ILAE Classification and Definition of Epilepsy Syndromes with Onset at a Variable Age: Position Statement by the ILAE Task Force on Nosology and Definitions

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Summary

The goal of this paper is to provide updated diagnostic criteria for the epilepsy syndromes that have a variable age of epilepsy onset based on expert consensus of the International League Against Epilepsy (ILAE)'s Nosology and Definitions Taskforce (2017-2021). Epilepsy syndromes that typically begin in the neonate/infant or in childhood are covered elsewhere.[1, 2] We use language consistent with current accepted epilepsy and seizure classifications and take into account knowledge from advances in genetics, EEG and imaging. Our aim in delineating the epilepsy syndromes that onset at a variable age is to aid diagnosis, and guide investigations for etiology and treatments for these patients.

Key words: focal epilepsy syndromes; progressive myoclonus epilepsies; Rasmussen encephalitis; epilepsy with reading induced seizures, mesial temporal lobe epilepsy - hippocampal sclerosis.

Introduction

Epilepsy can onset across the lifespan. Incidence is highest (>60/100,000) in those aged <5 years of age,[3] but is still around 21/100,000 in adolescence[4] and 35/100,000 in adulthood.[5] While many epilepsy syndromes typically begin in the neonatal, infant and childhood periods, and traditionally greater emphasis on epilepsy syndrome identification occurs in these ages, there are a number of important syndromes that have an age of onset that is not limited to these ages for which patient outcomes can be improved by prompt recognition. The purpose of this paper is to describe the specific phenotypes of these epilepsy syndromes that have epilepsy onset at a variable age. The methodology employed in achieving the definitions of these

syndromes, based on expert consensus opinion of the ILAE's Nosology and Definitions Taskforce (2017-2021), is described in detail by Wirrell et al., 2021.[6]

The epilepsy syndromes presenting at a variable age (**Figure 1**) are broadly divided into the following groups:

- generalized epilepsy syndromes, with presumed polygenic etiologies – the idiopathic generalized epilepsies (juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME) and epilepsy with generalized tonic-clonic seizures alone (GTCA)
- focal epilepsy syndromes with genetic, structural or genetic-structural etiologies - sleep related hypermotor epilepsy (SHE), familial focal epilepsy with variable foci (FFEVF), epilepsy with auditory features (EAF)
- a combined generalized and focal epilepsy syndrome with polygenic etiology - epilepsy with reading-induced seizures (EwRIS)
- a specific group of developmental and/or epileptic encephalopathies (DEEs) - progressive myoclonus epilepsies (PME).

In this paper we also discuss important illustrative examples of *etiology-specific epilepsy* syndromes[6] that have seizure onset at a variable age:

- the focal epilepsy syndromes of mesial temporal lobe epilepsy with hippocampal sclerosis (mTLE-HS, with principally acquired etiologies) and Rasmussen encephalitis (RE, with immune etiology).

While the above grouping of syndromes is employed in this paper, it is worth noting that this can be done flexibly, for example RE, some patients with SHE (e.g. those with *KCNT1* pathogenic gene variants) and some patients with mTLE-HS might be considered best described as DEEs, as these disorders have associated neurocognitive impairments that are

contributed to both by the underlying etiology and the epilepsy. The epileptic encephalopathy may only be transient, for example resolved by epilepsy surgery in mTLE-HS. Similarly, some patients with PME may predominantly have a generalized epilepsy syndrome at presentation, indistinguishable from JME. How epilepsy syndromes presentating at a variable age are categorized, therefore, may depend on the clinical evolution in specific patients.

The nomenclature for each syndrome presented in this paper has been reviewed to ensure the name chosen reflects the key features of the electroclinical phenotype (such as mandatory seizure type) and/or the etiology where this is important for syndrome diagnosis. Thus, the syndrome name reflects the characteristic seizures in JAE, JME, GTCA, SHE, EAF, mTLE-HS, EwRIS and PME. The term FFEVF reflects the familial nature of this focal epilepsy syndrome. While there has been a move away from the use of syndromes named after individuals, the nomenclature of RE has been retained. The rationale for choosing Rasmussen encephalitis chosen over Rasmussen syndrome is the prevalence of this term in published literature.

Definitions of epilepsy syndromes that begin at a variable age

Generalized epilepsy syndromes with polygenic etiology

Idiopathic generalized epilepsies (IGEs)

The most frequent epilepsies that begin in adolescence and adulthood are the idiopathic generalized epilepsies (IGEs), namely JAE, JME and GTCA. The IGEs are a sub-group of genetic generalized epilepsies (GGEs) that have particular epidemiological importance, as it is estimated that 15-20% of all persons with epilepsy have IGE.[7] For this reason, the IGE

syndromes, including those presenting at a variable age (JAE, JME and GTCA) are presented separately in a discussion paper by Hirsch et al.[8]

Focal epilepsy syndromes with genetic, structural or genetic-structural etiologies

The group of focal epilepsy syndromes presenting at a variable age includes a number of syndromes that have been adapted and updated from previous ILAE Commission reports.[9] These syndromes are: sleep-related hypermotor epilepsy (SHE), familial focal epilepsy with variable foci (FFEVF) and epilepsy with auditory features (EAF). A wider range of possible etiologies is now associated with these syndromes, derived from advances in imaging, genetic and EEG investigations. Thus, where relevant, these syndromes have been expanded to encompass both structural and genetic etiologies that may result in the same electro-clinical presentation. Pathogenic variants in several genes have been identified as causing these syndromes (**Table 1**); which may be inherited, arise *de novo* or be due to somatic pathogenic gene variants. The name of the syndrome of 'autosomal dominant nocturnal frontal lobe epilepsy' has been updated to SHE. This change reflects current understanding that this electro-clinical syndrome includes characteristic motor seizure types (hyperkinetic seizures and/or motor seizures with tonic/dystonic features), predominantly from sleep, but acknowledges that these can be of extra-frontal onset. While other focal epilepsies that relate to specific brain networks could be considered epilepsy syndromes, for example epilepsies with seizures in cingulate, orbitofrontal or insular-opercular networks, these often have more variable semiological and EEG features and can often only be distinguished in tertiary care (epilepsy surgery) centres. They are therefore not included as epilepsy syndromes at this time.

Helpful for diagnosis of most of these focal epilepsy syndromes is their distinct seizure semiology (**Table 2**). The typical seizure semiology of the hyperkinetic seizures occurring during sleep in SHE or the focal sensory auditory seizures in EAF suggests the syndrome diagnosis and helps target investigations to specific brain regions and genetic etiologies. The diagnosis of many of these syndromes requires careful review of family history. Family history may be missed due to reduced penetrance, a wide range of age of seizure onsets and variable severity and semiology of seizures and misdiagnosis in affected family members.[10, 11] If family members have focal aware seizures (for example auditory symptoms, déjà vu or brief nocturnal motor events alone), these may not have been identified as epileptic, unless family members are asked by a clinician who is aware of their significance. In some families, only detailed study of all affected individuals with clinical, EEG and imaging phenotyping (for example excluding family members with acquired structural brain abnormality) together *with* genetic investigation, will allow a confident clinical diagnosis of the specific familial focal epilepsy syndrome to be made.[12] Complicating assessment of focal epilepsy syndrome diagnosis is that the same pathogenic gene variants can underlie different focal epilepsy syndromes (for example pathogenic variants in *DEPDC5* have been identified in SHE and FFEVF). The epilepsy syndrome diagnosed in a family may therefore depend on whether all family members can be confirmed to have the same phenotype (i.e. SHE) or whether there is variable focal seizure semiology in different family members (FFEVF).

Sleep-related hypermotor epilepsy (SHE)

Sleep-related hypermotor epilepsy (SHE, **Table 3**) is a distinct focal epilepsy syndrome characterized by clusters of motor seizures occurring from sleep. Seizures are abrupt in onset and offset, typically brief (< 2 minutes) with preserved awareness and a stereotyped hyperkinetic or asymmetric dystonic/tonic motor pattern. SHE encompasses previous epilepsy

syndromes of hypnogenic-nocturnal paroxysmal dystonia-epilepsy, nocturnal frontal lobe epilepsy (NFLE) and autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) and can have both genetic and/or structural etiology. This epilepsy syndrome, particularly if associated with a structural brain abnormality or specific gene (e.g. *KCNT1*), can be drug resistant.

Epidemiology:

SHE is a rare syndrome, with an estimated prevalence of the non-familial form in the adult population of 1.8–1.9 per 100,000.[13, 14]

Clinical context:

Age at seizure onset is mostly in the first two decades of life, typically in adolescence (11-14 years), but has ranged from 2 months to 64 years of age.[11, 13, 15, 16] There is a slight male sex predominance.[13] Neurological examination and head size are normal. Perinatal history, developmental milestones and cognition are typically normal. Intellectual disability and neuropsychiatric or behaviour disorders have been reported in SHE.[17-19]

Course of Illness:

The course of SHE is predominantly related to the underlying etiology.[13] Most patients have normal intellect, normal imaging and respond to first line anti-seizure medication (ASM).[20] Patients with intellectual disability, neurological or imaging abnormality or seizures in wakefulness are less likely to achieve sustained seizure remission.[13, 20] Epilepsy surgery, in selected etiologies, may transform outcome from uncontrolled drug-resistant seizures to full remission of epilepsy. The best surgical outcome is seen when the etiology is a well-defined structural pathology, especially focal cortical dysplasia (FCD) type IIb.

Seizures:

Focal motor seizures with vigorous hyperkinetic or asymmetric tonic/dystonic features are seen, usually with autonomic signs (tachycardia, tachypnoea, irregular respiratory rhythm), vocalization and negative emotional expression such as fear.[21] There may be head and eye deviation. Hyperkinetic movements involve proximal limb or axial muscles, producing irregular large amplitude movements, such as pedaling, pelvic thrusting, jumping, thrashing or rocking movements.[22] Focal motor seizures may be subtle clinically (previously termed 'paroxysmal arousals') or may have longer duration and greater complexity (such as 'epileptic wandering').[11] Patients may describe a focal aware sensory or cognitive seizure before the motor features commence. Focal to bilateral tonic-clonic seizures can occur.[11, 13, 20] While occurrence of seizures from sleep is characteristic of this syndrome, seizures from the awake state occur in 27-45% of patients at some time in their life.[11, 13, 15]

EEG:

The EEG background is typically normal. The awake EEG is non-epileptiform in most (50-90%) patients.[11] During sleep, interictal epileptiform abnormalities are seen over the frontal areas in around 50% of patients, **Figure 2A**.[11] Ictal EEG may not show definitive ictal patterns, be obscured by movement artefact, or show evolving sharp/spike-wave discharges, rhythmic slow activity or diffuse background flattening over frontal areas (**Figure 2B)**. Postictal focal slowing may be seen. Prolonged video–EEG recording is the best diagnostic test to identify events with stereotyped semiology from sleep to confirm the diagnosis, especially in cases without a clear surface ictal EEG correlate. Intracranial EEG recordings (e.g. stereo-EEG) have demonstrated that ictal discharges may start in various extra-frontal areas (insulo-opercular, temporal and parietal cortices).[21, 23-25]

Imaging:

Neuroimaging is usually normal. Occasionally, a structural brain abnormality is found, most commonly FCD (**Figure 2C**) but also, less commonly, an acquired structural pathology.

Genetics:

The etiology of SHE may be genetic, genetic-structural or acquired. Family history should be carefully sought.[20] Familial SHE is usually inherited in an autosomal dominant fashion (ADSHE), with a penetrance of around 70%.[15] A pathogenic gene variant is found in around 19% of ADSHE and in 7% of sporadic SHE.[26] Genetic causes of ADSHE include pathogenic variants in GATOR1 complex genes (*DEPDC5,* less frequently *NPRL2, NPRL3*),[27-30] in acetylcholine receptor subunits genes (*CHRNA4,* less frequently *CHRNB2 or CHRNA2*)[31-33] and in the sodium-activated potassium channel *KCNT1*.[17] Individuals with GATOR complex pathogenic gene variants may have FCD, with implications for epilepsy surgery.[26] Individuals with *KCNT1* pathogenic variants have a more severe form of SHE with intellectual disability, psychosis and sometimes regression,[17, 18] and higher penetrance in families. Rare families with autosomal recessive SHE (ARSHE) are described, and pathogenic variants in *PRIMA1* have been identified in one family.[34]

Differential diagnoses:

- Non-REM parasomnias - patients with SHE may be mis-diagnosed as having parasomnias, often for some time before the epilepsy is recognized.[35] Seizures in SHE are typically brief (<2 minutes) with abrupt onset/offset, have stereotyped motor features from seizure to seizure, can occur nightly with clustering through the night (from sleep onset to the early morning), and there is often preserved awareness during the seizure. Parasomnias are longer in duration (>10 minutes), have variable features from event to event, are less frequent, often singular in a night,

are prominent 1-2 hours after falling asleep and the patient is confused during the event, with no memory of it afterwards.

- Psychogenic non epileptic seizures (PNES) - patients with SHE may be mis-diagnosed as having PNES, because they may have preserved awareness in the presence of bilateral movements during their seizures, and the ictal EEG may not show definitive ictal patterns. SHE may be differentiated from PNES by the stereotyped hyperkinetic features, brevity and clustering of seizures through the night from sleep, whereas events in PNES are less stereotyped and occur during wakefulness.
- REM behavior disorder (RBD) – this is a REM parasomnia that begins usually later in life (> 50 years), motor hyperkinetic events are not stereotyped and correspond to vivid dreaming.
- Familial focal epilepsy with variable foci (FFEVF) – if there is a family history of focal seizures, familial SHE is distinguished from FFEVF by all individuals in the family having SHE.[12]
- Other focal seizures occurring predominantly from sleep – these do not have the characteristic hyperkinetic or asymmetric tonic/dystonic features seen in SHE.

