

Pediatric Neurology

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1. Introduction

The subject of pediatric neurology is often intimidating to even the best of pediatric residents. Yet, if approached in a systematic, problem-oriented fashion, it can become a comprehensible subspecialty, providing great satisfaction to those who venture to manage the care of children with special needs. It is not a mysterious “black box;” it builds on the principles of adult medicine/neurology and the basic sciences of medical school.

Some of the most challenging problems of pediatrics include neurological problems, particularly: 1) seizures and other paroxysmal events; 2) headaches; and 3) developmental delays. These three areas constitute the majority of referrals to pediatric neurologists. If basic principles are applied, patients can be better and more quickly managed. Given the current shortage of pediatric neurologists, this chapter should be especially helpful.

2. Seizures and Other Paroxysmal Events

Epilepsy in infants and children differs from adult epilepsy in seizure semiology, EEG characteristics, and seizure development and propagation, which reflects the developmental stages of the immature brain. In addition, the underlying substrates of epilepsy are very different, and the most common etiologies are either genetic or derive from remote central nervous system (CNS) lesions. The etiologic differences have resulted in uniquely pediatric epilepsy syndromes. Some of the epilepsy syndromes are catastrophic and malignant; others are idiopathic, age-limited, and probably genetically predetermined. Epilepsy syndromes require a compilation of data, including seizure types, age of onset, developmental history, neurological exam, family history, EEG data, and neuroimaging results. The catastrophic epilepsy syndromes are generally found in infants and young children. This, in large part, is due to significant CNS pathology as well as the immaturity of the brain and its unique vulnerabilities. In the context of an ongoing epileptic encephalopathy, the immature brain undergoes aberrant apoptosis and synaptogenesis. The comorbidities associated with these catastrophic epilepsies include neurological abnormalities, developmental delays, cognitive impairments, and behavioral difficulties.¹

The first step in evaluating a child who may have had a seizure is to determine if the event was an epileptic seizure or some other paroxysmal event. Appropriate classification of the spell type—either epileptic or nonepileptic—is critical in identifying the appropriate treatment plan. If the events are seizures, identification of the type of seizure and the epilepsy syndrome is very helpful in developing a treatment plan and providing accurate information to the families with respect to prognosis.

In the classification of epilepsy, seizures can be divided into two types: generalized or partial (Table 1).

Partial seizures are seizures that emanate from a focal area of the brain, producing behavioral changes that correspond with the activation of specific areas of the brain. Simple partial seizures are partial seizures not associated with any alteration of consciousness. Complex partial seizures are partial seizures associated with an alteration in level of responsiveness (not necessarily a loss of consciousness). The behavioral man-

ifestation of a partial seizure will depend on where the epileptogenic focus resides. For example, partial seizures coming from the temporal lobe typically begin with an “aura” (simple partial seizure) characterized by a feeling of doom or dread, olfactory hallucination, déjà vu, jamais vu, or epigastric discomfort that rises in the chest. This aura is usually followed by staring, decreased responsiveness, automatisms, and occasional tonic stiffening (complex partial seizure). The patient may be able to respond to questions, but the responses will often be slow, monotone, and in single word phrases. Seizures emanating from the frontal lobe are classically brief nocturnal seizures associated with head and eye deviation and tonic stiffening. Complex partial seizures can secondarily become generalized tonic-clonic seizures. In fact, the majority of generalized tonic-clonic seizures begin

focally and progress to generalized seizures. The chronology of the seizure—how it began and how it evolved—is important in determining whether a generalized seizure began focally.

Generalized seizures are seizures associated with generalized discharges in the brain without focal features. Generalized seizures can be myoclonic, tonic, tonic-clonic, or absence. Myoclonic seizures are characterized by sudden extension or flexion of the arms and legs. Tonic seizures consist of sustained tonic stiffening of the arms (and usually the legs). Tonic clonic seizures begin with tonic stiffening followed by rhythmic clonic activity, ie, what used to be called “grand mal” seizures. Absence seizures represent the new nomenclature for “petit mal” seizures. These seizures are characterized by

Table 1

Classification of Epileptic Seizures

1. Partial Seizures

- A. Simple partial seizures
 - 1. With motor signs, such as focal clonic activity
 - 2. With somatosensory or special-sensory symptoms such as lateralized numbness, tingling, visual or auditory hallucinations, abnormal odors or smells
 - 3. With automatic symptoms or signs such as tachycardia, diaphoresis
 - 4. With psychic symptoms such as fear, anxiety, déjà vu, jamais vu, confusion

- B. Complex partial seizures
 - 1. With simple partial seizures (aura) at onset
 - 2. With impairment of consciousness at onset

- C. Partial seizures evolving to secondarily generalized seizures

2. Generalized Seizures

- A. Absence seizures

- B. Myoclonic seizures

- C. Clonic seizures

- D. Tonic seizures

- E. Tonic-clonic seizures

- F. Atonic seizures

episodes of staring unresponsively, sometimes in association with eyelid fluttering or subtle myoclonic jerks of the upper extremities. All staring spells, however, are not absence seizures. As discussed above, seizures associated with staring can be complex partial seizures emanating from the temporal lobe. Absence seizures can be differentiated from their counterpart, complex partial seizures, usually on the basis of history alone. Absence seizures are brief (lasting seconds), occur frequently throughout the day, are not associated with complex automatisms, and are not accompanied by a postictal state. The EEGs are very different as well, with absence seizures being associated with generalized 3-Hertz spike and slow wave discharges. On the other hand, complex partial seizures characterized by staring (usually emanating from the temporal lobe) contain other features, especially automatisms, which are repetitive stereotypic movements (eg, repetitive swallowing or chewing movements; repetitive picking at clothing). These seizures usually last 1-2 minutes, occur far less frequently than absence seizures, and are followed by a

postictal phase. In infants, complex partial seizures are often very subtle. For example, seizures emanating from the temporal lobe may manifest themselves as periods of behavioral arrest (often with perioral cyanosis) but no other clinical signs.

All paroxysmal events are not seizures. In fact, if one looks at the differential diagnosis of staring spells, there can be multiple causes for staring episodes, including absence seizures, complex partial seizures, attention deficit disorder, daydreaming, and even defiance-avoidance. Other paroxysmal events that can mimic seizures are listed in Table 2.

Breath-holding spells are worth elaborating on. Cyanotic breath-holding spells are precipitated by prolonged crying episodes, often stimulated by frustration or anger, followed by involuntary breath-holding, cyanosis, decreased oxygen saturation, and brief loss of consciousness. This can be accompanied by brief tonic-clonic activity. Pallid breath-holding spells, on the other hand, are typically precipitated by a fall or sudden surprise.^{1,2,3} These spells are truly vasovagal events resulting in bradycardia or even brief asystole accompanied by facial pallor, loss of consciousness, and sometimes brief tonic-clonic activity. Both types of breath-holding spells are benign and rarely require any intervention. Breath-holding spells decrease in frequency during the second year of life, are substantially reduced by 4 years of age, and disappear by 7-8 years of age. Vasovagal syncope may occur in up to 17% of these patients by late childhood/adolescence. The pathophysiology of breath-holding spells remains incompletely understood, but they are not volitional or associated with a “temperamentally difficult” child; instead, they are probably secondary to autonomic nervous system dysfunction/immaturity. The most important aspect of treatment is parental reassurance of the benign, self-limited nature of these spells. Iron deficiency may play a role in breath-holding spells, as there is one clinical study documenting a significant decrease in the frequency and severity of the breath-holding spells with iron therapy. Iron is important for catecholamine metabolism and neurotransmitter function; this may explain its role in eliminating breath-holding spells.²

Table 2

Nonepileptic Paroxysmal Events That Can Mimic Epilepsy

- Breath-holding spells
 - Cyanotic
 - Pallid
- Vasovagal syncope
- Motor tics
- Migraine, headaches, particularly confusional migraine
- Paroxysmal vertigo
- Paroxysmal choreoathetosis or dystonia
- Shuddering spells
- Pseudoseizures (conversion disorder)
- Sleep disorders, such as physiologic myoclonus of sleep

3. Epilepsy Syndromes

Specific epilepsy syndromes are defined on the basis of seizure type, taking into account the age of onset, family history, physical examination, electroencephalographic (EEG) findings, and neuroimaging studies. The identification of an epilepsy syndrome greatly assists the clinician in the choice of an antiepileptic drug or other therapy and provides important prognostic information to the family. In the following section, several common pediatric epilepsy syndromes are discussed (Tables 3 and 4).

Table 3

Classification of Epileptic Syndromes

Localization-related (Focal, Local, Partial)

Epilepsies and Syndromes

Idiopathic

Benign rolandic epilepsy

Benign occipital epilepsy

Symptomatic

Generalized Epilepsies and Syndromes

Idiopathic, age-related

Benign neonatal familial convulsions

Benign idiopathic convulsions

Benign myoclonic epilepsy in infancy

Childhood absence epilepsy

Juvenile absence epilepsy

Juvenile myoclonic epilepsy

Epilepsy with tonic-clonic seizures on awakening

Idiopathic and/or symptomatic

Infantile spasms (West's syndrome)

Lennox-Gastaut syndrome

Epilepsy with myoclonic-astatic seizures

Epilepsy with myoclonic absences

Symptomatic: early myoclonic encephalopathy

Epilepsies and Syndromes Undetermined as to Whether They are Focal or Generalized

Neonatal seizures

Severe myoclonic epilepsy in infancy

Epilepsy with continuous spike waves during slow-wave sleep

Acquired epileptic aphasia (Landau-Kleffner syndrome)

Infantile Spasms (West Syndrome)

Infantile spasms typically begin between four and eight months of age. Ninety percent of infantile spasms begin before 12 months of age. The pathophysiology of infantile spasms remains poorly understood. Theoretically, there is probably an enhanced excitability in the subcortical structures, resulting in the repetitive clusters of myoclonic jerks that are the hallmark of infantile spasms. The spasms can be classified as flexor, extensor, or mixed flexor-extensor types. They can be very subtle, with only a slight head drop or an abdominal "crunch." The spasms commonly occur in clusters, with the clusters typically occurring upon awakening from sleep. The presence of focal features, such as eye deviation, usually indicates an underlying focal brain lesion, such as a porencephalic cyst or malformation of cortical development.^{4,5}

Interictally, the EEG typically demonstrates a hypsarhythmia pattern defined by high amplitude background slowing and multifocal epileptogenic discharges over both hemispheres. However, it should be noted that the clinical infantile spasms may precede the changes in the EEG by over one-two weeks. In addition, the hypsarhythmia pattern may only be seen during sleep. Therefore, the EEG must be performed during both wakefulness and sleep. In addition, if the first EEG is normal and the clinical symptoms persist, the EEG should be repeated in one-two weeks.

