Early-Onset Epileptic Encephalopathies

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23.1 Introduction

Early myoclonic epilepsy (EME) and Ohtahara syndrome (OS) or early infantile epileptic encephalopathy (EIEE) are the earliest presenting within the age-dependent epileptic encephalopathy syndromes. These are electro-clinical syndromes, defined by their clinical features and electroencephalographic findings [1, 2].

These two entities share many features, including age at presentation, a similar electroencephalographic pattern, intractable seizures, and poor prognosis. Tonic seizures and focal motor seizures are frequently observed in both syndromes. Differentiating between the two conditions can be difficult, especially early in their course. As far as considerable clinical overlap between these conditions can occur [2], these two conditions have been conceptualized as part of the same continuum of disease.

EME and EIEE are traditionally distinguished according to different types of seizures, differences in the pattern of suppression-burst, and aetiologies. Specifically, in its original form, Ohtahara syndrome is thought to result mostly from structural malformations, whereas EME is associated with metabolic abnormalities [3].

New understandings of the genetic and pathophysiologic mechanisms underlying these diseases revealed further similarities between them. Both syndromes frequently seem associated with conditions that lead to abnormal neuronal migration, possibly leading to both structural brain abnormalities and a functional disconnection between the cortex and the deep brain and brainstem [4]. The prominence of brainstem abnormalities in both syndromes similarly indicates a disconnection between the cortex and subcortical structures [4].

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23.2 Ohtahara Syndrome

Ohtahara syndrome or early infantile epileptic encephalopathy (EIEE) was firstly described by Ohtahara in 1976, who named it "early infantile epileptic encephalopathy with suppression-burst" [5]. Ohtahara syndrome starts early in infancy, within the first 3 months of age and often within the first 2 weeks [6]. Ohtahara syndrome can result from a variety of aetiologies, but the majority of cases have been associated with structural brain abnormalities [7–10]. Cases related to genetic mutations and metabolic abnormalities have also been reported, although at least some of these cases also exhibited associated structural malformations [7]. Even in some cases when no structural lesions were evident on imaging, post-mortem examinations demonstrated evidences of a migration disorder or dysgenesis not previously appreciated on neuroimaging [7, 10].

A variety of structural malformations have been associated with Ohtahara syndrome, including hemimegalencephaly, agenesis of the corpus callosum, and porencephaly. Hypoxic injury, cortical dysplasia, and cerebral migration disorders are also frequently described [7, 9].

Among metabolic disorders, non-ketotic hyperglycinemia, cytochrome C oxidase deficiency, pyridoxine dependency, and carnitine palmitoyltransferase deficiency are the most frequently associated with Ohtahara syndrome [11–13].

Underlying genetic mutations have been increasingly reported with Ohtahara syndrome. Mutations in the syntaxin-binding protein 1 (STXBP1) gene, for example, have been described in Ohtahara syndrome since 2008 [14]. A variable proportion of patients, ranging from 10% to 38% with Ohtahara syndrome, might be caused by STXBP1 genetic variants [14]. Similarly, mutations of the ARX gene have also been associated with Ohtahara syndrome [15, 16]. Finally, mutations in the mitochondrial glutamate carrier family 25 (SLC25A22) gene have been identified as cause of Ohtahara syndrome.

Epilepsy onset is within the first 3 months of age and often within the first 2 weeks [6]. Infants acutely develop

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tonic spasms that can be either generalized or lateralized, can occur both isolated or in clusters, and are independent from the sleep cycle. Spasms typically last up to 10 s and can occur hundreds of times per day [6, 17]. One third of patients with Ohtahara syndrome might also develop other seizure types, most commonly focal motor seizures, hemiconvulsions, or focal to bilateral tonic-clonic seizures [6, 17].

The prognosis is universally poor. Only anecdotal evidence supports the use of specific antiepileptic drugs in these conditions. Phenobarbital, valproate, pyridoxine, zonisamide, and benzodiazepines have all demonstrated limited effects in seizure control in Ohtahara syndrome [18]. Adrenocorticotropic hormone therapy also exerts limited efficacy and may be particularly beneficial in cases of Ohtahara syndrome that progress to West syndrome [17]. The correction of underlying metabolic disorders may lead to a more favourable outcome. In particular, patients with Ohtahara syndrome have been reported to do relatively well after the correction of underlying pyridoxine deficiencies or biotinidase deficiencies [12]. Cases with structural abnormalities such as hemimegalencephaly or cortical dysplasia can benefit from surgery with focal resection or hemispherectomy [19].

