**ILAE Classification & Definition of Epilepsy Syndromes in the Neonate and Infant: Position Statement by the ILAE Task Force on Nosology and Definitions**

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**Abstract**

The ILAE Task Force on Nosology & Definition proposes a classification and definition of epilepsy syndromes in the neonate and infant with onset up to 2 years of age. The incidence of epilepsy is high in this age group and frequently associated with significant comorbidities and mortality. The licensing of syndrome specific anti-seizure medications following randomised controlled trials and the development of precision, gene related therapies are two of the drivers for defining the electroclinical phenotypes of syndromes with onset in infancy. The principal aim of this proposal, consistent with the 2017 ILAE Classification of the Epilepsies, is to support clinical management and emphasise the importance of classifying epilepsy in an individual both by syndrome and etiology. Syndromes are separated into self-limited syndromes, where there is likely to be spontaneous remission and the *developmental and epileptic encephalopathies* (DEE), diseases where there is developmental impairment related to both the underlying etiology independent of epileptiform activity and the epileptic encephalopathy. The emerging class of etiology-specific epilepsy syndromes is presented and includes genetic, genetic-metabolic, structural and genetic-structural causes. Epidemiology, clinical course, seizure types, EEG, neuroimaging, genetics and differential diagnosis are reported. The proposal defines the most common epilepsy syndromes and a selected number defined by etiology for which specific treatments are recommended. The number of etiology-defined syndromes will continue to increase, and these newly described syndromes will in time be incorporated into this classification. Tables summarise mandatory features, cautionary alerts and exclusionary features for the common syndromes. Guidance is given on the criteria for syndrome diagnosis in resource-limited regions where laboratory confirmation, including EEG, MRI and genetic testing, is not available.

## Introduction

The International League Against Epilepsy (ILAE) Task Force on Nosology & Classification proposes a framework for classification and definitions of epilepsy syndromes with onset in the neonatal period and infancy. This group includes infants from birth, whether premature or term, to two years of age. The Task Force proposes definitions for well-established electro-clinically defined epilepsy syndromes. Furthermore, we introduce the concept of epilepsy syndromes determined primarily by aetiology. This group includes syndromes where pathogenic variants in a gene or structural lesions have a consistent relationship with a well-defined electroclinical syndrome or are suggestive of a novel electroclinical syndrome. With all novel associations, the phenotypic spectrum will become better defined with time. In common with all ILAE classifications the focus of our Task Force was to develop a document reflecting the latest scientific knowledge which prepares the epilepsy community for emerging developments in epilepsy diagnosis and management.

A pure biological classification of the epilepsies is not possible given current levels of scientific knowledge, however broadening the definition of epilepsy syndromes to include etiology reflects the current reality of clinical epilepsy diagnosis and management. Precision therapies for genetically determined epilepsies, which may not only attenuate or stop seizures but also address many of the comorbidities of these disorders, are in development. The concepts presented in this proposal build on the work of many ILAE Commissions and Task Forces over several decades and further develop the 2017 ILAE Framework for Classification of the Epilepsies and the 2021 modification for seizures in the neonate where etiology is considered at all levels of classification from seizure type, to epilepsy type and epilepsy syndrome[1, 2]. The Task Force proposes the new classification and definitions of epilepsy syndromes as a hybrid combining electroclinical features with etiology. There is a complex relationship between etiology and clinical features in individuals with epilepsy where one etiology may relate to several different epilepsy syndromes and where one syndrome may be associated with different etiologies. More rarely, specific etiologies are associated with a unique electroclinical syndrome in most affected individuals. This requires that, in any individual with epilepsy, both the electroclinical syndrome and the etiology are considered together when developing a management plan. In resource-limited regions where such an approach is challenging due to limited access to specialized investigations, carefully defining the epilepsy syndrome can often suggest the etiology and guide optimal treatment. International collaborations through global networks and the International League Against Epilepsy may enhance equity of care.

## Definition of an epilepsy syndrome

The Proposal for Classification of Epilepsies and Epileptic Syndromes, published by the ILAE in 1985, defined an epilepsy syndrome as “an epileptic disorder characterized by a cluster of signs and symptoms, customarily occurring together[2]. The most recent Classification of the Epilepsies retained this definition, describing an epilepsy syndrome as a cluster of features incorporating typical seizure types, EEG and imaging features that tend to occur together, often with age-dependent features such as age at onset and remission (where applicable), seizure triggers, diurnal variation, sometimes prognosis and distinctive comorbidities such as intellectual and

psychiatric dysfunction[1]. It was noted that syndromes may have etiological, prognostic and treatment implications.

Our Task Force proposes the following definition for an epilepsy syndrome:

*"a characteristic cluster of clinical and EEG features, often supported by specific etiological findings (structural, genetic, metabolic, immune and infectious)". A syndrome diagnosis in an individual with epilepsy, carries prognostic and treatment implications. Syndromes often have age-dependent presentations and a range of specific co-morbidities[3].*

**Epilepsy with onset in the neonatal period and infancy**

Epilepsy incidence is age-dependent, with the highest incidences (> 60 per 100,000) found in those under the age of five years and those over the age of 65 years[4]. Several population-based studies have noted a much higher incidence of epilepsy in the first year of life than in older children (82.1-118 *versus* 46 per 100,000 person-years)[5-7]. A recent prospective, population-based study showed an incidence at 195/100,000 live births, considerably higher than previous estimates from retrospective studies[8]. These population-based studies are from high resource countries and it is noteworthy that acquired epilepsies have a higher incidence in resource-limited populations[9-11].

Children presenting with epilepsy very early in life experience a high burden of cognitive and behavioural comorbidity[12], higher rates of drug-resistance[13] and mortality[14], with up to 50% showing global developmental delay two years after presentation [8]. Comorbidities are more frequent among children who develop drug-resistant seizures[13] and those with a high seizure burden[15, 16].

Traditionally syndromes have been primarily defined by electroclinical features however, in the last two decades gene discovery in the epilepsies has allowed cohorts of cases with a shared genetic etiology to be studied. Consistent electroclinical phenotypes have emerged, examples including *CDKL5*[17], *MeCP2*[18, 19], *PCDH19*[20-22], *STXBP1*[23] and inv dup 15[24]. Furthermore, some structural, metabolic, immune and infectious etiologies also have characteristic electroclinical phenotypes[3]. Therefore, epilepsies due to specific genetic, structural, metabolic, immune or infectious etiologies may also meet criteria for a syndrome, when they are associated with consistent electroclinical features and have management and prognostic implications. Epilepsies in early childhood can be classified by syndrome in 41-42% of patients and by etiology in 54% when the latest neuroimaging, metabolic and gene testing techniques are used[6, 8]. By comparison, infants with severe epilepsies beginning under 18 months can be classified with an epilepsy syndrome at presentation in 64%, with the etiology being determined in 67%[25].

The etiology-defined epilepsy syndromes are restricted in this document to those with homogeneous electroclinical features and which, although they are individually rare diseases, are common enough to be seen in the practice of paediatric epilepsy specialists. The number of recognizable etiology-defined syndromes will increase and further development of associated precision therapies is anticipated. We have not included

response to therapy as part of the epilepsy syndrome definition although when there is evidence for specificity of response to medication, either reduction or exacerbation of seizure frequency, we have discussed this in the text.

**Methods**

The Task Force met face to face at ILAE meetings and had online discussions between 2018-2021. The syndrome descriptions were developed from those prepared by the ILAE EpilepsyDiagnosis.org Task Forces 2009-2013 & 2013-2017 and published online (www.epilepsydiagnosis.org). The definitions presented here were based on an iterative process within the Task Force[3]. A Delphi process incorporating 2 rounds of comments and involving additional expert clinicians outside the authorship group helped build consensus for any areas of disagreement[3].

**Framework for Classification**

The goal of this paper is to address the specific clinical and laboratory features of epilepsy syndromes with onset in the neonatal and infantile period (prior to age 2 years) and to provide rationale for any significant nomenclature or definitional changes.

**Syndromes**

We have divided epilepsy syndromes with onset in neonates and infants into two major groups; *self-limited epilepsy syndromes*, where there is likely to be spontaneous remission and the *developmental and epileptic encephalopathies* (DEE), diseases where there is developmental impairment related to both the underlying aetiology independent of epileptiform activity and the epileptic encephalopathy (Figure 1). Most etiology-specific syndromes that begin in the neonatal or infantile period are DEEs.

Within the group of self-limited epilepsies, there are syndromes in which both *de novo* and inherited pathogenic variants produce broadly similar electro-clinical features in familial and non-familial cases. We have therefore assigned a name for the syndrome and the inheritance as a secondary descriptor. The reasons for replacing the term "benign" in the epilepsy lexicon with "self-limited" have been described previously[1, 26]. In the self-limited epilepsy syndromes beginning under two years of age, the tendency to have seizures is age-limited, the seizures are typically pharmaco-responsive and the syndromes are associated with normal cognition or minor cognitive impairments.

The concept of the "developmental and epileptic encephalopathy (DEE)" recognises that in infants presenting with severe early-onset epilepsy, neurodevelopmental comorbidity may be attributable to both the underlying cause and to adverse effects of uncontrolled epileptic activity[1].

We have divided the DEEs into Early Infantile DEE with onset under 3 months of age and other syndromes which either typically present after 3 months of age or have a spectrum of age of onset which includes early and

late infantile periods. We discuss the typical age of presentation for each syndrome. We have not sub-divided the Early Infantile DEE into neonatal onset and later onset conditions as presentation can occur at any time from birth to a few months of age.

## A. Self-Limited Epilepsy Syndromes

### 1. Self-Limited (Familial) Neonatal Epilepsy (Table 1)

Self-limited neonatal epilepsy and self-limited familial neonatal epilepsy have similar clinical and electrical features but can be distinguished on the basis of family history[27-29]. These entities have similar genetic etiologies, with *de novo* pathogenic gene variants responsible for non-familial cases. A family history should be carefully sought as it can support diagnosis and guide decisions on investigation, treatment and prognosis. The familial syndrome was previously known as benign familial neonatal seizures or convulsions.
Seizures typically start between day 2 and 7 of life and often have focal clonic or focal tonic features or may progress to have sequential features. Focal seizures may alternate sides from seizure to seizure. Seizures can recur over hours to days. Developmental milestones are typically normal[29].

*Epidemiology:*

The estimated incidence of self-limited neonatal epilepsy is 5.3/ 100,000 live births[8].

*Clinical Context**:***

These syndromes typically present between days 2 and 7 of life[27-29]. If children are born prematurely, seizures may occur within days of the corrected gestational age of 40 weeks. Both sexes are affected equally.
Pregnancy and birth history are unremarkable. Infants appear otherwise developmentally appropriate for age. Head size and neurological examination are normal.

*Course of Illness:*

Seizures typically remit by 6 months of age, the majority ceasing by 6 weeks of age. If anti-seizure medication has been commenced, it can often be stopped within weeks. Developmental progress is usually normal although a minority of cases may have learning difficulties or mild motor impairment. Studies report that up to one third of individuals have seizures in later life[28]. These include febrile seizures, clusters of focal seizures, isolated generalised tonic-clonic seizures and in a minority, seizures with a self-limited epilepsy with centro-temporal spikes phenotype[27, 28, 30]. Some patients with specific pathogenic gene variants may have myokymia (continuous muscle activity causing stiffness and subtle twitching), which may present later in infancy[31].

*Seizures:*

Seizures are typically characterized by focal clonic and tonic features, affecting the face and limbs[27, 28, 32]. These may progress in a sequential pattern with tonic, clonic, myoclonic and autonomic features following each other without a single predominant feature. There is often changing lateralization within or between seizures. Vocalization and/or automatisms may be seen. Autonomic features such as apnoea and cyanosis are present in one third of seizures and may be the predominant manifestation. Seizures may last several minutes and are

characteristically longer in duration than seizures due to acute causes such as stroke and hypoxic-ischemic injury. Clusters of seizures may occur over hours or days, with the neonate behaving normally between events. Clinical examination is normal between events except in the immediate post-ictal period or if the infant is sedated by medication.

*EEG:*

The EEG background may be normal or may show minor non-specific abnormalities such as mild discontinuity or slowing[32]. Focal interictal epileptiform abnormalities can be seen in approximately two thirds of cases, most commonly in the central, centrotemporal or frontotemporal regions[32]. However, a "theta pointu alternant" pattern (Figure 2), can be seen in approximately half of cases or there may be focal or multi-focal sharp waves. The theta pointu alternant pattern consists of runs of theta activity intermixed with sharp waves, seen in awake and asleep states, that often alternates sides and does not change in response to various stimuli such as sound, touch or light[33, 34]**.** This pattern may persist for up to two weeks after cessation of seizures. Such a pattern is not specific for this syndrome and can be seen in neonatal seizures due to a range of other causes. The EEG abnormality may be enhanced in sleep. During periods of more active seizures, focal or widespread slowing may be seen, however in contrast to KCNQ2 developmental and epileptic encephalopathy, a burst-suppression pattern, or more marked, persistent slowing is not observed.

A typical ictal pattern has been described with an initial attenuation of the EEG lasting up to 20 seconds, followed by repetitive spike discharges (mainly centrotemporal although other regions can be affected – Figure 3) which are often bilateral but asynchronous and with shifting laterality[32, 34]. The topography can change from one seizure to the next.

*Imaging:*

Neuroimaging is normal.

*Genetics:*

Autosomal dominant inheritance patterns are seen within families (sometimes with incomplete penetrance). Self-limited neonatal epilepsy may be due to *de novo* pathogenic variants in the same genes, *KCNQ2* and *KCNQ3*, as self-limited familial neonatal epilepsy. The *KCNQ2* and *KCNQ3* genes code for potassium channel subunits which come together to form a heterotetrameric potassium ion channel (the M channel)[35-37].

A family history of self-limited neonatal seizures is required for self-limited familial neonatal epilepsy. There is often variability in the duration of the epilepsy in affected family members. In over 90% of families, a pathogenic variant is identified[28]. Pathogenic variants in *KCNQ2* are the most common cause of the syndrome, being present in over 80%, and include stop codons, deletions, and frameshift mutations resulting in haploinsufficiency, as well as certain missense variants that cause mild to moderate loss of channel function[38, 39]**.** *KCNQ3* and *SCN2A* pathogenic variants are much less frequent.

*Differential Diagnosis:*

• Neonatal seizures due to acute etiologies such as hypoxic-ischemic injury, infection, stroke or metabolic etiologies.
• Focal structural causes should be considered in infants with persistently focal stereotyped seizure
• Non-epileptic events such as benign neonatal sleep myoclonus.

## 2. Self-Limited (Familial) Neonatal-Infantile Epilepsy (Table 2)

Self-limited (familial) neonatal-infantile epilepsy is an autosomal dominant syndrome with onset in the neonatal or infantile period in different family members[40]. This disorder was identified in families and found to be due to dominantly inherited *SCN2A* pathogenic variants[41]. In addition, rare families have *KCNQ2* pathogenic variants[42]. D*e novo* pathogenic gene variants are likely to cause non-familial cases. A family history is helpful as it supports diagnosis and guides decisions on investigation, treatment and prognosis. Seizures start between day 2 and 7 months of life and have similar semiology to self-limited neonatal epilepsy, with focal clonic or focal tonic features, often occurring in clusters. Seizures can recur over hours to days. Developmental milestones are typically normal.

*Epidemiology:*

The estimated incidence is unknown.

*Clinical Context**:***

Self-limited (familial) neonatal-infantile epilepsy presents from 1 day to 23 months of life (mean 11 weeks, median 13 weeks)[43]. Both sexes are affected equally. Perinatal history is unremarkable. Infants are developmentally appropriate for age with normal examination and head circumference. No other clinical features are seen (such as movement disorders).

*Course of Illness:*

Seizure frequency varies with some infants having only a few seizures and not requiring treatment, while others have clusters of many seizures per day. Seizures cease by age 12-24 months, with no recurrences later in life. Seizures are readily controlled with anti-seizure medications.

*Seizures:*

Seizures comprise predominantly afebrile focal to bilateral tonic-clonic seizures. Initially focal features are observed with head and eye deviation, followed by tonic and clonic features. Some have prominent apnea and staring. Seizures vary in duration from 20 seconds to 4 minutes. Seizures with fever are rare.

*EEG:*

The EEG background may be typically normal. During periods of more active seizures, focal discharges, which are mainly in posterior regions or widespread slowing may be seen. The interictal EEG may show discharges in the posterior or central region or may be normal[44].

*Imaging:*

Neuroimaging is normal.

*Genetics:*

Autosomal dominant inheritance with high penetrance is seen with different family members showing a mixture of neonatal and infantile onset. This syndrome is primarily associated with pathogenic variants in the sodium channel subunit gene, *SCN2A*. Some families with self-limited seizures associated with *KCNQ2* may have individuals presenting outside the neonatal period[40, 42].

Patients with *de novo* pathogenic variants have also been reported.

*Differential Diagnosis:*

- Self-limited (familial) neonatal seizures. Self-limited (familial) infantile seizures.
- Neonatal or infantile acute symptomatic seizures due to hypoxic-ischemic injury, infection, stroke or metabolic etiologies.
- Other focal structural causes should be considered in infants with persistently focal stereotyped seizures.

## 3. Self-Limited (Familial) Infantile Epilepsy (Table 3)

Self-limited (familial) infantile epilepsy, formerly called benign familial (and non-familial) infantile seizures, is a syndrome characterized by the onset of seizures in the infantile period. Seizures are often frequent and may be difficult to control at onset, but spontaneously resolve. Children have normal developmental progress. It was first described in families with dominant inheritance of infantile seizures[45]. Later, it was expanded to include the familial syndrome of Infantile Convulsions Choreo-Athetosis syndrome (ICCA) with a movement disorder of paroxysmal kinesigenic dyskinesia/dystonia with affected family members having either seizures, movement disorder or both[46].

Self-limited familial infantile epilepsy and self-limited non-familial infantile epilepsy are identical except for the presence of a family history. Pathogenic variants in *PRRT2* are the most common genetic etiology. Familial cases show autosomal dominant inheritance, with incomplete penetrance.

*Epidemiology:*

Self-limited (familial) infantile epilepsy is relatively common, accounting for 7 - 9% of all epilepsies beginning prior to 2 years of age[47]. The incidence is estimated at 14.2/100,000 live births[8].

*Clinical context:*

Age at onset ranges from 3 to 20 months with a peak of 6 months. The antenatal, birth and neonatal history is typically normal. Head size and neurological examination are normal.

*Course of Illness*

Seizures may be frequent at onset but usually remit within 1 year from the onset. In untreated cases there can be isolated or brief clusters of seizures within the period from onset to remission[48]. A minority of individuals may have epilepsy persisting into later life.

Patients with *PRRT2* pathogenic variants may develop paroxysmal kinesigenic dyskinesia/dystonia beginning from childhood to adult life[49, 50]. Symptoms of the movement disorder should be sought for specifically as the events are very brief, lasting seconds, and the diagnosis often missed; it is easily controlled with carbamazepine.

*Seizures:*

Focal seizures are mandatory for diagnosis, and occur with behavioural arrest, impaired awareness, automatisms, head/eye version, and clonic movements. Focal clonic seizures may alternate from one side to the other and progress to a bilateral tonic-clonic seizure. Seizures are brief (<3 minutes) but can be frequent (e.g. 5-10 per day over 1-3 days at onset). One third of patients present with a single isolated seizure 10-15 days before frequent seizures commence. Longer seizures can occur but are rare. Seizures remit but recur after 1-3 months in a third of patients[51].

Focal hemiclonic seizures longer than 10 minutes are not seen in this syndrome. If these occur, particularly in the context of fever or following immunization, Dravet syndrome should be considered. If a migrating pattern within the same seizure is seen, particularly in the context of a developmental encephalopathy or regression, Epilepsy of Infancy with Migrating Focal Seizures should be considered.

