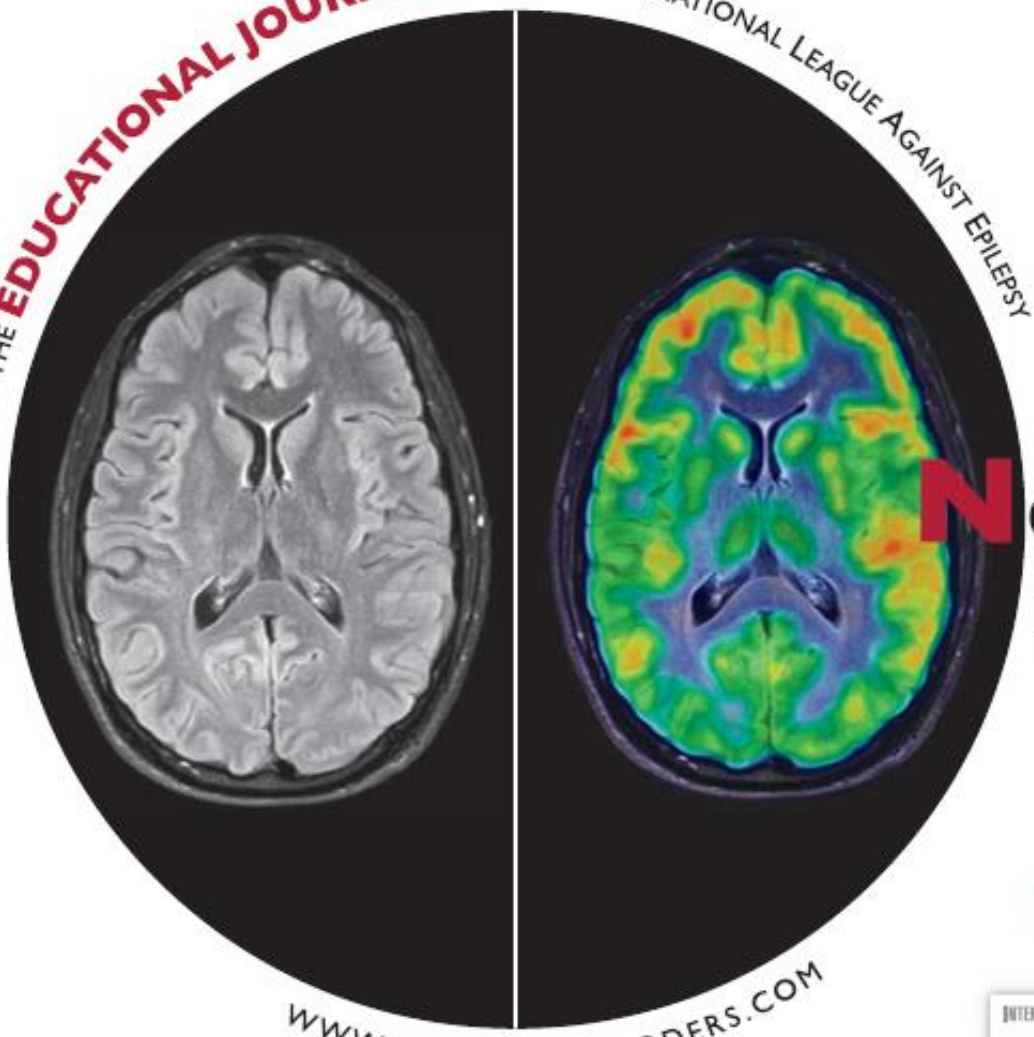
Epileptic Disorders

THE EDUCATIONAL JOURNAL OF THE INTERNATIONAL LEAGUE AGAINST EPILEPSY



No. 4
VOLUME 19
DECEMBER 2017

VIDEOS ONLINE

WWW.EPILEPTICDISORDERS.COM

John Libbey EUROTEXT
ISSN : 1294-9361

INTERNATIONAL LEAGUE AGAINST EPILEPSY
Established 1909

Epileptic Disord 2017; 19 (4): 385-437

The role of EEG in the diagnosis and classification of the epilepsy syndromes: a tool for clinical practice by the ILAE Neurophysiology Task Force (Part 2)*

Michalis Koutroumanidis [1], Alexis Arzimanoglou [2,3], Roberto Caraballo [4], Sushma Goyal [5], Anna Kaminska [6], Pramote Laoprasert [7], Hirokazu Oguni [8], Guido Rubboli [9], William Tatum [10], Pierre Thomas [11], Eugen Trinka [12], Luca Vignatelli [13], Solomon L. Moshé [14]

[1] St Thomas' Hospital, London, UK
[2] University Hospitals of Lyon (HCL), Department of Paediatric Clinical Epileptology, Sleep Disorders and Functional Neurology, Member of the European Reference Centre EpiCARE, Lyon, France
[3] Epilepsy Unit, Department of Paediatric Neurology, San Juan de Deu Hospital, Member of the European Reference Centre EpiCARE, Barcelona, Spain
[4] Hospital J P Garrahan, Neurology, Capital Federal, Buenos Aires, Argentina
[5] Evelina Hospital for Children, London, UK
[6] APHP, Hopital Necker-Enfants Malades, Department of Clinical Neurophysiology, Paris, France
[7] Children's Hospital, Neurology, Aurora, Colorado, 80045, USA
[8] Tokyo Women's Medical University, Department of Pediatrics, Shinjuku-ku, Tokyo, Japan
[9] Danish Epilepsy Centre, Department of Neurology, Dianalund, Denmark
[10] Mayo Clinic, Neurology, Jacksonville, Florida, USA
[11] Hopital Pasteur, Neurology, Hôpital Pasteur 24C, Nice, France
[12] Paracelsus Medizinische Privatuniversitat, Salzburg, Austria
[13] IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy
[14] Albert Einstein College of Medicine, Neurology, Neuroscience, and Pediatrics, Bronx, New York, USA

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Correspondence:
Michalis Koutroumanidis
St Thomas' Hospital,
London, UK
<michael.koutroumanidis@gstt.nhs.uk>

doi:10.1684/epd.2017.0952

*This report was written by experts selected by the International League Against Epilepsy (ILAE) and was approved for publication by the ILAE. Opinions expressed by the authors, however, do not necessarily represent the policy or position of the ILAE.

Part 1 was published in the September 2017 issue of *Epileptic Disorders* : Koutroumanidis M, Arzimanoglou A, Caraballo R, *et al*. The role of EEG in the diagnosis and classification of the epilepsy syndromes: a tool for clinical practice by the ILAE Neurophysiology Task Force (Part 1). *Epileptic Disord* 2017; 19(3): 233-98.

ABSTRACT – The concept of epilepsy syndromes, introduced in 1989, was defined as "clusters of signs and symptoms customarily occurring together". Definition of epilepsy syndromes based on electro-clinical features facilitated clinical practice and, whenever possible, clinical research in homogeneous groups of patients with epilepsies. Progress in the fields of neuroimaging and genetics made it rapidly clear that, although crucial, the electro-clinical description of epilepsy syndromes was not sufficient to allow much needed development of targeted therapies and a better understanding of the underlying pathophysiological mechanisms of seizures. The 2017 ILAE position paper on Classification of the Epilepsies recognized that "as a critical tool for the practicing clinician, epilepsy classification must be relevant and dynamic to changes in thinking". The concept of "epilepsy syndromes" evolved, incorporating issues related to aetiologies and comorbidities. A comprehensive update (and revision where necessary) of the EEG diagnostic criteria in the light of the 2017 revised terminology and concepts was deemed necessary. Part 2 covers the neonatal and paediatric syndromes in accordance with the age of onset. [*Published with educational EEG plates at www.epilepticdisorders.com*].

Key words: epilepsy syndromes, EEG and epilepsy diagnosis, EEG protocols, EEG Telemetry, EEG Atlas

1. Introduction

Part 2 of this work includes the main neonatal and paediatric epilepsy syndromes, presented according to age at onset (Scheffer *et al*., 2017). CAE (Childhood Absence Epilepsy) and Eyelid Myoclonia with or without Absences have already been discussed in Part 1 (Koutroumanidis *et al*., 2017a) amidst the genetic (idiopathic) generalized epilepsies (GGE/IGE).

As in Part 1, the structure of each chapter includes:

– (i) a brief *overview* of the presented syndrome;

– (ii) a description of the symptoms and semiology of each of the seizure types that are associated with the syndrome;

– (iii) an EEG section with the pertinent background, interictal and ictal characteristics in the awake state and sleep;

– (iv) recording protocols developed according to the evidence presented in the preceding EEG section to maximize diagnostic yield at two levels of complexity (*see section 1.5 of Part 1*);

– (v) levels of EEG diagnostic confidence in accordance with the strength of the EEG findings (*see section 1.3 of Part 1*).

The importance of adequate pertinent clinical information for the use of the appropriate recording protocol *and* the correct interpretation of the EEG findings and clinically useful final EEG report *across all ages* cannot be overemphasized (*figure 1.01 of Part 1)*.

In contrast to the important role of the EEG in the clinical diagnosis and the characterization of epilepsy syndromes, its contribution for the diagnosis of the underlying aetiology is overall moderate. Certain EEG patterns and combinations may strongly indicate specific genetic syndromes (such as GGE/IGE, progressive myoclonus epilepsy, or Dravet syndrome [DS]), but others, such as the commonly encountered focal spikes in association or not with focal slowing, are in keeping with aetiologies as diverse as genetic, structural, or unknown (*see also section 1.6 of Part 1*). In the latter case, the EEG may localize the focus, highlight the high probability of a structural lesion, and guide brain imaging studies.

There is a dominant maturational element in the clinical and EEG presentation of the structural focal epilepsies during childhood (Nordli *et al*., 2001), which may render localization and even lateralization of the responsible lesion very difficult, particularly in younger children. In children up to 2-3 years of age, for example, the repertoire of seizure manifestations has been shown to be limited, with four seizure types (epileptic spasms, tonic, clonic, and hypermotor seizures) constituting up to 80% of the total ictal semiologies (Hamer *et al*., 1999). In addition, the interictal and ictal EEG findings in infants and young children are frequently diffuse, even when the responsible structural lesion is small (*supplementary figures 1.01-1.03*), a phenomenon presumably related to age-dependent hyperexcitability. Such bilateral or diffuse/generalized epileptic discharges may not *per se* preclude epilepsy surgery (Wyllie *et al*., 2007; Arzimanoglou *et al*., 2016) or, on the other hand, prompt unsuitably early invasive procedures. It is important to emphasize that in this period of life, regional interictal background abnormalities, such as polymorphic delta activity (PDA) (*supplementary figure 1.04*), are much more important indicators of the epileptic focus and the associated underlying structural lesion (Noh *et al*., 2013). As in

Abbreviations

ABFEC: atypical benign partial epilepsy of childhood
BFIE: benign familial infantile epilepsy
BFNE: benign familial neonatal epilepsy
BFNIE: benign familial neonatal-infantile epilepsy
BFNIS: benign familial neonatal-infantile seizures
BIE: benign infantile epilepsy
BRE: benign rolandic epilepsy
CAE: childhood absence epilepsy
CSWS: continuous spike-and-wave during slow sleep
CTS: centrotemporal spikes
DS: Dravet syndrome
ED: epileptic discharge
EIMFS: epilepsy of infancy with migrating focal seizures
ELMA: eyelid myoclonia with absences
EMA: epilepsy with myoclonic absences
EMAS: epilepsy with myoclonic-atonic seizures
EME: early myoclonic encephalopathy
ESES: electrical status epilepticus during sleep
FOS: fixation-off sensitivity
FS: febrile seizure
GSPWD: generalized spike/polyspike-and-wave discharges
GSWD: generalized spike-and-wave discharges
GTCS: generalised toni-clonic seizure
HV: hyperventilation
ICCA: infantile convulsions and paroxysmal choreoathetosis
IED: interictal epileptic discharges
IPS: intermittent photic stimulation
IS: infantile spasms
LKS: Landau-Kleffner syndrome
LGS: Lennox-Gastaut syndrome
MAE: myoclonic-atonic epilepsy
MAS: myoclonic absence seizures
MEI: myoclonic epilepsy in infancy
MS: myoclonic seizure
OE-G: occipital childhood epilepsy of Gastaut
OLE: occipital lobe epilepy
OS: Ohtahara syndrome
PDA: polymorphic delta activity
PKD: kinesigenic dyskinesia
PPR: photoparoxysmal responses
PS: Panayiotopoulos syndrome
RMEI: reflex myoclonic epilepsy in infancy
S-B: suppression burst
SES: status epilepticus during sleep
SSW: slow spike-waves
SWI: spike-wave index
TA: typical absences
TLE: temporal lobe epilepsy
WS: West syndrome

the adolescent and the adult patient, sleep recordings should be pursued because they can activate epileptic discharges, which acquire higher lateralizing and localizing value during rapid eye movement (REM) sleep (Ochi *et al*., 2011).

Clinical-EEG presentation changes with brain maturation such that by the age of 6-7 years and in adolescents, seizure symptoms and semiology, as well as interictal and ictal EEG findings, become similar to those in adults, providing valuable information about the topography of the primary neural network that generates focal seizures.

Neonatal structural focal epilepsies are comprehensively discussed in Section 2 of this paper, while EEG changes in specific paediatric epilepsy syndromes that may also relate to structural brain lesions (such as West syndrome [WS] or Lennox Gastaut syndrome [LGS]) are fully covered in the relevant chapters here. Structural epilepsies in adults (also applicable to adolescents and older children) have already been described in Part 1 under *specific lobar syndromes*. A specific chapter on structural focal epilepsies in infancy and early and late childhood across the various aetiologies is not included in this paper, but will be the topic of a later publication. Readers are referred to the relevant chapters of excellent textbooks (Bureau *et al*., 2012; Arzimanoglou *et al*., 2016).

2. NEONATAL SEIZURES AND SYNDROMES

2.1 Overview of neonatal seizures and epilepsies

Neonatal seizures require rapid diagnosis, aetiological workup, and therapy, as delayed recognition of a treatable cause can have a significant impact on the child's neurodevelopment. In conjunction with advances in neuroimaging, metabolic, and genetic testing, electroclinical characterization with video-EEG recording allows more rapid determination of seizure aetiology and implementation of targeted treatment (*e.g.* in metabolic disorders with treatable conditions such as pyridoxine- and pyridoxal 5′-phosphate dependent epilepsy) (*for review see Pearl, 2016*).

Major aetiologies of neonatal seizures are acute cerebral injury including hypoxic-ischaemic encephalopathy, intracranial haemorrhage and infarctions, central nervous system infection, metabolic disturbances, congenital structural brain lesions, and drug withdrawal (Kang and Kadam, 2015; Arzimanoglou and Duchowny, 2018). Epilepsies beginning in the neonatal period represent, therefore, an uncommon but not rare cause of neonatal seizures (Mizrahi and Kellaway, 1998; Co *et al*., 2007; Volpe, 2008; Sands and McDonough, 2016).

Stereotyped focal seizures beginning in the neonatal period in the absence of metabolic or infectious disturbances may reveal an underlying structural anomaly, as focal cortical dysplasia or cortical tubers in tuberous sclerosis complex (TSC), or more diffuse anomalies associated with major congenital brain malformations, such as hemimegalencephaly or lissencephaly. Advances in identification of genetic causes of cerebral dysgenesis in recent years include somatic mutation associated with hemimegalencephaly, type IIb Focal Cortical Dysplasia, and Tuberous Sclerosis Complex resulting from mutations in various components of the mTOR pathway (D'Gama *et al*., 2015).

Beside the focal structural epilepsy with neonatal onset, three electroclinical syndromes with neonatal onset are recognized by the International League Against Epilepsy (ILAE). One of these, Benign Familial Neonatal Epilepsy, is characterized by transient seizures and good neurodevelopmental outcome. The two other syndromes belong to the encephalopathies with epilepsy, are associated with a burst suppression EEG pattern, and their prognosis is in most patients extremely poor with high mortality during the first months of life and severe development impairment.

In neonatal-onset epilepsies without metabolic or structural alteration, at least three groups with related functions were identified: ion channels (*i.e*. KCNQ2), regulators of forebrain development (*e.g*. ARX), and regulators of synaptic function (*e.g*. STXBP1) (Weckhuysen and Korff, 2014). Epilepsy with Infantile Migrating Focal Seizures (EIMFS) (with *de novo* gain-of-function mutation of *KCNT1* as the most common cause) can present near the end of the neonatal period. In addition to anamnestic, clinical, and imaging data, ictal and interictal EEG can direct to a possible aetiology, which helps determine the degree of cerebral dysfunction and prognosis, but also in the evaluation of treatment response. The neonatal EEG recording should be at least 60 minutes long (to include wakefulness and sleep) with elementary polygraphy (ECG, respiration) and bilateral EMG if abnormal movements are suspected (Beal *et al*., 2017).

2.2 Neonatal epileptic encephalopathies: Early-Infantile Epileptic Encephalopathy with suppression-burst pattern (Ohtahara syndrome) and Early Myoclonic Encephalopathy (EME)

Overview

Early Myoclonic Encephalopathy (EME) and Ohtahara syndrome (OS) are severe neonatal or early infantile epileptic/developmental encephalopathies. They share some types of seizure and also a pertinent EEG feature, namely the suppression-burst (S-B) pattern. The strategy for diagnostic EEG recording is essentially the same (Ohtahara and Yamatogi, 2003; Aicardi and Ohtahara, 2005). EME is typically associated with metabolic disorders and a degree of familial occurrence (*i.e*. pyridoxine-dependency, nonketotic hyperglycinaemia, methylmalonic academia, proprionic acidaemia, molybdenum co-factor deficiency, sulphite oxidase deficiency, Menkes disease, and Zellweger syndrome), while in OS, congenital or acquired structural brain lesions are more frequent (hemimegalencephaly, lissencephaly, polymicrogyria, Aicardi syndrome, dentato-olivaro dysplasia, and diffuse cerebral migration disorders) (Schlumberger *et al*., 1992; Miller *et al*., 1998; Ohtahara and Yamatogi, 2006; Arzimanoglou and Duchowny, 2018). Numerous mutations have been associated with OS, including *ARX*, mitochondrial glutamate transporter, *SLC25A22*, *STXBP1*, and *SCN2A* (Weckhuysen and Korff, 2014). Evolution to WS or multifocal epilepsy occurs more frequently in OS. Both syndromes, EME and OS, are fairly similar in terms of age at onset, EEG aspect of suppression-burst, and overlapping seizure types, and therefore their distinction is often difficult and sometimes impossible in the beginning of the disease (Schlumberger *et al*., 1992). Moreover, some children present motor manifestations during the bursts of activity that may be impossible to classify.

Seizures: symptoms and semiology

In the two syndromes, seizures begin very soon after birth, usually within the first month of life (Yamatogi and Ohtahara, 2002).

In OS, the most characteristic seizures are ***epileptic spasms*** and ***tonic seizures***, in clusters or isolated (Ohtahara and Yamatogi, 2006). They can be lateralized, or generalized but asymmetric particularly in neonates with lateralized structural lesions. Other seizure types such as ***focal motor*** seizures and ***hemiconvulsions*** occur in about a third of patients (Yamatogi and Ohtahara, 2002).

In contrast, ***myoclonic seizures (MS)*** (axial, segmentary, or erratic) are typical in EME and rare in OS. In EME, the frequency of seizures is variable but can be almost continuous. Erratic and segmentary myoclonus occur early on, often within the first few days or month of life (Guerrini and Aicardi, 2003). In erratic myoclonus, jerks appear to shift randomly from one area of the body to another, mainly involving the face or extremities. Axial myoclonus is less common. Focal clonic or subtle seizures may follow myoclonus.

Not infrequently, however, complex ictal movements that are usually stereotyped in the given child and associated with EEG bursts of paroxysmal activity can be difficult to classify as either spasms or myoclonias.

Focal seizures occur more or less equally in both conditions and are very common. These may be

motor with deviation of the eyes, tonic posturing, or hemiconvulsions. Subtle seizure with autonomic phenomena, such as flushing or apnoea, can also occur (Yamatogi and Ohtahara, 2002; Beal *et al*., 2017).

EEG section

Background

In EME, EEG can be normal at the onset of the seizures, and repetitive EEGs may be necessary for the diagnosis (Ozyurek *et al*., 2005). When the presentation is complete, there is no spatial or temporal organization (background rhythms are not different between cerebral areas and do not cycle/change with time and state of vigilance), and there are no physiological features in either wakefulness or sleep. S-B is the prevailing interictal pattern, however, clinical seizures concomitant with the bursts have been reported (Fusco *et al*., 2001).

Interictal abnormalities

In EME and OS, the suppression-burst (S-B) pattern consists of bursts of high-voltage asynchronous delta or theta waves, mixed with spikes and polyspikes (from 150 up to 350 μV) that last from 1 to 6 seconds and alternate with inter-burst intervals of low-voltage (<10 μV) activity or complete suppression that last usually 2-5 seconds (Aicardi and Ohtahara, 2005; Yamatogi and Ohtahara, 2002); at times, inter-burst intervals can last up to 18 seconds (Yamatogi and Ohtahara, 2002) (*supplementary figure 2.01*). The pattern may show multiple variations concerning configuration and inter-hemispheric synchrony/asynchrony of bursts (and may predominate over one hemisphere, especially when associated with lateralized structural anomalies, such as focal cortical dysplasia or hemimegalencephly) (*supplementary figure 2.02*). Bursts are shorter and periods of hypoactivity or silence are much longer in EME than in OS. Asynchrony is not common and has been described in Aicardi syndrome (Yamatogi and Ohtahara, 2002). Focal epileptiform discharges have also been described during the periods of suppression (Al-Futaisi *et al*., 2005). The S-B pattern in OS occurs in both wakefulness and sleep, in contrast to the S-B pattern in EME, which can be present only during sleep or be enhanced by sleep (Ohtahara and Yamatogi, 2006). The S-B pattern can persist beyond the first year of life. It can also evolve into hypsarrhythmia between three to six months of age, coincident with the development of more typical epileptic spasms (Yamatogi and Ohtahara, 2002; Ohtahara *et al*., 1987). Later transition into slow-spike and wave morphology (characteristic of LGS) has also been reported. This early transition into hypsarrhythmia is less common in EME wherein the suppression burst (S-B) pattern can persist into childhood after a transient evolution into hypsarrhythmia in middle to late infancy (Ohtahara and Yamatogi, 2006).

Ictal EEG

Epileptic spasms. EEG during tonic spasms principally shows desynchronization with or without evident rapid activity (Yamatogi and Ohtahara, 2002). Using video-EEG with surface electromyographic recordings from deltoid muscles, Fusco and co-workers found each burst to be associated with tonic contraction of variable duration (Fusco *et al*., 2001) (*supplementary figure 2.03A and B*). The erratic myoclonus usually has no EEG correlate, while limb/axial myoclonus is usually associated with bursts of spikes and polyspikes within the bursts of the S-B pattern (*supplementary figure 2.04*).

Complex stereotyped movements that are difficult to classify as either spasms or myoclonias are also associated with bursts of activity (high-amplitude spikes, polyspikes, waves, and sharp waves). There is no clear correlation between the duration of the burst and the type of seizure (*supplementary figure 2.05 and 2.06*).

Focal seizures are associated with focal discharges of spikes or sharp waves, clinically associated with tonic eye deviation, unilateral clonic contractions, or subtle or subclinical phenomena (*supplementary figure 2.07A, B and C*). There is no particular localization of ictal discharges on the EEG, however, focal seizures arising from a fixed focus and followed by tonic spasms in series have been described (*supplementary figure 2.08*) (Yamatogi and Ohtahara, 2002).

Recording protocols

Basic level

Schedule recording for at least one hour to increase the probability of recording seizures and ascertaining adequate representation of awake and sleep states. Employ polygraphy (ECG, bilateral deltoid EMG). Monitoring of respiration and full 10-20 EEG montage in term neonates are desirable.

Advanced level

Long-duration video-EEG from a few to 24 hours in order to ensure all seizure types are recorded. Extended polygraphy may include electro-oculogram and thoracic and abdominal respiration bands.

Levels of EEG diagnosis

(On clinical suspicion of neonatal epileptic encephalopathy with suppression-burst, including metabolic disorders such as pyridoxine-dependency [*supplementary figure 2.09*]).

A. Confirmatory of diagnosis

For both basic and advanced recording levels: non-reactive/invariant S-B EEG pattern with recording of typical seizure types.

B. High diagnostic certainty (probable)
The EEG shows stable/invariant S-B pattern without seizures. This also applies to basic level recording given the specificity of S-B in the absence of other conditions that can show a similar/reminiscent EEG picture (hypoxia, phenobarbital, fentanyl, *etc.-see differential diagnosis below*).

C. Low diagnostic certainty (possible)
No S-B is registered on the EEG, which may have been recorded too early during the course of the disease. Repeat basic or advanced recordings once seizures are established to register the typical S-B pattern/seizures and move diagnostic certainty to probable or confirmatory level.

Differential diagnosis
– (1) A discontinuous EEG pattern that may have some similarities to S-B can be seen in neonatal hypoxic ischaemic encephalopathy. However, in this condition, the pattern is usually transient and can be reactive or unstable in character.
– (2) A pattern reminiscent of S-B may be secondary to treatment for neonatal status epilepticus with medication, such as midazolam infusion and sometimes with opioids such as sufentanyl and fentanyl.

Indications for repeating advanced video-EEG recording level
– (1) Failure to record seizures.
– (2) Clinical suspicion of other types of seizure and/or epileptic syndrome (focal structural epilepsy).
Note. Repeat video-EEG basic level recording to monitor response to treatment for possible metabolic causes.

Atypical EEG/video-EEG features to be highlighted in the EEG report, which may cast doubts on (or refute) the diagnosis of a neonatal epileptic encephalopathy
Low amplitude of bursts, rare or absent spikes, and moderate flattening during the hypoactivity period would suggest other causes of neonatal encephalopathy.
Persistence of physiological background features during wakefulness and sleep.

2.3 Benign familial neonatal epilepsy (BFNE)

Overview
Benign Familial Neonatal Epilepsy (BFNE), previously known as Benign Familial Neonatal Seizures, belongs to a group of autosomal dominant benign epileptic syndromes with onset during the first year of life. Seizures typically start on the second or third day of life (in neonates born at full-term) or at around 40 post-menstrual weeks in premature neonates; rare cases with seizure onset after the first four weeks of life have also been described. Prenatal and perinatal history is unremarkable and there is family history of neonatal seizures. Two autosomal dominant epilepsy syndromes may present with neonatal seizures: BFNE and benign familial neonatal-infantile epilepsy/seizures (BFNIE/BFNIS) (Zara *et al.,* 2013).

Note. BFNE was the first proper genetic epilepsy described, hence some more information on its genetics was deemed appropriate. Genetic mutation in BFNE is found in around 90% of cases, with the *KCNQ2* encoding the voltage dependent K+ channel subunit being the most common gene; occasionally *KCNQ3* and *SCN2A* mutation were found in BNFE families (Grinton *et al.,* 2015). *KCNQ2* mutations have also been found in families, in which one or more family members had more severe outcome, including a variable degree of intellectual disability, suggesting that the clinical disease severity may be related to the extent of the mutation-induced functional K+ channel impairment. Recently, *de novo KCNQ2* mutations were found in patients with neonatal-onset drug-resistant seizures, psychomotor retardation, and important interictal abnormalities including "suppression burst" and abnormal neuroradiological features, thus defining a so-called "*KCNQ2 encephalopathy*" and the variable phenotype of KCNQ2-related epilepsies (Weckhuysen *et al*., 2012; Kato *et al*., 2013).

Seizures: symptoms and semiology
Seizures usually start with tonic posture, head or eye deviation or staring, apnoea, and other autonomic features, and often progress to unilateral or bilateral clonic movements. The postictal state is brief, interictal examination is unremarkable and feeding is normal. Biochemical examinations and cerebral imaging are normal (Hirsh *et al.,* 1993; Ronen *et al.,* 1993; Grinton *et al.,* 2015).
Seizure remission in BFNE occurs at around 4-6 months of age, irrespective of treatment. Development is usually normal and febrile or afebrile seizures are widely known to occur later in life after a prolonged seizure-free period in approximately 15-25% of BFNE cases (Grinton *et al.,* 2015).

EEG section

Background
Normal or subnormal.

Interictal abnormalities
Interictal recordings are normal or show minor epileptiform or non-epileptiform focal or multifocal

abnormalities (Grinton *et al.,* 2015). A pattern called "*theta pointu alternant*" can rarely occur in children with BFNE. It is defined as a dominant theta activity that is non-reactive, alternating or discontinuous, may be intermixed with sharp waves, and frequently shows inter-hemispheric asynchrony. It is present during active and quiet sleep, impeding precise definition of maturational age. "*Theta pointu alternant*" can be found in other conditions and therefore is not considered as specific for BFNE.

Ictal EEG

Focal seizures with initial tonic phase. When recorded on video-EEG, semiology is typical and stereotyped with initial diffuse hypertonia (symmetric or asymmetric), associated with apnoea/cyanosis and followed by clonic movements, unilateral or involving the whole body, symmetric or not. The semiology may also consist of "staring" with the arrest of activity being associated with autonomic or oculo-facial features without clonic movements. Pure clonic seizures are rare. Generalized seizures have never been reported in this syndrome. Seizures are brief and last for less than two minutes and may be very frequent, with up to 30 seizures per day.

On the EEG, seizures begin with diffuse bilateral, eventually asymmetric, flattening of the background activity for 5-20 seconds (which corresponds to the tonic and/or apnoeic phase), followed by focal or bilateral rhythmic, high-amplitude slow waves, and then by sharp waves over the frontal, temporal or central areas (corresponding to vocalizations, chewing, or unilateral or bilateral clonic movements). The preponderance of the ictal EEG changes and associated motor manifestations may vary between the left and right side, from one seizure to the next, in the same child (Ronen *et al.,* 1993; Hirsch *et al.,* 1993) (*supplementary figure 2.10 and 2.11*).

Recording protocols

Basic level

Attempt to record during wakefulness and sleep, if possible with polygraphy (ECG, respiration, and bilateral deltoid EMG to record autonomic and other ictal signs). Seizures are expected to occur within a few hours, as they are very frequent at onset and before treatment, sometimes amounting to status epilepticus.

Advanced level

Perform long video-EEG recordings for up to 24 hours to recover seizures. Polygraphy, as described in the basic level, is mandatory.

Levels of EEG diagnosis

A) Confirmatory of suspected BFNE in neonates with relevant family history

(For both basic and advanced recording levels)

Recording of typical ictal and interictal patterns.

B) High diagnostic certainty (probable)

(For both basic and advanced recording levels)

Normal background activity but no seizures recorded.

C) Low diagnostic certainty (possible)

(For both basic and advanced recording levels)

Slightly abnormal background activity with few focal, mostly multifocal, spikes or sharp waves), or atypical seizures recorded

Indications for repeating advanced level video-EEG recording

– (1) Failure to record seizures.

– (2) Clinical suspicion of other types of seizures or of acute underlying pathologies, such as hypoxia-ischaemia, infectious processes, metabolic disturbances, or diseases or other epileptic syndromes (structural focal epilepsies).

Atypical EEG/video-EEG features to be highlighted in the EEG report, which may cast doubts on or eliminate a diagnosis of BFNE

– Abnormal background activity
– Abundant focal or multifocal interictal abnormalities
– Suppression-burst pattern
– Focal seizures without typical features of BFNE
– Epileptic spasms
– Myoclonias

2.4 Focal structural epilepsy of neonatal onset

Overview

Among neonatal epilepsy syndromes, focal structural epilepsies are rare and may overlap with OS, as both can share similar electroclinical presentation. Indeed, studies focusing on electroclinical aspects of focal structural epilepsies with neonatal onset other than those on epileptic encephalopathies with suppression-burst (S-B; *see relevant chapter*) are scarce. Among 38 infants with seizures beginning within the first two months (mean: 0 months), not related to acute symptomatic causes (anoxic-ischaemic encephalopathies, neonatal stroke, metabolic, or infectious), the main seizure types were focal (76%) and epileptic spasms (24%) (Akiyama *et al.*, 2010); 34 of those (89%) had focal seizures and epileptic spasms in combination, with the second seizure type appearing after a median of three months. Multiple correspondence analysis, performed on electroclinical features, showed that the presence or absence of S-B pattern and of an asymmetry in the EEG background were the most meaningful variables to separate these very-early-onset epilepsies into

subgroups, thus confirming the relevance of the S-B pattern in the classification of neonatal-onset epilepsy syndromes (Akiyama *et al*., 2010; Yamamoto *et al*., 2011). While the asymmetry in interictal EEG was often associated with the presence of a structural brain abnormality, the S-B pattern was also associated with cerebral lesions in around half of the patients, as previously reported for OS (*see relevant section and Aicardi and Ohtahara [2005], Akiyama et al. [2010], and Yamamoto et al. [2011]*).

Typically, the presence of a focal lesion is suggested by stereotyped focal seizures, electrographically arising from the same region (but potentially multifocal in the case of tuberous sclerosis complex), or by asymmetries in voltage or frequency of background activities (Beal *et al*., 2017), however, interictal EEG can also be normal. Although EEG findings can sometimes be fairly characteristic (for instance periodic focal abnormalities in focal cortical dysplasia or cortical tubers [Domańska-Pakieła *et al*., 2014; Kotulska *et al*., 2014]), or high-voltage monomorphic theta or delta activity in lissencephaly), precise diagnosis relies on neuroimaging. Typically, treatment relies on epilepsy surgery, but response to medical treatment may be good (Kröll-Seger *et al*., 2007).

Seizures: symptoms and semiology

Ictal semiology relates to the topography of the epileptic discharge. Seizures may be tonic or clonic, or exhibit only subtle motor manifestations or autonomic symptoms, or be sub-clinical, especially when arising from temporal regions (Volpe, 1989; Mizrahi and Kellaway, 1987; Mizrahi and Kellaway, 1998; Beal *et al*., 2017).

***Focal clonic*.** These seizures consist of rhythmic (usually one to three jerks per second), repetitive movements of the face, proximal or distal limb, or axial muscles.

Focal tonic. Sustained posturing of a limb or lateralized axial flexion characterizes these seizures that can also be accompanied by sustained conjugate eye deviation to one side. Like focal clonic seizures, tonic seizures are usually associated with synchronized EEG discharges.

Myoclonic. These seizures manifest as sudden brief irregular, single or multiple contractions of muscles or muscle groups in the face, the proximal and distal parts of the limbs, or the trunk.

Epileptic spasms. Spasms manifest as sudden flexion, extension or mixed flexion and extension of limbs, neck, and body, which can be bilateral symmetric or asymmetric, or focal. A spasm is longer than a myoclonic jerk, but less sustained than a tonic seizure.

***Motor automatisms*.** Also called "subtle", these seizures occur frequently in the new-born and consist of minimal motor manifestations, with or without autonomic signs.

Autonomic. These seizures manifest with a variety of paroxysmal autonomic changes such as alterations in breathing, heart rate or blood pressure, salivation, sweating, and colour changes. Autonomic manifestations are often encountered in association with seizure discharges that originate from the temporal areas (Watanabe *et al*., 1982), and have also been described in subtle seizures.

EEG section

Background

The background is usually normal on the non-affected hemisphere, but shows variable alterations on the affected side that range from mild to complete absence of physiological features and contain paroxysmal abnormalities, or hemi-suppression-burst (*supplementary figure 2.12 and 2.13*).

Interictal abnormalities

The interictal paroxysmal patterns depend on the type and the extent of the lesion. Spikes, polyspikes and sharp waves, but also slow delta waves, sometimes of pseudo periodic occurrence (*supplementary figure 2.14*), and focal rapid rhythms may be found over the affected side. Abnormalities may also include hemi-suppression bursts concerning the whole hemisphere, in which case they are highly suggestive of focal cortical dysplasia or hemimegalencephaly (*supplementary figure 2.15A*). Nevertheless, absence of EEG abnormalities does not exclude the diagnosis of structural focal epilepsy.

Ictal EEG

Focal seizures may or may not be associated with epileptic spasms in the given patient. Focal seizures always begin in the same side or area of the brain and show stereotyped electroclinical course that relates to the topography of the lesion, however, those in neonates with tuberous sclerosis complex may be multifocal. Coexistent **epileptic spasms** are usually asymmetric and may precede, follow a focal seizure, or occur during its evolution (*supplementary figure 2.15B and C*).

The ictal EEG depends on the seizure type with focal flattening in ***focal tonic seizures***, rhythmic, periodic or irregular spiking in **clonic seizures** (*supplementary figure 2.15C and 2.16*), and rhythmic or periodic very-low-amplitude slow-wave discharges in **"subtle" or subclinical seizures** (*supplementary figure 2.17*).

Focal myoclonic jerks, unilateral or predominating on one side, may be present in cortical malformations that involve central areas (*supplementary figure 2.18 and 2.19*).

Recording protocols

Basic and advanced level recordings are exactly the same as for neonatal epileptic encephalopathies with suppression-burst (*see relevant chapter*).

Levels of EEG diagnosis

Clinical suspicion of focal structural epilepsy in untreated neonates *after* exclusion of the most frequent causes of acute symptomatic neonatal seizures, which are mostly focal (such as in stroke) or multifocal (such as in neonatal hypoxic ischaemic encephalopathy).

A. Confirmatory of diagnosis

(For both basic and advanced recording levels)

Recording of typical ictal and interictal features.

B. High diagnostic certainty (probable)

(For both basic and advanced recording levels)

Typical focal interictal abnormalities, but no seizures recorded. Proceed with, or repeat advanced level EEG to register seizures and move diagnostic certainty to level A.

C. Low diagnostic certainty (possible)

(For both basic and advanced recording levels)

Bilaterally abnormal background activity with focal, multifocal or diffuse interictal epileptiform abnormalities, or non-stereotyped seizures with multifocal onset (*see below*).

Indications for repeating advanced level video-EEG recording

– (1) Failure to record seizures.

– (2) Clinical suspicion of other types of seizure or of acute underlying pathologies (*as cited above*).

Atypical EEG/video-EEG features to be highlighted in the EEG report, which may cast doubts on a diagnosis of focal structural epilepsy

Multifocal interictal abnormalities and multifocal and non-stereotyped seizures.

3. INFANCY/EARLY CHILDHOOD

3.1 Infantile Spasms (IS) and West Syndrome (WS)

Overview

WS is a unique, age-dependent epilepsy that frequently presents in the first year of life, most commonly between the first three to nine months of life. Traditionally, the triad of clusters of epileptic spasms, developmental regression, and *hypsarrhythmia* on the EEG is termed as WS. It is now recognized that infantile spasms (IS) may not always be associated with the prototypical hypsarrythmic EEG pattern and can also affect children later in life, though rarely beyond the age of two years. The term "infantile spasms", particularly when used synonymously to "West syndrome" should be reserved to very young children. The recent ILAE classification included the term "epileptic spasms" when this seizure type is observed at other ages. Hypsarryhthmia can also be incidentally recorded in the absence of spasms.

In the vast majority of cases, IS are associated with structural brain abnormalities, including perinatal ischaemia/hypoxia, congenital or early acquired infections, abnormalities of cortical development, neurocutaneous conditions, *etc*., while familial cases are rare. Prognosis depends on aetiology and is better in children without apparent structural cause. In nearly half of the patients, WS evolves into LGS or multifocal epilepsies.

Seizures: symptoms and semiology

Epileptic spasms *(ES)* are the defining seizure type, although they are not exclusive for WS (*see also section on neonatal epileptic encephalopathies*). ES are brief muscle contractions that predominate in proximal and truncal muscles and cause sudden flexion (also known as "salaam spasms"), extension, or mixed movements. EEG-EMG polygraphy recordings have shown that a spasm reaches the maximum contraction more slowly compared to myoclonia, but faster compared to a tonic seizure (Vigevano *et al*., 2001). ES may be isolated but most frequently occur in clusters. The intensity and frequency of the sequential ES in each cluster often increase gradually to a peak, and then progressively decrease until they stop. ES can be "subtle", limited to only grimacing, eye deviation, and head nodding, or even be subclinical. ES may be asymmetric, or asynchronous, associated with various focal components that may involve the limbs, head, or eyes, or show compartmental and vegetative features (Watanabe *et al*., 2001). ES may be preceded or followed by, or intermixed with, focal seizures (Gaily *et al*., 1995). Stereotyped focal seizures preceding epileptic spasms suggest a focal lesion and polygraphic video recording is required for detailed analysis.

Focal seizures. Occur mainly in infants with overt cerebral lesions and can be multifocal. A focal seizure may trigger a cluster of spasms, or occur independently of them.

EEG section

Background

Continuously abnormal during wakefulness and sleep.

Interictal abnormalities

Hypsarrhythmia, a term coined by Gibbs and Gibbs in their atlas of electroencephalography in 1952, describes a high-voltage (hypsos=height), completely

disorganized and chaotic (without any discernible normal background rhythm=arrhythmia) EEG pattern (*supplementary figure 3.01*), which is the characteristic interictal presentation in WS. At onset, hypsarrhythmia may be present only during drowsiness and light sleep, but it soon becomes abundant during wakefulness.

Wakefulness. The main (typical) pattern of hypsarrhythmia occurs during wakefulness: it consists of random high-amplitude slow wave and spikes that vary from moment to moment, both in duration and location (*supplementary figure 3.01*). Occasionally, spike discharges appear to be focal, or multifocal, but never as a rhythmically repetitive and highly organized pattern. The abnormality is almost continuous, but early during the clinical course, the age-dependent physiological background may be intermittently preserved. Most frequently, hypsarrhythmia may predominate over the posterior head regions, while anterior predominance is rare and only seen after the first year of age.

Sleep. Hypsarrhythmia remains maximal in sleep Stage 1, but becomes less continuous during sleep Stages 2 and 3, and disappears during REM sleep. During Stages 2 and 3, a tendency of the multifocal spike and sharp wave discharges to group results in a quasi-periodic appearance of the paroxysmal activity (*supplementary figure 3.02*). Physiological graphoelements of sleep (vertex sharp transients, spindles, and K-complexes) are usually absent.

A number of different variants of hypsarrhythmia have been reported beyond its typical presentation (Hrachovy and Frost, 2003). These include hypsarrhythmia with increased inter-hemispheric synchronization (examples in *supplementary figure 3.02 and 3.03*), asymmetric hypsarrhythmia (*supplementary figure 3.04*), hypsarrhythmia with episodes of voltage attenuation (*supplementary figure 3.05*), hypsarrhythmia with a consistent focus of epileptic discharges (*supplementary figure 3.06*) or focal slowing, and other patterns.

An underlying structural origin can be suspected when the EEG reveals atypical hypsarrhythmia: for instance, predominating focal spikes or spike-waves or slow complexes may indicate a focal lesion, additional abnormal rhythms (*i.e.* diffuse high-voltage theta-alpha activity) may indicate lissencephaly or pachygyria, and persistent asymmetry or asynchrony may indicate a focal lesion or agenesis of the corpus callosum; asymmetric ictal patterns or interspersing focal seizures (*supplementary figure 3.07A to 3.07B*) may be of similar significance (*see ictal EEG below*).

Ictal EEG

Ictal discharges associated with ES include:

– (i) a diffuse high-amplitude triphasic slow wave;
– (ii) a low-amplitude brief fast discharge;
– (iii) a short-lasting diffuse flattening of ongoing activity (*supplementary figure 3.08 and 3.09*).

The frequency of occurrence of these three patterns and their terminology has varied according to different authors, but the first pattern may be the most frequent (Fusco and Vigevano, 1993; Vigevano *et al.*, 2001). A transient disappearance or reduction of the hypsarrhythmic pattern is usually seen during a cluster of ES (*supplementary figure* 3.08). Symmetric epileptic spasms (*supplementary figure 3.10*) may be idiopathic or of structural origin. Infants with brain lesions may show an asymmetry of the ictal high-amplitude slow wave, reflecting the pathologically more involved hemisphere. Focal or unilateral fast discharges immediately preceding the high-voltage slow wave are highly suggestive of focal cortical lesion.

Recording protocols

Basic level

Time: any time of the day, but preferentially during spontaneous sleep and after feeding (planning arrangements with parents are essential).

Activation: sleep is strongly recommended, and if achieved, further recording of at least 10 minutes after awakening is required, as ES occur very often in that period.

Polygraphy: bilateral deltoid EMG is desirable, even at the expense of complete 10-20 EEG cover.

Advanced level

Time: anytime of the day, but lengthy recordings are recommended to include spontaneous sleep and a period after feeding; if necessary induce sleep. Allow the patient to reach Stage 2 for at least 10-15 minutes and record for at least 30 minutes after awakening.

Polygraphy: bilateral deltoid EMG is mandatory.

Levels of EEG diagnosis

Clinical suspicion of IS/WS in <u>untreated</u> infants

A. Confirmatory of IS/WS

Ictal recording of epileptic spasms with interictal EEG showing typical hypsarrhythmia or any of its variants. Recording of hypsarrhythmia and history of ES in clusters upon awakening are sufficient for diagnosis of WS at level 1 (if video-EEG is not available or if epileptic spasms do not occur during the recording; asking parents to bring along video recordings of the typical spasms on portable phones will allow clinical confirmation; there is no need for SD recording level 2 (*however, see clinical indications below*).

B. High diagnostic certainty

(Probable IS/WS, for both recording levels 1 and 2).

No hypsarrhythmia or spasms recorded, but presence of multifocal spike discharges during sleep recording and history of epileptic spasms in clusters upon

awakening: repeat recordings level 1 and 2 (if possible) to record epileptic spasms or hypsarrhythmia.

C. Low diagnostic certainty

(Possible IS/WS, for both recording levels 1 and 2).

No hypsarrhythmia, but presence of multifocal spike discharges during sleep recording and history of possible (subtle) epileptic spasms (for instance, head nodding or eye deviation): Repeat recordings level 1 and 2 (if possible) to record the ictal EEG of the attacks and confirm the diagnosis of IS by showing that the ictal EEG pattern is compatible with that of epileptic spasms.

Indications for repeating advanced level SD recording

– (1) First EEG (recording level 1 or 2) normal or inconclusive.

– (2) Resistance to appropriate AED (vigabatrin, adrenocorticotropine, predonine).

Indications for video telemetry

– (1) Clinical suspicion of additional seizure type.

– (2) Confirm the treatment response.

3.2 Dravet syndrome (DS)

Overview

Dravet Syndrome is an infantile-onset epilepsy syndrome, first described in 1978 by Charlotte Dravet as "severe myoclonic epilepsy in infancy". Estimated prevalence is around 1% of epilepsy syndromes in infancy and childhood with males being more often affected. The natural course of DS during childhood is traditionally divided into an early phase (roughly corresponding to the first year of life) and a steady phase within the next 2-5 years, during which the full electroclinical picture becomes established. In the early phase, prolonged hemi- or generalized convulsive seizures occur, typically associated with fever, while some children show generalized photoparoxysmal responses (PPR) to photic stimulation, an unusual finding for this age. During the steady phase, MS, atypical absences, complex partial seizures (CPS), and episodes of non-convulsive status may also appear, while cognitive development slows leading to moderate/severe intellectual disability usually after the age of 4-5 years; some children may also show non-progressive ataxia, pyramidal signs, or hypotonia. Seizure evolution may vary in some children; for instance, clear association with fever may be lacking and myoclonic or CPS may start early. Such course variability and the overall seizure polymorphism, as well as the largely non-specific interictal EEG findings, may delay diagnosis. Long-term outcome is invariably unfavourable. DS is highly pharmaco-resistant and seizure freedom remains an exception, while patients remain cognitively impaired, often severely. Early mortality, sometimes due to sudden unexpected death in epilepsy (SUDEP), occurs in about 10% of patients.

DS is a channelopathy due to mutation in the *SCN1A* gene which encodes the alpha 1 subunit of the voltage-gated sodium channel. *SCN1A* abnormalities (mostly mutations and deletions) in DS are reported in 80% of patients. Identifying *SCN1A* mutations might be helpful in some patients as a means of supporting an early diagnosis of DS. However, *SCN1A* aberrations can be associated with several epilepsy syndromes, ranging from mild phenotypes found in families with genetic epilepsy with febrile seizures plus (GEFS+) to the severe infant-onset DS. Thus, diagnosis of DS is still based on the constellation of the many different seizure types and their EEG characteristics, and their evolution, as described by Dravet.

Seizures: symptoms and semiology

Seizures start in the first year of life in previously healthy children. Initial seizures are unilateral or generalized convulsive, mainly clonic or tonic-clonic and often prolonged (>10 min), evolving into status epilepticus. They are typically triggered by fever (giving initially the impression of atypical febrile convulsions), or occur after immunization, but may also be afebrile. Other types of seizure, mostly afebrile, occur in the second or third year of life in addition to the convulsive seizures that are present throughout the evolution (Bureau and Dalla Bernardina, 2011; Dravet *et al.*, 2012). Myoclonic seizures may be absent at the first stages of the syndrome (Guerrini and Aicardi, 2003).

A. Convulsive seizures are traditionally classified into:

– (i) "***Unilateral***" with clear hemi-clonic or tonic convulsions that, on different occasions, may alternate sides in the same child; such alternating unilateral seizures can offer a significant clue to early diagnosis of DS. These seizures become rarer with age.

– (ii) "***Generalized tonic-clonic***" seizures as in IGE/GGE, although of somewhat shorter duration.

– (iii) "***Falsely generalized***" and "***unstable***" seizures. These are ***bilateral convulsive*** but with asymmetric clonic or tonic movements and postures, at times predominating on one side, or switching sides during the seizure. For falsely generalized seizures, the description reported by the family appears to correspond to a generalized tonic-clonic seizure (GTCS), but polygraphic video-EEG recordings have shown that the onset of the bilateral motor manifestations may lag behind a brief period of eye opening and unresponsiveness, associated or not with eye deviation and facial jerking. The EEG onset is bilateral synchronous but often asymmetric in the falsely generalized seizure

and focal in the unstable seizure (*see EEG section*). Both these types tend to mainly occur during non-REM sleep.

B. Focal seizures, usually of the complex partial type, are frequently associated with autonomic symptomatology (pallor, cyanosis, respiratory changes, and drooling), oral automatisms and hypotonia, and sometimes with eyelid or distal jerks. They last from one to a few minutes; when longer they can evolve into a unilateral motor or secondary generalized seizure.

C. Myoclonic seizures can be either massive axial movements leading to falls or mild (isolated or grouped) manifesting as a few jerks. Erratic myoclonias may also occur.

D. Atypical absences may be at times associated with a myoclonic component.

E. Non-convulsive status epilepticus (NCSE), also known as ***obtuntation status***: NCSE episodes consist of prolonged (hours or days) impairment of consciousness with loss of contact or variably reduced responsiveness, hypotonia and somnolence, and erratic or segmental myoclonus. Obtundation status may be initiated, punctuated or terminated by generalized tonic-clonic seizures, or be combined with other seizure types, such as axial myoclonic, myoclonic-atonic or clonic.

F. Tonic seizures are exceptional.

Seizures may be triggered by intermittent photic stimulation (IPS), visual patterns, hot water immersion, and physical effort (Dravet *et al*., 2012), and sensitivity to photic or pattern stimulation is noted in approximately 40% of patients, particularly in younger children.

Status epilepticus or at least worsening of seizures may be provoked by inappropriate AEDs (carbamazepine, lamotrigine, and vigabatrin). In adults, MS, atypical absences, and focal seizures tend to remit, but long-lasting clonic seizures or short tonic-clonic seizures may persist, particularly during sleep (Ohki *et al*., 1997).

EEG section

Although abnormalities are non-specific, interictal EEG is helpful for differential diagnosis and patient management. Moreover, sequential EEG recordings may demonstrate the evolution of DS, while ictal recordings with EMG polygraphy document seizure polymorphism, which is diagnostically very important.

Background

Wakefulness. Background activity is normal at onset despite the frequent seizures; rhythmic theta activities of 4-5 Hz may be present over the central-parietal areas and vertex. Diffuse or asymmetric slowing may be seen if EEG is performed immediately after a seizure; sometimes, focal postictal abnormalities may linger on for a few days (*supplementary figure 3.11*).

Sleep. Normal patterns, at least initially.

After the first year, there is usually a gradual slowing of the background activity, more marked if seizures are frequent. Theta band waves predominate over the central areas with persistence of physiological patterns (*supplementary figure 3.12*). Physiological sleep phenomena and organization generally remain preserved, unless frequent nocturnal seizures occur.

Interictal abnormalities

Interictal abnormalities may be present at onset (22% of patients) and increase during evolution (77%) (Specchio *et al*., 2012). Generalized, focal and multifocal abnormalities, spikes, and spike-wave or polyspike-wave discharges, symmetric or not, are more frequent over the frontal and central areas, but also occur over the temporal and occipital areas (*supplementary figure 3.13*).

Interictal abnormalities are usually enhanced during sleep (*supplementary figure 3.14*). Generalized PPR occur in 9% of patients at onset, increasing to 22-44% during evolution (Specchio *et al*., 2012; Caraballo and Fejerman, 2006). Slow waves occur mainly over the central regions at onset and tend to diffuse during evolution. Both generalized and focal spikes and spike-wave discharges and slow waves are enhanced if seizures are more numerous.

There is no homogeneous evolution of the EEG aspects with age, with the overall pattern in the individual patient being dependent on the number and duration of seizures. A distinctive EEG pattern of frontal slow bi- or triphasic spikes, followed or not by slow waves when awake and activated by sleep with diffuse 5-10-second discharges of 8-9-Hz polyspikes, has been noted in a minority of adolescents with DS, some of whom had tonic seizures (Nabbout *et al*., 2008); despite some similarities with LGS, this pattern does not indicate transition of DS to LGS (*see also section on LGS*).

Ictal EEG

A. Convulsive seizures

– (i) ***Unilateral.*** These are frequent at the onset of the disease. The ictal discharge is characterized by rhythmic (2-3/second) bilateral slow waves of higher amplitude over the hemisphere contralateral to the clinical manifestations and intermixed with 10/second recruiting rhythms.

In other focal unilateral seizures, the EEG pattern can be variable with onset over the frontal or frontal-central regions of one hemisphere, or with bilateral asymmetric onset, but always predominant over the frontal areas (*supplementary figure 3.15A, B*). The EEG onset consists of "pseudo-rhythmic" spikes and waves, contralateral to the clinical manifestations, and may be

periodically interrupted by a 1-2-second flattening of the EEG.
– (ii) ***Generalized tonic-clonic seizures*** (See section on IGE/GGE).
– (iii) ***"Falsely generalized"*** and ***"unstable"*** seizures.
In the ***falsely generalized seizures,*** the EEG discharge is of bilateral symmetric or asymmetric onset with a slow spike or SW, sometimes followed by a brief attenuation, and fast activities intermixed with slow waves. These seizures can be preceded by isolated massive jerks for several minutes, increasing progressively in frequency and amplitude.
Unstable seizures are characterized by varying topographic changes of the ictal discharge. The seizure can start over one area of one hemisphere and then spread to another area of the same hemisphere or to the entire hemisphere, or asymmetrically to both hemispheres. The pattern of propagation is variable from one seizure to another in the same patient.
In general, polygraphic video-EEG recordings of both these seizure types have documented complex ictal evolution and a degree of discrepancy between clinical and EEG manifestations (*for further details see Bureau and Dalla Bernardina [2011] and Dravet et al., 2012*).

B. Focal (complex partial) seizures

Ictal EEG consists of a rhythmic sequence of fast polyspikes intermixed with theta activity during the last part of the seizure, involving, for the duration of the seizure, the temporal-parietal-occipital region of one hemisphere or more rarely a frontal region (Bureau and Dalla Bernardina, 2011) (*supplementary figure 3.16*).

C. Myoclonic seizures

These are accompanied by generalized spike- or polyspike-wave discharges at 3Hz or more, lasting 1-3 seconds and of higher voltage over the central-parietal areas (*supplementary figure 3.17 and 3.18*).

D. Atypical absences

These are associated with generalized regular or irregular spike-wave discharges at 2-3.5 Hz, lasting 3-10 seconds, and are accompanied by impaired consciousness and sometimes a myoclonic component (*supplementary figure 3.19*).

E. NCSE (obtuntation status)

EEG background activity is replaced by diffuse delta slow waves, superimposed with multifocal spikes and spike-waves, sharp waves, and generalised spike-and-wave discharges (GSWD) predominating over frontal-central areas, associated with myoclonic jerks or without a clinical correlate (atypical absence status).

F. Tonic seizures

These occur only exceptionally and are associated with diffuse discharges of polyspikes at 8-9 Hz (Nabbout *et al*., 2008).

Recording protocols

Basic level

Planned recording during wakefulness and sleep with polygraphy (ECG, respiration, bilateral deltoid EMG) with hyperventilation (HV) and IPS. IPS is important to record early photoparoxysmal responses.

Advanced level

Long-duration video-EEG with polygraphy, as above (with at least bilateral deltoid EMG). Include IPS and HV, as in level 1. Hospitalization of the child during a cluster of febrile or afebrile seizures provides a good opportunity.
Sleep is important to enhance the probability of recording interictal discharges and unstable and falsely generalized seizures. More extensive EMG polygraphy will better demonstrate the ictal polymorphism of these seizure types.
Repeat sleep EEGs when clinically indicated (*i.e.* appearance of a new seizure type) to better document the evolution of the syndrome.

Levels of EEG diagnosis

As already discussed, diagnosis of DS relies on the clinical evolution and is supported by serial (and as frequent as possible) video-EEG evidence that will document seizure polymorphism. Early EEG photosensitivity and video-recorded falsely generalized or unstable seizures provide pertinent diagnostic clues. It follows that ***confirmatory (level A)*** and ***probable (level B)*** levels are not applicable here, as for most of the other syndromes; in DS, there are no specific interictal features, and seizure polymorphism is unlikely to be shown by even an ictal EEG.
In the untreated child with suspected DS, the first EEG (both basic and advanced recording levels) can increase diagnostic certainty if it shows a combination of the following:
– (1) Background showing focal or diffuse slowing in postictal recordings, following repeated admissions for atypical febrile seizures (FS) or status epilepticus.
– (2) Early-onset photosensitivity.
– (3) Myoclonic *and* either unstable or falsely generalized seizures.

C) Low diagnostic certainty (possible)

(For both basic and advanced recording levels)
Monomorphic epilepsy syndrome with only myoclonus.
Development remains unaffected.

Indications for video-EEG telemetry
– (1) Worsening with suspicion of minor status epilepticus.
– (2) Clinical suspicion of other types of seizures and/or epilepsy syndrome.

Atypical EEG/video-EEG features to be highlighted in the EEG report, which may cast doubts on a diagnosis of DS
Persistent focal slowing of background activity associated with spike or polyspike-wave focus, suggesting focal structural epilepsy.
Frequent tonic seizures associated with diffuse bursts of polyspikes (*however, see also Nabbout et al. [2008]*).

3.3 Myoclonic Epilepsy in Infancy (MEI)

Overview

Myoclonic Epilepsy in Infancy (MEI) is characterized by brief generalized myoclonic seizures (MS) that are associated with brief generalized spike/polyspike-and-wave discharges (GSWD/GSPWD) and occur between three months and four years of life in previously healthy children (Auvin *et al*., 2006; Darra *et al*., 2006; Guerrini *et al*., 2012; Caraballo *et al*., 2013). There are no other seizure types. A history of earlier FS is noted in up to 18% of children, while a family history of epilepsy and FS has been described in 29% and 16% of children, respectively.
Although these children usually have good prognosis for seizures, cognitive and behavioural disturbances have been reported in around 40% of patients (Zuberi and O'Regan, 2006; Guerrini *et al*., 2012; Auvin *et al*., 2013). Some children have mainly reflex myoclonus activated by unexpected auditory, tactile, and photic stimulation. This presentation has been considered as a variant, termed "reflex myoclonic epilepsy in infancy (RMEI)", with some differentiating features (Ricci *et al*., 1995; Verrotti *et al*., 2013) that include: earlier mean age at onset (10 months, compared to 20 months for MEI), shorter duration of the MS, most of which are provoked by sudden and unexpected stimuli, better response to antiepileptic medication, and better cognitive outcome.
On rare occasions, other genetic generalized epilepsies may develop after MEI remits, including epilepsy with myoclonic-atonic seizures, JME, childhood absence epilepsy, and eyelid myoclonia with absences.
Note. Recognizing MEI is not difficult in children with the typical clinical/EEG presentation. Differential diagnosis should include some other syndromes and conditions in infancy and early childhood, such as Glut-1 deficiency, non-epileptic events including benign non-epileptic myoclonus and head atonic attacks, and IS without hypsarrhythmia. Neurometabolic conditions, such as mitochondrial cytopathies (myoclonic epilepsy with red ragged fibres; MERRF), storage disorders, neuronal ceroid lipofuscinosis, hexoamidase deficiency, and biopterin deficiency, may all present with MS and need to be considered in the differential diagnosis.

Seizures: symptoms and semiology

Myoclonic seizures (MS) typically start between 16 and 18 months of age and are often subtle at onset (Zuberi and O'Regan, 2006; Caraballo *et al*., 2013). They occur several times daily, usually in isolation, but also in clusters, and are easily controlled by antiepileptic medication, especially valproic acid.
MS are commonly brief and isolated, and can occur during wakefulness and the first two stages of sleep. A variant with predominantly nocturnal MS has also been described (Prabhu *et al*., 2014). Intensity varies. They predominantly involve the upper limbs with brief arm abduction and the head, appearing as head drops. They involve the lower limbs less commonly, but may rarely cause sudden drop attacks when strong.
Longer MS can occur as a sequence of arrhythmic or rhythmic jerks lasting 3-7seconds. When the duration is >4 seconds, alertness may be affected. MS may also be subtle, with eye blinking, rolling-up of the eyeballs, or a brief head movement. Reflex myoclonus can be seen along with spontaneous MS.
A rare coexistence of MS with absences during the active course of MEI has been described (Caraballo *et al*., 2013).

EEG section

Background
Normal in wakefulness and sleep with preserved sleep architecture (*supplementary figure 3.20*). Occasionally, monomorphic synchronous 4-6-Hz theta activity can be seen in the central regions.

Interictal abnormalities
GPSWD/GSWD are rare during wakefulness, but are activated by drowsiness and slow sleep (*supplementary figure 3.21 and 3.22*). However, a given sleep EEG may be normal.
When present, interictal GSWD/GPSWD are brief and can be asymmetric. Photoparoxysmal responses are rarely seen, though IPS-triggered fast (3-4-Hz) GSWD/GPSWD with concomitant MS may occur at the onset. Focal interictal epileptic discharges (such as low-voltage fronto-central spike or spike-wave discharges) are rarely seen.
GPSWD/GSWD and photoparoxysmal responses may persist for many years after the clinical remission of MEI (Caraballo *et al*., 2013).

Ictal EEG
MS are associated with fast (3-4-Hz) GSWD/GPSWD (*supplementary figure 3.23-3.26*). These GSWD/GPSWD complexes are often preceded by anterior predominant spike-and-wave discharges (Ricci *et al*., 1995). Eye blinking can be the mildest form of a MS

(Darra *et al*., 2006). Some children exhibit photosensitive MS associated with GPSWD (Ricci *et al*., 1995; Auvin *et al*., 2006).

Recording protocols

Basic level

Record during wakefulness and, at least, drowsiness; include sleep if possible.

Employ EMG polygraphy (at the expense of two EEG channels if not enough channels are available) to obtain a definite diagnosis of MS. Technologists should observe closely and annotate, particularly if video is not available.

Time: anytime of the day.

Activation: IPS/HV (blowing a windmill); specific activation should include unexpected tactile stimulation and noises (*supplementary figure 3.26*).

Advanced level

As in basic level, but perform prolonged video-EEG-EMG polygraphy to include sleep (for instance, day telemetry), to recover interictal GSWD and capture MS.

Levels of EEG diagnosis

A. Confirmatory of suspected MEI (in the absence of abnormal neuroimaging)

Recording of MS with the typical EEG-EMG polygraphy features and typical interictal presentation (normal background, with or without interictal GSWD), as stated above.

No atypical features or other types of seizure including epileptic spasms, myoclonic-atonic, tonic, or absence seizures.

B. High diagnostic certainty (probable)

No MS recorded, but typical interictal presentation (normal background with interictal GSWD), as stated.

No atypical background or interictal features; no other seizure types.

Proceed with prolonged advanced level recording to register MS and move diagnostic certainty to level A.

C. Low diagnostic certainty (possible)

Normal EEG without MS or any other seizure type. Proceed with (or repeat) prolonged advanced level recording to register MS or interictal GSWD and move diagnostic certainty to level A or B.

Indications for long video telemetry/ambulatory EEG

When basic or advanced EEG of limited length is normal (as in level C above), or when they show atypical features. The latter include:

– (i) *Background activity*: persistent diffuse slowing, persistent focal/lateralized PDA, or distortion of normal sleep architecture.

– (ii) *Florid interictal epileptiform discharges*: multifocal spikes, frequent GSWD or hypsarrythmic features.

– (iii) Other types of seizure beyond MS: for instance atonic, myoclonic-atonic, tonic, spasms, etc. (see chapters on epilepsy with myoclonic-atonic seizures, WS, LGS, etc.).

3.4 Benign Infantile Epilepsy (BIE)

Overview

BIE, or *benign infantile seizures (BIS),* is characterized by focal seizures that often occur frequently or in clusters, and appear resistant to treatment at onset, but spontaneously resolve weeks or months later. Pregnancy and perinatal history, neurological examination, and developmental milestones before the onset of seizures are normal. Diagnostic workups, including metabolic and neuroimaging studies, are unremarkable. The patients ultimately achieve normal development milestones.

BIE can be sporadic (Watanabe *et al*., 1993) or familial, showing autosomal dominant (AD) mode of inheritance; the latter is known as "benign familial infantile epilepsy/seizures" (BFIE) (Vigevano *et al*., 1992). BFIE shows incomplete penetrance and genetic heterogeneity. Four susceptibility loci for BIFE have been identified so far: chromosome 19q (BFIE1), 2q24 (BFIE3), 1p36.12-p35.1 (BFIE4), and 16p12-q12 (BFIE2), with the latter being by far the most frequently mapped (Striano *et al*., 2006).

A combination of BFIE with paroxysmal kinesigenic dyskinesia (PKD), occurring in 17% of BFIE, is called infantile convulsions and paroxysmal choreoathetosis (ICCA). Mutation in the proline-rich transmembrane protein 2 gene (PPRT2) located on chromosome 16p12-q12 has been identified as the major cause of PKD, ICCA and BFIE and may be present in 80-90% of familial cases (Heron *et al*., 2012).

De novo PRRT2 mutations have been found in cases with non-familial benign infantile seizures (Specchio *et al*., 2013), but the majority of sporadic cases remain genetically unexplained. The phenotypic spectrum of infantile epilepsy with PPRT2-related pathology has been further expanded. *PPRT2* mutation was also found in BFIE and heterogeneous phenotypes including FS and SUDEP (Labate *et al*., 2013) and benign myoclonus of early infancy (Maini *et al*., 2016).

Other conditions that may be related to BIE include:

Benign focal epilepsy in infancy with midline spikes and waves during sleep (Capovilla *et al*., 2006). Patients presented with focal seizures and typical midline interictal spikes solely during sleep with a benign outcome. Seizures were characterized by brief episodes of cyanosis, staring, and rare lateralizing signs.

Convulsions with mild gastroenteritis caused by either rotavirus or norovirus (Imai *et al*., 1999). The patients had mild gastroenteritis associated with focal seizures with secondary generalization. Seizure foci were noted in occipital, parietal, and frontal, but not in the temporal areas. Clinical manifestations were similar regardless of the site of origin (Maruyama *et al*., 2007). *Benign familial neonatal-infantile epilepsy or seizures (BFNIE or BFNIS)*, shares many clinical features with BFIE (Vigevano, 2005). The typical hallmark of BFNIE is the occurrence of seizures by age four months. SCN2A mutation has been identified (Berkovic *et al*., 2004).

Seizures: symptoms & semiology

The typical characteristic of BIE is clustering of brief seizures lasting between one and three days. Seizures are usually longer at the onset and became shorter after treatment. Isolated seizures can occur 10 to 15 days prior to the cluster. The onset of seizures is in the first or second year of life in the absence of definite causes. The patients are normal between the seizures and subsequently have normal developmental milestones (Vigevano *et al*., 2012). Clinical features of BIE are not diagnostic, although the presence of family history of seizures, PKD, and choreoathetosis are very helpful. However, a lack of family history of these conditions in small families cannot exclude BFIE. Sporadic forms are more difficult to diagnose and early diagnosis is possible only in the familial forms (Okumura *et al*., 2000; Specchio and Vigevano, 2006). Although the recognition of BIE is possible at the beginning of epilepsy (Espeche, 2010), a recent study showed that around 30% of patients initially diagnosed with BIE did not have a benign clinical course, and their clinical features during the acute phase did not distinguish individuals with BIE from those with non-benign infantile seizures (Kikuchi *et al*., 2015). Seizure semiology includes behavioural arrest, slow head and eye version with shifting predominance, bilateral tonic posturing, cyanosis, and unilateral followed by bilateral clonic limb jerking (Vigevano, 2005). Treatment is practically required during the initial seizure clustering, as there are no diagnostic electroclinical features of BIE. There are no electroclinical differences between BFIE and BNFIE (Lispi and Vigevano, 2001; Caraballo *et al*., 2003).

EEG section

Background

Normal in wakefulness and sleep

Note. Mildly diffuse background slowing may be caused by sedative medications. Consider other epilepsy syndromes if EEG background is consistently diffusely slow.

Focal slowing may occur but should not be persistent in a single area. Persistent focal slowing in one area should prompt search for a structural brain abnormality.

Interictal abnormalities

***Wakefulness*.** Typically absent.

Sleep. typically absent although a variant with low-voltage midline spikes during slow sleep has been described (Capovilla *et al*., 2006).

Note that interictal EEG performed during a cluster of seizures may show lateralized slow waves and spikes in the occipital-parietal areas (*supplementary figure 3.27*) (Specchio and Vigevano, 2006).

Ictal EEG

Seizures are accompanied by focal ictal epileptiform discharges, which may spread to both hemispheres. The ictal discharge often ends in the hemisphere contralateral to the ictal onset. The ictal onset may vary from lobe to lobe or from hemisphere to hemisphere in different seizures in the same patient. In familial cases, the seizures originate mostly in the parieto-occipital, but not the temporal areas (Vigevano, 2005).

Recording protocols

Basic level

Routine EEG during wakefulness and sleep: Sleep recording may activate low-voltage midline spikes.

Time: any time of the day.

Activation: photic stimulation and sleep.

Advanced level

Prolonged video-EEG, up to 24 hours, to evaluate longer portions of sleep and recover interictal epileptiform discharges (IED) and record seizures during a cluster.

Levels of EEG diagnosis

A. Confirmatory of suspected BIE (in the presence of normal development, positive family history [if present] and negative neuroimaging)

Recording a typical seizure or a cluster of characteristic focal seizures, as described above (ictal EEG).

B. High diagnostic certainty (probable)

Normal EEG background.

Absence of IED, except low-voltage midline spikes.

Interictal EEG performed during a cluster of seizures showing lateralized PDA and spikes in the occipital-parietal areas.

Note. The diagnosis of BIE is unlikely in the presence of:

– persistent diffuse background EEG;

– persistent focal/lateralized PDA;

– IEDs beyond low-voltage midline spikes during sleep;
– focal spikes shifting from one region to another in sequential EEGs, as in epilepsy of infancy with migrating focal seizures (*see relevant chapter*);
– atypical clinical seizures and ictal EEG, especially with persistent localization/lateralization of seizure semiology and ictal EEG suggesting structural epilepsy.

Indications for video telemetry/ambulatory EEG
To capture seizures during a cluster and confirm diagnosis.
Clinical and EEG suspicion of other types of epileptic syndromes.

3. 5 Epilepsy of Infancy with Migrating Focal Seizures (EIMFS)

Overview

EIMFS, previously called malignant migrating partial seizures of infancy, is a rare and severe condition that belongs to the group of early-onset epileptic encephalopathies. EIMFS was first described in 1995 (Coppola *et al*., 1995), and to date, approximately 125 patients have been reported. EIMFS is characterized by drug-resistant focal "migrating" or "random" seizures beginning within the first six months of life, severe global developmental delay, and acquired microcephaly. Brain MRI is usually normal at onset, but it later shows delayed myelination with thin corpus callosum and cerebral atrophy (Barcia *et al.,* 2012). Patients whose seizures are brought under control may show steady neurological improvement. Those with intractable seizures show progressive deterioration with development of major axial and limb hypotonia, loss of visual contact, and a complete loss of other motor and social skills; some children may show pyramidal and/or extrapyramidal manifestations with athetotic movements; 18% of the so far reported patients died (McTague *et al.,* 2013).
Recently, *de novo KCNT1* mutations with KCNT1 channel gain of function have been reported in around 50% of patients with sporadic EIMFS (Barcia *et al.,* 2012; McTague *et al*., 2013). Other mutations have been reported in familial cases with recessive autosomal transmission (in *SLC12A5*, *TBC1D24*, and *SLC25A22*) (Ohba *et al.,* 2015).

Seizures: symptoms and semiology

The natural history of EIMFS is recognised by three distinct phases, as described in the first report in 1995 (Coppola *et al*., 1995). A first phase, generally starting in the first six months after birth and lasting a few weeks or months, is characterized by sporadic seizures, usually recurring every few weeks or months. Seizures are mainly focal motor with rapid secondary generalization or with autonomic manifestations such as apnoea, flushing or cyanosis (Coppola *et al*., 1995; Caraballo *et al.,* 2008a).
In the second "stormy phase", which can occur between one and 12 months, seizures become very frequent, occurring in clusters several times a day or being almost continuous for several days. Seizure semiology more often includes lateral deviation of the head and eyes, twitches of the eyelids, unilateral clonic or tonic jerks of one or both limbs, apnoea, flushing and/or cyanosis of the face, chewing movements, mastication, and secondary tonic-clonic convulsions. Milder clinical manifestations may be easily overlooked and full detection of the frequent ictal manifestations is possible only by long-term video-EEG recordings (Coppola, 2009). Furthermore, clinical manifestations may be "subtle" or absent despite the long duration of seizures. Prolonged video-EEG recordings show a clear correlation between the topography of the ictal discharges and the clinical features.
The age at onset of the third phase may vary widely, ranging from the end of the first year to the fifth year of age and over. This phase is relatively seizure-free, although interspersing illnesses can trigger clusters of seizures or occasionally status epilepticus. Later, IS may occur (Coppola *et al.,* 1995; McTague *et al.,* 2013).

EEG section

Background
This is usually normal during the first months of the disease with the exception of slowing for many hours after long-lasting seizures (*see below*). As the disease evolves, background activities become progressively diffusely slower with reduction of physiological features.

Interictal abnormalities
Usually absent at onset, spikes rapidly increase in frequency and become multifocal within a few months. Multifocal spike-and-wave foci do not show any specific pattern and are not activated in sleep. Background activity may show alternating asymmetries, with one hemisphere exhibiting slower activity on a given trace and the other hemisphere showing slower rhythms on another trace (Coppola *et al.,* 1995). During seizure-free periods, sleep and wakefulness are clearly differentiated, but sleep spindles are rare, asynchronous, and asymmetric.

Ictal EEG
Migrating focal seizures
Seizures occur typically in clusters that last for a few days and are then followed by a few weeks or months of recovery. Within a cluster, seizures are very frequent

and may even amount to status epilepticus (*supplementary figure 3.28*).
Clusters increase in frequency within the first two years of life. It is important for the diagnosis to record the typical ictal EEG pattern during such a cluster. Typically, ictal discharges sequentially involve various areas in apparently migrating random fashion. The ictal pattern consists of mainly rhythmic monomorphic activity in the alpha-theta frequency range, although delta waves and rhythmic spikes and spike-waves may also occur. Usually, seizure activity remains restricted to one region for some time before it slows down in frequency and stops, as it appears to progressively involve an adjacent area (*supplementary figure 3.28 and 3.29*). Ictal discharges are followed by postictal slow wave activity without prolonged attenuation (Coppola *et al.*, 1995; Coppola, 2009).
When seizures are frequent, ictal onsets shift from one region to another and from one hemisphere to the other. Consecutive focal ictal discharges overlap, with a new one beginning before the end of the previous one, resulting in continuous, but shifting, multifocal ictal activity and a very complex pattern of status epilepticus (*supplementary figure 3.29*). Simultaneous independent discharges occur frequently without following usual propagation patterns or a stereotyped topographic course. Seizure activity may involve all cerebral regions with a clear correlation between the topography of the ictal discharge and the clinical features. Caraballo *et al*. (2008b) distinguished three different clinical patterns:
– (i) recurrence of ample rhythmic focal spikes or rhythmic sharp theta or alpha activity over the rolandic region;
– (ii) polymorphic theta-delta activity over a temporo-occipital region;
– (iii) initial flattening or small discharge of ample fast polyspikes in one hemisphere. With increasing age, the amplitude of the ictal discharges tends to increase, and frontal areas are more frequently affected (Dulac, 2005).
At the onset of the disease, focal seizures may be monofocal or multifocal without the typical "migrating" aspect. When the clinical picture is suggestive of the diagnosis, few long-duration EEG recordings may be required to convincingly show the multifocal and "migrating" nature of the seizures.

Recording protocols
Basic level
EEG should be recorded during wakefulness and sleep for as long as possible to recover seizures. Record during a cluster of seizures, if possible.
Use polygraphy (ECG, respiration, bilateral deltoid EMG), if possible, to detect ictal autonomic changes and subtle movements.

Advanced level
Perform long-duration video-EEG with polygraphy, as described for basic level. Attempt to record from a few to 24-48 hours during a cluster of seizures to capture multiple seizures and document their "migrating" character.

Levels of EEG diagnosis
A) Confirmatory of suspected EIMFS in untreated children
(For both basic and advanced recording levels)
Recording of typical "migrating" ictal presentation.
B) High diagnostic certainty (probable)
(For both basic and advanced recording levels)
No atypical interictal presentation; focal or multifocal seizures are recorded, but without the typical "migrating" expression. A second 24-48-hour recording is required to record the typical migrating seizures and confirm the diagnosis.
C) Low diagnostic certainty (possible)
(For both basic and advanced recording levels)
No atypical interictal features (*see below*), but without any seizures recorded.

Indications for repeating video-EEG recording
level 2
– (1) Failure to record seizures.
– (2) Focal seizures are recorded, but are monofocal or multifocal without a typical "migrating" aspect.
– (3) New clinical features suggesting another seizure type or epileptic syndrome or degenerative, chromosomal, and/or metabolic disease.

Atypical EEG/video-EEG features to be highlighted in the EEG report, which may cast doubts or eliminate the diagnosis of epilepsy of infancy with migrating focal seizures
– (1) Interictal abnormalities suggestive of a focal lesion, such as constant focus of spikes, polyspikes, rapid rhythms, or slowing.
– (2) Monofocal seizures associated or not with epileptic spasms.
– (3) Myoclonic seizures.

4. CHILDHOOD

4. 1 Febrile seizures (FS) and Genetic Epilepsy with Febrile Seizures *plus* (GEFS+)

Overview
The term "Febrile Seizures" defines any seizure accompanied by fever (temperature >100.4°F or 38°C by any method), without central nervous system infection occurring in children between six months and

five years of age (Subcommittee on Febrile Seizures; American Academy of Paediatrics, 2011).
The term "generalised epilepsy with febrile seizure *plus*" (Scheffer and Berkovic, 1997) has been renamed "genetic epilepsy with febrile seizure plus" because it is now recognised that some of the associated epilepsies may be focal (Camfield and Camfield, 2015; Zhang *et al*., 2017). The diagnosis of GEFS *plus* can only be made at a familial level (individuals may have "febrile seizures *plus*", a term reserved to febrile seizures alone persisting above the age of 5 years old).
GEFS+ is an important familial epilepsy disease state (rather than a homogenous epilepsy syndrome) with complex inheritance and clinical and genetic heterogeneity. Mutations are most frequently reported in sodium channel and GABA (A) receptor subunit genes, segregating in large autosomal dominant families. The two main phenotypes in these families include: (i) FS -generalised tonic-clonic seizures occurring with fever between two months and five years of life, and (ii) FS+ -generalised tonic-clonic seizures that occur after or extend beyond six years of age. In some children, afebrile seizures occur in addition to FS.
Additional phenotypes within the affected GEFS+ families include:
– FS/FS+ with other generalised seizures such as absences, and myoclonic and atonic seizures
– Afebrile generalised tonic-clonic seizures
– Classic genetic generalised epilepsies
– FS/FS+ with focal seizures
– Focal epilepsies alone
– Epilepsy with myoclonic-atonic seizures
– Dravet syndrome

Febrile seizures

The lower age at onset of febrile seizures (FS) is debatable and for practical purposes a lower cut off of two months is considered useful. The peak incidence is at 18 months with about 80% of seizures occurring at between one and three years of age. Febrile seizures are the most common phenotype in the GEFS+ families tested (Zhang *et al*., 2017).
The classic clinical distinction into "simple" and "complex" or "complicated" FS is based on prognostic implications: the majority of FS are simple, *i.e*. brief, usually generalized in their clinical expression, do not repeat in the same clinical illness, and have excellent prognosis and therefore do not require further diagnostic tests, including EEG (Subcommittee on Febrile Seizures; American Academy of Pediatrics, 1996). The "complex" group includes focal, prolonged (>15-20 minutes) or numerous FS in the same illness (or any combination of these attributes), and make almost a third of the total FS; complex FS are associated with increased risk of developing spontaneous seizures in later life (Annegers *et al*., 1987), particularly in the presence of an underlying neurological disorder. One should recognize that descriptions given by the carers in an emergency setting may be biased as early focal signs can be missed.
About 20-40% of children with a first FS will have a recurrence. If children present at a young age (<18 months) and have a positive family history of FS in a first degree relative, a low degree of fever while in the emergency department, and a brief duration between onset of fever and the initial seizure, the risk of recurrence increases to 70%. (Berg *et al*., 1997).
Febrile status epilepticus (FSE) is defined as a single seizure lasting >30 minutes, or a series of seizures, without full recovery in between, which also meet the definition of a FS.

Seizures: symptoms and semiology

Most FS are described by parents as generalized motor (diffuse stiffening or shaking), while focal seizures usually manifest with unilateral or strongly lateralized motor phenomena, version of head/eyes or lateralized postictal weakness; initial behavioural arrest is also suggestive of focal onset. Focal features at the onset may be missed by distressed parents. Carers often find it difficult to recall witnessed descriptions of limb movements and postictal behaviour.

EEG section

Note. **EEG is not indicated after simple FS in neurologically normal children.** There is no evidence that an EEG performed at the time of presentation or within the following month after a simple FS is predictive of recurrence of FS or the development of afebrile seizures epilepsy within the next two years.
However, it is conceivable that FS may still be a reason for EEG referral, particularly when complex, or when there is positive family history of epilepsy, or when underlying neurological pathology is clinically suspected. Maytal and colleagues reported that all sleep EEGs in their 33 patients with complex FS were normal (Maytal *et al*., 2000). On the other hand, Yücel and colleagues proposed that if neurological examination is normal, an EEG should be performed after seven days at the earliest, or at 10 days for more accurate prognostication (Yücel *et al*., 2004). A subsequent Cochrane review found no randomised control trial evidence to support or refute the use of EEG and it's timing in complex FS in neurologically normal children (Shah *et al*., 2017).
Given the lack of concrete evidence, for practical purposes the timing of the EEG should be based on available resources and, if possible, it should be done as soon as possible if the child is an in-patient, and repeated during follow-up, ideally after 10 days.

Background
Normal, as a rule. Postictal regional slowing or attenuation of background rhythms may occur in focal complex FS.
In ***FSE***, EEGs performed within 72 hours can show focal slowing, focal attenuation or focal slowing with attenuation. Focal slowing can also be associated with diffuse background slowing (*supplementary figure 4.01*). The slowing is significant if in the delta range and the attenuation if the voltage of the activity is less than half of the contralateral side. When present, the focal features are mostly over the temporal region (Nordli *et al.*, 2012). The key findings of this paper are that of the 199 EEGs, 90 (45.2%) were abnormal with the most common abnormality being focal slowing (n=47) or attenuation (n=25); these were maximal or more pronounced over the temporal areas in almost all cases. Epileptiform abnormalities were present in 13 EEGs (6.5%). Based on adjusted analysis, the odds of focal slowing were significantly increased by focal FSE (odds ratio [OR]: 5.08) and hippocampal T2 signal abnormality (OR: 3.50) and significantly decreased with high peak temperature (OR: 0.18). Focal EEG attenuation was also associated with hippocampal T2 signal abnormality (OR: 3.3).

Interictal abnormalities
Typically absent in the vast majority of simple and also complex FS. Occasional focal or generalised spike-wave discharges can be seen.
Note. The occasional occurrence of a generalized (or focal) spike-wave discharge may simply reflect a non-specific genetic trait and is not necessarily predictive of future generalized epilepsy or further FS (*supplementary figure 4.02 and 4.03*).

Recording protocols
After simple FS: an EEG is not recommended (*see note in EEG section above*).
After complex FS: irrespective of recording level (use of video or length of recording), the EEG should include sleep and IPS.

Levels of EEG diagnosis
Simple FS: the EEG is of limited diagnostic value.
Complex FS (focal, prolonged, or repeated): the following clinical practice statements can be made in accordance with given EEG findings:
– (1) Normal EEG: point out that no further EEG studies are needed.
– (2) Abnormal EEG:
  • Age >18 months: normal background, non-specific abnormalities including brief spike-wave discharges in children older than three years of age; avoid over-interpretation and point out that this may simply reflect a non-specific genetic trait and is not necessarily predictive of future generalized epilepsy or further FS (*see "interictal paroxysmal abnormalities" above*). In children with a family history of febrile or afebrile seizures, suggest that it may indicate later evolution to GEFS+ (which can help with possible genetic studies).
  • Age <18 months: a normal background with spontaneous epileptiform discharges indicates seizure susceptibility; recommend clinical follow-up and repeat EEG as required.

