UPDATE

The 2022 International League Against Epilepsy Classification and Definition of Childhood Epilepsy Syndromes: An Update for Pediatricians

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ABSTRACT

The 2017 classification of the epilepsies of International League Against Epilepsy (ILAE) defined three diagnostic levels, including seizure type, epilepsy type and epilepsy syndrome. Epilepsy syndromes have been recognized as distinct electroclinical entities well before the first ILAE classification of Epilepsies and Epilepsy Syndromes in 1985. A formally accepted classification of epilepsy syndromes was not available, and hence, the 2017-2021 Nosology and Definitions Task Force of ILAE was formulated. The ILAE position papers were published in 2022, which classified epilepsy syndromes into (1) syndromes with onset in neonates and infants (up to 2 years of age), (2) syndromes with onset in childhood, (3) syndromes that may begin at a variable age and (4) idiopathic generalized epilepsies. This classification recognized the concept of etiology-specific syndrome. These papers have addressed the specific clinical and laboratory features of epilepsy syndromes and specify the rationale for any significant changes in terminology or definition. This paper will review some pertinent changes and essential points relevant to pediatricians.

Keywords: *Developmental and epileptic encephalopathy, EEG, electroclinical syndromes, Seizures*

The 2017 classification of the epilepsies of International League Against Epilepsy (ILAE) defined three diagnostic levels, including seizure type, epilepsy type and epilepsy syndrome [1]. According to an ILAE report, an epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain [2]. In 2014, ILAE defined epilepsy as a disease of the brain characterized by any of the following conditions: *a*) At least two unprovoked (or reflex) seizures occurring > 24 h apart; *b*) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next ten years; *c*) diagnosis of an epilepsy syndrome [3].

Epilepsy syndromes are electroclinical syndromes recognized on the basis of clinical features such as seizure type, age at onset, co-morbid developmental delay, etc., and specific EEG findings. Common examples include West syndrome, Childhood absence epilepsy and Benign Childhood epilepsy with centro-temporal spikes. Epilepsy syndromes have been recognized as distinct electroclinical entities well before the first classification of Epilepsies and Epilepsy Syndromes was proposed by ILAE in 1985 [4]. However, a formally accepted classification and diagnostic criteria of epilepsy syndromes was not available, and hence, the 2017-2021 Nosology and Definitions Task Force of ILAE was assigned this task. This led to the publication of the ILAE 2022 position papers.

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The ILAE position papers are classified into *a*) syndromes with onset in neonates and infants (up to 2 years of age), *b*) syndromes with onset in childhood, *c*) syndromes that may begin at a variable age and *d*) idiopathic generalized epilepsies. For each syndrome, electroclinical criteria, expected results of investigations (imaging, genetics), common co-morbidities, and natural history are provided. This paper will review some relevant changes and important points pertinent to pediatricians.

The Concept of Epilepsy Syndromes

An epilepsy syndromeis defined as "a characteristic cluster of clinical andelectroencephalographic features, often supported by specific etiological findings (structural, genetic, metabolic, immune, and infectious)." The diagnosis of epilepsy syndrome in a child typically has prognostic and treatment implications. These syndromes frequently have age-dependent presentations and a gamut of specific comorbidities.

Epilepsy syndromes are further subdivided into generalized, focal, or generalized and focal, based on the prototype seizure(s), with a separate grouping for syndromes with developmental and epileptic encephalopathy (DEE) or progressive neurological deterioration. The 2017, classification proposed the term DEE to denote epilepsy associated with a developmental impairment that may be due to both the underlying etiology (developmental encephalopathy) and superimposed epileptic activity (epileptic encephalopathy). This approach delineates this group of syndromes associated with cognitive impairment with or without additional manifestations of neurological deterioration. It recognizes that this impairment may be due to the underlying etiology, superimposed epileptic activity, or both.

Moreover, this classification identified the concept of etiology-specific syndrome to define entities with a distinct phenotype associated with a specific etiology; examples include monogenic epilepsies, such as *CDKL5*-DEE, TSC-related epilepsy and *PCDH19* epilepsy, and structural epilepsies, such as mesial temporal lobe epilepsy with hippocampal sclerosis.

These papers have addressed the specific clinical and laboratory features of epilepsy syndromes and provide the rationale for any significant changes in terminology or definition. For each syndrome, three categories of criteria are provided [5].

Mandatory: Criteria that must be present to diagnose the syndrome. If any mandatory criterion is absent, the syndrome cannot be diagnosed.

