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Indice

Early-Onset Epileptic Encephalopathies

23

Marina Trivisano and Nicola Specchio

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

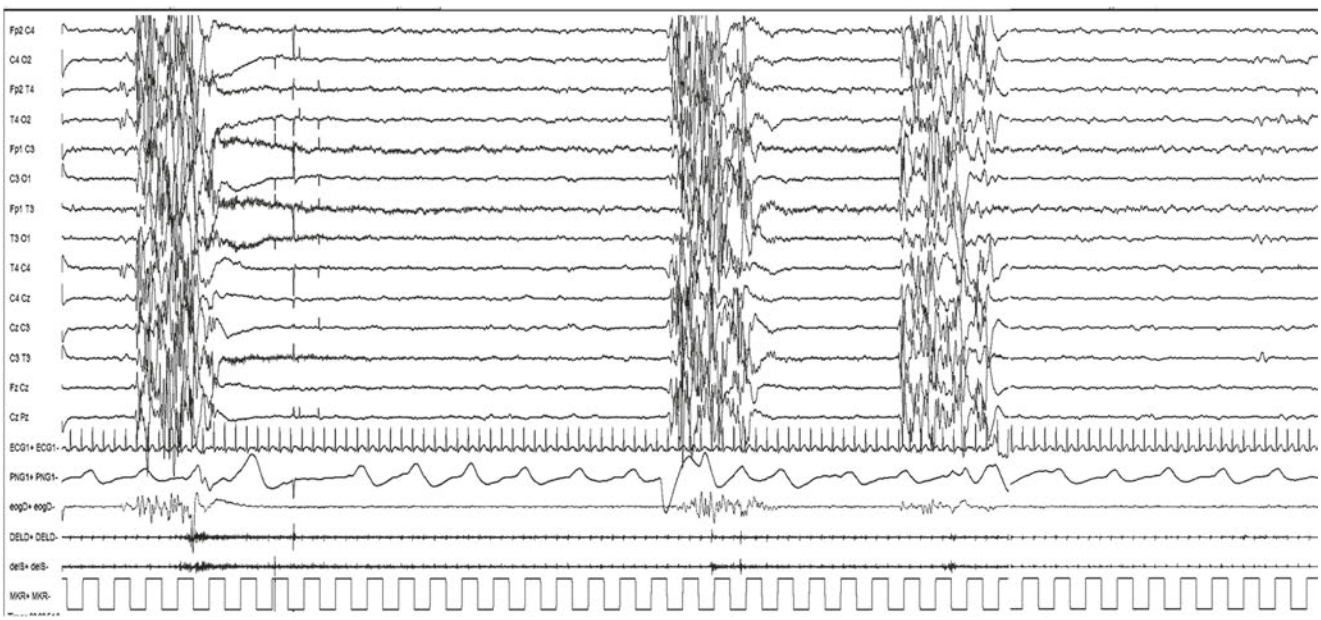

Fig. 23.1 Suppression-Burst pattern in a patient 1 month old boy with hypoxic-ischemic damage at birth. The EEG pattern is characterized high voltage bursts of spikes alternating with almost flat suppression phases at an approximately regular rate

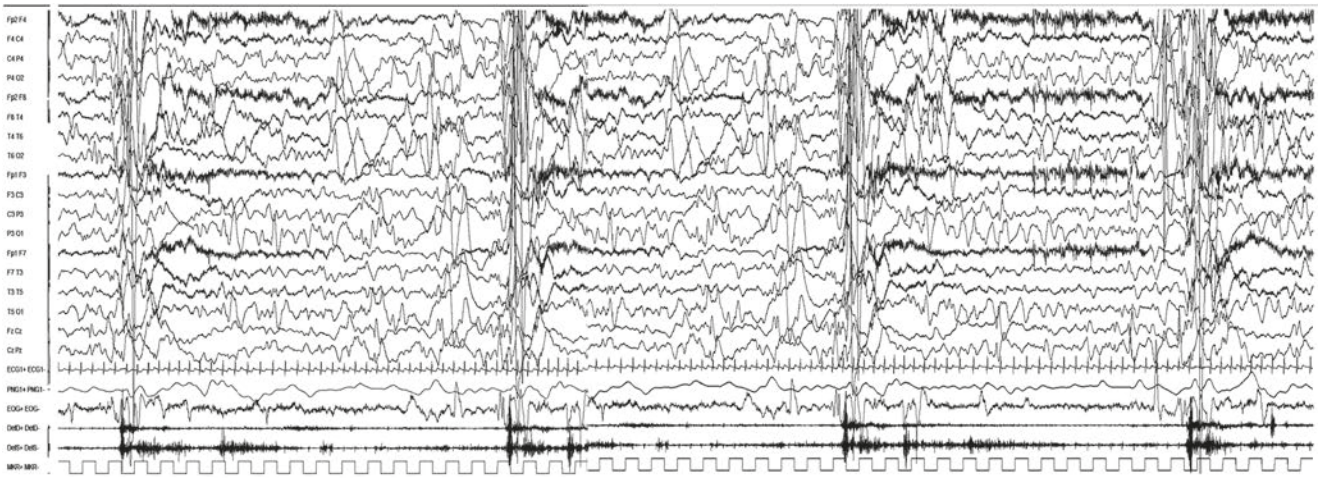

Fig. 23.2 Epileptic spasms in a 4 months old boy with STXBP1 gene mutation during awake state. Documentation of tonic-spasms

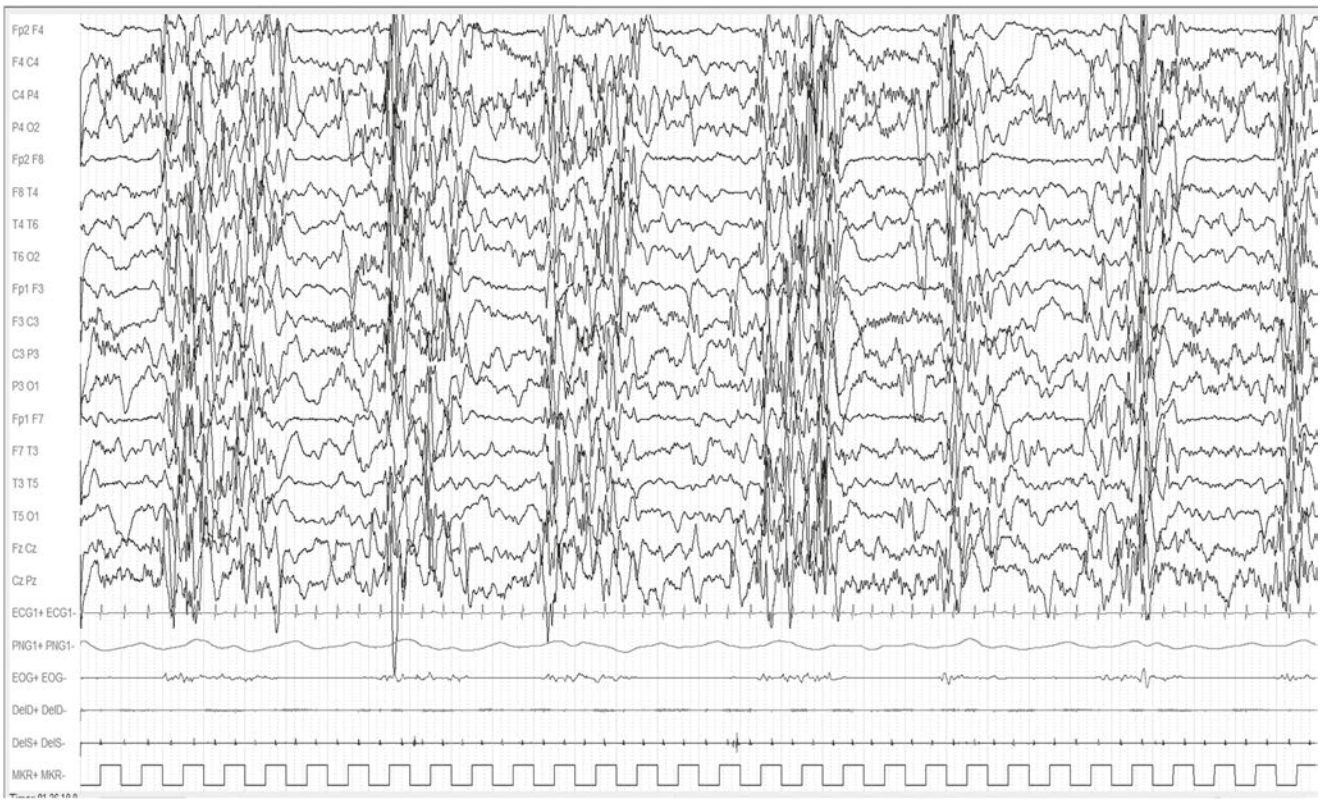

Fig. 23.3 Sleep EEG in a patient with STXBP1 gene mutation during sleep state. It's evident an increasing of epileptiform abnormalities, grouped in bursts of diffuse poly-spikes, intermingled with suppression of cerebral activities

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].

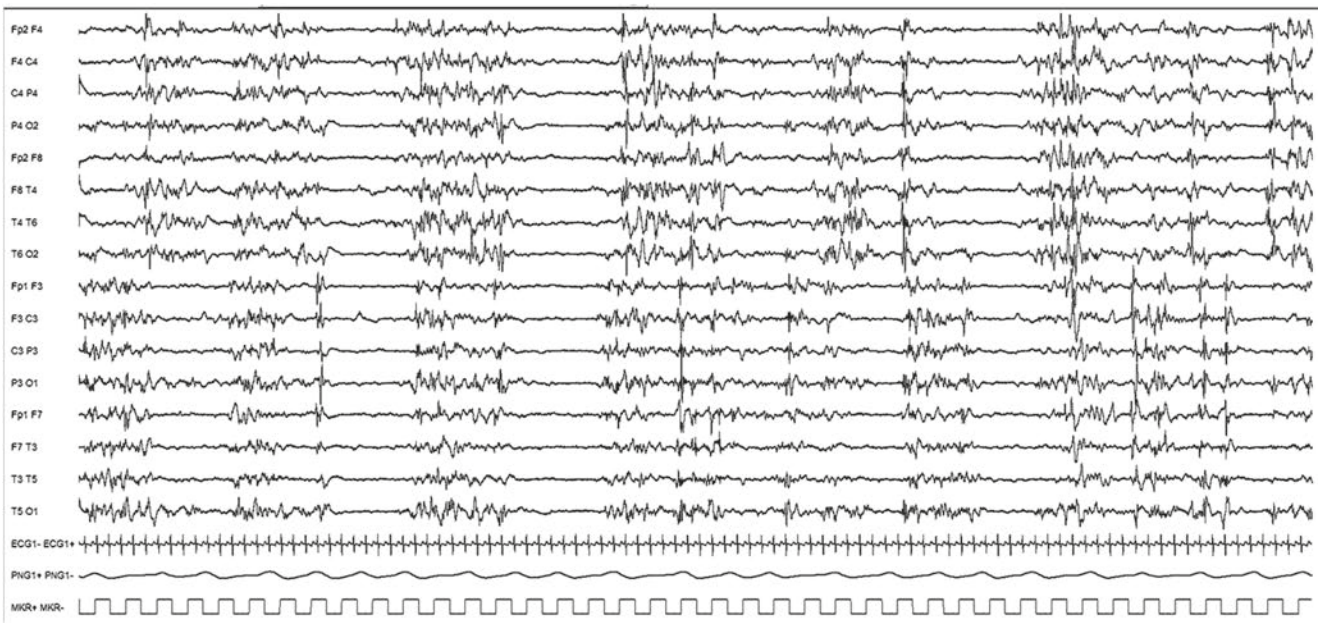

Fig. 23.4 Suppression-burst with multifocal epileptiform abnormalities in a patient with pyridoxine-deficiency encephalopathy

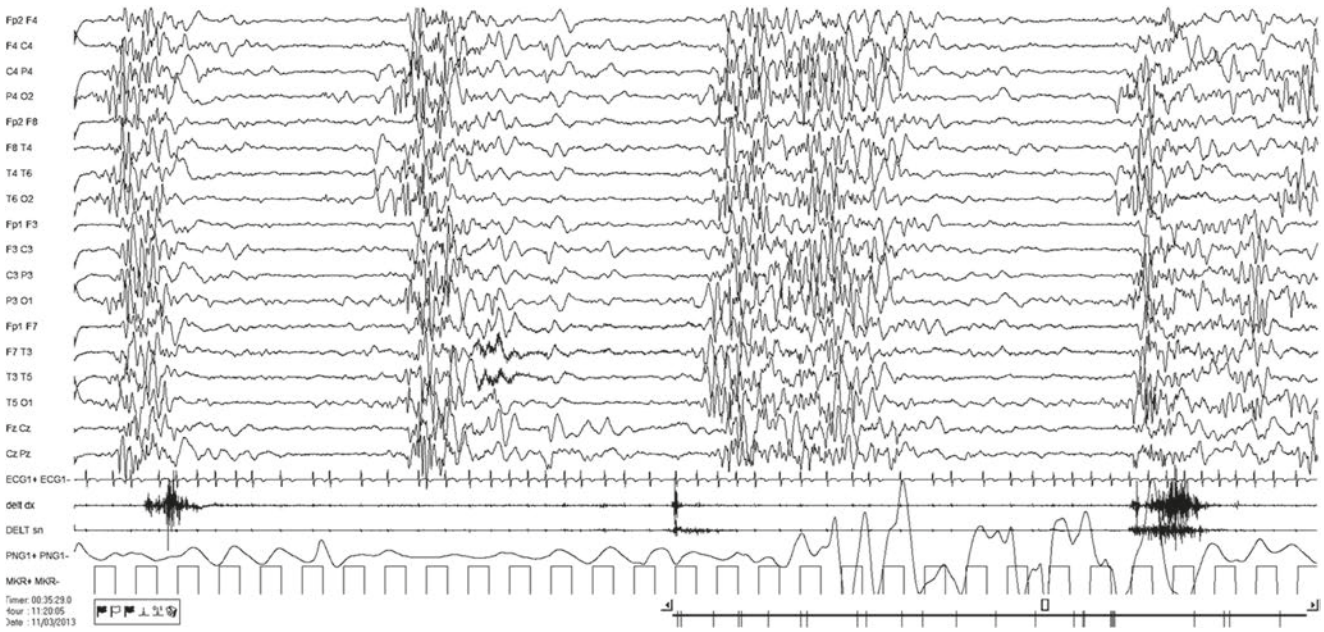

Fig. 23.5 EEG during awake state of a 6 month old boy with suppression-burst pattern due to CDG type 1 disorder due to ALG11 mutation. EEG indicates typical suppression burst pattern that can be observed in both Ohtahara syndrome and early myoclonic encephalopathy

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

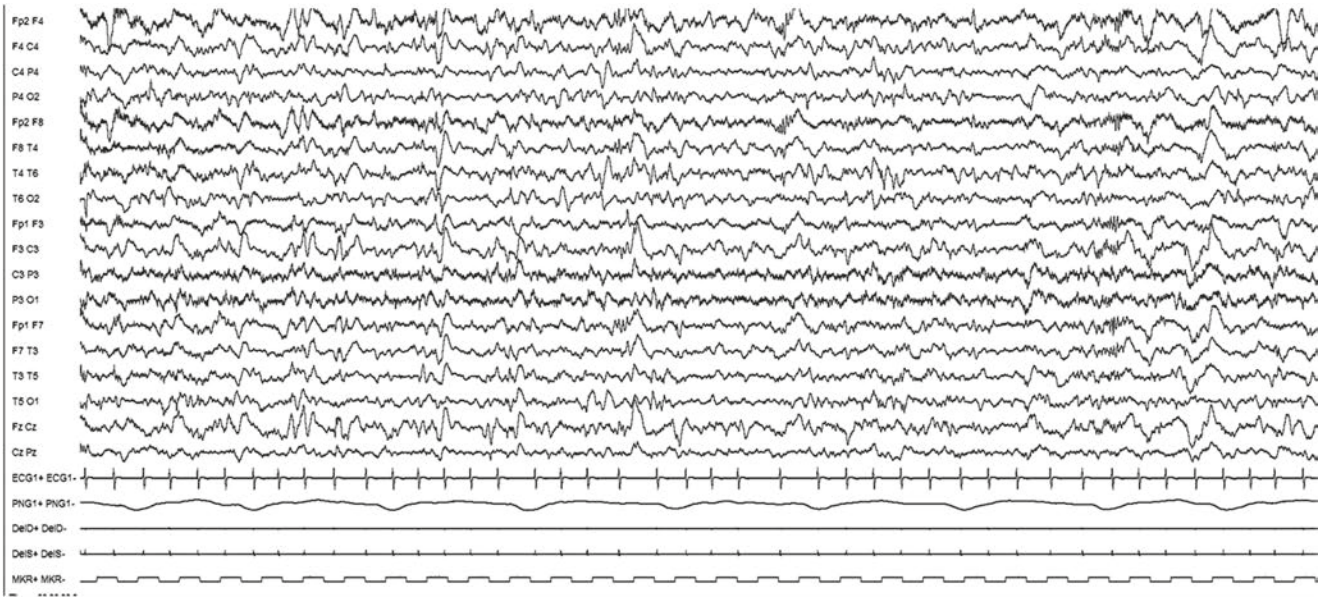

Fig. 23.6 Interictal EEG of a 8 years old girls with CDKL5-related encephalopathy. Bilateral epileptiform abnormalities are intermingled with brief phases of flattening of cerebral activity

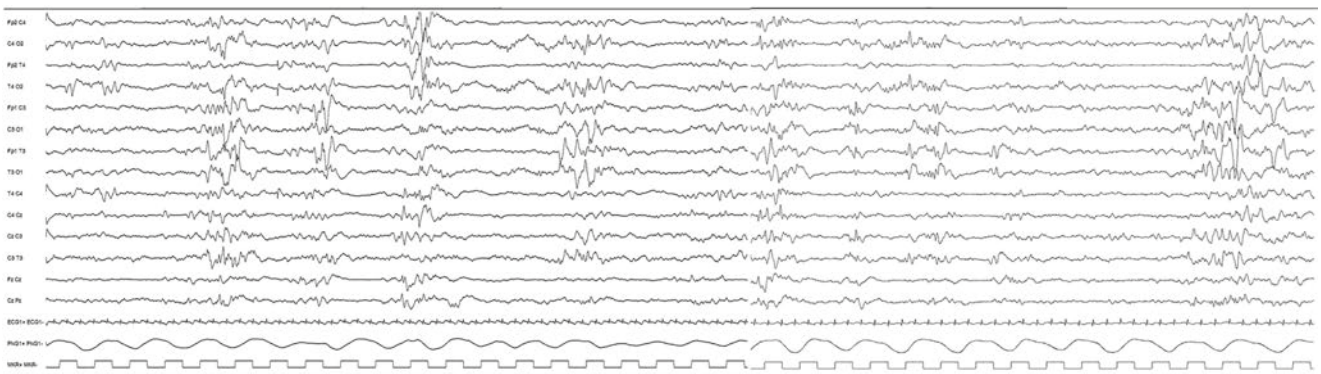

Fig. 23.7 Multifocal epileptiform abnormalities intermingled with diffuse suppression of cerebral activity in a patient with KCNQ2 at onset

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

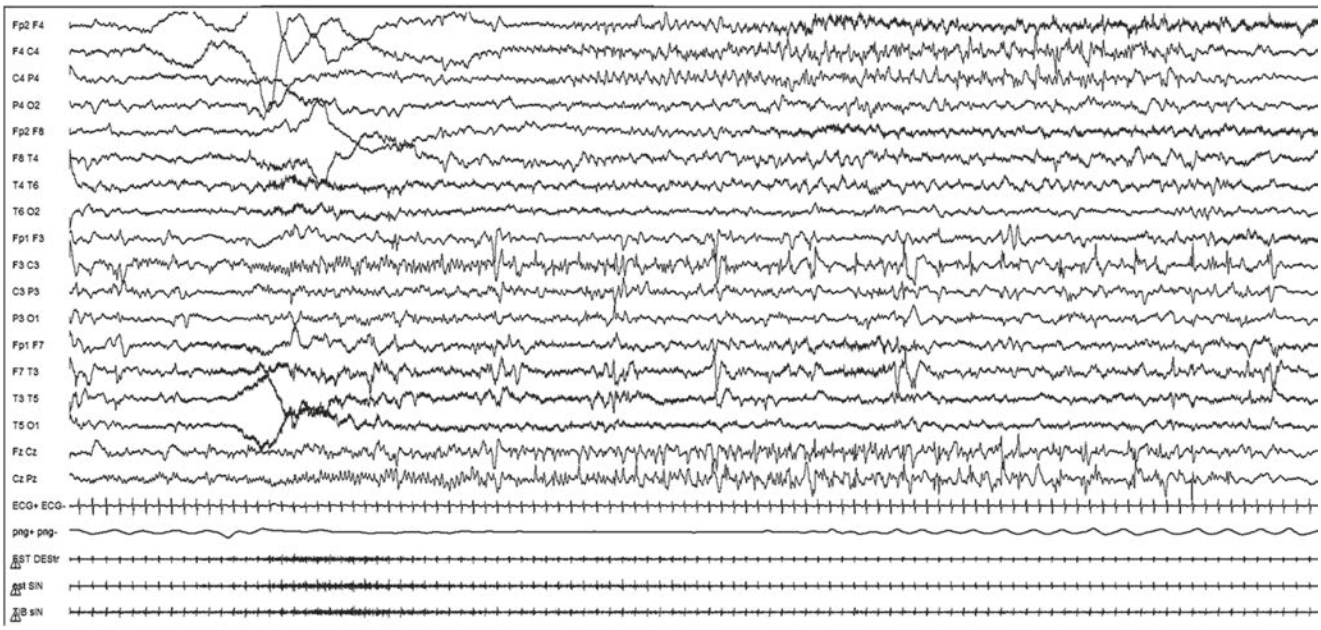

Fig. 23.8 Bilateral indipendent epileptiform abnormalities over left and right frontal regions in a 1 month old girl with early-onset epileptiform encephalopathy due to SCN2A mutation

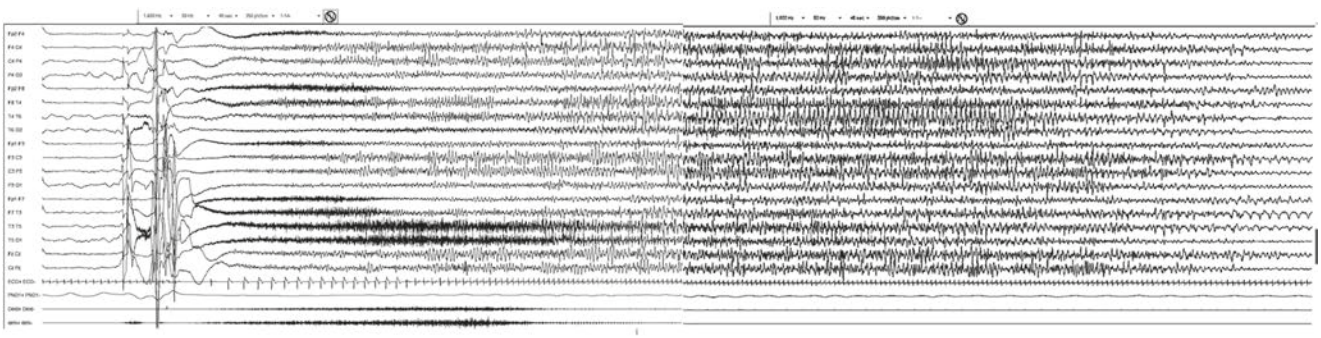

Fig. 23.9 Ictal EEG of a 4 months old boy with SCN8A mutation. Tonic seizure with diffuse onset, consisting of a flattening of cerebral activity, later on recruiting and increasing in amplitude. The ECG trace, shows an ictal bradicardia as one of the first signs of seizure

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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Epileptic Encephalopathies of Infancy and Childhood

24

Mario Brinciotti and Maria Matricardi

24.1 Introduction

Epilepsies associated with encephalopathy or cerebral damage were defined in the past with the term *epileptic encephalopathies*. Recently this concept has been deeply revised, restricting the criterion of inclusion to the forms in which the epilepsy itself is responsible of brain dysfunctions with mental and neurologic decline [1–4]. This implies that some syndromes, once included in this chapter, according to the new definition, are no longer considered today. Incidence and prevalence of these epilepsies are generally low, and many syndromes are included in the National Register of Rare Diseases of several countries in order to provide specific supports and related health services to patients. The electroclinical features are often influenced by the underlying processes of brain maturation and therefore by age (some forms are typically age-dependent); in addition, some syndromes present a clear continuity with evolution from one type to another. The etiology is variable, often characterized by brain structural damage, although the role of genetic factors has recently been emphasized in some forms [5, 6].

The prognosis is variable, depending on clinical features and underlying etiology, but it is generally unfavorable both for seizure outcome and neurocognitive development.

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24.2 West Syndrome

It is the most common epileptic encephalopathy in the first 2 years of life, with incidence ranging from 2.2 to 4.5 per 10,000 live births, very similar among different ethnic groups [7–10]. The onset occurs within the 1st year of life, usually between 3 and 12 months, with a peak at 5 months in 90% of cases. The electro-clinical feature is characterized by a triad: (a) infantile spasms, (b) typical EEG pattern (*hypsarrhythmia*), and (c) developmental arrest or psychomotor delay with intellectual impairment. In many cases, it is preceded by other types of seizures, especially partial, or by Ohtahara syndrome [11, 12].

The etiology is variable, often linked to infectious during pregnancy (rubella, toxoplasmosis, cytomegalovirus, etc.), severe pre-perinatal anoxic-ischemic encephalopathies, neurocutaneous diseases (tuberous sclerosis, neurofibromatosis), cerebral malformations (microgyria, pachygyria, heterotopias, etc.), and chromosomal abnormalities (trisomy 21). Recently, genetic studies based on complementary cytogenetic and genomic approaches provided evidence for the involvement of de novo mutations in children with infantile spasms of unknown etiology [6, 13].

Infantile spasms are a well-defined type of epileptic seizure, originally described by West [14], characterized by a brief axial contraction. They may be typical (anti-flexion of the head and simultaneous flexion of the limbs on the trunk) or atypical (in extension, asymmetric, asynchronous) and usually tend to repeat in cluster, with rapid succession for several minutes, almost always stereotypic [15–17].

Some clinical variants of spasms (tonic, atonic) have been recently described in some patients [18, 19]. Infantile spasms may be found in other epileptic encephalopathies other than West syndrome, such as Lennox-Gastaut syndrome, epilepsy with myoclonic-atonic seizures, Dravet syndrome, and epilepsy of infancy with migrating focal seizures [20]. The appearance of spasms can be preceded, accompanied, and followed by other types of seizures, especially focal.

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Hypsarrhythmia is the typical interictal EEG feature of West syndrome and occurs in two-thirds of patients. It is characterized by a disorganized high-amplitude background activity with a chaotic mixture of arrhythmic and asynchronous slow and sharp waves of high-voltage, multifocal spikes and polyspikes, interspersed with short periods of low voltage (Fig. 24.1). This pattern may be present in wakefulness or be more evident during non-REM sleep, generally associated with poor or absent representation of physiological figures such as spindles and K-complexes (Fig. 24.2). In sleep, epileptic anomalies tend to be grouped in short sequences; the track then becomes discontinuous in deep sleep. The hypsarrhythmia can be atypical, and several variants have been reported [21], among which an asymmetric or unilateral one can be found especially in patients with unilateral or clearly prevailing brain damage in a hemisphere (Figs. 24.3, 24.4, and 24.5). Ictal EEG, corresponding to the spasms, shows paroxysmal generalized slow waves followed by a brief period (1–2 s) of diffuse voltage attenuation, sometimes associated with rapid activity.

In about 3% of cases, West syndrome is preceded by Ohtahara syndrome [11, 12, 22], and the hypsarrhythmia represents a progressive transition from a previous pattern of suppression-brust (Figs. 24.6 and 24.7). Over one-third of patients suffering from West syndrome evolve to a Lennox-Gastaut syndrome, usually after 2–4 years of age [23, 24]; in these cases, the hypsarrhythmia is followed by an intermediate phase characterized by multifocal epileptic anomalies with subsequent appearance of typical generalized slow spike-and-wave complexes.

24.3 Dravet Syndrome

Initially described as severe myoclonic epilepsy in infancy by Dravet [25], it has a rare incidence, probably less than 1 in 30/40,000 [26, 27]. Even if the etiology is not completely clarified, the high family incidence of both epilepsy and febrile convulsions and the finding of genetic mutations in about 80% of patients, especially for SCN1A and PCDH19

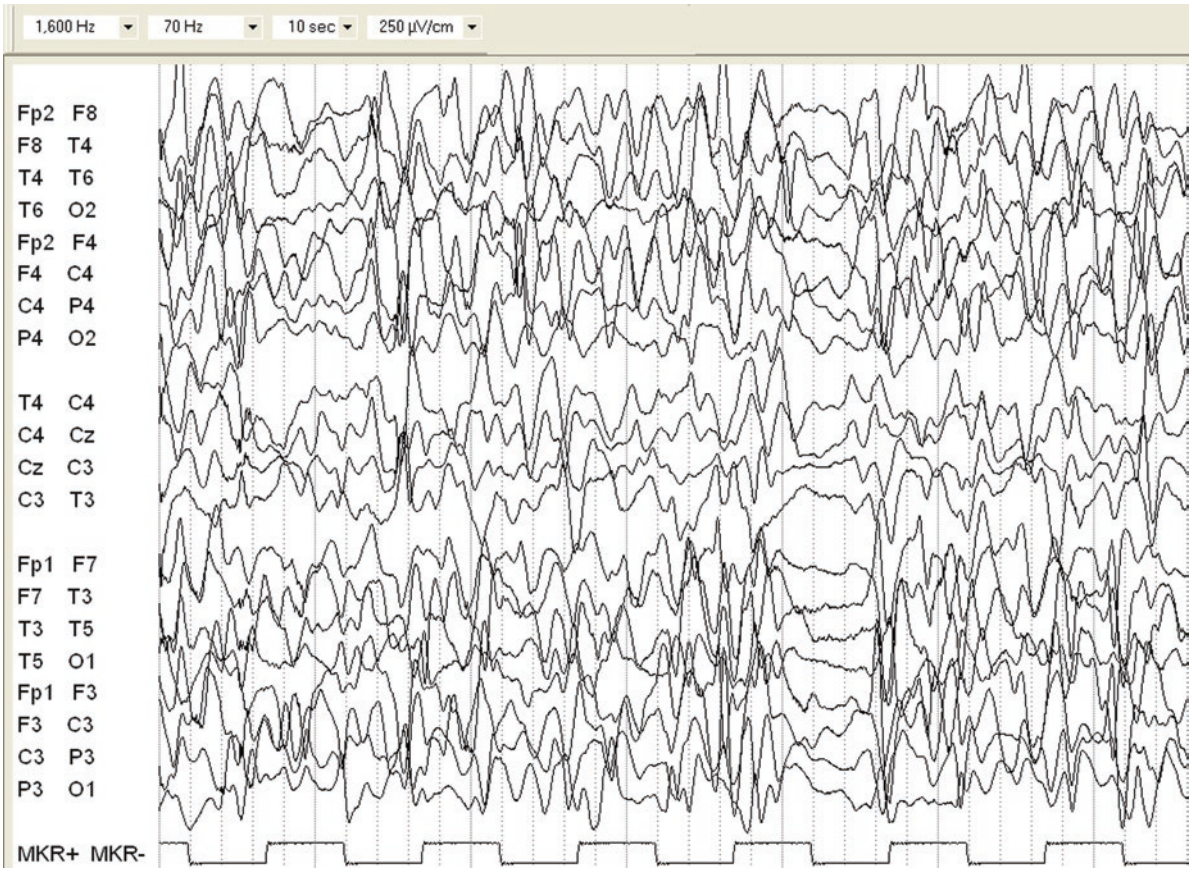

Fig. 24.1 Hypsarrhythmia (awake EEG). Disorganized high-amplitude background activity with a chaotic mixture of arrhythmic and asynchronous slow and sharp waves of high-voltage, multifocal spikes and polyspikes, with short periods of diffuse low voltage

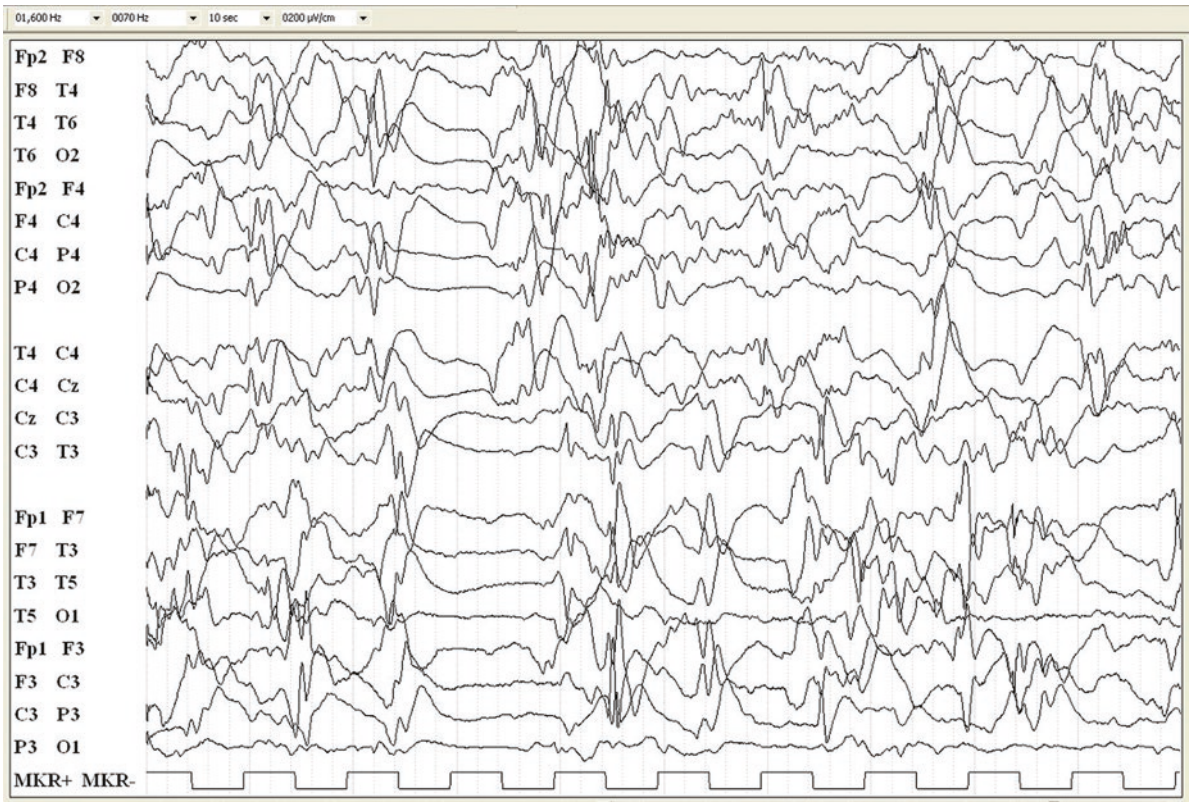

Fig. 24.2 Hypsarrhythmia (sleep EEG). Poor representation of physiological elements. Spikes, sharp waves, slow waves, and atypical synchronous and asynchronous spike-wave complexes, sometimes grouped in irregular sequences tending to diffusion, with short periods of diffuse low voltage

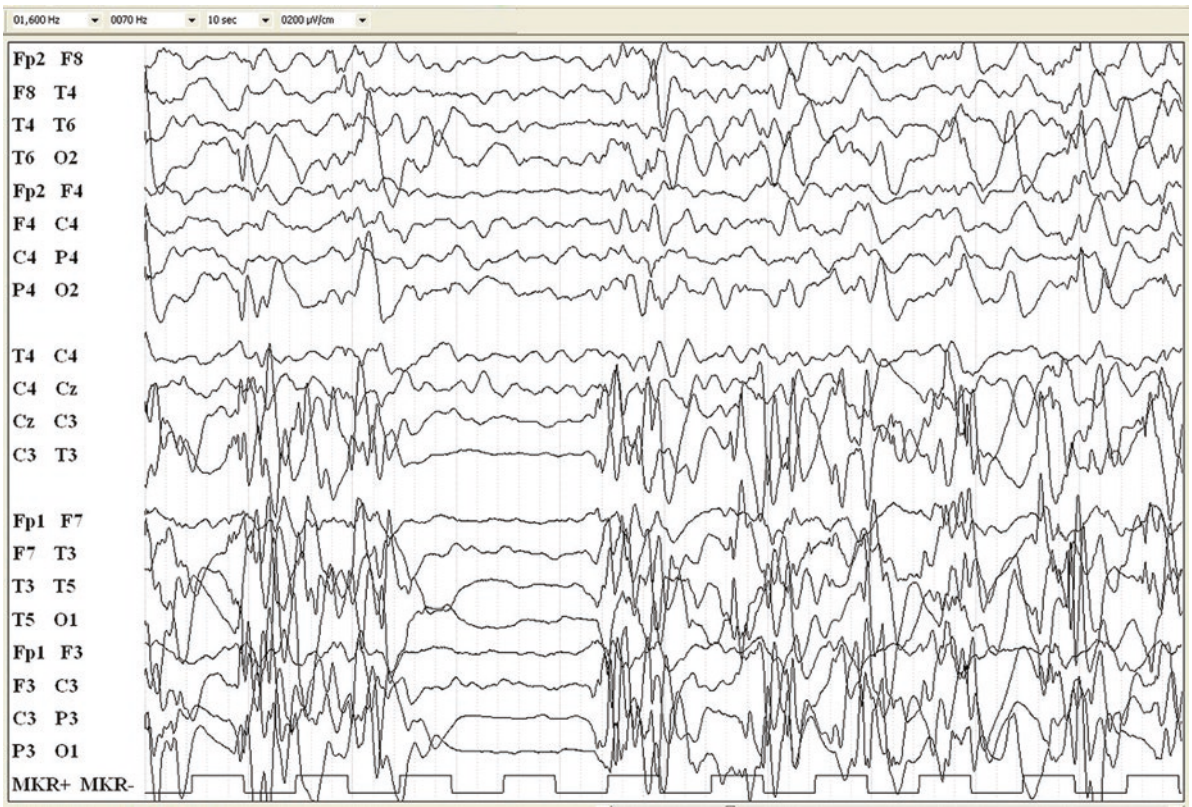

Fig. 24.3 Hemi-hypsarrhythmia (awake EEG). Asymmetrical EEG with hypsarrhythmic pattern on the left hemisphere and a better organized background activity on the right

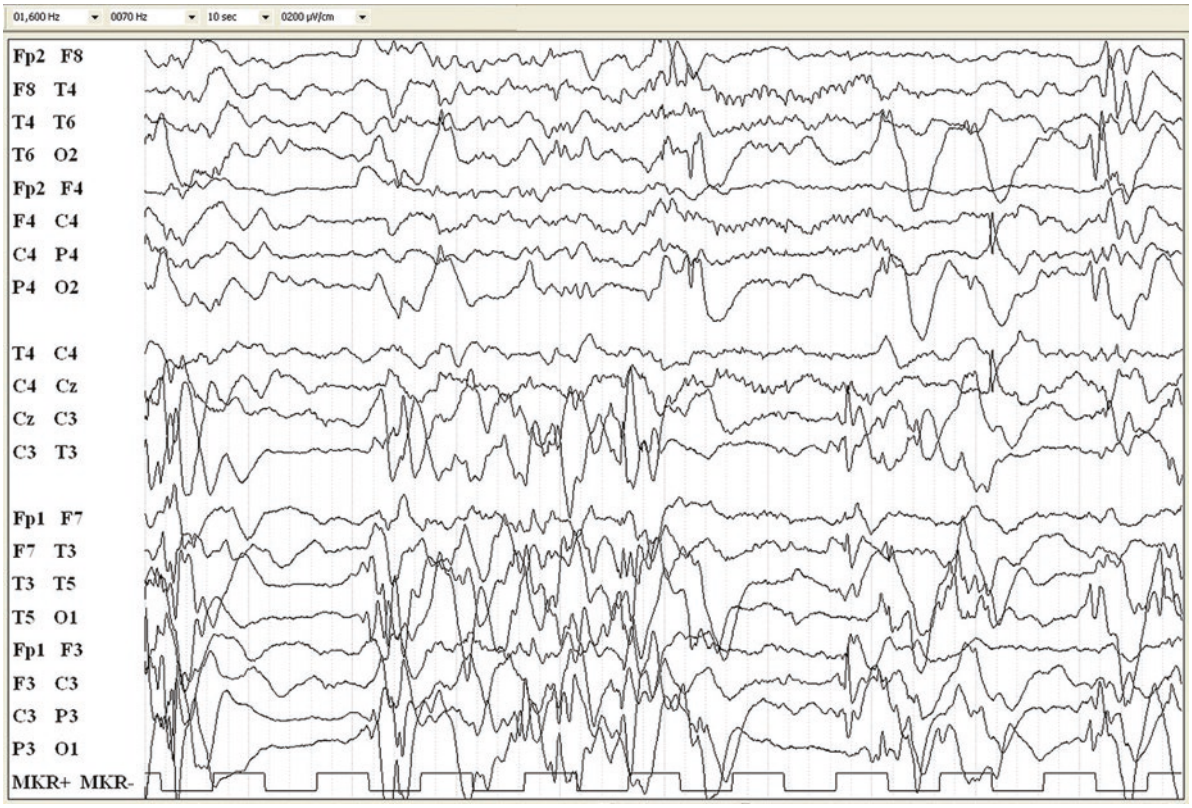

Fig. 24.4 Hemi-hypsarrhythmia (sleep EEG; same patient of Fig. 24.3). The EEG asymmetry persists with hypsarrhythmic pattern on the left and occurrence of delta activity and epileptic anomalies in the right posterior areas, inscribed on background activity however better organized and with well-represented physiological elements (note the presence of the spindles)

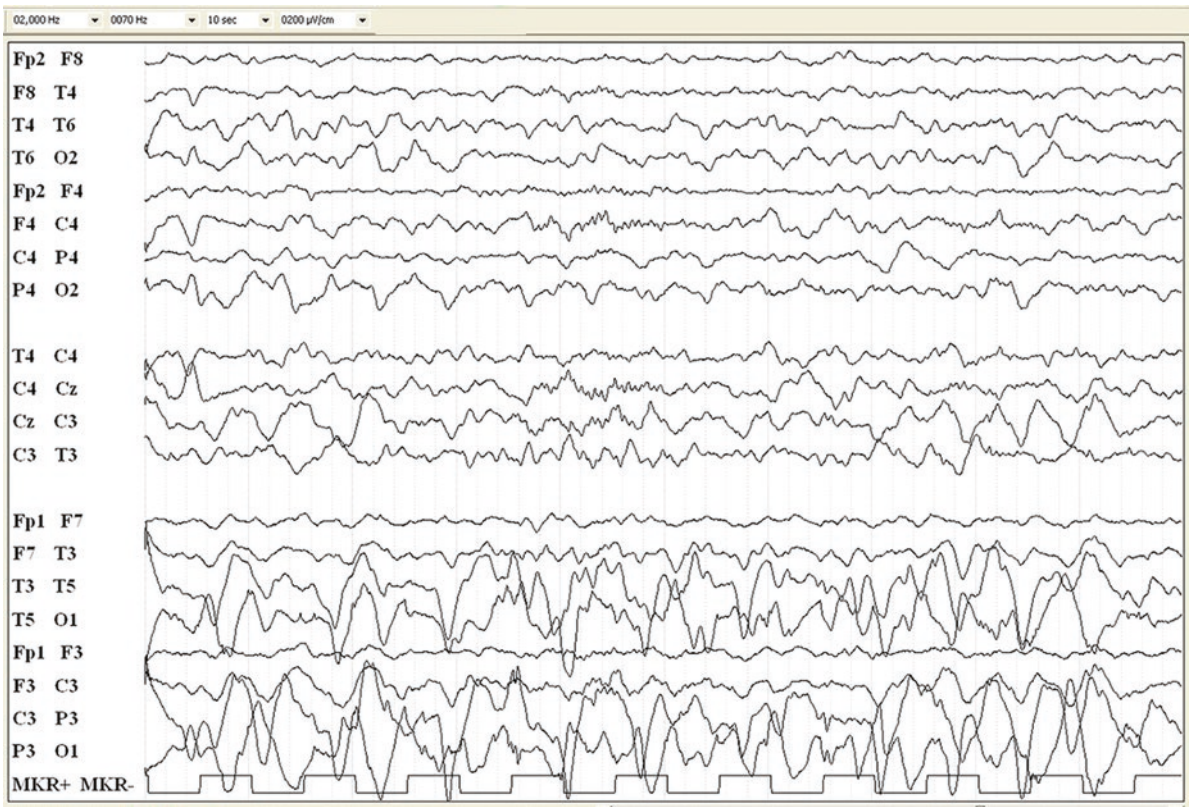

Fig. 24.5 Evolution of hemi-hypsarrhythmic pattern (same patient of Figs. 24.3 and 24.4—sleep EEG recorded after 16 months from the previous ones). Hypsarrhythmic pattern is no longer evident, whereas interhemispheric asymmetry persists, with slower and wider activity in the left posterior regions and the absence of the physiological elements on the left hemisphere

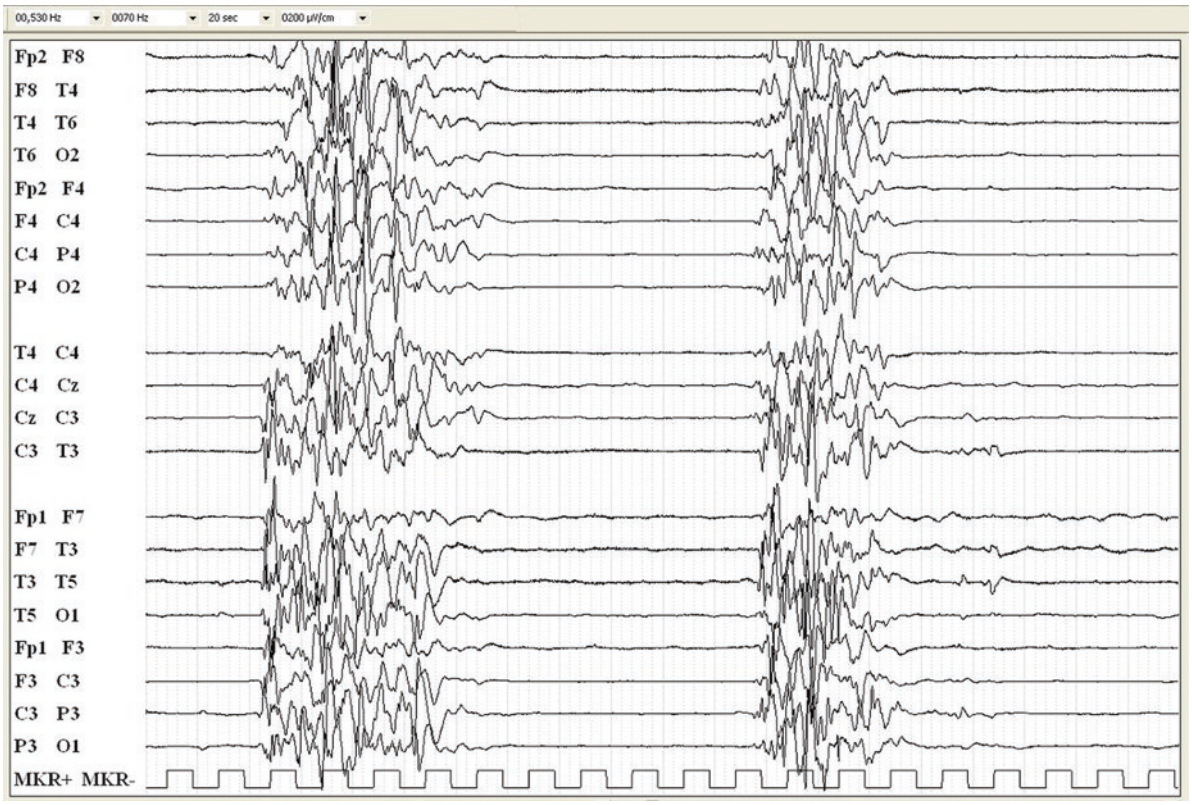

Fig. 24.6 Suppression-burst (awake EEG). Brief bursts (2–4 s) of spikes, sharp waves, slow waves, and atypical spike-wave complexes on diffuse low-voltage EEG

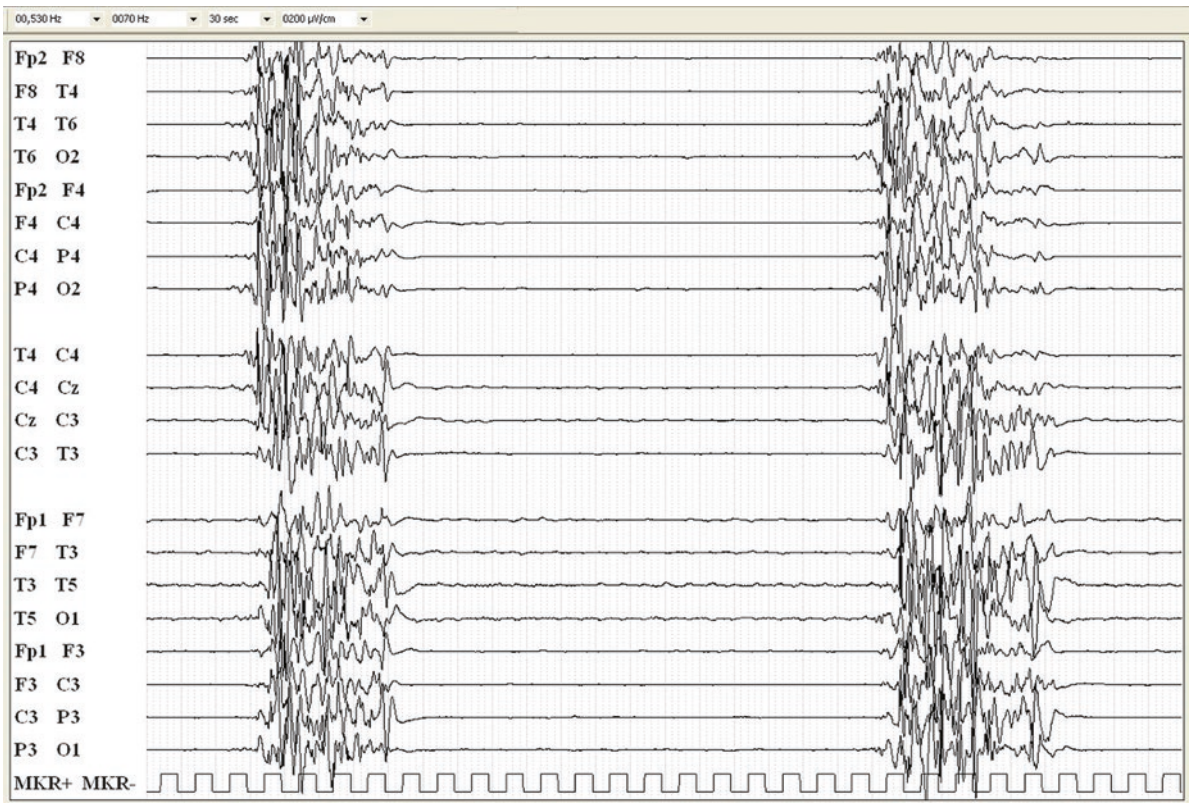

Fig. 24.7 Suppression-burst (sleep EEG). Longer periods of low-voltage interposed among epileptic discharges

genes, identify a causal role in genetic factors [28]. The clinical onset occurs within the 1st year of life (between 5 and 8 months) with a generalized or unilateral clonic seizure, even prolonged, often associated with fever, which tends to recur. Subsequently, other seizure types appear [29]: (1) Generalized tonic-clonic seizures and/or unilateral clonic seizures, often evolving to status. (2) Myoclonic seizures usually start between the ages of 1 and 5 years, with massive jerks involving all muscles, particularly the axial ones. (3) Atypical absences occur isolated or accompanied by myoclonic component such as rapid eyelid myoclonia. Episodes of *obtundation status* have been reported in 30–40% of patients [30, 31], consisting of consciousness' impairment, variable in intensity, associated with segmental and erratic myoclonus. (4) Focal seizures occur in 43–79% of patients [31–33], with motor signs or more complex semiology, including prominent autonomic symptoms, and with or without secondary generalization. (5) Tonic seizures are unusual. The presence of seizure-triggering factors (slight temperature variations, hot baths, photo and pattern sensitivity, environmental light, physical exercise, emotions, etc.) is a characteristic feature of this syndrome [29]. Developmental delay, cognitive deficits, and behavioral disturbances are common and usually start progressively from the 2nd year of life. Even if no regression is observed after 5 years in the stabilization stage, the evolution is however unfavorable in all cases, with constant intellectual impairment (severe in 60%) often associated with behavioral disturbances and psychosis [29].