Epileptic spasms and/or myoclonic seizures are exclusionary for this diagnosis.

*EEG:*

The background EEG is typically normal, although focal slowing may occur post-ictally[52]. If there is persistent focal slowing in one area, a structural brain abnormality should be considered. Diffuse, persistent slowing would suggest a different syndrome. The interictal EEG is typically normal, but a variant with midline spikes during slow sleep has been described[53, 54].

The ictal recording is characterized by focal discharges, which often onset in temporal or posterior head regions, and which may spread to both hemispheres[52]. The seizure onset may vary from lobe to lobe or from hemisphere to hemisphere in different seizures in the same patient. However, the ictal pattern within the same seizure does not show a migrating pattern.

*Imaging:*

Neuroimaging is normal. If the electroclinical diagnosis is clear and there is a family history, and/or a *PRRT2* pathogenic variant, neuroimaging is not mandatory.

*Genetics:*

*PRRT2* is the most commonly implicated gene[8, 38, 50]**.** Other genes associated with this syndrome include *SCN8A*, in which a movement disorder is also observed[55]**.** Infantile onset is also seen in patients with pathogenic variants in *SCN2A (see above section on self-limited familial neonatal-infantile seizures)*. In familial cases, inheritance is autosomal dominant with high penetrance. A genetic aetiology can be identified in about 80% of cases[8].

*Differential diagnosis:*

- Self-limited (familial) neonatal-infantile epilepsy: the distinction is made largely on age at presentation in affected family members (see above section).
- Infantile seizures due to acute causes e.g. bleed, infection, hypoglycaemia.
- Structural etiologies such as malformations of cortical development or brain injury.
- Epilepsy of infancy with migrating focal seizures: neurodevelopmental delay and a migrating pattern on EEG seen within the same seizure is suggestive of EIMFS.
- Dravet syndrome: prolonged hemiclonic seizures, rather than short seizures, should suggest Dravet syndrome
- Metabolic disorders: progressive encephalopathy and/or other organ dysfunction should prompt consideration of a metabolic disorder.

## 4. Genetic Epilepsy with Febrile Seizures Plus (GEFS+) spectrum: including Febrile Seizures Plus (Table 4)

GEFS+ was initially described as an autosomal dominant familial epilepsy with variable penetrance[56]. GEFS+ includes a spectrum of epilepsy phenotypes including Myoclonic-Atonic Epilepsy, Dravet syndrome[57], Genetic Generalized Epilepsy syndromes[58] and Focal Epilepsies[59], with heterogeneous phenotypes typically present in the same family. While febrile seizures are the hallmark of GEFS+ and occur in many affected family members, not all affected family members have febrile seizures. GEFS+ has heterogeneous genetic etiologies with pathogenic variants in several genes identified.

While the most common phenotype in GEFS+ is classical Febrile Seizures, the next most common phenotype is Febrile Seizures plus (FS+). Children with FS+ may have several different presentations: the most frequent is where typical febrile seizures continue beyond the age of 6 years, the classical age at which most febrile seizures stop. In infancy, a strong family history of GEFS+ phenotypes suggests this diagnosis but more recently, cases with GEFS+ phenotypes have been identified without a family history and a *de novo* pathogenic variant in a GEFS+ gene[60].

*Epidemiology:*

GEFS+ is a common familial syndrome, however epidemiological data on the incidence is lacking.

*Clinical context:*

The following describe the specific Febrile Seizures Plus Phenotype. Specific syndromes are described elsewhere.

Febrile seizures in GEFS+ families may begin prior to 6 months of age unlike typical febrile seizures (which onset after age 6 months), and persist beyond 6 years of age[56, 61]. Other afebrile seizure types may develop at various ages. Prolonged hemiclonic/focal clonic seizures with fever prior to 9 months, particularly if recurrent should suggest Dravet syndrome.

Neurological examination and cognitive abilities are usually normal.

*Course of Illness:*

Febrile Seizures Plus is typically responsive to antiseizure medications, although not all patients require prophylactic treatment. This syndrome is usually self-limiting with resolution of seizures by puberty[56].

*Seizures:*

Febrile seizures, which may be generalized or focal are mandatory for diagnosis. In addition, a variety of other generalized or focal afebrile seizures may be seen[56, 58, 59, 61, 62].

*EEG:*

The background EEG is normal. Occasionally, focal or generalized spike and wave may be seen.

The ictal EEG varies according to the seizure type.

*Imaging:*

Brain MRI, if done, does not show a causal etiology in patients with GEFS+ syndromes.

*Genetics:*

Inheritance is autosomal dominant, with variable penetrance[56, 58, 61]. Members of the same family may present with different types of seizures or epilepsy syndromes that may or may not be associated with fever or febrile seizures[56, 61, 62].

Although *SCN1B* was the first gene identified[63], it is not the most common gene associated with GEFS+, with *SCN1A* pathogenic variants identified in approximately 10% of GEFS+ families[58, 64]. Other gene variants encoding voltage-gated sodium, calcium, and potassium channels, and ligand-gated ion channels including nicotinic cholinergic receptor subunits, the gamma-aminobutyric acid A receptor and syntaxin 1B (*STX1B*) have also been linked to the syndrome[65, 66].

*Differential Diagnosis:*

- Febrile seizures without a family history suggestive of GEFS+.
- Infantile seizures due to acute causes e.g. ischemia, infection, hypoglycaemia.
- Structural etiologies such as malformations of cortical development or prior brain injury.
- Dravet syndrome should be considered with prolonged hemiclonic seizures under 1 year of age.
- Myoclonic-atonic epilepsy should be considered if myoclonic-atonic seizures are seen.

## 5. Myoclonic Epilepsy in Infancy (Table 5)

This syndrome presents with myoclonic seizures at onset, which may be activated by sudden noise, startle or touch, and less commonly by photic stimulation. Some authors propose that the term "Reflex Myoclonic Epilepsy in Infancy" should be used if myoclonic seizures are activated by triggering factors, and propose that children with this syndrome have a slightly earlier age at onset, better response to antiseizure medication, higher remission rate and more favorable cognitive outcome[67]. However, this syndrome should be considered a subgroup of Myoclonic Epilepsy in Infancy (MEI). Seizures are self-limiting in most cases. An EEG, ideally with video and EMG, is mandatory to confirm the epileptic nature of the myoclonus and to exclude Infantile Spasms Syndrome, which is much more common and severe than MEI.

*Epidemiology:*
Myoclonic Epilepsy in Infancy is a rare disorder, accounting for less than 0.8% of children with epilepsy treated at a specialty center[68]. It accounted for 1.1% of all epilepsy with onset prior to 36 months of age in a population-based cohort[8].

*Clinical context:*
The syndrome typically begins between the ages of 4 months and 3 years, with a peak age of 6-18 months. Males are more commonly affected, with a M:F ratio of approximately 2:1[68]. Development prior to seizure onset is typically normal. Cognitive, behavioral and motor difficulties may co-exist at onset but are incidental. Neurological examination is normal.

*Course of Illness:*
Myoclonic seizures remit in nearly all cases, typically within 6 months to 5 years from onset and most children can discontinue antiseizure therapy. Rarely, generalized tonic-clonic seizures may be seen in later life. Approximately 10% develop other epilepsies in late childhood or adolescence, mostly juvenile myoclonic epilepsy[68]. Patients with photosensitivity may have seizures that are more difficult to control.
At long-term follow-up, developmental outcome was normal in 63-85% of cases[68-73]. Occasionally, mild intellectual disability, learning disorders or attention problems evolve over time. Rarely, moderate to severe intellectual disability can be seen, and is not necessarily correlated with seizure frequency.

*Seizures:*
Myoclonic seizures are mandatory for diagnosis and involve the head and the upper arms. They typically occur multiple times per day, both in wakefulness and sleep. They can occur in clusters and can lead to falls. Reflex-induced myoclonic seizures are seen in approximately one third of cases and are triggered by sudden noise, touch or startle[68].
Febrile seizures are present in up to one third of cases[68] and may either precede or follow myoclonic seizures. Epileptic spasms, tonic, absence and focal seizures are exclusionary. Additionally, generalized tonic-clonic or generalized clonic seizures present at epilepsy onset are exclusionary.

*EEG:*

The EEG background in wakefulness is normal. Interictally, generalized discharges in the form of spike-and-wave, or less frequently, polyspike-and-wave, may be seen, and are more common in the early stages of sleep (Figure 4).

Photic stimulation does not provoke spike-wave discharge without concomitant myoclonus, but a photoparoxysmal response can be seen after disappearance of myoclonic seizures in a minority of patients.

The ictal EEG shows brief bursts of generalized spike-and-wave, polyspike and polyspike and wave at approximately 3 Hz during myoclonus. Myoclonic seizures are more commonly recorded from sleep, and may be triggered by sudden noise, touch or startle, or occasionally by intermittent photic stimulation[69, 74]. Concurrent EMG recording facilitates diagnosis.

*Imaging:*

Brain MRI is normal.

*Genetics:*

A family history of epilepsy or febrile seizures is reported in approximately 10% of cases[68]. No causal genes have been found.

*Differential diagnosis:*

*Epileptic:*

- Infantile spasms syndrome is distinguished by clusters of epileptic spasms, not myoclonic seizures. Spasms are most commonly seen shortly after waking, in comparison to myoclonus in MEI which may be seen both during wakefulness and sleep. Spasms typically last longer than 1 second. The EEG in infantile spasms syndrome is in most cases very abnormal with hypsarrhythmia or multifocal discharges.
- Dravet syndrome presents with prolonged seizures triggered by fever and status epilepticus. Myoclonus typically presents later.
- Lennox-Gastaut syndrome is distinguished by prominent atonic, tonic and atypical absence seizures which are not seen in MEI. In addition, Lennox-Gastaut presents later in the preschool years.
- Myoclonic Atonic Epilepsy is distinguished by myoclonic-atonic seizures, atypical absences, generalized tonic-clonic seizures and episodes of nonconvulsive status epilepticus, which are not seen in MEI. MAE also presents later in the preschool years.
- Early-infantile DEEs are distinguished by multiple seizure types in addition to myoclonus, marked developmental delay and severely abnormal EEG.
- Various neurometabolic disorders including both small molecule, mitochondrial and storage disorders may present with myoclonic seizures in early life. These are typically associated with progressive neurological deterioration and other organ dysfunctions.
- Glucose Transporter Deficiency is distinguished by relative microcephaly, other seizure types in addition to myoclonus, by low CSF glucose and, a low CSF/plasma glucose ratio.

- Progressive myoclonic epilepsies are distinguished by the presence of significant language or motor delay, frequent association with other seizure types besides myoclonus, frequent atrophy on MRI and photoparoxysmal response to low photic frequencies (suggesting CLN2 disease).

*Non-Epileptic*:

- Benign myoclonus of infancy is distinguished by the lack of EEG correlate to the myoclonic jerks.
- Hyperekplexia presents with pathological startle responses, which have no EEG correlate.
- Hypnagogic jerks
- Shuddering attacks present with repetitive, quick shudders, often provoked by excitement. There is no EEG correlate.

## B. Developmental and Epileptic Encephalopathies (DEE)

### 1. Early-Infantile Developmental and Epileptic Encephalopathy (Table 6)

Early-Infantile Developmental & Epileptic Encephalopathy is a syndrome characterized by:

- Onset of epilepsy in the first 3 months of life with frequent seizures that are typically drug resistant
- Abnormal neurological examination findings e.g. abnormalities of posture, tone or movement
- Moderate to profound developmental impairment evident with time
- Abnormal inter-ictal EEG which may include a burst-suppression pattern, diffuse slowing or multi-focal discharges
- Neuroimaging, metabolic and genetic testing allows precise etiological classification in approximately 80% of cases[8, 25].

Predominant seizure types include focal tonic, generalised tonic, myoclonic, focal clonic and epileptic spasms. Sequential seizures may occur[75, 76].

Early infantile DEE includes neonates and infants previously classified as Ohtahara syndrome and Early Myoclonic Encephalopathy (EME)[76, 77]. The syndrome may have many and varied underlying aetiologies including genetic, metabolic and structural. The electroclinical descriptions of Ohtahara syndrome (predominantly burst suppression EEG pattern and tonic seizures) and EME (predominantly myoclonic seizures and either burst-suppression or other significant EEG abnormalities) have been extremely valuable in epilepsy classification[78, 79]. This nomenclature allowed clinicians and researchers to study the causes, outcomes and treatment of neonates and infants with severe early onset epilepsy and provided families with crucial information on prognosis. However, the electroclinical features of these two syndromes have considerable overlap and furthermore share similar underlying etiologies[77, 80, 81]. The Task Force proposed that separating Early Infantile DEE into individuals with Ohtahara versus EME no longer provides valuable information for clinical decision making or determination of prognosis.

*Epidemiology:*

The incidence of Early Infantile DEE is estimated as 10/100,000 live births[8].

*Clinical context:*

This syndrome begins in the early infantile period (range 0-3 months) and affects boys and girls equally. The neurological examination is often severely abnormal with abnormalities of tone (most frequently central hypotonia), posture, and motor behaviour with cortical visual impairment.
Abnormal neurological behaviour or development often presents prior to onset of seizures but may be challenging to recognize due to extremely early onset (review of early videos can be helpful). Most children have moderate to profound developmental impairment.
Family, pregnancy and birth history are typically normal. Head size varies dependant on etiology but may be normal at birth.

*Course of Illness:*
The seizures are typically drug resistant unless metabolic or genetic targets for precision therapy or structural abnormalities amenable to surgery are identified[82, 83]. Many of these patients show favourable response to sodium channel agents, often at high dose[84-86]. Early-Infantile DEE, regardless of whether epileptic spasms are a presenting seizure type, may evolve into Infantile Spasms Syndrome with the burst-suppression or multi-focal EEG abnormalities changing to a hypsarrhythmia pattern. In very young neonates and infants the extent of any developmental impairment may be difficult to assess however almost all infants with Early-Infantile DEE will have moderate to profound intellectual disability. The exceptions include some individuals with early effective treatment of pyridoxine dependant epilepsy or pyridox(am)ine 5'-phosphate deficiency[87].
Infants with Early-Infantile DEE often have co-morbid movement disorders including myoclonus, chorea, dystonia and tremor. These may present prior to seizure onset, early in the evolution of the syndrome or develop with time. Differentiating paroxysmal movement disorders from seizures can be challenging particularly in the context of a severely abnormal interictal EEG. In such cases, prolonged video-EEG with EMG leads recording of the events should be considered[83].
Co-morbidities associated with global neurological disability including cortical visual impairment, motor impairment, orthopaedic concerns, behavioural problems, feeding difficulties, early and increased mortality are recognised associations with the syndrome[88].

*Seizures:*
Diagnosis of Early Infantile DEE requires one or more of the following seizure types:

1. tonic seizures
2. myoclonic seizures
3. epileptic spasms
4. sequential seizures, may include tonic, clonic and/or autonomic components as well as automatisms without a single predominant seizure type

**Tonic seizures** are typically frequent and can occur in isolation or in clusters with 10-20 clusters a day. If these occur in clusters, distinguishing features from spasms include (1) tonic seizures usually occur independent of the sleep cycle, unlike epileptic spasms, and (2) tonic seizures typically last longer than 5 seconds whereas epileptic spasms usually last <3 seconds. Tonic seizures are focal or asymmetric in the neonatal period.

**Focal or multifocal myoclonus** may be the predominant seizure type. The frequency of the myoclonus varies from occasional to almost continuous. Myoclonus can be erratic or massive and bilateral. Erratic myoclonus is typically asynchronous, asymmetric and random. It can occur in the face or extremities or may be restricted to only an eyebrow, lip, or finger. It occurs during both wakefulness and sleep. Erratic myoclonus is more commonly associated with a metabolic etiology.

**Epileptic spasms** occur in some patients. They are more frequently seen beyond the first month of life. They typically occur in clusters, often on awakening.

**Sequential seizures** are characterised by several seizure manifestations occurring in sequence in a given seizure[75]. For example, an event may begin with focal tonic features followed by focal clonic features and then epileptic spasms without one predominant manifestation.

In addition to the above seizure types, focal motor seizures may also occur.

*EEG:*

The background is abnormal and may show burst-suppression, multifocal spikes / spike waves / sharp waves with or without slowing, discontinuity and/or diffuse slowing (Figure 5). Very rarely the background activity is within normal limits at onset of seizures but will deteriorate quickly with increasing seizure frequency. Burst suppression pattern consists of high voltage bursts (150-300uV) of mixed spikes, sharp and slow waves lasting 1-5 seconds alternate with periods of marked suppression (< 5 μV) lasting 3-10 seconds, however the duration might be influenced by concomitant medications. It is usually seen both in wakefulness and sleep and is unresponsive to stimulation. A burst suppression pattern is usually bilateral but can be asymmetric, asynchronous or even unilateral. Random focal attenuation can sometimes be seen. In some children, an abnormal EEG background pattern may be seen prior to seizures with the burst-suppression pattern only becoming obvious post-ictally.

The burst-suppression pattern may disappear with age, but the EEG will remain abnormal. For infants who evolve to infantile spasms syndrome, hypsarrhythmia may appear with age. If the aetiology is treatable (metabolic or structural lesion amenable to surgery), the EEG may improve or even normalize.

The ictal pattern depends on seizure type.

With tonic seizures the burst-suppression pattern attenuates with emergence of low-voltage, high frequency fast activity. In the neonatal period ictal patterns are focal or asymmetric.

Myoclonus may have a spike/sharp wave correlate. Erratic/fragmented myoclonus may not have an ictal correlate.

Focal seizures are associated with a focal ictal recruiting rhythm.

The ictal pattern in a sequential seizure will change through the seizure as the clinical manifestations change.

Epileptic spasms are accompanied by a high voltage generalized or focal sharp or slow wave followed by low amplitude fast activity and attenuation. Furthermore, ictal EEG patterns may be seen with or without clinical seizures.

*Imaging:*

Structural brain abnormalities are an important and frequent cause of Early Infantile DEE and should be sought in all children. Where seizures are drug resistant and focal features are prominent, further imaging modalities should be considered to exclude a surgically remediable lesion. For certain genetic aetiologies, imaging is often normal initially or may show reduced brain volume or evidence of white matter hypo/dys-myelination. Over time cerebral atrophy may develop.

*Genetics:*

The following investigations should be considered:

- Chromosomal microarray, karyotype (eg. ring chromosome 14)
- Gene panel, whole exome or genome sequencing – it can be helpful for the quality of the resulting test report to highlight phenotypic features consistent with specific genes, where present (see below)
- Causative pathogenic gene variants can be identified in more than half of patients with Early Infantile DEE[8, 81]. Over time an increasing number of pathogenic gene variants are being identified in this syndrome.

**The seizure type(s) and EEG with other phenotypic features may predict genotype:**

- *KCNQ2*- DEE pathogenic variants are associated with sequential seizures (with a tonic component mostly but also with clonic, tonic, myoclonic, epileptic spasms or autonomic seizures) (see section below). This variant is also seen with exclusively tonic seizures associated with a burst-suppression or a multifocal EEG. Family history may include individuals with self-limited familial infantile epilepsy[84, 89-94].
- *SCN2A*-DEE pathogenic variants may include sequential seizures with predominantly tonic and autonomic features[86, 95].
- *SCN8A-DEE* pathogenic variants are associated with focal seizures[96].
- *STXBP1-DEE* pathogenic variants are associated with asymmetric tonic or sequential seizures (tonic, autonomic, clonic, and epileptic spasms)[97, 98].
- *CDKL5*-DEE is associated with tonic seizures. Seizures typically recur with a "hypermotor-tonic-spasms" phenotype[17, 99] (see below).
- *KCNT1*-DEE pathogenic variants can present with focal tonic seizures with autonomic symptoms[99].
- *UBA5*-DEE pathogenic variants can present with predominant myoclonic seizures[100].

