ILAE Classification and Definition of Epilepsy Syndromes with Onset in Childhood: Position Paper by the ILAE Task Force on Nosology and Definitions

N Specchio[1], EC Wirrell[2]*, IE Scheffer[3], R Nabbout[4], K Riney[5], P Samia[6], SM Zuberi[7], JM Wilmshurst[8], E Yozawitz[9], R Pressler[10], E Hirsch[11], S Wiebe[12], JH Cross[13], P Tinuper[14], S Auvin[15]

1. Rare and Complex Epilepsy Unit, Department of Neuroscience, Bambino Gesu' Children's Hospital, IRCCS, Member of European Reference Network EpiCARE, Rome, Italy
2. Divisions of Child and Adolescent Neurology and Epilepsy, Department of Neurology, Mayo Clinic, Rochester MN, USA.
3. University of Melbourne, Austin Health and Royal Children's Hospital, Florey Institute, Murdoch Children's Research Institute, Melbourne, Australia.
4. Reference Centre for Rare Epilepsies, Department of Pediatric Neurology, Necker–Enfants Malades Hospital, APHP, Member of European Reference Network EpiCARE, Institut Imagine, INSERM, UMR 1163, Université de Paris, Paris, France.
5. Neurosciences Unit, Queensland Children's Hospital, South Brisbane, Queensland, Australia. Faculty of Medicine, University of Queensland, Queensland, Australia.
6. Department of Paediatrics and Child Health, Aga Khan University, East Africa.
7. Paediatric Neurosciences Research Group, Royal Hospital for Children & Institute of Health & Wellbeing, University of Glasgow, Member of European Refence Network EpiCARE, Glasgow, UK.
8. Department of Paediatric Neurology, Red Cross War Memorial Children's Hospital, Neuroscience Institute, University of Cape Town, South Africa.
9. Isabelle Rapin Division of Child Neurology of the Saul R Korey Department of Neurology, Montefiore Medical Center, Bronx, NY USA.
10. Programme of Developmental Neurosciences, UCL NIHR BRC Great Ormond Street Institute of Child Health, Department of Clinical Neurophysiology, Great Ormond Street Hospital for Children, London, UK
11. Université de Paris, AP-HP, Hôpital Robert-Debré, INSERM NeuroDiderot, DMU Innov-RDB, Neurologie Pédiatrique, Paris, France.
12. Department of Clinical Neurosciences, University of Calgary, Calgary, AB, Canada.
13. Programme of Developmental Neurosciences, UCL NIHR BRC Great Ormond Street Institute of Child Health, Great Ormond Street Hospital for Children, London and Young Epilepsy Lingfield, UK.
14. Department of Biomedical and Neuromotor Sciences. University of Bologna. IRCCS Istituto delle Scienze Neurologiche. Bologna, Italy.
15. Université de Paris, AP-HP, Hôpital Robert-Debré, INSERM NeuroDiderot, DMU Innov-RDB, Neurologie Pédiatrique, Paris, France.

Number of text pages: 59

Number of words: 13524

Number of references: 182

Number of figures: 9

Number of tables: 12

Number of Supplementary Figures: 5

*Corresponding Author

Elaine Wirrell MD

Child and Adolescent Neurology, Mayo Clinic

200 First St SW

Rochester MN USA 55902

Email: wirrell.elaine@mayo.edu

Phone 507-266-0774

Fax 507-284-0727

Summary:

The 2017 ILAE classification has defined a three-tier system with epilepsy syndrome identification at the third level. While a syndrome cannot be determined in all children with epilepsy, identification of a specific syndrome provides guidance on management and prognosis. In this paper, we describe here the childhood-onset epilepsy syndromes. Most of these syndromes have both mandatory seizure type(s) and interictal EEG features. Based on the 2017 Classification of Seizures and Epilepsies, some syndrome names have been updated using terms directly describing the seizure semiology. Epilepsy syndromes beginning in childhood have been divided into three categories: 1. Self-limited focal epilepsies, comprising four syndromes: Self-Limited Epilepsy with Centrotemporal Spikes, Self-Limited Epilepsy with Autonomic Seizures, Childhood Occipital Visual Epilepsy and Photosensitive Occipital Lobe Epilepsy; 2. Generalized Epilepsies comprising three syndromes: Childhood Absence Epilepsy, Epilepsy with Myoclonic Absence and Epilepsy with Eyelid Myoclonia; 3. Developmental and epileptic encephalopathies, comprising five syndromes: Myoclonic-Atonic Epilepsy, Lennox-Gastaut syndrome, Developmental and/or epileptic encephalopathies with spike-wave activation in sleep, Hemiconvulsion-Hemiplegia-Epilepsy and Febrile Infection-Related Epilepsy Syndrome. We define each highlighting the mandatory seizure(s), EEG features, phenotypic variations and findings from key investigations.

Keywords:

Childhood epilepsy with centrotemporal spikes, Panayiotopoulos syndrome, Lennox-Gastaut syndrome, benign occipital epilepsy, continuous spike-wave in sleep, Landau-Kleffner syndrome, Myoclonic atonic, Febrile Infection-related Epilepsy Syndrome, Eyelid Myoclonia, Myoclonic Absences, Hemiconvulsion-Hemiplegia Epilepsy

Introduction

The goal of this paper is to describe epilepsy syndromes that begin in childhood (age 2 to 12 years). Additional syndromes that have a variable age at onset, including in childhood, are described in the paper on Epilepsy Syndromes with Onset in Adolescents, Adults and at Variable Ages[1]. The childhood-onset syndromes can be broadly divided into three main groups; (1) focal epilepsy syndromes of unknown cause, most of which are self-limited, (2) generalized epilepsy syndromes, which are thought to have a genetic basis, and (3) developmental and epileptic encephalopathies (DEE) which often have both focal and generalized seizures, including Lennox-Gastaut syndrome (LGS) and Developmental and/or Epileptic Encephalopathy with spike-wave activation in sleep (D/EE-SWAS), or may have generalized seizures alone, such as Myoclonic Atonic Epilepsy (MAE), or just focal/multifocal seizures alone, such as Hemiconvulsion Hemiplegia Epilepsy (HHE) and Febrile Infection-Related Epilepsy Syndrome (FIRES).

Childhood is also the typical age of onset of Childhood Absence Epilepsy (CAE), this syndrome is covered in a separate paper on the Idiopathic Generalized Epilepsy syndromes (IGEs)[2].

Recognition of these childhood syndromes requires careful analysis of seizure semiology, evolution over time, developmental course 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. At times, childhood syndromes may have evolved from other epilepsy syndromes or types, such as Infantile Spasms syndrome, which may evolve to LGS, or Self-limited Epilepsy with Centro-Temporal Spikes (SeLECTS - formerly known as Benign Rolandic epilepsy or Benign Epilepsy with Centro-Temporal Spikes) or structural focal epilepsy evolving to D/EE-SWAS. In other syndromes, children with prior normal development present with a severe, acute encephalopathy followed by drug-resistant epilepsy, as typically seen in Febrile Infection-related Epilepsy Syndrome (FIRES), or Hemiconvulsion-Hemiplegia Epilepsy (HHE). Moreover, for some Self-limited Focal Epilepsies (SeLFE), there may be overlap with the IGEs or even evolution to them, reflecting the patient's underlying susceptibility to epileptic seizures [3,4].

The exact proportion of children with epilepsy who meet criteria for a specific syndrome has not been well-studied prospectively, however retrospective data suggest that an epilepsy syndrome is identified in at least one third of cases [5,6].

This paper will address the specific clinical and laboratory features of epilepsy syndromes that begin in childhood and provide rationale for any significant nomenclature or definitional changes. Table 1 summarizes the epilepsy syndromes with updated nomenclature and acronyms discussed in this paper.

Methodology

The methodology for syndrome definitions is described in "Methodology for Classification and Definition of Epilepsy Syndromes: Proposal by the ILAE Task Force on Nosology and Definitions"[7]. A working group consisting of Task Force members with expertise in pediatrics was convened. One member of the group was assigned to draft a template for each proposed syndrome, using data from a literature review through to July 2019, the most recent edition of "Epileptic Syndromes of Infancy, Childhood and Adolescence"[8] and current criteria listed on www.epilepsydiagnosis.org, which was circulated to all members. Each draft was discussed either at an on-line or in-person meeting of Task Force members and modified based on further input and clinical experience of Task Force members, together with additional literature searches.

For each syndrome, mandatory features (must be present for diagnosis) and exclusionary features (must be absent for diagnosis) were proposed, along with Alerts (features that are atypical for the

syndrome and should prompt consideration of other diagnoses). A Delphi process was then undertaken, surveying all Task Force members, in addition to recognized external experts in Pediatric Epilepsy, from all ILAE regions (Europe, Oceania/Asia, North America, Latin America, Africa and the Eastern Mediterranean region), to reach consensus.

For each syndrome, the core diagnostic criteria, along with a summary of other features are provided. Based on the Delphi process, Tables with the mandatory and exclusionary criteria and Alerts for each syndrome are provided at the end of the manuscript.

Proposed syndromes are subdivided into (1) Self-Limited Focal Epilepsies of Childhood, (2) Genetic Generalized Epilepsies and (3) Developmental and/or Epileptic Encephalopathies of Childhood.

Self-Limited Focal Epilepsies of Childhood (SeLFE) syndromes

Focal epilepsies with onset during childhood are often self-limited and usually of unknown cause [9,10]. Many self-limited childhood focal epilepsies have a characteristic electro-clinical presentation and fall within one of the SeLFE syndromes (Fig. 1). These conditions have been referred to in the past as "benign" or "idiopathic". The term benign is no longer recommended as it fails to acknowledge the comorbidities present in some individuals. The term idiopathic is now restricted to describing the 4 syndromes termed the idiopathic generalized epilepsies. Given the typical evolution of these conditions, with age-dependent onset and remission, it has been proposed to use the term "self-limited" when referring to such epilepsies [11]. The Nosology and Definitions Task Force of the International League Against Epilepsy (ILAE) proposes the term "Self-Limited Focal Epilepsies" (SeLFEs) of Childhood to encompass this group of epilepsy syndromes.

Presumed genetic factors play an important etiological role, as supported by the higher incidence of a positive family history of epilepsy and age-dependent, focal EEG abnormalities. However, no specific genetic variants have been identified so far. Rarely, genetic variants may be associated with more severe phenotypes of these syndromes, i.e. *GRIN2A* in SeLECTS evolving to D/EE-SWAS [12–15].

The SeLFEs account up to 25% of all pediatric epilepsies [16,17]. They comprise a group of syndromes which share the following features:

1. Age-dependent occurrence, specific for each syndrome
2. No significant structural lesion of the brain.
3. Birth, neonatal and antecedent history is usually unremarkable.
4. Cognition and neurological examination are typically normal
5. Remission usually occurs by adolescence
6. Pharmaco-responsiveness if treated
7. Genetic predisposition for the EEG trait
8. Classical seizure semiology for each syndrome. Seizures are focal motor or sensory with or without impaired awareness and may evolve to bilateral tonic-clonic seizures.
9. Specific EEG features: epileptiform discharges with distinctive morphology and location (depending on the epilepsy syndrome), often activated with sleep. The EEG has a normal background.

In most cases, children with SeLFEs have features characteristic of one specific syndrome. However, some have a mixed picture, or may evolve from one syndrome to another over time [18]. Furthermore, rare cases also show overlap with the Idiopathic Generalized Epilepsies [3,4].

Specific syndromes which fall under the SeLFE umbrella include:

1. Self-Limited Epilepsy with Centrotemporal Spikes (SeLECTS) (formerly called childhood epilepsy with centrotemporal spikes, benign epilepsy of childhood with centrotemporal spikes or benign rolandic epilepsy)
2. Self-Limited Epilepsy with Autonomic Seizures (SeLEAS) (formerly called Panayiotopoulos syndrome or early-onset benign occipital epilepsy)
3. Childhood Occipital Visual Epilepsy (COVE) (formerly called late-onset benign occipital epilepsy or Gastaut syndrome or Idiopathic childhood occipital epilepsy – Gastaut type)
4. Photosensitive Occipital Lobe Epilepsy (POLE) (formerly called idiopathic photosensitive occipital lobe epilepsy)

All of the above nomenclature changes were carefully evaluated by our working group. The main goal was to have a uniform classification and terminology for the self-limited childhood focal epilepsy syndromes. Our aim was to improve diagnosis and management of these epilepsy syndromes, for both counselling and treatment purposes.

Self-Limited Epilepsy with Centrotemporal Spikes (SeLECTS)

SeLECTS is a self-limited epilepsy syndrome, formerly known as Benign Rolandic epilepsy or Benign Epilepsy with Centro-Temporal Spikes, which begins in children in their early school years[19] (Table 2). Seizures are often brief, and typically involve focal clonic or tonic activity of the throat/tongue and one side of the lower face, which may then evolve to a focal to bilateral tonic-clonic seizure. This epilepsy syndrome occurs in children who are otherwise neurologically and cognitively normal, and imaging studies, if done, show no causal lesion. The EEG shows a normal background with high amplitude centrotemporal sharp-and-slow-wave complexes, which are activated in drowsiness and sleep[20]. Seizures cease by mid-adolescence. The finding of a positive family history and focal EEG abnormalities in family members supports underlying genetic factors contributing to the etiology of SeLECTS[21,22].

Epidemiology:

SeLECTS is the most frequent SeLFE and accounts for about 6- 7% of all childhood epilepsies[5,23]. Its incidence is approximately 6.1 per 100,000 children aged <16 years per year[24,25].

Clinical context:

The age at onset ranges between 4 and 10 years in 90% of patients, with a peak around 7 years[26]. Both sexes are affected, with a slight male predominance (60%)[25,27,28].

Antecedent, birth and neonatal history is typically normal. A history of febrile seizures is seen in 5-15% of cases. Rarely, a history of SeLEAS may be present[29]. Development, cognition, neurological exam and head size prior to seizure onset are typically normal. SeLECTS may be seen in children with a history of prior neurological injury or intellectual disability, however, these features are considered coincidental and not causal. Prior to epilepsy onset, ADHD and specific cognitive function deficits, mainly related to language and executive function may be seen[30].

Course of illness:

Seizures usually resolve by age 13 years but can occasionally continue until 18 years of age[31]. While the epilepsy is active, behavioral and neuropsychological deficits may emerge or worsen, particularly in language and executive functioning[32,33]. These deficits often improve or resolve with age[34]. The social outcome in adults is very good[35]. Seizures typically respond well to antiseizure medication. The prognosis for seizure remission is excellent even for those whose seizures are initially difficult to control[36].

Seizures:

Focal seizures with characteristic fronto-parietal opercular features and/or nocturnal bilateral tonic-clonic seizures are mandatory for diagnosis. Seizures are brief, typically less than 2-3 minutes, usually few in number (most children have less than 10 lifetime seizures) and may occur sporadically, with frequent seizures seen over a few days or weeks and then several months until the next seizure.

Characteristic semiology of the focal seizures includes (i) somatosensory symptoms, with unilateral numbness or paresthesia of the tongue, lips, gums, and inner cheek [27], (ii) orofacial motor signs, specifically tonic or clonic contraction of one side of the face, mouth and tongue, then involving one side of the face; (iii) speech arrest – children have difficulty or are unable to speak (dysarthria or anarthria) but can understand language; and (iii) sialorrhea, a characteristic ictal symptom - it is unclear whether it is due to increased salivation, swallowing disturbance, or both. In some cases, focal seizures in sleep evolve rapidly to tonic-clonic activity of the ipsilateral upper limb, to an ipsilateral hemiclonic seizure, or to a focal to bilateral tonic-clonic seizure. Todd's paresis may occur post-ictally. In nocturnal seizures, the initial focal component may often not be witnessed.

Seizures occur during sleep in 80-90% of patients and only while awake in fewer than 20% of children [37]. In seizures associated with SeLECTS, cognitive (e.g. gustatory hallucinations), emotional (e.g. fear), and autonomic features are not seen. Moreover, focal motor or focal to bilateral tonic-clonic status epilepticus, defined as seizure persisting for >30 minutes, is rare [37] and, if present, should lead to review of the diagnosis. The occurrence of atypical absence seizures, focal atonic seizures and focal motor seizures with negative myoclonus with loss of balance and falls, should suggest evolution to D/EE-SWAS and evidence for cognitive impairment or regression should be sought. If patients present with prolonged focal non-motor seizures with prominent autonomic features, especially ictal vomiting, SeLEAS should be considered.

Generalized tonic-clonic seizures, as distinct from focal to bilateral tonic-clonic seizures, during wakefulness are exclusionary, but may be difficult to differentiate clinically.

EEG:

Background activity is typically normal, with the presence of normal sleep architecture. If sustained focal slowing without centrotemporal spikes or diffuse slowing is recorded, another epilepsy syndrome or a structural lesion should be considered, and brain imaging is recommended.

High amplitude centrotemporal sharp-and-slow wave complexes that activate in drowsiness and sleep are mandatory for diagnosis. They are triphasic, high-voltage (100-microvolts to 300-microvolts) sharp waves (initial low-amplitude positivity, then high amplitude negativity followed again by low amplitude positivity), with a transverse dipole (frontal positivity, temporo-parietal negativity), often followed by a high voltage slow wave [37,38]. The discharges may be isolated or occur in trains of doublets and triplets, and focal, rhythmic, slow activity is occasionally observed in the same region as the spikes. The discharges may be unilateral or bilateral and independent (Figure 2A). There may be discharges seen outside the centrotemporal region (midline, parietal, frontal, occipital). If a continuous spike-and-slow-wave pattern is present in sleep, the child should be evaluated for progressive language or cognitive impairment or regression. This EEG pattern should only lead to a diagnosis of D/EE-SWAS if developmental plateauing or regression is also present [21,39].

A marked increase in the frequency of epileptiform activity in drowsiness and sleep always occurs. The EEG pattern may also change such that sharp- or spike-and-slow waves have a broader field

and become bilaterally synchronous (Figure 2B). In 10-20% of children, centrotemporal sharp- or spike-and-slow wave may be activated by sensory stimulation of the fingers or toes [40].

Seizures are typically infrequent - it is rare to obtain an ictal recording and there are few published reports in the literature [41]. Seizures may be accompanied by a brief decrease in amplitude of the background EEG, followed by diffuse sharp wave discharges of increasing amplitude, predominantly in one centrotemporal region[41], followed by high amplitude slowing and then a return to the usual interictal EEG (Figure 2C). With focal to bilateral tonic-clonic seizures, ictal rhythms may become bilaterally synchronous (as opposed to generalized) sharp- or spike-and-slow-wave activity [42–44].

Imaging:

Neuroimaging is normal or may show non-specific findings. If the electroclinical diagnosis of SeLECTS is made and there are no atypical features, neuroimaging is not required. If there are clinical, developmental, EEG features, or evolution that are not consistent with this diagnosis, neuroimaging should be considered. Nonspecific MRI findings, such as hippocampal asymmetry, white matter abnormalities, and enlargement of the lateral ventricles, should not exclude a diagnosis of SeLECTS [45]. Patients with focal epilepsy due to structural abnormalities such as focal cortical dysplasia, heterotopia, or low-grade brain tumors may mimic SeLECTS but usually show atypical features such as unilateral EEG abnormality or drug-resistance.

Genetics:

Genetic factors play an important etiological role, as supported by the higher incidence of a positive family history for epilepsy or febrile seizures, and age-dependent, focal EEG abnormalities in the relatives of SeLECTS patients. Siblings may show the EEG trait of centrotemporal discharges in an age-dependent, autosomal dominant fashion without clinical seizures [22]. However, the clinical epilepsy syndrome is likely complex in inheritance, as pedigrees with multiple individuals with SeLECTS are very rare [41]. At this time, there are no identified pathogenic gene variants found in most children with SeLECTS. Heterozygous pathogenic variants in *GRIN2A* can be found in individuals with SeLECTS who may show evolution to D/EE-SWAS with associated language and cognitive impairment [13–15]. Also copy number variants have been detected in rare cases [46].