The most specific EEG feature is the suppression-burst (SB). This pattern is characterized by high-voltage bursts alternating with almost flat suppression phases at an approximately regular rate [1, 5] (Fig. 23.1).

It should be stressed that distinguished features of SB in Ohtahara syndrome are similar in both waking and sleeping states and regular appearance of periodicity [20]. This finding has critical importance for the diagnosis of this syndrome [20]. SB pattern differs definitely from the periodic type of hypsarrhythmia where it becomes remarkable in sleep (Figs. 23.2 and 23.3).

23.3 Early Myoclonic Encephalopathy

Early myoclonic encephalopathy (EME) can be associated with structural, metabolic, and genetic abnormalities. As in Ohtahara syndrome, also in the pathogenesis of EME seems to be involved a diffuse dysfunction which particularly involves brainstem and white matter, leading to deafferentation and hyperexcitability of the cortex [4].

Focal structural abnormalities are not frequently observed, while progressive, diffuse cortical atrophy – suggestive of an underlying metabolic or degenerative disorders [17] – has been reported in most cases [3].

Metabolic abnormalities are frequently associated with EME, particularly non-ketotic hyperglycinemia. Cases have also been reported in association with D-glyceric acidemia, propionic aciduria, molybdenum cofactor deficiency, pyridoxine deficiency (Fig. 23.4), methylmalonic acidemia, sulphite oxidase deficiency, Menkes disease, Zellweger syndrome, and CDG disorders (Fig. 23.5) [21, 22].

Pathologic findings in early myoclonic encephalopathy include demyelination, multifocal spongy changes in the white matter, imperfect lamination of the deep cortical layers, perivascular concentric bodies, and astrocytic proliferation [4]. Autopsy findings revealed prevalent white matter abnormalities and brainstem pathology [4, 10]. The presence

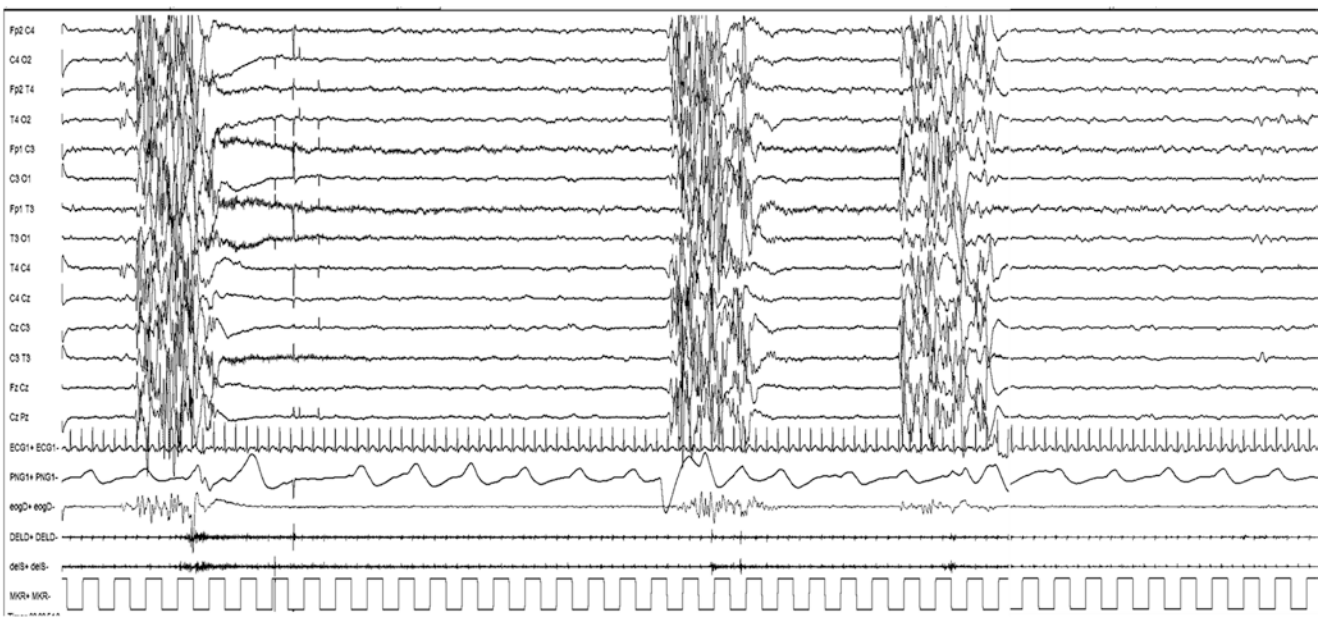

Fig. 23.1 Suppression-Burst pattern in a patient 1 month old boy with hypoxic-ischemic damage at birth. The EEG pattern is characterized high voltage bursts of spikes alternating with almost flat suppression phases at an approximately regular rate

