Review Article

Clinical review of pediatric epilepsy

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ABSTRACT

Seizure disorders are very common and represent the most common cause of referrals to pediatric neurology. Epilepsy, defined as recurrent unprovoked seizures, is also common with a frequency of 4-8 cases per 1000 children. In Saudi Arabia, inherited neurological disorders, including epilepsy and genetic epilepsy syndromes, are more common because of the high rate of consanguinity. This article attempts to provide an updated overview of pediatric epilepsy and review the most recent diagnostic and therapeutic guidelines. Seizures in children have wide variations in clinical expression with age specific presentation. Although epilepsy is a clinical diagnosis, EEG often provides supportive evidence and helps in seizure classification. Epilepsy syndromes are more common in younger children, and their proper diagnosis provides valuable genetic, therapeutic, and prognostic information. Magnetic resonance imaging is superior in identifying congenital or developmental abnormalities and should be performed in preference to CT. Monotherapy is the best management approach for better compliance and to prevent interactions or side effects. To conclude, epilepsy remains a clinical diagnosis and therefore, careful and detailed history remains the cornerstone of an accurate clinical diagnosis.

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Seizures are the most common cause of referral to pediatric neurology and represent an important cause of pediatric morbidity. Epilepsy is a common neurological disorder in children with a frequency of 4-8 cases per 1000 children.[1] In Saudi Arabia, inherited neurological disorders, including epilepsy and genetic epilepsy syndromes, are more common because of the high rate of consanguineous marriages.[2] Seizures in children have wide variations in clinical expression with age specific presentation. For example, primary generalized tonic clonic and absence seizures are extremely uncommon in infants and never occur in neonates. Benign rolandic epilepsy of childhood has an onset at 5 years and usually remits by age 15. Physicians are frequently faced with anxious parents and are required to make rational decisions regarding the workup and management of childhood epilepsy. They are subsequently required to provide counseling and information about the prognoses to the involved families. The aim of this article is to provide an updated overview of pediatric epilepsy and review the most recent diagnostic and therapeutic recommendations.

Definitions. A seizure (ictus) represents transient neurological manifestations because of abnormal, excessive neuronal discharges originating from the cerebral cortex. This discharge can result in many different neurological manifestations according to the seizure origin and spread (for example sensory, motor, somatosensory, psychic). A convulsion refers to a seizure with motor manifestations, usually generalized tonic clonic. A "fit" is a term that should not be used as it may imply a psychogenic etiology. Epilepsy (to be attacked in Greek) is recurrent (2 or more) unprovoked seizures. Transient provoked seizures caused by fever, illness, electrolyte imbalance, toxic exposure, or head injury, are not classified as epilepsy. Epilepsy is not a specific disease, but rather a

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manifestation of a variety of congenital or acquired brain insults.[3]

Classification. Seizures can be clinical or subclinical (electrographic) with EEG but no clinical manifestations. The International League against Epilepsy (ILAE) classification system is summarized in **Table 1**.[4] A partial (focal) seizure can be simple with normal consciousness or complex when consciousness is impaired (not necessarily completely lost). Patients may become confused disoriented or have no memory of a complex partial seizure, however, they always remember a simple attack (aura). Therefore, an aura is a simple partial seizure with clinical manifestations that depends on the involved region of the brain. Partial seizures can be motor (frontal), sensory (parietal), visual (occipital), autonomic or psychic (temporal). An initial simple partial seizure may spread to neighboring or remote brain regions resulting in impaired consciousness (simple to complex) or in a generalized tonic-clonic seizure. This later type is called a secondarily generalized seizure, to differentiate it from seizures that are generalized from the onset (primary generalized). Myoclonic, atonic, and absence seizures are all primary generalized seizures. Note that the majority of generalized tonic clonic seizures in children are secondarily generalized, which has important diagnostic and therapeutic implications. Epilepsy syndromes (**Table 1**) are associated with one or more seizure types and other characteristic clinical, EEG, or prognostic characteristics. For example, febrile seizures are a common special (situation related) benign epilepsy syndrome characterized by focal (atypical) or generalized (typical) seizures.[5]

Table 1 - International classification of seizures and epilepsy syndromes.