With respect to etiology, infantile spasms can be divided into three categories: 1) symptomatic; 2) cryptogenic; and 3) idiopathic. The most common etiologies for symptomatic infantile spasms include: 1) tuberous sclerosis (approximately 25% of patients with tuberous sclerosis have infantile spasms); 2) malformations of cortical development (eg, Aicardi's syndrome or malformations in the posterior quadrants of the brain); 3) chromosomal abnormalities (eg, Trisomy 21); 4) inborn errors of metabolism (eg, amino acidopathies, mitochondrial cytopathies); 5) asphyxia; 6) meningitis/encephalitis; and 7) trauma.⁵

Magnetic resonance imaging (ie, MRI brain imaging with at least 1.5 Tesla strength) is important, as CT scans have inadequate resolution to be helpful in this

Table 4**Epilepsies**

Generalized	Age of Onset	Clinical Characteristics	EEG Characteristics	Etiology	Prognosis	AEDs
Ohtaharas Syndrome	Birth	Tonic spasms	Burst suppression Ictal correlate — Electrodecremental response	Malformations of cortical development	Poor	Phenobarbital — May need high dose TPX — May require high doses at 20-40 mg/kg/d FBM — Start at 15 mg/kg/d Max dosage-90 mg/kg/d VPA-1:500 risk of hepatotoxicity Dosage will vary — 15-60 mg/kg/d Avoid CBZ, PHT
Early Infantile Myoclonic Epilepsy	Birth	Myoclonus — fragmental, segmental or generalized	Burst suppression Ictal correlate — Generalized burst of polyspikes	Neurometabolic disorders, esp. propionic acidemia, (nonketotic) hyperglycinemia, D-glyceric acidemia	Poor	Same as above
Infantile Spasms	2-6 months	Myoclonic seizures in clusters	Hypsarhythmia, ie, generalized high - amplitude delta activity with multifocal independent spikes	Tuberous sclerosis (TS), neurometabolic D/O, MCD, infection, genetic, trauma, asphyxia, idiopathic	Guarded, dependent on etiology and ability to normalize EEG and eliminate seizures	ACTH-150 u/m ² /day x 2wk Then 75 u/m ² /day x 2wk Then taper over 1 month If TS, consider vigabatrin, using dosages of 100-150 mg/kg/d Vitamin B6 (pyridoxine), up to 300 mg/d has been reported to work TPX-20-40mg/kg/day anecdotal evidence VPA-45-60mg/kg/day, risk of hepatotoxicity

Key: PS, S, & SWD/Cs = polyspike, spike, & slow wave discharges; D/O = disorder; VNS = vagal nerve stimulator; MCD = malformation of cortical development
LMT = lamotrigine; Oxcarb = oxcarbazepine; KD = ketogenic diet; PHT = phenytoin; CBZ = carbamazepine; TPX = topiramate; FBM = felbamate; VPA = valproate
(continued)

Table 4 (continued)

Generalized	Age of		EEG	Etiology	Prognosis	AEDs
	Onset	Clinical Characteristics				
Lennox-Gastaut Syndrome	12 mos-6 yrs	Tonic, atonic, myoclonic, absence, GTCS	Generalized ps, s & sw D/Cs at 1-2 1/2 Hz	Same as infantile spasms	Guarded, dependent on etiology and ability to normalize EEG and eliminate seizures	TPX — 10-20 mg/kg/d FBM — Start at 15 mg/kg/d Max 90 mg/kg/d LMT — 5-15 mg/kg/d VPA — 15-60 mg/kg/d Ketogenic diet (KD) Vagal nerve stimulator (VNS) Avoid CBZ Benzodiazepine for sz clusters
Myoclonic/Astatic Epilepsy of Doose	2-5 yrs Boys > Girls	Absence sz with myoclonic and atonic features, tonic, atonic, GTCS	Normal background Generalized ps, s, & sw D/Cs	Genetic predisposition	Guarded	VPA VPA and LMT FBM — May have special indication with this syndrome TPX
Severe Myoclonic Epilepsy of Dravet	12-24 mos Girls > Boys	1 — GTCS or complex febrile sz during 1st yr 2 — Subsequently atonic, GTCS, D/Cs 3 — Status epilepticus freq.	Normal EEG during 1st yr, then slow background with generalized ps, s, & sw D/Cs as well as multifocal D/Cs	Genetic	Poor	No AEDs are effective Efficacy of KD & VNS unknown Benzodiazepines helpful with sz clusters
Childhood Absence Epilepsy	5-10 yrs	Absence sz If <9 yr old at onset, 16% chance of concomitant GTCS If >9 yr old, 50% chance of GTCS	Generalized s & sw D/Cs at 3cps	Genetic	Good	For all absence syndromes Ethosuximide, if absence sz only VPA — 15-60 mg/kg/d VPA & LMT — May only need 2-3 mg per kg/d of LMT LMT — 5-10 mg/kg/d TPX — 5-10 mg/kg/d KD — Difficult in older pts.

Key: PS, S, & SW D/Cs = polyspike, spike, & slow wave discharges; D/O = disorder; VNS = vagal nerve stimulator; MCD = malformation of cortical development
LMT = lamotrigine; Oxcarb = oxcarbazepine; KD = ketogenic diet; PHT = phenytoin; CBZ = carbamazepine; TPX = topiramate; FBM = felbamate; VPA = valproate
(continued)

Table 4 (continued)

		EEG				
Generalized	Age of Onset	Clinical Characteristics	Characteristics	Etiology	Prognosis	AEDs
Juvenile Absence Epilepsy	12-17 yrs	1 — Absence 2 — GCS in 80%	Generalized s & sw D/Cs at 3cps	Genetic	Good—May not be able to discontinue meds	Same as above
Juvenile Myoclonic Epilepsy	12-18 yrs	1 — Myoclonus 2 — Absence 3 — GTCS-in 90%	Generalized s & sw D/Cs at 3cps	Genetic	Good control, but lifelong epilepsy	VPA — Efficacy demonstrated TPX LMT Primidone Levetiracetam
Localization Related						
Benign Rolandic Epilepsy	5-14 yrs Boys > Girls	Primarily nocturnal seizures, with drooling & focal motor clonic activity — May secondarily generalize	Drowsiness and sleep-activated central-temporal spikes	Genetic	Excellent - Remission by puberty	May not require AED Rx CBZ, OXCZB, LMT, Levetiracetam
Benign Occipital Epilepsy	5-7 yrs	1 — Ictal event usually heralded by visual aberrations progressing to complex partial sz with dizziness, confusion, ataxia 2 — Severe postictal headache	High amplitude ps & sw D/Cs over bioccipital regions, suppressed with eye opening	Genetic	May be two types, one with excellent prognosis; other variable	CBZ OXCZB LMT VPA TPX
Benign Infantile Familial Convulsions	3-7 mos	Sz characterized by behavior arrest, head & eye deviation, tonic stiffening	Lateralized spikes, usually over parietal-occipital head region	Genetic (Chromosome 9 localization)	Excellent — Remission in all	CBZ Phenobarb LMT VPA TPX

Key: PS, S, & SWD/Cs = polyspike, spike, & slow wave discharges; D/O = disorder; VNS = vagal nerve stimulator; MCD = malformation of cortical development
LMT = lamotrigine; Oxcarb = oxcarbazepine; KD = ketogenic diet; PHT = phenytoin; CBZ = carbamazepine; TPX = topiramate; FBM = felbamate; VPA = valproate
(continued)

Table 4 (continued)

Generalized	Age of Onset	Clinical Characteristics	EEG Characteristics	Etiology	Prognosis	AEDs
Rasmussen's syndrome	Variable Preschool- Adolescence	1 — Progressive unilateral sz Epilepsia partialis continuans 2 — Progressive hemiparesis 3 — Progressive cognitive D/O	Multifocal spikes over one hemisphere, may be maximal over parasagittal region	? Autoimmune	Variable	Hemispherectomy is only long-term therapy AEDs Steroids, IV immunoglobulin, and plasma exchange — anecdotal reports of transient efficacy
Special Syndromes						
Febrile seizures	6mos-3yrs	1 — GTCS 2 — High fever 3 — No evidence of intracranial infection	Normal — A & S	Genetic	Excellent — remission by 5 yrs	Diastat, if sz prolonged >5min
Neonatal seizures	Neonatal- Within first month	1 — Subtle 2 — Focal clonic 3 — Tonic 4 — Apnea	Various abnormalities — usually presence of epileptogenic D/Cs	Hypoxia — ischemic Hypocalcemia Hyponatremia Hypoglycemia Sepsis Pyridoxine dependency MCD Genetic/chromosomal Glucose transporter deficiency Other metabolic D/O	Variable, depends on etiology	Phenobarb Lorazepam Phenytoin (IV only) Vit B6 If glucose transporter deficiency, use ketogenic diet

*Key: PS, S, & SW/D/Cs = polyspike, spike, & slow wave discharges; D/O = disorder; VNS = vagal nerve stimulator; MCD = malformation of cortical development
LMT = lamotrigine; Oxcarb = oxcarbazepine; KD = ketogenic diet; PHT = phenytoin; CBZ = carbamazepine; TPX = topiramate; FBM = felbamate; VPA = valproate*

setting. In addition, because tuberous sclerosis is a common cause of infantile spasms, a detailed Wood's lamp examination of the skin should be performed in addition to ophthalmologic examination, renal ultrasound, and echocardiogram. Metabolic studies, including serum lactate and pyruvate, plasma amino acids, biotinidase level, serum ammonia, carnitine level and acylcarnitine profile, peroxisomal panel, and urine organic acids should be performed in all infants with infantile spasms of undetermined etiology, but especially in those with vomiting, lethargy, failure to thrive, or peculiar odors.⁵ Cerebrospinal fluid (CSF) evaluation is also critical, and one should look for glucose transporter syndrome (low CSF glucose: plasma glucose ratio), nonketotic hyperglycinemia, neurotransmitter disorders, and infection.

Because both pyridoxine dependency and biotinidase deficiency have been reported in association with infantile spasms, pyridoxine 100 mg should be administered intravenously during EEG monitoring. In pyridoxine dependent children, there is typically an immediate improvement in EEG and seizures. If this test is negative, 10-20 mg/day of biotin should be considered as empiric therapy. In those with biotinidase deficiency, seizures will stop within 24 hours.

ACTH remains the treatment of choice for most children with infantile spasms in the United States.⁷ The dosage among practitioners varies considerably. There has never been a prospective placebo controlled study that has critically looked at the various dosage schedules and compared efficacy. The high dose protocol is most commonly used, ie, 150 units/meters squared/day for one week followed by weekly reductions.⁶ The mechanism by which ACTH works to abort infantile spasms remains unknown, but it may act as a neurotransmitter or affect the GABA (gamma amino butyric acid) receptor. GABA is the primary inhibitory neurotransmitter in the brain. ACTH can produce significant side effects; the side effects are typical of steroid administration: Cushingoid obesity, growth retardation, severe irritability, hypertension, osteoporosis, hyperkalemic alkalosis, electrolyte disturbances, acne, and opportunistic infections due to immunosuppression. The high rate of side effects and the fact that ACTH is given as an injection dampens enthusiasm for ACTH as a treatment option.