Familial focal epilepsy with variable foci (FFEVF)

Familial focal epilepsy with variable foci (FFEVF, **Table 4**) is an autosomal dominant familial focal epilepsy syndrome, with incomplete penetrance, characterized by focal seizures arising from different cortical regions (most commonly frontal or temporal) in different family members with variable severity, but with each individual in a family having a single focal seizure type. This syndrome was previously known as ‘familial partial epilepsy with variable foci’ and ‘autosomal dominant partial epilepsy with variable foci’.[10, 12] The underlying etiology may include genetic and structural causes. Most cases are responsive to ASM. In appropriately selected patients with drug-resistant seizures and focal cortical dysplasia, epilepsy surgery may

result in full remission of epilepsy. Surgical assessment and counselling may be informed by identification of specific genetic etiologies.

Epidemiology:

There are no epidemiological studies of the prevalence of this epilepsy syndrome. It is considered rare.

Clinical context:

Age at seizure onset is typically in the first to second decade (peak 12-13.5 years) but has a wide range even in the same family, ranging from 1 month to 52 years.[10, 12] There is no reported sex predominance. Antecedent, birth and neonatal history are typically normal. Neurological examination and head size are normal. Early developmental milestones, intellect and cognition are typically normal, though mild intellectual disability, neuropsychiatric features including autism spectrum disorder and behavioral disorders have been reported.[36, 37]

Course of illness:

Most cases are responsive to ASM, however drug resistance rates may be up to 30%.[38] Epilepsy surgery, in selected cases, may transform the epilepsy from drug-resistant to full remission.[39]

Seizures:

Focal seizures occur, with semiology depending on the focal network involved in the individual. Each individual in a family typically has one focal seizure type. Focal cognitive, sensory, autonomic or motor seizures have been described. Seizures can arise from sleep, wakefulness or both. Focal to bilateral tonic-clonic seizures may occur.

EEG:

The EEG background is normal. The interictal EEG usually shows focal epileptiform abnormalities (frontal, temporal, centroparietal more than occipital).[12] In each individual in a family this focal area remains constant over time. Epileptiform discharges are enhanced by sleep deprivation and sleep. Ictal EEG demonstrates focal ictal patterns related to the focal brain network involved in the individual.

Imaging:

Neuroimaging may be normal or may show FCD (which may be subtle).[27, 39]

Genetics:

The etiology of FFEVF may be genetic or genetic-structural with co-occurring FCD (typically FCD II).[39] Inheritance is autosomal dominant with incomplete penetrance.[12, 40] Pathogenic variants in *DEPDC5*, *NPRL2* and *NPRL3* have been identified in families with FFEVF.

Differential diagnoses:

- Familial SHE – while nocturnal seizures compatible with SHE are common in *individuals* in families with FFEVF,[12] for this syndrome, *all* affected individuals in the family must have seizures compatible with SHE. A predominance of awake seizures is also reported to be a useful distinction between FFEVF and SHE.[12]
- Familial EAF – for this syndrome, all affected individuals in the family must have seizures compatible with EAF.

Epilepsy with auditory features (EAF)

Epilepsy with auditory features (EAF, **Table 5**) is a focal epilepsy syndrome that presents in adolescence/adulthood without any antecedent history and is characterized by focal aware seizures with auditory symptoms and/or receptive aphasia. Patients may have rare focal to bilateral tonic-clonic seizures. Some patients have seizures precipitated by sounds. This syndrome was previously known as autosomal dominant lateral temporal lobe epilepsy (ADLTE) and autosomal dominant partial epilepsy with auditory features (ADPEAF). EAF may occur as a familial focal epilepsy syndrome, familial EAF (FEAF), which may be inherited in an autosomal dominant fashion (ADEAF) with reduced penetrance.

Epidemiology:

The prevalence of this syndrome is unknown.

Clinical context:

Age at seizure onset is typically 10-30 years, range 0.5-54 years.[41] There is no reported sex predominance. Antecedent, birth and neonatal history are typically normal. Neurological examination and head size are normal. Early developmental milestones and intellect/cognition are typically normal.

Course of illness:

Seizure outcomes can range from mild seizures with spontaneous remission to highly drug-resistant seizures. Those with structural lesions may be treated surgically.[41] The cumulative rate of seizure remission in those followed for at least 5 consecutive years was about 50% by 30 years from epilepsy diagnosis.[41] Predictors of poor long-term prognosis are early age at onset (under 10 years), focal epileptiform discharges on interictal EEG and focal aware cognitive seizures with complex auditory hallucinations.[41]

Seizures:

Focal aware sensory (auditory) and/or cognitive (receptive aphasia) seizures are mandatory for this syndrome. They implicate Heschl's gyrus or Wernicke's area in the dominant hemisphere. Auditory sensory symptoms typically consist of simple unformed sounds (i.e. humming, buzzing, or ringing), or less commonly auditory distortions (such as alteration in volume) or complex sounds (i.e. specific songs or voices). Ictal receptive aphasia consists of a sudden onset of inability to understand spoken language in the absence of a general impairment of awareness. Other focal seizure symptoms can also occur, including vision alteration (distortions of faces/objects) and vertigo.[42, 43] Focal impaired awareness and focal to bilateral tonic-clonic seizures (often from sleep) may occur. The focal aware seizures may not have been appreciated as epileptic until these seizures occur; therefore careful history is important to elicit a history of these prior seizure types. Reflex seizures precipitated by sound (e.g. a ringing telephone) occur in some patients.[41]

EEG:

The interictal EEG is normal in most patients. If abnormality is seen, this is characterized by focal (usually temporal) sharp waves or spikes, these may also be widespread.[41] The EEG may be activated by hyperventilation, sleep deprivation and when asleep. Ictal EEG recordings are rarely reported.

Imaging:

Neuroimaging is usually normal, but rarely a structural etiology may be found.[42]

Genetics:

EAF mostly occurs sporadically, though familial EAF also occurs, with autosomal dominant inheritance (ADEAF) with incomplete penetrance.[41] Pathogenic variants (or microdeletions) in *LGI1* (epitempin) or *RELN* account for approximately half of ADEAF cases.[44-47] Pathogenic gene variants in *MICAL-1* are a rarer cause.[46] Pathogenic variants in *DEPDC5*, *CNTNAP2* and *SCN1A* have also been reported.[48]

Differential diagnoses:

- FFEVF - FEAF is distinguished from FFEVF by the semiology of the initial symptoms of the seizures. While seizures compatible with EAF can occur in an *individual* in a family with FFEVF, for FEAF to be diagnosed *all affected individuals* in the family must have seizures compatible with EAF.
- Psychiatric disorders - auditory hallucinations are easily distinguished from EAF by the more chronic nature and complexity of psychiatric auditory hallucinations.
- Tinnitus – this disorder is common and may be present in the patient's family. This is distinguished from focal sensory auditory seizures by the usually longer duration of tinnitus and the presence of other features of seizures accompanying ictal auditory sensations.

Focal etiology-specific epilepsy syndromes

Etiology-specific epilepsy syndromes can be identified when there is a specific etiology, that has a clearly defined, relatively uniform and distinct clinical phenotype in most affected individuals (clinical presentation, seizure types, comorbidities, course of illness and/or response to specific therapies), as well as consistent EEG, neuroimaging and genetic correlates.[6] Illustrative etiology-specific epilepsy syndromes that onset at a variable age are discussed in this section.

Mesial temporal lobe epilepsy with hippocampal sclerosis (mTLE-HS)

Mesial temporal lobe epilepsy (mTLE) is a frequent focal epilepsy in adults, though also presents in childhood. While mTLE may have many causes, including genetic, genetic-structural and immune pathologies, the syndrome of mesial temporal lobe epilepsy with hippocampal sclerosis (mTLE-HS, **Table 6**) requires imaging confirmation of hippocampal sclerosis for diagnosis. This epilepsy syndrome is often drug resistant; however, epilepsy surgery may transform outcome to full remission of the epilepsy.

Epidemiology:

There are few population-based epidemiological studies of mTLE. Most studies derive from tertiary care (e.g. epilepsy surgery) centres with referral bias towards drug-resistant patients. The prevalence of TLE was calculated at 1.7/1000 people in one population study.[49] The estimated prevalence of drug-resistant mTLE-HS is much lower, at 0.51-0.66 per 1000 persons, with an estimated incidence of 3.1-3.4 per 100,000 people per year.[50]

Clinical context:

Age at seizure onset is typically in adolescent and young adult years, though later or earlier onset is reported. There is no sex predominance. Antecedent, birth and neonatal history are typically normal. Neurological examination and head size are normal, although reduced facial movement may be noted on the contralateral side.[51] A past history of febrile seizures in early childhood can be found,[52-54] and prolonged febrile seizures in childhood have been shown to cause HS.[52, 55] Early developmental milestones are within normal limits. Cognitive co-morbidity is recognized, with deficits in verbal memory associated with mTLE-HS affecting the dominant (usually left) mesial temporal lobe and deficits in visual memory associated with mTLE-HS affecting the non-dominant temporal lobe.

Course of illness:

mTLE-HS is often drug resistant. Epilepsy surgery, in selected etiologies, may transform outcome from uncontrolled drug-resistant seizures to full remission of epilepsy. The best surgical outcome is seen when the structural abnormality is well-defined on imaging.

Seizures:

Focal aware or impaired awareness seizures occur with semiological features referable to medial temporal lobe networks. Focal aware seizures may be autonomic (e.g. a rising epigastric sensation, abdominal discomfort, nausea, retching, pallor, flushing, tachycardia), cognitive (e.g. déjà vu, jamais vu), emotional (e.g. fear) or sensory (e.g. olfactory, gustatory) seizures. Focal aware seizures may be the only initial seizure type and may occur for some time before a diagnosis of epilepsy is considered. In focal impaired awareness seizures, there is usually behavioral arrest and often automatisms which may be oral (chewing, lip-smacking, swallowing), vocal (speech, in non-dominant mTLE-HS) or gestural. Upper limb automatisms may be unilateral and may lateralize the seizure to the ipsilateral hemisphere. Unilateral pupillary dilatation can occur and can also lateralize the seizure to the ipsilateral hemisphere. Contralateral upper limb dystonia may develop and head and eye version to the contralateral side can occur.[56, 57] Speech may be preserved in seizures of nondominant mTLE-HS. Conversely, aphasia is common with dominant mTLE-HS. Seizures have a gradual offset, and typically last 1-5 minutes, though focal aware seizures can be briefer. After focal impaired awareness seizures, patients may experience a postictal state of confusion lasting several minutes. Focal to bilateral tonic-clonic seizures may occur and may have progression to contralateral (face before arm and leg) clonic jerking and head turning to the contralateral side before the focal to bilateral tonic-clonic phase.

Focal autonomic, cognitive, emotional and sensory seizures can also arise in other brain networks, however the onset symptoms and signs during seizure progression and postictal period are different. The following onset symptoms and signs suggest seizure onset in brain networks other than those in the mesial temporal region: throat discomfort, clonic or dystonic movements, somatic sensory symptoms, hyperkinetic activity, visual symptoms, auditory symptoms, laughter.

EEG:

The EEG background is normal or may show focal slowing over the temporal region(s). Focal slowing can be enhanced with hyperventilation. Anterior or mid temporal spikes and sharp waves are characteristic and are often increased during sleep (**Figure 3**). Temporal intermittent rhythmic delta activity (TIRDA) may also be present.[58] Discharges may occasionally be activated by hyperventilation.[59] Epileptiform discharges may be bilateral and independent, or bilaterally synchronous. Ictal EEG (**Figure 4**) commonly commences with focal electro-decrement and low voltage fast activity replacing the normal EEG background. This evolves to rhythmic fronto-temporal alpha or theta, with or without superimposed spikes or sharp waves. The first clinical symptoms or signs may precede the emergence of surface ictal rhythm on EEG. Postictal ipsilateral slowing is common.

Imaging:

Hippocampal sclerosis is characterized by decreased hippocampal volume (best demonstrated on coronal (at right angles to the long axis of the hippocampus) MPRAGE or T1-weighted sequences, **Figure 5**) with increased hippocampal signal intensity (best demonstrated on coronal FLAIR and T2 sequences on coronal MRI, **Figure 6**). Up to 15% of patients may have

hippocampal sclerosis co-existing with another structural abnormality, such as FCD or acquired pathologies ("dual pathology"),[60-62] these lesions should therefore be carefully sought. The occurrence of FCD with HS in ILAE classifications of FCD is categorized as FCD type IIIa,[62] this may be associated with earlier age of seizure onset in childhood and warrants extra care in pre-surgical evaluation to determine the primary lesion driving the epilepsy.

Genetics:

mTLE-HS is predominantly an acquired pathology,[52] therefore genetic studies are not often indicated. Febrile seizures, especially if prolonged, can cause HS, therefore genetic epilepsies that are accompanied by febrile seizures, especially if prolonged (e.g. Dravet syndrome or GEFS+; genes *SCN1A* or *SCN1B*), can predispose an individual to the development of mTLE-HS. Finding one of these genes may drive changes in treatment (e.g. ceasing sodium channel blockers) which may improve seizure control, but is unlikely to prevent the need for surgery in drug resistant patients.[63]

Differential diagnoses:

- Viral (e.g. HSV, HHV6) and autoimmune limbic encephalitis – can initially present with seizures with temporal semiology, but subsequently patients develop acute or subacute encephalopathy.
- mTLE due to causes other than HS – examples include FCD and genetic causes[64, 65]
- Extratemporal seizures that propagate to medial temporal lobe networks, especially from the orbitofrontal cortex and insula-opercular region but also from the occipital or parietal lobes.
- Non-epileptic seizures may be difficult to differentiate from mTLE when seizures do not progress to impaired awareness, or motor features, as the surface EEG may be normal during focal aware seizures and incidental abnormalities of the hippocampus (such as asymmetry in

size) are not uncommon. Adding to the challenge is that anxiety and mood disorders are common co-morbidities in patients with mTLE.