Differential Diagnosis:

Other Epilepsies:

- *D/EE-SWAS*: Patients with D/EE-SWAS may present with similar seizures but can be distinguished by cognitive and language regression. Children with SeLECTS may rarely evolve to this syndrome.
- Focal seizures due to structural brain abnormality.
- Other *SeLFEs* – the morphology of the EEG abnormalities in the various SeLFEs may overlap and their seizure localization may change with age.
- Fragile X syndrome should be excluded in males with intellectual impairment, as EEG changes in Fragile X syndrome may mimic those seen in SeLECTS [47,48]. In Fragile X syndrome, seizures are most commonly focal impaired awareness seizures, and less likely focal motor without impaired awareness or focal to bilateral tonic-clonic seizures.

Self-Limited Epilepsy with Autonomic Seizures (SeLEAS)

SeLEAS, formerly known as Panayiotopoulos syndrome or early-onset benign occipital epilepsy, is characterized by the onset in early childhood of focal autonomic seizures that are often prolonged. EEG shows high amplitude focal spikes with variable localization which are typically activated by

sleep. Seizures are infrequent in most patients, with 25% only having a single seizure. The epilepsy is self-limited with remission typically within a few years from onset [49]. The mean duration of the disease is around 3 years [50] (Table 3).

Epidemiology:

The prevalence of SeLEAS depends on the age range studied. It accounts for 5% of childhood epilepsies between 1-14 years [50] and 13% of childhood epilepsies between 3 and 6 years [51]. SeLEAS is the most common cause of afebrile nonconvulsive status epilepticus in childhood [52].

Clinical context:

The usual age at onset is between 3 and 6 years (70% of cases), and ranges from 1 to 14 years [53]. Both sexes are affected equally. Antecedent and birth history is normal. A history of febrile seizures is seen in 5-17% of patients. Head size and neurological examination are normal. Development and cognition are normal [50,54,55].

Course of illness:

Seizure frequency is typically low, with approximately 25% of children having a single seizure only, and the majority having fewer than 5 seizures in total [56]. Seizures typically remit within 1-2 years with normal neurodevelopment, although approximately 20% of patients may evolve to other SeLFEs, most commonly SeLECTS [56]. Rarely, SeLEAS may evolve to D/EE-SWAS.

Seizures:

Focal autonomic seizures, with or without impaired awareness, are mandatory for diagnosis. Autonomic features at onset may vary, but most frequently include retching, pallor, flushing, nausea, malaise and abdominal pain. Vomiting, the most common autonomic manifestation, occurs in about 75% of children and leads to misdiagnosis of acute gastroenteritis or migraine. Additional autonomic features include pupillary changes (e.g. mydriasis), temperature, and cardiorespiratory (breathing, pallor, cyanosis and heart rate) changes. Syncope may rarely occur. Seizures frequently evolve with eye and/or head deviation, generalized hypotonia, and focal clonic (hemiclonic) or focal to bilateral tonic-clonic seizure activity. Awareness is usually preserved at seizure onset and may fluctuate in degree of impairment as the seizure progresses. More than 70% of seizures occur from sleep. Seizures are often prolonged and can last longer than 30 minutes [17].

EEG:

The background activity is normal. If persistent focal slowing is present, a structural brain abnormality should be sought as an alternative etiology. Generalized slowing is not seen except in the post-ictal period.

Multifocal, high voltage spike- or sharp-and-slow-waves are typically seen, often over the posterior regions. Discharges may show marked variability in terms of localization in sequential EEGs, and generalized discharges may also be seen [29]. EEG discharges are activated both by sleep deprivation and by sleep, when discharges often have a wider field and may be bilaterally synchronous (Supplemental Figure 1A-B). Eye closure (elimination of central vision and fixation off sensitivity) typically activates posterior discharges, but this finding is not pathognomonic of this syndrome.

If seizures are recorded, ictal onset varies, but most have posterior onset. The ictal pattern shows rhythmic slow activity intermixed with small spikes and/or fast activity [57] (Supplemental Figure 1C).

Imaging:

Neuroimaging, if performed, shows no causal lesion. MRI should be considered in cases with recurrent seizures or atypical presentations. Nonspecific MRI findings should not exclude a diagnosis of SeLEAS.

Genetics:

SeLEAS is probably genetically determined, however no causative gene variants have been detected so far. There is a higher prevalence of febrile seizures in first-degree relatives, and case reports of siblings with other self-limited focal epilepsies [18,50]. There is no clear indication to perform genetic testing in most patients, however, rare cases with *SCN1A* pathogenic variants have been reported [58–60].

Differential Diagnosis:

Other epilepsies:

- Focal seizures due to structural brain abnormalities. Temporal lobe epilepsy in early childhood and structural occipital epilepsies may present with ictal vomiting.
- *SeLECTS* should be diagnosed if seizures have prominent fronto-parietal-opercular features.
- *COVE* is distinguished by prominent visual symptoms, as opposed to autonomic features.
- *Familial focal epilepsy with variable foci:* different focal epilepsies occur in other family members but SeLEAS is not usually seen.

Other conditions:

- Migraine-associated disorders such as benign paroxysmal vertigo
- Syncope
- Other medical disorders associated with intermittent vomiting

Childhood Occipital Visual Epilepsy (COVE)

Childhood occipital visual epilepsy syndrome, formerly known as late-onset benign occipital epilepsy, Gastaut syndrome or Idiopathic childhood occipital epilepsy – Gastaut type, begins in later childhood and is self-limited in the majority of patients. This syndrome occurs in developmentally normal children with frequent, brief seizures during wakefulness, with visual phenomena without altered awareness, which are often followed by headaches with migrainous features. Seizures may be controlled and remission of seizures often, but not invariably, occurs within 2-7 years from onset [61] (Table 4).

Epidemiology:

COVE has a prevalence of 0.3% of children with newly-diagnosed, afebrile seizures [26].

Clinical context:

Age at onset is typically at 8-9 years, with a range from 15 months to 19 years [62]. Both sexes are equally affected. Antecedent and birth history is normal. Patients have normal development and cognition, although mild cognitive impairment has been described. Head size and neurological examination are normal [63].

Course of illness:

Remission occurs in 50-80% of patients within 2-7 years after onset with or without administration of antiseizure medication [64,65]. Seizures are often responsive to antiseizure medication. Remission

is more likely in the 90% of patients who only have focal seizures [63]. Occurrence of bilateral tonic-clonic seizures is associated with a lower rate of remission. Development usually remains normal.

Seizures:

Focal sensory visual seizures during wakefulness are mandatory for diagnosis. They have abrupt onset, are brief (typically seconds, most lasting less than 3 minutes, rarely up to 20 minutes), and frequent without treatment. Typically, elementary visual phenomena occur, described as small multi-colored circles seen in the peripheral vision, increasingly involving more of the visual field and moving horizontally across to the other side. This may be followed by deviation of the eyes or turning of the head (to the side ipsilateral to the hemisphere of seizure onset) [66].

Other features consistent with occipital lobe onset may occur, including ictal blindness, complex visual hallucinations or illusions (such as palinopsia, micropsia, metamorphopsia), orbital pain, eyelid fluttering or repeated eye closure [67,68]. The seizure may spread outside the occipital lobe resulting in hemiparaesthesia, impaired awareness (14%), hemiclonic (43%) or a focal to bilateral tonic-clonic (13%) seizure [62]. Typical absence seizures may rarely occur in some patients after onset of the focal sensory seizures [69].

There may be ictal or post-ictal headache, nausea or vomiting. Post-ictal headache with migraine-like features is common (in 50% of patients) and may be associated with nausea and vomiting.

EEG:

The background activity is normal. Interictal occipital sharp- or spike-and-slow-wave complexes are typically seen but may only occur in sleep. Centrotemporal, frontal or generalized discharges are also present in 20% of cases [70]. Fixation-off sensitivity (facilitation of epileptiform discharges with elimination of central vision) is seen in 20-90% of patients but is not pathognomonic of this syndrome [62,65,71]. EEG discharges are enhanced by sleep deprivation and sleep (Supplemental Figure 2 A-B). COVE may rarely evolve to D/EE-SWAS, therefore if cognitive regression occurs, a sleep EEG should be performed.

At ictal onset, there is a reduction in the usual background occipital spike or spike-and-slow-wave with the sudden appearance of unilateral occipital fast rhythms with spikes of low amplitude. There may be slower spike-and-slow-wave discharges during oculo-clonic seizures or ictal blindness [67,68] (Supplemental Figure 2C).

Imaging:

Neuroimaging is normal. Brain MRI is required to exclude a structural brain abnormality [72].

Genetics:

Genetic testing is not required as there are no genes identified for this epilepsy syndrome. It is presumed that the etiology is genetic, and likely complex/polygenic in inheritance [18]. A family history of febrile seizures or epilepsy occurs in up to a third of cases and a family history of migraine is reported in 9-16% of cases [62,65].

Differential Diagnosis:

Other epilepsies:

- Focal seizures due to a structural brain abnormality
- Celiac disease, epilepsy and cerebral calcification syndrome is distinguished by occipital lobe calcification, best seen on CT brain.
- Myopathy, encephalopathy, lactic acidosis and stroke-like syndrome (MELAS)

- Lafora Disease is distinguished by the presence of regression, prominent myoclonus, progressive ataxia and spasticity.

Other conditions:

- Migraine with visual aura can be distinguished by the more gradual development and longer duration of the aura, and the character of the visual phenomena (linear, zig-zag or fortification spectral phenomena as opposed to colored circles or light flashes that change in size or move horizontally).
- Posterior reversible encephalopathy syndrome presents with acute symptomatic seizures, which resolve with control of hypertension.

Photosensitive Occipital Lobe Epilepsy (POLE)

Photosensitive Occipital Lobe Epilepsy (POLE) is a rare epilepsy syndrome that has onset in childhood and adolescence and is characterized by the presence of photic-induced, focal seizures involving the occipital lobe in individuals with normal development, neurological examination and intellect. At seizure onset, the patient experiences a visual aura with involuntary head version with intact awareness. Prognosis is variable. See Table 5.

Epidemiology

The prevalence of POLE is low. Epidemiological data is limited but estimates suggest that POLE accounts for 0.7% of childhood epilepsies[73].

Clinical Context:

Age at onset is between 4 and 17 years of age (mean 11 years), although rare cases with adult onset are also reported [74]. There is a strong female predominance [75]. Antecedent and birth history is unremarkable, and development is normal. Head size and neurological examination are normal.

Course of illness:

Prognosis varies, some patients will only have a few seizures, others have seizure remission over time and others continue to have photic-induced seizures [76].

Seizures:

Photic-induced, focal sensory visual seizures (induced for example by flickering sunlight) are mandatory for diagnosis and the main seizure type. Young children may find the aura hard to describe but they can sometimes draw a picture of what they see. Visual sensory symptoms include lights, colored spots, formed visual hallucinations or visual blurring/loss that moves across the visual field. There is associated head and eye version in which the patient feels they are following the visual phenomenon. Seizures can be induced by video games or other photic stimuli, and in the past were often induced by older analog televisions with slower frequency outputs [77].

Seizures are typically brief (<3 minutes) although prolonged seizures may occur. Seizures may progress to a cephalic sensation (including headache), autonomic epigastric sensation or vomiting, and impaired awareness or to a focal to bilateral tonic-clonic seizure [73,78]. Infrequently, seizures can arise from sleep without photic induction. Some patients also have focal sensory visual occipital seizures without visual induction [75]. An overlap between this syndrome and the IGEs is well-described [79–81] and thus myoclonic, absence and generalized tonic clonic seizures may also be seen. The frequency of seizures is variable.

EEG:

The background EEG is normal. Interictal occipital spike or spike-and-slow-wave discharges may occur. Generalized spike-wave, or centrotemporal spikes may co-exist. Occipital spike-and-wave or polyspike-and-slow-wave is facilitated by eye closure and intermittent photic stimulation (Supplemental Figure 3). Generalized spike-wave or polyspike-wave (with posterior predominance) may also occur with photic stimulation [73,75]. Epileptiform activity is elicited by sleep deprivation and by sleep.

Ictal onset is in the contralateral occipital lobe to the visual field containing the visual sensory phenomena, and to the direction of head and eye deviation [73,76]. Occipital ictal patterns may spread to the ipsilateral temporal lobe or the contralateral occipital lobe.

Imaging:

Neuroimaging is normal.

Genetics:

A family history is reported in one third of patients [73]. A few families with affected members in multiple generations have been reported [79,82,83]. There is considerable overlap with the IGEs and with SeLECTS [80,84]. No known gene exists.

Differential diagnosis:

Other epilepsies:

- *Epilepsy with eyelid myoclonia* is differentiated by the prominent eyelid myoclonia and by the absence of visual hallucinations and head and eye version.
- *SeLEAS* is differentiated by prominent dry retching/vomiting and other or autonomic features which are seen at seizure onset.
- *COVE* is distinguished by frequent focal sensory seizures with visual symptoms which are not triggered by photic stimuli.
- Focal seizures due to a structural brain abnormality – if present, focal sensory seizures with visual symptoms are not triggered by photic stimuli.
- *CLN2 disease* presents in younger children (<5 years of age) and the EEG characteristically shows a photoparoxysmal response at low frequencies (1-3 Hz). Children have progressive cognitive regression, ataxia and visual loss.
- *Lafora disease* presents with focal sensory visual seizures but is associated with a progressive myoclonic epilepsy with disabling myoclonus, cognitive impairment and ataxia.

Other conditions:

- *Migraine with visual aura* has visual phenomena which are longer in duration and qualitatively different (linear, zig-zag or fortification spectral phenomena as opposed to colored circles or light flashes that change in size or move horizontally).

The Genetic Generalized Epilepsy Syndromes of Childhood

Essentially all generalized epilepsy syndromes that have onset in childhood have a genetic etiology. They are regarded as following complex inheritance, which means they have a polygenic basis, with or without a contribution from environmental factors. Amongst the Genetic Generalized Epilepsies (GGEs), with onset in childhood the most common and best delineated is the IGE syndrome of Childhood Absence Epilepsy, which is discussed in the IGE paper[2]. Recent studies have highlighted that some IGE syndromes may also be due to monogenic disorders such as GLUT1 deficiency syndrome [85]. Among the more severe DEE, syndromes often have rare genetic

etiologies (such as Angelman syndrome, 15q inversion-duplication) typically arising *de novo* in the patient.

Other childhood genetic generalized epilepsy syndromes include two distinct syndromes, Epilepsy with Myoclonic Absence and Epilepsy with Eyelid Myoclonia. These syndromes have a more variable prognosis than Childhood Absence Epilepsy, with a higher proportion of cases having drug-resistant seizures and more frequent cognitive co-morbidities. While there is often a positive family history of epilepsy, the type of epilepsy in family members may include IGE syndromes as well as Genetic Epilepsy with Febrile Seizures Plus. Myoclonic-Atonic Epilepsy is also a generalized epilepsy syndrome that is classified under the DEE as children typically show developmental stagnation or regression during the period of frequent seizures. See Figure 3.

Epilepsy with Eyelid Myoclonia (E-EM)

Overview:

This syndrome (previously known as Jeavons syndrome) is characterized by the triad of frequent eyelid myoclonia, with or without absences, induced by eye closure and photic stimulation. Eyelid myoclonia is often most prominent on awakening (Table 6).

A subgroup of patients with Epilepsy with Eyelid Myoclonia (E-EM) have prominent photic induction of eyelid myoclonia (with or without absence), absence or myoclonic seizures [86]. This subgroup has been previously referred to as “Sunflower Syndrome”, due to sun-seeking behavior as they turn their faces to the sun as a light source at seizure onset [87]. This subgroup can be termed “Epilepsy with Eyelid Myoclonia With Prominent Photic Induction”.

Epidemiology:

This syndrome is rare and there are no population-based studies on incidence. Several studies from epilepsy centers have shown that it accounts for 1.2-2.7% of all epilepsy cases seen [88,89].

Clinical context:

The peak age at onset is 6-8 years of age, with a range of 2-14 years [89–91]. There is a 2:1 female:male predominance [89–91]. Antecedent and birth history is normal. Development and cognition are often normal although individuals with borderline intellectual functioning and intellectual disability are seen. In the subgroup with prominent photic induction, approximately half have intellectual disability or attentional problems, which may become more apparent with age [87]. Neurological examination is normal.

Course of illness:

E-EM, is often, but not invariably, drug-resistant [92–94]. Generalized tonic-clonic seizures are often controlled with antiseizure medications, whereas eyelid myoclonia are not fully controlled. In adult life, eyelid myoclonia alone may not be associated with EEG change, and thus represent a movement disorder [95]. Epilepsy with eyelid myoclonia is often a life-long condition [93,94].

In the subgroup with prominent photic induction, behavioral management may be important to avoid excessive medication, but is very challenging particularly in those with intellectual disability. Environmental measures to reduce light exposure are important in these patients, which include wearing wide-brimmed hats and wrap-around sunglasses. Specific blue lenses (Z1) may attenuate the photosensitive response in some patients [96].

Seizures:

Eyelid myoclonia, consisting of brief, repetitive and often rhythmic, 3-6 Hz myoclonic jerks of the eyelids, with simultaneous upward deviation of the eyeballs and extension of the head, are mandatory for diagnosis. These seizures are very brief (typically < 1 to 3 seconds, always <6 seconds) and occur multiple times each day, often multiple times per hour. They are typically induced by involuntary or voluntary slow eye closure or exposure to bright light or sunlight [97]. During eyelid myoclonia, awareness may be intact or mildly impaired; impaired awareness may be subtle and not recognized by the patient.

Up to 20% of patients develop eyelid myoclonic status epilepticus, with repetitive, recurrent eyelid myoclonia associated with mildly impaired awareness and responsiveness. Eyelid myoclonia may also be associated with absence seizures, with mildly impaired awareness. In addition, some patients have typical absence seizures without eyelid myoclonia.

Generalized tonic-clonic seizures occur in the majority of cases but are usually infrequent. They may be provoked by sleep deprivation, alcohol or photic stimulation.

In the patients with prominent photic induction, eyelid myoclonia (with or without absence), absence or myoclonic seizures are typically associated with behaviors such as facing a light source and hand-waving in front of the eyes, rubbing the forehead, going up close to an analog television, or using other means to create a flickering effect of light [86,87,98]. Sustained triggering can result in a generalized tonic-clonic seizure.

Febrile seizures occur in 3-13% patients [92,99]. Patients may also have myoclonic and typical absence seizures even if at relatively lesser frequency than eyelid myoclonias. The presence of frequent limb myoclonus should suggest an alternative syndrome diagnosis. Focal seizures are exclusionary.

EEG:

The background activity is normal - significant EEG background slowing should suggest an alternative diagnosis. Interictally, brief bursts of fast (3-6 Hz) irregular generalized polyspike-wave are frequent. Fixation-off sensitivity, which can be induced by eye-closure, and intermittent photic stimulation activate the epileptiform abnormality and often elicit eyelid myoclonia with/without absence seizures [100,101] (Figure 4). Young patients typically show photic sensitivity, which becomes less apparent with age and antiseizure medication. Similarly, sensitivity to eye closure may reduce with age. The epileptiform activity is also elicited by hyperventilation.

In the subgroup with photic induction, generalized spike-wave discharges are also provoked by photic induction.

Bursts of generalized spike-wave activity often become briefer and fragmented in sleep. Fragmented generalized spike-wave can appear as focal or multi-focal spike-and-slow-wave but is not consistently localized to one area. The morphology of the focal spike-wave resembles that of the generalized spike-wave.

Ictal recordings of eyelid myoclonia show high-amplitude, irregular generalized polyspike or polyspike-wave complexes, which may be followed by rhythmic spike or polyspike-wave at a frequency of 3-6 Hz. Eyelid myoclonia with/without absence are terminated with complete elimination of light. Eyelid myoclonia may or may not be associated with loss of awareness.

In those with photic induction, intermittent photic stimulation may trigger brief eyelid myoclonia, typical absence or myoclonic seizures.

Imaging:

An MRI is not required with a typical clinical presentation, but if done, shows no causal abnormality.

Genetics:

This syndrome likely has shared genetic etiologies with other idiopathic generalized epilepsies. A family history of seizures or epilepsy is present in 25-83% of cases, with nearly all affected relatives having generalized seizures [92,99]. In approximately 20% of cases, there is a family history of an IGE: Childhood Absence Epilepsy (CAE), Juvenile Absence Epilepsy (JAE), Juvenile Myoclonic Epilepsy (JME) or Generalized tonic-clonic seizure Alone (GTCA), and nearly half the patients have a family history consistent with genetic epilepsy with febrile seizures plus (GEFS+) [99].