Infantile spasms have also been treated with: 1) oral prednisone: the effectiveness is not as compelling as ACTH; 2) the benzodiazepines (clonazepam and nitrazepam), which are associated with significant side effects, including increased bronchopulmonary secretions, sedation, and tachyphylaxis (the development of tolerance); and 3) valproate (clinical studies estimating an efficacy rate of approximately 40%). In this age group, however, valproate carries a high risk of fatal hepatotoxicity of 1:500.⁸

Vigabatrin, a structural analog of GABA, has been shown to be very effective in the treatment of infantile spasms, particularly in patients with tuberous sclerosis. This medication is not approved by the U.S. Food and Drug Administration (FDA) for a variety of reasons, one of which is the occurrence of retinopathy in some patients. In Europe and Canada, however, vigabatrin is the first line drug for patients with tuberous sclerosis and infantile spasms. Many parents learn about vigabatrin over the internet and ask to have their child placed on this medication. The dosage varies from 100-200 mg/kg/day.^{9,10}

Preliminary research demonstrates that topiramate and felbamate effectively treat infantile spasms; however, because of the possible risk of aplastic anemia and liver failure, felbamate is not typically used for this purpose. There are only anecdotal reports of efficacy in treating infantile spasms using tiagabine and lamotrigine. A few newly released studies using zonisamide for this purpose indicate that it is effective in approximately one-third of patients.

Epilepsy surgery in the form of cortical resection (usually multilobar) has been beneficial in some patients with underlying focal cortical dysplasias. These patients usually have cortical dysplasias in the posterior quadrants of the brain and present with the combination of partial seizures and infantile spasms.¹²

Lennox-Gastaut Syndrome

Lennox-Gastaut syndrome (LGS) is another generalized epilepsy syndrome predominantly confined to children. The definition for Lennox-Gastaut syndrome is generalized, multiple seizure types (ie, tonic, atonic, absence, and myoclonic) with generalized slow spike and wave discharges at 1¹/₂ Hz to 2¹/₂ Hz

and cognitive impairments. The degree of cognitive impairment is correlated with the underlying substrate of epilepsy and seizure control. As with infantile spasms, LGS can be divided into categories of symptomatic, cryptogenic, and idiopathic. Because 40% of patients with infantile spasms evolve into older children with LGS, the etiologies for LGS are very similar to patients with infantile spasms. The etiologies for LGS include perinatal hypoxic-ischemic encephalopathy, infarction (antenatal and perinatal), CNS infections, malformations of cortical development, tuberous sclerosis, chromosomal abnormalities, inborn errors of metabolism, head trauma, and rarely, brain tumors.¹³

There are relatively few AEDs that have been shown to be effective in the treatment of LGS. The ketogenic diet is one of the oldest known treatments for pediatric epilepsy and status epilepticus and it remains an important alternative therapy for LGS (see Treatment section). Unfortunately, phenobarbital and phenytoin have never been shown to be effective in the treatment of LGS, probably because of their sedative effects, which produce an activation of the epileptiform discharges on EEG.

The introduction of valproate in the late 1970s provided one of the first major breakthroughs in the treatment of LGS (although there is no Class I evidence of its efficacy). Other AEDs that have been shown to be effective in the treatment of LGS in clinical research studies include topiramate, lamotrigine, and felbamate. Felbamate was released in 1993 and was almost removed from the market because of reported cases of aplastic anemia and liver failure. Because of its efficacy and active lobbying by parents, felbamate remains on the market for the treatment of medically refractory epilepsy. The benzodiazepines are also helpful in the treatment of LGS if given intermittently to abort seizure clusters, eg, rectal diazepam. Benzodiazepines, given on a daily basis, are too sedating and many patients develop tachyphylaxis.^{14,15,16}

In some patients, none of the AEDs are helpful. Corpus callosotomy has been utilized effectively in patients with intractable atonic/tonic seizures uncontrolled by medical treatment. In addition, vagal nerve stimulation has recently been tried in patients with medically refractory Lennox-Gastaut syndrome; preliminary studies are encouraging.

There are also patients with Lennox-Gastaut syndrome who have underlying focal structural lesions that may be surgically remediable. These patients have a “generalized epilepsy syndrome,” but EEG source localization paradigms and neuroimaging strongly indicate an underlying focal generator. A number of surgical successes have been reported in the literature.

The long-term prognosis of children with Lennox-Gastaut syndrome is unfavorable. Cognitive and motor impairments are found in the majority of patients. The main risk factors for overall outcome depends on the underlying etiology and the ability to effectively control the seizures. The history of infantile spasms, early age of onset (before three years of age), high seizure frequency, and repetitive status epilepticus predict a poor prognosis.¹⁷

Generalized Idiopathic Epilepsy Syndromes—Childhood Absence, Juvenile Absence, and Juvenile Myoclonic Epilepsy

The idiopathic generalized epileptic syndromes of childhood and adolescence include *childhood absence epilepsy*, *juvenile absence epilepsy*, and *juvenile myoclonic epilepsy*.⁷ These epilepsy syndromes may be different phenotypic expressions of the same gene, with other genes required to activate the epilepsy gene. Children with these syndromes have normal neurological examinations and normal or above average intelligence. Depending on the age of onset, the children and adolescents with these epileptic syndromes may have varying clinical manifestation—absence, myoclonic and/or generalized tonic-clonic seizures—and varying prognoses.

Childhood absence epilepsy accounts for 2% - 8% of all cases of childhood epilepsy. Age of onset is generally between 5-10 years of age. The seizure semiology is characterized by absence seizures, ie, brief episodes of staring often accompanied by eyelid fluttering, facial clonic activity, or upper extremity myoclonus. These seizures are brief (they last only 2-10 seconds), occur multiple times per day, and do not feature a concomitant postictal phase. The absence seizures can be induced with hyperventilation. If the epilepsy begins before 9 years of age, the risk of having concomitant generalized tonic-clonic seizures is only 16%. If the epilepsy begins

later, the risk of generalized tonic-clonic seizures is close to 50%. Myoclonic seizures are rare.¹⁸

Juvenile absence epilepsy usually begins between 10-17 years of age and is associated with absence seizures and generalized tonic-clonic seizures. Absence seizures occur in all patients; generalized tonic-clonic seizures occur in almost 80%.

Juvenile myoclonic epilepsy (JME) typically begins during adolescence between 12-18 years of age. The earliest typical clinical symptom is early morning sudden myoclonic jerks of the shoulders and arms. Generalized tonic-clonic seizures evolve in 90% of patients and 33% also have absence seizures.¹⁹

The interictal electroencephalogram (EEG) in all cases demonstrates generalized spike and slow wave discharges. With the earlier onset, the generalized spike and slow wave discharges are at 3 cps. With JME, the generalized discharges consist of a faster, more complex pattern of generalized polyspike, spike, and slow wave discharges at 4-5 Hz.

The treatment for these three epileptic syndromes is similar. Ethosuximide (Zarontin[®]) is efficacious for absence seizures, but it can cause gastritis, hiccups, and behavioral changes.² Valproate (Depakote[®]) is effective for both absence and generalized tonic-clonic seizures, but given the recent association of valproate use with polycystic ovaries and anovulatory cycles, the American Epilepsy Society and the American Academy of Neurology have stated that valproate is relatively contraindicated in women of reproductive age.²⁰ Preliminary clinical research indicates that lamotrigine may be very effective in these epilepsy syndromes. Topiramate also shows promise in the treatment of generalized tonic-clonic seizures and myoclonic seizures but not absence seizures.

Prognosis varies depending on the age of onset. JME requires lifelong treatment because of the high rate of relapse when AED therapy is discontinued. On the other hand, childhood absence epilepsy has a much better prognosis, with over 50% of patients outgrowing their epilepsy by the age of puberty.

Localization-Related Epilepsies

The localization-related epilepsies can be divided into two categories: symptomatic and idiopathic. The symptomatic localization-related epilepsies are the result of underlying CNS pathology, eg, tumor, stroke, encephalomalacia from head trauma, hemorrhage, or malformation of cortical development. The idiopathic epilepsies are felt to have an underlying genetic predisposition.

Benign rolandic epilepsy of childhood (benign epilepsy of childhood with central-temporal spikes) is the most common epilepsy condition of childhood, and it accounts for approximately 25% of all epileptic seizures in children between the ages of 5-14 years of age. It is genetically determined and is probably autosomal-dominant, with variable penetrance and age-limited expression. Boys outnumber girls by 2:1. Children with this syndrome enjoy normal growth and development, although there have been some reports of comorbid learning disabilities. The seizure description is classically defined by sensorimotor symptoms and clonic activity in the face, arm, and/or leg, with associated drooling (hypersalivation) and speech arrest. There may be secondary generalization. The seizure frequency varies, but typically seizures are rare and are precipitated by sleep deprivation. They are predominantly nocturnal, occurring in the early morning hours prior to awakening or soon after falling asleep.²¹

The interictal awake EEG can be normal. With drowsiness and sleep, there is activation of central-temporal spikes that can be asymmetric and/or have a wide field spread. At times, the sleep EEG can be highly epileptogenic and produce a pattern resembling the electrical status epilepticus of slow wave sleep (ESES).

The most important fact about this epilepsy syndrome is that by the time of adolescence, it is outgrown. Treatment with AEDs does not appear to alter prognosis. In fact, AEDs are seldom used in patients with rare seizures. Medication may be indicated for those patients who are experiencing more frequent seizures that disrupt sleep, school performance, or psychosocial well-being. The AEDs typically chosen for this syndrome include carbamazepine, gabapentin, valproate, and lamotrigine.

Benign occipital epilepsy, also a genetically determined localization-related epilepsy, occurs in school-aged children and is relatively rare. Approximately 50% have a significant family history of epilepsy. The seizure is characterized by visual hallucinations, including flashing lights or blurred vision. There is progression to a complex partial seizure characterized by dizziness, disorientation, slurred speech, and ataxia. Hemiclonic seizures occur frequently. The postictal phase is almost invariably accompanied by a pounding migrainous headache.²²

Classically, the interictal EEG contains high amplitude spike and slow wave complexes at 2-3 Hz localized to the bioccipital and posterotemporal head regions, suppressed by eye opening.

The seizures are usually easily controlled with any of the AEDs, although there are reports of some children with a more severe form of this epilepsy. These seizures usually remit spontaneously during adolescence.

Localization-related epilepsy with mesial temporal sclerosis is classically found in patients who have a history of one or more prolonged febrile seizures followed by the development of seizures without fever. The reasons for the development of mesial temporal sclerosis remain poorly understood. There is increasing evidence to suggest that the temporal lobe in these children may contain a malformation of cortical development or other abnormality predisposing this site to epilepsy. This type of epilepsy is usually medically refractory. Epilepsy surgery is very effective, providing complete seizure freedom off AEDs in nearly 85% - 90% of patients.^{23,24}

Landau-Kleffner syndrome, ie, acquired epileptic aphasia, is a poorly understood syndrome characterized by a regression in expressive and receptive language in association with either focal or multifocal epileptiform EEG. These patients commonly have complex partial seizures in addition to their regression in speech and language; however, in 30%, the sole clinical manifestation is the regression in expressive and receptive language.²⁵

The underlying pathophysiology of Landau-Kleffner syndrome remains a mystery, and perhaps as a direct

result of this uncertainty, its treatment remains equally controversial. The goal of therapy is normalization of the EEG and a concomitant improvement in speech and language. AEDs are used (particularly valproate) and carbamazepine has been reported to worsen the condition. Steroids and ACTH have also been tried with some anecdotal success. In refractory cases, multiple subpial transactions have been performed over the epileptogenic zone. A multicenter, double-blinded, placebo-controlled treatment trial is needed to determine appropriate, effective therapies. The prognosis for this disorder is variable. Interestingly, the clinical seizures may remit before puberty, as do many of the EEG changes. Unfortunately, language disorder and neuropsychological consequences commonly remain.²⁶

Some clinicians have broadened the definition of Landau-Kleffner syndrome to include those children with developmental aphasia and underlying epileptiform EEGs. This encompasses the 20% of children with autism who have epilepsy. As a result, some children with autism have been treated with AEDs and even steroids to see if there is an improvement in clinical symptoms. This type of therapy remains an area of considerable controversy among child neurologists.²⁷

Rasmussen's syndrome is a special epileptic syndrome characterized by a triad of three symptoms: progressive hemiparesis, progressive epilepsy with focal motor seizures (often continuous), and cognitive decline.²⁸ The neurologic deterioration evolves as the seizures progress. This syndrome can affect all ages, typically young children. The pathophysiology is poorly understood, but there is some indirect evidence to suggest that the syndrome may be the result of an autoimmune disorder directed against the glutamate receptor.²⁹ Pathological specimens contain evidence of inflammation, but there has never been a specific virus identified with this syndrome.