Rasmussen encephalitis (RE)

Rasmussen encephalitis (RE, previously known as Rasmussen syndrome, **Table 7**) is a presumed immune-mediated epilepsy that presents in children, adolescents and young adults. It is a progressive hemispheric syndrome characterized by focal seizures (usually motor seizures, including epilepsia partialis continua), which progress over time in frequency and severity. A progressive hemiparesis develops. On neuroimaging studies, progressive hemiatrophy contralateral to the hemiparesis is seen. The cause of RE is not known, and no causative antibody has been identified to date. CSF can show normal findings, but may show a mild pleocytosis, mildly elevated protein and oligoclonal bands. The diagnosis is based on the characteristic clinical presentation and imaging findings.[66, 67] Brain biopsy may not be required, but if performed shows multifocal cortical inflammation, neuronal loss and gliosis confined to one hemisphere.

Epidemiology:

Rasmussen encephalitis is a rare disease, with an incidence of 1.7 to 2.4 per 10 million individuals.[68, 69]

Clinical context:

The age of onset is 1-10 years (median 6 years). Late onset forms, starting in adolescent or adult life, comprise approximately 10% of cases.[70] Both sexes are equally affected. Antecedent and birth history is usually normal; however pregnancy or perinatal complications have been reported in 19% of patients in one surgical series operated on between 1945-1987.[71] At initial

presentation, children are typically developmentally normal. Over time, cognitive impairment emerges. At onset, neurological examination is usually normal. Rarely, children may initially present with unilateral limb dystonia or choreoathetosis prior to seizure onset. Over time, patients develop a progressive hemiparesis, and may develop hemianopia. Acquired language dysfunction is seen in cases that affect the dominant hemisphere. Progression of RE is slower in patients with adolescent or adult onset than in those with childhood onset, and final deficits may be less severe.[70, 72]

Course of illness:

Rasmussen encephalitis is a progressive disorder with drug resistant frequent seizures and progressive neurological impairment (hemiparesis, homonymous hemianopia, cognitive impairment). There are typically three stages of RE: an initial *prodromal* phase (lasting months to years, though shorter in younger children) with infrequent seizures and mild hemiparesis, an *acute* phase (lasting months to years, though shorter in younger children) with increasingly frequent seizures, at times with epilepsia partialis continua, and progressive hemiparesis, hemianopia, cognitive and language (the latter if dominant hemisphere) deterioration and finally a *chronic* phase with permanent stable hemiparesis and other neurological disabilities, and continued seizures (though less frequent than in the acute stage).[67] Hemispheric disconnection surgery (so called hemispherotomy) or hemispherectomy are the only known definitive treatments for seizures that can alter the course of the condition.

Seizures:

Focal seizures, usually motor seizures, occur and may be clinically subtle at onset. In childhood-onset RE, seizures are typically focal aware seizures, whereas in older onset patients, focal impaired awareness seizures are more commonly seen.[72] The clinical motor

manifestations are contralateral to the affected hemisphere. Seizures typically increase in frequency over weeks to months and can include epilepsia partialis continua, with ongoing twitching of one side of the body, most commonly the face and upper extremity. Focal seizures may evolve to bilateral tonic-clonic seizures. Focal atonic seizures may also occur. Seizures may rapidly engage bilateral brain networks and seizures that appear generalized may be seen.

EEG:

The background EEG may be normal at initial presentation, but usually shows slowing with loss of normal rhythms and sleep architecture on the affected side. With time, background asymmetry becomes more prominent. Epileptiform activity is typically seen maximally over the affected hemisphere (**Figure 7)**. With time, epileptiform discharges may spread to the contralateral hemisphere; this does not exclude a patient from surgical evaluation. Discharges can be facilitated by sleep. The ictal EEG shows focal ictal discharges with focal seizures. Seizures may arise from several foci within the affected hemisphere. Epilepsia partialis continua is often not accompanied by a clear ictal rhythm on scalp EEG. With atrophy of the affected hemisphere, ictal EEG may show asymmetric emphasis of the seizure on the contralateral side. However true independent focal seizure onset in both hemispheres ('bilateral' RE) has also rarely been reported (2% of cases).[67]

Imaging:

MRI is usually normal in the early phase of the disease. T2/FLAIR hyperintensity may be noted in the insular region. With time, there is progressive atrophy of the affected hemisphere, often starting in the insular region, with enlargement of the temporal horn of the lateral ventricle and Sylvian fissure.[67, 73] Ipsilateral atrophy of the caudate head is also an early sign (**Figure 8**).

Atrophy is usually seen within the first year of onset and correlates with progressive hemiparesis.

Genetics:

This disorder is not considered genetic in etiology.

Differential diagnoses:

- Autoimmune encephalitides – these are not expected to be limited to one hemisphere and cognitive, behavioural and psychiatric symptoms and movement disorders typically predate seizures.
- Metabolic disorders (mitochondrial disorders such as POLG, MELAS)
- Hemispheric structural abnormalities (e.g. vascular, FCD type 1) – these may be associated with seizures, hemiparesis and hemiatrophy on MR imaging, however progressive decline in motor and cognitive function over time is not expected.
- Hemiconvulsion-hemiplegia syndrome (HHE) – this condition is characterized by an initial prolonged seizure, which is then followed immediately by non-progressive hemiparesis.

Combined generalized and focal epilepsy syndrome with polygenic etiology

Epilepsy with reading-induced seizures (EwRIS)

Epilepsy with reading-induced seizures (EwRIS, **Table 8**) is a rare combined generalized and focal epilepsy syndrome, characterized by *reflex* myoclonic seizures affecting orofacial muscles triggered by reading. If reading continues these may worsen and a generalized tonic-clonic seizure may occur. Good history-taking is therefore critical for diagnosis, as is awareness of this syndrome as the task-specific eliciting of symptoms can result in

misdiagnosis of seizures as non-epileptic events, as tics or as stuttering. Seizures are elicited mainly by reading, but also by other tasks related to language. Prognosis is favourable, as spontaneous seizures are not expected, seizures are responsive to treatment and can be avoided through reducing exposure to the triggering stimulus. In most patients, seizures require long-term treatment, though some patients may experience remission in time.

Epidemiology:

This is a rare epilepsy syndrome therefore true incidence is unknown.

Clinical context:

Age at onset is typically in the late teens, but earlier or later onset is described. A male sex predominance (~2:1) is recognized.[74, 75] Antecedent, birth and neonatal history are typically normal. Development and cognition are typically normal. Neurological examination and head size are normal.

Course of illness:

Due to the rarity of this syndrome (case reports only), little is known about its course. Prognosis is generally considered to be favourable, with a good response to specific ASM described in the literature, and potential for remission in a minority of patients with age.[75] Reducing exposure to the triggering stimulus may be successful in reducing seizures, however limiting reading can result in significant restrictions in capacity for education, employment, lifestyle or even for religious practice.[76]

Seizures:

Low amplitude myoclonic jerks occur, mainly affecting the masticatory, oral and perioral muscles (jaw, lip, tongue). These can cause a clicking sensation, stuttering or altered speech.[77] They occur in minutes to hours after starting reading. If the patient continues to read after the myoclonus appears, the myoclonus can increase in severity, spread to trunk and limb muscles, have associated impaired awareness or a tonic-clonic seizure may emerge. Orofacial myoclonic jerks may be precipitated not only by reading, but also by other language-related tasks (language-induced epilepsy) in the same patient, for example by talking (when tense or argumentative), writing or by making complex decisions.[74, 78] Hand myoclonic jerks are seen in those with writing precipitation of seizures (graphogenic epilepsy). In an individual patient the trigger may be specific, for example seizures may occur when reading silently but not when reading aloud,[79] when reading a specific language but not mathematics,[75] when reading music, or when reading one language but not another.[76] A minority of patients with EwRIS have been described to have co-occurring ocular and visual ictal manifestations (e.g. blinking, difficulty with ocular fixation, nystagmus or complex visual hallucinations)[74, 78] or rare spontaneous myoclonus.[74]

EEG:

The EEG background is normal. Interictal discharges may not be seen, though may be facilitated during sleep or on awakening. Myoclonic seizures are accompanied by brief (i.e. single or very short paroxysm of) sharp, spike or spike wave complexes (which may be low voltage), see **Figure 9**. Approximately 75% of cases show generalized ictal discharges, approximately 25% have bilateral but asymmetric or unilateral discharges (lateralizing to the dominant hemisphere in all, 10% have focal temporal-parietal discharges).[74] These may be difficult to distinguish from accompanying myogenic artefact. Seizure features may be difficult

to appreciate on video, due to the subtle nature of the orofacial myoclonus and limited resolution of facial features during video-EEG.

Imaging:

Neuroimaging is expected to be normal. If there are atypical features to the clinical presentation, imaging may be considered to exclude a structural etiology.

Genetics:

A positive family history of epilepsy, usually one of the IGE syndromes or a GGE, is found in 20-40% of patients with EwRIS.[74, 78] This is considered to reflect a strong genetic contribution.[75]

Differential diagnoses:

- Non-epileptic stuttering – EwRIS is distinguished by the 'myoclonic' nature of the epileptic stuttering, while non-epileptic stuttering is characterized by involuntary repetitions, prolongations of sounds, syllables, words or phrases as well as involuntary silent pauses where the person who stutters is unable to produce sounds.
- JME - in EwRIS the myoclonus is all or nearly all (e.g. 80-90%) reading or language-related,[75, 80] localized to the jaw and is not predominantly in the morning.[74] In JME, the myoclonus occurs spontaneously (though cognitive induction by praxis – thinking or decision-making - has been recognized,[81] affects the upper extremities, is more frequently seen in the morning and a photoparoxysmal response may be seen on EEG.
- Focal seizures in occipito-temporal networks rarely can be induced by reading, but there is no orofacial myoclonus.[82]

Developmental and epileptic encephalopathies

In epilepsies that begin in adolescence or adulthood, after developmental milestone acquisition, the term *developmental encephalopathy* (DE) can be applied when there is clinical onset of a condition manifesting with cognitive, neurological or psychiatric impairment, stagnation or regression, if this is considered related directly to the underlying etiology and not to frequent epileptic activity. In contrast, an *epileptic encephalopathy* (EE) is defined 'where there is no preexisting developmental delay' and the etiology of the epilepsy is not thought to cause encephalopathy in its own right, but the encephalopathy is believed to be related to the frequency and severity of epileptic activity.[83] Patients may have a DE or EE, however when both factors contribute to a patient's functioning the patient is considered to have a *developmental and epileptic encephalopathy (DEE).* In this section of the paper, we discuss PME.

The progressive myoclonus epilepsies (PME)

The syndrome of progressive myoclonus epilepsy (PME, **Table 9**) is rare, and comprises a heterogenous group of underlying genetic etiologies recognized in the presence of 1) myoclonus, 2) progressive motor and cognitive impairment, 3) sensory and cerebellar signs and 4) abnormal background slowing on EEG,[84] that 5) appear in an individual with prior normal development and cognition. The severity of the condition depending on the etiology. There may be a family history, with autosomal recessive inheritance in most cases, but PME can be sporadic. The prevalence varies from one region to another with higher prevalence in isolated regions or in cultures that favour consanguineous marriages. The geographical and ethnic background of the patient is important data for the diagnosis of the underlying genetic cause.

The following entities account for the majority of PME: Unverricht-Lundborg disease, Lafora disease, neuronal ceroid lipofuscinosis, mitochondrial disorders (MERRF, POLG1, MELAS) and sialidosis. Three of these are discussed further in this paper and summarized in **Table 10**. Less commonly, the following entities may be identified: dentatorubo-pallidoluysian atrophy, juvenile Huntington disease, action-myoclonus-renal failure syndrome, juvenile neuroaxonal dystrophy, pantothenate-kinase associated neurodegeneration, neuroserpin inclusion body disease, leukoencephalopathy with vanishing white matter, early-onset Alzheimers disease, GOSR2 pathogenic variants, myoclonic epilepsy in Down syndrome, GM2 gangliosidoses, tetrahydrobiopterin deficiency, non-infantile neuronopathic Gaucher's disease, Niemann Pick type C and celiac disease. Genetic testing is required for most of these conditions to confirm the clinical diagnosis and identify the etiology. Histological or biochemical testing can be used to support the diagnosis in specific circumstances e.g. Lafora bodies in sweat duct cells or ragged red fibres in biopsied muscle.