When background shows focal/regional slowing, attenuation of faster rhythms, or both, with or without associated focal spikes, raise the possibility of later development of focal epilepsy and recommend clinical and EEG follow-up. A structural cause may need to be excluded.
Early (within the first year of life) occurrence of generalized spike-wave discharge on IPS raises the possibility of DS (*see relevant section*).

Febrile seizures plus (FS+)
The term "febrile seizures plus" (FS+) encompasses FS that persist beyond the age of six, or very rarely start after the age of six. Children may have afebrile GTCS in addition to their FS. The afebrile GTCS may occur in various patterns: either limited to the time frame of classic FS, or begin as the FS peter out, or not occur until several years after the FS cease. They usually settle by the second decade, although may recur in later life. FS+ may occur with other generalised seizures such as absences or myoclonic, myoclonic-atonic or atonic seizures. In GEFS+ families, focal epilepsy can occur with or without preceding FS/FS+. Also reported was the occurrence of temporal lobe epilepsy (TLE), which was more commonly associated with a history of preceding FS/FS+ (Zhang *et al.*, 2017).

EEG findings

Background
Normal, as a rule. Regional slowing or focal attenuation of the background rhythms may occur in children with focal seizures (Abou-Khalil *et al.*, 2001).

Interictal abnormalities
Typically absent in the vast majority of children with GEFS+. When present, their type corresponds to the clinical phenotype, for example ~3-Hz generalized spike-wave discharges occur in children with FS+ and absences, while focal spikes of corresponding topography occur in those with temporal or frontal seizures (*supplementary figure 4.04*).

Recording protocols
Both recording levels should include sleep and IPS.
If absences or myoclonic or focal seizures are suspected, follow the relevant protocols, as described in the corresponding sections (for example, when

history is suggestive of possible absences, perform sleep-deprived EEG with HV on awakening to record ~3-Hz spike-wave discharges or absences; *see chapter on CAE*). Similarly, use relevant recording protocols when possible myoclonic-atonic epilepsy or Dravet syndrome phenotypes are suspected (*see relevant chapters*.

Levels of EEG diagnosis

The first important point is to raise the possibility of GEFS+ in a child presenting with FS or FS+. When the family history is suggestive of GEFS+, the second aim is to define the phenotype of the affected proband, based on possible background abnormalities and interictal (or ictal) epileptic activity. A third aim is to collect information about the epilepsy phenotypes of the affected family members, or even perform EEG studies on them if possible. This would delineate the particular family GEFS+ profile.

A) Confirmatory of suspected GEFS+ when there is a history of FS/FS+ and a positive family history.

Normal background EEG with ictal recording of a generalised tonic-clonic seizure.

Normal background with absences associated with generalized 2-3-Hz spike-wave discharges, or myoclonic, myoclonic-atonic, or atonic seizures associated with generalized polyspike-wave discharges.

Normal background and ictal recording of a focal frontal or temporal lobe seizure.

B) High diagnostic certainty (probable)

Normal background with subclinical generalized discharges; proceed with advanced level recording (prolonged video monitoring) if there is a history suggestive of absences, myoclonic or atonic seizures; recommend clinical follow-up and repeat EEG when needed. Also consider Glut-1 deficiency.

Focal/regional background slowing, or attenuation of faster rhythms, or both, with or without associated focal spikes may be suggestive of GEFS+ with focal seizures (temporal or frontal); recommend clinical EEG follow-up and repeat EEG when needed.

C) Low diagnostic certainty (possible)

Normal EEGs.

4.2 Benign childhood epilepsy with centrotemporal spikes (CTS) or Benign Rolandic Epilepsy (BRE)

Note. The term "benign" refers to the clinical course and not to the neuropsychological development that may show neuropsychological impairments in literacy and language. The term "self-lmited" epilepsy is used in the recently published 2017 ILAE Classification (Scheffer *et al*., 2017).

Overview

Definition: BRE is the best known and commonest idiopathic childhood focal epilepsy, within the spectrum of the age-related focal seizure susceptibility syndrome (Panayiotopoulos *et al.,* 2008) that also comprises Panayiotopoulos syndrome (PS) and childhood occipital epilepsy of Gastaut. BRE is probably genetically determined. The age at onset peaks at around 7-10 years and the clinical course is considered benign. In very few cases, an atypical evolution may be seen.

Seizure symptoms and semiology

Seizure frequency is generally low, with 10% having only one attack and half having fewer than five. In about 20% of children, seizures are frequent and may even occur several times per day. Seizures generally last from 30-60 seconds with the majority of them (80-90%) occurring from sleep. The most frequent clinical manifestations of the typical rolandic seizures are (Dalla Bernardina *et al.,* 2005; Panayiotopoulos *et al.,* 2012):

Orofacial motor signs, specifically tonic or clonic contractions of one side of the face with predilection of the labial commissure (contralateral to centrotemporal spikes). Involvement of the ipsilateral eyelids is not unusual. More rarely, clonic convulsions may appear simultaneously in the ipsilateral upper extremity, while involvement of the leg is even rarer. There are also contractions of the tongue or jaw, guttural sounds, and drooling from hypersalivation and swallowing disturbance.

Speech arrest, most probably due to tonic contractions of pharyngeal and buccal muscles, leads to anarthric seizures. Laryngeal sounds may be uttered, particularly at the beginning. There is no impairment of the cortical language mechanism, and this may explain why ictal arrest of speech is equally common in left or right-sided seizures (Fejerman and Caraballo, 2007). Children are unable to speak during the seizure, either because they wake up with hemifacial contractions, or because when having a fit whilst awake, they open the mouth with the intention to speak but their mouth stays locked in that position. In exceptional cases, postictal dysarthria may persist for a few minutes after the seizure.

Somatosensory symptoms. Unilateral numbness or paresthesia of the tongue, lips, gums, and inner cheek are frequent, but one may need to specifically ask for such symptoms.

Sialorrhea. It is not clear whether this reflects increased salivation, a swallowing disturbance, or both. Sialorrhea is a characteristic ictal symptom of BRE and may be associated with oro-facial motor signs, speech arrest, or both.

Focal unilateral or bilateral motor seizures reflecting unilateral or bilateral involvement of the frontal motor areas may occur.

Generalized convulsive seizures are not infrequently observed, particularly in younger children (Fejerman and Caraballo, 2007). The initial event is often a nocturnal hemifacial convulsion, which may spread to the arm and the leg or may become secondarily generalized. It is highly probable that in these cases children start with a focal seizure during sleep, but the rapid generalization and loss of consciousness impairs their ability to remember what happened at seizure onset (Dalla Bernardina *et al.,* 2005). In children aged 2-5 years, hemiclonic seizures last sometimes more than 30 minutes and may be followed by transient ipsilateral deficits, generally not including the face.

Other seizure types

Autonomic seizures associated with motor manifestations, and visual manifestations have been described (Fejerman and Caraballo, 2007; Caraballo *et al.,* 2008b).

EEG section

Background

The background is symmetric, well organized, and normally reactive during wakefulness, and shows normal physiological patterns during sleep.

Interictal epileptiform abnormalities

The ***typical centrotemporal spikes (CTS)*** are located over the rolandic areas, and are frequently of maximal amplitude (peak negativity) over the lower central electrodes (C5/C6), positioned halfway between the central (C3/C4) and the mid-temporal (T3/T4) electrodes (Legarda *et al.,* 1994) and not over the mid-temporal area. They are broad, diphasic, and of high voltage (100-300 microvolts), often followed by a slow wave. The dipole could be assumed perpendicular to the cortex within the rolandic fissure and therefore almost parallel to the anterior-posterior axis of the brain, producing the classic anterior-posterior dipole with anterior positivity (*supplementary figure 4.05*).

CTS can be of small voltage (*supplementary figure 4.06*) or of high voltage (*supplementary figure 4.07*), may be sporadic or occur in clusters, and are not affected by eye opening or closure, HV, or photic stimulation. Focal rhythmic slow activity is occasionally observed in the region where the spikes are seen, but there is no disturbance of faster background rhythms (*supplementary figure 4.08*).

CTS may be unilateral or bilateral (independent or synchronous). Bilateral CTS occur during wakefulness or sleep in about one third of the cases. CTS tend to increase and diffuse to adjacent regions during sleep, but do not change morphology (for instance, they do not evolve into polyspike-wave) (*supplementary figure 4.09*). There is no correlation between abundance of CTS in the EEG and frequency, length, or duration of clinical seizures.

Spikes in other areas and multifocal spikes can be seen from the first EEG recording or during evolution (Dalla Bernardina *et al.,* 2005). Like CTS, multifocal spikes may increase or become evident during sleep (*supplementary figure 4.07 and 4.09*). The possible presence of multifocal spikes with the same morphology and behaviour both during wakefulness and sleep does not seem to correlate with the frequency of seizures.

Generalized spike-wave discharges are rarely seen during wakefulness, but are not infrequent during drowsiness (*supplementary figure 4.10*); they do not occur during sleep (Fejerman and Caraballo, 2007). The incidence of GSWD varies widely between studies (7-65%) (Dalla Bernardina *et al.,* 2005).

Ictal EEG

Given the generally low frequency of seizures and their mainly nocturnal occurrence, ictal EEG recordings are rare. The ictal EEG pattern is generally characterized by a sequence of rhythmic spikes which remain fairly monomorphous throughout the seizure discharge (*supplementary figure 4.11A, B*).

Recording protocols

Basic level

Sleep recording is desirable because typical findings may only be seen in sleep. If only EEG during wakefulness can be planned, or if the EEG during wakefulness is inconclusive and a sleep recording has not been scheduled, it is worth allowing some extra time for drowsiness or light sleep, if possible (*see below*).

Activate with HV and IPS; use polygraphy with ECG and bilateral deltoid EMG, if extra channels are available.

Advanced level

Awake and sleep recording after partial sleep deprivation or melatonin-induced EEG with HV and photic stimulation. Sleep Stages 1 and 2 are important to activate CTS when the recording during wakefulness is unremarkable and to assess for possible atypical features (*see below*). Sleep may also activate independent centro-temporal spikes over the other hemisphere or generalized spike-wave discharges that would argue against a structural cause.

Indications for prolonged video-EEG recording (telemetry)

– (1) Frequent refractory rolandic-type seizures with interictal EEG findings consistent with BRE (may indicate the possibility of structural epilepsy even though MRI is normal).

– (2) Appearance of drop attacks/atypical absences/MS in a child previously diagnosed with BRE (*see atypical evolution in BRE*).
– (3) Non-convulsive status/sudden and marked neuropsychological impairment in a child previously thought to have BRE (*see atypical evolution in BRE*).
– (4) Two normal interictal EEGs, including a sleep recording, in a child clinically thought to have BRE with frequently reported seizures.

Levels of EEG diagnosis
(For both basic and advanced levels)
A) Confirmatory (based on clinical suspicion of BRE in developmentally normal untreated children with ictal symptoms and semiology as above)
– (1) Ictal recording with appropriate clinical symptoms and EEG discharge over the centrotemporal area, with or without secondary generalization.
– (2) Interictal typical CTS, unilateral or bilateral, with or without spikes of similar morphology and behaviour outside the rolandic areas (extrarolandic) or generalized spike-wave discharges.
B) High diagnostic certainty (probable)
– (1) Unilateral CTS which increase in frequency during sleep without a change in their morphology.
– (2) Extrarolandic focal or multifocal spikes with the typical CTS morphology and behaviour in sleep.

Atypical EEG/video-EEG features to be highlighted in the EEG report, which may cast doubts on a diagnosis of BRE, as suggested by the clinical picture
– (1) Isolated rolandic spikes and/or spikes located in anterior regions that are not activated by sleep.
– (2) A change in morphology of the CTS during sleep (particularly the appearance of fast spikes or polyspikes, or a marked increase in the slow component, or a brief depression of voltage) may evoke the possibility of symptomatic aetiology even when the clinical ictal features are suggestive of BRE (Dalla Bernardina *et al*., 2005).
– (3) Prominent slowing of the background rhythms, either focally or diffusely.
– (4) Runs of diffuse bilateral/generalised spike-and-wave discharges, lasting for more than three seconds in wakefulness.
– (5) Evidence of electrical status epilepticus during sleep (ESES)/CSWS during sleep.
Note. Indications for brain MRI in suspected BRE: the EEG evidence.
Imaging is not indicated in children presenting with typical features of BRE even though about 15% of these children may exhibit an abnormal MRI. Non-causal structural abnormalities do not influence the favourable prognosis of the epilepsy (Gelisse *et al.,* 2003). Rarely though, patients with electroclinical phenotypes of BRE associated with cortical dysplasia have been reported (Fejerman and Caraballo, 2007; Pal *et al.,* 2016) (*supplementary figure 4.12*). MRI is recommended if there are atypical electroclinical features such as age at onset, abnormal neurological or intellectual development, difficult-to-treat seizures, or unusual course. From the EEG viewpoint, any of the atypical EEG features (particularly 1-3), as discussed above, also warrant consideration.

Atypical evolution of benign focal epilepsies in childhood
This condition does not refer to children with atypical clinical and EEG features of BRE, but to a subset of children who initially appear to have a typical form of BRE (or Panayiotopoulos syndrome-PS), but subsequently present a period of severe aggravation of epileptic seizures and/or language and cognitive dysfunction, and/or behavioural disturbance (Pal *et al.,* 2016). Aicardi and Chevrie (1982) were the first to report this unusual evolution in seven children with BRE who presented periods with new types of seizure, mainly atonic and myoclonic, associated with continuous spike-and-wave discharge in slow sleep on the EEG, and transitory deterioration in school performance; they used the term "atypical benign partial epilepsy of childhood" (ABFEC). Subsequently, Fejerman *et al*. (2000) reported a series of children with typical clinical-EEG features of BRE, who, years later, presented, not only the aforementioned features of ABFEC, but also AED-resistant continuous status while awake and during sleep, consisting of bilateral facial twitching, speech arrest, and sialorrhea, associated with continuous paroxysms of higher amplitude over the rolandic areas; evolution to Landau-Kleffner syndrome (LKS) and continuous spike-and-wave during slow sleep (CSWS) was also noted (*supplementary figure 4.13 and 4.14*). Tassinari (2009) proposed this to be an epileptic encephalopathy with heterogenous clinical manifastations (cognitive, motor, and behavioural in different associations and with various seizure types) associated with ESES in slow wave sleep. Children with occipital epilepsies of Gastaut and PS, who have similar atypical evolution with continuous spike-and-wave and severe neuropsychological impairment, have also been reported (Caraballo *et al.,* 2001, 2015; Ferrie *et al.,* 2002).

4.3 Panayiotopoulos syndrome (PS)

Overview
PS is a distinct type of idiopathic focal epilepsy of childhood with infrequent and often prolonged autonomic

seizures. Prevalence is noted to be up to 5.2% in children between 1-14 years, presenting with an afebrile seizure. In the majority, the onset is between the age of three and six years, with disease duration up to three years and remission by the age of 10 years. Seizures are rather infrequent with only 5% of children reported to have more than 10 seizures in total. PS can also present with autonomic status epilepticus and is a common cause of afebrile non-convulsive status epilepticus in children.

Seizure symptoms and semiology

The hallmark of this syndrome is the presence of autonomic seizures with emesis (70-80%). Most seizures (70%) occur from sleep, 17% during wakefulness, and 13% upon awakening (Specchio *et al.,* 2010a). Seizures typically begin with nausea, feeling unwell or retching in association with autonomic features such as pallor, flushing, pupillary dilatation, thermoregulatory changes, and hypersalivation. These manifestations may be followed by impairment of consciousness and non-autonomic signs, such as deviation of the eyes or hemi-clonic or generalised convulsions. Ictal vomiting is a key feature and is more frequently observed in seizures occurring from sleep (84.6%) than whilst awake (50%). Seizures are usually prolonged up to 30 minutes (range: 5-90 minutes). Visual symptoms are very rare.

Syncope-like seizures, in which the child suddenly becomes flaccid and unresponsive, irrespective of body position, may occur in many children, either in association with other ictal manifestations or not (Koutroumanidis *et al.,* 2012). Because of its protean clinical ictal features, PS should be differentiated from non-epileptic conditions that include atypical migraine, gastroenteritis, or syncope (when relatively brief seizures are concerned), while prolonged seizures can imitate encephalitis or other serious cerebral insults (Kivity and Lerman, 1992; Panayiotopoulos, 2002).

EEG section

Background

Normal. If EEG is performed postictally, focal or diffuse slowing may be noted.

Interictal abnormalities

Wakefulness. Interictal EEG shows great variability. Typically, high-voltage sharp-slow-wave complexes are seen in up to 90% of children with PS in at least one EEG of a possible series of recordings (*supplementary figure 4.15 and 4.16*). These are usually multifocal, although they tend to predominate over the occipital regions, or even occur exclusively over the occipital areas in some children. Occipital spikes may occur in paroxysms (*for occipital paroxysms, see chapter on occipital epilepsy of Gastaut*). On the other hand, occipital spikes may not occur at all in up to a third of children. Multifocal spikes may occur over any area (frontal, central, parietal or temporal) and shift from one region to another and from side to side in a series of EEGs, while they may not be associated with occipital spikes. Ohtsu *et al*. (2003) noticed the occurrence of multifocal spikes months or years after seizure onset in children who initially had occipital spikes (*supplementary figure 4.15 and 4.16*).

"Clone-like", repetitive spikes or sharp-wave discharges (*supplementary figure 4.17 left panel, supplementary figure 4.18*) and small, as opposed to high-voltage, spikes may also occur.

The first routine EEG may be normal in 66-85% of children (Sanders *et al.,* 2004; Caraballo *et al*., 2007).

Sleep. Irrespective of voltage and topography, spike-wave discharges are activated in sleep or only occur in sleep, as in other idiopathic focal epilepsies, such as BRE. The diagnostic sensitivity of the sleep EEG ranges from 80% to 100% (Ohtsu *et al*., 2003; Sanders *et al.,* 2004; Tata *et al.,* 2014). However, there are instances when epileptiform discharges may occur in only one of the interval EEGs.

Atypical evolution with continuous spike-wave during sleep (CSWS) in association with impairment of motor, language, and cognitive function can occur, though it is considered rare.

The frequency, location, or persistence of the spike-wave discharges do not influence clinical manifestations and their severity, or prognosis. Spikes may persist for many years after clinical remission and usually disappear completely by adolescence.

Ictal EEG.

Like the interictal spike-wave discharges, seizure onsets are also variable, starting from wide posterior or frontotemporal areas (*supplementary figure 4.17, middle and right panels*), usually with rhythmic theta waves, intermixed with or followed by small spikes and spike-waves and fast rhythms with diffusion to both hemispheres. The ictal EEG onset can occur several minutes prior to the clinical onset (Panayiotopoulos, 2002; Koutroumanidis, 2007; Specchio *et al*., 2010b).

Recording protocols

Basic level

Sleep recording is desirable because typical findings may only be seen in sleep. If only an awake EEG can be planned, or if the awake EEG is inconclusive and a sleep recording has not been scheduled, it is worth allowing some extra time for drowsiness or light sleep, if possible (*see below*).

Activate with HV and IPS; use polygraphy with ECG and bilateral deltoid EMG, if extra channels are available.

Advanced level

Recording during sleep is mandatory to increase diagnostic yield; plan EEG during wakefulness and sleep, melatonin-induced or after partial sleep deprivation with HV and PS. The occurrence of occipital paroxysms raises the possibility of fixation-off sensitivity (FOS), which can be tested by using goggles covered with opaque tape (that ensure complete darkness) and +10 spherical lenses or underwater goggles covered with a transparent tape (that allow light but impede fixation) (*see chapter on FOS*).

Differential diagnosis

PS may need to be differentiated from TLE because of the associated autonomic symptoms; nausea, vomiting, *etc*. (*for relevant diagnostic EEG criteria, see chapters on TLE*).

Differentiation from structural occipital lobe epilepsy (OLE) relies on the co-existence of extra-occipital spikes in PS, particularly over the centrotemporal areas which occur both during wakefulness and sleep (Tata *et al.,* 2014) (*see also chapters on structural OLE and OLE of Gastaut*).

Indication for prolonged video-EEG recording

As seizures are infrequent, prolonged video-EEG monitoring is not considered. However, review of home videos of the seizures can be very helpful, though often the onset may be missed. If seizures are frequent and the diagnosis is in doubt, then telemetry may be considered.

Levels of EEG diagnosis

Note. An EEG will be requested once the emetic and other autonomic symptoms are recognized by the referring physician as potential seizure manifestations. The vast majority of the EEGs are recorded in the interictal state. Sometimes, in the acute phase of a prolonged seizure or in the case of autonomic status, a postictal recording may be obtained (supplementary figure 4.20 and 4.21). Ictal recordings are rare.

A) Confirmatory of PS (based on clinical suspicion of PS in untreated children)

Basic or advanced EEG: recording of an autonomic seizure (very rare) with typical electroclinical presentation.

B) High diagnostic certainty (probable)

– Basic or advanced EEG: typical clinical presentation with recording of interictal occipital spikes or occipital paroxysms and FOS, or

– Typical clinical presentation with interictal extra-occipital multifocal typical spikes, with or without associated occipital spikes, or

– Typical presentation with serial EEGs that show changes in the topography of interictal spikes.

Postictal recording after autonomic status showing focal slowing with or without associated spikes; full clinical recovery of the child within a few hours makes diagnosis of PS highly probable.

C) Low diagnostic certainty (possible)

Normal basic level EEG: advanced EEG is recommended to record occipital or multifocal spikes during sleep and increase diagnostic certainty to level B. The vast majority of children will show typical spikes in 2-3 sequential EEGs, particularly when they include sleep.

Indications for repeating advanced EEG

– (1) Normal first sleep (advanced) EEG.

– (2) Resistance to appropriate AEDs (carbamazepine, valproate, and clobazam) with frequent seizures. Consider imaging (see BRE).

– (3) Focal or generalized seizures lacking autonomic symptoms with typical interictal epileptiform EEG abnormalities or autonomic seizures without typical interictal epileptiform EEG abnormalities.

4.4 Occipital childhood epilepsy of Gastaut (OE-G)

Overview

Occipital childhood epilepsy of Gastaut (OE-G) is a distinct, purely occipital epilepsy syndrome within the spectrum of the age-related focal seizure susceptibility syndrome (called self-limited syndromes in the 2017 ILAE Classification) that also comprises Benign Rolandic Epilepsy (BRE) with CTS and PS (Panayiotopoulos *et al.,* 2008), and for which a genetic contribution can be reasonably presumed (*see introduction Part 1*). The age at onset peaks at around 7-8 years and the clinical course is considered benign, although rates of full remission are reported lower than for BRE and PS (Caraballo *et al.,* 2009).

Seizure symptoms and semiology

The initial ictal symptoms and signs in OE-G are similar to those in occipital or posterior cortex epilepsies of structural aetiology, since both types of OLE reflect epileptic disturbance of the same (visual) brain area (*see section on structural OLE*). Due to the different aetiology however, there are important differences, mainly concerning the symptoms and signs that arise from the involvement of extra-occipital areas, either at seizure onset or during seizure propagation, and associated seizure types. These clinical differences contribute characteristically to the overall EEG picture of OE-G.

In OE-G, duration of seizures is usually brief, lasting less than two minutes, though longer seizures up to 15

minutes can occur. Most seizures occur during wakefulness, but nocturnal seizures can also occur.

Patterns of ictal propagation
TLE-like semiology, reflecting unilateral or bilateral involvement of the temporal areas through infrasylvian seizure propagation, is infrequent (11-15%) in all studies (Gastaut and Zifkin, 1987; Panayiotopoulos, 1999; Caraballo *et al.,* 2008c) and when it occurs, typically follows visual auras; on the other hand, infrasylvian seizure propagation is frequent (40-88%) in all series of structural OLE/posterior cortex epilepsy (Blume *et al.,* 1991; Salanova *et al.*, 1992; Williamson *et al.*, 1992; Panayiotopoulos, 1999; Fogarasi *et al.*, 2005) and can occur without warning, mimicking TLE.
Deviation of the eyes and head, when present, are noted after the onset of visual hallucinations. Hemiconvulsions, following initial visual symptoms, are frequent in OE-G (34% according to Gastaut and Zifkin [1987] and 45.5% according to Caraballo *et al.* [2008]), sometimes alternating sides. In contrast, hemiconvulsions are conspicuously absent or only scarcely reported in the major surgical series of structural OLE/posterior cortex epilepsy in which contralateral jerking/numbness or dystonic posturing may occur, due to fast ictal propagation to frontal motor or supplementary motor areas.

Associated seizure types
Absences associated with 3-Hz generalized spike-wave discharges may occur concurrently ors after the onset of visual seizures in up to 15% of children with OE-G (Caraballo *et al.,* 2008c; Wakamoto *et al.,* 2011), while rolandic seizures are reported in up to 6% (Caraballo *et al.,* 2008c). No absences or rolandic seizures have been reported in structural posterior cortex or OLE.

EEG section

Background
Normal.

Interictal abnormalities
(see also *table 1* in the structural OLE section)
Typical interictal EEG shows high-amplitude occipital (electronegative to O1-O2) spikes occurring either randomly or in long rhythmic clusters (occipital paroxysms) when the eyes are closed (*supplementary figure 4.22*), but also during sleep (*supplementary figure 4.23*).
Occipital paroxysms while eyes are closed should prompt assessment for FOS (*supplementary figure 4.24; see also relevant section in Part 1*).
FOS is present in more than 90% of the children with OE-G (Gastaut and Zifkin, 1987), but occurs only occasionally in structural OLE. Occipital spikes and paroxysms are not associated with regional background rhythm disturbance, and are bilateral in up to 60% of children in OE-G (Caraballo *et al.,* 2008c), reflecting constitutional occipital hyper-excitability, as opposed to structural OLE in which occipital spikes are typically recorded over the site of the lesion. In structural OLE; bilateral synchronous (occipital or wider posterior) spikes occur in 10% (Williamson *et al.*, 1992) to 34% (Salanova *et al.*, 1992), possibly in relation to secondary bilateral synchrony (Salanova *et al.*, 1992). In OE-G, centro-temporal spikes (CTS) coexist in up to 24% of patients (Caraballo *et al.,* 2008c), principally in those with hemiclonic seizures (Gastaut and Zifkin, 1987). Generalized spike-wave discharges (GSWD) have been reported in 17% (Wakamoto *et al.,* 2011), 27% (Caraballo *et al.,* 2008c), and 38% (Gastaut and Zifkin, 1987) of patients, usually in the form of brief, diffuse, and rather irregular bursts (*supplementary figure 4.25*), but also occur in more robust 3-4-Hz GSWD, identical to those in IGEs (Caraballo *et al.,* 2004). In contrast, from the eight major series of around 170 patients with structural OLE in total, only one patient (0.6%) (Williamson *et al.*, 1992) had diffuse spike-wave discharges.
HV has no significant effect on the occipital spikes/paroxysms, but can facilitate the occurrence of (or enhance) GSWD (*supplementary figure 4.26*).
EEG photosensitivity occurs in 11% (Gastaut and Zifkin, 1987) to 15% (Caraballo *et al.,* 2008c) of children with OE-G, but is not expected in structural OLE. In OE-G, the effect of sleep can vary; occipital spikes may attenuate or even disappear, or may appear for the first time during drowsiness and light sleep. In addition, centro-temporal spikes and GSWD tend to occur during sleep, as well as electrographic occipital seizures (Gastaut and Zifkin, 1987).

Ictal EEG
Typically, ictal discharges are limited in the occipital lobe, at least at seizure onset, and consist of fast rhythms, fast spikes, or both, and are of smaller amplitude than the interictal occipital spikes (*supplementary figure 4.27*) (Gastaut and Zifkin, 1987).

Recording protocols
Basic level
Awake with HV and photic stimulation. If recording during wakefulness is inconclusive, an attempt should be made to let the patient drowse even when a sleep recording has not been scheduled (*see advanced level below*).
Advanced level
Awake and sleep after partial sleep deprivation with HV and PS. Sleep Stages 1 and 2 are important to activate occipital spikes when recording during wakefulness is

unremarkable and further assess for integrity of posterior background rhythms, including POSTS. Sleep is also important because it may activate CTS or GSWD that would argue against a structural cause. Occurrence of occipital spikes or paroxysms only when the eyes are closed should prompt assessment for FOS (*see relevant section in Part 1*).

Levels of EEG diagnosis

Clinical suspicion of OE-G (developmentally normal children with ictal symptoms and semiology, as above):

A) Confirmatory of OE-G

(For both recording levels)

Ictal recording with appropriate clinical symptoms and EEG discharge over the occipital areas, unilateral or bilateral, with or without extra-occipital propagation and interictal typical unilateral or bilateral occipital paroxysms with centro-temporal spikes or generalized spike-wave discharges.

B) High diagnostic certainty (probable)

(For both recording levels)

The above findings without centro-temporal spikes or generalized spike-wave discharges are highly suggestive of OE-G, although imaging may be required to rule out the rare possibility of celiac disease that may produce an identical EEG picture (Gobbi, 2005).

C) Low diagnostic certainty (possible)

(For both recording levels 1 and 2)

Unilateral random interictal occipital spikes without regional background disturbance; the EEG findings are consistent with the diagnosis of OE-G, but other conditions, including structural occipital or posterior cortex epilepsy, must be ruled out. Repeat recording level 2 or proceed with telemetry to move diagnostic certainty up to levels A or B.

Note. In developmentally normal children with focal seizures, the clinical features of which suggest overlap between BRE, PS, and OE-G, perform advanced level sleep-deprived recording.

Indications for video telemetry

– (1) Extra-occipital ED without posterior cortex ED in clinically suggested OLE/occipital seizures.

– (2) Normal interictal advanced level EEG.

– (3) Normal EEG during visual symptoms suggestive of OLE or occipital seizures.

4.5 Epilepsy with Myoclonic-Atonic seizures (EMAS)

Overview

In 1970, Herman Doose reported 51 previously normal children between one and five years of age with "primary" generalized seizures. He described their seizures as myoclonic and astatic, often combined with absences and GTCS and tonic seizures, and proposed a genetic aetiology to differentiate these children from those with LGS (Kaminska and Oguni, 2013). In contrast to all other epilepsy syndromes, defined at that time exclusively on the basis of electro-clinical criteria, what characterized Doose's cases was the genetic predisposition (Arzimanoglou *et al*. 2004). He later refined his criteria and emphasized that tonic seizures are an uncommon feature (Doose, 1992). In 1989, the ILAE proposed the syndrome of myoclonic-astatic epilepsy with the following features:

– (1) Normal development before the onset of epilepsy.

– (2) Onset of myoclonic, myoclonic-astatic, or astatic seizures between seven months to six years of age.

– (3) Presence of generalized spike or polyspike-and-wave EEG discharges.

A genetic predisposition was acknowledged and in 2010 the term "epilepsy with myoclonic-atonic seizures" (EMAS) was introduced for the syndrome, keeping the 1989 diagnostic considerations, as above. Epilepsy with myoclonic-atonic seizures constitutes 1-2% of childhood epilepsy. Onset peaks at around three years with the ratio of boys to girls at about 2:1. MAES displays an age-dependent course and clinical spectrum, with a variable outcome. A long-term follow-up study by Oguni and colleagues of 81 patients showed a common evolution which was classified into favourable, intermediate, and unfavourable forms according to the ultimate seizure outcome (Oguni *et al*., 2005). Cumulative percentage remission reached 40% within six months, 63% within one year, and 89% within three years after seizure onset (Oguni *et al*., 2005). Thus, myoclonic, myoclonic-astatic, or astatic seizures disappeared within one to three years in 89% of 81 patients. Even in children with a favourable clinical course, seizures can be initially resistant to AEDs, sometimes requiring additional corticotropin (ACTH) or ketogenic diet. In unfavourable cases, epilepsy remains refractory to treatment and the course of the EMAS is altered by the occurrence of long-lasting episodes of non-convulsive status epilepticus. During these episodes, which are often punctuated by other types of seizure, vigilance is altered with loss of contact with the surroundings or somnolence. In addition, there is significant cognitive decline and patients may be left with a major mental defect.

EMAS is considered a unique age-dependent epilepsy syndrome, in which epileptogenesis progresses to a peak within one year after the onset. Intelligence is usually within the normal range during the first months of the disease, although patients are often severely hyperkinetic. Intellectual outcomes range from favourable to unfavourable (Kelley and Kossoff, 2010). Overall prognosis is also variable (Trivisano *et al*., 2011).

Seizures: symptoms and semiology

At present, EMAS should be recognized as an epileptic syndrome with a relatively wide clinical spectrum in which the main seizure types range from myoclonic to atonic.

Myoclonic seizures (MS), atonic seizures (or astatic) and myoclonic-atonic seizures. These typically occur a few days or weeks after the onset of generalised tonic-clonic or clonic seizures.

Generalised tonic-clonic or clonic seizures. These are often the presenting seizures in previously normal children and may be preceded by febrile seizures (FS).

Atypical absences. Within a mean of three months, seizure frequency gradually increases and atypical absences can be added to the clinical picture.

Non-convulsive status epilepticus presents as clusters of myoclonic-atonic, myoclonic or atypical absence status and is initially resistant to treatment.

Tonic seizures. Some patients with an unfavourable outcome have brief tonic seizures in the later part of the course that may still persist by the end of the second decade.

EEG section

Interictal background

During wakefulness, background activity is normal at the very onset of the disease (*supplementary figure 4.28A*).

A characteristic 4-7-Hz diffuse theta rhythm, usually predominating over the central-parietal areas (central theta waves), is often present, intermixed with normal waking activities and increasing during drowsiness (*supplementary figure 4.29A, B*). In some children, background may be diffusely slow (*supplementary figure 4.30*). During sleep, physiological features are usually seen at the onset. Diffuse slowing with loss of sleep architecture can occur during the evolution, particularly in the severe end of the MAE spectrum.

Interictal abnormalities

Wakefulness. There may be no epileptiform discharges. When present, generalized spike-waves discharges (GSWD) are at 2-3 Hz, and predominant or of maximal amplitude over the frontal-central areas. They may show asymmetries between the hemispheres, but these asymmetries are not consistent. Focal or multifocal spikes may also be present (*supplementary figure 4.31 and 4.33 upper trace*). These are seldom abundant and may predominate on one side but not consistently so, and are not associated with focal slowing (*see focal discharges under GGE/IGE in the introduction and the relevant chapters in Part 1*).

Sleep. Focal and generalized spike-wave discharges may enhance and acquire a distinctive polyspike component (*supplementary figure 4.28B, 4.32 and 4.33 lower trace*).

Ictal EEG.

(1) Epileptic drop attacks (*i.e.* seizures that cause falls) can be differentiated into three types according to the postural change, the temporal sequence of falling, and the associated EMG potential, as recorded by EMG polygraphy.

A. *Myoclonic flexor* seizures are characterized by sudden flexion or extension of the head and trunk, causing the patient to fall. On video inspection the body appears to be hurling toward the ground rather than slumping or collapsing (*supplementary figure 4.34*).

B. *Myoclonic-atonic* seizures are characterized by the same initial change as the myoclonic flexor type, but subsequent falling is caused by loss of muscle tone. EMG polygraphy has shown simultaneous EMG potentials in the sternocleidomastoid (SCM) muscles and interruption of potentials in the trapezius and erector spinae muscles (*supplementary figure 4.35*).

C. *Atonic* seizures are characterized by sudden slumping or collapsing to the floor as a result of transient loss of muscle tone (*supplementary figure 4.36 and 4.37*); there may be transient symptoms immediately before the fall (minimal myoclonic contraction of facial muscles and/or twitching of the extremities). EMG discharges from the trapezius muscle are interrupted suddenly, whereas those of the SCM persist (Oguni *et al*., 1992; Oguni *et al*., 1997).

Generalized bilaterally synchronous single or multiple spike-and-wave discharges with 2-4-Hz frequency are commonly associated with all three seizures types, although spike-wave discharges are briefer for myoclonus. The temporal relationship between the spike-wave discharge and the clinical seizure shows that the EMG phenomena of both myoclonic and atonic seizures correspond to the period between the spike component and the ascending portion of the slow wave.

The EMG correlate of the jerk is a burst of muscle activity lasting 100 ms. This is followed by a post-myoclonic silent period of EMG inhibition that lasts for 60-500 ms (Oguni *et al*., 1992; Oguni *et al*., 1997) (supplementary figure 4.35), which is synchronous for the recorded muscles and time-locked to the onset of the slow wave. Both the brisk jerk and the post-myoclonic silent period concur to produce the typical drop.

(2) Generalized clonic seizures occur during both wakefulness and sleep. The clonic component frequently resembles the repetition of massive MS (*supplementary figure 4.38*). Rhythmic opening of the mouth and movement of the arms and legs start after

a sudden collapse backwards on the floor, when the patient is sitting. Clonic movements usually increase in frequency and may become very rapid resulting in a "clonic vibratory" seizure that usually ends with gradually reducing frequency of the clonic jerks (*supplementary figure 4.39*).

(3) Generalised tonic-clonic seizures. In this type, the clonic component is preceded by a tonic phase lasting a few seconds (*supplementary figure 4.40*).

(4) Atypical absences. These correspond to runs of generalized irregular spike-wave discharges at 1.5-3 Hz (*supplementary figure 4.41*).

Some patients may have prolonged recurrent atypical absences with associated clouding of consciousness and often random segmental myoclonus, or head nodding. This atypical absence status is a type of non-convulsive status (*see NCSE below*), tends to start after awakening, and may last for hours. The EEG shows disorganised, markedly slow, background activity with random spike-wave discharges, identical to that of NCSE (*supplementary figure 4.42*).

(5) Non-convulsive (also known as minor) status epilepticus (NCSE). This state may consist of a series of myoclonic-astatic or MS and atypical absences. During these episodes, vigilance is altered with loss of contact or somnolence. Children may drool and have speech difficulties that may range from dysarthria to mutism. They exhibit erratic myoclonus predominating in the face and the upper limbs, mainly in the eyelids, mouth, tongue, and fingers; they are ataxic with hypotonia and tremor, and walking is difficult or impossible. EEG shows no normal background activity and is characterized by diffuse and irregular spikes and slow waves persisting continuously throughout the episode, in combination with erratic myoclonus recorded on the EMG (*supplementary figure 4.43*).

(6) Generalized tonic seizures with or without few clonic components occur during sleep. When predominant, these seizures are associated with unfavourable outcome, and they are most resistant to treatment. These seizures are termed "myo-tonic" when the tonic phase is preceded by a myoclonic jerk (*supplementary figure 4.44 and 4.45*). In some patients, the tonic seizures are clinically very subtle with only eye opening and irregular respiration for 10 seconds or more, corresponding to bursts of generalized spikes during sleep and eventually wakefulness.

Generalized tonic seizures may also acquire a "vibratory" clinical presentation (*supplementary figure 4.46*).

Recording protocols

Basic level

Schedule recording to contain both wakefulness and sleep with polygraphy (ECG, bilateral deltoid EMG). MS are expected to occur within an hour. HV (not infrequently effected by crying) may activate atypical absences. PPR have been reported in some children, but clinical photosensitivity is not among the characteristic features of MAES.

Note. Recording (under close supervision to prevent a fall) while children are sitting or standing is important to demonstrate the atonic component of the atonic or the myoclonic-atonic seizures.

Advanced level

Long-duration video-EEG (including sleep and wakefulness as above) to record the characteristic seizure types and delineate the clinical-EEG phenotype.

In addition to the basic level, employ extended polygraphy (respiration and bilateral trapezius, sternocleidomastoid, and paraspinal EMG).

Levels of EEG diagnosis

A) Confirmatory of suspected EMAS in <u>untreated</u> children

(For both recording levels)

Recording of typical myoclonic and/or atonic and/or myoclonic-atonic seizures (the latter while the child is sitting upright or standing under close supervision), with the typical clinical and EEG ictal and interictal presentation, and no atypical features (*see below*).

B) High diagnostic certainty (probable)

(For both recording levels)

Recording of typical interictal paroxysmal abnormalities with or without the characteristic 4-7-Hz central-parietal theta rhythm, but without myoclonic/myoclonic-atonic seizures. Proceed with (or repeat) advanced level recording to register the characteristic seizures and move diagnostic certainty to level A.

C) Low diagnostic certainty (possible)

(For both recording levels)

No typical 4-7-Hz central-parietal theta rhythm in background, or typical interictal epileptiform discharges, or seizures. No atypical features. Repeat basic or advanced level recording to register the characteristic EEG features and seizures and move diagnostic certainty to level B or A.

Indications for repeating video-EEG recording

level 2

– (1) Failure to record MS.

– (2) Clinical deterioration and/or suspicion of non-convulsive status epilepticus.

– (3) Clinical suspicion of other types of seizure and/or epileptic syndrome: epileptic spasms, frontal seizures, progressive myoclonic epilepsy, or LGS.

Atypical EEG/video-EEG features to be highlighted in the EEG report, which may cast doubts on a diagnosis of EMAS

– (1) Focal slowing of background activity with constant spike or polyspike focus.Focal slowing of background activity with constant spike or polyspike focus.

– (2) Focal slowing of background activity with constant spike or polyspike focus.Absence of MS despite long-duration video-EEG.

– (3) Focal slowing of background activity with constant spike or polyspike focus.Tonic seizures at presentation or as the main seizure type.

4.6 Absence seizures in the first three years of life

Overview

Children with typical absences (TAs) of early onset (before the third year of life, which is widely considered as the low cut-off limit for the age at onset of childhood absence epilepsy (CAE)) comprise a rare heterogeneous group with an overall poor prognosis; only a few of them can be classified into well-known syndromes (Chaix *et al*., 2003), such as epilepsy with myoclonic absences (EMA), eyelid myoclonia with absences (ELMA), idiopathic MS in infancy (Caraballo *et al*., 2011), or other genetic aetiologies, such as Glut-1 deficiency (Leary *et al*., 2003). It follows that specific syndrome recognition, when possible, is important for the definition of the aetiology, and also for treatment and prognostication (Caraballo *et al*., 2011). Although the overall prognosis is unfavourable and cognition may be variably affected, some of these children may have good outcome (Shahar *et al*., 2007), which - to all intents and purposes - would suggest that CAE may sometimes have an earlier onset.

Seizures: symptoms and semiology

Typical absences (TA). Essentially, TAs of early onset do not differ from those of later onset. They are brief, lasting 3-12 seconds (*supplementary figure 4.47 and 4.48*) and exceptionally longer (*supplementary figure 4.49 and 4.50*), and can be simple (with impairment of consciousness only) or complex (associated with other signs, especially motor manifestations). TA may bear the characteristics of a particular clinical syndrome (such as EMA or ELMA) or be non-descript and therefore difficult to define nosologically. Neurological examination and development are typically normal before the onset of absences, while outcome and response to treatment depend on the syndrome (*see chapters on CAE, ELMA and EMA*) or aetiology. For instance, Glut-1 deficiency is resistant to anti-absence antiepileptic drugs, but responsive to ketogenic diet (Suls *et al*., 2009).

TAs of early onset may be the only type of seizure or may be associated with generalized tonic-clonic seizures, eyelid myoclonias and eye-closure abnormalities, and MS (Caraballo *et al*., 2011).

EEG section

Background

Normal and sleep organization is preserved (Caraballo *et al*., 2011).

Interictal abnormalities

Wakefulness. EDs include brief or incompletely generalized spike-wave, polyspike, and polyspike-wave paroxysms and focal or multifocal non-localizing spikes (*supplementary figure 4.47A; also compare with CAE*).

IPS may elicit generalized spike waves and polyspike waves (*supplementary figure 4.47B*) (Caraballo *et al*., 2011).

Sleep. Focal and multifocal non-localizing slow spikes or rare fast spikes or polyspikes enhance or appear for the first time over the frontal, central, and posterior regions (*supplementary figure 4.51, 4.52B and 4.53*). Generalized ED acquire a polyspike component and become briefer and less synchronous as sleep deepens (*supplementary figure 4.52, 4.53B and 4.54*).

Ictal EEG.

TAs are associated with generalized spike-wave discharges that last three seconds or more (*supplementary figure 4.47-4.50 and 4.55-4.57*). Ictal discharges may have bilateral synchronous or lateralized/regional onset (*supplementary figure 4.49 and 4.50*), and sometimes may be fragmented (*supplementary figure 4.55*). Specific syndromes retain their own ictal clinical EEG characteristics (*see chapters on EMA and ELMA*).

Recording protocols

Basic level

Hyperventilation (HV) may induce TAs associated with the typical EEG pattern in children who may collaborate with this method of activation. Using a windmill can be effective and is amusing for the children.

IPS and tactile stimulation: the latter may activate MS associated with generalized spike/polyspike-wave discharges, as in benign/reflex myoclonic epilepsy in infancy, which some authorities include within the spectrum of absences before the age of three years.

Employ EMG polygraphy; although this is regarded as mandatory, it may not be possible when limited channels are available.

Attempt to record during sleep, if possible (discharge rate tends to increase during drowsiness and in the first stages of sleep, and focal and multifocal non-localizing

spikes may appear only during sleep). When sleep is achieved, repeat HV on awakening.

Advanced level

Awake and sleep EEG with HV on awakening (as for all IGE/GGE) and IPS/tactile stimulation, as for basic level. Sleep Stages 1 and 2 are important to activate generalized spike-and-wave discharges, which are important when the recording during wakefulness is unremarkable. Sleep may also activate focal and multifocal non-localizing spikes.

Polygraphy, as for basic level, is mandatory.

Levels of EEG diagnosis

Note 1. In children with a suggestive history and typical clinical and EEG features, similar to those of CAE, the diagnosis is not in doubt, and therefore neuroimaging for early-onset absences has not been regarded as necessary.

Note 2. In children with early-onset absences and cognitive deterioration or no response to anti-absence antiepileptic drugs, GLUT-1 deficiency should be ruled out by screening for mutations in *SLC2A1*, the gene encoding the GLUT1 glucose transporter (*supplementary figure 4.48*) (Suls *et al*., 2009).

A. Confirmatory of the diagnosis (based on clinical suspicion of early-onset absences in developmentally normal untreated children with ictal symptoms and semiology, as above).

For both basic and advanced recording levels: Ictal recording with appropriate clinical symptoms and EEG discharges compatible with typical absences (TA), with or without focal or multifocal non-localizing spikes and/or brief interictal generalized spike-wave discharges.

B. High diagnostic certainty (probable)

(For basic recording level): Interictal generalized spike-wave discharges with or without focal, non-localizing spikes are highly suggestive of early-onset absences when no TAs are recorded, either spontaneously or during HV. Perform advanced recording including sleep to activate absences and move diagnostic certainty to level A. Repeat advanced recording if the first attempt fails to record TAs.

C. Low diagnostic certainty (possible)

(For both basic and advanced awake recordings): Focal, non-localizing spikes, without interictal generalized discharges. Findings are still in keeping with a diagnosis of IGE/GGE (in the presence of suggestive clinical evidence), but advanced level EEG recording that contains sleep is recommended to activate interictal generalized discharges and move diagnostic certainty up to level B (or to level A if TAs occur on awakening).

Note. The diagnosis of early absences is unlikely when basic and advanced recordings (with the latter containing sleep) fail to demonstrate any epileptiform discharges.

Indications for video-EEG telemetry

– (1) Focal slowing of background activity with constant spike or polyspike focus.To quantify absences and fully explore the clinical phenotype (when there is history suggestive of MS or eyelid myoclonia).

– (2) Focal slowing of background activity with constant spike or polyspike focus.Repeatedly normal interictal advanced level EEG.

– (3) Focal slowing of background activity with constant spike or polyspike focus.Normal basic or advanced EEG during ictal symptoms (indicative of non-epileptic events) to explore possible co-existent TAs.

4.7 Lennox-Gastaut syndrome (LGS)

Overview

LGS belongs to the group of epileptic encephalopathies and concerns 2-4% of childhood epilepsies, affecting boys more often than girls (Markand, 2003). The electroclinical syndrome was delineated by the Marseille School between 1966 and 1972, but was first reported by Lennox and Davis as an epilepsy beginning in childhood and characterized by diffuse slow spike-waves (SSW) at <2.5 Hz and several types of seizures including tonic seizures, atypical absences, and "drop attacks" (Markand, 2003). The electroclinical delineation of LGS was proposed by Beaumanoir and was adopted by the International League Against Epilepsy Classification Commission in 1989 (Beaumanoir and Blume, 2005). In around 70-75% of patients, LGS is associated with a multitude of inherited or acquired structural anomalies or chromosomal disorders (including perinatal or post-natal insults, infections, malformations of cortical development, radiotherapy, and Down syndrome), while in the remainder 25-30%, there is no identifiable aetiology (Camfield, 2011). Prognosis is classically poor with children having seizures into adulthood and most with intellectual disability and behavioural and psychiatric disorders (75-95%) (Camfield, 2011).

Despite the different aetiologies, patients with LGS have a similar electroclinical phenotype, consistent with a common underlying mechanism (Arzimanoglou et al 2009). Functional neuroimaging has indicated that epileptic activity in LGS recruits widespread areas of association cortex and that tonic seizures are expressed through the reticular formation of the pons (Archer *et al*., 2014). LGS has been recently conceptualized as "secondary network epilepsy" in which the epileptic activity is expressed through largescale brain networks; cortical lesions, when present, appear to chronically interact with these networks to produce

network instability rather than triggering each individual epileptic discharge (Archer *et al.*, 2014). There is significant overlap between LGS and other epilepsy syndromes (Kaminska and Oguni, 2013), making the differential diagnosis particularly challenging. A thorough evaluation of the medical history along with an EEG during wakefulness and sleep is critical for the accurate diagnosis of the syndrome. The main differential diagnoses of LGS include frontal epilepsies with secondary bilateral synchrony, epilepsy with myoclonic-atonic seizures, Dravet disease, late-onset epileptic spasms, atypical benign partial epilepsy of childhood (Aicardi-Chevrie syndrome), and Ring chromosome 20 epilepsy syndrome.

Seizures: symptoms and semiology

Seizures begin between 3-10 years, usually before eight, but onset may occur in younger or older ages, even into adulthood. LGS may follow other types of epilepsy or syndromes, such as focal epilepsies, Ohtahara syndrome, and West syndrome (WS). Diagnosis requires the classic LGS triad of:

– (i) many types of seizure, but *including* tonic seizures and atypical absences, which are the main seizure types;

– (ii) cognitive impairment;

– (iii) typical interictal and ictal EEG patterns (Markand, 2003; Beaumanoir and Blume, 2005; Arzimanoglou *et al.*, 2009).

Tonic seizures are required for the diagnosis of LGS. They are diurnal and nocturnal, facilitated in NREM sleep, and typically occur in clusters. They are axial and involve mainly the proximal parts of the limbs, symmetrically or with unilateral predominance. They consist of sudden flexion of the neck and body, raising of the arms in flexion or extension, extension of the legs, contraction of the face muscles (that sometimes can be very subtle and restricted to the lower lip), rolling of the eyes and autonomic manifestations (apnoea and facial flushing tachycardia), and can culminate in what appears as diffuse tremor (rapid, small-amplitude jerks affecting the whole body). The distal limb muscles are relatively spared. Tonic seizures can result in sudden falling, associated or not with brief loss of consciousness, but they may also be brief and subtle involving only the eyes and changes in respiratory rhythm.

Atypical absences are the second most common seizure type in LGS, present in around 75% of patients. They are subtle and difficult to recognize without concurrent formal assessment of cognition and responsiveness. The main clinical manifestation is a brief lapse in consciousness, although some awareness may be preserved (Camfield, 2011). They are of long duration with the EEG discharge lasting >20 seconds, but their onset and termination are not always clinically discernible, as they begin and end progressively and patients may seem to fade in and out of consciousness. Associated clinical features may include eyelid and mouth myoclonias and a decrease in muscle tone that may lead to a collapse.

"Drop attacks" or sudden falls are less frequent, affecting 30-60% of patients, and are not specific to LGS; they are mostly provoked by a brief tonic seizure or an epileptic spasm, the latter being frequent in patients with a history of WS (Markand, 2003). Video-EEG and polygraphic recording are required to accurately determine the seizure type causing the "drop attacks".

Other seizure types include ***tonic-clonic***, ***focal***, ***myoclonic,*** and ***myoclonic-atonic***, which, like the drop attacks, are not specific to LGS.

Episodes of ***status epilepticus*** may occur in about 60% of patients, consisting of alteration of consciousness with continuous SSW, and may or may not be associated with serial tonic seizures (Arzimanoglou *et al.*, 2009).

EEG section

Background

Wakefulness and sleep: EEG is variable depending on aetiology (structural, chromosomal, or idiopathic) and age (young age when LGS follows WS), ranging from sub-normal to, most frequently, poorly structured without physiological features and mainly altered by continuous interictal abnormalities (*see below*).

Interictal abnormalities

Focal abnormalities are usually present in patients with structural lesions; they are non-specific and depend on the underlying pathology: focal or multifocal spikes, spike-waves, polyspikes, slow waves, and focal bursts of rapid rhythms.

Generalized interictal abnormalities during wakefulness and sleep are *required* for diagnosis of LGS:

Wakefulness. high-amplitude, diffuse and synchronous slow SSW at 1.5-2.5 Hz with maximal amplitude over frontal areas and ranging in duration from a few seconds to a few minutes, or sub-continuous during wakefulness (*supplementary figure 4.58*). The complexes typically consist of a spike (duration <70 mseconds) or a sharp wave (70-200 mseconds), followed first by a positive deep "trough," and then by a negative wave (300-500 mseconds) (Markand, 2003). It may be difficult to range them as ictal (atypical absences) or interictal because the assessment of cognition/responsiveness is difficult with usually non-cooperative children with intellectual disability. Stimuli, such as eye opening, noise, calling the patient's name, and pain, tend to decrease the occurrence of SSW or terminate SSW sequences in progress (Markand, 2003). Relaxation

and drowsiness favour their occurrence. HV and IPS generally have little influence on the SSW activity (Markand, 2003).

Sleep. Diagnosis of LGS requires:

– (i) previously described SSW discharges that are activated during slow sleep, showing a more marked tendency towards bilateral synchrony than in wakefulness;

– (ii) bursts of high-amplitude generalized polyspikes and polyspike-waves (*supplementary figure 4.59*);

– (iii) sequences of rhythmic activity at 10-25 Hz that last for a few seconds (2-10 seconds) during NREM sleep, called "paroxysmal fast activity", and considered by some authors as an essential diagnostic criterion.

These may be subclinical or, if of longer duration, accompanied by subtle change of axial muscle tone, which is detectable only by EMG electrodes as the ictal expression of a tonic seizure (Markand, 2003) (*supplementary figure 4.60*). Interictal abnormalities and seizures decrease in REM sleep.

Ictal EEG

Typical seizures of LGS

A. Tonic seizures correspond to fast bilateral rhythmic spikes at 15-25 Hz. Amplitude is low at onset, but increases as the discharge progresses, predominating over the anterior areas and the vertex and showing little or no change in frequency throughout their course; sometimes diffuse slow waves follow after the end of the seizure (*supplementary figure 4.61*) (Markand, 2003). Diffuse flattening of the background activity or high-amplitude SSW may precede these fast bilateral rhythmic spike discharges.

B. Atypical absences are concomitant with an irregular, diffuse, high-amplitude, more or less symmetric SSW that predominates over the frontal areas at 1.5- 2.5 Hz. Atypical absences may be difficult to differentiate from the interictal SSW (*supplementary figure 4.62*).

Recording protocols

Basic level

Schedule to record during both wakefulness and NREM sleep; a duration of a few hours may be needed to record tonic seizures.

Employ polygraphy with ECG, respiration, and bilateral deltoid EMG, if possible.

Advanced level

Long-duration video-EEG to include overnight sleep and record all types of seizure reported for the given patient.

Polygraphy, as for basic level, is mandatory.

Levels of EEG diagnosis

A) Confirmatory of suspected LGS in <u>untreated</u> children

(For both recording levels)

Recording of typical seizures (mainly tonic) with typical clinical and EEG ictal and interictal presentation, no atypical features (*see below*).

B) High diagnostic certainty (probable)

(For both recording levels)

Recording of typical interictal abnormalities during wakefulness and sleep stages, but no tonic seizures recorded.

C) Low diagnostic certainty (possible)

(For both recording levels)

No typical interictal abnormalities or seizures; no atypical features.

Indications for performing or repeating video-EEG recording (advanced level)

– (1) Failure to record seizures.

– (2) Worsening with suspicion of status epilepticus.

– (3) Clinical suspicion of other types of seizure and/or different epileptic syndrome: late-onset epileptic spasms, focal frontal seizures/epilepsy, myoclonic-atonic epilepsy, atypical benign partial epilepsy of childhood, and encephalopathy with continuous spike-waves in slow sleep.

Atypical EEG/video-EEG features to be highlighted in the EEG report, which may cast doubts on a diagnosis of LGS

Absence of typical interictal and ictal features during wakefulness and sleep.

Bursts of 2-3-Hz SSW, sub-clinical or associated with myoclonic jerks as the predominating seizure type and/or high-amplitude slow waves intermixed with multifocal spikes associated with erratic myoclonias (minor status epilepticus), suggesting epilepsy with myoclonic-atonic seizures.

Predominance of unilateral frontal slow waves, spikes or SW, and/or polyspikes suggesting frontal epilepsy with bilateral synchrony.

Long-lasting sequences (up to 20-30 minutes) of rhythmic, monomorphic SSW or slow waves at 4-1.5 Hz, more or less symmetric, predominating over the frontal areas, associated or not with tonic seizures, or frontal/frontal-temporal seizures suggesting ring chromosome 20 epilepsy syndrome.

4.8 Epilepsy with Myoclonic Absences (EMA)

Overview

Epilepsy with myoclonic absences (EMA) is included in the spectrum of age-dependent syndromes and is characterized by a distinctive seizure type, *i.e.* myoclonic absences (MA), with specific clinical and EEG/polygraphic features. The syndrome is rare,

accounting for less than 1% of all epilepsies in childhood. The age at onset ranges from one to 12 years (with the mean at around seven years). In contrast to CAE, boys are more frequently affected by EMA (70%). Aetiology appears heterogeneous; about 25% of these children have a family history of epilepsy, but other possible aetiological factors include immaturity, perinatal damage, or congenital hemiparesis. EMA is also briefly discussed in the chapter on absences before the age of three years.

Note. Variants of myoclonic absences (MA) with atypical EEG features can be seen in other conditions (*see below*).

Seizures: symptoms and semiology

As a seizure type, myoclonic absences (MA) are characterized by loss of contact and impairment of consciousness of variable intensity, typically associated with rhythmic myoclonic jerks of the muscles of the shoulders, arms and legs, and rarely of the face. Myoclonias are superimposed on a more or less evident axial tonic contraction that progressively increases during the absence seizure, resulting in a fairly recognizable clinical pattern of rhythmic jerking accompanied by a gradual elevation of the upper limbs. During MA, lateralized deviation of the eyes, head and body, or backward or forward oscillations can be seen when the patient is standing; falling is uncommon. Onset and offset is abrupt and the duration can vary from 10 to about 60 seconds. MA can be activated by HV and may occur during drowsiness or light sleep, awakening the child.

In about two thirds of cases, other seizure types can be observed before onset or diagnosis of EMA, including TAs or rare generalized tonic-clonic seizures. Seizure types that may occur after the onset of myoclonic absences are most frequently generalized tonic-clonic seizures (in about 45% of cases); absence status and, more rarely, TAs (Bureau and Tassinari, 2012). The association of myoclonic absences with GTCS, particularly when the latter are numerous, bears a worse prognosis with persistence of seizures or appearance of other seizure types (such as atypical absences, or clinical or subclinical tonic seizures either during wakefulness or light sleep).

Background

Normal for age; sinusoidal slow posterior rhythm, as in CAE, has never been reported. Sleep organization is intact.

Interictal abnormalities

Brief or incomplete generalized spike-waves occur during wakefulness in about a third of cases (*supplementary figure 4.63A*). Focal or multifocal spikes or SW have been rarely reported. As in CAE, sleep discharges tend to become brief and acquire a polyspike component (*supplementary figure 4.63B*), but may also occur as a regular 3-4-Hz discharge (*supplementary figure 4.63C*). Longer spike-wave discharges may become fragmented without associated myoclonic components (*supplementary figure 4.64*), but typical MA may also occur in light sleep (*supplementary figure 4.65*).

Ictal EEG

EEG of MA is characterized by rhythmic, bilateral, synchronous symmetric spike-wave discharges at 3 c/sec with bilateral synchronous or regional onset, as in CAE (*supplementary figure 4.65 and 4.66*).

Usually, onset and offset of SW discharge are abrupt, although rarely the end can be gradual with delta waves at frontal leads (*supplementary figure 4.66 and 4.67*). Polyspikes can be intermingled within the spike-wave complexes.

Polygraphic recording shows a fairly recognizable pattern of bilateral, rhythmic myoclonia at the frequency of the spike-wave discharge, recorded from the deltoids, usually after one second from the onset of the discharge (*supplementary figure 4.65-4.67*). During the course of the absence, a progressively increasing tonic contraction, maximal in the shoulder and deltoids, and the superimposed myoclonias result in the typical rhythmic elevation of the arms. A particularly prominent tonic contraction may dominate the motor pattern, in which case myoclonias can be barely appreciated. Sometimes, both the myoclonia and the tonic contraction can be asymmetric or even unilateral despite a generalized EEG pattern. Detailed analysis of the relationship between spike-waves and myoclonias has shown a strict and constant association between the spike of the spike-wave complex and the myoclonic jerk. Each myoclonia is followed by a brief EMG silent period which breaks the tonic contraction (Tassinari *et al*., 2008) (*supplementary figure 4.68*).

Bursts of SW discharges, sometimes associated with myoclonia, can be detected during sleep Stages II or III. Notably, no trains of fast rhythms at 10 HZ, as in LGS, have been observed (*supplementary figure 4.64 and 4.65*).

Variants of MA. Atypical MA have been described in various conditions. Indeed, MA with a very early onset, brief duration, and mild intensity of motor manifestations, either myoclonic or tonic, have been described in patients with chromosomal abnormalities (Angelman syndrome, 12 trisomy, and inv dup 15) (Elia *et al*., 1998). In addition, MA with irregular SW complexes, gradual onset and offset, and associated myoclonic and atonic phenomena have been reported in epileptic encephalopathies (Tassinari *et al*., 1996). Finally, MA

triggered by opening or closing the eyes, myoclonia of the eyelids and arms, or slow falls have also been described. In these cases, the EEG showed atypical features such as fast rhythms intermixed with, or preceding, the SW discharge (Giovanardi Rossi *et al*., 1988).

Recording protocols

Basic level

Obtain prolonged recording during wakefulness with HV and photic stimulation; allow light sleep if possible (see advanced level below).

HV can trigger myoclonic absences; therefore, this procedure can be repeated during the test in order to record a seizure. The patient should lay down on the recording bed or sit on the recording chair and be relaxed with eyes closed (the sitting condition allows the elevation of the arms to be detected more easily during MA). Polygraphy is required with EMG recording of the deltoids bilaterally.

Advanced level

Prolonged awake and sleep EEG after partial sleep deprivation with HV and photic stimulation using continuous video-EEG/polygraphic monitoring. As above, HV should be performed repeatedly. An afternoon nap can allow drowsiness to be recorded until Stages II-III of sleep. Sleep recording may show occurrence of SW complexes and exclude fast rhythms possibly associated with tonic contractions. Polygraphy is required to register EMG activity from the neck muscles, deltoids, and biceps, bilaterally. Since the tonic or myoclonic component can be variably expressed in different muscles, adding EMG leads increases the probability of detecting both the myoclonic and tonic manifestations (*supplementary figure 4.69*).

Levels of EEG diagnosis

Clinical suspicion of epilepsy with myoclonic absences in untreated children

A) Confirmatory of diagnosis

(For both basic and advanced EEG recording levels)

Recording of myoclonic absences, spontaneous or triggered by HV, with the typical EEG spike-wave discharge and polygraphic pattern in at least one of the recorded muscular areas (neck or bilateral deltoids or biceps).

B) High diagnostic certainty (probable EMA)

(For basic EEG level)

Recording of absence seizures with typical spike-wave discharges and rhythmic myoclonia in the deltoids, time-locked to the SW complex, without the associated tonic contraction. These findings may support the clinical diagnosis with high diagnostic certainty, particularly if the clinical picture is appropriate. To confirm the diagnosis, recording level 2 (with video-polygraphic recording and additional EMG leads) is recommended. Recording of brief absences with rhythmic myoclonia without tonic contraction, gradual onset and offset of the spike-wave discharge, and fast rhythms preceding or intermixed with the spike-wave discharge can be interpreted as atypical MAs when embedded in the proper clinical context (*see above*).

C) Low diagnostic certainty (possible EMA)

(For basic EEG level)

Recording of absence seizures associated with 3-Hz spike-wave discharges *without* concomitant polygraphic myoclonic phenomena in children with a clinical history suggestive of MS does not rule out EMA. Advanced level recording is recommended; if this fails to reach level A or B, the diagnosis of EMA is not likely. *Note*. The diagnosis of myoclonic absence epilepsy is unlikely when EEG recordings are normal, even after sleep deprivation and repeated HV.

Indications for repeating advanced level EEG

– (1) When there is suspicion of changes in seizure semiology or appearance of new seizure types, which can occur in the evolution of EMAs with less favourable course.When there is suspicion of changes in seizure semiology or appearance of new seizure types, which can occur in the evolution of EMAs with less favourable course.

– (2) Resistance to appropriate AEDs (valproic acid, ethosuximide, and lamotrigine)

Indications for repeating basic level EEG recording

– (1) To evaluate the effectiveness of AEDs.

– (2) To monitor the course of this condition.

Indications for video telemetry (a short period of daytime telemetry can replace level 2 recording, if available)

When standard EEG without EMG (deltoids) has shown typical SW discharges and there is clinical suspicion of EMA. Video telemetry can document the typical clinical manifestations of myoclonic absences.

4.9 Encephalopathy with Electrical Status Epilepticus during Slow Sleep (ESES)

Overview

Encephalopathy with ESES (otherwise labelled as encephalopathy with continuous spike and waves during sleep; CSWS) is an epileptic encephalopathy of which the main features are seizures of various types and neurological deterioration in different domains (cognitive, motor, and behavioural). The encephalopathy is attributed to the appearance of a peculiar EEG pattern characterized by the striking activation of epileptic abnormalities during non-REM sleep (Patry *et*

al., 1971), which is a condition of EEG status epilepticus during sleep (SES) (*supplementary figure 4.70C, 4.71, 4.72 right panel and 4.73B*). Anti-seizure drugs, immune modulatory agents, and surgery (Loddenkemper *et al*., 2009) have been used to treat conditions associated with ESES.

Note 1. SES can also be seen in children with atypical evolution of idiopathic/possibly genetic focal epilepsies, as well as in some children with brain lesions such as neuronal migrational disorders, hydrocephalus, and thalamic pathologies.

Note 2. The terms SES and CSWS refer both to the EEG phenomenon only, and can be used interchangeably. The term ESES will be used in this chapter to avoid undue confusion.

Seizures: symptoms and semiology

The clinical picture of ESES syndrome is characterized by (1) epilepsy and (2) encephalopathy:

1. Epilepsy. Seizures can occur before the recognition of SES. Age at onset of epilepsy can vary from two to 12 years, with a peak at around 4-5 years. In the majority of cases, seizures are present during SES, but in some cases there is no history of clinical seizures at all. Semiology and frequency of seizures are variable; tonic seizures during sleep have never been reported. Based on seizure patterns, three groups have been proposed (Tassinari *et al*., 2012). Group 1 includes patients with motor seizures, rare and nocturnal throughout the evolution of the syndrome. Group 2 includes patients with unilateral partial motor seizures or "secondary generalized" tonic-clonic seizures, mainly occurring during sleep, who also have absences during wakefulness; these are similar to TAs of CAE and occur at SES onset. Group 3 includes patients with rare nocturnal seizures in whom atypical absences develop during the course of ESES, after a variable period of evolution; these atypical absences are frequently associated with negative myoclonus or atonic components leading to sudden falls (*supplementary figure 4.74 and 4.75*).

2. Encephalopathy. This manifests itself most frequently as the appearance or the worsening of neuropsychological disturbances (such as global cognitive regression and various degrees of language impairment including acquired aphasia, as in Landau-Kleffner syndrome - LKS), behavioural disorders (including hyperactivity, attention deficits, and disturbances of personality with psychotic characteristics), and derangements of motor abilities (resulting in dystonia, dyspraxia, ataxia, and negative myoclonus) (Tassinari *et al*., 1977, 2012). Encephalopathy is by definition associated with SES. Despite the long-term favourable outcome of epilepsy and SES, the prognosis is guarded because of the persistence of severe cognitive and behavioural disturbances in about a half of the patients.

EEG section

Background

During wakefulness depends on the underlying aetiology (*see below*).

Interictal abnormalities

During wakefulness, the EEG is usually characterized by focal or multifocal slow spikes, frequently intermixed with diffuse slow spikes and waves. In some children, the interictal EEG may show epileptic paroxysms similar to those observed in idiopathic focal epilepsies (*supplementary figure 4.70A, B and supplementary figure 4.76*). In other cases, a clear background asymmetry, the presence of polyspikes or repetitive fast spikes, or other features may indicate underlying organic pathologies (disorders of neuronal migration are among the most common) (*supplementary figure 4.73 and 4.77*). Pre-existing interictal EEG epileptic abnormalities may increase when SES starts (Beaumanoir, 1995); in addition, diffuse bursts of 2-3-Hz spike-and-wave discharges may appear (*supplementary figure 4.72; left panel*).

As soon as patients fall asleep, an EEG pattern of extreme activation of epileptic abnormalities appears throughout all non-REM sleep stages overnight. This EEG picture is mainly observed between the ages of four and 14 years, developing one or two years after the appearance of seizures. The typical EEG pattern that was originally described (Patry *et al*., 1971) consisted of (sub) continuous slow spike-and-waves, mainly at 1.5-2.5 Hz, persisting through all non-REM sleep stages. The topography of the epileptic discharges during non-REM sleep can vary from mainly regional (frontal, centrotemporal, *etc*.) or multiregional, in relation to various factors (aetiology [*supplementary figure 4.73 and 4.77*], topography of interictal spikes during wakefulness [*supplementary figure 4.70*], evolution, *etc*.), to unilateral (*supplementary figure 4.78*), or diffuse (sometimes with shifting from a unilateral to a diffuse pattern in the same patient). In the original study (Patry *et al*., 1971), a spike-wave index (SWI), ranging from 85 to 100% and measured during overnight sleep EEG recording, was considered an essential feature for the diagnosis. However, SWIs below 85% have been used for the diagnosis of ESES syndrome as well (*see below*). A correlation between a SWI lower than 85% and less regression in performance scores, compared to higher sleep-related SWI, has been reported (Beaumanoir, 1995). Morphology and distribution of the paroxysms during slow-wave sleep can be relevant as well. During REM sleep, paroxysmal activity becomes fragmented

and less continuous, whereas focal discharges may become more evident.

Recording protocols

(For both recording levels)

Allow extra time for EEG recording during sleep.

Basic level

EEG recording during a nap that also includes a period of wakefulness pre- and post-sleep (to allow evaluation of the type and amount of epileptic abnormalities during the awake state). To obtain satisfactory recording post-awakening, it is advisable that sleep is natural, achieved by partial sleep deprivation. The EEG should be recorded with the 10-20 electrode array. Recording of at least one sleep cycle is advised. ECG should be routinely monitored. Muscle tone should be monitored by surface EMG from one antigravity muscle (either the mylohyoideus or submentalis, or mentalis muscle), if possible. In most instances, basic level recordings should be adequate to monitor evolution.

Advanced level

Overnight sleep video-EEG/polygraphic recording including wakefulness pre-and post-sleep. The recording procedure should include a 10-20 electrode array, EMG activity of one antigravity muscle (either the mylohyoideus or submentalis, or mentalis muscle), ECG, electro-oculogram, respiration, and video monitoring. Alternatively, a 24-hour ambulatory EEG with a 10-20 electrode array, and possibly with video monitoring (such as home video telemetry), could be employed. Ideally, advanced level recordings should be used to make the initial diagnosis of ESES, but this may not always be possible.

Levels of EEG diagnosis

The main EEG diagnostic criteria for ESES are based almost exclusively on the abundance of epileptic abnormalities during sleep. However, no consensus exists on which quantitative and qualitative parameters should be used to define the degree of EEG activation. The SWI, proposed initially by Patry *et al*. (1971), was expressed by the percentage of the duration of slow wave sleep occupied by epileptic activity. Since that report, a wide range of different threshold values have been used, ranging from a SWI >85% (Patry *et al*., 1971; Tassinari *et al*., 2000) to 25% (Van Hirtum-Das *et al*., 2006). In addition, the methods to determine SWI also vary considerably across different studies (*see review by Scheltens-de Boer, 2009*). Furthermore, based on the SWI *per se,* it is not possible to illustrate other EEG features that are potentially relevant to determining the clinical picture, such as, for example, the topography of the paroxysms or the temporal evolution of the SES through the night that, even if never quantified in detail, has been variably described as continuous, but also sub-continuous, fragmented, or periodic. Finally, recent data has suggested that besides the direct effect of epileptic activity, possible derangements of physiological homeostatic processes that occur during slow-wave sleep could play a role in the pathophysiology of ESES, suggesting that parameters related to sleep physiology should also be assessed (Tassinari and Rubboli, 2006; Bölsterli *et al*., 2011; Bölsterli Heinzle *et al*., 2014; Tassinari *et al*., 2012).

In the absence of universally accepted diagnostic criteria (*see discussion above*), and until these are uniformly agreed, it was felt that the following proposals are reasonable.

A) Confirmatory of suspected ESES in <u>untreated</u> children

As mentioned above, recording level 2 should be used to make the initial diagnosis of ESES, when possible. Recording of a pattern of strong activation of epileptic activity, occurring in a (sub)continuous, periodic or fragmented fashion during non-REM sleep, and coupled with a clinical picture compatible with ESES, can indicate the diagnosis of ESES. With the data available at present, it is difficult to set a cut-off for SWI, although most of the studies have used a SWI of at least 50%. Confirmation of the diagnosis may be supported also by repeating sleep EEG (recording level 1 is acceptable) during the evolution, particularly when clinical changes occur.

B) High diagnostic certainty (probable ESES)

The first basic diagnostic EEG recording shows (sub)continuous, periodic or fragmented epileptic activity during a limited period of slow sleep. In such cases, it is strongly advisable to obtain an advanced recording containing complete overnight sleep, if possible.

C) Low diagnostic certainty (possible)

(For both recording level 1 and 2)

Modest activation of epileptic activity during sleep associated with a clinical picture of ESES does not rule out the diagnosis. To increase diagnostic certainty, repeat the advanced recording level or proceed with advanced if only basic recording level was carried out.

Note 1. When the EEG shows SES without a clinical picture of ESES, repeat neuropsychological examination and level 2 recording is advised. Lack of evidence of cognitive/behavioural regression or worsening in association with the appearance of SES is not sufficient to establish a diagnosis of ESES.

Note 2. (*For both levels 1 and 2*): Diagnosis of ESES cannot be made when the EEG is normal, or when there is no observed activation of epileptic abnormalities, during wakefulness and sleep.

Indications for repeating advanced recording level

– (1) When the first advanced level recording has provided level C diagnostic level.

– (2) When the clinical picture has changed and repeating basic level recording has resulted inconclusive.

Indications for repeating basic level recording
– (1) To monitor the evolution, particularly when the clinical picture has changed.
– (2) To monitor the effect of treatment.

4.10 Landau-Kleffner syndrome (LKS)

Overview

LKS is an acquired epileptic aphasia or auditory agnosia, occurring in a previously normal child with already developed age-appropriate speech. LKS is associated with epileptic EEG abnormalities which are particularly prominent during sleep, with or without apparent clinical seizures. By convention, LKS is not related to brain organic lesions and occurs in previously normal children. However, there are reports of "clinically defined" LKS in patients with congenital or acquired brain lesions. Recently, LKS has been proposed to be considered within the spectrum of ESES syndrome (Tassinari *et al*., 2012).

Epileptic aphasia and seizure symptoms and semiology

LKS makes its appearance usually between two and eight years of age. The first symptom is epilepsy in about 60% of cases and aphasia in the remaining cases (Beaumanoir, 1992). The type of aphasia typically is a verbal auditory agnosia usually with a subacute onset, followed by rapid reduction of spontaneous speech, characterized by perseverations, paraphasias, phonological errors, and verbal stereotypies. The speech disorder can progress to complete mutism. Aphasia often shows a waxing and waning course with remissions and exacerbations, usually, but not necessarily, related to quantitative variations of paroxysmal activity during sleep (Landau and Kleffner, 1957; Mantovani and Landau, 1980; Hirsch *et al*., 1990). The duration of the language disorder is extremely variable, however, if it persists unchanged for more than a year, spontaneous recovery is rare. After a variable time, aphasia stabilizes and usually improves before adulthood (Deonna *et al*., 1989).
Epileptic seizures occur in about 70-80% of cases (Beaumanoir, 1992), are usually rare, and some children may have a single event, often nocturnal. Seizures can be clinically heterogeneous including subtle events with minor motor manifestations (eye blinking and brief ocular deviation), simple partial motor seizures, atypical absences, unilateral motor seizures, and occasionally secondary generalized tonic-clonic seizures. Complex partial seizures are rare, whereas tonic seizures have never been reported. The course of the epilepsy is typically benign and seizures respond easily to antiepileptic drugs. Seizures eventually disappear over time, generally by around the age of 15 years.

EEG section

Background
Normal.

Interictal paroxysmal abnormalities
Wakefulness. Interictal focal epileptic discharges (ED) are represented by high-amplitude repetitive spikes and spike-waves with variable topography over time. Unilateral discharges are more common early in the course of LKS, usually located in the temporal regions (in more than 50% of the children) or in the parietal-occipital regions (in about 30% of the children) (*supplementary figure 4.79-4.82*). Generalized spike-wave discharges have also been reported. The morphology of the ED resembles that of the "rolandic" spikes of BECTS. ED usually disappear after the age of 15 years. Generally, HV and photic stimulation do not elicit epileptic paroxysms.
Sleep. Sleep, particularly sleep onset, remarkably activates epileptic activity (*supplementary figure 4.83*). Focal EDs usually show predominantly posterior temporal topography, and in a given night, they are usually focal or unilateral (*supplementary figure 4.81, 4.82 and 4.83*). Unilateral subclinical seizure discharges can be detected alternatively over either hemisphere. At some time during the course of LKS, sleep EEG can show a pattern of continuous or sub-continuous, bilateral spike-wave activity for more than 85% of the time in slow sleep, consistent with the pattern of the ESES syndrome. This finding has suggested a partial or complete overlap between the two conditions (Hirsch *et al*., 1990) and more recently has led to the proposal that LKS is a clinical subtype included in the wide spectrum of the clinical manifestations of ESES syndrome (Tassinari *et al*., 2012).

Recording protocols and diagnostic levels

Considering the widely accepted consensus on LKS as part of the clinical spectrum of the ESES syndrome at present (*for a detailed review, see Tassinari et al. [2012]*), we refer readers to the ESES syndrome for recording protocols and diagnostic levels.

Acknowledgements and disclosures.
We wish to express our gratitude to all our EEG physiologists at St Thomas' and Evelina hospitals, for their high quality clinical EEG recordings on our patients through the years, and for their invaluable comments on important technical issues described in this work. The authors have no conflict of interest to declare.

References

Abou-Khalil B, Ge Q, Desai R, *et al*. Partial and generalized epilepsy with febrile seizures plus and a novel SCN1A mutation. *Neurology* 2001; 57: 2265-72.

Aicardi J, Chevrie JJ. Atypical benign partial epilepsy of childhood. *Developmental Med Child Neurol* 1982; 24: 281-92.

Aicardi J, Ohtahara S. Severe neonatal epilepsies with suppression-burst pattern. In: Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P, eds. *Epileptic Syndromes in Infancy, Childhood and Adolescence*, 4th Ed. John Libbey Eurotext Ltd, 2005.

Akiyama T, Kobayashi K, Ohtsuka Y. Electroclinical characterization and classification of symptomatic epilepsies with very early onset by multiple correspondence analysis. *Epilepsy Res* 2010; 91: 232-9.

Al-Futaisi A, Banwell B, Ochi A, *et al*. Hidden focal EEG seizures during prolonged suppressions and high-amplitude bursts in early infantile epileptic encephalopathy. *Clin Neurophysiol* 2005; 116: 1113-7.

Annegers JF, Hauser WA, Shirts SB, Kurland LT. Factors prognostic of unprovoked seizures after febrile convulsions. *N Engl J Med* 1987; 316: 493-8.

Archer JS, Warren AE, Jackson GD, Abbott DF. Conceptualizing Lennox-Gastaut syndrome as a secondary network epilepsy. *Front Neurol* 2014; 5: 225.

Arzimanoglou A, French J, Blume WT, *et al*. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. *Lancet Neurol* 2009; 8: 82-93.

Arzimanoglou A, Duchowny M. Epilepsy and other seizure disorders. In: Arzimanoglou A, O'Hare A, Johnston M, Ouvrier R, eds. *Aicardi's Diseases of the Nervous System in Childhood*, 4th Ed. McKeith Press, 2018.

Arzimanoglou A, Cross H, Gaillard WD, *et al*. *Pediatric Epilepsy Surgery*. Montrouge: John Libbey Eurotext, 2016.

Auvin S, Pandit F, De Bellecize J, *et al*. Benign myoclonic epilepsy in infants: electroclinical features and long-term follow-up of 34 patients. *Epilepsia* 2006; 47: 387-93.

Auvin S, de Bellescize J, Dravet C. Myoclonic epilepsy in infancy: one or two diseases? *Epileptic Disord* 2013; 15: 241-2.

Barcia G, Fleming MR, Deligniere A, *et al*. De novo gain-of-function KCNT1 channel mutations cause malignant migrating partial seizures of infancy. *Nat Genet* 2012; 44: 1255-9.

Beal JC, Eisermann M, Misra S, *et al*. Seizures and epilepsy in preterm and term neonates, infants, children and adolescents. In: Schomer DL, Lopes da Silva FH, eds. *Niedermeyer's Electroencephalography: Basic Principles, Clinical Applications, and Related Fields 7th Edition*. Montrouge: Oxford University Press, 2017 (In press).

Beaumanoir A. The Landau-Kleffner syndrome. In: Roger J, Bureau M, Dravet C, Dreifuss FE, Perret A, Wolf P, eds. *Epileptic Syndromes in Infancy, Childhood, Adolescence*. London: John Libbey, 1992.

Beaumanoir A. About continuous or subcontinuous spike-wave activity during wakefulness: electroclinical correlations. In: Beaumanoir A, Bureau M, Deonna T, Mira L, Tassinari CA, eds. *Continuous Spikes and Waves during Slow Sleep. Electrical Status Epilepticus during Slow Sleep*. London: John Libbey, 1995.

Beaumanoir A, Blume WT. The Lennox-Gastaut syndrome. In: Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P, eds. *Epileptic Syndromes in Infancy, Chlidhood and Adolescence (4th Edition)*. London: John Libbey, 2005.

Berg AT, Shinnar S, Darefsky AS, *et al*. Predictors of recurrent febrile seizures. A prospective cohort study. *Pediatr Adolesc Med* 1997; 151: 371-8.

Berkovic SF, Heron SE, Giordano L, *et al*. Benign familial neonatal-infantile seizures: characterization of a new sodium channelopathy. *Ann Neurol* 2004; 55: 550-7.

Blume WT, Whiting SE, Girvin JP. Epilepsy surgery in the posterior cortex. *Ann Neurol* 1991; 29: 638-45.

Bölsterli BK, Schmitt B, Bast T, *et al*. Impaired slow wave sleep downscaling in encephalopathy with status epilepticus during sleep (ESES). *Clin Neurophysiol* 2011; 122: 1779-87.

Bölsterli Heinzle BK, Fattinger S, Kurth S, *et al*. Spike wave location and density disturb sleep slow waves in patients with CSWS (continuous spike waves during sleep). *Epilepsia* 2014; 55: 584-91.

Bureau M, Tassinari CA. Myoclonic absences and absences with myoclonias. In: Bureau M, Genton P, Dravet C, *et al*. *Epileptic Syndromes in Infancy, Childhood and Adolescence*. London: John Libbey Eurotext Ltd, 2012.

Bureau M, Dalla Bernardina B. Electroencephalographic characteristics of Dravet syndrome. *Epilepsia* 2011; 52: 13-23.

Bureau M, Genton P, Dravet C, *et al*. *Epileptic Syndromes in Infancy, Childhood and Adolescence*. Montrouge: John Libbey Eurotext, 2012.

Camfield PR. Definition and natural history of Lennox-Gastaut syndrome. *Epilepsia* 2011; 52: 3-9.

Camfield P, Camfield C. Febrile seizures and genetic epilepsy with febrile seizures *plus* (GEFS+). *Epileptic Disord* 2015; 17: 124-33.

Capovilla G, Beccaria F, Montagnini A. 'Benign focal epilepsy in infancy with vertex spikes and waves during sleep'. Delineation of the syndrome and recalling as 'benign infantile focal epilepsy with midline spikes and waves during sleep' (BIMSE). *Brain Dev* 2006; 28: 85-91.