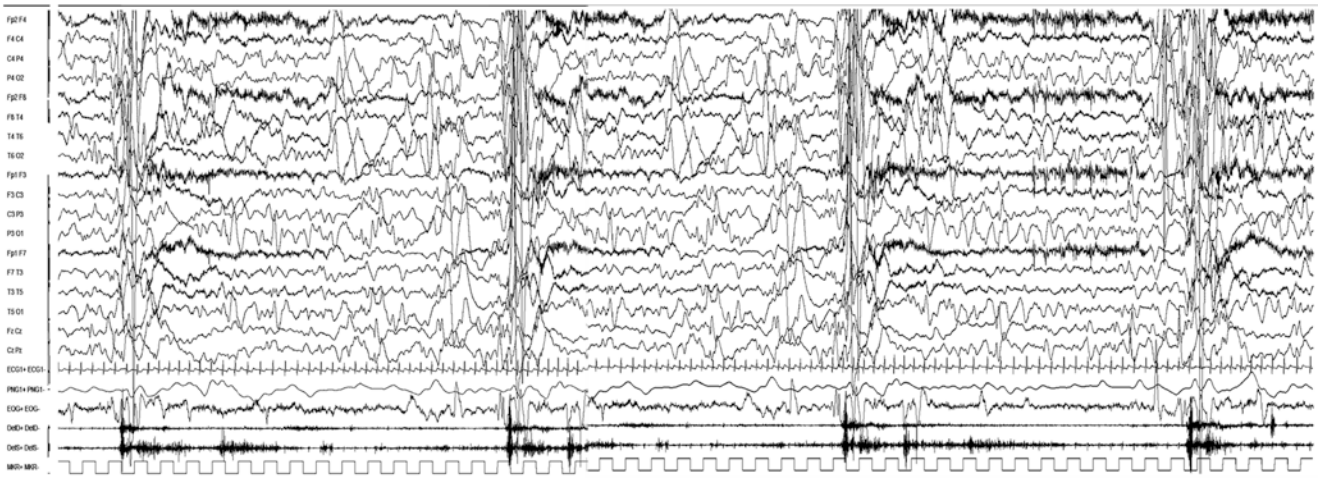

Fig. 23.2 Epileptic spasms in a 4 months old boy with STXBP1 gene mutation during awake state. Documentation of tonic-spasms