No single pathogenic gene variant is identified in the majority of patients. In patients with this syndrome in the setting of a DEE, several monogenic disease genes have been implicated including *CHD2*[102], *SYNGAP1*[103] and *NEXMIF* [104](formerly known as *KIAA2022)*; some patients with pathogenic variants in these genes have this syndrome without a DEE.

Differential diagnosis:

Other epilepsies:

- *IGE syndromes* with absence seizures (CAE, JAE and JME) may have photosensitivity on EEG, however prominent eyelid myoclonia is not seen.
- *POLE* presents with visually induced seizures but without eyelid myoclonia.
- Other early-onset epilepsies with myoclonus and photosensitivity [97], including rare monogenic epilepsies such as neuronal ceroid lipofuscinosis.

Other conditions:

- Facial tics
- Compulsive blinking

Epilepsy with Myoclonic Absence (E-MA)

Epilepsy with Myoclonic Absence (E-MA) is a very rare childhood epilepsy syndrome that presents with daily myoclonic absence seizures (Table 7).

Epidemiology:

The exact incidence is unknown. This syndrome accounted for 0.5-1% of all epilepsies observed in a specialty epilepsy clinic, Centre Saint-Paul in Marseille[105].

Clinical context:

Peak age at onset is approximately 7 years with a range of 1-12 years and males are more commonly affected (70%)[105,106]. The antecedent and birth history are unremarkable, however at presentation approximately half of patients have developmental impairment. Intellectual disability may become evident with age and is ultimately seen in 70% of cases [105–107]. Neurological examination is typically normal.

Course of illness:

The evolution of E-MA is variable [105,106]. Remission occurs in approximately 40% of patients. In the remainder, myoclonic absences persist, or the epilepsy may evolve with the development of other generalized seizure types. Prognosis is more favorable if myoclonic absence seizures are the only seizure type and are controlled with medication [105].

Seizures:

Myoclonic absence seizures are mandatory for diagnosis [105]. Absence seizures are associated with rhythmic 3 Hz jerks of the upper limbs, superimposed on tonic abduction of the arms during the seizure (giving a ratcheting appearance). The seizures have an abrupt onset and offset. The patient, if standing, typically bends forward during the seizure, but falling is uncommon. The myoclonic jerks are typically bilateral and symmetric but can be unilateral or asymmetric. Perioral myoclonia and rhythmic jerks of the head and legs may also occur. Seizures last 10-60 seconds and occur multiple times per day [107]. Level of awareness varies from complete loss of awareness to retained awareness. Occasionally, autonomic manifestations such as a change in breathing or urinary incontinence [105] or complex gestural automatisms may be seen [108]. Myoclonic absences are the only seizure type seen in a third of patients. Myoclonic absence status epilepticus is rare. Generalized tonic-clonic (seen in 45%), clonic, atonic or typical absence seizures may also occur; multiple seizure types may indicate a more unfavorable prognosis. Only 4% of patients also have typical absence seizures without myoclonic jerks. Focal seizures are exclusionary.

EEG:

The background activity is normal. Occipital intermittent rhythmic delta activity is typically not seen [105]. Interictal 3 Hz generalized spike-wave and polyspike-wave discharges may occur (around 1/3 of cases). Focal discharges that arise consistently from one region should raise consideration of an alternative diagnosis of a structural etiology.

Generalized spike-wave discharges may be provoked by hyperventilation, which may also trigger myoclonic absence seizures. Intermittent photic stimulation triggers generalized spike-wave in a minority of patients (14%). Generalized spike-wave is also activated by sleep deprivation, drowsiness and in sleep. Similar to other generalized epilepsies, generalized spike-wave often becomes fragmented with sleep deprivation or sleep. It may appear as focal or multi-focal spike-and-slow-wave but is not consistently seen in a single area. The morphology of the focal discharges appears similar to the generalized spike-wave activity.

Ictally, regular 3 Hz generalized spike-wave accompanies myoclonic absence seizures. The 3 Hz discharge is time-locked with the myoclonic jerks (Figure 5). The EMG recording shows that the myoclonic jerks precede the marked tonic contraction of both deltoids [105].

Imaging:

An MRI should be considered to exclude other causes, but if done, it should be normal or may show mild diffuse atrophy.

Genetics:

A family history (usually of generalized seizures) is present in 20% of cases. Rarely there is a family history of febrile seizures. While E-MA is considered to be genetic, there are only isolated case reports of specific pathogenic genetic variants [109,110], with most cases likely to be polygenic. This syndrome is presumed to have shared genetic etiologies with the IGEs [111].

Differential Diagnosis:

Other epilepsies:

- *Childhood Absence Epilepsy*: while subtle myoclonic jerks may be seen with absences in CAE, they are low amplitude, do not have the sustained rhythmicity and are not associated with the stepwise (ratcheting) tonic abduction of the arms.

- *Lennox-Gastaut syndrome* often has atypical absences with rhythmic jerking or loss of tone, however the presence of slow spike-wave (≤ 2.5 Hz), generalized paroxysmal fast activity and tonic seizures should suggest the diagnosis.
- Myoclonic absence seizures may rarely be seen in other DEE but are not the predominant seizure type [110].

The Developmental and Epileptic Encephalopathies or Epileptic Encephalopathies with Onset in Childhood

Epileptic encephalopathies are defined as diseases in which the epileptic activity itself contributes to severe cognitive and behavioral impairments above and beyond that expected from the underlying etiology alone. These disorders are characterized by frequent epileptiform activity associated with developmental slowing and often regression. They may occur on a background of normal or abnormal development.

In the 2017 Classification of the Epilepsies, additional terminology was introduced with the word 'developmental' added to denote those children who had abnormal development secondary to the underlying cause in addition to an epileptic encephalopathy [112]. This term was introduced because many pathogenic gene variants cause developmental impairment in their own right, with the epileptic encephalopathy superimposed on the pre-existing impairment further impacting developmental outcome [113].

Conversely, a *developmental encephalopathy* refers to developmental impairment without frequent epileptiform activity, such as in a child or adult with intellectual disability [112]. In this section, we describe Myoclonic-Atonic Epilepsy, Lennox-Gastaut syndrome and Developmental and Epileptic Encephalopathy with Spike-Wave Activation in Sleep. We also include two syndromes characterized by acute encephalopathy, followed by a developmental and epileptic encephalopathy, namely Febrile Infection-Related Epilepsy Syndrome (FIRES) and Hemiconvulsion-Hemiplegia-Epilepsy (HHE) syndrome.

Myoclonic-Atonic Epilepsy (MAE)

Myoclonic-Atonic Epilepsy (MAE), formerly known as Epilepsy with Myoclonic-Atonic Seizures (Doose syndrome), begins in early childhood, in the setting of normal development in two-thirds of cases [114]. The full complement of clinical and EEG features may be absent early in the course and take time to appear. These children typically show developmental stagnation or even regression during the active seizures (stormy) phase, which improves once seizures are controlled. See Table 8.

Epidemiology:

MAE has an incidence of approximately 1 in 10,000 children and accounts for approximately 2% of childhood epilepsies [115].

Clinical context:

MAE typically begins between 2-6 years. Boys are more commonly affected [116]. Approximately one quarter of children have a history of a febrile seizure [117–120] and such a history is associated with a more favorable long-term outcome [120]. Development prior to seizure onset is normal in two-thirds of patients and neurological examination is typically unremarkable at onset.

Course of illness:

The onset of MAE is often abrupt, with explosive 'stormy' onset of many seizures and seizure types often generalized tonic-clonic, and myoclonic. In other cases, it evolves more slowly, requiring careful follow-up over the first year to distinguish it from Lennox-Gastaut syndrome. Seizures often are drug-resistant, particularly during the high seizure frequency (explosive or stormy) phase, and recurrent bouts of non-convulsive status epilepticus with increased frequency of other generalized seizure types are seen. During this phase, developmental plateauing or even regression, predominantly on behavior and executive functions, and ataxia are often evident. Behavior disorders such as hyperactivity and aggression, and sleep disturbances are also common during the active phase, and typically improve or remit after seizure control is achieved.

Despite seizures being drug-resistant initially, two thirds of children achieve remission, usually within three years of onset, and are able to wean off antiseizure therapies [120,121]. In the remaining third, persisting seizures, cognitive impairment, aggression and hyperactivity are often seen. Once seizures are controlled and the EEG improves, developmental progress is seen. Development may return to premorbid levels of function or the child may be left with a variable degree of intellectual disability. Factors predictive of poorer outcome include tonic seizures, recurrent nonconvulsive status epilepticus and an EEG showing very frequent or near continuous irregular generalized spike-wave, slow spike-wave or generalized paroxysmal fast activity [120–124].

Seizures:

Myoclonic-atonic seizures are mandatory for diagnosis and are characterized by a brief myoclonic jerk affecting the proximal muscles, often associated with a slight vocalization, followed by a very brief atonic component, which may be subtle, with a head nod, or more prominent with an abrupt fall. Conversely, pure atonic seizures, which are also commonly seen, lack the myoclonic component at onset, and lead to an abrupt, but brief loss of axial tone, with head nods or a sudden fall.

Other seizures which are frequently seen include myoclonic (which are brief <100 msec and can also lead to falls), absence and generalized tonic-clonic seizures. The latter may occur with or without fever and are the presenting seizure type in approximately two thirds of cases [117,119,121].

Tonic seizures appear in some patients later in the course and are associated with a poorer long-term outcome [120].

Non-convulsive status epilepticus is also common and may be inaugural. It manifests as impaired awareness, lasting hours to days, with atypical absence, myoclonic and atonic features, associated with somnolence, unsteadiness, drooling and speech disorders and erratic myoclonus predominating in the face and upper limbs. Recurrent nonconvulsive status epilepticus is associated with a less favorable outcome [120,123]. Epileptic spasms and focal seizures are exclusionary.

EEG:

The background activity shows a normal, age-appropriate posterior dominant rhythm at epilepsy onset. Monomorphic, biparietal theta rhythms are characteristic of MAE but are not seen in all patients. With increased seizure frequency, generalized, higher amplitude, background slowing may be seen.

Interictal discharges comprised of generalized 3-6 Hz spike-and-slow-wave or polyspike-and-slow-wave often occurring in bursts lasting 2-6 seconds are seen (Figure 6A). Long sequences of generalized irregular spike-and-slow-wave discharges should raise the question of non-convulsive status epilepticus. While the generalized discharges can become fragmented, a consistent spike focus is not seen. Generalized spike-wave discharges are activated with sleep. Generalized

paroxysmal fast activity, consisting of bursts of diffuse, or bilateral fast (10 Hz or more) polyspikes during sleep is rarely seen and should suggest Lennox-Gastaut syndrome. Hyperventilation may elicit generalized spike-wave discharges and absence seizures. Photosensitivity is rare.

Ictal recording of myoclonic-atonic seizures shows a generalized polyspike or spike discharge with the myoclonus, followed by a high voltage, slow wave accompanying the atonic component (Figure 6B-C). Simultaneous recording of EMG with EEG is recommended for ictal recordings - polyspikes correlate with brief myoclonus in the neck muscles, whereas the slow wave correlates with loss of muscle activity in the proximal limb muscles. Absence seizures are associated with 2-6 Hz generalized spike-and-slow-wave complexes.

During non-convulsive status epilepticus, the EEG shows long runs of high-amplitude, 2-3 Hz irregular, generalized spike-wave activity, with background slowing.

Imaging:

The MRI is normal.

Genetics:

A family history of epilepsy or febrile seizures is found in approximately one third of cases [117,119,121,122,125] and is associated with a more favorable long-term outcome [120]. The familial epilepsy syndrome of Genetic Epilepsy with Febrile Seizures Plus is seen in families of probands with MAE [126,127].

In the majority of children, MAE has complex inheritance with a polygenic pattern. In some cases, pathogenic variants have been seen in genes including *SCN1A*[128], *SCN1B*[129], *SCN2A*[130], *STX1B*[131], *SLC6A1*[132], *CHD2*[102], *SYNGAP1*[103], *NEXMIF*[104] *KIAA2022* [133]. Approximately 5% of patients with myoclonic-atonic epilepsy have glucose transporter 1 (GLUT1) deficiency associated with pathogenic variants in *SLC2A1* [85].

Differential Diagnosis:

Other epilepsies:

- *Lennox-Gastaut syndrome* can be distinguished by the presence of tonic seizures early in the disease and the EEG, which shows slow spike-wave $\leq$ 2.5 Hz and generalized paroxysmal fast activity in sleep. Additionally, children with Lennox-Gastaut syndrome more commonly have delayed development prior to seizure onset and may have a history of infantile spasms syndrome.
- *Myoclonic Epilepsy of Infancy* is distinguished by the lack of myoclonic-atonic and atypical absence seizures, and typically presents earlier than MAE.
- *Dravet syndrome* is distinguished by prolonged, hemiclonic seizures triggered by fever/illness in the first year of life and absence of myoclonic-atonic seizures.
- *D/EE-SWAS* is associated with regression and marked activation of epileptiform discharges in sleep, with nearly continuous diffuse spike-wave; myoclonic-atonic seizures are not seen.
- *CLN2 disease* typically begins in children with normal development or isolated speech delay. Children may present with a phenotype of myoclonic-atonic epilepsy; however, there is progressive motor and cognitive decline and ataxia. The EEG shows a photoparoxysmal response at 1-3 Hz so low frequency testing is important.

Lennox-Gastaut Syndrome (LGS)

Lennox-Gastaut syndrome (LGS) is a DEE associated with a wide range of etiologies, It results from high-frequency, synchronized activity in bilaterally distributed brain networks, that develops in a susceptible age period in childhood [134]. This syndrome is characterized by the presence of (1) multiple types of drug-resistant seizures with onset prior to 18 years (one of which must include tonic), (2) cognitive and often behavioral impairments, which may not be present at seizure onset, and (3) diffuse slow spike-wave and generalized paroxysmal fast activity on EEG (Table 9). Many clinicians use the term "Lennox-Gastaut syndrome" to describe any severe, early-onset epilepsy with intractable seizures leading to falls. This approach is incorrect as it fails to recognize the specific features of LGS, and distinguish it from MAE, which often has a markedly better outcome, and many other severe epilepsies starting in childhood. The full complement of clinical and EEG features is often absent early in the course and takes time to appear. Young children presenting with characteristic seizure types but lacking all the features need close follow-up for evolution to LGS. In particular, a number of severe infantile epilepsy syndromes, such as Infantile Spasms Syndrome, Early Infantile DEE, and Epilepsy of Infancy with Migrating Focal Seizures, often evolve to LGS. Repetitive assessment for LGS criteria may be helpful to access to anti-seizure medicines licensed for LGS

Epidemiology:

LGS accounts for approximately 1-2% of all persons with epilepsy. In children, LGS is rarely diagnosed at initial seizure onset (0.6%). LGS often evolves from another severe infantile epilepsy syndrome or etiology, with approximately 20% of cases evolving from Infantile Spasms Syndrome [135]. Ultimately, 3.6% of all children with epilepsy, and 19% of children with seizures starting in infancy, evolve to have LGS [136].

Clinical context:

LGS usually begins between 18 months and 8 years of age, with a peak age at onset of 3-5 years. Onset in the second decade is rare [137]. It is slightly more common in males. Abnormalities on neurological examination (for example pyramidal signs) are often found and are related to the underlying etiology. Most children have developmental impairment which predate seizure onset in LGS, but developmental stagnation or decline can occur with onset of frequent seizures. Less commonly, development and behavior may be normal at seizure onset.

Course of illness:

LGS persists into adulthood in nearly all cases and seizures remain drug-resistant [137]. Atypical absence and tonic seizures remain frequent in adults whereas atonic seizures often settle [138].

Over time, there is developmental slowing, plateauing or regression, culminating in moderate to severe intellectual disability in over 90% of patients [138–140]. Behavior disorders such as hyperactivity, aggression, autism spectrum disorder and sleep disturbances are common in childhood and adolescence [138,139].

Seizures:

Tonic seizures, consisting of a sustained increase in axial and limb muscle contraction lasting from 3 seconds to two minutes, are mandatory for diagnosis and are most prominent in sleep. They may be subtle, with slow upward eye rolling or deviation, at times with facial grimace or flexor movements of the head and/or trunk, or more clinically obvious, with a brief cry, apnea, abduction and elevation of the limbs with a vibratory component and bilateral fist clenching. If occurring while standing, they may forcefully throw the patient off balance leading to a fall (drop attack), with the patient often sustaining an injury. Tonic seizures may be exacerbated by medications that lead to increased sleepiness, such as acute use of high-dose benzodiazepines.

In addition to tonic seizures, a second seizure type is mandatory for the diagnosis of LGS and may include any of the following seizure types:

i. Atypical absence seizures: These are often frequent and consist of periods of impaired awareness. They may be challenging to identify with confidence due to their gradual onset and offset in a patient with underlying cognitive impairment.

ii. Atonic seizures: These lead to an abrupt loss of axial tone, with head nods or a sudden fall (drop attacks), often causing injury. They are frequent, particularly in younger children with LGS. They are typically brief, lasting only one to a few seconds.

iii. Myoclonic seizures: Myoclonic seizures are also very brief (<100 ms) and may lead to falls (drop attacks). If myoclonic-atonic seizures are present, the diagnosis of Myoclonic-Atonic Epilepsy should be strongly considered.

iv. Focal impaired awareness seizures: These may remain focal or evolve to bilateral tonic-clonic seizures.

v. Generalized tonic-clonic seizures.

vii. Non-convulsive status epilepticus: Approximately half to three quarters of patients with LGS have one or more episodes of non-convulsive status epilepticus, which consist of ongoing atypical absence seizures with altered awareness, with erratic, generalized or multifocal myoclonic and atonic components, and interspersed clusters of brief tonic seizures.

viii. Epileptic spasms

EEG:

The background activity is abnormal with diffuse theta-delta slowing, which may be more pronounced focally, depending on the underlying etiology. If prominent biparietal theta rhythms are seen, MAE should be considered. Two interictal patterns are mandatory for the diagnosis of LGS.

i. Generalized slow spike-wave: This interictal slow spike-wave pattern is characterized by spikes (<70 ms) or sharp waves (70-200 ms), followed by negative high voltage slow waves (350-400 ms), which are bilaterally synchronous, often anterior predominant, and occur at a frequency of $\leq$ 2.5 Hz (Figure 7A). The slow spike-wave pattern is abundant and often occurs in runs. It can be associated with atypical absence seizures, but often waxes and wanes without any clinical correlate both in wakefulness and particularly in sleep. Generalized slow spike-wave ($\leq$ 2.5Hz) is more frequently present in young children, while in adolescence and adulthood there is a decrease in the frequency of the spike-wave pattern. After the age of 16 years, the majority of patients no longer exhibit the typical slow spike-wave [141–143].

ii. Generalized paroxysmal fast activity: This pattern consists of bursts of diffuse or bilateral fast (10 Hz or more) activity often seen during sleep. These typically are brief, lasting a few seconds or less (Figure 7B).

Focal or multifocal slow spike-and-slow-wave may also be seen. Discharges are not typically activated by photic stimulation.

Tonic seizures, which are often subtle, and may not be recognized by families, are typically recorded on sleep EEG. The EEG pattern of tonic seizures consists of a burst of bilateral 10 Hz or higher frequency fast activity with a recruiting rhythm – an initial diffuse decrement followed by gradual increase in amplitude (Figure 7C). Polygraphic recordings during tonic seizures often show

a brief apnea with electromyographic axial muscle contraction. Because of these findings, a sleep recording can be beneficial to distinguish LGS from other epilepsy syndromes.

Atypical absence seizures are associated with slow spike-wave although it can be challenging to clearly distinguish between ictal and interictal slow spike-wave patterns.

Imaging:

As structural causes are the most common etiology, MRI at onset is strongly recommended as this may impact on treatment decision-making [144]. A variety of structural etiologies may be found including focal or diffuse cortical malformations, tuberous sclerosis complex, tumors or acquired brain injury such as hypoxic-ischemic encephalopathy. Re-investigation of older patients with LGS can result in identification of structural etiologies missed on previous imaging [145]. MRI may also be normal.