I. Seizure classification

1. Partial (focal) seizures
- A. Simple (normal consciousness)
- B. Complex (disturbed level of consciousness)
- C. Simple evolving to complex partial

2. Generalized
- A. Primary generalized (generalized from the onset)
- B. Secondary generalized (starting as simple or complex partial)

3. Unclassified

II. Classification of epilepsy syndromes

1. Localization related (focal)
- A. Idiopathic (benign rolandic epilepsy)
- B. Cryptogenic (non-lesional partial epilepsy)
- C. Symptomatic (mesial temporal sclerosis, glioma)

2. Generalized
- A. Idiopathic (Absence epilepsy)
- B. Cryptogenic (Myoclonic astatic epilepsy)
- C. Symptomatic (Infantile spasms, Lennox Gastaut syndrome)

3. Undetermined (severe myoclonic epilepsy of infancy)

4. Special (situation related such as febrile seizures)

Epidemiology. The overall prevalence of epilepsy ranges between 4-8/1,000 population.[6] Children <10-years have a lifetime prevalence of 6/1,000. Up to 5% of children will have a febrile seizure in the first 5 years of life.[5] Most seizures start at the extremes of age.[7] The incidence is highest in the first year of life and lowest in early and middle adulthood. It begins increasing in the 50s, with a dramatic increase after age 60 when the incidence exceeds that of infancy. Males are at higher risk; however, no significant racial differences exist. Partial seizures are the most common type accounting for more than 50% of all seizures, complex partial seizures being the most common.[6] Up to 12% of epilepsy patients present in status epilepticus. Of the children with epilepsy, 35% had an associated developmental disorder such as mental retardation, cerebral palsy, visual impairment, or hearing impairment.[6]

Etiology. A seizure may be an isolated event with no obvious cause or triggered by acute metabolic disturbances or fever. Epilepsy may be idiopathic (usually genetic), cryptogenic (undiagnosed cause with associated neurological or developmental deficits), or symptomatic (known cause). This etiologic classification also applies to epilepsy syndromes (**Table 1**). Epilepsy results from an insult to the cerebral cortex, particularly the neocortical gray matter and the limbic system (hippocampus and amygdala). Most patients have no underlying organic pathology. Causes include congenital anomalies, developmental disorders (such as migration defects), vascular, traumatic, hypoxic, infectious, neoplastic, and degenerative disorders.[6,8-10] With the advent of neuroimaging, particularly MRI, subtle brain malformations and migration disorders are increasingly recognized. Advances in genetic research also allowed the identification of the chromosomal location and the abnormal gene in familial epilepsy. Mesial temporal sclerosis (MTS) is the most common lesion encountered in patients referred for temporal lobectomy. Patients with MTS often have history of atypical febrile seizures.[5]

Semiology. Seizures are stereotyped and random events; however, some children have several seizure types. Different seizures may be attributable to varying cortical involvement or propagation to neighboring cortex. A seizure may be characterized by flashing lights in one visual field (occipital), followed by eye deviation away from the side of onset (spread to association cortex), followed by loss of awareness and automatic behavior (spread to the temporal lobe), and then culminates in a generalized tonic-clonic seizure (secondarily generalized). Facial twitching followed by speech arrest support the diagnosis of a partial seizure originating from the dominant hemisphere.[11] During

complex partial seizures, the patient may have simple oral-buccal automatisms (chewing, swallowing, sucking), or complex motor phenomena (bicycling, flailing, walking). On some occasions, the patient may experience only the first stage of the seizure without progression. Only close questioning of the parents and child will uncover this valuable localizing information. We see many children with a referral diagnosis of generalized tonic clonic seizures for whom close questioning yields information that the seizures are focal in origin. Generalized motor seizures cannot be interrupted by vocal or painful stimulation, distinguishing them from non-epileptic events. Atonic seizures (drop attacks) usually occur in neurologically abnormal children with multiple seizure types such as Lennox-Gastaut syndrome (LGS). Absence seizures (previously called Petit Mal) cannot be interrupted by vocal or tactile stimulation when compared to non-epileptic staring spells (day dreaming or inattention) seen in children with attention deficit hyperactivity disorder. Absence seizures are very repetitive and often result in brief interruptions of conversation or physical activity for seconds (usually less than 30 seconds). This helps in distinguishing absence seizures from the staring spells due to complex partial seizures, which are usually less frequent (up to 2-4/day), longer in duration (1-2 minutes), and may be associated with aura, cyanosis, or postictal sleep. Children with absence seizures have no memory of the event and no postictal sleep.