The EEG at the onset shows normal background activity during wakefulness and normal organization of physiologic patterns during sleep. A peculiar 4–5 Hz rhythmic theta activity may be recorded over the rolandic areas and the vertex in some cases, starting at the end of the 1st year of life and persisting throughout the follow-up [34, 35]. Afterward, the interictal EEG shows both generalized and focal (more often, multifocal) epileptic abnormalities (spike, polyspikes, spike-wave and polyspike-wave complexes) accentuated by sleep [36]. Photoparoxysmal responses (PPR) may be induced by intermittent light stimulation (ILS) and/or pattern stimulation in 26–40% of cases [36, 37], even at an early stage, representing an unusual finding at this age. The background activity, initially normal, tends to gradually deteriorate over time [36, 37].

The ictal abnormalities are characterized by generalized spike-wave complexes and/or fast polyspikes, diffuse or

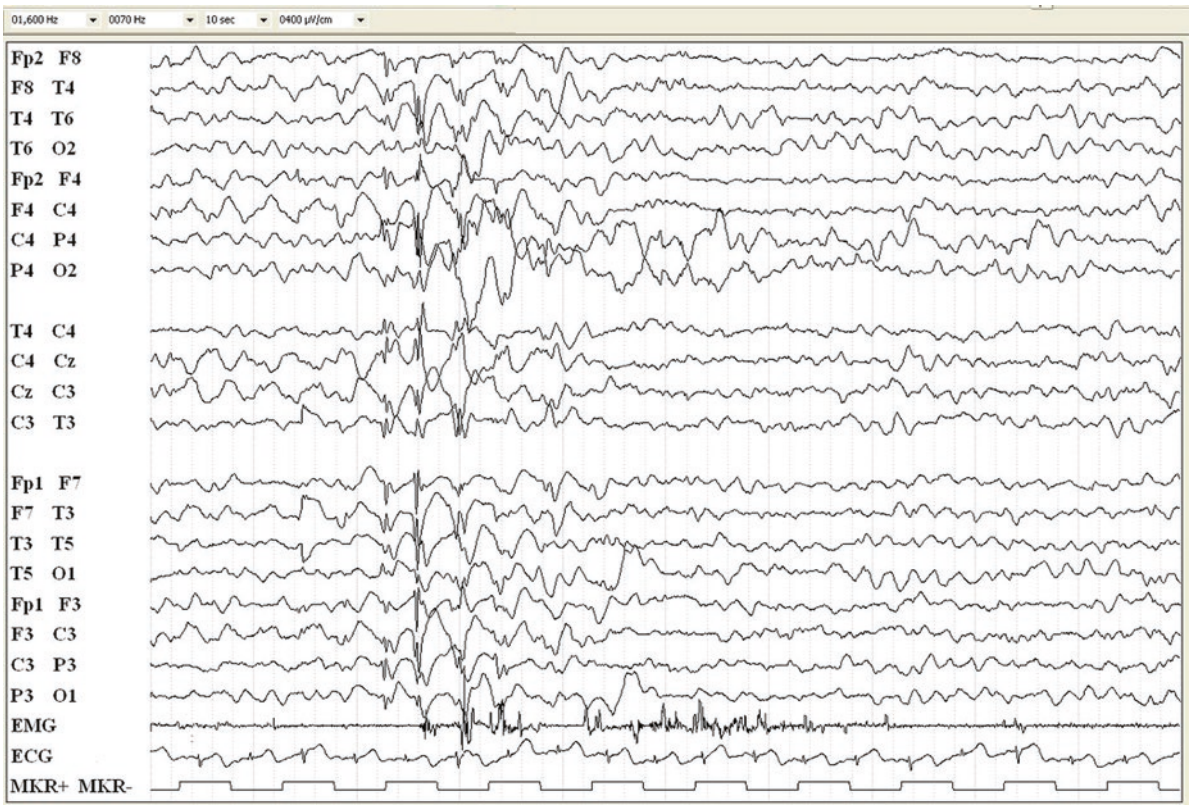

Fig. 24.8 Polygraphic EEG during non-REM sleep (*EMG* right deltoid muscle). Generalized spike-wave and polyspike-wave complexes associated with proximal myoclonia of the upper limbs

involving mainly the frontocentral regions, often associated with focal and multifocal fast spikes or polyspikes [36, 37]. Paroxysms vary according to seizure type:

- Myoclonic seizures are associated with brief bursts of generalized spike-wave and polyspike-wave complexes or fast polyspikes, mainly involving the frontocentral regions especially at onset (Fig. 24.8).
- Atypical absences coincide with generalized, often irregular, spike-wave complexes.
- Focal seizures are accompanied by spikes, sharp waves, spike-wave complexes, and polyspike-wave complexes tending to transmission or generalization.

24.4 Lennox-Gastaut Syndrome

Lennox-Gastaut syndrome is one of the most severe epileptic encephalopathies of childhood [38, 39]. The incidence is low (only 0.6% of all new-onset epilepsies), but, due to its poor treatability, its prevalence varies from 1 to 10% of all childhood epilepsies [40, 41]. The etiology is symptomatic in 75% of cases, with considerable heterogeneity with respect to the type of lesion [40]. The onset is between 2 and 6 years of age, often in children with previous West syndrome or other forms of severe epilepsy and episodes of status epilepticus. The diagnosis is based on a characteristic triad of electro-clinical signs [38–42]:

(a) *Multiple seizure types*: atypical absences, tonic seizures especially during sleep, tonic and atonic drop attacks with fall, and more rarely myoclonic seizures
(b) *Specific (but not pathognomonic) EEG abnormalities*: interictal slow spike-wave complexes (<3 Hz) and paroxysmal fast activity (PFA), consisting of bursts of diffuse fast rhythms, during non-REM sleep
(c) *Cognitive impairment*: intellectual slowing/regression and behavioral problems

The interictal EEG during wakefulness and sleep shows typical slow spike-wave complexes at 1.5–2.5 Hz. These abnormalities consist most often of a sharp wave (70–200 ms), followed by a sinusoidal slow wave (300–500 ms) of high voltages (200–800 μV) or, less often, by a spike (duration <70 ms) or polyspikes followed by a slow wave. These abnormalities are generally diffused, prevailing in the frontal areas (Fig. 24.9), synchronous and symmetrical, but sometimes may be arrhythmic, asynchronous, or prevalent

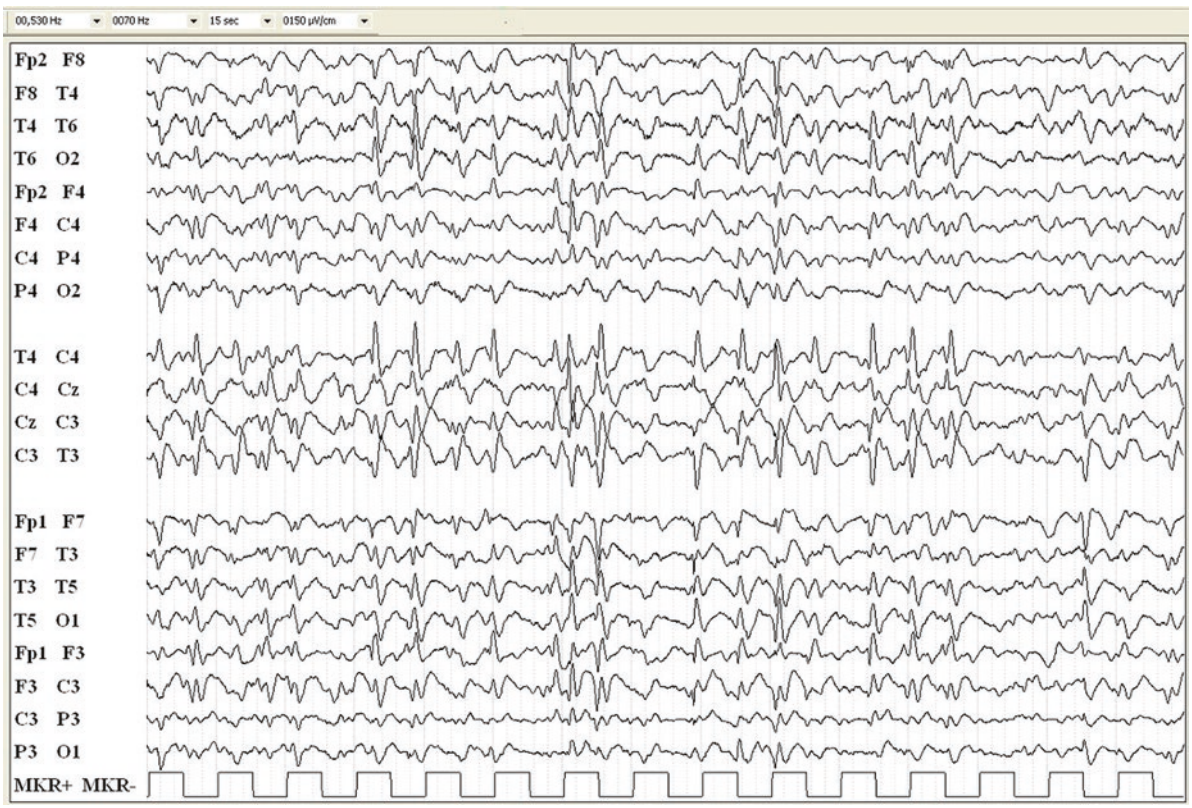

Fig. 24.9 Awake EEG. Generalized 2–2.5 Hz spike-wave complexes of high amplitude on poorly organized background activity

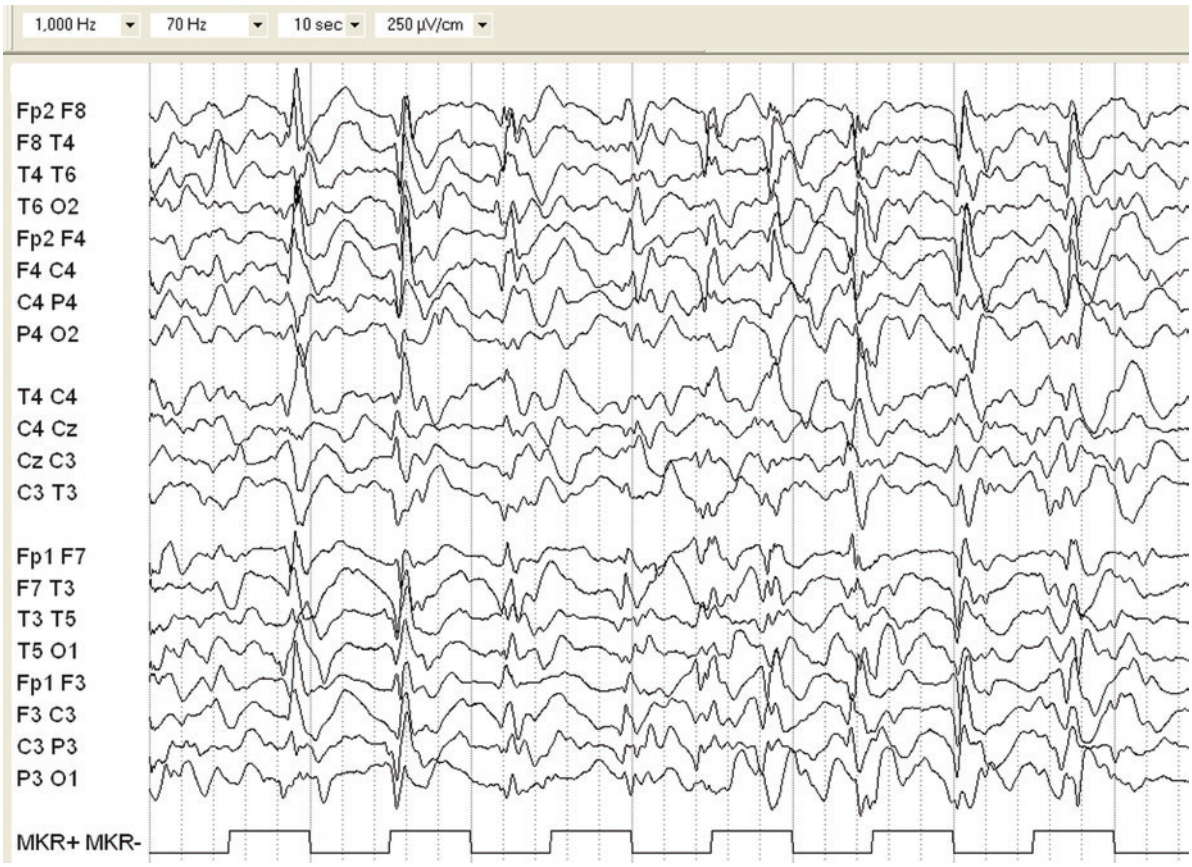

Fig. 24.10 EEG during non-REM sleep. Slow (1.5–2 Hz) spike-wave complexes of high voltage, more synchronous and symmetrical than waking state

in a hemisphere. Hyperventilation and intermittent photic stimulation (IPS) have little influence on this paroxysmal activity. Usually, spike-wave complexes increase during non-REM sleep and become more synchronous, symmetrical, and slower (Fig. 24.10). Focal or multifocal abnormalities (spikes, spike-waves, polyspikes, slow waves, and focal bursts of rapid rhythms) may also be found in the awake state and tend to become bisynchronous during sleep. These focal abnormalities are more common in patients with structural brain lesions and are nonspecific, depending on the underlying pathology.

The background EEG activity appears disorganized and slowed, with the posterior alpha rhythm poorly structured or absent. The slowdown of background activity may be moderate to severe, and its degree correlates with the severity of cognitive impairment.

The sleep EEG is also poorly structured, with alterations of the cyclic architecture and a lesser representation of physiological elements (vertex waves, spindles, K-complexes). During non-REM sleep, periods of electrodecremental activity alternated with periods of irregular high-amplitude sharp and slow activity may also be observed [39].

The ictal EEG varies according to seizure type:

- Tonic seizures, required for the diagnosis [38], may be associated with four types of ictal patterns [39]: (a) diffuse desynchronization; (b) discharge of PFA, progressively increasing in amplitude; (c) initial flattening followed by PFA; and (d) rhythmic discharge at 10–15 Hz of high amplitude from the beginning. The typical pattern of PFA is characterized by brief sequences (from 2 to 10 or more seconds in duration) of rapid rhythmic activity (10–25 Hz), sometimes preceded by a brief burst of slow spike-wave complexes (Fig. 24.11).
- Atypical absences are accompanied by generalized discharges of slow spike-wave complexes at 2–2.5 Hz of high voltage.
- Atonic seizures are associated with bursts of irregular spike-wave and/or polyspike-wave complexes, polyspikes, or rapid rhythms.
- Drop attacks constitute the third most common seizure types. The falling seizures may be pure atonic, myoclonic-atonic, myoclonic, and tonic and may involve the whole body or just the head (head drop) [39]. The EEG correlates of drop/falling seizure are heterogeneous. During atonic or myoclonic-atonic seizures, the ictal EEG shows diffuse polyspike-and-wave complexes, with loss of tone related to the wave of complex.

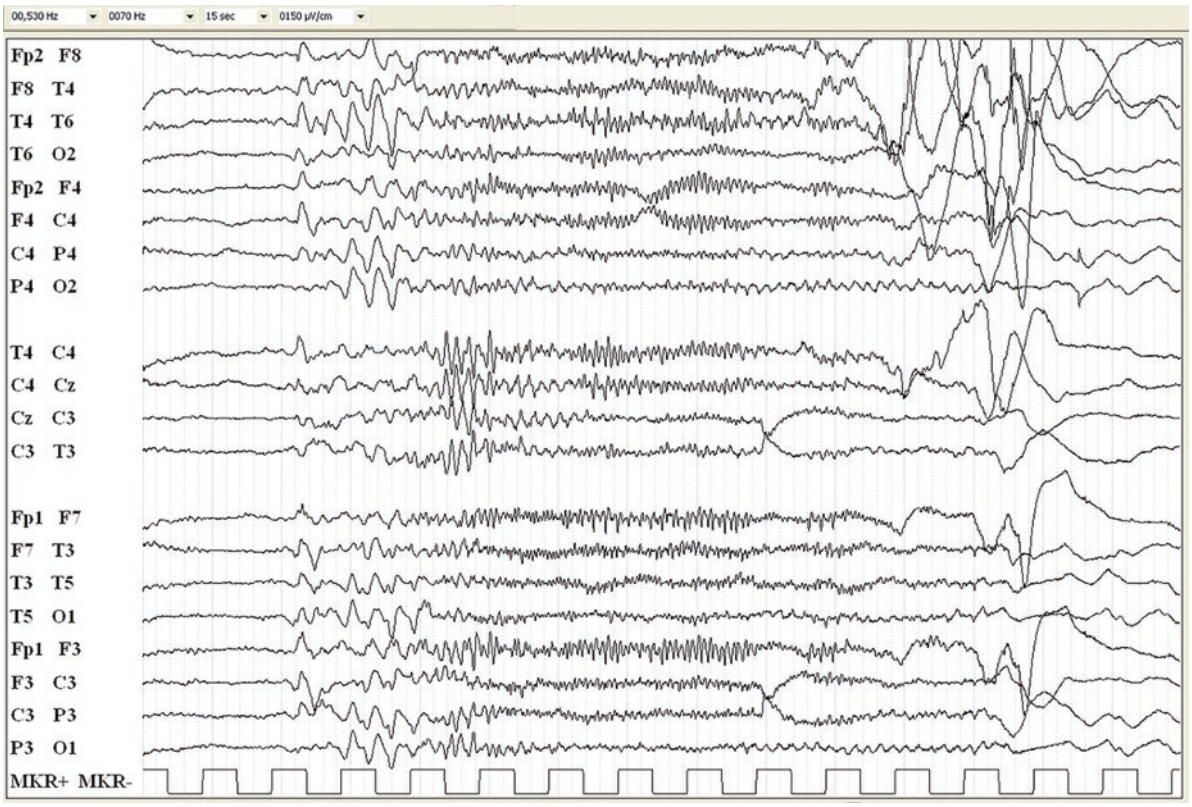

Fig. 24.11 Ictal EEG during non-REM sleep. Sequence of recruiting rhythms at 10–15 Hz, dominant in anterior regions, clinically associated with tonic seizure

Myoclonic drop attacks are accompanied by bursts of polyspikes or polyspike-wave complexes. Brief tonic seizure may produce only desynchronization of the EEG activity.

– Status epilepticus is common in these patients, and it can be convulsive (tonic status) or nonconvulsive (atypical absence status) [39]. The EEG during status epilepticus is similar to the interictal EEG, with diffuse slow spike-wave complexes more persistent.

The long-term outcome of Lennox-Gastaut syndrome is generally poor for the persistence of pharmacoresistant epilepsy and cognitive deficits. The typical EEG pattern of slow spike-wave complexes persists in more than one-third of adult patients, whereas in the remaining ones, the diffuse discharges are replaced by focal or multifocal epileptic abnormalities [43, 44].

24.5 Epilepsy with Myoclonic-Astatic Seizures (Doose Syndrome)

It is a generalized epilepsy syndrome of young children characterized by multiple seizure types, predominantly myoclonic, astatic, and myoclonic-astatic seizures, as well as generalized tonic-clonic, absence, myoclonic absence, and tonic seizures [45–48].

The incidence is not known, while the prevalence is estimated to be between 1 and 2% of all epilepsies of infancy and childhood. The onset occurs between 2 and 5 years of age in children, especially males (74%) [45, 46]. At the beginning, psychomotor development is normal in 84% of cases (with a slight delay, prevalent in language, in the remaining ones). In more than half of the cases, the onset is characterized by generalized tonic-clonic or clonic seizures, even prolonged and repeated, which precede the appearance of typical myoclonic-astatic and myoclonic seizures [45–48]. Myoclonic-astatic seizures consist of sudden massive myoclonic contractions, followed by brief and abrupt loss of muscle tone with fall (*drop attack*). Repeated and protracted episodes of status epilepticus occur in about 36% of patients, accompanied by intellectual deterioration especially of some functions (praxis and language). The unfavorable epilepsy outcome, especially with the appearance of tonic seizures, is constantly associated with progressive global intellectual impairment [45–48]. At the onset, the interictal EEG during waking may show abnormal 4–7 Hz rhythms prevailing in the central areas. Afterward, generalized epileptic abnormalities appear: bilateral, synchronous and symmetrical, regular

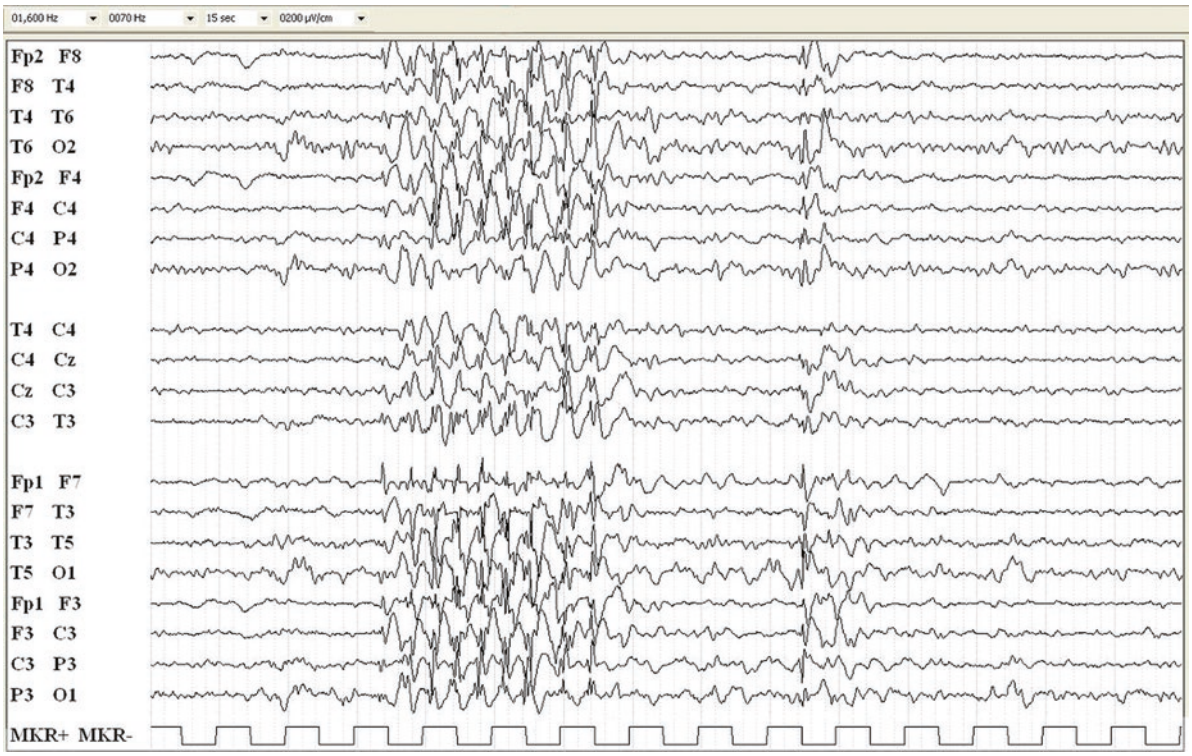

Fig. 24.12 Awake EEG. Short discharge of bilateral synchronous and symmetrical spike-wave and polyspike-wave complexes at 2–3 Hz of high voltage

or more often irregular, spike-wave and polyspike-wave complexes at 2–3 Hz of wide voltage (Fig. 24.12), often more evident during non-REM sleep phases (Fig. 24.13).

The ictal EEG shows bursts of generalized spike or polyspikes-and-wave complexes; in the atonic seizures, the spike-and-wave morphology was characterized by a positive-negative-deep-positive wave followed by a large negative slow wave [45].

24.6 Progressive Myoclonic Epilepsies

This name indicates a heterogeneous group of neurodegenerative disorders distinguished by etiology but brought together by clinical symptomatology and unfavorable prognosis [49–52]. Clinical feature includes a triad of signs common to all forms: myoclonic seizures, tonic-clonic seizures, and progressive neurological dysfunctions (especially, ataxia and dementia). Their incidence is rare, and the onset varies from adolescence to adulthood. Based on their relative frequency, five forms are considered as major (Lafora disease, Unverricht-Lundborg disease, myoclonus epilepsy with ragged-red fibers or MERRF, neuronal ceroid lipofuscinosis, sialidosis-galactosialidosis) compared to other rare or sporadic ones [49–52] (Table 24.1).

Lafora disease is the most common form in childhood (estimated prevalence, less than 1/1,000,000). It is a genetically heterogeneous disease caused by mutations of the genes EPM2A for laphorine (22–58% of cases) and EPM2B for malin (35–72%) [49–53]. The pathological picture is characterized by typical cytoplasmic inclusions consisting of accumulations of polyglucosans (bodies of Lafora) both in the nervous system (especially cerebral and cerebellar cortex) and in extracerebral parenchyma (the skin, muscles, and liver) [49–52]. The onset occurs between 6 and 19 years, more frequently during adolescence, with generalized tonic-clonic or clonic-tonic-clonic seizures and massive and/or segmental myoclonia. Myoclonus, often associated with negative myoclonus, may be spontaneous as well as intentional, or of action, and tends to rapid progression. About half of the patients have occipital lobe seizures with transient amaurosis or visual hallucinations. The course is characterized by a rapid deterioration of movement (ataxia, extrapyramidal stiffness) and mental disorders (dementia, behavior disorders), accompanied by a progressive increase in intensity and frequency of seizures and myoclonia [49–53]. The interictal EEG at the onset can detect generalized polyspikes and polyspike-wave complexes inscribed on a well-organized background activity both in wakefulness and in sleep. Isolated erratic myoclonia, not associated with evident EEG abnormalities, can be documented with polygraphic recordings. As the disease develops,

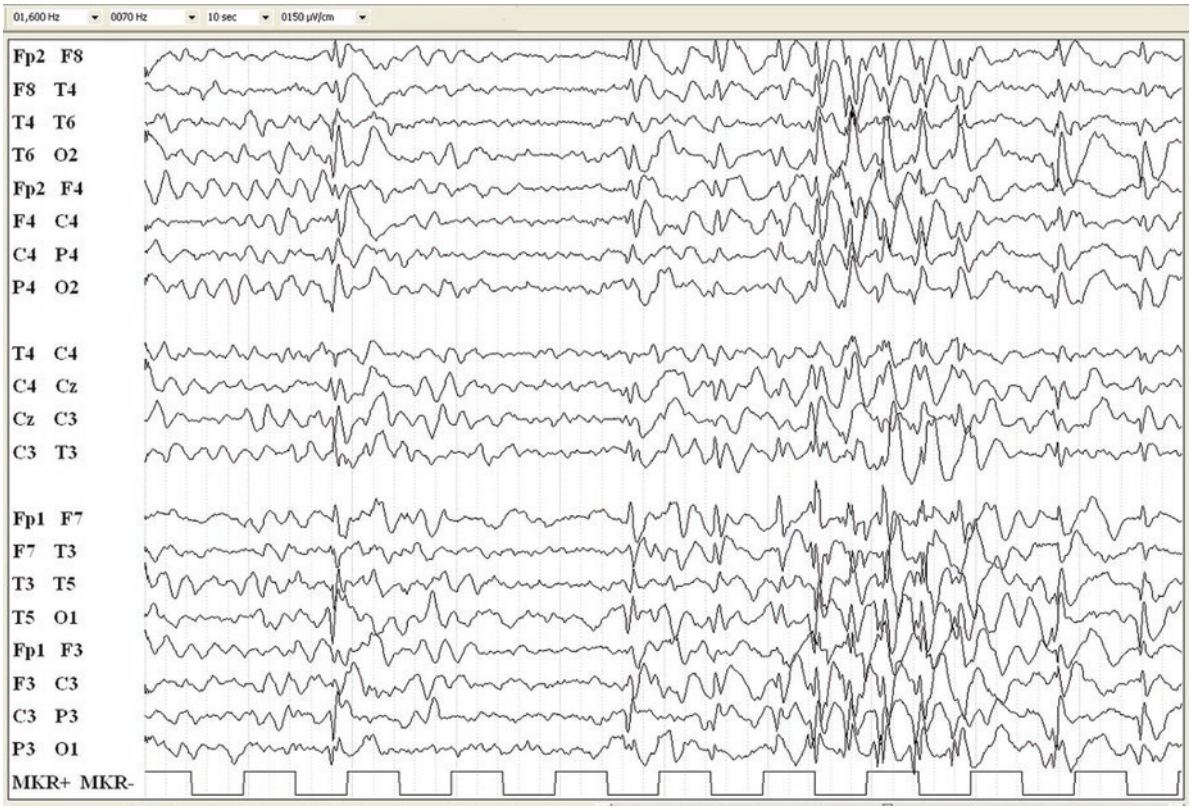

Fig. 24.13 EEG during non-REM sleep. Spikes and spike-wave and polyspike-wave complexes at 2–4 Hz, of high voltage, bilateral, synchronous and symmetrical, isolated, and in sequence, evident in drowsiness

Table 24.1 Progressive myoclonic epilepsies: hereditary transmission and involved genes

Main forms	Transmission	Chromosome	Gene
Lafora disease	AR	6q24	EPM2A (laforin)
	AR	6p22	EMP2B (malin)
Unverricht-Lundborg disease	AR	21q22.3	EPM1 (cystatin B)
MERRF	Maternal	mt-DANN	tRNA $^{Lys\ (8344,\ 8356,\ 8363,\ 8361)}$ tRNA $^{Phe\ (611)}$
MERRF-MELAS	Maternal	mt-DANN	tRNA $^{Leu\ (pos.\ 3243)}$ ND5 $^{(13042)}$
Neuronal ceroidolipofuscinosis			
– Late infantile (Jansky-Bielschowsky)	AR	11p15.5	CLN2
– Juvenile (Spielmeyer-Vogt-Sjogren)	AR	16p	CLN3
Sialidosis			
– Type 1	AR	6p21.3	Neuraminidase
– Type 2	AR	6p21.3	Neuraminidase
– Galactosialidosis	AR	20q13.1	PPCA
Rare forms			
Dentatorubro-Pallido-Luysiana atrophy	AD	12p13.31	B 37 (athrophin)
Gangliosidosis GM2	AR	15q23-q24	HEXA
Gaucher disease type III	AR	1p21	Glucocerebrosidase
Hallervorden-Spatz disease	AR	20p13-p12.3	Pank-2
Juvenile Huntington's disease	AD	4p16.3	Huntingtin

AD autosomal dominant, *AR* autosomal recessive, *MERRF* myoclonus epilepsy with ragged-red fibers, *MELAS* mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

the background activity becomes slower and disorganized, the physiological elements of sleep tend to disappear, while the epileptic anomalies become more active, with generalized or bi-frontal spike-wave and polyspike-wave complexes, almost constantly associated with focal epileptic anomalies, located mainly in the occipital regions. At this stage, myoclonia and negative myoclonus become increasingly frequent and can be well documented by suitable polygraphic recordings (Figs. 24.14 and 24.15). IPS evokes PPR, both interictal and ictal, often throughout the course of the disease (Fig. 24.16). As in the other forms of this group, the prognosis is unfavorable with progressive deterioration and death after 2–10 years from the onset of symptoms.

Unverricht-Lundborg disease is a rare progressive myoclonic epilepsy, found mainly in Mediterranean and Baltic countries (in Finland, estimated incidence of 1/20,000) [54]. It is an autosomal recessive disease, caused by mutations of the EPM1 gene for cystatin B. It starts, insidiously, in the second infancy or adolescence (in 86% of the cases between 9 and 13 years) with action myoclonus, characteristically more evident after the awakening, associated with clonic or clonic-tonic-clonic seizures during sleep. Myoclonus gradually becomes invalidating due to its severe interference on motor activity, especially in the execution of complex praxies. Generally in this phase there is also a cerebellar ataxia of variable entity. The disease progresses by alternating periods of remission, to periods of worsening with increased frequency of myoclonia and epileptic seizures. Gradually, a mild to moderate degree of cognitive impairment occurs. The EEG at onset shows a normal organization of the background activity which subsequently presents a modest slowing of the posterior alpha rhythm. Later on, sequences of delta activity appear which become progressively more and more evident. Spike-wave and polyspike-wave discharges are occasionally associated with massive myoclonia, whereas the action myoclonus is never accompanied by EEG anomalies. In 90% of patients, ILS evokes a PPR. With the progression of the disease, epileptic abnormalities tend to decrease, while the slowing and disorganization of the background activity become increasingly evident.

MERRF syndrome is a progressive myoclonic epilepsy with maternal transmission, due to a mutation in the tRNA of the mitochondrial lysine [55]. It begins in children or young adults, and the complete clinical picture includes myoclonic

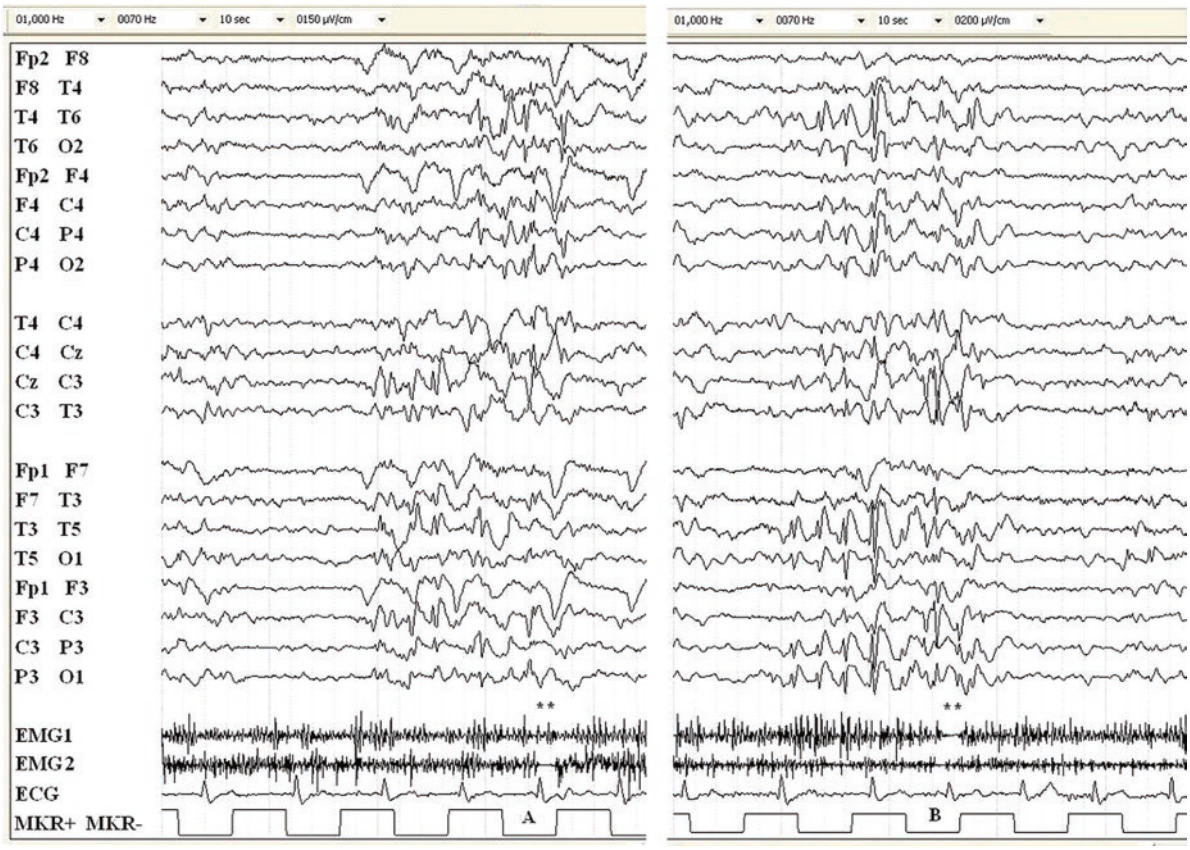

Fig. 24.14 Polygraphic EEG in wakefulness (*EMG 1* right deltoid muscle, *EMG 2* left deltoid muscle). Two episodes of negative myoclonus (**) evident during antigravity contraction of the arm muscles, both left (*A*) and right (*B*), associated with rapid spikes, polyspikes, and spike-wave complexes in frontocentral regions contralateral to the interested limb. Note the simultaneous presence of spikes and spike-wave complexes in the posterior regions, prevalent on the left (the patient reported short episodes of amaurosis and visual hallucinations)

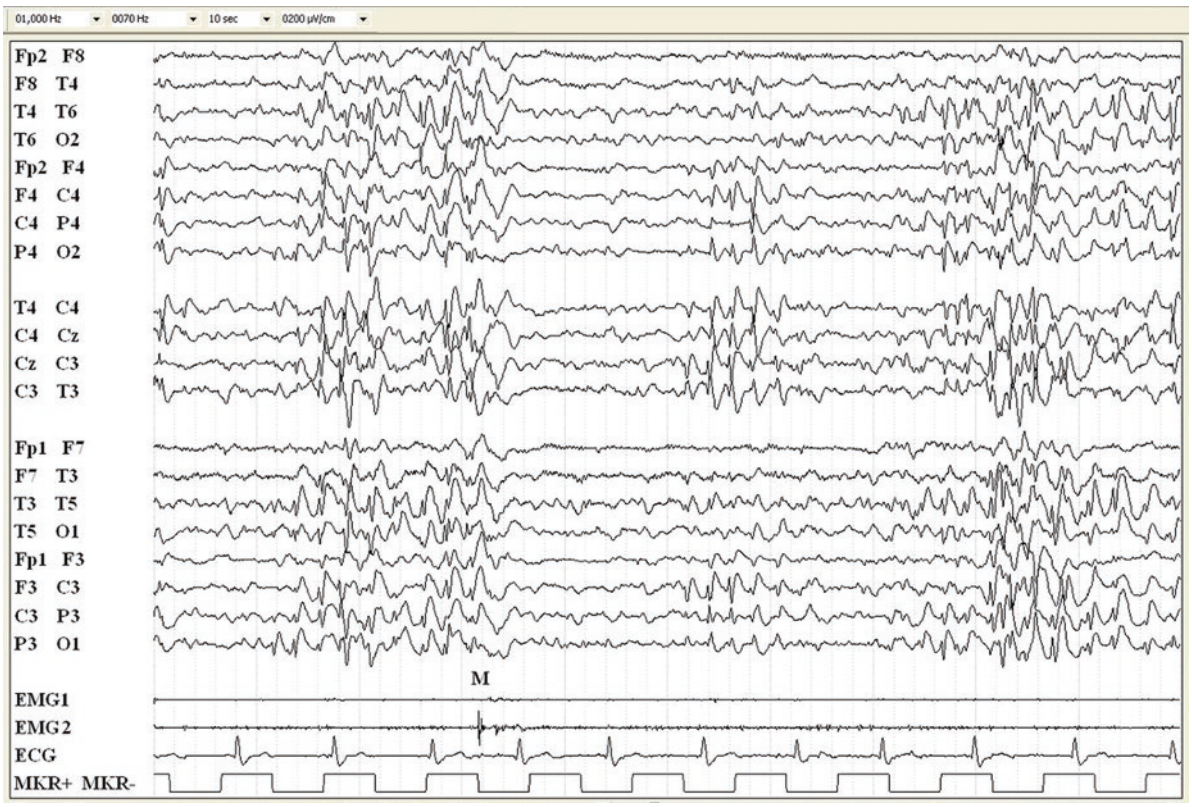

Fig. 24.15 Polygraphic EEG in wakefulness (*EMG 1* right deltoid muscle, *EMG 2* left deltoid muscle; same patient of Fig. 24.14). Isolated myoclonus (*M*) in the upper left limb, recorded under conditions of basic muscle relaxation

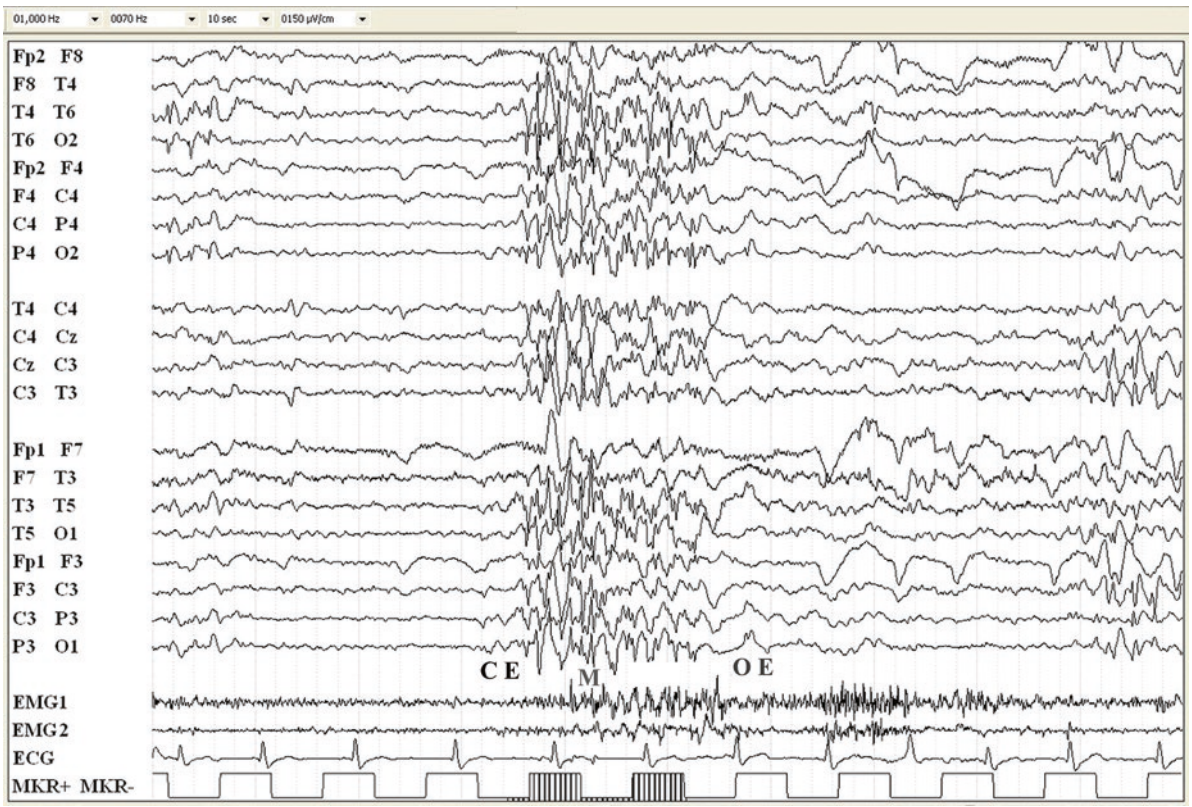

Fig. 24.16 Polygraphic EEG during ILS (*EMG 1* right deltoid muscle, *EMG 2* left deltoid muscle, *CE* closed eyes, *OE* open eyes, *M* myoclonus; same patient of Figs. 24.14 and 24.15). Photoparoxysmal response characterized by a generalized sequence of spikes, polyspikes, and spike-wave and polyspike-wave complexes, synchronous and symmetrical, associated with axial and limb myoclonia

seizures, ataxia, muscular hyposthenia, dysarthria, optic atrophy, nystagmus, short stature, gradual hearing loss, and progressive mental deterioration. Clinical findings and progression are very variable, and many patients can be asymptomatic even for a long time.

