Diagnosis and Treatment of Pediatric Epilepsy

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The management of childhood epilepsy begins with diagnostic evaluations of (1) seizure confirmation, (2) seizure classification, (3) syndrome identification, and (4) etiology investigations. In evaluating a child with recurrent paroxysmal events, a differential diagnosis that includes non-epileptic spells is crucial to prevent delay of appropriate managements for mimickers of seizures and to avoid unnecessary treatment with antiepileptic drugs. A detailed history of stereotyped clinical features among the recurring events is suggestive of epilepsy. While electroencephalogram (EEG) can be supportive of epilepsy diagnosis, lack of abnormal EEG findings does not exclude this diagnosis. Establishing the epilepsy syndrome diagnosis and identification of underlying cause can direct management and help with counselling of long-term prognosis. When pharmacologic therapies fail, consideration may be given to non-pharmacologic therapies or updated etiology evaluations in children with drug resistant epilepsy.

Classification of seizure types and epilepsy syndrome identification

Seizure classification begins with determining the mode of seizure onset, whether the initial manifestations of the seizure are focal, generalized, or unknown. In the most recent 2017 scheme [1], classification of seizure are "focal onset" or "generalized onset" along with more detailed descriptions when available: "focal motor seizure," "generalized nonmotor absence seizures with eyelid myoclonic," etc (Table 1). Specific seizure types can be determined from supportive evidences such as videos that family provides, interictal EEG patterns, and neuroimaging. Laboratory results of autoimmune epilepsy, gene mutations, or epilepsy syndromes known to be associated with specific mode of seizure onset points towards specific seizure classification. Some seizure types are not exclusively focal or generalized onset. Epileptic spasms and tonic seizures may be focal, generalized, and unknown onset. Video-EEG recording may be required to distinguish seizures which mode of onset is unknown or unclassified.

Epilepsy syndromes are classified by the age of seizure onset, seizure type(s), developmental history, neuroimaging, and EEG findings. A specific epilepsy syndrome may be apparent at initial diagnosis in 28% children with new onset epilepsy [2]. The epilepsy syndrome can predict long-term prognosis of childhood onset epilepsy (Table 2). Some electroclinical syndromes are pharmacoresponsive and remits in childhood or early adolescence (childhood absence epilepsy, benign epilepsy with centrotemporal spikes). Others such as juvenile absence epilepsy and juvenile myoclonic often require life-long therapy despite response to antiepileptic drugs.

About a third of children with childhood onset epilepsy may have drug resistant epilepsy. Lack of specific epilepsy syndrome, however, does not equate with poor prognosis. Among otherwise normal children with nonlesional focal epilepsies not fitting into a specific syndrome, 55%-67% were in remission, and pharmacoresistance was rare [3].

Choice of antiepileptic drug depends on seizure type or epilepsy syndrome. Some antiepileptic drugs have a narrow spectrum and are effective for selected seizure type or epilepsy syndrome (ethosuximide for childhood absence epilepsy). Other antiepileptic drugs may worsen certain seizures: carbamazepine, oxcarbazepine, and phenobarbital in absence seizures. When classification of focal or generalized seizures cannot be made, a broad-spectrum antiepileptic drug able to treat both focal and generalized seizures is preferred.

The goal of epilepsy management is seizure-free control with minimal medication side effects. The goal is not to normalize or correct interictal EEG findings. An exception is electrical status epilepticus in sleep (ESES), in which the EEG shows marked activation of the discharges in sleep to a near continuous spike-wave in slow-wave sleep pattern. *Continuous spike-wave in slow wave sleep* and *Landau-Kleffner syndrome* are two epilepsy syndromes associated with ESES pattern on EEG. Children typically presents between ages of 3 and 10 years. In CSWS, children exhibit a global regression in language, attention, memory, mood, and motor domains. In Landau-Kleffner syndrome, children develop acquired auditory agnosia, resulting in progressive loss of spontaneous speech and developmental regression. First line therapies include benzodiazepines, steroids, acetazolamide, ethosuximide, and valproate. Certain antiepileptic drugs should be avoided as they may exacerbate the condition (carbamazepine, oxcarbazepine, phenytoin). The goal of ESES treatment is not only to stop the seizures but also to resolve the continuous epileptiform discharges in order to maximize the child's development.

Etiology investigations

The etiology of pediatric epilepsy is diverse and includes structural, metabolic, genetic, autoimmune, and unknown causes.