History taking. Careful and detailed history remains the cornerstone of an accurate diagnosis. A timed description of the child's behavior during the event is needed for accurate classification and localization. The first encounter may require follow-up visit or phone call to other witnesses, such as a teacher or an older sister. Asking one of the parents to videotape the event, whenever possible, can be diagnostic. The physician should remember to include the child in the conversation who may provide valuable information. If the description is not clear, the physician can ask the parent to mimic the event, or the physician may mimic different seizures to find a match for the child's events. A previous diagnosis of epilepsy should not be accepted without a confirmatory history. The history of each event should be divided into 4 stages including preictal, beginning of the seizure, ictal, and postictal phase. In the preictal phase, provoking or precipitating factors should be sought of such as fever, illness, ingestion, compliance, and head injury. The time of the seizure is important as some occur predominantly in sleep (benign rolandic seizures, tonic seizures in LGS, and frontal lobe seizures). History of any brief focal signs or symptoms (aura) at the beginning of the more dramatic seizure should be obtained. Anxious parents tend to describe the most dramatic part of the seizure and ignore the more subtle initial focal symptoms. Aura should not be confused with prodrome, which precedes a generalized tonic clonic seizure by several hours to a day. Prodromal symptoms include headache, irritability, and personality change; all are rare in children and are not part of the ictus. Tonic seizures immediately preceded by crying or minor trauma should alert the physician to the diagnosis of breath-holding spells. Falls following standing in a stressful situation (classroom) and preceded by dizziness suggests vasovagal syncope. A cardiac cause, such as prolonged QT interval, should be considered if the child is pale during the event. During the seizure, the exact description of the clinical manifestations and their duration is needed. Clusters of tonic spasms upon awakening suggest infantile spasms. A non-epileptic seizure should be suspected if the patient has minimal or no movements during a prolonged unresponsive event. Waxing and waning motor activity with tight eye closure are consistent with a pseudoseizure, particularly if passive eye opening is resisted.[12] Postictal unilateral headache or transient weakness (Todd's paresis) has a lateralizing value indicating a contralateral hemispheric origin. Postictal aphasia (inability to talk despite being able to follow simple commands) suggests a seizure originating from the speech area of the dominant hemisphere. Visual field defects have localizing value indicating occipital lobe origin. Other important aspects of the history include development, past medical, family and social histories. Inquiring about history of meningitis, encephalitis, head injury, and febrile seizures is mandatory in every child with epilepsy. Positive family history of epilepsy or consanguinity should raise the suspicion of an inherited genetic epileptic disorder.

Physical examination. Anthropometric parameters should be measured and plotted on age appropriate percentile charts. Abnormal head size, weight, and height may be associated with certain disorders and syndromes that may have neurological manifestations.[13] In the acute situation, vital sign measurements are critical. Fever or hypothermia, particularly in infants, may indicate an underlying CNS infection. In patients with disturbed level of consciousness, high blood pressure and bradycardia (Cushing reflex) indicate increased intracranial pressure due to hemorrhage or a space-occupying lesion. Examination for meningeal irritation signs is important to exclude raised intracranial pressure. Neck stiffness may indicate meningitis, meningo-encephalitis, subarachnoid hemorrhage, or cerebellar herniation. The blood pressure should be measured in the supine and standing positions to assess postural drop in patients with vasovagal syncope. Skin exam is important as the skin and the nervous

system have the same embryologic origin (ectoderm). Therefore, developmental CNS disorders may have associated skin signs (neurocutaneous disorders) such as ash leaf spots of tuberous sclerosis, facial angioma of Sturge-Weber syndrome, café-au-lait spots of neurofibromatosis, nevi of the linear nevus syndrome, and swirling hypopigmentation of Ito syndrome.[14] Examination of the skull for shape, fontanel size and tenseness, sutures for premature fusion or wide separation are important. As well, skull auscultation for bruits may indicate an underlying arteriovenous malformation. Many syndromes may have associated CNS anomalies or features. It is important therefore to carefully assess the patient for dysmorphic features (face, mouth, palate, hands, and feet). Ophthalmologic examination may provide clues to the child's seizures (leish nodules or retinal hamartomas). Abdominal examination may reveal organomegaly in storage diseases. Cardiac examination is necessary if a cardiogenic cause for the child's episodes is suspected. Careful CNS examination is needed to exclude focal neurological signs. Some seizures can be provoked in the examination room such as absence seizures (hyperventilation) or startle precipitated seizures (auditory stimuli).

Investigations. Investigations are directed toward confirming the clinical diagnosis, seizure classification, and uncovering the underlying etiology. Extensive diagnostic testing may not be necessary if the history and physical examination provide an obvious etiology for the seizure.[5] Initial laboratory investigations include serum electrolytes, calcium, phosphorous, alkaline phosphatase, magnesium, and glucose. In febrile children, complete blood count and appropriate cultures are indicated, however, meningitis and meningo-encephalitis are the main concern. Seizures can be the presenting, but not the only feature, of up to 15% of children with meningitis. Infants with meningitis may not display meningeal signs, however, they have other symptoms and signs that strongly suggest the diagnosis (for example, altered state of consciousness, persistent vomiting, bulging fontanel, abnormal neurological signs). It is recommended that lumbar puncture (LP) be strongly considered in infants less than 12 months, considered in infants 12-18 months, and if clinically indicated in those greater than 18 months of age.[5] A LP should also be strongly considered if the child had received prior oral antibiotics that may mask the clinical manifestations of meningitis or results in transient improvement. Routine LP in all children with febrile convulsions is clearly not warranted.[5] Infants with a history of vomiting, diarrhea, and altered fluid intake should have serum electrolyte profiles to exclude hypernatremia or hyponatremia. Clinical evidence of dehydration and prolonged drowsiness or postictal obtundation are also indications for measurement of serum electrolytes, blood sugar, calcium, and urea nitrogen. If an acute cause cannot be found, the child may be experiencing the initial seizure of an epileptic disorder. An EEG and neuroimaging should be considered in these children. Testing for metabolic or genetic disorders should be performed if these disorders were suspected clinically.