Caraballo RH, Fejerman N. Dravet syndrome: a study of 53 patients. *Epilepsy Res* 2006; 70: S231-8.

Caraballo RH, Astorino F, Cersosimo R, Soprano AM, Fejerman N. Atypical evolution in childhood epilepsy with occipital paroxysms (Panayiotopoulos type). *Epileptic Disord* 2001; 3: 157-62.

Caraballo RH, Cersósimo RO, Espeche A, Fejerman N. Benign familial and non-familial infantile seizures: a study of 64 patients. *Epileptic Disord* 2003; 5: 45-9.

Caraballo RH, Sologuestua A, Grañana N, *et al*. Idiopathic occipital and absence epilepsies appearing in the same children. *Pediatr Neurol* 2004; 30: 24-8.

Caraballo R, Cersósimo R, Fejerman N. Panayiotopoulos syndrome: a prospective study of 192 patients. *Epilepsia* 2007; 48: 1054-61.

Caraballo RH, Fontana E, Darra F, *et al*. Migrating focal seizures in infancy: analysis of the electroclinical patterns in 17 patients. *J Child Neurol* 2008a; 23: 497-506.

Caraballo R, Fontana E, Darra F, *et al*. Childhood absence epilepsy and electroencephalographic focal abnormalities with or without clinical manifestations. *Seizure* 2008b; 17: 617-24.

Caraballo RH, Cersósimo RO, Fejerman N. Childhood occipital epilepsy of Gastaut: a study of 33 patients. *Epilepsia* 2008c; 49: 288-97.

Caraballo RH, Koutroumanidis M, Panayiotopoulos CP, Fejerman N. Idiopathic childhood occipital epilepsy of Gastaut: a review and differentiation from migraine and other epilepsies. *J Child Neurol* 2009; 24: 1536-42.

Caraballo R, Darra F, Fontana E, Garcia R, Monese E, Dalla Bernardina B. Absence seizures in the first three years of life: an electroclinical study of 46 cases. *Epilepsia* 2011; 52: 393-400.

Caraballo RH, Flesler S, Pasteris MC, Lopez Avaria MF, Fortini S, Vilte C. Myoclonic epilepsy in infancy: an electroclinical study and long-term follow-up of 38 patients. *Epilepsia* 2013; 54: 1605-12.

Caraballo RH, Pasteris MC, Portuondo E, Fortini PS. Panayiotopoulos syndrome and diffuse paroxysms as the first EEG manifestation at clinical onset: a study of nine patients. *Epileptic Disord* 2015; 17: 143-9.

Chaix Y, Daquin G, Monteiro F, Villeneuve N, Laguitton V, Genton P. Absence epilepsy with onset before age three years: a heterogeneous and often severe condition. *Epilepsia* 2003; 44: 944-9.

Co JP, Elia M, Engel Jr. J, *et al*. Proposal of an algorithm for diagnosis and treatment of neonatal seizures in developing countries. *Epilepsia* 2007; 48: 1158-64.

Coppola G. Malignant migrating partial seizures in infancy: an epilepsy syndrome of unknown etiology. *Epilepsia* 2009; 50: 49-51.

Coppola G, Plouin P, Chiron C, Robain O, Dulac O. Migrating partial seizures in infancy: a malignant disorder with developmental arrest. *Epilepsia* 1995; 36: 1017-24.

Dalla Bernardina B, Sgro V, Fejerman N. Epilepsy with centrotemporal spikes and related syndromes. In: Roger J, Bureau M, Dravet Ch, Genton P, Tassinari CA, Wolf P, eds. *Epileptic Syndromes in Infancy, Childhood and Adolescence*. Montrouge: John Libbey Eurotext, 2005.

Darra F, Fiorini E, Zoccante L, *et al*. Benign myoclonic epilepsy in infancy (BMEI): a longitudinal electroclinical study of 22 cases. *Epilepsia* 2006; 47: 31-5.

Deonna T, Peter CL, Ziegler A. Adult follow-up of the acquired aphasia epilepsy syndrome in childhood: report of seven cases. *Neuropediatrics* 1989; 20: 132-8.

D'Gama AM, Geng Y, Couto JA, *et al*. Mammalian target of rapamycin pathway mutations cause hemimegalencephaly and focal cortical dysplasia. *Ann Neurol* 2015; 77: 720-5.

Domańska-Pakieła D, Kaczorowska M, Jurkiewicz E, Kotulska K, Dunin-Wąsowicz D, Jóźwiak S. EEG abnormalities preceding the epilepsy onset in tuberous sclerosis complex patients - a prospective study of 5 patients. *Eur J Paediatr Neurol* 2014; 18: 458-68.

Doose H. Myoclonic-astatic epilepsy. *Epilepsy Res Suppl* 1992; 6: 163-8.

Dravet C, Bureau M, Oguni H, Cokar O, Guerrini R. Dravet syndrome. In: Bureau M, Genton P, Dravet C, Delgado-Escueta A, Tassinari CA, Thomas P, Wolf P, eds. *Epileptic Syndromes in Infancy, Childhood and Adolescence, 5th Edition*. Montrouge: John Libbey Eurotext, 2012.

Dulac O. Malignant migrating partial seizures in infancy. In: Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P, eds. *Epileptic Syndromes in Infancy, Childhood and Adolescence, 4th Edition*. Montrouge: John Libbey Eurotext, 2005.

Elia M, Guerrini R, Musumeci SA, Bonanni P, Gambardella A, Aguglia U. Myoclonus absence-like seizures and chromosome abnormality syndromes. *Epilepsia* 1998; 39: 660-3.

Espeche A. Benign infantile seizures: a prospective study. *Epilepsy Res* 2010; 89: 96-103.

Fejerman N, Caraballo R. *Benign Focal Epilepsies in Infancy, Childhood and Adolescence*. London: John Libbey Eurotext, 2007.

Fejerman N, Caraballo R, Tenembaum SN. Atypical evolutions of benign localization-related epilepsies in children: are they predictable? *Epilepsia* 2000; 41: 380-90.

Ferrie CD, Koutroumanidis M, Rowlinson S, Sanders S, Panayiotopoulos CP. Atypical evolution of Panayiotopoulos syndrome: a case report. *Epileptic Disord* 2002; 4: 35-42.

Fogarasi A, Tuxhorn I, Hegyi M, Janszky J. Predictive clinical factors for the differential diagnosis of childhood extratemporal seizures. *Epilepsia* 2005; 46: 1280-5.

Fusco L, Vigevano F. Ictal clinical electroencephalographic findings of spasms in West syndrome. *Epilepsia* 1993; 34: 671-8.

Fusco L, Pachatz C, Di Capua M, Vigevano F. Video/EEG aspects of early-infantile epileptic encephalopathy with suppression-bursts (ohtahara syndrome). *Brain Dev* 2001; 23: 708-14.

Gaily EK, Shewmon DA, Chugani HT, Curran JG. Asymmetric and asynchronous infantile spasms. *Epilepsia* 1995; 36: 873-82.

Gastaut H, Zifkin BG. Benign epilepsy of childhood with occipital spike and wave discharges. In: Andermann F, Ugaresi E, eds. *Migraine and Epilepsy*. Stoneham MA: Butterworth, 1987.

Gelisse P, Corda D, Raybaud C, Dravet C, Bureau M, Genton P. Abnormal neuroimaging in patients with benign epilepsy with centrotemporal spikes. *Epilepsia* 2003; 44: 372-8.

Giovanardi Rossi P, Ricciotti A, Melideo G, Santucci M, Gobbi G. Atypical myoclonic absences: clinical, electroencephalographic and neuropsychological aspects. *Clin Electroencephalogr* 1988; 19: 87-94.

Gobbi G. Coeliac disease, epilepsy and cerebral calcifications. *Brain Dev* 2005; 27: 189-200.

Grinton BE, Heron SE, Pelekanos JT, *et al*. Familial neonatal seizures in 36 families: clinical and genetic features correlate with outcome. *Epilepsia* 2015; 56: 1071-80.

Guerrini R, Aicardi J. Epileptic encephalopathies with myoclonic seizures in infants and children (severe myoclonic epilepsy and myoclonic-astatic epilepsy). *J Clin Neurophysiol* 2003; 20: 449-61.

Guerrini R, Mari F, Dravet C. Idiopathic myoclonic epilepsies in infancy and early childhood. In: Bureau M, Genton P, Dravet C, *et al*, eds. *Epileptic Syndromes in Infancy, Childhood and Adolescence, 5th Edition*. Montrouge: John Libey Eurotext Ltd, 2012.

Hamer HM, Wyllie E, Lüders HO, Kotagal P, Acharya J. Symptomatology of epileptic seizures in the first three years of life. *Epilepsia* 1999; 40: 837-44.

Heron SE, Grinton BE, Kivity S, *et al*. PRRT2 mutations cause benign familial infantile epilepsy and infantile convulsions with choreoathetosis syndrome. *Am J Hum Genet* 2012; 90: 152-60.

Hirsch E, Marescaux C, Maquet P, *et al*. Landau-Kleffner syndrome: a clinical and EEG study of five cases. *Epilepsia* 1990; 31: 756-67.

Hirsch E, Velez A, Sellal F, *et al*. Electroclinical signs of benign neonatal familial convulsions. *Ann Neurol* 1993; 34: 835-41.

Hrachovy RA, Frost Jr. JD. Infantile epileptic encephalopathy with hypsarrhythmia (infantile spasms/West syndrome). *J Clin Neurophysiol* 2003; 20: 408-25.

Imai K, Otani K, Yanagihara K, *et al*. Ictal video-EEG recording of three partial seizures in a patient with the benign infantile convulsions associated with mild gastroenteritis. *Epilepsia* 1999; 40: 1455-8.

Kaminska A, Oguni H. Lennox-Gastaut syndrome and epilepsy with myoclonic-astatic seizures. *Handb Clin Neurol* 2013; 111: 641-52.

Kang SK, Kadam SD. Neonatal seizures: impact on neurodevelopmental outcomes. *Front Pediatr* 2015; 3: 101.

Kato M, Yamagata T, Kubota M, *et al*. Clinical spectrum of early onset epileptic encephalopathies caused by KCNQ2 mutation. *Epilepsia* 2013; 54: 1282-7.

Kelley SA, Kossoff EH. Doose syndrome (myoclonic-astatic epilepsy): 40 years of progress. *Dev Med Child Neurol* 2010; 52: 988-93.

Kikuchi K, Hamano S, Higurashi N, *et al*. Difficulty of early diagnosis and requirement of long-term follow-up in benign infantile seizures. *Pediatr Neurol* 2015; 53: 157-62.

Kivity S, Lerman P. Stormy onset with prolonged loss of consciousness in benign childhood epilepsy with occipital paroxysms. *J Neurol Neurosurg Psychiatry* 1992; 55: 45-8.

Kotulska K, Jurkiewicz E, Domańska-Pakieła D, *et al*. Epilepsy in newborns with tuberous sclerosis complex. *Eur J Paediatr Neurol* 2014; 18: 714-21.

Koutroumanidis M. Panayiotopoulos syndrome: an important electroclinical example of benign childhood system epilepsy. *Epilepsia* 2007; 48: 1044-53.

Koutroumanidis M, Ferrie CD, Valeta T, Sanders S, Michael M, Panayiotopoulos CP. Syncope-like epileptic seizures in Panayiotopoulos syndrome. *Neurology* 2012; 79: 463-7.

Koutroumanidis M, Arzimanoglou A, Caraballo R, *et al*. The role of EEG in the diagnosis and classification of the epilepsy syndromes: a tool for clinical practice by the ILAE Neurophysiology Task Force (Part 1). *Epileptic Disord* 2017a; 19: 233-98.

Koutroumanidis M, Sakellariou D, Tsirka V. Electroencephalography. In: Mills K, ed. *Oxford Textbook of Clinical Neurophysiology*. Oxford: Oxford University Press, 2017b, 119-30.

Kröll-Seger J, Kaminska A, Moutard ML, *et al*. Severe relapse of epilepsy after vigabatrin withdrawal: for how long should we treat symptomatic infantile spasms? *Epilepsia* 2007; 48: 612-3.

Labate A, Tarantino P, Palamara G, *et al*. Mutations in PRRT2 result in familial infantile seizures with heterogeneous phenotypes including febrile convulsions and probable SUDEP. *Epilepsy Res* 2013; 104: 280-4.

Landau W, Kleffner FR. Syndrome of acquired aphasia with convulsive disorder in children. *Neurology* 1957; 7: 523-30.

Legarda S, Jayakar P, Duchowny M, Alvarez L, Resnick T. Benign rolandic epilepsy: high central and low central subgroups. *Epilepsia* 1994; 35: 1125-9.

Lispi ML, Vigevano F. Benign paroxysmal tonic upgaze of childhood with ataxia. *Epileptic Disord* 2001; 3: 203-6.

Loddenkemper T, Cosmo G, Kotagal P, *et al*. Epilepsy surgery in children with electrical status epilepticus in sleep. *Neurosurgery* 2009; 64: 328-37.

Maini I, Iodice A, Spagnoli C, *et al*. Expanding phenotype of PRRT2 gene mutations: a new case with epilepsy and benign myoclonus of early infancy. *Eur J Paediatr Neurol* 2016; 20: 454-6.

Mantovani JF, Landau WM. Acquired aphasia with convulsive disorder: course and prognosis. *Neurology* 1980; 30: 524-9.

Markand ON. Lennox-Gastaut syndrome (childhood epileptic encephalopathy). *J Clin Neurophysiol* 2003; 20: 426-41.

Maruyama K, Okumura A, Sofue A, Ishihara N, Watanabe K. Ictal EEG in patients with convulsions with mild gastroenteritis. *Brain Dev* 2007; 29: 43-6.

Maytal J, Steele R, Eviatar L, Novak G. The value of early postictal EEG in children with complex febrile seizures. *Epilepsia* 2000; 41: 219-21.

McTague A, Appleton R, Avula S, *et al*. Migrating partial seizures of infancy: expansion of the electroclinical, radiological and pathological disease spectrum. *Brain* 2013; 136: 1578-91.

Miller SP, Dilenge ME, Meagher-Villemure K, O'Gorman AM, Shevell MI. Infantile epileptic encephalopathy (Ohtahara syndrome) and migrational disorder. *Pediatr Neurol* 1998; 19: 50-4.

Mizrahi EM, Kellaway P. Characterization and classification of neonatal seizures. *Neurology* 1987; 37: 1837-44.

Mizrahi EM, Kellaway P. *Diagnosis and Management of Neonatal Seizures. 1st Edition*. Oxford: Lippincott Williams & Wilkins, 1998.

Nabbout R, Desguerre I, Sabbagh S, *et al*. An unexpected EEG course in Dravet syndrome. *Epilepsy Res* 2008; 81: 90-5.

Noh BH, Berg AT, Nordli DR Jr. Concordance of MRI lesions and EEG focal slowing in children with nonsyndromic epilepsy. *Epilepsia* 2013; 54: 455-60.

Nordli DR Jr, Kuroda MM, Hirsch LJ. The ontogeny of partial seizures in infants and young children. *Epilepsia* 2001; 42: 986-90.

Nordli Jr. DR, Moshé SL, Shinnar S, *et al*. Acute EEG findings in children with febrile status epilepticus: results of the FEBSTAT study. *Neurology* 2012; 79: 2180-6.

Ochi A, Hung R, Weiss S, *et al*. Lateralized interictal epileptiform discharges during rapid eye movement sleep correlate with epileptogenic hemisphere in children with intractable epilepsy secondary to tuberous sclerosis complex. *Epilepsia* 2011; 52: 1986-94.

Oguni H, Fukuyama Y, Imaizumi Y, Uehara T. Video-EEG analysis of drop seizures in myoclonic astatic epilepsy of early childhood (Doose syndrome). *Epilepsia* 1992; 33: 805-13.

Oguni H, Hayashi K, Imai K, *et al*. Idiopathic myoclonic-astatic epilepsy of early childhood-nosology based on electrophysiologic and long-term follow-up study of patients. *Adv Neurol* 2005; 95: 157-74.

Ohba C, Kato M, Takahashi N, *et al*. De novo KCNT1 mutations in early-onset epileptic encephalopathy. *Epilepsia* 2015; 56: e121-8.

Ohki T, Watanabe K, Negoro T, *et al*. Severe myoclonic epilepsy in infancy: evolution of seizures. *Seizure* 1997; 6: 219-24.

Ohtahara S, Yamatogi Y. Epileptic encephalopathies in early infancy with suppression-burst. *J Clin Neurophysiol* 2003; 20: 398-407.

Ohtahara S, Yamatogi Y. Ohtahara syndrome: With special reference to its developmental aspects for differentiating from early myoclonic encephalopathy. *Epilepsy Res* 2006; 70: S58-67.

Ohtahara S, Ohtsuka Y, Yamatogi Y, Oka E. The early-infantile epileptic encephalopathy with suppression-burst: developmental aspects. *Brain Dev* 1987; 9: 371-6.

Ohtsu M, Oguni H, Hayashi K, Funatsuka M, Imai K, Osawa M. EEG in children with early-onset benign occipital seizure susceptibility syndrome: Panayiotopoulos syndrome. *Epilepsia* 2003; 44: 435-42.

Okumura A, Hayakawa F, Kato T, Kuno K, Negoro T, Watanabe K. Early recognition of benign partial epilepsy in infancy. *Epilepsia* 2000; 41: 714-7.

Ozyurek H, Turanli G, Aliefendioglu D, Coskun T. Repetitive EEG recordings are necessary for the diagnosis of early myoclonic encephalopathy. *Neurol India* 2005; 53: 235-7.

Pal DK, Ferrie C, Addis L, *et al*. Idiopathic focal epilepsies: the "lost tribe". *Epileptic Disord* 2016; 18: 252-88.

Panayiotopoulos CP. Visual phenomena and headache in occipital epilepsy: a review, a systematic study and differentiation from migraine. *Epileptic Disord* 1999; 1: 205-16.

Panayiotopoulos CP. The EEG in Panayiotopoulos syndrome is a multifocal EEG. In: Panayiotopoulos CP, ed. *Panayiotopoulos Syndrome, a Common and Benign Childhood Epileptic Syndrome*. London: John Libbey Eurotext, 2002.

Panayiotopoulos CP, Michael M, Sanders S, Valeta T, Koutroumanidis M. Benign childhood focal epilepsies: assessment of established and newly recognized syndromes. *Brain* 2008; 131: 2264-86.

Panayiotopoulos CP, Bureau M, Caraballo R, Dalla Bernardina B, Valeta T. Idiopathic focal epilepsies in childhood. In: Bureau M, Genton P, Dravey C, *et al*, eds. *Epileptic Syndrome in Infancy, Childhood and Adolescence*. Montrouge: John Libbey Eurotext, 2012.

Patry G, Lyagoubi S, Tassinari CA. Subclinical electrical status epilepticus induced by sleep in children. *Arch Neurol* 1971; 24: 242-52.

Pearl PL. Amenable treatable severe pediatric epilepsies. *Semin Pediatr Neurol* 2016; 23: 158-66.

Prabhu AM, Pathak S, Khurana D, Legido A, Carvalho K, Valencia I. Nocturnal variant of benign myoclonic epilepsy of infancy: a case series. *Epileptic Disord* 2014; 16: 45-9.

Ricci S, Cusmai R, Fusco L, Vigevano F. Reflex myoclonic epilepsy in infancy: a new age-dependent idiopathic epileptic syndrome related to startle reaction. *Epilepsia* 1995; 36: 342-8.

Ronen GM, Rosales TO, Connolly M, Anderson VE, Leppert M. Seizure characteristics in chromosome 20 benign familial neonatal convulsions. *Neurology* 1993; 43: 1355-60.

Salanova V, Andermann F, Olivier A, Rasmussen T, Quesney LF. Occipital lobe epilepsy: electroclinical manifestations, electrocorticography, cortical stimulation and outcome in 42 patients treated between 1930 and 1991. Surgery of occipital lobe epilepsy. *Brain* 1992; 115: 1655-80.

Sanders S, Rowlinson S, Manidakis I, Ferrie CD, Koutroumanidis M. The contribution of the EEG technologists in the diagnosis of Panayiotopoulos syndrome (susceptibility to early onset benign childhood autonomic seizures). *Seizure* 2004; 13: 565-73.

Sands TT, McDonough TL. Recent advances in neonatal seizures. *Curr Neurol Neurosci Rep* 2016; 16: 92.

Scheffer IE, Berkovic SF. Generalized epilepsy with febrile seizures plus. A genetic disorder with heterogeneous clinical phenotypes. *Brain* 1997; 120: 479-90.

Scheffer IE, Berkovic S, Capovilla G, *et al*. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017; 58: 512-21.

Scheltens-de Boer M. Guidelines for EEG in encephalopathy related to ESES/CSWS in children. *Epilepsia* 2009; 50: 13-7.

Schlumberger E, Dulac O, Plouin P. Early-infantile epileptic syndrome(s) with suppression-bursts. Nosological considerations. In: Roger J, Bureau M, Dravet C, *et al*, eds. *Epileptic Syndromes in Infancy, Childhood and Adolescence*. Montrouge: John Libbey & Company Ltd, 1992.

Shah PB, James S, Elayaraja S. EEG for children with complex febrile seizures. *Cochrane Database Syst Rev* 2017; 10: CD009196.

Shahar E, Genizi J, Nevo Y, Kaufman R, Cabot S, Zelnik N. Typical absence epilepsy presenting prior to age of 3 years: an uncommon form of idiopathic generalized epilepsy. *Eur J Paediatr Neurol* 2007; 11: 346-52.

Specchio N, Vigevano F. The spectrum of benign infantile seizures. *Epilepsy Res* 2006; 70: S156-67.

Specchio N, Trivisano M, Di Ciommo V, *et al*. Panayiotopoulos syndrome: a clinical, EEG, and neuropsychological study of 93 consecutive patients. *Epilepsia* 2010a; 51: 2098-107.

Specchio N, Trivisano M, Claps D, *et al*. Documentation of autonomic seizures and autonomic status epilepticus with ictal EEG in Panayiotopoulos syndrome. *Epilepsy Behav* 2010b; 19: 383-93.

Specchio N, Balestri M, Trivisano M, *et al*. Electroencephalographic features in Dravet syndrome: five-year follow-up study in 22 patients. *J Child Neurol* 2012; 27: 439-44.

Specchio N, Terracciano A, Trivisano M, *et al*. PRRT2 is mutated in familial and non-familial benign infantile seizures. *Eur J Paediatr Neurol* 2013; 17: 77-81.

Striano P, Lispi ML, Gennaro E, *et al*. Linkage analysis and disease models in benign familial infantile seizures: a study of 16 families. *Epilepsia* 2006; 47: 1029-34.

Subcommittee on Febrile Seizures, American Academy of Pediatrics. Neurodiagnostic evaluation of the child with a simple febrile seizure. *Pediatrics* 2011; 127: 389-94.

Suls A, Mullen S, Weber Y, *et al*. Early-onset absence epilepsy caused by mutations in the glucose transporter GLUT1. *Ann Neurol* 2009; 66: 415-9.

Tassinari CA. Encepahlopathy with status epilepticus during slow wave sleep: "the Penelope syndrome". *Epilepsia* 2009; 50: 4-8.

Tassinari CA, Rubboli G. Cognition and paroxysmal EEG activities: from a single spike to electrical status epilepticus during sleep. *Epilepsia* 2006; 47: 40-3.

Tassinari CA, Dravet C, Roger J. ESES: encephalopathy related to electrical status epilepticus during slow sleep. In: *Proceedings of the ninth congress international federation of EEG and clinical neurophysiology*. Amsterdam: Elsevier Science, 1977.

Tassinari CA, Michelucci R, Rubboli G, *et al*. Myoclonic absence epilepsy. In: Duncan JS, Panayiotopoulos CP, eds. *Typical Absences and Related Syndromes*. London: Churchill Livingstone, 1996.

Tassinari CA, Rubboli G, Volpi L, *et al*. Encephalopathy with electrical status epilepticus during slow sleep or ESES syndrome including the acquired aphasia. *Clin Neurophysiol* 2000; 111: 94-102.

Tassinari CA, Michelucci R, Gardella E, Rubboli G. Epilepsy with myoclonic absences. In: Engel J, Pedley TA, eds. *Epilepsy. A Comprehensive Textbook*. Philaldelphia: Walters Kluwer-Lippincott Williams & Wilkins, 2008.

Tassinari CA, Cantalupo G, Rubboli G. Polygraphic recording of epileptic seizures. In: Panayiotopoulos CP, ed. *Atlas of Epilepsies*. London: Springer-Verlag Limited, 2010.

Tassinari CA, Cantalupo G, Dalla Bernardina B, *et al*. Encephalopathy related to status epilepticus during slow sleep (ESES) including Landau-Kleffner syndrome. In: Bureau M, Genton P, Dravet C, *et al*, eds. *Epileptic Syndromes in Infancy, Childhood and Adolescence*. London: John Libbey Eurotext Ltd, 2012.

Tata G, Guveli BT, Dortcan N, *et al*. Panayiotopoulos syndrome and symptomatic occipital lobe epilepsy of childhood: a clinical and EEG study. *Epileptic Disord* 2014; 16: 197-202.

Trivisano M, Specchio N, Cappelletti S, *et al*. Myoclonic astatic epilepsy: an age-dependent epileptic syndrome with favorable seizure outcome but variable cognitive evolution. *Epilepsy Res* 2011; 97: 133-41.

Van Hirtum-Das M, Licht EA, Koh S, Wu JY, Shields WD, Sankar R. Children with ESES: variability in the syndrome. *Epilepsy Res* 2006; 70: S248-58.

Verrotti A, Matricardi S, Pavone P, Marino R, Curatolo P. Reflex myoclonic epilepsy in infancy: a critical review. *Epileptic Disord* 2013; 15: 114-22.

Vigevano F. Benign familial infantile seizures. *Brain Dev* 2005; 27: 172-7.

Vigevano F, Fusco L, Di Capua M, Ricci S, Sebastianelli R, Lucchini P. Benign infantile familial convulsions. *Eur J Pediatr* 1992; 151: 608-12.

Vigevano F, Fusco L, Pachatz C. Neurophysiology of spasms. *Brain Dev* 2001; 23: 467-72.

Vigevano F, Bureau M, Watanabe K. Idiopathic focal epilepsies in infants. In: Bureau M, Genton P, Dravet C, *et al*, eds. *Epileptic Syndromes in Infancy, Childhood and Adolescence (5th Ed)*. Paris: John Libbey Eurotext, 2012.

Volpe JJ. Neonatal seizures: current concepts and revised classification. *Pediatrics* 1989; 84: 422-8.

Volpe JJ. Neonatal seizures. In: Saunders WB. *Neurology of the Newborn*. Philadelphia: 2008.

Wakamoto H, Nagao H, Fukuda M, *et al*. Idiopathic childhood occipital epilepsy of Gastaut: report of 12 patients. *Pediatr Neurol* 2011; 44: 183-6.

Watanabe K, Kuroyanagi M, Hara K, Miyazaki S. Neonatal seizures and subsequent epilepsy. *Brain Dev* 1982; 4: 341-6.

Watanabe K, Negoro T, Aso K. Benign partial epilepsy with secondarily generalized seizures in infancy. *Epilepsia* 1993; 34: 635-8.

Watanabe K, Negoro T, Okumura A. Symptomatology of infantile spasms. *Brain Dev* 2001; 23: 453-66.

Weckhuysen S, Korff CM. Epilepsy: old syndromes, new genes. *Curr Neurol Neurosci Rep* 2014; 14: 447.

Weckhuysen S, Mandelstam S, Suls A, *et al*. KCNQ2 encephalopathy: emerging phenotype of a neonatal epileptic encephalopathy. *Ann Neurol* 2012; 71: 15-25.

Williamson PD, Thadani VM, Darcey TM, Spencer DD, Spencer SS, Mattson RH. Occipital lobe epilepsy: clinical characteristics, seizure spread patterns, and results of surgery. *Ann Neurol* 1992; 31: 3-13.

Wyllie E, Lachhwani DK, Gupta A, *et al*. Successful surgery for epilepsy due to early brain lesions despite generalized EEG findings. *Neurology* 2007; 69: 389-97.

Yamamoto H, Okumura A, Fukuda M. Epilepsies and epileptic syndromes starting in the neonatal period. *Brain Dev* 2011; 33: 213-20.

Yamatogi Y, Ohtahara S. Early-infantile epileptic encephalopathy with suppression-bursts. Ohtahara syndrome; its overview referring to our 16 cases. *Brain Dev* 2002; 24: 13-23.

Yücel O, Aka S, Yazicioglu L, Ceran O. Role of early EEG and neuroimaging in determination of prognosis in children with complex febrile seizure. *Pediatr Int* 2004; 46: 463-7.

Zara F, Specchio N, Striano P, *et al*. Genetic testing in benign familial epilepsies of the first year of life: clinical and diagnostic significance. *Epilepsia* 2013; 54: 425-36.

Zhang YH, Burgess R, Malone JP, *et al*. Genetic epilepsy with febrile seizures plus: refining the spectrum. *Neurology* 2017; 89: 1210-9.

Zuberi SM, O'Regan ME. Developmental outcome in benign myoclonic epilepsy in infancy and reflex myoclonic epilepsy in infancy: a literature review and six new cases. *Epilepsy Res* 2006; 70: S110-5.

Visit www.epilepticdisorders.com to discover the commented educational figures with EEG plates (see Legends below).

Appendix 1. Legends of supplementary figures

Figure 1.01. Video-EEG monitoring during FDG uptake period of a four-year-old boy with previously normal development, who started having nocturnal seizures associated with generalized stiffening at the age of three years. Brain MRI showed a single focal structural change at the junction of the superior and middle right frontal gyrus, consistent with **cortical dysplasia**. The FDG PET scan showed right frontal hypometabolism extending to the bilateral anterior temporal areas, although to a lesser degree. Note the normal background and the brief generalised spike-wave discharge with slight accentuation over the left hemisphere that, *per se*, would suggest GGE/IGE rather than focal epilepsy.

Figure 1.02. Same recording as in *figure 1.01*, during sleep. Note the focal spikes over the right frontotemporal area (blue arrows) and the bilateral diffuse discharge (green arrow), which now has left-sided emphasis. This EEG also showed independent left frontal spikes, as well as other generalized discharges with fluctuating side emphasis. Sleep architecture was normal.

Figure 1.03. Long, 23sec GSWD of bilateral and synchronous onset, associated with motionless staring during a positron emission tomography (PET) scan. There are no "triggering" focal ED leading to the GSWD (the criteria of spatial and temporal constrains), but SBS can be assumed from the faster activities over the left temporal-parietal areas compared to the right in the first 4 sec of the GSWD. The PET scan revealed left frontal hypometabolism.

Figure 1.04. Focal regular 3Hz spike-wave discharge over the right frontal area in a child with a history of "blank spells" and left focal motor seizures. Note the regional background disturbance which consists of irregular slow rhythms and sharp waves (arrow) maximal over the right central area. Brain MRI showed a large subependymal heterotopia on the right associated with cortical thickening.

Figure 2.01. Suppression-Burst pattern in a six-day-old new-born: bursts of high-voltage asynchronous delta and theta waves, mixed with high-amplitude spikes and polyspikes, lasting around two seconds and alternating with inter-burst intervals of low-voltage activity or complete suppression lasting around seven seconds.

Figure 2.02. Suppression-Burst pattern over the left hemisphere in an eight-day-old new-born with left **hemimegalencephly**.

Figures. 2.03. (A, B) OS with S-B pattern. Note the asymmetric tonic seizures that are concomitant with the bursts, as recorded by bilateral deltoid EMG leads.

Figure. 2.04. Myoclonus of both upper limbs recorded from deltoid EMG during the bursts of spikes and polyspikes within the bursts of the S-B pattern in a six-day-old new-born with EME.

Figure. 2.05. EME with S-B. Note some erratic limb movements concomitant with the bursts that are difficult to classify. This neonate also had jerks involving the face.

Figure. 2.06. EMG activity of both deltoids associated with bursts of activity (high-amplitude spikes, polyspikes, waves, and sharp waves) in a five-day-old new-born.
Figure.2.07. A five-day-old neonate with **OS** and supression burst. (A) A focal motor seizure was recorded with deviation of the eyes to the right, right arm jerks, and head deviation to the right. Ictal EEG onset (B) shows a generalied attenuation followed by a left hemisphere ictal pattern with bilateral evolution and offset (C).
Figure. 2.08. Series of tonic spasms followed by focal seizures in an eight-day-old new-born with **OS**.
Figure. 2.09. Pyridoxine-dependent epilepsy in a 14-week-old boy: status epilepticus with epileptic spasms, S-B pattern with bursts of high-amplitude spikes, polyspikes, and slow waves concomitant with contraction of deltoids (A); clonic status epilepticus with successive myoclonic jerks associated with rhythmic slow spike-waves (B); EEG a few minutes after intravenous injection of pyridoxine; note the disappearance of the spike and the diffuse flattening of the tracing (C); and EEG during wakefulness after a few days of treatment with oral pyridoxine showing normal background activity (D).
Figure 2.10. Two consecutive seizures recorded in a three-day-old neonate with **BNFE**, born at full-term. (A) diffuse bilateral flattening of the background activity predominating on the right side (arrow) that lasts for 10 seconds and corresponds to the tonic extension of the left arm and deviation of the head to the left (video snapshot). The flattening is followed by rhythmic slow spike and wave activity over the right frontal area that increases in amplitude while diffusing to the left frontal area. (B) Similar ictal EEG pattern on the left side.
Figure 2.11. Ictal EEG in a neonate with **BNFE**, with polygraphic EMG recording from both deltoids showing tonic contraction of both upper limbs.
Figure 2.12. Interictal EEG during wakefulness in a two-day-old new-born with right **hemimegalencephaly** (*see MRI in figure 2.19*). Note the inter-hemispheric asymmetry with continuous high-amplitude spikes, polyspikes, and sharp waves that diffuse to the left hemisphere. There are no discernible physiological rhythms on the right (EMG1: right deltoid; EMG2: left deltoid).
Figure 2.13. EEG during active sleep in a 10-day-old neonate with left **hemimegalecephaly**. Note the normal background activity on the right and the S-B pattern on the left.
Figure 2.14. EEG during active sleep in a two-day-old neonate with **tuberous sclerosis complex**. Background activity is normal. Note a sequence of pseudo-periodic sharp waves over the right temporal-occipital region (arrow).
Figure 2.15. EEG recording in a 14-day-old new-born with right **frontal cortical dysplasia**, identified on brain MRI at the age of four years (red arrow). (A) Interictal right-sided hemi-S-B pattern during active sleep; note that the bursts contain spikes and rapid rhythms intermixed with sharp waves. (B) Ictal EEG showing asymmetric epileptic spasms (arrows), concomitant with high-amplitude right hemisphere spike and polyspike-waves that predominate over the central area. (C) An epileptic spasm (green arrow) is followed by an asymmetric tonic seizure predominating in the left upper limb (grey arrow), concomitant with a flattening of the tracing and a sequence of rhythmic, bilateral frontal-central sharp waves that predominate over the right hemisphere (EMG 1: right deltoid; EMG 2: left deltoid).
Figure 2.16. Ictal EEG in a 15-day-old neonate with right **frontal cortical dysplasia**. The seizure is asymmetric tonic, then clonic with interspersing epileptic spasms. The ictal discharge begins with a flattening of the tracing over the right hemisphere, particularly over the frontal region (green arrow), and continues with rapid rhythmic spiking. Epileptic spasms occur during the evolution of the focal seizure discharge and at its end (grey arrows), concomitant with high-amplitude brief diffuse slow wave complexes that also appear to predominate over the right hemisphere (EMG 1: right deltoid; EMG 2: left deltoid).
Figure 2.17. "Subtle" right temporal-occipital seizure in a 10-day-old neonate with **tuberous sclerosis complex**.
Figure 2.18. Ictal EEG in a 20-day-old neonate with **tuberous sclerosis complex**: left frontal-central seizure with tonic, then-clonic movements of the right upper limb. Notice the clonic rather than myoclonic jerks that are concomitant with high-amplitude spikes over the left frontal-central region.
Figure 2.19. Ictal EEG in the two-day-old neonate from *figure 2.12*. The EEG pattern appears similar to that in *figure 2.12* (asymmetric with high-amplitude, continuous spikes, polyspikes, and sharp waves diffusing to the left hemisphere), but some discharges are now concomitant with myoclonic jerks recorded on the left deltoid (EMG 2).
Figure 3.01. Typical **hypsarrhythmia** during natural sleep.
Figure 3.02. Hypsarrhythmia during awake EEG. A six-month-old girl developed epileptic spasms in clusters three weeks before this study. She was given a diagnosis of **cryptogenic West syndrome** based on the neurological and laboratory examination, as well as neuroimaging studies. Background activity was occupied by

irregular slow wave and spikes or polyspikes, most predominantly in both temporal regions. Physiological background activity was intermittently preserved.
Figure 3.03. Hypsarrhythmia during sleep EEG. Note the enhanced synchronization of the hypsarrhythmic discharges, which became almost continuous during slow sleep; same patient as in *figure 3.02*.
Figure 3.04. Asymmetric **hypsarrhythmia**.
Figure 3.05. Hypsarrhythmia associated with background attenuation.
Figure 3.06. Interictal EEG showing an epileptic focus over the left posterior quadrant (panels). The baby has **epileptic spasms** but the pattern here, although of high voltage, cannot be characterized as hypsarrhythmic.
Figure 3.07. (A) Same baby as in *figure 3.03*. The seizure starts with an asymmetric epileptic spasm (blue arrow). Note the pronounced activation of the right deltoid EMG compared to the left. A prolonged, also asymmetric, tonic posturing follows (green arrow), associated with deviation of the eyes to the left (red arrow). (B) (continued): The ictal discharge involves the left parietal-occipital area; clinically, the right arm appears to become fisted and immobile as she continues to stare. (C) At the offset of the focal seizure, a cluster of asymmetric epileptic spasms are recorded (note the EMG artefacts in the lower two channels). The paper speed is very slow and the gain reduced to appreciate the ictal changes.
Figure 3.08. Ictal EEG with polygraphy. **Epileptic spasms** (arrows) are associated with a diffuse high-amplitude triphasic slow wave, followed by -also diffuse- transient suppression of background activity.
Figure 3.09. Typical morphology of ictal EEG. In the monopolar montage, a large positive slow wave is followed by a negative slow wave, corresponding to EMG discharge of the spasm.
Figure 3.10. Slow paper speed (upper and lower traces) and reduced sensitivity (lower trace) provides better resolution of epileptic spasms against a chaotic high-voltage hypsarrhythmic background. Note the bilateral EMG from the deltoid muscles at the bottom of each trace (reproduced with permission from Koutroumanidis et al., 2017b).
Figure 3.11. A 20-month-old boy presented with a **one-hour febrile tonic-clonic seizure**, requiring intubation and ventilation; he had already suffered two febrile seizures. This EEG was performed four days later. Note the non-specific slowing over the posterior regions (L>R) and the occasional bursts of slow waves over the left hemisphere and the right fronto-temporal areas, against an otherwise preserved background. Background rhythms were normal four months later.
Figure 3.12. Diffusely slow background within the theta frequency range (with frontal emphasis) in an eight-year-old boy with **Dravet Syndrome** of infantile onset.
Figure 3.13. Awake EEG in a seven-year-old boy, showing slow background activity in the theta band with bifrontal spikes and slow waves.
Figure 3.14. Same child as in *figure 3.12*. Sleep EEG shows bursts of focal spikes over the right anterior quadrant and independent sharp waves and spikes over the left anterior quadrant.
Figure 3.15. (A, B) Unilateral tonic-clonic seizure in the child of *figure 3.14*. On this occasion, the seizure mainly involved the left side of his body, but other unilateral seizures were reported to involve the right side. Note the bilateral ictal EEG onset (R>L).
Figure. 3.16. Focal seizure in a seven-year-old boy with asymmetric tonic-clonic movements, beginning on the left frontal-central area with high-amplitude spike/polyspike activity that diffuses to the entire left hemisphere and the right frontal-central areas. Notice the tonic, then tonic-clonic movements on the right EMG. The seizure discharge ends first on the left hemisphere and is followed by diffuse postictal suppression that is more pronounced on the left hemisphere.
Figure. 3.17. Awake EEG in a six-year-old boy with **Dravet Syndrome**. High-amplitude generalized, 3-Hz spike-wave discharges predominating over the frontal-central areas are associated with myoclonic jerks recorded on deltoid EMG. Note the slow background within the theta band, particularly over the frontal-central areas.
Figure 3.18. Sleep EEG in a two-year-old girl with genetically confirmed **Dravet Syndrome**. Brief generalized spike/polyspike-and-wave discharges are at times associated with myoclonic jerks (lower two EMG channels recorded both deltoids). She first presented jerky movements of arms at the age of six months, on a background of previously normal development. These gradually became more florid and interfered with her crawling. A prolonged tonic-clonic seizure occurred at the age of one, she had subsequent bouts of status epilepticus, and her development was noted to plateau. She has frequent daily myoclonic jerks and absences (*see figure 3.19*), which can occur at any time.
Figure 3.19. Myoclonic absence in **Dravet Syndrome**. Note the regular 2.5-Hz spike-and-wave discharge with the associated bilateral myoclonic jerks that are time-locked to the spike component (lower two EMG channels recorded both deltoids).

Figure 3.20. Video-EEG showing normal background activity during wakefulness of a 12-month-old boy with episodes of brief arm jerks which would result in him dropping objects. **Myoclonic jerks** most often occurred when he was about to sleep.
Figure 3.21. Interictal EEG during light sleep (N1) in the same child as in *figure 3.20*. Note the normal background and a brief diffuse spike-and-wave discharge with no clinical correlate.
Figure 3.22. A 13-month-old boy with normal development who presented with **recurrent myoclonic jerks** of both arms and mild head drops. Brain MRI was normal. Metabolic workups were unremarkable. Myoclonic seizures initially responded to treatment with VPA. During drowsiness and light sleep, interictal GSWD increased in frequency, producing an arousal on this occasion (note the appearance of alpha rhythm after the offset of the discharge).
Figure 3.23. Ictal EEG during early drowsiness in the same child as in *figures 3.20 and 3.21*. Note the single axial myoclonic jerk which is associated with a two-second burst of irregular 3-Hz generalised spike-and-wave discharge, registered by EMG polygraphy (lower two channels).
Figure 3.24. (Same child as in *figures 3.20, 3.21 and 3.23*). Two **myoclonic jerks** in rapid succession during sleep, recorded on EMG channels in association with a brief burst of generalised spike-and-wave discharge on the EEG. The patient became seizure-free upon treatment with levetiracetam. Sleep EEG at three years of age was normal.
Figure 3.25. Video-EEG of a 10-month-old boy who was healthy until eight months of age when he developed **recurrent myoclonic jerks** of the arms with occasional head drops; the latter were captured on the video while he was sitting. Note the increased muscle activity in the deltoid muscle in association with the GSWD. EEG-EMG polygraphy confirmed that the head drop was myoclonic rather than atonic seizure. Background EEG was normal.
Figure 3.26. A 22-month-old girl with recurrent **myoclonic jerks** of both arms, particularly noticeable when something came in contact with her head. Brain MRI was normal. Interictal EEG was normal. The patient had a typical, sudden episode of bilateral arm abduction associated with GSWD (asterisk).
Figure 3.27. A two-month-old boy who developed sudden onset of **focal seizures**, described as head and eye deviating to the right side with brief stiffening of both arms occurring in clusters for 4-5 days. He appeared to be normal in between the seizures. Brain MRI was normal. Seizures resolved two months later after treatment with levetiracetam. His mother had a history of infantile seizures. Infantile epilepsy panel was positive for *PPRT2* gene mutation. The interictal EEG during a cluster shows spikes over the left parietal region.
Figure 3.28. Focal migrating seizures from the left frontotemporal area (A, red arrow) to the right frontotemporal (B, red arrow) and then to the right posterior areas (B, blue arrow) recorded during status epilepticus in a five-month-old girl. Traces A and B show two 20-second epochs selected from the same migrating seizure (back arrows). The density spectral array (DSA) (0-30 Hz) at the bottom of both traces depicts activities from C4 and C3 electrodes over eight hours of recording. Migrating seizures occurred with a frequency of 1-2/hour and lasted for 5-15 minutes each.
Figure 3.29. Focal migrating seizure recorded during status epilepticus in the same girl. Nine 20-second sections have been selected from this five-minute continuous seizure. The seizure onset occurs over the left frontal-central areas with rhythmic theta waves and sharp waves intermixed with slow spikes (A, red arrow). After a few minutes, the seizure activity "migrates" to the contralateral frontal-central areas (D, red arrow), while it slows down on the left and ends (D, blue arrow and E). The seizure continues on the right with rhythmic alpha-like activity (E-H) and then theta rhythmic waves (I) intermixed with spikes.
Figure 4.01. A five-year-old girl presented with a first episode of **febrile status epilepticus**. Seizures were noted to be focal at onset, with right arm involvement. Note the diffuse slowing of the EEG background in this recording, performed 24 hours after the resolution of the status. Also, note asymmetries, as spindles are still seen over the right hemisphere (rectangle), whereas the left temporal region appears comparatively attenuated, suggestive of left hemisphere pathology.
Figure 4.02. A 22-month-old boy with a history of four seperate episodes of complex febrile generalised tonic-clonic seizures. Interictal EEG shows normal backgroud and a single burst of spike-and-wave discharge mainly over the left centro-parietal region.
Figure 4.03. Follow-up EEG of the previous child, now 29 months old. He had no further seizures and he is not on any anti-seizure medication. Sleep EEG showed a single irregular burst of bilateral high-voltage slow waves, associated with focal spikes.

Figure 4.04. Three-year-old girl with **recurrent febrile and subsequent afebrile generalised tonic-clonic seizures** since the age of five months. Family history was positive (for sister, mother, and maternal aunt). The patient had maternally inherited variants of *SCN1A*. Early EEGs at age one and two years were normal. At age eight, she continues to have seizures on medication, but subsequent sleep EEGs have been normal. Her EEG at the age of three years shows: notched slow waves over the left frontal region during wakefulness, diffusing to the right frontal region (A); brief bursts of diffuse bilateral slow waves with a bifrontal emphasis and embedded spikes (note the right frontal lead-in to the burst of more diffuse and widespread slow waves associated with spikes (B, arrow); and a brief burst of irregular diffuse slow waves in sleep, associated with bilateral spikes, more evident on the right (C, D). (C) and (D) show the same discharge on common average and double banana, respectively.
Figure 4.05. Comparison between the typical mid-temporal focal spike in **symptomatic lateral temporal lobe epilepsy** (left half of traces) and the **also typical rolandic spike** in the self-limiting BRE with CTS. Note the differences in the spike topography and polarity over the anterior brain areas and the differences between the two montages (bipolar anterior-posterior or "double banana" and average reference). Reproduced with permission from Koutroumanidis *et al*. (2017).
Figure 4.06. An eight-year-old boy presenting with three nocturnal seizures with mouth and tongue deviation followed by clonic jerking. Note the run of relatively small sharp waves over the right temporal electrode (T4).
Figure 4.07. A seven-year-old boy presented with two seizures in the early hours of the morning, not associated with high temperature. During the seizures, he shook all over and drooled; he tried to talk during the seizures, but his speech was slurred. The patient had normal delivery at full term and normal development, without a family history of epilepsy. He had a possible febrile convulsion at age five. Note the high-voltage right centrotemporal spikes and independent left parietal-posterior temporal, as well as a few mid-parietal, spikes.
Figure 4.08. Note a mild excess of theta/fast delta activity over the left temporal area, associated with the typical spikes.
Figure 4.09. Sleep EEG of the child in *figure 4.07*. Note the activation of the independent spikes over the right centro-sylvian, mid-parietal, and left centro-parietal electrodes.
Figure 4.10. Generalized spike-wave discharge during light sleep (Stage 1) of the child in *figure 4.06*.
Figure 4.11. (A) **Typical rolandic seizure** arising from sleep Stage 2 in a 10-year-old boy with BRE. He suddenly woke and sat up with his eyes open. Initially, the left side of the mouth contorted and deviated to the left (snapshot taken at the time marked by the vertical green arrow), followed by left facial clonus that involved the eyelids. There was a short bilateral tonic posturing and then clonic movements of the left limbs. The seizure lasted one minute and 40 seconds, and promptly after offset he was well oriented in time and place and able to recall the word "red" given to him during the seizure. Postictally, the left side of the mouth appeared to droop, his speech was slurred for a while but not dysphasic, and voluntary movements of the left arm appeared reduced for a few minutes. The electrographic onset of the seizure occurs over the right lateral temporal-central area (horizontal green arrow) and is presented in more detail in *figure 4.11B*. (B) Electrographic onset of the rolandic seizure of *figure 4.11A*. Note the typical interictal centrotemporal spikes on the left side of the figure (panels) and their relationship with the k-complex and the associated sleep spindles. The onset of the ictal activity occurs over the right centro-temporal area (blue arrows) and consists of alpha-like rhythm that soon incorporates rhythmic spikes, which show exactly the same topography and polarity as the interictal CTS, but are much smaller in voltage.
Figure 4.12. EEG recording of a four-year-old girl showing normal background activity with superimposed spikes in the left centro-temporal region. FLAIR MRI scan showed **focal cortical dysplasia** involving the left rolandic region (from Guerrini R and Pisano T; Pal *et al*. [2016]).
Figure 4.13. A 10-year-old boy with typical rolandic seizures developing atonic seizures and **ESES**. The green arrow marks the time when his head drops to the right and backwards.
Figure 4.14. A three-year-old girl presented with nocturnal seizures consistent with **BRE** (though atypical for age at onset). At age four, she showed decline in cognition and frequent nocturnal seizures and falls (drop attacks) during the day. Brain MRI was normal. Awake video EEG shows runs of bilateral spike-and-wave discharges clinically associated with subtle head drops (blue arrow).
Figure. 4.15. Evolution of epileptiform discharges in a girl with **Panayiotopoulos syndrome**. The first sleep EEG was recorded at age five years and seven months, and showed bilateral parietal-occipital sharp-slow discharges. Discharges involved the bilateral frontopolar regions at age seven years and nine months and became almost diffuse at age eight years and 10 months. They finally localized in the right centro-temporal-parietal region at age 10 years and six months.

Figure. 4.16. Evolution of epileptiform discharges in a boy with **Panayiotopoulos syndrome**. The first sleep EEG, performed incidentally at age two years and eight months, showed sharp waves over the wider left central-temporal-posterior temporal regions. At age four years and three months, the sleep EEG showed independent and synchronous occipital and frontopolar spike discharges, which became more active three months later.
Figure. 4.17. Interictal EEG (left panel) and an electrographic EEG seizure (middle and right panels) in a six-year-old girl with **Panayiotopoulos syndrome**. The sleep EEG showed interictal left frontopolar and bilateral parietal-occipital spike-wave discharges, occurring synchronously. The seizure discharge started from and remained confined to the left frontopolar region. There were no clinical accompaniments (subclinical seizure).
Figure. 4.18. Clone-like spikes in **Panayiotopoulos syndrome**.
Figure. 4.19. Generalized spike-wave discharge during hyperventilation in a six-year-old boy with **Panayiotopoulos syndrome**. Note the similarities to the generalized discharges in occipital epilepsy of Gastaut and benign rolandic epilepsy and the differences with the robust generalized spike-wave discharges in childhood absence epilepsy (*see relevant chapters*).
Figure. 4.20. Video-EEG recorded for a three-year-old girl with **Panayiotopoulos syndrome** two days after an episode of non-convulsive autonomic status epilepticus. She suddenly became pale and started vomiting. Several minutes later, she collapsed and became unresponsive, and subsequently eyes deviated to the left with left limb jerking. The seizure lasted more than 30 minutes and resulted in admission to the paediatric intensive care unit. At the time of this recording, the girl was fully alert and cooperative. Note the postictal slowing that still persists over the right posterior quadrant. An EEG three months later was normal.
Figure. 4.21. Sleep EEG of the girl of *figure 4.19*, now four years old. Her seizures continued and she could describe a warning of a headache. She would then become floppy and unresponsive for about 10 minutes. Note the typical high-voltage spike-wave complexes over the parietal midline that occurred only during sleep.
Figure 4.22. Occipital paroxysms during wakefulness while eyes are closed.
Figure 4.23. Occipital spikes/sharp waves during sleep in an eight-year-old boy with **occipital epilepsy of Gastaut type**.
Figure 4.24. Effect of eyes closed and open on occipital paroxysms in routine EEG recording. Upper trace: high-amplitude, continuous occipital sharp and slow wave complexes (occipital paroxysms) occur immediately after closing of the eyes and last for as long as the eyes remain closed. The EEG normalises immediately after opening of the eyes and for as long as the eyes are open with visual fixation (the child is looking at an object). Lower trace: effect of the elimination of central vision and fixation on occipital paroxysms in a well-lit room. Here, this is achieved by +10 spherical lenses, although underwater goggles covered with semi-transparent tape could also be used.
Figure 4.25. Generalized spike-wave discharge in a child with **Occipital Epilepsy-Gastaut type**. Identical discharges also occur in BRE and PS (*see relevant chapters*). Compare these GSWD with the typical 3-Hz GSWD of IGE (*see chapter on CAE*).
Figure 4.26. GSWD in the child of *figure 4.24* during hyperventilation. Note the longer duration and also that the child made a mistake in breath counting (marked by the technologist with the red line at the end of the discharge).
Figure 4.27. Ictal discharge occurs over both occipital regions (black arrow) nearly simultaneously with the first clinical events (white arrow) which consist of blurring of vision. The seizure also consisted of forced eye-lid closures and lasted for less than a minute.
Figure 4.28. A two-year-old boy presented with a second afebrile generalized tonic-clonic seizure. A sleep video-EEG at that time showed normal background during drowsiness and sleep (A) and myoclonic jerks associated with generalized spike-wave discharges during drowsiness and light sleep (B).
Figure 4.29. (A) A three-year-old child with prominent centro-parietal theta rhythms presented with febrile seizures and later developed myoclonic and atonic seizures. (B) Another example of central theta slowing.
Figure 4.30. A three-year-old child with **epilepsy with myoclonic-atonic seizures**. Note that the EEG background on this occasion is slow with diffuse theta-delta.
Figure 4.31. A seven-year-old with **epilepsy with myoclonic-atonic seizures**. Interictal EEG during wakefulness shows bilateral bursts of polyspikes at times with a left parasagittal emphasis.
Figure 4.32. A five-year-old boy presented with **generalized clonic seizures during sleep**. Interictal sleep EEG shows brief generalised bursts of polyspike-wave discharges at times associated with mycolonic jerks.
Figure 4.33. A girl presenting with sudden falls at the age of 18 months, causing minor injuries. She then developed myoclonic and generalized tonic-clonic seizures, but became seizure-free at the age of three years following treatment with sodium valproate. Upper trace: normal physiological rhythms during sleep with

low-voltage focal spikes over the superior frontal areas (F4, Fz and F3). Lower trace: brief bursts of generalized spike/polyspike-and-wave discharges during sleep.
Figure 4.34. Myoclonic extensor-type jerk in an 18-month-old child with drop attacks. Arrow points to the bilateral massive axial myoclonus with extension and elevation of arms.
Figure 4.35. Myoclonic-atonic seizure. Note initial myoclonic jerk (first arrow) preceded by the burst of generalised discharges, followed by the atonic drop associated with the electroclinical silent period with loss of EMG signal from the deltoids (second arrow).
Figure 4.36. Atonic seizures; note the sudden loss of EMG signal (arrow) with the associated atonic drop.
Figure 4.37. This two-year-old girl is sitting, playing with a toy, when she had what appeared to be a sudden jerk followed by an atonic drop forwards (her head hit the toy on her lap). Note the EMG silent period (arrow). There is no preceding EMG potential to verify a myoclonic component and therefore the seizure appears to be atonic (negative epileptic myoclonus), rather than myoclonic-atonic.
Figure 4.38. EEG-EMG polygraphy showing a long **clonic seizure**.
Figure 4.39. Generalised clonic seizure in a three-year-old child with EMAS. Note that as the seizure progresses there is marked increase in the frequency of the clonic movements (arrow) resulting in a "vibratory" appearance. The frequency of the clonic movements diminishes towards seizure offset.
Figure 4.40. Generalised tonic-clonic seizure. Note the initial myoclonic component (red arrow) at the onset of the tonic phase (green arrow). This myoclonic-tonic combination is also known as "myo-tonic" (see also section on tonic seizures below). The clonic phase (blue arrow) of the seizure ensues.
Figure 4.41. Atypical absence with 2-2.5 anteriorly dominant generalised spike-and-wave discharges in a four-year-old boy with refractory **epilepsy with myoclonic-atonic seizures**. During the discharge, he appears still and stops drinking from his bottle.
Figure 4.42. A two-year-old boy presented with initially febrile then afebrile seizures, and went on to have **atypical absences** and **myoclonic-atonic seizures**. This EEG showed sequential long runs of diffuse slow spike-and-wave discharges that were separated from one another by only a few seconds. During this period, the boy appeared unresponsive and at times had head drops.
Figure 4.43. Non-convulsive status epilepticus (NCSE). This 10-year-old girl presented at the age of six months with generalised tonic-clonic seizures and myoclonic and atonic seizures. She has remained refractory to treatment and had several episodes of NCSE. During this episode, she was intermittently vacant and confused, and exhibited continuous erratic upper limb and facial myoclonias.
Figure 4.44. Myo-tonic seizure in light sleep. Note the initial brief EMG potential (arrow) that correlates with the generalized spike-wave discharge, followed by the prolonged bilateral tonic contraction that is associated with the diffuse attenuation with superimposed low-voltage fast-recruiting rhythms.
Figure 4.45. Brief bilateral **myo-tonic seizure** associated with a 5-6-second burst of high-voltage generalised polyspikes. Note the initial myoclonic component (arrow).
Figure 4.46. In this **generalised tonic seizure**, no initial myoclonic component is detectable at the onset of the tonic phase (green arrow). Also note the diffuse rapid spike-waves that associate with very rapid tonic movements (blue arrow), which are of high amplitude and account for the "vibratory" clinical presentation. The associated rapid spiking is different from the diffuse low-voltage fast rhythms of the classic tonic seizure in LGS. This child had unfavourable outcome.
Figure 4.47. (A) Spontaneous typical brief generalized spike-wave discharge accompanied by fleeting staring in a two-year-old girl with **absences** since the age of seven months and a single generalized tonic-clonic seizure at the age of 18 months. Her mother has well controlled IGE/GGE with absences and photosensitivity. Note an isolated left posterior temporal "non-localizing" focal spike-wave discharge (green arrow) and a posterior onset for the generalized paroxysm. (B) Similar generalized spike-wave discharge elicited by IPS at 18 Hz; the effect was consistent.
Figure 4.48. Routine video-EEG of a 3.5-year-old boy with diagnosed **Glut1 deficiency** and **absences** since the age of two years. (A) Brief spontaneous absence; (B, C) absences during hyperventilation. He is now 10 years old and on ketogenic diet and VPA 400 mg bd; he has 5-10 absences per day. He was also diagnosed with an autism spectrum disorder.
Figure 4.49. A **typical absence** associated with sudden behavioural arrest and staring of a three-year-old girl with alpha mannosidosis diagnosed at the age of two years; the patient had daily episodes of "freezing" for a few seconds since the age of around 18 months. A video-EEG recorded several absences at age two years and three months, but these were not treated. Note the bilateral synchronous onset of an 18-second

long generalized regular 3-Hz spike-wave discharge that shows no asymmetries of fragmentations. The girl remained unresponsive throughout the seizure discharge.
Figure 4.50. Another **typical absence** of the same girl from *figure 4.49*. Clinical semiology was the same as in *figure 4.49*, but the associated generalized 3-Hz spike-wave discharge shows a left-sided electrographic onset. The rest of the EEG features are the same, *i.e.* regular frequency and frontal emphasis without asymmetries or fragmentations. Compare these discharges with the examples in the chapter on childhood absence epilepsy.
Figure 4.51. Sleep EEG of the girl from *figures 4.49 and 4.50*. Note the left occipital spikes (A), left frontal spikes (grey arrows in B), and right frontal spikes (green arrow in C).
Figure 4.52. Sleep EEG of a three-year-old boy with **staring attacks** since the age of 19 months. (A) Four-second generalized 3-Hz spike-wave discharge during Stage 1 of sleep; note the electrographic arousal that follows, manifested by the diffuse appearance of theta rhythms. (B) single generalized 3-Hz spike-wave discharge with bilateral occipital emphasis during sleep Stage 2; note the preceding non-localising focal spikes over the right occipital (grey arrows) and left occipital (black arrows) regions. (C) Diffuse spike-wave discharges in Stage 3 sleep; note the brevity and irregular/fragmented morphology of the spike-wave discharges and the left occipital spikes that continue to occur. Compare with the sleep EEG findings in childhood absence epilepsy.
Figure 4.53. Sleep EEG of the girl from *figure 4.47*, now aged three. Note the degradation of the generalized spike-wave discharges during Stage 3 sleep occurring on the left (A), bilaterally but not entirely synchronously (B), and right side (C). Also, note the left anterior temporal (C, green arrow) and right anterior temporal non-localizing spike wave (D, green arrow).
Figure 4.54. Bursts of high-voltage, frontally dominant sharp theta or fast spike-wave discharges during sleep in the girl from *figures 4.49 and 4.50*. Note the variable side emphasis: left (A), bilateral with mild left-sided emphasis (B), bilateral with mild right-sided emphasis (C), and right-sided (D).
Figure 4.55. Video-EEG of the boy from *figure 4.52*. TA during hyperventilation: the boy stops blowing, drops the windmill, and stares with eye blinking. Note the right temporal onset of the ictal 3-Hz generalized spike-wave discharge which continues on that side, effectively "linking" two otherwise **typical absences**.
Figure 4.56. Video-EEG of the boy from *figure 4.55* two years later (five years old), showing a **long typical absence** during hyperventilation. In this recording, he is still off antiepileptic medication as his parents had declined treatment. He is now 13 years old and on LTG and TPM, and is still having absences and infrequent GTCS. Previous treatment with LEV and ethosuximide was unsuccessful.
Figure 4.57. Spontaneous **brief 3-Hz generalized spike-wave** discharge during drowsiness in the girl from *figure 4.47*, now aged three. Note the right frontotemporal lead-in.
Figure 4.58. Interictal EEG during wakefulness of a five-year-old boy with **Lennox-Gastaut syndrome**. Note the high-amplitude diffuse, synchronous slow spike-waves (SSW) at <2.5 Hz with maximal amplitude over the frontal areas. In the lower part, density spectral array (DSA) (0-30 Hz) shows activity from FP2 and FP1 electrodes over nine hours of recording. Each red vertical line corresponds to a sequence of SSW lasting for a few minutes; these sequences are sub-continuous during wakefulness.
Figure 4.59. Interictal EEG of the same boy as in *figure 4.58* during NREM sleep, showing bursts of high-amplitude generalized polyspikes and polyspike-waves.
Figure 4.60. Interictal/ictal EEG of an eight-year-old girl with **Lennox-Gastaut syndrome** during NREM sleep, showing fast bilateral rhythms/spikes (10-20-Hz) predominating in the anterior areas and on the vertex, lasting 2-3 seconds (paroxysmal fast activity). These could be subclinical (A) or, when of longer duration, accompanied by slight increase of axial muscle tone (B, C), detected by EMG electrodes placed on both deltoids; these are considered as subtle tonic seizures.
Figure 4.61. Tonic seizure during NREM sleep of the boy of *figures 4.58 and 4.59*, showing fast bilateral rhythms/spikes at 10-20 Hz, predominating over the anterior areas and the vertex, lasting for 9 seconds (concomitant to the tonic contraction of both deltoids recorded on EMG1 and EMG2 electrodes), followed by diffuse SSW. In the density spectral array (DSA) (0-30 Hz) from FP2 and FP1 electrodes, the black arrow shows the beginning of the tonic seizure at the onset of the NREM sleep. Each red vertical line corresponds to a sequence of SSW and polyspike-waves during NREM sleep.
Figure 4.62. Atypical absence of a 10-year-old girl with **Lennox-Gastaut syndrome**. The seizure lasted for one minute and is presented in three EEG sections. Note the diffuse SSW discharge at 2-2.5 Hz that predominates over the frontal areas, which is more or less symmetric and shows gradual onset and offset.
Figure. 4.63. Interictal generalized spike-wave discharges during wakefulness (A) and slow sleep (B, C) in a girl of four years and three months old, with only a two-day history of frequent vacant spells. Parents described that she would become vacant and unresponsive with jerking of the arms and sometimes head for 15-20 seconds,

every 30 minutes to an hour. A paternal cousin had similar episodes as a child. Note the difference in the amplitude of the two types of discharge in (B) and (C). The gain is the same in all three panels.

Figure. 4.64. Long **generalized spike-wave discharge** of the girl of *figure 4.6*3 during slow sleep: note the fragmentations in the discharge and the absence of myoclonus on the EMG channels. Apart from intermittent very mild eyelid fluttering, no other clinical manifestations were noticeable on the video. The girl continued sleeping without any evidence of post-discharge electrographic arousal.

Figure 4.65. Myoclonic absence during slow sleep (same EEG as that for the girl in *figures 4.63 and 4.64*): note the bilateral synchronous onset of the rhythmic 3-Hz generalized spike-wave discharge that (in contrast to that in *figure 4.64*) appears robust and without fragmentation or distortion of rhythmicity. Also, note the associated rhythmic (and symmetric on video) myoclonic jerks of both upper limbs at the same frequency as that of the spike-wave discharge, as recorded by EMG electrodes placed over the deltoids. As in *figure 4.64*, this myoclonic absence did not cause electrographic arousal.

Figure 4.66. Myoclonic absence during hyperventilation: note the left frontal onset (arrow) and the post-discharge high-voltage bilateral frontal delta activity.

Figure 4.67. Myoclonic absence during wakefulness (the same girl in *figures 4.63-4.66*): note the consistent bilateral rhythmic myoclonias on the EMG channels and the high-voltage bursts of delta after the offset of the ictal discharge, followed by diffuse faster delta activity at 3-4 Hz.

Figure 4.68. EEG-EMG polygraphy relationships in **myoclonic absences**. (A) Slow speed recording to evidence the progressive build-up (1-3) of the spike-and-wave discharge and the appearance of myoclonus with the first downward spike positive component. Myoclonus is associated with a tonic activity of the trapezius and deltoid, and, to a lesser extent, the cervical and sternocleidomastoid muscles. (B) Detail from (A) showing the myoclonus (in red) with increasing tonic activity and decreasing inactivity (in yellow) between the myoclonias on the EMG. (C) EEG (FZ-CZ) and EMG (right wrist) at fast speed showing the constant relationship between each positive spike component and the following myoclonus. (D) Detail from (C) showing the positive (PT) spike component on the EEG and the myoclonus. Note the spike complex (100-ms duration) with its positive (downward; in green) component followed by the negative (upward) spike component; the large 300-ms slow wave (grey) follows (from Tassinari *et al*., 2010 with permission).

Figure 4.69. Extended EMG polygraphy in **myoclonic absences**. The first three spikes and wave complexes are not accompanied by myoclonias. EMG shows rhythmic myoclonus at the same frequency as the spike and wave in the deltoid, flexor, and extensor of the wrist on the right and left, associated with a build-up of tonic activity (from Tassinari *et al*. [2010] with permission).

Figure 4.70. A boy with infrequent **nocturnal seizures** at age nine with **left centro-temporal spikes** during wakefulness (A) that increase during sleep (B). He was initially diagnosed with benign rolandic epilepsy, but a year later he presented with cognitive decline. An EEG during sleep at age 10 showed SES (C).

Figure 4.71. Status Epilepticus during Sleep in a four-year-old girl with a history of nocturnal seizures manifested with drooling and choking sounds. Note the temporary disruption of the continuous spike-wave pattern due to accidental noises (arrows). She also had day-time absences (*figure 4.74*). She gradually presented language and global regression (*figure 4.78*). Brain MRI was normal.

Figure 4.72. Left panel: interictal bifrontal and diffuse, and rather symmetric, ~3-Hz spike-and-wave discharge during wakefulness, in a nine-year-old boy with **Landau-Kleffner syndrome**, manifested at the age of seven years and nine months, and focal seizures since the age of three years and six months. The LKS was considered to be resolved two years and six months after its appearance; during this period, he also had behavioural disturbances, inattentiveness, and impairment of executive functions. He is now 12 years old and still has some language problems and learning difficulties. Right panel: continuous spike-wave discharges during slow sleep showing a similar distribution to that of the interictal spike-wave discharges (spike-wave index: 70%).

Figure 4.73. This nine-year-old girl had frequent daytime seizures with speech disturbance, head drops, eyelid flickering, and facial clonus. The EEG shows near-continuous focal discharges over the right central electrode during wakefulness (A) and SES (R>L) during slow sleep (B). Brain MRI shows **right peri-sylvian polymicrogyria**.

Figure 4.74. Atypical absence during hyperventilation in the girl of *figure 4.71*. The patient stops blowing the windmill and remains unresponsive, exhibiting eyelid flickering.

Figure 4.75. Atypical absence associated with sudden head drop (arrow), hypersalivation, and changes in breathing in a seven-year-old boy with **ESES** of presumably structural aetiology. Brain MRI showed developmental malformation with bilateral, predominantly perisylvian, polymicrogyria and underdeveloped cerebellum.

Figure 4.76. Interictal EEG abnormalities during wakefulness in the boy of *figure 4.75*. Note the frequent bilateral independent multifocal (temporal, centro-temporal, and parietal) spike-wave discharges.

Figure 4.77. Status Epilepticus during Sleep in the boy from *figures 4.75 and 4.76*. A left hemispheric run of spike-and-wave discharges, approximately 10 seconds in duration, becomes diffuse and bilateral, and almost continuous from sleep onset (arrow).
Figure 4.78. Sleep EEG in the girl of *figures 4.71 and 4.74*, one year later, showing **Status Epilepticus during Sleep** during Stage 2 sleep (note the k-complexes marked by arrows and nearby spindles), recorded over the left side. At that stage, concerns about her language and cognition had already been raised (verbal IQ: 70; non-verbal IQ: 120). Long runs of left central spikes also occurred during wakefulness.
Figure 4.79. (A) Run of high-voltage left mid- to posterior temporal spike-wave discharges during wakefulness (panel) in an eight-year-old boy with significant speech delay since the age of six years; the patient had mainly nocturnal brief right-sided motor seizures with mostly retained awareness and a family history of LKS (older sister and twin brother). His mother also had seizures until her early twenties. This EEG also showed independent left frontal and right posterior temporal/parietal spikes (arrows). Treatment with VPA, and later with LEV and steroids, reduced the frequency of seizures and improved receptive language, but not motor speech; the EEG at this stage showed left pre-frontal spikes diffusing to the right frontal area, but no temporal paroxysms (B).
Figure 4.80. High-voltage left occipital (panel), left central-temporal / parietal (green arrow), right mid -to posterior temporal (grey arrow), and right frontal (black arrow) spike-wave discharges in the twin brother of patient from *figure 4.79*. The patient also presented with global language regression and mainly nocturnal seizures, but showed better response to treatment with steroids; his language function improved and his follow-up EEG normalized. A sleep recording was impossible to obtain for any of the siblings at any stage, despite multiple attempts in the EEG laboratory. Testing for continuous spike-wave during sleep (SES) would only be possible by examining overnight sleep EEG (*see advanced EEG recording protocol in the ESES chapter*).
Figure 4.81. Right centro-temporal-parietal spikes in a 12-year-old boy with **Landau-Kleffner syndrome** during wakefulness (A), becoming more frequent during slow sleep (B).
Figure 4.82. Left posterior temporal-parietal paroxysms and independent, less frequent, right posterior temporal-parietal spikes during wakefulness (A) in a 10-year-old boy with **epileptic aphasia**, associated with nocturnal rolandic-type seizures and atypical absences. Note the continuous occurrence of the left posterior temporal-parietal discharges during slow sleep (B). Both aphasia and seizures improved after treatment with prednisolone and valproic acid.
Figure 4.83. Activation of continuous spike-wave activity over the left central and bilateral mid-posterior temporal areas during sleep (right panel) in a nine-year-old boy with **Landau-Kleffner syndrome**. Note the paucity of epileptic discharges during wakefulness (left panel).
Figure 4.84. First sleep EEG of a six-year-old boy who presented with **subacute behavioural speech disturbance**; note the frequent spike-wave discharges over the right mid- to posterior temporal area, diffusing to the central-parietal region. Background activity during wakefulness was normal. His speech showed some improvement after treatment with steroids and his follow-up EEG showed less frequent spikes. No overt epileptic seizures were reported by his family or recorded in any of his two EEGs.

FIGURES _ Part 2

INTRODUCTORY SECTION: MATURATIONAL ISSUES

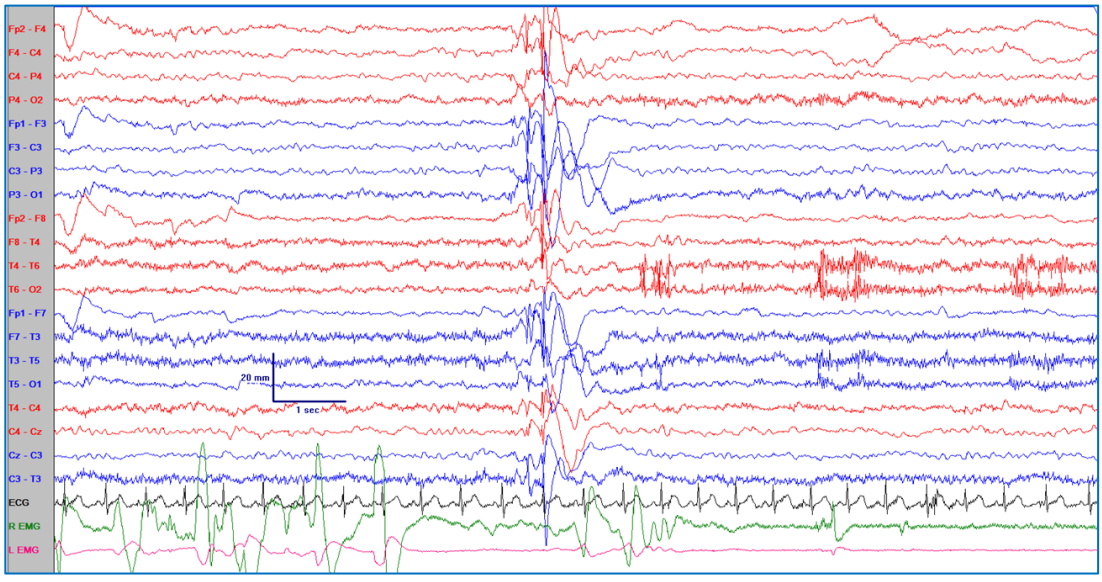


Figure 1.01. Video-EEG monitoring during FDG uptake period of a four-year-old boy with previously normal development, who started having nocturnal seizures associated with generalized stiffening at the age of three years. Brain MRI showed a single focal structural change at the junction of the superior and middle right frontal gyrus, consistent with **cortical dysplasia**. The FDG PET scan showed right frontal hypometabolism extending to the bilateral anterior temporal areas, although to a lesser degree. **Note the normal background and the brief generalised spike-wave discharge with slight accentuation over the left hemisphere that, *per se*, would suggest GGE/IGE rather than focal epilepsy**.

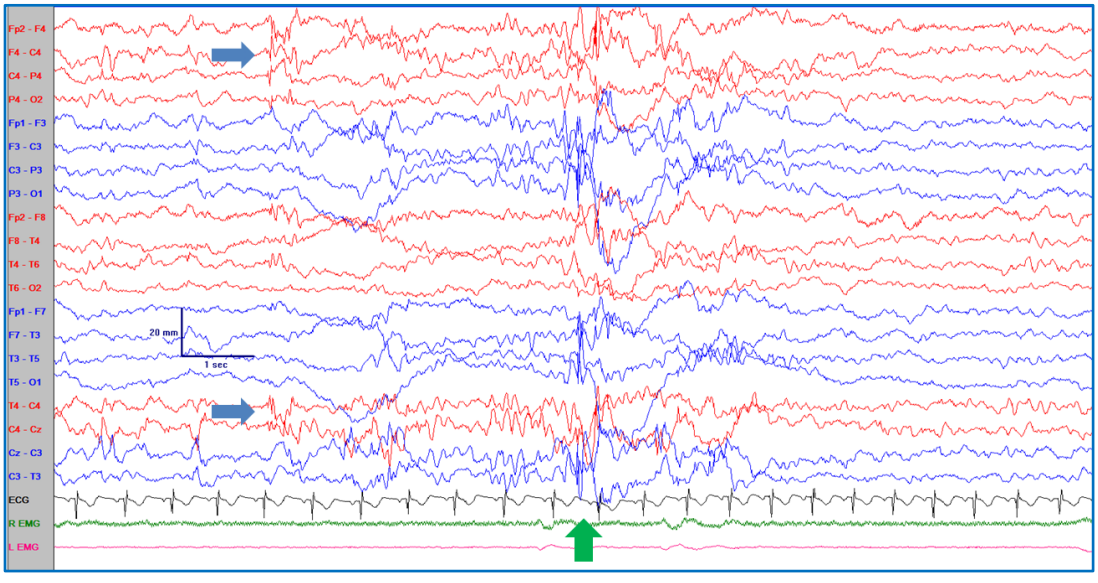


Figure 1.02. Same recording as in *figure 1.01*, during sleep. Note the focal spikes over the right frontotemporal area (blue arrows) and the bilateral diffuse discharge (green arrow), which now has left-sided emphasis. This EEG also showed independent left frontal spikes, as well as other generalized discharges with fluctuating side emphasis. Sleep architecture was normal.

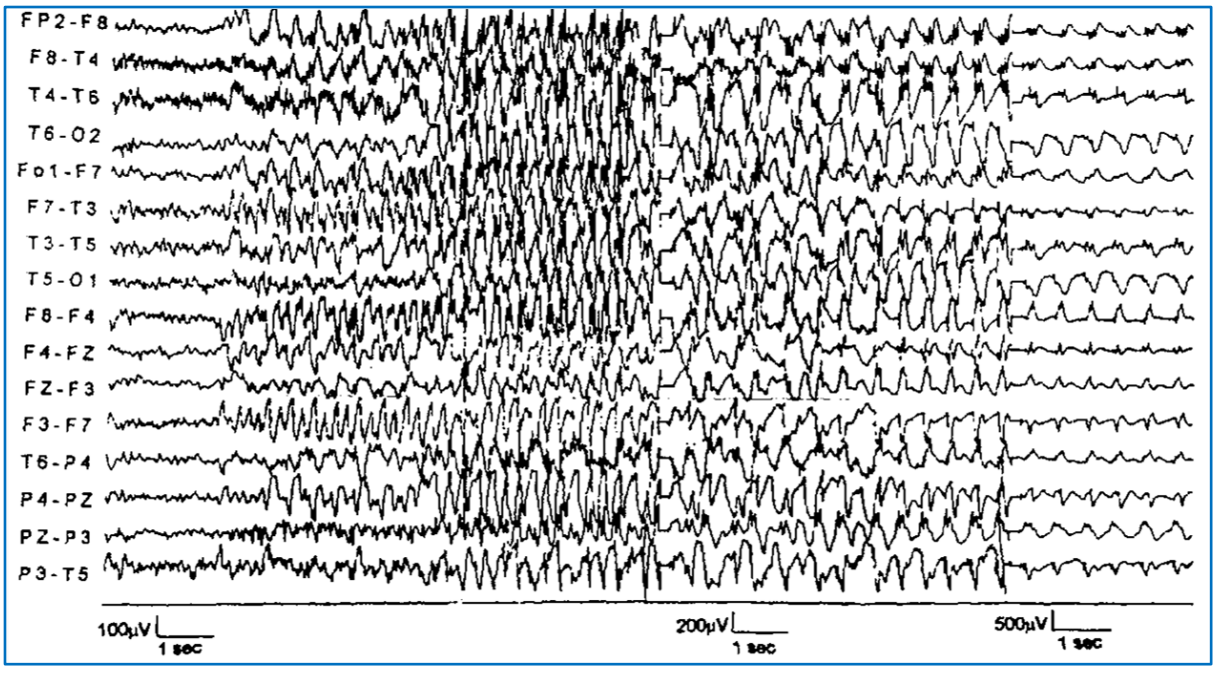


Figure 1.03. Long, 23sec GSWD of bilateral and synchronous onset, associated with motionless staring during a positron emission tomography (PET) scan. There are no "triggering" focal ED leading to the GSWD (the criteria of spatial and temporal constrains), but SBS can be assumed from the faster activities over the left temporal-parietal areas compared to the right in the first 4 sec of the GSWD. The PET scan revealed left frontal hypometabolism.

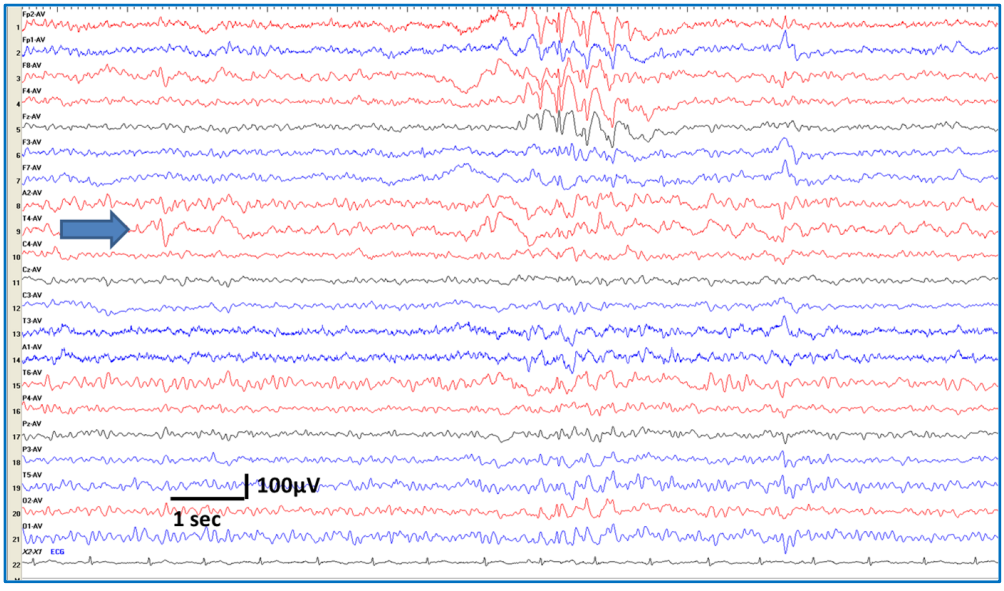


Figure 1.04. Focal regular 3Hz spike-wave discharge over the right frontal area in a child with a history of "blank spells" and left focal motor seizures. Note the regional background disturbance which consists of irregular slow rhythms and sharp waves (arrow) maximal over the right central area. Brain MRI showed a large **subependymal heterotopia** on the right associated with cortical thickening.

NEONATAL SEIZURES & SYNDROMES

SECTION 2.2: NEONATAL EPILEPTIC ENCEPHALOPATHIES

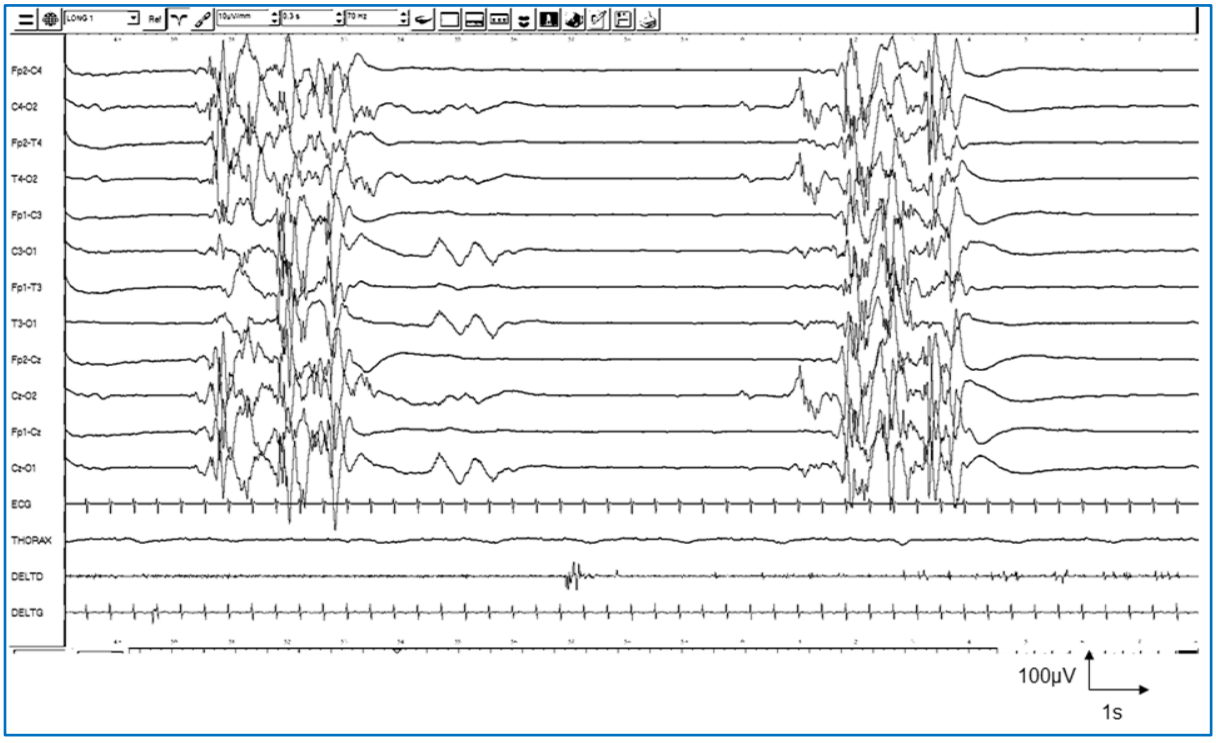


Figure 2.01. Suppression-Burst pattern in a six-day-old new-born: bursts of high-voltage asynchronous delta and theta waves, mixed with high-amplitude spikes and polyspikes, lasting around two seconds and alternating with inter-burst intervals of low-voltage activity or complete suppression lasting around seven seconds.