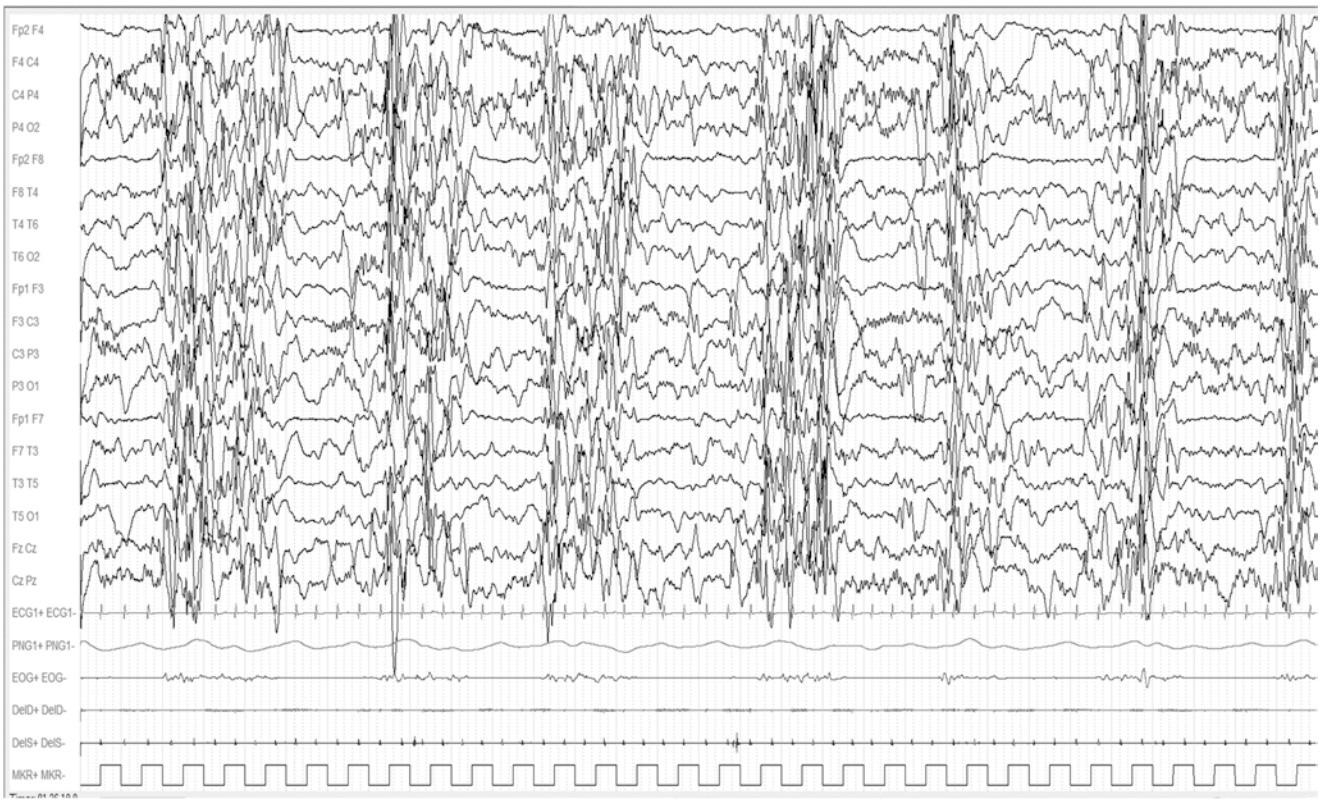

Fig. 23.3 Sleep EEG in a patient with STXBP1 gene mutation during sleep state. It's evident an increasing of epileptiform abnormalities, grouped in bursts of diffuse poly-spikes, intermingled with suppression of cerebral activities

of numerous spiny neurons dispersed in the white matter has also been reported, which is suggestive of impaired neuronal migration and apoptosis [11]. Also a dysfunction of basal ganglia and thalami has been documented [10].

Dealing with genetic aetiology, in 2009, EME was reported in association with a mutation of the verba erythroblastic leukaemia viral oncogene homologue 4 (ErbB4 gene), which is involved in the migration of interneurons to the cortex [23]. This genetic abnormality is consistent with the persistence of spiny neurons in the white matter on pathologic examination and of the functional deafferentation described by Hirose et al. [4]; both of them seem to indicate impaired neuronal migration to the cortex, suggesting a degree of "cortical isolation" in the brains of these patients [4].