Electroencephalography. The EEG is a very important tool in investigating children with epilepsy. Although epilepsy is a clinical diagnosis, accurate EEG interpretation often provides supportive evidence and helps in seizure classification.[15] However, the EEG does not rule out or diagnose epilepsy. In other words, it only confirms the clinical impression. Some non-epileptic events may simulate epilepsy including breath holding spells, syncope, tics, migraine related phenomena (for example, benign paroxysmal vertigo), and psychogenic seizures.[16,17] The neurological examination and interictal EEG are usually normal; however, a complete event description accurately identifies the nature of these events.[15] The yield of routine EEG is low in neurologically normal children with febrile seizures even if the seizure is atypical.[5] When the clinical suspicion of epilepsy is high, and the awake-recorded EEG is normal, sleep EEG may provide additional diagnostic information.[18] Falling asleep normally is superior to drug induced sleep as spike activation may occur mainly in the lighter stages of sleep. Sleep deprivation is therefore used to achieve this goal. Occasionally, achieving natural sleep is difficult in young children and drugs need to be used. Benzodiazepines and barbiturates should not be utilized because of their antiepileptic properties and induction of faster EEG frequencies, and the drug of choice is chloral hydrate.[18] Chloral hydrate is safe and effective for sleep induction; however, the sleep onset is frequently missed which may alter the EEG interpretation.[18] The sedative effect was not sustained in many children, particularly those with chronic neurological abnormalities.[18] In general, the EEG should be obtained as soon as possible after a seizure as the incidence of epileptiform discharges is highest in the first few days.[19] If the diagnosis is still in question, a repeat EEG is indicated. In one study, an initial EEG was abnormal in 56% of newly diagnosed epilepsy.[20] Repeat EEG identified an additional 11% of those with an initially normal result. Abnormal slowing may occur shortly after the seizure, which can serve to confirm the clinical impression that a seizure has occurred.[21,22] Up to 20% of children with epilepsy have repeatedly normal EEGs. As well, epileptiform activity may be seen in up to 5% of normal children who may never develop epilepsy, highlighting that epilepsy is a clinical diagnosis.[23]

Neuroimaging. Neuroimaging is not routinely recommended for children with benign epilepsy syndromes or primary generalized epilepsy. Computed tomography (CT) scan is satisfactory to screen for large tumors, old infarction, calcifications, and major malformations. A CT scan is preferred in emergencies and for critically ill children who may not tolerate anesthesia. Magnetic resonance imaging is superior in identifying cortical developmental lesions (dysplasia), small tumors, malformations, neurocutaneous syndromes, post traumatic and hypoxic insults. If both modalities are available, MRI should be performed in preference to CT. Special thin cuts and sequences (coronal flair images) are necessary to assess hippocampal abnormalities if MTS is suspected. However, MRI is more expensive than CT, not readily available in some centers, and requires heavy sedation in young uncooperative children.

Epilepsy syndromes. The ILAE classification of epilepsy syndromes (**Table 1**) provides valuable genetic, therapeutic, and prognostic information.[24] Syndromes are recognized on the basis of the clinical, developmental, neurological, and EEG characteristics.[25] Some benign syndromes need no treatment (rolandic, occipital epilepsy) while others (juvenile myoclonic epilepsy) may need life long treatment.[26,27] Overall, the etiology of the syndrome is idiopathic in 25%, cryptogenic in 49%, and symptomatic in 26%.[28] Most children (63%) have localization related (partial) epilepsy syndrome, 12% have a generalized epilepsy syndrome, and 26% are classified as undetermined.[28] Favorable prognosis was associated with idiopathic syndromes, while symptomatic syndromes carry a poorer prognosis.[29] Three important syndromes that are frequently missed or misdiagnosed are discussed in the next section. Making the correct diagnosis is critical for proper investigations, management, and counseling.

Benign rolandic epilepsy. Seizures originating from the centrotemporal (rolandic) region characteristically involve the face and throat with excessive salivation.[30] The seizures are usually simple partial as the child can recall the symptoms of choking, facial twitching, drooling, and inability to speak despite trying. Seizures mainly occur during sleep and may rapidly generalize. The interictal EEG shows characteristic spike and slow wave discharge in one or both centrotemporal regions that usually activate with sleep. If the history and EEG findings are consistent with this syndrome, imaging studies are not necessary.[30] Rolandic seizures may occur quite infrequently (once in 30%), and therapy often is not recommended, particularly if the seizures are simple partial and the child and family are comfortable without treatment. Indications for treatment include frequent or prolonged seizures and seizures during wakefulness. Controlled release carbamazepine as a single bedtime dose is the drug of choice.