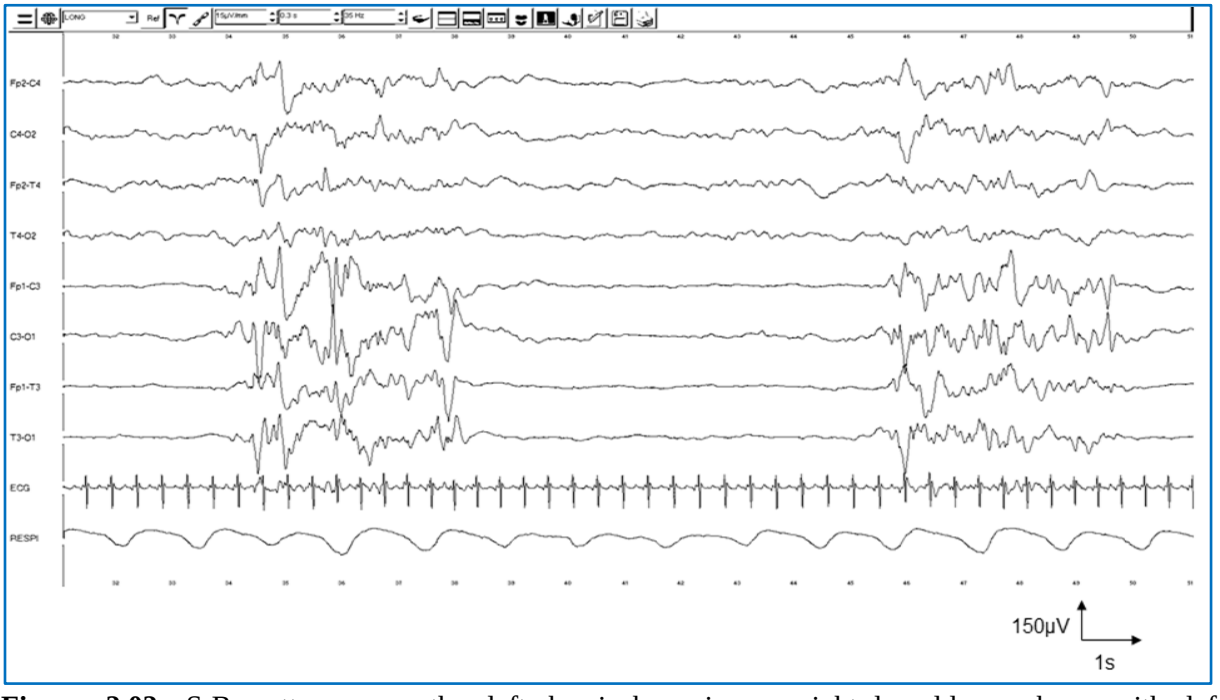
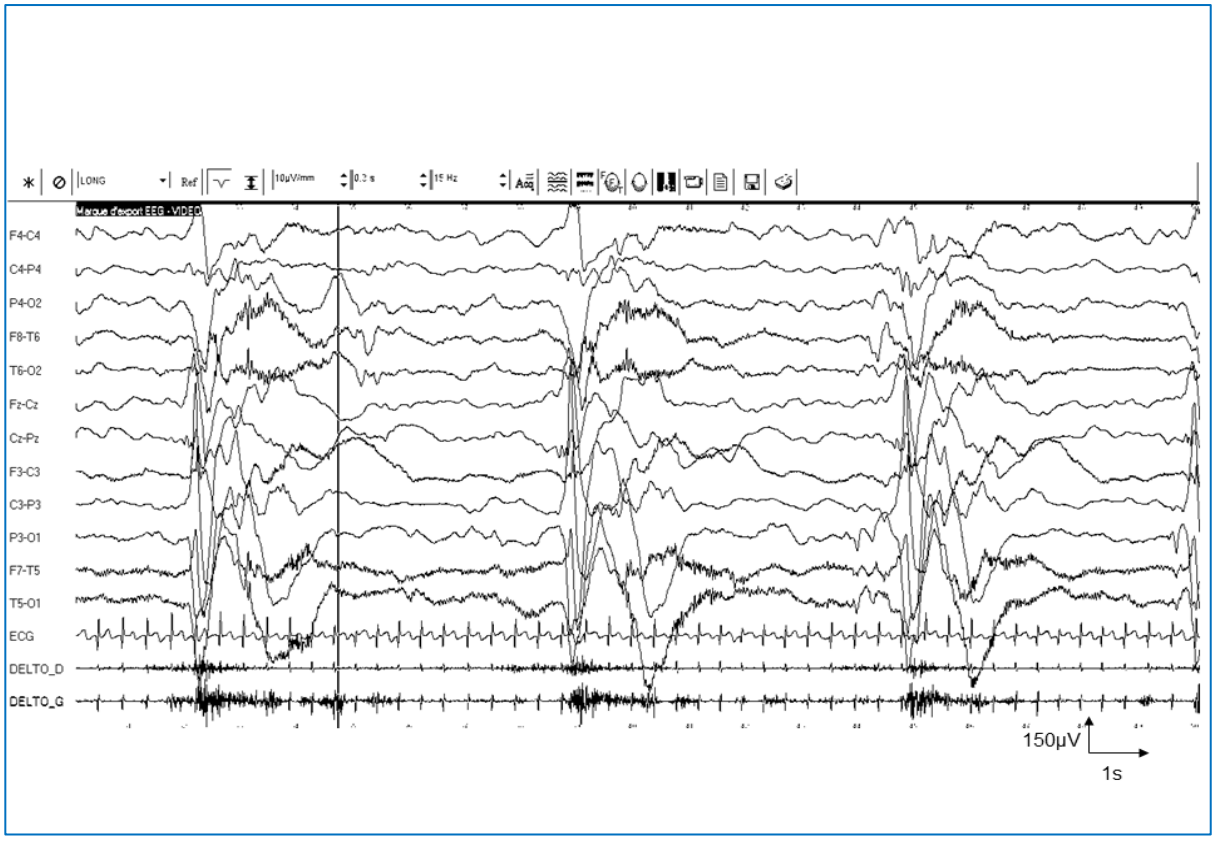


Figure 2.02. S-B pattern over the left hemisphere in an eight-day-old new-born with left **hemimegalencephly**.



Figures. 2.03 A, B. **Ohtahara Syndrome with S-B pattern**. Note the asymmetric tonic seizures that are concomitant with the bursts, as recorded by bilateral deltoid EMG leads.

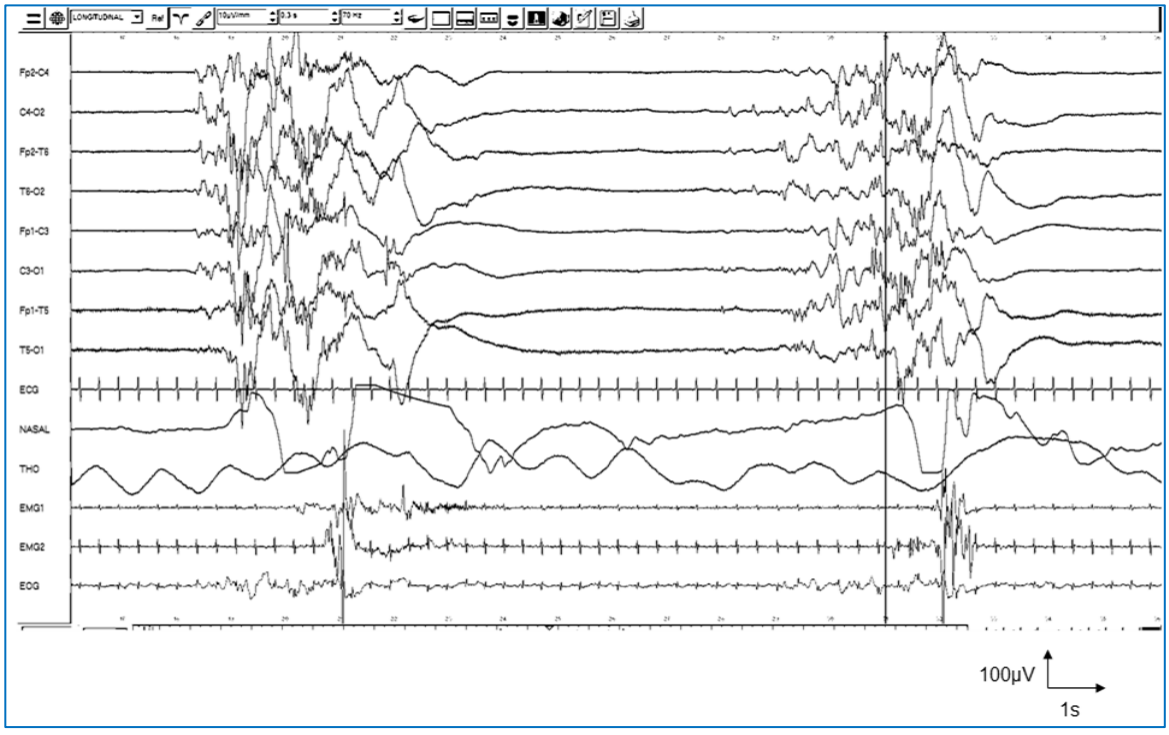


Figure. 2.04. Myoclonus of both upper limbs recorded from deltoid EMG during the bursts of spikes and polyspikes within the bursts of the S-B pattern in a six-day-old new-born with **EME**.

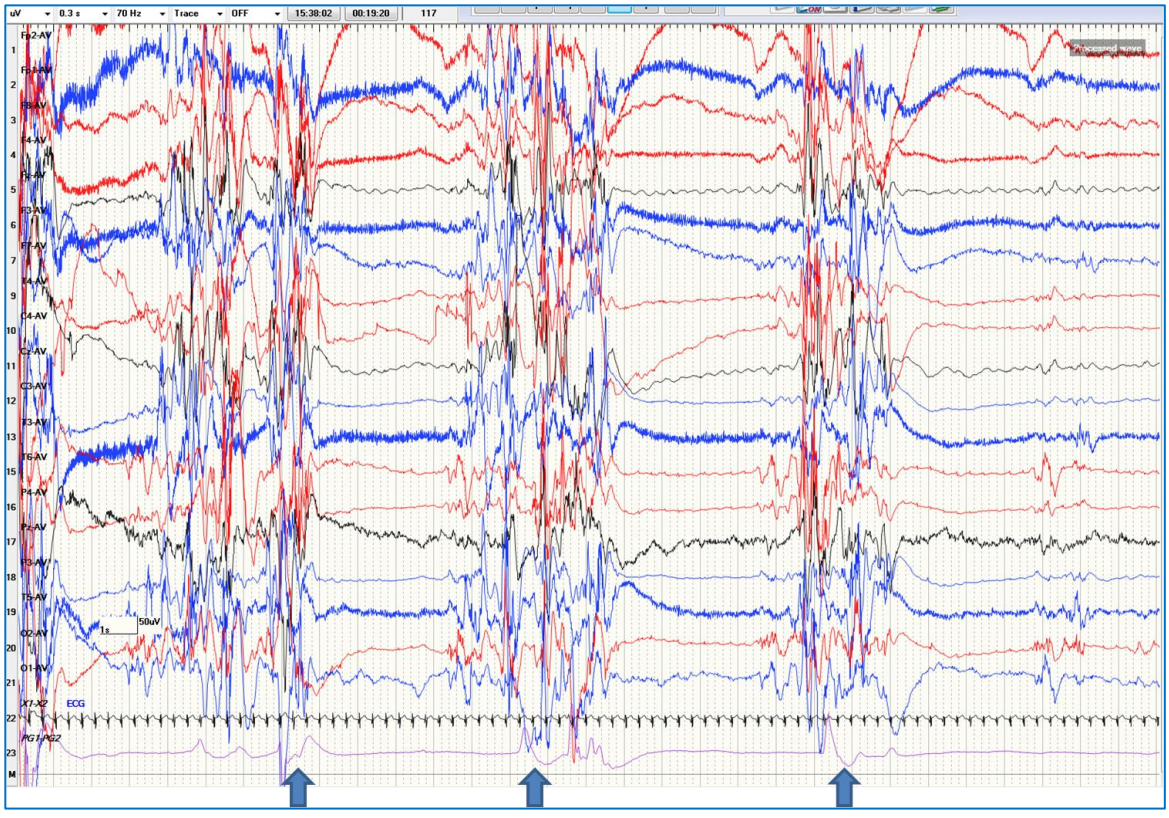


Figure. 2.05. **Early Myoclonic Encephalopathy with S-B**. Note some erratic limb movements concomitant with the bursts that are difficult to classify. This neonate also had jerks involving the face.

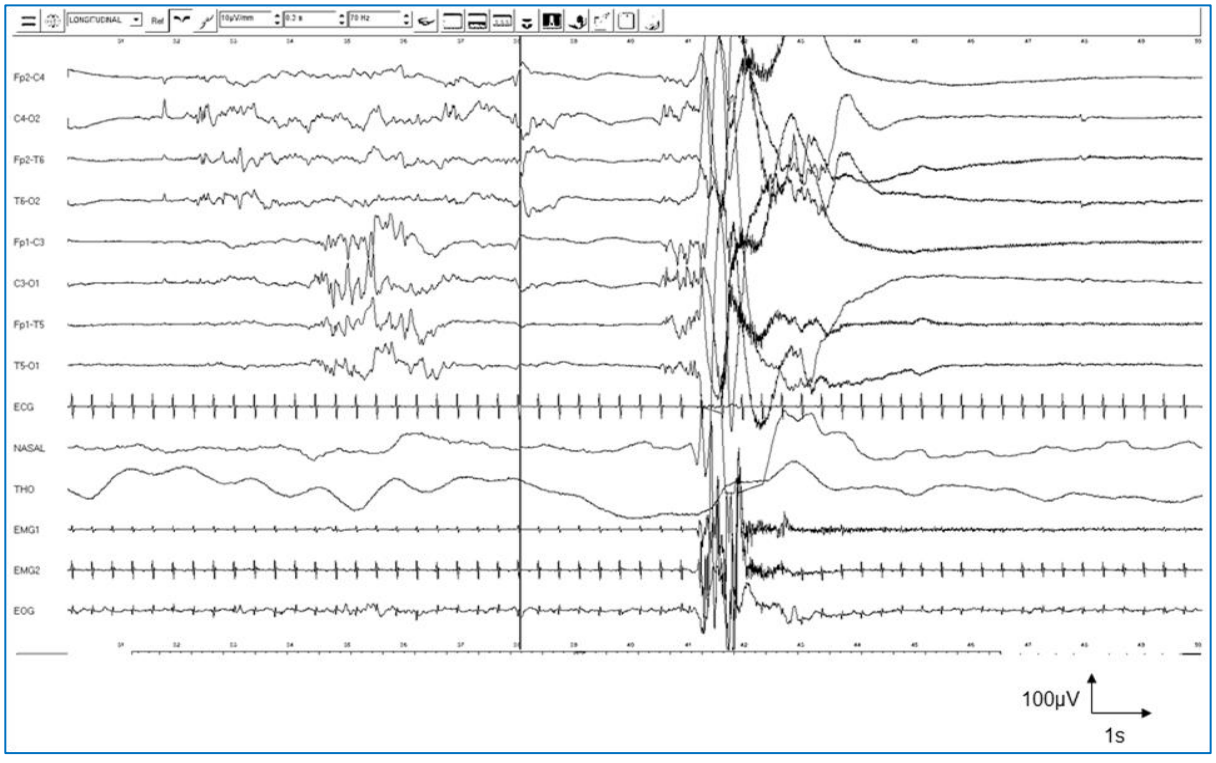
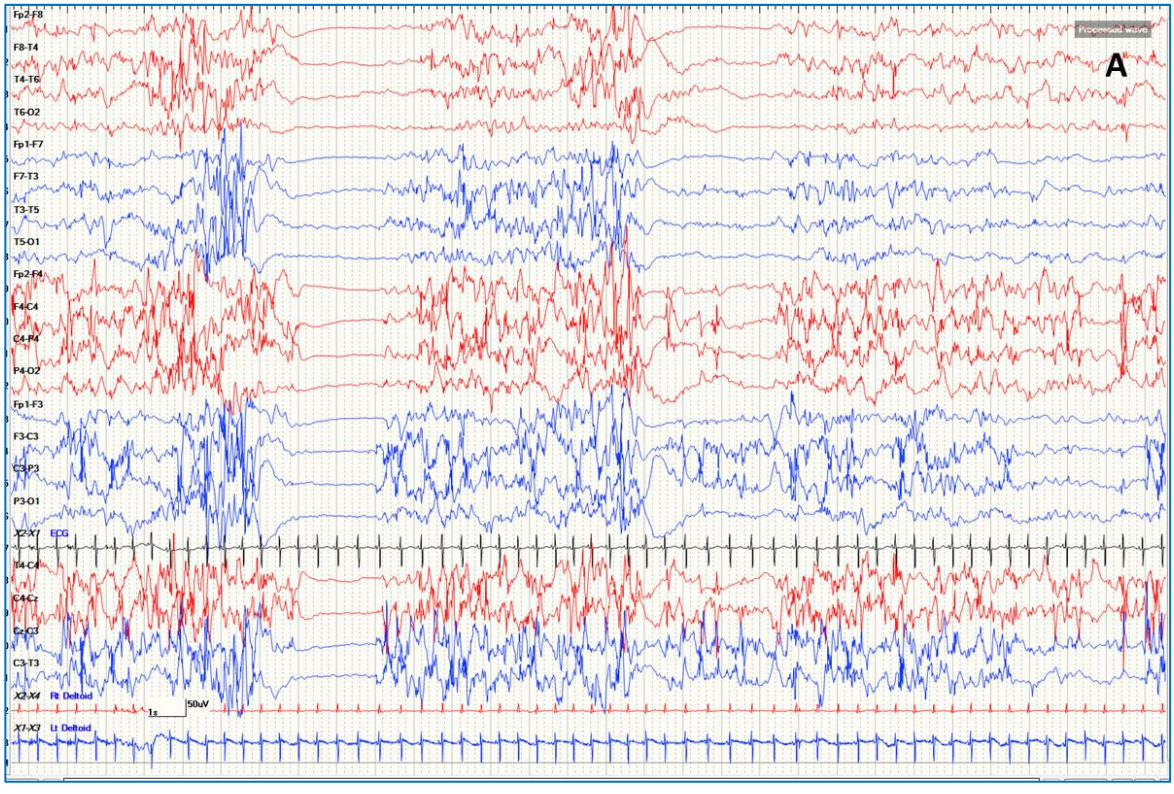


Figure. 2.06. EMG activity of both deltoids associated with bursts of activity (high-amplitude spikes, polyspikes, waves, and sharp waves) in a five-day-old new-born.



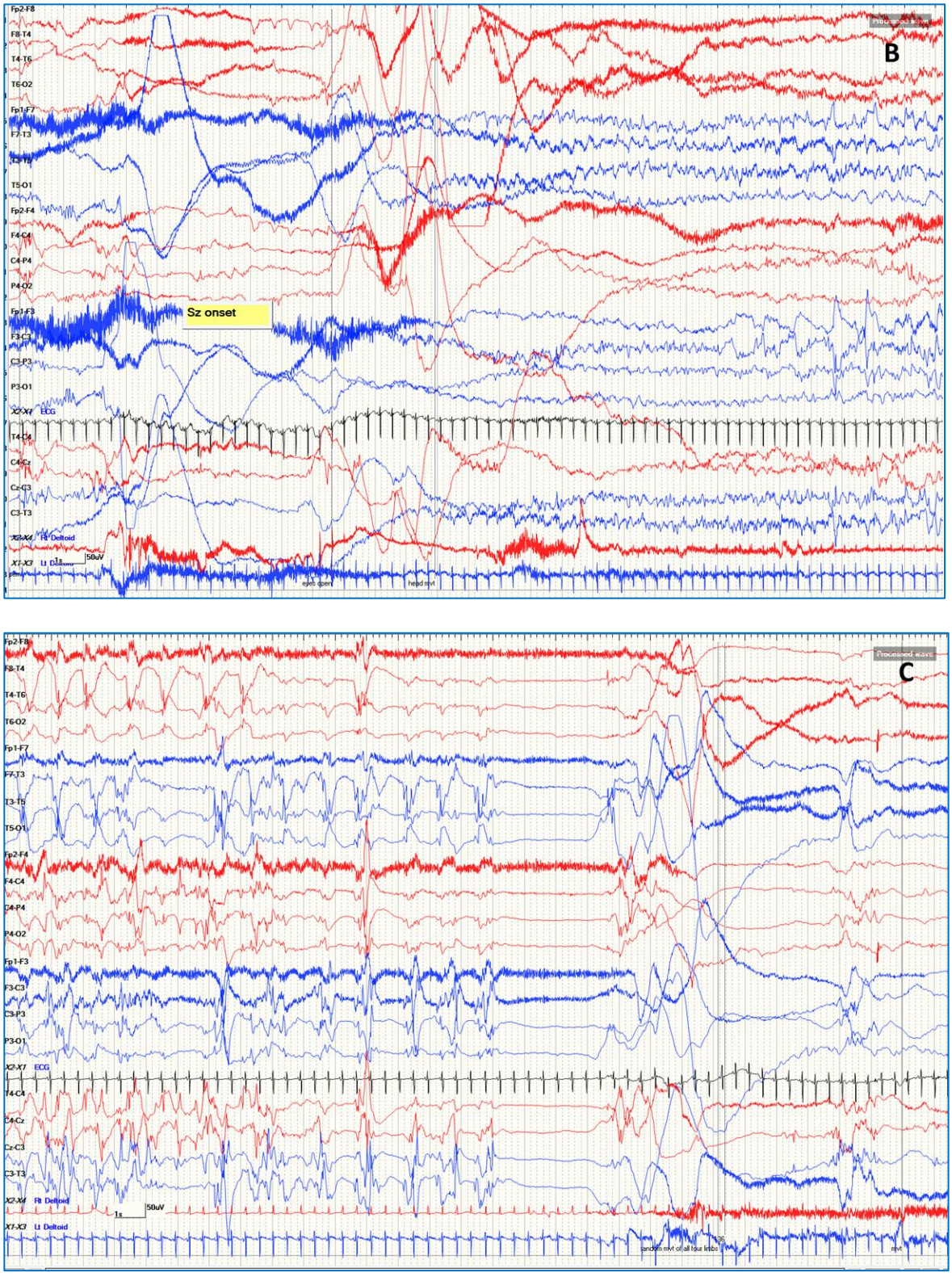


Figure.2.07. A five-day-old neonate with **Ohtahara Syndrome** and supression burst.
(**A**) A focal motor seizure was recorded with deviation of the eyes to the right, right arm jerks, and head deviation to the right. Ictal EEG onset (**B**) shows a generalied attenuation followed by a left hemisphere ictal pattern with bilateral evolution and offset (**C**).

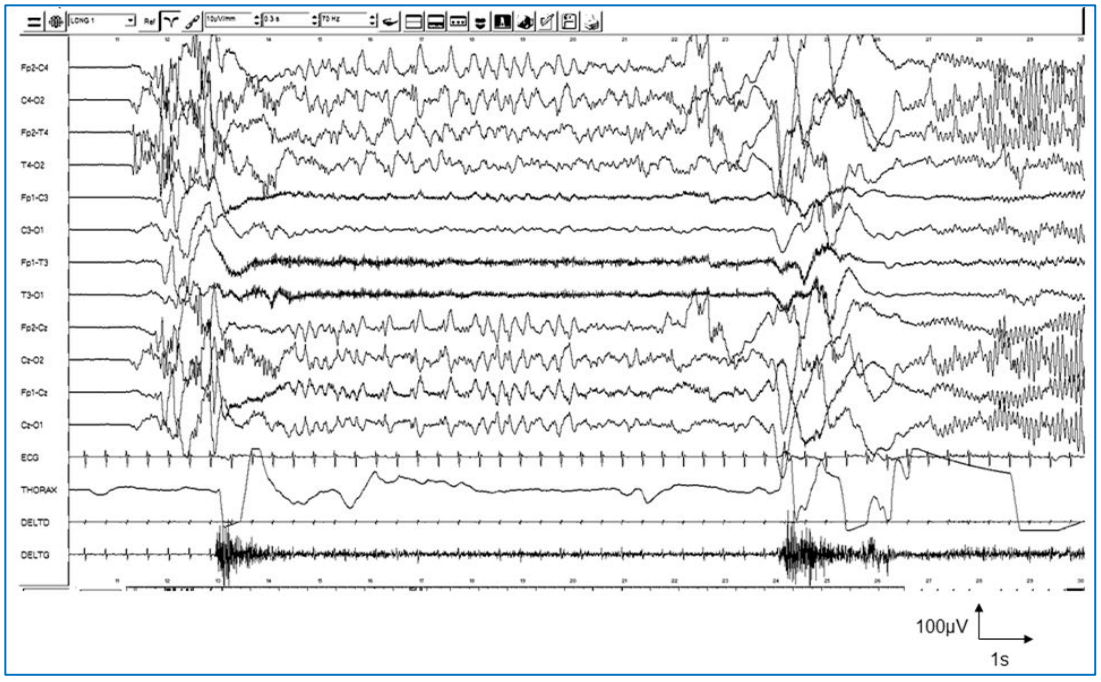


Figure. 2.08. Series of tonic spasms followed by focal seizures in an eight-day-old new-born with **Ohtahara Syndrome**.

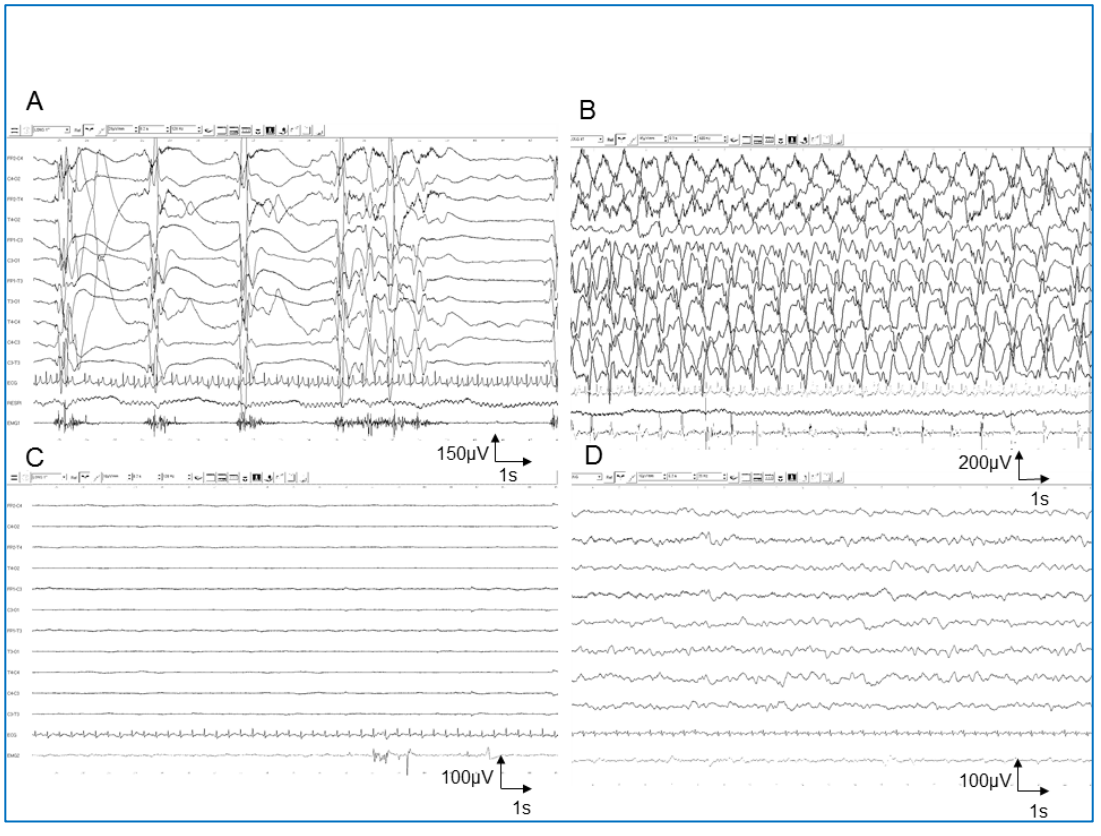


Figure. 2.09. Pyridoxine-dependent epilepsy in a 14-week-old boy: status epilepticus with epileptic spasms, S-B pattern with bursts of high-amplitude spikes, polyspikes, and slow waves concomitant with contraction of deltoids (**A**); clonic status epilepticus with successive myoclonic jerks associated with rhythmic slow spike-waves (**B**); EEG a few minutes after intravenous injection of pyridoxine; note the disappearance of the spike and the diffuse flattening of the tracing (**C**); and EEG during wakefulness after a few days of treatment with oral pyridoxine showing normal background activity (**D**).

SECTION 2.3: BENIGN FAMILIAL NEONATAL EPILEPSY (BNFE)

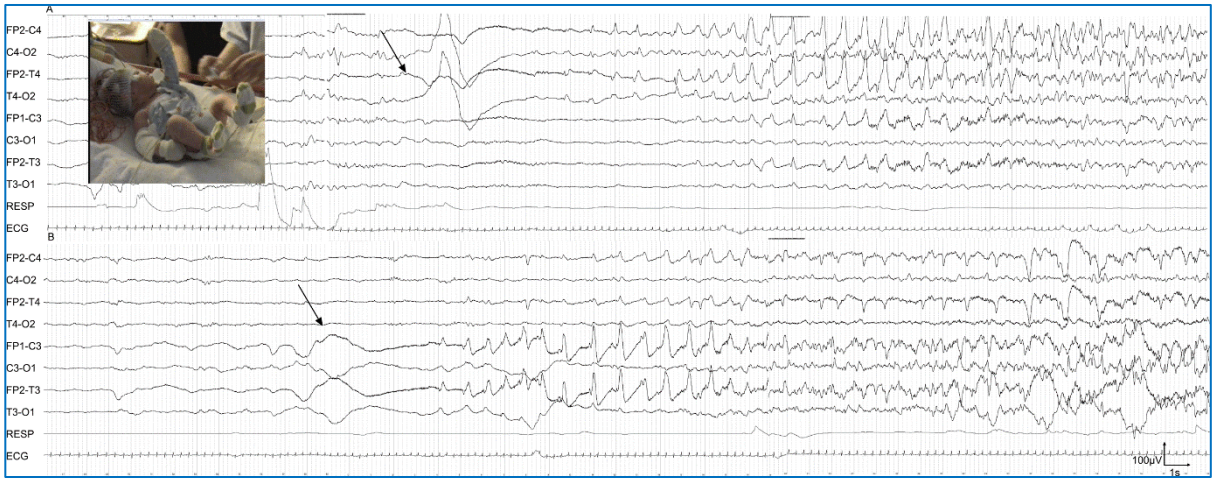


Figure 2.10. Two consecutive seizures recorded in a three-day-old neonate with **BNFE**, born at full-term. (**A**) diffuse bilateral flattening of the background activity predominating on the right side (arrow) that lasts for 10 seconds and corresponds to the tonic extension of the left arm and deviation of the head to the left (video snapshot). The flattening is followed by rhythmic slow spike and wave activity over the right frontal area that increases in amplitude while diffusing to the left frontal area. (**B**) Similar ictal EEG pattern on the left side.

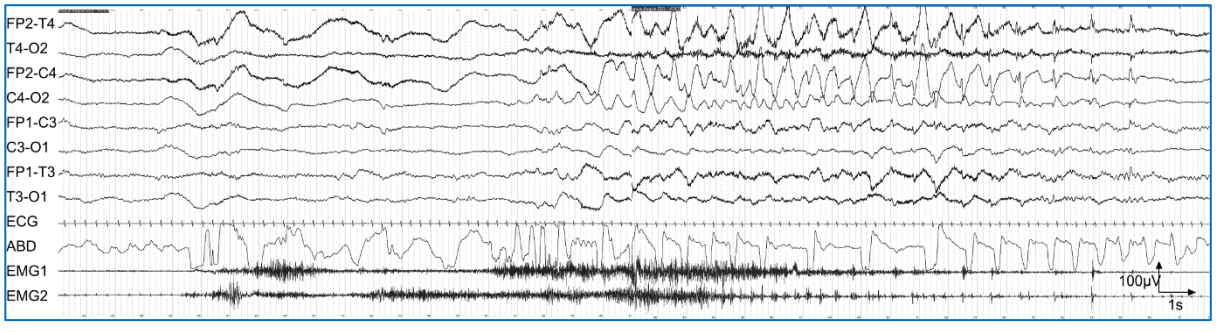


Figure 2.11. Ictal EEG in a neonate with **BNFE**, with polygraphic EMG recording from both deltoids showing tonic contraction of both upper limbs.

SECTION 2.4: FOCAL STRUCTURAL EPILEPSY OF NEONATAL ONSET

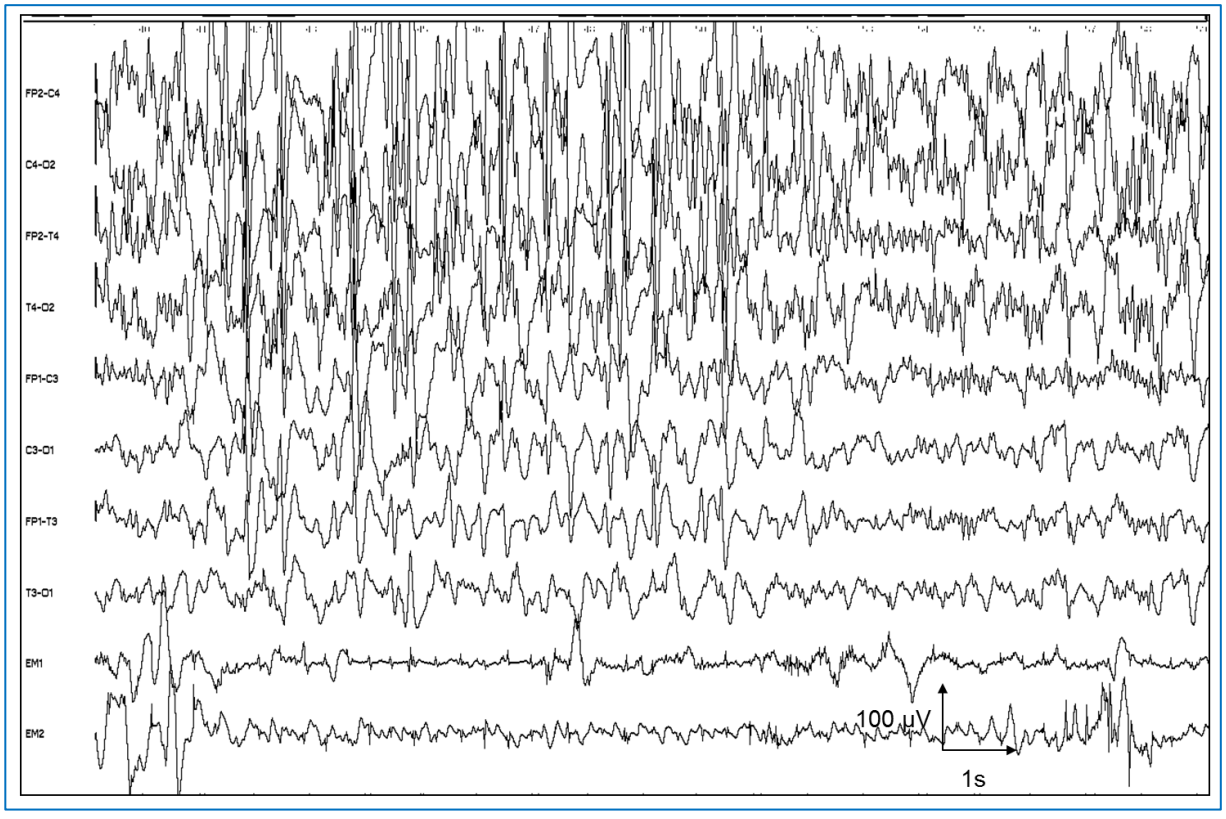


Figure 2.12. Interictal EEG during wakefulness in a two-day-old new-born with right **hemimegalencephaly** (*see MRI in figure 2.19*). Note the inter-hemispheric asymmetry with continuous high-amplitude spikes, polyspikes, and sharp waves that diffuse to the left hemisphere. There are no discernible physiological rhythms on the right (EMG1: right deltoid; EMG2: left deltoid).

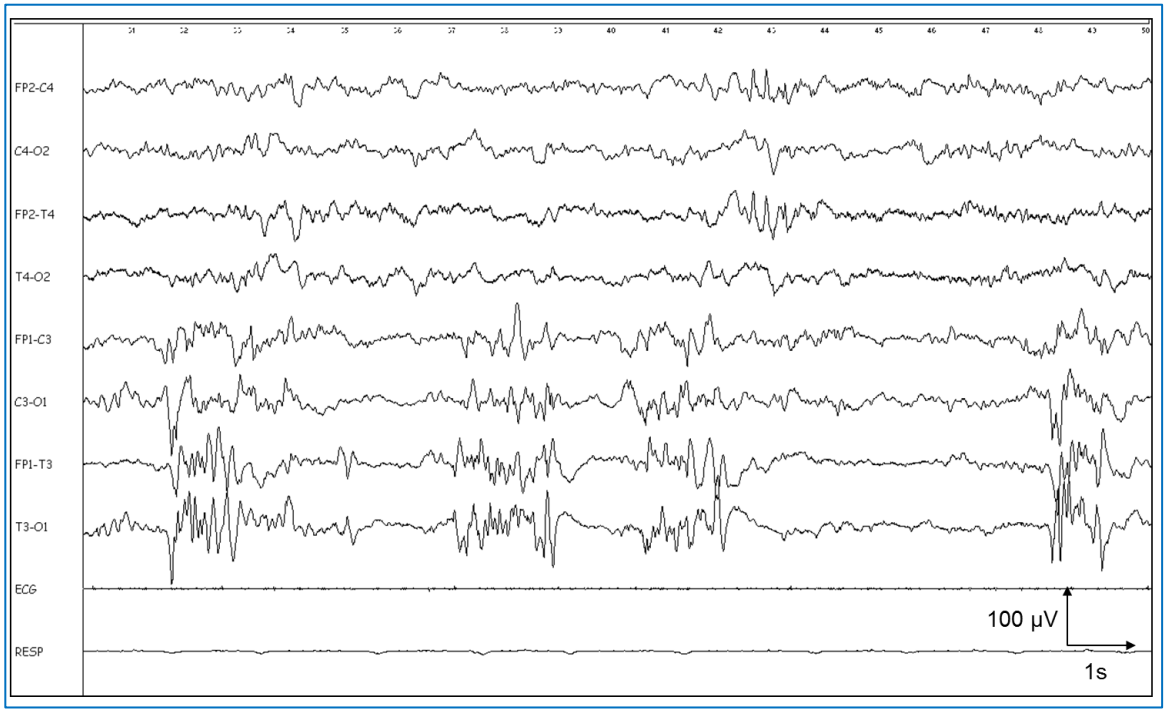


Figure 2.13. EEG during active sleep in a 10-day-old neonate with left **hemimegalecephaly**. Note the normal background activity on the right and the S-B pattern on the left.

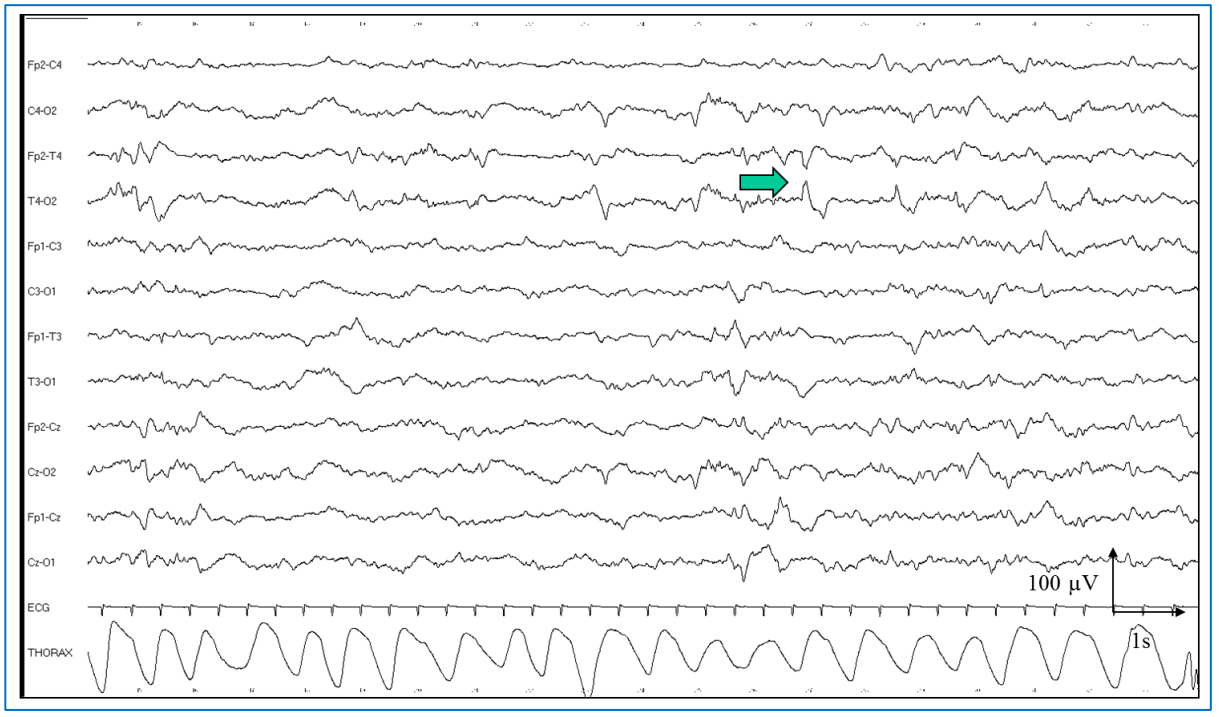


Figure 2.14. EEG during active sleep in a two-day-old neonate with **tuberous sclerosis complex**. Background activity is normal. Note a sequence of pseudo-periodic sharp waves over the right temporal-occipital region (arrow).

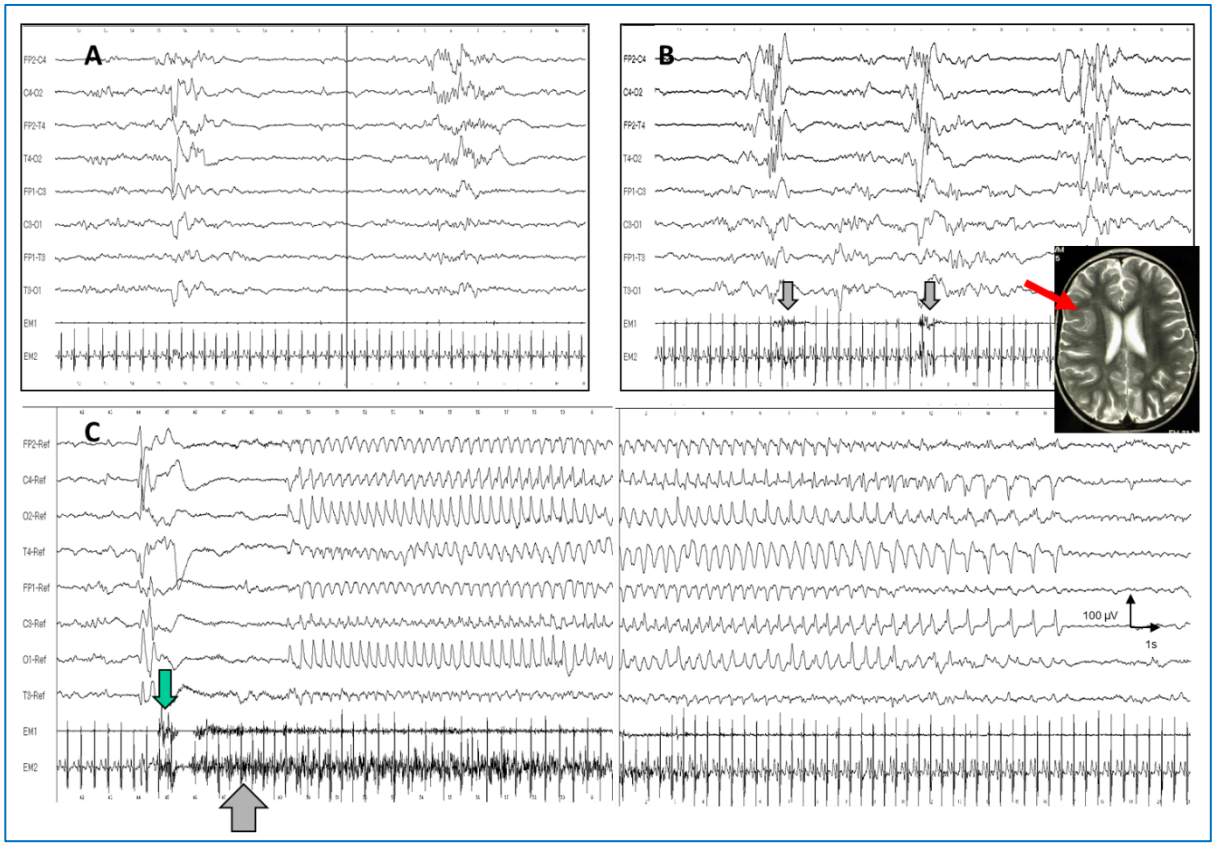


Figure 2.15. EEG recording in a 14-day-old new-born with right **frontal cortical dysplasia**, identified on brain MRI at the age of four years (red arrow). (**A**) Interictal right-sided hemi-S-B pattern during

active sleep; note that the bursts contain spikes and rapid rhythms intermixed with sharp waves. (**B**) Ictal EEG showing asymmetric epileptic spasms (arrows), concomitant with high-amplitude right hemisphere spike and polyspike-waves that predominate over the central area. (**C**) An epileptic spasm (green arrow) is followed by an asymmetric tonic seizure predominating in the left upper limb (grey arrow), concomitant with a flattening of the tracing and a sequence of rhythmic, bilateral frontal-central sharp waves that predominate over the right hemisphere (EMG 1: right deltoid; EMG 2: left deltoid).

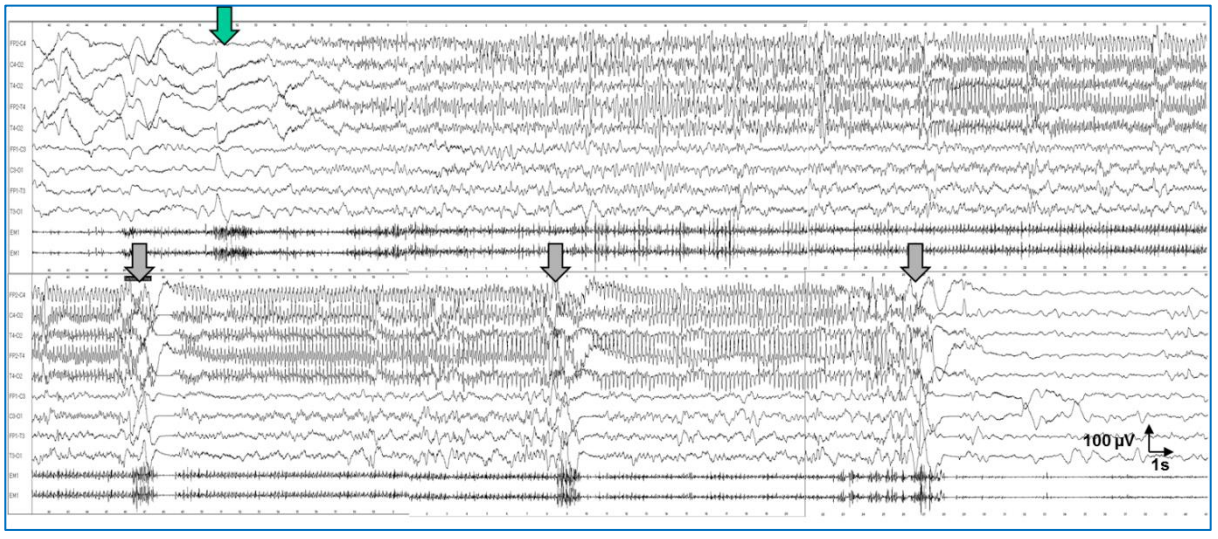


Figure 2.16. Ictal EEG in a 15-day-old neonate with right **frontal cortical dysplasia**. The seizure is asymmetric tonic, then clonic with interspersing epileptic spasms. The ictal discharge begins with a flattening of the tracing over the right hemisphere, particularly over the frontal region (green arrow), and continues with rapid rhythmic spiking. Epileptic spasms occur during the evolution of the focal seizure discharge and at its end (grey arrows), concomitant with high-amplitude brief diffuse slow wave complexes that also appear to predominate over the right hemisphere (EMG 1: right deltoid; EMG 2: left deltoid).

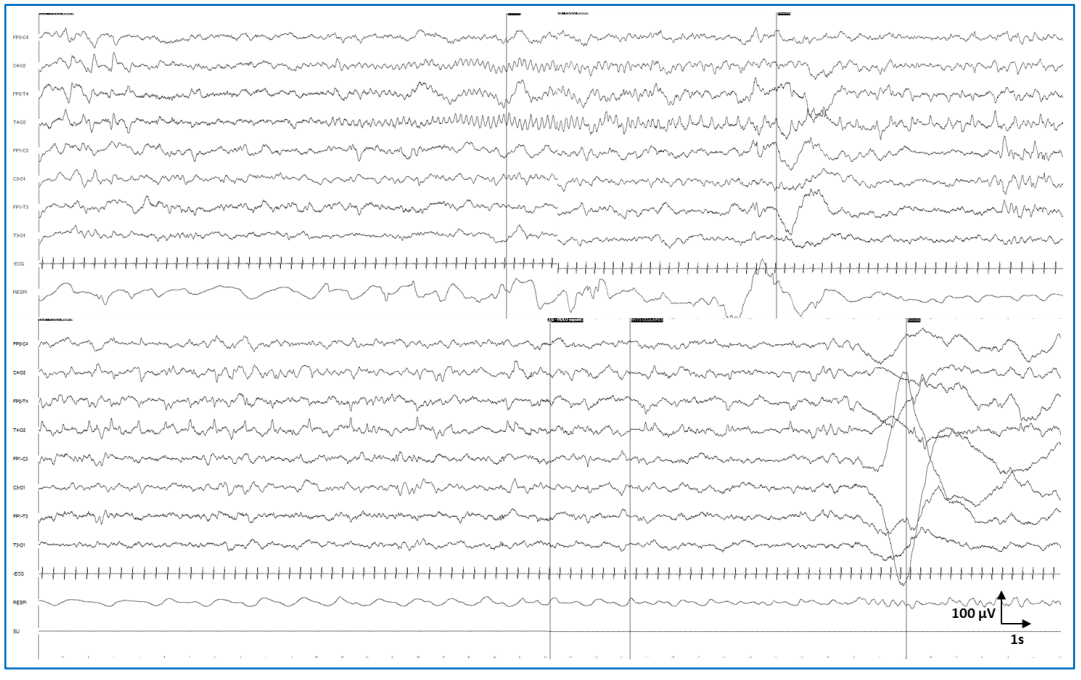


Figure 2.17. "Subtle" right temporal-occipital seizure in a 10-day-old neonate with **tuberous sclerosis complex.**

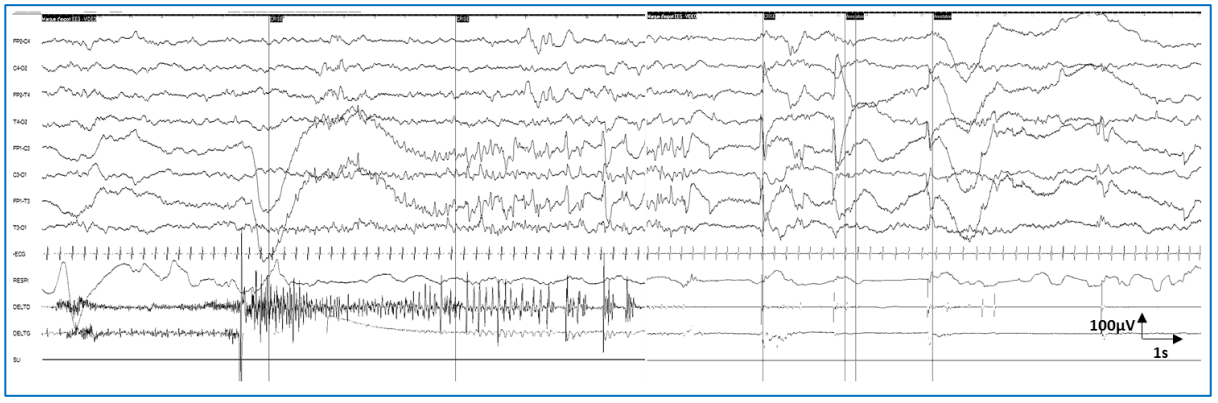


Figure 2.18. Ictal EEG in a 20-day-old neonate with **tuberous sclerosis complex**: left frontal-central seizure with tonic, then-clonic movements of the right upper limb. Notice the clonic rather than myoclonic jerks that are concomitant with high-amplitude spikes over the left frontal-central region.

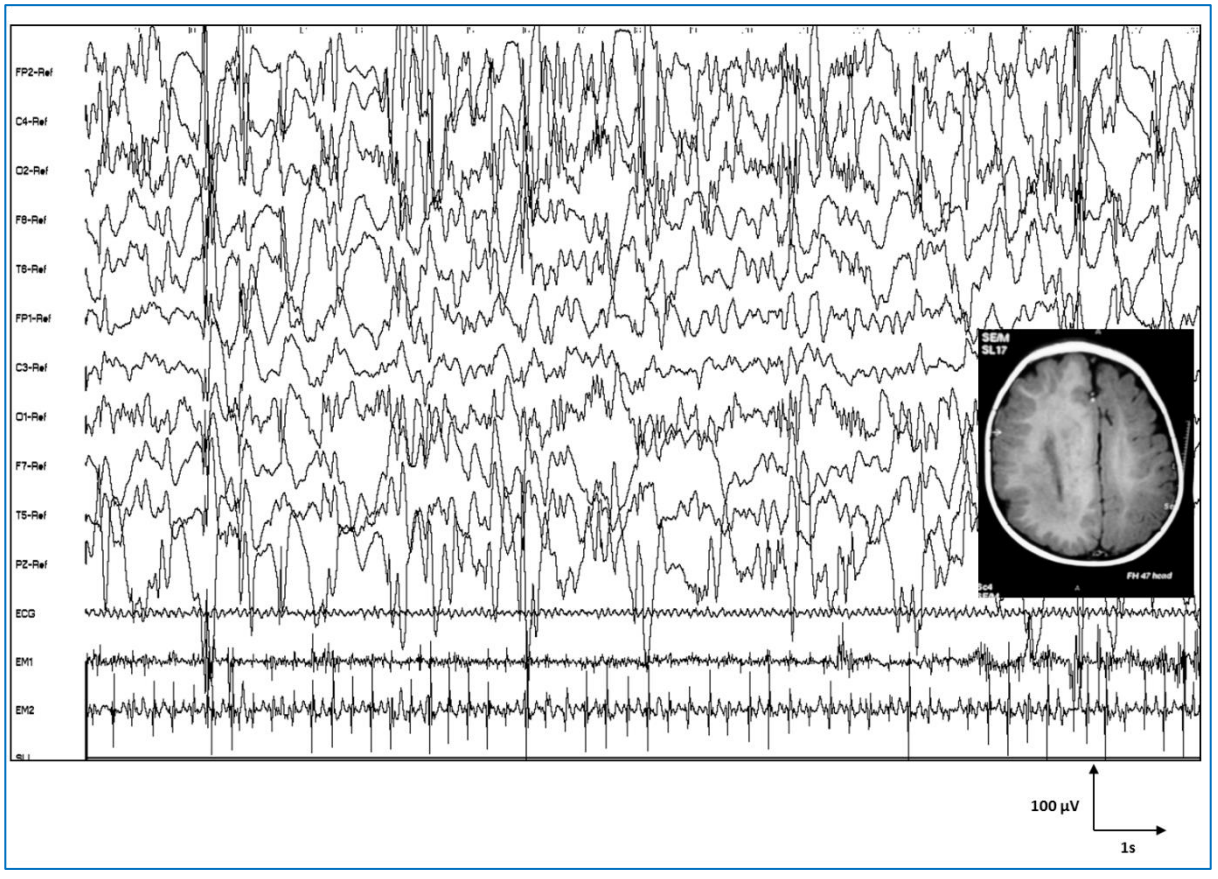


Figure 2.19. Ictal EEG in the two-day-old neonate from *figure 2.12*. The EEG pattern appears similar to that in *figure 2.12* (asymmetric with high-amplitude, continuous spikes, polyspikes, and sharp waves diffusing to the left hemisphere), but some discharges are now concomitant with myoclonic jerks recorded on the left deltoid (EMG 2).

INFANCY & EARLY CHILDHOOD

SECTION 3.1: INFANTILE SPASMS & WEST SYNDROME

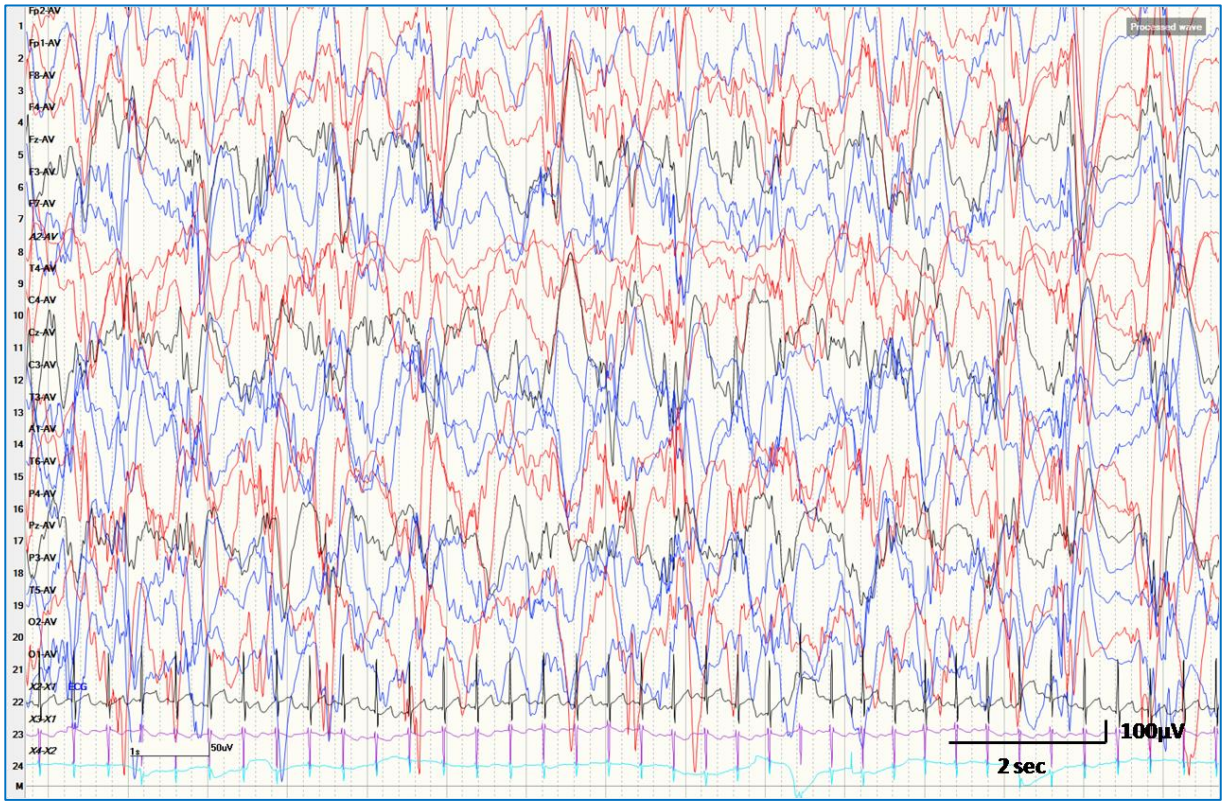


Figure 3.01. Typical hypsarrhythmia during natural sleep.

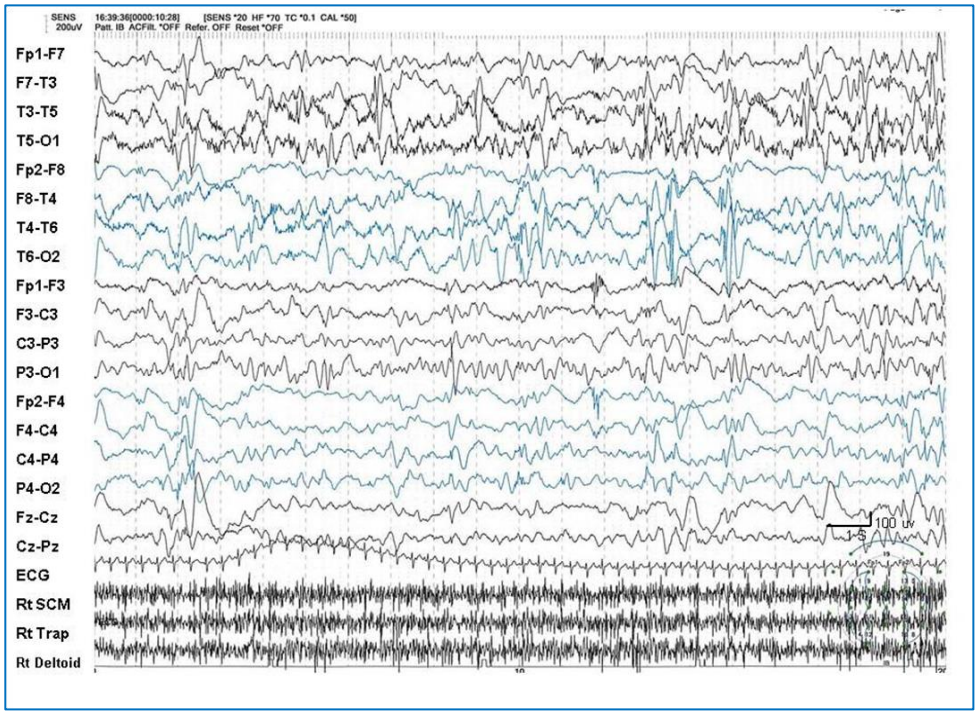


Figure. 3.02. Hypsarrhythmia during awake EEG. A six-month-old girl developed epileptic spasms in clusters three weeks before this study. She was given a diagnosis of cryptogenic West syndrome based on the neurological and laboratory examination, as well as neuroimaging studies. Background activity was occupied by irregular slow wave and spikes or polyspikes, most predominantly in both temporal regions. Physiological background activity was intermittently preserved.

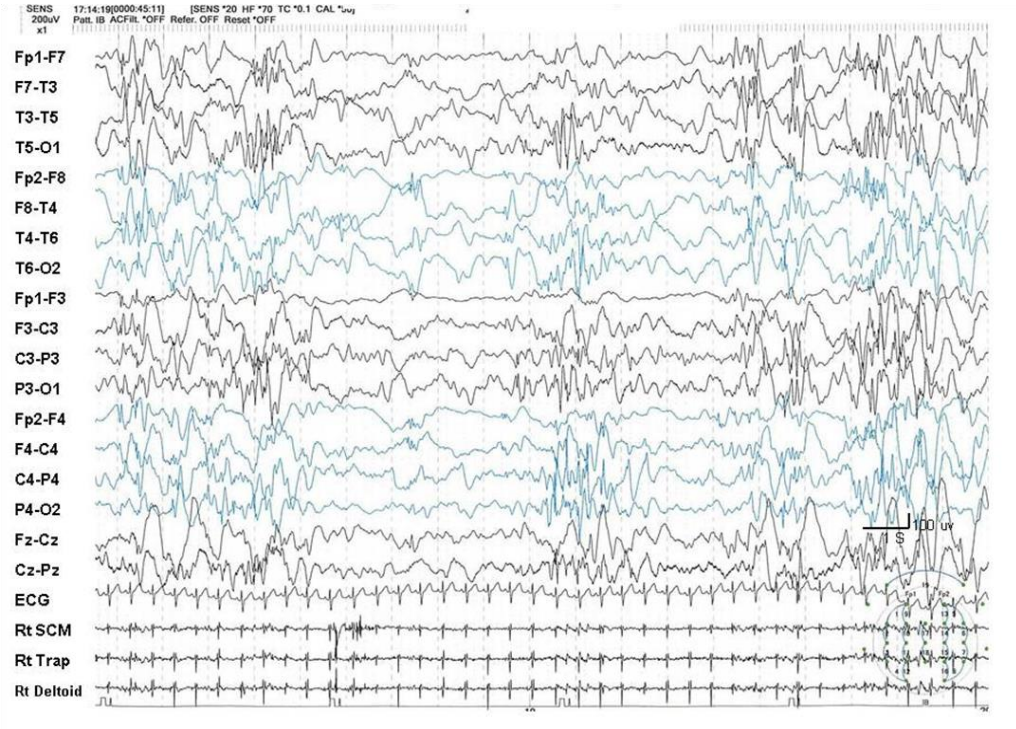


Figure. 3.03. Hypsarrhythmia during sleep EEG. Note the enhanced synchronization of the hypsarrhythmic discharges, which became almost continuous during slow sleep; same patient as in *figure 3.02*.

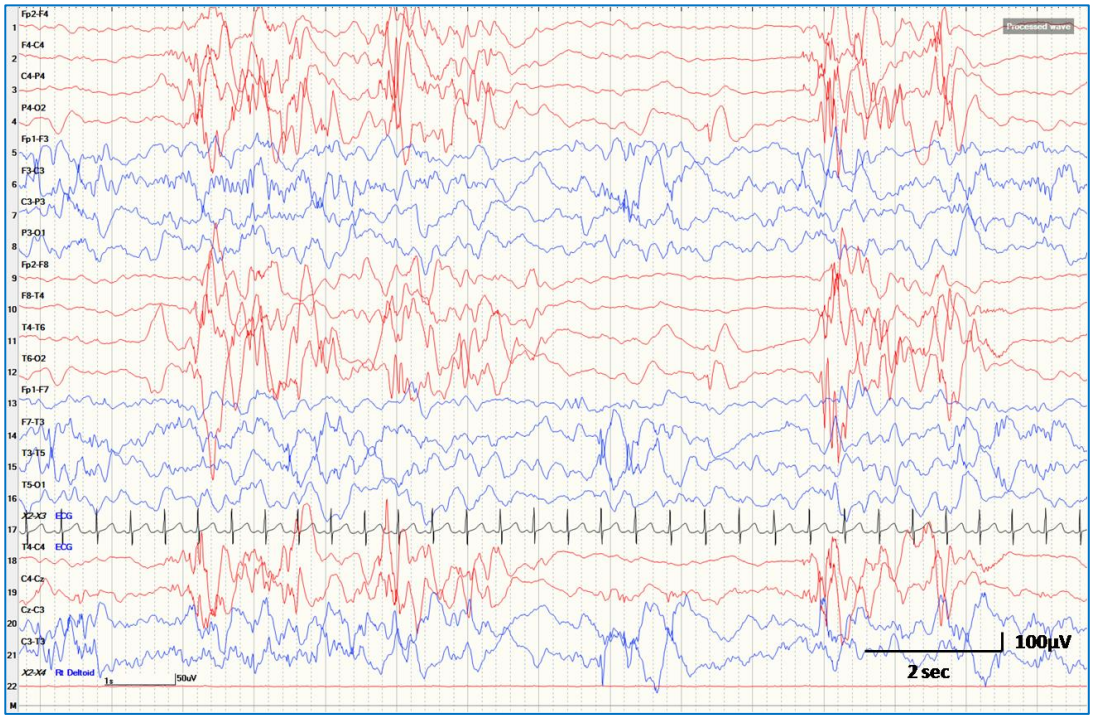


Figure. 3.04. Asymmetric hypsarrhythmia.

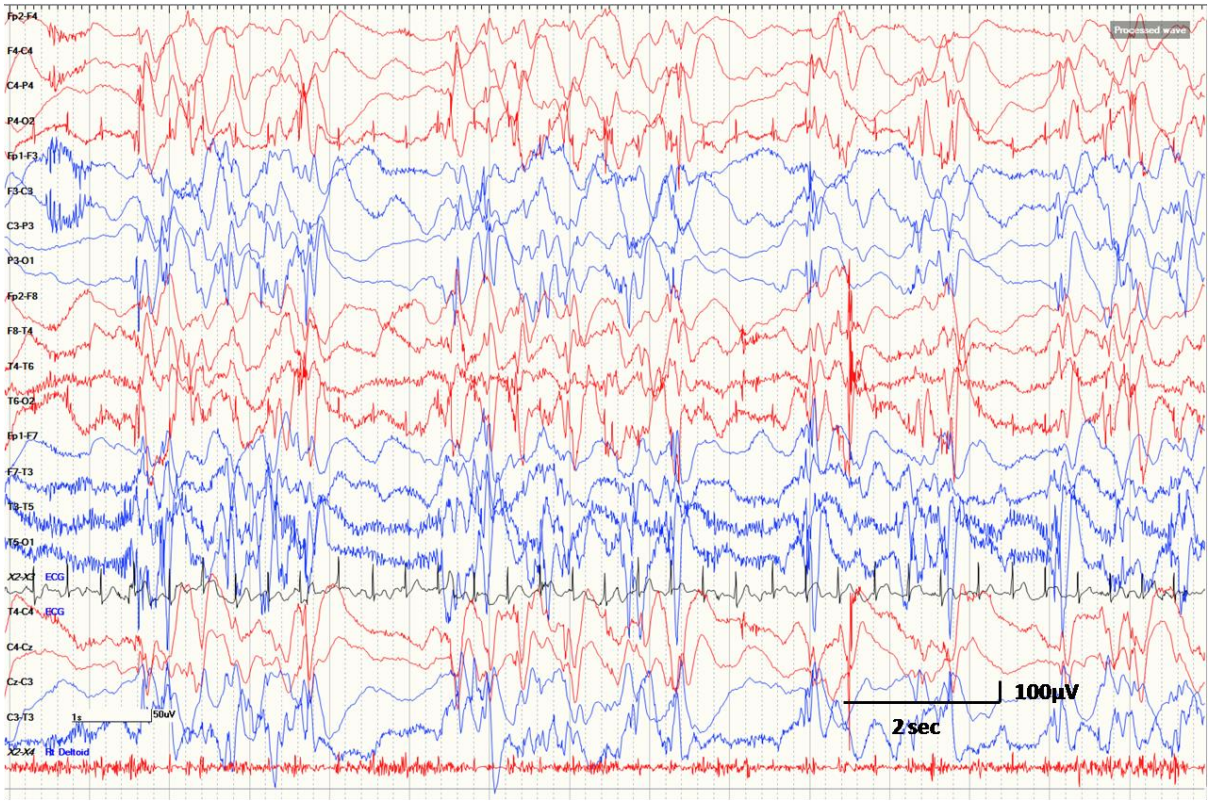


Figure. 3.05. Hypsarrhythmia associated with background attenuation.

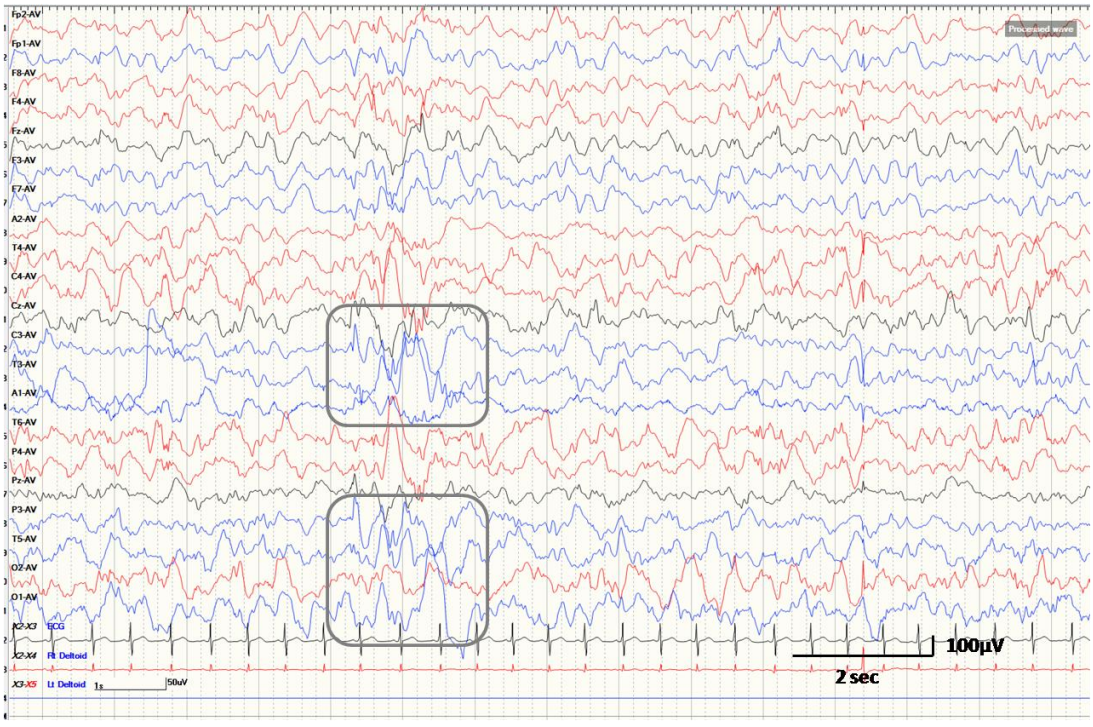
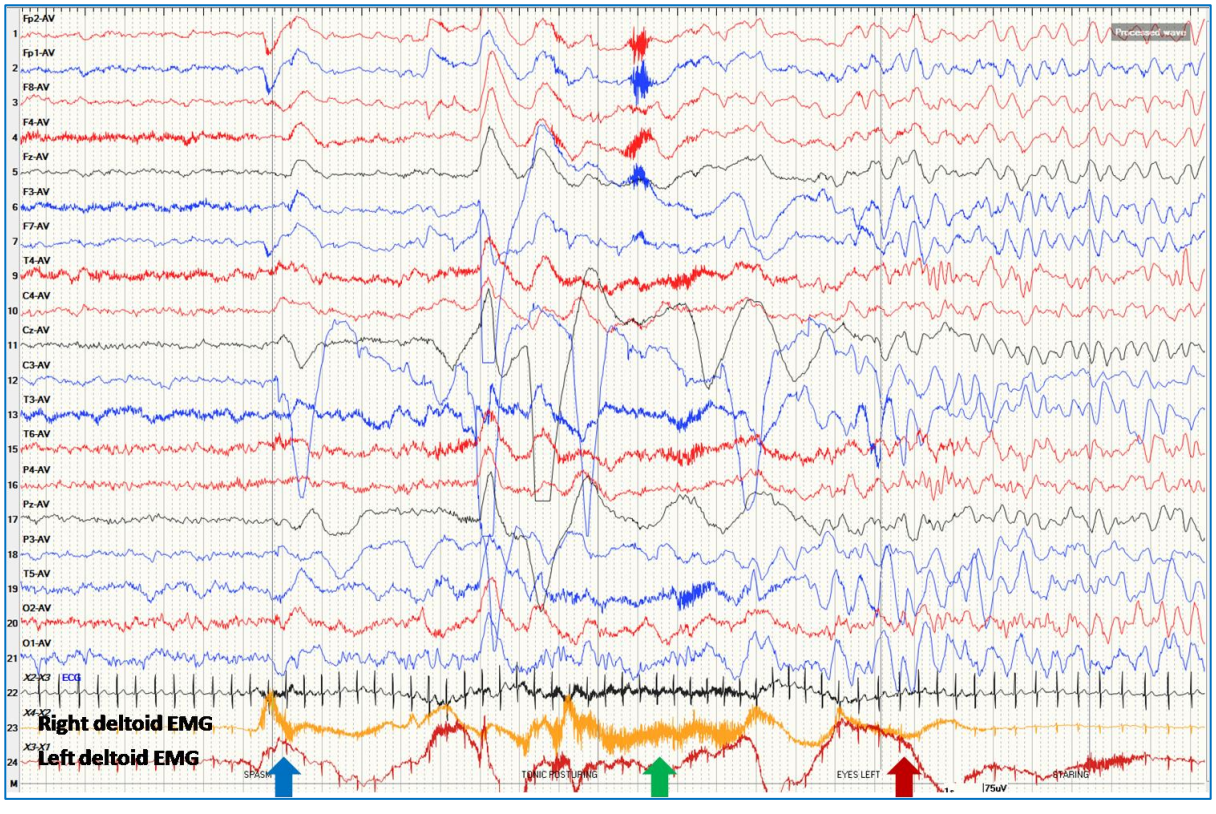


Figure.3.06. Interictal EEG showing an epileptic focus over the left posterior quadrant (panels). The baby has epileptic spasms but the pattern here, although of high voltage, cannot be characterized as hypsarrhythmic.



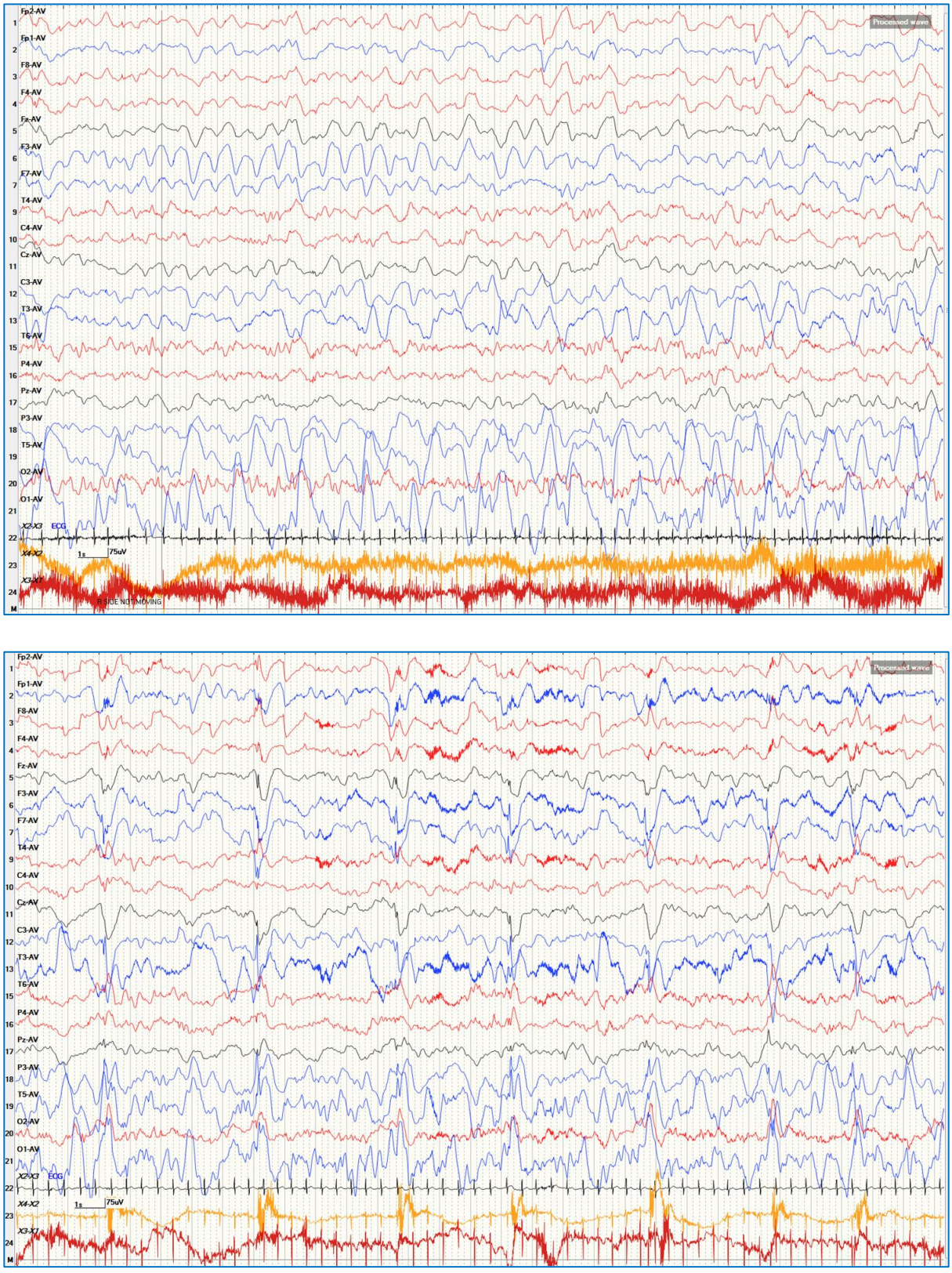


Figure. 3.07. (**A**) Same baby as in *figure 3.03*. The seizure starts with an **asymmetric epileptic spasm** (blue arrow). Note the pronounced activation of the right deltoid EMG compared to the left. A prolonged, also asymmetric, tonic posturing follows (green arrow), associated with deviation of the eyes to the left (red arrow). (**B**) (continued): The ictal discharge involves the left parietal-occipital area; clinically, the right arm appears to become fisted and immobile as she continues to stare. (**C**) At the offset of the focal seizure, a cluster of asymmetric epileptic spasms are recorded (note the EMG artefacts in the lower two channels). The paper speed is very slow and the gain reduced to appreciate the ictal changes.

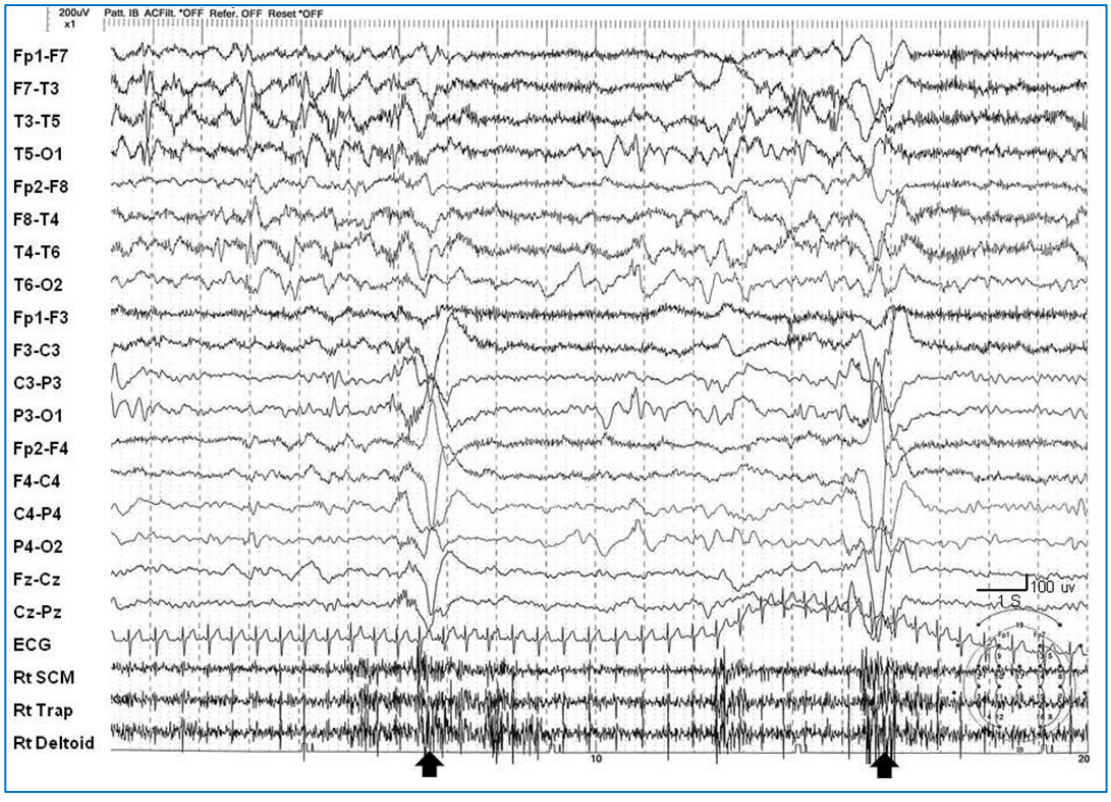


Figure. 3.08. Ictal EEG with polygraphy. **Epileptic spasms** (arrows) are associated with a diffuse high-amplitude **triphasic slow wave**, followed by -also diffuse- transient suppression of background activity.