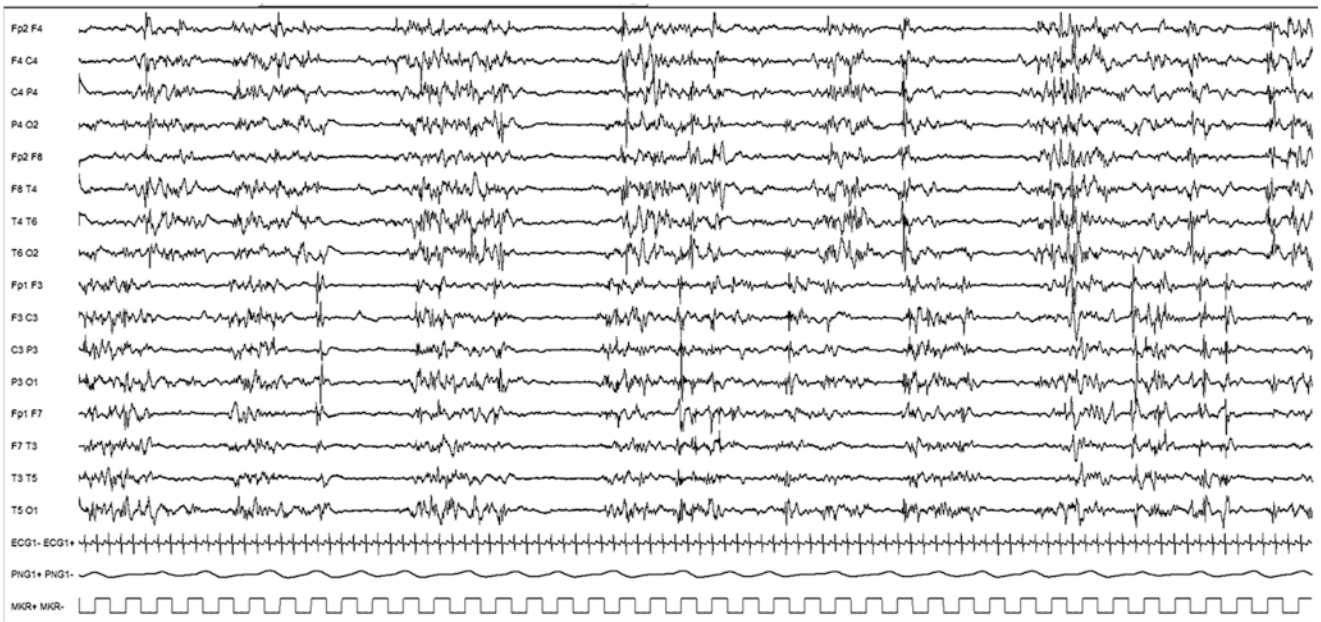

Fig. 23.4 Suppression-burst with multifocal epileptiform abnormalities in a patient with pyridoxine-deficiency encephalopathy

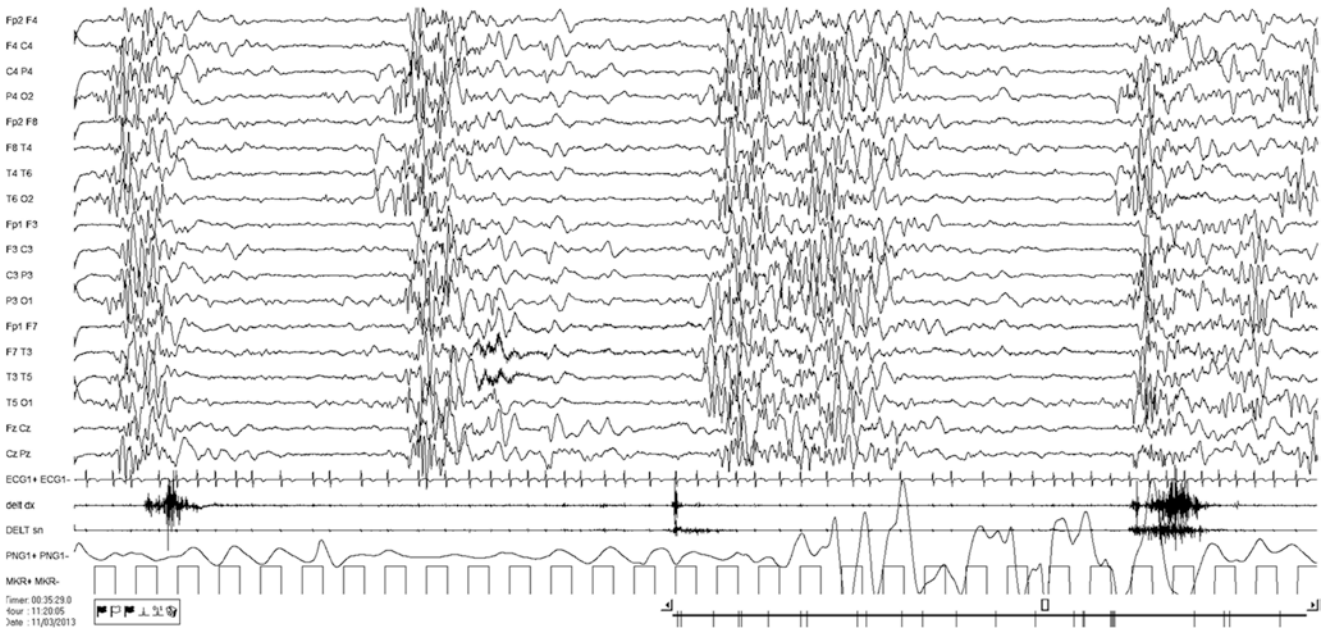

Fig. 23.5 EEG during awake state of a 6 month old boy with suppression-burst pattern due to CDG type 1 disorder due to ALG11 mutation. EEG indicates typical suppression burst pattern that can be observed in both Ohtahara syndrome and early myoclonic encephalopathy