Alerts: Criteria absent in most cases within a syndrome but rarely can be seen. Alerts alone would not exclude the syndrome but should alert the physician to reappraise the diagnosis and perform further investigations to rule out other conditions. The more alerts present, the less confident one can be about diagnosing a specific syndrome.

Exclusionary: Criteria that must be absent to diagnose the syndrome. If an exclusionary criterion is present, the syndrome cannot be diagnosed.

Other valuable points include how the syndrome may be diagnosed in low-resource settings. For example, some syndromes, e.g. Dravet syndrome, may be diagnosed based on the clinical features alone, and EEG, MRI and genetic testing are not essential for diagnosis in a low-resource setting. The other significant change is that the terminology of "benign" has been replaced by "self-limited", recognizing that these formerly "benign" termed syndromes do have intellectual and behavioral co-morbidities. For example, benign childhood epilepsy with centro-temporal spikes (BECTS) has been renamed Self Limited Childhood Epilepsy with Centro-temporal spikes (SeLECTS). Lastly, most named syndromes have been replaced with descriptive nomenclature. For example, West syndrome is now called "Infantile Epileptic Spasms Syndrome". However, there are some exceptions where the eponyms have been preserved, e.g. Lennox Gastaut syndrome and Dravet syndrome.

It is beyond the scope of this article to discuss the criteria for the individual syndromes. This review will be restricted to the nomenclature and classification. The reader is encouraged to refer to the original ILAE papers for the criteria required for syndromic diagnosis of various epilepsy syndromes. For a basic understanding of seizure and epilepsy classification in children and its modification in neonates, the reader is referred to the relevant papers [1,6]. A list of electroclinical syndromes with their previous and current terminology according to recent ILAE classification has been provided in **Table I**.

Epilepsy with Onset in the Neonatal Period and Infancy

This subset has been divided into two major groups: self-limited epilepsy syndromes, where spontaneous remission is the rule, and the DEEs, where there is developmental/cognitive impairment related to both the underlying etiology independent of epileptiform activity and the epileptic encephalopathy. Most etiology-specific syndromes that have onset in the neonatal or infantile period are DEEs [7].

The term "benign" has been replaced with self-limited as explained earlier. The common entity "Benign familial neonatal convulsions" has been replaced with "self-limited neonatal epilepsy."

As explained earlier, transparent terms that describe the clinical condition, such as Infantile epileptic spasms syndrome (IESS), have been proposed instead of the eponymous West syndrome. The aim is toenable early diagnosis and appropriate treatment. Many infants do not fulfill the triad of West syndrome, as they may lack hypsarrhythmia or regression hence, the term IESS is proposed.

Previous classifications for infantile-onset epileptic encephalopathy included two syndromes: Ohtahara syndrome and Early Myoclonic Encephalopathy. There is an electroclinical overlap between these two, sharing genetic and structural etiologies. Furthermore, many infants do not meet the criteria for either syndrome, highlighting the broad spectrum of presentations within Early-infantile developmental and epileptic encephalopathy (EIDEE). Thus, the Task Force amalgamated these into one syndrome called EIDEE. Syndromes that

Table I List of Electroclinical Syndromes With Their Previous and Current Terminology According to Recent ILAE Classification

	Current terminology	*Previous term*
Self-limited epilepsies	Self- limited (familial) neonatal epilepsy (SeLNE) Self- limited familial neonatal- infantile epilepsy (SeLFNIE) Self-limited infantile epilepsyGenetic epilepsy with febrile seizures plus (GEFS+) spectrum Myoclonic epilepsy in infancy (MEI)	Bening familial neonatal convulsions Bening familial neonatal/infantile seizures
Developmental epileptic encephalopathies (DEE)	Early infantile developmental epileptic encephalopathy Epilepsy in infancy with migrating focal seizures Infantile epilepsy spasms syndrome Dravet syndrome	Ohtahara syndrome and Early myoclonic encephalopathy of infancy Migrating partial seizures of infancy West syndrome Severe myoclonic epilepsy of infancy
Etiology specific syndrome	KCNQ2- DEE Pyridoxine-dependent (ALDH7A1)- DEE (PD- DEE) and pyridox (AM) INE 5'-phosphate deficiency (PNPO)- DEE (P5PD- DEE) CDKL5- DEE PCDH19 clustering epilepsy GLUT1DS Sturge–Weber syndrome	
Self- limited focal epilepsies Epilepsy syndromes with focal seizures	Self- limited epilepsy with centrotemporal spikes (SeLECTS)	Childhood epilepsy with centrotemporal spikes, (benign) Rolandic epilepsy, (benign) epilepsy with centrotemporal spikes
	Self- limited epilepsy with autonomic seizures (SeLEAS)	Panayiotopoulos syndrome, early onset (benign) occipital epilepsy
	Childhood occipital visual epilepsy (COVE)	Late onset (benign) occipital epilepsy or idiopathic childhood occipital epilepsy–Gastaut type
	Photosensitive occipital lobe epilepsy (POLE)	Idiopathic photosensitive occipital lobe epilepsy
Genetic generalized epilepsies	Childhood absence epilepsy (CAE)	Pyknolepsy, petit mal
Epilepsy syndromes with generalized seizures	Epilepsy with eyelid myoclonia (EEM)	Jeavons syndrome
DEEs	Epilepsy with myoclonic absence (EMA)	Bureau and Tassinari syndrome
	Epilepsy with myoclonic atonic seizures Lennox–Gastaut syndrome DEE-SWAS and EE-SWAS Febrile infection- related epilepsy syndrome (FIRES) Hemiconvulsion–hemiplegia–epilepsy syndrome (HHE)	Doose syndrome.