Genetics:

Pathogenic variants in many genes have been associated with the etiologies that causes LGS and are usually *de novo* in the child [146,147]. A range of chromosomal abnormalities and copy number variants have been associated with LGS, so chromosomal microarray is essential. A range of next generation sequencing approaches can be taken, ideally with whole exome sequencing, or an epilepsy gene panel, particularly if no etiology is found after clinical examination and MRI. Furthermore, genetic testing should also be considered for patients with structural brain disorders suggestive of an underlying genetic cause.

Metabolic Testing:

Rarely, LGS can be due to a neurometabolic disorder. Metabolic testing should be considered if an underlying etiology is not found with imaging or genetic studies.

Differential Diagnosis:

Other Epilepsies:

- *Infantile spasms syndrome* may progress to LGS and distinction between these syndromes type during the transition can be challenging. In distinction to spasms, tonic seizures are typically longer than 3 seconds and do not occur in clusters on waking.
- *Myoclonic-atonic epilepsy* is distinguished by normal development prior to seizure onset in many cases, myoclonic-atonic seizures, and faster generalized spike-wave which is typically greater than 3 Hz.
- *Dravet syndrome* is distinguished by prolonged, hemiclonic seizures triggered by seizures in the first year of life; tonic seizures (if present) do not occur until later.
- Other *early-onset DEEs* with multiple seizures types.
- *D/EE-SWAS* is associated with regression and marked activation of epileptiform discharges in sleep, with nearly continuous diffuse spike-wave.
- *Frontal lobe epilepsy* may present with bilateral tonic seizures, often with asymmetrical features. Slow spike-wave and generalized paroxysmal fast activity are not seen.
- *Rare metabolic disorders* may lead to a LGS phenotype*. CLN2 disease* typically begins in children with normal development or isolated speech delay. Following onset of seizures, there is progressive motor and cognitive decline and ataxia. The EEG characteristically shows a photoparoxysmal response at 1-3 Hz.

Developmental and/or Epileptic Encephalopathy with spike-wave activation in sleep (D/EE-SWAS)

Developmental and/or Epileptic Encephalopathy with spike-wave activation in sleep (D/EE-SWAS), refers to a spectrum of conditions that are characterized by the EEG feature of spike-wave activation in sleep, share similar clinical features (Table 10) and management implications. This syndrome now incorporates several well-known syndromes previously named Landau-Kleffner syndrome, Epileptic Encephalopathy with Continuous Spike-Wave in Sleep and Atypical Benign Partial Epilepsy (pseudo-Lennox syndrome) (Figure 8) and it is recommended that these terms no longer be used. They are grouped together because they carry similar implications and the syndrome highlights the need to inquire about specific clinical features when seeing a child such as auditory agnosia, global regression of behaviour and motor skills and negative myoclonus.

The EEG pattern previously required for this syndrome was known as continuous spike-wave in sleep (CSWS) [11,148] and the clinical correlate previously known as electrical status epilepticus in sleep (ESES). The literature often defines CSWS as nearly constant epileptiform activity that occupies >85% of slow wave sleep, however, lower percentages of sleep may also be associated with significant regression or fluctuation in cognitive or behavioral function.

These all have cognitive, behavioral and/or motor regression that occurs at the same time or within a few weeks of the EEG showing marked spike-wave activation in sleep (SWAS), with almost continuous, slow (1.5-2Hz) spike-wave in slow sleep, usually occupying >50% of slow sleep.

Sleep EEG must be performed to confirm the diagnosis. The EEG abnormalities occur in association with marked cognitive and/or behavioral regression. The diagnosis of D/EE-SWAS requires that the child show temporally related cognitive, behavioral or motor regression with the EEG pattern.

EE-SWAS occurs in a child with normal development, whereas D/EE-SWAS occurs in one with pre-existing developmental delay or just language delay.

The severity of cognitive regression varies widely, but typically results in a reduction in the patient's intelligence quotient. Regression may be limited to speech or can be more global, including motor regression. Children may present with an auditory agnosia where they do not recognize common sounds, such as the doorbell or telephone ringing. They show loss of understanding and have an acquired aphasia. Seizures do not occur in all children. Where they do, they may range from easily controlled focal motor seizures to drug-resistant seizures of multiple types.

Specific focal epilepsy syndromes, such as SeLECTs and SeLEAS, or other structural focal epilepsies may evolve to D/EE-SWAS, either transiently or for a prolonged period.

Epidemiology:

D/EE-SWAS is rare, accounting for 0.5-0.6% of all epilepsy presentation seen at pediatric tertiary epilepsy centers [149–151].

Clinical context:

D/EE-SWAS is characterized by onset of seizures between 2 and 12 years of age (peak 4-5 years), with the EEG developing spike-wave activation in sleep 1-2 years after seizure onset in association with cognitive or behavioral regression. Both sexes are affected equally. Antecedent and birth history are often normal; however, structural brain lesions are a risk factor for D/EE-SWAS. Specifically, thalamic injury in early life [152], and malformations such as bilateral perisylvian polymicrogyria are associated with this syndrome. Neurological examination and developmental level may be normal or reflect an underlying structural brain abnormality. Regression in cognitive,

behavioral or psychiatric functioning is the cardinal symptom of this syndrome. All cognitive domains can be affected including language and communication, temporo-spatial orientation, attention and social interaction. Motor regression with dyspraxia or dystonic features may also occur [153]. Follow-up visits with clinical assessment, EEGs, and neuropsychological testing should be scheduled in order to assess the evolution [154].

Course of illness:

Clinical seizures typically remit around puberty, even in patients with a structural lesion [155]. Resolution of clinical seizures may precede, coincide with, or follow the resolution of the EEG pattern [155]. The SWAS pattern on EEG also resolves, typically by adolescence [156,157]. Focal discharges may persist both during wakefulness and sleep. Sleep architecture normalizes with resolution of SWAS [156].

Neurocognitive and behavioral improvement is typically seen with resolution of the SWAS on EEG [158]. However, many patients have residual impairment, which is severe enough to limit independent functioning in approximately half of the patients [159,160]. The duration and etiology of D/EE-SWAS is the most important predictor of cognitive outcome – the risk of poor outcome is higher if it is present for more than 2 years [161]. Poorer outcomes are also seen with younger onset of D/EE-SWAS [161]. Thus, early diagnosis is of paramount importance to enable initiation of treatment to improve long term outcome even if some causes are not treatable (the etiology prevails), and there may be no clinical improvement for some when you abolish the EEG pattern. Nevertheless, residual deficits may remain following remission of seizures and SWAS, which may occur from months to 7 years after onset.

Seizures:

There is no mandatory seizure type. Seizure type is dependent on the underlying etiology. Furthermore, D/EE-SWAS may occur in patients who do not have clinical seizures.

In most patients, infrequent and drug-responsive seizures are observed during the initial phase between 2 and 5 years of age. These early seizures are typically focal motor, with or without impaired awareness, and focal to bilateral tonic-clonic seizures. As the child shows cognitive and/or behavior regression, seizures typically worsen with the evolution of multiple seizure types. These include focal seizures with or without impaired awareness, typical and atypical absence seizures, atonic seizures and focal motor seizures with negative myoclonus.

EEG:

The EEG pattern depends on the underlying etiology. The background activity during wakefulness may show focal or diffuse slowing and often contains focal or multifocal discharges, but it may be normal (Figure 9A). Epileptiform discharges during wakefulness are not continuous. In drowsiness and sleep, there is marked activation of epileptiform activity, with almost continuous, slow (1.5-2Hz) spike-wave in slow sleep, often occupying >50% of slow sleep. Typically, this activity is also seen in Stage II sleep (Figure 9B). SWAS is usually diffuse but may occur more focally (typically frontally) or multifocally. In REM sleep, the discharges become less frequent or may even be absent. Normal sleep architecture (vertex sharp waves, sleep spindles and K complexes) is absent or difficult to distinguish. An overnight sleep EEG may be required, as slow-wave sleep may not be achieved on an outpatient sleep EEG. The ictal EEG correlates with the seizure type.

Imaging:

Neuroimaging may be normal or demonstrate underlying structural brain abnormalities that may be developmental (e.g. perisylvian polymicrogyria) or acquired (thalamic abnormalities can be observed).

Genetics:

Some cases have a genetic basis and may follow monogenic or complex inheritance. A family history of seizures is seen in up to 50% patients with D/EE-SWAS [162]. The major monogenic cause is *GRIN2A*, which encodes the NMDA glutamate receptor alpha 2 subunit [12]. Pathogenic variants are associated with a range of severity of D/EE-SWAS phenotypes [13–15]. These individuals have a characteristic speech pattern which may persist into adult life [163].

Differential diagnosis:

Other epilepsy syndromes:

- *SeLFEs* can have marked activation of epileptiform discharges in sleep, but there is not temporally related cognitive or behavioral regression with the EEG finding of SWAS.
- *Structural focal epilepsies* may have abundant focal discharges which may activate in sleep, but there is not temporally related cognitive or behavioral regression with the EEG finding of SWAS.
- *Lennox-Gastaut syndrome* is distinguished by the EEG which shows prominent slow spike-wave during *both* wakefulness and sleep, and by the sleep EEG which shows generalized paroxysmal fast activity, and often tonic seizures are captured.

Other conditions:

- Children with autism spectrum disorders with or without intellectual disability but without regression may show activation of epileptiform discharges in sleep.
- Cognitive regression due to other etiologies.

Febrile Infection-Related Epilepsy Syndrome (FIRES)

FIRES (previously also known as acute encephalitis with refractory, repetitive partial seizures – AERRPS, or devastating epileptic encephalopathy in school-aged children – DESC) is one form of New-Onset Refractory Status Epilepticus (NORSE), that occurs predominantly in children and adolescents (Table 11). A prior febrile infection occurs, starting between 24 hours and 2 weeks, prior to an explosive onset of super-refractory status epilepticus, there may or may not be fever at onset of status epilepticus [164]. The acute phase, during which the seizure burden is very high, lasts 1-12 weeks [165], and during this phase, mortality and morbidity is significant. This is followed by a chronic phase where most survivors are left with drug-resistant multifocal epilepsy and a variable degree of intellectual disability or learning difficulties. The cause is not known, but growing evidence suggests a heterogeneous etiology resulting in fulminant non-antibody-mediated neuroinflammation [166,167].

Epidemiology:

This is a rare syndrome, which is likely under-recognized, with an estimated incidence of 1 per million [168].

Clinical context:

FIRES occurs most commonly in school-aged children (mean 8 years) with a typical range of 2-17 years [164,169,170]. It is exceedingly infrequent under age two years but may rarely occur in young

adulthood. Both sexes are affected, with a slight male predominance [169]. Perinatal history is typically normal. At presentation, children are developmentally normal without a history of prior neurological disease including epilepsy and have normal head size.

All children have a history of a prior febrile infection, most commonly upper respiratory or gastrointestinal, between 24 hours and 2 weeks before onset of refractory status epilepticus. At the time of seizure onset, patients may still be febrile, or may have had recent resolution of the fever.

At presentation, patients are typically encephalopathic and have frequent seizures despite antiseizure medications. Head size is normal. Persistent focal abnormalities on exam are unusual, but transient Todd's paresis may be seen.

Course of illness:

The prognosis is variable but often poor [169]. Mortality is approximately 10% in the acute phase, due to intensive care complications such as sepsis, or uncontrolled status epilepticus. Following the acute phase, most children are left with drug-resistant, multifocal epilepsy.

Developmentally, in the acute stage, most children regress and at follow-up, in the chronic phase, the majority are left with varying degrees of intellectual disability [169]. Approximately one third of survivors have normal or borderline cognition (often learning disorders), one third have mild to moderate intellectual disability and one third have severe to profound disability or are vegetative. Poorer outcome was associated with longer duration of medically induced burst-suppression coma and younger age at onset [169]. Attention and behavior problems, including aggression are also common in survivors.

In the chronic phase, many patients will have evidence of motor dysfunction.

Seizures:

Focal or multifocal seizures are mandatory for diagnosis and may evolve to bilateral tonic-clonic seizures. Seizures progress in frequency and severity rapidly to culminate in super-refractory status epilepticus (defined as > 24 hours) in the acute phase.

EEG:

The EEG background activity is typically abnormal with slowing and multifocal discharges. Recurrent extreme delta brush, consisting of a paroxysmal beta-delta complex of 15-18 Hz beta superimposed on 1-3 Hz delta in the frontal and central head regions is often seen [171] (Supplemental Figure 4 A-B). This pattern may be modified by anesthetic agents used for the treatment for status epilepticus.

Prolonged video-EEG monitoring at diagnosis shows a gradual increase in seizure burden over the first days to week of illness. Initially, seizure burden may be low, but over time, frequent, multifocal subclinical and clinical seizures are recorded, usually with a frequency of several per hour [171]. A typical seizure pattern, consisting of focal activity of >10 Hz of low to moderate amplitude, evolving to well-formed, rhythmic spike and spike-wave complexes are seen, and ictal activity often shifts from one hemisphere to the other [171] (Supplemental Figure 4 C).

Neuroimaging:

During the acute stage, the MRI is normal in approximately two thirds of cases. Approximately one third may show T2 hyperintense changes in bilateral temporal regions, insula, basal ganglia and/or thalami, which may be subtle. Leptomeningeal enhancement may also be seen but is not specific to this syndrome [172].

During the chronic stage, the MRI usually shows variable degrees of diffuse cerebral atrophy, and/or signal changes over the temporal lobes, cerebral cortex, periventricular white matter, hippocampi and basal ganglia [172].

Genetics:

This disorder is not suspected to be genetic, and no causal genes have been identified. There is usually no family history of seizures.

Other Laboratory Studies:

Examination of CSF is required to exclude infection. The CSF is typically normal but may show a mild pleocytosis. CSF protein and lactate are normal. Oligoclonal bands are negative. An immune etiology should be excluded but in FIRES, no causal antibodies have yet been found [167]. Serum and CSF autoimmune panels are negative. Metabolic studies are unremarkable. In some cases, excessive neuroinflammation, which may be secondary to functional deficiency in interleukin-1 receptor antagonist has been reported [173,174].

Differential diagnosis:

Other epilepsy syndromes

- *Dravet syndrome* is distinguished by its presentation predominantly in the first year of life, and history of intermittent prolonged seizures with interval recovery, as opposed to a singular super-refractory status epilepticus with the development of persistent morbidity.
- *PCDH19 related epilepsy* is distinguished by its presentation in the first three years of life, and history of cluster of seizures usually induced by fever. Super-refractory status epilepticus is unusual.

Other conditions

- Meningitis or encephalitis
- Specific autoimmune-mediated encephalopathies such as anti-NMDA receptor encephalitis
- Toxic encephalopathies
- Metabolic disorders such as mitochondrial disease

Hemiconvulsion-Hemiplegia-Epilepsy syndrome (HHE)

Hemiconvulsion-Hemiplegia-Epilepsy (HHE) syndrome is a rare consequence of focal motor status epilepticus in infancy and early childhood (Table 12). The initiating event for this syndrome is a focal clonic status epilepticus typically occurring in the context of a febrile illness in a children less than 4 years of age [175]. Neuroradiological studies at the time of the status epilepticus show unilateral edematous swelling of the affected hemisphere. The acute phase is followed by hemispheric atrophy with subsequent appearance of focal seizures which are drug resistant. The majority of patients have a resultant permanent motor deficit. The etiology and the underlying mechanisms are not understood.

Epidemiology:

HHE is a rare syndrome, and its incidence has declined markedly in resource equipped countries over the last 30 years since the instigation of aggressive treatment for prolonged seizures or status epilepticus [176].

Clinical context:

Age at onset is typically less than 4 years of age, and there is no sex predilection [176,177]. Birth and antecedent history are non-contributory and previous development and neurological examination are normal. Children present with prolonged focal status epilepticus and then develop immediate hemiparesis. The diagnosis of HHE syndrome should be considered when a persistent hemiplegia is observed after febrile status epilepticus in a child under 4 years of age. Aphasia may also be present acutely in up to a quarter of cases, if the dominant hemisphere is involved [178].

Course of illness:

The majority of children are left with a permanent motor deficit. However, this deficit may be minimal or resolve within 12 months in 20% [175]. If present, aphasia most commonly resolves within two months [178] but may persist [179]. Subsequent focal seizures appear after a variable duration, with 85% having seizure onset within 3 years of the initial status epilepticus [176]. Focal seizures during the chronic phase are typically drug-resistant [177], but may be amenable to surgical treatment, such as hemispherotomy [176,180]. Many children are also left with variable degrees of intellectual disability [176].

Seizures:

The first seizure is typically focal clonic febrile status epilepticus status epilepticus. The clonic component may be subtle. There is typically a seizure-free period after the focal status epilepticus that can last months to years. After a variable period, focal motor seizures and/or focal to bilateral tonic-clonic seizures appear, and usually become drug-resistant. Seizures may localize solely to the temporal lobe or may arise from extratemporal regions or be multifocal [180].

EEG:

If an EEG is obtained during the acute focal status epilepticus, the ictal discharge is characterized by rhythmic (2-3 Hz) slow waves that are usually bilateral with higher amplitude over the affected hemisphere [176] (Supplemental Figure 5 A-B). In addition, over the affected hemisphere recruiting rhythms (10 Hz) are frequently seen [176]. The background activity may be normal at onset but during the chronic phase, there is excess slowing (often asymmetric) and epileptiform discharges, which are most prominent over the affected hemisphere, but may be bilateral.

Imaging:

MRI immediately following the status epilepticus demonstrates diffuse hemispheric signal abnormalities with T2 hyperintensity and restricted diffusion, predominantly of the subcortical white matter of the affected hemisphere [181]. Edema of the affected hemisphere can be severe, leading to mass effect and possible herniation [176] (Supplemental Figure 5 C-F). If MR spectroscopy is done, it shows decreased N-acetyl aspartate [NAA] and mildly increased lactate in the affected hemisphere. On day 8-15 post status epilepticus, cytotoxic edema decreases, with normalization of apparent diffusion coefficient (ADC) images and ongoing T2 hyperintensity with evolving volume loss. Within one month, atrophy of the affected cerebral hemisphere is clearly evident. Hippocampal sclerosis is also commonly seen [180] (Supplemental Figure 5 G-J).

Genetics and other testing:

Genetic testing, evaluation for coagulation disorders and metabolic, infective and immune disorders are typically normal [176,182].

Differential diagnosis:

Other epilepsy syndromes:

- *Dravet syndrome* presents in infancy with prolonged hemiclonic seizures in the context of a febrile illness which may result in transient Todd's paresis. However, this deficit resolves and the typical MRI abnormalities of HHE are not present.
- *Sturge-Weber syndrome* may present with focal motor status epilepticus, but the skin lesions and MRI showing the typical features of this syndrome should suggest the diagnosis.
- *Rasmussen encephalitis* presents with unilateral focal motor seizures, but the progression is much slower and focal status epilepticus is seen later in evolution and is a more persistent feature when it occurs. MRI may be normal at seizure onset or show mild insular atrophy but evolves to focal white matter changes and hemispheric atrophy over months to years.
- Focal *febrile status epilepticus* or *focal status epilepticus due to other etiologies* can be followed by a Todd's paresis which typically resolves within 24 hours.

Other conditions:

- Meningitis and encephalitis
- Hemorrhagic or ischemic stroke
- POLG or MELAS-related mitochondrial disease

Discussion

While not every child with epilepsy can be classified as having a specific epilepsy syndrome, identification of a syndrome can provide guidance on management and prognosis. An electroclinical approach, combining a detailed clinical history and an EEG recording is needed to reach a syndrome diagnosis. Most of the syndromes described above have a mandatory seizure type(s) and often mandatory interictal EEG features. A diagnostic hypothesis is crucial to ensure adequate EEG studies, including both wakefulness and sleep, are recorded to inform syndrome diagnosis. A sleep EEG is required to identify mandatory EEG patterns in some syndromes, such as LGS and D/EE-SWAS. Moreover, detailed seizure semiology based on history is adequate to diagnose many seizure types without obtaining an ictal recording. However, for seizure types in certain syndromes, an ictal EEG recording is required for diagnosis. For example, it is not easy to determine a specific seizure type for a "drop attack" based on history alone. Even the use of home video recordings, that are undoubtedly helpful in many cases, cannot always confirm a definitive seizure type. Based on the diagnostic hypothesis, a specific EEG type (sleep-deprived, prolonged video-EEG) may be required to confirm a syndrome diagnosis.