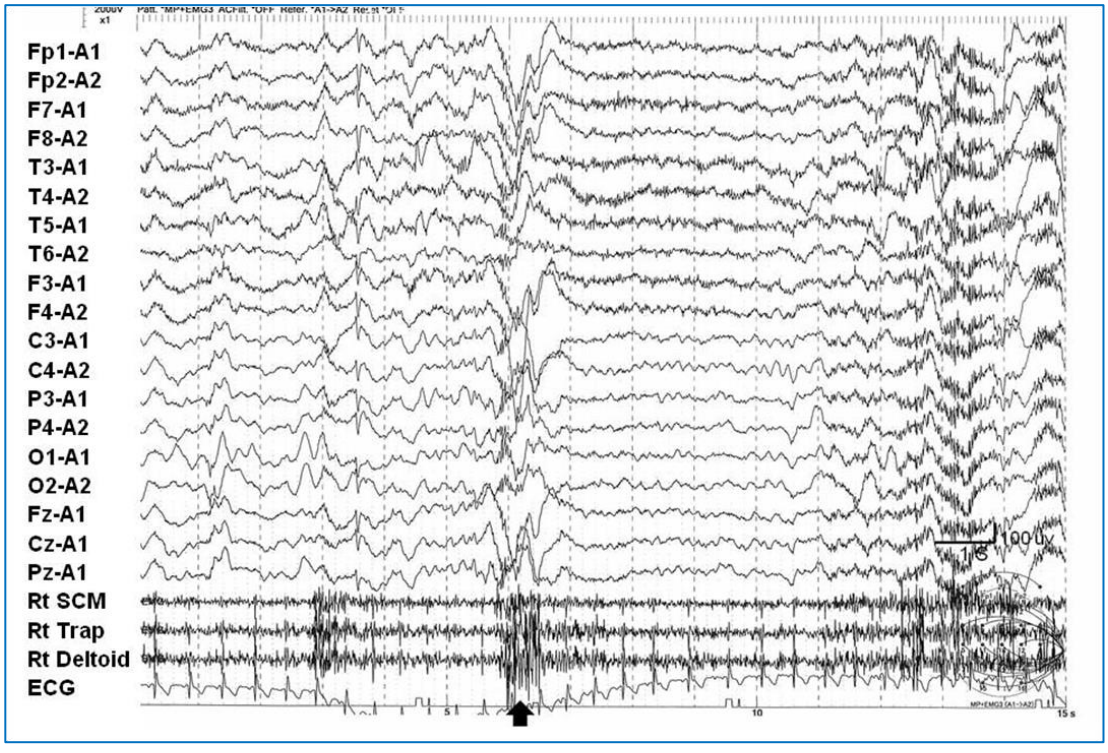


Figure. 3.09. Typical morphology of ictal EEG. In the monopolar montage, a large positive slow wave is followed by a negative slow wave, corresponding to EMG discharge of the spasm.

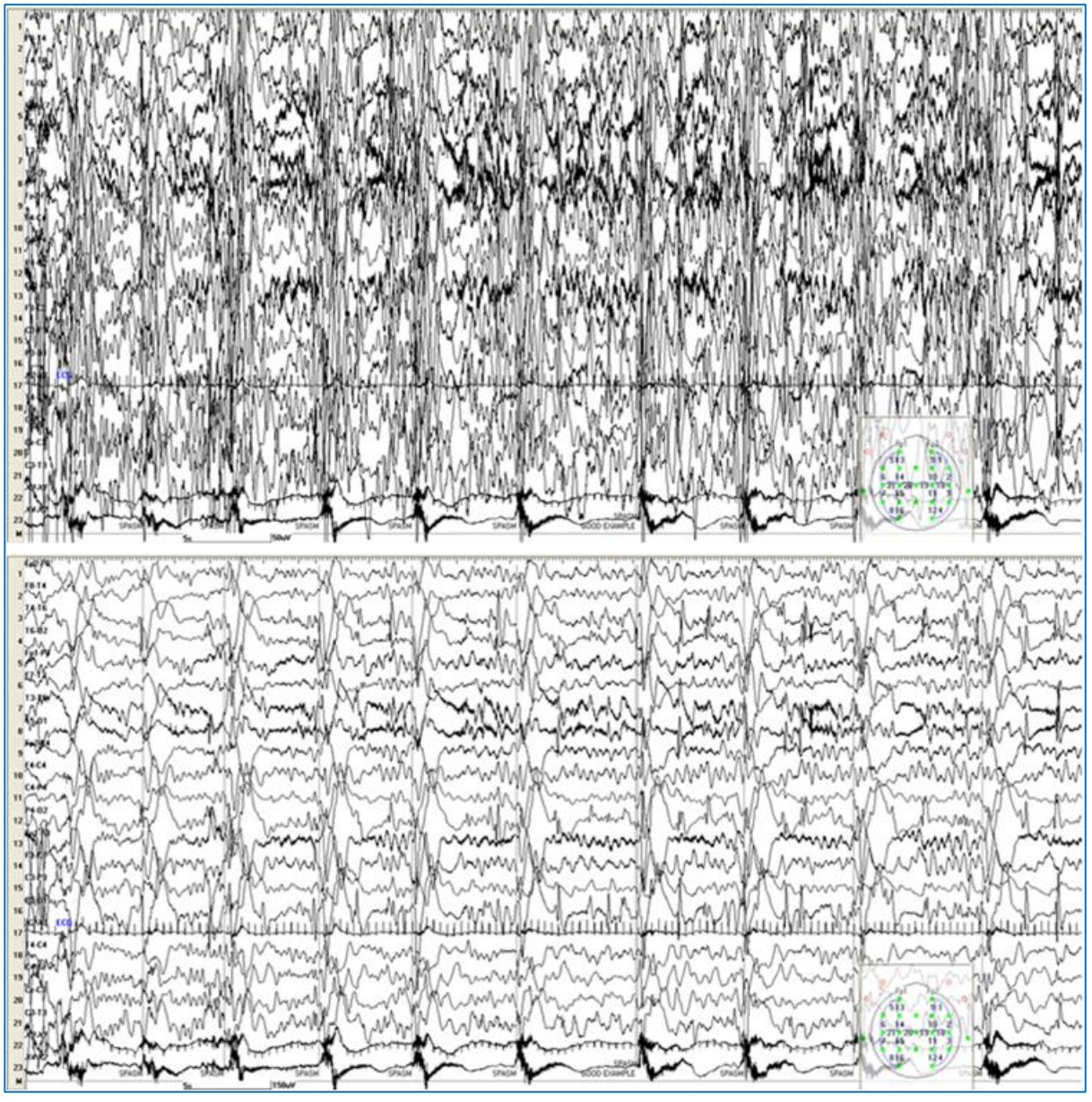


Figure 3.10. Slow paper speed (upper and lower traces) and reduced sensitivity (lower trace) provides better resolution of **epileptic spasms** against a chaotic high-voltage **hypsarrhythmic** background. Note the bilateral EMG from the deltoid muscles at the bottom of each trace (reproduced with permission from Koutroumanidis *et al*. [2017]).

SECTION 3.2: DRAVET SYNDROME (DS)

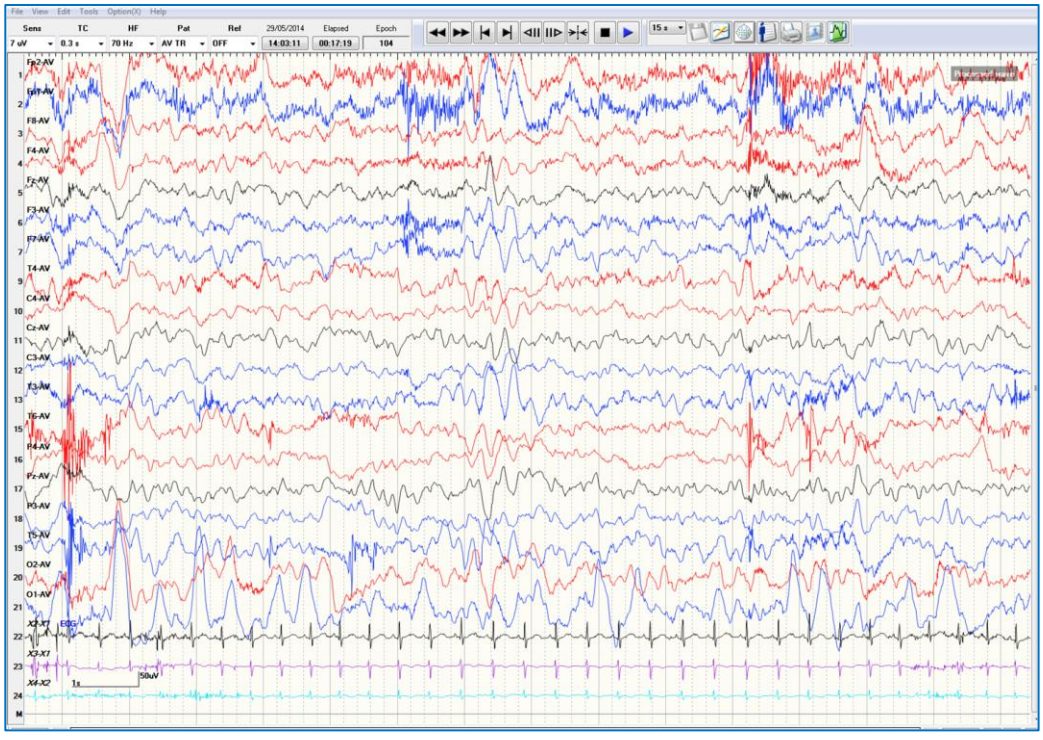


Figure 3.11. A 20-month-old boy presented with a one-hour febrile tonic-clonic seizure, requiring intubation and ventilation; he had already suffered two febrile seizures. This EEG was performed four days later. Note the non-specific slowing over the posterior regions (L>R) and the occasional bursts of slow waves over the left hemisphere and the right fronto-temporal areas, against an otherwise preserved background. Background rhythms were normal four months later.

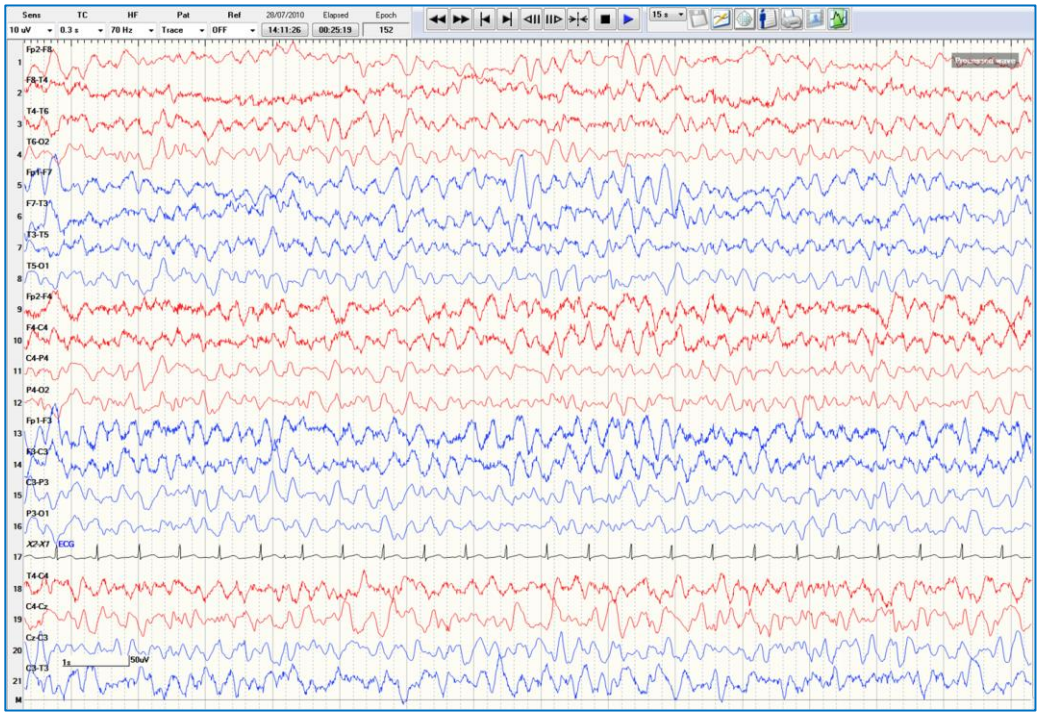


Figure 3.12. Diffusely slow background within the theta frequency range (with frontal emphasis) in an eight-year-old boy with **Dravet Syndrome** of infantile onset.

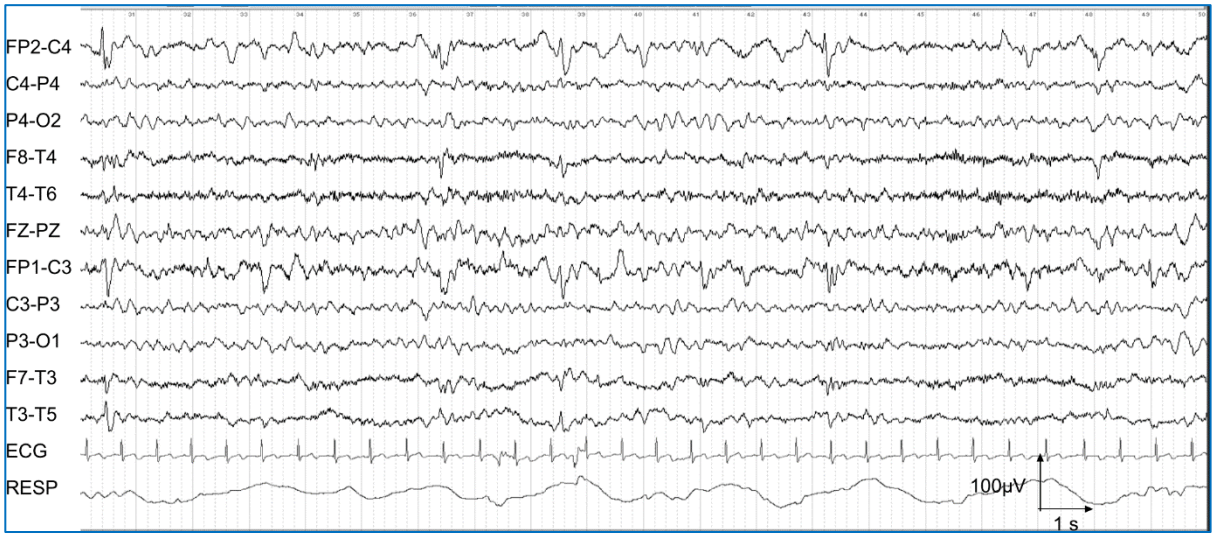


Figure 3.13. Awake EEG in a seven-year-old boy, showing **slow background activity** in the theta band with bifrontal spikes and slow waves.

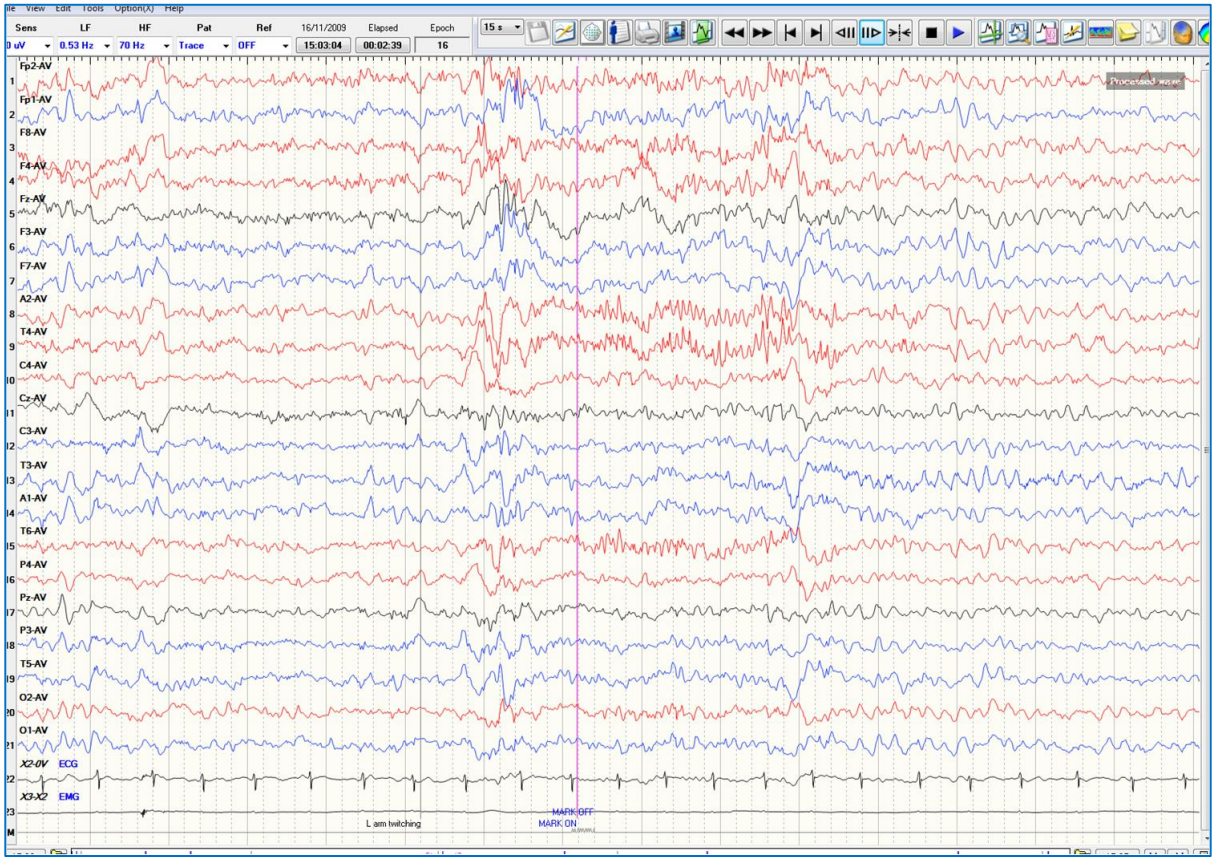


Figure 3.14. Same child as in *figure 3.12*. Sleep EEG shows **bursts of focal spikes** over the right anterior quadrant and independent sharp waves and spikes over the left anterior quadrant.

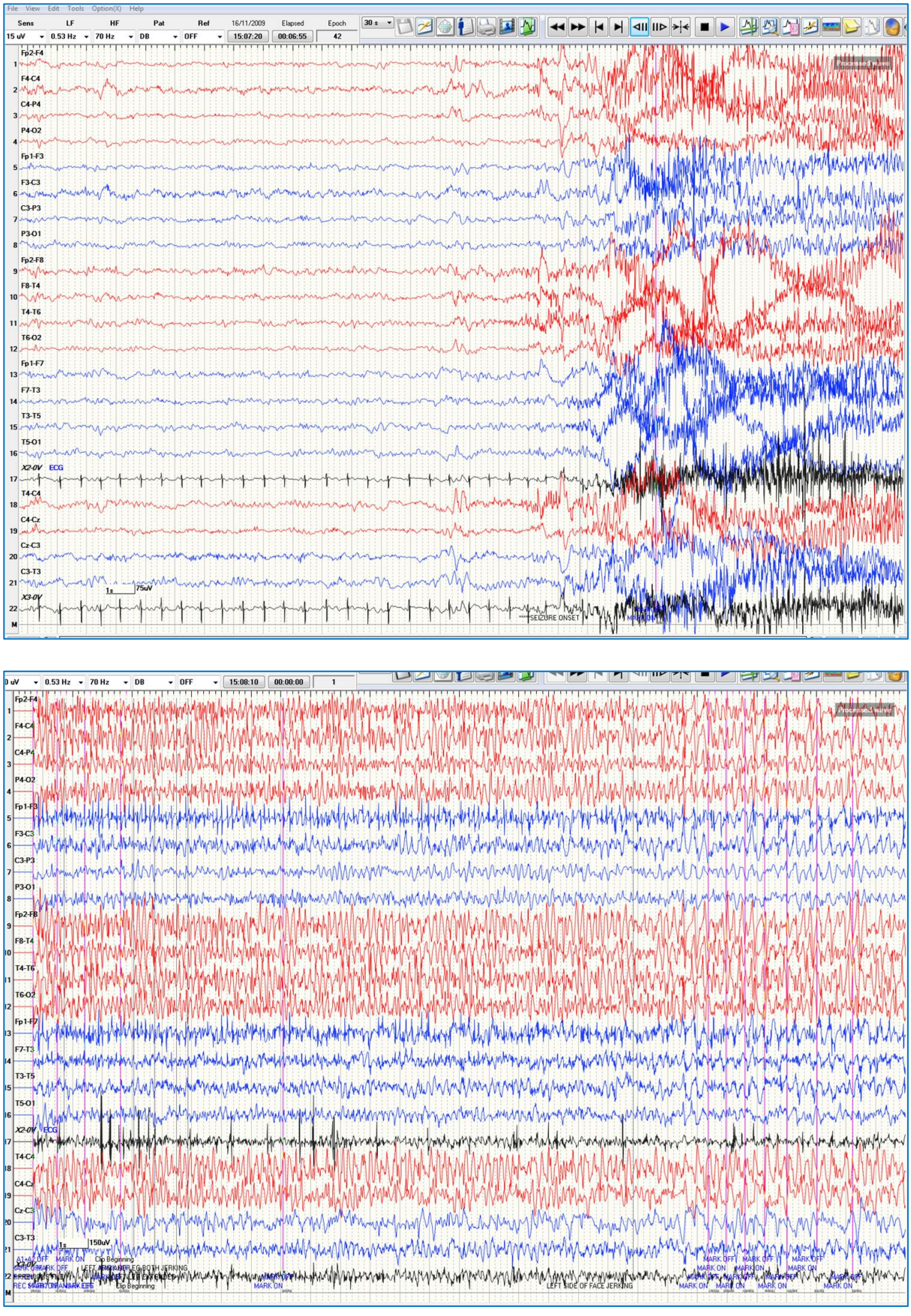


Figure 3.15A, B. Unilateral tonic-clonic seizure in the child of *figure 3.14*. On this occasion, the seizure mainly involved the left side of his body, but other unilateral seizures were reported to involve the right side. Note the bilateral ictal EEG onset (R>L).

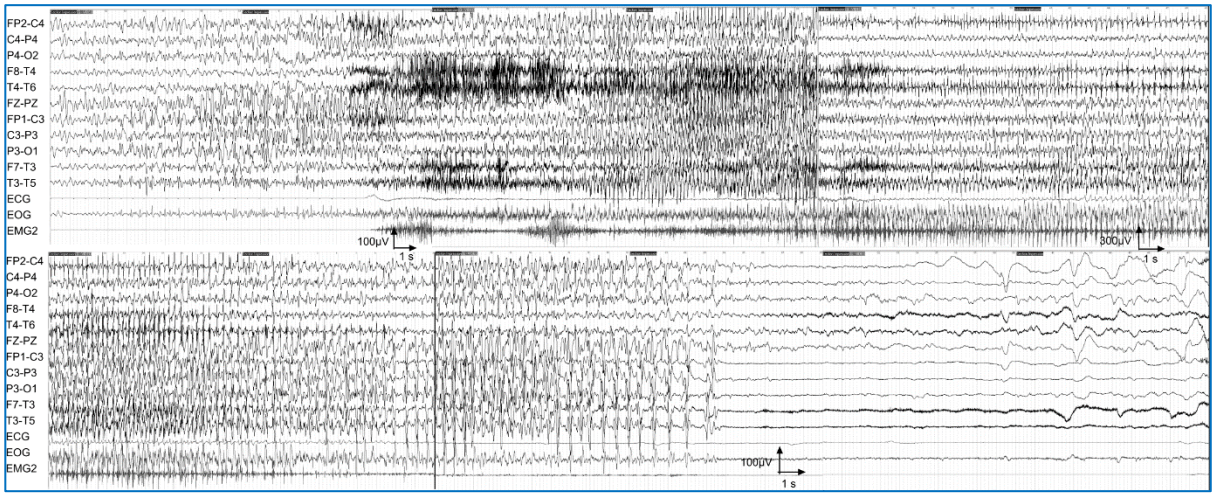


Figure. 3.16. Focal seizure in a seven-year-old boy with asymmetric tonic-clonic movements, beginning on the left frontal-central area with high-amplitude spike/polyspike activity that diffuses to the entire left hemisphere and the right frontal-central areas. Notice the tonic, then tonic-clonic movements on the right EMG. The seizure discharge ends first on the left hemisphere and is followed by diffuse postictal suppression that is more pronounced on the left hemisphere.

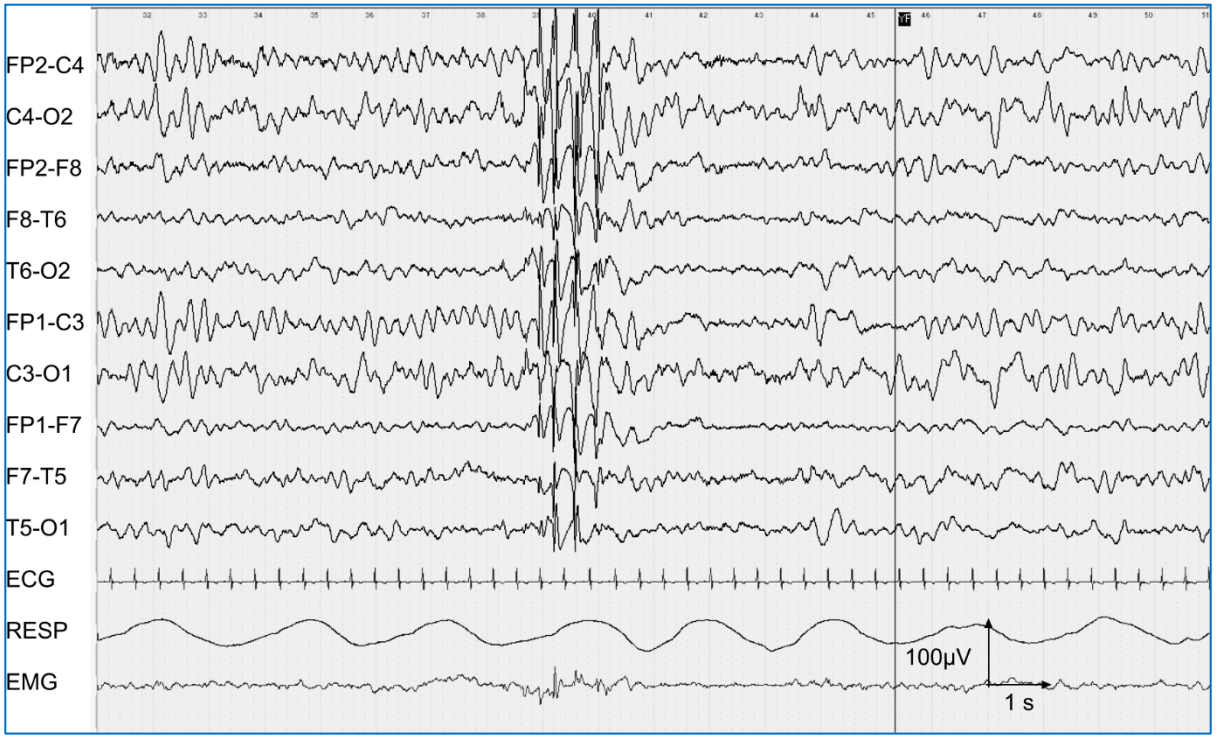


Figure. 3.17. Awake EEG in a six-year-old boy with **Dravet Syndrome**. High-amplitude generalized, 3-Hz spike-wave discharges predominating over the frontal-central areas are associated with myoclonic jerks recorded on deltoid EMG. Note the slow background within the theta band, particularly over the frontal-central areas.

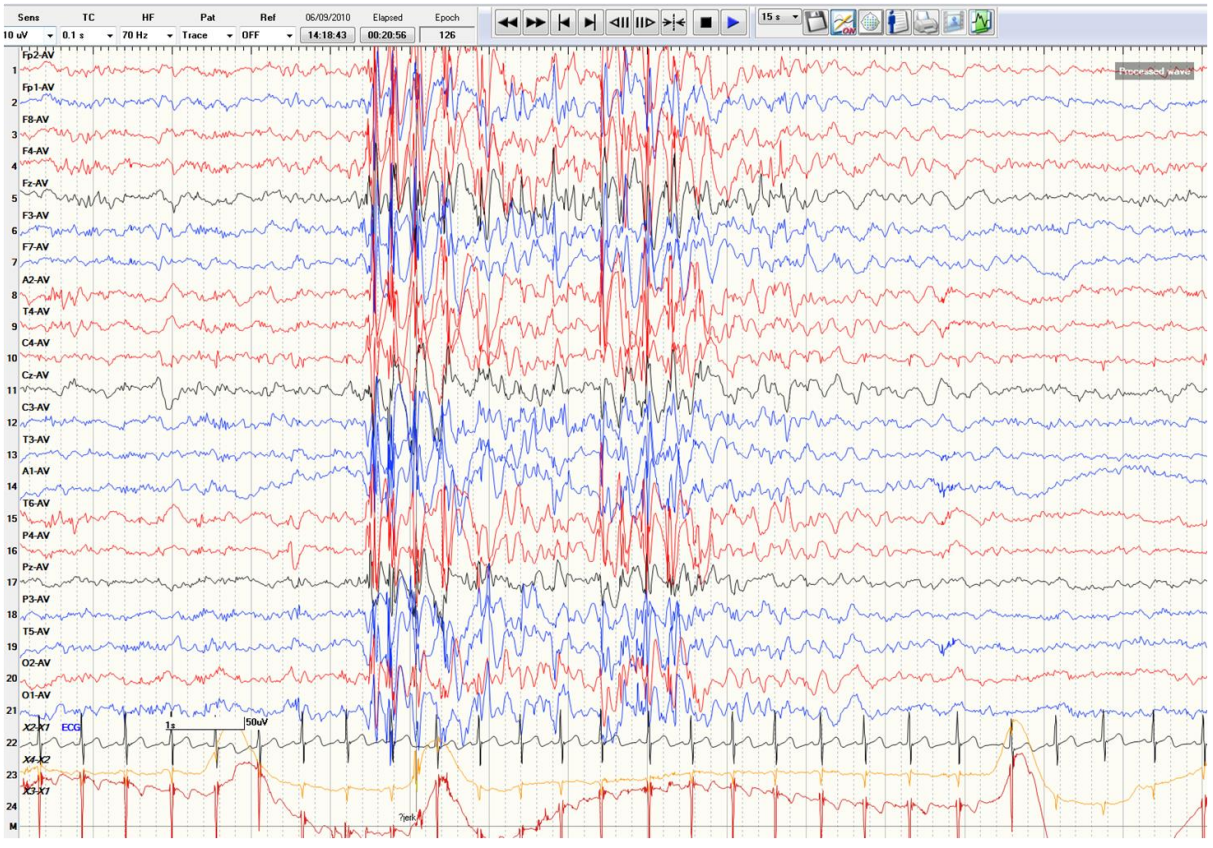


Figure 3.18. Sleep EEG in a two-year-old girl with genetically confirmed **Dravet Syndrome**. Brief generalized spike/polyspike-and-wave discharges are at times associated with myoclonic jerks (lower two EMG channels recorded both deltoids). She first presented jerky movements of arms at the age of six months, on a background of previously normal development. These gradually became more florid and interfered with her crawling. A prolonged tonic-clonic seizure occurred at the age of one, she had subsequent bouts of status epilepticus, and her development was noted to plateau. She has frequent daily myoclonic jerks and absences (*see figure 3.19*), which can occur at any time.

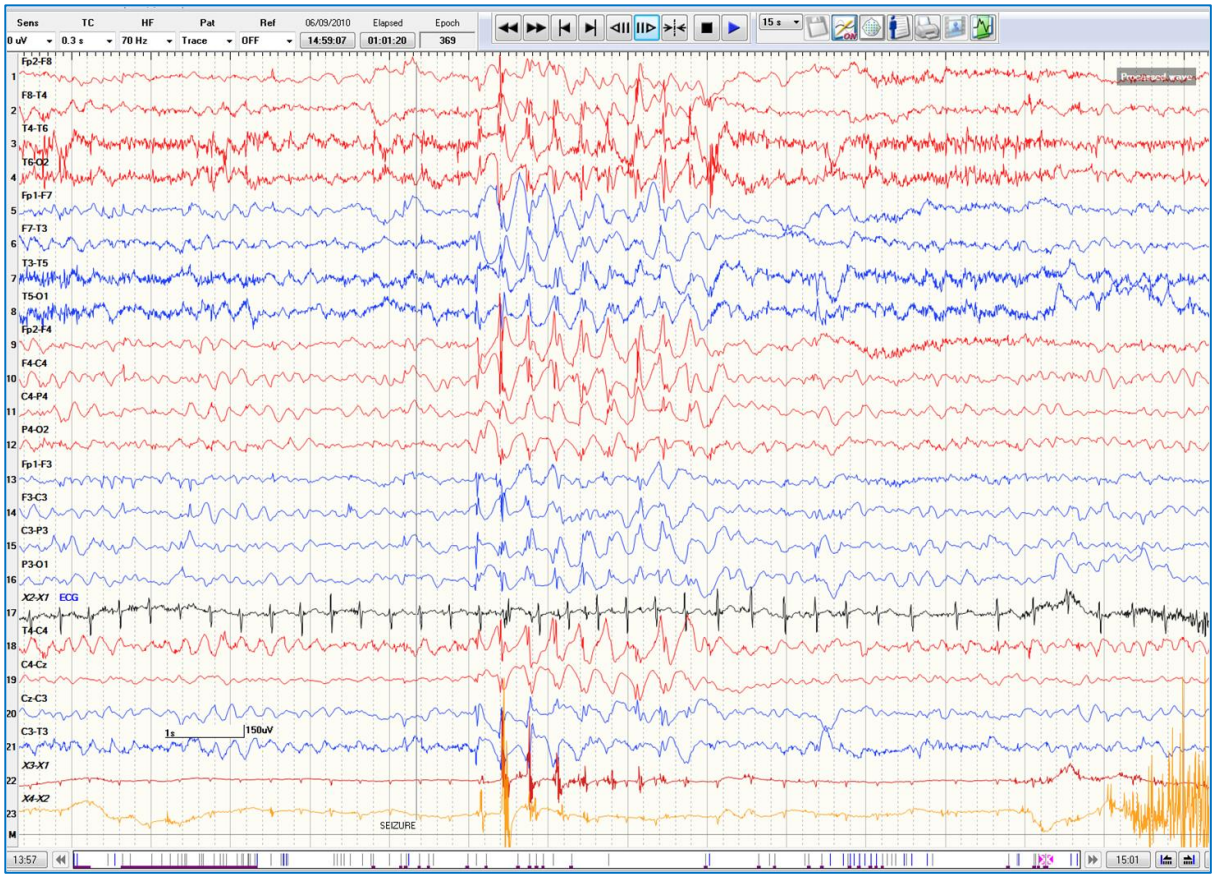


Figure 3.19. Myoclonic absence in Dravet Syndrome. Note the regular 2.5-Hz spike-and-wave discharge with the associated bilateral myoclonic jerks that are time-locked to the spike component (lower two EMG channels recorded both deltoids).

SECTION 3.3: MYOCLONIC EPILEPSY IN INFANCY (MEI)

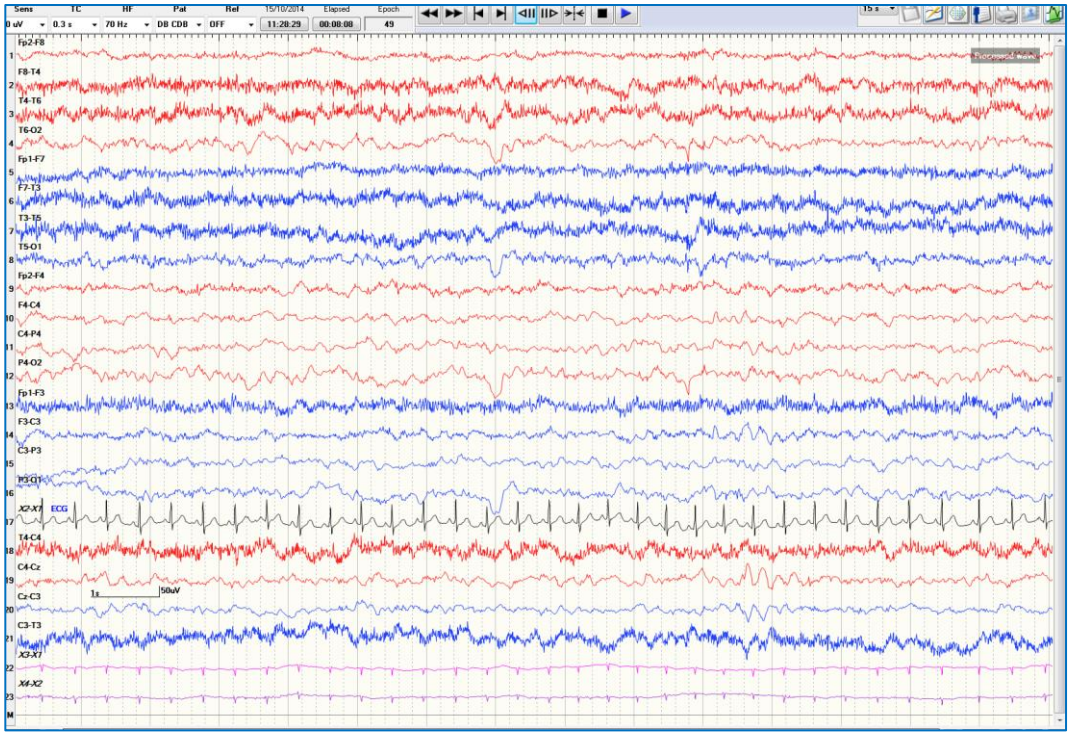


Figure 3.20. Video-EEG showing normal background activity during wakefulness of a 12-month-old boy with episodes of brief arm jerks which would result in him dropping objects. Myoclonic jerks most often occurred when he was about to sleep.

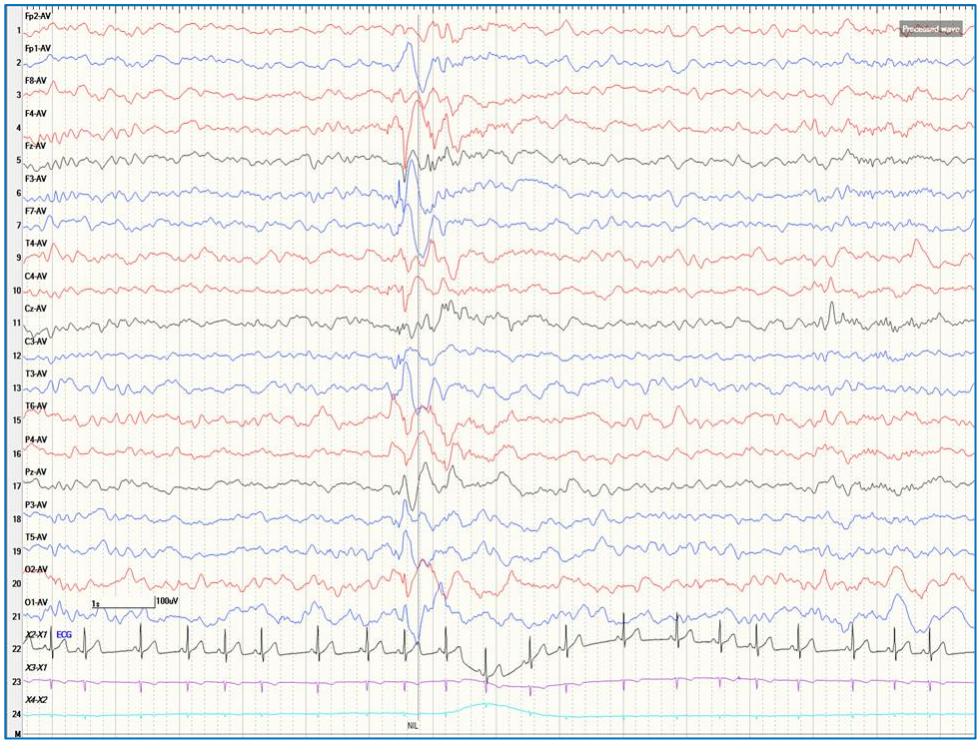


Figure 3.21. Interictal EEG during light sleep (N1) in the same child as in *figure 3.20*. Note the normal background and a brief **diffuse spike-and-wave discharge with no clinical correlate**.

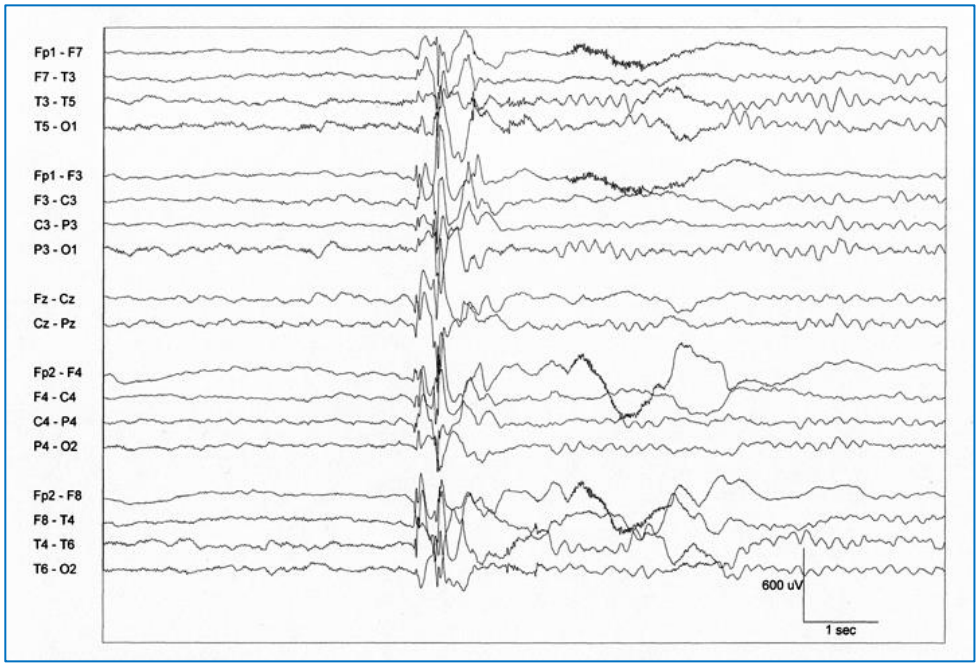


Figure 3.22. A 13-month-old boy with normal development who presented with recurrent **myoclonic jerks** of both arms and mild head drops. Brain MRI was normal. Metabolic workups were unremarkable. Myoclonic seizures initially responded to treatment with VPA. During drowsiness and light sleep, interictal GSWD increased in frequency, producing an arousal on this occasion (note the appearance of alpha rhythm after the offset of the discharge).

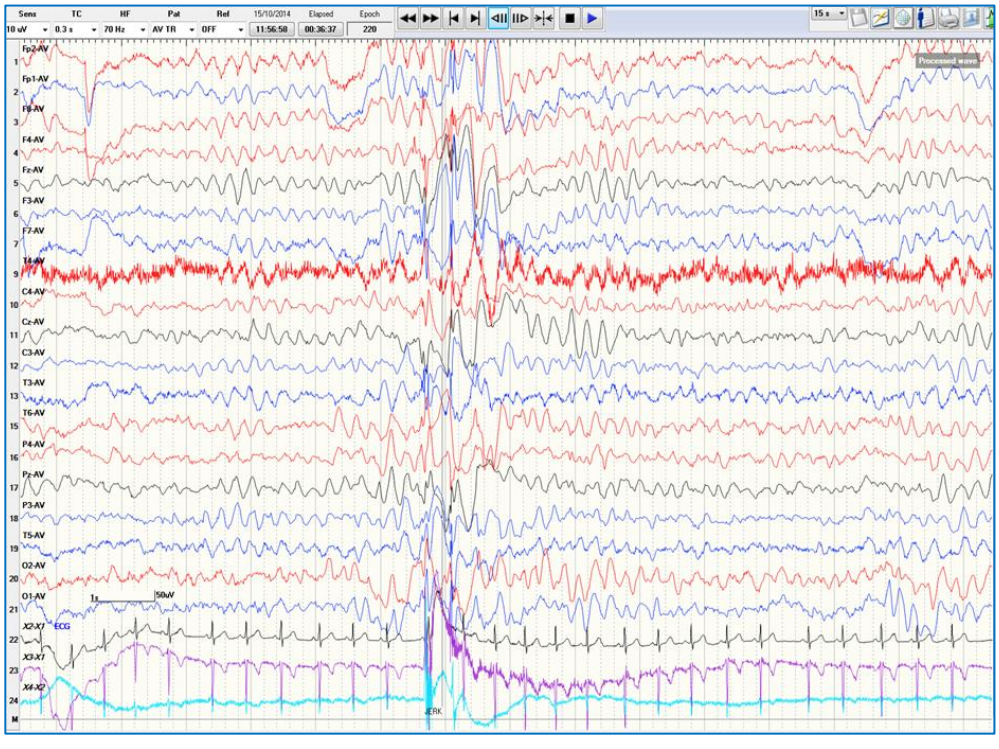


Figure 3.23. Ictal EEG during early drowsiness in the same child as in *figures 3.20 and 3.21*. Note the single **axial myoclonic jerk** which is associated with a two-second burst of irregular 3-Hz generalised spike-and-wave discharge, registered by EMG polygraphy (lower two channels).

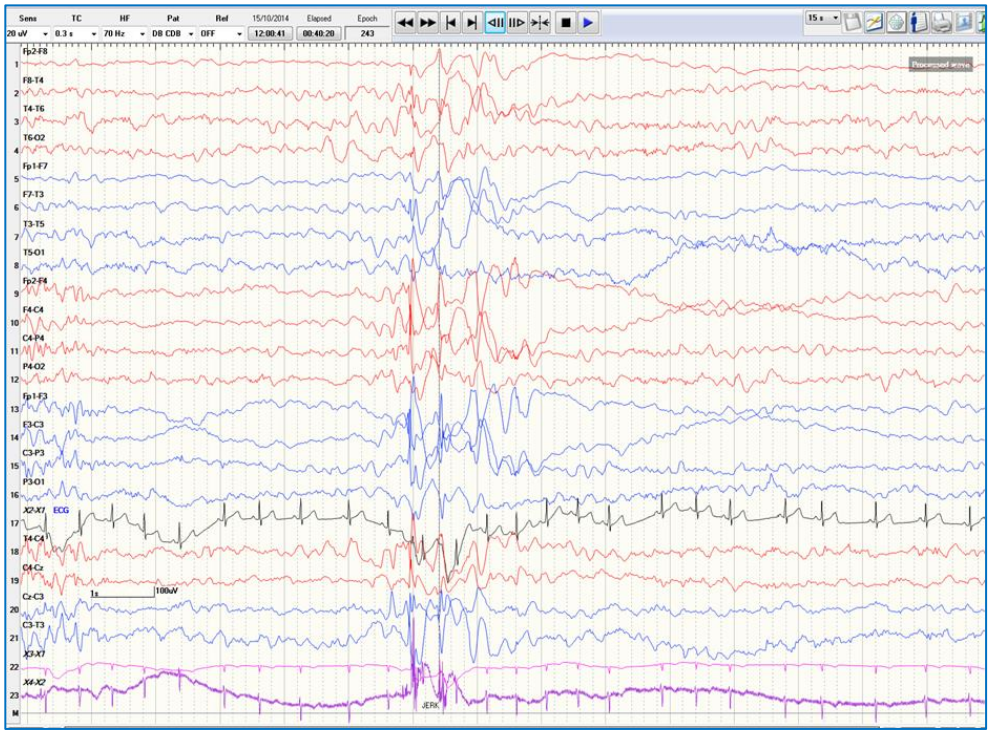


Figure 3.24 (Same child as in *figures 3.20, 3.21 and 3.23*). Two **myoclonic jerks** in rapid succession during sleep, recorded on EMG channels in association with a brief burst of generalised spike-and-wave discharge on the EEG. The patient became seizure-free upon treatment with levetiracetam. Sleep EEG at three years of age was normal.

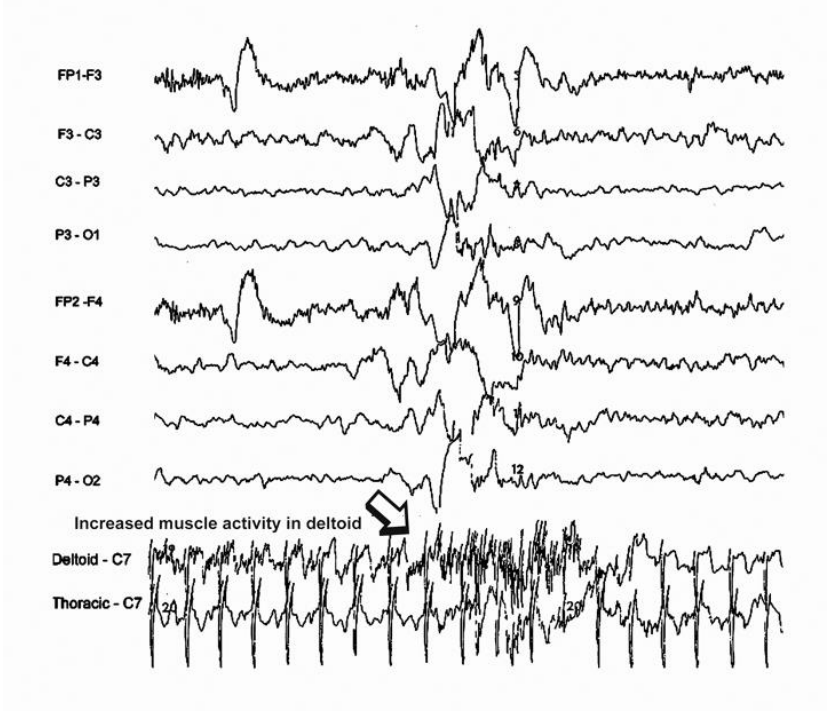


Figure 3.25. Video-EEG of a 10-month-old boy who was healthy until eight months of age when he developed recurrent myoclonic jerks of the arms with occasional head drops; the latter were captured on the video while he was sitting. Note the increased muscle activity in the deltoid muscle in association with the GSWD. EEG-EMG polygraphy confirmed that the head drop was myoclonic rather than atonic seizure. Background EEG was normal.

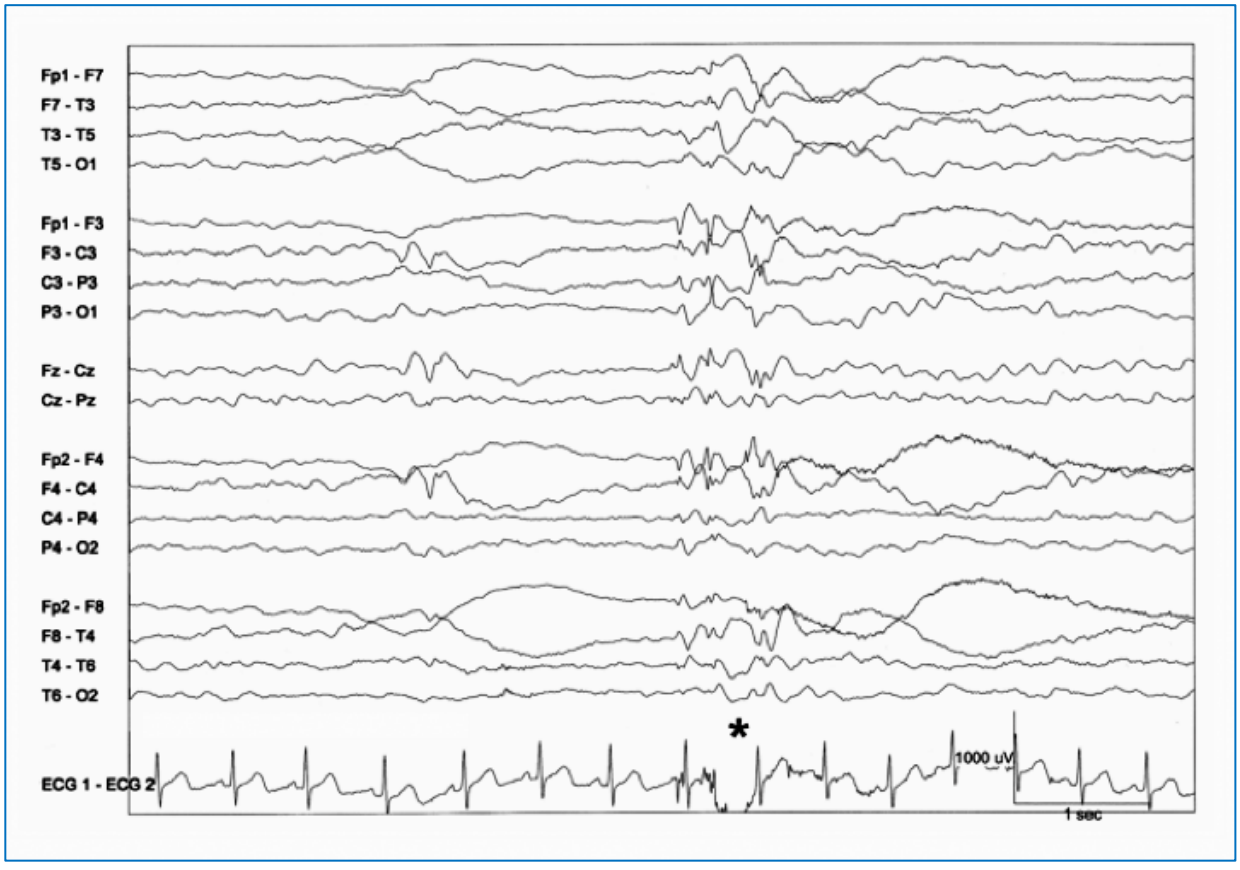


Figure 3.26. A 22-month-old girl with **recurrent myoclonic jerks** of both arms, particularly noticeable when something came in contact with her head. Brain MRI was normal. Interictal EEG was normal. The patient had a typical, sudden episode of bilateral arm abduction associated with **GSWD** (asterisk).

SECTION 3.4: BENIGN INFANTILE EPILEPSY (BIE)

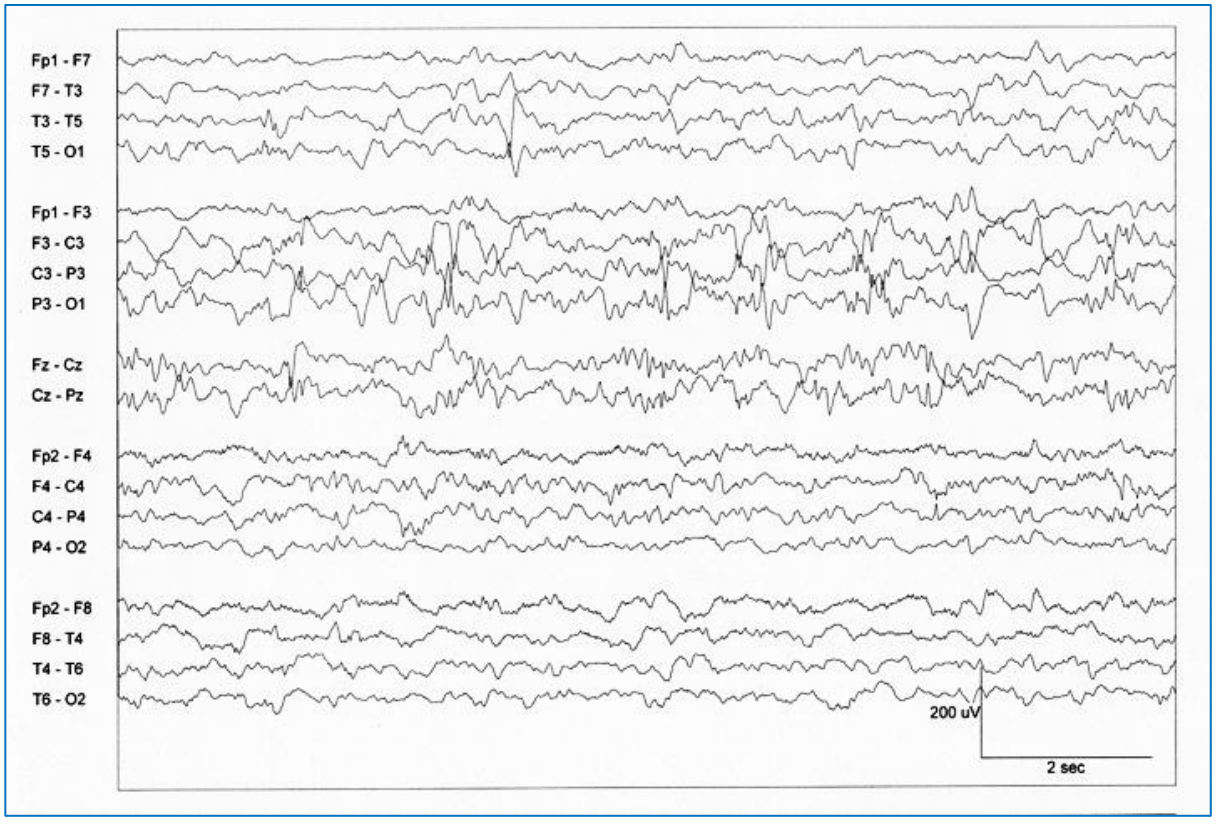


Figure 3.27. A two-month-old boy who developed sudden onset of **focal seizures**, described as head and eye deviating to the right side with brief stiffening of both arms occurring in clusters for 4-5 days. He appeared to be normal in between the seizures. Brain MRI was normal. Seizures resolved two months later after treatment with levetiracetam. His mother had a history of infantile seizures. Infantile epilepsy panel was **positive for *PPRT2* gene mutation**. The interictal EEG during a cluster shows spikes over the left parietal region.

SECTION 3. 5: EPILEPSY OF INFANCY WITH MIGRATING FOCAL SEIZURES

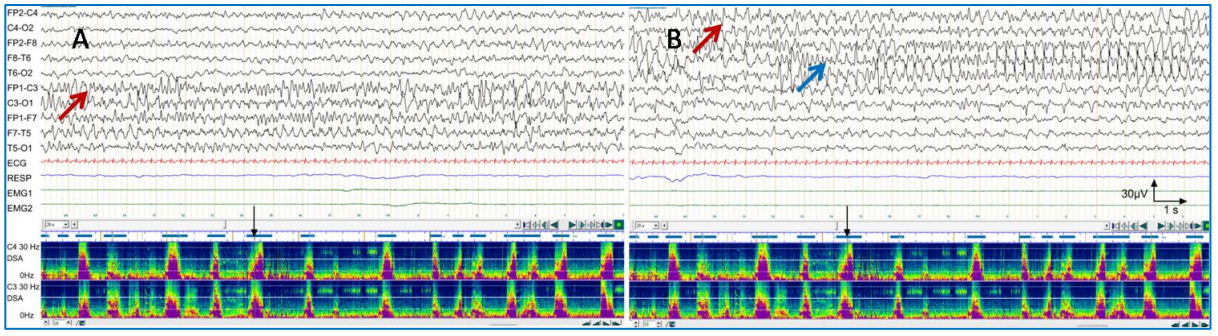


Figure 3.28. Focal migrating seizures from the left frontotemporal area (**A**, red arrow) to the right frontotemporal (**B**, red arrow) and then to the right posterior areas (**B**, blue arrow) recorded during status epilepticus in a five-month-old girl. Traces A and B show two 20-second epochs selected from the same migrating seizure (back arrows). The density spectral array (DSA) (0-30 Hz) at the bottom of both traces depicts activities from C4 and C3 electrodes over eight hours of recording. Migrating seizures occurred with a frequency of 1-2/hour and lasted for 5-15 minutes each.

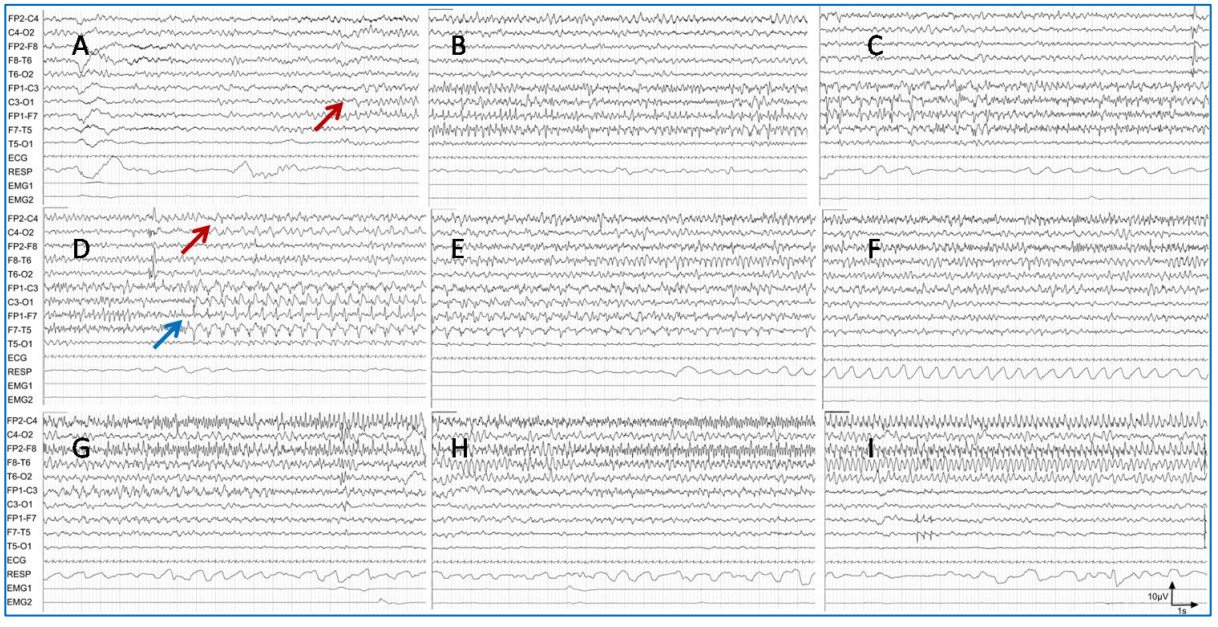


Figure 3.29. Focal migrating seizure recorded during status epilepticus in the same girl. Nine 20-second sections have been selected from this five-minute continuous seizure. The seizure onset occurs over the left frontal-central areas with rhythmic theta waves and sharp waves intermixed with slow spikes (**A**, red arrow). After a few minutes, the seizure activity "migrates" to the contralateral frontal-central areas (**D**, red arrow), while it slows down on the left and ends (**D**, blue arrow and **E**). The seizure continues on the right with rhythmic alpha-like activity (**E-H**) and then theta rhythmic waves (**I**) intermixed with spikes.

4. CHILDHOOD

SECTION 4.1: FEBRILE SEIZURES AND GEFS+

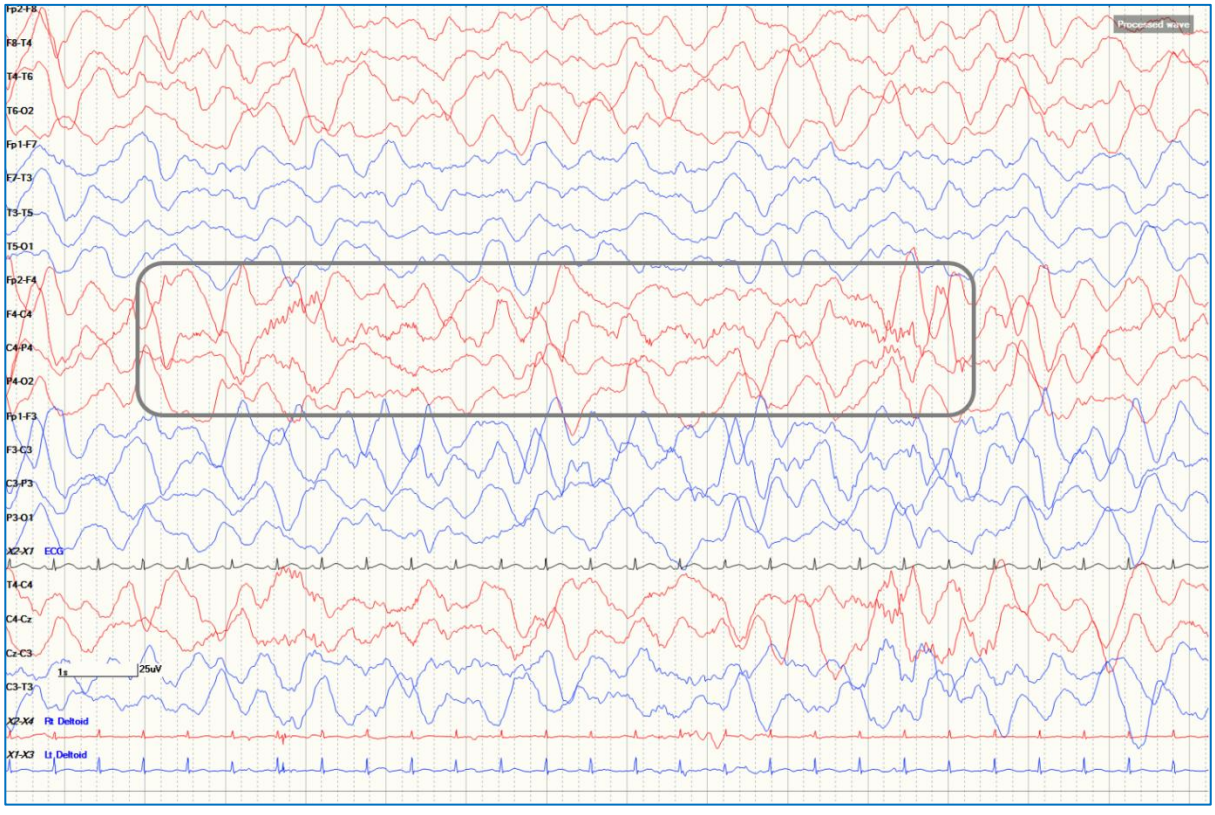


Figure 4.01. A five-year-old girl presented with a first episode of **febrile status epilepticus**. Seizures were noted to be focal at onset, with right arm involvement. Note the **diffuse slowing of the EEG background** in this recording, performed **24 hours after the resolution of the status**. Also, note asymmetries, as spindles are still seen over the right hemisphere (rectangle), whereas the left temporal region appears comparatively attenuated, suggestive of left hemisphere pathology.

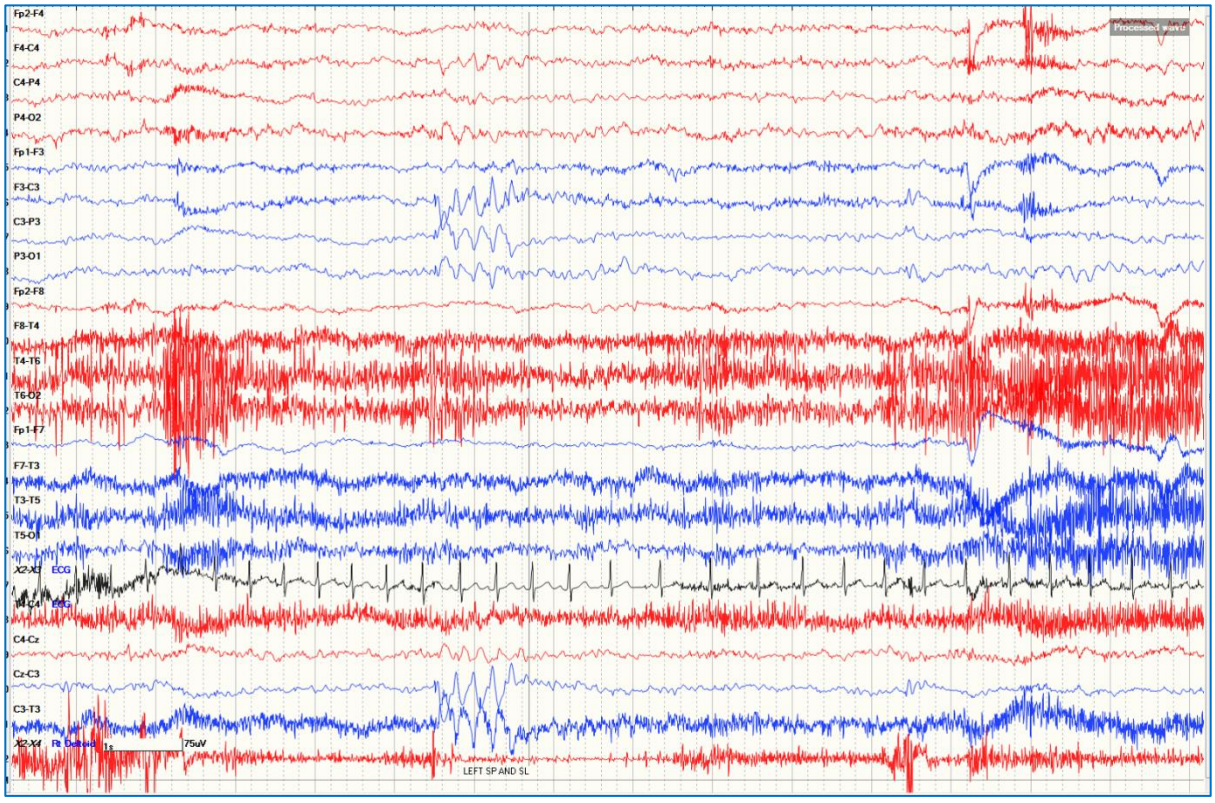


Figure 4.02. A 22-month-old boy with a history of four seperate episodes of **complex febrile generalised tonic-clonic seizure**s. **Interictal EEG** shows normal backgroud and a single burst of spike-and-wave discharge mainly over the left centro-parietal region.

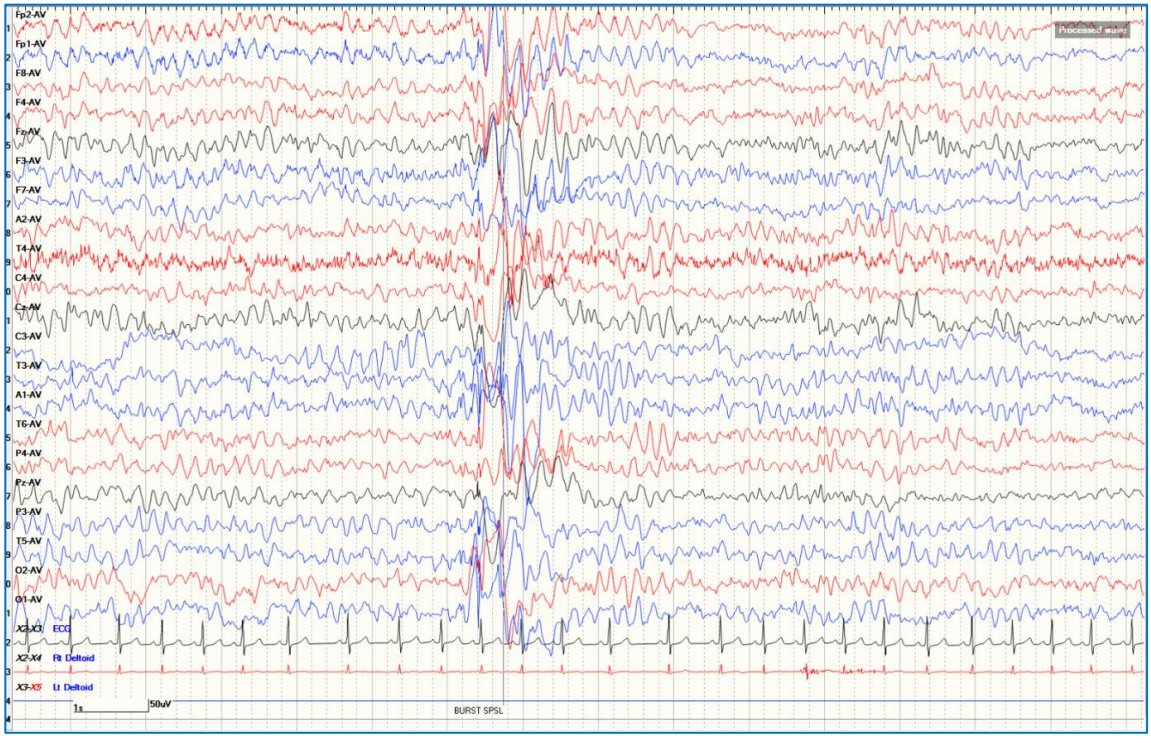
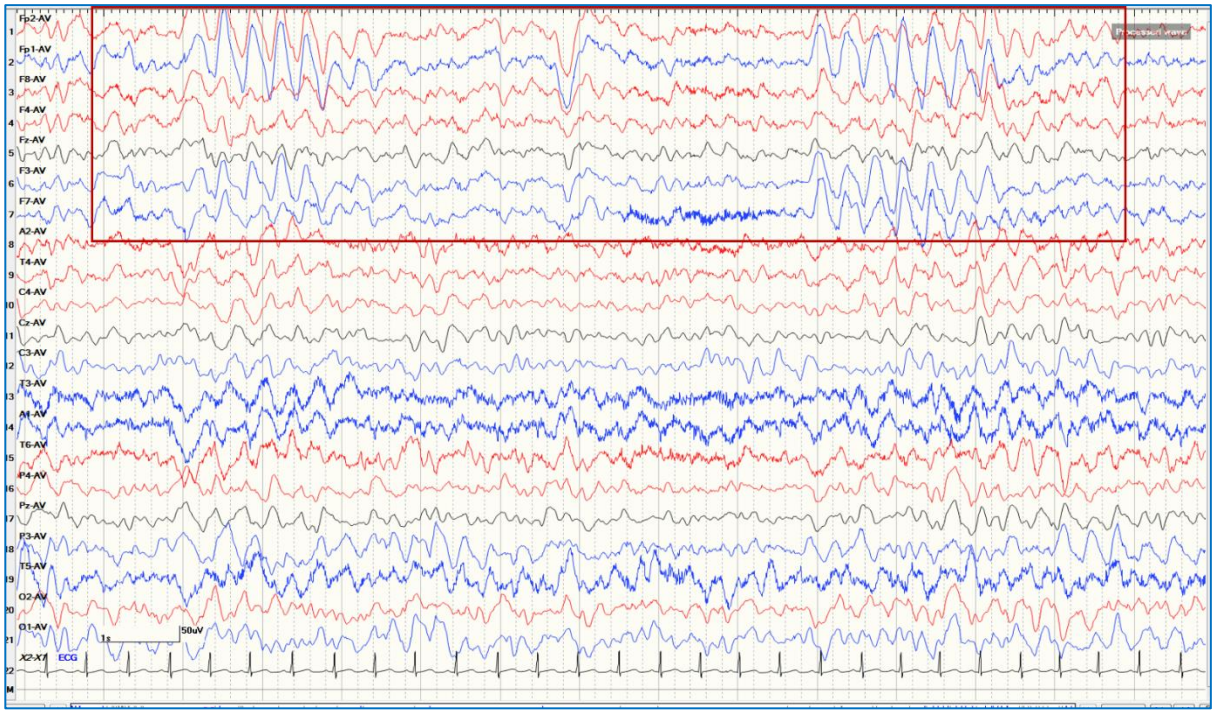
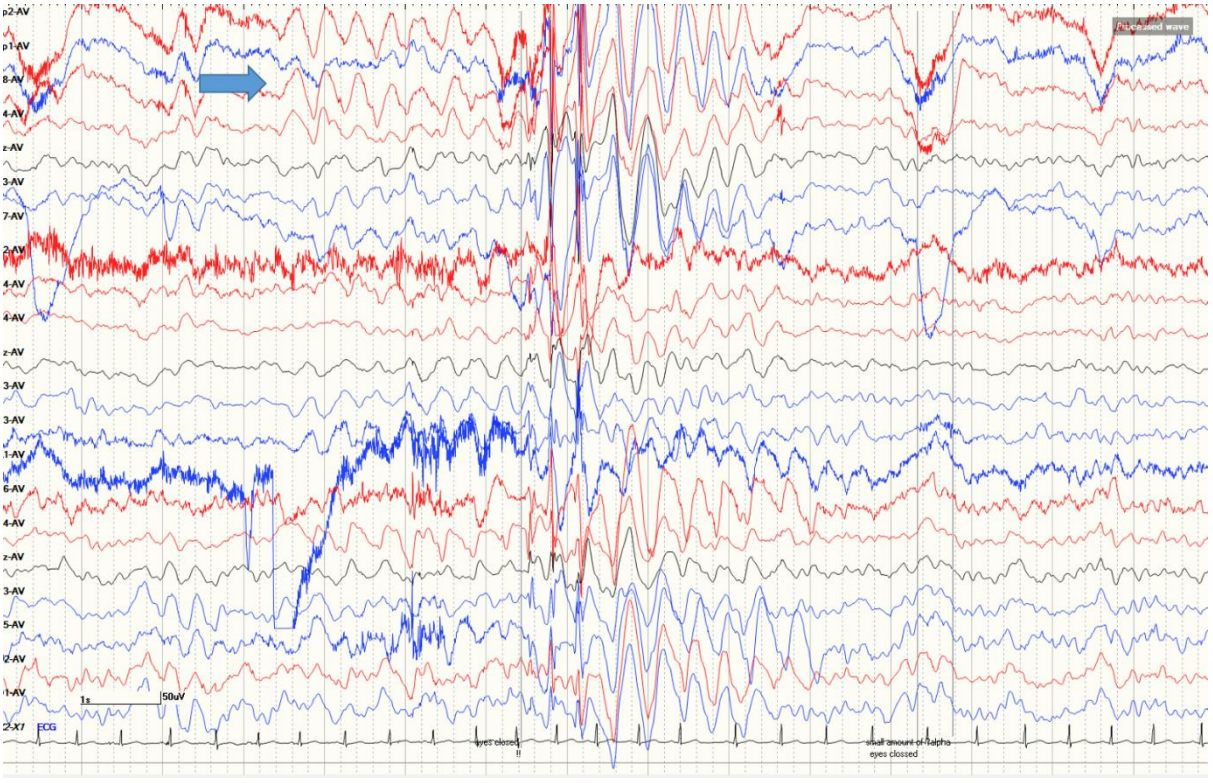


Figure 4.03. Follow-up EEG of the previous child, now 29 months old. He had no further seizures and he is not on any anti-seizure medication. Sleep EEG showed a single irregular burst of bilateral high-voltage slow waves, associated with focal spikes.


Fp2-AV
Fp1-AV
F8-AV
F4-AV
Fz-AV
F3-AV
F7-AV
A2-AV
T4-AV
C4-AV
Cz-AV
C3-AV
T3-AV
A1-AV
T6-AV
P4-AV
Pz-AV
P3-AV
T5-AV
O2-AV
O1-AV
1s
50uV
X2-X1
ECG


Processed wave
1s
50uV
X2-X1
ECG
eyes closed
small amount of alpha
eyes closed

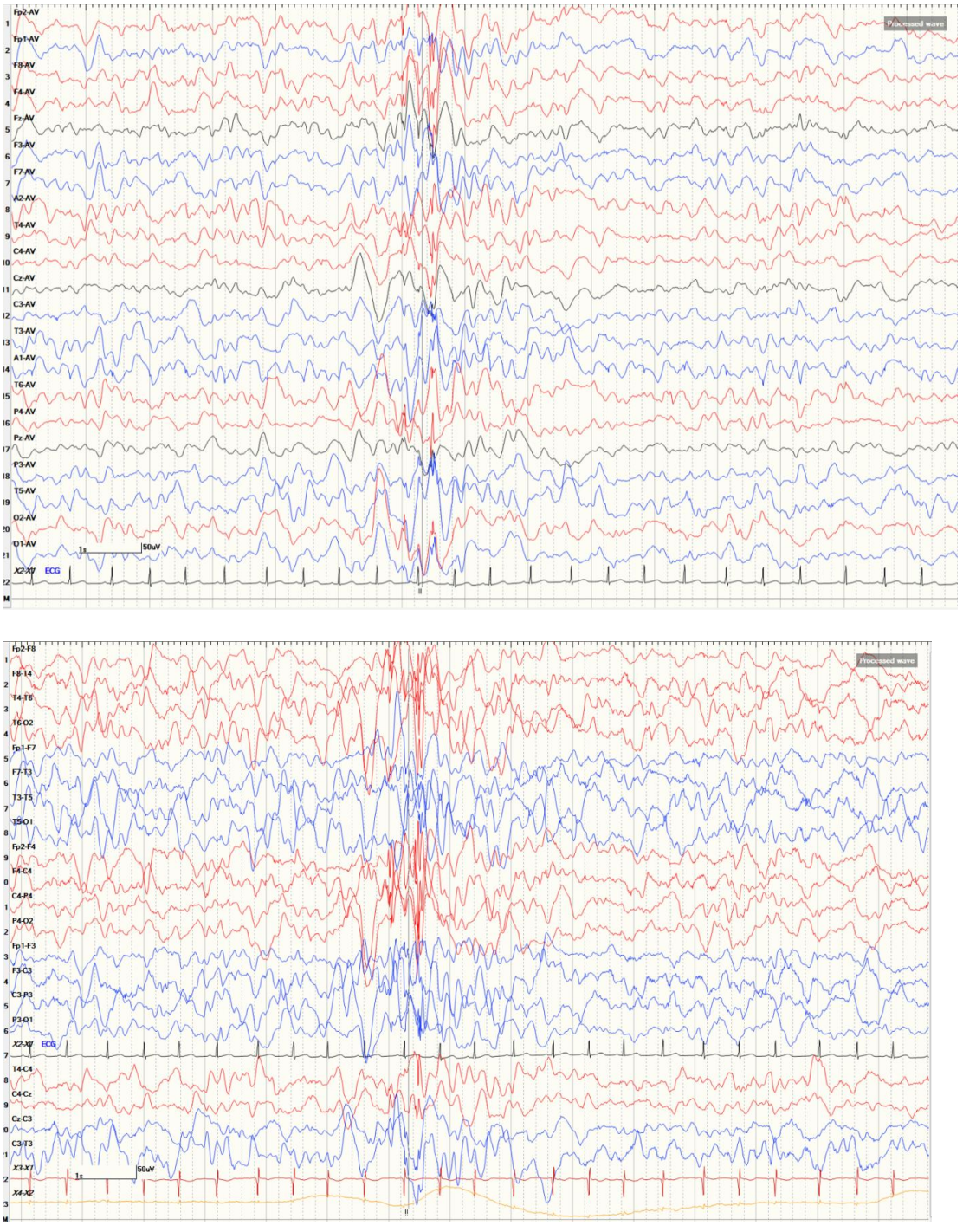


Figure 4.04. Three-year-old girl with **recurrent febrile and subsequent afebrile generalised tonic-clonic seizures** since the age of five months. Family history was positive (for sister, mother, and maternal aunt). The patient had maternally inherited variants of *SCN1A.* Early EEGs at age one and two years were normal. At age eight, she continues to have seizures on medication, but subsequent sleep EEGs have been normal. Her EEG at the age of three years shows: notched slow waves over the left frontal region during wakefulness, diffusing to the right frontal region (**A**); brief bursts of diffuse bilateral slow waves with a bifrontal emphasis and embedded spikes (note the right frontal lead-in to the burst of more diffuse and widespread slow waves associated with spikes (**B**, arrow); and a brief burst of irregular diffuse slow waves in sleep, associated with bilateral spikes, more evident on the right (**C**, **D**). (**C)** and (**D)** show the same discharge on common average and double banana, respectively.

SECTION 4.2: SELF-LIMITED ROLANDIC EPILEPSY

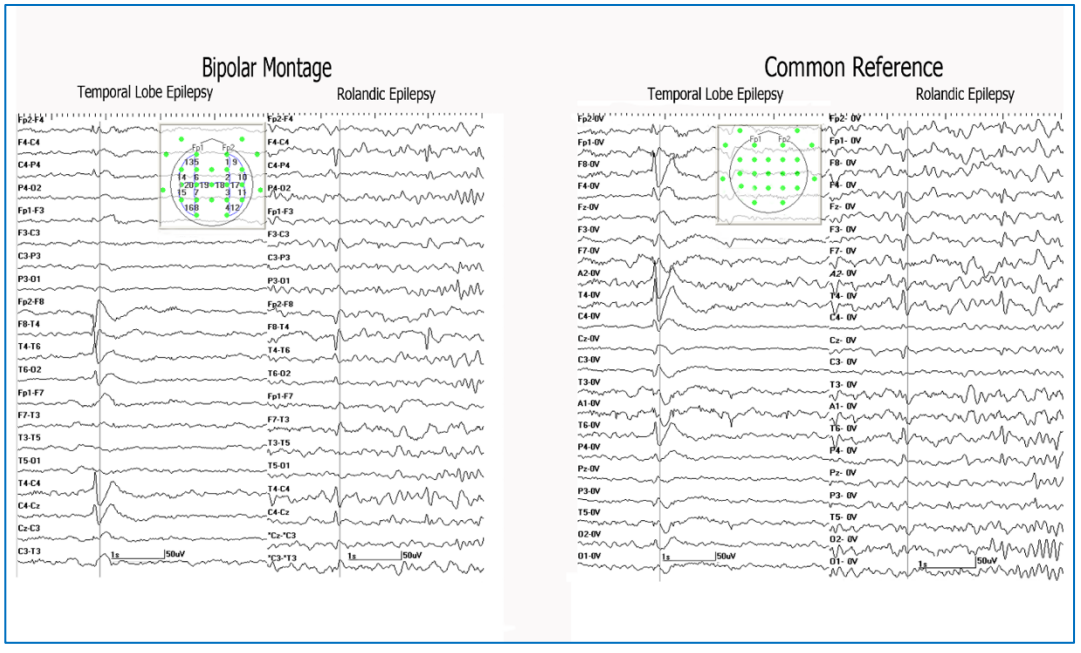


Figure 4.05. Comparison between the typical mid-temporal focal spike in **symptomatic lateral temporal lobe epilepsy** (left half of traces) and the also **typical rolandic spike** in the self-limiting BRE with CTS. Note the differences in the spike topography and polarity over the anterior brain areas and the differences between the two montages (bipolar anterior-posterior or "double banana" and average reference). Reproduced with permission from Koutroumanidis *et al*. (2017).