contained terms such as severe (severe myoclonic epilepsy in infancy), malignant (malignant migrating partial seizures in infancy), and benign (benign neonatal seizures) were changed to align with the most recent update.

Similarly, the term "partial seizures" has been replaced by "focal-onset seizures." To avoid confusion between seizure types and epilepsy syndrome, the term "convulsions" was replaced with "epilepsies" in some syndromes such as Self-Limited Neonatal Epilepsy. Moreover, because only family history differentiates between Familial and Non- familial Self-limited neonatal and infantile epilepsies, they merged these using the terms "Self-limited (Familial) Neonatal Epilepsy" and "Self-limited (Familial) Infantile Epilepsy," which allows the term "familial" to be used wherever appropriate. Finally, the concept of etiology-specific syndromes for certain

genetic and structural etiologies have been introduced. Gene discoveries have allowed the delineation of new electro-clinical syndromes, such as KCNQ2-DEE and CDKL5- DEE. Etiology-specific syndromes would mean rapid diagnosis and optimization of anti-seizure medications for the specific syndrome if available (e.g. sodium channel blockers for KCNQ2-DEE), and they allow the possibility for precision medicine trials/therapies, which will improve long-term prognosis.

Epilepsy Syndromes with Onset in Childhood

Epilepsy syndromes of childhood onset (age 2-12 years) have been divided into three categories: *a*) self-limited focal epilepsies (SeLFE), comprising four syndromes: self-limited epilepsy with centrotemporal spikes, self-limited epilepsy with autonomic seizures, childhood occipital visual epilepsy, and photosensitive occipital lobe epilepsy; *b*) generalized epilepsies, comprising three syndromes: childhood absence epilepsy, epilepsy with myoclonic absence, and epilepsy with eyelid myoclonia; and *c*) developmental and/or epileptic encephalopathies (DEEs), comprising five syndromes: epilepsy with myoclonic–atonic seizures, Lennox–Gastaut syndrome, developmental and/or epileptic encephalopathy with spike and wave activation in sleep, hemiconvulsion–hemiplegia–epilepsy syndrome (HHES), and febrile infection-related epilepsy syndrome (FIRES) [8].

Recognition of these childhood syndromes requires knowledge of seizure semiology, temporal evolution, and the developmental status of the child, as well as electroencephalographic (EEG) features (background, interictal, and ictal patterns) and, in some cases, brain magnetic resonance imaging (MRI) and genetic studies. The name "SeLFE" was chosen to reflect the key features of the natural history and the clinical phenotype. The term "benign" is inappropriate, as some children have associated cognitive and behavioral comorbidities. For each syndrome, the terms used reflect the major phenotypic features, such as centrotemporal spikes in SeLECTs, autonomic seizures in SeLEAS, occipital semiology and EEG findings in childhood occipital visual epilepsy (COVE), and photic-induced focal sensory visual seizures and genetic predisposition in photosensitive occipital epilepsy (POLE).

Regarding the childhood-onset DEEs, not uncommonly, childhood syndromes may have evolved from pre-existing epilepsy syndromes, such as infantile epileptic spasms syndrome, which typically evolve to LGS in up to one-third of patients, or self-limited epilepsy with centrotemporal spikes (SeLECTS; formerly known as benign rolandic epilepsy or benign epilepsy with centrotemporal spikes) or structural focal epilepsy evolving to epileptic encephalopathy with spike-wave activation in sleep (EE-SWAS). In acquired syndromes, they are typically developing children present with a profound acute encephalopathy followed by drug-resistant epilepsy, as seen in FIRES, or HHE. Moreover, some self-limited focal epilepsies may overlap with the idiopathic generalized epilepsies (IGEs) or even evolution to IGEs.