In many, but not all cases, syndrome identification informs likely etiology. This allows clinicians to initiate the highest-yield investigations to minimize discomfort and invasive investigations for the patient, and to reach a specific diagnosis, in the most cost-effective manner. Specific comorbidities also correlate strongly with specific syndrome, and thus identification of an epilepsy syndrome may assist in their earlier recognition and management. In the context of a specific epilepsy syndrome, the occurrence of comorbidities is of paramount importance as they may be responsible for a greater burden for the patient than the seizures. Increasingly, precision therapies are being identified which target specific etiologies, and recent clinical trials in epilepsy are targeting specific syndromes.

While some syndromes are highly correlated with specific etiologies, others are associated with a diverse group of etiologies. Despite well recognized electro-clinical epilepsy syndromes, evolution and outcome are often still challenging to predict accurately and often depend upon the underlying etiology. With rapid advances in genetics, immunology and imaging, it is likely that further etiology-specific syndromes will be identified, and it might be possible to predict which patients will respond best to a specific treatment, or to identify a specific or novel therapy based on the causative genes or pathway responsible for the disorder. Use of therapies that target the underlying neurobiological process which leads to epileptogenesis may significantly ameliorate comorbidities as well as seizures.

Furthermore, it is well recognized that specific antiseizure medications may exacerbate certain conditions, such as sodium channel agents for many of the idiopathic generalized epilepsies. Moreover, some antiseizure medications are more likely to be effective for several seizure types such as absence seizures and generalized tonic-clonic seizures. Thus, early syndrome identification will allow for selection of the optimal therapy, which is most likely to lead to early seizure control and to prevention of other seizure types that may evolve in a specific syndrome.

Accurate syndrome definition will often inform natural history and likelihood of remission. Some syndromes are self-limiting over time. For these, we can provide reassurance to families of the favorable long-term outcome and can also avoid excessively prolonged use of chronic antiseizure medications, and unnecessary diagnostic tests or treatments. Conversely, other syndromes have a much poorer outcome, such as LGS, HHE syndrome, or FIRES. In those, we understand from their onset that evolution will be unfavorable, typically with drug-resistant and life-long seizures and adverse neurodevelopmental sequelae. In such cases, a more aggressive treatment approach may be undertaken, with regular review, in order to attempt to ameliorate overall function and quality of life outcomes. However, it should be acknowledged that treatment options for these syndromes are often limited, the choice of the most appropriate medication is not always clear from studies to date, and polytherapy might increase the risk for adverse events or in some cases, cause seizure aggravation. Many patients with these syndromes might benefit from participation in future clinical trials of novel medications. Some syndromes do not fall clearly in a self-limited epilepsy or DEE, but rather they might have an uncertain evolution: Epilepsy with Myoclonic Absence, Epilepsy with Eyelid Myoclonia, Myoclonic-Atonic Epilepsy, and D/EE-SWAS. Outcome is variable, both terms of seizure remission and cognitive and psychiatric comorbidities. In these latter conditions, there is a spectrum of severity - patients might present with or evolve to intellectual disability ranging from mild to severe, with variable degrees of neurological impairment. Sometimes, even if seizures remit, neurological sequalae persist.

As described above, some syndromes may evolve to another syndrome over time, such as SeLEAS to SeLECTS, and SeLECTS to D/EE-SWAS. This raises the question of the possible neurobiological links between these syndromes. To date, it is unclear why the majority of children have just one syndrome while others evolve. Such evolution is likely to be due to underlying neurobiological factors. As future research provides insights into the underlying etiology, we may be able to more accurately distinguish the patients who will not show progression from one syndrome to another. Such insights will modify therapeutic approaches from the onset of their epilepsy. Identification of biomarkers may allow intervention to prevent such evolution.

The most significant nosological changes in the childhood syndromes are in the Self-limited Focal Epilepsies which were formerly known as “benign” or “idiopathic” focal epilepsies, and D/EE-SWAS which was formerly known by several terms (LKS, EE-CSWS).

The nomenclature “SeLFE” was chosen to reflect the key features of the natural history, and the clinical phenotype. The term “benign” is inappropriate as many children have associated cognitive and psychiatric comorbidities. For each syndrome, the nomenclature used reflects the major phenotypic features: such as centro-temporal spikes for SeLECTs, autonomic seizures in SeLEAS, occipital semiology and EEG findings in COVE, photic-induced focal sensory visual seizures and genetic predisposition in POLE. Similarly, the term D/EE-SWAS comprises the two essential components, cognitive regression and the characteristic EEG pattern.

We elected to keep the term LGS for several reasons. Most importantly, the term LGS is crucial in allowing patients to acquire the multiple supports including medical and disability support therapies that they require on a daily basis. Replacing this term would lead to a lapse in services that these patients critically require. Additionally, the syndrome comprises multiple seizure type and etiologies which would be challenging to capture in a succinct name.

Our hope is that using clearer language with terms directly expressing the seizure semiology, which are consistent with the 2017 Epilepsy and Seizure classification, will facilitate both recognition and accurate diagnoses, for healthcare professionals and families caring for children with epilepsy.

Acknowledgements:
We gratefully acknowledge the input from the following persons outside of our Nosology Task Force who assisted with the Delphi Panels:
Drs Birinus Adikaibe, Raidah Al Baradi, Danielle Andrade, Thomas Bast, Ahmed Beydoun, Christian Bien, Roberto Caraballo, Ana Carolina Coan, Mary Connolly, John Dunne, Sheryl Haut, Floor Jansen, Barbara Jobst, Reetta Kalviainen, Angela Kakooza, Mitsuhiro Kato, Kelly Knupp, Silvia Kochen, Lieven Lagae, Luis Carlos Mayor, Natela Okujava, Kurupath Radakishnan, Eliane Roulet-Perez, Loreto Rios, Lynette Sadleir, Daniel San Juan-Orta, Jose Serratosa, Renee Shellhaas, Meng-Han Tsai, Vrajesh Udani, Helen Yue-Hua Zhang and Dong Zhou

Disclosures:
We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.
N Specchio has served on scientific advisory boards for GW Pharma, BioMarin, Arvelle, Marinus and Takeda; has received speaker honoraria from Eisai, Biomarin, Livanova, Sanofi; has served as an investigator for Zogenix, Marinus, Biomarin, UCB, Roche.
E Wirrell has served as a paid consultant for Encoded Therapeutics and Biomarin. She is the Editor-in-Chief of Epilepsy.com.
IE Scheffer has served on scientific advisory boards for UCB, Eisai, GlaxoSmithKline, BioMarin, Nutricia, Rogcon, Chiesi, Encoded Therapeutics and Xenon Pharmaceuticals; has received speaker honoraria from GlaxoSmithKline, UCB, BioMarin, Biocodex and Eisai; has received funding for travel from UCB, Biocodex, GlaxoSmithKline, Biomarin and Eisai; has served as an investigator for Zogenix, Zynerba, Ultragenyx, GW Pharma, UCB, Eisai, Anavex Life Sciences, Ovid Therapeutics, Epigenyx, Encoded Therapeutics and Marinus; and has consulted for Zynerba Pharmaceuticals, Atheneum Partners, Ovid Therapeutics, Care Beyond Diagnosis, Epilepsy Consortium and UCB.
R Nabbout has served as principal investigators in clinical trials for Novartis, Nutricia, Eisai, UCB, GW Pharma, Livanova. She received consulting fees from Biogene, BioMarin, GW Pharma, Zogenix, Novartis, Nutricia, Stoke, Ionis, Targeon, Takeda and honoraria from Nutricia, Biocodex, Zogenix, GW Pharma, Advicennes and Eisai. She received unrestricted research grants from Eisai, UCB, Livanova and GW Pharma and academic research grants from EJP-RD (horizons 2020) and IDEAL-EPISTOP.
SM Zuberi has received research support from Epilepsy Research UK, Tenovus Foundation, Glasgow Children's Hospital Charity, Scottish Government Technology Enabled Care. He has received honoraria for educational symposia, advisory boards and consultancy work from GW Pharma, Zogenix, Arvelle Therapeutics and Encoded Therapeutics.
JM Wilmshurst has received paid honorarium for activities as Associate Editor of Epilepsia.
E Yozawitz reports no conflicts of interest.
R Pressler has acted as an investigator for studies with UCB, Johnson & Johnson. She received consulting fees and/or honoraria from UCB, Eisai, Natus and GW. Her research is supported by the National Institute of Health Research (NIHR) Biomedical Research Centre at Great Ormond Street Hospital, Cambridge Biomedical Research Centre, NIHR and GOSH Charity.
E Hirsch has received honoraria from UCB, Eisai, Livanova, Novartis and GW Pharmaceuticals.
S Wiebe has received unrestricted educational grants from UCB Pharma, Eisai and Sunovion.
JH Cross has acted as an investigator for studies with GW Pharma, Zogenix, Vitaflo and Marinius. She has been a speaker and on advisory boards for GW Pharma, Zogenix, and Nutricia; all remuneration has been paid to her department. Her research is supported by the National Institute of Health Research (NIHR) Biomedical Research Centre at Great Ormond Street Hospital.

She holds an endowed chair at UCL Great Ormond Street Institute of Child Health; she holds grants from NIHR, EPSRC, GOSH Charity, ERUK, and the Waterloo Foundation.
P Tinuper received speaker's or consultancy fees from Arvelle, Eisai, GW Pharma, LivaNova, UCB Pharma, Xenon Pharma and Zogenix.
S Auvin has served as consultant or received honoraria for lectures from Biocodex, Biomarin, Eisai, GW Pharma, Neuraxpharma, Nutricia, UCB Pharma, Xenon, Zogenix. He has been investigator for clinical trials for Eisai, UCB Pharma and Zogenix. He is Associate Editor for Epilepsia.
K Riney has received speaker honoraria, advisory board payments and/or research funding from: UCB, Eisai, Novartis, Zogenix Inc., SK Lifesciences, AFT Pharmaceuticals, Liva Nova, Queensland Genomic Health Alliance, Department of Health (Australia), Medicure International Inc, Novartis, Janssen-Cilag.
P Samia report no conflicts of interest.

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Table 1. Childhood epilepsy syndromes

Epilepsy syndromes with focal seizures	Formerly known as	Epilepsy syndromes with generalized seizures	Formerly known as	Developmental and epileptic encephalopathies	Formerly known as
Self-limited Focal Epilepsies (SeLFE)		***Genetic Generalized epilepsies (GGE)***		***Developmental and epileptic encephalopathies (DEE)***	
SeLECTS *Self-Limited Epilepsy with Centrotemporal Spikes*	Childhood Epilepsy with Centrotemporal Spikes, (Benign) Rolandic Epilepsy, (Benign) Epilepsy with Centrotemporal Spikes	***MAE*** *Myoclonic-Atonic Epilepsy*	Epilepsy with Myoclonic-Atonic Seizures (Doose syndrome)	***LGS*** *Lennox-Gastaut syndrome*	No changes
SeLEAS *Self-Limited Epilepsy with Autonomic Seizures*	Panayiotopoulos syndrome, Early Onset (Benign) Occipital Epilepsy	***CAE*** *Childhood absence epilepsy**	Pyknolepsy, Petit mal	***D/EE-SWAS*** *Developmental and Epileptic Encephalopathy with spike-wave activation in sleep*	Landau-Kleffner syndrome, Epileptic Encephalopathy with Continuous Spike-Wave in Sleep, Atypical (Benign) Partial Epilepsy (pseudo-Lennox syndrome)
COVE *Childhood Occipital Visual Epilepsy*	Late-onset (Benign) Occipital Epilepsy or Idiopathic childhood Occipital Epilepsy – Gastaut type	***E-EM*** *Epilepsy with Eyelid Myoclonia*	Jeavons Syndrome	***FIRES*** *Febrile Infection-Related Epilepsy Syndrome*	Acute encephalitis with refractory, repetitive partial seizures (AERRPS), devastating epileptic encephalopathy in school-aged children (DESC)
POLE *Photosensitive Occipital Lobe Epilepsy*	Idiopathic Photosensitive Occipital Lobe Epilepsy	***E-MA*** *Epilepsy with Myoclonic Absences*	Bureau and Tassinari syndrome	***HHE*** *Hemiconvulsion-Hemiplegia-Epilepsy*	No changes

This table includes identified syndromes of this age group and not all epilepsy types.

* CAE is addressed in the paper on Idiopathic Generalized Epilepsies[2]

Table 2. Self-Limited Epilepsy with Centrotemporal Spikes (SeLECTS)

	Mandatory	Alerts	Exclusionary
Seizures	Focal seizures with dysarthria, sialorrhea, dysphasia and unilateral clonic or tonic-clonic movement of mouth in wakefulness or sleep and/or nocturnal focal to bilateral tonic clonic seizures in sleep only If seizures occur during sleep, they are seen within 1-2 hours of falling asleep or 1-2 hours prior to awakening	Focal motor or generalized convulsive status epilepticus >30 min Usual seizure frequency more than daily Daytime seizures only	Generalized tonic-clonic seizures during wakefulness Atypical absences Seizures with gustatory hallucinations, fear and autonomic features
EEG	High amplitude, centrotemporal biphasic spike-wave discharge	Sustained focal slowing not limited to the postictal phase Persistently unilateral centrotemporal discharges on serial EEGs Lack of sleep activation of centrotemporal discharges	
Age at onset		Age >12 years at onset	Onset <3 years of >14 years of age
Development at onset		Moderate to profound intellectual disability	Neurocognitive regression with a continuous spike-wave pattern in sleep (suggests EE-SWAS)
Neurological exam		Hemiparesis or focal neurological findings, other than Todds paresis	
Imaging			Causal lesion on brain MRI
Course of illness	Remission by mid to late adolescence No developmental regression		Neurocognitive regression with a continuous spike-wave pattern in sleep suggests evolution to EE-SWAS
Are MRI or ictal EEG required for diagnosis? An MRI is not required for diagnosis but should be strongly considered in cases with Alerts. An ictal EEG is not required for diagnosis.			
Syndrome without laboratory confirmation: In resource-limited regions, SeLECTs can be diagnosed without EEG and MRI in children without Alerts who meet all other mandatory and exclusionary criteria			

Table 3. Self-Limited Epilepsy with Autonomic Features (SeLEAS)

	Mandatory	Alerts	Exclusionary
Seizures	Focal autonomic seizures, with or without impaired awareness. Autonomic symptoms often involve prominent retching and vomiting, but may also include malaise, pallor, flushing, abdominal pain, pupillary or cardiorespiratory changes	Seizure frequency greater than monthly	
EEG	High amplitude, focal or multifocal discharges which increase in drowsiness and sleep	Sustained focal slowing not limited to the postictal phase Unilateral focal discharges in a consistent focal area across serial EEGs	
Age at onset		Age at onset <3 years or >8 years	Age at onset <1 year or >15 years
Development at onset		Moderate to profound intellectual disability	Neurocognitive regression with a continuous spike-wave pattern in sleep (suggests EE-SWAS)
Neurological exam		Hemiparesis or focal neurological findings, other than Todds paresis	
Imaging			Causal lesion on brain MRI
Course of illness	Remission by early to mid-adolescence No developmental regression		Neurocognitive regression with a continuous spike-wave pattern in sleep suggests evolution to EE-SWAS

Are MRI or ictal EEG required for diagnosis?
An MRI is not mandatory for diagnosis but should be done in the presence of any Alerts.
An ictal EEG is not required for diagnosis.

Syndrome without laboratory confirmation: In resource-limited regions, at a minimum, an interictal EEG is required to confidently diagnose this syndrome.

Table 4. Childhood Onset Visual Epilepsy (COVE)

	Mandatory	Alerts	Exclusionary
Seizures	Focal sensory visual seizures with elementary visual phenomena (multi-colored circles), with or without impaired awareness, and with or without motor signs (deviation of the eyes or turning of the head. Seizures arise predominantly or exclusively from wakefulness	Prolonged seizure lasting >15 minutes GTCS during wakefulness	Drop (tonic or atonic) seizures Atypical absences Progressive myoclonus
EEG	Occipital spikes or spikes-and-wave discharges (awake or sleep).	Sustained focal slowing not limited to the postictal phase	
Age at onset		Age at onset <6 years >14 years	Age at onset <1 year or >20 years
Development at onset		Intellectual disability	Neurocognitive regression
Neurological exam		Any significant neurological examination abnormality	Persistent visual field deficit
Imaging			Causal lesion on brain MRI Cerebral occipital lobe calcifications
Course of illness			Neurocognitive regression Development of myoclonic seizures, ataxia, spasticity
Are MRI or ictal EEG required for diagnosis? An MRI is required for diagnosis to exclude a causal lesion. An ictal EEG is not required for diagnosis.			
Syndrome without laboratory confirmation: In resource-limited regions, at a minimum, an interictal EEG and MRI are required to confidently diagnose this syndrome.			

Table 5. Photosensitive Occipital Lobe Epilepsy (POLE)

	Mandatory	Alerts	Exclusionary
Seizures	Focal sensory visual seizures (see text), which may evolve to bilateral tonic-clonic seizures Seizures are triggered by photic stimuli, such as flickering sunlight	Prolonged seizures lasting >15 minutes	Eyelid myoclonia Progressive myoclonus
EEG	Occipital spike-wave or polyspike and wave is facilitated by eye closure and IPS	Sustained focal slowing not limited to the postictal phase Photoparoxysmal response at slow photic frequency (1-2 Hz) (suggest CLN2 disease)	
Age at onset		Onset of seizures before age 4 years or after age 17 years	Age at onset <1 year or >50 years
Development at onset		Moderate to profound intellectual disability	Neurocognitive regression
Neurological exam		Any significant neurological examination abnormality	Permanent visual field deficit
Imaging			Causal lesion on brain MRI
Are MRI or ictal EEG required for diagnosis? An MRI is required for diagnosis to exclude a causal lesion. An ictal EEG is required for diagnosis.			
Syndrome without laboratory confirmation: In resource-limited regions, at a minimum, an EEG and MRI are required to confidently diagnose this syndrome.			

Table 6. Epilepsy with Eyelid Myoclonia (E-EM)

	Mandatory	Alerts	Exclusionary
Seizures	Eyelid myoclonia (see text)	Inability to induce eyelid myoclonia in the office by slow eye closure during exposure to bright light in an untreated patient Myoclonic jerks affecting limbs – strongly consider JME	Any of the following seizure types: • Myoclonic-absence seizures • Focal seizures
EEG	Eye closure and intermittent photic stimulation elicits fast (3-6 Hz) generalized polyspikes or polyspike-and-slow-wave		Focal slowing Consistently unilateral focal spikes Generalized slow spike-wave at frequency <2.5 Hz (unless it is at the end of a higher frequency burst) Diffuse background slowing that is not limited to the postictal period Lack of EEG correlate with typical clinical event
Age at onset			<2 years or >14 years at onset
Neurological exam		Focal neurological findings	
Imaging		Potentially relevant abnormal neuroimaging, excluding incidental findings (see text)	Abnormal neuroimaging with causative lesion
Course of illness			*Progressive cognitive decline over the course of the epilepsy*

Are MRI or ictal EEG required for diagnosis?
An MRI is not required for diagnosis.
An ictal EEG is not required for diagnosis provided that eyelid myoclonia has been observed clinically by the diagnosing provider and the interictal study shows fast (3-6 Hz) generalized polyspikes or polyspike and slow-wave induced by eye closure or intermittent photic stimulation. However, most untreated patients will have recorded photo paroxysmal response with eyelid myoclonia on a routine EEG performed during intermittent light stimulation.

Syndrome without laboratory confirmation: In resource-limited regions, Epilepsy with Eyelid Myoclonia can be diagnosed in persons who meet all other mandatory and exclusionary clinical criteria if they have Eyelid myoclonia witnessed by the examiner or captured on home video.

Table 7. Epilepsy with Myoclonic Absences (E-MA)

	Mandatory	Alerts	Exclusionary
Seizures	Myoclonic absence seizures as predominant type (see text)		Focal seizures Atonic, Myoclonic-Atonic or Tonic seizures
EEG	Regular 3 Hz generalized spike-and-slow-wave time-locked with the myoclonic jerks		Focal slowing Consistently unilateral focal spikes Generalized slow spike-wave at frequency <2.5 Hz (unless it is at the end of a higher frequency burst) Diffuse background slowing that is not limited to the postictal period
Age at onset			<1 or >12 years at onset
Neurological exam		Moderate or greater intellectual disability Focal neurological findings	
Imaging			Abnormal neuroimaging with causative lesion
Course of illness			*Progressive cognitive decline over the course of epilepsy*

Are MRI or ictal EEG required for diagnosis?