The *neuronal ceroid lipofuscinoses* represent the most common form of lysosomal disease in childhood. They are genetically heterogeneous multisystem diseases in which the malfunctioning of lysosomes causes a progressive storage of characteristic lipopigments [56]. Patients present drug-resistant myoclonic seizures, progressive retinopathy with consequent loss of visual function, cerebellar ataxia, cognitive and global deterioration, and premature death.

Sialidoses are lysosomal storage diseases with autosomal recessive inheritance. The overall incidence is estimated at 1/4,200,000 live births. There are three main forms: (a) *sialidosis type 1*, also known as "cherry-red spot syndrome and myoclonus," generally normomorphic; (b) *sialidosis type 2*, which includes also complex facial dysmorphias, bone dysplasias, and psychomotor retardation; (c) *gangliosidosis.* The onset is variable, generally between 5 and 25 years, with progressive difficulty in walking, loss of visual acuity, which initially prevails on the chromatic vision, night blindness, corneal opacity, and, in some cases, nystagmus. Progressive multifocal myoclonus usually starts in the second decade of life, associated with seizures and ataxia, especially in sialidosis [57].

24.7 Landau-Kleffner Syndrome

Originally described by Landau and Kleffner in 1957 [58] as "syndrome of acquired aphasia with convulsive disorder," Landau-Kleffner syndrome is characterized by a progressive language dysfunction (verbal and/or auditory agnosia) associated with epileptic seizures, although not constantly (70–80% of cases). The onset is from 3 to 8 years (mean age of onset 4.8 years) in children with previously normal psychomotor and language development [59, 60]. Language regression is generally gradual and subtle but in some patients may be sudden and rapid. Behavior disorders with attention deficit and/or hyperactivity may coexist [59]. In 70–80% of patients, seizures of different types occur: focal seizures, secondarily generalized tonic-clonic seizures, absences, or atonic seizures [59, 60]. The interictal awake EEG shows spikes, sharp waves, and spike-wave complexes located at temporal or temporo-occipital regions, often bilateral, symmetrical, or asymmetric (Fig. 24.17). Sometimes the anomalies may be

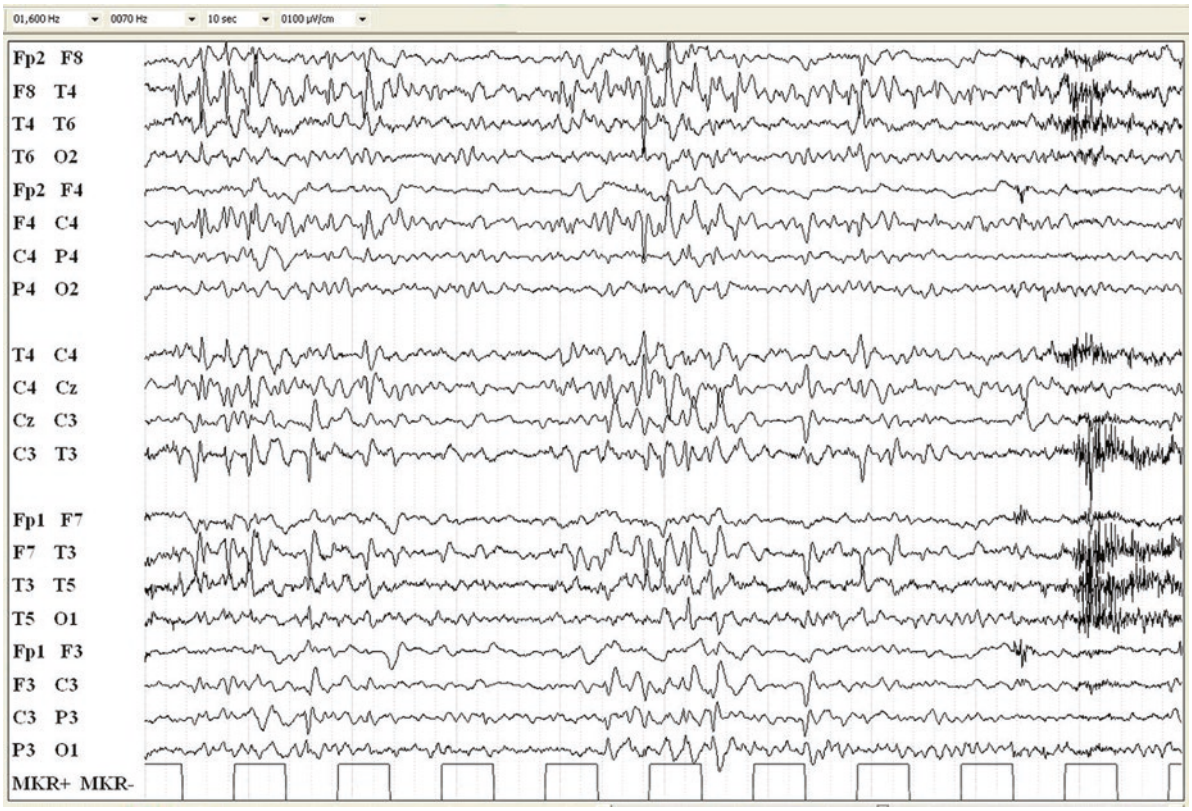

Fig. 24.17 Awake EEG. Spikes, sharp waves, and atypical spike-wave complexes dominant in the anterior temporal areas of both hemispheres

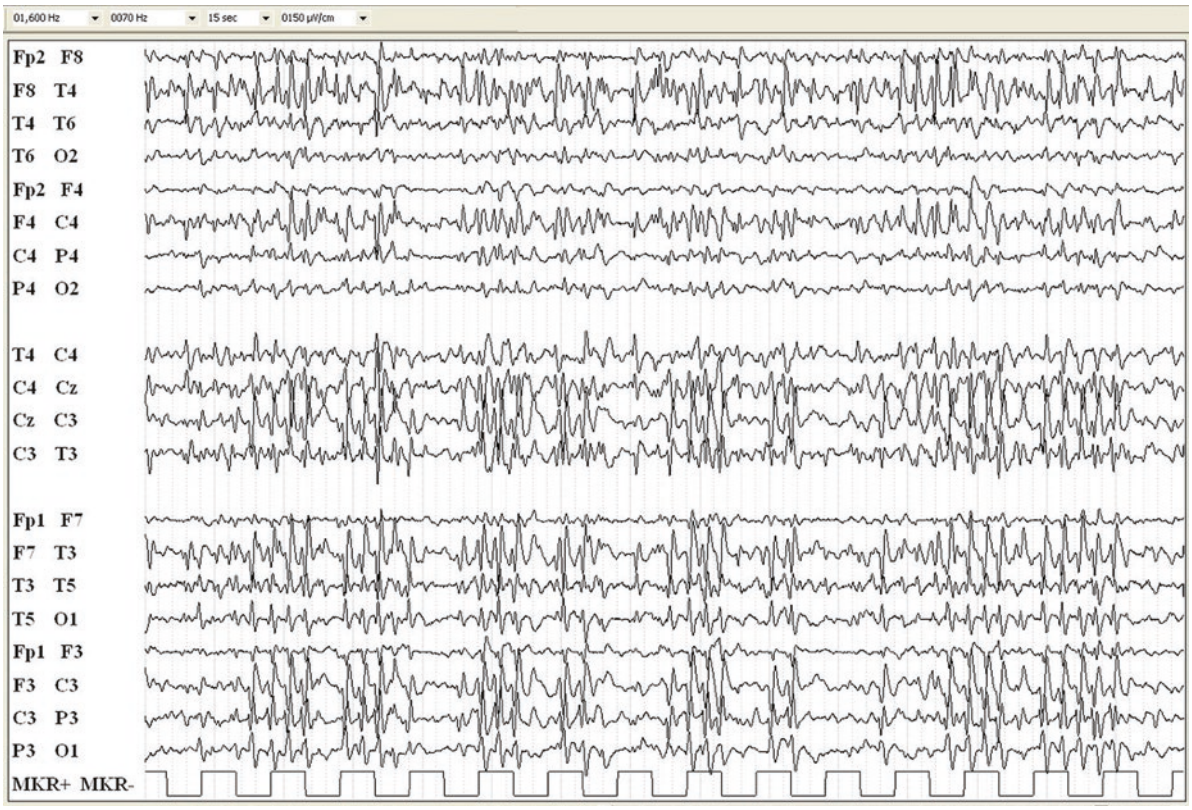

Fig. 24.18 EEG during non-REM sleep (same patient of Fig. 24.17). Sub-continuous spikes, sharp waves, and atypical spike-wave complexes at 3–5 Hz of high voltage on the anterior temporal regions of both hemispheres, with slight tendency to spread to the contiguous areas on the left

multifocal, but a clear prevalence in the temporal regions is always evident. The EEG becomes typical in sleep [59–61], due to the increase of epileptic anomalies, continuous or sub-continuous during non-REM sleep, clearly localized or dominant in temporal regions, with maximal amplitude in posterior temporal and/or parietal electrodes (Fig. 24.18). The ictal EEG has no peculiar features but correlates with seizure type. Background activity and sleep macro-architecture are usually normal. The prognosis of these patients is variable [62, 63]; seizures are generally controlled by therapy, and the EEG anomalies tend to resolve after some years, but this positive outcome of the epilepsy is not always associated with an equally favorable evolution of the language; usually, more or less serious language disorders persist even after the disappearance of the EEG anomalies [59–63].

24.8 Electrical Status Epilepticus During Slow Sleep

The main characteristic of this syndrome (electrical status epilepticus during slow sleep—ESES) is the strong activation of epileptic anomalies during non-REM sleep, with spike-wave complexes occurring for more than 85% of the duration of non-REM phases [64, 65]. This pattern tends to repeat every night for longer or shorter periods of time (months or years). No epidemiological data are available, but it is considered a rare condition (incidence of 0.5% on over 12,000 children studied over a 10-year period). Three types of clinical manifestations are associated with this EEG pattern:

– *Seizures of different type.* The age at onset varies from a few months to 12 years, with a peak around 4–5 years. Seizures may occur in children with normal psychomotor development as well as in those with signs of pre-existing brain damage. In about half of the patients, the first episode consists of a unilateral epileptic seizure during nighttime sleep. Ictal manifestations may be both focal and generalized, and about 60% of patients have multiple seizure types (clonic, tonic-clonic, focal motor, and/or with complex semiology), but there are never tonic seizures in sleep. At the beginning the seizure frequency is generally low, but it tends to increase when the typical EEG pattern arises. ESES generally occurs 1 or 2 years after the first seizure and is often associated with the appearance of other types of attacks (especially, atypical absences and drop attacks).

– *Deterioration of neuropsychological functions.* The appearance of the EEG pattern is accompanied by a progressive and often severe impairment of neuropsychological functions, with particular involvement of the language. Serial evaluations show a progressive reduction of the cognitive level both global and sectorial, with low scores especially in memory, attention, ability of orientation, and space-time organization. The functional profile is however variable from case to case, and behavioral disorders may appear with hyperactivity, aggressiveness, and psychotic manifestations.
– *Movement disorders.* The appearance of ESES interferes with the control of the motor action both at the cortical and cerebellar level (dyspraxia, dystonia, ataxia). Unilateral deficits, sometimes transient or fluctuating, and negative myoclonus may also occur.

The EEG in wakefulness does not show any specific aspects before, during, and after the ESES phase; there may be both generalized and focal epileptic anomalies, with the latter being more often located in the anterior regions. Predictive signs of the imminent onset of an ESES are considered: (a) the appearance of 2–3 Hz spike-wave complexes in short generalized discharges, apparently subclinical, (b) a greater tendency to the diffusion of focal anomalies, and (c) increased seizure frequency and appearance of other types of attacks.

The EEG during sleep typically presents continuous or sub-continuous epileptic activity (spike-wave index between 85 and 100%) during all non-REM phases. The anomalies are characterized by high-voltage synchronous and symmetrical spike-wave complexes, diffuse, often dominant in the anterior regions (Fig. 24.19). Although the anomalies are widespread, in many patients there is a clear prevalence in some areas, with consequent changes in the clinical picture: anomalies prevalent in the temporal regions of one or both hemispheres involve a greater interference on the language, while those dominant in the frontal regions are more frequently associated with the development of psychosis, especially in the autistic spectrum.

The ESES abruptly disappears during the REM phases; short discharges of diffuse spike-wave complexes or focal anomalies, mainly frontal, may persist. The cyclic alternating pattern of the non-REM and REM phases is discreetly conserved, but the microstructural organization and architecture of sleep are globally altered, which might have further adverse effects on cognitive function [64–66]. The presence of an ESES may be suspected by short

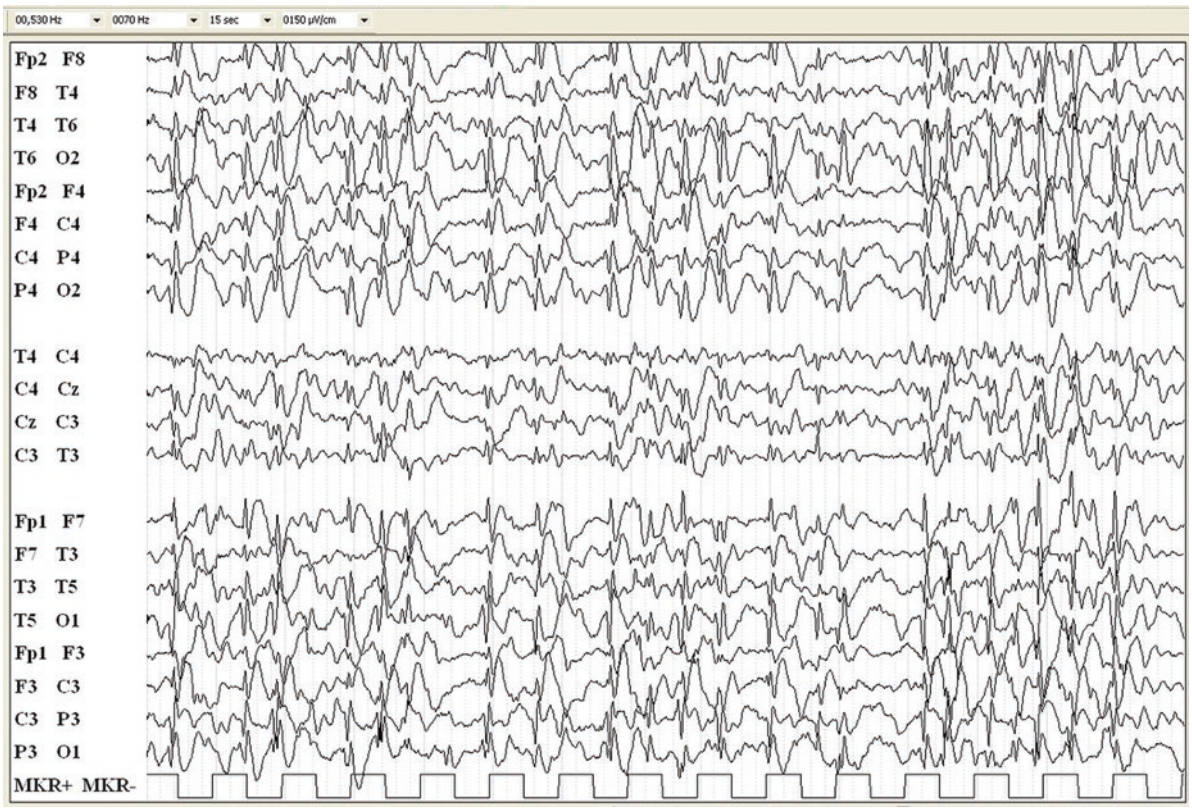

Fig. 24.19 EEG during non-REM sleep. Sub-continuous generalized 2–4 Hz spike-wave complexes of high voltage

EEG during sleep, but nocturnal sleep recording is generally essential to confirm the diagnosis and to better outline the prognosis. Although the long-term outcome of seizures and ESES is generally favorable, greater cautiousness must be placed in assessing the overall prognosis in individual patient. Indeed, the remission of ESES is generally associated with improvement of cognitive function, attention, language, and behavior, but in about half of the cases, serious neuropsychological and/or motor deficits may persist.

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Focal "Idiopathic" Epilepsies of Infancy

25

Elena Gardella and Gaetano Cantalupo

25.1 Introduction

Under the old term of focal "idiopathic" epilepsies of infancy are comprised a group of epilepsy conditions characterized by *focal (or localization-related)-onset seizures* and a relatively "benign" course. These conditions account for about the 20% of children with nonfebrile seizures.

The term "idiopathic epilepsy" means that epilepsy is not subtended by a detectable structural brain abnormality and probably is due to a genetically determined propensity to a certain type of seizures, EEG abnormalities, and evolution. Furthermore the term "idiopathic," from the Greek word "idios" ("self" or "proper"), points to the fact that epilepsy is not a manifestation of another disease, but it represents the disease in itself. In fact, this group of epilepsies arose in children without any other neurological or cognitive impairment, seizures are likely to be controlled with appropriate antiepileptic therapy (or even do not need drug treatment), and the seizure propensity is ultimately self-limited, since they are expected to have a spontaneous and definitive remission before adulthood. After the seizure onset, the neuropsychological development of these children is usually normal, but may present a transient or even long-lasting impairment. Therefore, the term "benign," often used in connection with this group of epilepsy syndromes, is not considered appropriate any longer and has been recently replaced by the term "self-limited" (ILAE Commission for Classification and Terminology [1]).

Three electro-clinical syndromes recognized by the International League Against Epilepsy (ILAE) (1989) [2] are Rolandic epilepsy (RE), Early-Onset Epilepsy with Occipital Paroxysms (Panayiotopoulos Syndrome) and Late-Onset Childhood Epilepsy with Occipital Paroxysms (Gastaut Type). Within each entity, although focal, seizures and EEG abnormalities usually affect asynchronously homologous regions in both hemispheres, thus leading to quite homogeneous and reproducible clinical and EEG features. This suggests that seizure propensity does not involve a single focus but primarily involves a particular system (e.g., the autonomic system in Panayiotopoulos syndrome or the sensorimotor system in Rolandic epilepsy); thus the term "system epilepsies" was proposed to unify all "idiopathic" epilepsies [3]. All those entities have been considered part of a spectrum of an age-related genetically determined focal "seizure susceptibility syndrome" (Panayiotopoulos et al. 2008).

Part of this spectrum are also some less frequent epilepsies with specific inter-ictal focal EEG patterns (e.g., with vertex spikes-and-waves during sleep or with giant somatosensory evoked spikes) or nonfebrile self-limiting seizure conditions, not requiring a diagnosis of epilepsy (benign familial and non-familial infantile seizures).

25.2 Rolandic Epilepsy (or Benign Childhood Epilepsy with Centrotemporal Spikes)

Rolandic epilepsy (RE), or self-limited epilepsy with centrotemporal spikes, formerly also called benign childhood epilepsy with centrotemporal spikes (BECTS), is the most common non-lesional focal epilepsy of childhood, accounting for about the 15% of nonfebrile focal epilepsies in otherwise normal children. The epilepsy onset peaks at the range of age 7–10 years.

Seizures typically are focal motor and occur from sleep, presenting with orofacial motor signs, specifically tonic or

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clonic contractions of one side of the face, mainly involving the oropharyngeal muscles, with guttural sounds, drooling (sialorrhea), swallowing, and in some cases speech arrest (anarthria). Somatosensory symptoms are also frequent, if the children are specifically asked, mainly consisting of unilateral paresthesia of the tongue, lips, gums, and inner cheek [4–7]. The lower limb is affected only in 8% of children, and in a minority of cases, postictal dysarthria, Todd's paresis, or exceptionally hemiplegia may persist for a few minutes [6, 8]. Other seizure types, with associated autonomic, motor, and visual manifestations, have been described [8].

Less frequently generalized tonic-clonic seizures are observed, particularly in younger children [8].

The seizure frequency is generally low, with half having fewer than five attacks in their life [5].

Some degrees of stable or intermittent neuropsychological deficits are quite common and may be related to the marked accentuation of the interictal epileptic abnormalities during sleep, which in very few children may lead to an atypical evolution consisting with encephalopathy with status epilepticus during sleep (ESES/CSWS see below).

25.2.1 Interictal EEG

The EEG background is well organized both during wakefulness and sleep.

The interictal epileptiform abnormalities have a characteristic morphology and topography. They are slow, dysphasic, and high-voltage spikes (100–300 μV), often followed by a slow wave; in some cases, the centrotemporal spikes can be of small voltage (Fig. 25.1a). They may be sporadic or occur in clusters and may be unilateral or bilateral and synchronous or asynchronous in the centrotemporal (Rolandic) regions. Their maximal amplitude is halfway between the central (C3/C4) and the mid-temporal (T3/T4) electrodes (Fig. 25.1a, b), corresponding to the lower central electrodes (C5/C6), in case of a montage with supplementary EEG derivations [9].

The orientation of the dipole of the spikes is perpendicular to the cortex within the Rolandic fissure (sagittal dipole) with anterior positivity (Fig. 25.1b). Integrated localization techniques (high-resolution EEG, MEG, source analysis, and fMRI) localize the generator of the Rolandic spikes in the lower part of the sensorimotor cortex, revealing two dis-

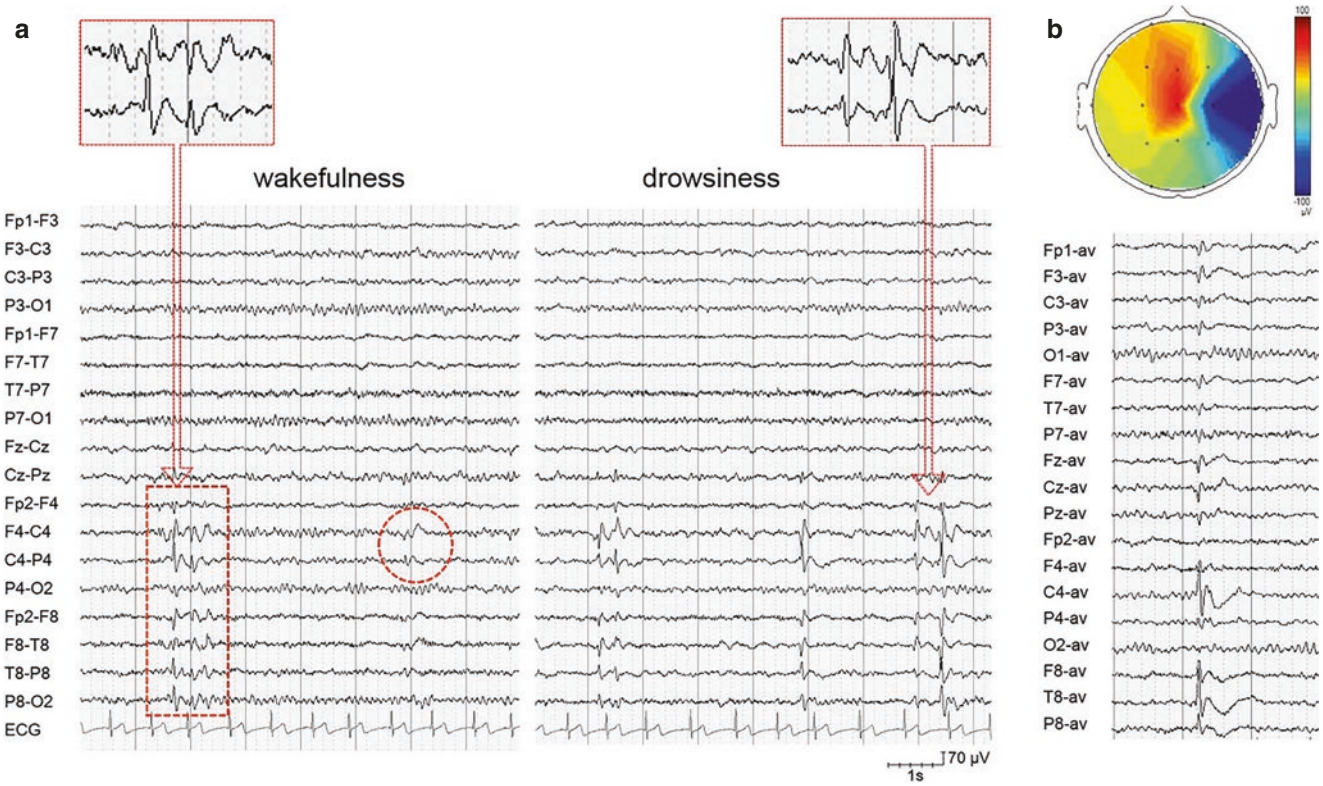

Fig. 25.1 Interictal EEG during wakefulness and drowsiness in a patient with Rolandic epilepsy. The characteristic slow, dysphasic spike-and-slow wave complexes show maximum in the centrotemporal (Rolandic) regions (maximal amplitudes C4 and T8). (**a**) The typical high-voltage spikes alternate sometimes to some small-voltage ones (circle). The spikes become more frequent during drowsiness, when a discrete focal rhythmic slow activity can also appear. (**b**) The map of amplitude corresponding to the negative peak of the spike shows the maximum of negativity in the mid-temporal regions with anterior positivity (sagittal dipole) *(EEG band-pass filter 1–70 Hz)*

tinct sources, one in the postcentral and the other in the precentral cortex [10].

The presence of a very fast EEG component (ripples) on top of the Rolandic spikes predicts a worst clinical outcome and need of a chronic pharmacologic treatment [11]. Focal rhythmic slow activity is occasionally observed in the region epileptic focus (Figs. 25.1 and 25.3).

The centrotemporal spikes are not affected by eye opening/closure, hyperventilation (HV), or photic stimulation (PS) but can be evoked or suppressed by protrusion of the tongue [12, 13].

Spikes in other areas and multifocal spikes can be seen from the first EEG recording or during evolution [4] (Fig. 25.2). The presence of multifocal spikes does not seem to correlate with the seizures frequency or semiology.

During drowsiness and NREM sleep is observed an accentuation of the epileptiform abnormalities, without changes in the morphology (Fig. 25.3). Sleep may also activate independent centrotemporal spikes over the other hemisphere or generalized spike-wave discharges that would argue against a structural cause. Sleep recording in these

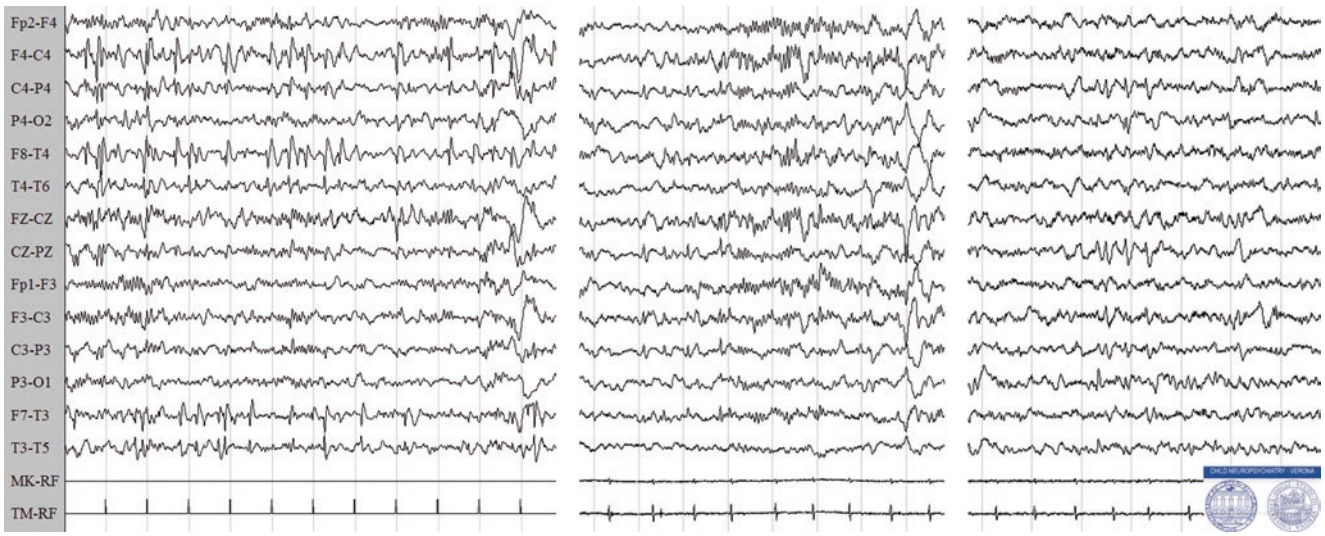

Fig. 25.2 Left panel: during sleep, stage N2, frequent and high-amplitude focal spike-and-waves, asynchronous on centrotemporal region of both hemispheres, can be observed in a patient with Rolandic epilepsy during the active phase (by age 7 years). In the middle and right panel, two EEGs from the same patient, during N2 sleep, at 9 and 10 years old, respectively (during the initial remission phase), in which small focal spikes or spike-and-waves are evident on central and vertex region. Please note that in the right panel, the spike component became longer in duration ("slow spikes" or "sharp waves") but with the same topographical distribution

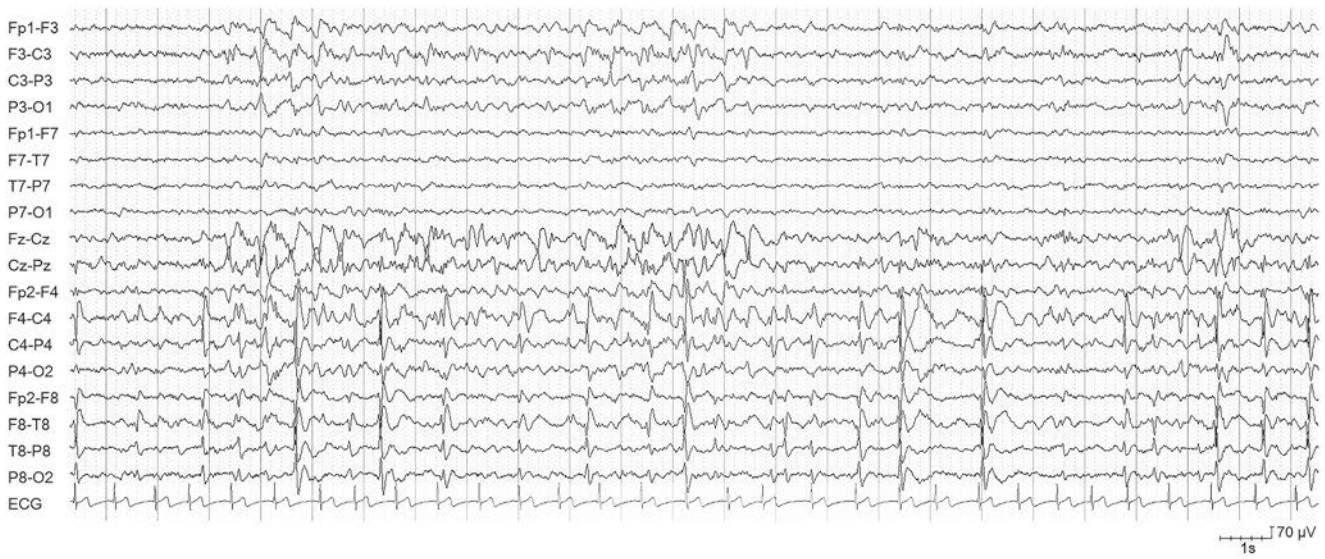

Fig. 25.3 Interictal EEG during sleep in a child with Rolandic epilepsy (same patient as in Fig. 25.1), where the right centrotemporal spikes and the intermixed rhythmic slow activity are accentuated. During N2 sleep some centrotemporal spikes and focal slow activity appear also in the left hemisphere, synchronously and asynchronously *(EEG band-pass filter 1–70 Hz)*

children is therefore highly recommended because typical EEG findings may only be seen during sleep [14].

Generalized spike-wave discharges are rare during wakefulness and do not occur during sleep, but are not infrequent during drowsiness [4, 8].

There is no correlation between amount of the interictal spikes and the frequency or severity of the seizures. Anyway, atypical EEG features (spike morphology or location, abnormal background, etc.) have been associated with a higher percentage of learning and behavioral disabilities [15]. The EEG renormalization occurs usually later than clinical remission [16].

25.2.2 Ictal EEG

Given the low seizure frequency and their preferential nocturnal occurrence, ictal EEG recordings are rare.

The ictal EEG pattern is generally characterized by fast rhythms in the Rolandic regions, contralateral to the motor manifestations, progressively increasing in amplitude and evolving to a spike- or polyspike-and-slow wave pattern (Fig. 25.4) with or in most cases without diffuse spreading and secondary generalization [17]. In the late part of a seizure, the ictal spikes show a maximum of positivity at the mid-temporal EEG derivations. That means, a reversal of the interictal dipole is observed, which has maximum negativity in the central and medial-temporal derivations [18].

25.2.3 Atypical Evolution

In a few patients with RE, a severe neuropsychological impairment may occur and become persistent for years. This is an age-related condition, associated with a peculiar EEG pattern, characterized by the striking activation of epileptic abnormalities during non-REM sleep, which may became almost continuous during NREM sleep. This condition is known as encephalopathy with status epilepticus during slow sleep (ESES) [19] or with continuous spike and waves during sleep (CSWS) (see [20], for a review).

Different patterns of EEG distribution have been described (diffuse, hemispheric, focal) (for a review, see [21]) (Fig. 25.5). The reasons why some children develop this EEG pattern are still not understood. In some cases, certain antiepileptic drugs seemed to be responsible [22]. The remission is spontaneous before puberty, but the cognitive recovery is not always complete [23].

25.3 Early-Onset Epilepsy with Occipital Paroxysms (Panayiotopoulos Syndrome)

The "early-onset" variant of the childhood occipital epilepsy, also called Panayiotopoulos syndrome (COE-PS), has a prevalence of about 5% in children with an afebrile focal seizure. The peak age of onset is 3–6 years, and the spontaneous remission is up to 3 years.

Seizures are infrequent; only a few children report to have had more than ten seizures in total. COE-PS seizures are usually prolonged (average duration 5–90 min) and sleep related, about 70% occurring out of sleep and 13% upon awakening [24].

The hallmark of the COE-PS is the prolonged autonomic seizures (nausea, retching and vomiting, pallor/flushing, pupillary dilatation, and hypersalivation) with emesis (70–

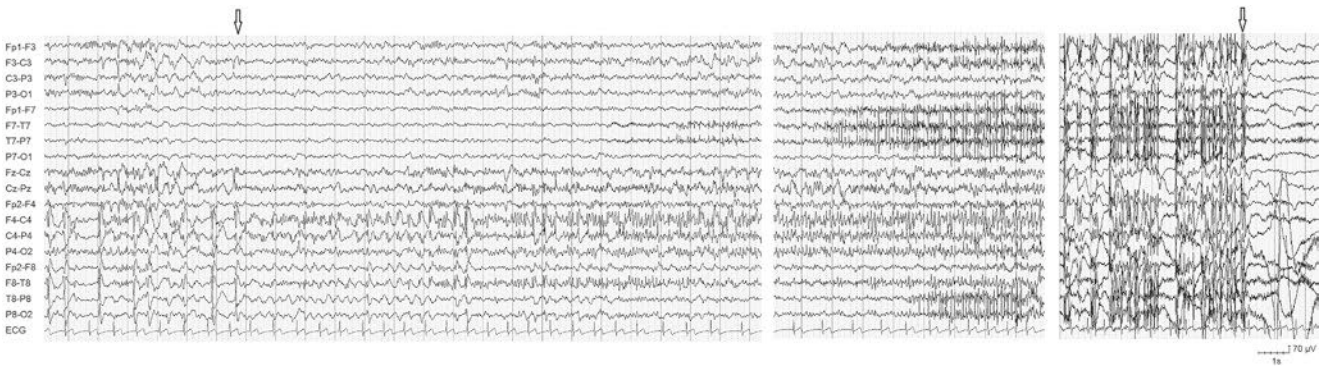

Fig. 25.4 Rolandic epilepsy. EEG recordings of a focal seizure with onset during sleep, characterized by myoclonia around the mouth and in the left part of the face, arousal and anartria. The duration of the seizure is 1 min and 2 s. On the EEG, the seizure starts with an arrest of the interictal epileptiform abnormalities consisting of trains of high-amplitude Rolandic spikes (left arrow) and with the appearance of a rhythmic 12–14 Hz activity on the right centro-frontotemporal regions, progressively increasing in amplitude with intermixed spike-and-slow waves. The right arrow indicates the seizure end *(EEG band-pass filter 1–70 Hz)*

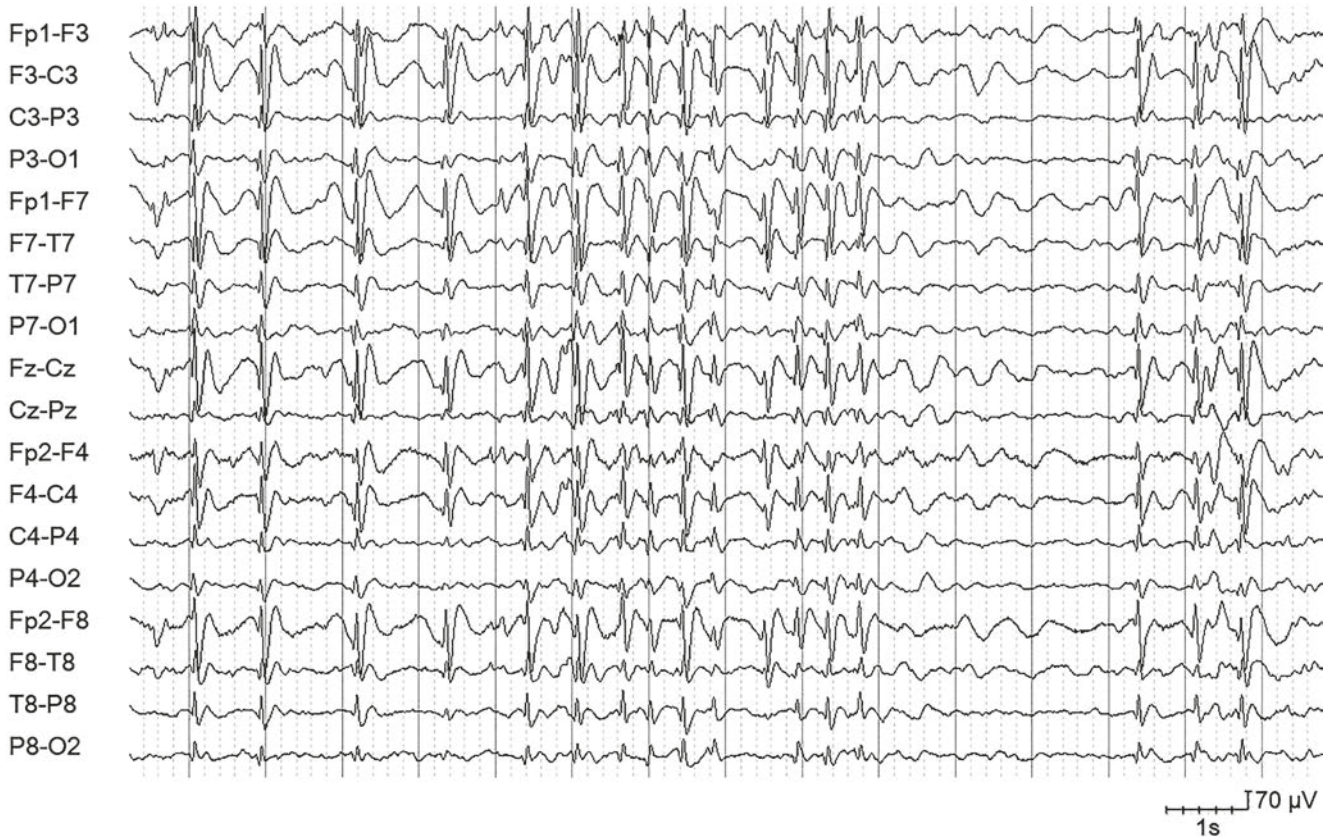

Fig. 25.5 Girl with Rolandic epilepsy, aged 9 years and 3 months, having had a few focal clonic seizures during sleep with onset at the age of 6 years and 9 months. Previous EEG showed infrequent epileptiform abnormalities in the Rolandic regions. She developed cognitive stagnation/regression from the age of 7.5 years. Twenty-four hours EEG recordings show almost continuous diffuse spike-and-slow waves (frontal predominance) during NREM sleep, consistent with the diagnosis of ESES/CSWS *(EEG band-pass filter 1.6–70 Hz)*

80%), up to autonomic status epilepticus. Impairment of consciousness and motor manifestations (deviation of the eyes, hemi-clonic or tonic-clonic manifestations) can also occur. Visual symptoms are very rare.

Many children also present syncope-like seizures characterized by sudden loss of consciousness and flaccidity [25].

25.3.1 Interictal EEG

The first routine EEG is normal in 66–85% of children [26]. The EEG background is generally normal also at follow-up but can show focal or diffuse slowing postictally.

Interictal EEG abnormalities show a great variability, ranging from completely normal EEG (21%) to focal spikes (any site) or even brief generalized discharges. The most common localization is in the occipital regions (Fig. 25.6a); anyway, "apparently" extra-occipital spikes are the only interictal abnormalities in about a third of cases, shifting from side to side and from one region to another in the same patient. However, it is important to note that apparently frontal spikes represent actually a fast spread of occipital spikes toward anterior regions (Fig. 25.7), as demonstrated by computer-aided analysis (Leal phenomenon [27]).

High-voltage and diffuse (Fig. 25.8a) or multifocal sharp-slow-wave complexes are seen in up to 90% of children at some point in their follow-up, particularly in drowsiness or sleep. Repetitive small-voltage spikes or sharp-wave discharges ("clone-like") are also present.

The epileptiform abnormalities are inhibited by eye opening in a minority of cases (Fig. 25.6a), can be induced by photic stimulation (Fig. 25.6b), and are typically markedly activated during sleep or only occur in sleep (Fig. 25.8b). The sensitivity of the sleep EEG ranges from 80 to 100%; therefore sleep EEG recording is considered mandatory [26, 28].