This syndrome is refractory to AED therapy. Because of the autoimmune theory of pathogenesis, corticosteroids (and ACTH), plasmapheresis, and intravenous immunoglobulin have also been tried. There are anecdotal reports in the literature of transient improvement.³⁰ Functional or anatomic hemispherectomy is still regarded as the definitive treatment in this devastating condition, and hemispherectomy usually results in effective seizure control and improvement of cognitive function.¹⁶

4. Special Syndromes

Neonatal seizures are commonly the result of hypoxic-ischemic injury, sepsis, hypoglycemia, or hypocalcemia.³¹ There are two rare causes of neonatal seizures that pediatric residents should be familiar with: pyridoxine dependency and glucose transporter deficiency. Pyridoxine dependence is related to an insufficient production of GABA, a primary inhibitory neurotransmitter. The glucose transporter deficiency is characterized by low cerebrospinal glucose concentration. There is an enzymatic defect in glucose transport that disrupts facilitative diffusion of glucose across the blood/brain barrier. The latter two are typically overlooked but eminently treatable, particularly if recognized early. Pyridoxine, in dosages of 10-15 mg/kg/day, should be administered to any neonate with status epilepticus or poorly controlled seizures. The defect in glucose transport is recognized by performing a lumbar puncture and comparing serum glucose to cerebrospinal fluid glucose. If the CSF glucose is abnormally low, the ketogenic diet should be used as a treatment for the concomitant epilepsy. Other rare metabolic causes for neonatal seizures include pyridoxal-5-phosphate deficiency and biotinidase deficiency.

Neonatal seizure semiology is different from that of older children and adolescents. Because of the primitive synaptic network, neonatal seizures can be quite subtle. Examples of neonatal seizures include eye deviation with apnea or multifocal clonic activity. A neonate will not have a generalized tonic-clonic seizure, although he can have a tonic seizure. The neonate can also have “subtle seizures,” eg, bicycling or chewing movements, that may have no EEG correlate. Some clinical researchers believe that these events may be “brain stem release phenomena,” not seizures.

The most important therapeutic intervention in neonatal seizures is recognition of the underlying etiology followed by its prompt treatment. This may, in and of itself, abort any further seizure activity without the use of chronic AEDs.

Febrile seizures represent a very common special developmental seizure disorder, occurring in 2% - 4% of young children. By definition, a simple febrile seizure is a generalized tonic-clonic seizure experienced in children between the ages of 6 months to 5

years that is associated with a high fever not related to an underlying CNS infection. Multiple reviews establish the benign nature of these seizures. Simple febrile seizures carry a low risk for epilepsy, ie, only 1% - 2% compared with the general population’s risk of 0.5% - 1%. There is an underlying genetic predisposition, with a positive family history in 33% of first-degree relatives. The risk of febrile seizure recurrence is quite high, and one-third of children have at least one recurrence. If a child is less than 12 months of age at the time of the first febrile seizure, the risk of recurrence is 50%.^{32,33}

If the history for a febrile seizure is clear, no diagnostic studies need to be performed. The physician should design the work-up in response to the most likely etiology for the fever. A lumbar puncture should be performed, particularly in young infants less than 12 months of age, because signs and symptoms of meningitis are unreliable in this age group. If the thought of meningitis crosses the physician’s mind, a lumbar puncture should be performed. In this age group, the procedure is done easily. Missing the diagnosis of meningitis can have fatal consequences.

Febrile seizures constitute the most common cause of status epilepticus (SE) in infants and children. A recent study assessed the short-term outcome of children with febrile status epilepticus (FSE) versus children with brief febrile seizures (FS). Compared with the controls, children with FSE were less likely to have a family history of febrile seizures but more likely to be neurologically abnormal and have a prior history of neonatal seizures with a positive family history of epilepsy.^{36,37}

Phenobarbital is no longer used in the treatment of febrile seizures. There is no evidence to suggest that treatment with phenobarbital decreases the risk for developing epilepsy. Furthermore, the side effects of phenobarbital in these children is significant, eg, 40% exhibit hyperactivity, aggressive behaviors, impulsivity, poor attention and concentration, and/or sleep disturbance. Oral or rectal diazepam can be given to prevent febrile seizure recurrence in those predisposed children. The dosage of oral diazepam is 0.33 mg/kg every 8 hours during the course of the febrile illness.³⁸ This medication can produce side effects including sedation and irritability. The dosage of rectal diazepam is 0.5 mg/kg in

children under the age of 5 years. It should be given for febrile seizure clusters or a prolonged febrile seizure (lasting greater than 5 minutes).

The prognosis for febrile seizures is excellent. Very few children develop epilepsy. The risk factors for the development of epilepsy (outlined above) suggest an underlying substrate of epilepsy and suggest that the seizure threshold was simply lowered by the fever.

Epilepsy develops in fewer than 5% of all children with simple febrile seizures. The identified risk factors for the development of epilepsy include: prolonged seizure, focal seizure, two or more seizures in the same illness, family history of epilepsy; developmental delays, or an abnormal neurological exam. The presence of one or two risk factors increases the risk of epilepsy to only 5% - 10%.³⁴ The recent identification of the epilepsy syndrome, called febrile seizure “plus” syndrome, underscores the need for better definition of these epilepsy syndromes. The febrile seizure plus syndrome is associated with febrile seizures as well as generalized tonic-clonic seizures without fever in the context of a positive family history with different seizure phenotypes. This syndrome has been linked with a mutation in the NA^+ channel 1 subunit gene, *SCN1B*.³⁵

Drug Therapy

When discussing antiepileptic drug therapy, it is important to recognize the seizure type as well as the epilepsy syndrome. This is the single most important criterion in making a decision about antiepileptic medication.

There are basic principles to remember in choosing antiepileptic drug therapy (AED):

1. AED monotherapy is effective in most patients and avoids drug interactions.
2. Therapeutic blood levels represent a range of efficacy and are not absolute levels, ie, they represent trough levels.

3. AEDs should be titrated slowly and only to the point of seizure control, not necessarily “into the therapeutic range.”

4. Seizure control should not be achieved at the expense of side effects.

5. Drug compliance is enhanced when medication is given once or twice daily. Therefore, sustained-release medication should always be considered.

When should treatment be instituted after a first seizure? As a general rule, it is not necessary to begin AED therapy after a single, unprovoked seizure. The work-up should include a non-urgent MRI scan of the brain and an EEG—both awake and sleep. In the pediatric population, 30% of the epileptiform discharges are seen in one state only—either wakefulness or sleep, but not both. Statistically, the chance of seizure recurrence after the first seizure is approximately 30% - 40%; however, there can be exceptions to this rule of thumb:

1. If the EEG demonstrates temporal epileptiform discharges or generalized spike and slow wave discharges, the chance of recurrence is much higher, approaching 90%.
2. If there is an underlying structural lesion on MRI, the chance of seizure recurrence is high.

If the child has a second seizure, the risk of recurrence is also much higher. Antiepileptic medication is generally recommended following a second seizure. There are exceptions to this, particularly if a benign epilepsy syndrome is identified, eg, benign rolandic epilepsy.

There should also be special consideration given to the adolescent or young adult who is driving. Following a single unprovoked seizure, the patient should not be allowed to drive. The statutes of each state differ. Some states require physicians to report a patient who has had a seizure and other states adopt a voluntary surrender plan. In addition, states vary greatly in the length of time required to be seizure-free before resumption of driving privileges, ie, 3 months to one year. If an adolescent or young adult relies on driving as a mode of transportation, one could consider starting an AED immediately following a single unprovoked seizure.

Table 5**Summary of Commonly Used Antiepileptic Drugs (New Drugs)**

AED	Indications	Maintenance Dosage (mg/kg/d)	Starting Dosage	Half-Life (h)	Therapeutic Range	Common Side Effects	Serious Idiosyncratic Side Effects
Felbamate (Felbatol®)	Partial Partial with 2° general Tonic Atonic	Maximal dosage 90	15 mg/kg/d; increase in 10 mg/kg increments to 60 mg/kg/ if necessary	13-24	Not established	Anorexia Insomnia Somnolence	Aplastic anemia Hepatotoxicity Rashes
Gabapentin (Neurontin®)	Partial Partial with 2° general	20-60	10 mg/kg/d; increase in 5 mg/kg increments	5-8	Not established	Lethargy Dizziness Irritability	None
Lamotrigine (Lamictal®)	Partial Partial with 2° general Absence	5-15; dosage dependent on other drugs used; if on enzyme inducers, use 10-15; if on valproate, use 2-3. Must titrate the dosage slowly	12.5-25 mg/d; increase slowly; be cautious if patient is on valproate	15-60 (highly dependent on concomitant AEDs)	Not established	Rashes Lethargy Irritability Movement disorder	Rashes
Tiagabine (Gabitril®)	Partial Partial with 2° general	0.5-1; dosage dependent on other drugs used; if on enzyme inhibitors, use 0.7-1.5; if on no enzyme inhibitors, use 0.3-0.4	0.1 mg/kg/d; increase weekly by 0.1 mg/kg/d	3-8	Not established	Lethargy Confusion Mental dullness Difficulties with concentration	None
Topiramate (Topamax®)	Partial Partial with 2° general	5-10	1-2 mg/kg/d; increase weekly by 1 mg/kg/d	12-30	Not established	Irritability Hyperactivity Cognitive slowing Weight loss Renal stones Oligohydrosis Metabolic acidosis	None

Abbreviations: AED = antiepileptic drug; 1° = primary; 2° = secondary.