Unverricht-Lundborg disease (ULD)

Also known as: epilepsy progressive myoclonus 1 (EPM1) or Baltic myoclonic epilepsy

This is the most frequent cause of PME world-wide, and is associated with a less severe PME.[85] Most cases originate from Scandinavian or Baltic regions of Europe, or Northern Africa. Prevalence may be as high as 1:20,000 in Finland.[86] The severity of the condition, and therefore life expectancy, varies widely.[85-87] ULD begins before 18 years of age, typically 7-13 years of age,[87] with tonic-clonic or myoclonic seizures, absence seizures can occur. Myoclonus may be induced by tactile or photic stimulation and is usually more pronounced upon waking. It can be significantly worsened by phenytoin. Progression is seen in adolescence, usually beginning in the first 6 years after seizure onset, with worsening of myoclonus, development of ataxia and mild cognitive decline. The condition tends to stabilize in early adulthood with minimal or

no further cognitive decline and myoclonus and ataxia may even improve. The EEG background may be normal at onset, but progressive slowing of the background appears over time. Photic stimulation facilitates spike-and-wave discharges on EEG in most cases,[84] this can be seen early in the condition. Interictal generalized spike and polyspike-wave discharges are seen, **Figure 10**. Ictal EEG during myoclonic seizures shows generalized polyspike-and-wave. MRI is usually normal in the early stages of the condition; later mild atrophy can be seen. A repeat expansion variation in the cystatin B (*CSTB, EMP1*) gene accounts for approximately 90% of the cases worldwide, inheritance is autosomal recessive. The type of pathogenic variant can relate to severity.[87] This condition is differentiated from other PME's by notable dysarthria, dysphagia and tremor.

Lafora disease

Also known as: Lafora body disease, progressive myoclonic epilepsy 2A and 2B, EMP 2A and 2B

Lafora disease is more prevalent in Southern Europe, Northern Africa and Central and Southern Asia.[88] The disorder is usually fatal around 10 years after onset. This PME begins between 6 and 19 years of age, typically 14-15 years, with cognitive decline, cerebellar signs (ataxia, incoordination), vision loss and myoclonic and generalized tonic-clonic seizures. Focal seizures with visual symptoms (transient blindness, elemental visual phenomena or visual hallucination) are characteristically an early manifestation.[88] Myoclonic seizures gradually worsen and become intractable and progressive cognitive decline continues. By 10 years after onset, affected individuals have near-continuous myoclonus with absence seizures, frequent generalized tonic-clonic seizures, and have profound dementia or are in a vegetative state. At onset, the EEG has a normal background, with interictal spike wave and polyspike discharges that are activated by photic stimulation at low frequencies. In contrast to JME, generalized

discharges are not activated during sleep,[88] though focal discharges in the posterior regions can be.[89] With time, the EEG background slows, the frequency of discharges increases and discharges may have emphasis in posterior regions **(Figure 11)**. Patients with Lafora disease can develop erratic myoclonus without EEG correlate, a further distinction from JME. MRI is usually normal, but MR spectroscopy may show significant reduction of the NAA/creatine ratio in frontal cortex, basal ganglia and cerebellar hemispheres.[90] FDG-PET can show extensive areas of decreased glucose metabolism, the severity of which may correlate with stage of disease.[91] Pathogenic gene variants in *EPM2A* (laforin) and *EPM2B* (malin) are found in 70% and 27% of cases respectively, with no pathogenic variant found in 3%.[92] Lafora bodies (accumulation of glycogen, **Figure 12**) are seen in sweat duct cells and in other tissues.[93] This condition is differentiated from ULD by the presence of cognitive decline early at the onset and rapid progression of the PME.

Neuronal ceroid lipofuscinosis (NCL, Batten disease, ceroid lipofuscinosis/CLN)

The neuronal ceroid lipofuscinoses are a group of neurodegenerative lysosomal storage disorders, resulting in excess accumulation of lipopigments (lipofuscin). They were originally classified by age at onset: the infantile-onset form ('Finnish form', not a PME), the late infantile-onset form, the juvenile-onset form and the adult-onset form. With the identification of causal gene variants, however, the NCLs are now classified according to the underlying pathogenic gene defect and age of onset. To date, more than a dozen genetically distinct diseases are recognized.[94, 95]. The diagnosis of NCLs is based on genetic testing and (in some types) assays of enzyme activity. Electron microscopy of lymphocytes or tissue may be useful for non-classical presentations. The most prevalent NCL's are:

- CLN2 (previously known as NCL type 2, the classic late infantile onset form NCL and Jansky-Bielschowsky disease). This is the most prevalent NCL and has been reported

in different ethnic groups.[96, 97] New onset of unprovoked seizures in a child aged 2 to 4 years of age, with a history of early language delay should prompt consideration of CLN2. Multiple seizures types can occur, including febrile, tonic–clonic, absence, myoclonic, atonic and focal (with or without focal to bilateral tonic-clonic seizures) seizures. Myoclonic seizures may not be present at onset. Delayed speech development is often recognized prior to onset of seizures. Disease progression is often rapid with loss of mobility and language by the age of 4–5 years. Further regression occurs, with loss of vision occurring over the next few years. Patients die between the ages of 8 and 12 years. EEG may show a photo-paroxysmal response at low frequencies of flash stimulation (1–3Hz, **Figure 13**),[98] the spike-waves are time locked to the photic stimuli. MRI shows posterior white matter signal alteration or cerebellar atrophy. Early diagnosis is important in CLN2 disease, because enzyme replacement treatment is available, this can delay motor and language decline.[99] CLN2 is caused by pathogenic gene variants in the tripeptidyl-peptidase1 (*TPP1*) *CLN2* gene, resulting in TPP1 enzyme deficiency and subsequent accumulation of lipopigments (lipofuscin) in neurons and other tissues. Variants of late infantile onset NCL may also be caused by pathogenic gene variants in *CLN1*, *CLN5*, *CLN6*, *CLN7*, *CLN8*, and *CTSD*.[94, 95]

- CLN3 (previously known as NCL type 3, the classic juvenile onset form NCL, Batten disease, or Spielmeyer-Vogt-Sjögren disease). This is frequent in Scandinavia (1% of Swedes carry the gene,[84] but is rare in other regions. This NCL is clinically similar to the late infantile form, but the age of onset is later (4 to 10 years) and the survival time longer (13 to 30 years). Visual loss is rapidly progressive, with macular degeneration, optic atrophy and retinitis pigmentosa.[100] This form is due to pathogenic variants in the *CLN3* gene. The mutant CLN3 protein retains residual function, explaining why this form of CLN shows later onset and less severe clinical manifestations compared to

other forms of CLN.[101] Variants of juvenile NCL may also be caused by pathogenic gene variants in *CLN1*, *CLN2*, *CLN9* and *ATP13A2*.[94, 95]

- *Adult onset NCL*. This NCL (previously known as Kufs disease) is rare and appears as a sporadic condition. It is present in two forms: type A is a PME with later development of dementia and ataxia, and type B (not a PME) is characterized by dementia with cerebellar or other extrapyramidal motor symptoms. Visual impairment does not occur. Age of onset is 11 to 50 years of age, typically 30 years.[102] The prognosis is poor with death around 10 years after the onset. The storage material of lipopigments has different ultrastructural patterns with mixed combinations of 'granular,' 'curvilinear,' and 'fingerprint' profiles, **Figure 14**. This NCL is caused by pathogenic variants in the *CLN6* gene[103] Variants of adult onset NCL may also be caused by pathogenic gene variants in *CTSD, CLN1*, *CLN3*, *CLN5*, *CLN6*, *CTSF*, *GRN*.[94, 95]

Discussion

While not every person with epilepsy can be characterized as having an epilepsy syndrome, where a syndrome is identified this can provide important guidance on investigation for etiology, management and prognosis. Syndromes remain predominantly identified and differentiated based on their electro-clinical presentation with specific seizure types in specific clinical contexts and specific interictal EEG patterns. In the modern era, clinical phenotyping has been enhanced through the use of home video of seizures allowing clinicians access to detailed review of seizure semiology, often complementing or superior to video obtained during video-EEG.[104] For suspected syndromes, clinicians may select targeted EEG investigations (awake with photic stimulation, asleep, prolonged or overnight) that assist with confirming the specific epilepsy syndrome. As epilepsy syndrome identification informs likely etiology, the presence of a syndrome allows clinicians to initiate the highest-yield most cost-

effective investigations to obtain an etiology diagnosis, limiting discomfort or risk to the patient. Work on investigating the individual's family history (including clinical, EEG and imaging phenotypes of every affected member) is increasingly essential for the diagnosis of many focal epilepsy syndromes presenting at a variable age, and enhances genetic variant curation during genomic investigation, which is increasingly utilized in the current era. As the focal epilepsy syndromes with genetic/structural etiologies are important contributors to the epilepsy syndromes presenting at a variable age (excepting the IGE's discussed elsewhere,[8] family phenotyping and genomic investigation incorporated into the early epilepsy care of every patient should allow better patient care. Identifying a syndrome or etiology can inform therapy, as specific ASM may optimize seizure control for generalized epilepsies whereas others (e.g. sodium channel blockers) may aggravate generalized seizures. A patient with JME can have aggravation of their epilepsy, to mimic PME, when treated with sodium-blockers (such as carbamazepine). PME can be aggravated significantly by sodium-blockers (such as phenytoin). Though apparently a focal epilepsy, patients with mTLE-HS may rarely have aggravation of their epilepsy with sodium-channel blockers, if there is a concomitant genetic sodium channelopathy. Further, for focal epilepsy syndromes (SHE, (F)FEVF, EAF, mTLE-HS and RE), epilepsy surgery may be critical to management if seizures do not respond to ASM. This includes when there is an underlying genetic-structural etiology (specifically mTOR pathway genes *DEPDC5*, *NPRL2*, *NPRL3*), but epilepsy surgery has not been associated with seizure freedom in Dravet syndrome associated mTLE-HS.[63] In this fashion, both the syndrome and genetic/structural etiology are important for tailoring treatment, and counselling regarding candidacy for surgery and likely surgical outcome. Finally, while autoimmune-associated epilepsies other than RE were not included in this paper, as their specific clinical presentations are covered elsewhere,[105] these conditions further illustrate the

importance of a focus on etiology in epilepsies that begin at a variable age, as their prompt recognition allows earlier appropriate treatments to optimize outcomes.

Fortunately, the progressive epilepsy syndromes presenting at a variable age are rare, specifically RE and PME. In these syndromes, cognitive and neurological impairment are eventually nearly always present. Therapeutic options are limited for these syndromes, for example hemispheric disconnection in RE, which though resolving the epilepsy results in a permanent hemispheric neurological deficit. Therapeutic options are not available for many PME's, though recently enzyme replacement therapy has been made available for CLN2.[99] There is a great need for better therapies for these disorders identified, through patients being included in clinical trials.

Historically, epilepsy syndromes evolved from patients (and families) being grouped into empirically delineated electro-clinical presentations, and then research reported data from those cohorts, describing their phenotype (clinical, EEG, imaging) and associated etiologies. This past approach has strongly influenced early characterization of epilepsy syndromes. As time passed, and with contributions from genetic research, the phenotypic spectrum for some syndromes have been expanded, for example Dravet syndrome, and etiology-specific epilepsy syndromes are increasingly being characterized. This is likely to continue into the future, and etiology-specific epilepsy syndromes will be increasingly important. Strictly delineation of epilepsy syndromes can be harmful if they exclude patients who do not precisely meet a syndrome's criteria from having appropriate investigation and treatment for the syndrome (and related etiology) that they approximate, but do not strictly meet. Syndromes should, therefore, be revised in the future to reflect expanded phenotypes, or alternatively more precise phenotypes, when these are recognized as relevant, and to include newly identified etiologies,

when these are discovered. This may have importance when specific family, pregnancy, preventative or mitigating therapies are available for the etiology and/or its neurodevelopmental and cognitive sequelae - for example emerging anti-epileptogenesis strategies before onset of seizures in specific mTORopathies.[106] Looking to the future, with ongoing research improving delineation of structural brain abnormalities, immune-mediated pathologies and pathogenic gene variants, it is likely that more etiology-specific epilepsy syndromes will emerge but epilepsy syndromes themselves will continue to have relevance as the phenotypes associated with some etiologies may not be specific (e.g. *DEPDC5*), and syndrome identification may remain important for targeting investigation towards a group of potential etiologies and initially guiding treatment and prognosis counselling. Future work establishing diagnostic criteria for etiology-specific epilepsy syndromes will be important for clinical research into the development of precision therapies, advancing knowledge of pathogenesis (for example the mTOR inhibitors for mTORopathies – *TSC1/2, DEPDC5, NPRL2, NPRL3*) or potentially identifying sub-groups within specific etiologies, where it might be possible to predict which patients will respond best to a specific treatment. It is anticipated that this will be the role of future Taskforce's of the ILAE.

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Tables:

Table 1. Genetic focal epilepsy syndromes and genes currently implicated

Focal epilepsy syndrome	**Related genes**
Sleep-related hypermotor epilepsy (SHE)	*CHRNA4, CHRNA2, CHRNB2, DEPDC5, KCNT1, NPRL2, NPRL3, PRIMA1*

Familial focal epilepsy with variable foci (FFEVF)	*DEPDC5*, *NPRL2*, *NPRL3*
Epilepsy with auditory features (EAF)	*LGI1*, *RELN*, *MICAL1*

Table 2. Distinguishing features of the genetic, structural and genetic-structural focal epilepsies of adolescence/adulthood/any age.

Syndrome	Onset (usual)	Clinical	Interictal EEG	Imaging
SHE	Second decade of life	From sleep, brief hyperkinetic or asymmetric tonic/dystonic motor seizures	Background interictal EEG is usually normal. Focal (usually frontal) sharp waves or spikes can be seen.	Normal, focal cortical dysplasia or acquired structural abnormality
(F)FEVF	First or second decade of life	Focal seizures semiology dependent on focal cortical area involved in an individual, but constant in that individual	Background interictal EEG is usually normal. Focal sharp waves or spikes can be seen.	Normal or focal cortical dysplasia

EAF	Second or third decade of life	Sensory – auditory Cognitive – receptive aphasia	Background interictal EEG is usually normal. Focal (usually temporal) sharp waves or spikes can be seen.	Usually normal, though posterior temporal neocortical malformations reported.