Lennox-Gastaut syndrome. This is a relatively common cryptogenic or symptomatic syndrome of intractable epilepsy due to a wide variety of etiologies.[31] Patients usually present in the first 7 years of life with multiple seizure types, particularly nocturnal tonic seizures, but also include atypical absence and atonic seizures. Mental retardation (occasionally progressive) and generalized slow spike-wave discharges (1-2.5 HZ) on EEG are the other 2 characteristic feature of this syndrome. Fast polyspikes are associated with the tonic seizures. Up to 25% of affected children have a history of infantile spasms. Children are usually intractable to multiple antiepileptic drugs (AEDs). The best drug combination is valproic acid and lamotrigine.[32]

Juvenile myoclonic epilepsy of childhood. This syndrome occurs in normal young teenagers and is frequently misdiagnosed.[33] Seizures include myoclonic jerks and generalized tonic-clonic seizures upon awakening, and history of absence seizures. Absence seizures at an earlier age (5-10 years) may lead to a diagnosis of absence epilepsy; only a family history of myoclonus or generalized seizures will suggest the diagnosis. The age of onset of myoclonic jerks is 8-15 years and generalized seizures at 9-16 years.[33] The EEG reveals fast (3.5-6 HZ) spike and polyspike wave discharges superimposed on normal background rhythms. In 25%, EEG photic stimulation (repetitively flashing light) results in epileptiform discharges (photoparoxysmal response) and occasionally clinical myoclonus (photoconvulsive response). Some investigators have found a linkage to chromosome 6p.[34] Juvenile myoclonic epilepsy is a chronic disorder and patients may need to be treated for life. Drug options include valproic acid, clobazam, lamotrigine and topiramate. Phenytoin and carbamazepine are contraindicated as they can exacerbate absence and myoclonic seizures.

Management. Once the diagnosis of epilepsy is established, communicating such news to the parents is often difficult and emotional.[35] Most physicians do not feel comfortable dealing with children with neurological disorders such as epilepsy.[36,37] At the same time, it is important that the transfer of such information is carried out well as the manner in which neurological bad news is conveyed to parents can significantly influence their emotions, beliefs, and attitudes towards the child, the medical staff, and the future.[35] Besides the seizures, children with epilepsy may have behavioral, cognitive, neurological, and sleep disorders.[38] These co-morbidities are the result of the underlying neurological etiology, associated recurring seizures, or AEDs. Sub-clinical seizures (non-convulsive status epilepticus) can result in cognitive decline and behavioral changes. Some

epilepsy syndromes are characterized by cognitive deterioration such as LGS. Parental education and explanations about what to do in acute situations are important as many parents may perform unnecessary maneuvers such as mouth to mouth breathing or inserting objects to keep the mouth open. The parent needs to put the child on the side to move the tongue away from the airway and avoid aspiration if the child vomits and remove tight clothing. Certain daily activities need to be modified if the epilepsy is active. Swimming without supervision by a trained adult swimmer, bathing in a full tub, biking without a helmet, and climbing, should be all avoided. Once the epilepsy is controlled, these restrictions can be lifted gradually. Physician should stress the importance of school and discourage overprotection. Some families need psychological counseling to help them deal with epilepsy. Several AEDs are available as shown in **Tables 2, 3, & 4**. A neurologically normal child with an idiopathic seizure has a 24% recurrence risk in the next year.[39] The risk increases to 37% with prior neurological insult such as cerebral palsy, and 70% if the child had 2 seizures. It is generally accepted to initiate AED treatment after having 2 seizures within a 6-month period. An abnormal EEG is also a valuable predictor of recurrence.[39] An initial presentation in status epilepticus also increases the risk of recurrence. Children with absence seizures, drop attacks, and infantile spasms are always treated

Table 2 - List of the available older and new antiepileptic drugs (AEDs).

Traditional AEDs	New AEDs	Newer AEDs
Phenobarbital (1912)*	Clobazam (1991)	Fosphenytoin (1996)
Phenytoin (1938)	Felbamate (1993)	Oxcarbazepine (1997)
Primidone (1954)	Gabapentin(1994)	Tiagabine (1998)
Ethosuximide (1960)	Vigabatrin (1994)	Zonisamide (1999)
Carbamazepine (1974)	Lamotrigine (1995)	Levetiracetam (2000)
Clonazepam (1975)	Topiramate (1997)	
Nitrazepam (1975)		
Valproic Acid (1978)		

*Year of introduction in North America

Table 4 - Comparison between the best 4 new AEDs, ordered according to efficacy, safety, pharmacokinetics and cost.