Table 6

Summary of Commonly Used Antiepileptic Drugs (Established Drugs)

AED	Indications	Maintenance Dosage mg/kg/d	Starting Dosage	Half-Life (h)	Therapeutic Range (ug/mL)	Common Side Effects	Serious Idiosyncratic Side Effects
Carbamazepine (Tegreto®)	Partial Partial with 2° general 1° general, tonic-clonic	10-20	5-10 mg/kg/d	8-25	8-12	Diplopia Lethargy Blurred vision Ataxia Incoordination	Rashes Hepatic dysfunction Pancreatitis Aplastic anemia Leukopenia
Ethosuximide (Zarontin®)	Absence	15-40; most children require 15-20	<6y: 10 mg/kg/d >6y: 250 mg/d	25-40	40-100	Gastrointestinal Distress Hiccups Lethargy	Rashes Leukopenia Pancytopenia Systemic lupus erythematosus
Phenobarbital	Partial Partial with 2° general 1° general, tonic-clonic	<1y: 3-5 >1y: 2-4 Teenagers, adults: 2-3	Same as maintenance	40-70	15-40	Irritability Hyperactivity Lethargy	Rashes
Phenytoin (Dilantin®)	Partial Partial with 2° general 1° general, tonic-clonic	5 (may need higher doses in children <5-6y)	Same as maintenance	Dependent on concentration	10-20	Lethargy Dizziness Ataxia Gingival hypertrophy Hirsutism	Rashes Hepatic dysfunction Lymphadenopathy Blood dyscrasias
Topiramate (Topamax®)	Partial Partial with 2° general 1° general, tonic-clonic	12-25	<6y: 50 mg qhs <12y: 100 mg qhs >12y: 150 mg qhs	5-8 (Phenobarbital 40-70)	5-12	Irritability Hyperactivity Lethargy Nausea	Rashes
Valproic Acid (Depakene®)	Partial Partial with 2° general 1° general, tonic-clonic Absence Myoclonic Tonic Atonic	15-60	5-15 mg/kg/d; increase by 10-15 mg/kg/d every 2 wk	4-14	60-100	Lethargy Weight gain or loss Hair loss Tremor	Hepatic dysfunction Pancreatitis Anemia Thrombocytopenia
Levetiracetam	Partial Partial with secondary generalization, myoclonic	60	10 mg/kg/day; increase by 10 mg/kg/week until at initial maintenance of 30 mg/kg/day	12-18	Not well established	Irritability Aggression	None to bone marrow or liver

Abbreviations: AED = antiepileptic drug; 1° = primary; 2° = secondary.

The last few years have seen a rapid escalation in the marketing of AEDs. The drugs of choice for partial seizures now include a broad range of AEDs, including carbamazepine, gabapentin, lamotrigine, levetiracetam, topiramate, valproate, zonisamide, phenobarbital, and phenytoin. The newer AEDs have all been approved by the Food and Drug Administration (FDA) as adjunctive therapy in the treatment of partial seizures in adults. Topiramate has received approval for treatment of partial seizures in children down to the age of 2 years. Lamotrigine has been approved for both the treatment of partial seizures as well as generalized tonic-clonic seizures. Levetiracetam has recently received FDA approval for the treatment of myoclonic seizures. See Table 5 and 6 for a listing of new and old AEDs, their dosages, indications, and side effects.³⁹⁻⁴⁵

Physicians in this country continue to frequently prescribe phenobarbital and phenytoin (over 50% of the time). Phenobarbital is used extensively in the treatment of neonatal seizures; however, in older children, it does carry a risk of significant side effects, particularly irritability, poor attention and concentration, hyperactivity, aggressive behaviors, and cognitive impairments. Phenytoin is very difficult to dose in children less than one year of age, given the fact that its bioavailability is erratic in children less than a year of age and that its first order pharmacokinetics makes it very difficult to dosage in young infants. In addition, the cosmetic side effects make it less attractive for long-term use.

Alternatives to Antiepileptic Drugs

The Ketogenic diet dates back to Biblical times when people with seizures were considered to be “possessed by the devil” (many had epilepsy) and subsequently sent out to the desert to fast and pray. The diet became repopularized in the twentieth century by Dr. Haddow Keith from the Mayo Clinic, who observed that children in status epilepticus stopped once they reached ketosis. The ketogenic diet provides most of a child’s calories as fat, resulting in ketosis. The diet must be strictly adhered to and requires that every piece of food be carefully weighed and measured for fat/carbohydrate/protein content. Any deviation from the diet will result in the loss of ketosis and recurrent seizures. The exact mechanism by which

the ketogenic diet provides seizure control remains unknown. It is presumed that the ketones have antiepileptic properties. In the appropriately chosen patients, the ketogenic diet can eliminate seizures in one-third, decrease seizure frequency by over 50% in another third, and lacks efficacy in the final third. The diet can be very challenging for children who already have dietary preferences.^{20,21}

A vagal nerve stimulator was approved by the FDA for use as adjunctive therapy in the treatment of medically refractory localization-related epilepsy in children and adults over the age of 12 years. The vagal nerve stimulator is a pacemaker implanted in the chest pocket below the clavicle that delivers pulses antidromically from a bipolar electrode connected to the vagus nerve. The exact mechanism(s) of action by which the vagal nerve stimulator works remains an enigma. Most likely, however, the VNS influence over the EEG is mediated via the brainstem, with its projections to the cortex. High stimulation of the vagus nerve appears to result in EEG desynchronization. The efficacy of the VNS is still a subject of considerable debate, but preliminary studies are encouraging. There may be special populations, including children with Lennox-Gastaut syndrome and children with tuberous sclerosis and intractable partial seizures. Efficacy may be enhanced over time.^{48,49}

Side effects include bleeding, infection, voice alteration (or hoarseness when the VNS cycles on), cough, throat pain, dyspepsia, and nausea. There are no reports of cardiac arrhythmias with this device.

Immunotherapy has been used in the treatment of a variety of rare epilepsy syndromes, including infantile spasms, Rasmussen’s syndrome, and Landau-Kleffner syndrome, as discussed in previous sections.

Epilepsy surgery should not be considered a treatment of last resort. It can be lifesaving and should be considered early in the child’s course. This is particularly true in the following conditions:

1. Children with lesional localization-related epilepsy, ie, presence of a tumor, tuber, or other structural lesion, whether or not it is controlled with AEDs.

2. Children with catastrophic epilepsies where the continuation of the epileptic encephalopathy and clinical seizures will result in substantial morbidity in terms of development and quality of life. Examples of this include patients with:

- a. Infantile spasms and an underlying malformation of cortical development
- b. Sturge-Weber syndrome with progressive hemiparesis and intractable seizures
- c. Rasmussen's syndrome with progressive encephalopathy, seizures, and hemiparesis
- d. Malformations of cortical development, eg, hemimegalencephaly

Other candidates for epilepsy surgery include:

1. Children with nonlesional localization related epilepsy who have failed two-to-three standard AEDs. (If a patient fails one AED, the chance of a second AED controlling the seizure disorder is only 10%).
2. Children with generalized or multifocal epilepsies in whom the clinical presentation, seizure semiology, EEG findings, MRI scan of the brain, or other tests strongly suggest a single focal generator for the epileptic condition.
3. Children with intractable generalized epilepsy who have tonic/tonic seizures may be candidates for corpus callosotomy.

The most important questions that must be asked before the consideration of a presurgical evaluation are:

- Is this an epileptic syndrome with a poor prognosis for remission?
- Will the continuation of the epileptic seizures have a significant impact on the child's ultimate development and/or quality of life?
- Have the seizures been refractory to several AEDs?

- Is the epileptogenic zone able to be localized, using EEG data and neuroimaging?
- Can the epileptogenic zone be resected without unacceptable neurologic deficits?^{23,50}

The type of epilepsy surgery performed depends on the localization of the epileptogenic zone. Some of the more common surgical procedures include *temporal lobectomy with amygdalohippocampectomy; focal cortical resection; hemispherectomy; and corpus callosotomy.*

5. Emergency Treatment of Status Epilepticus

Convulsive status epilepticus is a medical emergency. Status epilepticus is defined as a seizure that is enduring or repetitive without recovery and lasts more than 5 minutes. Any seizure that lasts greater than 20 minutes results in a cascade of events that can lead to neuronal cell loss. In addition, if not treated promptly, status epilepticus produces an alteration in gamma-aminobutyric acid (GABA) receptors that reduces the ability of the benzodiazepines to be effective. Status epilepticus must be treated promptly with intravenous medications.

The single biggest mistake made in the treatment of status epilepticus is the use of inadequate doses of medications to effectively abort the seizures. In Table 7,

the doses and medications of choice are listed. In most patients, status epilepticus can be treated effectively without intubation. On the other hand, if the airway is compromised, intubation should be performed quickly and without hesitation. Using smaller doses of medication to avoid intubation is inappropriate.⁵¹

In neonates and young infants, an intravenous dosage of 100-200 mg of pyridoxine should be given if the episode of status epilepticus remains unresponsive to conventional medication. Pyridoxine-dependent epilepsy is rare but eminently treatable.

Table 7

Treatment of Status Epilepticus

Maintain the ABCs—airway, breathing, and circulation

Stop clinical and electrographic seizures using intravenous medication

Lorazepam 0.1 mg/kg/dose x 2

Fosphenytoin 20 mg/kg

Phenobarbital 20 mg/kg

If intravenous access not readily available, may use diazepam rectal gel (Diastat®)

0.5 mg/kg for children less than 5 years of age

0.3 mg/kg for children between the ages of 5 and 11 years

0.2 mg/kg for children 12 years of age and over

Identify precipitating factors and treat reversible conditions

Prevent or correct systemic complications

If status epilepticus remains unaborted, patient should be transferred quickly to a tertiary care facility.

May give additional 7 mg/kg of fosphenytoin and additional 10 mg/kg boluses of phenobarbital in the interim.

Diastat can also be prescribed for home use by parents in the event of a seizure lasting greater than 5 minutes or a seizure cluster

6. Headaches

Headaches are very common in the pediatric population. Children's headaches can be appropriately divided into several categories, depending on symptomatology. These categories include:

Acute headaches

Acute recurrent headaches

Chronic progressive headaches

Chronic nonprogressive headaches.⁵²

The evaluation of headache pain should involve:

1. Careful physical examination
2. Detailed neurological examination
3. MRI brain imaging (only as directed on the basis of history and physical examination) (Table 8)
4. Laboratory tests (only as deemed appropriate on the basis of the history and physical examination)

Acute headaches may vary in quality and character. They are usually the result of an underlying infection, inflammation, or toxic exposure. Some of the most common causes of this headache type include:

Meningitis/encephalitis

Sinusitis

Otitis media

Impacted or decayed tooth

Influenza or other systemic viral illness

Hypertension

Inflammation

Clinical pearl. It is very rare that “eye strain” or allergies causes headaches in children. The key to diagnosis is performing a careful physical and neurological examination, paying special attention to the head and neck.

Table 8

Criteria for MRI Scan of the Brain in Patients with Headaches

Acute disabling headaches

Unifocal pain

Focal neurological deficit

Papilledema

Complicated migraine

Morning headache with valsalva sensitivity

Rapidly progressive headache

Alteration of consciousness with headache

Profound anxiety on the part of the parent or child

Acute recurrent headaches are usually either migraine headaches or tension headaches. Migraine headaches are common, even in young children. Approximately 20% - 30% of children experience their first migraine headache by five years of age. Most recurrent paroxysmal headaches prior to the age of 10 years are migrainous. The diagnosis of a migraine headache can be made with a detailed history and physical examination. Migraine is genetically based, with a positive family history in 70% - 90% of patients. These migraine headaches differ from adults' in several ways: they are generally shorter in duration; are commonly bilateral; and are associated with nausea and vomiting; photophobia, or phonophobia—but not necessarily all three. Sleep commonly brings relief from the headache pain. Many migraine headaches in children go unrecognized.