Key: SHE-sleep related hypermotor epilepsy, FFEVF-familial focal epilepsy with variable foci, EAF-epilepsy with auditory features.

Table 3. Core diagnostic criteria for Sleep-Related Hypermotor Epilepsy.

	Mandatory	**Alert**	**Exclusionary**
Seizures	Brief focal motor seizures with hyperkinetic or asymmetric tonic/dystonic features occurring predominantly during sleep	Seizures predominantly from the awake state	Seizures only during wakefulness Generalized onset seizures

EEG		Frequent epileptiform discharges outside of the frontal regions Generalized epileptiform discharges	
Age at onset		Onset <10 or > 20 years of age	Age at onset <2 months; > 64 years
Development at onset		Moderate to severe intellectual disability	
Neurological exam		Focal neurological examination abnormalities	
Are MRI or ictal EEG required for diagnosis? An MRI is not required for diagnosis but should be done to evaluate for underlying etiology. An ictal EEG is not required for diagnosis.			
Syndrome without laboratory confirmation: In resource limited regions, SHE can be diagnosed if other mandatory and exclusionary criteria are met, and the patient has witnessed or video-recorded hyperkinetic seizures during sleep.			

Table 4. Core diagnostic criteria for Familial Focal Epilepsy with Variable Foci.

	Mandatory	**Alert**	**Exclusionary**

Seizures	Focal onset seizures		Generalized onset seizures
EEG		Generalized epileptiform discharges	
Age at onset		Neonatal onset	
Development at onset			Moderate to profound intellectual disability
Neurological exam		Focal neurological examination abnormalities	
Imaging	Normal or focal cortical dysplasia		
Other studies – genetics, etc	Family history of individuals with focal seizures that arise from cortical		Family history of focal seizures which occur exclusively before 20 months of age

	regions that differ between family members		
Are MRI or ictal EEG required for diagnosis? An MRI is required for diagnosis. Familial focal seizures due to tuberous sclerosis should be excluded, family history of focal seizures might be incidental due to an acquired cause. An ictal EEG is not required for diagnosis.			
Syndrome without laboratory confirmation: In resource limited regions, FFEVF can be diagnosed without EEG in a patient who meets mandatory and has no exclusionary non-laboratory criteria. However, an MRI or CT is required to exclude other structural etiologies.			

Table 5. Core diagnostic criteria for Epilepsy with Auditory Features.

	Mandatory	**Alert**	**Exclusionary**
Seizures	Focal sensory auditory seizures and /or focal cognitive seizures		Generalized onset seizures Other focal onset seizures

	with receptive aphasia		
EEG		Generalized epileptiform discharges	
Development at onset			Moderate or severe intellectual disability
Neurological exam		Focal neurological examination abnormalities	
Imaging	Normal or focal cortical dysplasia		
Are MRI or ictal EEG required for diagnosis? An MRI is required for diagnosis to exclude other causes. An ictal EEG is not required for diagnosis.			
Syndrome without laboratory confirmation: In resource limited regions, MRI is required for to exclude other structural etiology.			

Table 6. Core diagnostic criteria for Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis.

	Mandatory	**Alert**	**Exclusionary**

Seizures	Focal aware or impaired awareness seizures with initial semiology referable to medial temporal lobe networks (see text)	Initial semiology referable to networks other than mesial temporal (see text)	Generalized onset seizures
EEG		Consistent absence of temporal interictal discharge despite repeated EEGs Generalized epileptiform discharges High amplitude, centrotemporal spikes with horizontal dipole	Recorded seizures with generalized onset EEG seizures recorded with onset in regions outside the temporal lobe

		Interictal epileptiform discharges or focal slowing outside of the temporal regions or over the posterior temporal region.	
Age at onset		Age at onset <2 years	
Development at onset		Moderate to severe intellectual disability	
Neurological exam		Focal neurological findings such as hemiparesis (excluding facial asymmetry)	
Imaging	Hippocampal sclerosis (unilateral or bilateral) on MRI		
Are MRI or ictal EEG required for diagnosis? An MRI documenting hippocampal sclerosis is required for diagnosis. An ictal EEG is not required for diagnosis.			

Syndrome without laboratory confirmation: In resource-limited regions, an MRI is required for confirmation of diagnosis.

Table 7. Core diagnostic criteria for Rasmussen encephalitis.

	Mandatory	**Alert**	**Exclusionary**
Seizures	Focal/hemispheric seizures which often increase in frequency over weeks to months	Focal onset independently in both hemispheres (only 2% of RS is bilateral)	Generalized seizure types
EEG	Hemispheric slowing and interictal discharges	Generalized spike-wave discharges	
Age at onset		Onset in adolescence or adulthood	
Development at onset		Abnormal development prior to seizure onset	
Neurological exam			Hemiparesis present at onset (if permanent hemiparesis is present immediately following

			status epilepticus consider HHE)
Imaging	Progressive hemiatrophy (early insula and head of caudate atrophy) (see text).	Lack of hyperintense signal and/or atrophy of the ipsilateral caudate head, and/or lack of T2/FLAIR hyperintense signal of grey or white matter	Imaging shows Sturge Weber Syndrome
Other studies – genetics, etc			Metabolic cause of epilepsia partialis continua Condition is due to specific antibody-mediated encephalitis
Long Term outcome	Drug resistant epilepsy Progressive neurological deficits		
Are MRI or ictal EEG required for diagnosis? An MRI is required for diagnosis. An ictal EEG is not required for diagnosis.			

Syndrome-in-evolution: Children with drug-resistant, focal hemispheric seizures that progressively increase in frequency, with progressive neurological deficits, but whose MRI remains normal, and where other metabolic and autoimmune etiologies have been excluded should be highly suspected of having emerging Rasmussen encephalitis.
Syndrome without laboratory confirmation: In resource-limited regions, Rasmussen encephalitis can be diagnosed without EEG in a patient with focal/hemispheric onset seizures, who shows the typical clinical evolution, who meets all other mandatory and exclusionary clinical criteria and has no alerts. However, imaging (CT or MRI) is required to exclude other causes.

Table 8. Core diagnostic criteria for Epilepsy with Reading-induced Seizures.

	Mandatory	**Alert**	**Exclusionary**
Seizures	Reflex myoclonic seizures affecting orofacial muscles triggered by reading/language related tasks	Prominent myoclonic jerks affecting the upper limbs	All other seizure types, except generalized tonic-clonic seizures
EEG			Background slowing on EEG, excluding in the

			post-ictal phase of a generalized tonic-clonic seizure
Age at onset		>20 years	
Development at onset	Normal		
Neurological exam	Normal		
Imaging	Normal		
Are MRI or ictal EEG required for diagnosis? An MRI is required for diagnosis to exclude a structural cause. An ictal EEG is not required however observation during reading (either directly or by video) is highly recommended as it shows the characteristic myoclonus affecting orofacial muscles.			
Syndrome without laboratory confirmation: In resource limited regions, this syndrome can be diagnosed in children and adults who meet all other mandatory and exclusionary criteria.			

Table 9. Core diagnostic criteria for Progressive Myoclonus Epilepsies.

	Mandatory	**Alert**	**Exclusionary**
Seizures	Myoclonic seizures		

EEG	Generalized spike/polyspike and wave		Persistent focal spikes other than occipital
Age at onset	2-50 years	>20years	
Development	Normal at onset		
Neurological exam	Normal at onset		
Comorbidities	Progressive neurocognitive deterioration (in some cases observation over time is necessary to distinguish PME from JME)		
Imaging	Normal at onset		
Course of illness	Progressive worsening of myoclonus, myoclonic and generalized tonic-clonic seizures, cognitive decline, progressive cerebellar signs.		

	EEG deterioration with progressive background slowing and/or increased paroxysmal activity		
Are MRI or ictal EEG required for diagnosis? An MRI is not required for diagnosis but is often done to evaluate for underlying etiology. An ictal EEG is not required for diagnosis.			
Syndrome without laboratory confirmation: In resource limited regions, PME can be suspected in persons who meet mandatory and exclusionary criteria, without alerts and who show a progressive worsening of myoclonic seizures and neurological and cognitive function.			

Table 10. Key characteristics of important progressive myoclonus epilepsies (PME).

PME type	Age of onset	Progression	Diagnosis
ULD	7-13 years	Slow cognitive and motor deterioration with stabilization in adulthood.	Cystatin B (EMP1) expansion variations account for ~90% of cases worldwide

LD	6-19 years	Early rapid cognitive, vision and motor deterioration; fatal around a decade after onset. Focal seizures with visual symptoms are an early feature.	Laforin (EMP2A) pathogenic gene variant in 70%, malin (EMP2B) pathogenic gene variant in 27%, no pathogenic variant found in 3%. Lafora bodies are seen in sweat duct cells or other tissues.
CLN2	2-4 years	Initial speech delay and seizures, subsequently deterioration in cognition and motor skills, and then vision loss emerges 4-6 years of age.	CLN2/TPP1 pathogenic gene variants. Tripeptidyl-peptidase 1 (TPP1) enzyme activity is reduced. EEG can show a photo-paroxysmal response at low (1-3Hz) frequency. Curvilinear bodies profile of lipofuscin accumulation in tissues (e.g. skin) or lymphocytes.
CLN3	4-10 years	Rapidly progressing vision loss, with macular degeneration, optic atrophy +/- retinitis pigmentosa. Survival late teens-30 years.	CLN3 pathogenic gene variants. Fingerprint profile of lipofuscin accumulation in tissue (e.g. skin) or lymphocytes. Lymphocytes are vacuolated.
Adult-onset NCL (type A)	11-50 years	Slow development of dementia and ataxia; visual impairment does not occur	CLN6 pathogenic gene variants (pathogenic variants in CTSD, PPT1, CLN3, CLN5, CTSF, GRN also reported). Mixed type inclusions (fingerprint, curvilinear,

			rectilinear) in tissue (e.g. skin) or lymphocytes.

Key: ULD=Unverricht Lundborg disease, LD=Lafora disease, NCL=neuronal ceroid lipofuscinosis.

Figure Legends:

Figure 1: The epilepsy syndromes that begin in adolescents, adults and at a variable age.

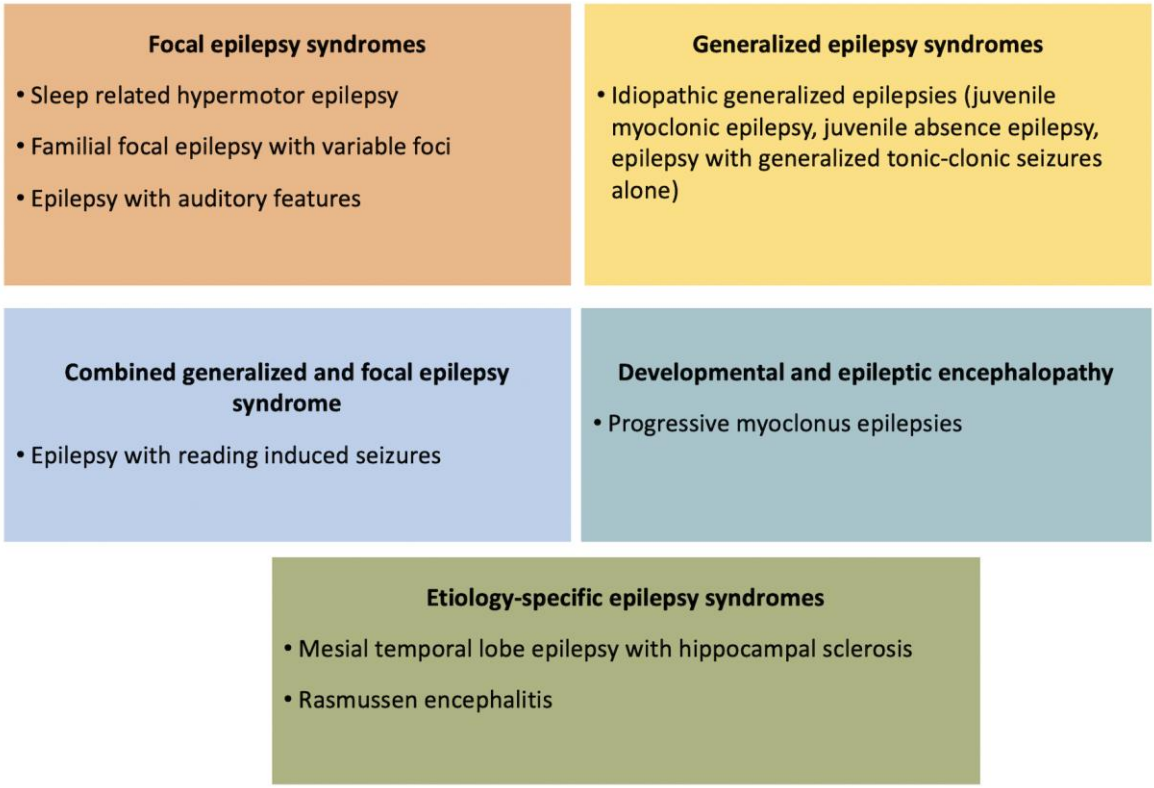

Figure 2. Interictal paroxysmal activity in an 8-year-old boy with sleep-related hypermotor epilepsy. **A)** EEG shows repetitive spiking over the anterior regions of the left hemisphere with phase reversal at F3 and F7; **B)** A hyperkinetic seizure during Non-REM sleep in the same boy. The tracing is almost masked by muscle artifact due to movement of the head, the trunk and the four limbs. It is possible to see fast activity (arrow) in the left frontal region; **C**) MRI shows a subtle band heterotopia in the subcortical white matter of the left frontal lobe (arrow).