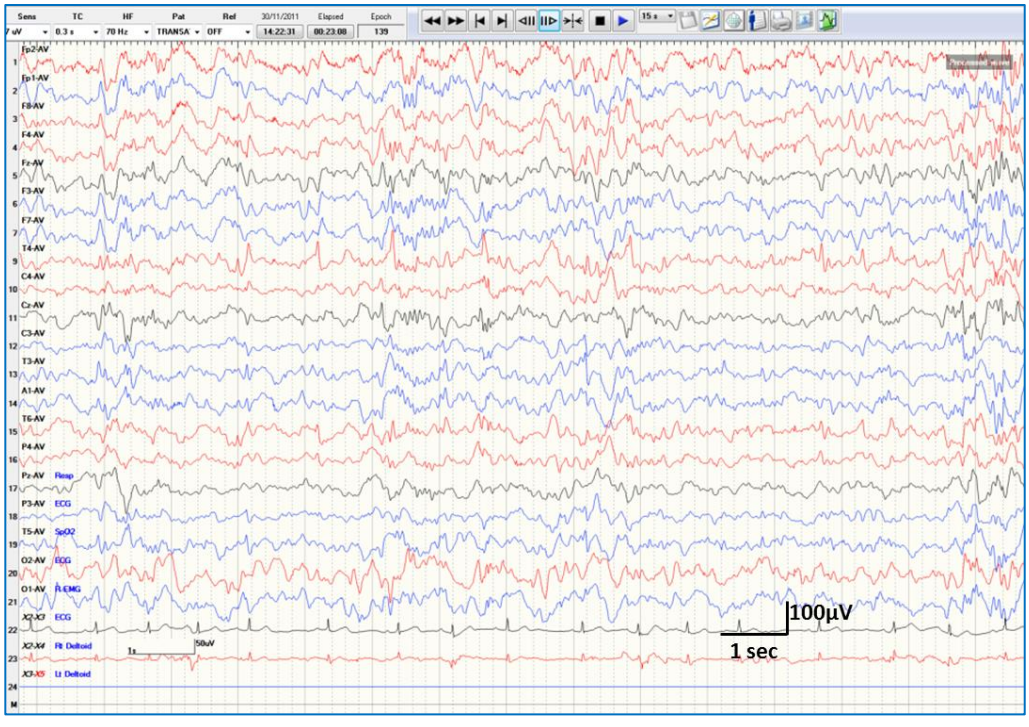


Figure 4.06. An eight-year-old boy presenting with three nocturnal seizures with mouth and tongue deviation followed by clonic jerking. Note the run of relatively small sharp waves over the right temporal electrode (T4).

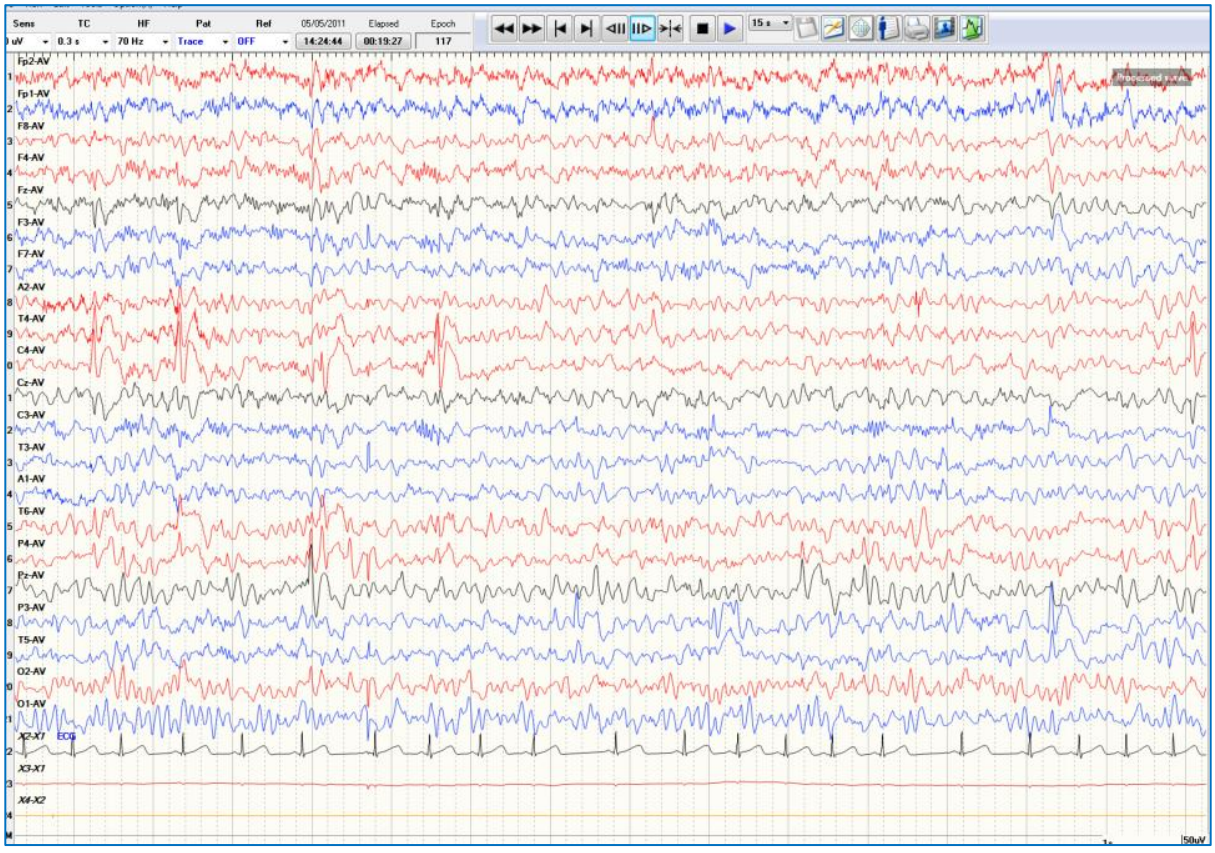


Figure 4.07. A seven-year-old boy presented with two seizures in the early hours of the morning, not associated with high temperature. During the seizures, he shook all over and drooled; he tried to talk during the seizures, but his speech was slurred. The patient had normal delivery at full term and normal development, without a family history of epilepsy. He had a possible febrile convulsion at age five. Note the high-voltage right centrotemporal spikes and independent left parietal-posterior temporal, as well as a few mid-parietal, spikes.

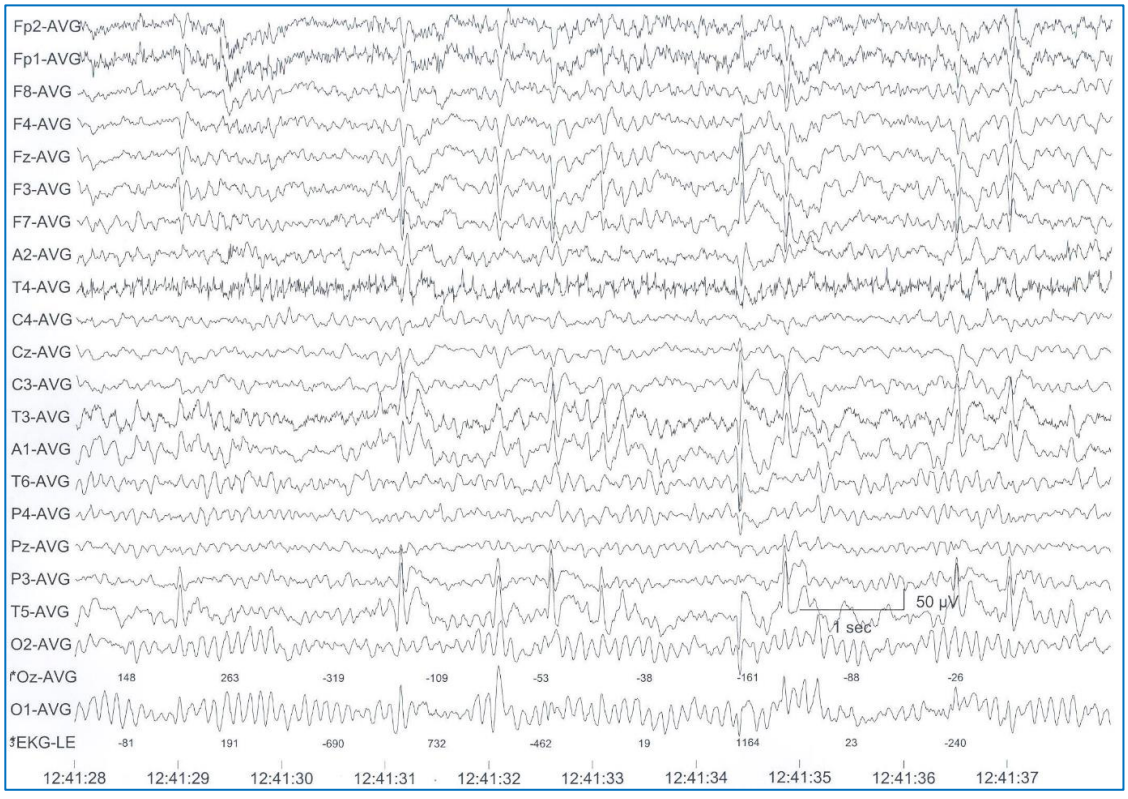


Figure 4.08. Note a mild excess of theta/fast delta activity over the left temporal area, associated with the typical spikes.

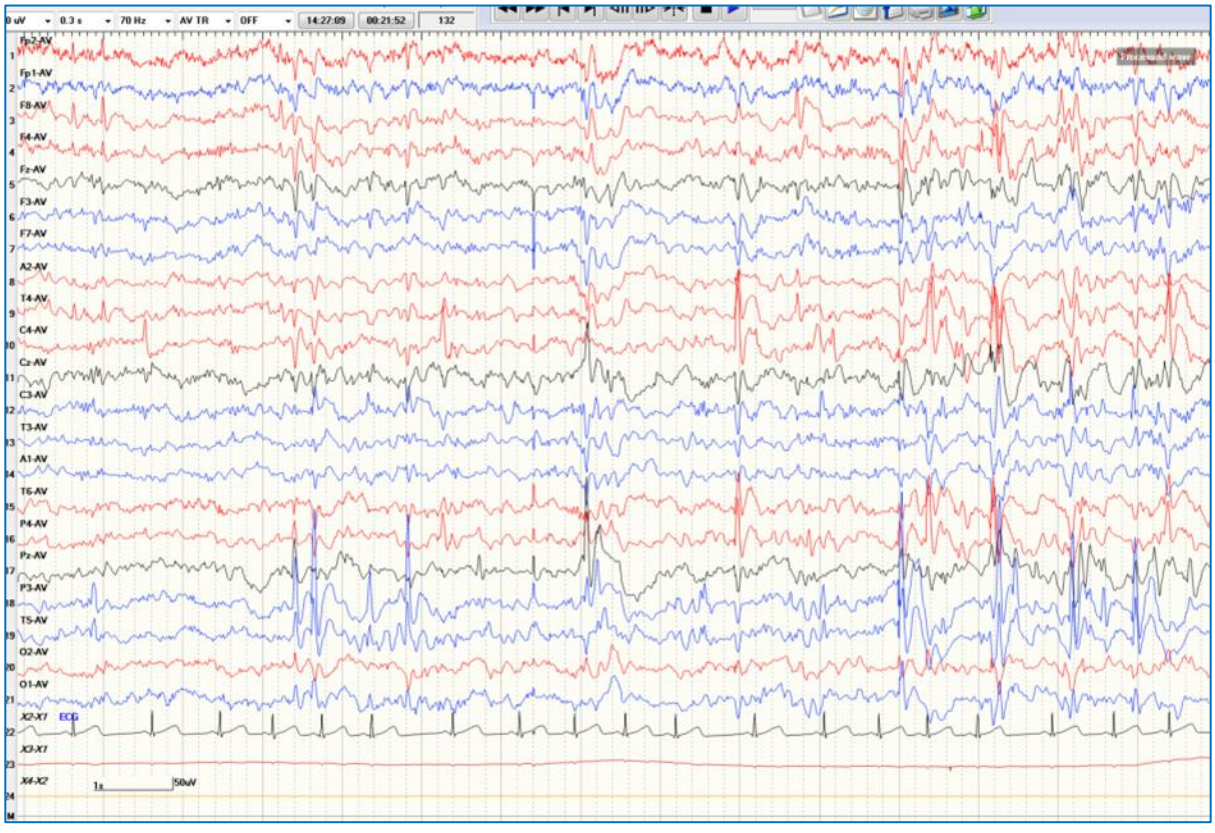


Figure 4.09. Sleep EEG of the child in *figure 4.07*. Note the activation of the independent spikes over the right centro-sylvian, mid-parietal, and left centro-parietal electrodes.

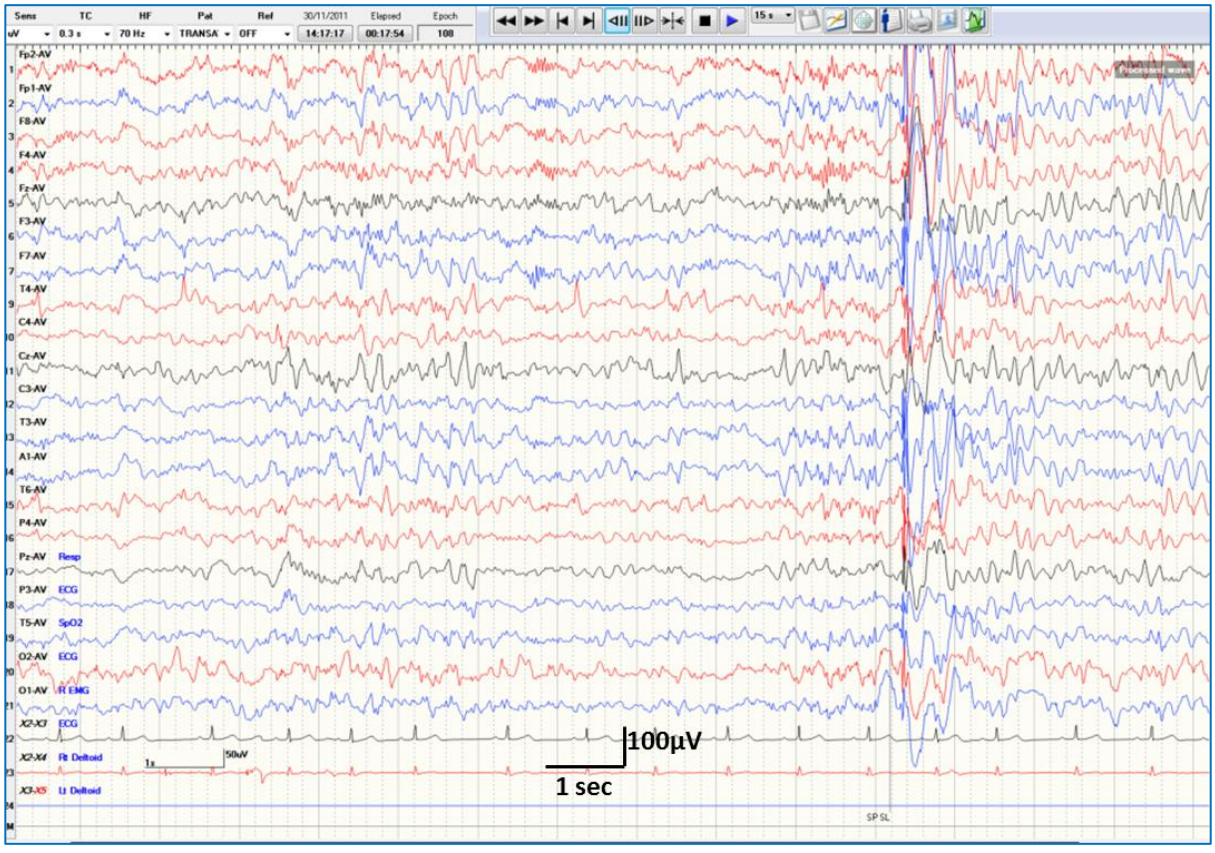


Figure 4.10. Generalized spike-wave discharge during light sleep (Stage 1) of the child in *figure 4.06*.

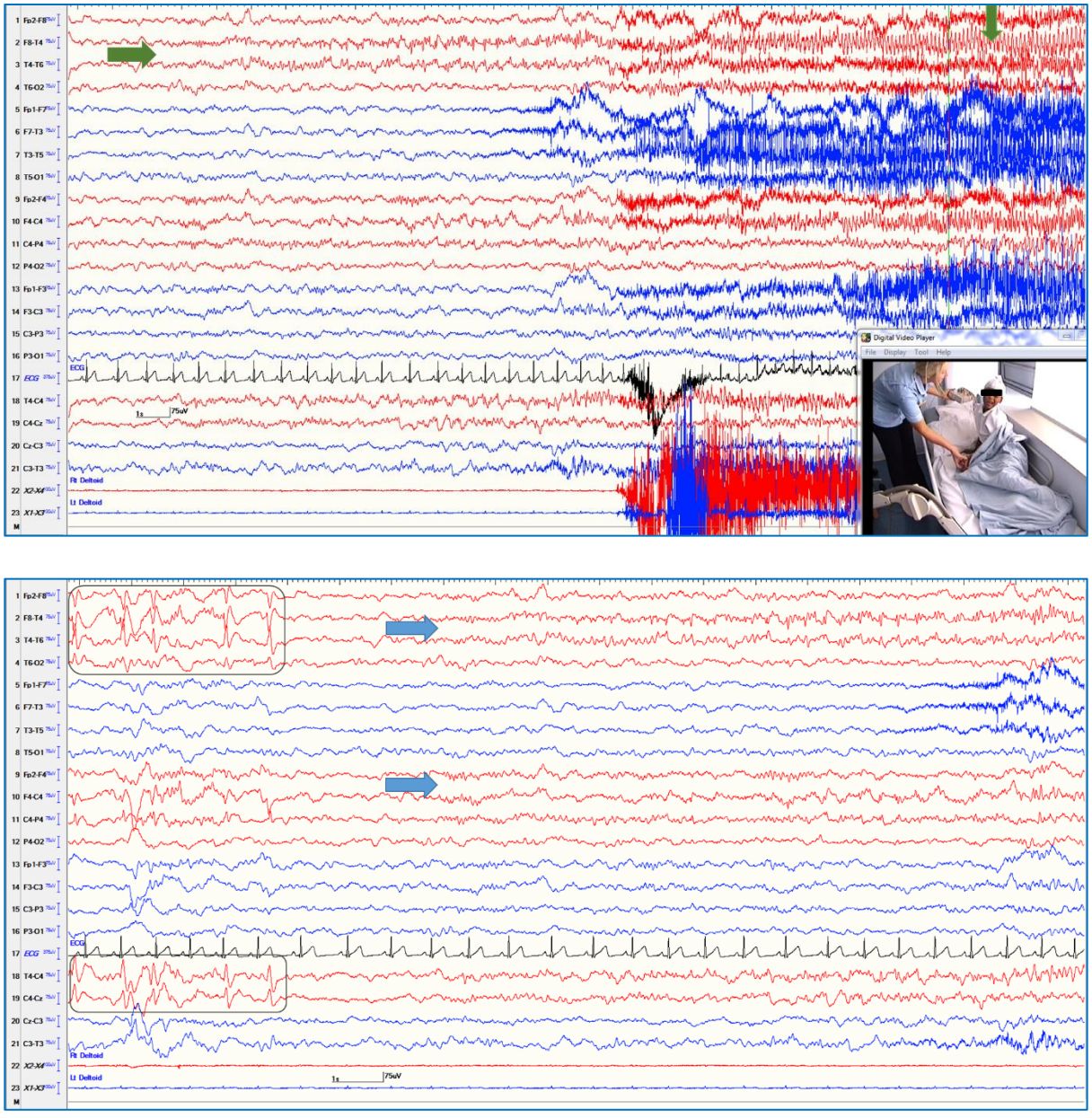


Figure 4.11. (**A**) **Typical rolandic seizure** arising from sleep Stage 2 in a 10-year-old boy with BRE. He suddenly woke and sat up with his eyes open. Initially, the left side of the mouth contorted and deviated to the left (snapshot taken at the time marked by the vertical green arrow), followed by left facial clonus that involved the eyelids. There was a short bilateral tonic posturing and then clonic movements of the left limbs. The seizure lasted one minute and 40 seconds, and promptly after offset he was well oriented in time and place and able to recall the word "red" given to him during the seizure. Postictally, the left side of the mouth appeared to droop, his speech was slurred for a while but not dysphasic, and voluntary movements of the left arm appeared reduced for a few minutes. The electrographic onset of the seizure occurs over the right lateral temporal-central area (horizontal green arrow) and is presented in more detail in *figure 4.11B.*

(**B**) **Electrographic onset of the rolandic seizure of *figure 4.11A*.** Note the typical interictal centrotemporal spikes on the left side of the figure (panels) and their relationship with the k-complex and the associated sleep spindles. The onset of the ictal activity occurs over the right centro-temporal area (blue arrows) and consists of alpha-like rhythm that soon incorporates rhythmic spikes, which show exactly the same topography and polarity as the interictal CTS, but are much smaller in voltage.

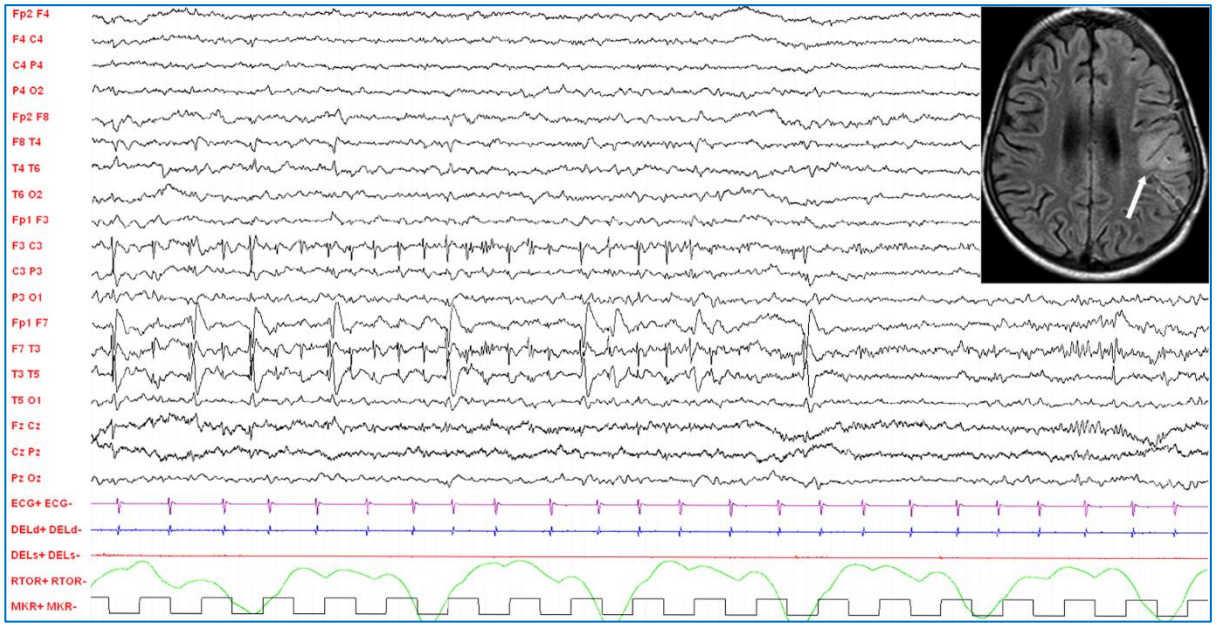


Figure 4.12. EEG recording of a four-year-old girl showing normal background activity with superimposed spikes in the left centro-temporal region. FLAIR MRI scan showed **focal cortical dysplasia involving the left rolandic region** (from Guerrini R and Pisano T; Pal *et al*. [2016]).

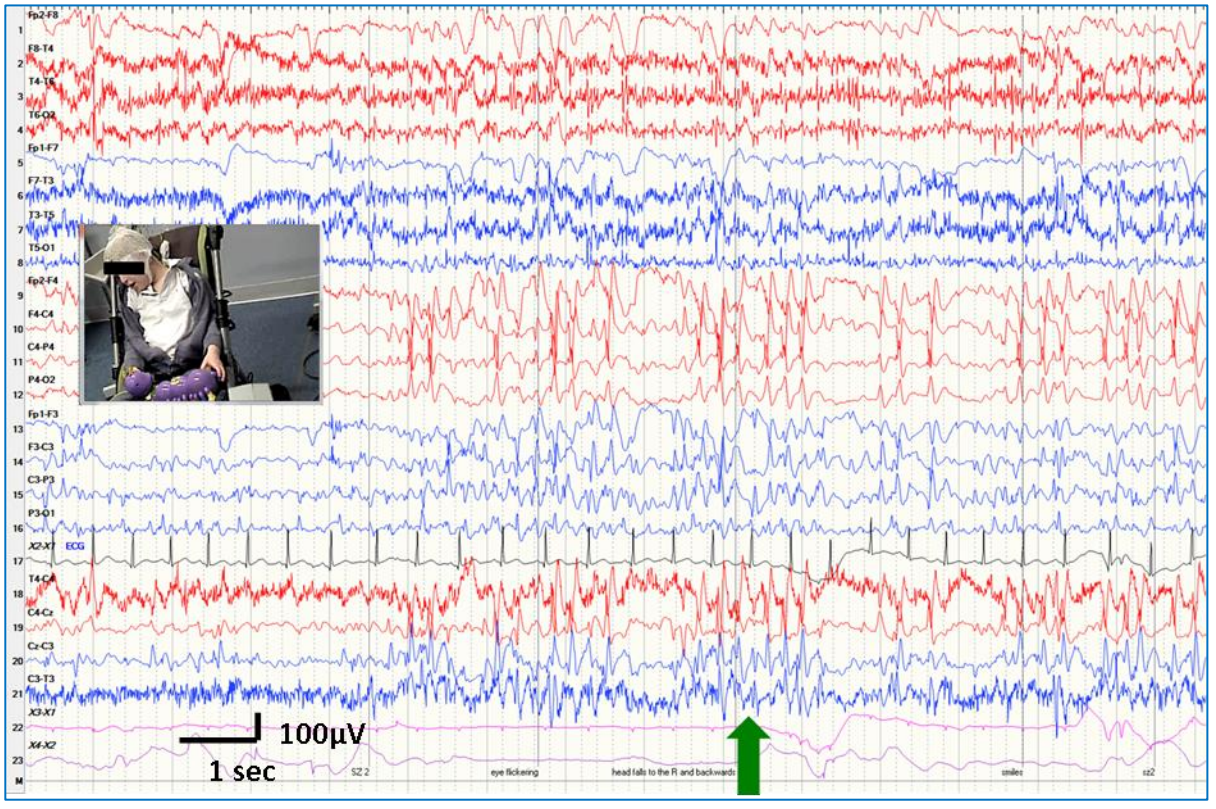


Figure 4.13. A 10-year-old boy with typical rolandic seizures developing atonic seizures and **ESES**. The green arrow marks the time when his head drops to the right and backwards.

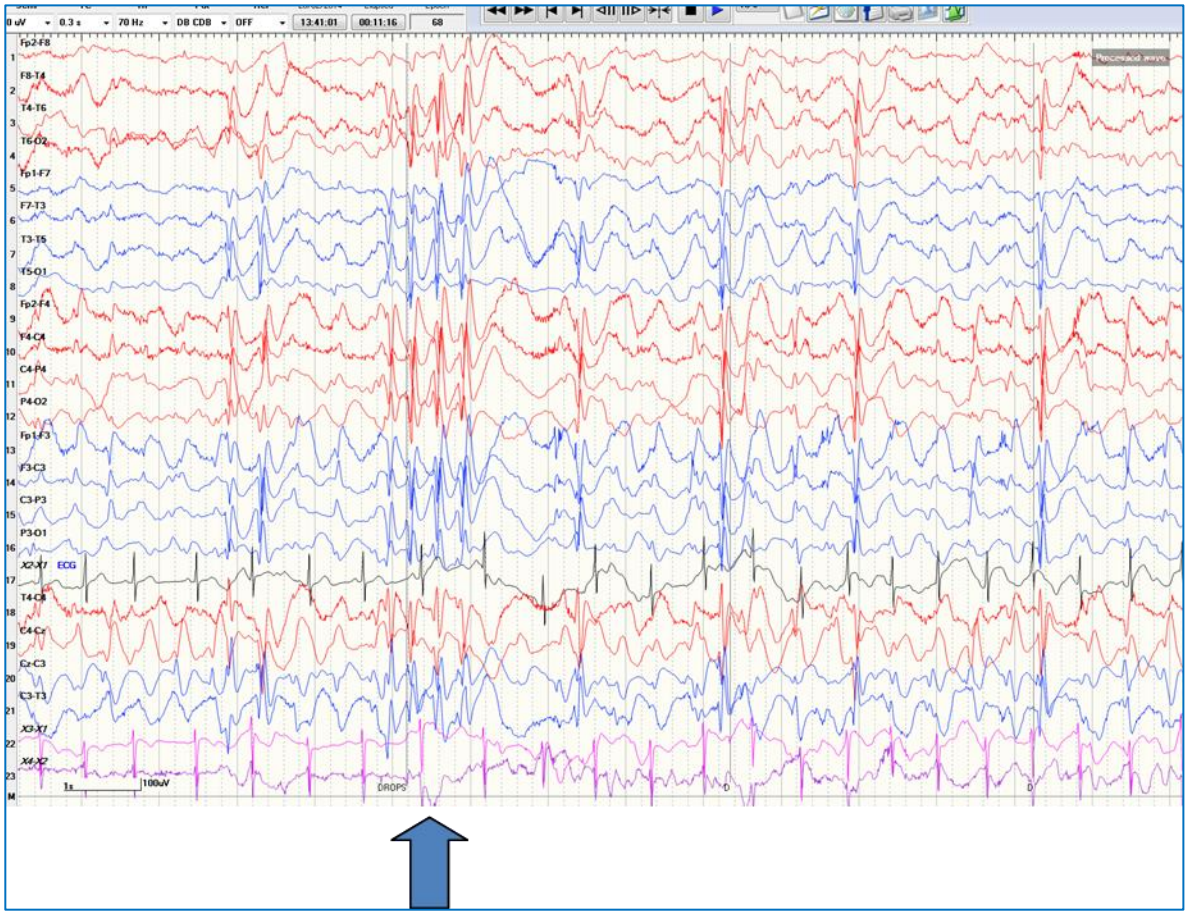


Figure 4.14. A three-year-old girl presented with nocturnal seizures consistent with **Rolandic Epilepsy** (though atypical for age at onset). At age four, she showed decline in cognition and frequent nocturnal seizures and falls (drop attacks) during the day. Brain MRI was normal. Awake video EEG shows runs of bilateral spike-and-wave discharges clinically associated with subtle head drops (blue arrow).

SECTION 4.3: PANAYIOTOPOULOS SYNDROME

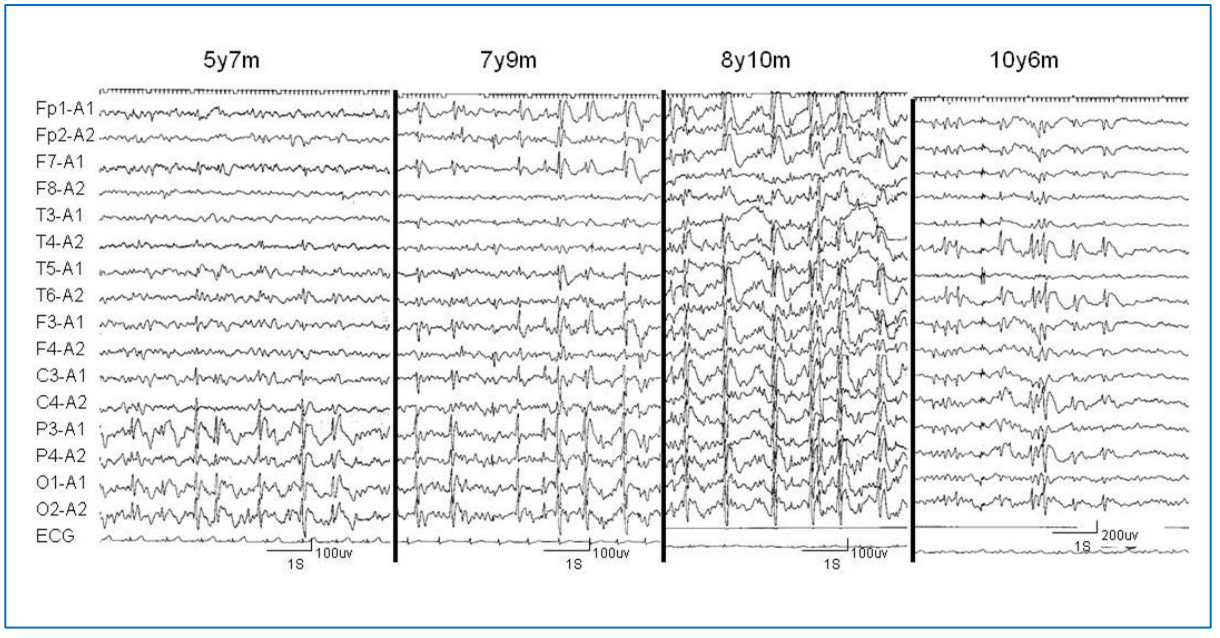


Figure. 4.15. Evolution of epileptiform discharges in a girl with **Panayiotopoulos Syndrome**. The first sleep EEG was recorded at age five years and seven months, and showed bilateral parietal-occipital sharp-slow discharges. Discharges involved the bilateral frontopolar regions at age seven years and nine months and became almost diffuse at age eight years and 10 months. They finally localized in the right centro-temporal-parietal region at age 10 years and six months.

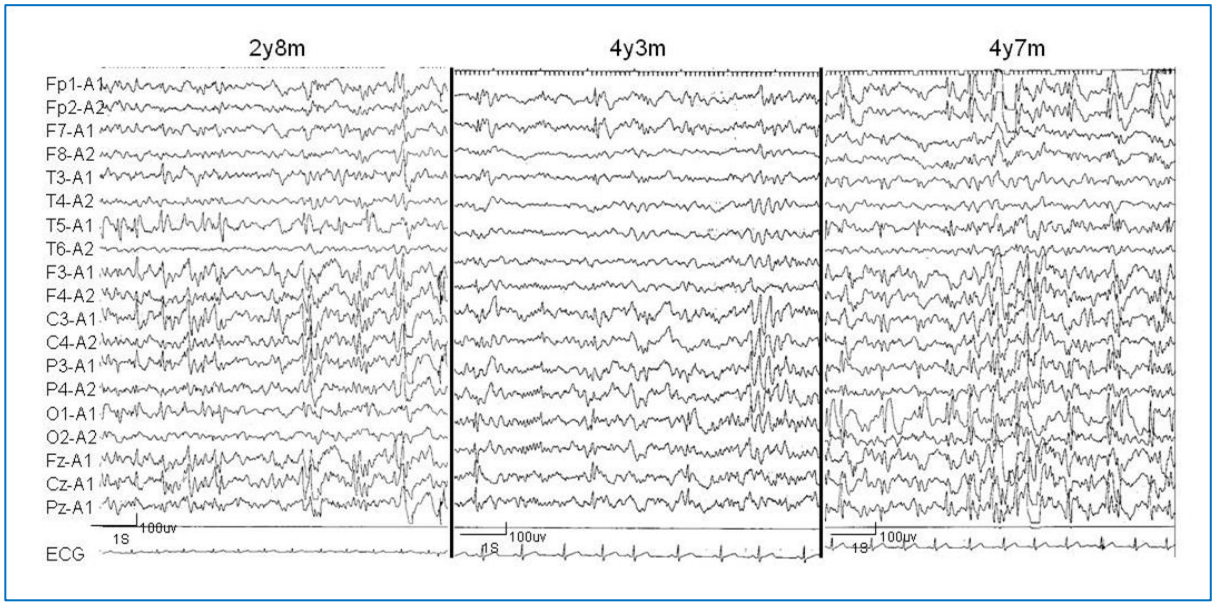


Figure. 4.16. Evolution of epileptiform discharges in a boy with **Panayiotopoulos Syndrome**. The first sleep EEG, performed incidentally at age two years and eight months, showed sharp waves over the wider left central-temporal-posterior temporal regions. At age four years and three months, the sleep EEG showed independent and synchronous occipital and frontopolar spike discharges, which became more active three months later.

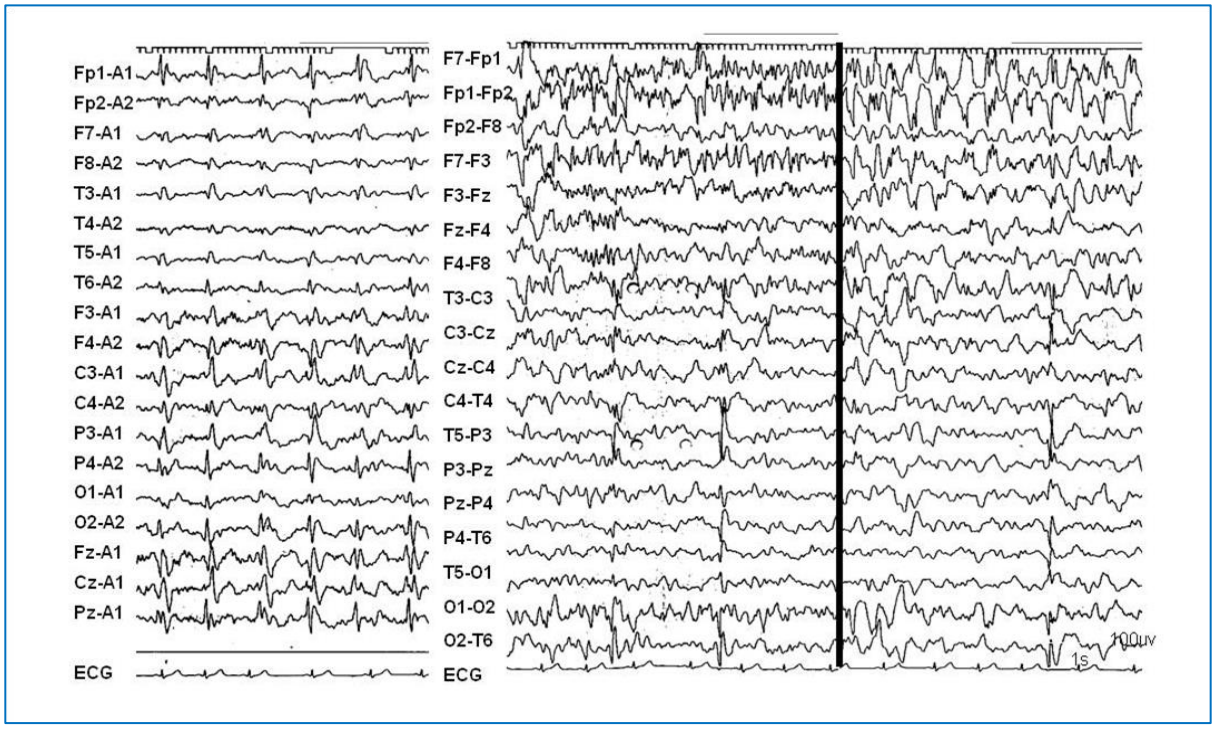


Figure. 4.17. Interictal EEG (left panel) and an electrographic EEG seizure (middle and right panels) in a six-year-old girl with **Panayiotopoulos Syndrome**. The sleep EEG showed interictal left frontopolar and bilateral parietal-occipital spike-wave discharges, occurring synchronously. The seizure discharge started from and remained confined to the left frontopolar region. There were no clinical accompaniments (subclinical seizure).

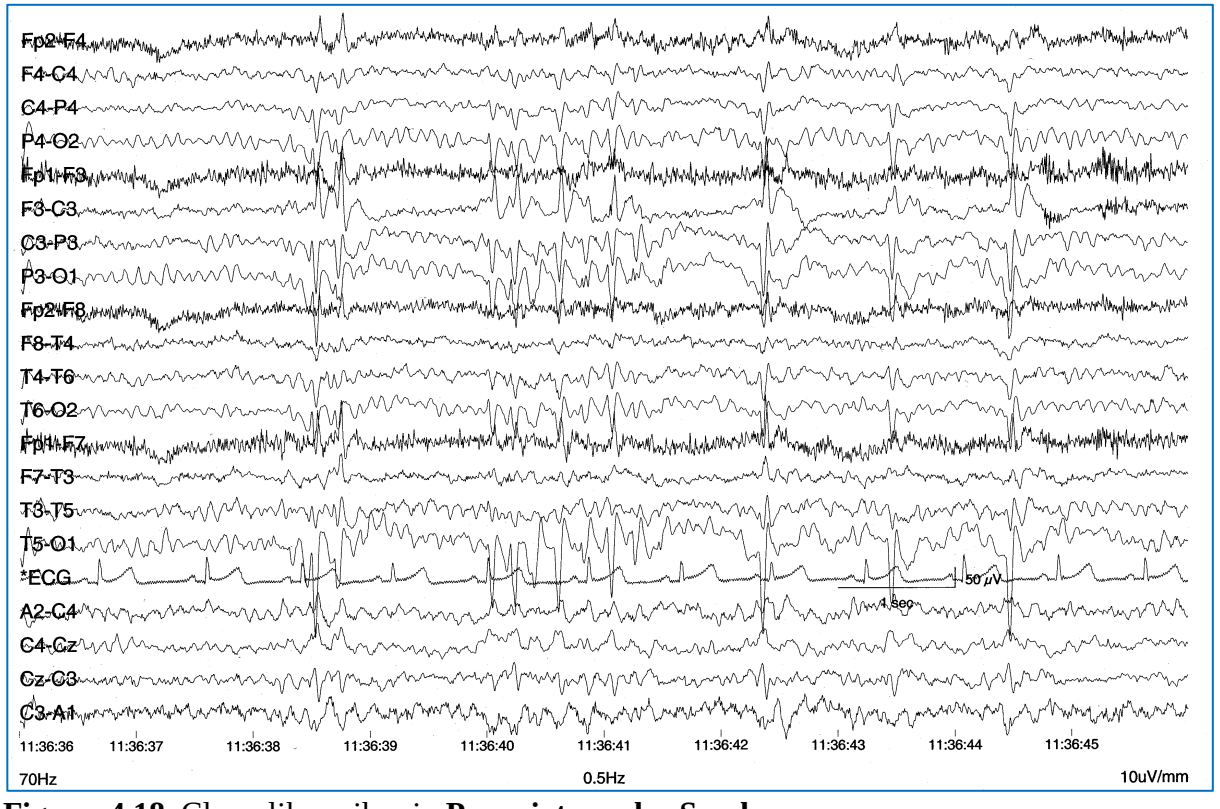


Figure. 4.18. Clone-like spikes in **Panayiotopoulos Syndrome**.

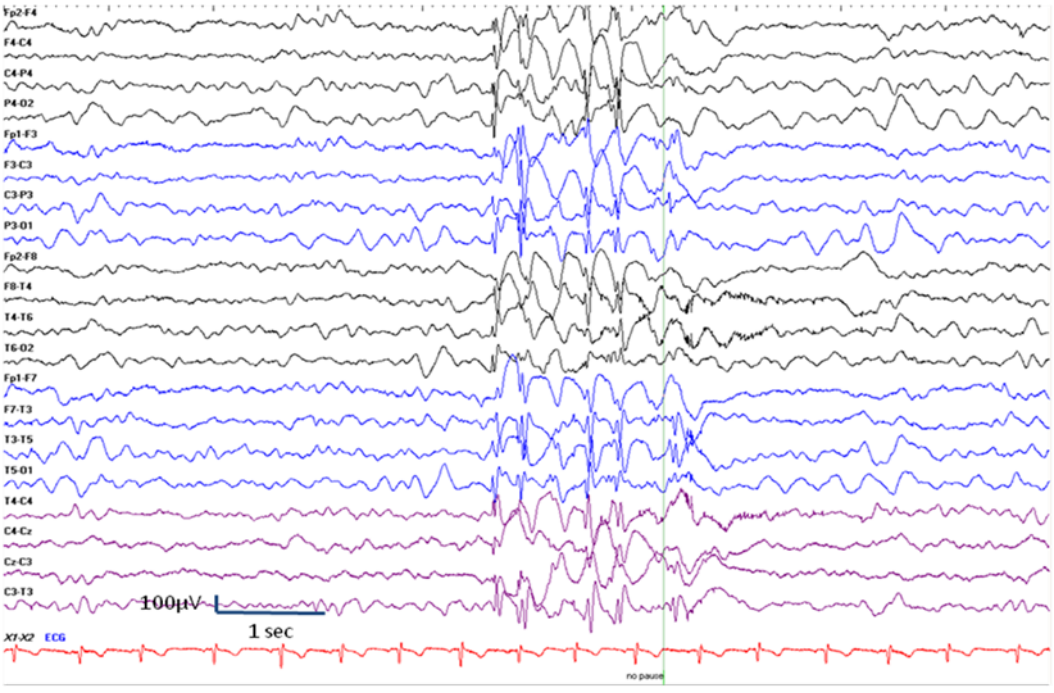


Figure. 4.19. Generalized spike-wave discharge during hyperventilation in a six-year-old boy with **Panayiotopoulos Syndrome**. Note the similarities to the generalized discharges in occipital epilepsy of Gastaut and benign rolandic epilepsy and the differences with the robust generalized spike-wave discharges in childhood absence epilepsy (*see relevant chapters*).

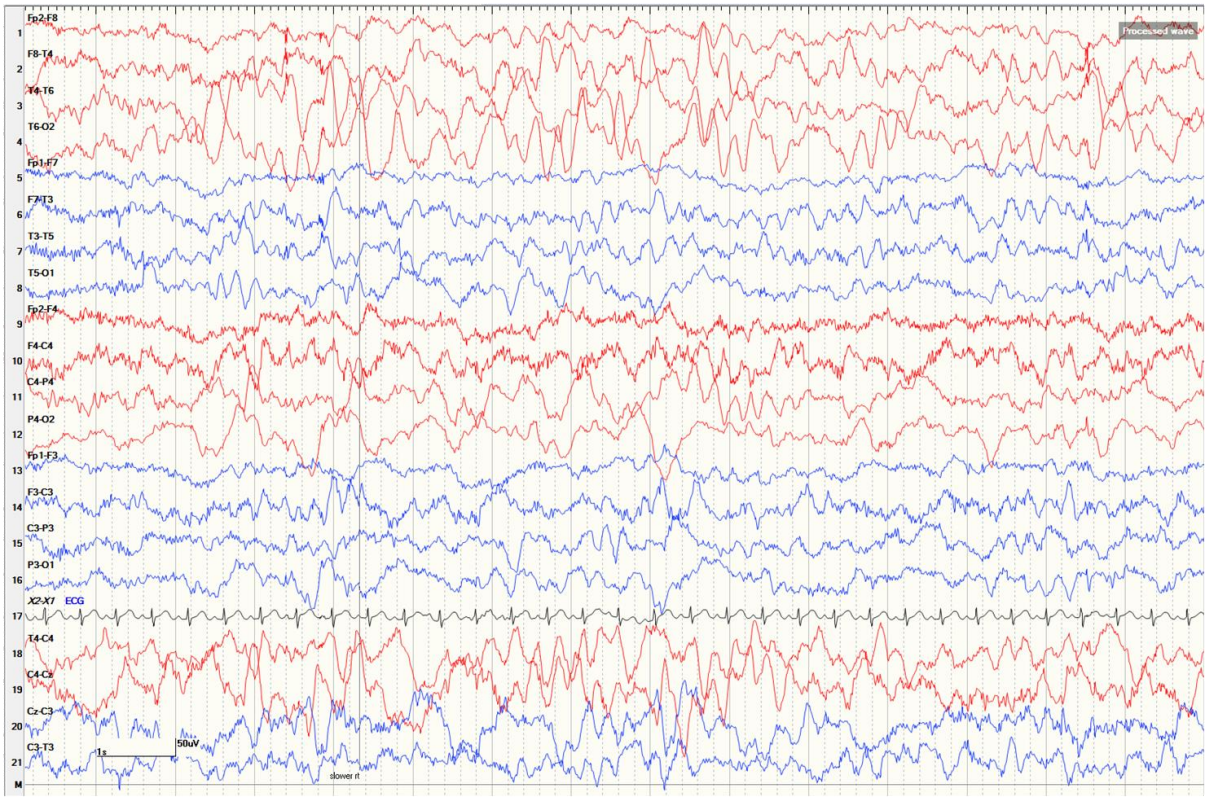


Figure. 4.20. Video-EEG recorded for a three-year-old girl with **Panayiotopoulos Syndrome** two days after an episode of non-convulsive autonomic status epilepticus. She suddenly became pale and started vomiting. Several minutes later, she collapsed and became unresponsive, and

subsequently eyes deviated to the left with left limb jerking. The seizure lasted more than 30 minutes and resulted in admission to the paediatric intensive care unit. At the time of this recording, the girl was fully alert and cooperative. Note the postictal slowing that still persists over the right posterior quadrant. An EEG three months later was normal.

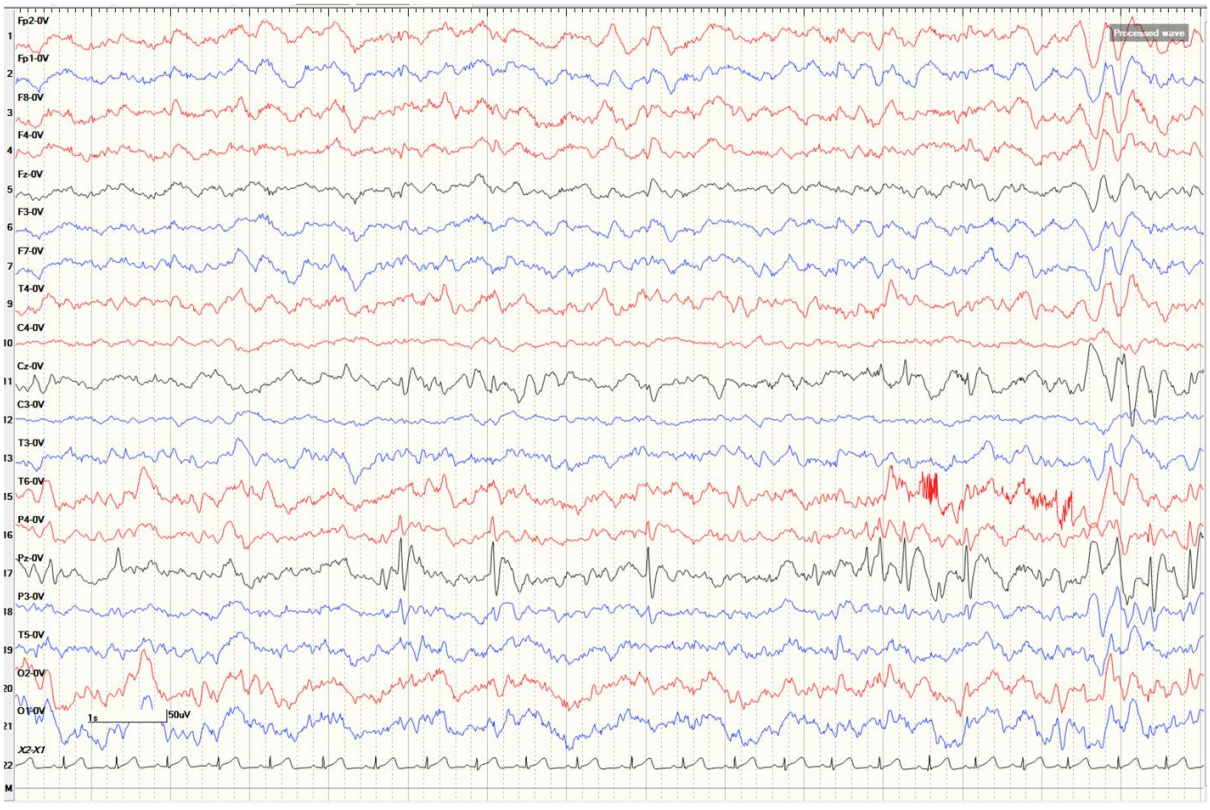


Figure. 4.21. Sleep EEG of the girl of *figure 4.19*, now four years old. Her seizures continued and she could describe a warning of a headache. She would then become floppy and unresponsive for about 10 minutes. Note the typical high-voltage spike-wave complexes over the parietal midline that occurred only during sleep.

SECTION 4.4: OCCIPITAL CHILDHOOD EPILEPSY OF GASTAUT TYPE

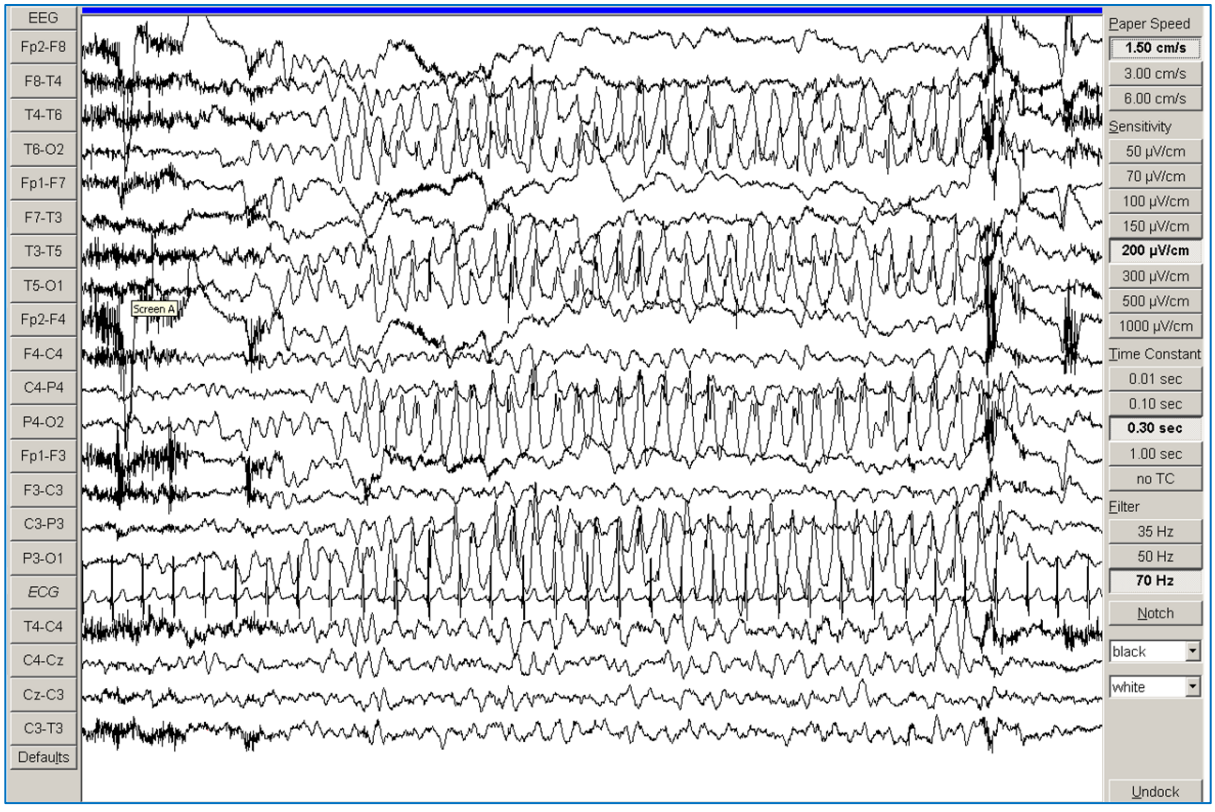


Figure 4.22. Occipital paroxysms during wakefulness while eyes are closed.

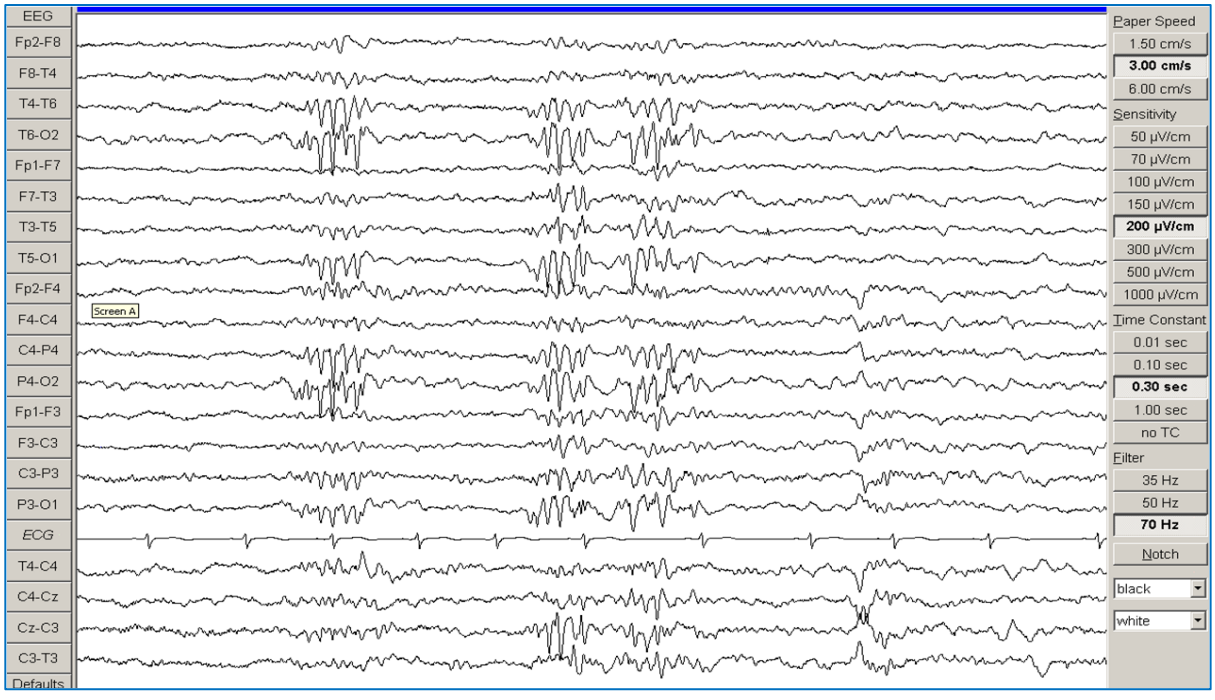


Figure 4.23. Occipital spikes/sharp waves during sleep in an eight-year-old boy with occipital epilepsy of **Gastaut type**.

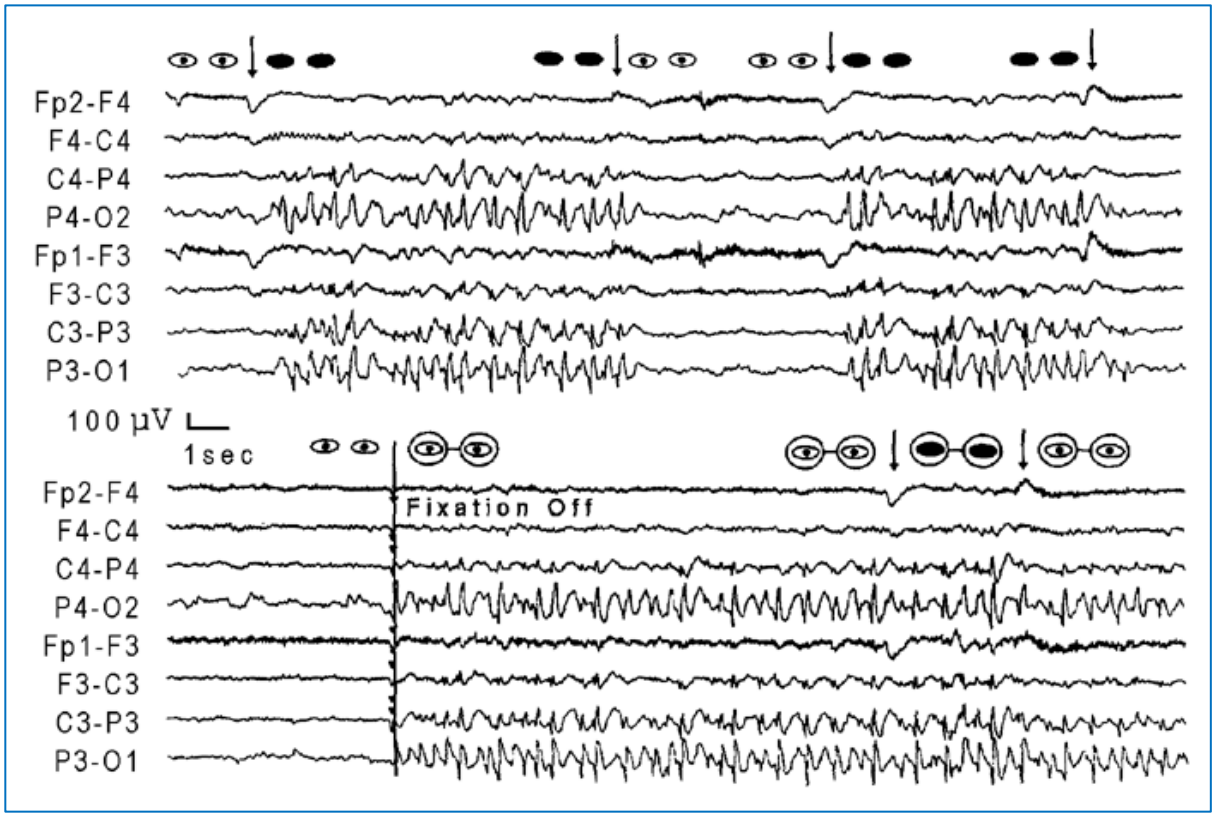


Figure 4.24. Effect of eyes closed and open on occipital paroxysms in routine EEG recording. Upper trace: high-amplitude, continuous occipital sharp and slow wave complexes (occipital paroxysms) occur immediately after closing of the eyes and last for as long as the eyes remain closed. The EEG normalises immediately after opening of the eyes and for as long as the eyes are open with visual fixation (the child is looking at an object). Lower trace: effect of the elimination of central vision and fixation on occipital paroxysms in a well-lit room. Here, this is achieved by +10 spherical lenses, although underwater goggles covered with semi-transparent tape could also be used.

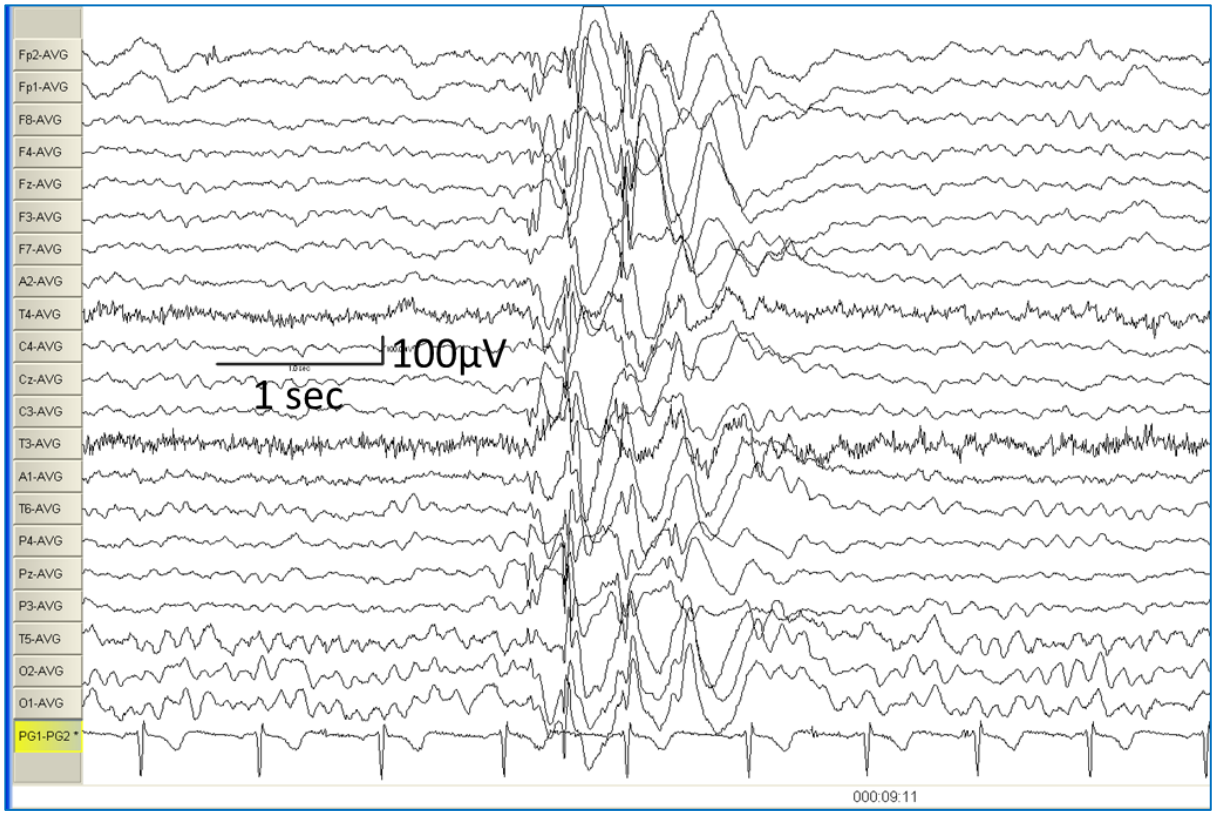


Figure 4.25. Generalized spike-wave discharge in a child with **OE-Gastaut type**. Identical discharges also occur in BRE and PS (*see relevant chapters*). Compare these GSWD with the typical 3-Hz GSWD of IGE (*see chapter on CAE*).

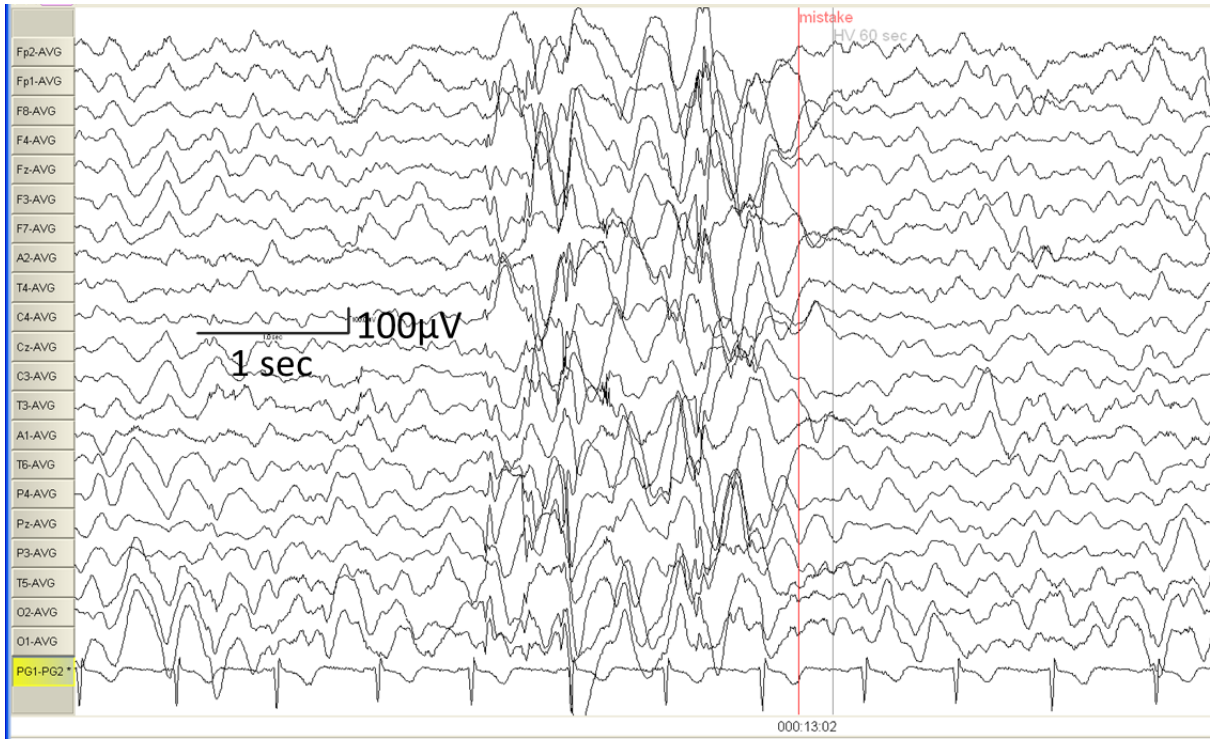


Figure 4.26. Generalized Spike-Wave Discharge in the child of *figure 4.24* during hyperventilation. Note the longer duration and also that the child made a mistake in breath counting (marked by the technologist with the red line at the end of the discharge).

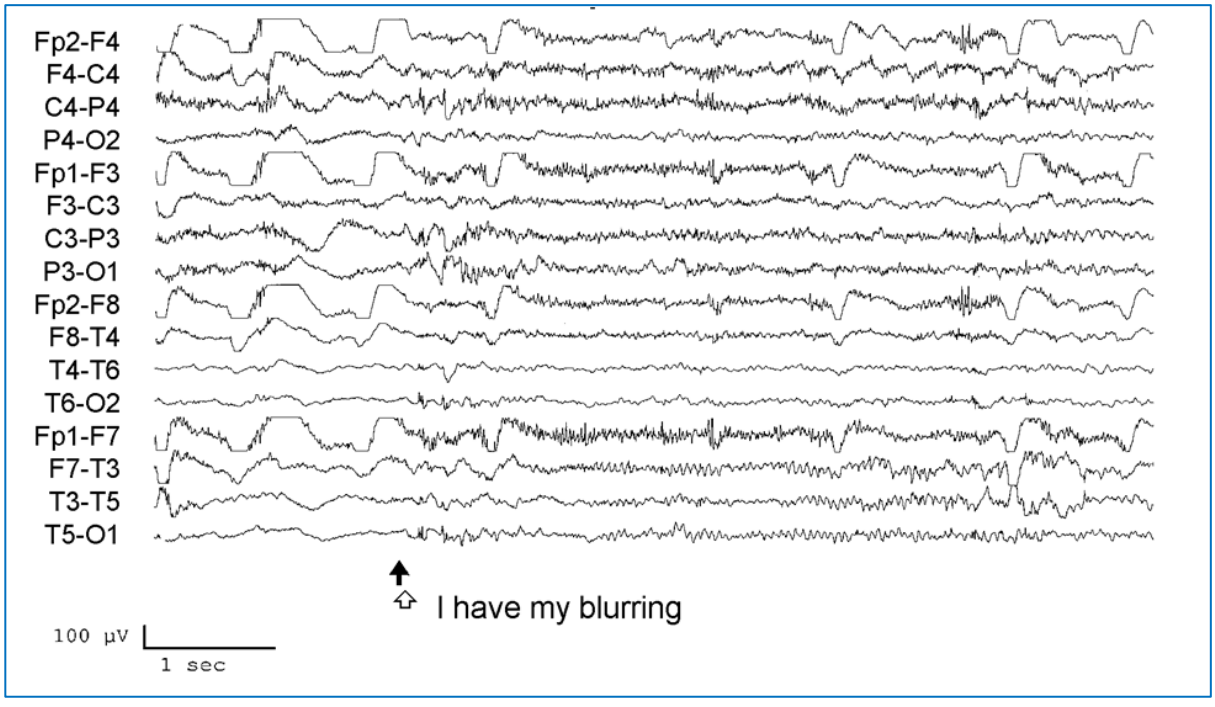


Figure 4.27. Ictal discharge occurs over both occipital regions (black arrow) nearly simultaneously with the first clinical events (white arrow) which consist of blurring of vision. The seizure also consisted of forced eye-lid closures and lasted for less than a minute.

SECTION 4.5: EPILEPSY WITH MYOCLONIC-ATONIC SEIZURES

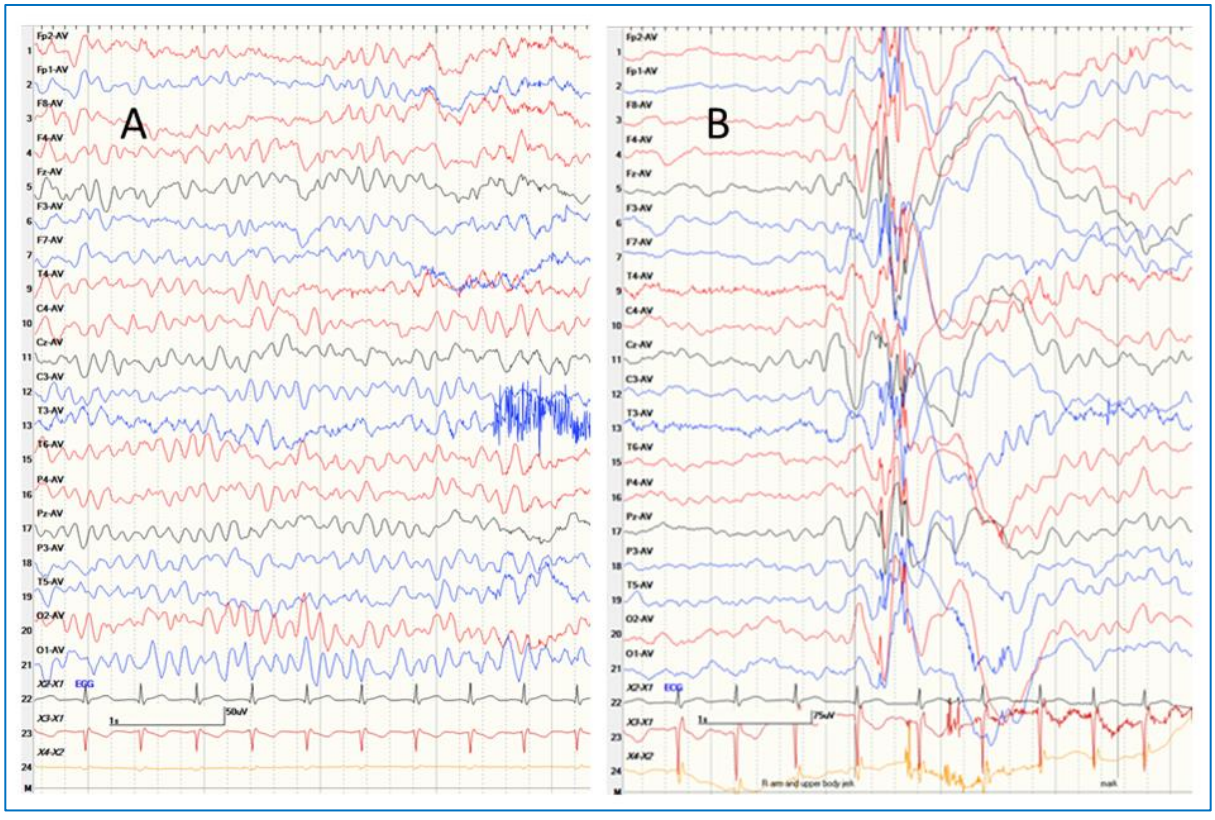


Figure 4.28. A two-year-old boy presented with a second afebrile generalized tonic-clonic seizure. A sleep video-EEG at that time showed **normal background** during drowsiness and sleep (**A**) and **myoclonic jerks** associated with generalized spike-wave discharges during drowsiness and light sleep (**B**).

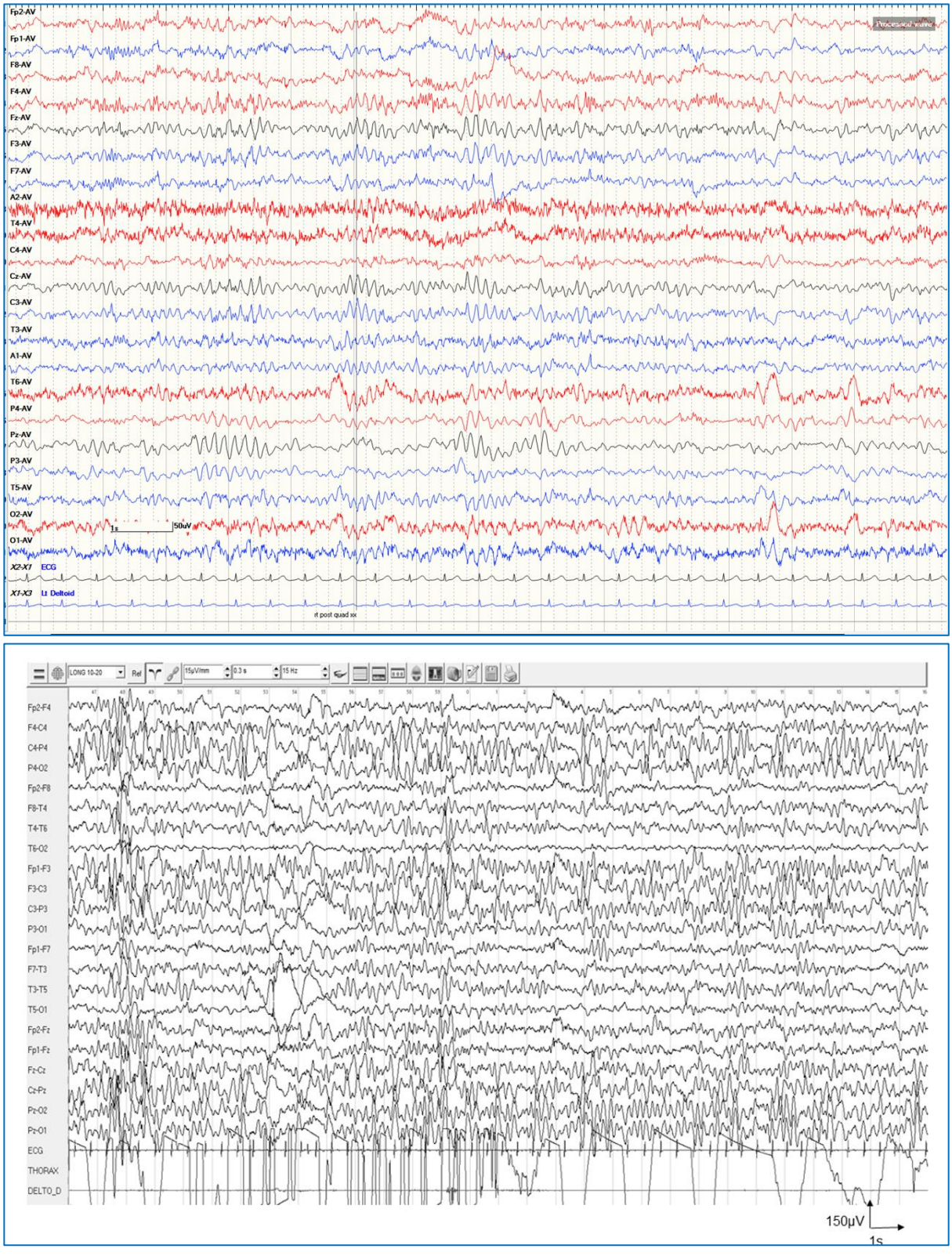


Figure 4.29 (A) A three-year-old child with prominent **centro-parietal theta rhythms** presented with febrile seizures and later developed myoclonic and atonic seizures. (**B)** Another example of central theta slowing.

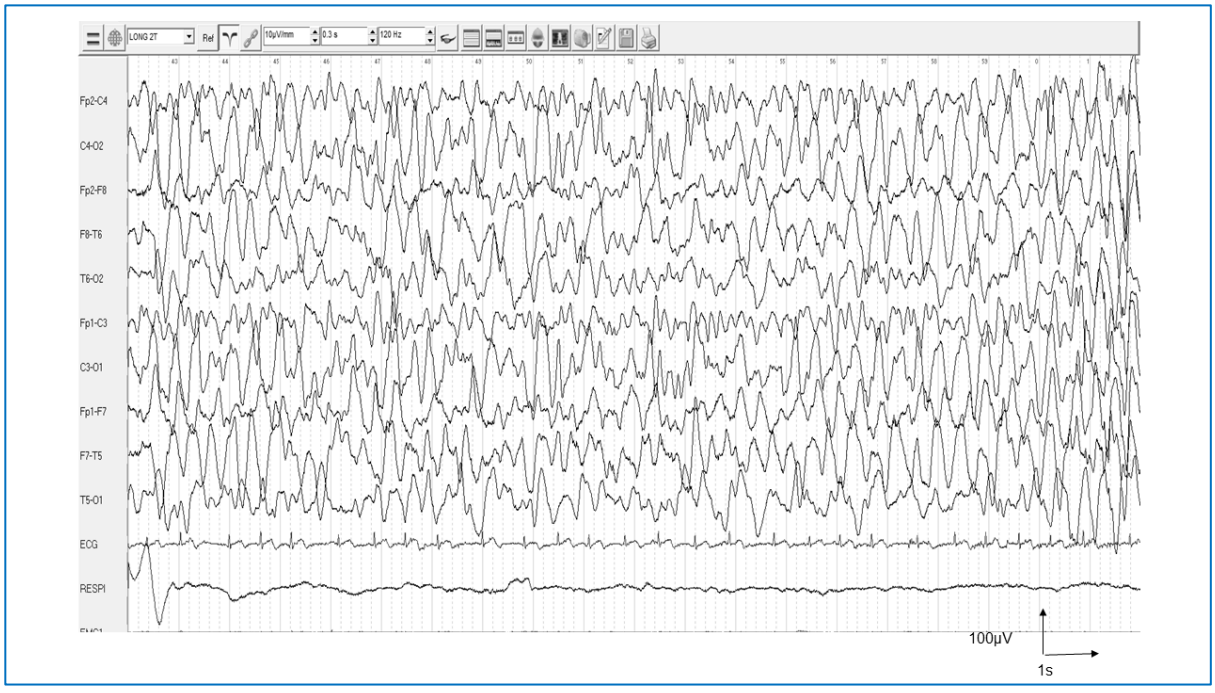


Figure 4.30. A three-year-old child with **epilepsy with myoclonic-atonic seizures**. Note that the EEG background on this occasion is slow with diffuse theta-delta.

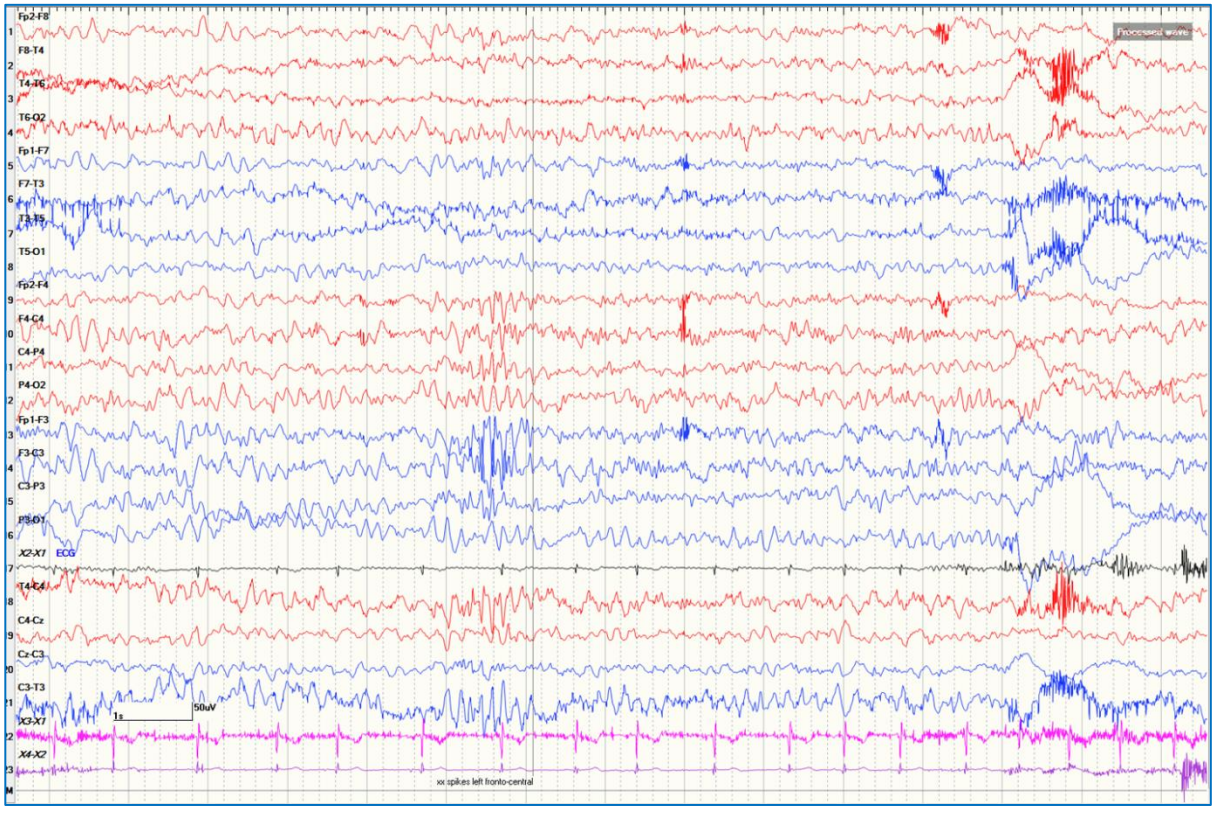


Figure 4.31. A seven-year-old with **epilepsy with myoclonic-atonic seizures**. Interictal EEG during wakefulness shows bilateral bursts of polyspikes at times with a left parasagittal emphasis.