The pathophysiology of migraine headaches is becoming increasingly understood. It is simplistic and erroneous to consider the pain of migraine headaches to be the result of vasoconstriction/vasodilation of blood vessels. The pain of the headache is synonymous with the depolarization of the perivascular sensory axons located in the trigeminovascular complex. These sensory axons are distributed along the intracranial and dural arteries and veins. The sensory axons release local vasodilating and permeability promoting peptides when stimulated. Modulation of the perivascular sensory axon thresholds can occur via several different mechanisms: 1) neurochemical transmissions of serotonin, substance P, histamine, hormones,

alcohol, bradykinin, and food; 2) mechanical stretch receptors; 3) ionic/synaptic transmissions, spreading an electrical depression across neuronal membranes; and 4) neurovascular sympathetic/parasympathetic responses.

Visceral (blood vessel) and somatic (forehead) inputs into the trigeminal nucleus complex in the brainstem may explain the referral of pain superficially on the scalp and may contribute to the poorly localized and concomitant autonomic symptoms. The trigeminovascular fibers may also contribute to the hyperemia during the headache phase.

In the new classification, migraine headaches are divided into several categories. Common migraine headaches are now classified as migraine headaches without aura; classic migraine headaches are termed migraine headaches with aura. Auras are typically visual, with either scintillating lights or visual scotomas. An aura, by definition, does not last greater than 60 minutes and the onset of headache pain is within 60 minutes of the onset of the aura.

Complicated migraine headaches are migraine headaches associated with transient neurologic deficits. Rarely are the neurologic deficits permanent. Complicated migraines require further noninvasive evaluation, including MRI scan of the brain; MR angiogram, as well as an EKG and echocardiogram looking for congenital heart disease, including PFO; blood tests for mitochondrial disorders and coagulopathies (protein C, protein S, anti-thrombin III, or Factor V Leiden deficiencies); antiphospholipid antibody syndrome; and lupus vasculitis. To exclude the possibility of nonconvulsive status epilepticus, an EEG should also be performed if the migraine is associated with confusion or disorientation. Treatment with vasoconstrictors or the triptans are contraindicated with complicated migraines.⁵³

Examples of complicated migraines in the pediatric population include:

Basilar migraines. These present with blurred or tunnel vision followed by slurred speech/ dysarthria, vertigo, ataxia, and/or diplopia. The symptoms may progress to obtundation or loss of consciousness.

The headache pain is usually occipital. Basilar migraines are the most common form of complicated migraine in the pediatric population.

Confusional migraines. These migraines are very frightening to parents. They typically occur in the adolescent population and present with agitation and confusion. When seen in the emergency room in this state, it is very appropriate and imperative to conduct a full-scale investigation, looking for structural CNS lesions, meningitis/encephalitis, drug/toxin exposure, trauma, or metabolic abnormalities. As the confusion clears (generally *after* all of the above tests have been completed), the patient begins to complain of a severe, throbbing headache.

Hemiplegic migraines. These are associated with headache and hemiplegia linked to chromosome 19p13 or chromosome 1q31a, therefore, they can be familial.

Ophthalmoplegic migraines. These are associated with headache and partial or complete paralysis of cranial nerve III. The paralysis is felt to be secondary to edema of the internal carotid artery in the cavernous sinus. Steroids have been used to reduce the pain and speed recovery from the ophthalmoplegia.

Retinal migraines. These result in transient monocular loss of vision. A careful search should be made for intraocular pathology and thromboembolic phenomena.

There are also migraine variants in the pediatric population that are not typically found in their adult counterparts. They include:

1. **Paroxysmal vertigo**, which is usually seen in children between the ages of 2-6 years. This condition is characterized by brief paroxysmal episodes of vertigo, facial pallor, and nystagmus. Patients often are frightened during the episodes; they do not lose consciousness. Children with these episodes often develop migraine headaches as they grow older.
2. **Paroxysmal torticollis**, which typically occurs in infants and consists of paroxysmal episodes of head tilt associated with presumed headache pain, agitation, nausea, and vomiting. The episodes can

last for hours to days. In rare instances, a cranio-cervical junction tumor can cause similar symptoms and radiological evaluation of this area is indicated.

3. **Cyclic vomiting syndrome** is a rare condition characterized by sudden onset of vomiting (usually in the early morning hours out of sleep). It is accompanied by abdominal pain and nausea. The vomiting is often profuse and unremitting for several hours, resulting in dehydration and hospitalization. Children with this syndrome need to have a thorough evaluation to exclude: 1) metabolic disorders (mitochondrial disorders, an intermittent branched chain aminoaciduria, or an intermittent urea cycle defect); 2) gastrointestinal obstruction or structural abnormality; and 3) underlying CNS structural abnormality.⁵⁴

Treatment

In approaching a patient with migraine headaches, one must take into account the patient's age, type of migraine, severity and frequency of attacks, known precipitating triggers, family/patient reliability, and the family/patient attitude toward medication.

One of the first steps in managing migraine headaches is to offer reassurance that the headache pain is not due to an underlying structural lesion in the brain. Next, it is usually very helpful to have the patient/family maintain a headache diary, so that precipitating or aggravating factors can be identified. Migraines can be triggered by stress, lack of sleep, relative dehydration, fasting, or even specific foods. However, in children, specific triggers may not be identified. Lifestyle modifications should be recommended in all migraineurs, including stress management, adequate hydration, regular meals, and good sleep hygiene. Techniques, such as relaxation exercises, meditation, and biofeedback may be very helpful in reducing the frequency of attacks.

The pharmacologic treatment of migraine headaches can be divided into two categories: symptomatic acute abortive and prophylactic therapy.

Acute abortive therapy usually includes one of the analgesic preparations, such as acetaminophen or the NSAIDs (nonsteroidal anti-inflammatory drugs). Clinical research indicates that the NSAIDs, especially when combined with sips of a caffeine-containing beverage, are more effective than acetaminophen in aborting migraine headaches.

Table 9

Acute, Abortive Treatment for Migraine Headaches

	Doses	Side Effects
Aspirin	15 mg/kg/4-6 hrs	Bleeding; GI upset; risk of Reye's syndrome if febrile and ill
Acetaminophen	15 mg/kg/4-6 hrs	
Nonsteroidal anti-inflammatory drugs (NSAIDs), ie, ibuprofen	15 mg/kg/4-6 hrs	Bleeding; GI upset
Sumatriptan* (Imitrex®) Also available as a nasal spray	.06 mg/kg SQ; 25-50 mg po 10 mg (<40 kg body weight) 20 mg (≥40 kg body weight)	Shortness of breath Unpleasant taste Facial flushing and feeling of warmth
Zolmatriptan*	Start with 2.5 mg; may give 5 mg	Shortness of breath Facial flushing and feeling of warmth

* Pediatric dosage, safety, and efficacy have not yet been established. Approved for children 18 years and older

Frequent use of NSAIDs may, however, cause rebound headaches. Aspirin therapy also carries a high risk of rebound headaches, as well as the risk of Reye's syndrome in acutely ill, febrile children and adolescents.

In an adolescent patient with infrequent severe migraines, the triptan preparations can be very effective in aborting headaches. The use of the triptans, and zolmatriptan, such as sumatriptan, has not been approved for children less than 18 years of age and is contraindicated in patients who have complicated migraines⁵⁵ (Table 9). The side effects experienced with the triptans (facial flushing and a feeling of warmth) are usually transient and tolerable.

Prophylactic medications should be initiated in those patients who have migraine headaches two to three times per week, requiring abortive therapy. It should also be considered in those patients who miss an excessive number of school days, have attacks that last several days, or have migraine headaches that are unresponsive to the abortive measures described above. Prophylactic medication should also be considered in those patients who have complicated migraines.

The common prophylactic medications are outlined in Table 10. None of these medications is FDA-approved for children in the prophylactic treatment of migraine headaches. However, these are the medications that are typically used by pediatric neurologists. Propranolol is one of the oldest medications used in the prophylactic treatment of migraines. It is usually well tolerated in young children but contraindicated in those children who have reactive airway disease/asthma. Propranolol can also cause exercise intolerance, depression, weight gain, and nightmares. Cyproheptadine is also commonly used for the prophylactic treatment of migraines. Its main side effects include sedation, dry mouth, and increased appetite with weight gain. Valproate is being used more commonly in the prophylactic treatment of migraine headaches. Generally, one can use lower doses than what is typically used to treat epilepsy. Common side effects include weight gain and tremor. Rare side effects include pancreatitis and liver toxicity. Topiramate has also been approved for the prophylactic treatment of migraines. Its main side effects include cognitive slowing, anorexia, weight loss, oligohydrosis, metabolic acidosis, and renal stones. Again, as

Table 10

Prophylactic Treatment of Migraine Headaches

Propranolol	2-4 mg/kg/day
Amitriptyline	1 mg/kg/day, usually 25-50 mg
Valproate	20-40 mg/kg/day
Cyproheptadine	0.25-1.5 mg/kg
Topiramate	1-4 mg/kg/day

with valproate, one can use much lower doses than what is typically used to treat epilepsy. The calcium channel antagonists have been touted as effective in the prophylactic treatment of migraine headaches, but recent clinical research sheds doubt on their efficacy. One of the most effective prophylactic treatments for migraine headaches is amitriptyline or nortriptyline. Many physicians do not use these medications because of their anti-cholinergic side effects and the need for serial EKG monitoring. Amitriptyline, in particular, is very effective and should definitely be tried in patients with migraines recalcitrant to other therapies.⁵⁵ Many patients respond to low doses of amitriptyline, as little as 25-50 mg per day.

In the pediatric population, there are four recognized headache syndromes that only respond to indomethacin. The dose is 25-150 mg per day and symptoms usually abate within 48-72 hours.

The recognized indomethacin-responsive headaches include:

- Exertional headaches, which are precipitated by exercise, cough, or coitus
- Cyclic cluster migraines, which occur daily for several days/weeks and then disappear for several months
- Chronic paroxysmal hemicrania
- Hemicrania continua

7. Status Migrainosis

The treatment of status migrainosis can be challenging. One must evaluate the patient carefully for contributing factors, including illness, dehydration, stress, medication abuse (such as the daily use of NSAIDs).

In addition, therapy should include:

- Adequate hydration, with intravenous fluids
- Sedation
- Antiemetics

The selective use of analgesics, triptans, intravenous steroids, or intravenous valproate is based on the clinician's own comfort level and familiarity with these medications. The use of intravenous ketorolac or steroids are my own personal favorites. There should be steadfast avoidance of the opiate medications. In addition, there are no publications or data on the use of intravenous valproate in the treatment of status migrainosis⁵⁶ (Table 11).

Chronic progressive headaches is a description that implies that there is an underlying structural lesion in

the cranial vault that is causing increased intracranial pressure or other related problems. These headaches are recognized by their progressive nature. If there is concomitant increased intracranial pressure, the headaches are exacerbated by change in position or Valsalva maneuver, worse in the early morning hours, and may cause nocturnal awakening from sleep. A careful neurological examination is warranted, as there are usually neurologic deficits such as papilledema or cranial nerve VI palsy.

The differential diagnosis included in this group includes: 1) hydrocephalus; 2) brain tumor; 3) brain abscess; 4) pseudotumor cerebri; 5) chronic subdural hematoma; 6) chronic/subacute meningitis; and 7) primary CNS vasculitis.