Drug	Advantages	Disadvantages
Lamotrogine (Lamictal)	Broad spectrum Very effective	Serious skin rash Drug interactions High cost
Topiramate (Topamax)	Broad spectrum Very effective Few drug interactions	Cognitive side effects Rare renal stones High cost
Gabapentin (Neurontin)	Very safe No drug interactions	Narrow spectrum of action Short half life High cost
Vigabatrin (Sabril)	Very effective No drug interactions	Behavioral side effects High cost Irreversible retinal toxicity

Table 3 - Summary of the newer antiepileptic drugs used in children.

Drug	Mechanism	Dose	Interactions	Side effects
Lamotrogine (Lamictal)	Na channel Inhibit glutamate and aspartate release GABA inhibitor	5-7 mg/kg divided BID	Decreased level with enzyme inducers Increased level with valproate Inhibit epoxide metabolism	Skin rash 10% (less if started at a low dose and increased very slowly), angioedema, Steven Johnson syndrome (higher with valproate), dizziness, headache, nausea, vomiting, ataxia, diplopia, somnolence, blurred vision, insomnia
Topiramate (Topamax)	Saccharide Na channels GABAergic CA inhibitor	5-10 mg/kg divided TID	Decreased level with enzyme inducers, e.g. phenytoin and carbamazepine	Psychosis, depression sedation, weight loss, dizziness, nephrolithiasis (1.5%), teratogenic, impaired concentration, finger tingling, ataxia, aphasia
Gabapentin (Neurontin)	Competitive inhibitor of amino acid transport into the CNS	25-45 mg/kg divided BID or TID	% absorbed decrease with higher dose (saturable L-AA gut transport)	Ataxia, somnolence, lethargy, dizziness, fatigue, nystagmus, nausea, weight gain, precipitation of myoclonus
Vigabatrin (Sabril)	GABA transaminase inhibitor	50-150 mg/kg divided BID	25% decrease in phenytoin level	Irritability, agitation, insomnia, hyperkinesis, drowsiness, ataxia, confusion, headache, psychosis (2-5%), depression, hallucinations, weight gain, retinal toxicity, precipitation of myoclonus, leukopenia

Na - sodium, GABA - gamma aminobutyric acid A, Ca - calcium, CNS - central nervous system, BID - 2 times per day, TID - 3 times per day, L-AA - L-amino acid

since they usually present with frequent seizures. The choice of AED is dependent upon the type of seizure, syndrome, and EEG patterns.[40] The AED should be effective with few side effects, and cost-effective. Drug options in a decreasing order for partial seizures (with or without secondary generalization) include carbamazepine, phenytoin, phenobarbitone, lamotrigine, valproic acid, topiramate, benzodiazepines, vigabatrin, and gabapentin. Both phenytoin and phenobarbitone are used less often because of their chronic side effects; however, they are very useful in emergencies. Options for primary generalized seizures include valproic acid, benzodiazepines, phenytoin, phenobarbitone, lamotrigine, topiramate and less commonly carbamazepine. Infantile spasms respond well to steroids, but other choices include vigabatrin, benzodiazepines, valproic acid, lamotrigine, and topiramate. Vigabatrin is used less frequently because of the high incidence of visual field restrictions due to irreversible retinal toxicity. Carbamazepine, phenytoin, phenobarbitone, and gabapentin should not be used in infantile spasms or myoclonic seizures. Interestingly, vigabatrin may exacerbate myoclonic seizures despite being effective in children with infantile spasms. Absence epilepsy responds to ethosuximide, valproic acid, lamotrigine, topiramate, and clobazam. Ethosuximide is not effective for any other seizure types. Valproic acid is a better option for children with juvenile absence epilepsy that may be associated with other seizure types. Vigabatrin, carbamazepine, phenytoin, phenobarbitone, and gabapentin should not be used for absence seizures. Atonic seizures (drop attacks) may respond to valproic acid, lamotrigine, topiramate, benzodiazepines, and occasionally phenobarbitone. Both carbamazepine and phenytoin may exacerbate this seizure type. Most AEDs should be started at a low dose and increased slowly for better tolerance. If the dose is increased with no response, drug levels are indicated to confirm compliance. Other indications for drug levels include drug interactions and toxicity. Routine levels should be discouraged. The best time for obtaining the test is before the morning dose. Monotherapy is best to avoid interactions and side effects and for better compliance. A second AED is added when seizures are resistant to the initial drug; however, this should not be performed unless a maximum dose is reached with therapeutic levels. Before switching to another drug, the diagnosis should be reevaluated to exclude non-epileptic events and confirm the seizure semiology. For example, staring spells due to absence epilepsy will get worse on carbamazepine. Combination therapy may be necessary for children with multiple seizure types or refractory epilepsy. Synergistic interaction, such as lamotrigine and valproic acid, results in improved seizure control.[32] However, the incidence of idiosyncratic skin rash is higher with this combination. Therefore, the dose of lamotrigine should be started and increased slowly to a maximum of 5 mg/kg/day. Carbamazepine and lamotrigine or topiramate is a powerful combination for intractable partial epilepsy, while valproate and topiramate or lamotrogine is favored for intractable generalized seizures. Certain combinations, such as phenobarbital and benzodiazepines should be avoided because of additive CNS depression and effects on muscle tone. Drugs with similar pharmacological actions should not be combined such as phenytoin and carbamazepine. Only under extreme circumstances should more than 2 drugs be used simultaneously to avoid interactions, side effects, and increased cost. Routine laboratory testing including complete blood count, liver or renal function, is not recommended.[41] Many side effects are idiosyncratic, including skin rash, Stevens-Johnson syndrome, hepatotoxicity, and pancreatitis, cannot be predicted by routine blood tests, unless the child is symptomatic. Valproic acid can be associated with elevations of liver enzymes and serum ammonia.[42,43] Most cases of fatal hepatotoxicity have been in infants with severe epilepsy.[44] Possibly, many of these children have an undiagnosed neurodegenerative or metabolic disorder such as mitochondrial disorders (Alper's Syndrome), which are exacerbated by the valproic acid. Valproic acid should be avoided if progressive or metabolic disorders are suspected.[45] In teenage girls, 5 mg of folic acid should be supplemented daily to prevent open neural tube defects associated with valproic acid.[46] The AEDs should be withdrawn after 1-2 years without seizures regardless of the etiology.[47] The recurrence risk is approximately 30-40%.[47] Several studies with 6-12 months treatment have shown only slightly higher recurrence rates.[48,49] Motor, cognitive, or EEG abnormalities increase the likelihood of future recurrence.[50] However, a normal EEG is not a must before tapering AEDs; it simply increases the recurrence risk, particularly in generalized epilepsy. Drugs are usually tapered over a 4-8 week period. Longer periods of weaning are not necessary except with phenobarbitone or benzodiazepines to minimize the likelihood of developing withdrawal seizures.