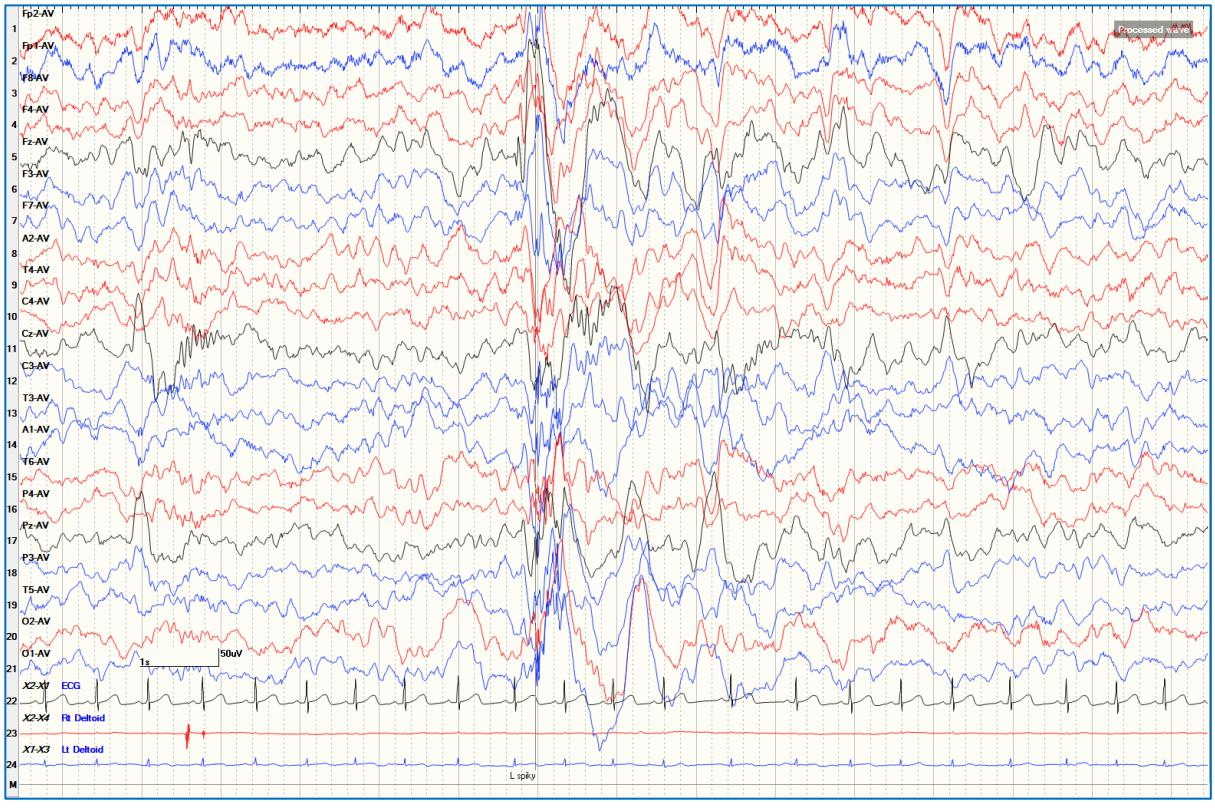


Figure 4.32. A five-year-old boy presented with **generalsied clonic seizures from sleep**. Interictal sleep EEG shows brief generalised bursts of polyspike-wave discharges at times associated with mycolonic jerks.

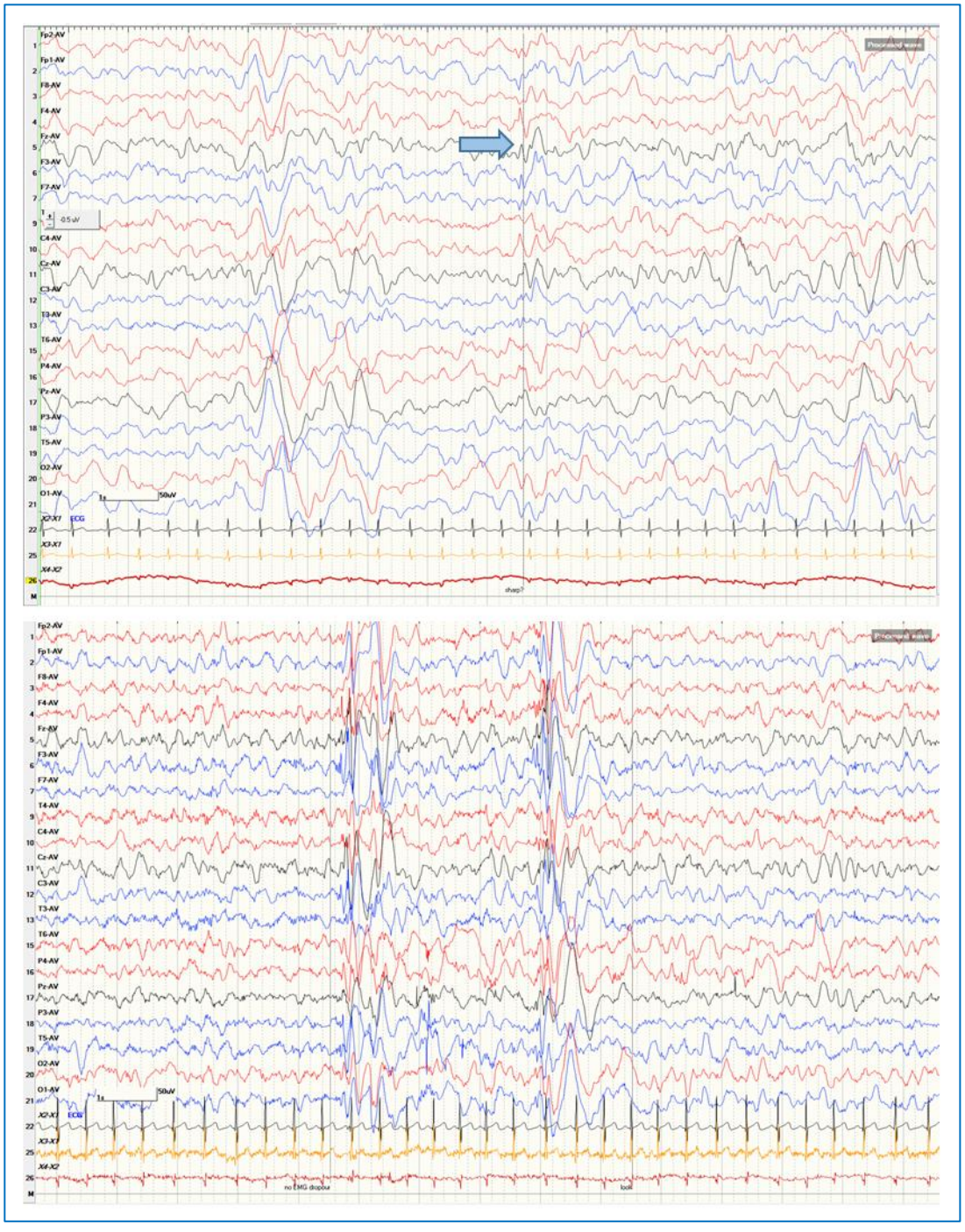


Figure 4.33. A girl presenting with sudden falls at the age of 18 months, causing minor injuries. She then developed myoclonic and generalized tonic-clonic seizures, but became seizure-free at the age of three years following treatment with sodium valproate. Upper trace: normal physiological rhythms during sleep with low-voltage focal spikes over the superior frontal areas (F4, Fz and F3). Lower trace: brief bursts of generalized spike/polyspike-and-wave discharges during sleep.

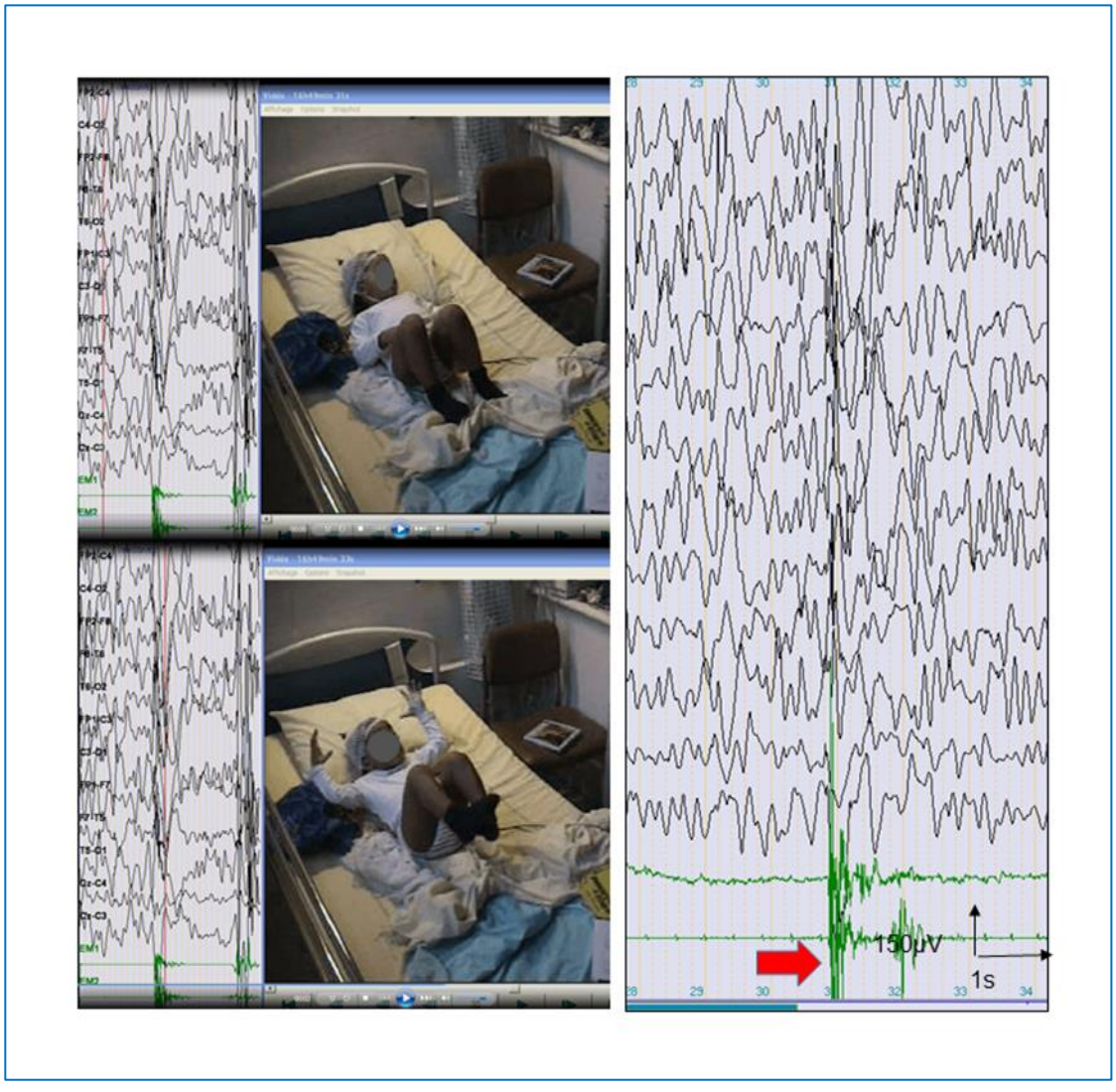


Figure 4.34. Myoclonic extensor-type jerk in an 18-month-old child with drop attacks. Arrow points to the bilateral massive axial myoclonus with extension and elevation of arms.

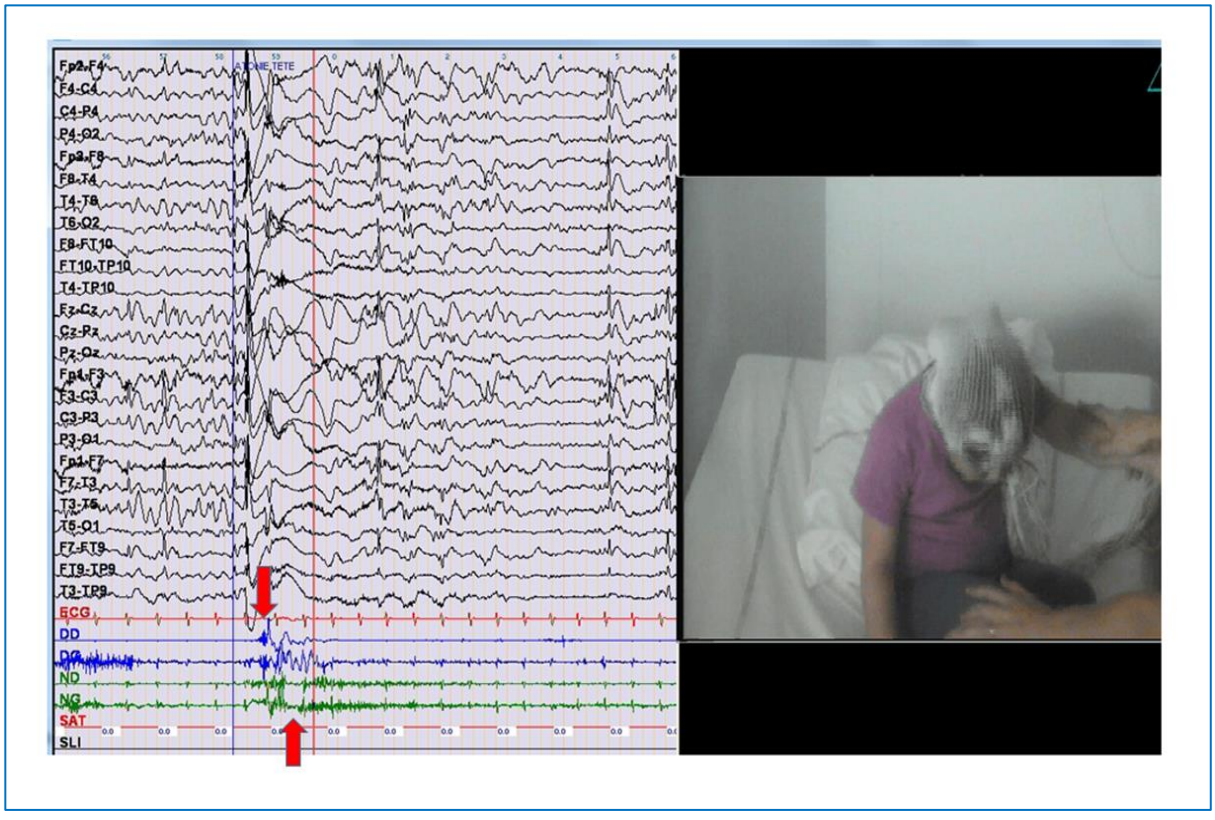


Figure 4.35. Myoclonic-atonic seizure. Note initial myoclonic jerk (first arrow) preceded by the burst of generalised discharges, followed by the atonic drop associated with the electroclinical silent period with loss of EMG signal from the deltoids (second arrow).

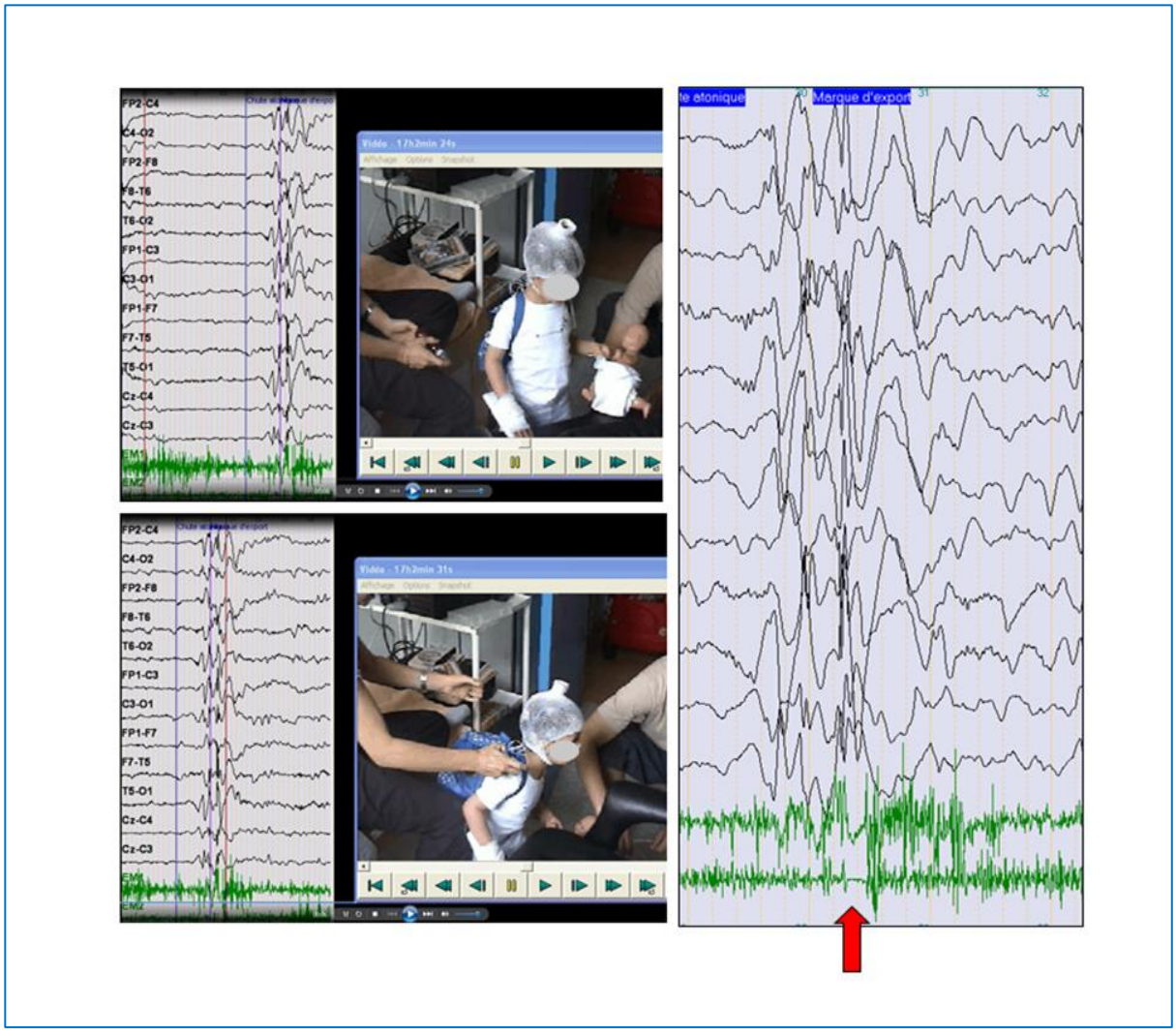


Figure 4.36. Atonic seizures; note the sudden loss of EMG signal (arrow) with the associated atonic drop.

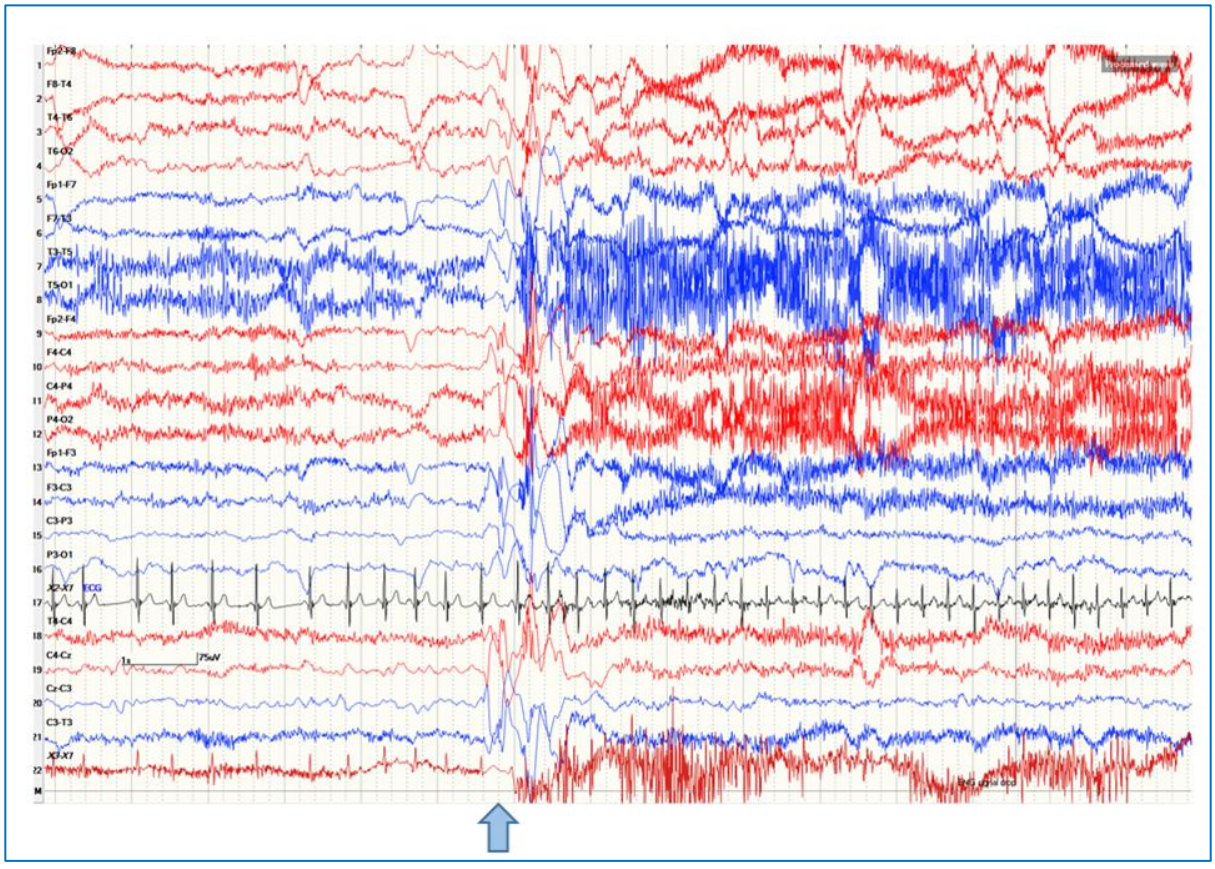


Figure 4.37. This two-year-old girl is sitting, playing with a toy, when she had what appeared to be a sudden jerk followed by an **atonic drop forwards** (her head hit the toy on her lap). Note the EMG silent period (arrow). There is no preceding EMG potential to verify a myoclonic component and therefore the seizure appears to be atonic (negative epileptic myoclonus), rather than myoclonic-atonic.

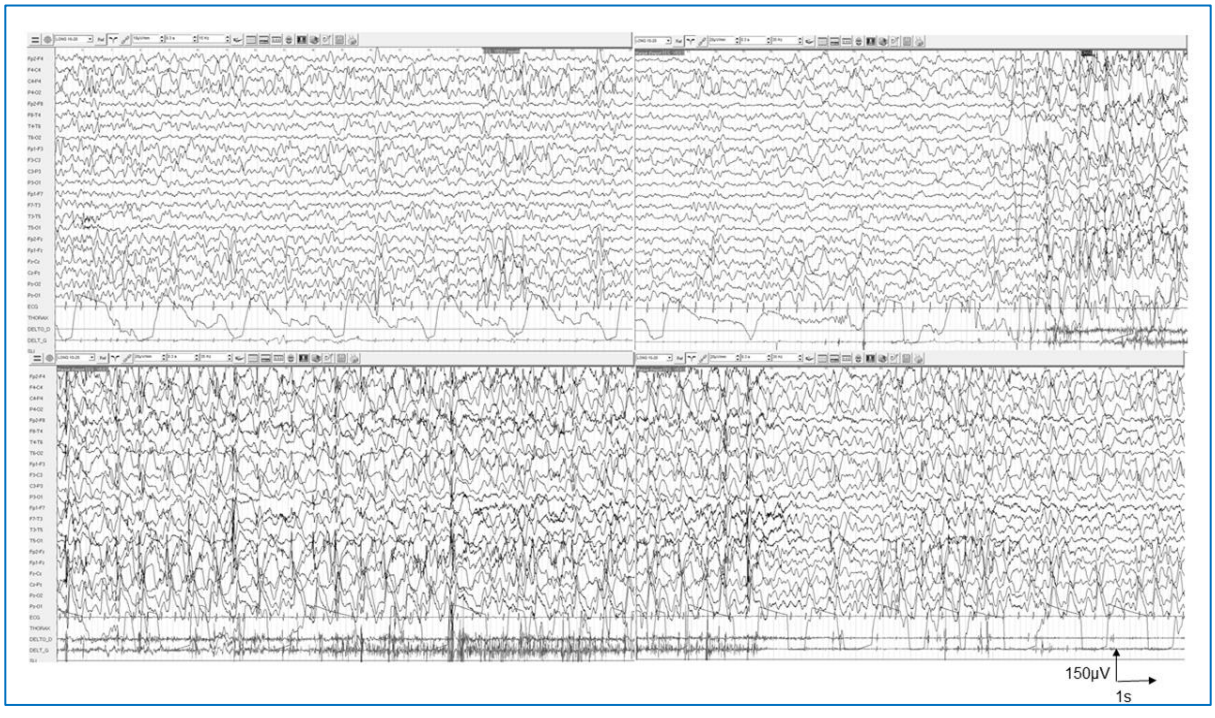


Figure 4.38. EEG-EMG polygraphy showing a long **clonic seizure**.

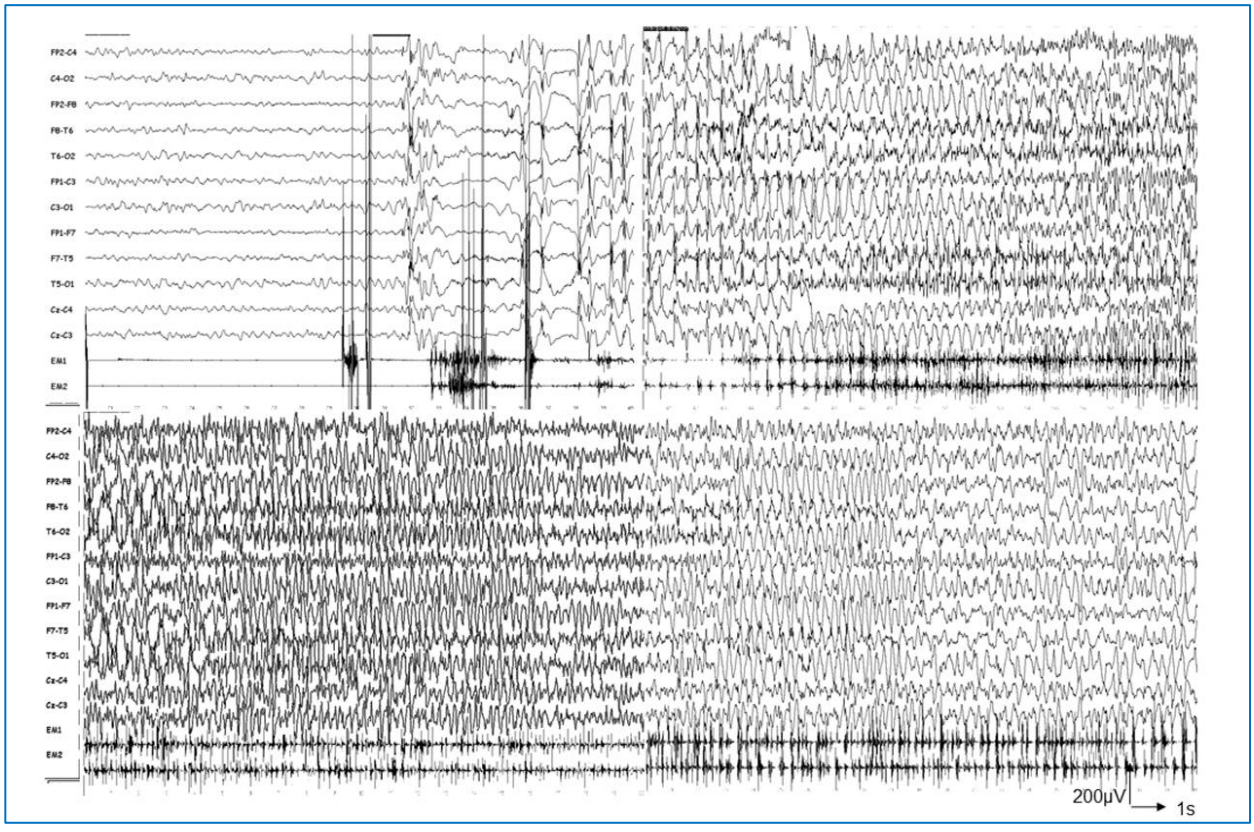


Figure 4.39. Generalised clonic seizure in a three-year-old child with **epilepsy with myoclonic-atonic seizures**. Note that as the seizure progresses there is marked increase in the frequency of the clonic movements (arrow) resulting in a "vibratory" appearance. The frequency of the clonic movements diminishes towards seizure offset.

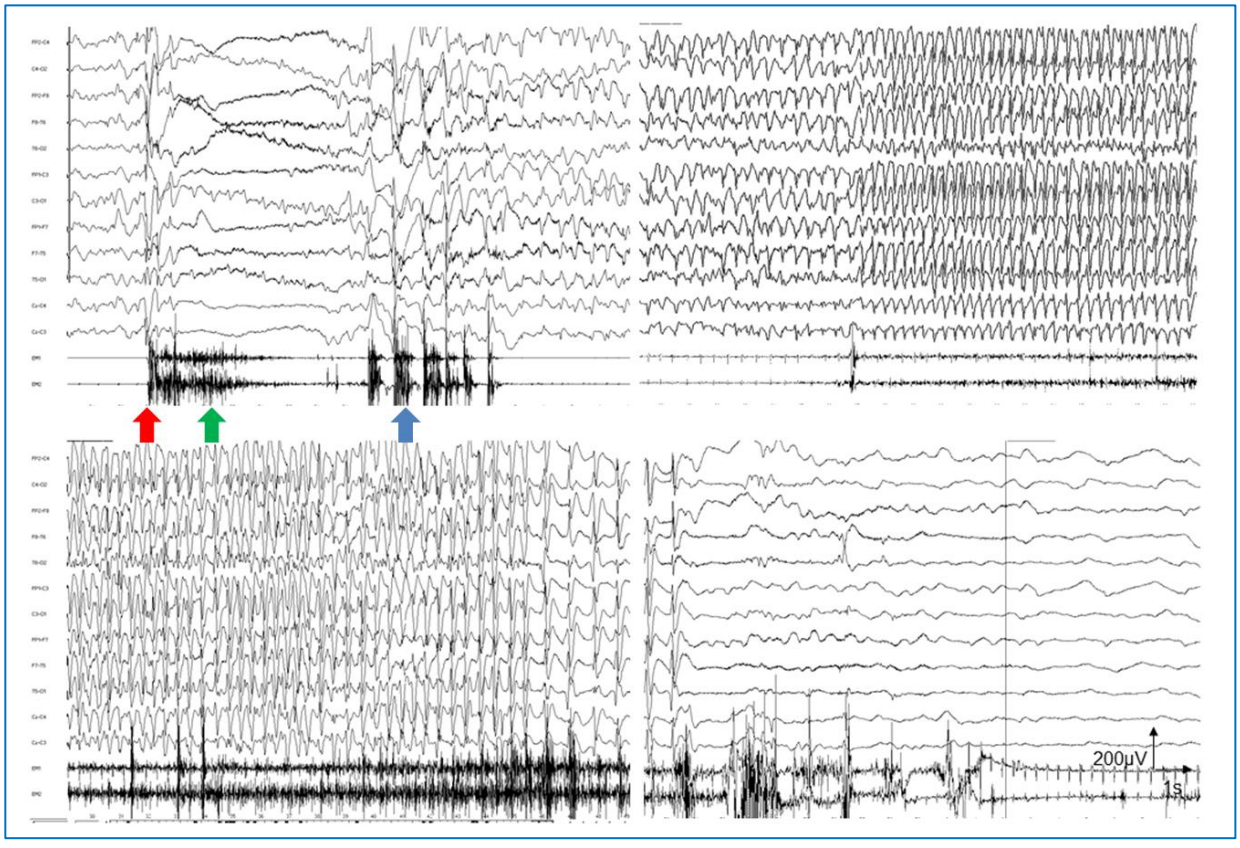


Figure 4.40. Generalised tonic-clonic seizure. Note the initial myoclonic component (red arrow) at the onset of the tonic phase (green arrow). This myoclonic-tonic combination is also known as "myo-tonic" (see also section on tonic seizures below). The clonic phase (blue arrow) of the seizure ensues.

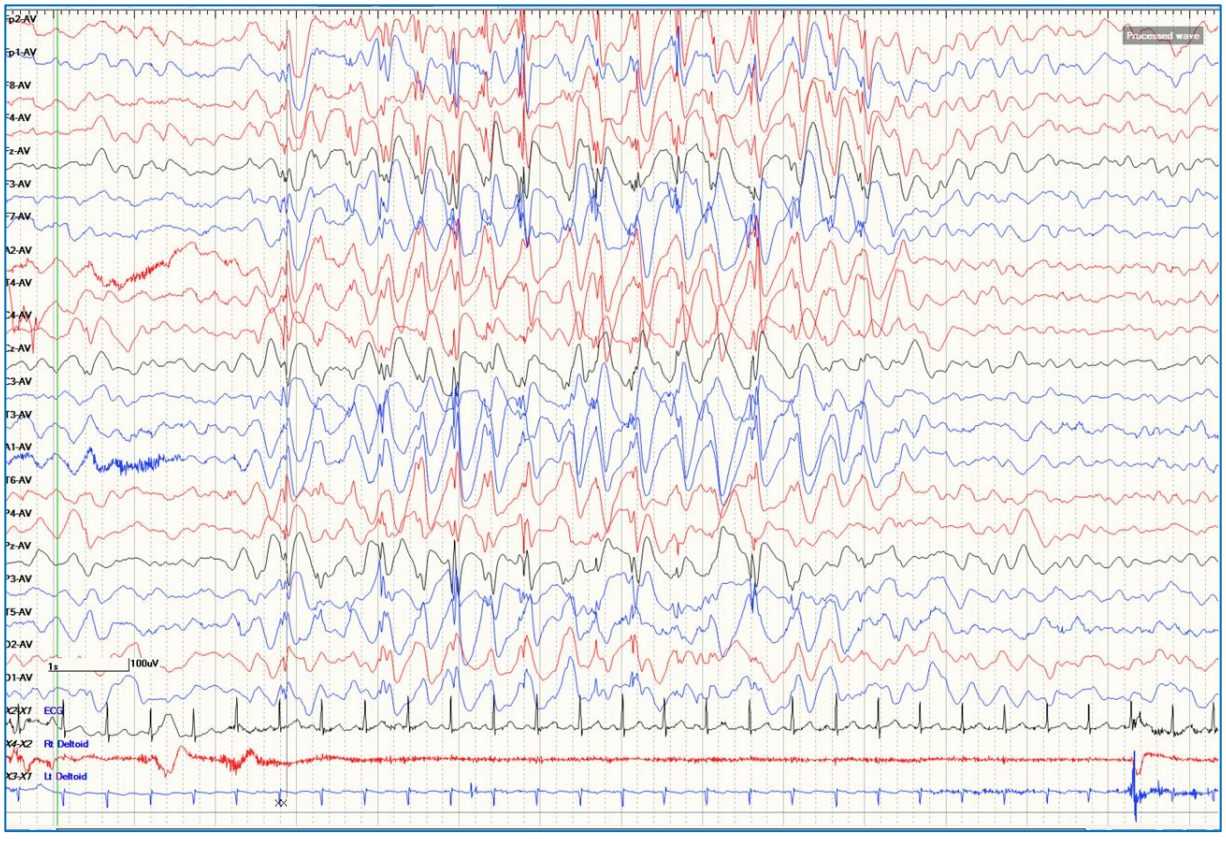


Figure 4.41. Atypical absence with 2-2.5 anteriorly dominant generalised spike-and-wave discharges in a four-year-old boy with refractory **epilepsy with myoclonic-atonic seizures**. During the discharge, he appears still and stops drinking from his bottle.

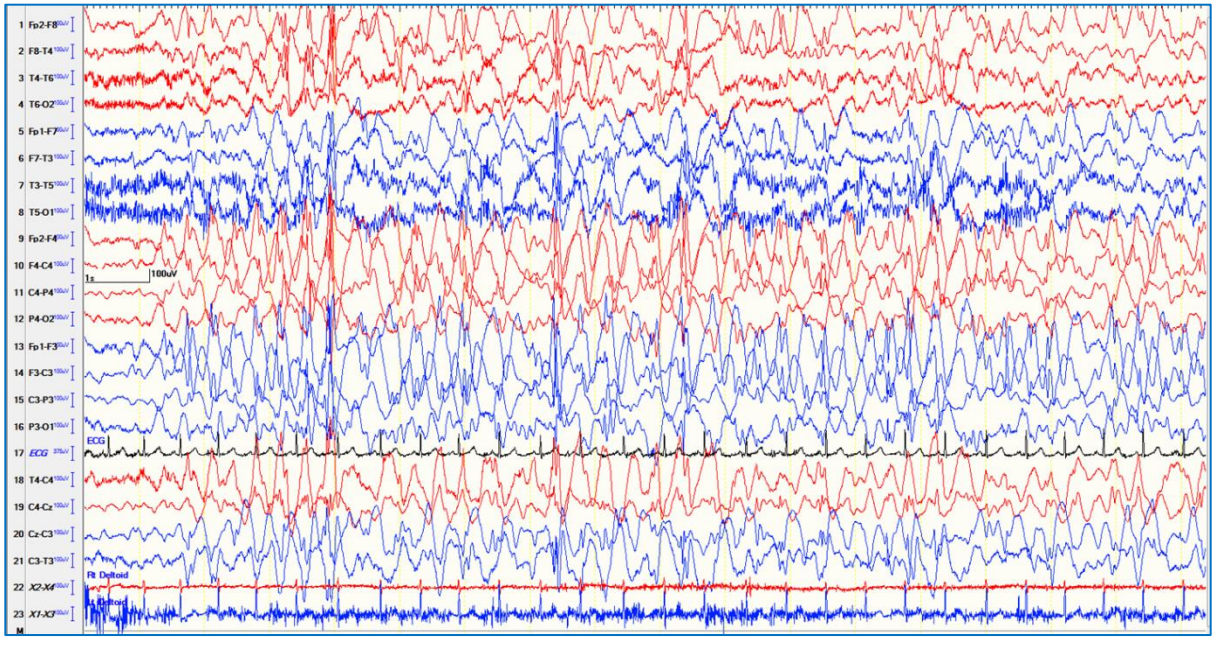


Figure 4.42. A two-year-old boy presented with initially febrile then afebrile seizures, and went on to have atypical absences and myoclonic-atonic seizures. This EEG showed **sequential long runs of diffuse slow spike-and-wave discharges** that were separated from one another by only a few seconds. During this period, the boy appeared unresponsive and at times had head drops.

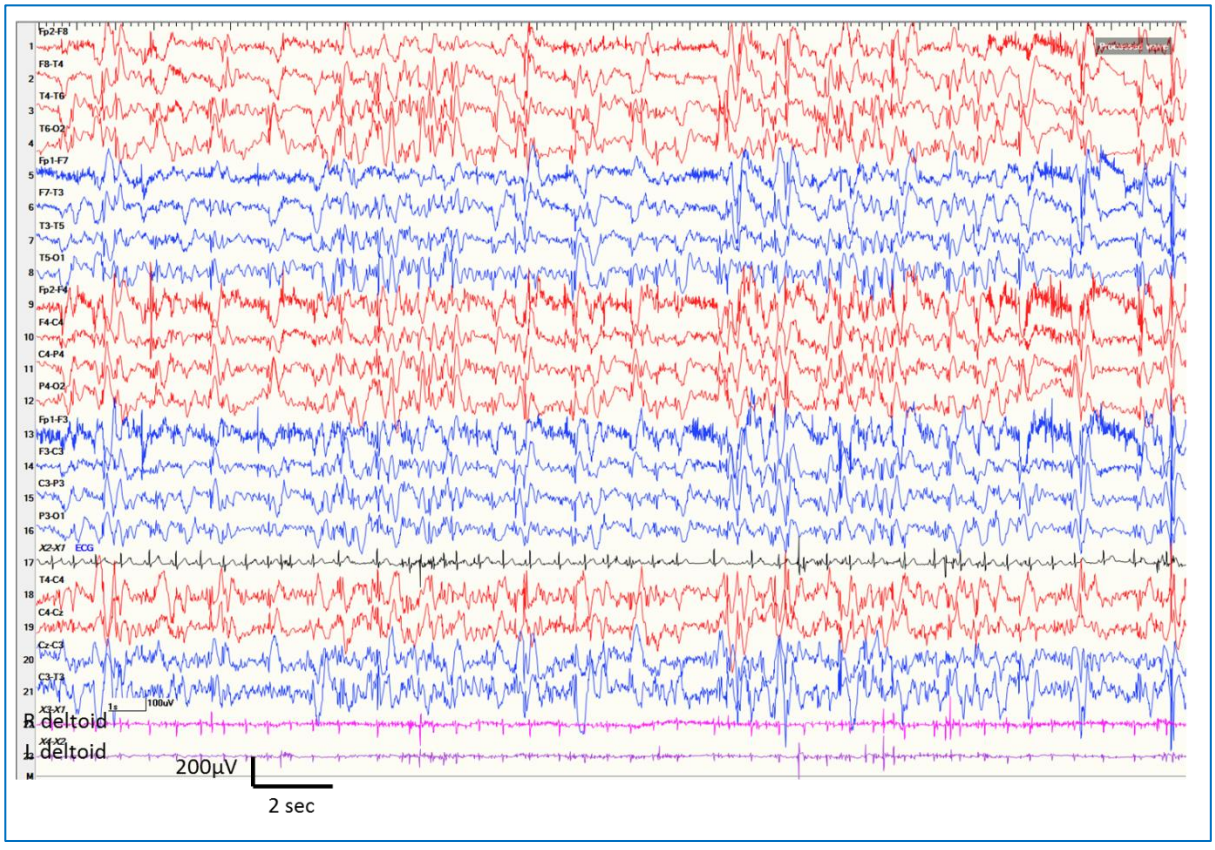


Figure 4.43. Non-convulsive status epilepticus (NCSE). This 10-year-old girl presented at the age of six months with generalised tonic-clonic seizures and myoclonic and atonic seizures. She has remained refractory to treatment and had several episodes of NCSE. During this episode, she was intermittently vacant and confused, and exhibited continuous erratic upper limb and facial myoclonias.

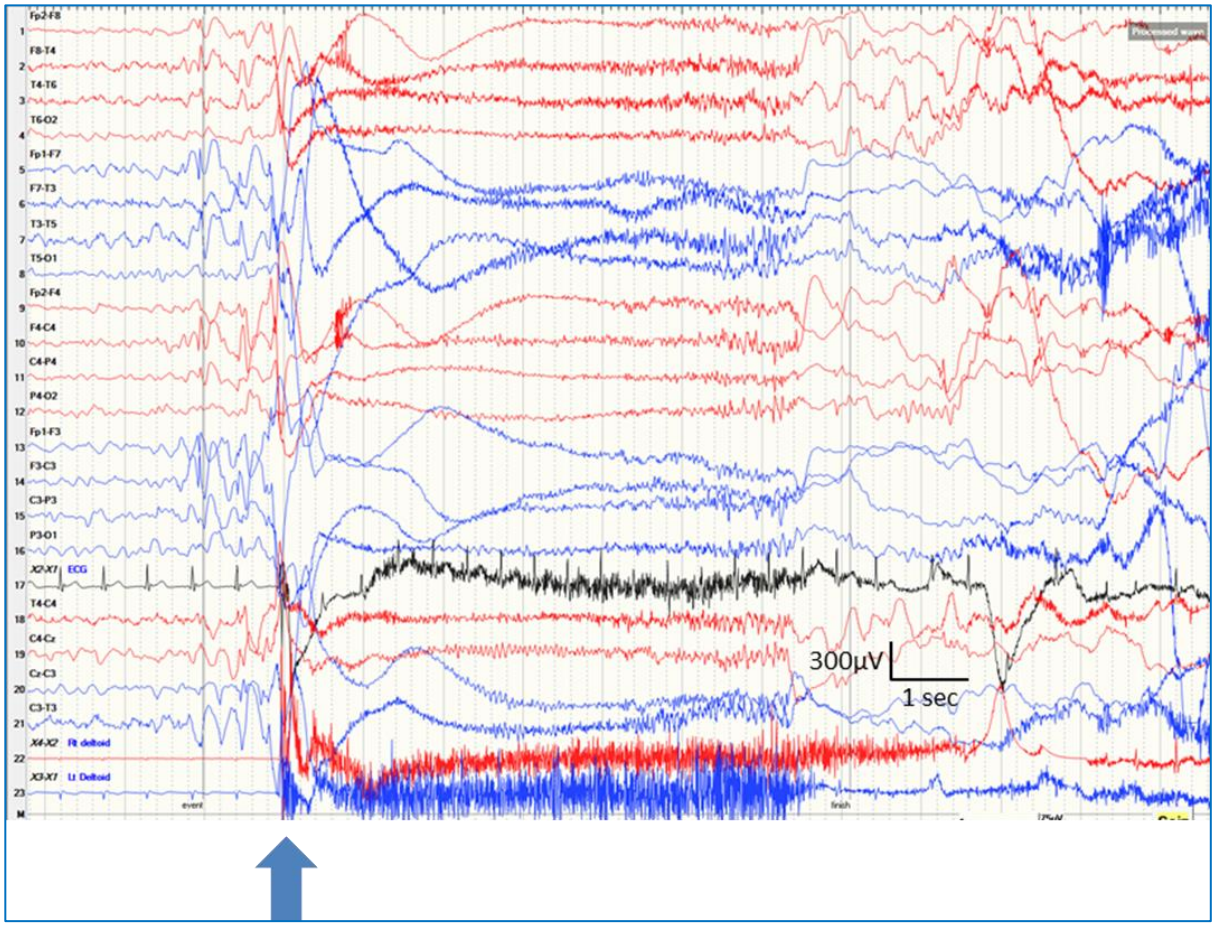


Figure 4.44. Myo-tonic seizure in light sleep. Note the initial brief EMG potential (arrow) that correlates with the generalized spike-wave discharge, followed by the prolonged bilateral tonic contraction that is associated with the diffuse attenuation with superimposed low-voltage fast-recruiting rhythms.

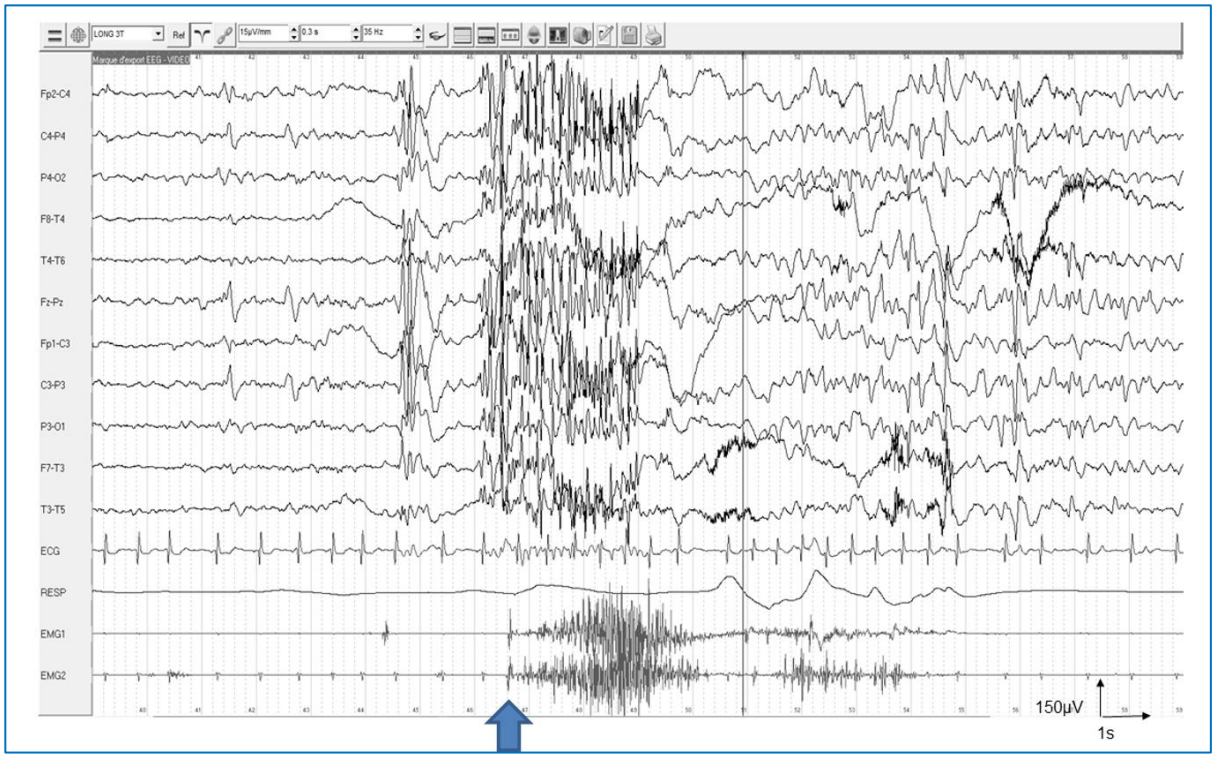


Figure 4.45. Brief bilateral myo-tonic seizure associated with a 5-6-second burst of high-voltage generalised polyspikes. Note the initial myoclonic component (arrow).

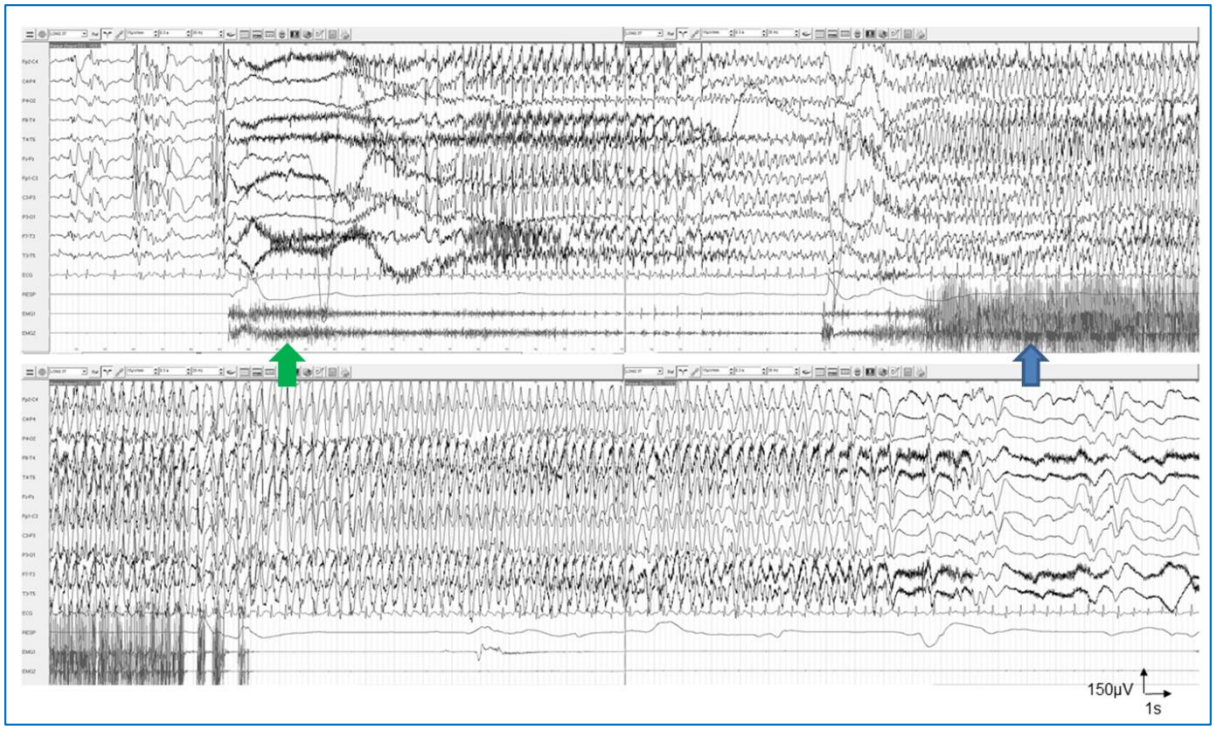


Figure 4.46. In this generalised tonic seizure, no initial myoclonic component is detectable at the onset of the tonic phase (green arrow). Also note the diffuse rapid spike-waves that associate with very rapid tonic movements (blue arrow), which are of high amplitude and account for the "vibratory" clinical presentation. The associated rapid spiking is different from the diffuse low-voltage fast rhythms of the classic tonic seizure in LGS. This child had unfavourable outcome.

SECTION 4.6: ABSENCE SEIZURES IN THE FIRST THREE YEARS OF LIFE

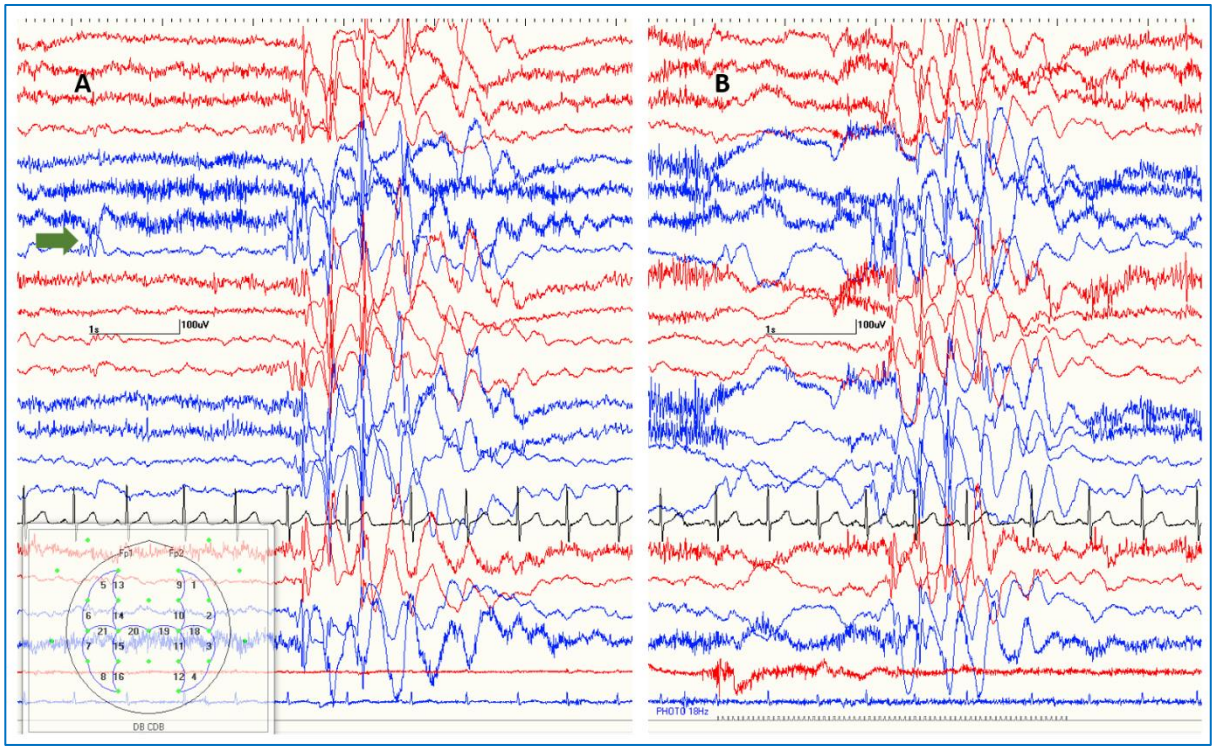


Figure 4.47. (**A**) Spontaneous typical brief generalized spike-wave discharge accompanied by fleeting staring in a two-year-old girl with **absences** since the age of seven months and a single generalized tonic-clonic seizure at the age of 18 months. Her mother has well controlled IGE/GGE with absences and photosensitivity. Note an isolated left posterior temporal "non-localizing" focal spike-wave discharge (green arrow) and a posterior onset for the generalized paroxysm. (**B**) Similar generalized spike-wave discharge elicited by IPS at 18 Hz; the effect was consistent.

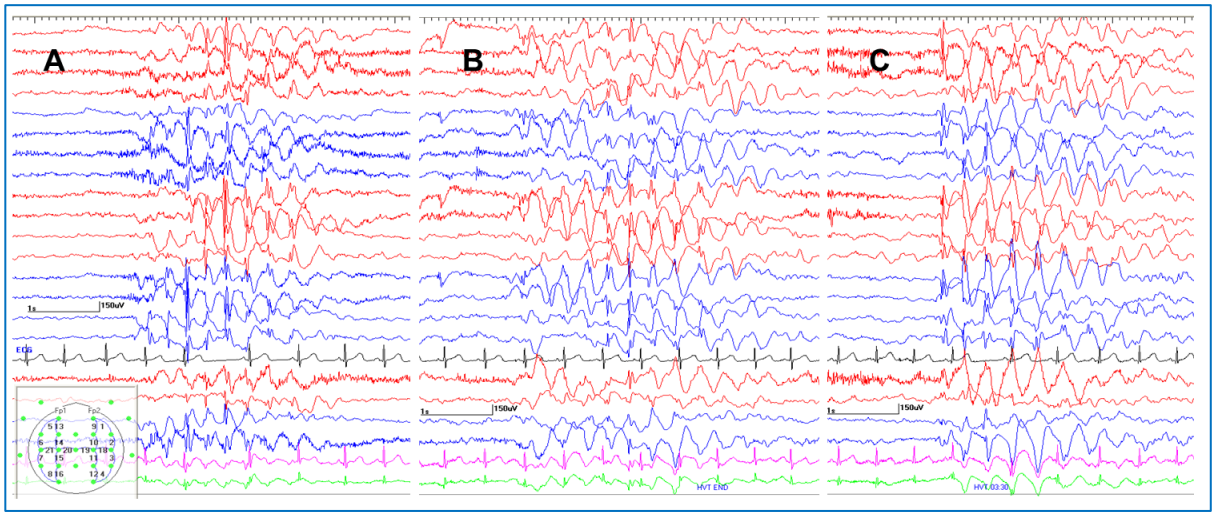


Figure 4.48. Routine video-EEG of a 3.5-year-old boy with diagnosed **Glut1 deficiency** and absences since the age of two years. (**A**) Brief spontaneous absence; (**B**, **C**) absences during hyperventilation. He is now 10 years old and on ketogenic diet and VPA 400 mg bd; he has 5-10 absences per day. He was also diagnosed with an autism spectrum disorder.

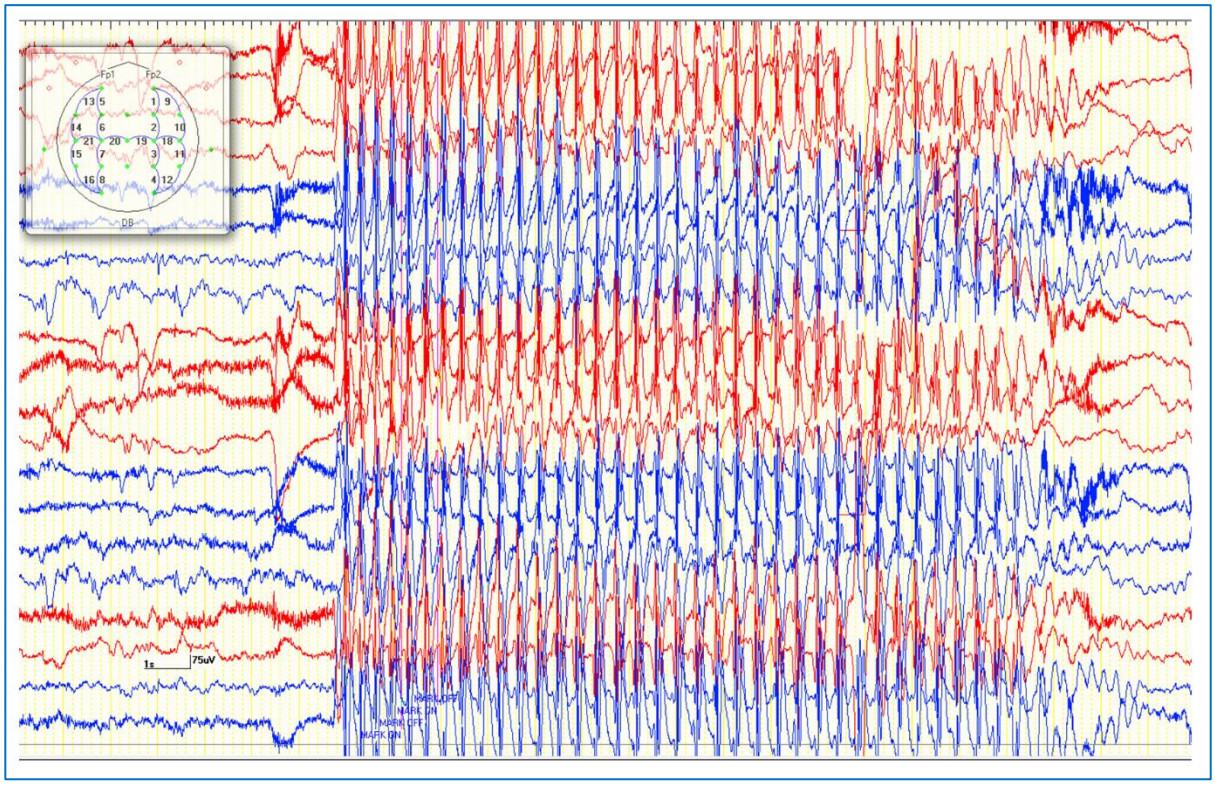


Figure 4.49. A **typical absence** associated with sudden behavioural arrest and staring of a three-year-old girl with alpha mannosidosis diagnosed at the age of two years; the patient had daily episodes of "freezing" for a few seconds since the age of around 18 months. A video-EEG recorded several absences at age two years and three months, but these were not treated. Note the bilateral synchronous onset of an 18-second long generalized regular 3-Hz spike-wave discharge that shows no asymmetries of fragmentations. The girl remained unresponsive throughout the seizure discharge.

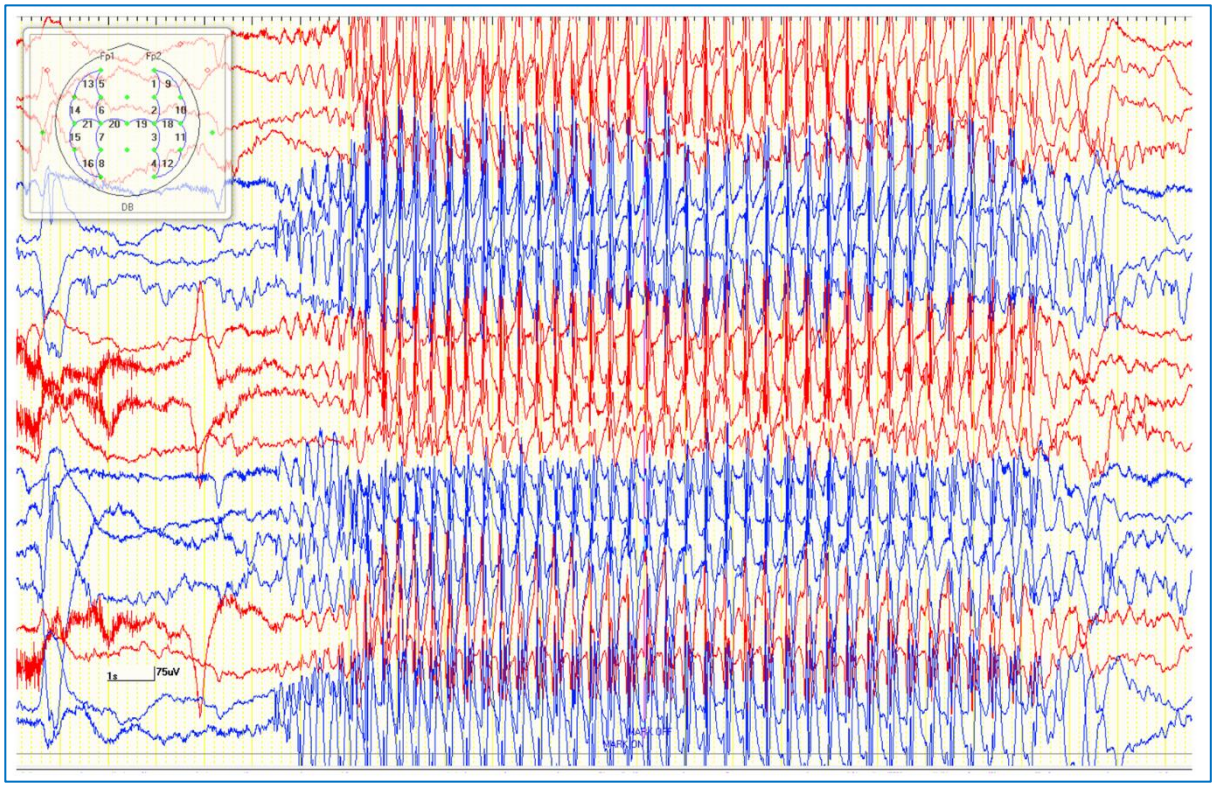


Figure 4.50. Another **typical absence** of the same girl from *figure 4.49*. Clinical semiology was the same as in *figure 4.49*, but the associated generalized 3-Hz spike-wave discharge shows a left-sided electrographic onset. The rest of the EEG features are the same, *i.e*. regular frequency and frontal emphasis without asymmetries or fragmentations. Compare these discharges with the examples in the chapter on childhood absence epilepsy.

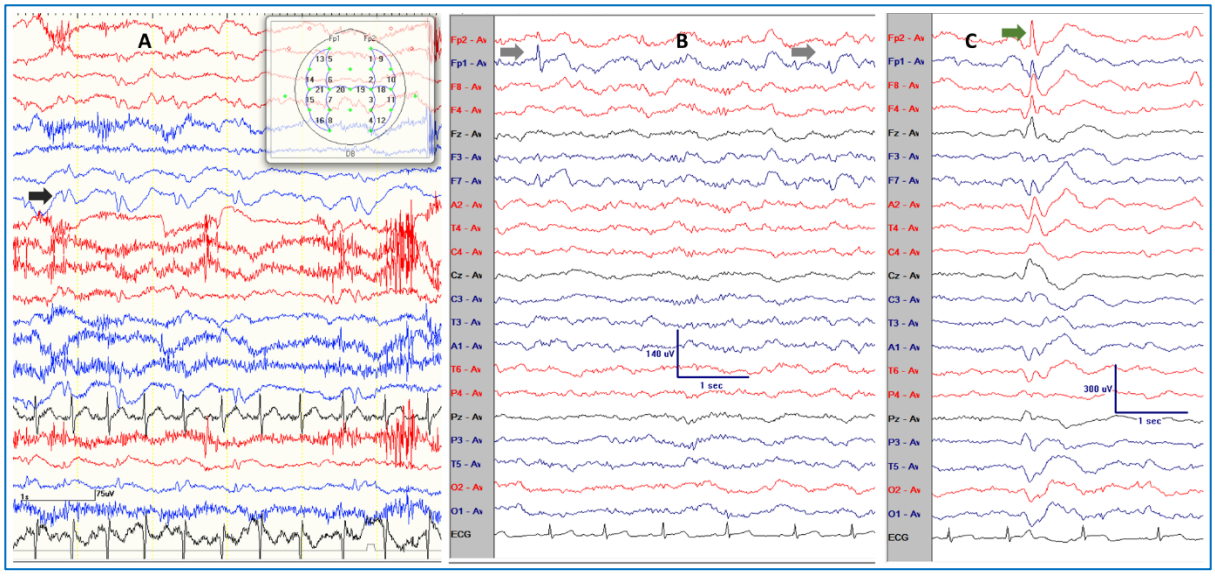


Figure 4.51. Sleep EEG of the girl from *figures 4.49 and 4.50*. Note the left occipital spikes (**A**), left frontal spikes (grey arrows in **B**), and right frontal spikes (green arrow in **C**).

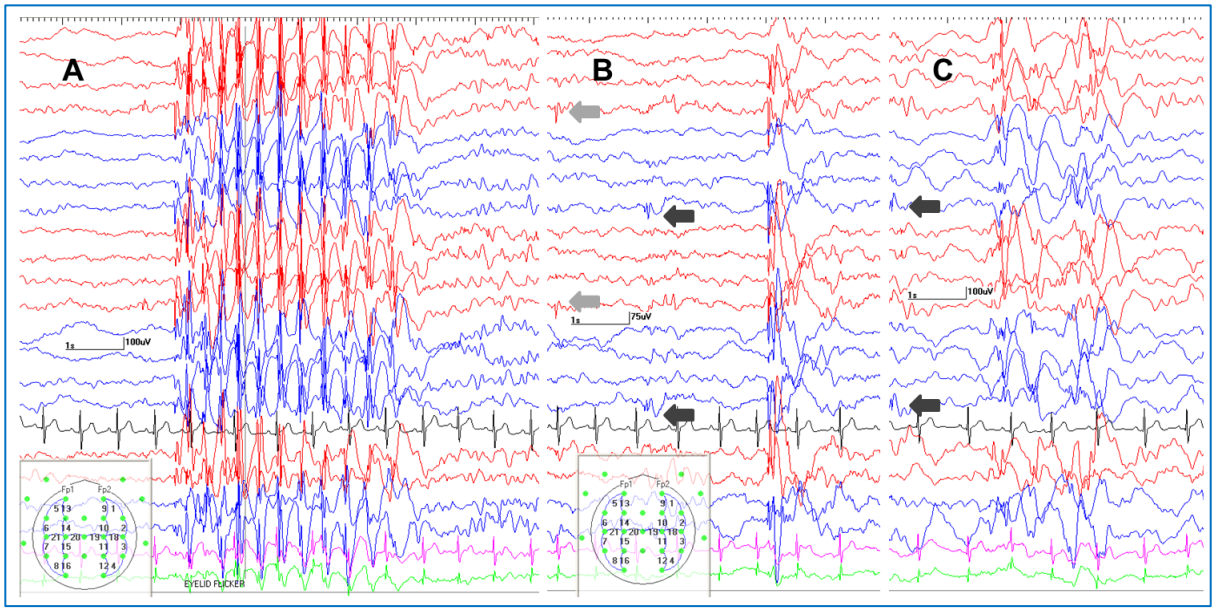


Figure 4.52. Sleep EEG of a three-year-old boy with **staring attacks** since the age of 19 months. (**A**) Four-second generalized 3-Hz spike-wave discharge during Stage 1 of sleep; note the electrographic arousal that follows, manifested by the diffuse appearance of theta rhythms. (**B**) single generalized 3-Hz spike-wave discharge with bilateral occipital emphasis during sleep Stage 2; note the preceding non-localising focal spikes over the right occipital (grey arrows) and left occipital (black arrows) regions. (**C**) Diffuse spike-wave discharges in Stage 3 sleep; note the brevity and irregular/fragmented morphology of the spike-wave discharges and the left occipital spikes that continue to occur. Compare with the sleep EEG findings in childhood absence epilepsy.

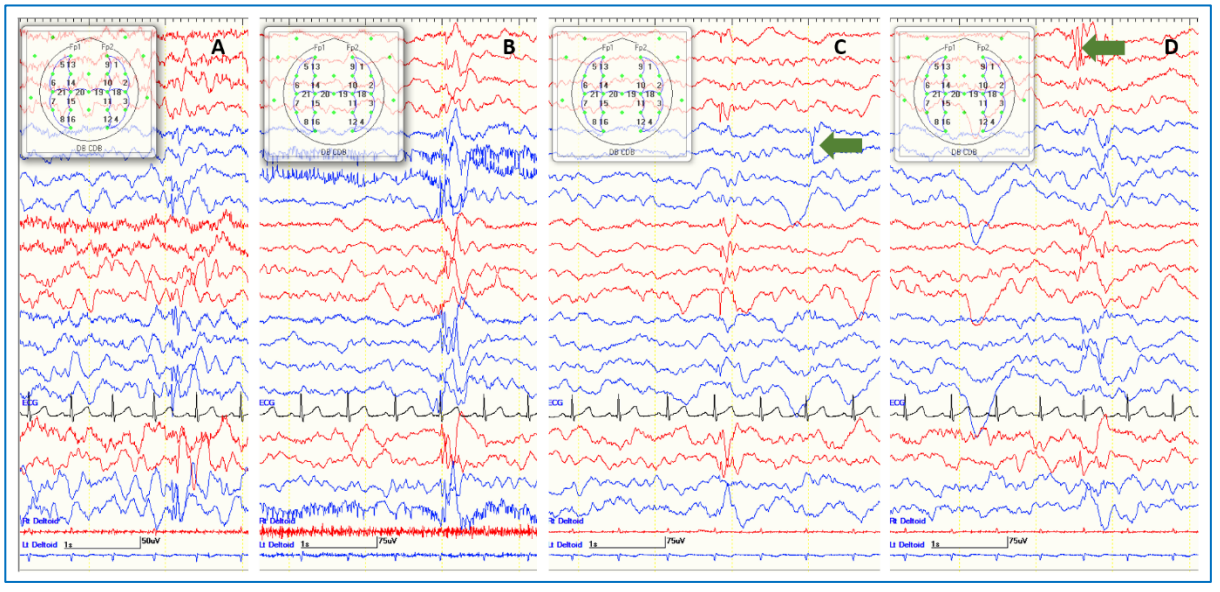


Figure 4.53. Sleep EEG of the girl from *figure 4.47*, now aged three. Note the degradation of the generalized spike-wave discharges during Stage 3 sleep occurring on the left (**A**), bilaterally but not entirely synchronously (**B**), and right side (**C**). Also, note the left anterior temporal (**C**, green arrow) and right anterior temporal non-localizing spike wave (**D**, green arrow).

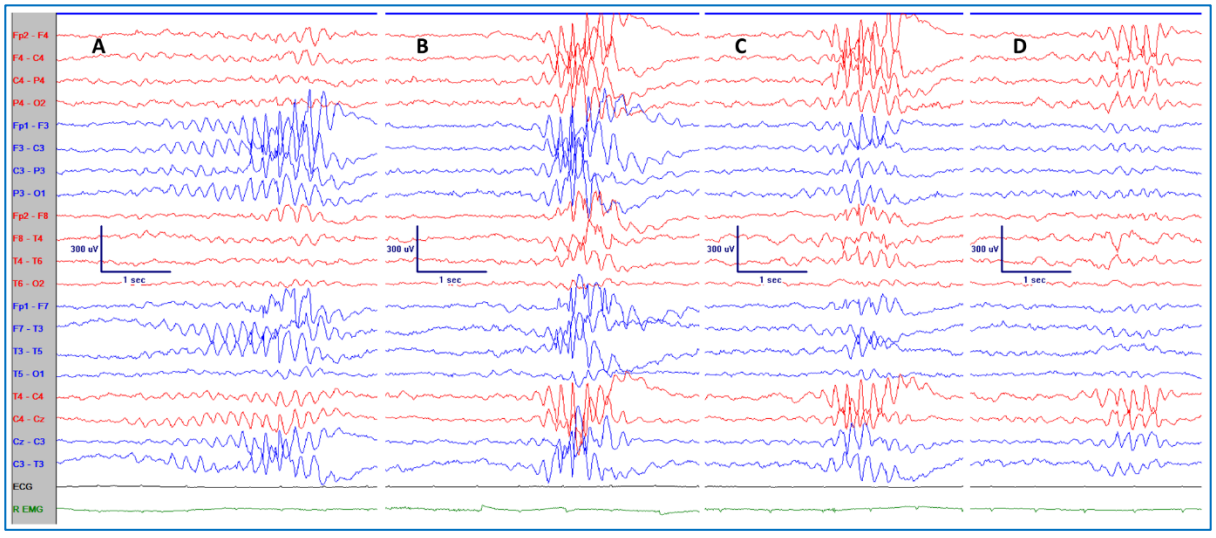


Figure 4.54. Bursts of high-voltage, frontally dominant sharp theta or fast spike-wave discharges during sleep in the girl from *figures 4.49 and 4.50*. Note the variable side emphasis: left (**A**), bilateral with mild left-sided emphasis (**B**), bilateral with mild right-sided emphasis (**C**), and right-sided (**D**).

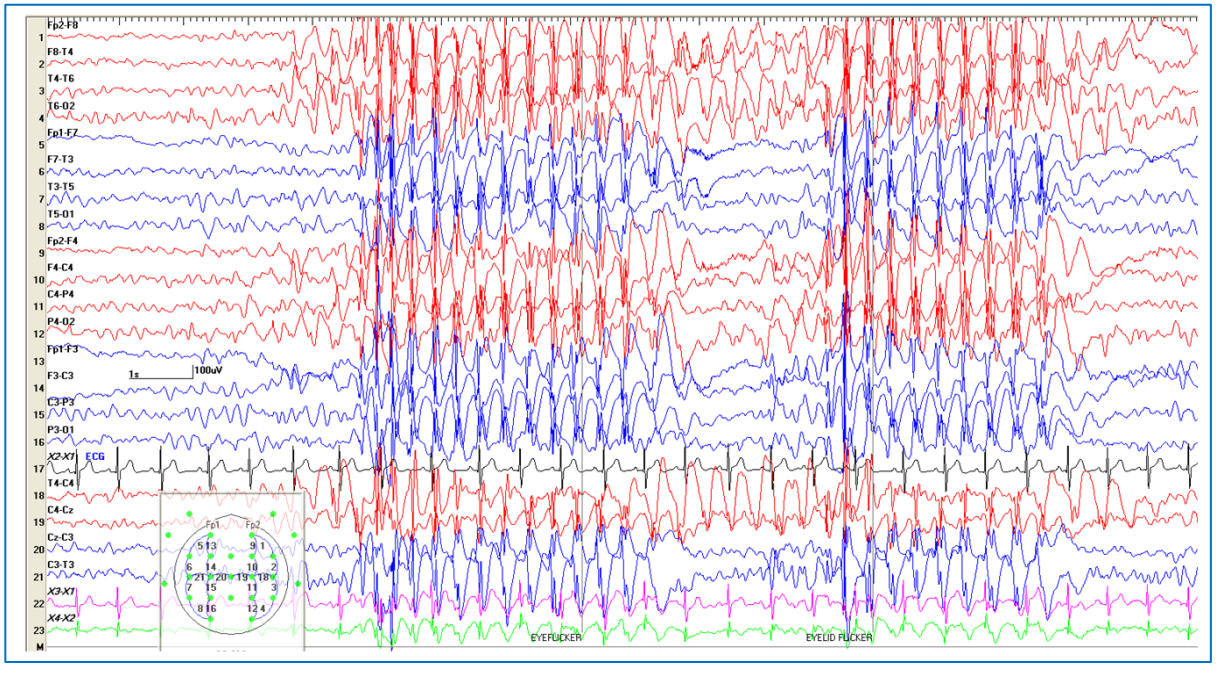


Figure 4.55. Video-EEG of the boy from *figure 4.52*. TA during **hyperventilation**: the boy stops blowing, drops the windmill, and stares with eye blinking. Note the right temporal onset of the ictal 3-Hz generalized spike-wave discharge which continues on that side, effectively "linking" two otherwise typical absences.

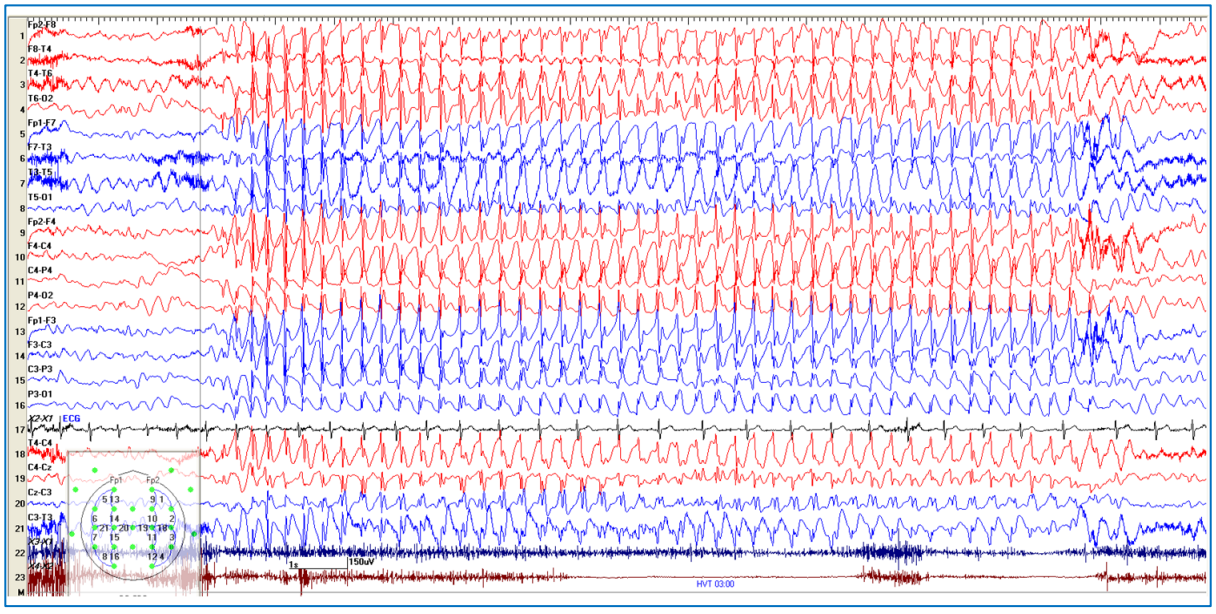


Figure 4.56. Video-EEG of the boy from *figure 4.55* two years later (five years old), showing a long typical absence during hyperventilation. In this recording, he is still off antiepileptic medication as his parents had declined treatment. He is now 13 years old and on LTG and TPM, and is still having absences and infrequent GTCS. Previous treatment with LEV and ethosuximide was unsuccessful.

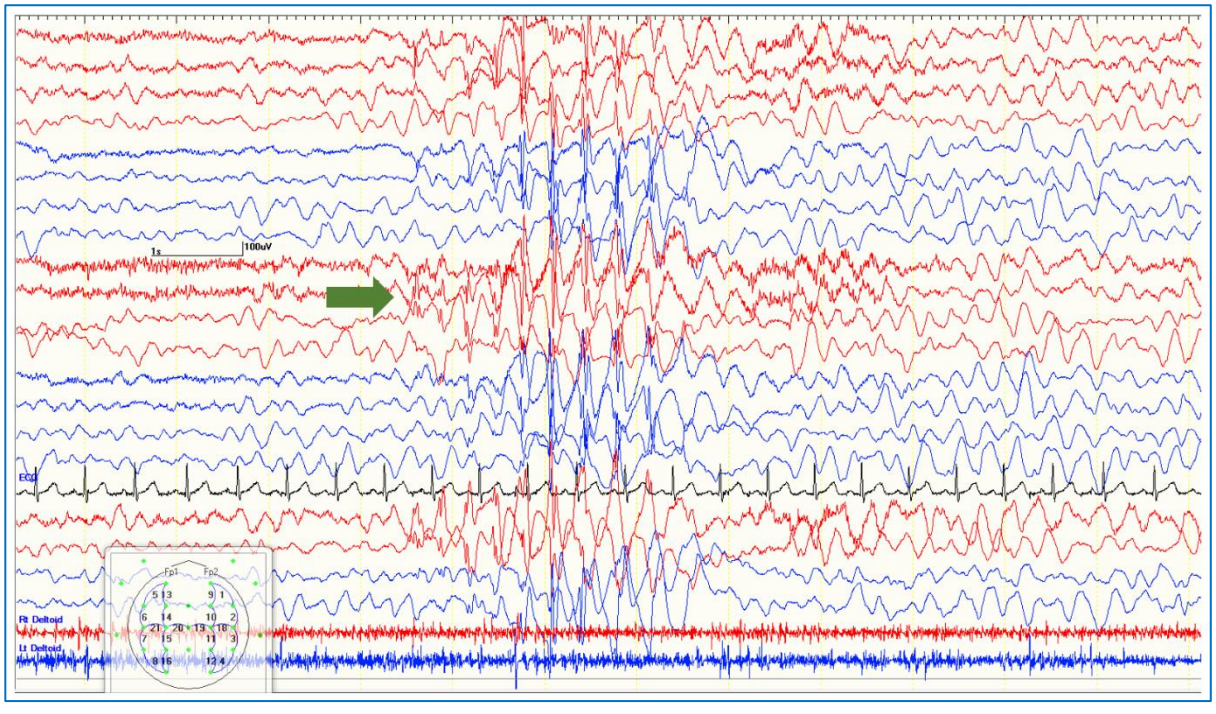


Figure 4.57. Spontaneous brief 3-Hz generalized spike-wave discharge during drowsiness in the girl from *figure 4.47*, now aged three. Note the right frontotemporal lead-in.