An MRI scan of the brain should be obtained when confronted with a patient with a chronic progressive headache. A CT scan is inadequate when looking for a lesion in the brain. The only time that it might be a first option is when there is a suspicion for hemorrhage or trauma. It can also be used to screen for hydrocephalus. Lumbar puncture may be required if CNS infection, vasculitis, or pseudotumor cerebri (see below) is suspected. A lumbar puncture should be obtained only after neuroimaging is completed, in order to ensure that there is no risk of herniation.

Table 11

Status Migrainosis Treatment Options

IV hydration is standard of care

Subcutaneous sumatriptan 2-6 mg (in adolescent population only)

Intravenous ketorolac 30-60 mg

Intravenous neuroleptics or antiemetics
Chlorpromazine 0.5-1.0 mg/kg/dose

Intravenous steroids
Methylprednisolone 30 mg/kg/dose, maximum 1 gm

Intravenous dihydroergotamine
Pretreat with antiemetic and sedative, such as chlorpromazine and lorazepam (.05 mg/kg)

Use test dose of 0.1 mg. Treatment dose is 0.1-0.2 mg/dose q8hr

Pseudotumor cerebri or “benign” increased intracranial hypertension is characterized by headache pain that is chronic, progressive, and typically, throbbing. It may be associated with blurred vision, visual obscurations, or diplopia. It most commonly occurs in overweight, adolescent girls. Risk factors for the development of pseudotumor cerebri fall into three broad categories: 1) drugs (eg, tetracyclines, corticosteroids, corticosteroid withdrawal, hypervitaminosis A, and oral contraceptives); 2) systemic disorders (eg, iron deficiency anemia, leukemia, polycythemia, antiphospholipid antibody syndrome, and systemic lupus erythematosus); and 3) metabolic-endocrinologic disorders (eg, hyperthyroidism, adrenal insufficiency, obesity, hypoparathyroidism, and pregnancy).

On physical examination, there is usually visual blurring, and an enlarged blind spot (70%), papilledema, and sometimes CN VI palsy. On MRI scan of the brain, there is no intraparenchymal abnormalities, but slit-like ventricles may be seen. A lumbar puncture is diagnostic, if it demonstrates increased opening pressure. Treatment is controversial, but most patients do best with the combination of serial lumbar punctures (where enough CSF is drained off to normalize pressure) and acetazolamide therapy (dosage of 20 mg/kg/day in two divided doses).⁵⁵

The pathophysiology of pseudotumor cerebri is poorly understood; however, elevated venous sinus pressure is consistently seen.

Chronic nonprogressive headaches are poorly understood and not easily treated. They are characterized by gradual onset and prolonged duration. They are typically bilateral or poorly localized, nonthrobbing, and do not improve with sleep. They are often associated with anxiety and depression, although it is difficult to tease out which symptom came first. The neurological examination is invariably normal. They are also a frequent endpoint of chronic analgesia overuse, ie rebound headache syndrome.

These headaches are infrequent in childhood, but they increase in adolescent years. They are seen most commonly in adolescent girls. Many clinicians

have ascribed a psychosomatic etiology to these headaches, but the current hypothesis is that the chronic nonprogressive daily headaches may be a variant of migraine headaches transformed into chronic headaches and/or the result of estrogen/progesterone changes. As the pain persists, many of these young women also develop muscle tension headaches, resulting in a mixed headache picture.

The treatment of chronic nonprogressive headaches is equally vexing. It is important to talk to the family and patient about the fact that the pathophysiology for this headache entity is poorly understood, treatments are largely unsatisfactory, and that the headache pain will subside slowly, usually in six months to one year.

The treatment approach should be multidisciplinary and should involve pharmacologic and nonpharmacologic therapies:

1. Tricyclic antidepressants, usually amitriptyline or nortriptyline. If insomnia is an issue, amitriptyline would be the most appropriate choice.
2. Biofeedback
3. Relaxation exercises
4. Regular aerobic exercise helps with the headache and concomitant depression.
5. Psychotherapy
6. Meditation
7. Adequate hydration with noncaffeinated beverages.
8. Diet modifications with regular, healthy meals.
9. Adequate sleep hygiene

8. Developmental Delays in Infants and Children

Developmental delays in infants and children must be approached in a systematic fashion; ie, asking questions in the clinical history and performing a detailed neurological examination that will assist in localization of the disease process (“white matter” vs. “gray matter,” upper motor neuron involvement vs. lower motor neuron involvement, or both) and ascertainment of whether the problem is static or progressive:

1. Onset of the problem
2. Static or progressive. Has there been a slowing in development, plateauing in development, or an actual loss of previously acquired developmental milestones?
3. Episodic symptoms or continuous ones?
4. Diffuse changes in the child’s state, encompassing cognitive, motor, and social arenas? Or more selective and focal changes?
5. Are there concomitant cognitive impairments?
6. Are there comorbidities, such as epilepsy, attention deficit disorder, or behavioral disinhibition?
7. Are the cranial nerves involved, ie, are there visual impairments, abnormalities in eye movements, facial asymmetry, hearing loss, or difficulty swallowing?
8. Is there hypotonia and weakness, hypotonia without weakness, spasticity?
9. Are the deep tendon reflexes hyperreflexic, hyporeflexic, or absent?
10. Is there ataxia, dysmetria, tremor, or abnormal movements such as chorea or dystonia?
11. What are the gait abnormalities?

Cerebral Palsy

Spasticity without obvious cognitive impairments or epilepsy suggests an upper motor neuron process involving predominantly the white matter. The most obvious diagnosis would be “cerebral palsy,” ie, a static encephalopathy involving the white matter, resulting in static motor deficits that can improve over time. In premature infants, due to the fragile nature of the germinal matrix near the ventricles, motor deficits classically involve the lower extremities more than the upper extremities. The corticospinal tract fibers to the legs pass closest to the ventricles and these fibers are preferentially affected in the event of ischemia or intraventricular hemorrhage. The term “cerebral palsy” is overused and should be confined to the above-stated strict definition. Most child neurologists have abandoned the term in favor of “*static encephalopathy*.” “Cerebral palsy” is still widely used in the school system, as “static encephalopathy” is not recognized. Therefore, if children with static encephalopathy are to obtain necessary physical therapy and occupational therapy, “cerebral palsy” must be indicated in the required paperwork.

Children with presumed cerebral palsy still deserve a full diagnostic evaluation, unless there are compelling data to suggest otherwise, as the diagnosis of cerebral palsy is a diagnosis of exclusion. There may be some obvious cases of cerebral palsy, such as a premature infant with a history of grade II-IV intraventricular hemorrhage and documented periventricular leukomalacia on MRI brain imaging.

The etiology of cerebral palsy remains poorly understood. The results of a NIH-funded perinatal collaborative project suggest that only a small portion of infants with the diagnosis of cerebral palsy have the condition as a result of hypoxic-ischemic injury at the time of birth. The factors associated with the development of cerebral palsy include maternal mental retardation, other somatic malformations, breech presentation (not breech delivery), and birth weight less than 1700 grams. Except for the last predictive factor (ie, prematurity), the others strongly suggest that the etiology of cerebral palsy may be genetic and begin in the first trimester.^{57,58}

Other etiologic possibilities must be considered when presented with a child who has cognitive deficits and/or epilepsy accompanied by spasticity. This suggests a more extensive process, as the condition lies outside the realm of a strictly “white matter” disease. In this case it is also important to determine, if at all possible, where the disease is localized and whether or not it is static or progressive. The differential diagnostic list would include:

Structural changes in the brain, eg, malformations of cortical development or encephalomalacia due to perinatal infarction, hypoxic-ischemic injury, trauma, or meningitis/encephalitis;

Chromosomal abnormalities or genetic syndrome, particularly if there are dysmorphic features;

Inborn errors of metabolism.

Inborn Errors of Metabolism

The inborn errors of metabolism are particularly difficult to navigate. There are clinical pearls, however:

1. In newborn infants, the typical presentation for an inborn error of metabolism is lethargy, vomiting, poor feeding, and failure to thrive. The most common cause for these symptoms in newborns is sepsis. If sepsis is excluded, along with electrolyte imbalances and respiratory problems, one must consider the possibility of a circulating neurotoxin. The most common inborn errors of metabolism that present in the newborn infant include: urea cycle defects, amino acidopathies, defects in beta oxidation, galactosemia, and pyridoxine dependency (invariably also associated with seizures).
2. Defects in fatty acid oxidation and urea cycle defects commonly present with intermittent vomiting and encephalopathy. The defects in beta oxidation can present in infancy, but some present later in infancy during the child’s first prolonged fast, eg, during viral gastroenteritis. Classically the child presents with nonketotic hypoglycemia and coma due to an inability to mobilize fats for energy after the exhaustion of glucose and glycogen stores. Urea cycle defects may present in infancy or may be intermittent, may follow a

large protein intake, may occur in intercurrent illness, or may accompany another stress.

3. Inborn errors of metabolism that result in metabolic acidosis include: the mitochondrial cytopathies (particularly pyruvate dehydrogenase deficiency); organic acidurias (often the result of defects in fatty acid oxidation); branched chain aminoacidopathies; and multiple carboxylase deficiencies.⁵⁹
4. **Mitochondrial diseases** can be divided into the following three major categories: defects in fatty acid oxidation, defects of pyruvate metabolism, and defects in the respiratory chain enzymes. Patients with defects in fatty acid oxidation experience metabolic decompensation with fasting (as mentioned above), usually resulting in nonketotic hypoglycemia, cyclic vomiting, and an encephalopathy indistinguishable from Reye’s syndrome. Defects in pyruvate metabolism are associated with elevated serum and tissue concentrations of pyruvate, lactate, and alanine. An inability to metabolize pyruvate results in an energy failure because of dysfunction of the Krebs’ cycle. Defects in respiratory chain enzymes also result in energy failure because of the inability to produce ATP. The clinical presentation of defects of the respiratory chain classically includes the brain and muscle, as these have a high oxidative metabolic demand.^{60,61}

Mitochondrial diseases are pleomorphic in their clinical presentation. The pleomorphism is related to the number of abnormal mitochondria, ie, where they segregate in the body, as well as the underlying enzymatic deficiency. The inheritance of mitochondrial diseases may be maternal, autosomal recessive, or sporadic. Maternal inheritance can occur because of the presence of mitochondrial DNA (mitochondria are found only in the egg, not in the sperm). Symptoms suggestive of mitochondrial diseases include: metabolic acidosis, progressive ophthalmoplegia, sensorineural hearing loss, ataxia, hypotonia, myoclonic seizures, intermittent vomiting and encephalopathy, cardiomyopathy, and endocrinopathies. Two or more of these symptoms should be highly suspicious for a mitochondrial disease and should prompt a thorough investigation, including muscle biopsy.^{59,60}