An MRI should be considered to exclude other causes.

An ictal EEG is not required for diagnosis, provided that myoclonic absences have been observed clinically by the diagnosing provider and the interictal study shows regular 3 Hz generalized spike and wave. However, most untreated patients will have recorded myoclonic absence seizure on routine EEG.

Syndrome without laboratory confirmation: In resource-limited regions, Epilepsy with Myoclonic Absences can be diagnosed in persons who meet all other mandatory and exclusionary clinical criteria if they have myoclonic absence seizures witnessed by the examiner or captured on home video.

Table 8. Myoclonic-Atonic Epilepsy (MAE)

	Mandatory	Alerts	Exclusionary
Seizures	Myoclonic-atonic seizures	Tonic seizures within 12 months of epilepsy onset	Epileptic spasms or ISS prior to diagnosis Focal seizures
EEG	Generalized 3-6 Hz spike-wave or polyspike-and-slow-wave discharges	Generalized paroxysmal fast activity in sleep Generalized slow spike-wave < 2.5 Hz Photoparoxysmal response at low frequencies (suggests *CLN2* disease)	Persistent focal discharges Hypsarrhythmia
Age at onset			Onset < 6 months or >8 years
Development at onset		Moderate to severe developmental delay preceding seizure onset	
Neurological exam		Focal neurological findings	
Imaging			Causal lesion on MRI

Are MRI or ictal EEG required for diagnosis?
An MRI is not required for diagnosis but is typically done to exclude other causes.
An ictal EEG is not required for diagnosis. However, in a child with Alerts or those with clinical features which may suggest Lennox-Gastaut syndrome or infantile spasms, a video at least is essential and ideally an ictal EEG
Syndrome-in-evolution: Myoclonic atonic epilepsy should be suspected if onset of explosive onset of multiple generalized seizure types in appropriately aged child without other Alerts or exclusionary features.

Syndrome without laboratory confirmation: In resource-limited regions, MAE can be presumptively diagnosed without EEG and MRI only in cases meeting all mandatory and exclusionary clinical criteria, without Alerts, where the clinician has personally witnessed myoclonic atonic seizures, either directly by observing the patient, or on video provided by the family. However, an EEG is strongly recommended.

Table 9. Lennox-Gastaut Syndrome (LGS)

	Mandatory	Alerts	Exclusionary
Seizures	Tonic seizures (see text) In addition to tonic seizures, at least one additional seizure type must be present which may include any of the following: • Atypical absences • Atonic • Myoclonic • Focal impaired awareness • Generalized tonic clonic • Nonconvulsive status epilepticus • Epileptic spasms		
EEG	Generalized slow spike-wave <2.5 Hz (or history of this finding on prior EEG) Generalized paroxysmal fast activity in sleep (or history of this finding on prior EEG)	Photoparoxysmal response at low frequencies (consider CLN2 disease)	Persistent focal discharge without generalized spike-wave
Age at onset	< 18 years	Onset > 10 years of age	
Long term outcome	Drug resistant epilepsy Mild to profound intellectual disability		

Are MRI or ictal EEG required for diagnosis?

An MRI is not required for diagnosis but is usually performed to evaluate for underlying etiology.

An ictal EEG is not required for diagnosis. However, it should be strongly considered in a child with Alerts or those with clinical features which may suggest Myoclonic-Atonic Epilepsy syndrome.

Syndrome-in-evolution: Approximately 50% of infants with a severe DEE, eg. ISS or Early-infantile DEE evolve over time to LGS.

Syndrome without laboratory confirmation: In resource-limited regions, at a minimum, an interictal EEG showing characteristic generalized slow spike wave during wakefulness is required for diagnosis.

Table 10. Developmental and Epileptic Encephalopathy with Spike-Wave Activation in Sleep (D/EE-SWAS)

	Mandatory	Alerts	Exclusionary
Seizures			Epileptic spasms
EEG	Continuous, slow (<2Hz) spike-wave in >50% of non-REM sleep The discharges are activated in sleep	Generalized paroxysmal fast activity in sleep (consider Lennox-Gastaut syndrome) Generalized slow spike-wave <2.5 Hz in both awake and asleep states (consider Lennox-Gastaut syndrome)	
Age at onset			Onset <2 yr or >12 years
Development at onset	Cognitive, behavioral or motor regression or plateauing temporally related to SWAS on EEG		
Long term outcome	Remission of SWAS pattern on EEG by mid adolescence, although EEG often remains abnormal		

Are MRI or ictal EEG required for diagnosis?
An MRI is NOT required for diagnosis but is often performed to evaluate for underlying etiology
A sleep EEG is mandatory for diagnosis.

Syndrome without laboratory confirmation: In resource-limited regions, this syndrome cannot be presumptively diagnosed without a sleep EEG.

Table 11. Febrile Infection-Related Epilepsy Syndrome (FIRES)

	Mandatory	Alerts	Exclusionary
Seizures	History of nonspecific febrile illness in the 2 weeks preceding seizure onset. Focal and multifocal seizures that often evolve to bilateral tonic-clonic seizures. Seizures progress in frequency and severity to culminate in super-refractory status epilepticus typically within 2 weeks of onset		History of epilepsy prior to onset of FIRES
EEG	Slowing of the background with multifocal discharges and frequent, focal electrographic and electroclinical seizures	Unifocal seizures	
Age at onset		Onset <2 years of age	Onset ≤12 months or ≥30 years of age
Development at onset	Acute encephalopathy with onset of frequent seizures	Intellectual disability prior to seizure onset	
Neurological exam		Neurological examination abnormalities prior to onset of seizures	
Imaging			At presentation – MRI shows an epileptogenic lesion concordant with seizure onset (see text)
Other testing			Lumbar puncture showing evidence of central nervous system infection. Causal antibody on CSF or plasma autoimmune testing Documented metabolic or genetic etiology Documented toxic encephalopathy
Long term outcome		Lack of drug resistant focal or multifocal epilepsy Lack of learning difficulties or ID Lack of variable degrees of cerebral atrophy on MRI	
Are MRI or ictal EEG required for diagnosis? An MRI is required for diagnosis to exclude a causal lesion. An ictal EEG is required for diagnosis to confirm frequency and multifocality of seizures.			
Syndrome without laboratory confirmation: In resource-limited regions, this syndrome cannot be presumptively diagnosed without EEG and MRI studies.			

Table 12. Hemiconvulsion-Hemiplegia-Epilepsy Syndrome (HHE)

	Mandatory	Alerts	Exclusionary
Seizures	Diagnosis requires both a history of acute stage and chronic stage disease (Acute stage) Episode of febrile, hemiclonic status epilepticus, which is immediately followed by permanent hemiparesis (Chronic stage) After a variable time (usually <3 years after initial status epilepticus), unilateral focal motor or focal to bilateral tonic clonic seizures appear		Transient hemiparesis (Todd's paresis) Unilateral focal motor seizures which progress in a crescendo pattern over months to years, with late development of progressive hemiparesis (consider Rasmussen encephalitis)
EEG	Slowing of background activity over the affected hemisphere Focal or multifocal epileptiform discharges over the affected hemisphere in the chronic phase		
Age at onset		Onset >4 years of age	Onset ≥6 yrs of age
Development at onset		Intellectual disability prior to seizure onset	
Neurological exam		Focal neurological abnormalities prior to initial episode of febrile status epilepticus Facial angioma suggestive of Sturge-Weber syndrome	
Imaging	MRI immediately following febrile status epilepticus (acute stage) shows diffuse signal change with T2 hyperintensity and restricted diffusion of the subcortical region of the affected hemisphere, often with severe edema. Over time (chronic stage), there is atrophy of the affected hemisphere		Other structural causes predisposing to focal status epilepticus
Other testing			Alternative cause of hemiparesis found such as acute ischemic stroke, intracranial infection, etc
Long term outcome	Drug-resistant epilepsy Permanent focal motor deficit		

Are MRI or ictal EEG required for diagnosis?

An MRI is required to diagnosis.

An ictal EEG is not required for diagnosis.

Syndrome-in-evolution: Children with acute permanent hemiparesis following an episode of focal convulsive febrile status epilepticus, with mandatory MRI findings but who have not yet progressed to the chronic phase of the disease with recurrent, drug-resistant focal motor or focal to bilateral tonic-clonic seizures should be suspected of having emerging HHE.

Syndrome without laboratory confirmation: In resource-limited regions, Hemiconvulsion-Hemiplegia-Epilepsy Syndrome can be presumptively diagnosed without EEG in cases who meet all mandatory and exclusionary clinical criteria without Alerts. However, an imaging study (CT or MRI) is required to exclude other causes.

Figure Legends

Figure 1.
Self-limited Focal Epilepsies of Childhood (SeLFE) syndromes are a group of conditions characterized by age dependent occurrence in otherwise normal children. Cognition and neurological evaluation are typically normal. Remission occurs in all patients. Presumed genetic factors have an important role. Seizure's semiology, and EEG features are specific for each of the syndromes included in this group. SeLFE encompasses for former syndromes of childhood epilepsy with centrotemporal spikes or benign epilepsy of childhood with centrotemporal spikes or benign rolandic epilepsy now renamed as Self-Limited Epilepsy with Centrotemporal Spikes (SeLECTS), of Panayiotopoulos syndrome or early-onset benign occipital epilepsy now renamed as Self-Limited Epilepsy with Autonomic Seizures (SeLEAS), of late-onset benign occipital epilepsy or Gastaut syndrome or Idiopathic childhood occipital epilepsy – Gastaut type now renamed as Childhood Occipital Visual Epilepsy (COVE), and of idiopathic photosensitive occipital lobe epilepsy now renamed as Photosensitive Occipital Lobe Epilepsy (POLE). In the figure are represented the typical age at onset and EEG findings for each of the syndromes.

Figure 2.
Typical EEG pattern seen in SeLECTS in a 9-year-old boy. **A.** Awake EEG showing high amplitude, spike and wave discharges over the right centro-temporal region. Abnormalities are isolated or occur in brief sequences. Synchronous or asynchronous similar spikes are seen also over the left central region or over the anterior vertex. B. In the same patient, sleep EEG shows an increase in interictal epileptiform abnormalities and a higher amplitude. C. Ictal EEG. Over the left central and temporal region there are rhythmic spikes which increase in amplitude and decrease in frequency. The discharge is focal and does not interfere with asynchronous interictal spikes seen over right frontal and central region.

Figure 3.
Genetic Generalized epilepsies of Childhood are a group of condition characterized by genetic etiology with complex inheritance, namely with polygenic basis. A positive family history of epilepsy is frequent. Cognition, neurological examination and response to drugs are variable. Seizure's semiology, and EEG features are specific for each of the syndromes included in this group. Genetic Generalized epilepsies of Childhood encompasses for Childhood Absence Epilepsy, which is discussed in the paper on IGE syndromes[2], the former Jeavons syndrome now called Epilepsy with Eyelid Myoclonia, Epilepsy with Myoclonic Absence and the former Epilepsy with Myoclonic-Atonic Seizures (Doose syndrome) now renamed as Myoclonic-Atonic Epilepsy. Epilepsy with Myoclonic Absence and Epilepsy with Eyelid Myoclonia have a variable prognosis. Myoclonic-Atonic Epilepsy is classified under the DEE as children typically show developmental stagnation or regression. In the figure are represented the typical age at onset and EEG findings for each of the syndromes.

Figure 4.

Ictal EEG in 14-year-old patient with Epilepsy with Eyelid Myoclonia. Background activity is normal. Each time the patient closes his eyes (eye closure artifact is seen) there is a generalized discharge of polyspikes and polyspike and wave lasting between 6 and 8 seconds clinically associated with eyelid myoclonia.

Figure 5.
Ictal EEG in an 8-year-old boy with Epilepsy with Myoclonic Absences showing a paroxysmal generalized 3 Hz spike and wave discharge with a higher amplitude over bilateral anterior regions. EMG channels (right and left deltoids) show bilateral myoclonic jerks synchronous with epileptiform abnormalities, and between jerks there is a sustained increase in muscle tone.

Figure 6.
Myoclonic Atonic Epilepsy in a 3-year-old child. **A.** Interictal EEG with polygraphic recording, showing bilateral posterior slow waves (4-6 Hz). There are generalized abnormalities characterized by high voltage spikes and spike and wave discharges intermingled with high amplitude delta waves. **B.** and **C.** Examples of myoclonic atonic seizures in the same patient. The paroxysmal event is associated with a generalized spike and wave discharge of brief duration. EMG channels show loss of tone in the deltoids (**B**) and in nuchal and sternocleidomastoid muscles (**C**). Clinically the patient experiences abrupt falls with both events.

Figure 7.
Interictal and ictal EEG in a patient with Lennox-Gastaut Syndrome. **A.** Diffuse slow spike and wave abnormalities (between 2 and 2.5 Hz) are seen, lasting 8 seconds, unassociated with clinical signs. **B.** Generalized paroxysmal fast activity characterized by diffuse bursts of fast activity (10 Hz). The discharge is seen during sleep and is not associated with clinical findings. **C.** Ictal EEG showing a diffuse low voltage fast activity lasting 4 seconds associated with bilateral tonic contraction of the upper limbs, consistent with a generalized tonic seizure.

Figure 8.
Developmental and/or Epileptic Encephalopathy with spike-wave activation in sleep (D/EE-SWAS) is a syndrome characterized by both (1) regression or plateauing of cognitive, behavioral and/or motor skills, AND (2) marked sleep activation of epileptiform discharges. D/EE-SWAS encompasses for former syndromes of Landau-Kleffner, Encephalopathy with CSWS and Atypical Benign Focal Epilepsy of Childhood. Importantly, other syndromes such as SeLECTS may also be associated with marked spike-wave activation in sleep but there is no regression or plateauing of skills. Thus, a diagnosis of D/EE-SWAS should only be made if both clinical and electrographic features are present.

Figure 9.
Awake and sleep EEG in a patient with D/EE-SWAS. **A**. Awake EEG shows a background activity characterized by 9-10 Hz rhythm, with a lower voltage, faster activity seen over the bilateral anterior regions. No clear-cut epileptiform abnormalities are seen. **B.** During sleep, diffuse and continuous spike and wave discharges are seen.

Supplementary Figure Legends

Supplementary Figure 1.
Awake and sleep EEG in a patient with SeLEAS. **A.** Awake EEG shows a symmetric 9-10 Hz background activity associated with rare and isolated spikes over bilateral posterior regions. **B.** During sleep, mixed theta and delta rhythms are seen, with a significant increase in frequency and amplitude of bilateral posterior spike and wave discharges.

Supplementary Figure 2.
Interictal and ictal EEG in a patient with COVE. **A.** Awake interictal EEG showing posterior repetitive spikes. **B.** During sleep, there is a significant increase of epileptiform abnormalities which are almost continuous over bilateral posterior regions. **C.** Ictal EEG in the same patient. The EEG shows bilateral, posterior, low voltage fast activity lasting for 10 seconds followed by rhythmic theta waves intermingled with spikes. The activity is most prominent over bilateral posterior regions, but also present over the posterior vertex and bilateral parietal regions.

Supplementary Figure 3.
Interictal EEG in patient with POLE. Diffuse spike and wave discharges are induced by eye closure. Discharges stop when the child opens her eyes.

Supplementary Figure 4.
Interictal and ictal EEG in patients with FIRES. **A**. Interictal EEG showing bilateral anterior slow waves during the acute phase. **B.** Over bilateral frontal and central regions with higher amplitude on the right, there are paroxysmal beta-delta complexes (15-18 Hz beta superimposed on 1-3 Hz delta). **C**. Ictal EEG in the same patient. EEG shows a right posterior temporal seizure characterized by low voltage spikes which increases in amplitude and decreases in frequency, associated with impaired awareness and sialorrhea.

Supplementary Figure 5.
EEG and brain MR in a patient with HHE. **A.** Intertical EEG showing an asymmetry of background activity together with multiple slow waves over frontal and central regions of the left hemisphere. **B.** In the same regions are seen multiple spikes and spike and wave discharges associated with theta and delta activity. **C-F** Acute brain MR showing left hemisphere signal abnormalities, which are hypointense on FLAIR sequence **(C)** and hyperintense on T2 sequences **(E).** Diffusion weighted sequences reveal signal abnormalities of the entire left hemisphere **(F)**. **G-J.** Brain MR in the same patient after 6 months showing marked atrophy of the left hemisphere.

Figure 1.

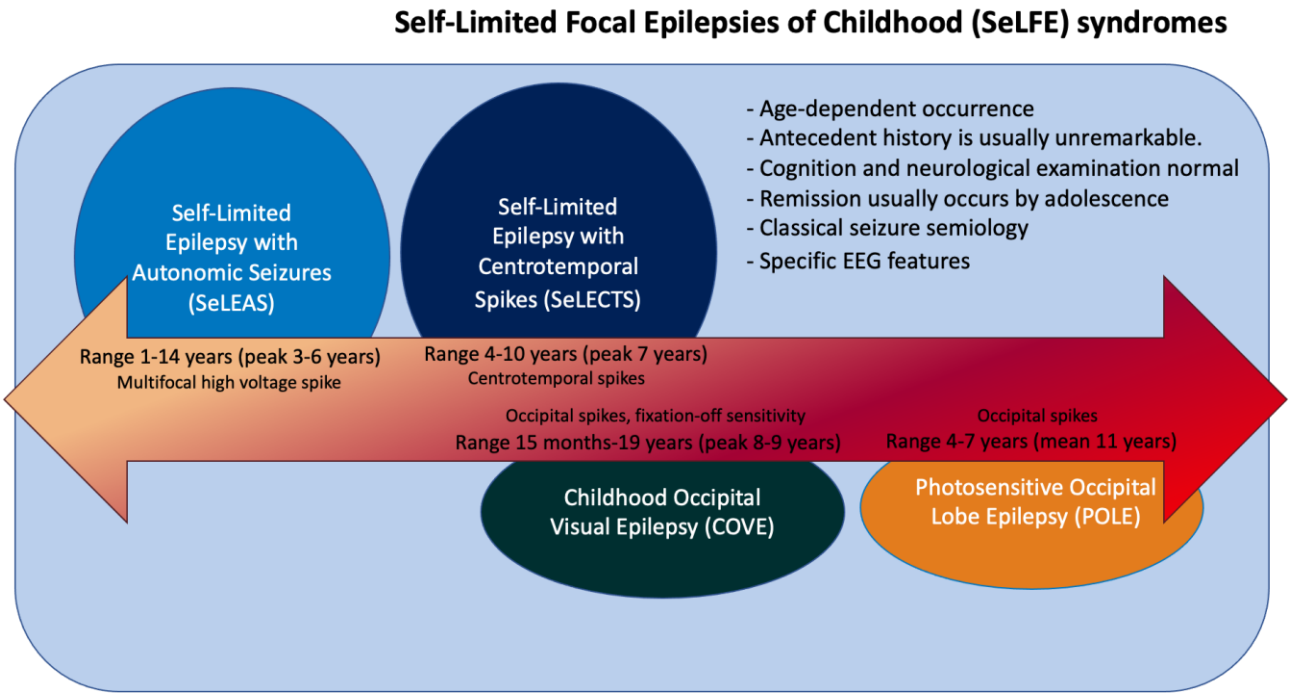

Self-Limited Focal Epilepsies of Childhood (SeLFE) syndromes
- Age-dependent occurrence
- Antecedent history is usually unremarkable.
- Cognition and neurological examination normal
- Remission usually occurs by adolescence
- Classical seizure semiology
- Specific EEG features
Self-Limited Epilepsy with Autonomic Seizures (SeLEAS)
Self-Limited Epilepsy with Centrotemporal Spikes (SeLECTS)
Range 1-14 years (peak 3-6 years)
Multifocal high voltage spike
Range 4-10 years (peak 7 years)
Centrotemporal spikes
Occipital spikes, fixation-off sensitivity
Range 15 months-19 years (peak 8-9 years)
Occipital spikes
Range 4-7 years (mean 11 years)
Childhood Occipital Visual Epilepsy (COVE)
Photosensitive Occipital Lobe Epilepsy (POLE)

Figure 2.