SECTION 4.7: LENNOX-GASTAUT SYNDROME

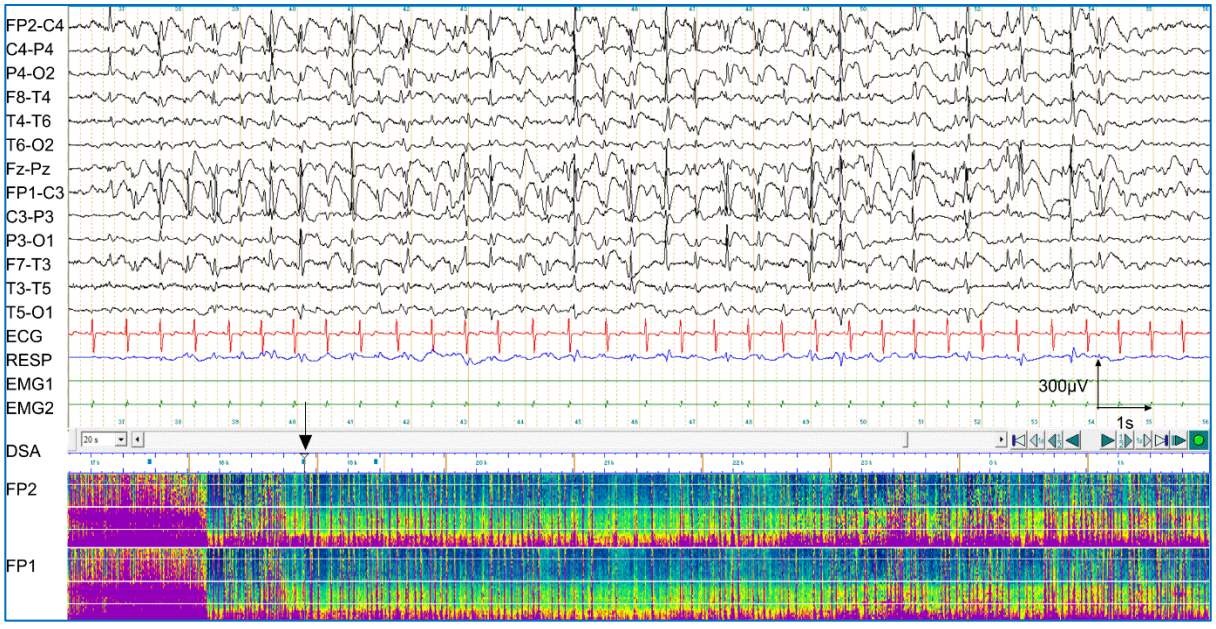


Figure 4.58. Interictal EEG during wakefulness of a five-year-old boy with **LGS**. Note the high-amplitude diffuse, synchronous slow spike-waves (SSW) at <2.5 Hz with maximal amplitude over the frontal areas. In the lower part, density spectral array (DSA) (0-30 Hz) shows activity from FP2 and FP1 electrodes over nine hours of recording. Each red vertical line corresponds to a sequence of SSW lasting for a few minutes; these sequences are sub-continuous during wakefulness.

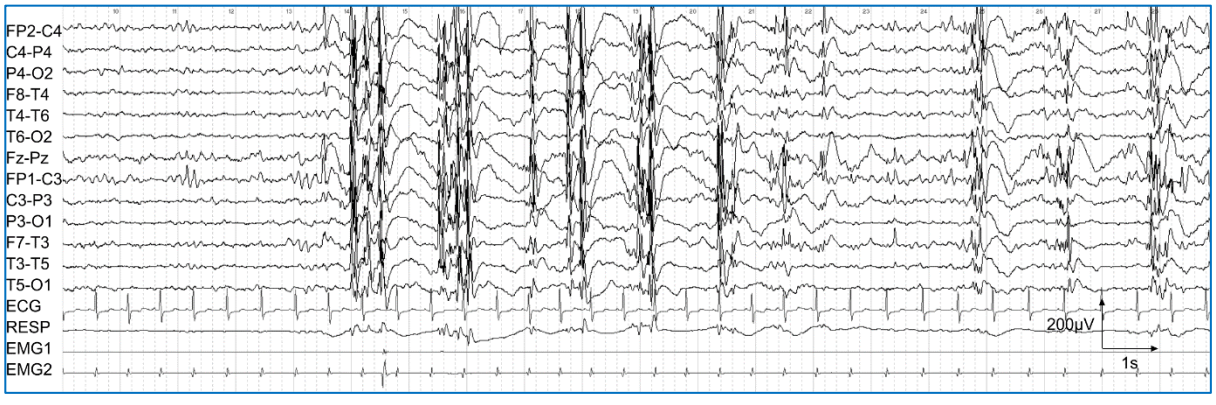


Figure 4.59. Interictal EEG of the same boy as in *figure 4.58* during NREM sleep, showing bursts of high-amplitude generalized polyspikes and polyspike-waves.

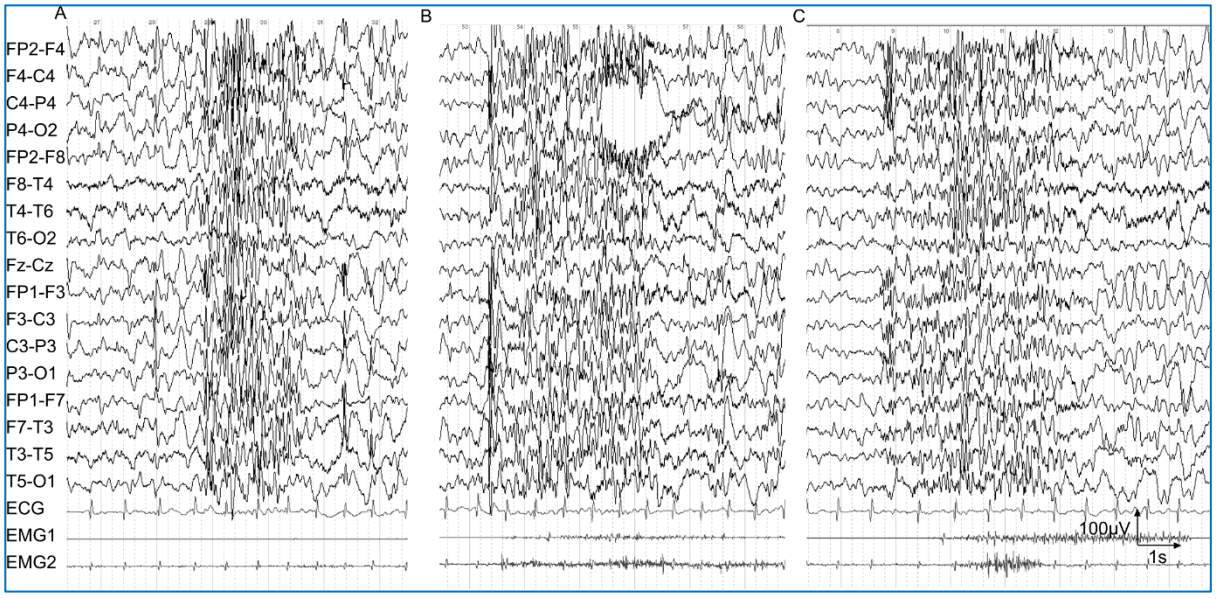


Figure 4.60. Interictal/ictal EEG of an eight-year-old girl with **LGS** during NREM sleep, showing fast bilateral rhythms/spikes (10-20-Hz) predominating in the anterior areas and on the vertex, lasting 2-3 seconds (paroxysmal fast activity). These could be subclinical (**A**) or, when of longer duration, accompanied by slight increase of axial muscle tone (**B**, **C**), detected by EMG electrodes placed on both deltoids; these are considered as subtle tonic seizures.

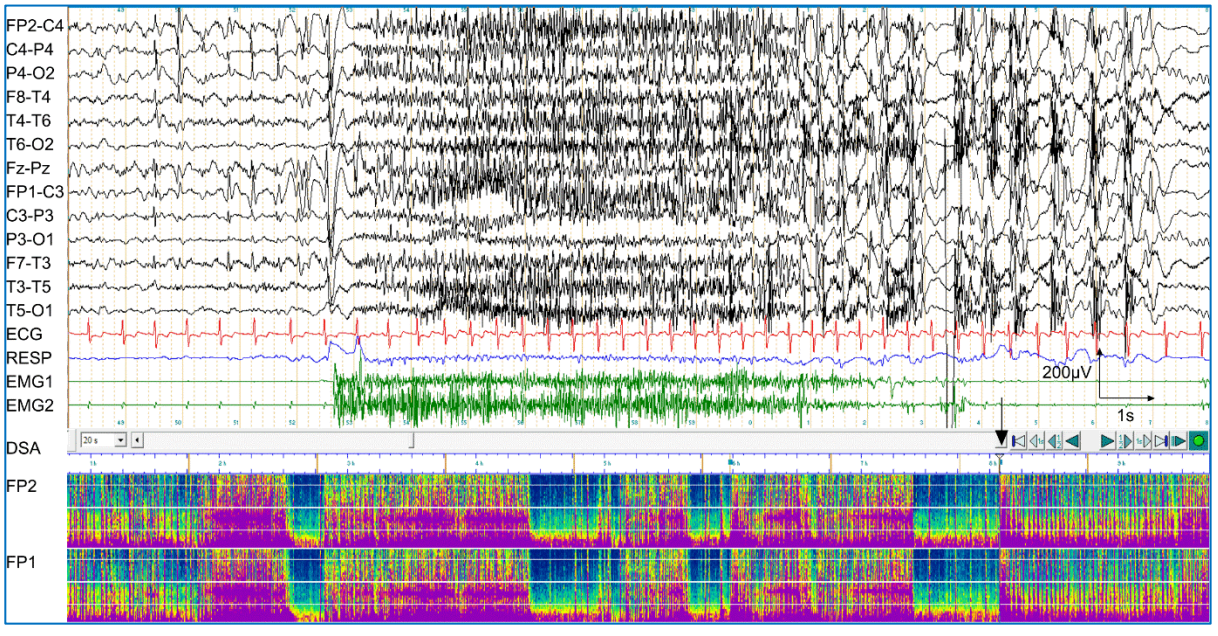


Figure 4.61. Tonic seizure during NREM sleep of the boy of *figures 4.58 and 4.59*, showing fast bilateral rhythms/spikes at 10-20 Hz, predominating over the anterior areas and the vertex, lasting for 9 seconds (concomitant to the tonic contraction of both deltoids recorded on EMG1 and EMG2 electrodes), followed by diffuse SSW. In the density spectral array (DSA) (0-30 Hz) from FP2 and FP1 electrodes, the black arrow shows the beginning of the tonic seizure at the onset of the NREM sleep. Each red vertical line corresponds to a sequence of SSW and polyspike-waves during NREM sleep.

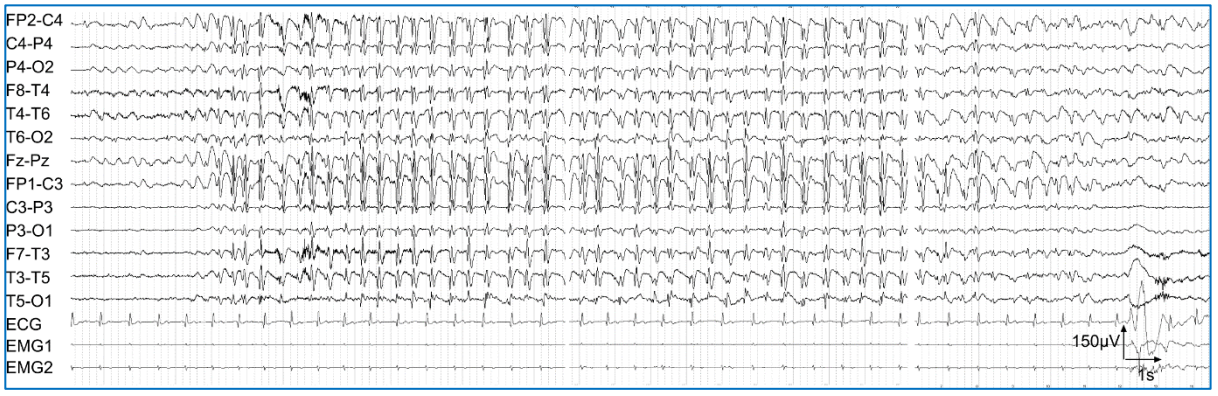


Figure 4.62. Atypical absence of a 10-year-old girl with **LGS**. The seizure lasted for one minute and is presented in three EEG sections. Note the diffuse SSW discharge at 2-2.5 Hz that predominates over the frontal areas, which is more or less symmetric and shows gradual onset and offset.

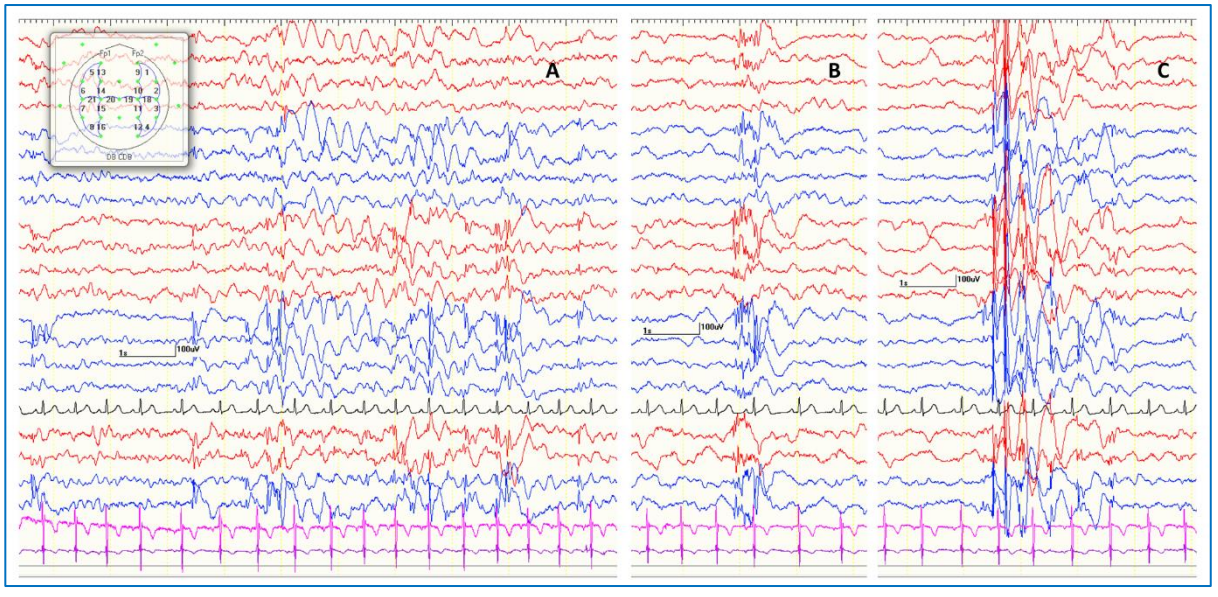


Figure. 4.63. Interictal generalized spike-wave discharges during wakefulness (**A**) and slow sleep (**B**, **C**) in a girl of four years and three months old, with only a two-day history of frequent vacant spells. Parents described that she would become vacant and unresponsive with jerking of the arms and sometimes head for 15-20 seconds, every 30 minutes to an hour. A paternal cousin had similar episodes as a child. Note the difference in the amplitude of the two types of discharge in (**B**) and (**C**). The gain is the same in all three panels.

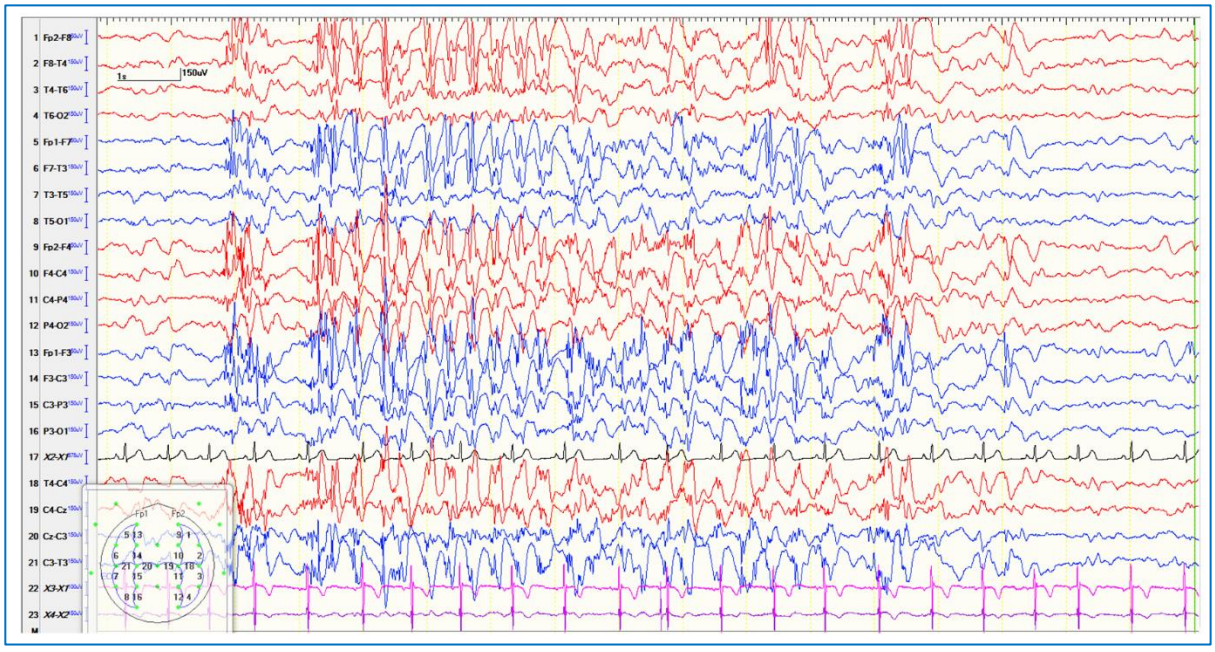


Figure. 4.64. Long generalized spike-wave discharge of the girl of *figure 4.6*3 during slow sleep: note the fragmentations in the discharge and the absence of myoclonus on the EMG channels. Apart from intermittent very mild eyelid fluttering, no other clinical manifestations were noticeable on the video. The girl continued sleeping without any evidence of post-discharge electrographic arousal.

SECTION 4.8: EPILEPSY WITH MYOCLONIC ABSENCES

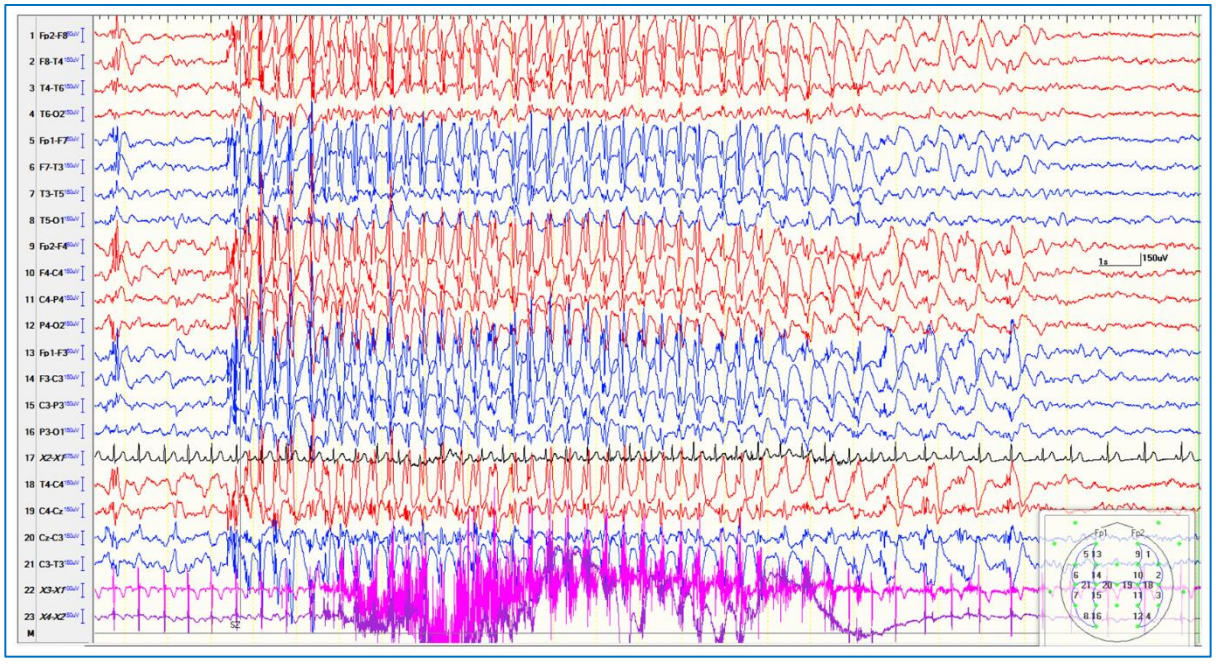


Figure 4.65. Myoclonic absence during slow sleep (same EEG as that for the girl in *figures 4.63 and 4.64*): note the bilateral synchronous onset of the rhythmic 3-Hz generalized spike-wave discharge that (in contrast to that in *figure 4.64*) appears robust and without fragmentation or distortion of rhythmicity. Also, note the associated rhythmic (and symmetric on video) myoclonic jerks of both upper limbs at the same frequency as that of the spike-wave discharge, as recorded by EMG electrodes placed over the deltoids. As in *figure 4.64*, this myoclonic absence did not cause electrographic arousal.

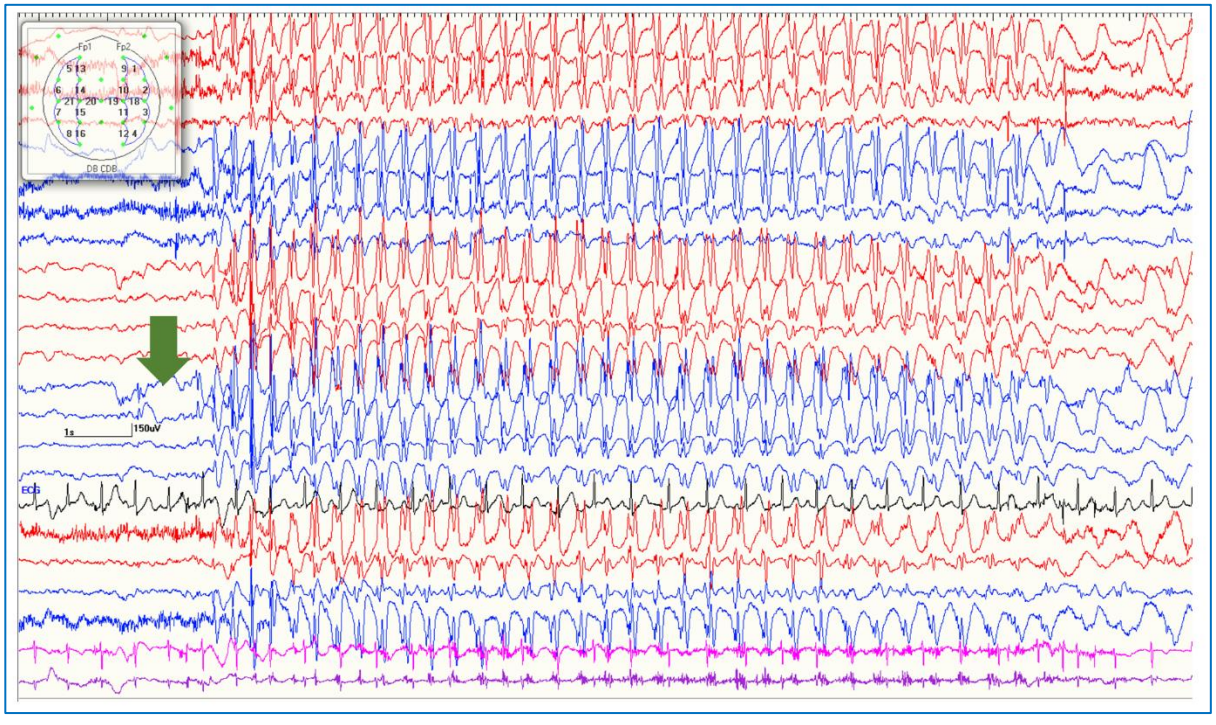


Figure 4.66. Myoclonic absence during hyperventilation: note the left frontal onset (arrow) and the post-discharge high-voltage bilateral frontal delta activity.

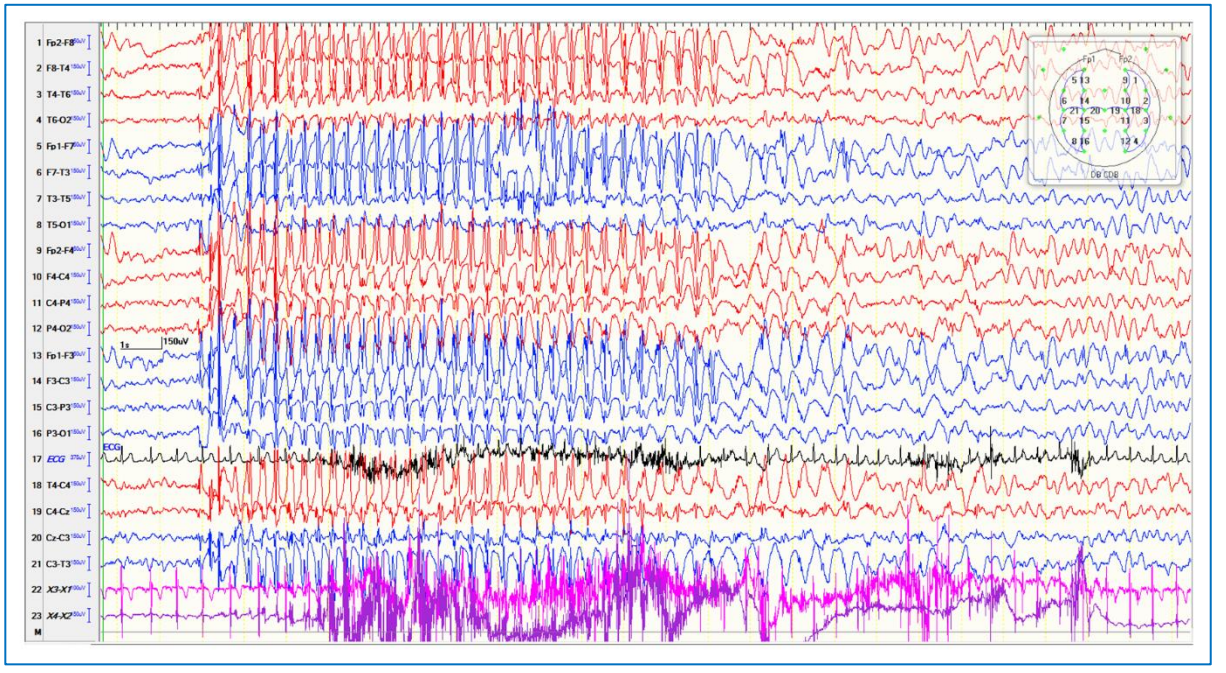


Figure 4.67. Myoclonic absence during wakefulness (the same girl in *figures 4.63-4.66*): note the consistent bilateral rhythmic myoclonias on the EMG channels and the high-voltage bursts of delta after the offset of the ictal discharge, followed by diffuse faster delta activity at 3-4 Hz.

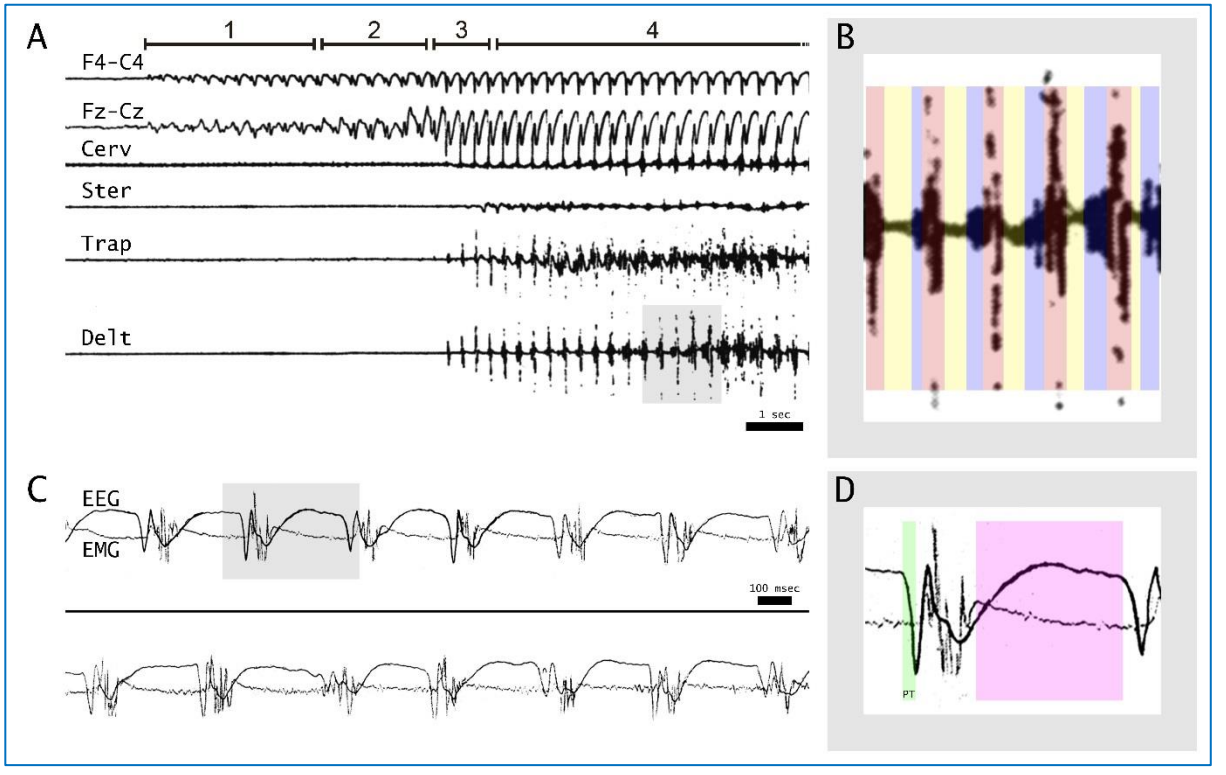


Figure 4.68. EEG-EMG polygraphy relationships in **myoclonic absences**. (**A**) Slow speed recording to evidence the progressive build-up (1-3) of the spike-and-wave discharge and the appearance of myoclonus with the first downward spike positive component. Myoclonus is

associated with a tonic activity of the trapezius and deltoid, and, to a lesser extent, the cervical and sternocleidomastoid muscles. (**B**) Detail from (**A**) showing the myoclonus (in red) with increasing tonic activity and decreasing inactivity (in yellow) between the myoclonias on the EMG. (**C**) EEG (FZ-CZ) and EMG (right wrist) at fast speed showing the constant relationship between each positive spike component and the following myoclonus. (**D**) Detail from (**C**) showing the positive (PT) spike component on the EEG and the myoclonus. Note the spike complex (100-ms duration) with its positive (downward; in green) component followed by the negative (upward) spike component; the large 300-ms slow wave (grey) follows (from Tassinari *et al.* [2010] with permission).

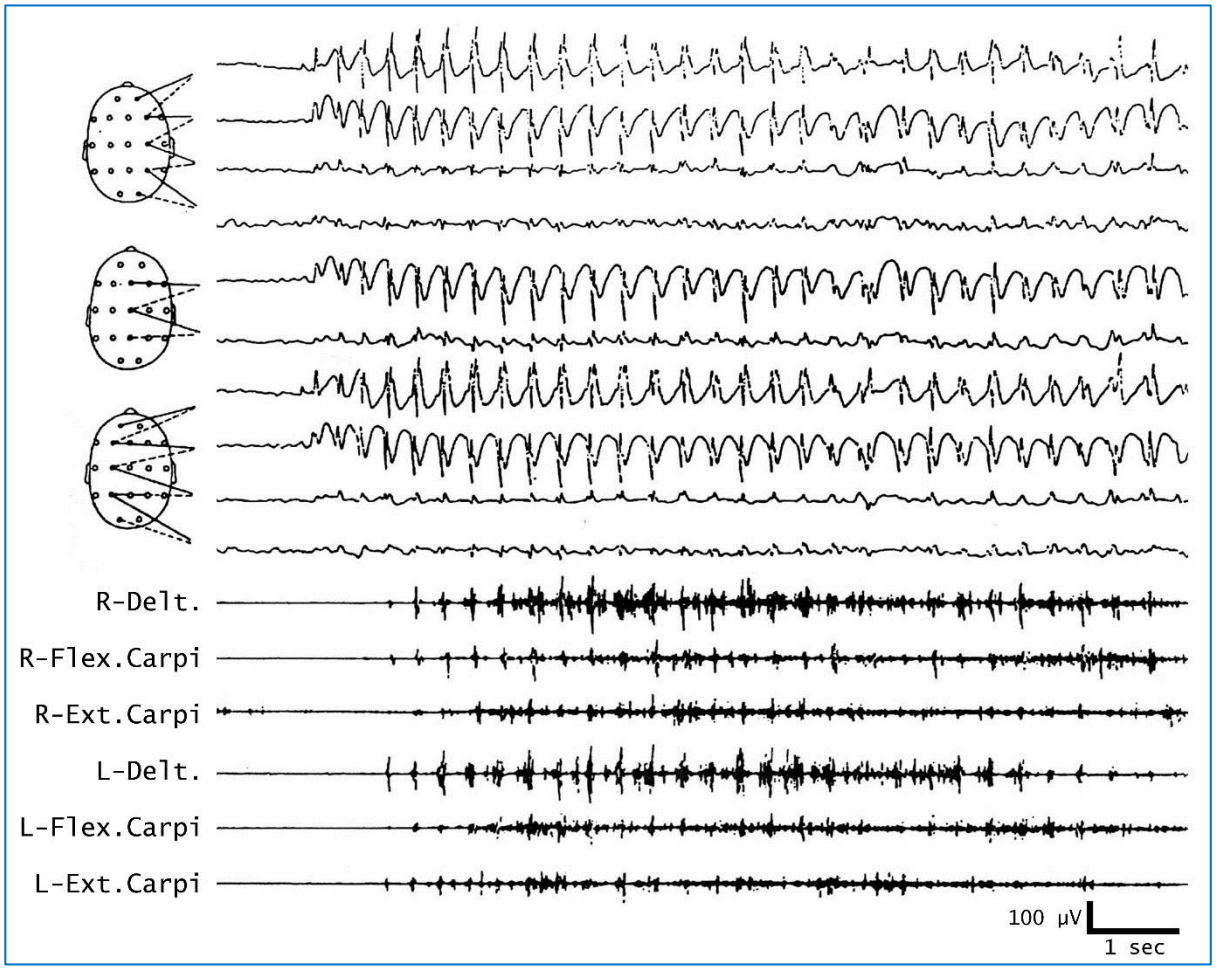


Figure 4.69. Extended EMG polygraphy in **myoclonic absences**. The first three spikes and wave complexes are not accompanied by myoclonias. EMG shows rhythmic myoclonus at the same frequency as the spike and wave in the deltoid, flexor, and extensor of the wrist on the right and left, associated with a build-up of tonic activity (from Tassinari *et al*. [2010] with permission).

SECTION 4.9: ENCEPHALOPATHY WITH ELECTRICAL STATUS EPILEPTICUS DURING SLEEP (ESES)

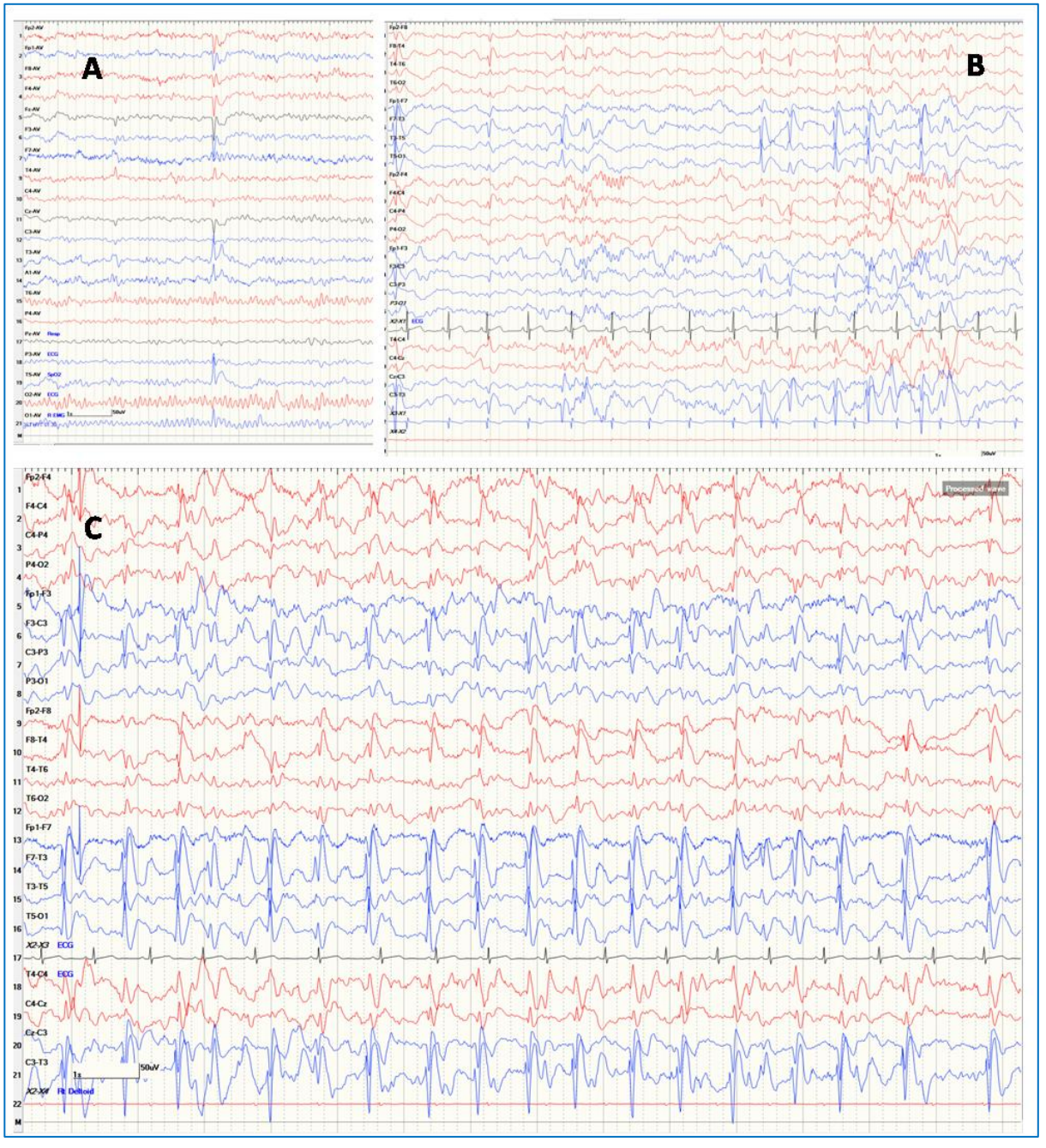


Figure 4.70. A boy with infrequent nocturnal seizures at age nine with left centro-temporal spikes during wakefulness (**A**) that increase during sleep (**B**). He was initially diagnosed with benign rolandic epilepsy, but a year later he presented with cognitive decline. An EEG during sleep at age 10 showed SES (**C**).

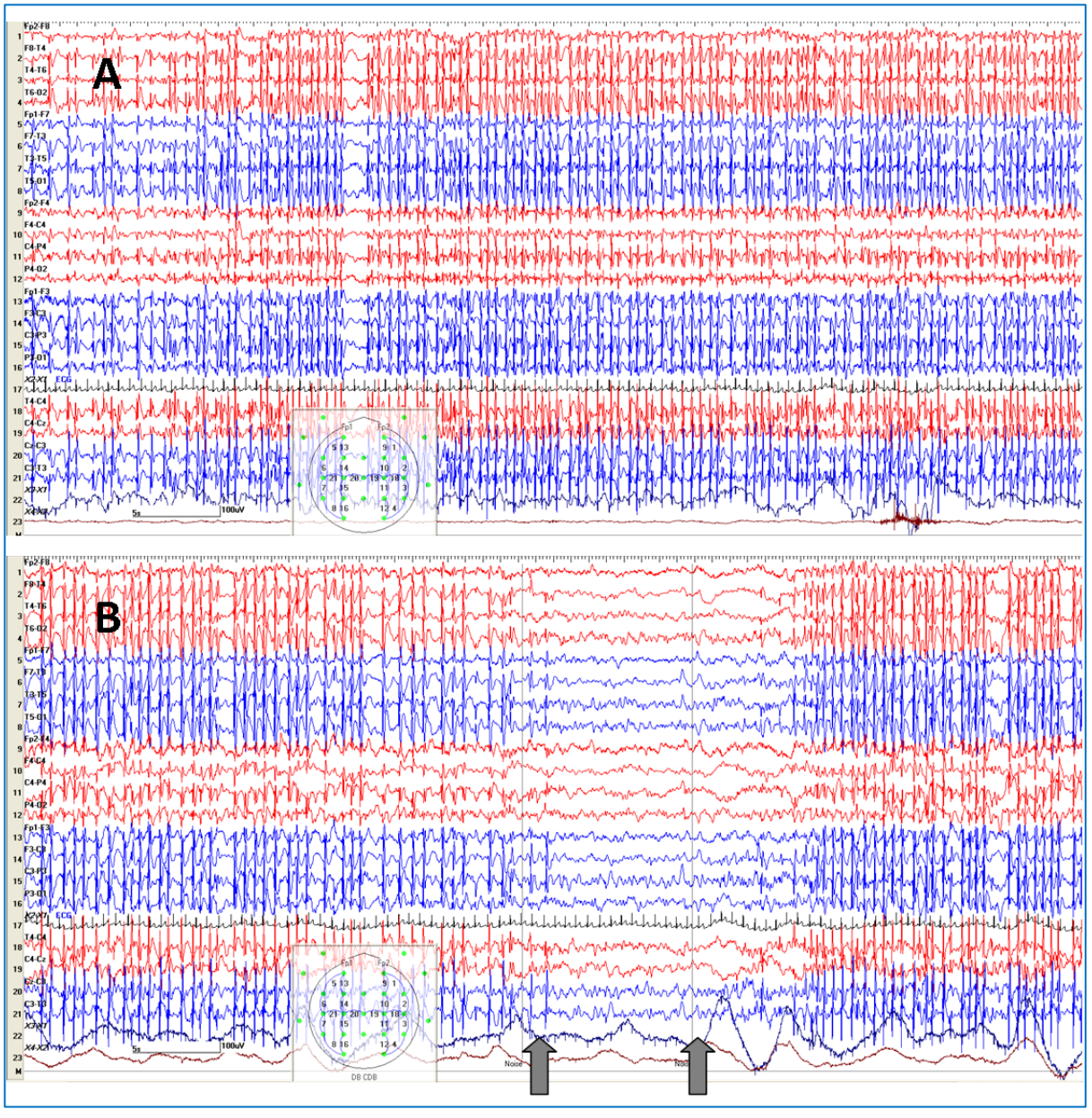


Figure 4.71. ESES in a four-year-old girl with a history of nocturnal seizures manifested with drooling and choking sounds. Note the temporary disruption of the continuous spike-wave pattern due to accidental noises (arrows). She also had day-time absences (*figure 4.74*). She gradually presented language and global regression (*figure 4.78*). Brain MRI was normal.

SECTION 4.10: LANDAU-KLEFFNER SYNDROME

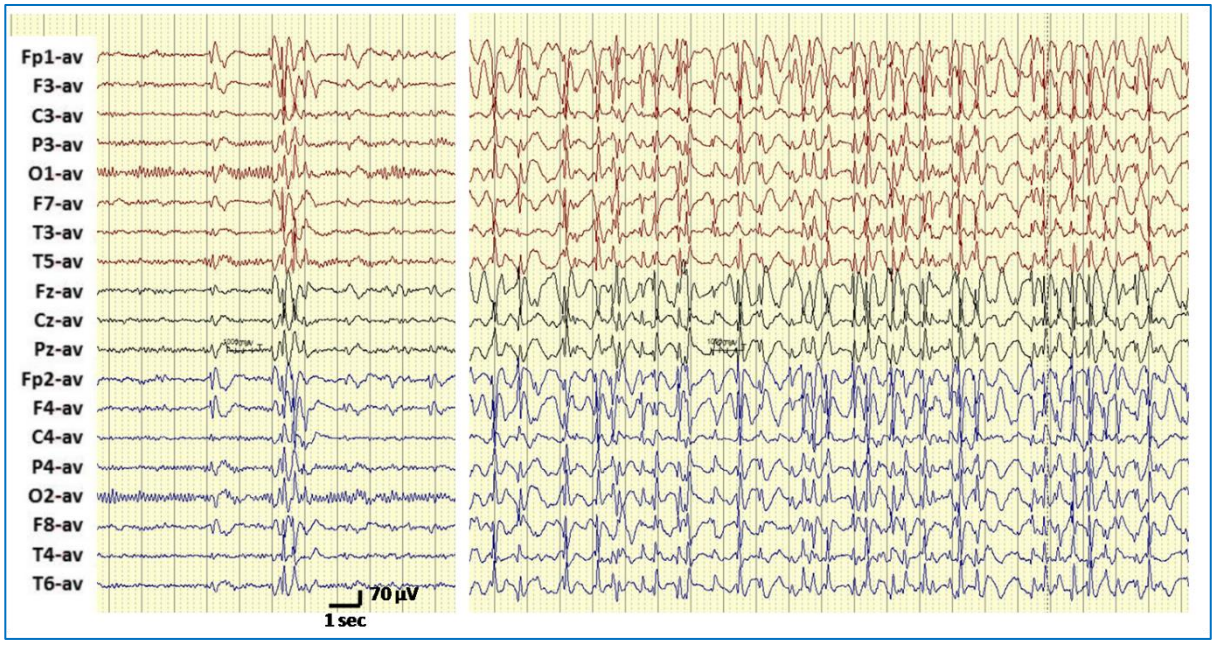


Figure 4.72. Left panel: interictal bifrontal and diffuse, and rather symmetric, ~3-Hz spike-and-wave discharge during wakefulness, in a nine-year-old boy with **Landau-Kleffener Syndrome**, manifested at the age of seven years and nine months, and focal seizures since the age of three years and six months. The LKS was considered to be resolved two years and six months after its appearance; during this period, he also had behavioural disturbances, inattentiveness, and impairment of executive functions. He is now 12 years old and still has some language problems and learning difficulties. Right panel: continuous spike-wave discharges during slow sleep showing a similar distribution to that of the interictal spike-wave discharges (spike-wave index: 70%).

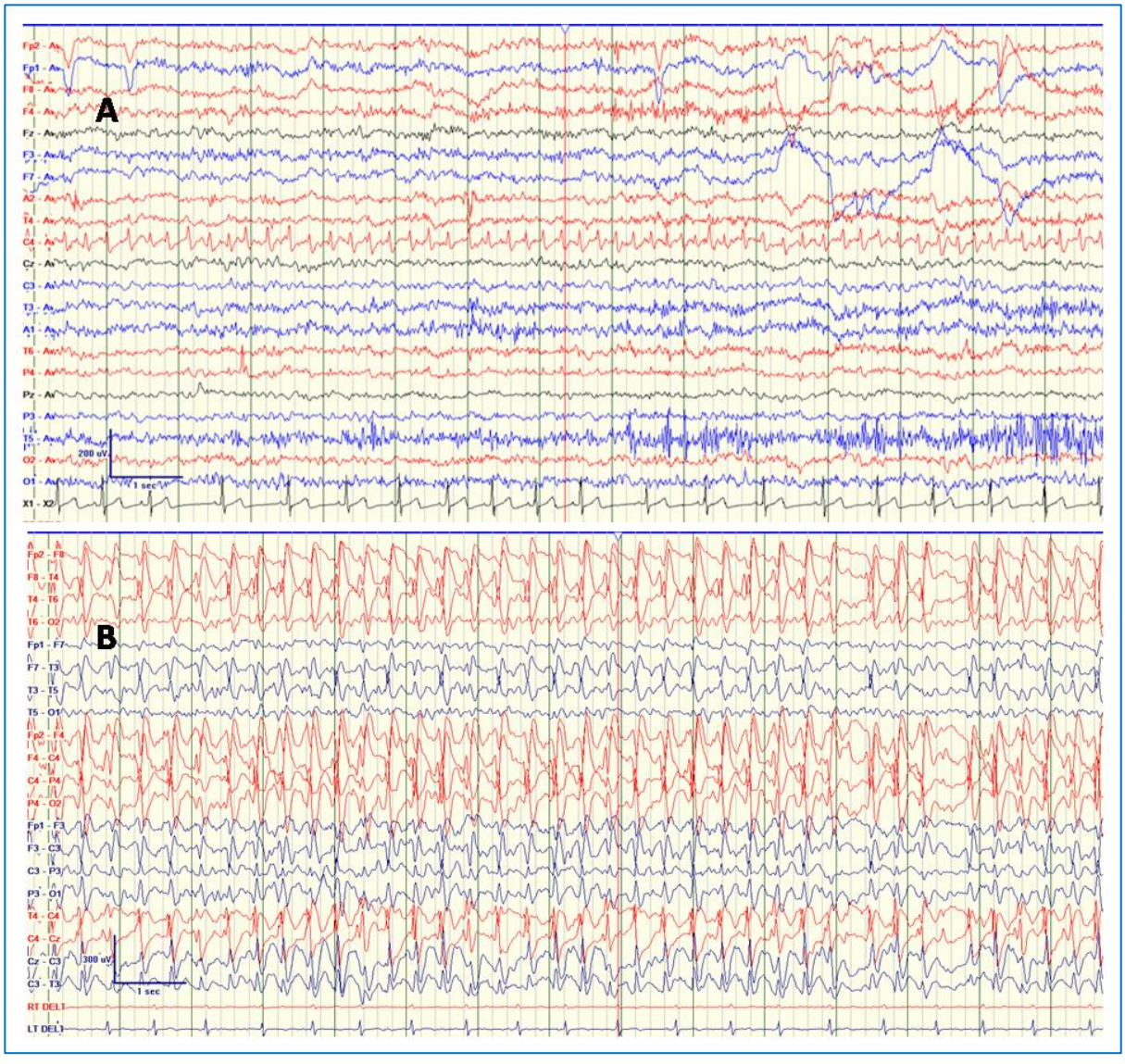


Figure 4.73. This nine-year-old girl had frequent daytime seizures with speech disturbance, head drops, eyelid flickering, and facial clonus. The EEG shows near-continuous focal discharges over the right central electrode during wakefulness (**A**) and SES (R>L) during slow sleep (**B**). Brain MRI shows right peri-sylvian polymicrogyria.

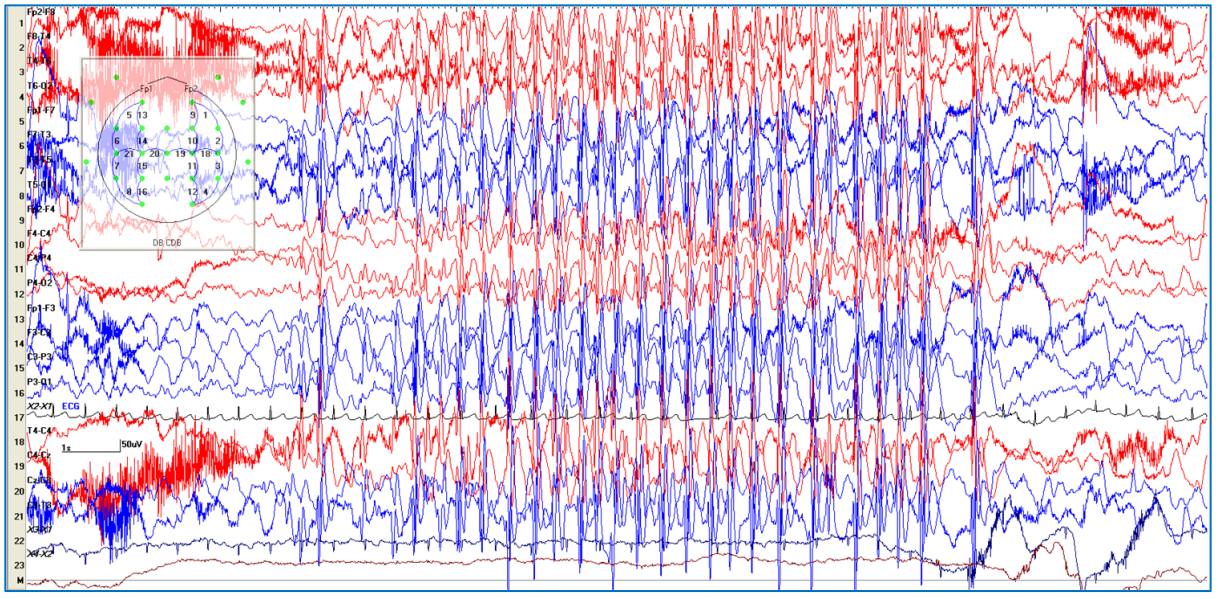


Figure 4.74. Atypical absence during hyperventilation in the girl of *figure 4.71*. The patient stops blowing the windmill and remains unresponsive, exhibiting eyelid flickering.

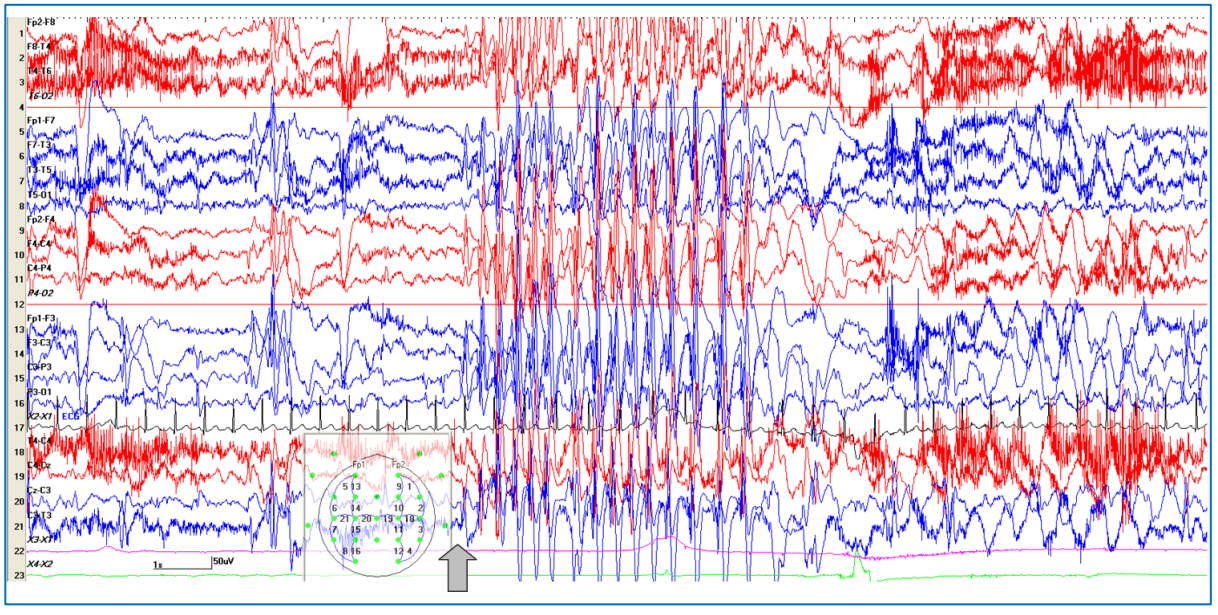


Figure 4.75. Atypical absence associated with sudden head drop (arrow), hypersalivation, and changes in breathing in a seven-year-old boy with **ESES** of presumably structural aetiology. Brain MRI showed developmental malformation with bilateral, predominantly perisylvian, **polymicrogyria** and underdeveloped cerebellum.

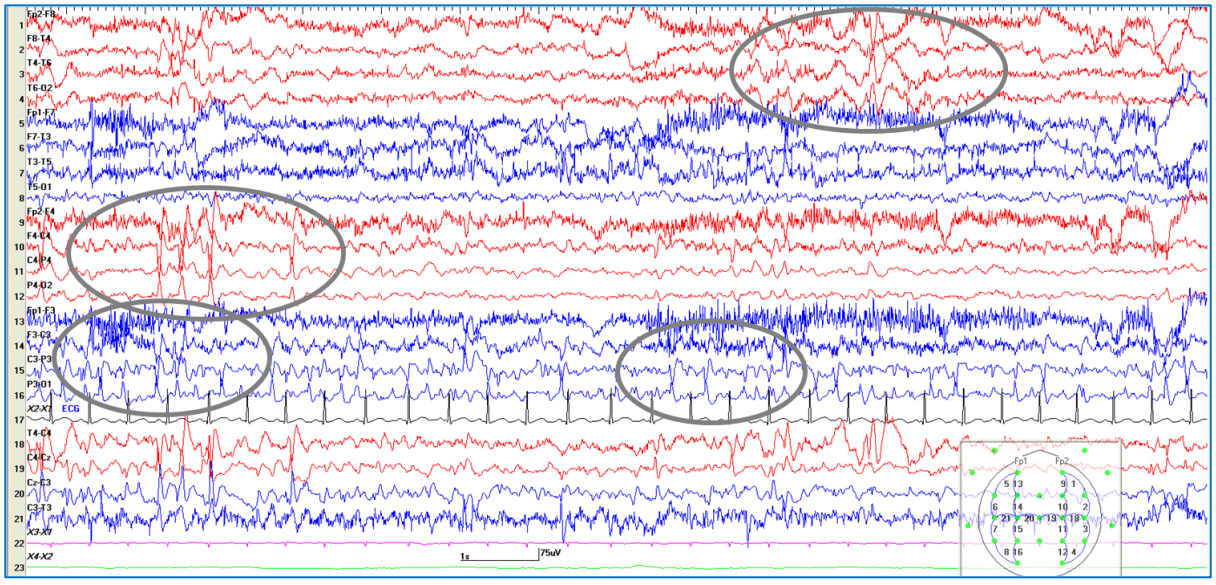


Figure 4.76. Interictal EEG abnormalities during wakefulness in the boy of *figure 4.75*. Note the frequent bilateral independent multifocal (temporal, centro-temporal, and parietal) spike-wave discharges.

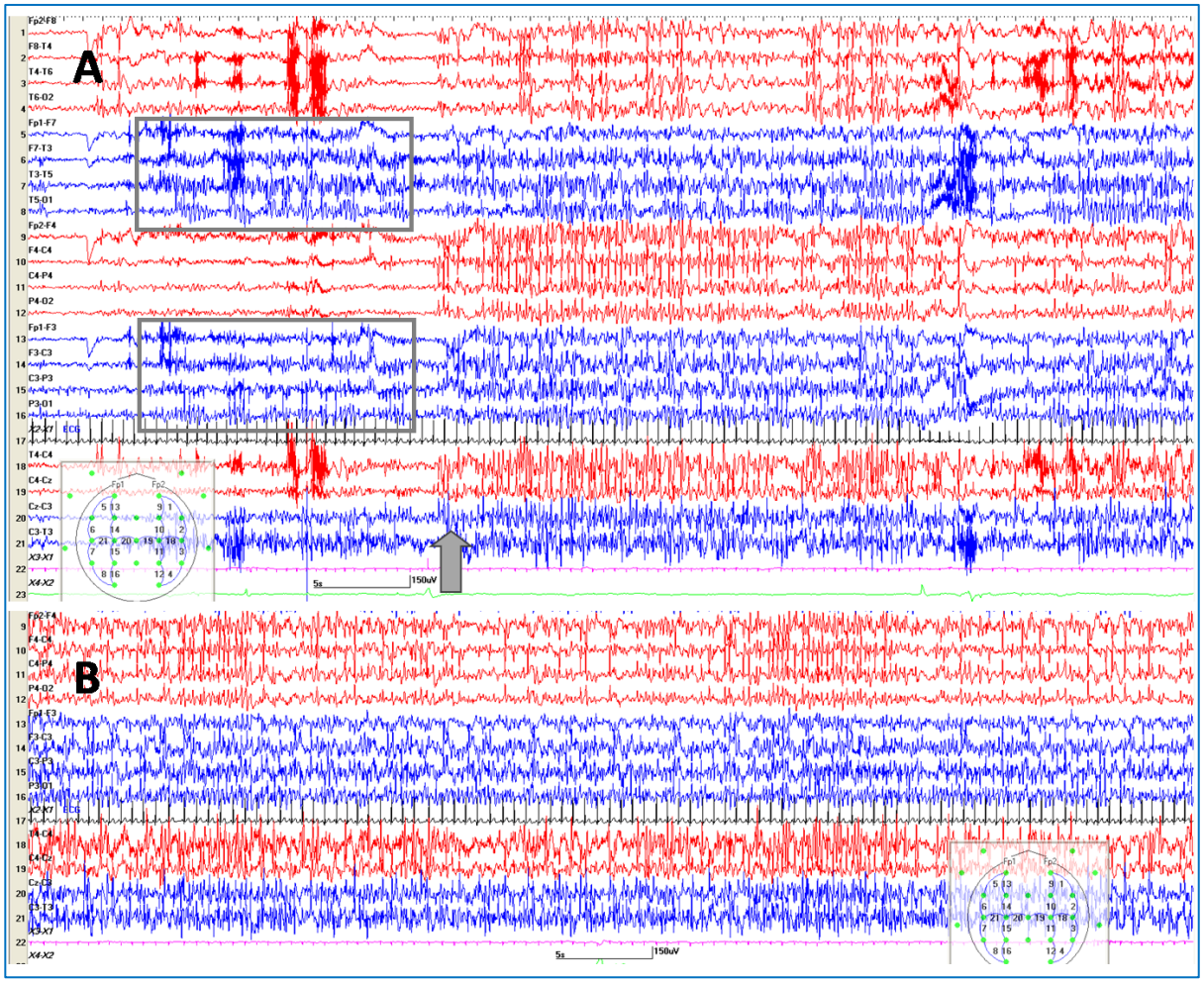


Figure 4.77. ESES in the boy from *figures 4.75 and 4.76*. A left hemispheric run of spike-and-wave discharges, approximately 10 seconds in duration, becomes diffuse and bilateral, and almost continuous from sleep onset (arrow).

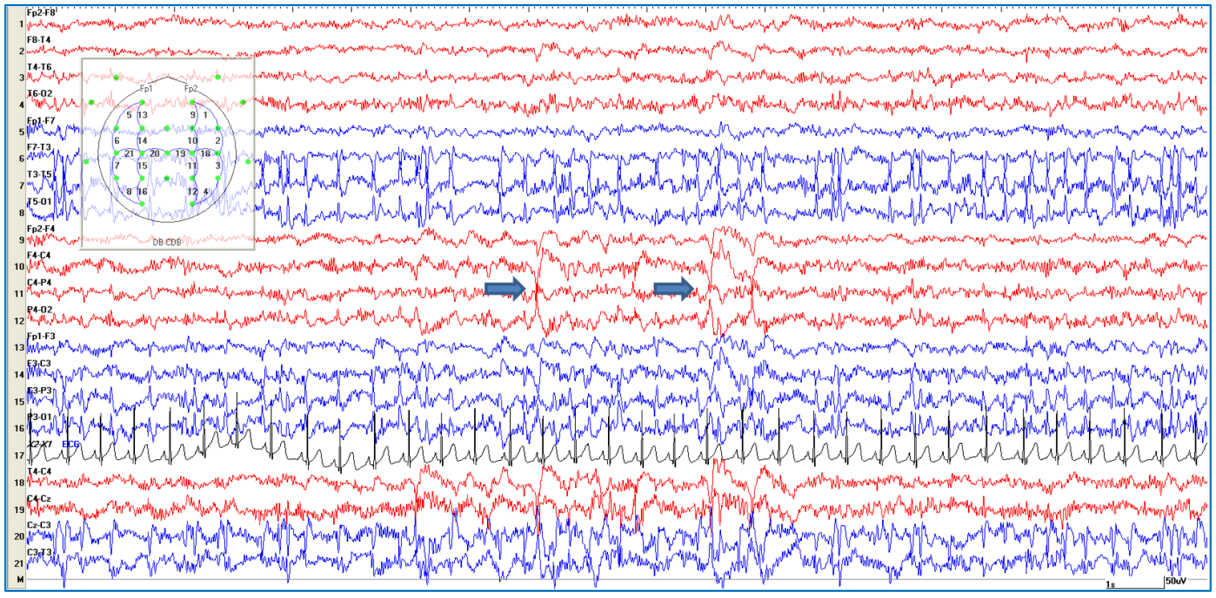


Figure 4.78. Sleep EEG in the girl of *figures 4.71 and 4.74*, one year later, showing SES during Stage 2 sleep (note the k-complexes marked by arrows and nearby spindles), recorded over the left side. At that stage, concerns about her language and cognition had already been raised (verbal IQ: 70; non-verbal IQ: 120). Long runs of left central spikes also occurred during wakefulness.

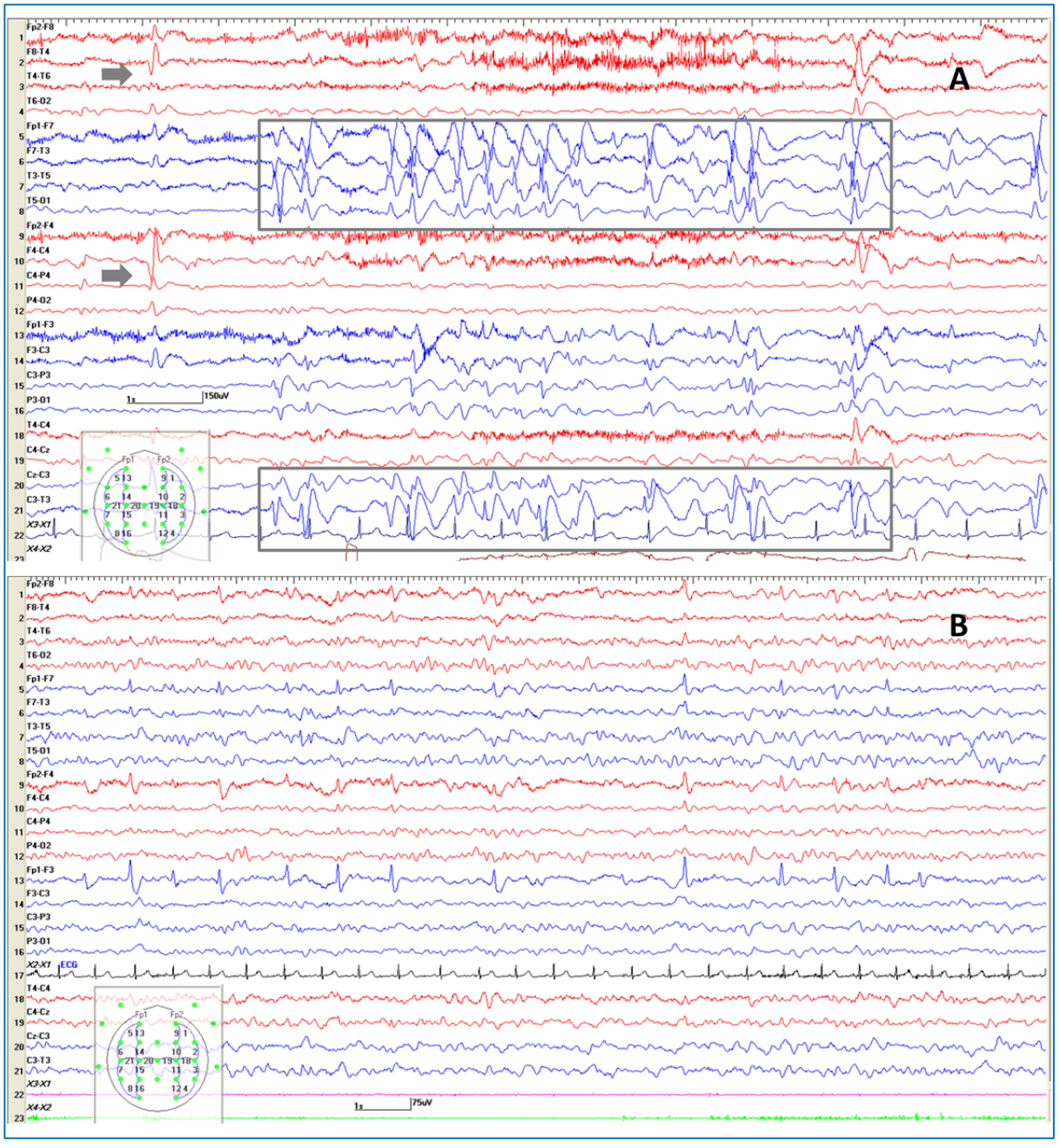


Figure 4.79. (**A**) Run of high-voltage left mid- to posterior temporal spike-wave discharges during wakefulness (panel) in an eight-year-old boy with significant speech delay since the age of six years; the patient had mainly nocturnal brief right-sided motor seizures with mostly retained awareness and a family history of **LKS** (older sister and twin brother). His mother also had seizures until her early twenties. This EEG also showed independent left frontal and right posterior temporal/parietal spikes (arrows). Treatment with VPA, and later with LEV and steroids, reduced the frequency of seizures and improved receptive language, but not motor speech; the EEG at this stage showed left pre-frontal spikes diffusing to the right frontal area, but no temporal paroxysms (**B**).

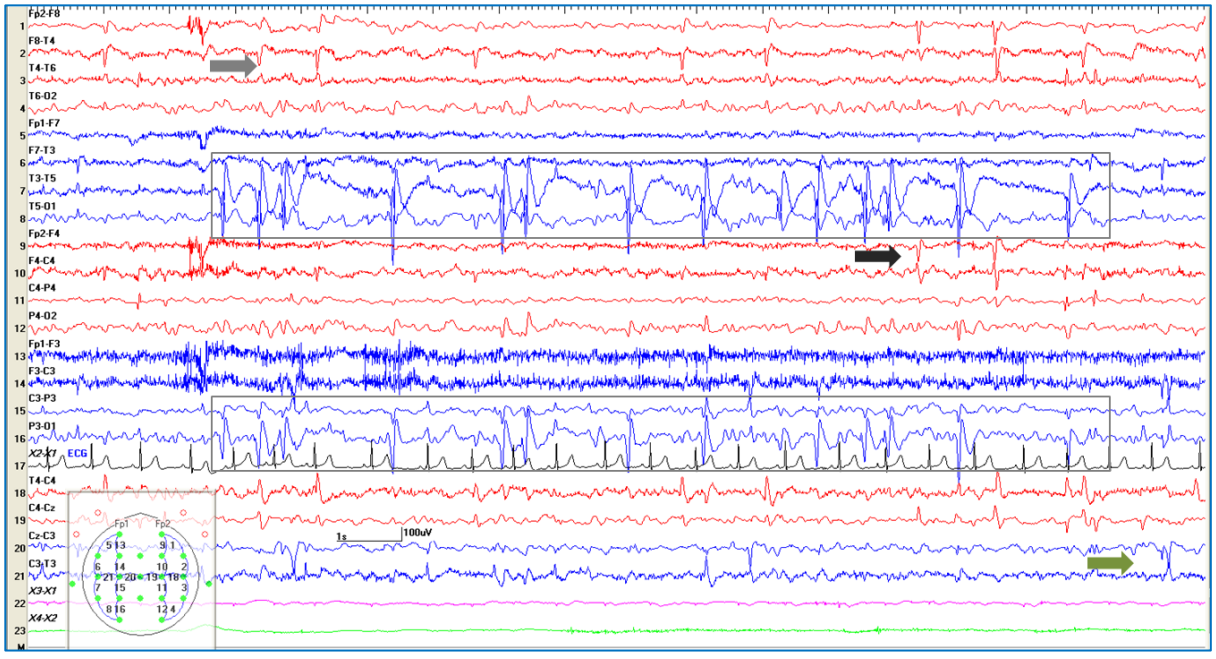


Figure 4.80. High-voltage left occipital (panel), left central-temporal / parietal (green arrow), right mid -to posterior temporal (grey arrow), and right frontal (black arrow) spike-wave discharges in the twin brother of patient from *figure 4.79*. The patient also presented with global language regression and mainly nocturnal seizures, but showed better response to treatment with steroids; his language function improved and his follow-up EEG normalized. A sleep recording was impossible to obtain for any of the siblings at any stage, despite multiple attempts in the EEG laboratory. Testing for continuous spike-wave during sleep (SES) would only be possible by examining overnight sleep EEG (*see advanced EEG recording protocol in the ESES chapter*).

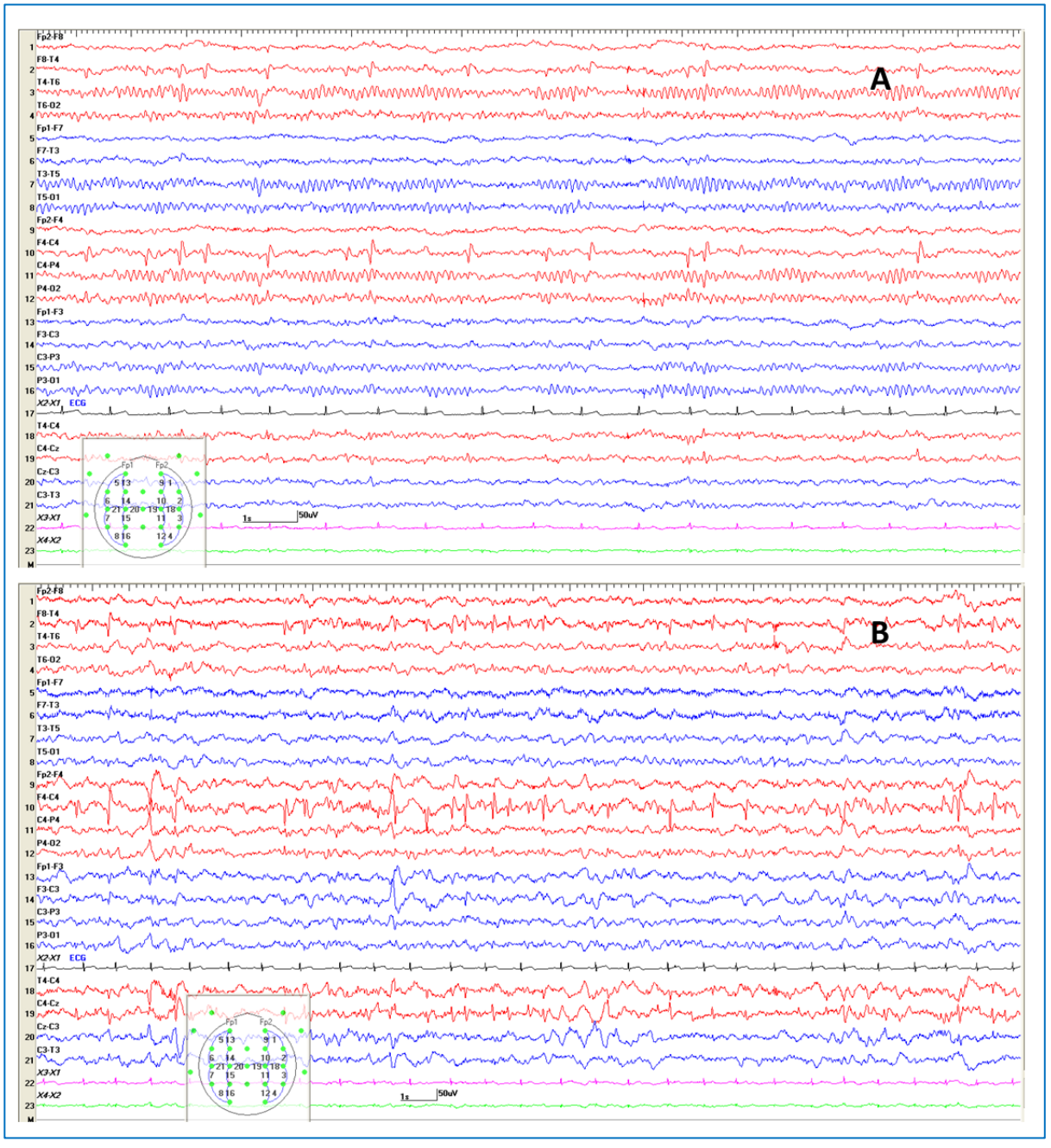


Figure 4.81. Right centro-temporal-parietal spikes in a 12-year-old boy with **LKS** during wakefulness (**A**), becoming more frequent during slow sleep (**B**).

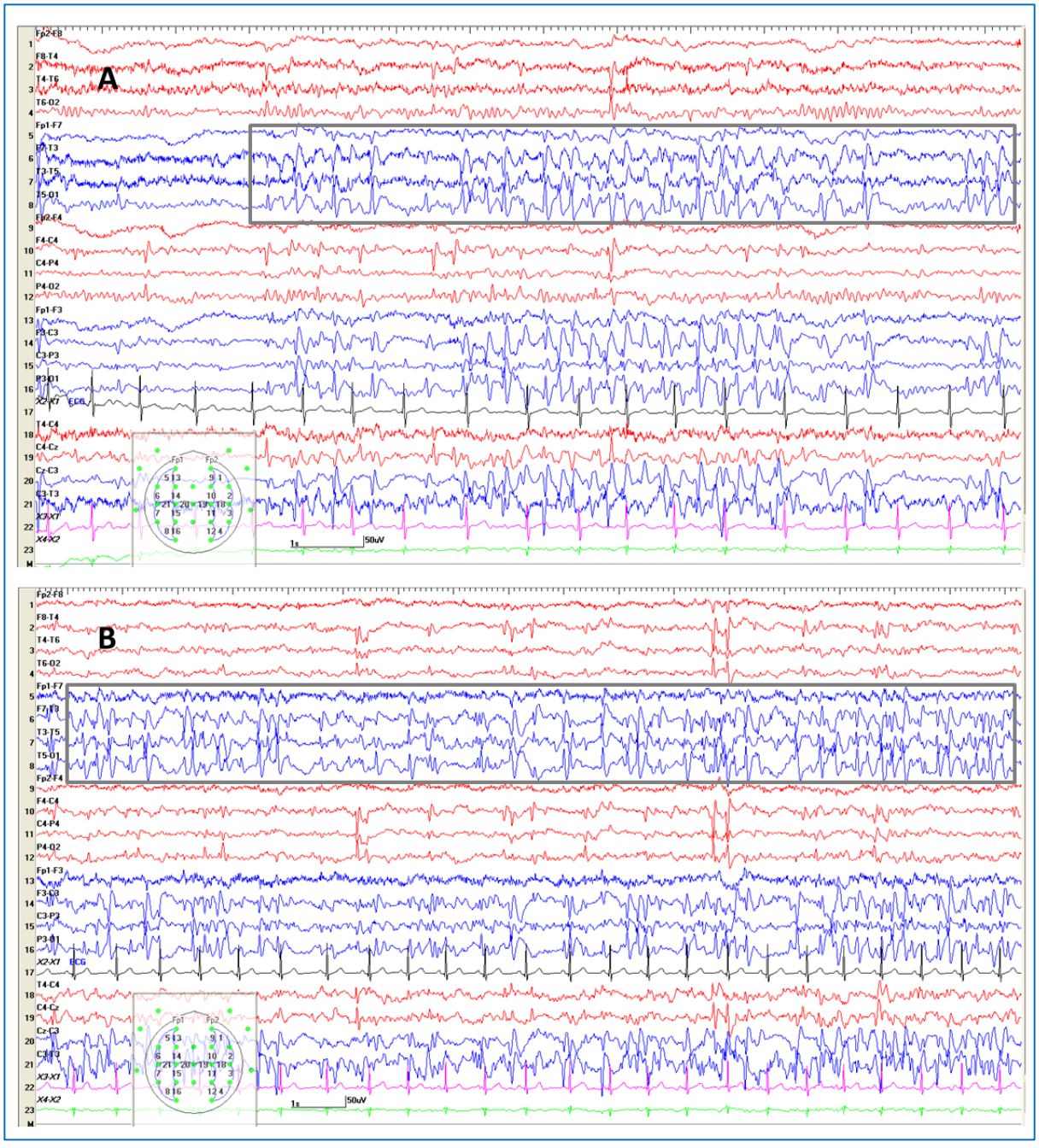


Figure 4.82. Left posterior temporal-parietal paroxysms and independent, less frequent, right posterior temporal-parietal spikes during wakefulness (**A**) in a 10-year-old boy with epileptic aphasia, associated with nocturnal rolandic-type seizures and atypical absences. Note the continuous occurrence of the left posterior temporal-parietal discharges during slow sleep (**B**). Both aphasia and seizures improved after treatment with prednisolone and valproic acid.

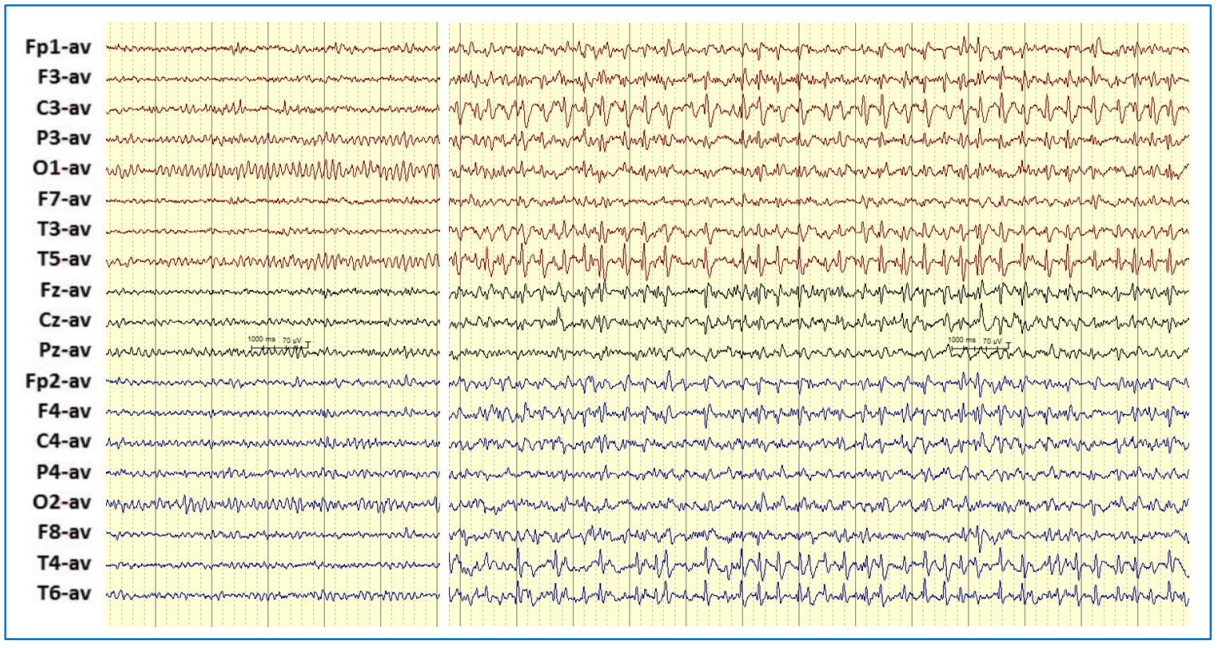


Figure 4.83. Activation of continuous spike-wave activity over the left central and bilateral mid-posterior temporal areas during sleep (right panel) in a nine-year-old boy with **LKS**. Note the paucity of epileptic discharges during wakefulness (left panel).

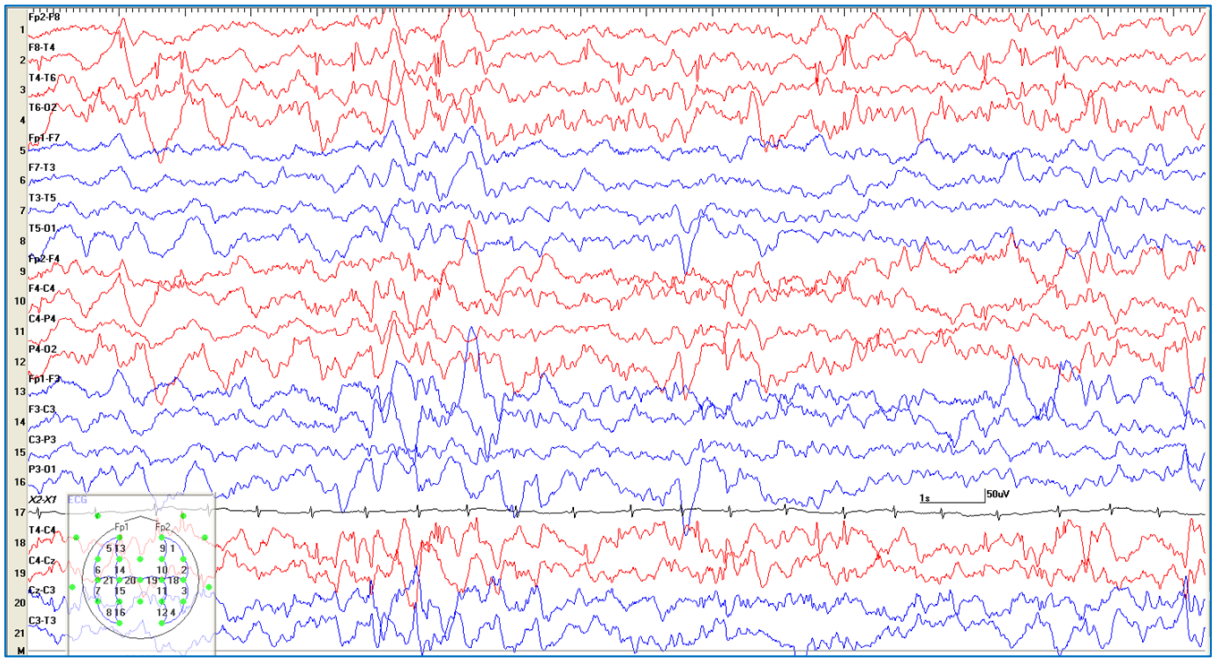


Figure 4.84. First sleep EEG of a six-year-old boy who presented with subacute behavioural speech disturbance; note the frequent spike-wave discharges over the right mid- to posterior temporal area, diffusing to the central-parietal region. Background activity during wakefulness was normal. His speech showed some improvement after treatment with steroids and his follow-up EEG showed less frequent spikes. No overt epileptic seizures were reported by his family or recorded in any of his two EEGs.