Genetic etiology. Genetic testing should be considered in infants and young children with early onset epilepsy, profound intellectual disability, and developmental regression. Testing for genetic causes may include chromosome analysis, array comparative genomic hybridization, targeted epilepsy gene panels, or whole exome sequencing. The yield of chromosome analysis is low unless there is clear dysmorphic features or multiple congenital anomalies are present The diagnostic yield of genetic testing in childhood epilepsy ranges between 10% and 50%, with disease-causing genetic variants seen most frequently in patients with neonatal onset epilepsies, followed by epileptic encephalopathies [4]. Genetic heterogeneity exists for many syndromes, with multiple genes resulting in a similar phenotype. Additionally, phenotypic heterogeneity exists for many genes, with a single gene mutation resulting in multiple possible phenotypes. However, despite this genetic and phenotypic heterogeneity, genetic diagnosis in some cases can provide data that modify care and direct treatment targeted at underlying cause. Example includes Dravet syndrome due to SCN1A mutations, in which there is proposed loss of sodium channel function in inhibitory interneurons. Sodium channel blockers (lamotrigine, phenytoin, carbamazepine), which further depress neuronal inhibition, have been shown to worsen seizures in Dravet and typically contraindicated. In patients with gain of function SCN2A and SCN8A mutations, high dose phenytoin a sodium channel blockers have been shown to be beneficial. Other examples of precision treatment targeted at disease pathophysiology include carbamazepine in PRRT2, ezogabine in KCNQ2, quinidine in KCNT1, and memantine in GRIN2A [5].

Structural etiology. Infants and young children may have generalized ictal and interictal discharges despite findings of congenital or early acquired focal lesions on MRI neuroimaging. Focal lesions should be suspected if there are lateralizing features to the seizure semiology, persistent asymmetries on the ictal or interictal EEG, and if there are focal abnormalities on the neurologic exam. An MRI with seizure protocol should be performed if a focal lesion is suspected. Between ages 6 months and 24 months, MRI can be limited as immature myelination can appear isointense to cortex on T1 and T2 images, limiting detection of cortical dysplasias. In young children with epilepsy of unknown cause, MRI should be repeated after 24 to 30 months given that myelination is largely completed around this age.

Children with focal drug resistant epilepsy should be referred to tertiary centers for surgical evaluation. The underlying causes for surgically remediable epilepsy are diverse in children. The type of surgery depends on the extent of epileptogenic zone (the area of cortex needed to be removed in order to render seizure free control) and its relation with functional cortex as determined from noninvasive and phase II evaluations. In those patients with diffuse hemispheric abnormality, modified hemispherotomy or multilobar resection may be needed. The presence of a single focal anatomic lesion identified on MRI and seizure localization to the temporal lobe are favorable prognosticators for surgical outcome. In cases where the MRI does not provide localizing information, but a single epileptogenic zone is suspected, ancillary testing including functional neuroimaging (SISCOM or FDG-PET) or magnetoencephalogram is often useful. Focal resection surgery in carefully selected patients may render seizure free control in 60%-80% of patients with lesional temporal lobe epilepsy versus in 40%-70% in nonlesional extratemporal epilepsy. Complete resection of the epileptogenic zone also predicts better outcome.

Focal cortical dysplasia (FCD) is the most common histopathology found in pediatric epilepsy surgery cohort. FCD refers to a spectrum of abnormalities involving the laminar structure of the cortex, with or without dysmorphic neurons and balloon cells. Seizures typically start during early childhood with high seizure burden and may remain refractory to medical management. About a third to one half of patients with pathology-confirmed FCD have normal brain MRI, however this depends on type of FCD. About 90% of patients with FCD type II have MRI abnormalities compared to only 30% patient with FCD type I. In MRI-negative epilepsy, FDG-PET shows corresponding areas of hypometabolism in up to 90% of patients later found to have focal cortical dysplasia. The MRI findings of FCD include cortical thickening, abnormal gyration pattern, loss of gray-white differentiation, presence of transmantle sign (subcortical white matter hyperintensity extending from cortical thickening in the overlying cortex), and bottom of the sulcus dysplasia to the lateral ventricle.