Developmental/Epileptic Encephalopathy with Spike Wave Activation on Sleep (DEE-SWAS) (DEE-SWAS) and Epileptic Encephalopathy with Spike Wave Activation on Sleep (EE-SWAS) refer to a spectrum of conditions that are characterized by various combinations of cognitive, language, behavioral, and motor regression associated with striking spike and wave activation in NREM sleep. DEE- SWAS and EE- SWAS share similar clinical features. These were previously called by various terms such as Landau Kleffner Syndrome, Electrical Status Epilepticus in Sleep, and epileptic encephalopathy–continuous spike and waves during sleep. Similarly, the terms DEE-SWAS and EE-SWAS comprise two essential components, cognitive regression and the characteristic EEG pattern.

Epilepsy Syndromes with Onsset at a Variable Age

Although many epilepsy syndromes typically begin in the neonatal period, infancy, or childhood, several important syndromes begin at a variable age, which have treatment implications if recognized appropriately [9].

Syndromes that begin at a variable age can begin in those aged ≤ 18 years and in those aged ≥ 19 years. These syndromes can be broadly classified into generalized, focal, and combined generalized and focal epilepsy syndromes. Some syndromes can be associated with developmental and/or epileptic encephalopathy in children or with progressive neurological deterioration if they begin later in life.

Generalized epilepsy syndromes with polygenic etiologies, include idiopathic generalized epilepsies (IGEs), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and epilepsy with generalized tonic–clonic seizures alone (GTCA).

Focal epilepsy syndromes include self-limited focal epilepsy syndromes with presumed complex inheritance: childhood occipital visual epilepsy (COVE) and photosensitive occipital lobe epilepsy (POLE).

Focal epilepsy syndromes with genetic, structural, or genetic–structural etiologies: sleep-related hypermotor (hyperkinetic) epilepsy (SHE), familial mesial temporal lobe epilepsy (FMTLE), familial focal epilepsy with

variable foci (FFEVF), and epilepsy with auditory features (EAF)

A combined generalized and focal epilepsy syndrome with polygenic etiology: epilepsy with reading-induced seizures (EwRIS)

Epilepsy syndromes with developmental encephalo-pathy (DE), epileptic encephalopathy (EE), or both, and epilepsy syndromes with progressive neurological deterioration: progressive myoclonus epilepsies (PME) and febrile infection-related epilepsy syndrome (FIRES).

Two other etiology-specific epilepsy syndromes have seizure onset at variable ages, which are of importance under this category:

- Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE- HS)
- Rasmussen syndrome (RS)

Idiopathic Generalized Epilepsy Syndromes

The term idiopathic generalized epilepsies (IGEs) had historically included the syndromes childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and epilepsy with generalized tonic–clonic seizures alone (GTCA). The 2017 ILAE classification suggested that the term "genetic generalized epilepsies" (GGEs) be used for the broad group of epilepsies with generalized seizure types and generalized EEG abnormalities based on a presumed genetic etiology. The task force proposed that the term IGE should pertain to a distinct subgroup of the GGEs comprising of these four syndromes for the following reasons: They are the most common GGE syndromes. They typically have a good prognosis for seizure control. They typically do not evolve to epileptic encephalopathy. There is clinical overlap between CAE, JAE, and JME. They may evolve with age to another IGE syndrome (e.g., CAE evolving to JME). They have similar electroencephalographic (EEG) findings, including a normal background activity with 2.5-6 Hz generalized spike-wave and/or polyspike-wave discharges that may activate on hyperventilation and photic stimulation [10].

These current definitions and classifications of epilepsy syndromes by ILAE will enable clinicians to early characterize epilepsy syndromes, offer appropriate treatments and prognostication. With contributions from genetic research, the phenotypic spectrum for epilepsy syndromes has expanded and etiology-specific epilepsy syndromes are increasingly recognized. There is a word of caution about the strict delineation of epilepsy syndromes, which can be potentially harmful if they exclude patients who do not precisely meet the criteria. Future work establishing diagnostic criteria for etiology-specific epilepsy syndromes will be necessary for research into precision therapies [e.g., Mammalian target of rapamycin (mTOR) inhibitors for tuberous sclerosis], advancing knowledge of pathogenesis and identifying subgroups within specific etiologies with a better treatment response. Future ILAE classifications may throw more light on this perspective.

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