23.4 Other Early-Onset Epileptic Encephalopathies due to Specific Genetic Aetiology

23.4.1 CDKL5-Related Epileptic Encephalopathy (OMIM 300672)

Early infantile epileptic encephalopathy type 2 (EIEE2, OMIM #300672) is an X-linked dominant severe neurologic disorder characterized by onset of seizures in the first months of life and severe global developmental delay resulting in mental retardation and poor motor control [24]. The epilepsy course has been distinguished into three successive stages: (stage I) early epilepsy (onset 1–10 weeks) with normal interictal EEG despite frequent convulsive seizures, (stage II) epileptic encephalopathy with infantile spasms and hypsarrhythmia, and (stage III) refractory epilepsy with tonic seizures and myoclonia [25]. Interictal EEG in this last phase is characterized by a marked

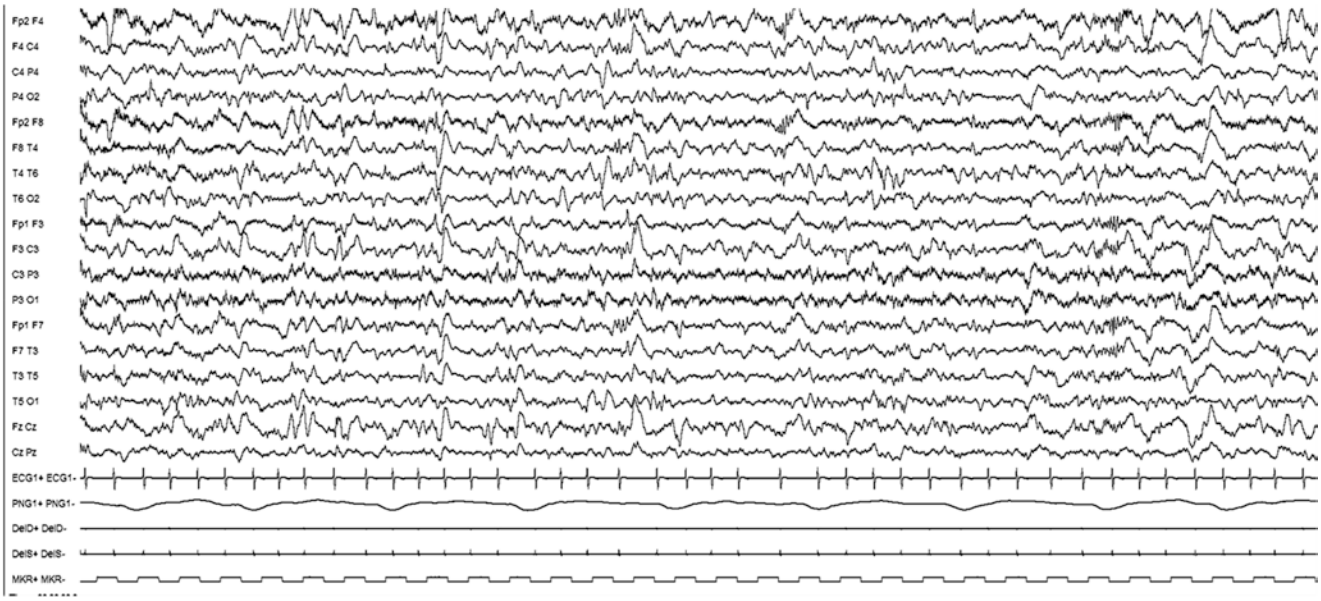

Fig. 23.6 Interictal EEG of a 8 years old girls with CDKL5-related encephalopathy. Bilateral epileptiform abnormalities are intermingled with brief phases of flattening of cerebral activity