*Metabolic Studies:*

Metabolic studies should be strongly considered, particularly if a clear structural abnormality is not found on imaging[82]. Furthermore, imaging or EEG features may suggest a specific metabolic etiology. Other sources should guide detailed neurometabolic testing however investigations should include urine organic and amino acids (including s-sulfocysteine), urine alpha aminoadipic semialdehyde, plasma amino acids, lactate, uric acid, copper/ceruloplasmin, ammonia, acylcarnitine profile, transferrin isoelectric focusing, very long chain fatty acids, and CSF glucose, lactate, pyruvate, amino acids and neurotransmitters.

*Differential Diagnosis*

- Provoked seizures associated with hypoxic ischaemic encephalopathy, infection, acute reversible metabolic disturbance, stroke or intracranial haemorrhage may be myoclonic, focal clonic and focal tonic. There may be a severe encephalopathy and a suppression burst EEG. Provoked seizures are much more common than those associated with EIDEE and relevant investigations to exclude acute causes should be performed. However, certain genetic causes of EIDEE including molybdenum cofactor deficiency and sulphite oxidase deficiency have imaging features which may mimic hypoxic brain injury.

## 2. Epilepsy of Infancy with Migrating Focal Seizures (EIMFS) (Table 7)

EIMFS is a rare developmental and epileptic encephalopathy beginning with drug-resistant, focal seizures in the first year of life, with associated severe encephalopathy. Focal seizures can arise in both hemispheres and migrate from one cortical region to another. Seizures are often prolonged with episodes of status epilepticus[101]. Prognosis is poor with severe neurological disability and reduced life expectancy, which may be, in part, related to the specific genetic mutation[101, 102] although a milder evolution has been reported in a few children. The cause is mainly genetic with *KCNT1*[103] as the major gene and more than 25 other genes linked to this syndrome[104].

*Epidemiology:*
EIMFS is rare, with an estimated prevalence of approximately 0.11 per 100,000 children[105].

*Clinical context:*
This syndrome usually begins in the first 6 months (mean 3 months) with rare cases beginning in the latter half of the first year of life)[101, 102, 106]. Males and females are equally affected. Head size and neurological examination are usually normal at onset; neurological examination findings later are consistent with severe neurological impairment. Most patients develop microcephaly by 1 year of age[106, 107]. Development may be normal at onset, however regression and subsequent severe delay is typical[101].

*Course of Illness:*
Prognosis is poor with ongoing drug resistant seizures, severe neurological disability and reduced life expectancy[101, 106], although a milder evolution has been reported in a few children. Some patients are also affected

by severe gut dysmotility and movement disorder[105], as is common to many genetic developmental epileptic encephalopathies.

*Seizures:*

Focal motor clonic or tonic seizures are mandatory for diagnosis. These are initially sporadic but the frequency rapidly increases in the weeks and months after seizure onset. Seizures may also be more subtle with behavioral arrest with or without head and eye version, and prominent autonomic features[101, 108].

Focal seizures show a migration pattern on EEG, which might be missed if a prolonged video EEG is not performed[102, 108, 109]. Clinically, migration is characterized by unilateral focal tonic or clonic activity at seizure onset, which then evolves to contralateral focal tonic or clonic activity over the course of the seizure. Status epilepticus is common[108].

Rare cases with a history of epileptic spasms have been reported[105, 110-112].

Myoclonic seizures are exclusionary.

*EEG:*

The EEG background can be normal at onset; however diffuse slowing of the background occurs with time[101, 105, 108]. Multifocal discharges appear with time in all cases. The EEG abnormality is enhanced by sleep deprivation and by sleep. Rarely hypsarrhythmia is reported[105, 111].

The ictal EEG correlates with clinical semiology and there is involvement of multiple independent cortical regions consecutively in the same single seizure event (Figure 6)[108, 109]. The ictal EEG is characterized by monotonic activity in the 4-10 Hz band, beginning in the temporo-occipital regions with a specific and pathognomonic pattern of propagation called migration[108, 109]. Recently, two EEG markers have been developed to differentiate *KCNT1*-EIMFS seizures from other focal seizures seen in neonates and infants, with variance in time and coherence of ictal rhythms of seizures[109].

*Imaging:*

Neuroimaging is typically normal at the outset, with reports of mild to moderate enlargement of subarachnoid and ventricular spaces. Brain atrophy, predominantly in the cerebellar region, has been reported on follow up of some cases. Delayed myelination with white matter hyperintensity on MRI and decreased N-acetyl aspartate on MR spectroscopy are often reported[103, 105, 106].

*Genetics:*

Familial inheritance is rare showing interfamilial variability (mildly affected parents with infants with EIMFS)[113, 114]. *De novo* gene abnormalities are most commonly implicated. *KCNT1* is the major gene and is reported in almost half of cases[103, 104, 115]. Other genes associated with this syndrome include mainly *SCN1A*, *SCN2A*, *SLC12A5*, *BRAT1* and *TBC1D24*[104].

*Metabolic testing:*

Some children presenting with migrating focal seizures have been found to have underlying congenital disorders of glycosylation[116].

*Differential diagnosis:*

- Self-limited familial and nonfamilial neonatal and infantile epilepsies are distinguished by normal development and lack of a migrating pattern on ictal EEG.
- Other focal, early-onset epilepsies due to a structural etiology are distinguished by the presence of stereotyped seizures, often with a single constant focus without a migrating pattern on EEG.
- Other early-onset genetic epileptic encephalopathies. These children may have multifocal and/or generalized seizures, with severe neurodevelopmental delay but do not show the characteristic migrating pattern within the same seizure on EEG. Many of these children may also develop movement disorders.
- Other inborn errors of metabolism.
- Dravet syndrome is distinguished by prolonged hemiclonic seizures that alternate from side to side with different seizures. However, these patients do not show a migratory pattern within the same seizure.

### 3. Infantile Spasms Syndrome (Table 8)

Infantile Spasms Syndrome is a term proposed to encompass both West syndrome as well as infants presenting with epileptic spasms who do not fulfil all the criteria for West syndrome. West syndrome classically referred to the triad of epileptic spasms, hypsarrhythmia and developmental stagnation or regression[117]. However, infants with Infantile Spasms Syndrome often lack one of these three criteria. For example, the developmental impact may not be apparent or typical hypsarrhythmia may not be present. This change emphasizes the importance of early diagnosis and therapy as shorter lag time to treatment is associated with a better outcome[118]. Infantile Spasms Syndrome is characterized by onset of epileptic spasms between 3 and 12 months of age, although later onset may occur. Infants may have no antecedent history, or the antecedent history may reflect the underlying cause e.g. acquired structural brain abnormality. In some cases, infants with Early Infantile DEE or other early onset epilepsies (typically with focal seizures) may evolve to have clinical and EEG features of Infantile Spasms Syndrome after 3-4 months of age[119].

*Epidemiology:*

The estimated incidence of Infantile Spasms Syndrome is 30/100,000 liveborn infants, with some studies suggesting higher incidence rates with higher geographic latitudes (Sweden, Finland, Denmark)[8, 120-122]. A population-based cohort showed that ISS accounted for 10% of epilepsies that begin prior to 36 months[8, 38]. Both sexes are affected, with a higher incidence in males.

*Clinical Context:*

Infantile Spasms Syndrome typically has onset between 3-12 months, with a range of 1-24 months. If onset occurs prior to 3 months, other early-onset developmental and epileptic encephalopathies should be considered. Prior to onset of Infantile Spasms Syndrome, development can be normal, but there is often a history of preceding clear or suspected abnormal development. Developmental slowing, arrest or regression, is typically seen with the onset of spasms. Parents may report isolated regression in visual attention or altered social

responsiveness in the days or weeks preceding onset of spasms. Developmental plateauing and regression typically worsen without urgent and effective treatment.
While head size and examination may be normal, careful neurological examination may provide clues to the etiology, including abnormal head size or neurological exam findings. Additionally, dermatological exam (for stigmata suggestive of a neurocutaneous disorder such as tuberous sclerosis complex), ophthalmologic assessment and examination for dysmorphic features can suggest an underlying cause.

*Course of Illness:*
Infantile Spasms syndrome frequently evolves to other epilepsy types or syndromes, especially Lennox-Gastaut syndrome, or drug-resistant focal epilepsies. About one third to half of the patients with Infantile Spasms syndrome evolve to Lennox-Gastaut syndrome (LGS)[123, 124]. Some infants may begin with focal epilepsy that evolves to Infantile Spasms syndrome, and then, as the child ages or in response to therapy, reverts back to focal epilepsy. In such cases, focal features are often seen on EEG and typical hypsarrhythmia may be absent. Co-existing focal seizures, asymmetric epileptic spasms and consistent focal features on EEG should also raise the possibility of a structural brain abnormality.
Spasms may persist in some cases, particularly with some of the genetic or structural encephalopathies. In some individuals, spasms resolve with effective therapy and subsequent epilepsy is not seen.
Developmentally, many infants are left with poor developmental outcome, regardless of seizure outcome. The severity of developmental delay relates predominantly to aetiology and promptness of treatment.

*Seizure types:*
Epileptic spasms are mandatory for diagnosis, and consist of brief tonic contractions of axial muscles, each typically lasting <3 seconds, which may be flexor, extensor or mixed. These usually occur in series or clusters, with increasing prominence of the motor features through the cluster, often over a period of minutes (though clusters may last 30 minutes or longer) and are often seen on awakening. These may be symmetric or asymmetric and may be subtle, with minor head nods, eye or chin movements.
Focal seizures may also be seen and may co-occur in an infant with spasms particularly in the setting of a structural aetiology, e.g. tuberous sclerosis, focal cortical dysplasia. Focal seizures may occur either independently of spasms or may precede, occur during or follow a cluster of epileptic spasms, or even occur throughout the series of epileptic spasms. Tonic seizures at onset are atypical and should raise concern for another early onset developmental and epileptic encephalopathy.

*EEG:*
Interictally, hypsarrhythmia (chaotic, high amplitude, excessive slowing, multifocal epileptiform discharges) is typically seen and the yield of detection is greatest if non-REM sleep is recorded (Figure 7A). However, some patients with Infantile Spasms do not have hypsarrhythmia, but the EEG is still significantly abnormal. A modified hypsarrhythmia pattern, representing greater interhemispheric synchrony, or consistent focal features may be present, including focal spasm complexes. A consistent focal epileptiform discharge or focal fast activity should suggest an underlying structural abnormality. Some infants may have a very active multifocal

epileptiform EEG without the chaotic background that typifies hypsarrhythmia. Very early in the course, or in older children, hypsarrhythmia may also be absent.
The ictal recording of a spasm is characterized by a high amplitude, generalized sharp or slow wave followed by low amplitude, fast activity which may appear as a brief electrodecrement (Figure 7B). Hypsarrhythmia typically attenuates or stops during a series of epileptic spasms. EMG helps to distinguish epileptic spasms from myoclonic seizures and tonic seizures (see Figure 8)[125].
A burst-suppression pattern on EEG is suggestive of early infantile developmental and epileptic encephalopathy.

*Neuroimaging:*
Early neuroimaging is strongly recommended to clarify the etiology, which may impact treatment decision-making. Brain MRI is abnormal in half to two thirds of children with Infantile Spasms[8, 126-130], and can show either acquired or congenital lesions that are focal, multifocal or diffuse. Early imaging should be repeated after 2 years of age when myelination is likely to be complete, if there is a suspicion of a focal structural lesion, or in infants with refractory infantile spasms of unknown etiology. Optimized imaging and analysis for the detection of subtle focal cortical dysplasias may be necessary, and modalities such as fluorodeoxyglucose (FDG) Positron Emission Tomography can be useful to detect focal structural anomalies in the presence of an apparently normal MRI. Such children should be referred early for epilepsy surgical assessment. In addition, MRI abnormalities may point to specific metabolic disorders.

*Genetics:*
Genetic studies should be considered if no etiology is found after clinical examination and MRI. In addition, genetic testing should be considered for patients with structural brain disorders known to be associated with a genetic basis.

Pathogenic variants in many genes have been associated with Infantile Spasms Syndrome and often are *de novo* in the child. A genetic etiology can be defined in up to 41% of cases[8]. Etiologies include Trisomy 21, *ARX*, *CDKL5*, *STXBP1*, *IQSEC2*, *TSC1*, *TSC2* and many others. A genetic mutation can be inherited from a parent with mild symptoms or an unaffected parent. Additionally, a range of chromosomal abnormalities and copy number variants have been associated with Infantile Spasms syndrome, so chromosomal microarray and routine karyotype should be considered.

*Metabolic and Other lab Studies:*
Metabolic etiologies are a rare but important cause of Infantile Spasms syndrome. Metabolic testing should be considered if an etiology is not found on clinical examination and no structural abnormalities on MRI.
In the absence of a known etiology, pyridoxine dependency should be considered. If laboratory studies are unavailable to rapidly exclude this diagnosis, infants should be considered for a trial of pyridoxine 100 mg/day for 3-7 days. However, given the rarity of this disorder, such a trial should be given at the same time as the first line therapy.

*Differential diagnosis:*

*Epileptic:*

- Early infantile developmental and epileptic encephalopathy begins before 3 months of age. While spasms may be present, other seizure types including tonic, myoclonic and sequential seizures typically co-exist.
- Myoclonic Epilepsy of Infancy presents with myoclonic seizures, not epileptic spasms. The EEG and EMG can distinguish myoclonus from epileptic spasms. There should be a normal background with generalized spike wave discharges.

*Non-epileptic:*

- Benign Sleep Myoclonus: Hypnic jerks in sleep are a normal phenomenon.
- Benign Myoclonus of Infancy presents with myoclonus and a normal interictal and interictal EEG.
- Infantile Colic presents with intermittent prolonged bouts of crying and stiffening. The EEG is normal.
- Benign Shuddering of Infancy.
- Benign Infantile Head Drops: frequent head drops with onset at 3-6 months of age. This entity is self-limited and the EEG is normal.

### 4. Dravet Syndrome (Table 9)

Dravet syndrome (previously known as Severe Myoclonic Epilepsy of Infancy), typically presents in the first year of life in a normal child with prolonged, febrile and afebrile, focal (usually hemiclonic) and generalized tonic-clonic seizures[131]. Other seizure types including myoclonic and atypical absence seizures appear between the age of 1 and 4 years. Seizures are usually intractable and from the second year of life children demonstrate cognitive and behaviour impairments[131]. Gait abnormalities including a characteristic crouch gait are usually seen by late childhood[132]. The clinical diagnosis is supported by the identification of pathogenic variants in the sodium channel gene *SCN1A* (found in over 80% of cases)[133].

*Epidemiology*:

Dravet syndrome affects approximately 6.5/100,000 live births[8, 38, 134].

*Clinical context:*

Onset of seizures is typically between 3-9 months, with a mean and median age of 6 months[131, 135, 136]. Rare cases can present as early as 1 month of age, or as late as 20 months of age. Development appears normal at seizure onset[135-137].

The neurological examination is normal at seizure onset. Walking is slightly delayed (mean 16-18 months) and gait instability may be present. Head size is normal during the first years. Significant developmental delay, neurological examination abnormalities, movement disorders or microcephaly at the time of seizure onset, should suggest an alternative diagnosis.

*Course of Illness:*

Seizures are pharmaco-resistant and present through life, although episodes of status epilepticus are more frequent before five years of age. They can however occur later, even into adult life, especially with illness or fever[135].

By adolescence/early adulthood, status epilepticus and atypical absences are rare – seizures are predominantly brief, nocturnal tonic and GTCS[138, 139].

Over time, developmental progress slows and delay may be evident from 12-60 months[140-142]. Speech delay is predominant, with most patients developing intellectual disability which ranges from severe (50%) to mild[137, 140]. Many patients develop behavior and motor disorder and some have inattention and hyperactivity[135, 142, 143].

Developmental regression can rarely be seen following episodes of status epilepticus. In most patients, however, the pattern is more of developmental slowing and consequent intellectual impairment[140].

Over time, most patients develop subtle pyramidal signs and gait disorder evolving to crouch gait, typically by late childhood to adolescence[132].

*Seizure Types*:

Recurrent hemiclonic seizures (unilateral clonic seizures affecting one side of the body), focal to bilateral tonic-clonic seizures or generalized tonic-clonic seizures at onset which are often prolonged and frequently triggered by fever, elevated environmental temperature or immunization, are mandatory for diagnosis[131, 136]. A prolonged, hemiclonic seizure with fever (especially low grade fever) prior to 9 months of age, in the absence of an infection or a structural brain lesion, in a previously normal infant, is highly suggestive of Dravet syndrome[135].

By 1.5 to 5 years of age, additional seizures types can occur (but are not always present)[135, 136]:

- Myoclonic seizures
- Focal impaired awareness seizures.
- Atypical absence seizures
- Atonic seizures
- Non-convulsive status epilepticus (originally termed obtundation status)
- Tonic and tonic-clonic seizures mainly in sleep and in clusters

By this age, in addition to illness, seizures can also be triggered by physical activity, change in environmental temperature, visual patterns (rarely), photic stimulation (15% of patients), and excitement[127, 135, 141].

Tonic and tonic-clonic seizures mainly in sleep and in clusters, may appear later in the course of the disease, from around age 4-5 years, and become more evident in adult life[138, 139, 144].

Epileptic spasms are exclusionary.

Seizures are typically exacerbated with the use of sodium channel blocking drugs (this can be a clue to the diagnosis) such as carbamazepine, oxcarbazepine and phenytoin. Lamotrigine should be avoided in young children as it may exacerbate seizures[145], but it may have a role in older patients[146].

*EEG*:

Background may be normal or slow prior to age 2 years. Slowing is typical after 2 years of age[136, 141, 147].

Interictal discharges are often focal, multifocal and generalized, and appear after 2 years of age[147].

A photoparoxysmal response occurs in 15% of patients and is more frequent in younger children[147].

Ictal recordings depend on seizure type. In patients with sleep clusters of seizures, interictal frontal discharges are often seen[144, 147].

*Neuroimaging:*

MRI is typically normal at seizure onset[148]. Over time, mild cerebral and cerebellar atrophy may evolve. About one-third of patients have hippocampal sclerosis[148, 149], however, epilepsy surgery is not indicated.

*Genetics:*

An *SCN1A* mutation is present in > 80-85% of cases[133]. Most are *de novo***,** however, up to 10% of patients who are thought to have a *de novo* mutation will have one parent who is mosaic for their mutation[150]. This carries implications for reproductive counselling. Dravet syndrome may occur in one member of a family with GEFS+. *SCN1A* mutations may be found in other epilepsy syndromes such as GEFS+ (genetic epilepsy with febrile seizures plus) and early infantile *SCN1A* encephalopathy with profound impairment. The diagnosis of Dravet syndrome requires the typical clinical features and cannot be made on the basis of the genetic mutation alone[143]. Treatment should not be delayed in the setting of a clinical diagnosis.

Onset prior to 3 months, significant delay preceding seizure onset and a movement disorder after seizure onset is suggestive of *SCN1A*-EIDEE rather than Dravet syndrome, and may be associated with specific *SCN1A* genotypes such as Thr226Met[151]. Some cases of early onset *SCN1A*-EIDEE are linked to gain-of-function variants, and thus responsive to sodium channel blocking agents[152].

Other genes have rarely been associated with Dravet syndrome including dominant, pathogenic variants in *GABRG2*, *GABRA1*, *STXBP1* and rare recessive cases with *SCN1B* mutations[153].