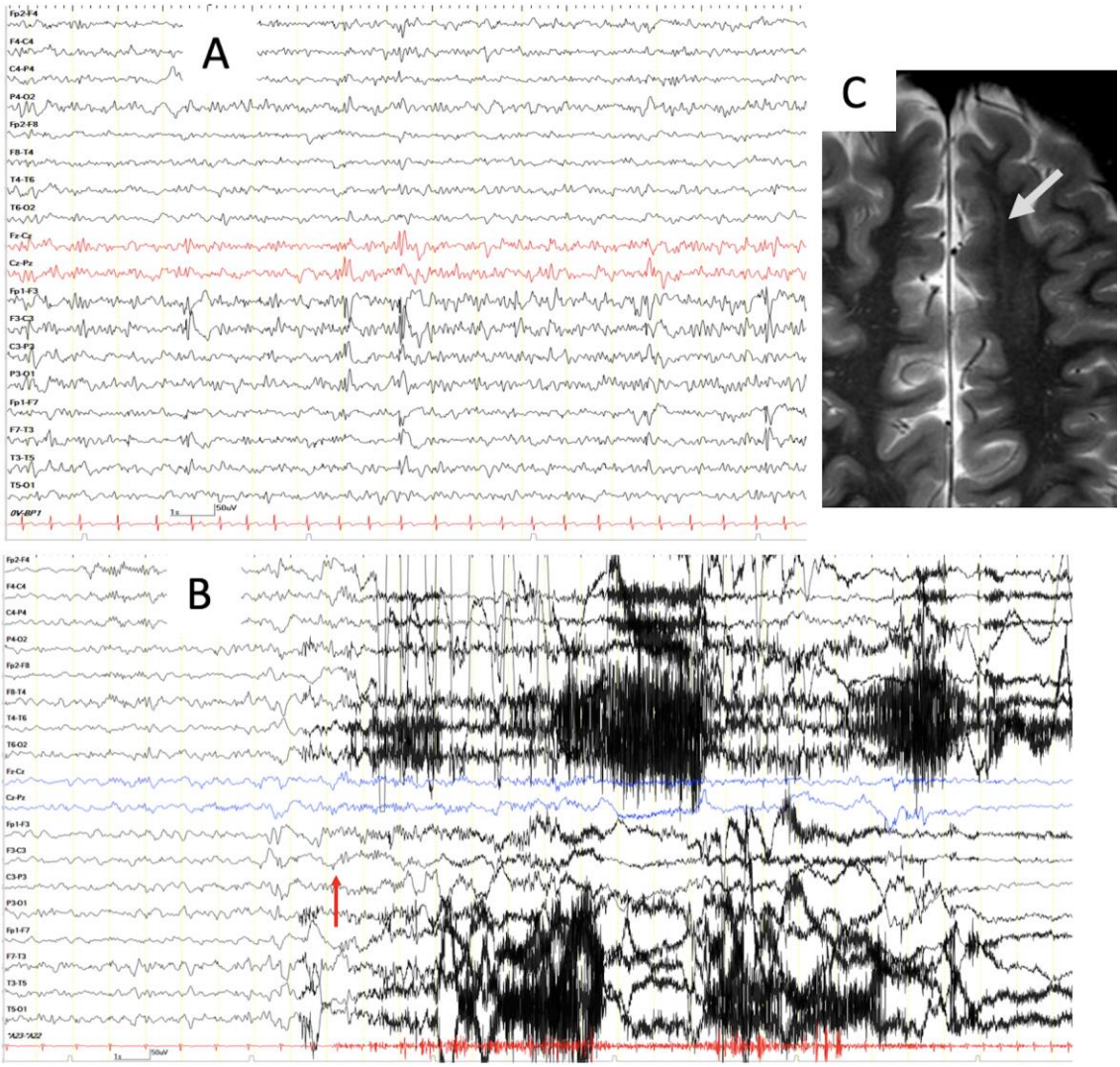
A
B
C

Figure 3: EEG in a patient with mTLE-HS (right sided hippocampal sclerosis). Theta activity over the right temporal regions; repetitive spike and waves complexes with phase reversal on T4 and T6 (drowsiness).

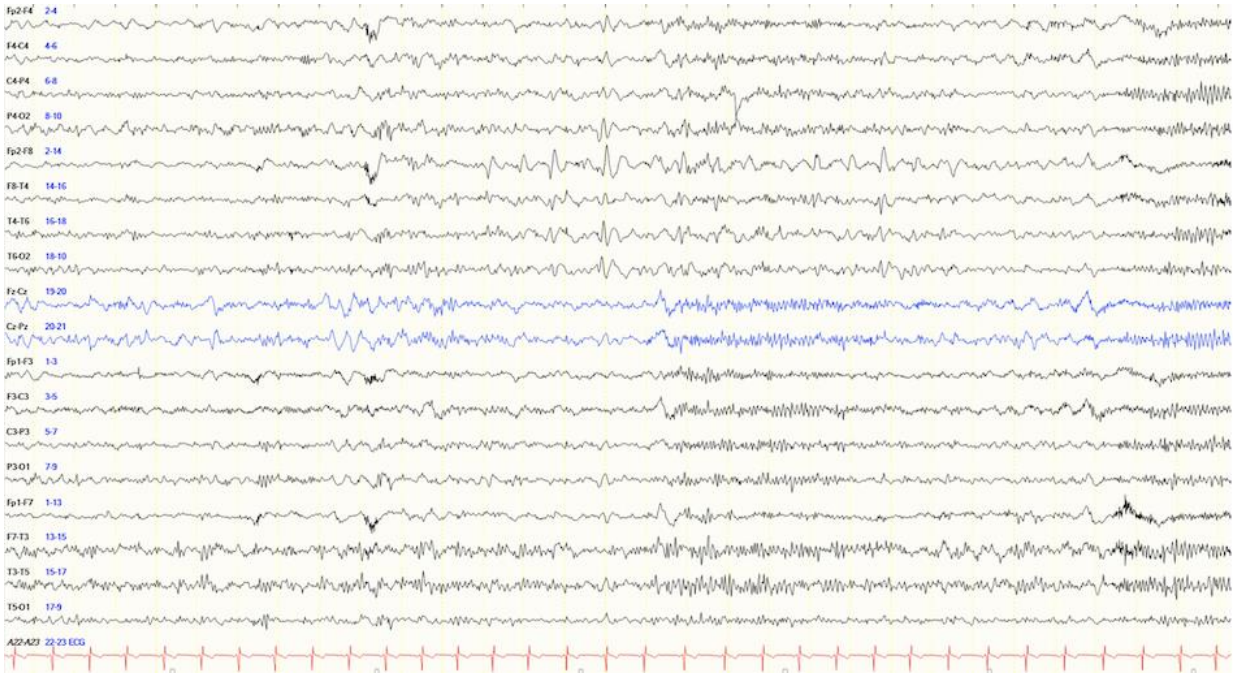

Figure 4: Left mesial temporal seizures in a 50-year-old woman with mTLE-HS (left sided hippocampal sclerosis). O) at the onset of the seizure, interictal spiking disappears; A) a low amplitude, high frequency activity over the left temporal regions appears; B) the patients describes a rising abdominal sensation; C) oro-mandibular automatisms appear, accompanied on the EEG by rhythmic sharp wave activity involving the temporal leads; D) the ictal discharge involves the supra-sylvian region and the patient becomes unaware.

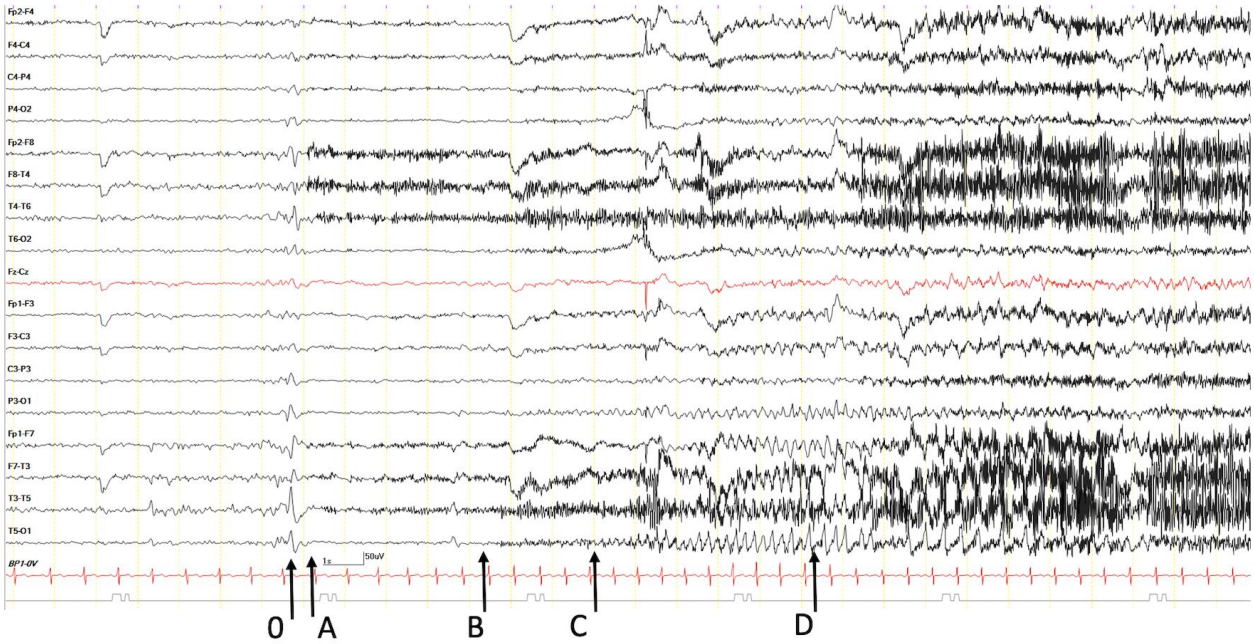

Figure 5: T1-weighted imaging in a coronal plane at right angles to the long axis of the hippocampus showing atrophy of the right hippocampus (arrow).

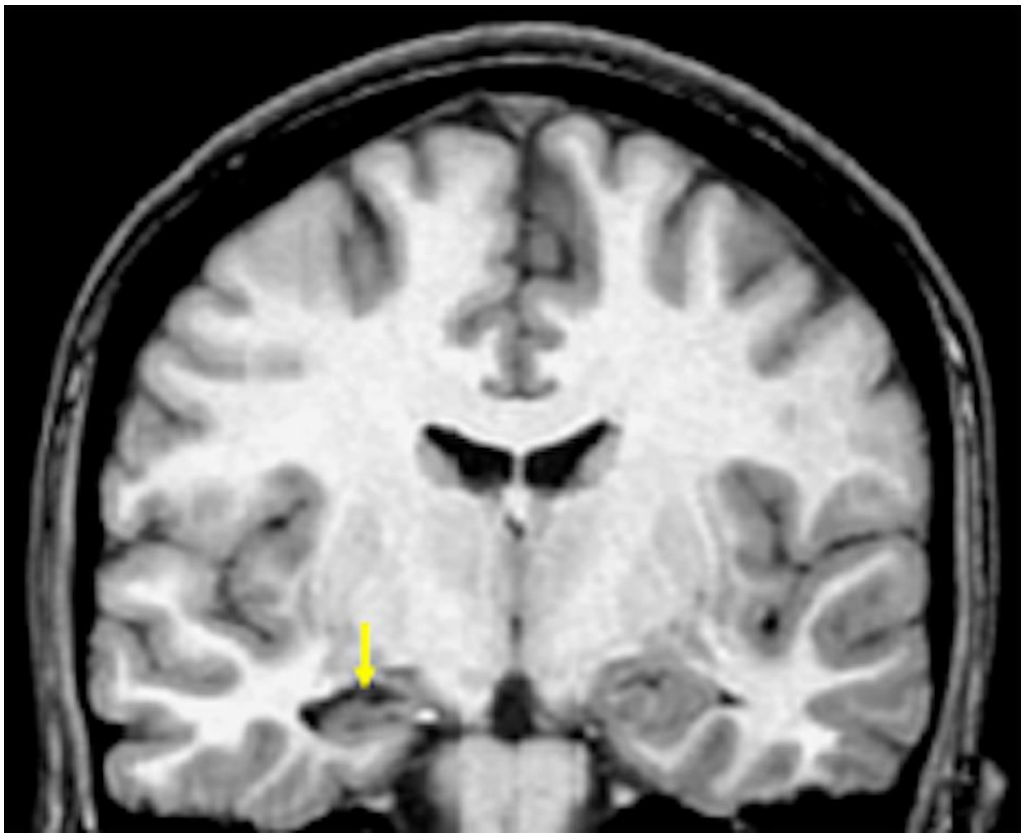

Figure 6: T2-weighted imaging in a coronal plane at right angles to the long axis of the hippocampus showing increased signal and loss of volume in the left hippocampus (arrow).