The frequency and location of the spike-wave discharges do not correlate with the severity of the clinical manifestations and prognosis. The EEG normalization

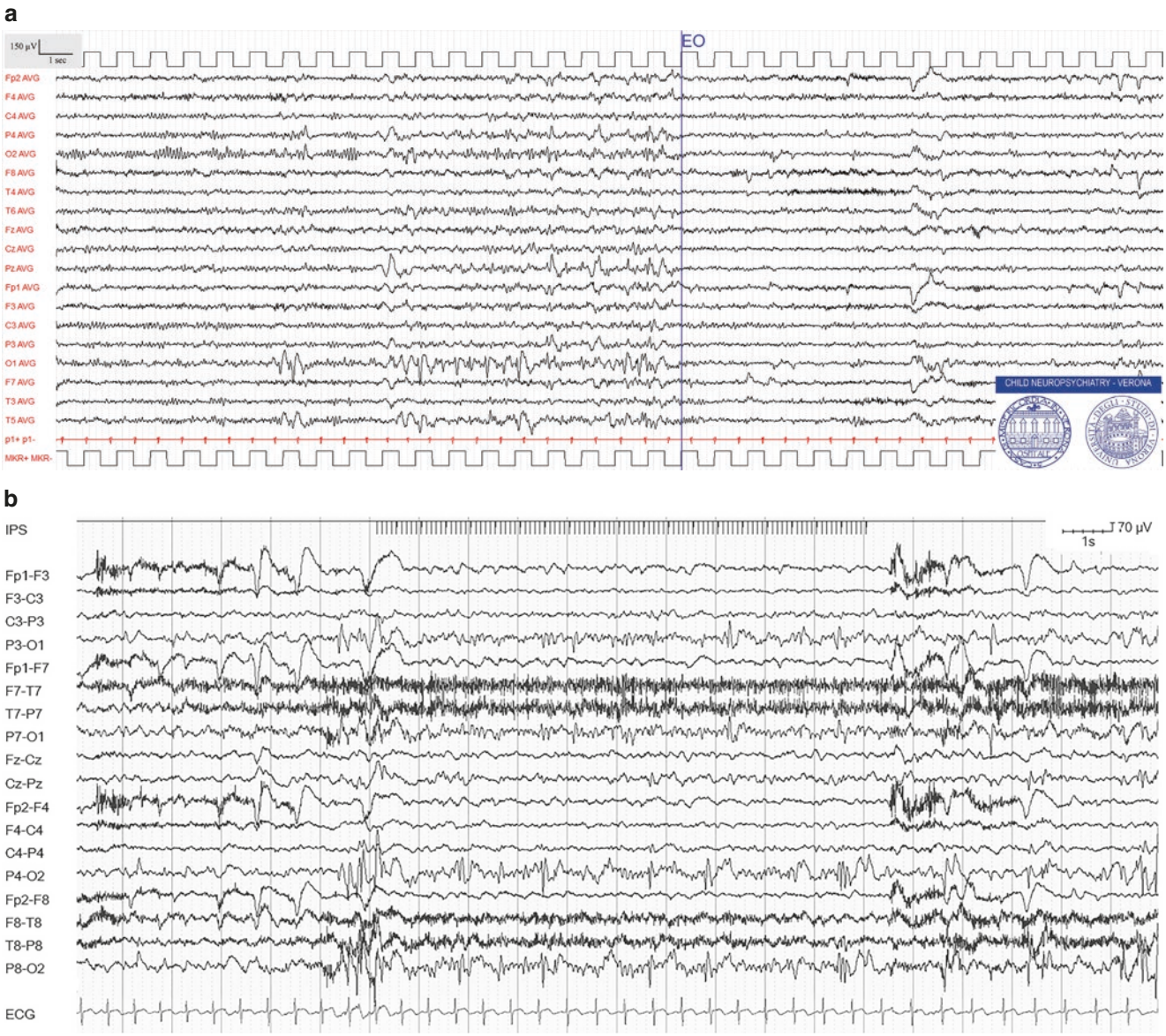

Fig. 25.6 (**a**) Typical focal posterior spike-and-waves (in this case more evident on the left occipital channels) in a case of focal idiopathic occipital epilepsy, inhibited by eye opening (EO) (**b**) In another patient, with eye closure sensitivity, the intermittent photic stimulation induces an occipital photoparyoxysmal response

can occur up to 7 years after clinical remission [29], and often interictal EEG abnormalities only disappear by adolescence.

25.3.2 Ictal EEG

Seizures are typically sleep related, and the ictal EEG onset can occur several minutes prior to the clinical onset [24, 30].

The seizure-onset zone is variable, either in a wide posterior region or in the frontotemporal regions, usually consisting of rhythmic theta waves, intermixed by small spikes and spike-and-slow waves, followed by a fast rhythm spreading to both hemispheres.

25.3.3 Atypical Evolution

As in the case of RE, in a minority of patients with COE-PS, an atypical evolution to encephalopathy with status epilepticus during sleep (ESES/CSWS) can occur, with impairment of cognitive and/or motor function.

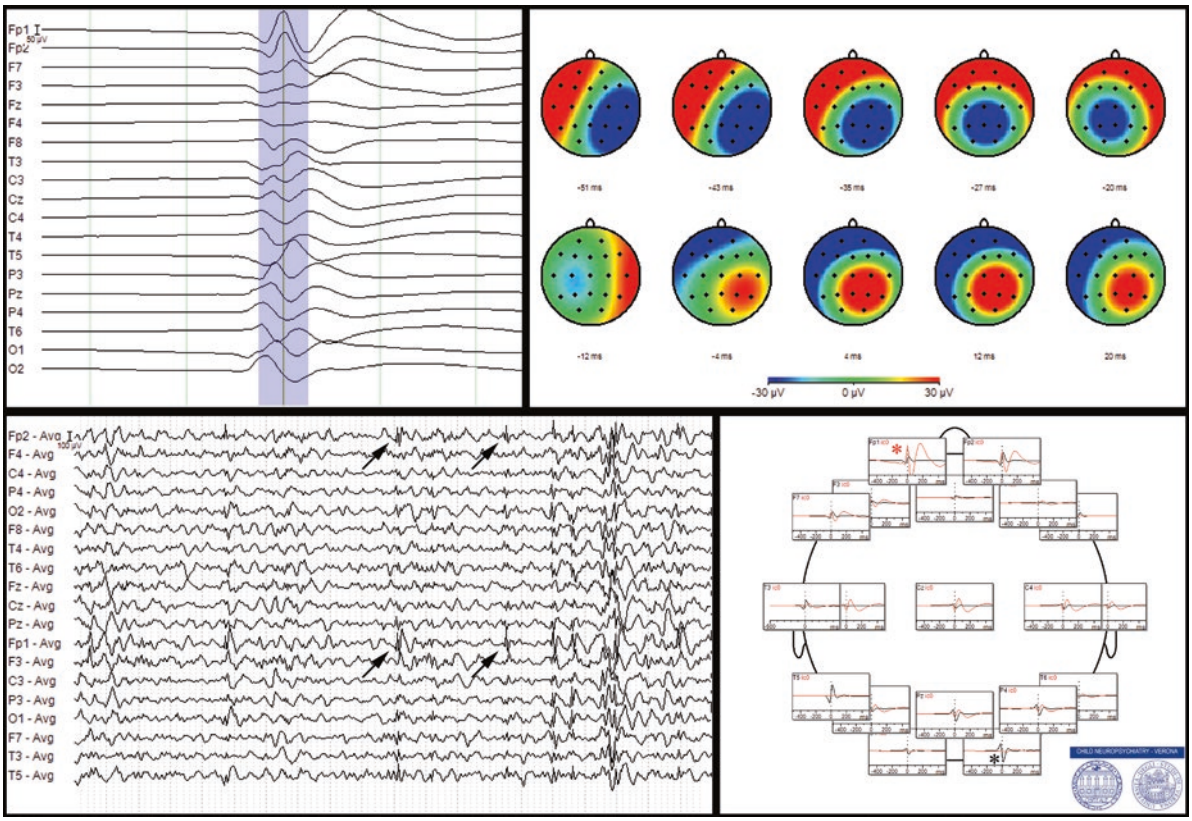

Fig. 25.7 Diffuse spike-and-wave during sleep in a patient with COE-PS. In this case the paroxysmal abnormalities are of higher amplitude and more evident on frontopolar channels (arrows), erroneously suggesting a frontal origin, representing instead a propagation of posterior abnormalities, as demonstrated by Leal et al. [27]. Actually, spike-averaging—centered on the frontopolar peak of the spike—demonstrates a negative transient on right posterior channels constantly preceding by 30 ms (peak-to-peak) the anterior one (upper line, left panel; blue-shaded area extends from −50 ms to 50 ms around 0). On the right—upper line—ten consecutive scalp voltage maps at 8 ms intervals showing the evolution from −51 ms to 20 ms across 0 line. In the lower right panel, the two principal components of the spike-and-wave complex, computed by independent component analysis (ICA) decomposition (Makeig et al. 1996), are overlaid, the red one representing the frontopolar component peaking at time 0 on Fp1 (red asterisk), while the black one is the earlier posterior component (black asterisk)

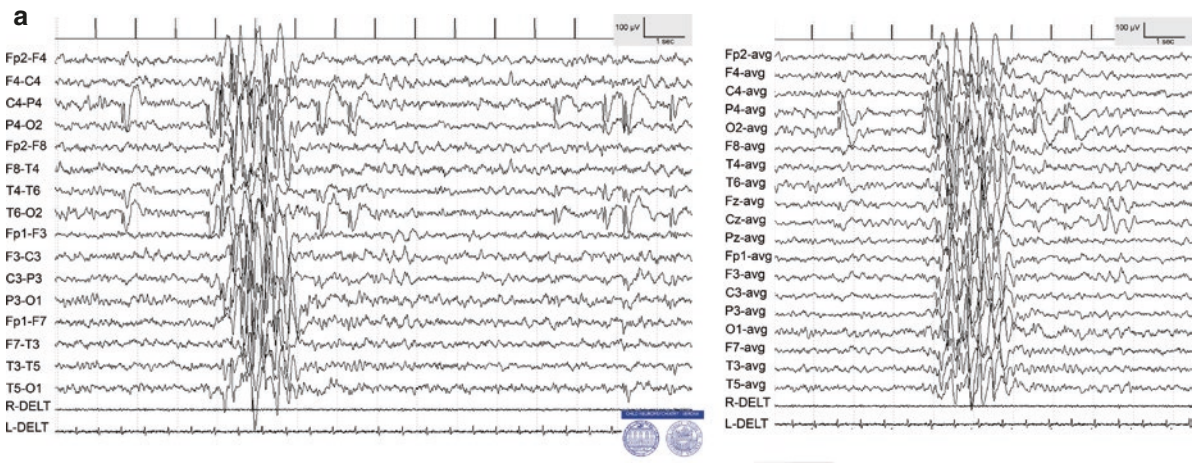

Fig. 25.8 (**a**) Drowsiness and sleep EEG findings in patients with COE-PS (same patient ads in Fig. 25.6b), showing frequent, high-amplitude 2–3 Hz spike/sharp-and-slow-wave complexes (SW) in the posterior quadrants, isolated or in short trains. The SW appears on eye closing (EC) (left panel) and is accentuated during NREM sleep (right panel) *(EEG band-pass filter 1–70 Hz, notch filter 50 Hz)*. (**b**) Typical focal posterior SW in a case of focal idiopathic occipital epilepsy (same patient ads in Fig. 25.6a). In this case, paroxysmal abnormalities are more evident on the right occipital channels, isolated or in brief sequences, sometimes organized in discharges with bilateral diffusion, constituting brief bouffées (bursts) of diffuse irregular SW complexes. Please note the different shape of the abnormalities in bipolar (left panel) and monopolar (right panel) montages

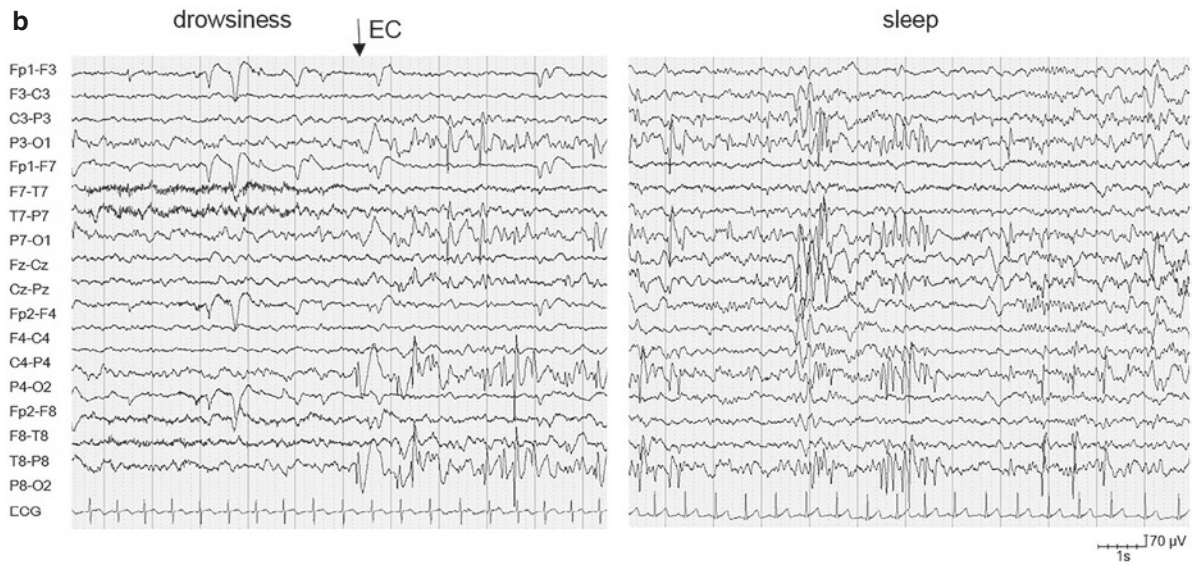

Fig. 25.8 (continued)

25.4 Late-Onset Childhood Epilepsy with Occipital Paroxysms (Gastaut Type)

The childhood occipital epilepsy of Gastaut (COE-G) is a purely occipital and probably genetic epilepsy syndrome, including the idiopathic photosensitive occipital lobe epilepsy, as a less common form with uncertain prognosis [31].

The peak age of onset is 7–8 years, and the clinical course is considered benign, although full epilepsy remission is lower than for RE and for COE-PS [32].

Most seizures occur during wakefulness, and their duration might be up to 15 min, though typically brief (<2 min). Seizure starts with visual symptoms (mainly simple hallucinations), followed by eye and head deviation and hemiconvulsions in 34–45% of case, sometimes alternating sides [33, 34]. Infrequently (11–15% of cases), visual aura can be followed by temporal lobe symptoms [34, 35].

The ictal symptoms of the occipital lobe seizures in COE-G are grossly similar to those in occipital epilepsies of structural origin. Therefore, recognizing the typical EEG pattern and ictal semiology of COE-G is important for their differential diagnosis.

In a minority of children, at any time during epilepsy course, may also occur absences associated with 3-Hz generalized spike-and-slow waves (<15%) or Rolandic seizures (<6%) [33, 36].

25.4.1 Interictal EEG

The background activity is normal. The interictal EEG abnormalities consist of high-amplitude occipital spikes, not associated with focal background slowing, occurring either as a single potential or in long rhythmic clusters with a peak of negativity on O1–O2.

In up to 60% of the children with COE-G, occipital spikes are bilateral synchronous and asynchronous [33], suggesting a diffuse occipital hyper-excitability (Fig. 25.9).

The epileptiform abnormalities are accentuated by eye closure and by drowsiness (Fig. 25.9) and sleep (Fig. 25.10). Fixation-off sensitivity is present in more than 90% of children with COE-G [34].

In about 24–38% of COE-G patients have been also reported centrotemporal spikes and brief bursts of generalized spike-and-slow waves [33, 34], more irregular than those observed in idiopathic generalized epilepsies.

Photosensitivity occurs in 11–15% [33, 34] of children (Fig. 25.9). The effect of sleep can result both in an accentuation of the epileptiform activity (Fig. 25.10), which in some children appears only during drowsiness and light sleep, and less frequently in an attenuation of the abnormalities. In addition, the centrotemporal spikes and generalized spike-waves occur typically during sleep [34].

Hyperventilation has no significant effect on the focal epileptiform abnormalities but can facilitate the occurrence of generalized spike-wave discharges.

Conversely, in structural occipital lobe epilepsy, the occipital spikes are often unilateral and are associated with focal background slowing [37, 38]; photosensitivity and fixation-off sensitivity are not expected.

25.4.2 Ictal EEG

In children with COE-G, the seizures occur typically during sleep and might be very prolonged. Typically, the ictal dis-

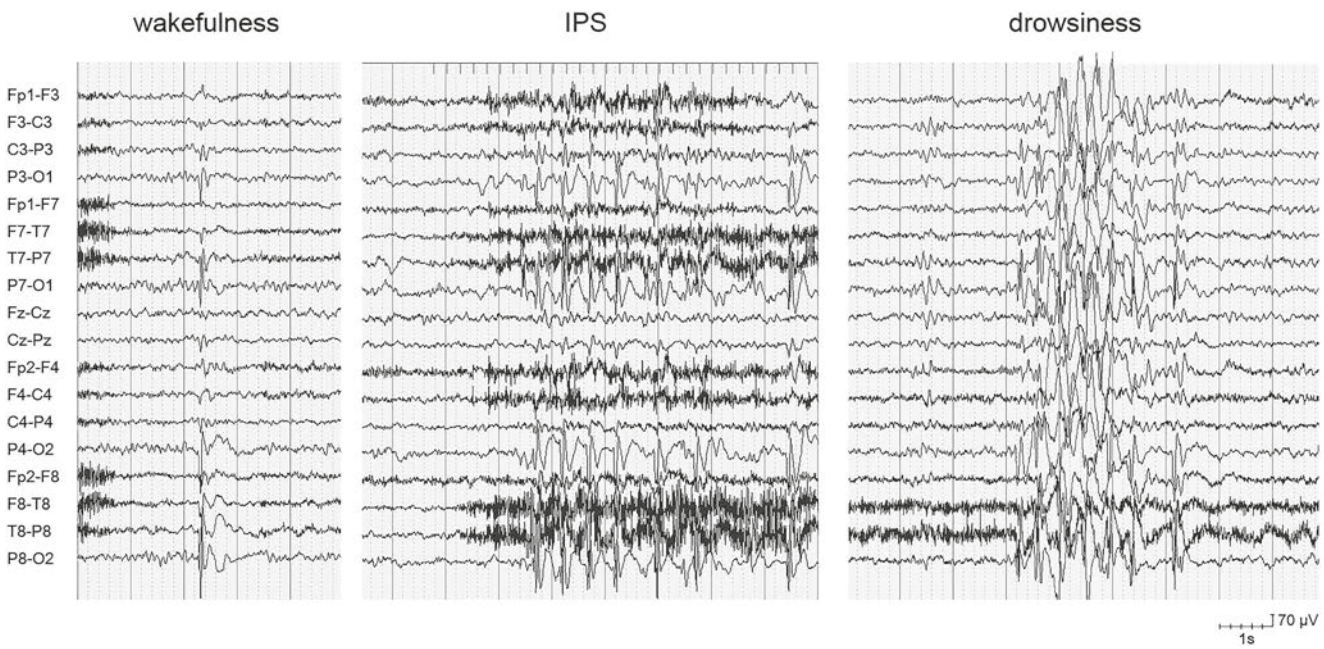

Fig. 25.9 In a patient with childhood occipital epilepsy of Gastaut (COE-G), the EEG during wakefulness showed isolated high-amplitude spike/sharp-and-slow-wave complexes (SW). The intermittent photic stimulation (IPS) induces an occipital photoparyoxysmal response, limited to the stimulus train. During drowsiness brief bursts of diffuse irregular SW complexes appeared, as observed in RE and COE-PS *(EEG band-pass filter 1–70 Hz)*

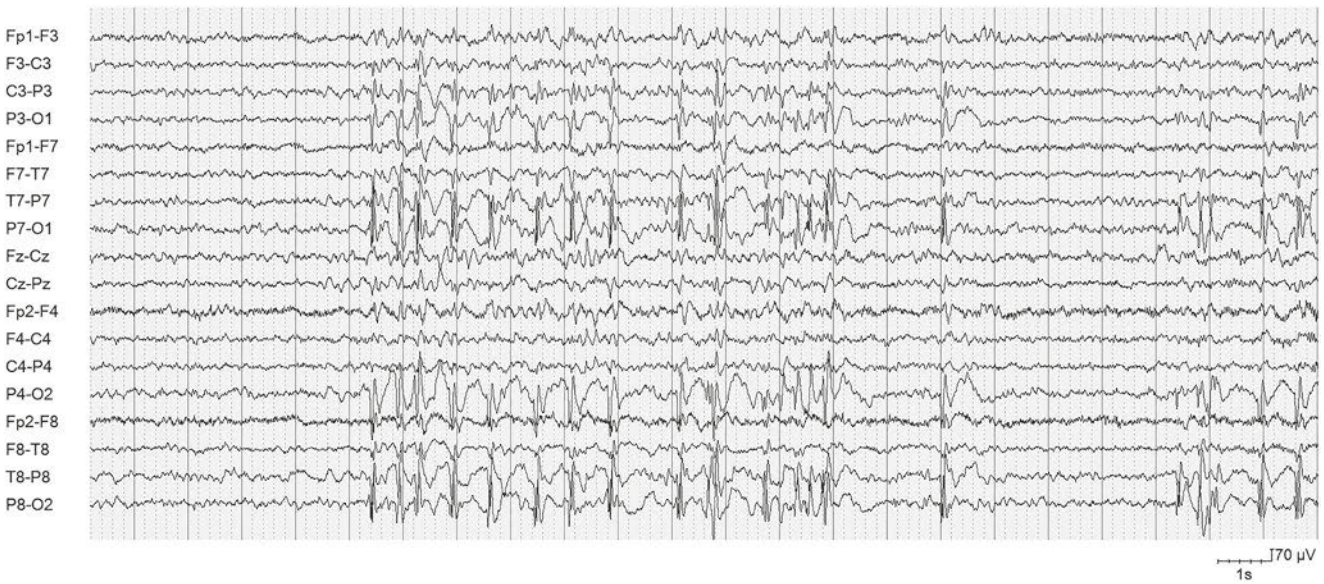

Fig. 25.10 Marked accentuation of the epileptiform abnormalities in the occipito-parieto-post-temporal regions in patients with COE-G (same patient ads in Fig. 25.9). The spike-and-slow-wave complexes appear isolated or in short trains *(EEG band-pass filter 1–70 Hz)*

charge consists of rhythmical fast spikes limited in the occipital lobe of one of both sides. The amplitude of the ictal occipital spikes is usually smaller than the one of the interictal occipital spikes (Fig. 25.11) [34]. In COE-G the pattern of EEG propagation is slow and suprasylvian, leading to hemiconvulsions.

In contrast, structural occipital lobe epilepsy frequently has a fast ictal propagation to the supplementary motor areas

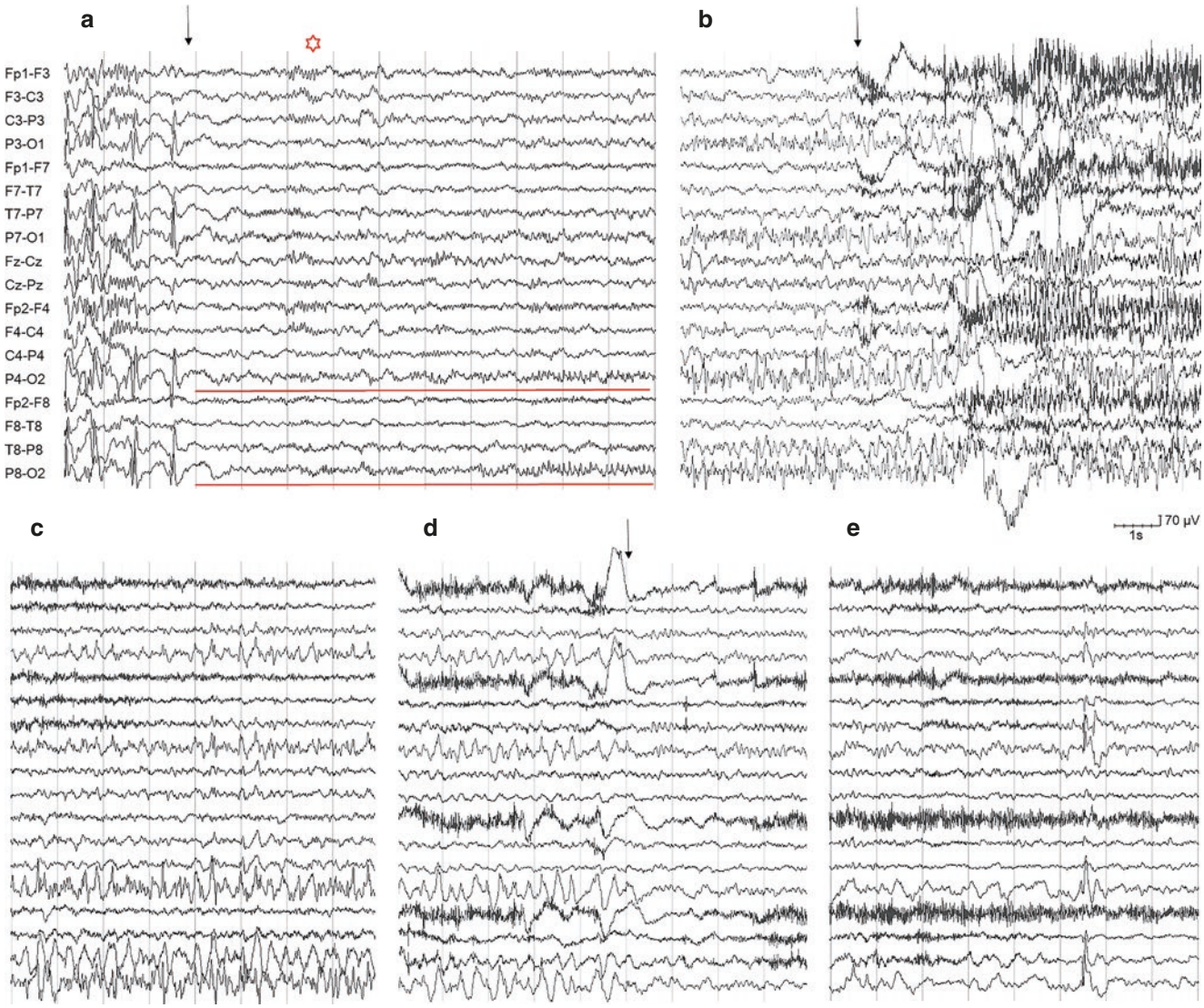

Fig. 25.11 A typical focal seizure in a patient with COE-G. (**a**) The seizure occurs out of N2 sleep, where there were very frequent, high-voltage 1 Hz spike-and-slow-wave complexes (SW) bilaterally in the posterior regions (occipital predominance). At seizure onset (arrow), the interictal epileptiform abnormalities stop abruptly, and a rhythmic low-voltage activity appears in the right occipito-post-temporal regions. Notably, in the anterior regions, the spindles are physiologically represented during the first part of the seizure (star). In this phase no evident clinical manifestations are observed. (**b**) The focal epileptiform discharge is gradually increasing in amplitude and spreading to the contralateral occipito-post-temporal regions. After 1 min and 22 s from seizure onset (arrow), the child wakes up crying and saying that he can't see; the eyes are deviated to the left. The amplitude of the ictal occipital spikes is smaller than the one of the interictal occipital spikes (see panels **a** and **e**). (**c**, **d**) The propagation of the ictal discharge remains confined to the occipito-post-temporal regions (right side prevalence). Fear, crying, and blindness still persist. A theta-delta component of increasing amplitude becomes more and more evident, intermixed to the focal rhythmic spikes. The seizure abruptly stops after 8 min and 9 s (arrow, panel **d**). (**e**) A postictal EEG slowing in the right posterior quadrant (max occipital: see $P4\text{-}O_2/P8\text{-}O_2$) is evident; a few minutes after seizure ends, the interictal SW appears in the posterior quadrants bilaterally (max in the right occipital region). The child experiences a gradual recovery of vision *(EEG band-pass filter 1–70 Hz)*

or an infra-sylvian propagation, mimicking temporal lobe seizures [35, 37, 38].

25.5 Other "Minor" Localization-Related Self-Limited Genetic Epilepsies

Other less defined and probably rare self-limiting epilepsy condition, described in otherwise normal children, are the "benign focal epilepsy with extreme somatosensory evoked potential" (ESEP) and the "benign infantile focal epilepsy with midline spikes and waves during sleep" (BIMSE).

The benign focal epilepsy with ESEP was described by de Marco and Tassinari in 1981 [39].

Initially, patients show only high-voltage ESEP elicited from the tapping on the feet, on an otherwise normal EEG. With variable delay, spontaneous interictal spikes

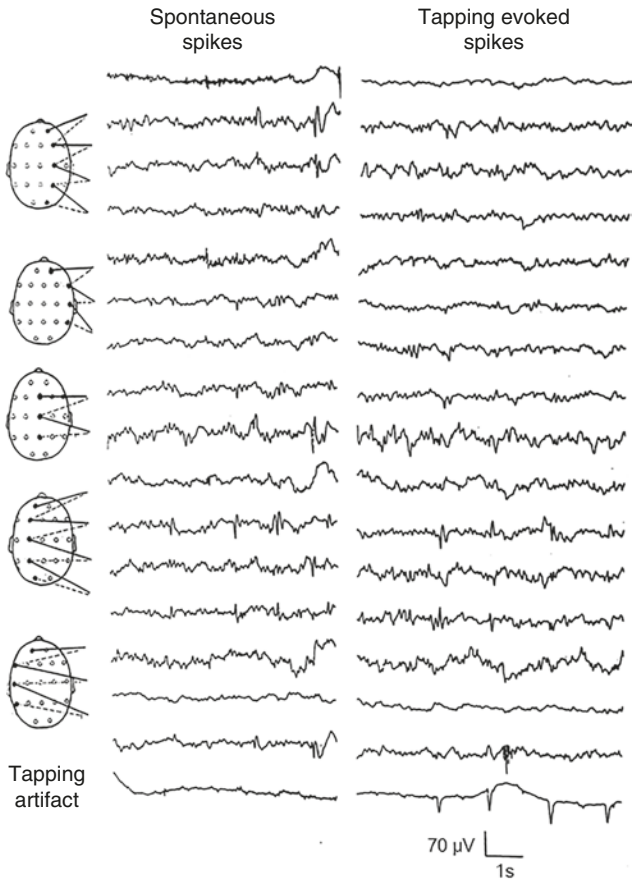

Fig. 25.12 Patients with ESEP showing spontaneous high-voltage spikes in the right centro-parietal and left centro-frontal and midline regions, asynchronously (left panel), and high-voltage spikes in the left centro-parietal elicited from the tapping on the right feet (right panel) *(Courtesy of Dr. Guido Rubboli)*

appear in the parietal and midline regions (same regions as ESEP), initially only during sleep (Fig. 25.12).

After 5 months to 2 years from the appearance of the spontaneous spikes, these patients have a few focal motor seizures (versive type), usually in clusters, mainly during wakefulness. Seizures might evolve to a generalized tonic-clonic phase or to status epilepticus and remit spontaneously after circa 1 year from their onset. ESEP and EEG abnormalities usually persist for several years. Accordingly with the idea of a spectrum, ESEP can be found also in patients with RE and BIMSE.

BIMSE was described by Capovilla and colleagues in 2000. The frequency of this condition is unknown, probably rare. The age of onset peaks between 16 and 20 months. All children have favorable outcomes, and the majority of them do not need to be chronically treated.

Seizure is sporadic, sometimes in clusters, and occurs mainly while awake. They are characterized by cyanosis, staring, and rare automatisms or lateralizing motor signs (duration 1–5 min).

The typical EEG pattern consists of spike followed by a bell-shaped slow-wave, localized in the mid-frontal regions, only present during sleep (Fig. 25.13) [40].

25.6 Non-familial and Familial Benign Infantile Seizures (Watanabe-Vigevano Syndrome)

Non-familial and familial benign infantile seizures (BIS/BFIS) represent a benign age-related idiopathic condition with focal seizures during early infancy, in otherwise normal infants [41, 42].

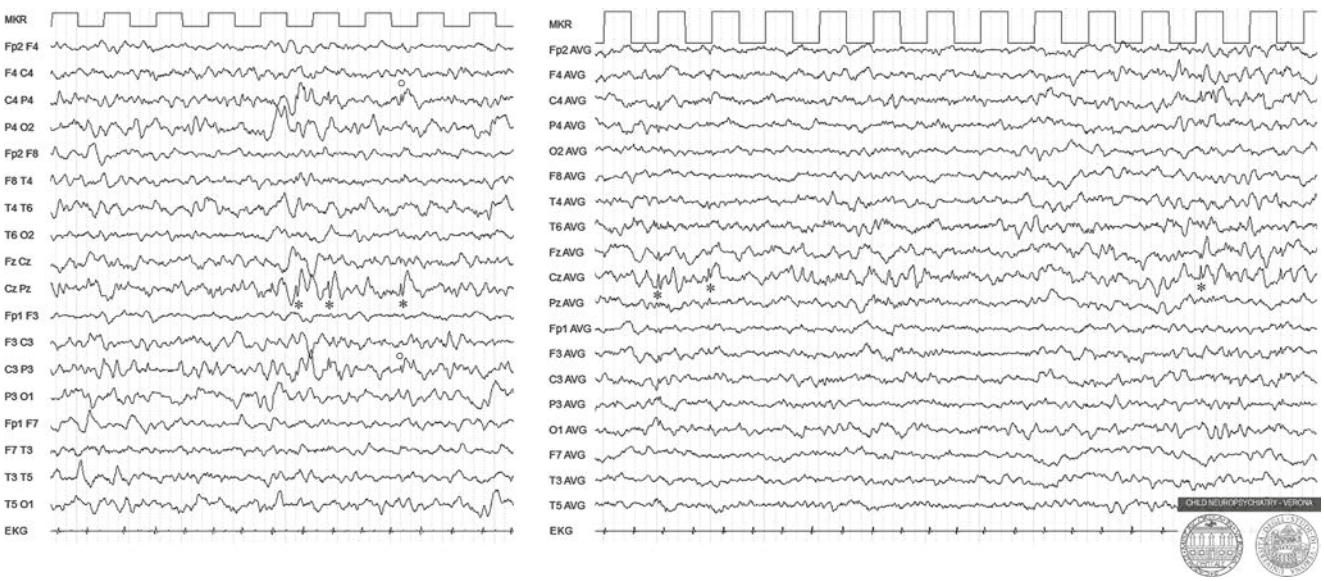

Fig. 25.13 Small spikes followed by a bell-shaped slow-wave, evident on the midline region (Cz-Pz channel, see asterisks), sometime with diffusion to centro-parietal channels of both hemispheres (circles). On the right panel are other examples of "Capovilla's spikes" (asterisks) in a monopolar average-reference montage

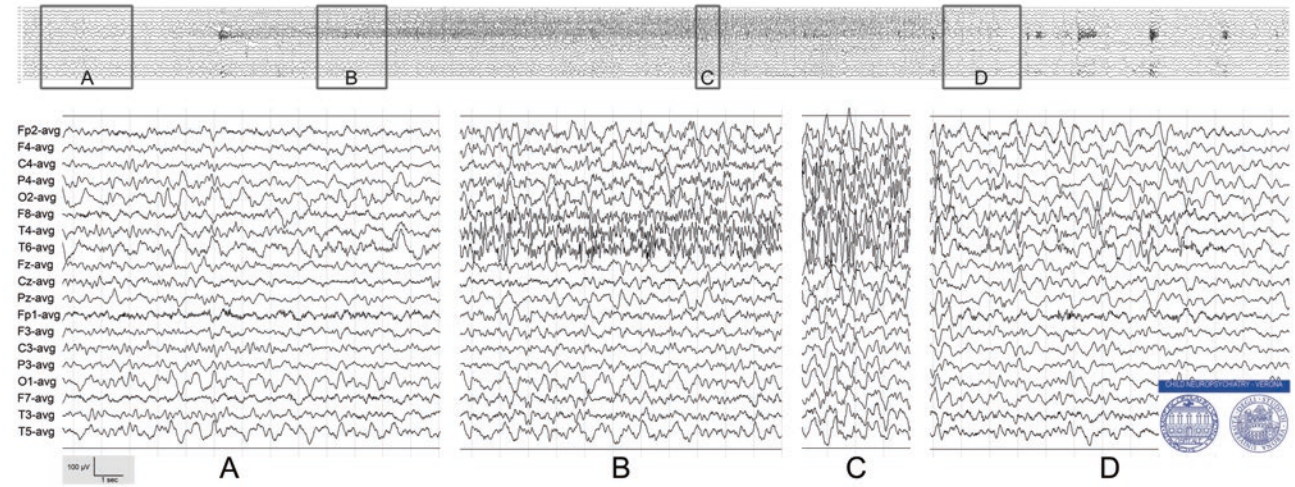

Fig. 25.14 A typical focal seizure in a patient carrying a mutation of PRRT2 gene, occurring during sleep. In the upper line is the entire evolution of the seizure, while in the lower line, four details are shown, corresponding to the four rectangles of the upper line and accordingly labeled. In (**a**) the seizure onset is visible as a low-amplitude fast activity on temporal region, superimposed to the slow background (arrowhead), increasingly becoming more evident over T6 (arrow); the paroxysmal discharge progressively involves all temporal channels (**b**), then the entire right hemisphere (**c**), ending within 3 min from seizure onset with a mild right hemisphere slowing (**d**)

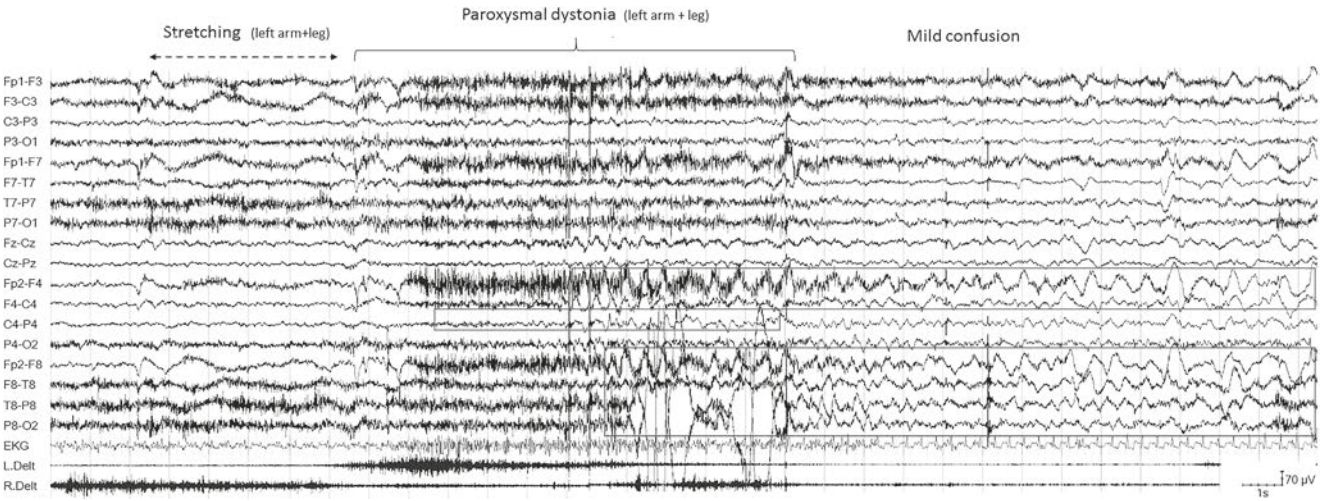

Fig. 25.15 This 14-year-old boy with BFIS developed brief but frequent episodes (several every day) of paroxysmal dystonia elicited by the abrupt onset of a voluntary movement or by stretching. He denied any impairment of consciousness during the episodes. Conversely, the video-EEG recordings documented a mild subconfusion during and after the episode of PD, together with an EEG correlate and a prolonged delta activity in the frontal regions, suggesting an ictal-cortical event. This further confirms the importance of ictal video-EEG recordings for the proper assessment of paroxysmal motor events in these patients [45]

Age of seizure onset ranges from 3 to 20 months (4–7 months in familial form). Seizures are predominantly diurnal in clusters for 1–3 days. The ictal symptoms are motor arrest/staring, eye and head deviation, simple automatisms and hemi-clonic jerks, and sometimes progression to a generalized tonic-clonic seizure. The seizures frequency is very low, and the response to anticonvulsive medication is prompt. A spontaneous seizure offset is expected before the age of 2 years.

About 20% of patients with BIFS might develop paroxysmal kinesigenic dyskinesia (PKD) after puberty; this combination of symptoms is called ICCA (infantile convulsions and paroxysmal choreoathetosis, [43]). Mutations in *PRRT2* have been identified as the major cause of BFIS and of ICCA [44]. Recently a causative association with *SCN8A* mutation, BFIS, and ICCA has been also described [45].

25.6.1 Interictal and Ictal EEG

The interictal EEG is usually normal. The ictal EEG is characterized by a variable side and site of onset (either frontal, temporal, parietal, or occipital), even among seizures of the same patient. EEG shows focal, low-amplitude fast activity, intermixed with spikes, with spreading to the neighboring areas or diffusely (Fig. 25.14).

The video-EEG recording of the episodes of PKD is rare; anyway these manifestations are generally assumed to be a subcortical event. Anyway, in a patient with SCN8A-ICCA, PKD turned out having an EEG correlate, suggesting an epileptic nature of the phenomenon is also possible (Fig. 25.15).

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Genetic Generalized Epilepsies

27

Aglaia Vignoli and Maria Paola Canevini

Genetic generalized epilepsies (GGE) are a cluster of epilepsy syndromes, diagnosed and classified according to clinical features and electroencephalographic (EEG) characteristics, the etiology has a known or presumed genetic defect, and seizures are the core symptom of the disorder.

Since hereditary predisposition seems to be the only identified cause of GGE, the ILAE Task Force on Classification has recently suggested to remove the term "idiopathic" from the International Classification and to replace it with the term "genetic," due to increasing recognition and discovery of the genes involved in many of these epilepsies, including those with monogenic (with inherited or de novo pathogenic variants) or complex (polygenic with or without environmental factors) inheritance [1].

The majority of GGE individuals are reported as sporadic, with no family history [2]. Indeed, this is consistent with complex inheritance believed to underlie GGE, so that different genetic mechanisms such as polygenic transmission, multifactorial etiology, and other factors have been encompassed. Mutated DNA sequences in genes encoding for ion channels or neurotransmitter receptors have been identified in GGE, but genotype-phenotype correlations are poor, arguing for additional factors determining the effect of a genetic predisposition, such as epigenetic factors [3].

In addition, several copy-number variants (CNVs) have been discovered to be associated to generalized epilepsies as risk alleles. The most frequently identified CNVs, each found in approximately 1% of GGE, are 15q13.3, 15q11.2, and 16p13.11 [4].

These syndromes, accounting for 15–20% of all epilepsies, are defined by an age-related onset and specific clinical features [5]. The most common electro-clinical syndromes recognized by the International League Against Epilepsy (ILAE) [1] are childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and generalized tonic-clonic seizures alone (GTCSa).

According to the current ILAE definition [1], GGE patients are required to be intellectually unimpaired, with standard magnetic resonance imaging (MRI) of the brain showing no abnormalities. Structural differences between GGE and healthy controls were observed only with volume detection techniques (reductions in whole brain and in other areas (especially in the thalamus-cortical networks)) [6].

The defining EEG characteristic of GGE is typical generalized, bisynchronous, and symmetric activity with spike-wave (SW) or polyspike-wave (PSW) discharges.

EEG research has focused on the origin of generalized SW discharges, as they remain a core sign of GGE. Many studies support the corticoreticular theory proposed by Gloor [7], which indicates that these generalized SWs could be generated by an interplay between the thalamus and a hyperexcitable cortex. Studies on animal models began to support the cortical focus theory [8, 9]. Recently, several EEG-functional MRI (fMRI) studies, EEG source analysis, MEG, PET, and TMS have suggested that generalized SW discharges and seizures have cortical onset and the thalamus has an essential role in the recruitment of the network comprising determine an activation in the frontal, parietal and occipital cortex and the default-mode network [10]. The involvement of thalamus-cortical networks, including frontal cortex, putamen, amygdala, and supplementary motor area (SMA), has been also demonstrated by functional connectivity studies [11, 12].

The diagnosis of GGE is based on clinical and EEG findings. The clinical criteria are:

– Seizure types: typical absences (TAs), myoclonic and generalized tonic-clonic seizures (GTCS) alone or in combination.

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– No etiologic factor could be found with the exception of genetic predisposition.

Besides, EEG criteria of GGEs are the following [13]:

– Normal background activity.
– Normal sleep organization with bilateral and symmetrical sleep patterns.
– Presence of interictal abnormalities such as generalized spikes, or polyspikes, generalized SW and PSW discharges at 3 Hz, or more.
– Increase of interictal abnormalities in slow sleep and no abnormalities during rapid eye movement sleep.
– Ictal discharges are generalized at their onset, bilateral, symmetrical, and synchronous.

In some clinical conditions, these criteria will not strictly apply:

– The background activity will be markedly slowed in the wake of a GTCS; such slowing may be found hours and in some cases days after the seizure.
– The ictal and interictal abnormalities are usually of higher voltage over the frontal and vertex areas; sometimes they can be slightly asymmetrical; however, whenever the discharges are irregular in their morphology or in their frequency, or are slower than 2.5 Hz, or constantly asymmetrical, the diagnosis of GGE must be reappraised.

Photosensitivity is not one of the core features of the syndrome; however during EEG, 20–30% of patients could present a photoparoxystic response, especially when at younger age and in the absence of therapy [14].

In adult patients interictal abnormalities may show an irregular morphology. Nonlocalizing abnormalities may occur, usually spikes over the fronto-central areas [13].

The occurrence of focal discharges constantly recorded in the same region should make the suspicion of a structural abnormality, as well as the hemispheric predominance of the discharges or its fragmentation during the evolution of the seizure.

The first EEG, ideally with video recording and performed before starting treatment, should be sufficiently long and include more than one hyperventilation (HV) session if needed. Sleep EEG recording should be recommended, and partial sleep deprivation the night before almost guarantees the natural occurrence of sleep and contributes to maximal activation in combination with the effects of drowsiness and light sleep, and of HV and intermittent photic stimulation (IPS), after provoked awakening. Basic EMG recording should be always required, with at least bilateral deltoid muscles and pneumogram, in order to demonstrate hesitation or interruption in breath effort and myoclonic jerks. All recordings should be individualized according to clinical information/questions [15].

27.1 Childhood Absence Epilepsy (CAE)

CAE is the most common type of childhood-onset epilepsy syndrome, occurring in neurologically normal children, between the age of 4 and 10 years, with a peak at 5–7 years. Girls are affected greater than boys [16]. Pathogenic variants of SLC2A1 leading to autosomal dominant GLUT1 deficiency account for up to 1% of cases, increasing to 10% of those with absence seizures starting before the age of 4 years [5].

The hallmark of the syndrome is the presence of TAs, characterized by sudden arrest of voluntary activities, although semi-voluntary preictal behaviors may persist for a few seconds after seizure onset. TAs usually last for 10–20 s and are typically associated with severe loss responsiveness. Staring or upward drifted eyes, with eyelid blinking, are common features. TAs may be associated with oroalimentary, gestural, or speech automatisms that are related to the duration of seizures, being present in up to 95% of those longer than 16 s [17]. Clonic movements of the eyelids or face, head turning, autonomic changes, and reduction of muscle tone can occur but are mild and do not persist throughout the seizure. TAs may be interrupted by sudden auditory stimuli (calling a child's name or clapping of hands). Offset is also sudden with resumption of the preictal activities as though the latter were never interrupted. There are no postictal symptoms [15].

GTCS are not expected early in the active absence phase. Their early occurrence may indicate a poor prognosis [18–20].

27.1.1 EEG Features

Background EEG activity is normal for age. In 13–20% of children with TAs, an occipital intermittent rhythmic delta activity (around 3 Hz) [21] (Fig. 27.1) can occur, which enhances with HV and sometimes evolves into the generalized SW discharges associated. This hallmark is related to a good prognosis, according to Loiseau [22].

The characteristic feature of the interictal and ictal EEG is a 3–4 Hz generalized symmetric SW discharge. Onset is bilateral synchronous, but regional (usually frontal or occipital), bilateral, or lateralized onsets are not infrequent, without a constant side in the same or subsequent recordings.