A family history of febrile seizures or other epilepsies may be seen in 30-50% of cases, and the semiology may be suggestive of GEFS+.

*Metabolic and other Lab Studies:*

No consistent abnormalities found.

*Differential Diagnosis:*

*Epileptic:*

- Febrile seizures plus: While this condition also may present with febrile seizures in early life, the presence of recurrent, prolonged, hemiclonic seizures in infancy should suggest Dravet syndrome.
- Lennox-Gastaut Syndrome: Lennox-Gastaut syndrome can readily be distinguished from Dravet syndrome, as tonic seizures are prominent early on, and prolonged hemiconvulsive seizures do not occur. Furthermore, the EEG in Lennox-Gastaut shows a slow background, with prominent, frontally-predominant slow spike-wave (<2.5 Hz) and paroxysmal fast activity in sleep.
- Myoclonic Atonic Epilepsy: Myoclonic atonic epilepsy begins later than Dravet syndrome, typically in the preschool years. Although some cases may have a history of febrile seizures, prolonged, hemiclonic seizures and focal seizures are not seen. Myoclonic atonic seizures are typical. Children may develop myoclonic non-convulsive status but recurrent convulsive status epilepticus is also rare.

- Protocadherin 19-DEE typically presents with clusters of seizures, as opposed to prolonged hemiconvulsive seizures, however, similar to Dravet syndrome, seizures are typically triggered by fever. Protocadherin 19-DEE predominantly affects females, and there is an X-linked mode of inheritance which spares males.
- *SCN1A*-DEE is distinguished from Dravet syndrome by very early onset (<3 months), preceding developmental delay and prominent movement disorder. These pathogenic variants most commonly correlate with gain-of-function variants.
- Structural focal epilepsy may begin with prolonged focal seizures triggered by fever, however recurrent seizures affect the same side or limb, as opposed to Dravet syndrome which results in hemiclonic seizures that often alternate sides. Myoclonic and atypical absence seizures are unusual. MRI often shows a causal lesion.
- Mitochondrial disorders: Children with mitochondrial disorders may also present with multiple seizure types early in life. However, there are typically other signs of mitochondrial disease, such as other organ dysfunction, elevated lactate, characteristic abnormalities on MRI.

***Non epileptic:***

- Intracranial infection such as meningitis or encephalitis must be excluded in the presence of a prolonged febrile seizure

## 5. Etiology-Specific Syndromes

Increasingly, consistent electroclinical phenotypes are being identified with strong associations to specific etiologies. Some known syndromes have specific etiologies (i.e. SCN1A pathogenic variants in Dravet syndrome), however for other etiologies, novel characteristic phenotypes are associated. In some cases, the etiology has just a single phenotype, while in others, particularly certain genetic disorders, the phenotype may vary depending on age and nature of the variant. Our Task Force did not aim to identify and describe all Etiology-Specific Syndromes, but provided definitions on a limited number, including the DEEs associated with *KCNQ2*, *CDKL5*, *PCDH19*, *SCL2A1,* Pyridoxine and Pyridox(am)ine 5'-Phosphate Dependent Epilepsy, Sturge-Weber syndrome and Gelastic Seizures with Hypothalamic Hamartoma.

### *a.* *KCNQ2*-DEE (**Table 10**)

*KCNQ2*-DEE causes a neonatal onset encephalopathy and is due to *de novo* missense variants that produce a disorder distinct from self-limited neonatal epilepsy. Seizures may respond to sodium channel blockers.

*Epidemiology:*
The incidence of *KCNQ2*-DEE is unknown.

*Clinical Context:*

Seizure onset is within the first few days of life in the context of a severe neonatal encephalopathy with abnormal neurological examination and behaviour[89, 93, 154-159]. Seizures are typically not responsive to first line medications such as phenobarbitone and levetiracetam. Sodium channel blocking agents such as carbamazepine and phenytoin should be considered early in this clinical context[84].

*Course of Illness:*
*Seizures* may respond partially or completely to sodium channel blockers. Epilepsy frequently remits however developmental outcome is typically moderately to severely impaired[157]. Over half of patients will become seizure free varying from a few months of age to several years[157]. As genetic testing becomes more readily available it is likely that more cases with intermediate outcome between self-limited neonatal epilepsy and *KCNQ2*-DEE will be identified. Milder phenotypes may be seen in cases with mosaicism.

*Seizure Types:*
Focal tonic seizures are seen most frequently though other seizure types including focal clonic and myoclonic may also be seen[93, 155, 157]. Autonomic features, apnoea and ictal crying may be prominent during seizures. Epileptic spasms have been recorded in some individuals however the evolution to infantile spasms syndrome is seen less frequently in *KCNQ2*-DEE than in other severe early infantile DEE syndromes. The seizure semiology in neonates is similar to that seen in Self-limited familial neonatal epilepsy however seizure frequency, EEG background abnormalities and abnormal neurological examination in *KCNQ2*-DEE allows the syndromes to be distinguished[157].

*EEG:*
In more than 60% of cases the EEG shows a burst suppression pattern which may be asymmetric at times (Figure 5)[92, 156]. In other cases, multifocal abnormalities including spikes, sharp waves, and hemispheric suppression may be seen.

*Neuroimaging:*
MRI signal abnormalities may be seen in the basal ganglia or thalamus during the neonatal period. In some cases, hyperintensities seen on T1 sequences in the globus pallidus may disappear with time. Mild atrophy of the frontal lobe and thin corpus callosum have been reported [90, 92].

*Genetics:*
*De novo* missense variants in particular regions (hot spots) of the *KCNQ2* gene produce a dominant negative, more severe loss of channel function than is seen in self-limited neonatal epilepsy[156, 158, 159].

### *b.* Pyridoxine-Dependent (*ALDH7A1*)-DEE & Pyridox(am)ine 5'-Phosphate Deficiency (*PNPO*)-DEE (Table 11)

Pyridoxine-dependent (PDE) and Pyridox(am)ine 5'-Phosphate deficiency (P5PD)-DEE are caused by genetic-metabolic defects within the same lysine degradation pathway[160]. Seizure control can be achieved in almost all

cases with pharmacological doses of pyridoxine and pyridoxal-5'-phosphate (PLP), respectively, emphasizing the importance of early recognition. Some infants with P5PD respond partially or completely to pyridoxine therapy[160].

*Epidemiology:*

Estimates of incidence are only available for PDE-*ALDH7A1* and vary from 1 in 65,000 births, 1 in 273,000 births to 1 in 783,000 births[161-163]. The incidence of P5PDE is unknown.

*Clinical Context:*

Patients with PDE and P5PD typically present shortly after birth with encephalopathy and seizures or with intrauterine convulsions but up to 25% of patients with PDE may present outside the newborn period, mainly in the first three years of life, though new onset of seizures has been reported at 17 years of age[164, 165]. Patients with P5PDE are often born prematurely, and both PDE and P5PD may show signs of neonatal distress, irritability and vomiting at times with acidosis and low Apgar scores, leading to a misdiagnosis of neonatal hypoxic-ischaemic encephalopathy [165, 166]. There may be a family history of early-infantile DEE, infertility and death in siblings[167]. Seizures are resistant to standard anti-seizure medications.

*Course of Illness:*

Evidence from small case series and observational studies suggests that lysine reduction therapies including a lysine restricted diet and L-arginine therapy may provide additional benefit in terms of seizure control and cognitive outcome[168]. Despite adequate seizure control, the majority of people have varying degrees of intellectual disability from mild to severe[169, 170]. Later seizure onset is associated with better cognitive outcome however this can be normal for patients with onset at any age with both PDE and P5PD, emphasising the importance of early and adequate treatment[171]. Seizure relapse may occur during febrile illnesses and treatment doses of pyridoxine may be doubled at these times[168]. Withdrawal of pyridoxine leads to a recurrence of seizures therefore treatment should be lifelong with dose adjustments as needed. Chronic use of pyridoxine may result in peripheral neuropathy but this is rare if doses do not exceed 200mg/d and can be monitored through testing deep tendon reflexes and nerve conduction studies[172]. People with P5PD may be exquisitely sensitive to dosing and timing of PLP with some benefiting from multiple doses per day.

Cirrhosis of the liver has been reported in P5PD and surveillance for this association is appropriate[173].

*Seizure Types:*

Seizures may manifest antenatally as excessive fetal movements and typically present in the first hours to days of life. Infants may be acidotic and hypotonic however seizures may manifest as frequent, at times continuous, multifocal myoclonus affecting limbs, trunk, eyes and facial muscles. A variety of seizure types may occur including focal seizures, spasms and generalised tonic and clonic seizures[168]. The semiology of a hyperkinetic, seemingly distressed and agitated infant with multifocal myoclonus and spasms should alert the clinician to the possibility of PDE or P5PDE. In older infants, presentation may be with febrile or febrile generalised tonic clonic seizures, status epilepticus or clusters of focal seizures. If doses of PLP are missed or not tolerated during vomiting illnesses, patients with P5PD may present with semiology suggesting occipital network involvement,

including coloured lights, ictal blindness and darting eye movements. Presentation with infantile spasms later in infancy is rare but has been reported in PDE[174]. The wide variety of seizure types at presentation necessitates that P5PD and PDE are considered in all infants with drug-resistant seizures in infancy. Some children with PDE may be partially responsive to anti-seizure medications.

*EEG:*

EEG in PDE and P5PD in neonates with severe encephalopathy prior to treatment can show a burst-suppression pattern. In other cases, focal or multifocal discharges may be seen against a background of slow rhythms. If pyridoxine is given intravenously to an encephalopathic patient (ideally this should be done under EEG control), it must be done in a setting where the child can be intubated for respiratory support should treatment cause an apnoea. A burst suppression EEG or EEG with multifocal sharp or spike complexes can become diffusely suppressed following pyridoxine administration and may take many hours or days to return to show normal background rhythms. Hypsarrhythmia has been reported in 1 out of 30 patients in one series[164].

*Neuroimaging:*

Neuroimaging may be normal but in both PDE and P5PD over half of patients have MRI abnormalities. These including white matter oedema in severely encephalopathic cases[164, 166]. Intraventricular haemorrhage, ventricular dilatation and corpus callosum hypoplasia can lead to misdiagnosis of a structural aetiology for the epilepsy[164].

*Genetics:*

Most cases of PDE are associated with biallelic variants in *ALDH7A1* also known as antiquitin (PDE-*ALDH7A1*) with a minority associated with biallelic variants in *PLBP* (previously known as *PROSC*)[167, 170, 175]. Pyridox(am)ine 5' phosphate deficiency is associated with biallelic variants in the *PNPO* gene[175]. The disorder previously termed folinic acid responsive epilepsy is a form of PDE associated with variants in *ALDH7A1* and has a better response to pyridoxine than folinic acid alone[87]. If a single pathogenic variant is identified, in the appropriate clinical context, then multiplex ligation probe amplification (MLPA) and chromosomal microarray should be undertaken to identify intragenic or whole gene deletions or duplications involving the relevant gene on the other allele. If variants of uncertain significance are identified metabolic investigations will help in assessment of pathogenicity. Antenatal genetic testing and maternal treatment with pyridoxine should be considered in subsequent pregnancies.

*Metabolic Testing:*

The biomarkers α-aminoadipic semialdehyde (αAASA) and pipecolic acid are elevated in urine, plasma and CSF[168]. Ideally urine and plasma samples should be taken prior to treatment with pyridoxine, however this should not delay therapy in suspected cases[172]. Following treatment these biomarkers may be reduced but typically remain elevated. α-AASA is considered the more reliable test. With the use of biomarkers and gene testing, withdrawal of therapy as a diagnostic test is now obsolete.

### c. *CDKL5*-DEE (Table 12)

*CDKL5*-DEE, also known as *CDKL5* deficiency disorder, is a DEE that is the result of mutations in the cyclin-dependent kinase like 5 (*CDKL5*) gene. It is an important cause of very early-onset epilepsy (median age 6 weeks) with pronounced hypotonia. The combination of clusters of infantile spasms and tonic seizures in the first few months of life is characteristic but multiple seizure types can occur. Seizures often have multiple phases, with a classical hypermotor-tonic-spasms sequence. Severe global delay is present in essentially all cases.

*Epidemiology:*

*CDKL5*-DEE is rare, with estimated incidence of between 1/40,000-1/60,000 live births[38, 176, 177]. This disorder is X-linked and females outnumber males by a ratio of 4:1[178, 179].

*Clinical Context:*

The median age of seizure onset is 6 weeks, and 90% of cases have onset before 3 months[180, 181]. Developmental concerns are typically present at the time of seizure onset but become more pronounced with time. True regression is rare[178].

Neurological examination shows diffuse hypotonia but normal head circumference at onset[17, 178]. Cortical visual impairment, with poor eye contact and lack of visual tracking is common[178]. Subtle dysmorphic features with deep set eyes, broad forehead, prominent lips, deep philtrum, puffy phalanges with tapered fingers have also been described[178].

*Course of Illness:*

Epilepsy typically remains pharmaco-resistant and most cases are left with severe intellectual disability. Most patients continue to have daily seizures, although occasional periods of seizure freedom up to 2 months or longer are seen in less than half of cases[178]. Independent walking and ability to speak single words is achieved in less than one quarter of cases[178]. Movement disorders including choreoathetosis, akathisia, dystonia and parkinsonism can affect a minority of patients[178]. Males are typically more severely affected.

*Seizure Types:*

The initial seizure type can vary, but are most commonly tonic seizures, spasms, generalized tonic clonic seizures or focal seizures are seen[179].

Over time, other seizure types can occur. The majority will have epileptic spasms and/or tonic seizures.

One characteristic seizure type, seen in many but not all cases, are hypermotor-tonic-spasms sequence seizures[182]. The first part of this seizure begins with a hypermotor phase with rocking, kicking, and vocalization which lasts 10–60 seconds. This is followed by a tonic phase, either with extension of all limbs or extension of the upper limbs and flexion of the lower limbs lasting 20–45 seconds. The seizure evolves to a series of extensor spasms which lasts 1–15 minutes. Similar seizures which involve multiple phases with clustering of tonic seizures and spasms, but with variety in the order, are common[179]. Autonomic features are commonly seen with the above seizures, with facial flushing, pupillary dilation and irregular respirations.

Myoclonic, clonic, absence and atonic seizures may be seen with time.

Characteristically, the epilepsy associated with *CDKL5*-DEE follows 3 successive stages[183]:

Stage 1: Early epilepsy onset with brief tonic seizures, often with facial flushing.

Stage 2: Epileptic encephalopathy with tonic seizures and infantile spasms.

Stage 3: Late multifocal and myoclonic epilepsy with tonic seizures, myoclonia, absences or multifocal seizures.

*EEG:*

In Stage 1, the interictal EEG is typically normal but ictal recordings show generalized attenuation followed by fast activity in frontal or central head regions during the tonic seizure[183]. A burst-suppression pattern is not seen in this stage.

In Stage 2, the interictal EEG is severely abnormal, showing either a modified hysarrhythmia pattern, or bilateral or generalized slowing with spikes or polyspikes[183]. A burst-suppression pattern has rarely been reported in this stage[184].

In Stage 3, the interictal recording shows diffuse, high-amplitude delta slowing with pseudo-periodic bursts of spikes, polyspikes and spike-wave complexes that are maximal in the central, temporal or temporal-occipital regions[183].

*Genetics:*

A pathogenic or likely pathogenic variant in the *CDKL5* gene, is required to confirm the diagnosis of *CDKL5*-DEE and multiple variants have been reported in affected individuals. There is limited data on genotype-phenotype correlation; however missense variants may correlate with a slightly less severe disorder than truncating variants[178].

**d. *PCDH19* Clustering Epilepsy (Table 13)**

*PCDH19* Clustering Epilepsy is an X linked disease, predominantly seen in females, caused by pathogenic variants in the *PCDH19* gene. Epilepsy onset is around the first year of life (mostly during the first 3 years) and the most characteristic feature is clusters of seizures typically induced by fever. Intellectual disability and psychiatric symptoms are reported in about two-thirds of cases. The severity of the phenotype seems to be correlated with the age of epilepsy onset[21, 185].

*Epidemiology*:

Data on incidence is limited but one study reports an estimated incidence of 1 in 42,000 live births[38]. Large cohorts of females with seizure clusters triggered by fever show rates of *PCDH19* mutations ranging from 2% to 20%[21].

*Clinical context:*

Seizures typically onset before one year of age, with a mean age of 10 months (1.5-60 months in females, 5-96 months in males)[20, 186]. Development and neurological examination are normal at seizure onset. Head circumference is normal.

*Course of Illness:*

Seizures occur in clusters which are typically triggered by fever and often pharmaco-resistant. After the first decade, a decrease in the frequency of the seizure clusters generally occurs regardless of the treatment and remission of seizures may occur in at least one quarter, usually in adolescence to mid adulthood[20, 21, 186-188].

A significant risk of intellectual disability and autism spectrum disorder, affecting up to 70%, emerges during the second year of life and often become the most relevant symptoms after the first decade. Behavioral disorders, with prominent hyperactivity and possible psychosis in up to 25% of women are often problematic in adolescence and adults[189].

*Seizure Types*:

At onset, seizures are focal impaired aware with tonic extension of the upper arms, deviation of head and eyes, pallor of the face, expression of fear, and screaming reported in half of the patients[20, 186].

Atypical absences may also be seen[186]. Seizures occur in clusters, often related to fever and status epilepticus has been reported[190].

*EEG*:

Interictal EEG showed slow background activity with rare focal spikes and slow waves that increase in frequency during clusters. With age, background activity may normalize. One third of patients show a photoparoxysmal response and few patients had generalised bursts of spike and waves[20, 186].

Seizures recorded on ictal EEG often arise from temporal regions, but parieto-occipital, frontal or central onset may also be seen. In half of cases, seizures appear focal but are not well lateralized or localized on EEG[20].

*Neuroimaging:*

MRI is typically normal at seizure onset.

*Genetics:*
*PCDH19* pathogenic variants were initially recognized in large pedigrees in which only females were affected by epilepsy and intellectual disability (Epilepsy in Females with Mental Retardation – EFMR). Currently, approximately half of reported cases are *de novo*[21].
Although the *PCDH19* gene is located on Xq22, this condition has an unusual X-linked mode of inheritance typically sparing transmitting males. Only heterozygous female and mosaic males are affected due to presumed cellular interference. Affected males have a similar phenotype (9 cases reported in the literature)[185, 191].

*SMC1A* DEE can mimic PCDH19 clustering epilepsy and can present with prolonged clusters of multiple focal and generalised seizures resistant to antiseizure medication sometimes lasting days. Infants with this disorder have a severe developmental encephalopathy and mild dysmorphic features[192].

*Metabolic and other Lab Studies:*

No consistent metabolic abnormalities are found.

**e. Glucose Transporter 1 Deficiency Syndrome (Glut1DS) (Table 14)**

Glut1DS is a complex neurological disorder associated with a range of neurological symptoms including infantile onset epilepsy, movement disorders and intellectual disability[193, 194]. Epilepsy is the most common presenting feature of Glut1DS and is typically drug-resistant unless treated with the ketogenic diet[195-197]. The syndrome is associated with pathogenic variants in the *SLC2A1* gene encoding the glucose transporter type 1, thus impairing glucose transport across the blood brain barrier[193].

*Epidemiology:*
The estimated incidence of Glut1DS presenting as epilepsy in infancy is 1/24,000 live births however the syndrome as a whole may be more common as individuals may present later in childhood and with symptoms other than epilepsy[38].

