need to perform a diagnostic lumbar puncture for neurometabolic diseases? Positive yield and retrospective analysis from a tertiary center. Turk J Pediatr. 2012 Jan-Feb;54(1):52-58.
24. Breese EH, Dalmau J, Lennon VA, Apiwattanakul M, Sokol DK. Anti-N-methyl-D aspartate receptor encephalitis: early treatment is beneficial. Pediatr Neurol. 2010;42:213–4.
25. Cellucci T, Van Mater H, Graus F, Muscal E, Gallentine W, Klein-Gitelman MS, Benseler SM, Frankovich J, Gorman MP, Van Haren K, Dalmau J, Dale RC.. Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. Neurol Neuroimmunol Neuroinflamm. 2020 Jan 17;7(2):e663. https://doi.org/10.1212/NXI.0000000000000663.. Print 2020 Mar.
26. Armangue T, Titulaer MJ, Malaga I, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis – clinical analysis and novel findings in a series of 20 patients. J Pediatr. 2013;12:157–65.

27. Pr¨obstel AK, Dornmair K, Bittner R, et al. Antibodies to MOG are transient in childhood acute disseminated encephalomyelitis. Neurology 2011;77:580–588
28. Binks S, Vincent A, Palace J. Myasthenia gravis: a clinical immunological update. J Neurol. 2016;263:826e34.
29. Varley JA, Irani SR. Antibody-associated autoimmune neurological disease. Medicine. 2016;44(9):563–9.
30. van Wezel-Meijler G, Steggerda SJ, Leijser LM. Cranial ultrasonography in neonates: role and limitations. Semin Perinatol. 2010 Feb;34(1):28-38. https://doi.org/10.1053/j.semperi.2009.10.002.
31. Ketonen LM, Valanne L. Neuroimaging of pediatric diseases. Semin Neurol. 2008 Sep;28(4):558-569. https://doi.org/10.1055/s-0028-1083692.. Epub 2008 Oct 8.
32. Wycliffe ND, Holshouser BA, Bartnik-Olson B, Ashwal S. Pediatric neuroimaging. In: Swaiman's pediatric neurology. Elsevier; 2017. p. 78–86.
33. Ment LR, Bada HS, Barnes P, Grant PE, Hirtz D, Papile LA, Pinto-Martin J, Rivkin M, Slovis TL. Practice parameter: neuroimaging of the neonate: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2002 Jun 25;58(12):1726-1738. https://doi.org/10.1212/wnl.58.12.1726.
34. Erdem E, Ağildere M, Eryilmaz M, Ozdirim E. Intracranial calcification in children on computed tomography. Turk J Pediatr. 1994 Apr-Jun;36(2):111-122.
35. Wells RG, Vetter C, Laud P. Intracranial hemorrhage in children younger than 3 years: prediction of intent. Arch Pediatr Adolesc Med. 2002 Mar;156(3):252-257. https://doi.org/10.1001/archpedi.156.3.252.
36. Radue EW, Weigel M, Wiest R, Urbach H. Introduction to magnetic resonance imaging for neurologists. Continuum. 2016;22(5):1379–98.
37. Baig MA, Klein JP, Mechtler LL. Imaging of brain tumors. Continuum. 2016;22(5):1529–52.
38. Lin MP, Liebeskind DS. Imaging of ischemic stroke. Continuum: Lifelong Learning. Continuum. 2016;22(5):1399.
39. Lapalme-Remis S, Cascino GD. Imaging for adults with seizures and epilepsy. Continuum. 2016;22(5):1451–79.
40. Balashov K. Imaging of central nervous system demyelinating disorders. Continuum. 2016;22(5):1613–35.
41. Covarrubias DJ, Luetmer PH, Campeau NG. Posterior reversible encephalopathy syndrome: prognostic utility of quantitative diffusion weighted MR images. Am J Neuroradiol. 2002;23(6):1038–48.
42. Feldman HM, Yeatman JD, Lee ES, Barde LH, Gaman-Bean S. Diffusion tensor imaging: a review for pediatric researchers and clinicians. J Dev Behav Pediatr. 2010 May;31(4):346-356. https://doi.org/10.1097/DBP.0b013e3181dcaa8b.
43. Taoka T, Sakamoto M, Nakagawa H, Nakase H, Iwasaki S, Takayama K, et al. Diffusion tensor tractography of the Meyer loop in cases of temporal lobe resection for temporal lobe epilepsy: correlation between postsurgical visual field defect and anterior limit of Meyer loop on tractography. Am J Neuroradiol. 2008;29(7):1329–34.
44. Vargas MI, Delavelle J, Jlassi H, Rilliet B, Viallon M, Becker CD, Lövblad KO. Clinical applications of diffusion tensor tractography of the spinal cord. Neuroradiology. 2008 Jan;50(1):25-29. https://doi.org/10.1007/s00234-007-0309-y.. Epub 2007 Oct 2.
45. Jang SH, Kim SH, Kim OL, Byun WM, Ahn SH. Corticospinal tract injury in patients with diffuse axonal injury: a diffusion tensor imaging study. NeuroRehabilitation. 2009;25(4):229–33. https://doi.org/10.3233/NRE-2009-0519.
46. Ducreux D, Meder JF, Fredy D, Bittoun J, Lasjaunias P. MR perfusion imaging in proliferative angiopathy. Neuroradiology. 2004 Feb;46(2):105-112. https://doi.org/10.1007/s00234-003-1045-6.. Epub 2004 Jan 16.