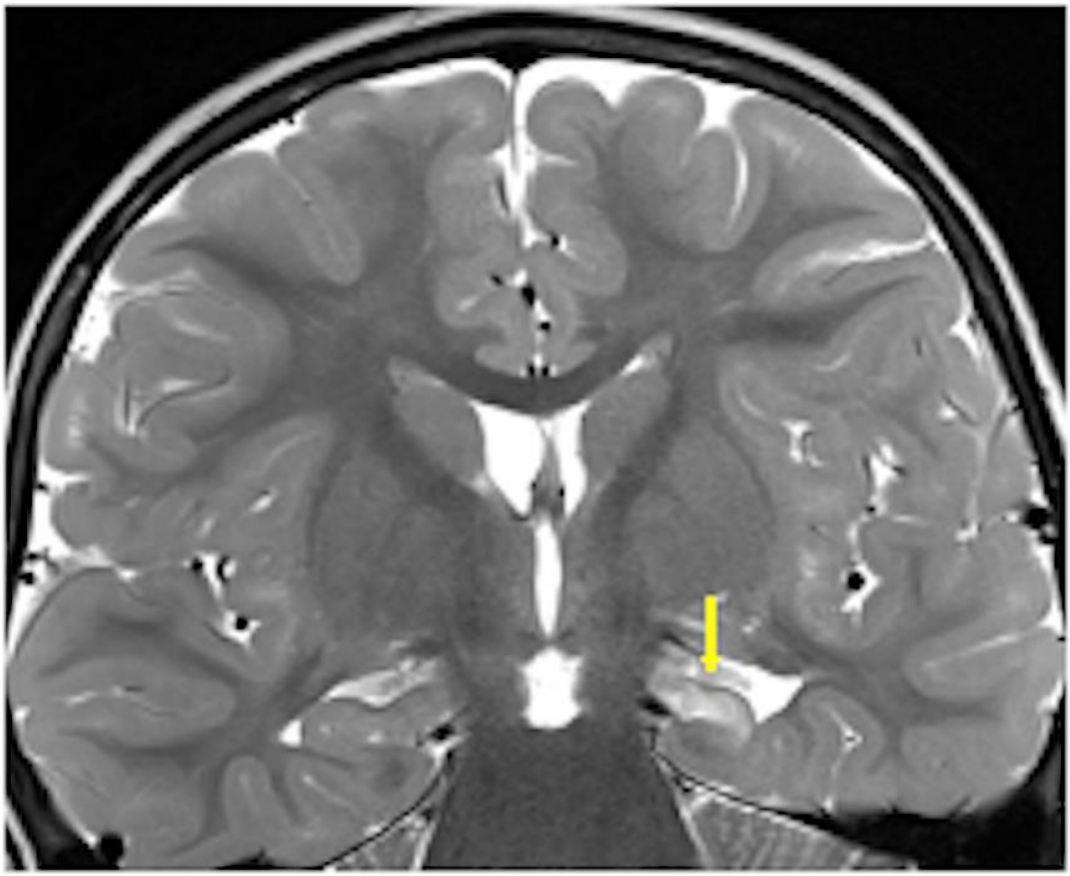

Figure 7. A twelve-year-old female with Rasmussen Encephalitis affecting the left hemisphere, 18 months after seizure onset: A) interictal EEG (bipolar montage) showing sharp waves (circled, maximum amplitude at Fz-Cz and Cz-Pz) with slow waves (square, Fz-Cz, Cz-Pz, Pz-Oz, F3-C3), and B) axial FLAIR MRI performed at the same age showing focal hyperintensity and atrophy in the left supplementary motor area.

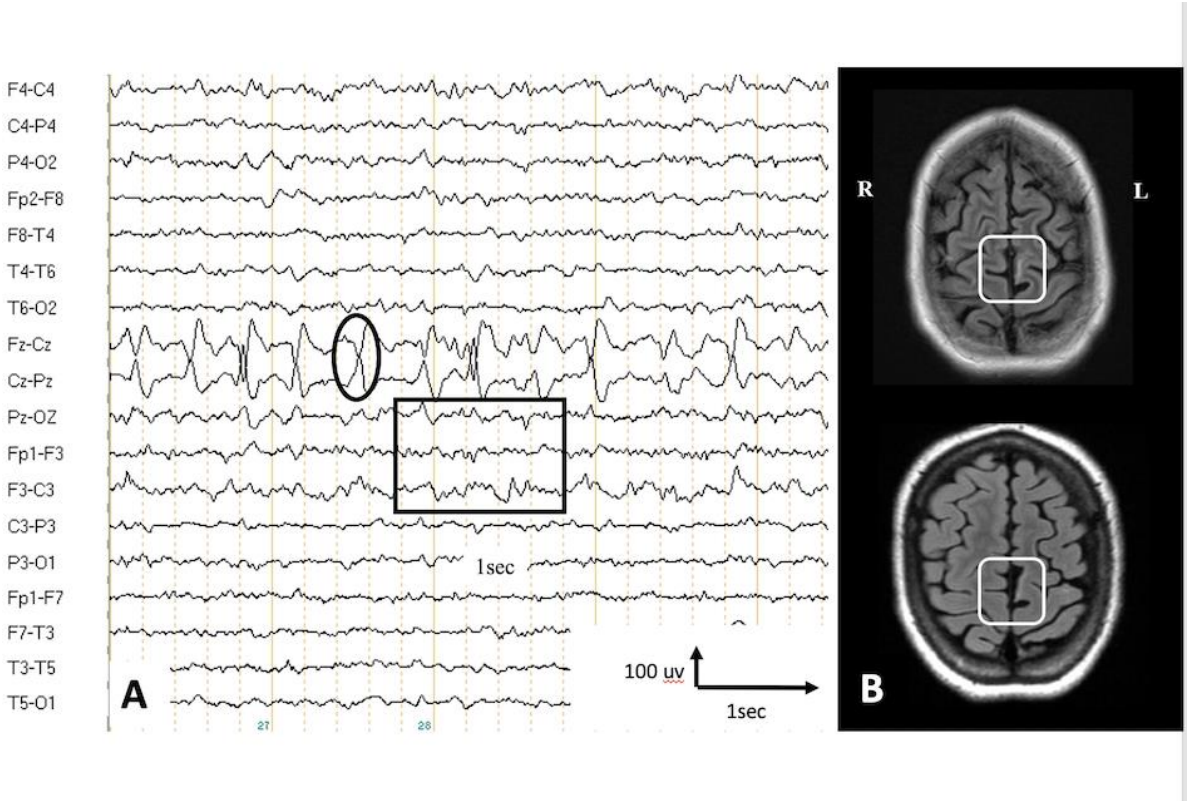

Figure 8. T2-weighted axial image showing atrophy of the caudate (arrow) with subtle loss of volume of the left insular region (evident as increased sulcal spaces).

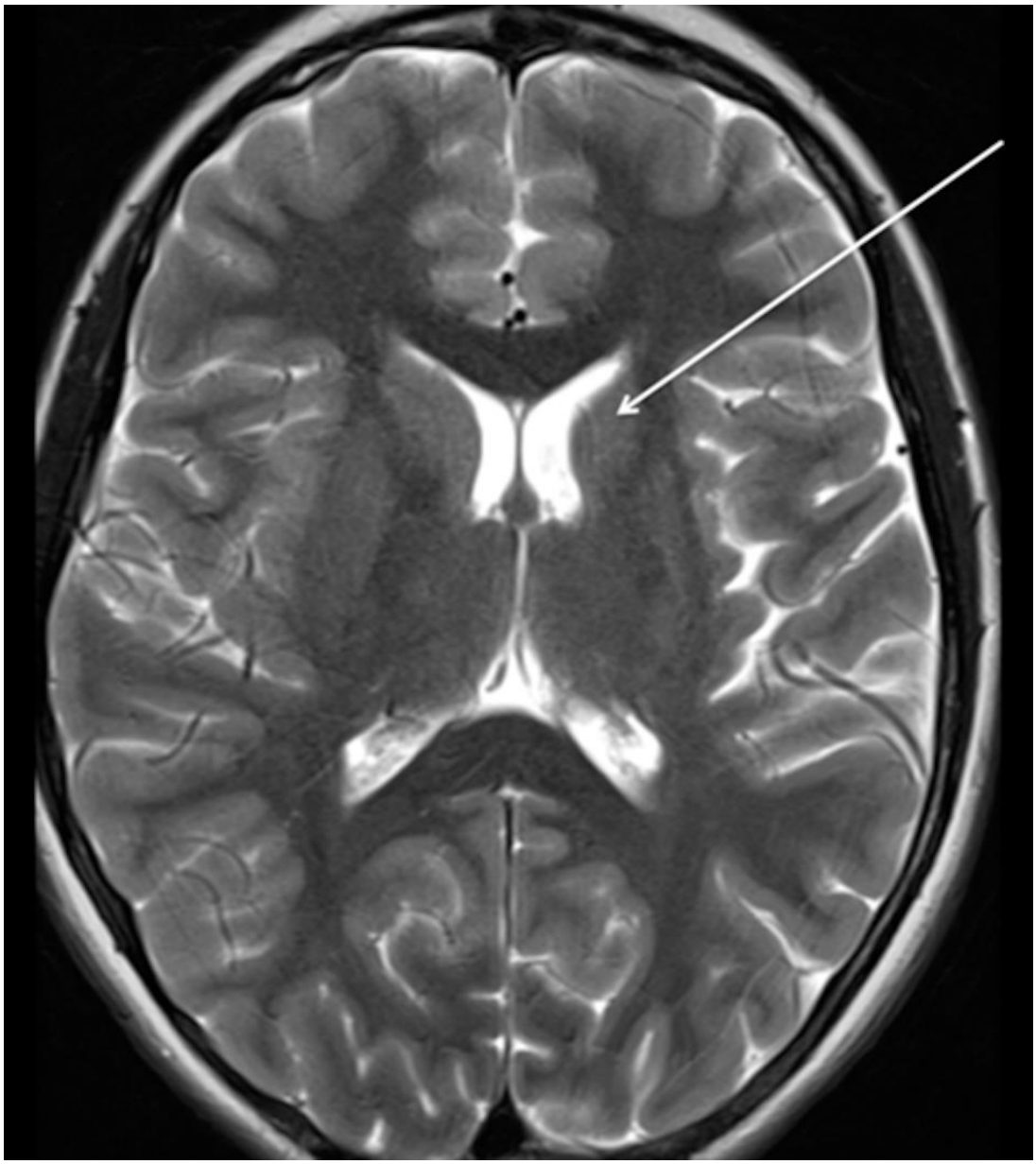

Figure 9: A 42-year-old woman with epilepsy with reading induced seizures from 18 years of age. EEG shows A) focal C3 and C4 spikes with perioral bilateral myoclonia, followed by an interictal bilateral spike-wave and B) interictal EEG showing 3-6 Hz generalized spike-wave discharges.

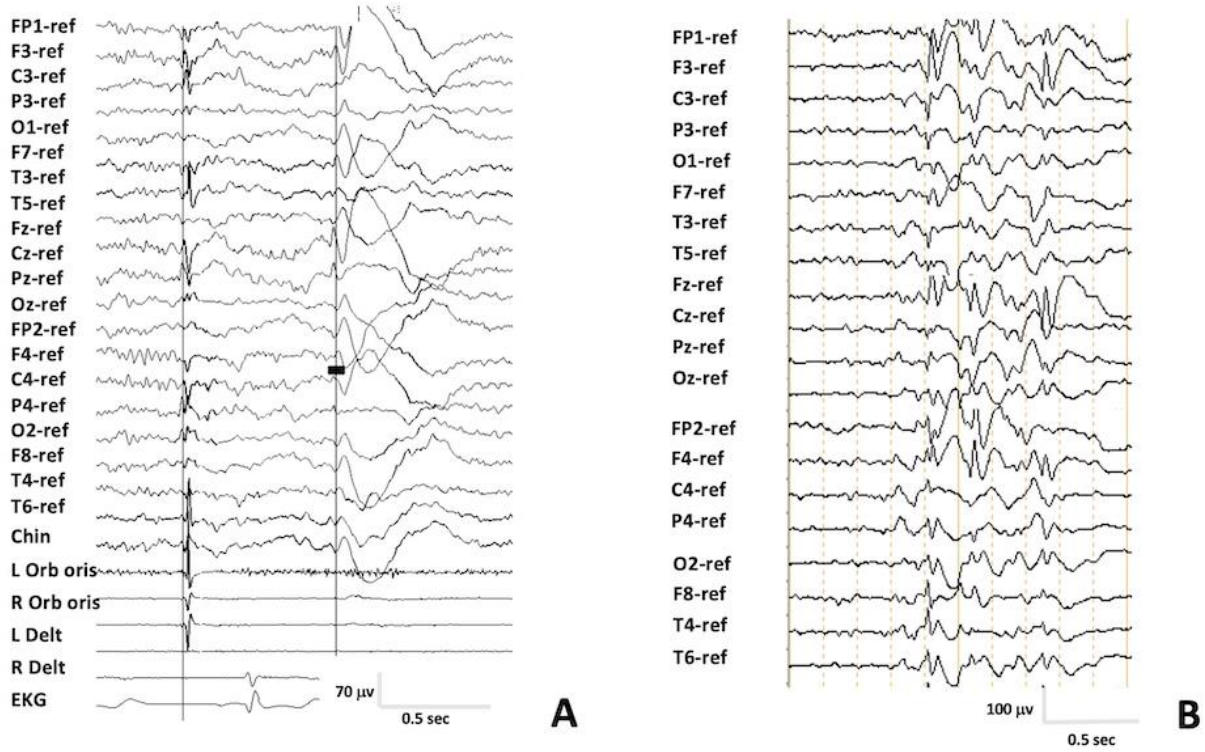

Figure 10: Polygraphic recording in a 16-year-old boy with Unverricht-Lundborg disease. **A)** in the awake state, abundant fast rhythms (due to benzodiazepines) and diffuse spike wave and sharp waves bursts are seen, on EMG there are bursts of myoclonic activity with and without an EEG burst; **B)** in stage 2 sleep, diffuse bursts of polyspike activity with anterior predominance are seen without myoclonic activity on EMG.