Centro-temporal spikes and waves similar to those usually recorded in children with benign epilepsy with centro-temporal spikes have been reported by Dalla Bernardina et al. in 14% of 119 children with TAs [23].

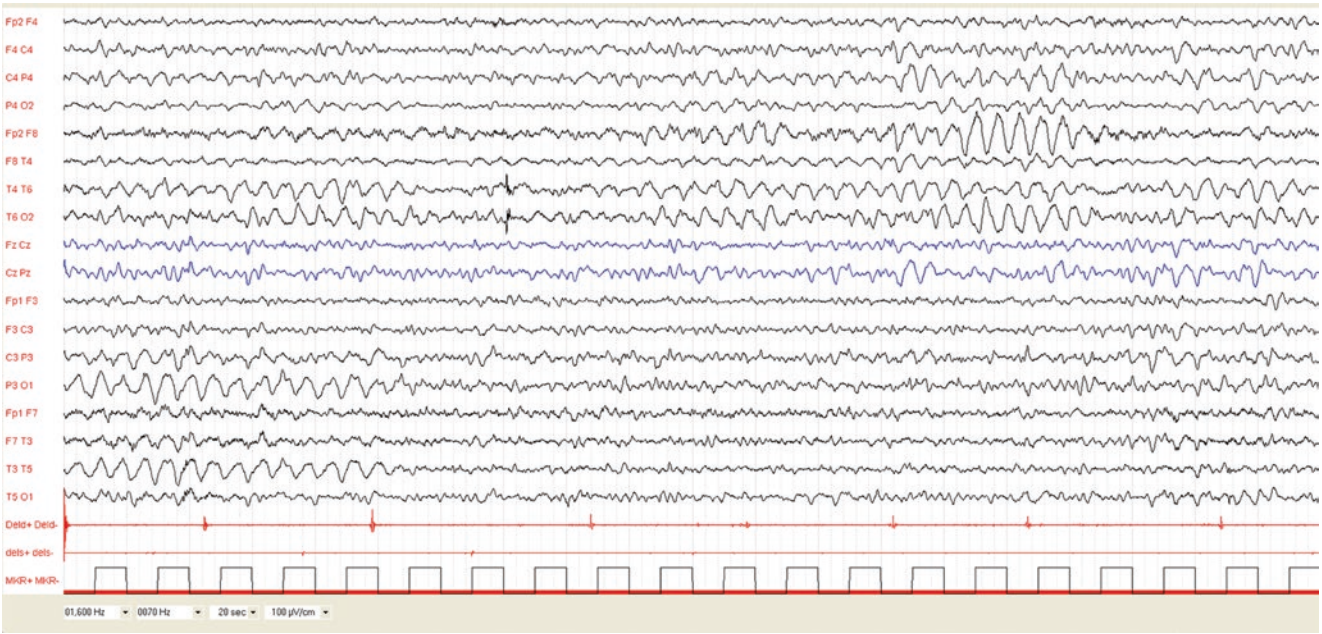

Fig. 27.1 Occurrence of trains of delta activity over the posterior region of both hemispheres, independently, in a 7-year-old girl with CAE

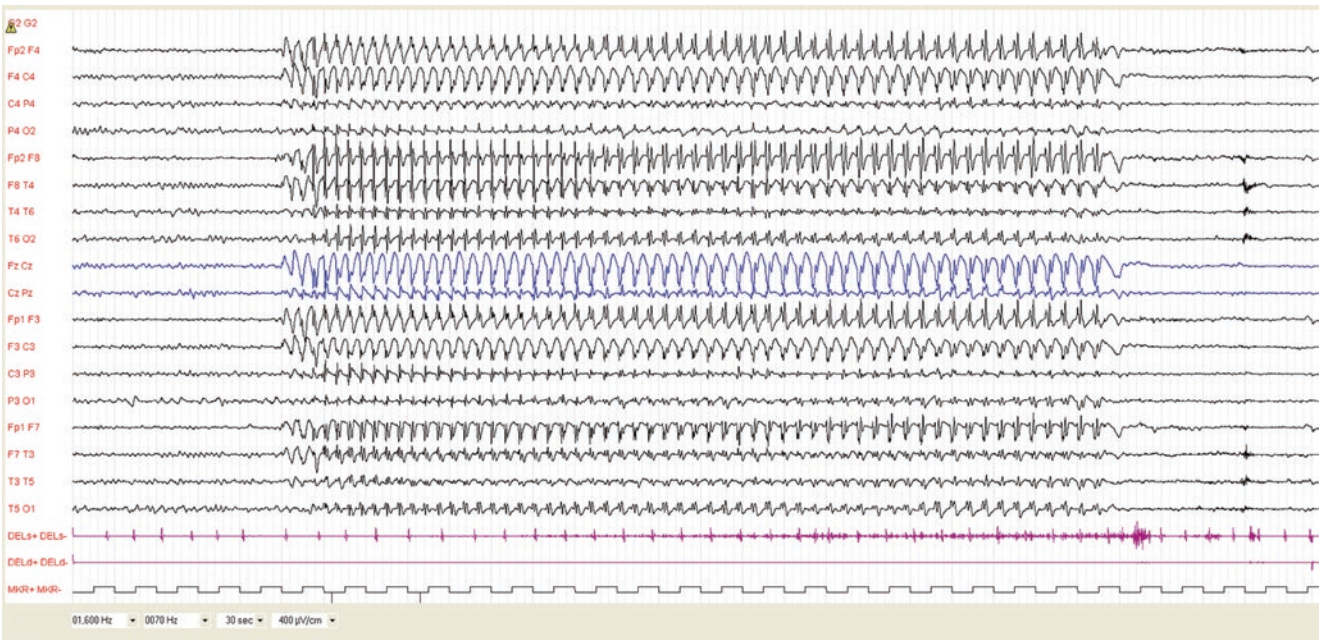

Fig. 27.2 Ictal recording of a typical absence seizure in a 5-year-old boy: 3 Hz spike and wave discharge lasts up to 20 s. Note the abrupt onset and end of the discharge. The boy does not answer to the acoustic stimulus (MRK) produced by the technician

In untreated children with CAE, absences are expected to occur during or immediately after HV. HV should be performed twice or more if the diagnostic suspicion of CAE is high.

Even though IPS can provoke TAs, nevertheless, when TAs are constantly related to IPS or specific visual patterns, CAE diagnosis cannot be performed [24, 25].

Sleep recordings show normal organization; paroxysmal discharges increase in frequency in NREM sleep (stages 2 and 3). Generalized SW discharges during drowsiness and sleep may be more frequent and brief than in wakefulness and may acquire a clear polyspike component, although less than in juvenile myoclonic epilepsy (JME).

Focal discharges may become more apparent during sleep [15].

EEG features of absence in CAE are shown in Figs. 27.2 and 27.3.

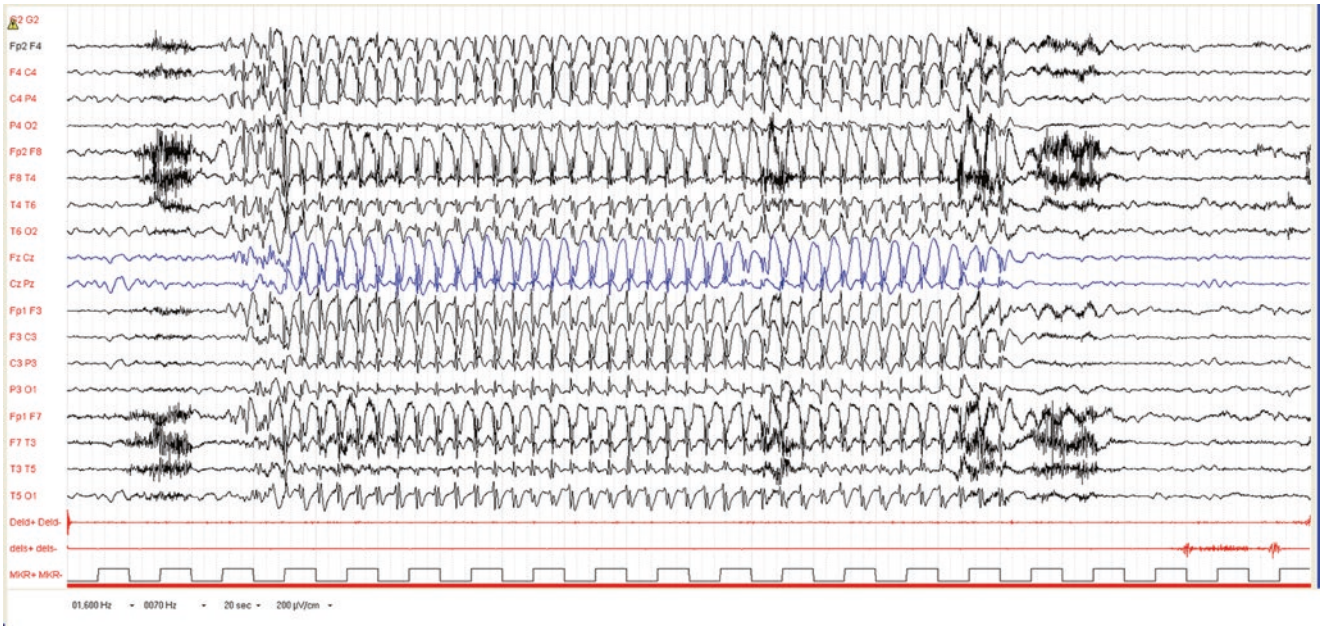

Fig. 27.3 Typical absence in an 8-year-old girl with CAE: the 3 Hz spike and wave discharge is preceded by bilateral spikes over the frontal regions

When absences continue in adulthood, generalized SW discharges tend to become irregular in their morphology, and, even when patients are correctly tested during the seizure, a complete loss of awareness cannot be clearly demonstrated. Adult patients with TAs generally report a sensation of dizziness or a vague woolliness in relation to the ictal event.

27.2 Juvenile Absence Epilepsy (JAE)

Age of seizure onset is usually around puberty (range 10–17 years with a peak at 10–12 years) [22]. Compared to CAE and JME, where a female preponderance is widely accepted, there are no sex difference in JAE [26].

A family history is frequent. Marini et al. [27] found a low phenotypic concordance within families with JAE (10%) compared to other GGE syndromes. Thirty-one percent of JAE relatives had CAE suggesting a close genetic relation.

The absences in JAE show the same characteristics of absences in CAE, but absences with retropulsive movements are less common, and often loss of consciousness is less pronounced than in CAE. The seizure frequency is lower than in CAE, with clinical absences occurring less frequently than every day, mostly sporadically. Clusters of absences at awakening are a possible occurrence. The majority of patients also have GTCS [28], and it may be that the diagnosis is often missed if absences are the only seizure type. The occurrence of GTCS often precedes absences more often than in CAE. Most frequently, patients experience GTCS at awakening [26].

Association with myoclonic seizures is more common than in CAE, probably of the order of 15–20% [29].

Few studies describe the clinical characteristics of seizures in JAE; in one video-based study [30] in three patients with JAE during absences, language functions were less rapidly abolished, consciousness was less severely impaired, and HV stopped later than in CAE.

In our personal series of patients with JAE, during absences awareness was only partially impaired and corresponded to an increasing latency between stimulus and response for discharges lasting more than 5 s [31].

It is not infrequent to record absence status in patients with JAE, precipitated by drug withdrawal or related to inappropriate treatment (especially carbamazepine) [32]. As in all GGE, other precipitating factors are sleep deprivation, abnormal lifestyle, and premenstrual period.

27.2.1 EEG Features

Background EEG activity is usually normal. The characteristic feature of the interictal and ictal EEG is symmetric generalized SW discharge, often prevalent on the frontal regions. The SW frequency is usually faster than 3 Hz (3.5–4 Hz), the first complex of a group sometimes being even faster. The slow wave could be preceded by two or three spikes. The generalized SW discharges could show fragmentation more than in CAE.

Sleep recordings show normal organization; paroxysmal discharges increase in frequency in NREM sleep and decrease in REM.

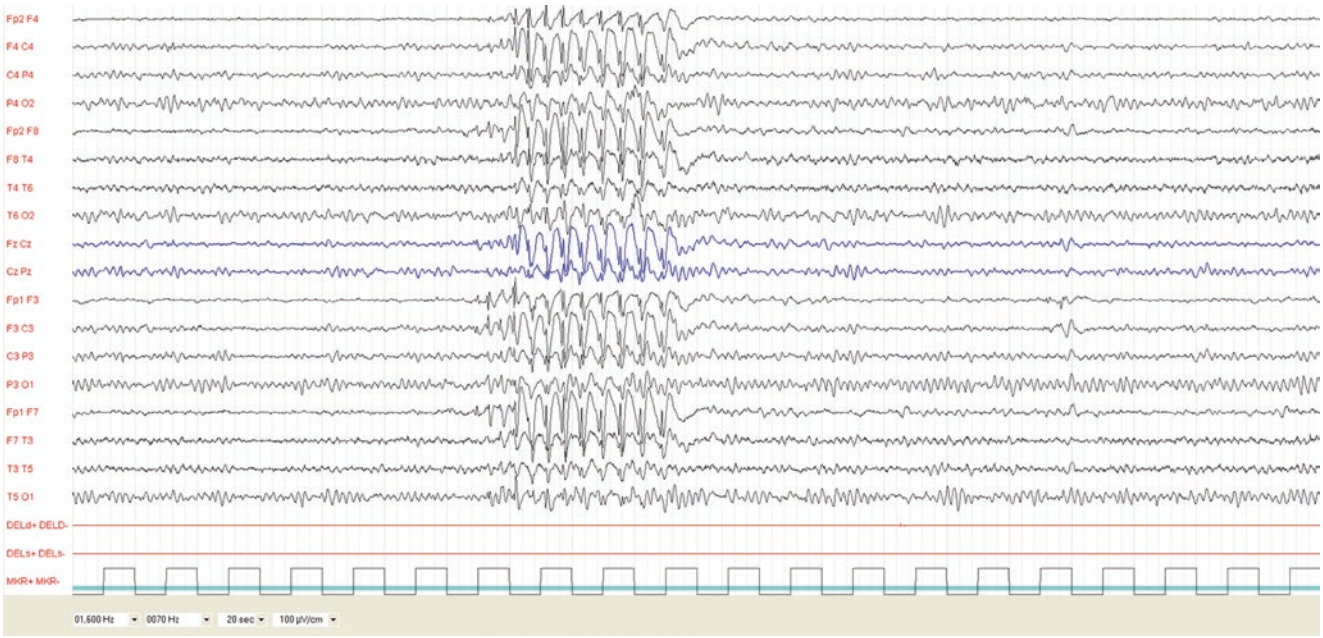

Fig. 27.4 Ictal discharge occurring during HV in an 18-year-old boy with JAE; note that absences are usually shorter than in CAE. At the onset of the ictal discharge, polyspikes followed by 3 Hz spike and waves

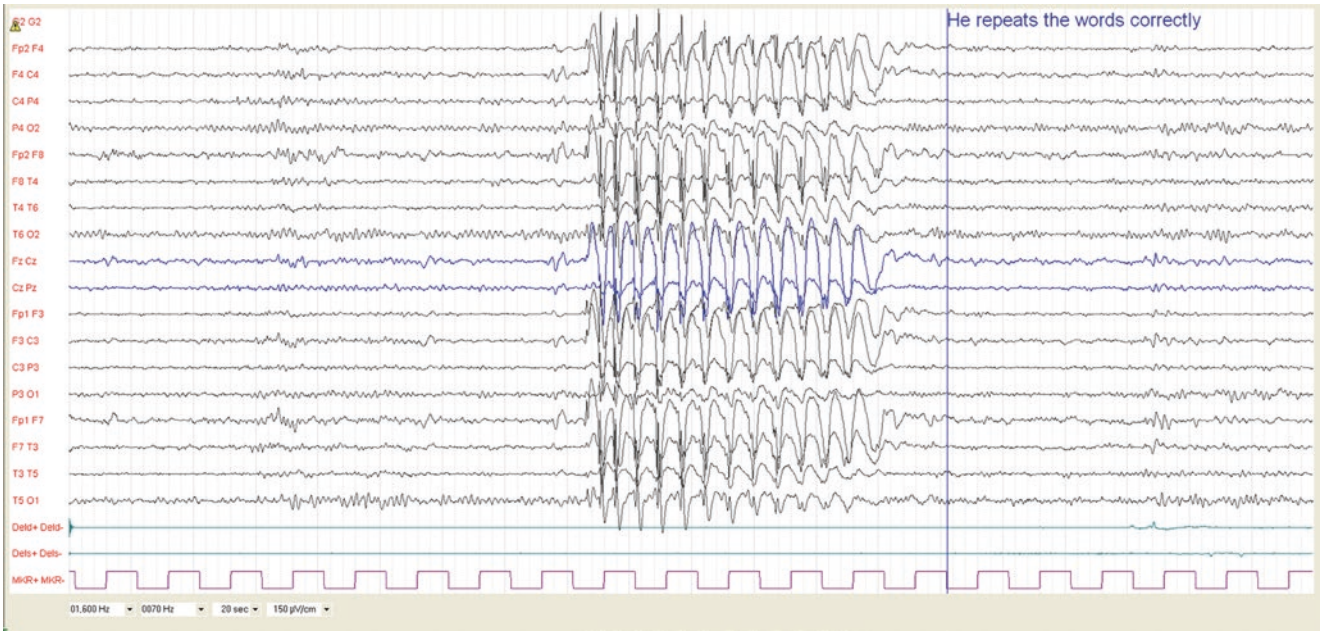

Fig. 27.5 Awareness can be preserved during absences in JAE, like in this 16 year old boy with 3 Hz ictal discharge with frontal predominance

EEG features of absences in JAE are shown in Figs. 27.4 and 27.5.

27.3 Juvenile Myoclonic Epilepsy (JME) (Janz Syndrome)

JME has been described by Janz and Christian in 1957 [33].

JME is a very common form of epilepsy (5–10% of all epilepsies) and one of the most frequent forms of GGE [34]. A family history of epilepsy is found in one third of cases. From a genetic point of view, though, JME appears very heterogeneous. Two main susceptibility genes (GABRA1 and EFHC1) and many other genes have been found in families with JME, and microdeletions in 15q13.3, 15q11.2, and 16p13.11 also contribute risk to JME, but research is still ongoing [35].

The seizure onset is clearly age-related, with a range between the ages of 8 and 26 and a mean age of 14. Even if JME has an equal sex distribution, myoclonic jerks occur sooner in girls than in boys, which can reflect different hormonal developments.

In the most typical cases, patients are usually referred following the first GTCS, which had been preceded by isolated jerks for several months. This first major seizure could be precipitated by provoking factors (e.g., sleep deprivation) [36]. When accurately investigated, the patients report that after waking up in the morning, they experience unprovoked jerks, mainly in the upper limbs, causing them to drop whatever they hold (generally the coffee cup, the toothbrush, or the razor). The jerks can present in clusters with an increasing course; sometimes they can escape to the attention of onlookers, but they can also make the patient fall, without loss of consciousness [37].

In the majority of patients, myoclonic jerks predominate on the upper limbs, grossly symmetric, even if they can be felt to be asymmetric or unilateral [38] or their amplitude can be dependent on the degree of tonic contraction of the arm involved (patients often report that jerks affect prominently their dominant limb) [36]. Myoclonic jerks infrequently involve the lower limbs, causing a sudden fall, after which the patient promptly recovers his balance [33].

Myoclonic jerks can be precipitate by lack of sleep and sudden provoked awakening, excessive alcohol intake and, in some patients, photic stimulation, eye closure [38, 39], and poor adherence to antiepileptic drugs [40].

Mental tasks that imply manual activity and decision-making may also trigger seizures, evoking a relationship between JME and certain reflex epilepsies [41] and can be attributed to hyperexcitability of distinctive brain networks [42].

Rarely myoclonic jerks occur in status with a full preservation of consciousness, being facilitated by acute drug withdrawal or by intake of inadequate drug (see below).

Most patients (80–95%) present myoclonic jerks and rare GTCS, which usually follow a longer series of jerks, with increasing amplitude and frequency, until myoclonic jerks melt into the initial tonic phase of the GTCS (Fig. 27.6). GTCS are not very frequent in the natural course of JME (one or two per year), but they can cluster over a short period during adolescence. They may be invalidating in noncompliant or mistreated patients, especially when lifestyle is grossly abnormal [36].

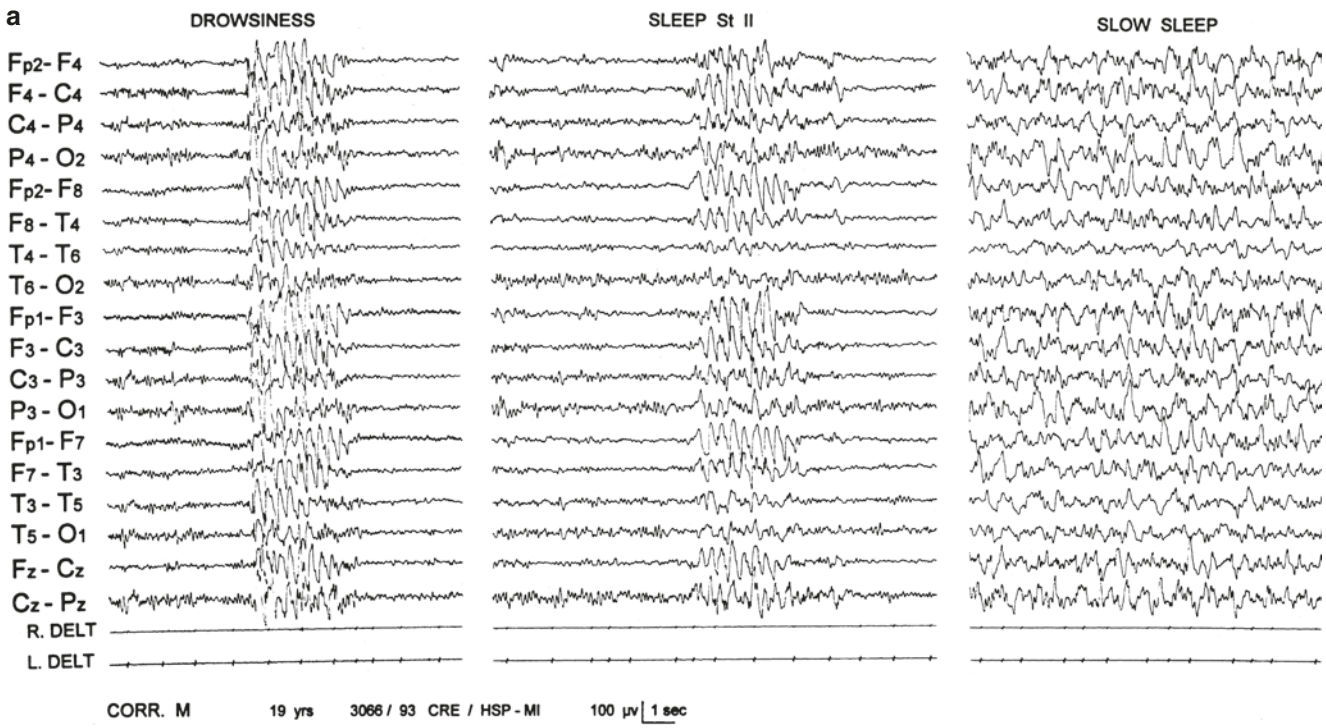

Fig. 27.6 A 19-year-old patient with JME. EEG recording after sleep deprivation. Panel (**a**): during drowsiness and sleep stage 2, sharp and slow wave discharges without clinical correlate. During slow sleep, rare slow abnormalities intermingled with slow background activity. Panel (**b**): 15 min after awakening myoclonic jerks at upper limbs, both at rest and during HV. Panel (**c**): After the myoclonic jerks, ictal recording of a generalized tonic-clonic seizure. EEG showed sharp and slow wave complexes at 3.5 Hz. Panel (**d**): EEG showed fast spike activity at 10 Hz, correlated to the tonic phase of the seizure; after 75 s from the onset, sharp wave discharges associated to the clonic phase of the seizure. Panel (**e**) At the end of the seizure, diffuse slow activity which progressively disappeared

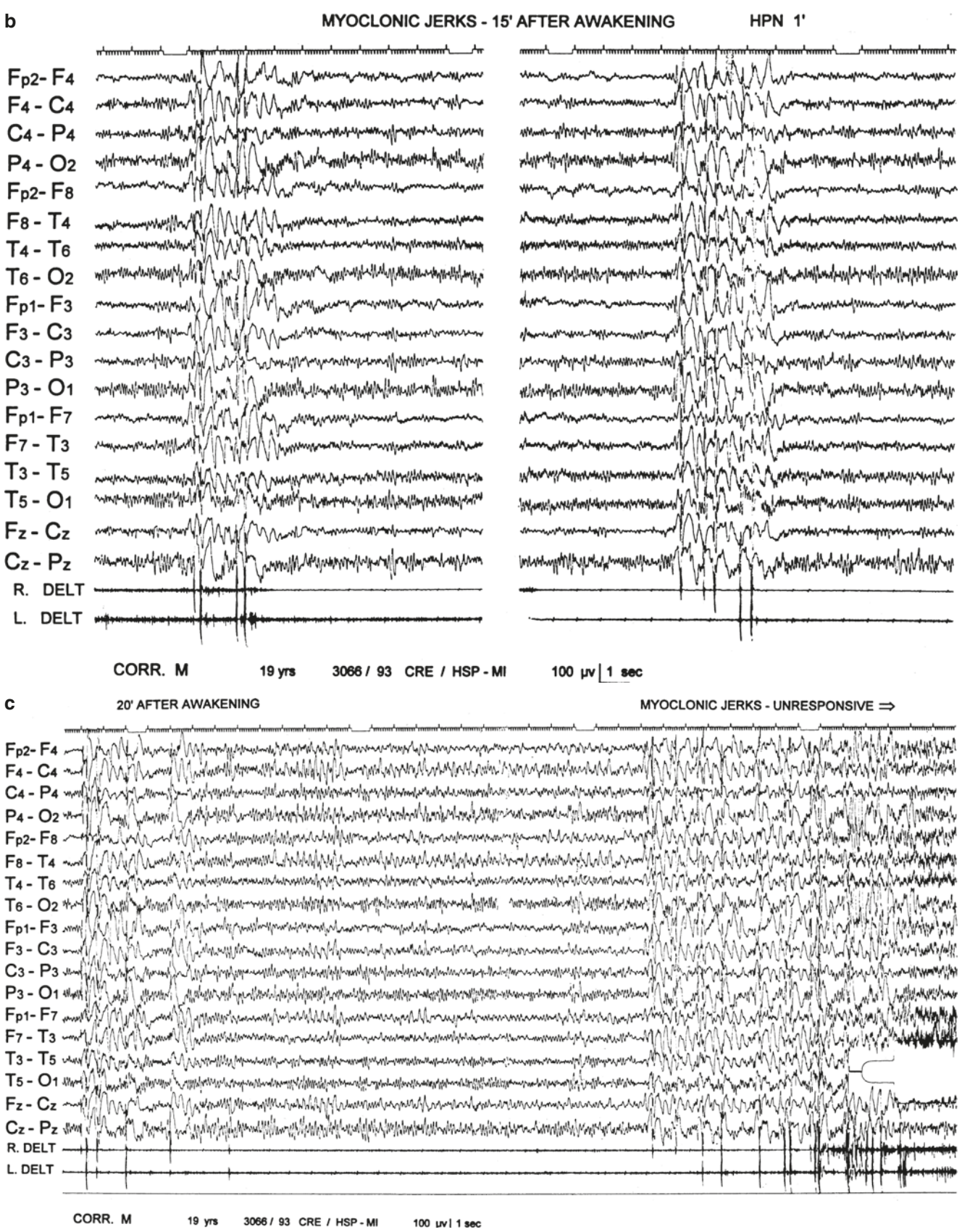

Fig. 27.6 (continued)

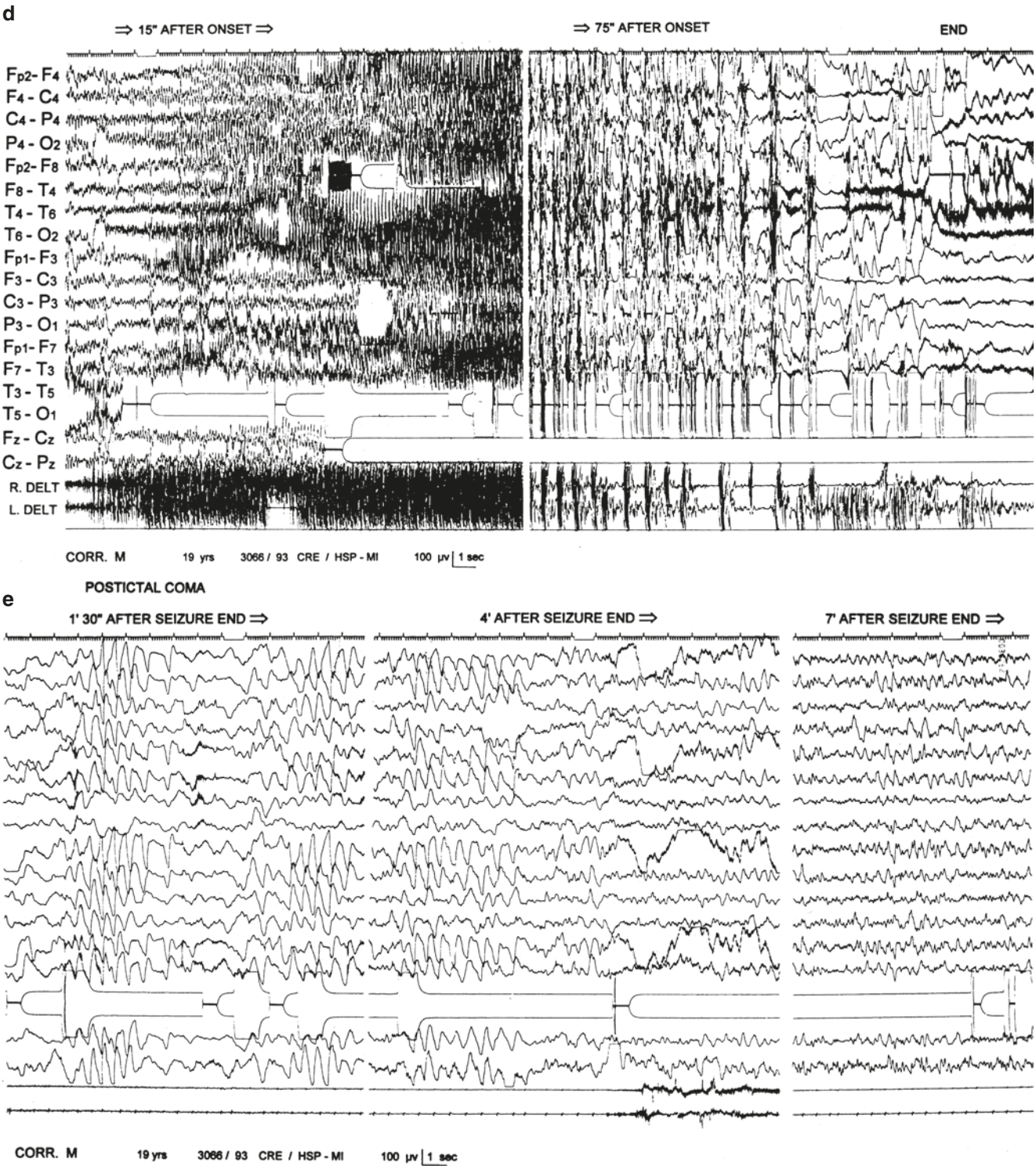

Fig. 27.6 (continued)

Asymmetric semeiological features, such as asymmetric myoclonic jerks and asymmetric evolution of GTCS, can be observed [43].

Patients with JME may also experience TAs with mild impairment of consciousness, as found in JAE [44].

27.3.1 Neurophysiology

Diagnosis of JME should be confirmed by an ictal recording, easily obtained by polygraphic video-EEG performed after a nocturnal sleep deprivation, before starting treat-

ment. The characteristic EEG trait is bilateral, synchronous, symmetric PSW discharges, that precede (about 20 ms) a myoclonic jerk recorded on polygraphic surface EMG deltoids. The amplitude of spikes is typically increasing and is maximal over the frontal areas (Fig. 27.7). Slow waves often precede or follow the polyspikes, resulting in a PSW complex that lasts longer than myoclonic jerks, around 2–4 s. The number of spikes appears to be correlated to the intensity of the jerks [36]. Back averaging of myoclonic jerks shows the characteristics of cortical myoclonus [45].

Interictal EEG recordings show normal background activity during wakefulness and sleep. Interictal generalized PSW may have anterior prevalence. Focal epileptiform discharges can be detected in the course of the disease [46].

In 30% of JME patients, especially in females, IPS determines PSW discharges sometimes associated with myoclonic jerks. This photosensitivity provoked in EEG laboratory in most of the cases does not correspond to a clinical problem in natural ambience.

27.4 Epilepsy with Generalized Tonic-Clonic Seizures Alone (GTCSa)

Although the clinical characteristics of this syndrome are not broadly described yet, this epileptic syndrome has been considered even in the new classification [1]. Epilepsy with GTCS alone includes the previously called "epilepsy with grand mal on awakening" (EGMA) listed in the 1989 classification besides other forms of IGE with GTCS, even if less well-defined entities.

Range of epilepsy onset is between ages 9 and 24 years, with a peak around puberty.

A slight male preponderance has been reported in some series [47], but sex distribution seems to be equal.

There is a family history of febrile convulsions and epilepsy [48].

Main seizure type is GTCS, but many patients have in addition minor generalized seizures, either absence or myoclonic or both, which can precede or follow the convulsive seizure. Seizure frequency is generally low [49].

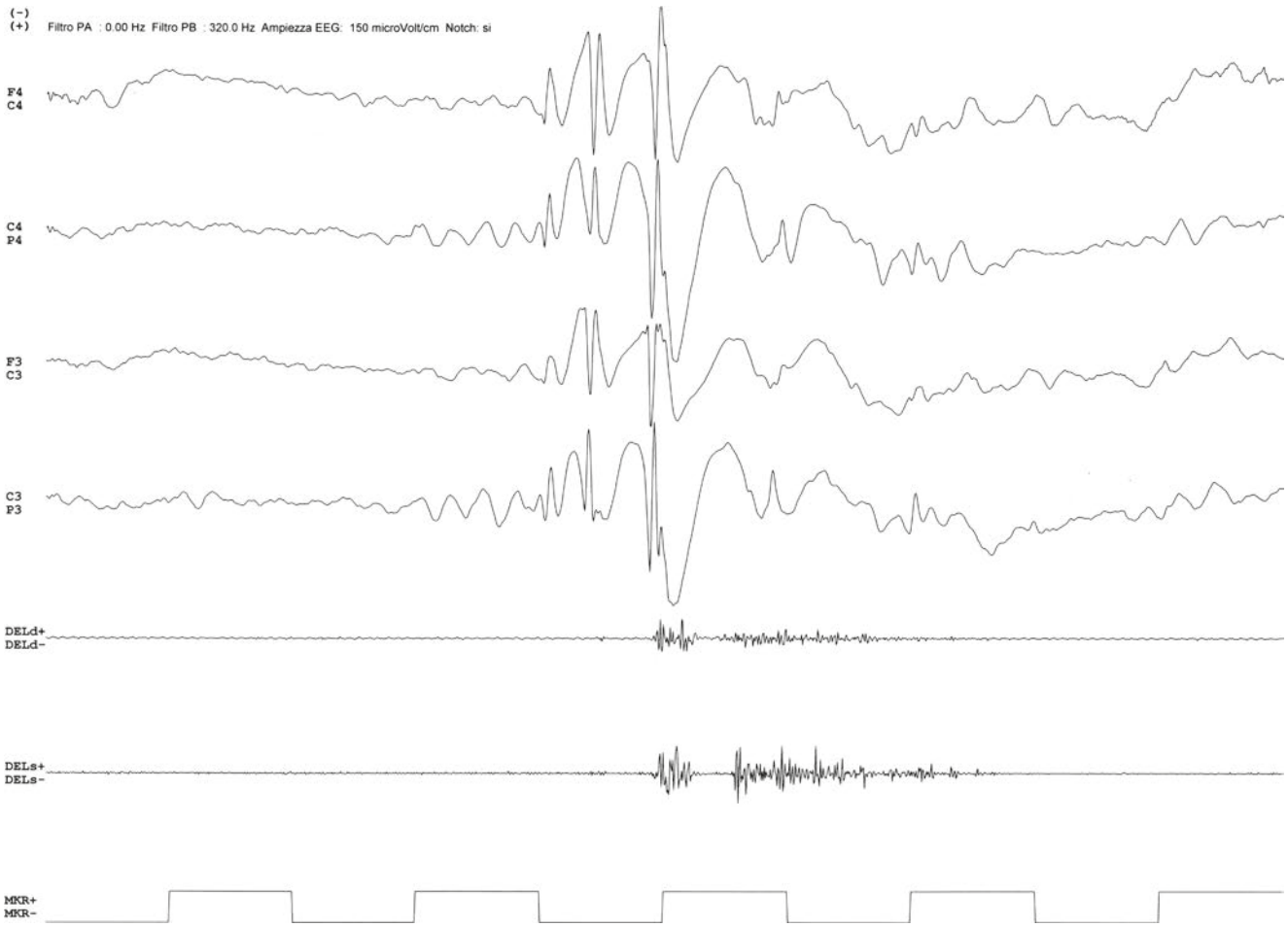

Fig. 27.7 Polyspike-wave discharges have a prominent amplitude on bilateral frontal regions. The polyspike component is related to the occurrence of myoclonic jerks

The clear majority of seizures in GTCS alone occur either in the 2 h after awakening (regardless of the time of the day) or in the second peak, during the evening relaxation phase [50].

EEG characteristics include occurrence of generalized SW and PSW activity. In order to confirm the diagnosis, since routine EEG can be uninformative, sleep-deprived recordings increase the opportunity of SW/PSW detection. It is recommended to provide a registration that includes awakening from a sleep period, where SWs are more probably be recorded. Focal abnormalities are extremely rare. In contrast with focal syndromes with convulsive seizures during sleep, GTCS alone is one of the epileptic syndromes that are related to photosensitivity.

27.5 Eyelid Myoclonia with/Without Absences (EMA) (Jeavons Syndrome)

The 2010 revised ILAE Report on Terminology and Classification recognized an additional type of absence seizures characterized by special features: eyelid myoclonia with absence (EMA) [51]. These seizures have been reported also in the recent ILAE classification of seizures [52], but a distinct syndrome has not been identified among the epilepsy syndromes [1]. Indeed, patients with EMA show very peculiar seizure features, which deserve a distinct description.

Moreover, recent studies demonstrated that the clinical genetics of EMA is suggestive of complex inheritance with shared genetic determinants overlapping with both classical GGE and GEFS+ [53].

Seizures in EMA are characterized as prominent jerking of the eyelids with upward deviation of the eyes, often triggered by eye closure, and retropulsion of the head. Impairment of awareness may be brief and subtle. Independent absence or myoclonic seizures may occur in some patients, triggered by HV or IPS or even spontaneously. Onset occurs in childhood (peak 6–8 years), with a female predominance (M:F = 1:3–4) [15].

The ictal EEG pattern for EMA has been described as 3–6 Hz generalized PSW complexes with occasional paroxysmal bursts in the occipital regions, which can precede the generalized discharges [54] (Fig. 27.8). It is unclear whether Jeavons syndrome should be classified as a type of absence epilepsy or as a myoclonic epilepsy, given its prominent eyelid myoclonia.

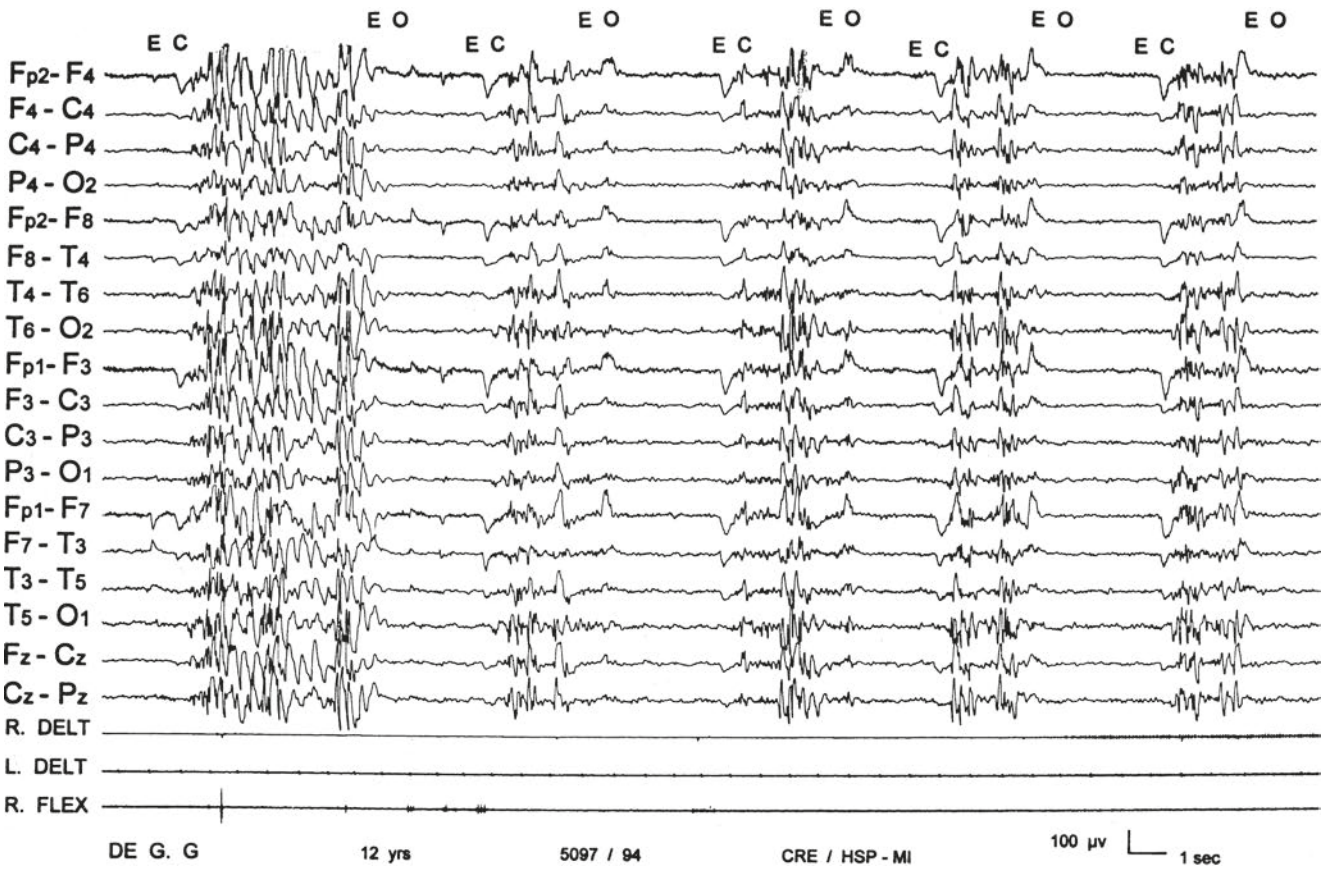

Fig. 27.8 Eyelid myoclonia without absence in a 12-year-old girl. Note that the discharge is characterized by polyspikes occurring at eye closure (EC), which disappear at eye opening (EO)

EMA can occur both in genetic and in symptomatic epilepsies. The genetic form is referred to as Jeavons syndrome, and EMA in this syndrome usually occurs following eyelid closure; all patients are photosensitive [39].

The distinctive feature of seizures in EMA has been recently studied by fMRI: alterations of the anatomo-functional properties of the visual system were demonstrated, involving a circuit encompassing the occipital cortex and cortical/subcortical systems physiologically activated in the motor control of eye closure and eye movements [55].

The outcome and prognosis for Jeavons syndrome is poorly understood. There is some evidence that GTCS, either light-induced or spontaneous, will occur in most patients over the long term [56]. Jeavons syndrome is thought to be a lifelong disorder, resistant to medical treatment [53].

27.6 Lifestyle and Drugs Can Influence EEG in GGE

In patients with GGE, lifestyle recommendations are mandatory: the sleep-wake rhythm must be regulated, and circumstances that can interfere with normal sleep and cause precocious awakening in the morning should be avoided. Alcohol intake should be restricted and permitted only in small quantities.

Even if easily controlled by AED therapy in most cases, JME should be considered a lifelong condition since relapses are very common after drug withdrawal, and only a third of the patients can remain off medication [33].

Choosing the appropriate drug can be challenging in patients with GGE; although valproate is still considered the drug of choice in JME, it should be possibly avoided in women in childbearing potential. Levetiracetam can be a therapeutic option in these patients [57], together with topiramate [58] and zonisamide [59].

The use of lamotrigine in JME is still controversial, as worsening in seizure frequency and severity has been reported with this drug, as well as with carbamazepine and vigabatrin, which can increase the occurrence of jerks and of subclinical interictal discharges.

27.7 Conclusion

In order to distinguish GGE from other forms of epilepsies, strict clinical and EEG criteria have been proposed by the ILAE classification; however, clinical experience shows that these criteria are not fulfilled by all patients all of the time. Epileptic conditions considered as representative of GGE are a heterogeneous group, and their clinical and EEG correlates may vary slightly, due to many factors, such as age, interfering drugs, time of the day, and state of vigilance.

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Febrile Seizures and Febrile Status Epilepticus

30

Nicola Specchio and Giusy Carfi' Pavia

30.1 Introduction

Febrile seizures (FS) are nosological entities that affect 2–5% of children aged 6 months to 5 years [1, 2]. In most cases, these seizures are isolated or sporadic, of short duration, and with no focal semiological features; in such cases they are defined as simple febrile seizures. However, a febrile seizure that lasts more than 15 min, which has focal signs, or that recurs within 24 h is defined as "complex" febrile seizure [2, 3]. Prolonged febrile seizure (PFS) is therefore a particular type of complex febrile seizure. PFS are events that last more than 10–15 min (there is debate about which is the cutoff to be considered): according to some authors, it would be more appropriate to consider 10 min, but for the risk assessment of status epilepticus or response to treatment, 15 min seems a most appropriate benchmark [4, 5]. In case the duration exceeds 30 min, the more appropriate definition is febrile status epilepticus (FSE). FSE occurs in approximately 5% of children with ongoing febrile seizures and in about 25% of all status epilepticus in childhood. There are reports concerning the possible association of PFS/FSE and hippocampal lesions, which might justify the subsequent onset of temporal lobe epilepsy [6].