Status epilepticus. Status epilepticus (SE) is defined as a seizure or series of seizures, which continue for at least 30 minutes without return of consciousness between the seizures.[51] Status epilepticus could be the initial presentation of an epileptic disorder (12%) and 20% of epileptics have SE in the first 5 years following the diagnosis. Overall, SE is the most common medical neurological emergency in childhood with an incidence of 4-6/10,000 population.[51] It is more common in younger children, particularly infants

with a mortality rate of up to 20%. Status epilepticus can be classified as idiopathic (35%) or symptomatic (65%) secondary to trauma, neoplasm, stroke, CNS infection or anomalies. Etiologically, it can be secondary to acute causes (toxic-metabolic) or chronic causes such as established epilepsy (breakthrough or drug related seizures). The chronic group tends to respond more favorably to treatment and have a lower mortality. Status epilepticus can also be classified as non-convulsive (absence or complex partial) or convulsive. Convulsive SE can be partial motor (epilepsia partialis continua) or generalized (tonic clonic or myoclonic). Non-convulsive SE is characterized by confusion, somnolence, automatic behavior, psychic or cognitive disturbances without any obvious motor phenomena, usually occurring in children with severe epilepsy such as LGS. The management of SE is outlined in **Table 5**. Taking a focused history and performing a focused examination are critical to identify medical illnesses, trauma, infection, intoxication, or child abuse. Benzodiazepines are effective (80%) and fast (2.5 minutes) in aborting the seizures (**Table 5**). Lorazepam has longer duration of effect (12-24 hours) when compared to diazepam (15-30 minutes). Phenytoin is preferred to phenobarbitone to avoid additional respiratory depression, hypotension, or further impairment of consciousness. Fosphenytoin is a phosphate ester prodrug of phenytoin with no propylene glycol leading to fewer side effects (hypotension, arrhythmia, and thrombophlebitis). The physician should be prepared for intubation once phenobarbital is given after benzodiazepines because of additive depressant effects. Other drug options for intractable SE are outlined in **Table 5**. Status epilepticus of longer duration tends to be less responsive to drug therapy. Midazolam and Propofol induce anesthesia with rapid clearance and less pronounced hypotensive effects. If used, they should be maintained for 12-24 hours then withdrawn gradually. Pentobarbital is an active metabolite of thiopental, both with possible neuroprotective effects. However, severe hypotension requires pressor therapy. They also have saturable metabolism with accumulation in lipoid tissues resulting in delays in post infusion recovery. Therefore, midazolam and propofol are increasingly popular when compared to these long acting barbiturates.

Table 5 - Management of pediatric status epilepticus.