Metabolic etiology. Although rare individually, inborn errors of metabolism accounts for 1 in 3000 live births. Seizures starting in the neonatal period and infancy, with global neurologic dysfunction and developmental regression are a common presentation of inborn errors of metabolism [6]. In a neonate, EEG showing a burst suppression pattern with myoclonic seizures, consistent with early myoclonic encephalopathy increases the suspicion of metabolic cause. Family history suggestive of inborn errors of metabolism includes consanguinity, relatives with metabolic disorder and unexplained neurologic conditions. The goal of evaluation for inborn errors of metabolism is to identify expeditiously those conditions with disease-modifying treatments, to preserve existing neurologic status and prevent progressive decline. Examples include pyridoxine for pyridoxine dependent epilepsy,

ketogenic diet for glucose transporter deficiency, and folinic acid for cerebral folate deficiency. In conditions without disease-modifying therapy, reasons for accurate diagnosis include avoidance of exacerbating agents (valproic acid-induced hepatic failure in POLG-1 mutation) and genetic counseling to inform family planning and prognosis for the index case. Initial metabolic studies include serum glucose, lactate, amino acids, urine organic acid to evaluate for mitochondrial disorder, aminoacidopathies, and organic acidurias. Further metabolic testing should be considered in the correct clinical context and can include alpha-aminoadipic semialdehyde (pyridoxine-dependent epilepsy), CSF for pyridoxal 5'-phosphate (pyridoxal 5'-phosphate-dependent epilepsy), neurotransmitters (neurotransmitter disorders), lactate (mitochondrial disorders and glucose transporter deficiency), and glucose (glucose transporter deficiency).

Autoimmune etiology. Autoimmune epilepsies should be considered in patients with medically refractory epilepsies from seizure onset and who have other concomitant neurological symptoms, including movement disorders, cognitive decline, and sleep disturbances. Clinical suspicion for an autoimmune etiology depends on a triad of acute or subacute onset of CNS dysfunction, serological detection of the pertinent antibody and a response to immunotherapy. Potential associations with occult neoplasm make accurate diagnosis imperative to allow timely initiation of immunotherapy and early cancer diagnosis. Early recognition through clinical and serological diagnosis is important since this may lead to an early diagnosis of cancer, expedited implementation of immunotherapy (high-dose corticosteroid, IVIg) and improved neurological long-term outcome.

Conclusion: With careful review of the patient's seizure history, the epilepsy syndrome classification and etiology diagnosis may be clear with supportive diagnostic testing. In patients in whom prior evaluations may not have produced a clear diagnosis, interval evaluations may be appropriate, as new diagnostic tools may have become available. In other cases, advancements in the pathophysiology mechanisms of known cause may have led to precision medication for the previously unavailable treatment.

Reference:

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Table 1. Seizure Types and Terminology Used in 1981, 2010, and 2017 [1, 7]

Mode of Onset	1981 Seizure Types	2010 Seizure Descriptions	2017 Seizure Classification
Focal	Simple partial seizures	Without impairment of consciousness or awareness:	Focal Aware
	Simple partial sensory	With observable motor or autonomic components	Motor Onset (automatisms, atonic, clonic, epileptic spasms, hyperkinetic, myoclonic, tonic)
	Simple partial motor		
	Simple partial special sensory (unusual smells or tastes)	Involving subjective sensory or psychic phenomena only (aura)	Nonmotor Onset (autonomic, behavior arrest, cognitive, emotional sensory)
	Speech arrest or unusual vocalization		
	Complex partial seizures	With impairment of consciousness or awareness (dyscognitive)	Focal Impaired Awareness
	Consciousness impaired at onset		Motor Onset (automatisms, atonic, clonic, epileptic spasms, hyperkinetic, myoclonic, ton
	Simple partial onset followed by impaired consciousness		Nonmotor Onset (autonomic, behavior arrest, cognitive, emotional sensory)
	Evolving to generalized tonic-clonic convulsions (secondary generalized tonic-clonic seizures)	Evolving to a bilateral, convulsive seizure	Focal to Bilateral tonic-clonic
	Simple evolving to generalized tonic-clonic		
	Complex evolving to generalized tonic-clonic (including those with simple partial onset)		
Generalized	Tonic-clonic	Tonic-clonic	Generalized Onset
	Myoclonic	Myoclonic	Motor Onset (Tonic-clonic, clonic, tonic, myoclonic, myoclonic-tonic-clonic, myoclonic-atonic, atonic, epileptic spasms)
	Absence and atypical absence	Absence	Nonmotor Onset (Absence)
		Typical	Typical, Atypical, myoclonic, eyelid myoclonia
		Atypical	
		With special features	
	Clonic	Clonic	
	Tonic	Tonic	
	Atonic	Atonic	
Not clear	Unclassified	Unknown (including epileptic spasms)	Unknown onset
			Motor Onset
			Nonmotor Onset
			Unclassified

Table 2. Selected epilepsy syndrome in infants and children [8, 9].