30.2 EEG in FS and FSE

Electroencephalogram (EEG) is not indicated in the routine evaluation of simple febrile seizures; on the other hand, the role of EEG in children with complex febrile seizures including febrile status epilepticus is not well-known [7]. One of the most remarkable findings in EEGs done within 1 week after febrile status epilepticus is focal slowing. The acute EEG findings after prolonged febrile seizures reveal abnormal activity in at least one third of cases across different series. Usually what is seen in those cases is slowing of background activity with wide amplitude over bilateral posterior regions (Fig. 30.1). Even if it has been estimated that about one third of patients with prolonged febrile seizures might develop epilepsy in the future, this has not been correlated with the presence of slowing at EEG, which therefore do not confer any added risk.

In old series it has been reported that focal slowing at EEG might be of added value in predicting the subsequent development of epilepsy [8] even if this is not completely clarified [9]. Moreover, in both reported series, the follow-up was limited to less than 5 years (Fig. 30.2).

Regarding the possible association with temporal lobe epilepsy, it is likely that the previous mentioned series had no sufficient follow-up in order to ascertain whether an initial abnormal EEG was predictive of subsequent temporal lobe epilepsy [10].

The FEBSTAT study [11] is a multicenter study that is prospectively identifying children with febrile status epilepticus. The children have both an MRI and EEG along with additional studies performed at baseline and at 1 year as well as if they develop epilepsy and are being followed long term. These EEGs are being interpreted by two readers blinded to the clinical histories and outcomes.

Consensus is reached on the findings in all studies. Early findings [12] confirm that focal slowing is a common finding with a frequency similar to that reported in the older series. Correlations between EEG findings and the MRI as well as the long-term outcomes are inconsistent. The study is adequately powered to eventually address the question of the relationship between prolonged febrile seizures and subsequent mesial temporal sclerosis and mesial temporal lobe epilepsy as well as the predictive value of the EEG for short- and long-term outcomes. The physiological mechanisms underlying the slowing are unknown.

A small portion of children at the age of 3 years and below with EEG was recorded soon after a febrile status epilepticus

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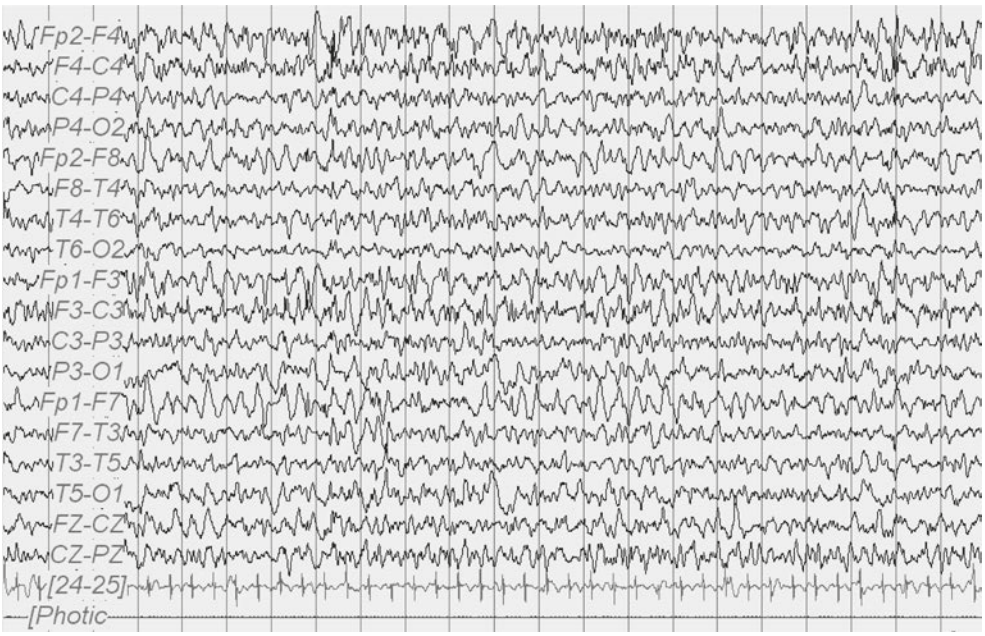

Fig. 30.1 Post-ictal EEG in a patient with complex febrile seizures (buccal midazolam was administered 30 min before the EEG). Background activity is slightly slow. Over frontal and fronto-temporal left regions some theta-delta waves are evident

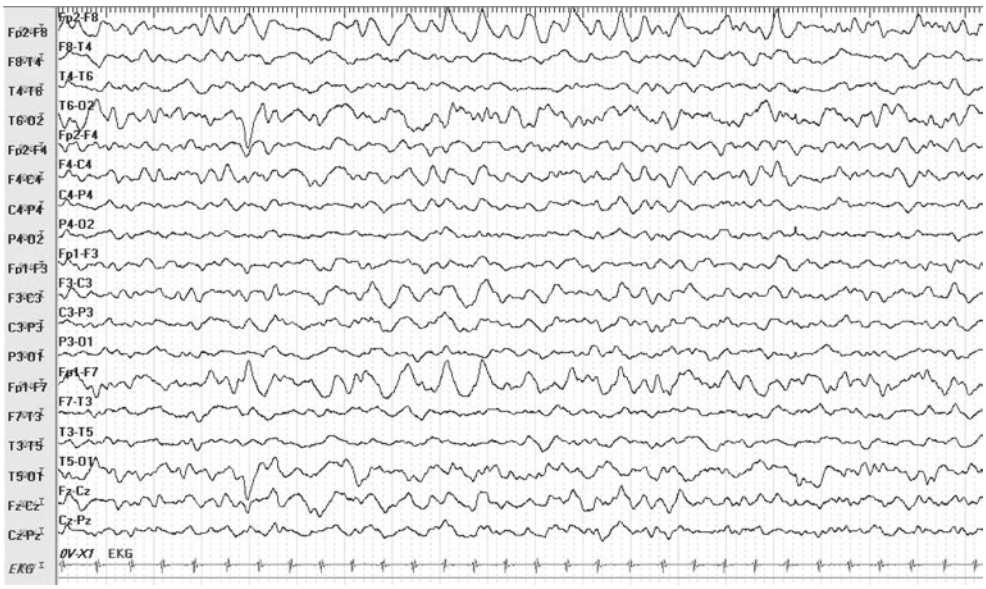

Fig. 30.2 Post-ictal EEG of a patient with simple febrile seizure. Rare slow waves are evident over frontal bilateral regions

revealed epileptiform discharges [13]. The clinical significance of these interictal epileptiform discharges is not clear. According to Yucel et al., detection of epileptiform activity is less common in the first week following the prolonged febrile convulsion [14]. The most common type of epileptiform activity to observe in the older children are bursts of generalized spike-wave discharges, although an association with centrotemporal spikes has also been noted [15]. Frantzen et al. reported that generalized spike-wave discharges did not usually appear in the acute EEG, but were found on follow-up, on average 16 months after the febrile convulsion [9]. It is possible that the occurrence of spikes indicates a genetic susceptibility. The long-term value of the early EEG findings after prolonged febrile seizures is not yet known, but the data so far suggest that the focal slowing is not associated with pre-existing focal structural lesions since it is only present for a short period of time. These data suggest that it might be important to correlate the findings with experimentally induced febrile status [16]. The precise relation between the focal slowing and epilepsy is uncertain. Studies to date were underpowered and lacked sufficient follow-up to rigorously assess the risk of focal slowing for the development of epilepsy. In addition the best studies were performed decades ago, long before the advent of MR, so the relationship with

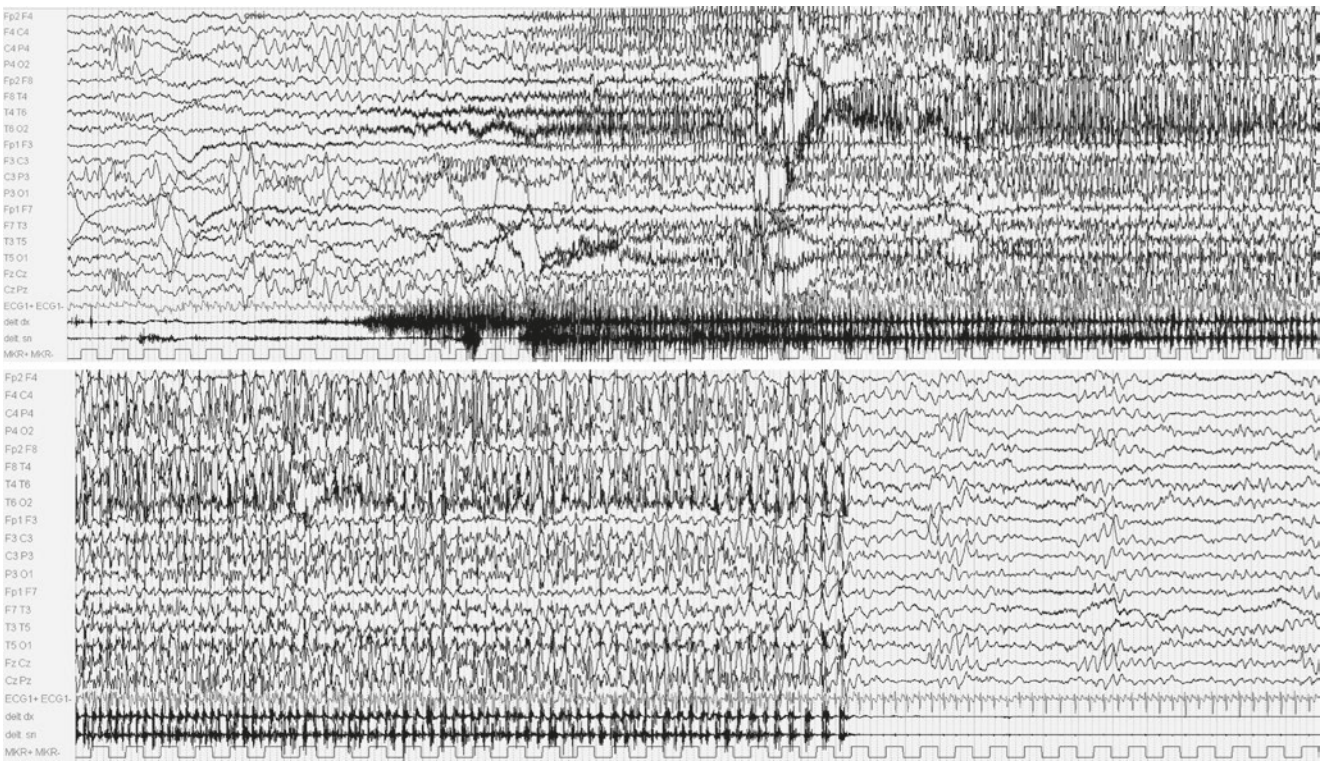

Fig. 30.3 EEG counterpart of a simple febrile seizure in a 2 years old patient. The EEG shows a diffuse attenuation of cerebral activity followed by repetitive spikes more prominent over left frontal region. The EMG trace show a bilateral hypertonus at beginning followed by clonic jerks

mesial temporal sclerosis, if any, is undetermined. Completion of existing prospective clinical studies, refinement of the existing animal models for febrile seizures to better match the clinical characteristics observed in children, and correlation between the two may help to accelerate our understanding of this very interesting phenomenon. Figure 30.3 shows an ictal recording of a simple febrile seizure.

30.3 Other Conditions with Seizures Induced by Fever

Febrile infection-related epilepsy syndrome (FIRES) is a catastrophic epileptic encephalopathy with refractory status epilepticus (SE) in developmentally normal children [17] without a diagnostic biologic marker. FIRES is characterized by the development of seizures in healthy children few days after a short febrile illness that rapidly exacerbated into a SE or a cluster of seizures, followed by a chronic drug-resistant epilepsy and cognitive function deficit [18].

Since most of the patients presented with seizures immediately following a febrile episode, an autoimmune mechanism has been considered. Different antibodies have been investigated in patients with FIRES with negative results; therefore up to now there are no evidence to support that autoantibodies are the etiology of FIRES. Furthermore, poor response to immunotherapy has been reported. FIRES is likely to represent an immune-inflammatory-mediated epileptic encephalopathy rather than an autoimmune process [19]. The syndrome invariably begins with a febrile illness, most commonly a minor upper respiratory tract infection or a gastroenteritis; fever during the infectious illness is sometimes low grade or absent (with a median duration of 4 days); in about half of the patients, it disappears at the time of first seizure occurrence [20] in contrast to febrile seizures and febrile status epilepticus. The clinical course of this disorder is typically biphasic with an initial acute catastrophic phase followed by a chronic refractory epilepsy phase.

After the onset, seizures rapidly became frequent or exacerbated into SE showing resistant to treatment with a variety of antiepileptic drugs (AEDs). It is not uncommon for children with FIRES to have hundreds of seizures a day during the acute phase. Seizures are focal (simple motor with facial twitching or complex partial seizures with lateral deviation of the head, chewing movements, and some autonomous features, suggesting a mesial temporal lobe involvement) with a strong tendency to become bilateral tonic-clonic. Also,

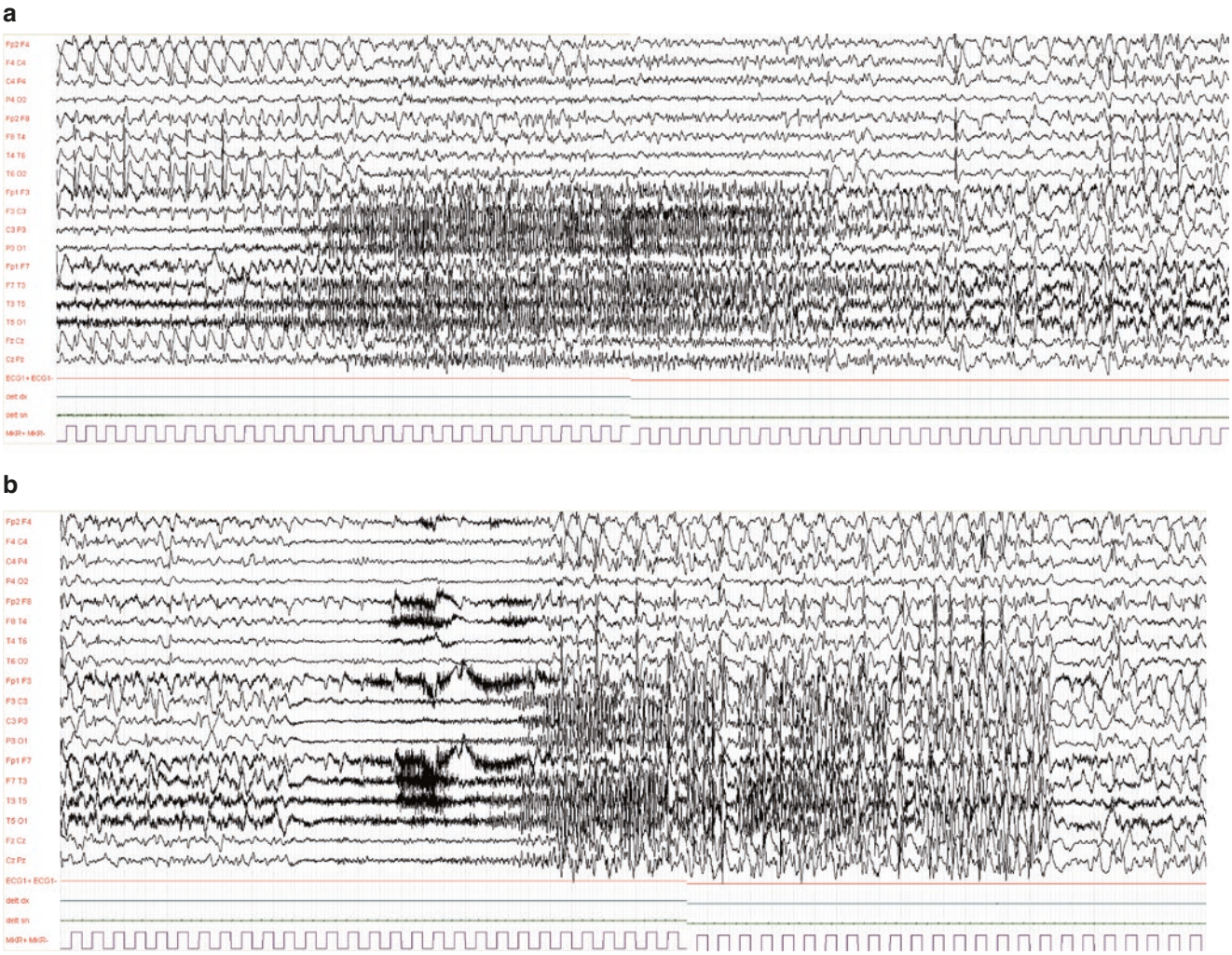

Fig. 30.4 Ictal EEG during a status epilepticus in a 4 years old patient with FIRES. Seizures are brief but subsequent. (**a**) On the right hemisphere there are spikes and spikes and waves discharges as last part of a previous seizure. At the same time a new seizure is staring on the left hemisphere characterized by repetitive spikes over left fronto-temporal region. (**b**) Seizure ends abruptly and after few seconds one more ictal clinical discharge is evident on the same side

myoclonic seizures of facial and oro-buccal muscles have been reported. Consciousness is decreased, including the interictal period. The duration of this acute phase is variable. It can last from a few days to several months. Usually no patient had neurological features other than seizures during the acute phase of illness. Ictal and interictal electroencephalography (EEG) studies revealed focal, generalized, or more frequently bilateral, multifocal pattern, and the location of the epileptic foci was predominantly frontotemporal (Fig. 30.4). Background focal or generalized slowing is common. The EEG between seizures shows slow waves resembling an "encephalitis" pattern.

30.4 Conclusions

Focal slowing is the main electroencephalographic abnormality seen acutely in children with febrile status epilepticus. The findings are quite consistent over time and in different patient populations. If focal slowing is associated with a development of epilepsy later in life is uncertain. Studies to date are not sufficient in order to assess the risk of focal slowing for the development of epilepsy. Future clinical studies, better understanding of animal models, and results from genetic studies might help in this field of knowledge.

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Chromosomal Abnormalities and Cortical Malformations

33

Maurizio Elia

33.1 Chromosomal Abnormalities

Chromosome abnormalities are often associated with neurodevelopmental disorders and particularly with intellectual disability (ID). They represent a relatively rare etiology of epilepsy, but seizures are more frequently present in patients with ID than in the general population. Consequently, chromosome abnormalities play an important role especially when there is the co-occurrence of epilepsy and ID.

Different genetic tools such as karyotyping, high-resolution chromosome banding, and fluorescent in situ hybridization (FISH) have contributed to the discovery of a certain number of abnormalities involving rather large chromosome regions. In the last few decades, some new "molecular karyotype" techniques have been implemented, based on DNA hybridization, such as array comparative genomic hybridization (aCGH), multiplex ligation-dependent probe amplification (MLPA), and single nucleotide polymorphisms (SNP) array. In particular, aCGH has allowed to investigate the entire genome for micro-rearrangements, namely, copy number variations (CNVs) in the same experiment.

However, many of the studies published have been carried out on small groups of patients or on single cases with chromosome abnormalities and epilepsy, usually without providing sufficient information on the clinical and EEG phenotype, in order to correctly classify epilepsy.

Discovering chromosome abnormalities in patients with epilepsy may be important in order to verify whether they are correlated with peculiar clinical and EEG phenotypes and to clarify whether epileptogenesis is determined by the abnormal function of a candidate gene localized in the region of the chromosome anomaly. This is the case, for instance, of fragile X syndrome (FraXS) and Angelman syndrome (AS) that will be included in this chapter. The former, originally diagnosed with the evidence of a fragile site at the Xq27.3 region, when lymphocytes are grown in a folic acid-deprived medium, is now recognized as caused by a mutation of FMR1 gene; the latter has been correlated with the maternal copy of the ubiquitin-protein ligase gene (UBE3A), localized on the 15q11–13 region.

I will discuss here only those chromosome abnormalities or gene mutations, discovered by means of older and newer techniques, that have been strongly associated with clinical and EEG patterns so characteristic to suggest to the clinician a specific genetic diagnosis.

33.1.1 1p36 Deletion Syndrome

1p36.3 deletions account approximately for 0.5–1.2% of idiopathic ID. The prevalence, once estimated 1:10.000, is now considered to be 1:5000, making this genetic condition the most common terminal deletion [1, 2]. According to a recent review, more than 300 cases of 1p36 deletion syndrome have been reported in literature [3]. 1p36 deletion may be the result of pure terminal deletions, interstitial deletions of varying sizes, or more complex rearrangements. Deletions of the paternally inherited chromosome are usually larger than those of the maternally inherited chromosome [1].

Haploinsufficiency for KCNAB2 has been proposed as a significant risk factor for epilepsy in subjects with 1p36.3 deletion syndrome [4], but probably this is not the only gene responsible for epileptogenesis in this syndrome. In fact, the human gamma-aminobutyric acid A receptor delta-subunit gene GABRD and the proto-oncogene SKI have also been suggested to contribute to pathogenesis of epilepsy and neurodevelopmental disorders in 1p36 deletion syndrome [3].

1p36.3 deletion syndrome is typically characterized by craniofacial dysmorphic features, brachydactyly/camptodactyly, short feet, and sensorineural hearing impairment. More rare findings are epicanthal folds, highly arched palate, oral-facial clefting, congenital heart malformations, hypothyroidism, and visual inattentiveness. All subjects present developmental delay or ID of moderate to profound degree,

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and more than 85% of them show early muscle hypotonia. The majority of the patients achieves independent walking, but gait appears broad-based or ataxic. Behavior disturbances have been reported, mostly characterized by aggressiveness, self-injury, and autism spectrum disorder [1].

Brain neuroimaging may show cerebral atrophy, dilation or asymmetry of the lateral ventricles, hydrocephalus, myelination delay, focal dysplasias, polymicrogyria, subependimal heterotopia, and leukodystrophy [1, 3, 5].

Interictal EEG—A multicenter retrospective study of 91 subjects with 1p36.3 deletion syndrome has reported an interictal EEG at the onset characterized by spikes, polyspikes, or spike-and-wave complexes over the rolandic regions (6 cases), the temporo-occipital regions (18 cases), or multifocal/generalized (14 cases). Furthermore, in the majority of the patients, a slow activity was evident over the temporo-parieto-occipital regions. Only three patients (two of whom with seizures) had a normal EEG and five showed a hypsarrhythmic pattern. Interictal EEG remained unchanged in almost all cases, showing high-voltage diffuse or multifocal spikes, intermixed with slow waves in patients with drug-resistant epilepsy, slow background activity, and focal spikes in subjects with partially controlled seizures or seizure-free [5]. A more recent review of the literature confirms these data, reporting 31 cases of focal spikes in the interictal EEG at the onset (7 rolandic, 18 temporo-posterior or temporo-occipital, 1 right centrotemporal, 1 bilateral frontal, and 4 no better specified focal). There were also 20 cases with multifocal or generalized spikes or polyspikes and 10 cases with spike-and-wave discharges. Abnormal delta-theta wave activity mainly on the posterior temporo-parieto-occipital areas and asymmetry of slow activities were present in most patients. Thirty-one patients with seizures had a normal EEG, and 29 showed hypsarrhythmia [3].

Seizures and ictal EEG—Seizures are present in more than 60% of cases, with a predominance for female sex, and they are polymorphous: more commonly spasms, but also focal, generalized tonic-clonic, myoclonic, atonic, and absence seizures. It is arduous to define the age at seizure onset, since most reports fail to specify it. Anyway, seizures usually start in the first year of life (about 80% of cases during the first 6 months of age). Approximately 22% of patients develop an epileptic encephalopathy at a median age of 5 months [1–3, 5].

Two different patterns have been recognized: (1) patients with a few seizures in infancy, transiently treated with antiepileptic drugs, with no recurrence of the seizures during or after the first year of age [6, 7], and (2) patients suffering from enduring convulsions and requiring long-term medication [8]. Taking in count the literature data, 18.8% (36/191) of subjects with seizures develop a drug-resistant epilepsy [3]. The onset of refractory epilepsy in 1p36 deletion syndrome might be associated with the onset of infantile spasms and their degree of response to high-dose steroids [5].

33.1.2 2q24.4 Deletion Syndrome

Patients with a clinical and EEG picture of Dravet syndrome (DS) who are negative for SCN1A mutations may present SCN1A exonic or larger deletions involving SCN1A and contiguous genes [9–12]. These deletions account for 2–3% of all DS cases and for about 12.5% of patients with DS who are negative for mutations on sequencing [13].

Deletions extending beyond SCN1A and including variable numbers of contiguous genes can be associated with additional dysmorphic features, depending on the genes involved [9], or with a more severe epilepsy phenotype when other voltage-gated sodium channels (VGSC) α subunit genes clustered on chromosome 2q such as SCN2A, SCN3A, SCN7A, and SCN9A are involved [12, 14]. Clinical phenotype may be characterized by microcephaly, bitemporal narrowing or frontal bossing, down-slanting or short palpebral fissures, bulbous nose or broad nasal bridge, low-implanted ears, thick helix, bow-shaped mouth, anterior open bite, single palmar creases bilaterally, and partial syndactyly between the second and third toes [9, 14]. In a review of 43 previously published cases with a del(2)(q24.3q31.1), for the 22 seizure-positive cases, 2q24.3 region constituted the smallest commonly deleted region among the majority of the cases. The most common dysmorphic features were ear abnormalities, microcephaly, micrognatia, and brachysyndactyly [12].

MRI is usually normal, although one patient at 14 months of age showed diffuse lesions in the periventricular white matter and basal ganglia. Postmortem brain examination showed abnormalities as seen in Leigh syndrome, with spongiosis and increased gliosis of the internal and external pallidum, and less pronounced lesions in the pons and mesencephalon (central tegmental tract) [11].

Interictal EEG—The interictal EEG picture is that typical of DS [13, 15].

Seizures and ictal EEG—Seizures start always in the first year of life, with severe drug resistance, mild to severe ID, autistic behavior, ataxia, and muscle hypotonia. Ictal EEG picture shows the typical patterns of DS, i.e., absences, generalized tonic-clonic, myoclonic, and focal seizures [13, 15].

33.1.3 4p⁻ Syndrome (Wolf-Hirschhorn Syndrome)

The 4p⁻ syndrome or Wolf-Hirschhorn syndrome (WHS) is a rare malformative condition caused by the distal deletion of the short arm of chromosome 4 (region 4p16), which is sporadic in approximately the 85% of cases or originates from an unbalanced translocation in the remaining 15% of cases. The deleted region can be of paternal or maternal origin. The frequency of WHS is estimated as 1:50,000 births with a female predilection of 2:1. However, this prevalence figure

may be underestimated, taking in count missed diagnoses due to lack of recognition or inadequate genetic analysis [16–19].

The shortest area regarded as the WHS critical region (WHSCR) is restricted to a 165-kb interval on 4p16.3. WHSC1 gene may be involved in the pathogenesis of WHS, such as in Pitt-Rogers-Danks syndrome which represents the result of an allelic variation and is usually milder than WHS [20]. Also the HOX7 (MSX1) gene has been found deleted in patients with WHS, and this was the first demonstration of the involvement of a homeobox gene in a human malformative condition Anyway, this gene anomaly has not been reported in all subjects with WHS [21, 22]. A new critical region has been proposed, WHSCR2, distally contiguous with WHSCR. One of the candidate genes included in WHSCR2 is LETM1 which likely plays a role in epileptogenesis. More recently, an additional chromosome region for seizures has been suggested, falling within the terminal 1.5 Mb on 4p, not including LETM1 [23]. On the basis of a genotype-phenotype analysis, WHS should be distinguished in a "classical" form and a "mild" form, the latter correlated with shorter deletions [20].

WHS is clinically characterized by severe prenatal and postnatal growth delay, low birth weight, severe ID, microcephaly, "Greek warrior helmet" profile of the face, cleft of the lip or palate, ocular coloboma, and heart septal defects. In about one third of cases, death occurs in the first year of age for systemic severe malformations, heart failure, and pulmonary infections [16–19].

In WHS, the following neuropathological abnormalities have been observed: microcephaly, anomalous pattern of the cortical gyri, heterotopia, dysplasia of the lateral geniculate bodies and dentate nuclei, and corpus callosum hypoplasia [24].

Interictal EEG—Two types of EEG patterns have been reported. The first type was characterized by frequent, diffuse, atypical slow spike and wave complexes, often occurring in long bursts, elicited by slow wave sleep. The second type included frequent, high-amplitude, fast spike-polyspike and wave complexes over the centro-posterior regions, triggered by eye closure (Fig. 33.1) [19, 25].

Seizure and Ictal EEG—Although the precise frequency of seizures in WHS is unknown, they occur in 50–100% of subjects reported in literature. Seizure onset is usually in the first year of age but definitely before 2 years of age [19, 26].

Clinical and EEG features of epilepsy in WHS have been described in detail only in a few cases. They are clonic or tonic, involving one side with or without secondary generalization, generalized tonic-clonic from the onset, in clusters, often triggered by fever. Unilateral or generalized tonic-clonic status epilepticus may occur. Focal seizures, myoclonic

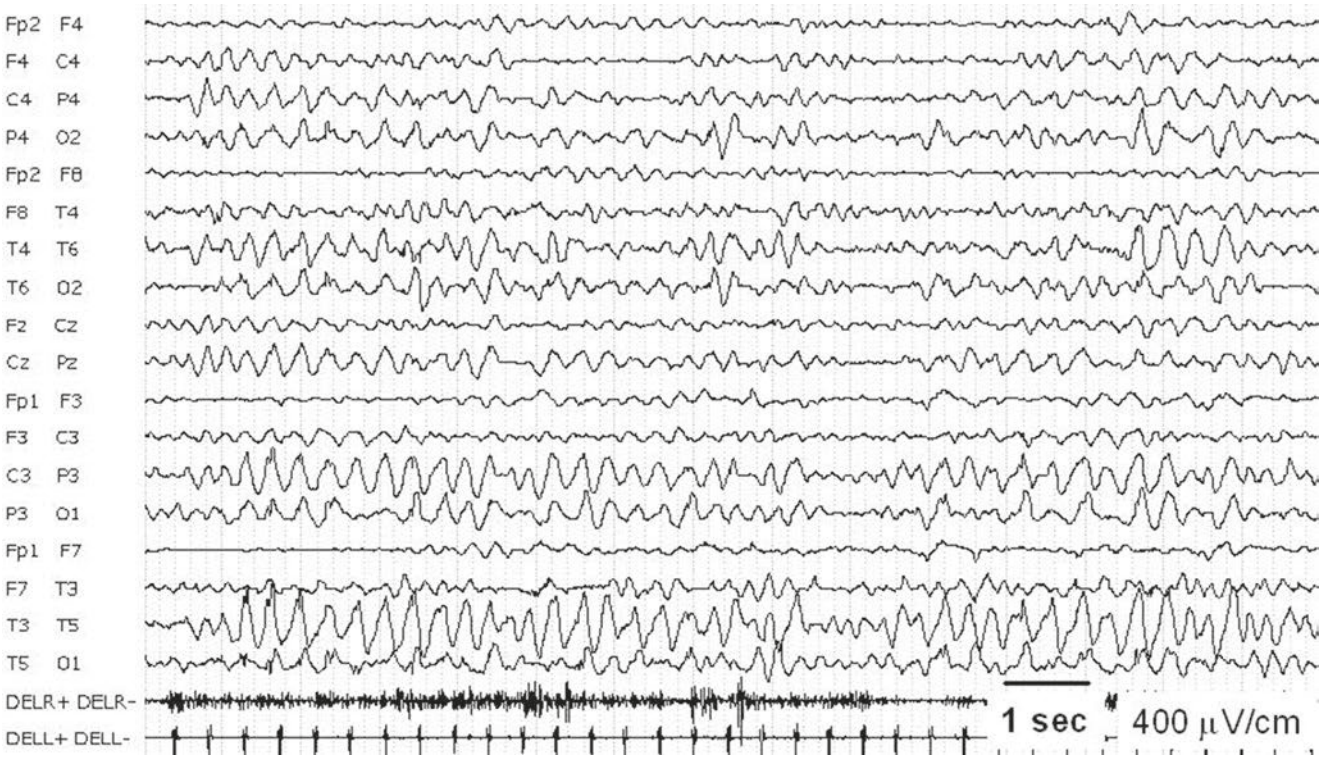

Fig. 33.1 Wakefulness EEG of a 1-year-old female with 4p⁻ syndrome. Long sequences of high-voltage slow waves and spike-and-wave complexes are evident over the parieto-temporo-occipital regions of both hemispheres, prominent on the left one (*R* right, *L* left, *DELT* deltoid muscle)

seizures, tonic spasms, or migrating partial seizures are rarer [19, 26–29].

A peculiar ictal EEG pattern has been observed in some studies. After the onset of unilateral or generalized tonic-clonic seizures in the first year of age, the patients develop frequent atypical absences accompanied by myoclonic jerks mainly involving the eyelids and axorizomelic muscles, induced by eye closure. EEG shows generalized spike-and-wave complexes [19, 30].

The prognosis of epilepsy in WHS is rather favorable. Seizures are controlled by valproic acid alone or in association with ethosuximide. In some cases, benzodiazepines and levetiracetam should be considered as treatment options. Sodium bromide is effective for preventing status epilepticus and for treating migrating partial seizures [19, 26–28, 31, 32].

33.1.4 5q14.3 Deletion Syndrome

Although 5q14.3 deletion has been associated with a Rett-like phenotype, most of the patients do not show acquired microcephaly and developmental regression after a normal interval but show muscle hypotonia, severe ID, early onset seizures, and sometimes autistic behavior, stereotypic hand movements, and episodic hyperventilation [33, 35].

Other characteristic dysmorphic signs include broad and high forehead, relatively large, backward rotated ear lobes, mildly upward-slanting palpebral fissures, and cupid bowed or tented upper lip [36]. Periventricular heterotopias or simplified gyral pattern on brain MRI are other possible features [34, 37].

MEF2C is the candidate gene for this syndrome. It encodes for a transcriptor factor, and its activity relies on the recruitment of many other transcription factors, as well as on translational and posttranscriptional modifications [38]. Patients with MEF2C defects showed diminished MECP2 and CDKL5 expression, and MEF2C mutations in vitro resulted in diminished transactivation of both the MECP2 and CDKL5 promoters [36]. A mutational screening for MEF2C microdeletion can be considered in patients with early onset Rett-like phenotype and negative for MECP2, CDKL5, and FOXG1 mutation or deletion.

Interictal EEG—Generalized spike-wave or polyspike-wave discharges have been reported in four patients [39].

Seizures and ictal EEG—Seizure onset is between 1 and 10 months of age, usually with infantile spasms. Febrile seizures, atypical absences, myoclonic, and focal seizures may also occur [15, 37, 39].

33.1.5 6q Terminal Deletion Syndrome

The 6q terminal deletion syndrome is a rare condition characterized by ID, facial dysmorphic features, genital hypoplasia, and structural CNS abnormalities. We described five patients with 6q terminal deletion (9 to 16 Mb large) and a specific electroclinical pattern [40]. Subsequently, other seven patients with 6q subtelomere deletion and a similar clinical and EEG pattern were reported with a size of the deletion ranging from 3 to 13 Mb [41, 42]. It has been calculated that 6q terminal deletion is present in about 0.05% of patients with ID and/or development delay [43].

Brain MRI is characterized by colpocephaly and dysgenesis of the corpus callosum, thalami, and brainstem [40].

In a more recent review, 28 cases with pure 6q terminal deletion were counted [43]. A comparison of the case with the smallest deletion (~0.4 Mb; 3 known genes) reported to date and the case that has the largest deletion (<11 Mb; >34 known genes) showed no specific phenotype differences. The region of greatest interest resulted the smallest overlapped portion of the most distal part of chromosome 6q. The genes located in the region within 0.4 Mb of the 6q terminus were PSMB1, TBP, and PDCD2. The TBP gene has been proposed as a candidate gene for phenotype in patients with 6q terminal deletion. However, the possibility of other genes playing a role in the phenotype resulting from this deleted region cannot be ruled out. To confirm this, a study on 12 patients with 6q terminal deletion and developmental brain abnormalities, including also periventricular nodular heterotopia, suggested that C6orf70 gene might play a major role in the control of neuronal migration [44].

Interictal EEG—Interictal EEG is characterized by posterior spike-and-wave complexes which become more pronounced during NREM sleep (Fig. 33.2) [40, 41].

Seizures and ictal EEG—There are no ictal EEG pictures of 6q terminal deletion in literature up to now. Epilepsy starts in the first or second decade of life. In almost all cases, seizures had a focal onset, characterized by the ictal signs of vomiting, cyanosis, and head and eye version with or without loss of consciousness. The ictal signs and the EEG patterns in these patients suggest that the seizures originate from the occipital lobes. Given the early onset of seizures, it is conceivable that an age-related low threshold of emetic centers causes the ictal vomiting, as occurs in Panayiotopoulos-type occipital epilepsy. No status epilepticus or prolonged seizures occur. Prognosis of epilepsy is generally good, in terms of both seizure control and evolution [40, 41].

33.1.6 Trisomy 12p Syndrome

This represents a rare condition (estimated prevalence 1:50,000), which can be caused by a de novo occurrence (also in a mosaic fashion) or by an unbalanced translocation, and is characterized by severe ID, absent language, and generalized hypotonia. The main dysmorphic features include round face, short neck, high and prominent forehead, flat

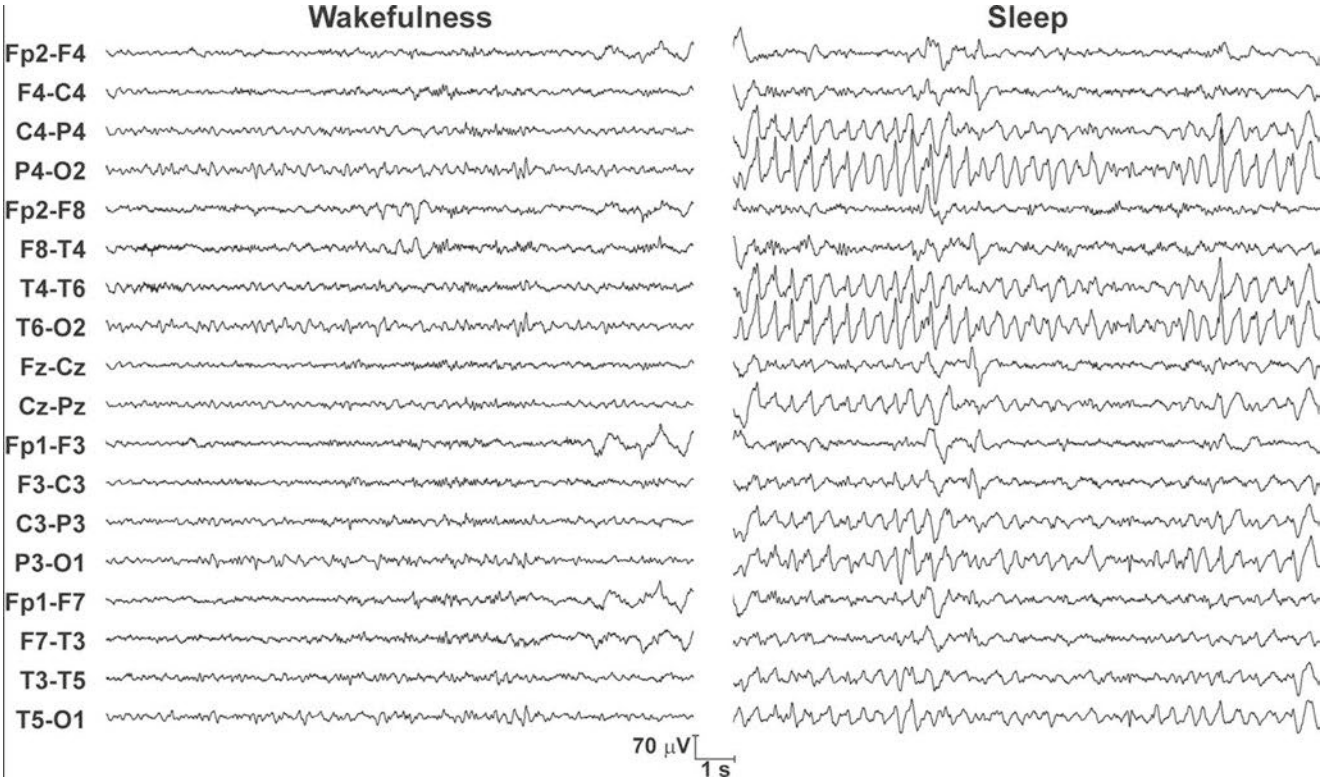

Fig. 33.2 Wakefulness EEG of a 19-year-old male with 6q terminal deletion showing sharp waves over the occipital regions of the right hemisphere (**a**). During non-REM sleep, high-voltage rhythmical delta activity is present over the temporo-parietal regions (**b**)

occiput, hypertelorism, epicanthus, broad nasal bridge, long philtrum, prominent lower lip, low-set ears, and micrognathia [45–47].

Brain neuroimaging discloses calcifications of the basal ganglia, cortical and subcortical atrophy, "mega cisterna magna," and signal alteration of the white matter [45–47].

It is noteworthy that in the 12p13 region, deleted in this chromosome abnormality, there is a cluster of three genes coding for potassium voltage-gated channels which might be relevant for epileptogenesis [45–47].

Interictal EEG, *seizures*, *and ictal EEG*—In some cases, a typical electroclinical pattern has been found, characterized by absences with myoclonias, starting after 3 years of age, associated with generalized spike- and polyspike-and-wave complexes at the interictal and ictal EEG (Fig. 33.3) [45–47].

Seizures are present in about 30% of cases, and they present mostly as febrile or afebrile generalized tonic-clonic, or myoclonic fits. They are usually controlled by valproic acid in monotherapy or associated with ethosuximide [45, 46].

33.1.7 Ring Chromosome 14 Syndrome

Ring chromosome 14 is a rare chromosomal anomaly which occurs as a mosaicism. The patients present early onset epilepsy, severe or profound ID, language disturbance, microcephaly, and facial dysmorphisms. Ocular anomalies, such as cortical cataract, retinopathy, and refractive errors, may be present [47].

Neuroimaging shows hypoplasia of the corpus callosum, left temporal hypodensity, cortical atrophy, mild dilatation of the left temporal horn, mild bilateral fronto-temporo-parietal atrophy, cystic hypophysis anomaly, mild external hydrocephaly, sphenoid wing cyst, cerebral and white matter hypoplasia, hippocampal dysmorphisms, and cerebellar structural anomalies [48–51].

Ring chromosome 14 represents the smallest form of 14q monosomy. Two hypotheses could explain the presence of seizures in r(14) syndrome: ring instability, resulting in monosomy 14 in a proportion of cells, or haploinsufficiency of critical genes, with a decreased expression of genes contained on the adjacent 14q arm. FOXG1B gene, included in the 14q11q13 region, with a well-known role in the development of the brain and telencephalon, has been suggested as a candidate gene for epilepsy [51].

Interictal EEG—In a recent retrospective study on 22 patients with ring 14 chromosome syndrome, 15 of them had a slow and poorly organized EEG background activity, with interposed discontinuous rhythmic monomorphous bifrontal or temporo-posterior high-voltage slow waves. Epileptiform abnormalities, such as spike-and-wave complexes, slow

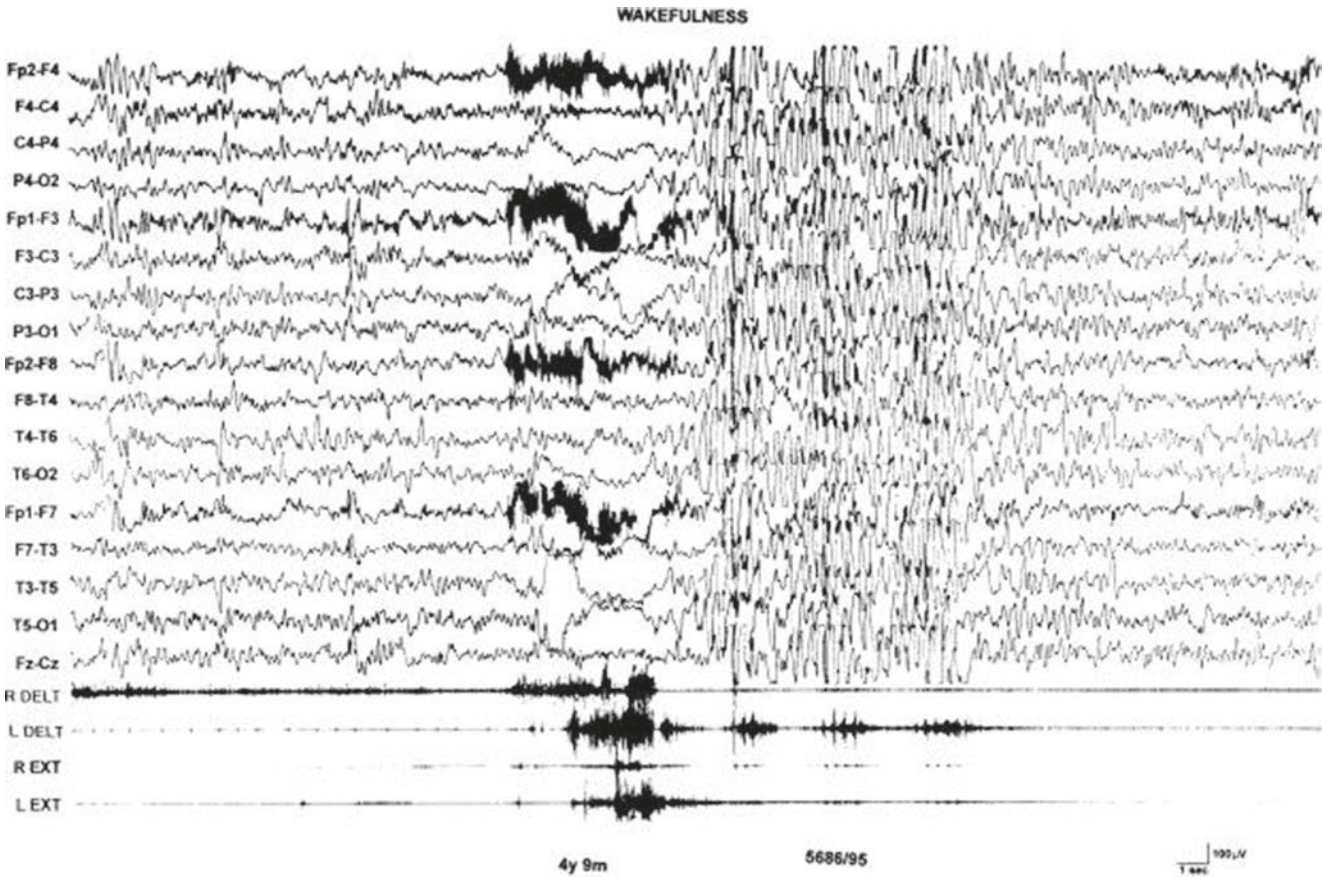

Fig. 33.3 Wakefulness EEG of a 4-year-old female with trisomy 12p syndrome. A myoclonic absence is recorded, characterized by a diffuse spike-and-wave discharge, accompanied by rhythmical myoclonic jerks, prevalent at the left deltoid muscle, superimposed over a tonic contraction (*R* right, *L* left, *DELT* deltoid muscle, *EXT* forearm extensor muscles)

spikes, sharp waves, fast rhythms over the fronto-central or fronto-temporal regions, and more diffuse during sleep, were present in seven subjects. In five patients, paroxysmal generalized abnormalities were preceded by unusual unilateral or bilateral posterior recruiting spikes or fast rhythms. Follow-up EEG evaluation showed the persistence of the bursts of rhythmic high-voltage slow waves over the posterior or fronto-central areas. In sporadic cases with a good seizure outcome, EEG revealed only theta activities over the temporal regions or was normal [51].