*Clinical Context:*
Infants may present with many different seizure types but generalised onset seizures are more common than focal[195, 198]. In any child presenting with epilepsy and a movement disorder Glut1DS should be considered[199]. A history of seizures associated with fasting or in the early morning may be present. Other clues to diagnosis include eye-head gaze saccades (consisting of rapid, multidirectional eye movements, accompanied by head movements in the same direction) in early infancy and microcephaly (present in 50% of cases) or deceleration of head growth[193, 197, 200]. Diagnosis is confirmed by lumbar puncture identifying low CSF glucose with normal or low CSF lactate after a 4-6 hour fast in the context of a normal blood glucose[201]. In Glut1DS, CSF glucose 5th percentile values range from 1.8 - 2.9 mmol/L, and CSF/plasma glucose ratio 5th percentile values range from 0.41 - 0.510. In the presence of a highly typical phenotype with a pathogenic *SLC2A1* variant, a lumbar puncture may not be necessary[197]. In later onset epilepsy associated with GLUT1 deficiency, CSF glucose levels may not be as low[202].

*Course of Illness:*
Seizures vary in frequency from multiple per day to only a few per year and are resistant to antiseizure medications. In general seizure frequency tends to decline later in childhood and adult life where intellectual disability, movement disorders and migraine may be the predominant features[197, 203]. Ketogenic diet with adequate ketosis may completely control seizures. While this therapy may ameliorate further cognitive decline, many patients are still left with variable degrees of intellectual disability.

*Seizure Types:*

Generalised seizures are typically myoclonic, myoclonic-atonic, generalised tonic-clonic or atypical or early onset absences. Early onset absences (less than age 4 years), often seen with a myoclonic component, should be investigated by lumbar puncture and genetic testing[204]. Additionally, this disorder should be considered in persons with myoclonic-atonic epilepsy or drug-resistant absence epilepsy, particularly if cognitive concerns are present. Epileptic spasms and generalised tonic clonic status epilepticus have also rarely been reported[38].

*EEG:*

Interictal EEG is often normal. There is some evidence for age-specific changes with focal or generalised slowing of background rhythms in infancy with or without intermittent focal or generalised spike and wave. In children older than 2 years generalised 2.5-4 Hz spike-wave is seen[205]. In some cases pre-prandial EEG abnormalities may be improved during the recording by feeding as glucose crosses the blood-brain barrier and EEG background rhythms may be less abnormal on the ketogenic diet (Figure 9)[206].

*Neuroimaging:*

Approximately 25% of patients have neuroimaging abnormalities including hyperintensity of subcortical U-fibers, prominence of perivascular Virchow spaces, prominent ventricles and delayed myelination for age[193, 207, 208]. 18F-deoxyglucose positron emission tomography may show a specific imaging signature including reduced signal from cerebral cortex, cerebellum and thalamus with apparent increased glucose in the striatum[209].

*Genetics & other investigations:*

Gene sequence analysis identifies heterozygous and less commonly recessive pathogenic variants in *SLC2A1* in 81-89% of cases[193]. Another 11-14% of cases with deletions or duplications in the gene may be identified by multiplex-ligation probe amplification and chromosomal microarray[193]. With a highly suspicious clinical phenotype, but nondiagnostic lumbar puncture and genetic testing, other investigations including erythrocyte uptake tests and measurement of GLUT-1 on surface of red blood cells should be considered[209, 210].

**f. Sturge-Weber syndrome (Table 15)**

Sturge-Weber syndrome (SWS) is a congenital neurocutaneous syndrome defined by the association of a facial capillary malformation named port-wine birthmark (PWB) with ipsilateral leptomeningeal angioma and frequent ipsilateral glaucoma. It is caused by somatic activating mutations in the guanine nucleotide-binding protein alpha-q (*GNAQ*) gene[211]. The prognosis of SWS is highly variable and related to the potential complications that develop often in early childhood, including epilepsy, focal neurological deficits and glaucoma[212]. The diagnosis is confirmed by brain imaging showing direct or indirect evidence of the leptomeningeal angioma.

*Epidemiology:*

Patients with a facial port wine stain on the forehead and/or the upper eyelid have an estimated risk of 20-70% of developing SWS[213, 214].

*Clinical context:*

The diagnosis of SWS is suspected at birth in newborns presenting a facial port wine stain covering the forehead and/or the upper eyelid. Careful examination under the hairline is important to detect more subtle lesions. Contrast-enhanced MRI can detect the leptomeningeal angioma before 3 months of age[215]. Rarely, the facial angioma may be absent[216].

Seizures are usually the first manifestation, affecting 75 to 85% of patients at a median age of 6 months[217]. Rare cases with onset of seizures in adulthood have also been reported[217].

In addition to epilepsy, 40 to 60% of SWS patients will develop glaucoma with the risk of early visual impairment[217].

*Course of Illness:*

Natural history is highly variable but typically marked by a progressive course with age-dependent neurological manifestations. Early manifestations during infancy include epilepsy, hemiparesis, psychomotor delay and stroke-like events. Later signs and symptoms at school age include headaches, academic difficulties, and behavioral problems. In adulthood, psychiatric disorders including depression can be significant and epilepsy and stroke-like events can continue throughout life.

Early seizure onset (before age 12 months), high seizure frequency and pharmaco-resistance are the most reliable predictors of poor outcome[217, 218]. Extensive unilateral or bilateral intracranial involvement is associated with earlier onset of seizures and worse cognitive development compared to unilateral leptomeningeal angioma[219]. Presurgical evaluation should be considered in patients with unilateral disease who are drug resistant[220].

*Seizures:*

The first seizures are usually focal motor[221]. Focal autonomic seizures with variable degrees of impaired awareness are also frequent[222]. Seizures can be subtle, and their prompt recognition is important as prolonged seizures and status epilepticus can occur frequently[221]. About 30% of cases may have onset of seizures during febrile episodes and there is an increased susceptibility for fever-induced seizures at any age in most patients[221]. Infantile spasms, myoclonic atonic seizures and gelastic seizures have also been reported[223]. Seizure clustering following a prolonged period of seizure freedom is common (40% of cases)[222, 223].

Due to the high incidence of early-onset seizures and their potential deleterious effects on the developing brain, parental education in early seizure recognition and individualized emergency plans including the use of rescue benzodiazepine therapy is recommended[224].

*EEG:*

The EEG characteristically shows asymmetric reduction in voltage and slowing of the background over the affected hemisphere (Figure 10)[225]. The background might be however normal during the first year of life.

Interictal epileptiform abnormalities may appear later and consists of focal sharp waves or frequent spike-wave bursts[225]. Such interictal epileptiform abnormalities before seizure onset might be a useful marker to identify patients with SWS at risk of developing epilepsy[226].
Ictal activity varies depending on seizure focus.

*Neuroimaging:*
Contrast-enhanced, cerebral MRI confirms the diagnosis of SWS by the direct visualization of leptomeningeal enhancement. Detection can be challenging in very young infants. Other indirect imaging features such as ipsilateral choroid plexus enlargement, enlarged transmedullary veins and T2 shortening of the white matter can help establish the diagnosis[215]. Cortical calcifications and cerebral atrophy appear over time.

*Genetics:*
Isolated port wine stain and SWS have a common genetic etiology with a somatic mosaic mutation that has been recently identified in the guanine nucleotide-binding protein alpha-q (*GNAQ*) gene[211].

g. **Gelastic Seizures with Hypothalamic Hamartoma (Table 16)**

Hypothalamic hamartomas are very rare, congenital, non-neoplastic lesions which are characteristically associated with gelastic (mirthless laughter) or, less commonly, dacrystic (crying) seizures that typically begin in infancy or early childhood. Other seizure types including focal impaired awareness or various generalized seizures may evolve, and with time, there is progressive cognitive plateauing or regression, and progressive behavioral abnormalities including impulsiveness and aggression. Precocious puberty is present in some cases. Seizures remain drug resistant but may improve significantly with surgical intervention. Early surgical therapy should be considered for seizure control and to prevent progressive cognitive and behavioral decline.

*Epidemiology:*
A single study in Sweden documented a prevalence of hypothalamic hamartoma with gelastic seizures of 0.5 per 100,000 in children less than 20 years of age[227].

*Clinical Context:*
Onset is in the first year of life in approximately 85% of cases[228]. A minority of cases can begin in early to mid-childhood[227, 229]. There is no sex predisposition. Neurological examination is normal however general physical examination may reveal features of precocious puberty.

*Course of Illness:*
Epilepsy due to hypothalamic hamartoma is typically drug resistant. There is progression over time in most cases, with development of focal impaired awareness and generalized seizures[230, 231]. Some patients may develop tonic, atonic or atypical absences suggestive of Lennox-Gastaut syndrome. Surgical therapy targeting the hypothalamic hamartoma can mitigate this unfavorable evolution.

Cognition is typically normal at seizure onset, but over time, developmental plateauing or regression is usually seen. Children can also develop progressive behavioral problems including aggression, impulsivity, hyperactivity and autism spectrum disorder.

*Seizure types:*

Gelastic seizures are the distinctive seizure type and mandatory for diagnosis. They are seen at epilepsy onset, and are brief, typically lasting less than one minute. They consist of mechanical, mirthless laughter, inappropriate to context. Awareness is often not impaired and postictal confusion is absent. Seizure frequency is high, typically multiple per day, and seizures may cluster.

Seizures with smiling alone, but without distinctive mirthless laughter are not gelastic seizures.

Dacrystic seizures, characterized by stereotypic lacrimation, and sobbing, grimacing or yelling, inappropriate to context may also be present. The combination of gelastic and dacrystic seizures in the same patient is particularly suggestive of a hypothalamic hamartoma. Other seizure types which can occur include focal seizures with frontal or temporal lobe semiology and rarely, epileptic spasms. Later in childhood, tonic and drop attacks, as well as atypical absences, may develop.

*EEG:*

The background is usually normal. Interictal discharges typically appear after infancy and initially are most commonly seen in the temporal regions, although focal spikes from any region may be present. Children with infantile spasms may show a hypsarrhythmia pattern[232].

By later childhood, generalized slow spike-wave, or generalized spike or spike-wave can occur, in addition to focal or multifocal discharges.

Ictal recordings of gelastic seizures may show no change, or alternatively may show subtle and nonspecific changes, such as decrease in amplitude, or reduction in frequency of interictal spikes. On scalp recording, seizures may appear to localize to the temporal or frontal region. However, depth electrodes in the hamartoma will confirm it as the focus of ictal onset[228, 233], and thus surgery should target the hamartoma, as opposed to focal temporal or frontal resection. By later childhood, patients with generalized seizure types will show generalized ictal onset.

*Neuroimaging:*

MRI shows a pedunculated or sessile lesion that lies between the infundibular stalk anteriorly and the mammillary bodies posteriorly[234]. The lesions are typically isointense to slightly hypointense to grey matter on T1-weighted studies, and hyperintense on T2 weighted studies. They usually do not enhance with contrast. In cases of suspected gelastic seizures, thin slices through the hypothalamic region should be obtained.

*Genetics:*

Most cases are sporadic. However, approximately 5% of cases have Pallister Hall syndrome with a *GL13* pathogenic variant[235].

*Differential diagnosis:*

- Gelastic seizures are not always associated with hypothalamic hamartomas but may arise from other foci (most commonly temporal and frontal). In patients without hypothalamic hamartomas, an epilepsy protocol MRI should be obtained to evaluate for other structural lesions.
- Complex stereotypies
- Infantile self-gratification

**Discussion**

In defining epilepsy syndromes in neonates and infants, we focus on the electroclinical picture, with careful descriptions of seizure type(s), significant antecedent factors, neurological examination, associated comorbidities, and the interictal and ictal EEG pattern. We hope that this classification will be relevant to all clinicians, regardless of health care resources. Although the proportion of infants with known etiologies is expanding, many are still left with unknown cause, but still fulfil criteria for an epilepsy syndrome, which provides physicians and families guidance regarding optimal therapies, comorbidities and prognosis.

The concept of an epilepsy syndrome was defined in the 1985 and 1989 Classifications of the Epilepsies, however specific syndromes were recognized well before that time. The initial description of West syndrome was published in *the Lancet* in 1841, describing the characteristic clusters of flexor spasms and cognitive decline in Dr. West's own son[236]. Early infantile epileptic encephalopathy with suppression-burst was described by Shunsuke Ohtahara and colleagues in 1976, and was also termed Ohtahara syndrome[78]. Charlotte Dravet and colleagues first described severe myoclonic epilepsy of infancy in 1978, which is now called Dravet syndrome[135]. This syndrome is the prototype of monogenic developmental and epileptic encephalopathy.
The Nosology Task Force wished to move away from eponymous names, with some exceptions. We elected to maintain a few syndromes, including Dravet syndrome, due to the ubiquitous use of this term in research, ongoing precision clinical trials and orphan drug designation and registration.
In general, we propose using transparent terms that describe the clinical condition, such as Infantile Spasms Syndrome. By defining the syndrome by the characteristic seizure type, our aim is to enable early diagnosis and appropriate treatment. Many infants do not fulfil the full triad of West syndrome, as they may lack hypsarrhythmia or regression. There is electroclinical overlap between Ohtahara syndrome and Early Myoclonic Encephalopathy, with both syndromes sharing genetic and structural etiologies. In addition, many infants do not meet criteria for either syndrome, highlighting the broad spectrum of presentations within early-infantile DEE. Thus, our Task Force merged both entities into one syndrome called Early-Infantile DEE.

We aligned our nomenclature with the previous classification efforts[1]. Syndrome names which contained terminology such as severe (severe myoclonic epilepsy in infancy), malignant (malignant migrating partial seizures in infancy) and benign (benign neonatal seizures) were changed to align with the most recent Classification[1]. Similarly, the term "partial seizures" was replaced by "focal seizures". To avoid any confusion between seizure types and epilepsy syndrome, we replaced the term "convulsions" with "epilepsies" in some syndromes such as Self-Limited Neonatal Epilepsy. Furthermore, as only family history differentiates between Familial and Non-familial Self-limited Neonatal and Infantile Epilepsies, we merged these together using the

term “Self-limited (Familial) Neonatal Epilepsy”, “Self-limited (Familial) Neonatal-Infantile and “Self-limited (Familial) Infantile Epilepsy”, which allows the term “familial” to be used where appropriate.

Finally, we introduce the concept of Etiology-Specific Syndromes for certain genetic and structural etiologies. Gene discoveries have allowed delineation of new electro-clinical syndromes, such as *PCDH19* Clustering Epilepsy and *CDKL5*-DEE. Etiology-specific syndromes inform rapid diagnosis, optimization of medical care and ensure readiness for precision medicine trials. Given the devastating consequences of many infantile epilepsies, prompt etiological diagnosis offers the hope that novel precision therapies will improve the long-term prognosis. Progress in this area relies not only on advances in genetics, imaging and immunology, but also requires clinicians to carefully phenotype electroclinical and developmental features and long-term outcome in children with early-life epilepsies.

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**Table 1: Diagnostic Criteria for Self-Limited (Familial) Neonatal Epilepsy**

| | **Mandatory** | **Alerts** | **Exclusionary** |
|---|---|---|---|
| Seizures | Focal clonic or focal tonic seizures which may alternate sides from seizure to seizure, which may evolve to bilateral tonic-clonic seizures | Clinical history suggestive of in-utero seizures | Epileptic spasms<br>Myoclonic seizures<br>Generalized tonic seizures<br>Generalized tonic-clonic seizures |
| EEG | | Mild background slowing | Persistent focal slowing or moderate or greater background slowing not limited to the postictal period<br>Burst suppression pattern<br>Hypsarrhythmia<br>Lack of EEG correlate with clinical symptoms |
| Age at onset | | | Onset after first month of age |
| Development at onset | | | Any degree of encephalopathy |
| Neurological exam | | Significant neurological examination abnormalities, excluding incidental findings (see text) | |
| Imaging | | | Neuroimaging documenting a causal lesion for seizures |
| Other studies – genetics, etc | | Lack of pathogenic variant in gene associated with this syndrome, most commonly KCNQ2 or KCNQ3<br>OR<br>Lack of family history suggesting AD inheritance with incomplete penetrance | Other acute symptomatic cause of seizures including intracranial infection, ischemic or hemorrhagic stroke, hypoxic-ischemic brain injury, significant metabolic disturbances |
| Course of illness | | *Mild neurodevelopmental delay long-term*<br>*Lack of remission of epilepsy after 6 months of age*<br>*Drug resistant epilepsy* | *Moderate to severe neurodevelopmental disability* |
| **Are MRI or ictal EEG required for diagnosis?**<br><br>A non-lesional MRI is required to diagnose this syndrome<br><br>An ictal EEG is not required for diagnosis | | | |
| **Syndrome without laboratory confirmation:** In resource-limited regions, SeLNE can be diagnosed without EEG and MRI in a neonate with a family history suggestive of familial SeLNE who meets all other mandatory and exclusionary clinical criteria and has no Alerts. However, the clinical history of affected family members should be consistent with the expected course for SeLNE, and careful follow-up of the patient is required to ensure their course is also consistent with this syndrome. | | | |

**Table 2: Diagnostic Criteria for Self-Limited (Familial) Neonatal-Infantile Epilepsy**

| | Mandatory | Alerts | Exclusionary |
|---|---|---|---|
| Seizures | Focal clonic or focal tonic seizures which may alternate sides from seizure to seizure, and may evolve to bilateral tonic-clonic seizures | Sequential seizures | Epileptic spasms<br>Myoclonic seizures |
| EEG | | Mild background slowing | Persistent focal slowing or moderate or greater background slowing not limited to the postictal period<br>Burst suppression pattern<br>Hypsarrhythmia<br>Lack of EEG correlate with clinical symptoms |
| Age at onset | 1 day to 23 months | | |
| Development at onset | | | Encephalopathy |
| Neurological exam | | Significant neurological examination abnormalities, excluding incidental findings (see text) | |
| Imaging | | | Neuroimaging documenting a causal lesion for seizures |
| Other studies – genetics, etc | | A history of prior acute symptomatic seizures including intracranial infection, ischemic or hemorrhagic stroke, hypoxic-ischemic brain injury, significant metabolic disturbances<br><br>Lack of pathogenic variant in genes associated with this syndrome (usually *SCN2A)* | |
| Course of illness | | *Mild neurodevelopmental delay long-term*<br>*Lack of remission of epilepsy by age 2 years*<br>*Drug resistant epilepsy* | *Moderate to severe neurodevelopmental disability* |
| **Are MRI or ictal EEG required for diagnosis?**<br><br>A non-lesional MRI is required to diagnose this syndrome.<br><br>An ictal EEG is not required for diagnosis. | | | |
| **Syndrome without laboratory confirmation:** In resource-limited regions, Self-limited neonatal-infantile epilepsy can be diagnosed without EEG and MRI in a neonate with a family history suggestive of familial self-limited neonatal-infantile epilepsy who meets all other mandatory and exclusionary clinical criteria and has no Alerts. However, the clinical history of affected family members should be consistent with the expected course for SeLNIE, and careful follow-up of the patient is required to ensure their course is also consistent with this syndrome. | | | |