47. Olejniczak P. Neurophysiologic basis of EEG. J Clin Neurophysiol. 2006 Jun;23(3):186-189. https://doi.org/10.1097/01.wnp.0000220079.61973.6c.
48. Hess R. Brain tumors and other space occupying processes. In: Remond A, editor. Handbook of electroencephalography and clinical neurophysiology; 1975.
49. Hockaday JM, Whitty CW. Factors determining the electroencephalogram in migraine: a study of 560 patients, according to clinical type of migraine. Brain. 1969;92(4):769–88. https://doi.org/10.1093/brain/92.4.769.
50. Keen JH, Lee D. Sequelae of neonatal convulsions. Study of 112 infants. Arch Dis Child. 1973 Jul;48(7):542-546. https://doi.org/10.1136/adc.48.7.542.
51. Eeg-Olofsson O. The development of the electroencephalogram in normal adolescents from the age of 16 through 21 years. Neuropadiatrie. 1971 Jul;3(1):11-45. https://doi.org/10.1055/s-0028-1091798.
52. Doose H, Gerken H, Hien-Völpel KF, Völzke E. Genetics of photosensitive epilepsy. Neuropadiatrie. 1969 Jun-Jul;1(1):56-73. https://doi.org/10.1055/s-0028-1091864.
53. Gastaut H, Roger J, Soulayrol R, Tassinari CA, Regis H, Dravet C, et al. Childhood epileptic encephalopathy with diffuse slow spike-waves (otherwise known as “petit mal variant”) or Lennox syndrome. Epilepsia. 1966;7(2):139–79.
54. Landau WM, Kleffner FR. Syndrome of acquired aphasia with convulsive disorder in children. Neurology. 1957 Aug;7(8):523-530. https://doi.org/10.1212/wnl.7.8.523.
55. Dusser A, Navelet Y, Devictor D, Landrieu P. Short- and long-term prognostic value of the electroencephalogram in children with severe head injury. Electroencephalogr Clin Neurophysiol. 1989 Aug;73(2):85-93. https://doi.org/10.1016/0013-4694(89)90187-9.
56. Slatter KH. Some clinical and EEG findings in patients with migraine. Brain. 1968 Mar;91(1):85-98. https://doi.org/10.1093/brain/91.1.85.
57. Scher MS. Pediatric neurophysiologic evaluation. In: Swaiman’s pediatric neurology. Elsevier; 2017. p. 87–96.
58. Pampiglione G, Harden A. Neurophysiological identification of a late infantile form of “neuronal lipidosis”. J Neurol Neurosurg Psychiatry 1973 Feb;36(1):68-74. https://doi.org/10.1136/jnnp.36.1.68.
59. Laan LA, Brouwer OF, Begeer CH, Zwinderman AH, van Dijk JG. The diagnostic value of the EEG in Angelman and Rett syndrome at a young age. Electroencephalogr Clin Neurophysiol. 1998 May;106(5):404-408. https://doi.org/10.1016/s0013-4694(98)00007-8.

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