Seizures and ictal EEG—Epilepsy has an early onset, mostly in the first year of age. Seizure at onset was reported to be of generalized, tonic-clonic, myoclonic-tonic, and clonic types in 9 out of 22 patients. Focal hemiclonic seizures were present in two subjects and focal seizures with secondary generalization, mainly starting from the mid-temporal and frontal regions, in 11 subjects. Seizures were often prolonged or in clusters, correlated with sleep, and resistant to the different antiepileptic drugs used; convulsive and nonconvulsive status epilepticus have been reported in some cases [51].

At the EEG, in focal seizures, the fast generalization of the ictal discharge can hide its focal origin, or focal discharge can appear during an apparently generalized seizure. Focal seizures originate mainly from fronto-temporal and mid-posterior regions. Generalized tonic seizures are characterized by a generalized desynchronization on EEG. Irregular or asymmetric 2.5–3 Hz spike-and-wave discharges clinically correlated with eyelid myoclonic absences may be rarely present. In patients with nonconvulsive status epilepticus, an EEG pattern with bilateral frontal high-voltage continuous rhythmic or pseudo-rhythmic delta activity is evident [51].

33.1.8 Angelman Syndrome

Angelman syndrome (AS) is a genetic malformative condition characterized by severe ID with absent or very limited verbal language, ataxia, myoclonus, paroxysmal laughter, and seizures [47, 52, 53].

The prevalence of AS has been reported as 1:62,000, but this epidemiological finding could be underestimated, and a

higher prevalence, 1:12,000, has been recently suggested [53, 54]. In more than 70% of cases, a deletion of the long arm of the chromosome 15 is recognizable, with a maternal origin (15q11–13 region); in approximately 2–3% of cases, a uniparental paternal disomy is present; about 3–5% of cases are associated with a defect of the *imprinting center*, leading to the absence of the typical maternal DNA methylation pattern. Furthermore, from 1997 up today, several sporadic and familial cases (5–10%) with mutations of the UBE3A (ubiquitin-protein ligase E3A) gene, located in the 15q11–13 region, have been reported. Fifty percent of these mutations involves exons 8 and 9 of UBE3A gene [47, 55].

The abovementioned genotypes determine AS variable phenotypes, more severe in subjects with 15q11–13 deletion, less severe in those with UBE3A mutations, and milder in those with uniparental paternal disomy and with *imprinting center* defect [47, 56].

Among the different known transgenic animal models, the GABRB3 knockout shows clinical and EEG features similar to those found in humans. Up to now, it is unclear how the inactivation of UBE3A gene is able to cause AS. It has been hypothesized that the UBE3A gene might act by means of a defect of activation of Plic-1 protein, which regulates the number of $GABA_A$ receptors containing the β3 subunit on the cell membrane, reducing the strength of the GABAergic synapses [57, 58].

Neuroimaging usually shows nonspecific anomalies. Frequently, cerebral atrophy of variable degree and dilation of lateral ventricles are observed [59].

Interictal EEG—EEG picture in AS is rather peculiar, is similar in the different phenotypes, and is characterized by a slow background activity and paroxysmal abnormalities, mostly spike-and-wave complexes, prominent over the occipital or frontal regions. Diffuse spike-and-wave complexes, accompanied by myoclonias, sometimes rhythmical and bilateral, sometimes quasi-continuous and apparently not correlated with the paroxysmal abnormalities are often recorded (Fig. 33.4).

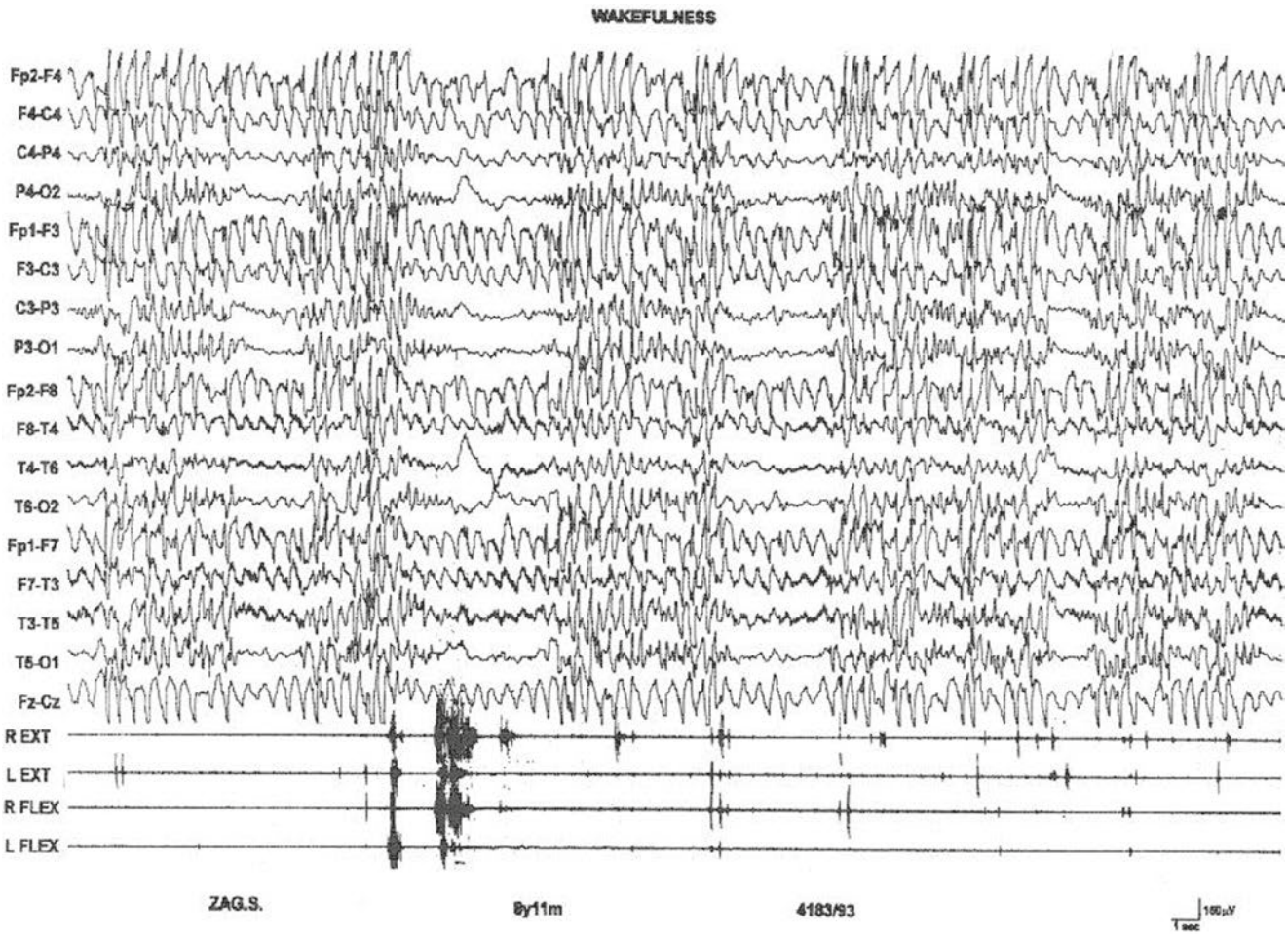

Fig. 33.4 An 8-year-old female with Angelman syndrome. At wakefulness EEG, a slow background activity and quasi-continuous spike-and-wave discharges, better represented over the frontal regions, are present. Surface EMG of forearm extensor and flexor muscles records numerous bilateral, sometimes rhythmical and bilateral, myoclonic jerks which are inconstantly correlated with paroxysmal abnormalities (*R* right, *L* left, *EXT* forearm extensor muscles, *FLEX* forearm flexor muscles)

In the sleep stages 1–2, spike-and-wave complexes become continuous, and spindles are not easily recognizable; in the stages 2–3 of the subsequent sleep cycles, the activation of paroxysmal abnormalities is reduced, and spindles are better represented (Fig. 33.5). In slow sleep, myoclonus disappears, and it reappears at the awakening and during REM sleep, when a theta activity on the vertex and rolandic regions is evident.

Two females have been reported with the typical EEG trait of AS but with mutations of MECP2 gene and a diagnosis of Rett syndrome [60, 61].

Back-averaging study of myoclonus in AS has demonstrated that it has a cortical origin, with a rostro-caudal activation pattern. Furthermore, in some patients, a quasi-continuous focal or multifocal rhythmical cortical myoclonus, at about 11 Hz of frequency, involving hands or face, has been described [62].

Seizures and ictal EEG—Seizures are present in approximately 90% of cases, start in the first year of age, and are polymorphous: spasms, myoclonic, myoclonic-atonic, generalized tonic-clonic, focal seizures, myoclonic absences, and febrile convulsions [47, 63]. The typical ictal EEG pattern of AS is the so-called myoclonic status, which is clinically correlated with an obtundation status, an impairment of the gait, more frequent myoclonic jerks, and hyperactivity. At the EEG, quasi-continuous spike-and-wave complexes diffuse over both hemisphere, correlated or not with myoclonic jerks, are evident (Figs. 33.6 and 33.7) [47, 64, 65].

An earlier onset and a greater severity of seizures are common in patients with 15q11–13 deletion, in comparison with the other genotypes [56].

Epilepsy is rather benign in the evolution, and treatment is based on valproic acid, also in association with ethosuximide, or benzodiazepines [47, 66]. Lamotrigine, topiramate, and levetiracetam have been reported as helpful in a few cases [47, 67]. Cortical myoclonus can be treated with high dosages of piracetam [62]. In adults, drug withdrawal might be considered in the management of epilepsy despite the persistence of epileptiform abnormalities [66].

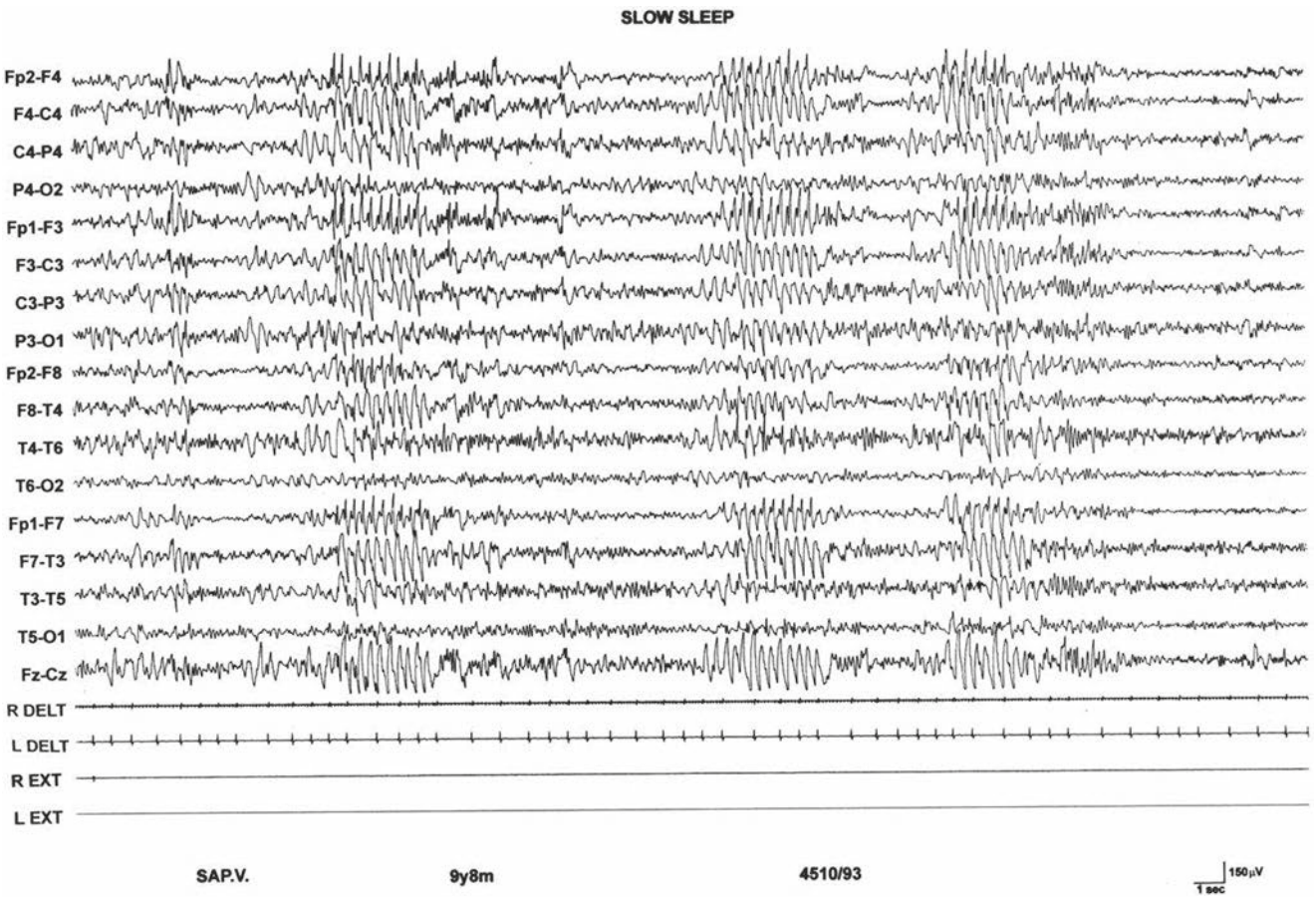

Fig. 33.5 A 9-year-old female with Angelman syndrome. Sleep EEG shows diffuse spike-and-wave discharges, prevalent over the anterior regions of both hemispheres and the vertex. Spindles are bilaterally and symmetrically represented. There are no myoclonic jerks at surface EMG of forearm muscles (*R* right, *L* left, *DELT* deltoid muscle, *EXT* forearm extensor muscles)

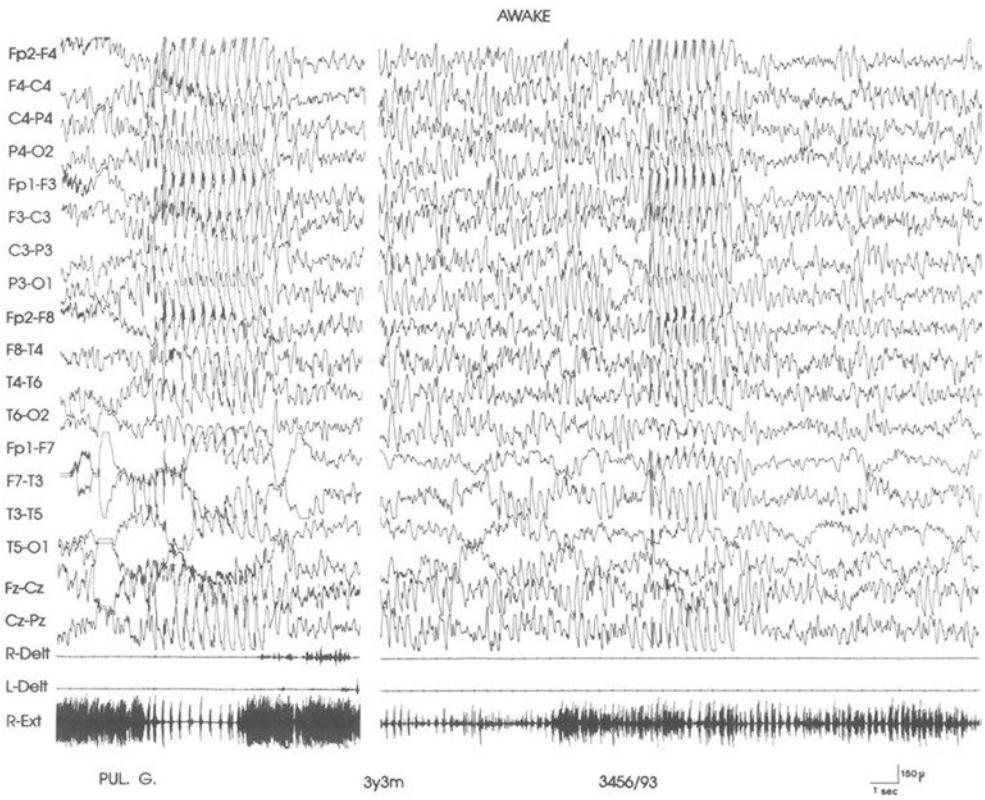

Fig. 33.6 A 3-year-old male with Angelman syndrome. On the left side, a short generalized discharge of spike-and-wave complexes is evident, and it is timely correlated with rhythmical losses of muscle tone, determining an absence with myoclonus. On the right side, EEG shows spike-and-wave complexes over the anterior regions of both hemispheres and another short spike-and-wave discharge. In this case, the correlation with myoclonus is less evident (*R* right, *L* left, *DELT* deltoid muscle, *EXT* forearm extensor muscles)

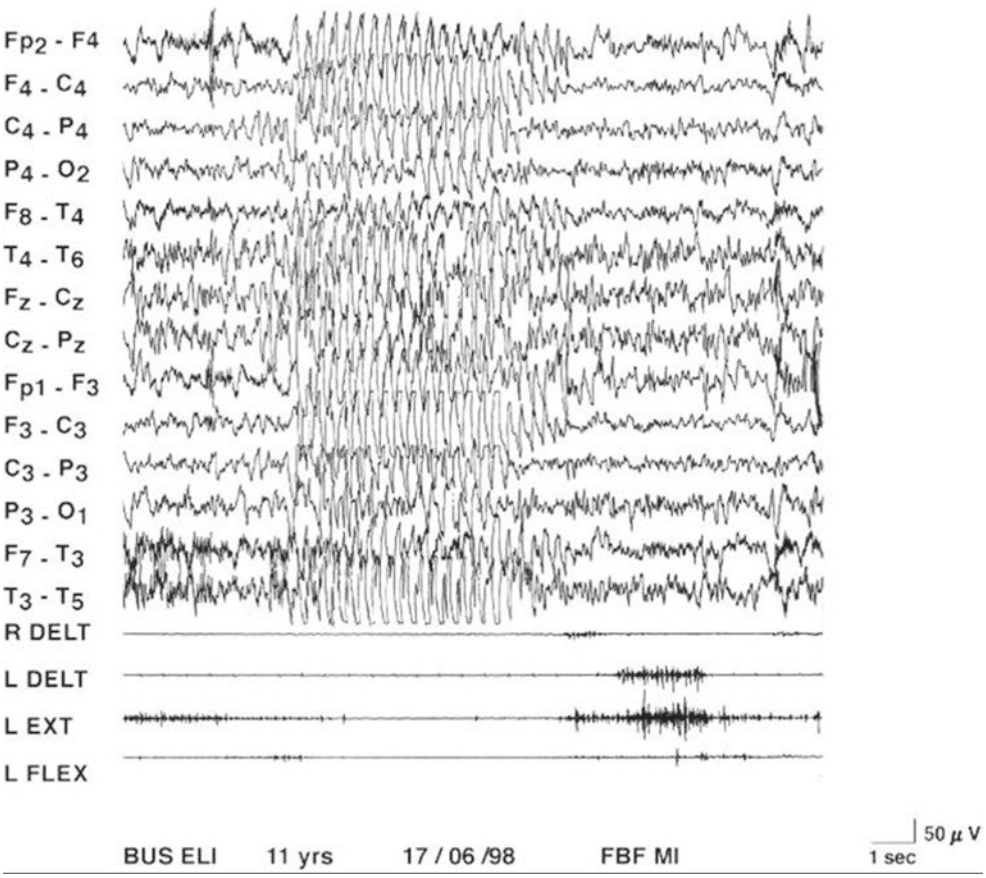

Fig. 33.7 An 11-year-old female with Angelman syndrome. Ictal EEG disclosing an atypical absence, correlated with an interruption of the motor activity at surface EMG of deltoid and forearm extensor muscles (*R* right, *L* left, *DELT* deltoid muscle, *EXT* forearm extensor muscle, *FLEX* forearm flexor muscle)

33.1.9 Inv Dup (15) Syndrome

The inverted duplication of proximal chromosome 15 [inv dup (5)] or isodicentric 15 chromosome [idic (15)] is the most common chromosome marker or extra structural abnormal chromosome (ESAC). Its prevalence is estimated to be 1:30,000 [47].

Phenotype is very variable, with ID, behavioral disturbances, autism spectrum disorder, and epilepsy. In the majority of cases, neuroimaging does not reveal specific alterations; enlarged ventricles, enlarged subarachnoid spaces, thinning of the corpus callosum and increased signal density around the posterior horns of the lateral ventricles, moderate volume increase of the cerebrospinal fluid surrounding the left temporal pole, and mild brain atrophy have been reported [68, 69].

There are many evidences that phenotype is more severe when the inverted and duplicated 15 chromosome segment is larger. Anyway, some other reports seem to contradict this statement [70]. Certainly, phenotype is strictly correlated with the extension of the region and with the gene dosages, when it contains the PWS/AS critical region. Among genes with a sure role in determining phenotype of inv. dup (15) syndrome, there are those coding for the subunits α5 and β3 of GABA receptor and P gene. Tetrasomy of these genes could alter the activity of GABA receptor and then cause some of the main clinical features of this syndrome, such as seizures, hyperactivity, aggressiveness, and autism spectrum disorder.

Other genes, such as SLC12A6, located more distally, coding for cation chloride cotransporter, and expressed in the brain, or CHRNA7, coding for a subunit of nicotinic acethylcholine receptors, located on 15q11.2–q13.3, could be involved in the pathogenesis of seizure [47, 71].

Interictal EEG—In a recent retrospective study of 35 patients with inv. dup (15), the interictal EEG was differentiated: slow or sharp waves, biphasic spikes-polyspikes more prominent over both frontal regions, often quasi-continuous, sometimes diffuse to the entire brain; fast ill-defined spike-and-wave complexes, usually in runs of variable duration, over both fronto-centro-temporal regions; fast activity at 12–20 Hz bilaterally over fronto-centro-temporal areas (Fig. 33.8); and slow background activity. Sleep spindles

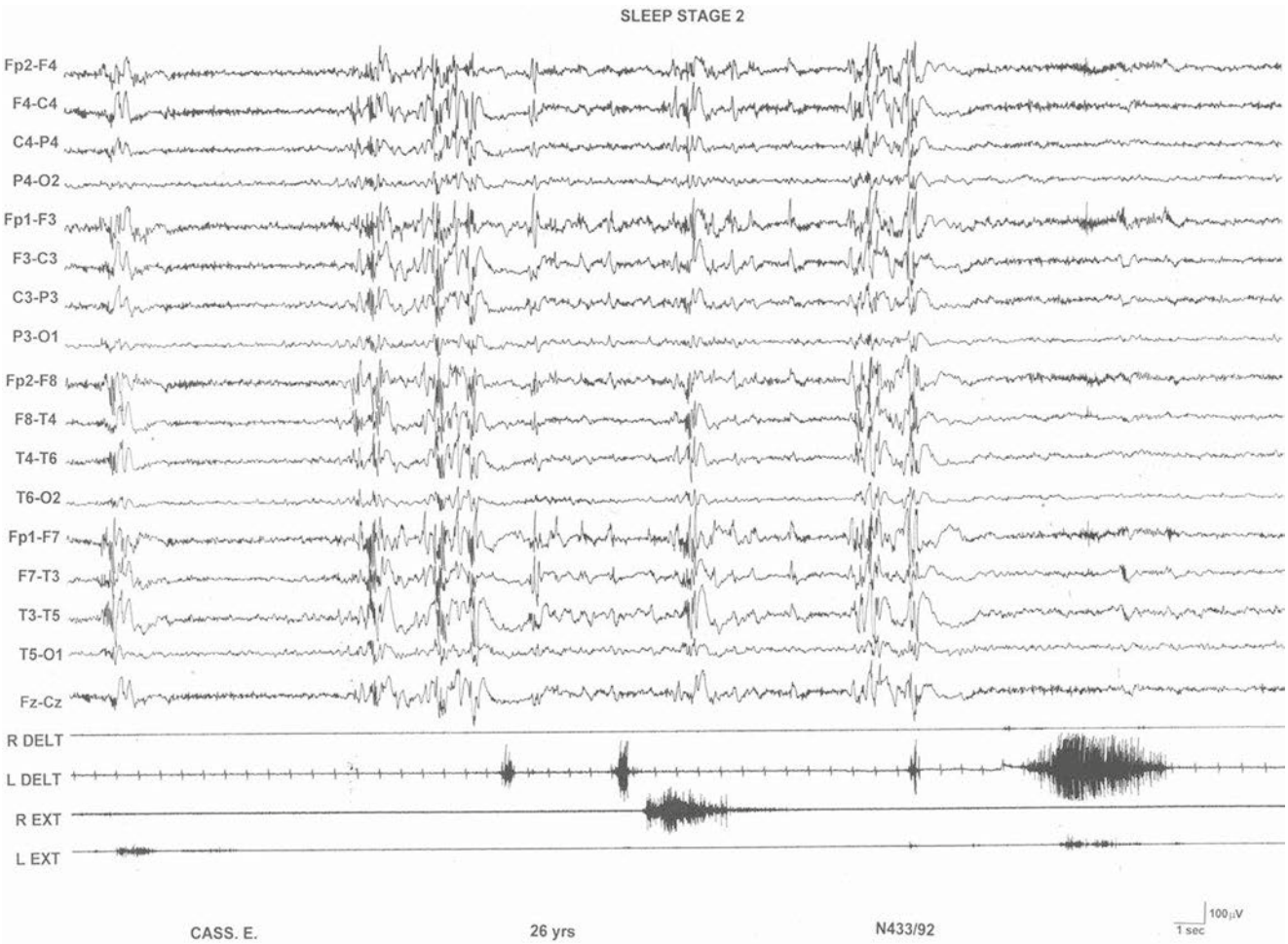

Fig. 33.8 A 26-year-old female with inv. dup (15) syndrome. Sleep EEG shows numerous short fast polyspike discharges, without clinical correlation, as in the typical Lennox-Gastaut syndrome (*R* right, *L* left, *DELT* deltoid muscle, *EXT* forearm extensor muscle)

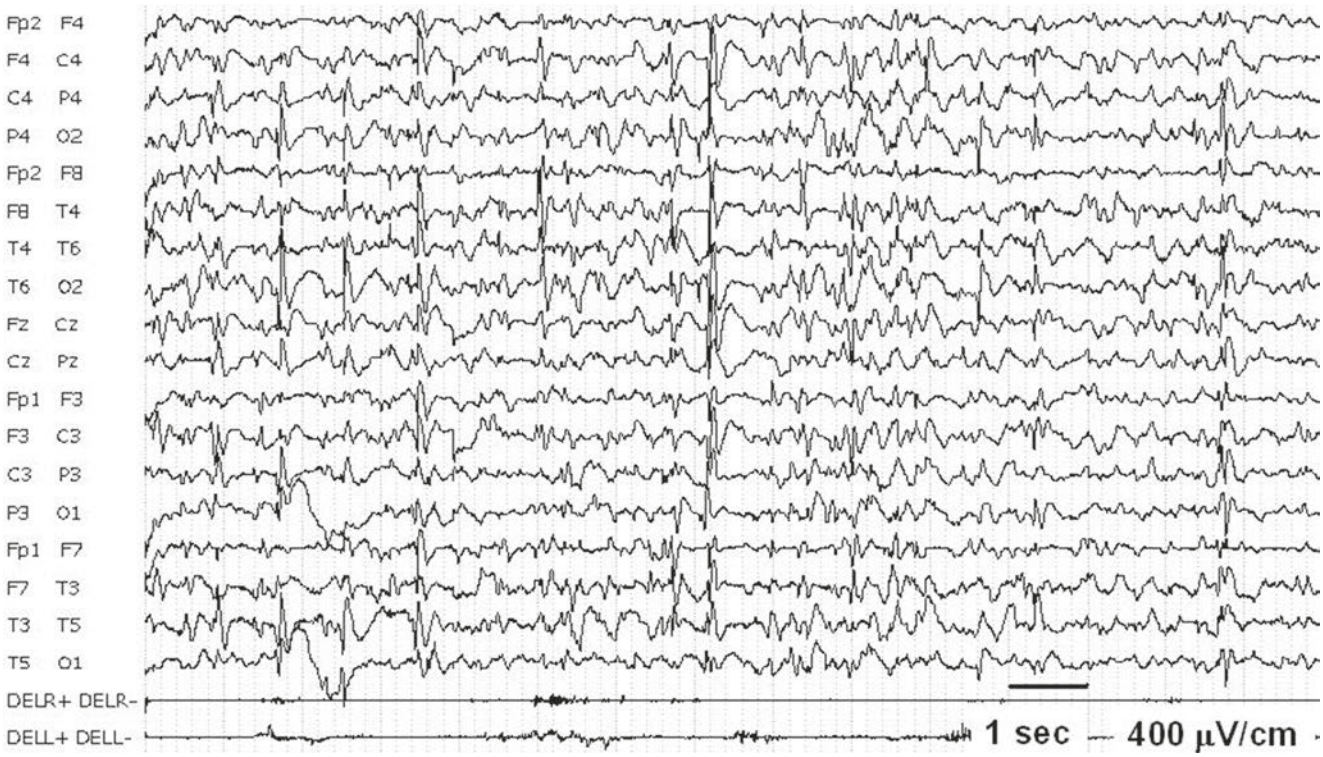

Fig. 33.9 A 2-year-old male with inv. dup (15) syndrome. Wakefulness interictal EEG is characterized by numerous high-voltage, multifocal or diffuse spikes and slow spike-and-wave complexes (*R* right, *L* left, *DELT* deltoid muscle)

were recognizable in most patients [71]. These findings were confirmed in a recent review of the literature [69].

In the first year of life, the EEG picture can be that of an epileptic encephalopathy, with a poorly organized and reactive background activity and numerous multifocal epileptiform abnormalities (Fig. 33.9).

Seizure and ictal EEG—Seizures usually start between 2 months and 9 years of age and affect 65–80% of patients. In about 32% of cases, the first seizures are infantile spasms associated with an hypsarrhythmic EEG [69, 71]. In the first year of age, also episodes with the EEG characteristics of very short tonic seizures, i.e., diffuse fast paroxysmal activity discharges, are typically recorded (Fig. 33.10).

In about 25% of cases, first seizures are tonic, either focal or generalized, triggered by sleep with a later onset (up to 10 years); 30% of patients develop atypical absences, by age 1–7 years. All such patients later developed a Lennox-Gastaut syndrome [71, 72]. Focal, myoclonic, and atonic seizures are present in about 30%, 27%, and 28% of cases, respectively [69]. On the basis of a further very recent retrospective study of 45 patients with inv. dup (15) syndrome, it was possible to define four definite epileptic syndromes: generalized epilepsy, focal epilepsy, epileptic encephalopathy with spasms as the only seizure type, and epileptic encephalopathy with epileptic spasms associated with other seizure types [73].

Ictal EEG has been recorded only sporadically and shows diffuse spikes followed by high-voltage spikes and waves in the right frontal-temporal regions during an episode of head rotation to the right followed by rotation to the left, tonic adduction of the arms, chewing movements, and loss of consciousness (Fig. 33.11a, b); diffuse fast spikes followed by voltage decrease; mild diffuse attenuation of background activity with low-amplitude, rhythmic theta activity; or diffuse delta bursts followed by an electrodecremental response [69].

Epilepsy results well controlled in 35.7% of patients, satisfactorily controlled (seizure reduction >75%) in 7.1%, partially controlled (seizure reduction <50%) in 21.4%, and drug-resistant in 35.7%. Valproate, lamotrigine, and rufinamide seem to be the most effective AEDs [71].

33.1.10 15q13.3 Deletion Syndrome

15q13.2–13.3 deletion has been first described as a recurrent CNV associated with ID and epilepsy [74]. Subsequently, many other papers described this abnormality in association with a broad phenotype including polymorphous dysmorphisms, schizophrenia, severe neurodevelopmental disorders, autism spectrum disorder, and epilepsy [75–78]. The most frequent dysmorphic features are hypertelorism,

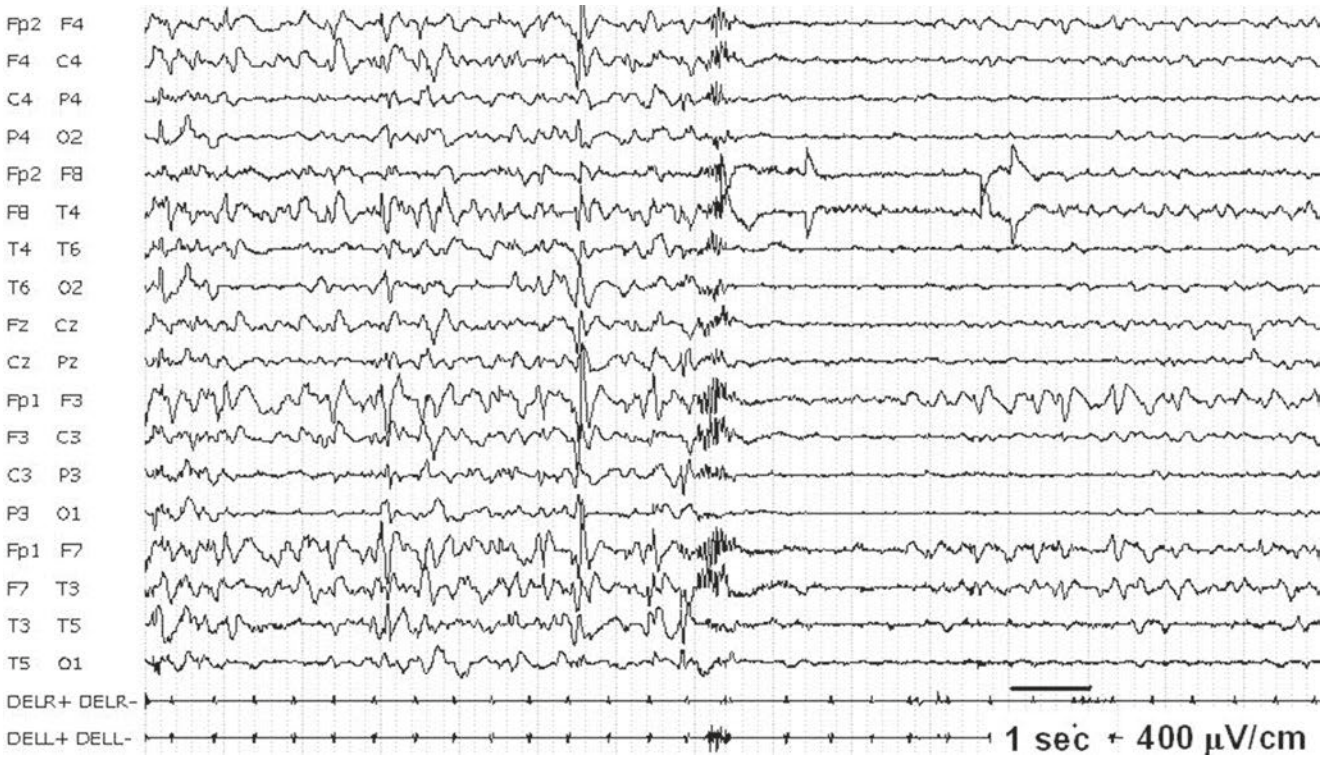

Fig. 33.10 The same patient of Fig. 33.9, at 3 years of age. EEG recording of a short tonic seizure, characterized by a short sequence of diffuse fast activity, followed by diffuse desynchronization. At surface EMG of deltoid muscles, a short tonic contraction, more intense on the left side, is evident (*R* right, *L* left, *DELT* deltoid muscle)

upslanting palpebral fissures, prominent philtrum with full everted lips, and clinodactyly [74].

The breakpoints 4 and 5 (BP4 and BP5) have been associated with the epilepsy phenotype [74]. A more severe phenotype has been found in the homozygous loss state [79, 80].

Recently, 15q13.3 deletion has been proposed as a common risk factor for epilepsy, since it is detected in about 1% of patients with idiopathic generalized epilepsy with or without other neurological manifestations [75, 81].

Haploinsufficiency of CHRNA7, which encodes for the α7 subunit of the acetylcholine receptor, is considered as the most likely responsible factor for the phenotype [75, 82]. No specific brain abnormalities have been reported in association to this CNV [15].

Interictal EEG—Focal (frontal, central, or parietal) spike/slow waves or generalized spike-and-wave complexes are present in some patients [77].

Seizures and ictal EEG—Absences have been recently reported in three patients with 15q13.3 deletion out of 570 children with epilepsy and ID [83]. Two other families with multiple affected individuals, presenting with absences or myoclonic absences associated to mild ID, have been described. The ictal EEG showed generalized polyspike-and-wave or spike-and-wave discharge. Apparently, the seizures persisted in the elderly and were difficult to control, requiring an association of at least two AEDs [84].

33.1.11 Ring Chromosome 20 Syndrome

Ring chromosome 20 is a rare chromosome anomaly. Until now, 170 cases of ring chromosome syndrome have been reported in literature [85]. Reported cases are almost exclusively sporadic and in mosaicism [47]. Phenotype is characterized by ID of variable degree, usually without major dysmorphic features; in approximately 90% of cases, drug-resistant seizures are present [47]. In some cases, MRI structural abnormalities (i.e., cortical dysplasias or hypoplasia of the corpus callosum or cerebellum) or PET neurotransmitter dysfunctions (i.e., reduced uptake of 18F-fluoro-l-DOPA) involving the frontal lobes and basal ganglia have been reported [86–89].

Telomeric regions involved in ring chromosome 20 contain some genes implied in the genesis of autosomal dominant epilepsies, such as benign neonatal familial convulsions or autosomal dominant frontal lobe epilepsies which are very different from ring chromosome 20 epilepsy. The mecha-

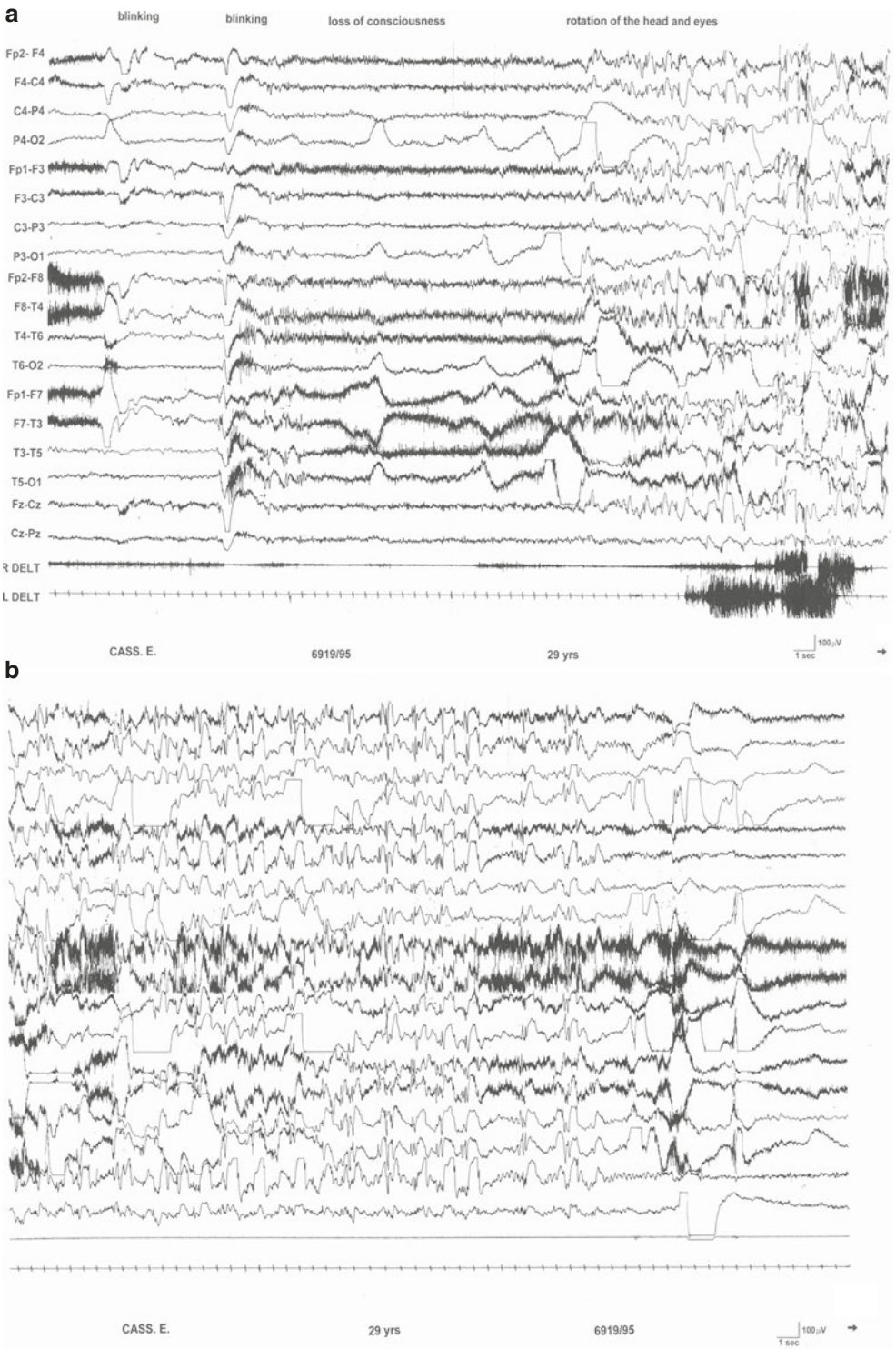

Fig. 33.11 (**a**, **b**) A 29-year-old female with inv. dup (15) syndrome. Ictal EEG is characterized by repetitive artifacts correlated with eye blinking, followed by diffuse desynchronization, and diffuse spikes (**a**) and spike-and-wave complexes (**b**). The patient presents loss of consciousness, generalized hypertonia, and head and eye deviation (*R* right, *L* left, *DELT* deltoid muscle)

nism of epileptogenesis in this syndrome is not well understood, since many of the patients have not deletions, and deleted genes are rather heterogenous. Alteration of gene expression derived from telomere position could be a possible explanation [47].

Interictal EEG—Slow waves, spikes, or spike-and-wave complexes most prominent over the fronto-central regions are often evident (Fig. 33.12). A peculiar EEG pattern, apparently subclinical, characterized by multifocal 5 Hz theta waves, mostly localized over the temporal regions, which persists after administration of diazepam intravenously [90]. More recently, a peculiar 3–7 Hz cortical rhythm has been found in ring chromosome 20 patients arising from the sensory-motor system [91].

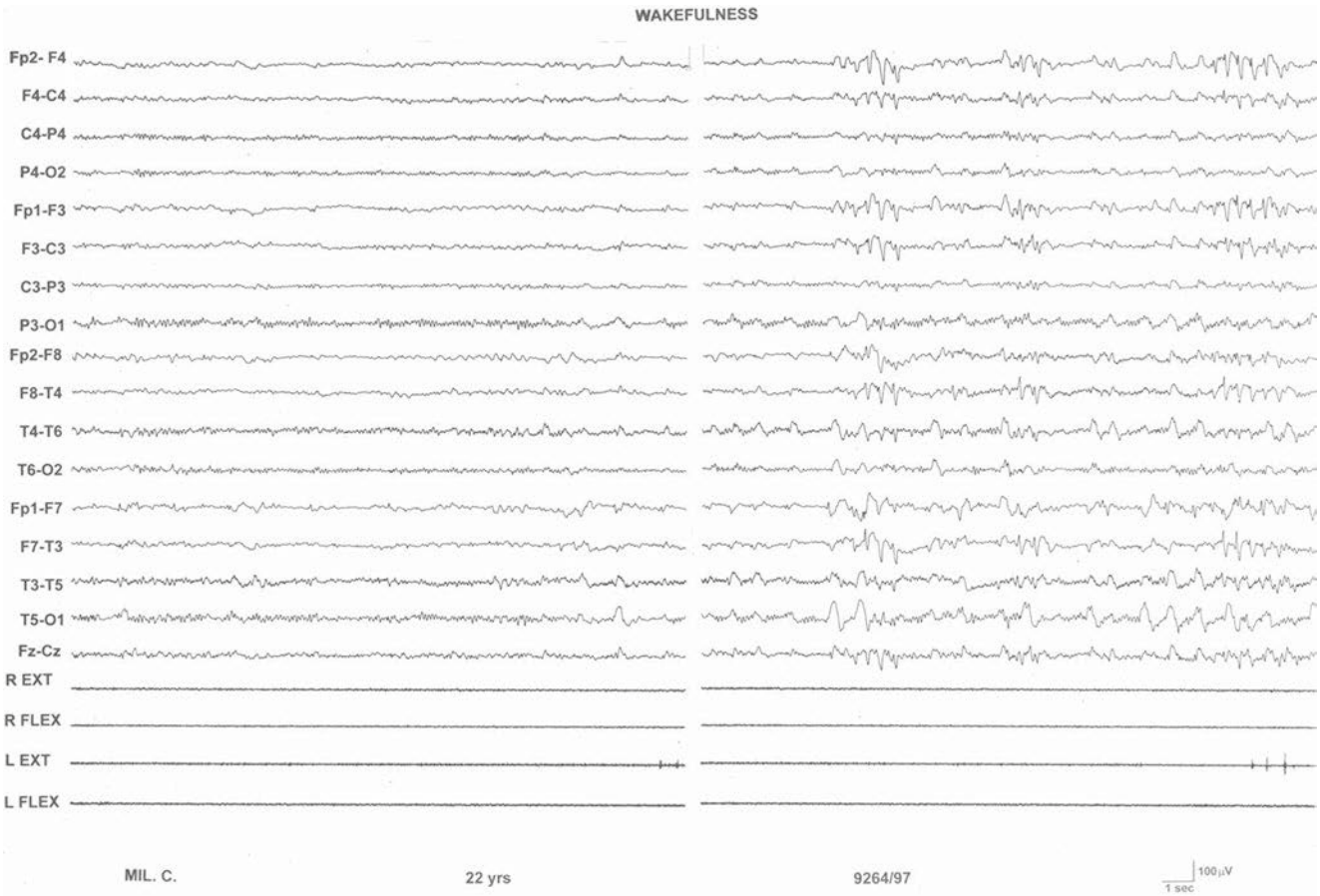

Fig. 33.12 A 22-year-old male with ring chromosome 20 syndrome. On the left side, wakefulness interictal EEG shows theta waves over the left temporal regions; on the right side, diffuse, repetitive sequences of theta waves and spike-and-wave complexes, prominent over the frontal regions of both hemispheres (*R* right, *L* left, *EXT* forearm extensor muscles, *FLEX* forearm flexor muscles)

The total duration of paroxysmal anomalies appeared significantly longer in patients (31–692 min) compared to controls (0–48 min) in a long-term EEG recording study [92].