Key: EMG – electromyogram, R Delt. – right deltoid, R/L Flex. – right/left arm flexors, R/L Ext. – right/ left arm extensors, L Quadr. Fem - left quadriceps femoralis.

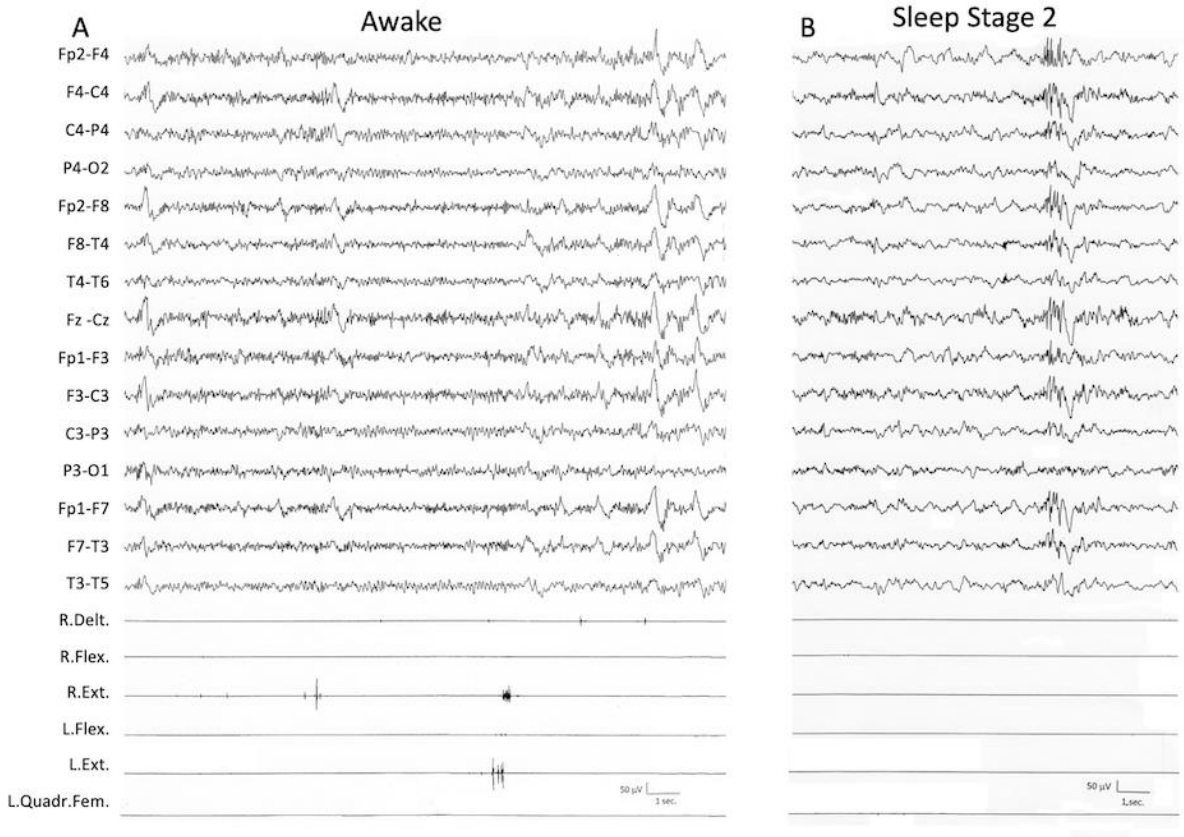

Figure 11: Polygraphic recording in a 16-year-old girl with Lafora disease. Diffuse slowing of the background activity is present, with abundant fast activity (due to benzodiazepines) overlaid. There are diffuse burst of irregular spike wave complexes. Low amplitude spikes are seen in the posterior regions. On EMG leads, almost continuous myoclonic activity is seen.

Key: EMG – electromyogram, R/L Flex.-Ext. – right/left flexor-extensor muscles of the arms, ECG – electrocardiogram, Resp – respiration.

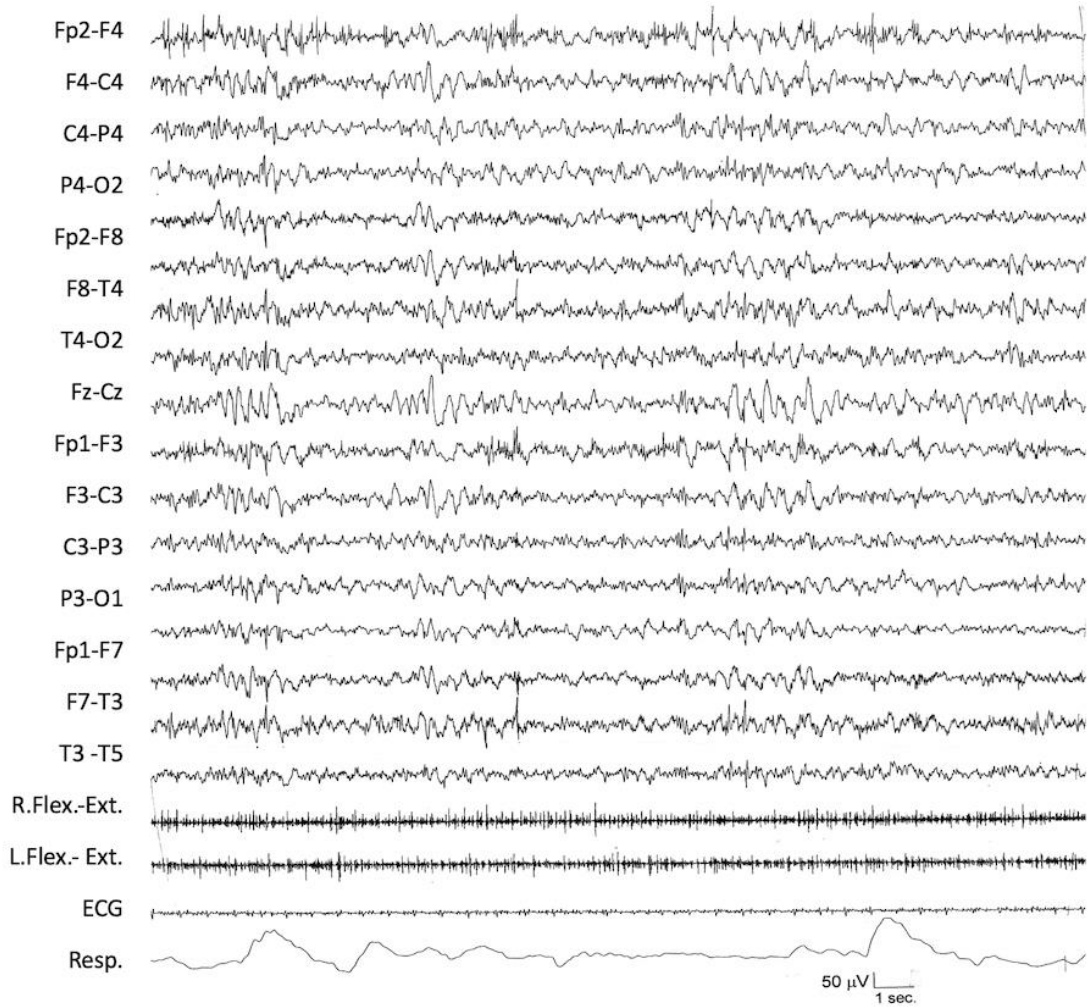

Figure 12: Axillary skin biopsy from a patient with Lafora disease. The picture is taken of apocrine gland cells under light microscopy. Intensely PAS-positive material (Lafora bodies) is observed scattered in the cytoplasm of several cells (circles).

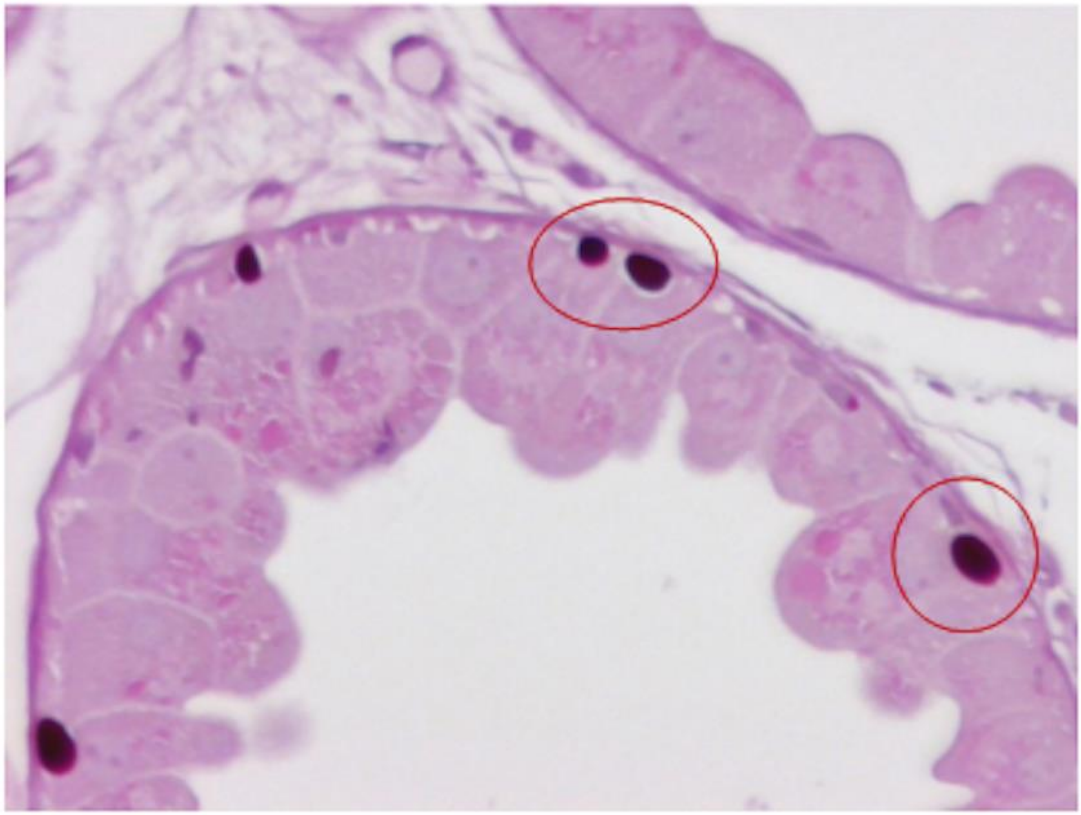

Figure 13: EEG showing slow photoparoxysmal response to 1 Hz photic stimulation in a 3 year 9-month-old child with CLN2 disease.

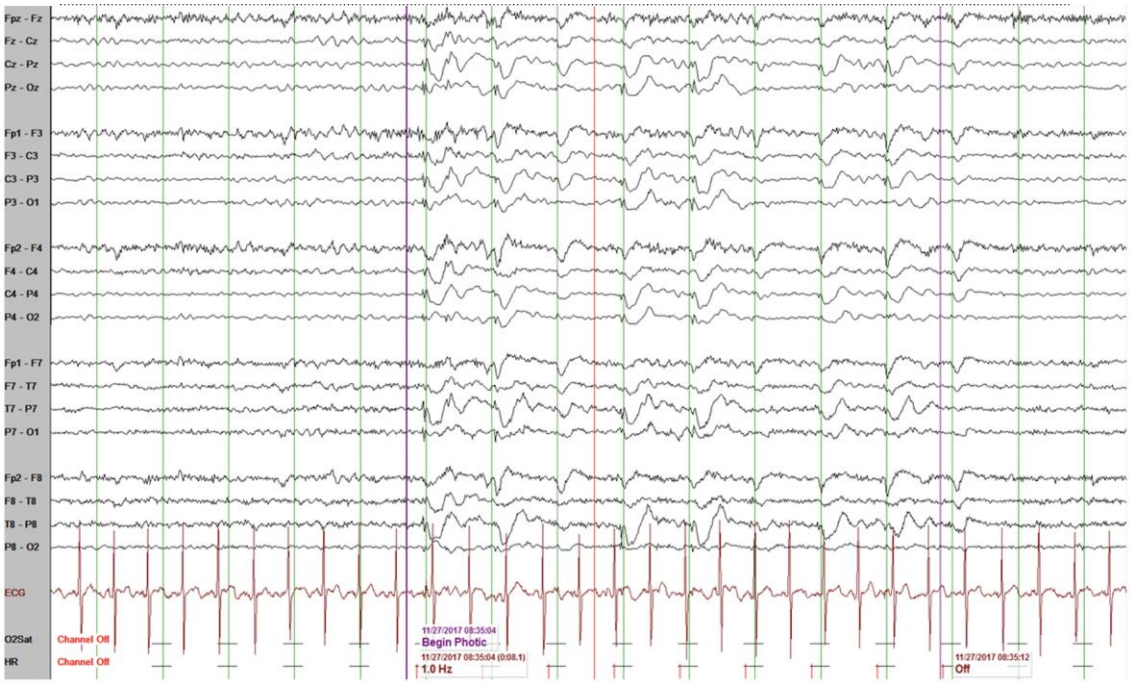

Figure 14: Typical ‘finger-print’ inclusion bodies (arrows) in a patient with adult onset NCL, seen on electron microscopy of a skin biopsy.