**Table 3: Diagnostic Criteria for Self-Limited (Familial) Infantile Epilepsy**

| | Mandatory | Alerts | Exclusionary |
|---|---|---|---|
| Seizures | Focal seizures occur with behavioural arrest, impaired awareness, automatisms, head/eye version, and clonic movements (often alternating from one side to the other and progressing to a hemiclonic or focal to bilateral tonic-clonic seizure). Seizures are usually brief (<3 minutes). | Prolonged or focal hemiclonic seizures (>10 minutes) | Epileptic spasms<br>Myoclonic seizures<br>Sequential seizures<br>Tonic seizures |
| EEG | | Mild background slowing | Persistent focal slowing or moderate or greater background slowing not limited to the postictal period<br><br>Hypsarrhythmia |
| Age at onset | | Onset 18-36 months of age | Age at onset <1 month or >36 months |
| Development at onset | | Mild developmental delay | Moderate to profound delay<br>Neurocognitive regression |
| Neurological exam | | Significant neurological examination abnormalities, excluding incidental findings (see text) | |
| Imaging | | | Causal lesion on brain MRI |
| Other studies – genetic, etc | | Lack of pathogenic variants found in PRRT2, SCN2A, KCNQ2 or KCNQ3<br>OR<br>Lack of family history suggesting AD inheritance with incomplete penetrance | |
| Course of illness | | *Lack of remission by late childhood* | *Neurocognitive regression with myoclonic seizures, ataxia, spasticity* |
| **Are MRI or ictal EEG required for diagnosis?**<br><br>A non-lesional MRI is required to diagnose this syndrome.<br><br>An ictal EEG is not required for diagnosis. | | | |
| **Syndrome without laboratory confirmation:** In resource-limited regions, SeLIE can be diagnosed without EEG and MRI in an infant with a family history suggestive of familial SeLIE who meets all other mandatory and exclusionary clinical criteria and has no Alerts. However, the clinical history of affected family members should be consistent with the expected course for SeLIE, and careful follow-up of the patient is required to ensure their course is also consistent with this syndrome. | | | |

**Table 4: Diagnostic Criteria for Febrile Seizures Plus**

| | Mandatory | Alerts | Exclusionary |
|---|---|---|---|
| Seizures | Febrile seizures persisting after 6 years of age and/or afebrile seizures | Prolonged Febrile seizures | Epileptic spasms |
| EEG | Normal background | | |
| Age at onset | | Age at onset prior to 6 months | |
| Development at onset | | Abnormal development at onset | |
| Neurological exam | | Significant neurological examination abnormalities, excluding incidental findings | |
| Imaging | | | Causal lesion on brain MRI |
| Other studies – genetic, etc | | Absence of familial history of GEFS+ (although in some cases, obtaining an accurate family history may be challenging) | Seizures due to other acute causes such as infection, metabolic disturbances |
| Course of illness | | *Drug resistant seizures*<br>*Lack of remission by puberty* | *Cognitive Regression* |
| **Are MRI or ictal EEG required for diagnosis?**<br><br>An MRI is not required for diagnosis.<br><br>An ictal EEG is not required for diagnosis. | | | |
| **Syndrome without laboratory confirmation:** In resource-limited regions, Febrile seizures Plus can be diagnosed without EEG and MRI provided the patient meets all other mandatory and exclusionary clinical criteria and has no Alerts. | | | |

**Table 5: Diagnostic Criteria for Myoclonic Epilepsy in Infancy**

| | Mandatory | Alerts | Exclusionary |
|---|---|---|---|
| Seizures | Myoclonic seizures (see text) | Afebrile generalized tonic-clonic seizure or generalized clonic at time of epilepsy onset | Any of the following seizure types:<br>• Absence seizures<br>• Atonic seizures<br>• Epileptic spasms<br>• Focal impaired awareness seizures<br>• Hemiconvulsive seizures<br>• Myoclonic-absence seizures<br>• Tonic Seizures |
| EEG | Normal background | PPR at low frequency photic stimulation (suggest CLN2 disease)<br><br>Lack of generalized spike-wave discharge on sleep recording | Recorded myoclonic event without EEG correlate<br><br>Hypsarrhythmia<br><br>Generalized slow spike-wave (<2.5 Hz) |
| Age at onset | | | Age at onset of myoclonic seizures ≤4 months or >3 years |
| Development at onset | | Speech delay at time of diagnosis<br>Moderate to profound ID | |
| Neurological exam | | Significant neurological examination abnormalities, excluding incidental findings (see text) | Dysmorphism or other congenital anomalies (suggests chromosomal disorder) |
| Imaging | | | Significant neuroimaging abnormalities |
| Other studies – genetics, etc | | | Low CSF glucose or pathogenic SLC2A1 variants |
| Course of illness | | | *Neurocognitive regression* |
| **Are MRI or ictal EEG required for diagnosis?**<br><br>A non-lesional MRI is required for diagnosis.<br><br>An ictal EEG is not required for diagnosis but should be strongly considered if the interictal sleep recording does not show generalized spike-wave to confirm that myoclonus is epileptic. | | | |
| **Syndrome without laboratory confirmation:** In resource-limited regions, at a minimum, a sleep EEG showing generalized spike-wave is required to make this diagnosis. | | | |

**Table 6: Diagnostic Criteria for Early Infantile Developmental and Epileptic Encephalopathy**

| | Mandatory | Alerts | Exclusionary |
|---|---|---|---|
| Seizures | Tonic and/or myoclonic seizures | | |
| EEG | Either burst suppression or multifocal discharges<br><br>Diffuse slowing | | |
| Age at onset | Birth to 3 months (adjusted for prematurity) | | |
| Development at onset | | Normal development at onset, although it is acknowledged that this can be challenging to accurately assess historically | |
| Neurological exam at onset | | Normal neurological examination, although it is acknowledged that this can be challenging to assess historically or in an infant who has had very frequent seizures and/or received ASMs that may alter their exam. | |
| Early Comorbidities | Developmental impairment is present prior to or shortly after seizure onset | | |
| Course of illness | *Abnormal neurodevelopment including intellectual disability (see text)* | | |
| **Are MRI or ictal EEG required for diagnosis?**<br><br>An MRI is not required for diagnosis but is strongly recommended to exclude structural causes.<br><br>An ictal EEG is not required in an infant with characteristic clinical features where the interictal EEG shows burst-suppression, multi-focal discharges with diffuse slowing. | | | |
| **Syndrome without laboratory confirmation:** In resource-limited regions, this syndrome cannot be diagnosed without an interictal EEG. | | | |

**Table 7: Diagnostic Criteria for Epilepsy of Infancy with Migrating Focal Seizures**

| | **Mandatory** | **Alerts** | **Exclusionary** |
|---|---|---|---|
| Seizures | Focal/multifocal tonic or clonic seizures, with or without subtle behavioral arrest and prominent autonomic features<br><br>Seizures migrate from one hemisphere or lobe to another clinically.<br><br>Seizure frequency rapidly increases in the first weeks and months, often progressing to status epilepticus | | Myoclonic seizures |
| EEG | Ictal recording shows a migrating pattern (this might be missed if a prolonged video EEG is not performed)<br><br>Multifocal discharges | Suppression burst pattern prior to medication<br><br>Single persistent epileptic focus on EEG<br><br>Hypsarrhythmia | |
| Age at onset | <12 months | Onset 6-12 months | |
| Development at onset | | Severe delay prior to seizure onset | |
| Neurological exam | | Significant abnormalities on neurological examination prior to seizure onset | |
| Comorbidities | Developmental plateauing or regression with frequent seizures | | |
| Imaging | | | Abnormal neuroimaging with structural causal lesion |
| Course of illness | *Neurodevelopmental delay* | *Seizure freedom*<br><br>*Lack of brain atrophy on MRI* | |
| **Are MRI or ictal EEG required for diagnosis?**<br><br>An MRI is required for diagnosis to exclude a causal structural etiology.<br><br>An ictal EEG may not be required if clinical migration is observed. However, an ictal EEG is strongly recommended to document a migrating pattern. | | | |
| **Syndrome without laboratory confirmation:** In resource-limited regions, EIMFS can be diagnosed on clinical observation of seizure migration without EEG or MRI, provided all other clinical mandatory and exclusionary criteria are met. | | | |

**Table 8: Diagnostic Criteria for Epilepsy of Infantile Spasms Syndrome**

| | Mandatory | Alerts | Exclusionary |
|---|---|---|---|
| Seizures | Clusters of flexor, extensor or mixed epileptic spasms | | |
| EEG | Either hypsarrhythmia, multifocal or focal epileptiform discharges | Normal interictal EEG<br><br>Suppression-burst pattern on EEG | Normal EEG during recorded clinical events of suspected spasms |
| Age at onset | 1-24 months (while epileptic spasms may begin later, this would not be ISS) | Age at onset 1-2 months | |
| Comorbidities | Developmental slowing after spasm onset | | |
| **Are MRI or ictal EEG required for diagnosis?**<br><br>An MRI is not required for diagnosis but is highly recommended to evaluate for underlying cause.<br><br>An ictal EEG is not required for diagnosis provided the interictal study shows hypsarrhythmia. In the absence of hysparrhythmia, an ictal recording is required. | | | |
| **Possible evolving syndrome**: Infants with preceding brain injury, developmental brain malformations or specific genetic conditions, including early-infantile DEE, who show significant interictal EEG abnormalities (high amplitude, background slowing and/or multifocal discharges) should be carefully watched for the development of clinical epileptic spasms. However, the syndrome of ISS cannot be diagnosed prior to onset of the mandatory seizure type. | | | |
| **Syndrome without laboratory confirmation**: In resource-limited regions**,** an interictal EEG is highly recommended. However, if EEG is unavailable, if clear clusters of typical epileptic spasms are witnessed by an experienced clinician (in person or on video recording), with the other clinical mandatory and exclusionary criteria, ISS can be diagnosed. | | | |

**Table 9: Diagnostic Criteria for Dravet Syndrome**

| | Mandatory | Alerts | Exclusionary |
|---|---|---|---|
| Seizures | Recurrent hemiclonic seizures (which often alternate sides from seizure to seizure), focal to bilateral tonic-clonic and/or generalized tonic clonic seizures | No history of prolonged seizures (>10 minutes)<br><br>Lack of fever sensitivity as a seizure trigger | Epileptic spasms<br>Early infantile SCN1A DEE |
| EEG | | Normal EEG background without interictal discharges after age 2 years | |
| Age at onset | 1-20 months | 1-2 months or 16-20 months | |
| Development at onset | | Developmental delay at seizure onset | |
| Neurological exam | | Focal neurological findings (other than Todds paresis) | |
| Imaging | | | MRI showing a causal focal lesion |
| Other testing: ie genetics etc | | Lack of pathogenic *SCN1A* or other causal variant | |
| Course of illness | *Drug resistant epilepsy*<br>*Intellectual disability* | *Good efficacy with prophylactic sodium-channel agents including carbamazepine, oxcarbazepine and phenytoin* | |
| **Are MRI or ictal EEG required for diagnosis?**<br><br>An MRI is not required for diagnosis but is highly recommended to exclude other causes.<br><br>An ictal EEG is not required for diagnosis. | | | |
| **Possible evolving syndrome**: In a child <12 months who presents with a prolonged hemiclonic or bilateral tonic-clonic seizure with fever, and no other underlying cause, the possibility of Dravet syndrome should be considered. Further convulsive seizures (often with fever, and if prolonged or hemiclonic) would allow more definitive diagnosis of Dravet syndrome. A diagnosis would be further supported by the finding of a pathogenic *SCN1A* variant. | | | |
| **Syndrome without laboratory confirmation:** In resource-limited regions, Dravet syndrome can be diagnosed in children without Alerts who meet all other clinical mandatory and exclusionary criteria, without EEG, MRI and genetic testing. | | | |

**Table 10: Diagnostic Criteria for *KCNQ2*-DEE**

| | **Mandatory** | **Alerts** | **Exclusionary** |
|---|---|---|---|
| Seizures | Tonic, myoclonic and / or focal seizures | | |
| EEG | Either burst suppression or multifocal discharges; diffuse slowing | | |
| Age at onset | < 3 months | Onset beyond the first week of life (corrected gestational age) | |
| Neurological exam | | Normal neurological examination | |
| Comorbidities | Neurodevelopmental slowing/encephalopathy is apparent at seizure onset | | |
| Other testing: ie genetics etc | Pathogenic variant in *KCNQ2* | | |
| Course of illness | *Abnormal neurodevelopment – with profound to moderate impairment* | | |
| **Are MRI or ictal EEG required for diagnosis?**<br><br>An MRI is not required for diagnosis but is strongly recommended to exclude other causes.<br><br>An ictal EEG is not required for diagnosis. | | | |
| **Syndrome without laboratory confirmation:** In resource-limited regions, *KCNQ2*-DEE cannot be diagnosed without genetic testing. | | | |

**Table 11: Diagnostic Criteria for Early-onset Vitamin-dependent (Pyridoxine/ Pyridox(am)ine 5'-Phosphate) DEE**

| | Mandatory | Alerts | Exclusionary |
|---|---|---|---|
| Seizures | Variable seizure types which may include:<br>• Focal/multifocal seizures<br>• Epileptic spasms<br>• Generalized tonic seizures<br>• Generalized clonic seizures<br><br>Seizures are drug-resistant and frequent (often evolving to status epilepticus) but rapidly respond to pyridoxine (pyridoxine-dependent-DEE) or pyridoxal-5-phosphate (Pyridox(am)ine 5'-Phosphate-DEE) supplementation | | |
| EEG | Abnormal with slowing and focal/multifocal discharges or burst suppression pattern | | |
| Age at onset | | Age >3 years at onset (there are rare, later-onset forms of pyridoxine-dependent epilepsy) | |
| Neurological exam | | Lack of encephalopathy and irritability | |
| Other testing: ie genetics etc | Laboratory testing providing confirmatory evidence, which may include either:<br>1. Metabolic features: Increased α-aminoadipic semialdehyde and/or pipecolic acid in urine, plasma and/or CSF (pyridoxine-dependent-DEE) or low pyridoxal-5-phosphate in CSF (Pyridox(am)ine 5'-Phosphate-DEE)<br>OR<br>2. Genetic features: pathogenic variants in *ALDH7A1* or *PLBP* (pyridoxine dependent-DEE) or *PNPO* gene (Pyridox(am)ine 5'-Phosphate-DEE) | | |
| Course of illness | *Seizures that show sustained marked reduction or cessation with lifelong pyridoxine or pyridoxal-5-phosphate.* | *Normal neurodevelopmental outcome* | |
| **Are MRI or ictal EEG required for diagnosis?**<br><br>An MRI is not required for diagnosis but is strongly recommended to exclude other causes.<br><br>An ictal EEG is not required for diagnosis. | | | |
| **Syndrome without laboratory confirmation:** In resource-limited regions, Pyridoxine or Pyridox(am)ine 5'-Phosphate-DEE can be diagnosed in children without Alerts who meet all other mandatory and exclusionary clinical criteria and whose seizures cease with pyridoxine or P5P supplementation, recur when supplementation is stopped, and cease again with re-introduction of supplementation. | | | |

**Table 12: Diagnostic Criteria for *CDKL5*-DEE**

| | Mandatory | Alerts | Exclusionary |
|---|---|---|---|
| Seizures | Seizures which may include tonic seizures, epileptic spasms, generalized tonic-clonic seizures and/or focal seizures. Hypermotor-tonic-spasms sequence seizures are characteristic but not seen in all cases | Absence of epileptic spasms in the first year of life | |
| EEG | | Normal EEG background without interictal discharges after 4 months of age | |
| Age at onset | | Onset of epilepsy >3 months | |
| Development at onset | | Normal development prior to seizure onset | |
| Neurological exam | | Normal tone<br>Lack of encephalopathy | |
| Other testing: ie genetics etc | Pathogenic variant in the *CDKL5* gene (X-linked but females outnumber males by 4:1) | | |
| Course of illness | *Profound to severe intellectual disability*<br>*Drug resistant epilepsy* | | |
| **Are MRI or ictal EEG required for diagnosis?**<br><br>An MRI is not required for diagnosis but is strongly recommended to exclude other causes.<br><br>An ictal EEG is not required for diagnosis. | | | |
| **Syndrome without laboratory confirmation:** In resource-limited regions, *CDKL5*-DEE cannot be diagnosed without confirmatory genetic testing. | | | |

**Table 13: Diagnostic Criteria for *PCDH19* Clustering Epilepsy**

| | Mandatory | Alerts | Exclusionary |
|---|---|---|---|
| Seizures | Focal seizures (fearful screaming typical) and tonic-clonic seizures, typically in clusters; may be triggered by fever | Prolonged hemiclonic seizures in infancy (consider Dravet)<br>No clustering | |
| EEG | | Absence of epileptiform discharge (which is usually focal, but rarely may be generalized) | |
| Age at seizure onset | 1.5-60 months in females; 5-96 months in males | | |
| Other testing: ie genetics etc | *PCDH19* pathogenic variant: see text regarding unusual inheritance pattern | | |
| **Are MRI or ictal EEG required for diagnosis?**<br><br>An MRI is not required for diagnosis but is strongly recommended to exclude other causes.<br><br>An ictal EEG is not required for diagnosis. | | | |
| **Possible evolving syndrome:** This syndrome should be considered in an infant girl who presents with a first cluster of febrile seizures. | | | |
| **Syndrome without laboratory confirmation**: In resource-limited regions, *PCDH19* clustering epilepsy could be a provisionally diagnosed without confirmatory genetic testing, specifically in the setting of a family history suggestive of X-linked dominant inheritance with male sparing. | | | |

**Table 14: Diagnostic Criteria for GLUT1DS-DEE**

| | Mandatory | Alerts | Exclusionary |
|---|---|---|---|
| Seizures | Seizures which may be focal or generalized, including absence seizures (often beginning before 3 years of age) | | |
| Neurological exam | | Focal neurological findings (other than Todds paresis) | |
| Other testing: ie genetics etc | Pathogenic *SLC2A1* variant<br>OR<br>Low fasting CSF glucose and CSF/plasma glucose ratio* | | Other documented etiology for hypoglycorrhachia |
| Course of illness | *Intellectual disability* | *Seizures that are controlled with medication*<br><br>*Lack of improvement in seizures with ketogenic diet*<br><br>*Lack of movement disorders such as ataxia, paroxysmal exercise-induced dyskinesia, dystonia* | |
| **Are MRI or ictal EEG required for diagnosis?**<br><br>An MRI is not required for diagnosis but is strongly recommended to exclude other causes.<br><br>An ictal EEG is not required for diagnosis. | | | |
| **Syndrome without laboratory confirmation:** In resource-limited regions, GLUT1DS-DEE can be diagnosed without EEG, MRI or genetic studies in children without Alerts who meet all other mandatory and exclusionary clinical criteria. CSF studies are required for diagnosis. | | | |

*CSF glucose may not be as low in later-onset epilepsies associated with GLUT1 deficiency

**Table 15: Diagnostic Criteria for Sturge Weber Syndrome**

| | Mandatory | Alerts | Exclusionary |
|---|---|---|---|
| Seizures | Focal motor or autonomic seizures with or without impaired awareness, which may evolve to bilateral tonic-clonic seizures | | |
| EEG | | Lack of asymmetrical background with reduction in voltage and slowing over the affected hemisphere | |
| Neurological exam | | Lack of facial capillary hemangioma affecting the V1 dermatome | |
| Imaging | MRI showing leptomeningeal enhancement suggestive of leptomeningeal angioma, with cortical calcification and focal cerebral atrophy developing with time | | |
| Course of illness | | *Lack of abnormal neurological examination – may be limited to visual field deficit*<br><br>*Lack of intellectual disability ranging from mild to profound* | |
| **Are MRI or ictal EEG required for diagnosis?**<br><br>An MRI is required for diagnosis. Changes may be very subtle or absent on MRI done prior to 2 months of age.<br><br>An ictal EEG is not required for diagnosis. | | | |
| **Syndrome without laboratory confirmation:** In resource-limited regions, Sturge Weber syndrome can be presumptively diagnosed without EEG or MRI in persons without Alerts who meet all other mandatory clinical criteria. | | | |

**Table 16: Diagnostic Criteria for Gelastic Seizures with Hypothalamic Hamartoma**

| | Mandatory | Alerts | Exclusionary |
|---|---|---|---|
| Seizures | Gelastic seizures with mechanical, mirthless laughter, inappropriate to context | Seizure frequency less than daily | |
| EEG | | Generalized or focal background slowing (excluding immediate postictal period)<br><br>Gelastic seizures may lack ictal EEG correlate | |
| Age at onset | | Onset >5 years of age | |
| Development at onset | | Clear developmental delay at seizure onset | |
| Neurological exam | | Focal neurological findings (other than Todds paresis) or generalized hypotonia | |
| Imaging | Hypothalamic hamartoma (may require thin slices through the hypothalamic region to confirm) | | |
| Course of illness | *Drug resistant epilepsy* | *Lack of behavioral problems including aggression, impulsivity and hyperactivity* | |
| **Are MRI or ictal EEG required for diagnosis?**<br><br>An MRI is required for diagnosis.<br><br>An ictal EEG is not required for diagnosis. Furthermore, gelastic seizures may lack ictal correlate on EEG. | | | |
| **Syndrome without laboratory confirmation:** In resource-limited regions, HH-GS cannot be diagnosed in the absence of an MRI, as gelastic seizures may arise from other brain regions. | | | |

**Figure Legends:**

**Figure 1: Organization of Epilepsy Syndromes that Begin in the Neonates and Infants**

Syndromes are broadly divided into Self-Limited Epilepsies (where there is likely to be spontaneous remission) and Developmental and Epileptic Encephalopathies (disorders where there is developmental impairment related to both the underlying aetiology independent of epileptiform activity and the epileptic encephalopathy). Etiology-specific epilepsy syndromes are due to specific genetic, structural, metabolic, immune or infectious etiologies, and have consistent electroclinical features, management and prognostic implications. Most etiology-specific syndromes that begin in the neonatal or infantile period are DEEs.