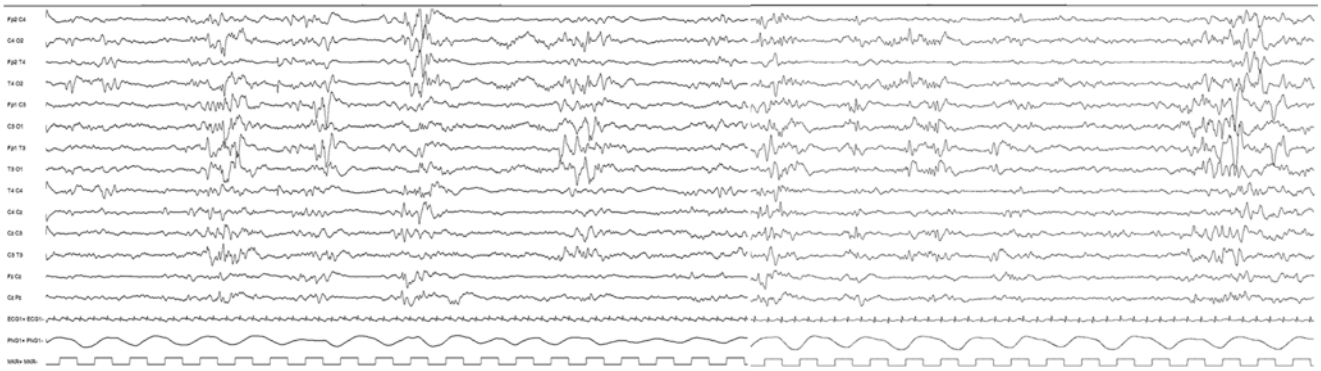

Fig. 23.7 Multifocal epileptiform abnormalities intermingled with diffuse suppression of cerebral activity in a patient with KCNQ2 at onset

slowing down of background activity and multifocal abnormalities (Fig. 23.6). The phenotypes associated with CDKL5 mutations range from a mild form with controlled epilepsy and ability to walk to a severe form with absolute microcephaly and poor motor development. Genotype-phenotype correlation is not still defined even if a relationship between severity and the type of CDKL5 mutation, depending on whether the catalytic domain is impaired or not, has been reported [24, 25].

23.4.2 KCNQ2-Related Epileptic Encephalopathy (OMIM 613720)

KCNQ2-related epileptic encephalopathy type 7 (OMIM #613720) is a neonatal-onset epilepsy characterized by daily seizures, predominantly tonic and drug-resistant, associated with intellectual disability [26]. Seizure onset is between 1 and 4 days of age with daily tonic asymmetric, focal, and clonic seizures. EEG is characterized by multifocal epileptiform abnormalities intermingled with disuse suppression of cerebral activity (Fig. 23.7).

Most patients reach seizure control within the first year of life and remain seizure-free thereafter; however, cognitive deterioration of variable degree remains evident. Sodium channel blockers, especially carbamazepine and phenytoin are the drugs of choice for effective seizure control [27].

23.4.3 SCN2A-Related Epileptic Encephalopathy (OMIM 613721)

Early infantile epileptic encephalopathy type 11 (EIEE11, OMIM #613721) is a recently recognized syndrome caused by de novo SCN2A missense variants. Epilepsy onset is reported within the first 3 months of life [28] About 40% of patients have an identifiable epilepsy syndrome, i.e. Ohtahara syndrome or epilepsy of infancy with migrating focal seizures (EIMFS) [28, 29]. The remaining patients have