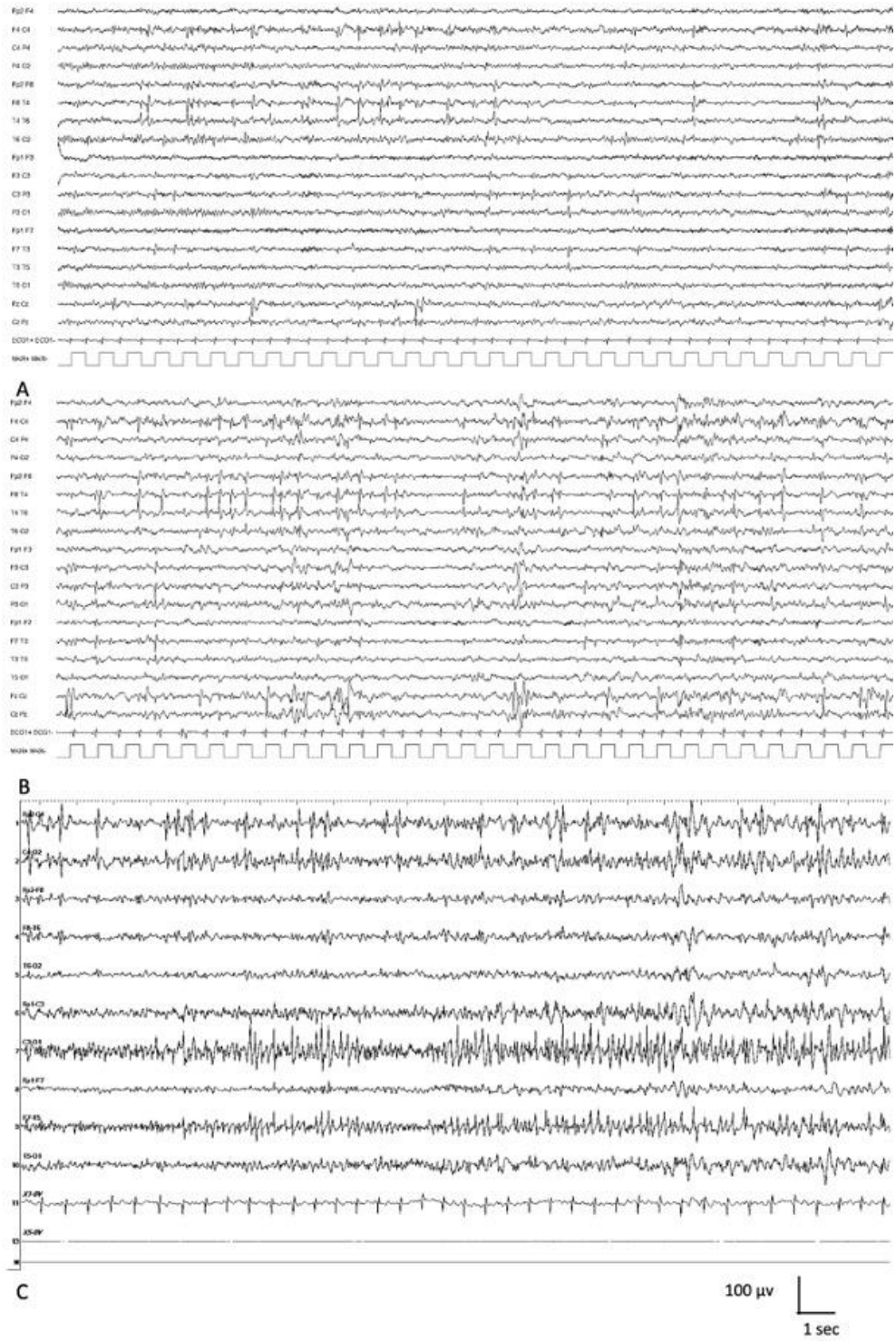
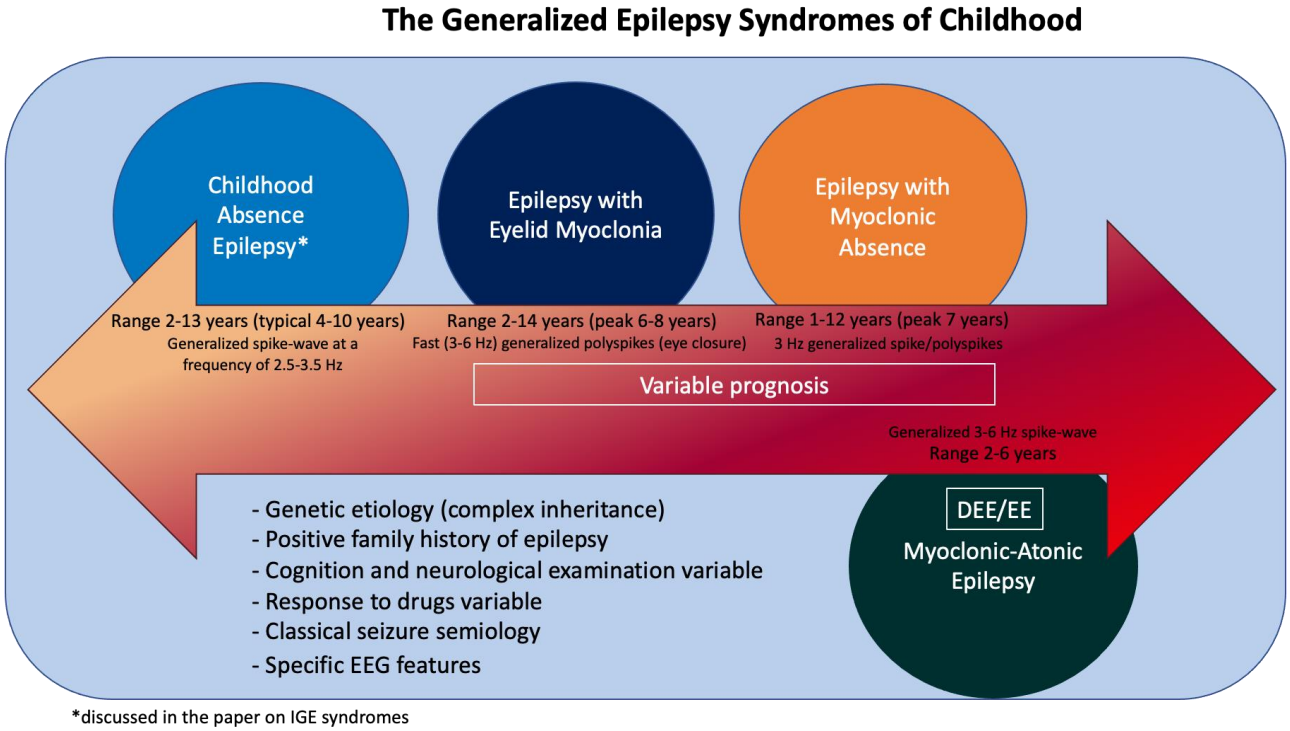


Figure 3.



*discussed in the paper on IGE syndromes

Figure 4.

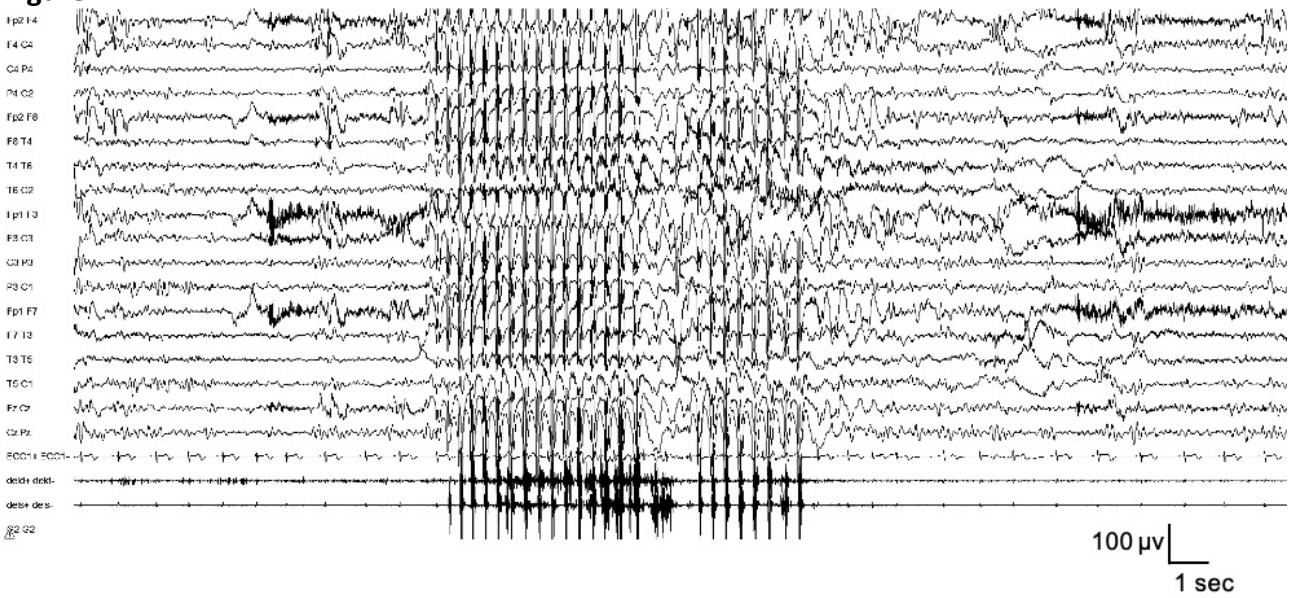
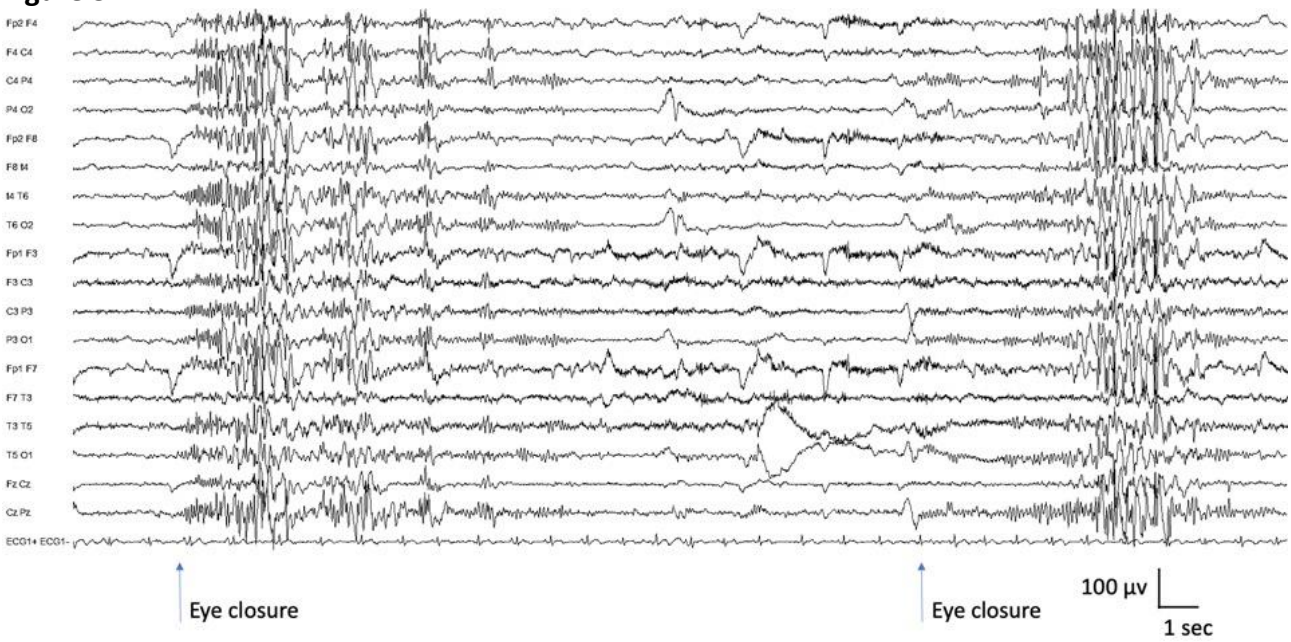


Figure 5.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F4 C4
C4 P4
P4 O2
Fp2 F8
F8 T4
T4 T6
T6 O2
Fp1 F3
F3 C3
C3 P3
P3 O1
Fp1 F7
F7 T3
T3 T5
T5 O1
Fz Cz
Cz Pz
ECG1+ ECG1-
Eye closure
Eye closure
100 µv
1 sec

Figure 6.

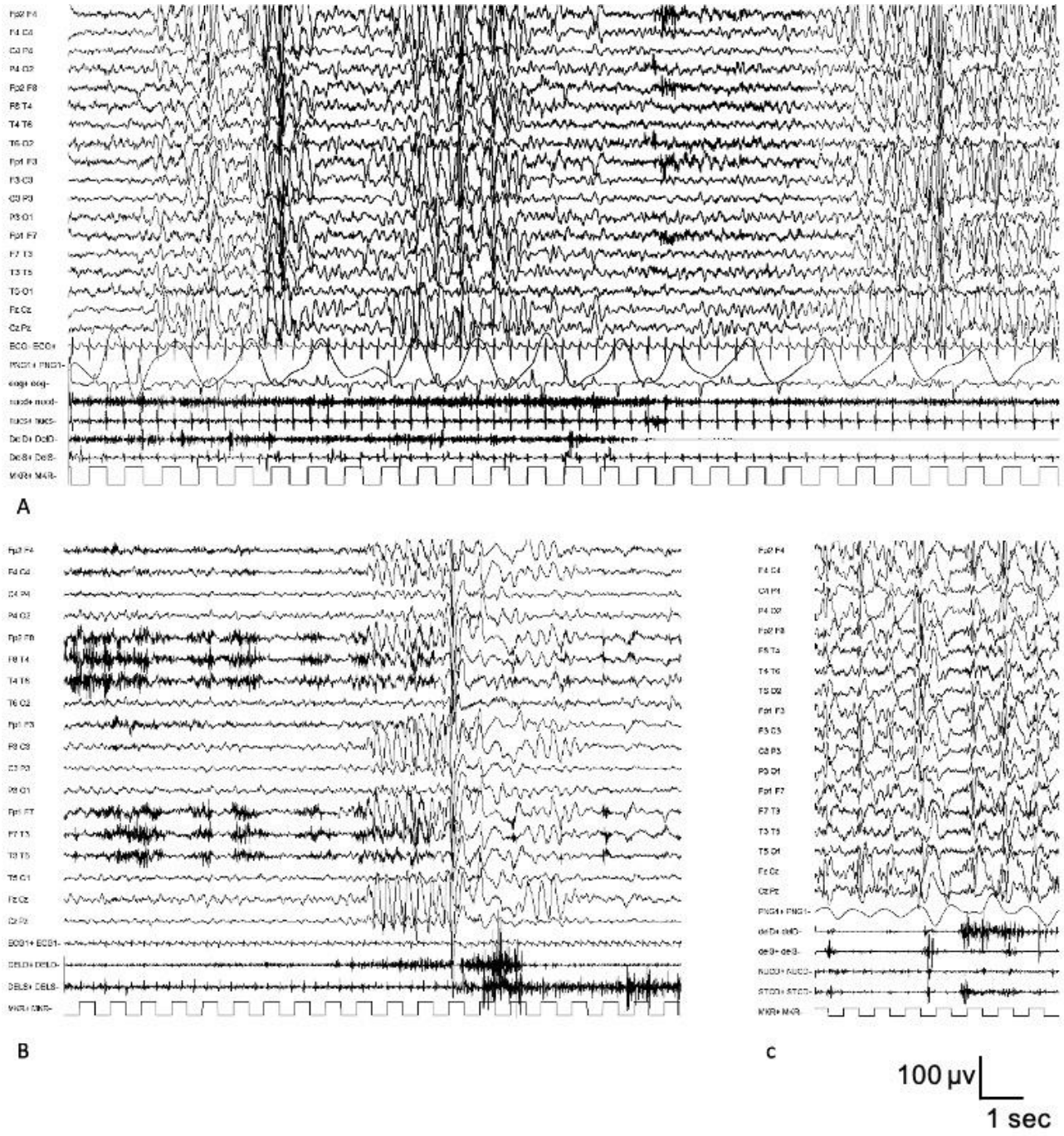
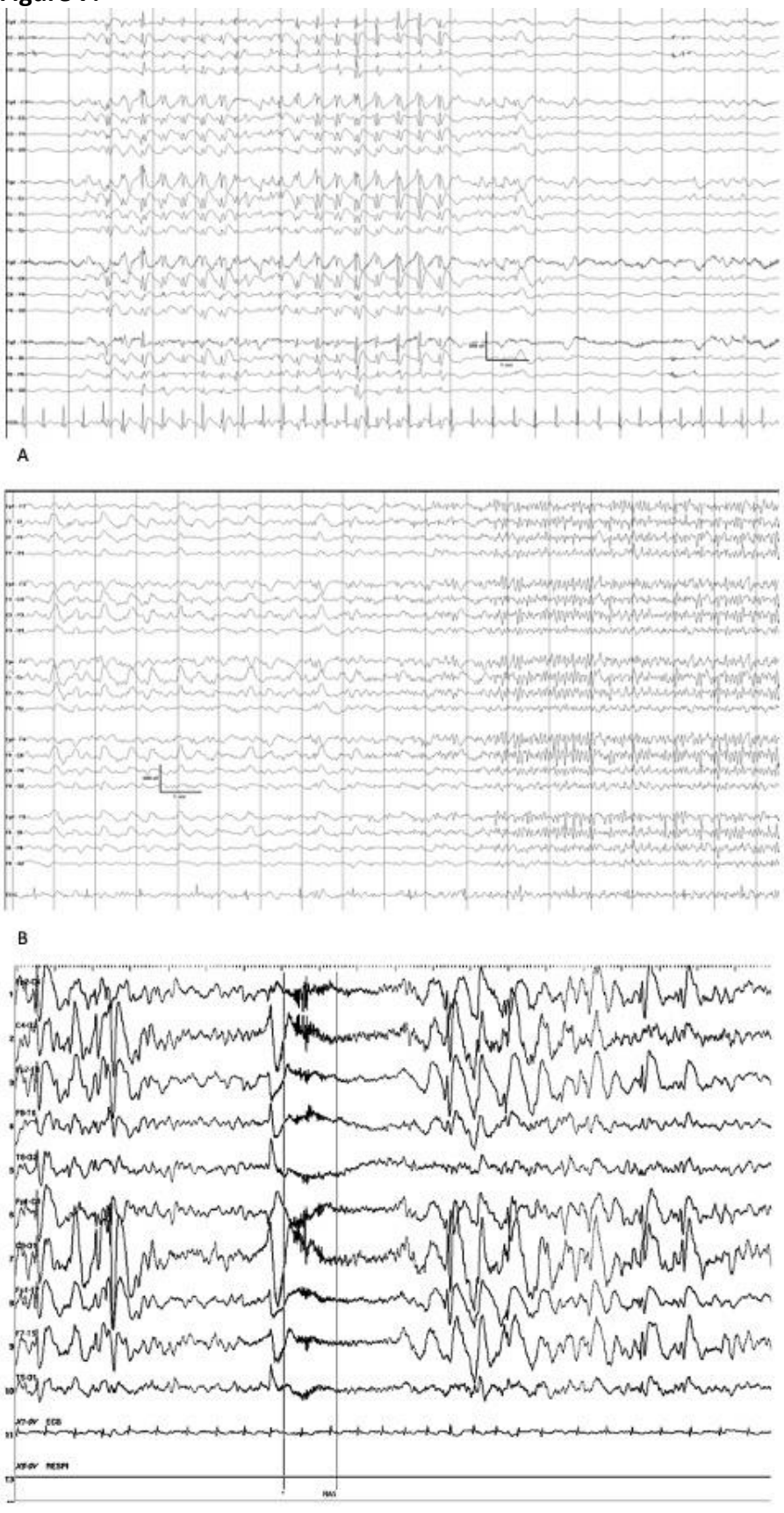


Figure 7.