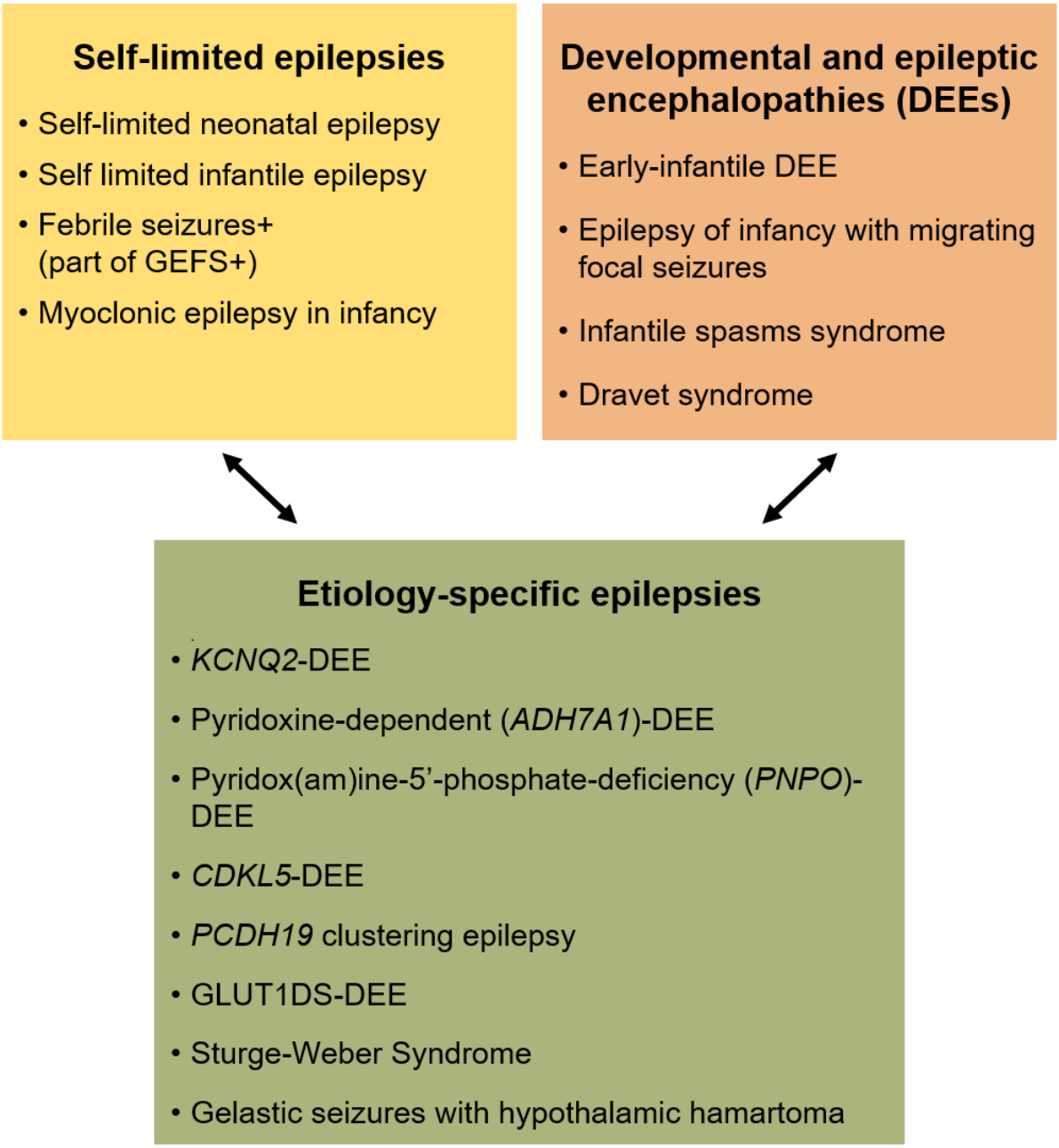


Figure 2: The ” theta pointu alternant ” interictal pattern on EEG. This pattern is characterized by runs of non-reactive theta activity, that may be intermixed with sharp waves, and frequently shows inter-hemispheric asynchrony.

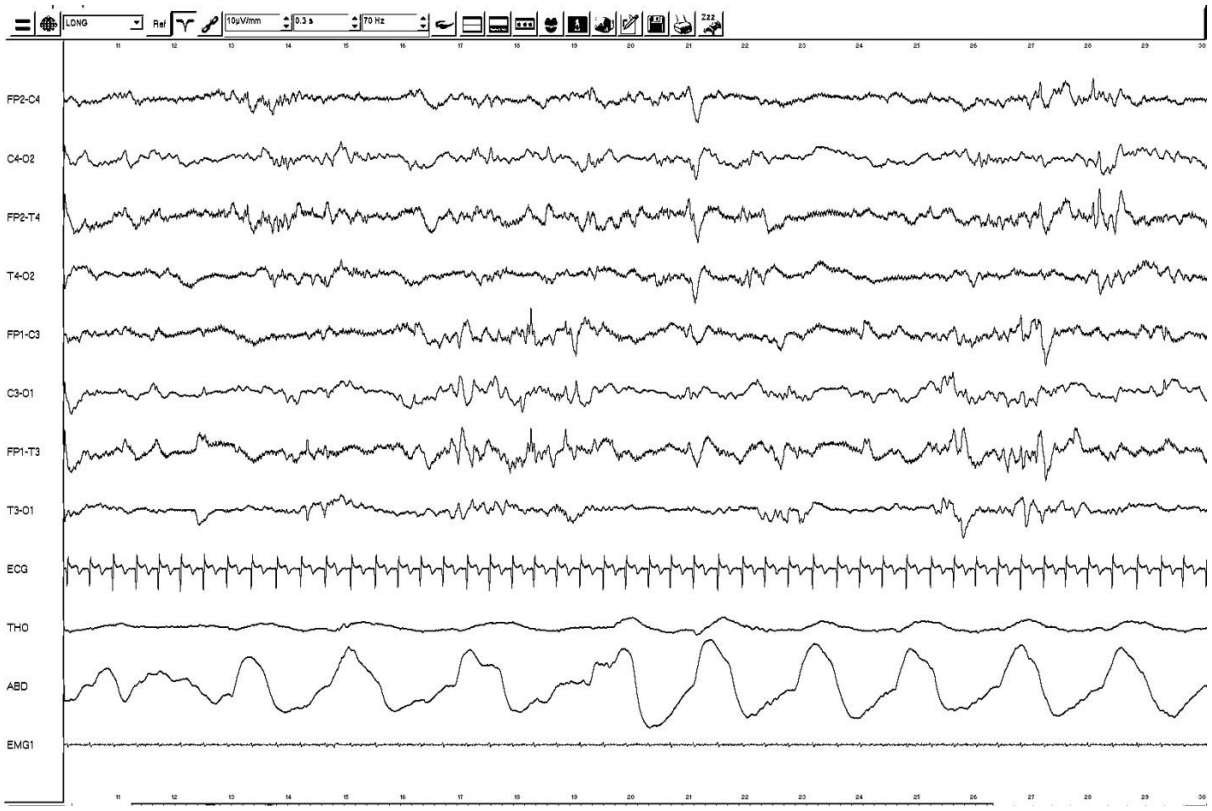


Figure 3: Seizure recorded in a three-day-old neonate with Self-limited Familial Neonatal Epilepsy, born at full-term. Seizures begin with a tonic and/or apneic phase concomitant with diffuse bilateral, but asymmetrical flattening of the background activity and polygraphic EMG recording from both deltoids showing tonic contraction of both upper limbs (tonic and/or apneic phase). This is followed by left frontal rhythmic, high amplitude slow waves, which evolve to sharp waves and spread to left temporal and central regions, and then to the right hemisphere, with eventual bilateral clonic movements of the limbs.

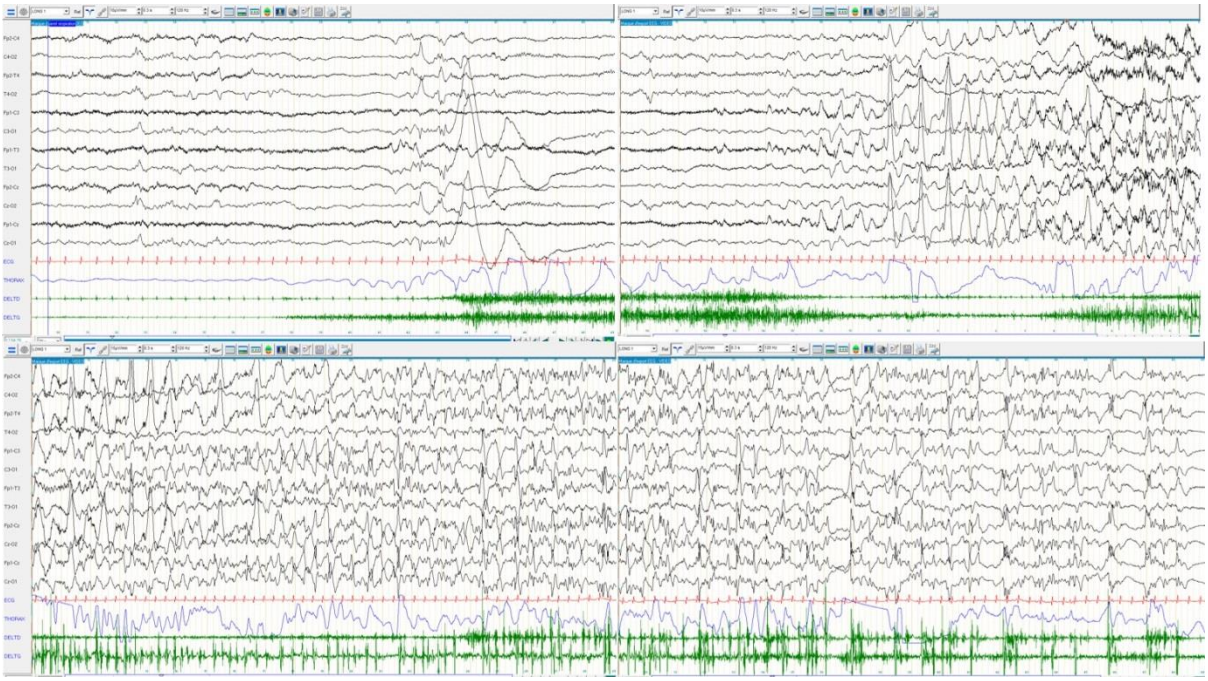


Figure 4: 14 month old boy, who presented with myoclonic seizures. His development was normal for age and he was diagnosed with Myoclonic Epilepsy in Infancy. The EEG shows generalized spike wave discharge, with a clinical myoclonic jerk seen in the EMG lead.

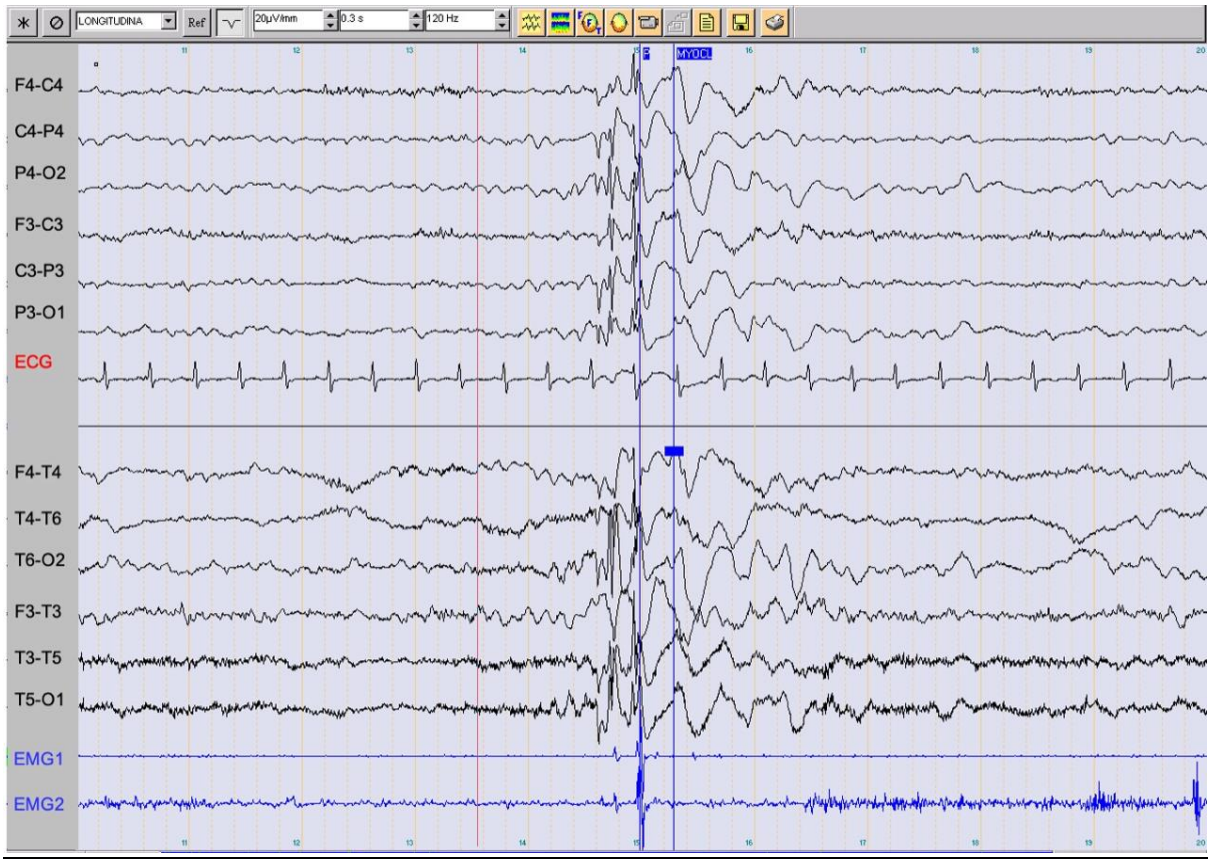


Figure 5:  4 week old boy with EIDEE. He presented on day 2 of life with sequential seizures with a prominent tonic component and severe encephalopathy. The EEG (20 microvolt/mm, 30 mm/sec) shows a burst-suppression pattern. Genetic testing showed a *KCNQ2* pathogenic variant. The patient showed a marked reduction in seizures with carbamazepine but remained profoundly delayed.

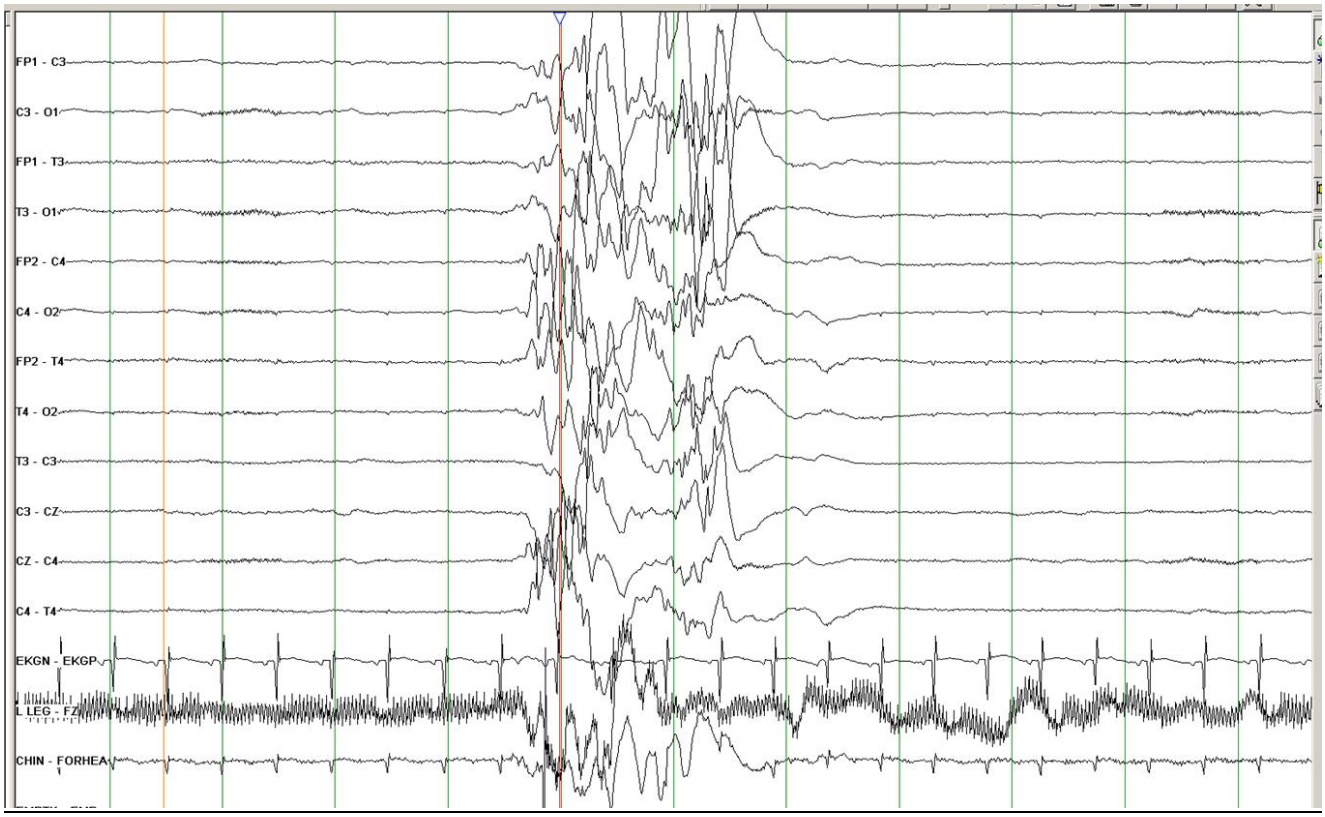


Figure 6: EEG recording of a 5-month girl with Epilepsy in Infancy with Migrating Focal Seizures related to SCN8A pathogenic variant. The EEG shows a prolonged seizure of 7 minutes starting in the left temporal area (green frame) and progressively becoming bilateral (pink frame) then migrates to the right hemisphere involving mainly the right temporal area (blue frame) and ending on the right hemisphere (orange frame).