5. *Lysosomal storage diseases* are characterized by the abnormal accumulation of normal substances and their catabolic products within lysosomes. These disorders consist of the sphingolipidoses, mucopolysaccharidoses, mucopolipidoses, and glycogen storage diseases. Some of the most common lysosomal storage diseases are neuronal ceroid lipofuscinosis, Tay-Sachs disease, and Nieman-Pick disease. The lysosomal storage diseases usually present in early or late infancy, but there are variations on the theme, with descriptions of childhood, juvenile, and adult presentations. The classic presentation is an observed indifference of the infant/child to his/her surroundings, lack of visual interest, and plateauing of developmental milestones. As the disease pro-

gresses, there is continued deterioration with loss of previously acquired developmental milestones, onset of epilepsy, hypotonia (usually combined with the evolution of spastic quadriplegia), and increasing loss of vision. The physical examination can provide important clues as to the diagnosis, including the presence of: hepatosplenomegaly, optic atrophy or a cherry red spot, myoclonus, progressive megalencephaly, peripheral neuropathy, progressive weakness, choreoathetosis, and skin, hair, or joint changes. A careful physical examination including ophthalmologic evaluation and skin biopsy often can be very helpful in identifying the specific diagnosis. The skin should be sent for electron microscopy (to look for inclusion bodies) and

Table 12a

Hypotonia and Weakness

Profound Weakness Absent DTRs	Weakness Hypoactive or Absent DTRs; Cranial Nerve Abnormalities	Weakness Hypoactive DTRs
Ddx: Spinal muscular atrophy (SMA) Poliomyelitis Guillain-Barré Leukodystrophies Polyneuropathy EMG/NCS Muscle biopsy Nerve biopsy MRI scan of the brain if CNS involved Genetic test for SMA If leukodystrophy, may need blood or skin fibroblasts for specific enzyme testing If neuropathy, obtain: Vitamin B12, folate levels Phytanic acid level Heavy metal screen – 24-hour urine Lipoprotein panel Vitamin E level	Ddx: Myopathy Mitochondrial disorder Myasthenia gravis (MG) Infantile botulism Muscular dystrophy (MD) Other metabolic disorders CPK and aldolase Tensilon test EMG/NCS Metabolic testing (Mitochondrial) Blood – Lactate, pyruvate, amino acids, biotinidase, peroxisomal panel, ammonia, carbohydrate transferrin, carnitine – total and free Urine – Organic acids Lumbar puncture – cell count, protein, glucose, lactate, pyruvate, amino acids Blood – mitochondrial DNA analysis	Ddx: Electrolyte imbalance Systemic infection Hypothyroidism Cystic fibrosis Electrolytes Mg and glucose TFTs Sweat chloride Ddx: Myopathies or muscular dystrophy Polymyositis Dermatomyositis EMG/NCS CPK and aldolase Muscle biopsy

Table 12b

Hypotonia without Weakness

Globally Delayed Brisk DTRs

- + Seizures
- + Dysmorphisms
- + Weakness

Ddx: Hypoxia/ischemia
 Malformation of cortical development
 Amino acidopathies
 Mitochondrial disorders
 Carnitine deficiency
 Fatty acid oxid defect
 Resp. chain enzyme def.
 Peroxisomal disorders
 Carbohydrate-deficient glycoprotein syndrome
 Urea cycle defect
 Chromosomal abnormalities

MRI scan of the brain
 Chromosomal analysis
 Lactate; pyruvate
 Serum and urine amino acids
 Ammonia
 Peroxisomal panel
 Carbohydrate transferring level
 Urine organic acids
 Carnitine – plasma and urine
 Lumbar puncture
 Cell count
 Protein
 Glucose
 Lactate
 Pyruvate
 Amino acids
 Ophthalmologic
 Muscle biopsy, if indicated

Neurologic Deterioration Globally Delayed Brisk DTRs

- Seizures**
- Often Progressing to Spasticity**

Ddx: Tay-Sachs
 Mucopoly-saccharidoses
 Other lysosomal storage disease (neuronal ceroid leukodystrophies)
 Lipofuscinosis

Clinical exam
 MRI scan of brain
 Ophthalmologic exam
 Leukocyte or skin biopsy
 Fibroblast culture for enzymatic analysis
 Electron microscopy (looking for inclusions)
 Nerve conduction studies (if leukodystrophy)

Cognitively Normal Brisk DTRs Positive Babinski

Ddx: Hypotonic cerebral palsy (diagnosis of exclusion)
 Must r/o
 Malformation of cortical development
 Inborn error of metabolism, including mitochondrial D/O
 Chromosomal analysis / genetic syndrome
 Hypoxia – ischemia
 Sepsis

Clinical exam
 MRI of the brain
 Metabolic screening
 Chromosomal analysis

Cognitively Normal Brisk DTRs in LE Motor and Sensory Levels

Ddx: Transverse myelitis
 Spinal cord transection

Clinical exam
 MRI of the spine

fibroblast culture (for lysosomal enzymatic analysis).⁶² Specific genetic testing is now available for the most common lysosomal storage disease, ie, neuronal ceroid lipofuscinosis.

6. **Peroxisomal disorders** are uncommon but do constitute a category of metabolic disorders. The peroxisomes are important small organelles that oxidize very long chain fatty acids and pipecolic acid. They are also involved in the synthesis of plasmalogens and bile acids. The most recognized peroxisomal disorder is X-linked adrenoleukodystrophy. Classic X-linked adrenoleukodystrophy, which presents between 4-8 years of age, features behavior problems and school failure followed by the development of spastic paraparesis, swallowing difficulty, and visual loss. There is also an impaired cortisol response.⁶³ These patients can present in Addisonian crisis.
7. **Intermittent ataxia** can be the result of an inborn error of metabolism generally seen in the branched chain aminoacidopathies and mitochondrial diseases; however, the most common cause of acute ataxia in a child is either acute cerebellar ataxia (probably autoimmune) or toxic exposure (alcohol being a common agent).

Developmental Delays and Hypotonia

Developmental delays and hypotonia are frequent clinical symptoms. By following the principle of localizing the lesion, one can easily develop a differential diagnosis and make appropriate decisions with respect to diagnostic tests (Tables 12a and 12b).

Hypotonia and developmental delays in infancy can be divided first into two broad categories and subsequently into several further subdivisions solely on the basis of clinical history and physical examination:

Hypotonia with Weakness

- a) Hypotonia, profound weakness, and absent deep tendon reflexes (DTRs) indicate a disorder of the muscle or nerve. Distal weakness is more indicative of a peripheral neuropathy; proximal weakness is more characteristic of a muscle disorder. If acute and presenting with ascending weakness, these symptoms would be strongly suggestive of Guillain-Barré syndrome.

- b) Hypotonia, weakness, hypoactive or absent DTRs, and cranial nerve abnormalities are most suggestive of a congenital myopathy, mitochondrial disease, or a defect of the neuromuscular junction. If acute, these symptoms may suggest Miller-Fischer variant of Guillain Barré syndrome.
- c) Hypotonia, weakness, and hypoactive DTRs could suggest a myopathic process but may also be found with more systemic illnesses, eg, electrolyte imbalance, infection, or hypothyroidism.

Hypotonia Without Weakness

- a) Hypotonia in conjunction with global delays and brisk DTRs suggests that the localization of the lesion is in the central nervous system or possibly in both the central and peripheral nervous systems. Often, the hypotonia is more axial in nature, with the eventual development of appendicular spasticity. Disorders that typically present in this fashion include hypoxic-ischemic encephalopathy, malformations of cortical development, chromosomal abnormalities, and many of the inborn errors of metabolism.
- b) Hypotonia in conjunction with neurologic deterioration is indicative of a neurodegenerative disorder, especially the lysosomal storage diseases.
- c) Hypotonia without weakness, in the context of an otherwise cognitively intact child, may be due to hypotonic “cerebral palsy,” while considering that this is a diagnosis of exclusion.
- d) Hypotonia with motor and sensory levels indicates a spinal cord abnormality such as transverse myelitis or a spinal cord transection. The clinical history is generally critical in identifying the etiology, nature, and progression of the symptoms.

Basal Ganglia Disease

Developmental delay with prominent abnormal movements (eg, chorea, dystonia, or rigidity) should raise the possibility of basal ganglia disease such as Wilson's disease, Halleorden-Spatz disease, or Fahr disease.

Static or Progressive Diseases Affecting the Spinocerebellar Tract

Developmental delay with prominent cerebellar ataxia should raise the suspicion of static or progressive diseases predominantly affecting the spinocerebellar tract, eg, cerebellar hypoplasia, Dandy-Walker malformation or variant, ataxia telangiectasia, vitamin E deficiency, and the dominantly-inherited spinocerebellar ataxias.

9. Summary

Many neurologic disorders were not covered in this chapter. The intent was to concentrate on the most commonly encountered problems in the pediatric population. For more detailed information about the above described disorders or other neurologic problems, the reader is referred to several of the excellent pediatric neurology textbooks and one new article on treatment of epilepsy: expert opinion.^{64,65,66,67}

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11. Questions

1. The signs and symptoms that would indicate a possible mitochondrial disorder include:
- A. Sensorineural hearing loss
 - B. Ataxia
 - C. Ophthalmoplegia
 - D. Cardiomyopathy
 - E. All of the above
2. The most common antecedents of cerebral palsy include:
- A. Maternal mental retardation
 - B. Birth weight less than 1800 gms
 - C. Perinatal asphyxia
 - D. Somatic malformations
 - E. All of the above
 - F. All but C.
3. In children with hypotonia, weakness, and cranial nerve findings, the most likely diagnosis is:
- A. CNS injury
 - B. Congenital myopathy
 - C. Spinal cord injury
 - D. Corticospinal tract injury

4. The risk factors for the development of epilepsy in patients with febrile seizures include:
- A. Focal seizure, prolonged seizure, family history of epilepsy
 - B. Focal seizure, prolonged seizure, family history of febrile seizures
 - C. Focal seizure, prolonged seizure
 - D. Focal seizure, prolonged seizure, greater than two febrile seizures during the course of the illness
5. The treatment for febrile seizures includes:
- A. Rectal diazepam, to be given in the event of a seizure lasting greater than 5 minutes
 - B. Oral diazepam, to be given during the course of the febrile illness
 - C. Phenobarbital
 - D. Depakote
 - E. A. and B. only
 - F. All of the above
6. Indications for an MRI scan of the brain in a patient with severe headaches include:
- A. Papilledema
 - B. Abnormal neurological examination
 - C. History of antecedent head trauma
 - D. Progressive headache
 - E. All except for C.
 - F. All of the above
7. The most common side effect of topiramate is:
- A. Renal stones
 - B. Oligohydrosis
 - C. Cognitive processing difficulties
 - D. Allergic rash
8. With a single unprovoked seizure, the most appropriate course of action would be:
- A. Urgent CT scan, nonurgent MRI scan, EEG
 - B. Nonurgent MRI scan of the brain, EEG—awake only, initiation of antiepileptic medication
 - C. Urgent CT scan, nonurgent MRI scan, EEG
 - D. Nonurgent MRI scan, EEG—awake and sleep
9. Developmental delays in which ataxia is prominent would include a work-up for:
- A. Cerebellar malformation
 - B. Dandy-Walker malformation
 - C. Aminoacidopathies
 - D. Mitochondrial disorder
 - E. All of the above
 - F. A. and B. only

10. Which drugs are approved by the FDA for prophylactic treatment of migraine headache in the pediatric population?

- A. Propranolol
- B. Valproate
- C. Cyproheptadine
- D. Amitriptyline
- E. None of the above

Answers

- 1. E.
- 2. F.
- 3. B.
- 4. A.
- 5. E.
- 6. F.
- 7. C.
- 8. D.
- 9. E.
- 10. E.