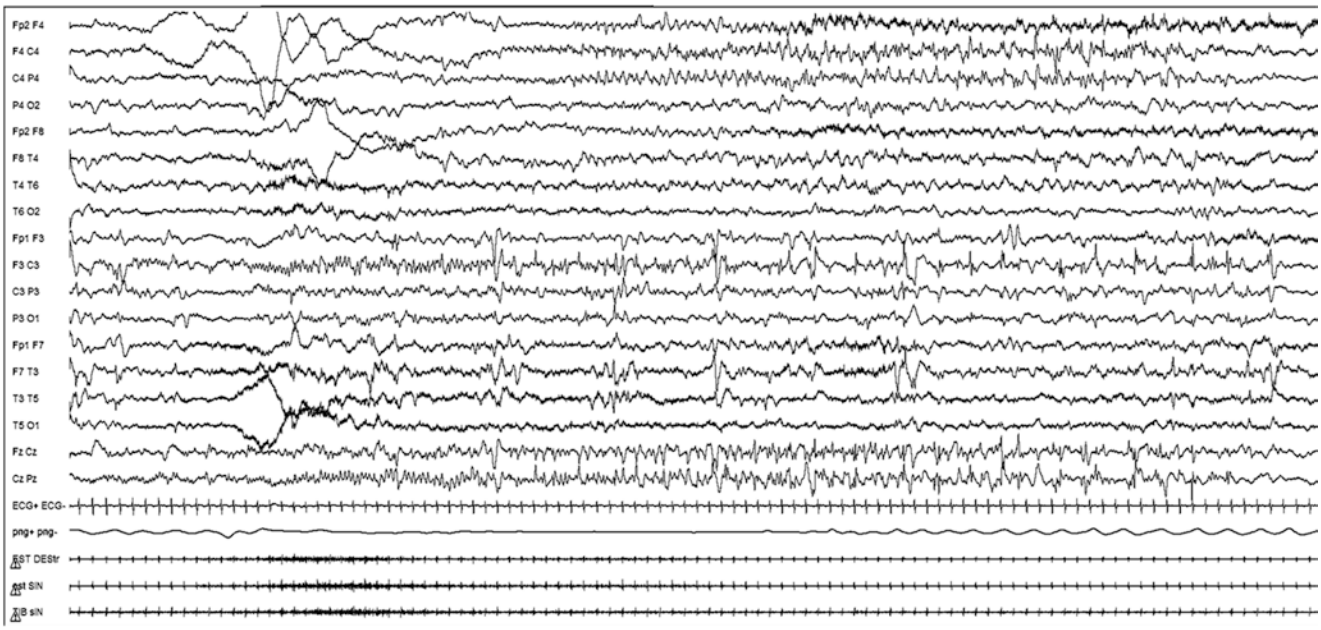

Fig. 23.8 Bilateral indipendent epileptiform abnormalities over left and right frontal regions in a 1 month old girl with early-onset epileptiform encephalopathy due to SCN2A mutation

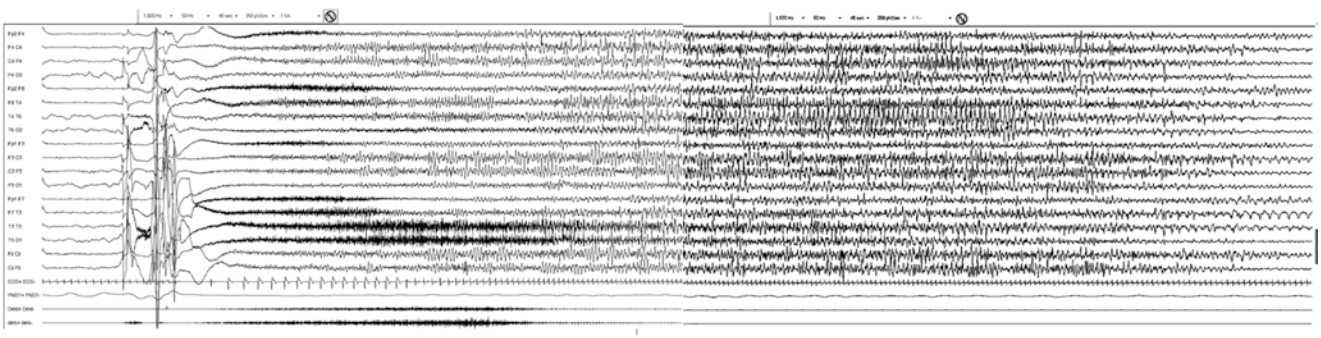

Fig. 23.9 Ictal EEG of a 4 months old boy with SCN8A mutation. Tonic seizure with diffuse onset, consisting of a flattening of cerebral activity, later on recruiting and increasing in amplitude. The ECG trace, shows an ictal bradicardia as one of the first signs of seizure

unclassifiable epilepsies. The predominant seizure types in these are focal (Fig. 23.8), tonic, and tonic-clonic seizures or spasms. Initial EEGs shows a suppression-burst pattern in one third of cases and multifocal spikes in the majority of the remaining cases [28].

Regardless of the epileptic syndrome, all patients present with intellectual disability, being severe in about two third of cases [28]. Sodium channel blockers, especially carbamazepine and phenytoin, are the drugs of choice for effective seizure control [30].

23.4.4 SCN8A-Related Epileptic Encephalopathy (OMIM 614558)

Early infantile epileptic encephalopathy type 13 (EIEE13, OMIM #614558) is a recently recognized syndrome caused by de novo SCN8A missense variants. Epilepsy starts before 18 months of age and is intractable and is associated with developmental impairment, usually severe, and pyramidal and extrapyramidal signs [31]. Also in SCN8A developmental and epileptic encephalopathy, it has been reported an improvement with sodium channel-blocking antiepileptic drugs [30].

Interictal EEG at epilepsy onset is reported normal in 35% patients and with discrete slowing and infrequent epileptiform abnormalities in 40%. More rarely hypsarrhythmia has been described. All patients develop during the following years a progressive slowing of background activity and multifocal epileptiform abnormalities, mainly over the temporo-parieto-occipital regions [31]. Multiple seizure types occur, including focal seizures, generalized seizures, and epileptic spasms [31]. Ictal bradycardia is frequently reported, mainly in tonic seizures (Fig. 23.9).

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