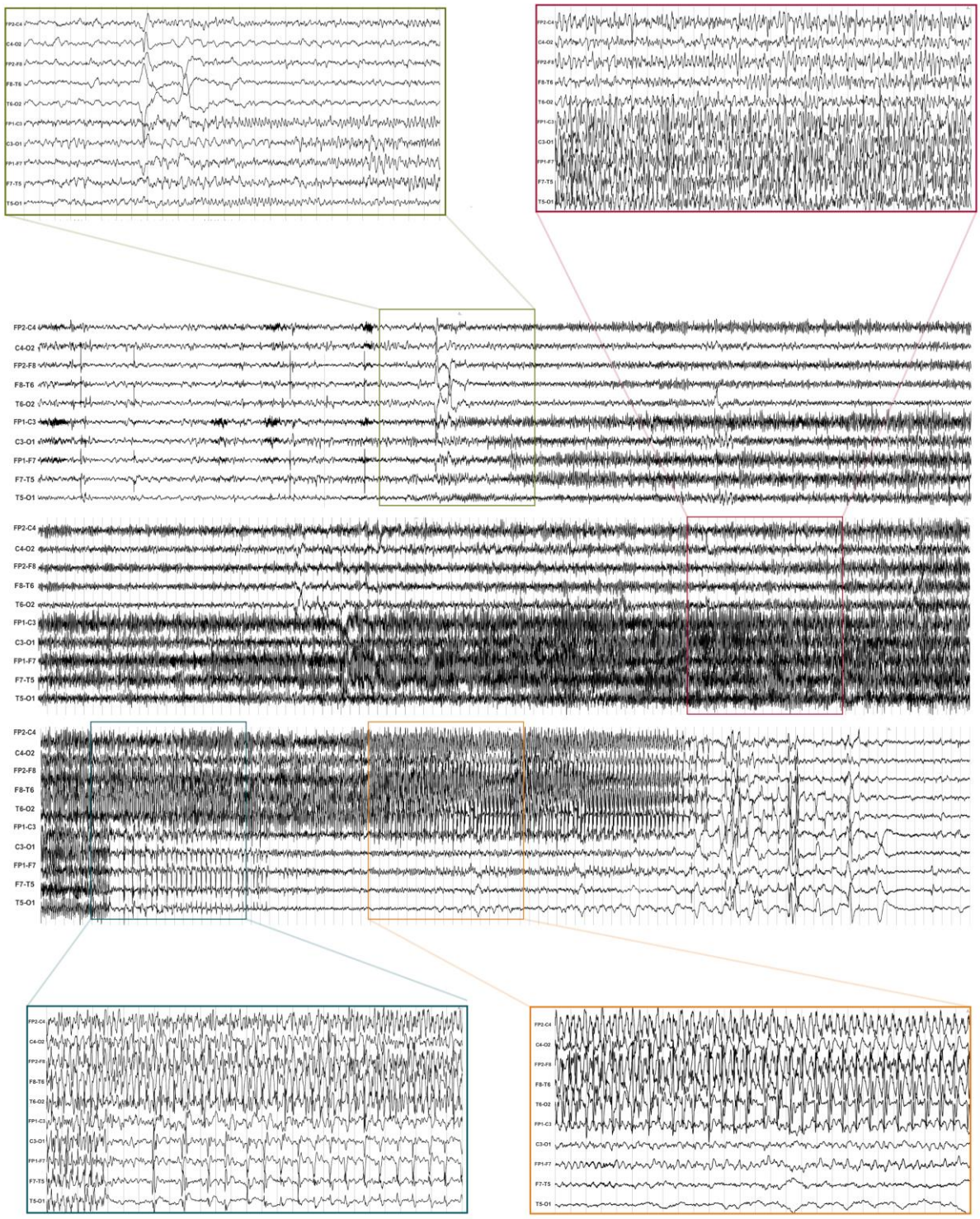


Figure 7A and B: A 7 month old boy presented with a 1 month history of flexor spasms. He had shown normal developmental progress until onset of spasms but then had decreased visual interest. His interictal EEG (Figure 7A) shows a hypsarrhythmia pattern. The ictal recording (Figure 7B) shows a high amplitude sharp wave followed by a relative decrement.

Figure 7A

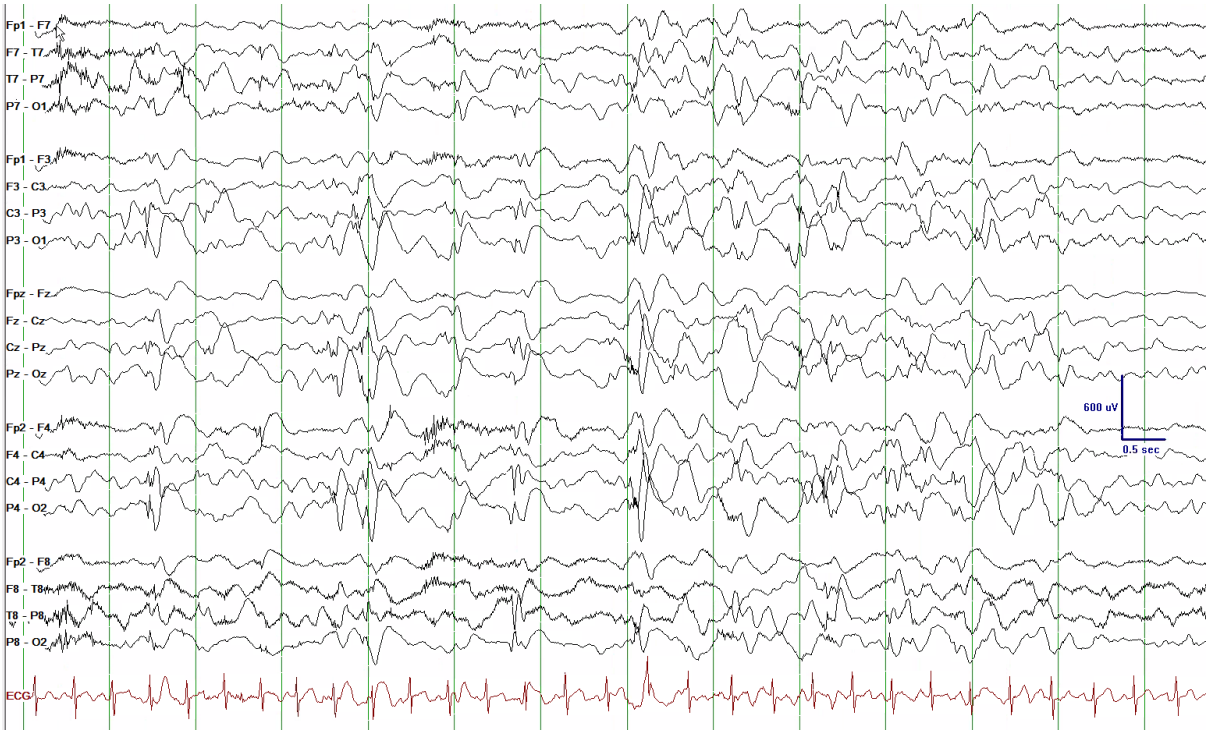



Figure 7B

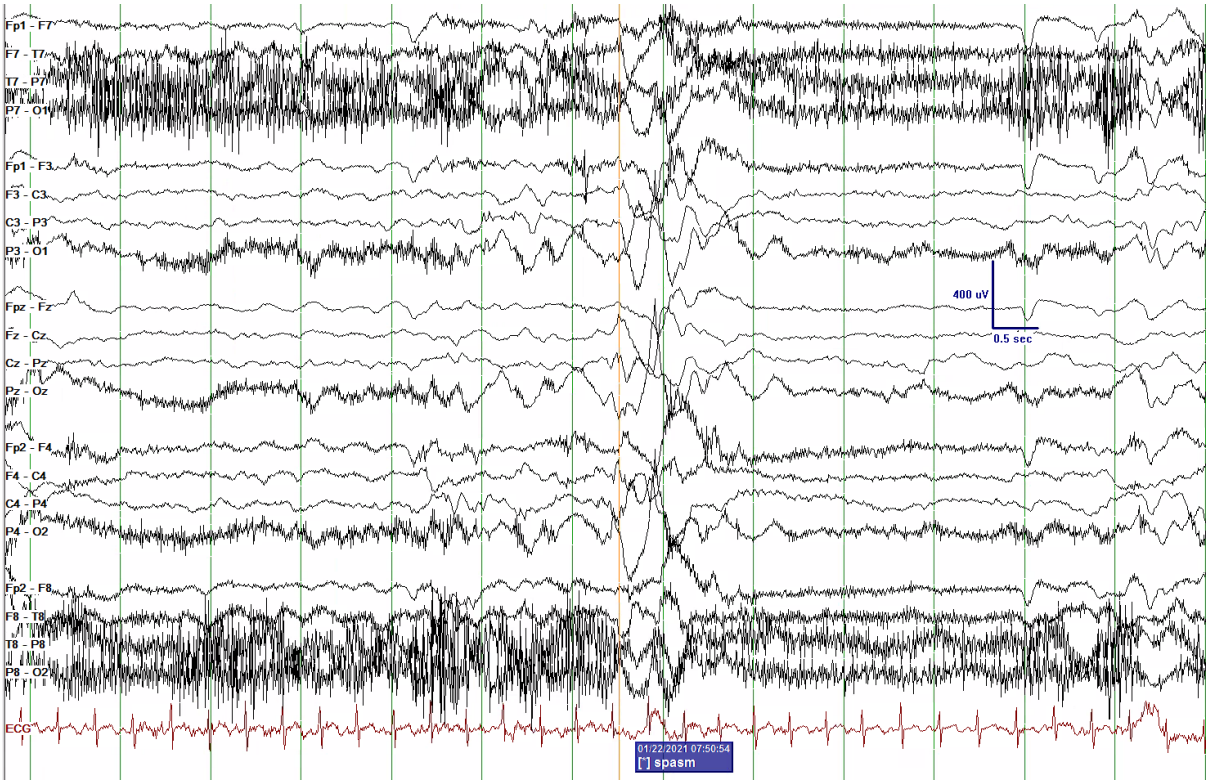



Figure 8: Differentiation of Spasm from Myoclonic and Tonic Seizure (from Fusco L and Vigevano F, Epilepsia 1993)[125] . Both EMG and EEG channels are shown. A: Myoclonic jerk, B: Tonic Seizure, C: Spasms. Note the EMG correlate of a spasm appears as a rhombus, and the EEG correlate as a slow wave, with an inverse phase reversal of the vertex region.

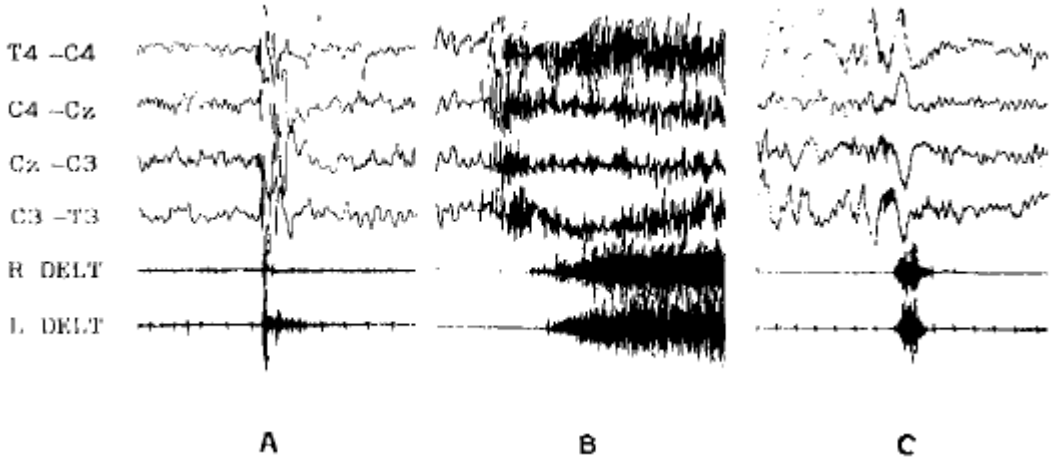
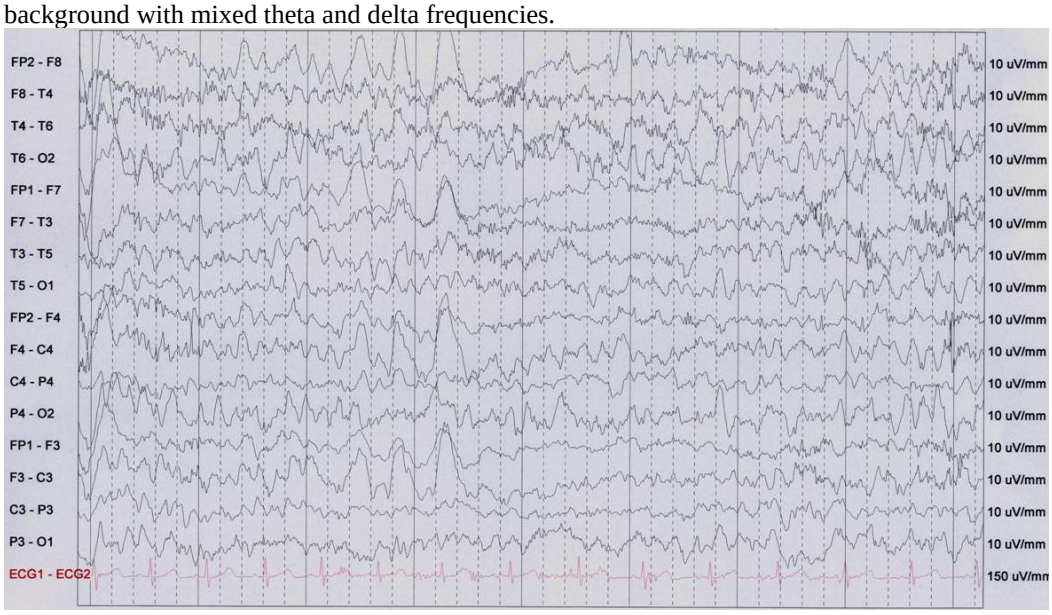


Figure 9: GLUT1 DEE

9a EEG in a 9 year old child with Glut1DS prior to ketogenic diet showing moderate to high amplitude slow background with mixed theta and delta frequencies.




9b EEG in same child as in 9a after 3 months on the ketogenic diet showing much faster background rhythms. A similar change can be seen with food taken immediately prior to or during the EEG.

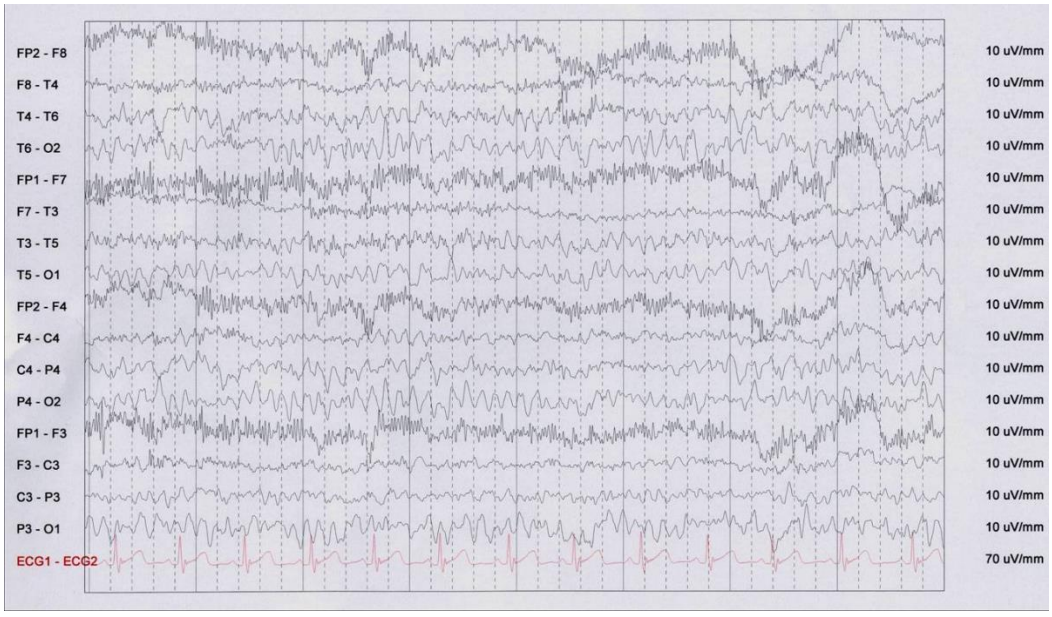
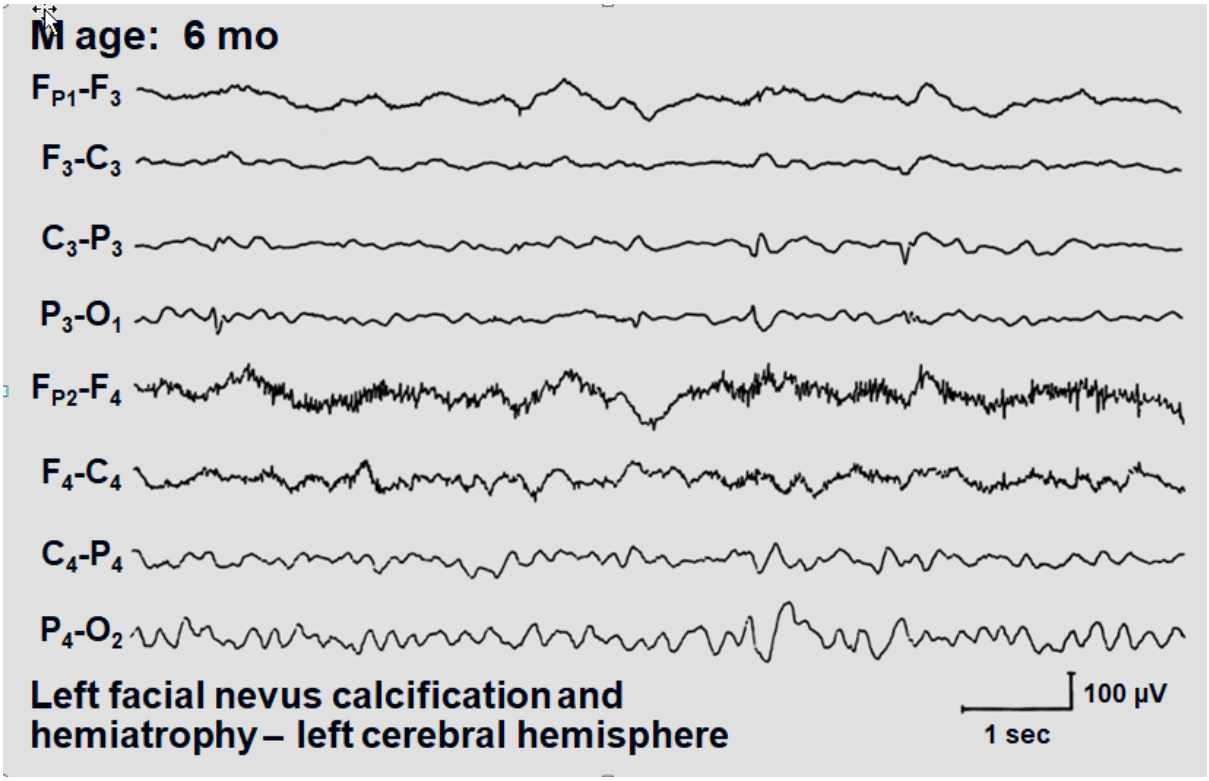


Figure 10: EEG in 6 month old child with Sturge Weber syndrome affecting the left hemisphere. Note the relative suppression through the left hemisphere, background slowing and epileptiform discharges at P3.



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