Epilepsy syndrome	**Age of seizure onset**	**Seizure types**	**EEG features**	**Underlying etiology**	**Prognosis (Change of long-term seizure control / Likelihood of remission)**
Early infantile epileptic encephalopathy (Ohtahara syndrome)	First 2 weeks of life	Tonic seizures	Background: Suppression burst pattern in awake and sleep; Interictal: High voltage (150-350 uV) paroxysm; Ictal: Generalized paroxysms or focal discharges	Cerebral structural abnormality, genetic abnormalities (i.e., *STXBP1*)	25% die by 2 years; or evolves to West syndrome and profound disability. (Very low / very low)
Early myoclonic encephalopathy	First weeks of life	Myoclonic seizures	Background: Suppression burst pattern, enhanced by sleep; Interictal: High voltage (150-350 uV) paroxysm; Ictal: Generalized paroxysms or focal discharges	Metabolic genetic etiologies (nonketotic hyperglycinemia, pyridoxine/pyridoxal-5-phosphate dependency, molybdenum cofactor deficiency, organic aciduria, amino-acidopathies)	50% die within first year; or profound disability. (Very low / very low)
West syndrome	3- 8 months	Epileptic spasms	Background: Poorly organized, high amplitude (500-1000 mV), generalized slowing; Interictal: multifocal epileptiform discharges with generalized electrodecrement; Ictal: generalized sharp wave followed by electrodecrement	Heterogeneous (congenital cortical malformations, tuberous sclerosis, trisomy 21, trisomy 18, CDKL5, ARX, MECP2)	Depends on etiology; other seizure types evolves by about 5 years (Low / Low)
Dravet syndrome	6 months	Febrile status epilepticus, alternating hemiconvulsions → absence, myoclonic seizures	Background: Normal, generalized or focal slowing; Interictal: Generalized, multifocal or focal discharges; photoparoxysmal response; Ictal: Generalized paroxysms or focal discharges.	80% SCN1A mutation	Mortality in childhood 10%; intellectual disability, crouched gait without spasticity in adults (Very low / very low)
Childhood absence epilepsy	5-8 years	Absence seizures occasionally with automatisms	Background: normal, periodic rhythmic delta activity; Interictal: 3 Hz spike and waves; Ictal: 3 Hz spike and waves.	Unknown	Normal development (moderate to high / moderate to high)
Benign epilepsy with centrotemporal spikes	5-12 years	Nocturnal focal seizures (lower face, drooling and dysarthria) to	Background: normal; Interictal: centrotemporal discharges, with frontal dipole Ictal: focal spikes	Unknown	Normal development (very high / very high)

		generalized tonic-clonic seizures.			
ESES related syndromes	5-8 years	Focal seizures	Background: Normal or focal/diffuse slowing; Interictal: focal/ multifocal/ generalized discharges; marked sleep activation with increased interictal spatial distribution or bilateral synchrony; sleep spike wave index > 85%; CSWS- frontal predominant LKS- temporal predominant; Ictal: focal discharges	CSWS- structural; LKS- unknown	Relapsing-remitting course; age-limiting by teenage years (CSWS - moderate / moderate to high; LKS – high / high)
Lennox-Gastaut syndrome	1-8 years	Generalized (tonic, atonic, absences, myoclonic) or Focal	Background: generalized slowing; Interictal: frequent slow spike waves 1.5 -2.5 Hz; or multifocal; Ictal: Absence -low spike and waves; Tonic- generalized attenuation with recruiting rhythm; Atonic- generalized polyspike/ spike waves, or attenuation; Myoclonic-generalized polyspike/spike waves.	Heterogeneous	Intellectual disability (very low / very low)
Myoclonic-atonic epilepsy	7 months - 6 years	Multiple (atonic, myoclonic, absences, rarely tonic)	Background: Normal or mild diffuse/ focal slowing; Interictal: Generalized polyspike-and-wave discharges; photoparoxysmal response; Ictal: Generalized spike or polyspike-and-wave	No consistent etiology	50% normal cognition at last follow-up (moderate / high)
Juvenile myoclonic epilepsy	12-16 years	GTC, myoclonic seizures in the mornings, occasional absences	Background: Normal; Interictal: 4-5 Hz generalized discharges, polyspike waves, photoparoxysmal response; Ictal: Generalized spike or polyspike-and-wave		Life long therapy typically required (moderate to high / low)

ESES- electrical status epilepticus in slow wave sleep; CSWS- continuous spike wave in sleep; LKS- Landau-Kleffner syndrome; GTC- generalized tonic-clonic.