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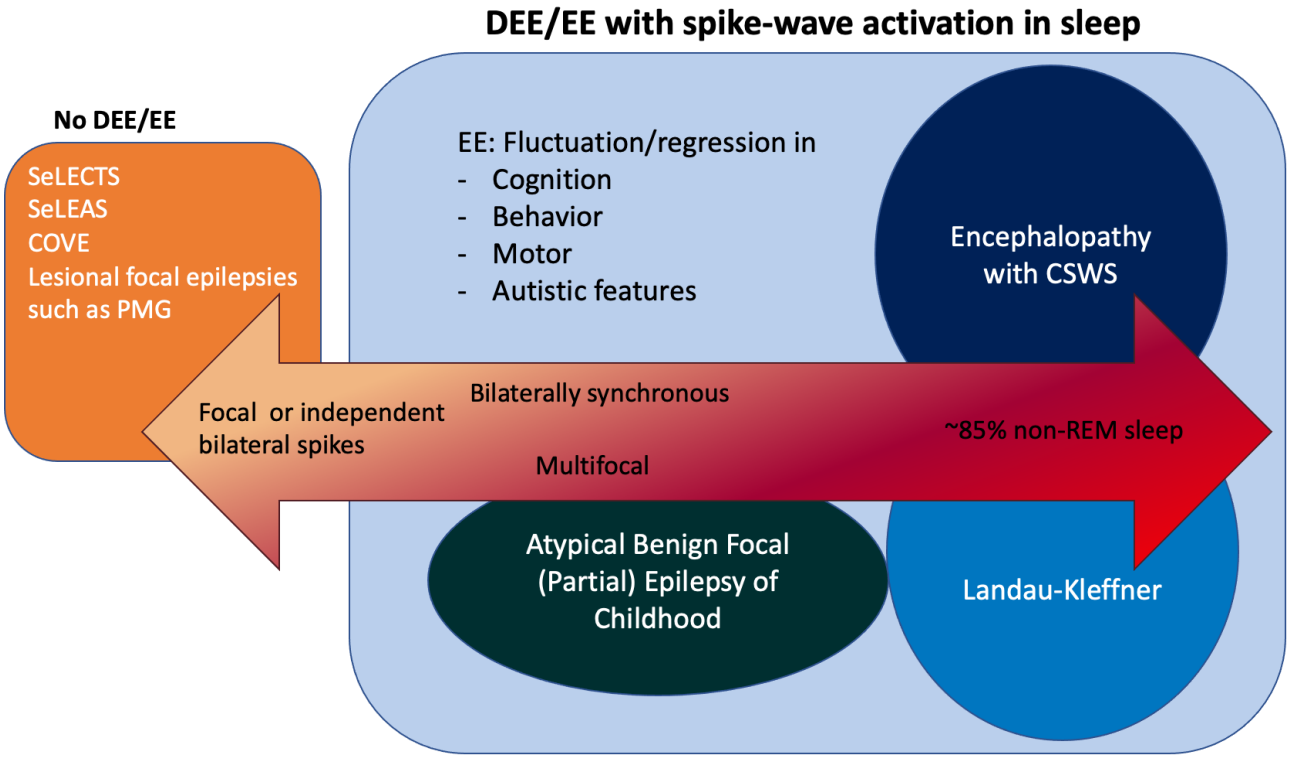
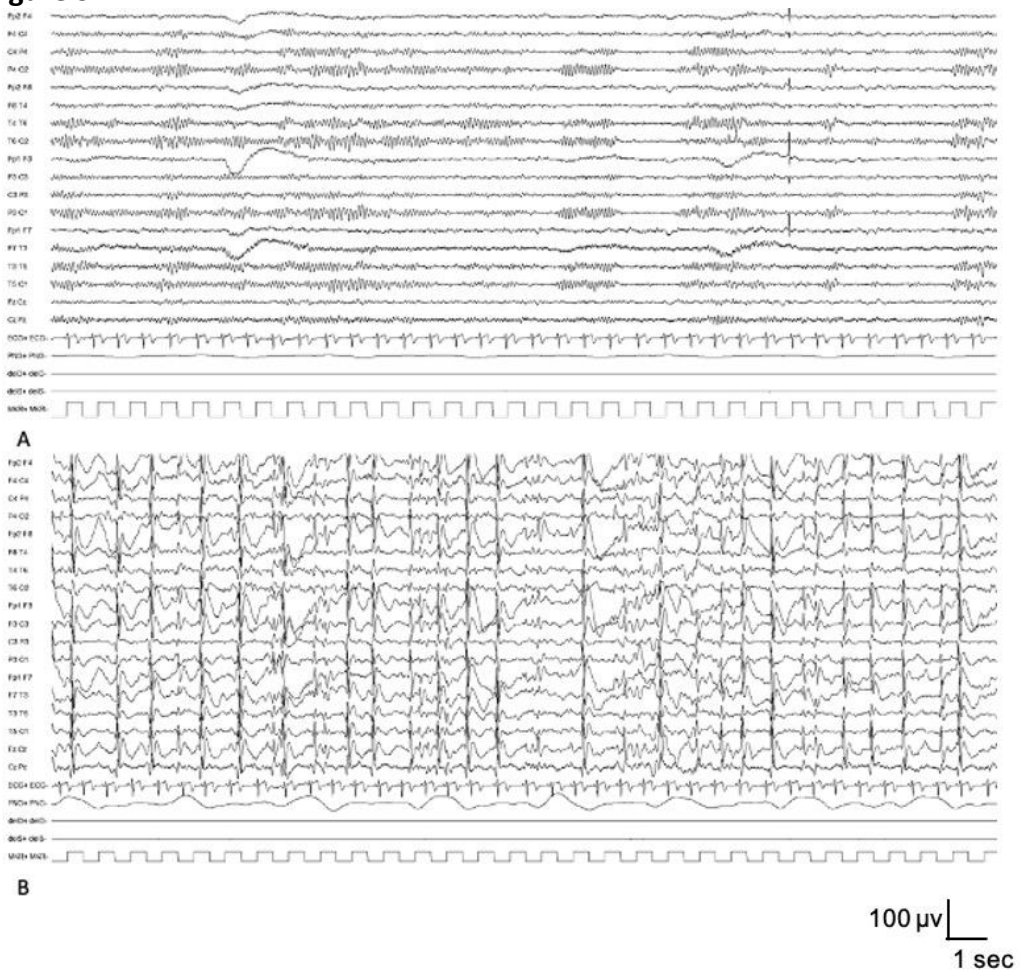


Figure 9



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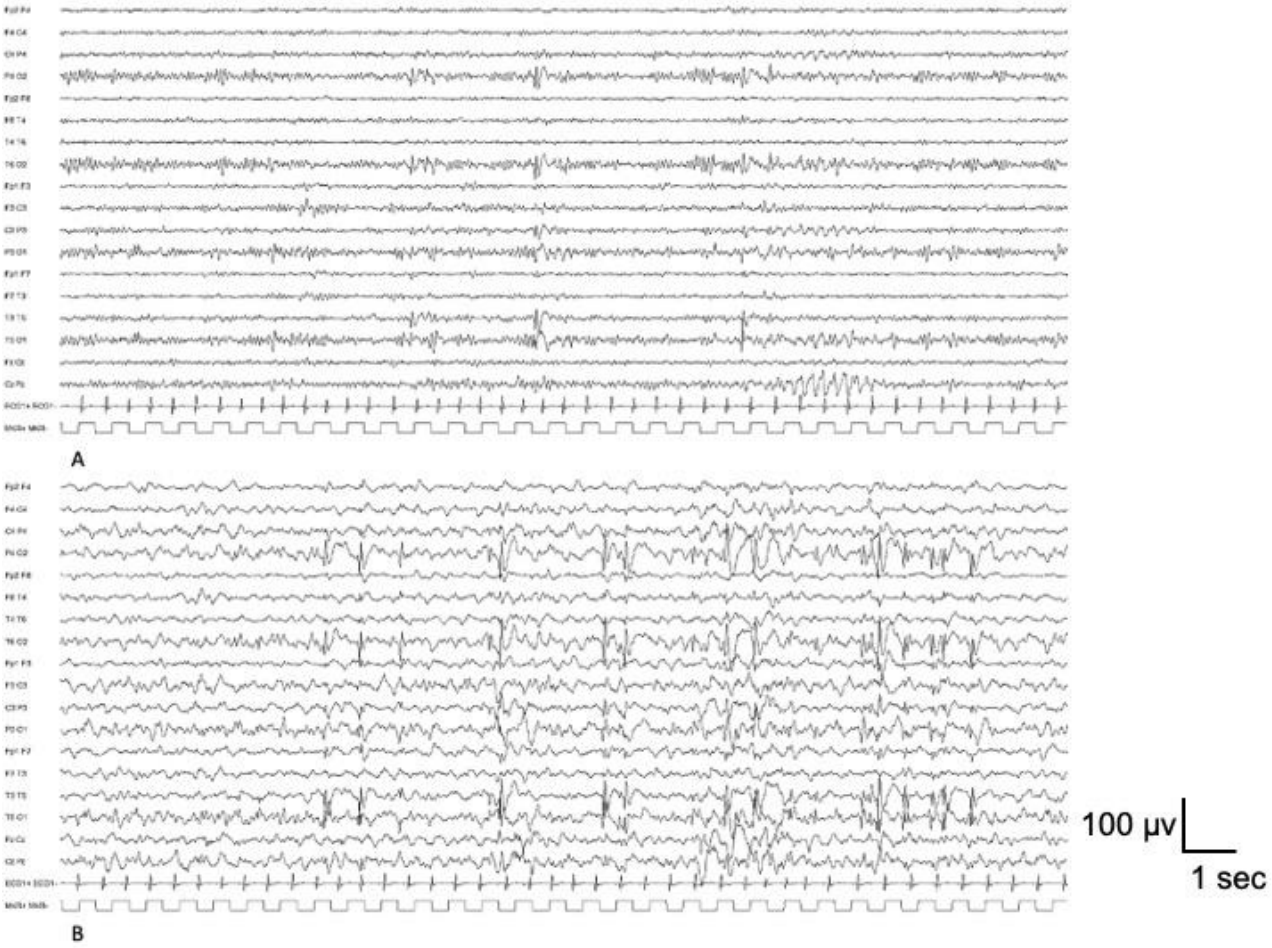
Supplementary Figure 1



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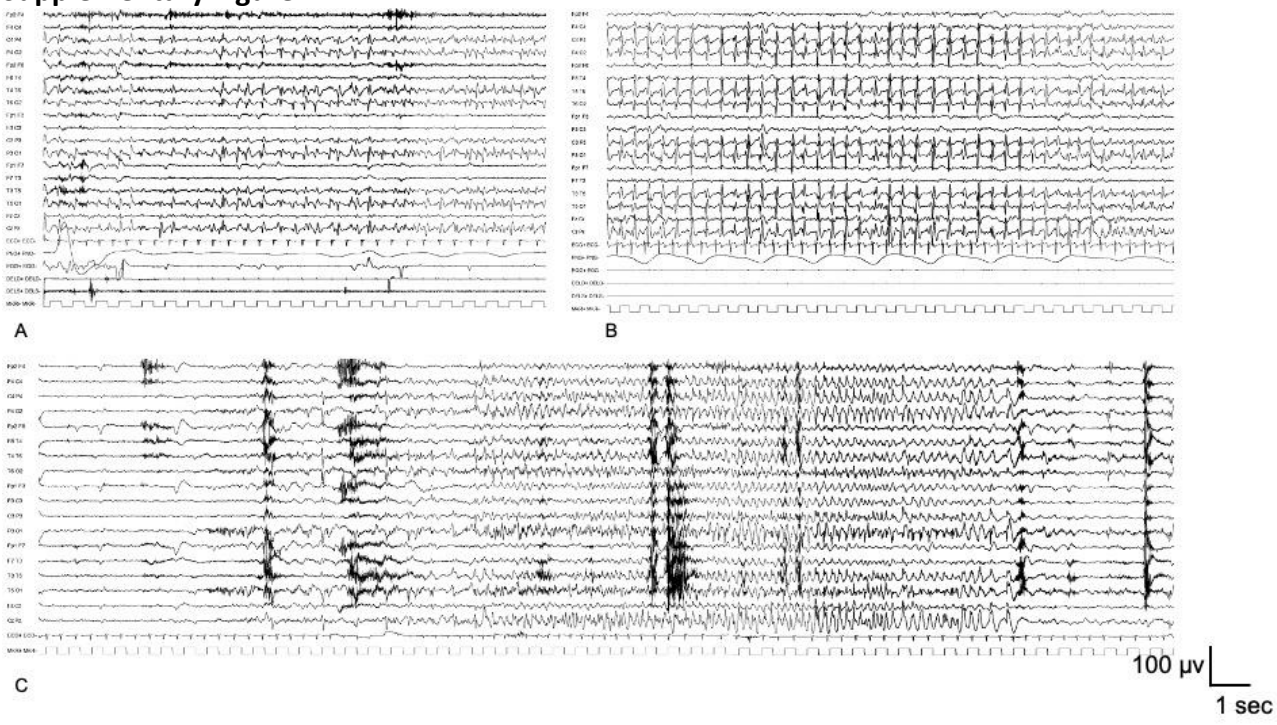
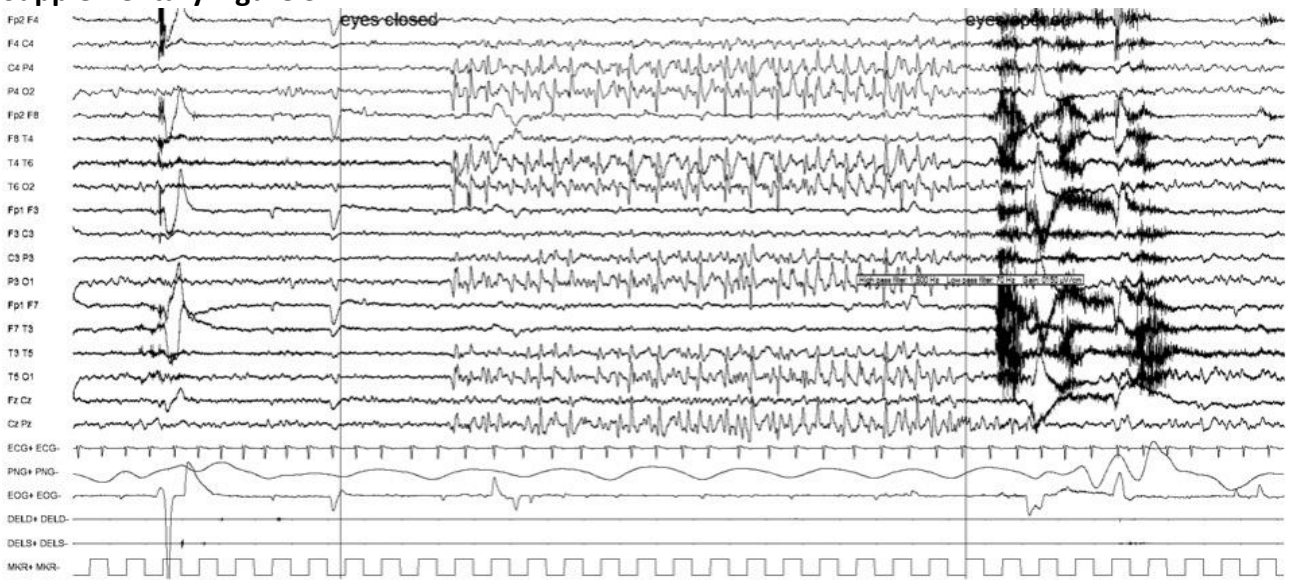


Supplementary Figure 3



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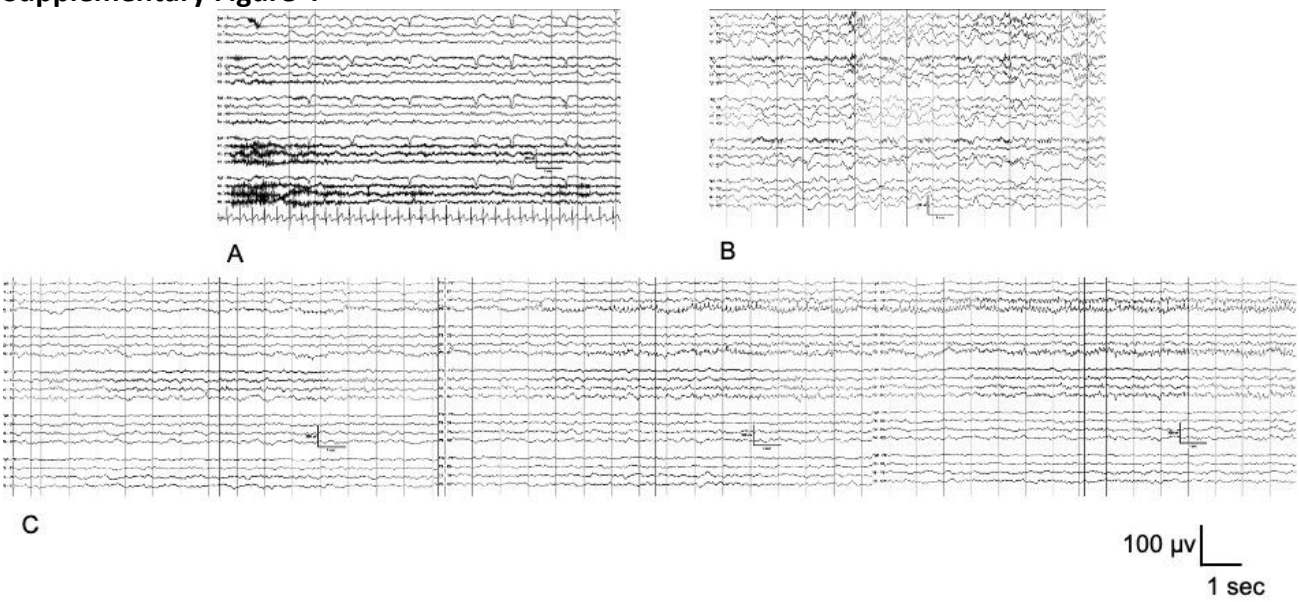

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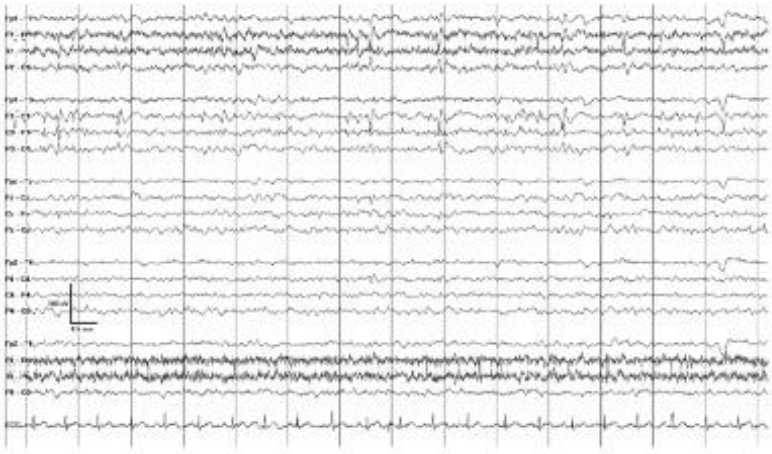

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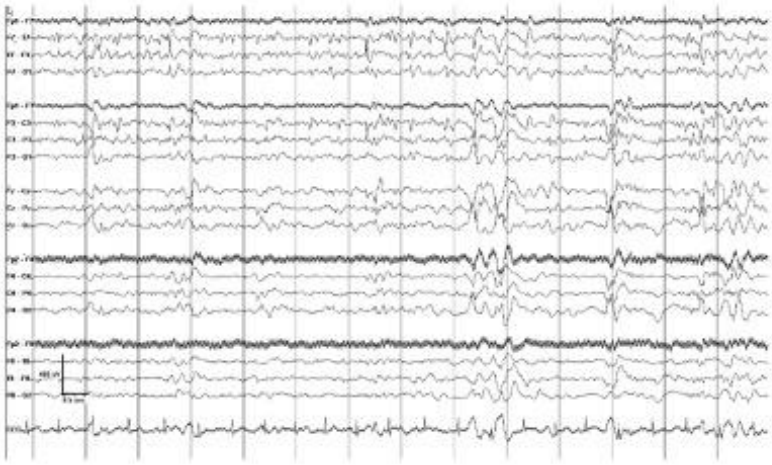

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