Initial assessment
ABC, vital signs Cardiac monitor, pulse oximetry, 100% O_2 Intravenous access, urgent glucose, gas, and electrolytes Start anticonvulsant therapy Focused history and exam (known epilepsy, illnesses, trauma, meningitis, focal signs)
Initial drug treatment
Lorazepam 0.1 mg/kg buccal or IV (2 mg/min) up to 4 mg/dose, or Diazepam 0.3 mg/kg IV or 0.4 mg/kg PR (up to 10 mg/dose)
Phenytoin 15-20 mg/kg (infuse at <50 mg/min), or Fosphenytoin 20 mg/kg IV (<150 mg/min)
Further steps if no response
Prepare for intubation and ventilation
Repeat Lorazepam (8 mg maximum total dose), or Repeat Diazepam (20 mg maximum total dose)
Phenobarbital 20 mg/kg IV (infuse at <75 mg/min)
Additional Phenytoin then Phenobarbital at 10 mg/kg
Refractory status epilepticus
Team approach including neurology and intensive care unit
Consider EEG monitoring, central line placement, and blood pressure support
Additional drug options include:
Paraldehyde 0.1 ml/kg PR or IV Midazolam 0.2 mg/kg IV slowly then infuse at 0.75-10 μg/kg/min Propofol 1-2 mg/kg IV then infuse at 2-10 mg/kg/hr Pentobarbital 5-15 mg/kg over 1 hr followed by 0.5-3 mg/kg/hr Thiopental 3-4 mg/kg followed by 0.2 mg/kg/min
ABC - airway, breathing, circulation, IV - intravenous, PR - as required

Intractable epilepsy. Intractable epilepsy is defined as recurrent seizures that fail to respond to at least 3 AED trials singly or in combination, despite using maximum doses or doses resulting in therapeutic drug levels.[52] Intractability has been associated with cognitive and behavioral problems and impaired psychosocial development.[53] These children have a high potential for long-term disability and difficulties in adjusting to school.[54] Recurrent seizures also increase the risk of injury and even death.[53] Three treatment modalities are available for such children including the ketogenic diet, epilepsy surgery, and vagal nerve stimulation (VNS). The ketogenic diet consists of 3-4 parts fat to one part carbohydrate. The nutritional content of all meals must be calculated and each food item weighed. The high fat content and relative absence of carbohydrate produces a persistent ketosis, which appears to have a direct anticonvulsant effect. The level of ketosis can be monitored daily in the urine. The diet is not curative, but it decreases seizure frequency in up to 60% of children.[55] It is also associated with improved awareness, however, it is unpalatable, results in many social limitations, and can be associated with diarrhea, growth failure, stones, and acidosis. The long-term effects on lipid homeostasis need further study. The diet should be supervised by a well-trained dietitian and continued for 1-2 years. Surgical approaches include focal

resection, corpus callosotomy, hemispherectomy, and multiple subpial transections.[56,57] The procedure selected depends upon the type and localization of the seizures. Children with focal epileptic zone, particularly if a lesion is present on imaging studies, do very well with regional resection. The most commonly performed procedure is temporal lobectomy, which can offer >80% chance of cure. The results of extratemporal resection are similar to those of temporal lobectomy if a lesion is present.[58] Results of non-lesional cases are less successful with <40% success rate.[59] Children with hemispheric syndromes such as hemimegalencephaly or Rasmussen syndrome may have an excellent response to undercutting of the cortex of an entire hemisphere (functional hemi-spherectomy). Other surgical options include corpus callosotomy for atonic or generalized tonic seizures and multiple subpial transactions for epilepsy involving the primary motor or sensory cortex. The vagus nerve stimulator is surgically implanted under the skin of the lateral chest wall and connected to stimulating electrodes attached to the left vagal nerve. The patient or parents also can activate the stimulator, when a seizure is anticipated, by passing a special magnet over the VNS. The VNS is approved as an adjunct treatment for intractable partial epilepsy and LGS. The exact mechanism of action is not known, however, it results in significant seizure reduction in up to 30% of children. The procedure is expensive and requires meticulous follow up.

In conclusion, this paper summarized many important aspects of pediatric epilepsy. Seizures in children have wider variations in clinical expression with age specific presentation. Epilepsy syndromes are also more common in children and proper diagnosis provides valuable genetic, therapeutic, and prognostic information. Careful and detailed history remains the cornerstone of an accurate diagnosis. Investigations are directed toward confirming the clinical diagnosis, seizure classification, and uncovering the underlying etiology. Although epilepsy is a clinical diagnosis, EEG often provides supportive evidence and helps in seizure classification. The MRI is superior in identifying congenital or developmental abnormalities and should be performed in preference to CT. Monotherapy is the best management approach for better compliance and to prevent interactions or side effects. Drug levels and periodic blood investigations are not recommended routinely. If the seizures are intractable to multiple AEDs, the physician could consider ketogenic diet, epilepsy surgery, and vagal nerve stimulation. The AEDs should be withdrawn after a 1-2 year seizure free interval. Drugs are usually tapered over a 6-8 week period. Motor, cognitive, and EEG abnormalities increase the likelihood of future recurrence, however, a normal EEG is not a must before tapering AEDs.

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