Seizures and ictal EEG—Epilepsy, invariably drug-resistant, has an age-dependent course, and cognitive outcome is inversely correlated with age at seizure onset. When seizure onset occurs in childhood, terrifying hallucinations associated with focal motor seizures, often sleep-related, or dyscognitive seizures, are often the typical features, with a possible evolution in epileptic encephalopathy and non-convulsive status epilepticus [93, 94]. Subsequently, epilepsy is associated with non-convulsive status epilepticus, focal seizures with motor and autonomic features, and eyelid myoclonia [94]. Reflex seizures evoked by video games or by psychical stimuli have been sporadically reported [86, 95]. During non-convulsive status epilepticus, patients present a consciousness disturbance with bizarre or persevering behaviors, motor or verbal automatisms, fear, and perioral or eye myoclonia. The episodes of status occur daily or weekly and last also for hours [47, 87].

Ictal EEG is characterized by sequences of slow waves mixed with spikes, and spike-and-wave frequency can change during the episode (Fig. 33.13).

Drug-resistant frontal lobe seizures, recurrent non-convulsive status epilepticus, and characteristic EEG features represent a typical electroclinical triad which is specifically observed in all the patients with ring chromosome 20 syndrome [85].

Regarding treatment, there are no effective antiepileptic drugs for this epileptic syndrome, although valproate associated with lamotrigine was helpful in two children with non-convulsive status epilepticus. Vagal nerve stimulation was beneficial in one case [96].

33.1.12 Down Syndrome

Down syndrome (DS) or trisomy 21 is the commonest chromosome abnormality in subjects with ID, with an estimated prevalence of 1:800 live births. The phenotype is typical: ID of variable degree, short stature, muscle hypotonia, microceph-

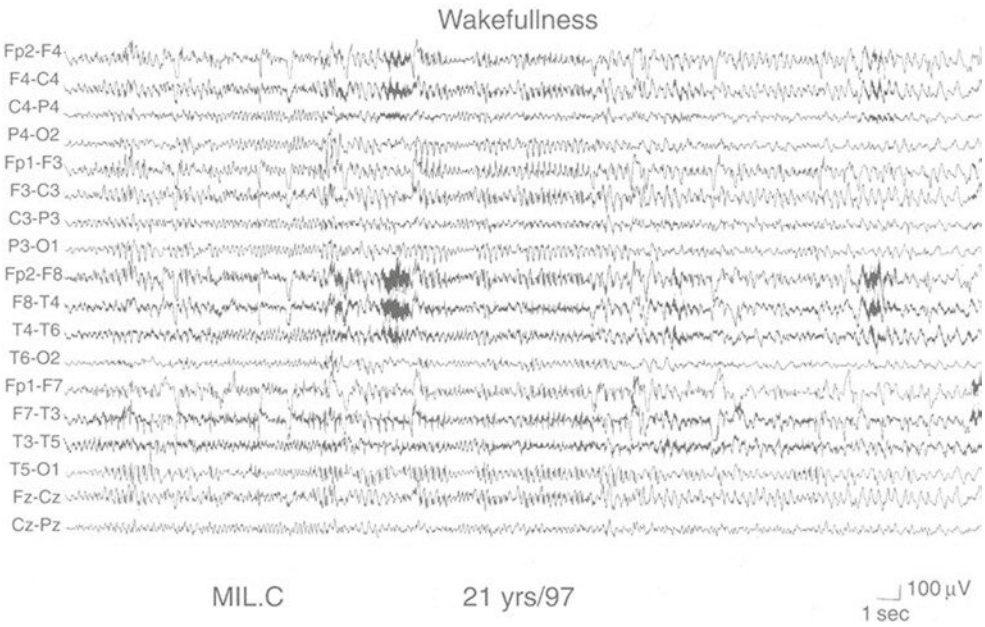

Fig. 33.13 The same patient of Fig. 33.12 at age 21 years. Ictal EEG, during nonconvulsive status epilepticus, characterized by sequences of slow waves intermixed with spikes; the frequency of the spike-and-wave complexes changes during the recording

aly, flat occiput, upslanting palpebral fissures, microtia, short neck, simian crease, and congenital heart malformations [47].

Trisomy 21 is due to a nondisjunction of chromosomes 21 during meiosis in 95% of cases; approximately 4% of patients present an unbalanced translocation and 1% a mosaicism; in a minimal percentage of cases, a duplication of the 21q22.3c critical region is present [59].

Gene imbalance in trisomy 21 determines developmental cell alterations in different tissues, such as the brevi and heart. Cortical gyri show a simplified pattern, and cytoarchitectural anomalies have been described, such as reduction of the GABAergic granular cells, lower neuronal density, delayed myelination, and dysgenesis of the dendritic spines [47].

Interictal EEG—Background activity is frequently slow, and bilateral hypsarrhythmia is evident in children with infantile spasms. Hypsarrhythmia reappears between spasms and clears after intravenous administration of diazepam, determining a pattern which is similar to that observed in idiopathic West syndrome (Fig. 33.14). In patients with Lennox-Gastaut syndrome, wakefulness EEG shows numerous slow waves mixed with spikes, prevalent over the frontal regions; during sleep, spike-and-wave complexes and polyspikes appear over the same regions [47, 59].

In adults, diffuse background slowing is the dominant EEG abnormality (60%). Epileptiform activity is present in 18% of cases, over the frontal, central, or temporal regions [97].

Seizures and ictal EEG—Seizures are present and heterogeneous in 10% of cases with DS [98]. In a large Italian cohort of patients with DS, 49% of subjects had infantile spasms, 33.7% had focal seizures, and 17.3% had generalized seizures. Febrile seizures were recorded in 4.8% subjects [99]. Patients with trisomy 21 may present a peculiar Lennox-Gastaut syndrome, characterized by late onset and high occurrence of reflex seizures, mostly precipitated by sudden unexpected sensory stimulations, usually preceding or accompanying the onset of the Lennox-Gastaut syndrome picture [100] (Fig. 33.15).

Some other cases have been reported with benign myoclonic epilepsy or with reflex seizures but without the features of the Lennox-Gastaut syndrome. The age at onset of spontaneous and reflex seizures tends to coincide in DS (2–24 years). Reflex seizures are evoked by different unexpected stimuli, their frequency is high. The same stimulus can evoke different types of seizures, such as atypical absences or tonic seizures [47, 59].

In adult patients with DS, a late myoclonic epilepsy with photosensitivity may appear, often associated with an Alzheimer-type dementia. At the EEG, myoclonic and generalized tonic-clonic seizures are recorded [47, 101, 102].

Outcome of seizures and response to treatment are strictly related to the type of epilepsy presented by the patients. In the majority of cases, myoclonic seizures are controlled by valproic acid or benzodiazepines; for drug-resistant infantile spasms, a short treatment with corticosteroids can be useful [47].

33.1.13 Fragile X Syndrome

The fragile X syndrome (FraXS) represents the most common familial form of ID known, affecting approximately 1:1500 males. Phenotype of FraXS includes ID, seizures, macroorchidism, large and prominent ears, narrow face, and signs of connective tissue dysplasia. A psychiatric phenotype is also recognizable in FraXS, with hyperactivity, language disorders, and autistic traits (i.e., tactile defensiveness, eye contact avoiding, stereotypies, hand biting, tantrums).

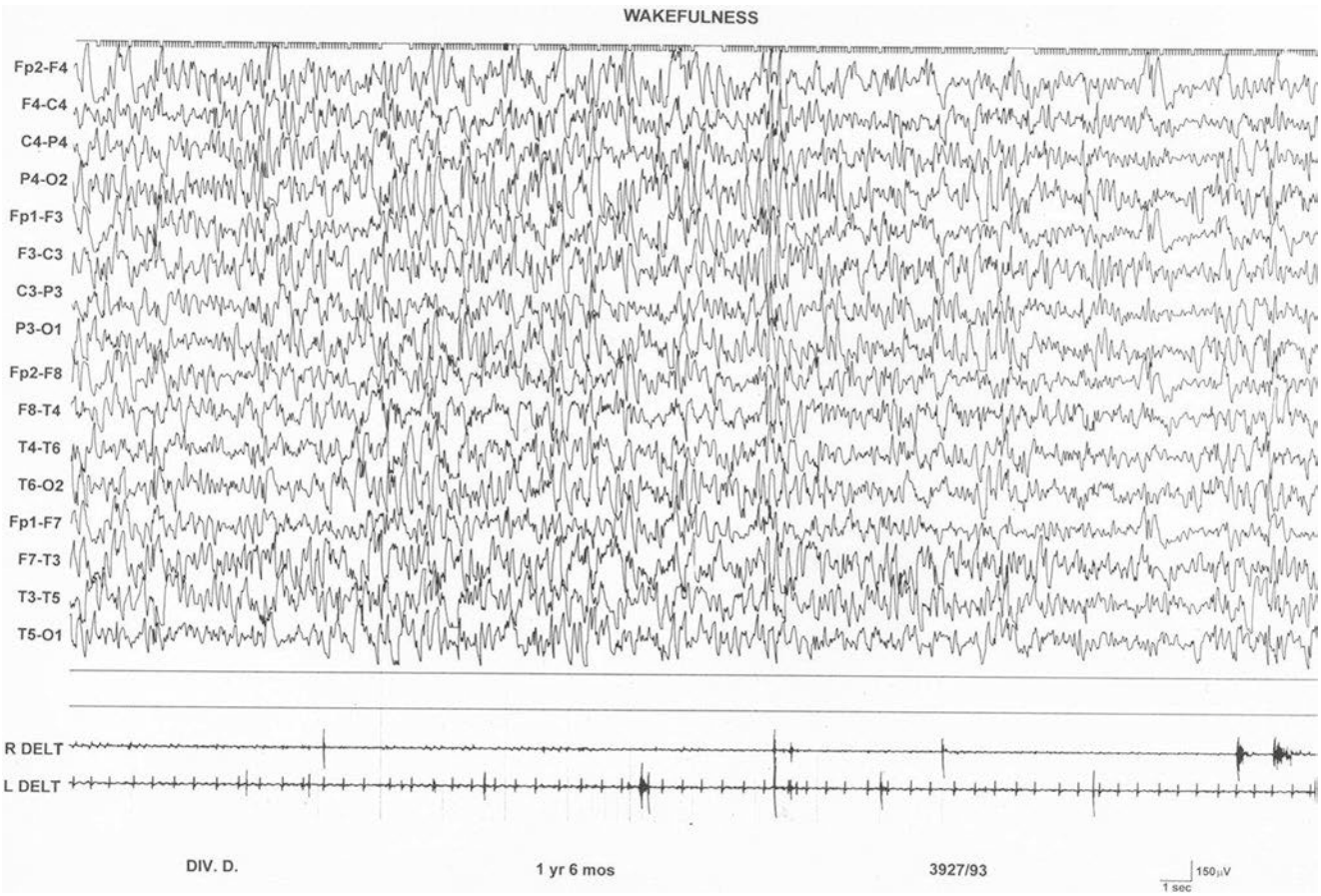

Fig. 33.14 A 1-year-old male with Down syndrome. Interictal EEG shows a hypsarrhythmic pattern (*R* right, *L* left, *DELT* deltoid muscle)

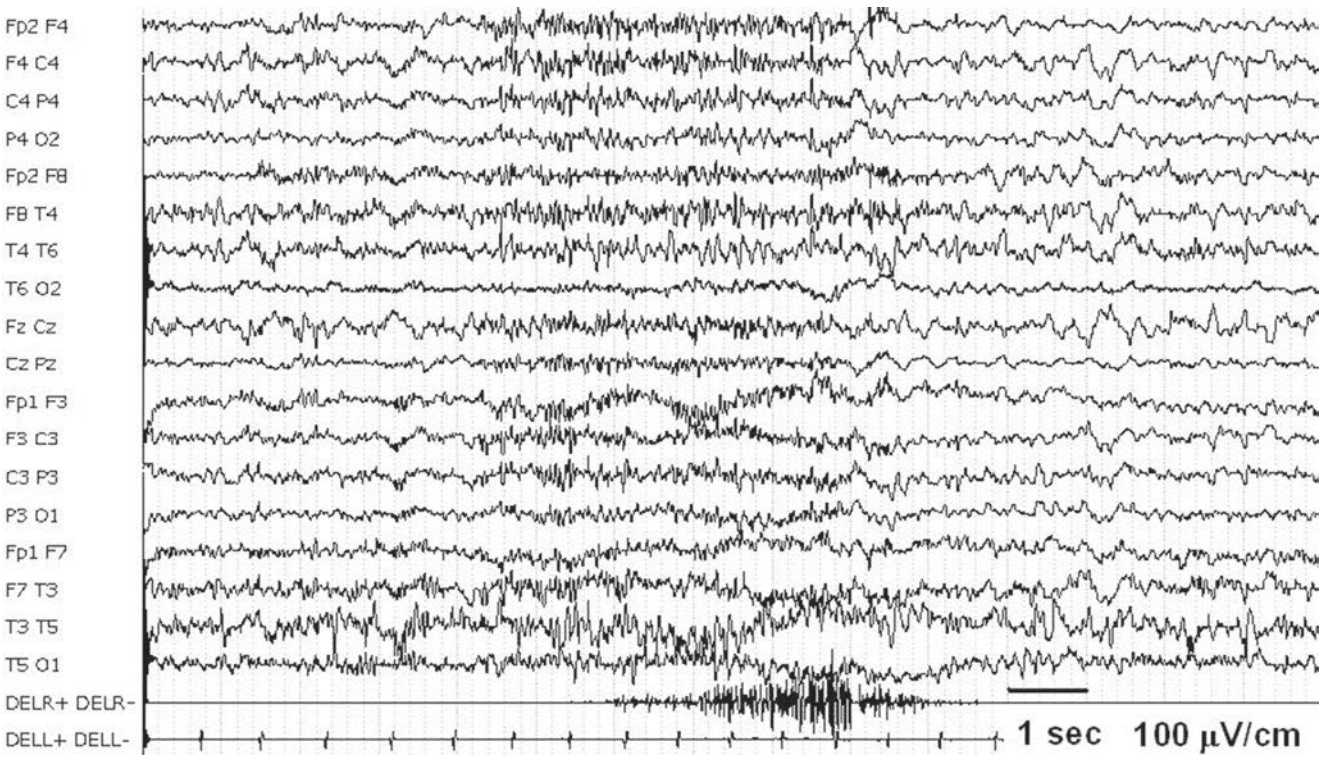

Fig. 33.15 A 43-year-old female with Down syndrome. Ictal EEG during sleep. The seizure is characterized by a diffuse fast activity discharge. At surface EMG of deltoid muscles, an asymmetrical tonic contraction, prevalent on the right side, is present (*R* right, *L* left, *DELT* deltoid muscle)

Originally, the demonstration of the fragile site at Xq27.3 region was dependent on the use of folate-deficient tissue culture media. More recently, molecular genetic studies revealed that FraXS results from a mutation in a (CGG) repeat in the FMR1 gene. In normal subjects, FMR1 allele contains 6–52 copies of the CGG repeat; in patients with FraXS, ≥200 repeats are present, and this determines the transcriptional silencing of the gene and the absence of the FMR protein (full mutation). An intermediate range of CGG repeats (50–200) characterizes the premutation status [47, 103].

The main neuropathologic findings in FraXS are abnormally long and thin cortical dendrites and abnormal dendrite spine morphology [104]. Furthermore, an abnormally enlarged hippocampal volume has been found in FraXS patients at MRI [105].

An increased susceptibility to audiogenic seizures is present in FraX knockout mice at all the ages tested, and these results support the validity of this animal model also for epilepsy and seizures in the human FraXS [106]. In addition, the introduction of the human FMR1 gene in knockout mice is able to revert the epileptic phenotype [107].

This evidence in the animal model and the presence of giant somatosensory evoked potentials (SEPs) in patients with FraXS seem indicate a relationship between FMR protein (FMRP) absence and cortical hyperexcitability [108]. FMRP may have a role in mRNA regulation in dendrites. Dendritic spines are longer and more frequently present an immature morphology in the pyramidal cells of the V stratum of the visual cortex in FMR1 knockout mice, mossy fibers of the hippocampal dentate gyrus have an altered distribution, GluR1 receptor cortical expression is depressed, and long-term potentiation is reduced [109–112]. A reduced number of mGlu5 receptors are tightly linked to the constituents of postsynaptic density and, in particular, to the constitutive forms of Homer proteins, with possible consequent alterations in synaptic plasticity [113].

Interictal EEG—Background activity is normal or slow, and a peculiar EEG pattern characterized by multifocal spikes, prevalently localized over the centro-temporal regions, is evident in approximately 40–50% of cases. These paroxysmal abnormalities appear at 3–4 years of age and persist up to 12–13 years, with a marked activation in NREM sleep (Fig. 33.16). In a retrospective and prospective study on 193 patients with FraXS, this EEG pattern was, respectively, found in 43.5% and 48% of cases at all ages, in 50.3% and 52% of subjects younger than 12 years. Spikes tended to disappear in adulthood, and if present, they were usually nonspecific [114].

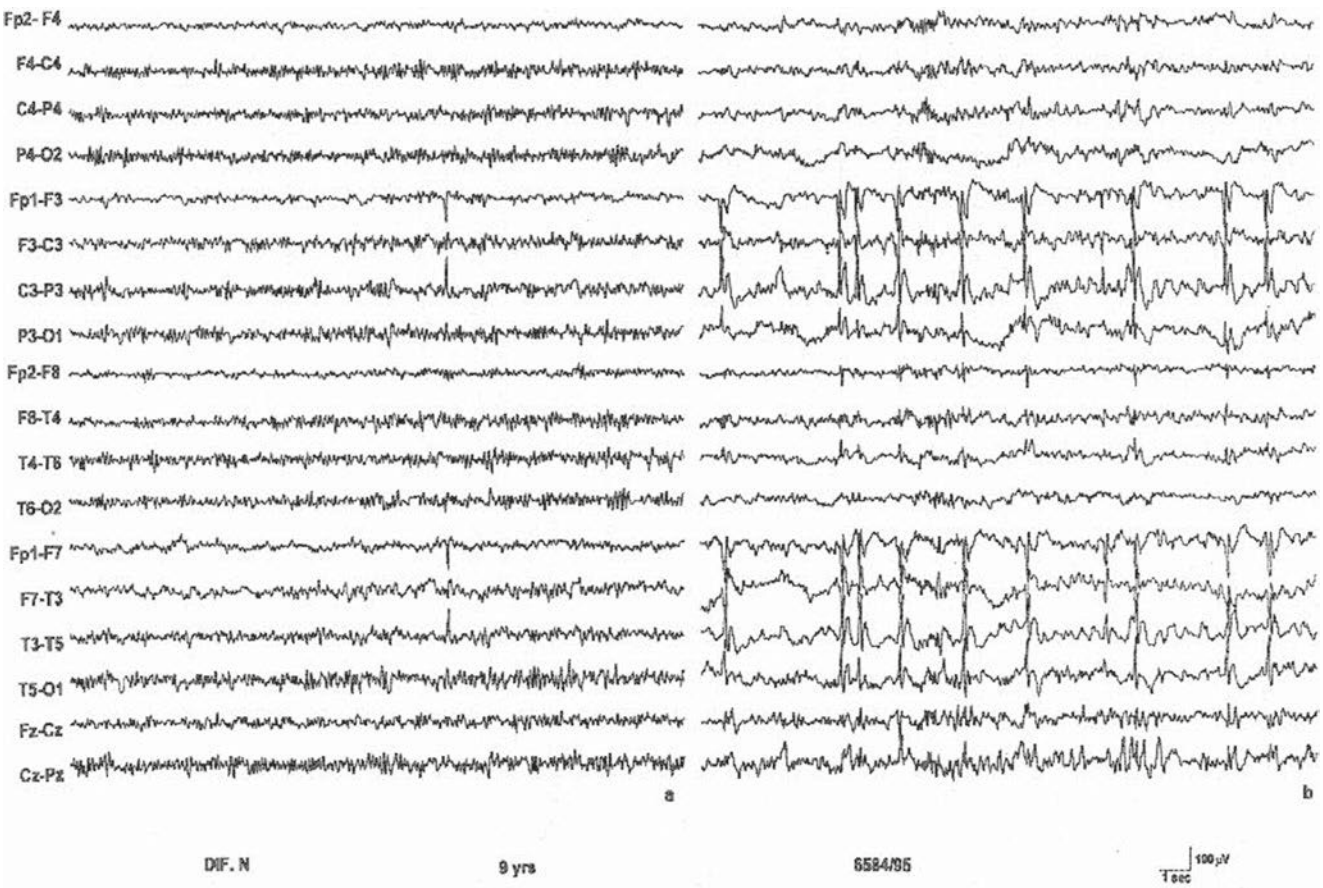

Fig. 33.16 A 9-year-old male with fragile X syndrome. On the left side, wakefulness EEG shows a single high-voltage spike localized over the right centro-temporal regions; on the right side, during sleep, there is a marked activation of paroxysmal abnormalities over the same regions

Seizures and ictal EEG—Ictal EEG figures of FraXS have never been published in literature. The prevalence of seizures ranges between 17 and 30%, respectively, in a retrospective and prospective population. The age at onset is between 2 and 9 years. Focal seizures with unawareness (originating from frontal or temporal lobes) predominate (>85%), in respect to other types of seizures, such as generalized tonic-clonic seizures or focal seizure without loss of consciousness [114]. Nine patients with FraXS and status epilepticus have been reported [115].

The choice of the antiepileptic drug depends from the type of epilepsy or seizures. At least 80% of patients reach a good control of seizures.

33.1.14 Klinefelter Syndrome

Klinefelter syndrome (KS) is a relatively common genetic condition characterized by mild or moderate ID, behavior disturbances, infertility, tall stature, long limbs, hypogonadism, ginecomasty, and reduced hair. The estimated prevalence is around 1.7:1000 males. The abnormality consists of a meiotic nondisjunction of sexual chromosomes, which determines the presence of one or more supplementary X chromosomes. The mosaic forms derive from a post-zygotic nondisjunction of X chromosomes [47, 59].

Neuropathology is not specific, and only one case with polymicrogyria and megalencephaly has been reported [116].

Interictal EEG—Background activity can be slow, and focal or generalized paroxysms are present (Figs. 33.17 and 33.18).

Seizures and ictal EEG—Seizures are present in 2–10% of cases. Generalized seizures are more frequent than focal ones, with atypical absences, generalized tonic-clonic seizures. One case with West syndrome has been described [117]. Seizures are easily controlled by therapy [47, 118, 119].

33.1.15 Xp11.22–11.23 Duplication Syndrome

A group of nine subjects with a microduplication at Xp11.22–11.23 has been identified at a diagnostic genome array screening of 2400 subjects with ID. The duplication was either familial or sporadic. The phenotype is characterized by a cognitive disturbance (from borderline functioning to severe ID), speech delay, poor speech articulation, hoarse and/or nasal voice, early puberty, overweight, nonspecific facial dysmorphic features, and lower-extremity anomalies, including flat or arched feet, fifth-toe hypoplasia, and syndactyly. Neuroimaging does not show specific abnormalities [120].

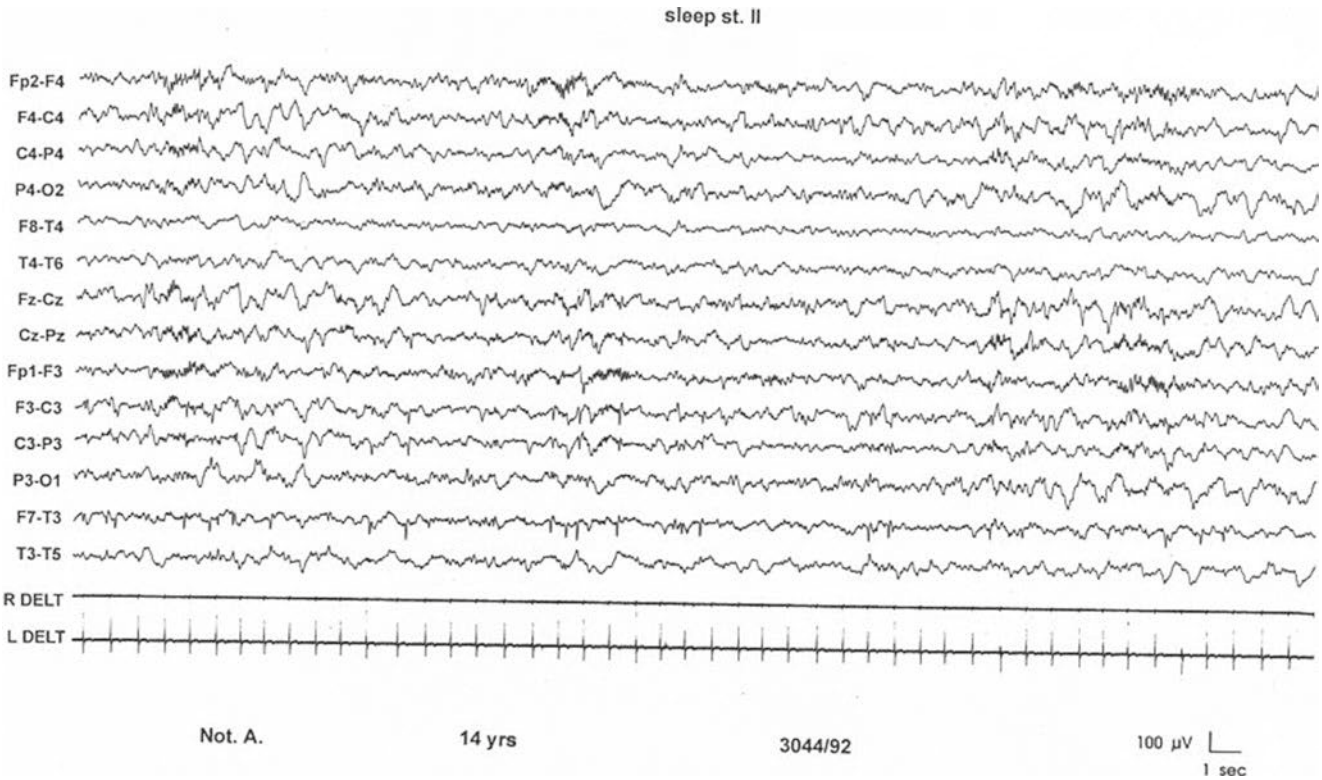

Fig. 33.17 A 14-year-old male with Klinefelter syndrome. During sleep EEG, focal spikes are recorded over the left fronto-centro-temporal regions and vertex (*R* right, *L* left, *DELT* deltoid muscle)

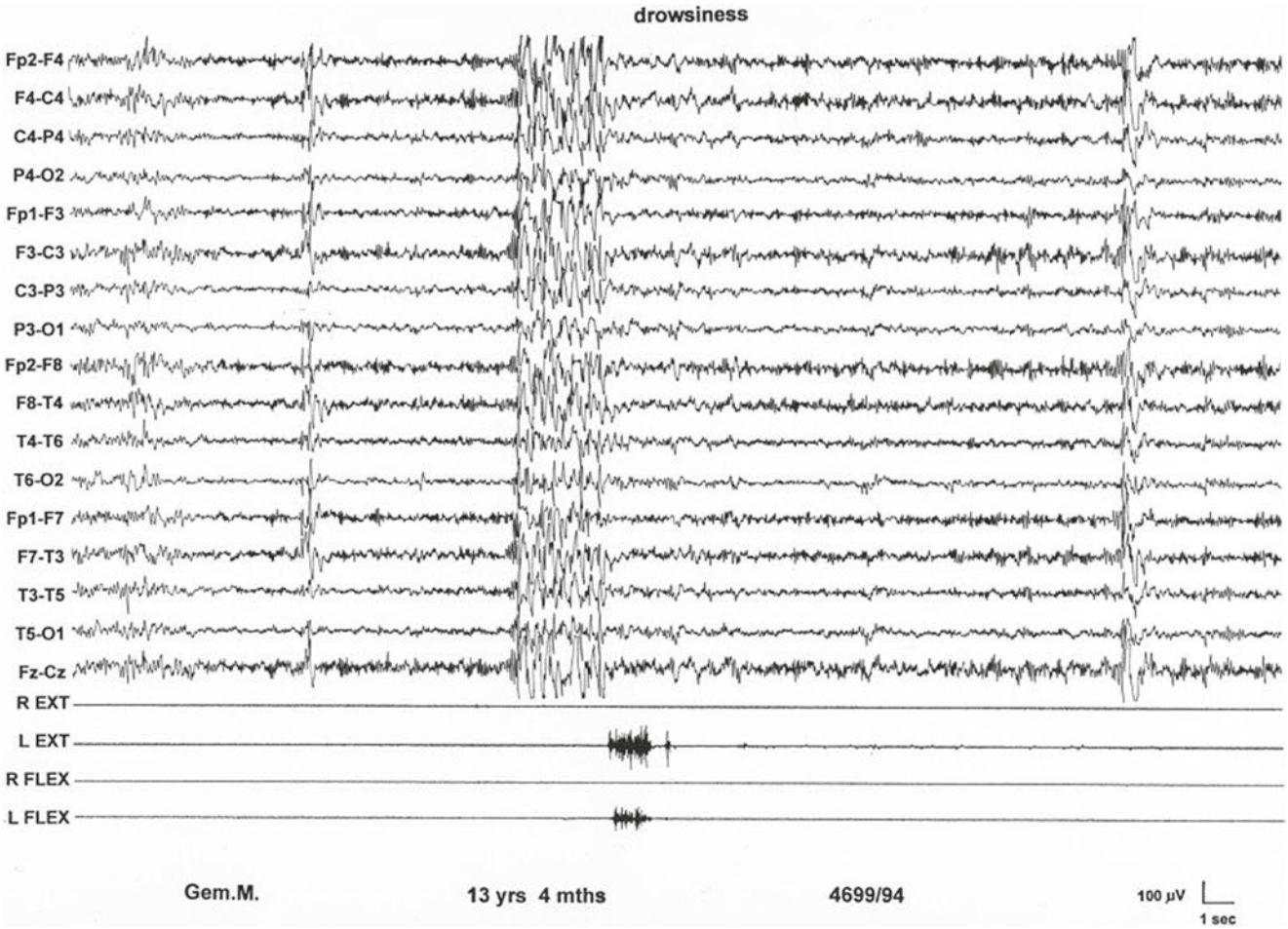

Fig. 33.18 A 13-year-old male with Klinefelter syndrome. EEG during drowsiness presents numerous diffuse spikes and spike-and-waves (*R* right, *L* left, *EXT* forearm extensor muscles, *FLEX* forearm flexor muscles)

Xp11.2 is a gene-rich, rearrangement-prone region within the critical linkage interval for several neurogenetic disorders harboring X-linked mental retardation (MRX) genes which could be responsible for the syndrome phenotype [121].

Interictal EEG—A study contributed to better define the neurological phenotype of this new syndrome [120]. Electrical status epilepticus during sleep (ESES) was present in five of nine patients, particularly in younger ones (from 5 to 13 years), and was associated with speech delay in all cases. ESES was controlled by antiepileptic drugs in three out of five patients; the other two patients remained untreated.

Seizures and ictal EEG—Epilepsy was reported in about one third of cases, with different types of seizures starting in infancy or in childhood, such as clonic jerks of the limbs and staring, generalized tonic-clonic seizures during sleep, and absences. Outcome was favorable [120].

33.1.16 XYY Syndrome

The XYY syndrome is characterized by an extra copy of the Y chromosome, with an incidence of 1:1000 males. Males with 47, XYY syndrome are sometimes taller than average and have a variable risk of cognitive, language, and behavioral deficits. Neuroimaging is generally normal in the cases reported [122].

Interictal EEG—In a series of four patients with XYY, EEG background activity was normal; focal EEG profile showed rolandic-like focal paroxysms localized over the vertex area or over central-temporal regions, markedly activated during sleep; these EEG traits were independent of the presence or not of seizures. However, other cases with slow background activity, with generalized or multifocal paroxysmal abnormalities, and with hypsarrythmia have been described [122].

Seizures and ictal EEG—Seizures, when present, may present features such as age of onset, clinical characteristic evolution, and good response to antiepileptic drugs, which are very similar to those of rolandic epilepsy [122].

33.2 Cortical Malformations

Malformations of cortical development represent another group of etiologies that can determine neurodevelopmental disorders and epilepsy in the first years of life. They are characterized by a wide spectrum of syndromes. There are very severe conditions that present with marked delay of psychomotor development and early and drug-resistant seizures but also milder clinical pictures that are discovered late, often after the occurrence of seizures in subjects without neurological signs.

Recently, the advances in the technology of noninvasive neuroimaging techniques, such as high-field MRI, facilitated diagnosis and structural and topographic classification of these syndromes.

Cortical malformations may occur as sporadic or familial forms. Genetic studies, i.e., Sanger sequencing, next-generation sequencing (NGS), and whole exome or genome sequencing (WES, WGS), allowed to discover a great number of genes regulating the development of the CNS.

Here, I will describe the main cortical malformative syndromes, focusing special attention to the specific interictal and ictal EEG pictures. They are classically distinguished taking into account the different phases of the intrauterine CNS development in which they occur: malformations secondary to abnormal neuronal and glial proliferation or apoptosis (tuberous sclerosis complex, focal cortical dysplasias type II, hemimegalencephaly); malformations due to abnormal neuronal migration (lissencephaly, subcortical band heterotopia, periventricular nodular heterotopia); and malformations secondary to abnormal postmigrational development (schizencephaly, polymicrogyria, focal cortical dysplasias type I and III).

33.2.1 Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is a neurocutaneous syndrome involving the CNS, retina, skin, kidney, heart, and lungs with an estimated prevalence ranging from 1:30,000 to 1:50,000. The characteristic cerebral lesions are represented by the cortical tubers, the subependymal nodules, and the giant cell tumors. Cortical tubers, highly epileptogenic, often multiple, are hamartomas easily recognizable at MRI, as enlarged gyri with an atypical form and with an altered signal intensity (Fig. 33.19) [123–125].

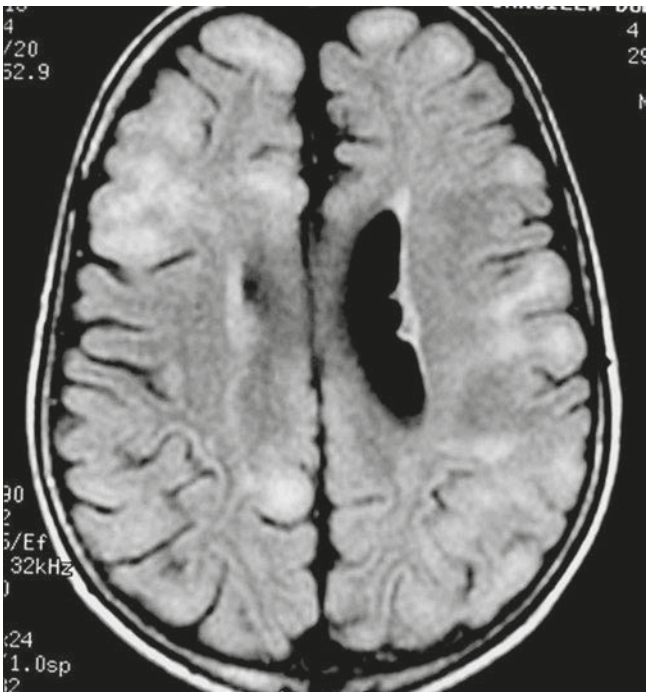

Fig. 33.19 Brain MRI of a 4-year-old male with tuberous sclerosis. Numerous cortical tubers are present over both hemispheres

TSC can occur in a sporadic or familial way, and in this case, it has autosomal dominant inheritance. TSC is caused by mutations of the TSC1 (tuberin) or TSC2 (hamartin) genes, respectively, localized in the 9q34 and 16p13.3 regions. The TSC1-TSC2 protein complex integrates cues from growth factors, the cell cycle, and nutrients to regulate the activity of mammalian target of rapamycin (mTOR), p70S6 kinase (S6K), 4E-BP1, and ribosomal S6 proteins. Mutations leading to loss of function of the TSC1 or TSC2 genes result in enhanced Rheb-GTP signaling and consequent mTOR activation, causing increased cell growth, ribosome biogenesis, and mRNA translation; the result is overgrowth of normal cells and production of abnormal cells in many organs [126].

Approximately 50% of the familial cases are caused by TSC1 mutations; among sporadic cases, TSC2 mutations are present in about 50% of cases, and TSC1 mutations are found in 10% of cases. Somatic mosaicism is present in 8–15% of cases.

Studies on genotype-phenotype correlation suggested that TSC1 mutations are usually correlated with a milder clinical picture: lower frequency of seizures, minor cognitive dysfunction, minor number of tubers and subependymal nodules, and milder impairment of the kidney, retina, and skin [123–125].

Interictal EEG—When EEG is recorded between the neonatal period and the seizure onset, focal or multifocal

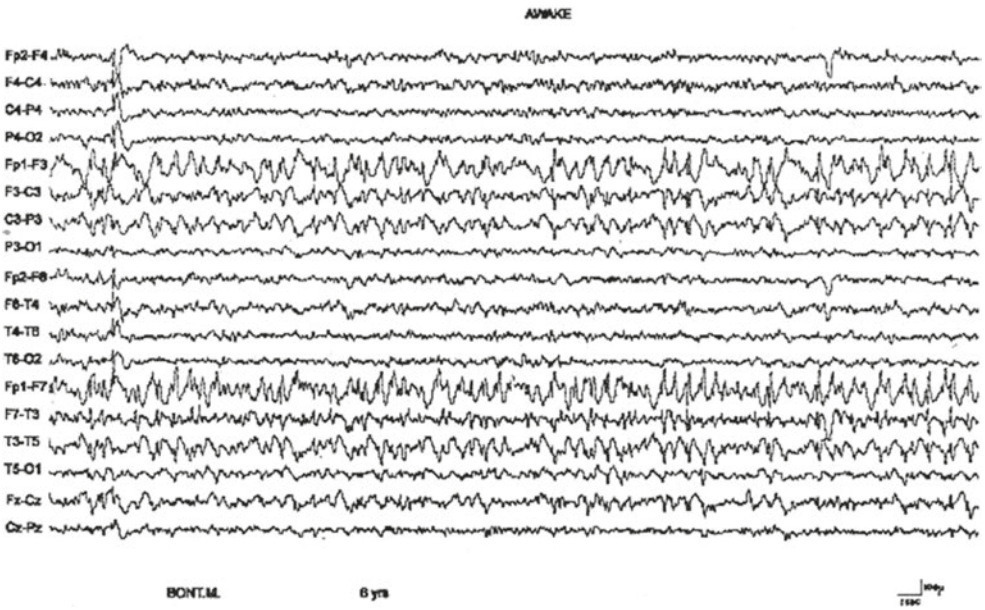

Fig. 33.20 A 6-year-old male with tuberous sclerosis. Wakefulness EEG shows quasi-continuous sharp waves and spikes over the left fronto-central-temporal (correlated with the localization of a large cortical tuber)

paroxysmal abnormalities are evident. Children with infantile spasms show a wakefulness EEG characterized by multifocal paroxysms, with the morphology of high-voltage spikes and irregular slow waves, at 2–3 Hz, sometimes with a typical hypsarrhythmic pattern.

Subsequently, this pattern tends to disappear, and interictal EEG shows only focal or multifocal spikes or slow waves (Fig. 33.20).

These paroxysms are localized over the temporal or occipital regions at first, often correlated with the tubers, but after 2 years of age, they can be observed also over the frontal regions.

NREM sleep is characterized by activation of paroxysmal abnormalities. They become generalized in the evolution and synchronous polyspike-and-wave discharges, sometimes followed by short abrupt flattenings are evident. Spindle can be poorly recognizable (Fig. 33.21). During REM sleep, epileptiform activity is less frequent, and diffuse paroxysms tend to disappear.

In some patients, interictal EEG is seen in Lennox-Gastaut syndrome, but this pattern actually could be the evolution of a frontal epilepsy to a secondary generalization [123, 124].

Seizures and ictal EEG—Seizures are polymorphous: infantile spasms in 50% of cases, but also tonic seizures, focal seizures, atypical absences, and generalized tonic-clonic seizures. They start before 15 months of age. In about one third of cases, prognosis is severe. A correlation between number and size of tubers and severity of epilepsy has been proposed.

Infantile spasms, at EEG, are characterized by a focal discharge of spikes or polyspikes originating from central, temporal, or occipital regions, followed by irregular diffuse slow waves and by a sudden desynchronization of the background activity. Paroxysmal activity disappears during the cluster of spasms and re-emerges at the end (Fig. 33.22).

It is possible to identify three different clinical and EEG phenotypes of epilepsy in TSC.

1. Onset with spasms or focal seizures; spasms may present a focal component (unilateral or bilateral with eye deviation or eye myoclonias) or may be "pseudoperiodic," in clusters lasting also many minutes; they can evolve in tonic seizures with a focal component.
2. An epileptic encephalopathy from the onset; the background activity is slow with quasi-continuous diffuse or multifocal paroxysmal abnormalities during wakefulness and sleep; seizures are polymorphous, frequent, and drug-resistant.
3. A focal epilepsy, with variable frequency of rather stereotyped seizures (Fig. 33.23) [123, 124].

Treatment of seizures in TSC depends from the specific clinical and EEG aspects of epilepsy.

Among the new antiepileptic drugs, vigabatrin demonstrated the higher efficacy in the treatment of infantile spasms associated to TSC. Response to vigabatrin is much quicker than that observed with steroids, benzodiazepines, and valproic acid; however, focal seizures can persist after the disappearance of spasms. However, the high risk of visual field alterations limits the use of this drug. Lamotrigine determines a seizure reduction higher than 50–80% of cases. Its efficacy is prolonged, but responders prevalently belong to the group of patients with focal seizures. Felbamate may be helpful, but it determines a risk of severe aplastic anemia. Also topiramate has been successfully used in patients with focal seizures with or without secondary generalization [123].

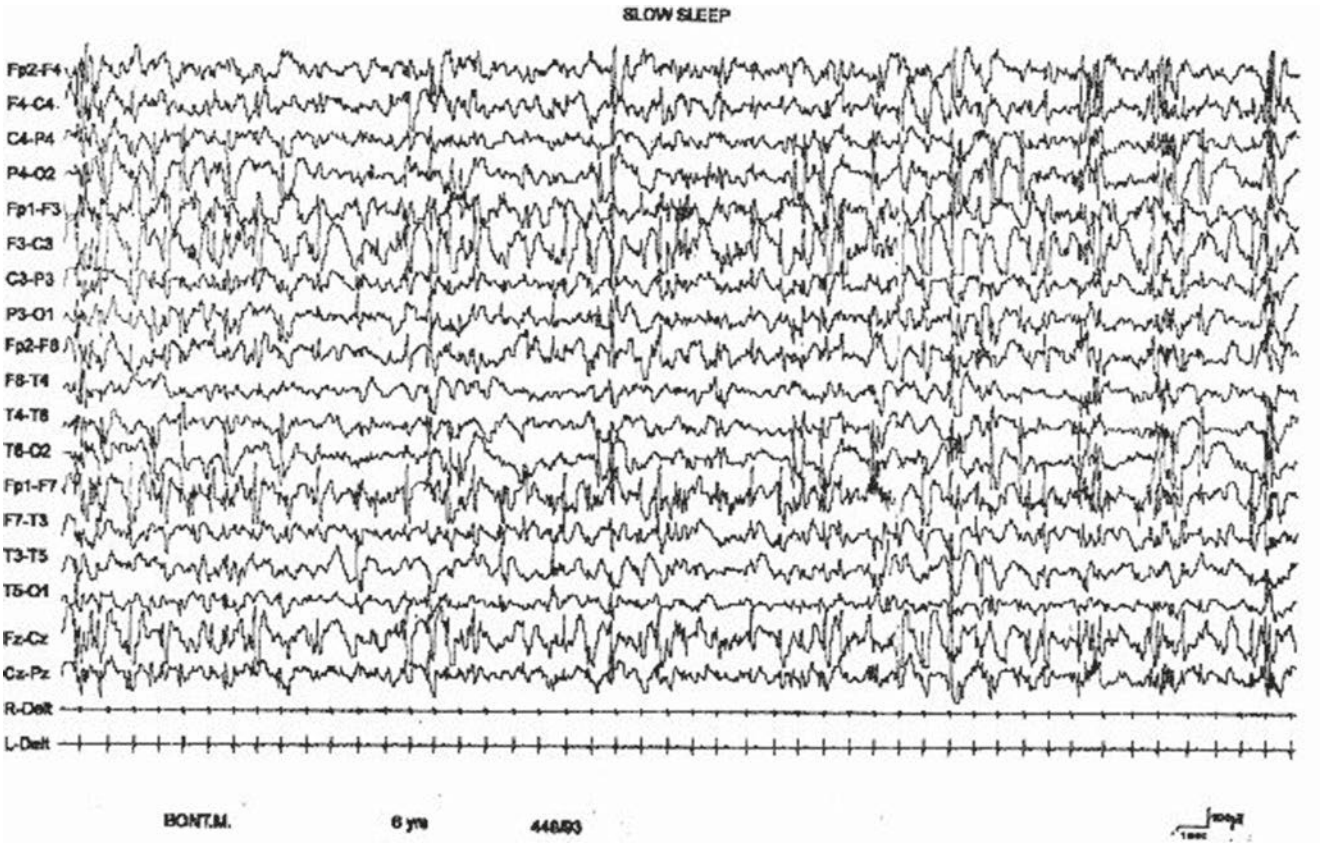

Fig. 33.21 The same subject of Fig. 33.20. During sleep, paroxysmal abnormalities become quasi- continuous over both hemispheres (*R* right, *L* left, *DELT* deltoid muscle)

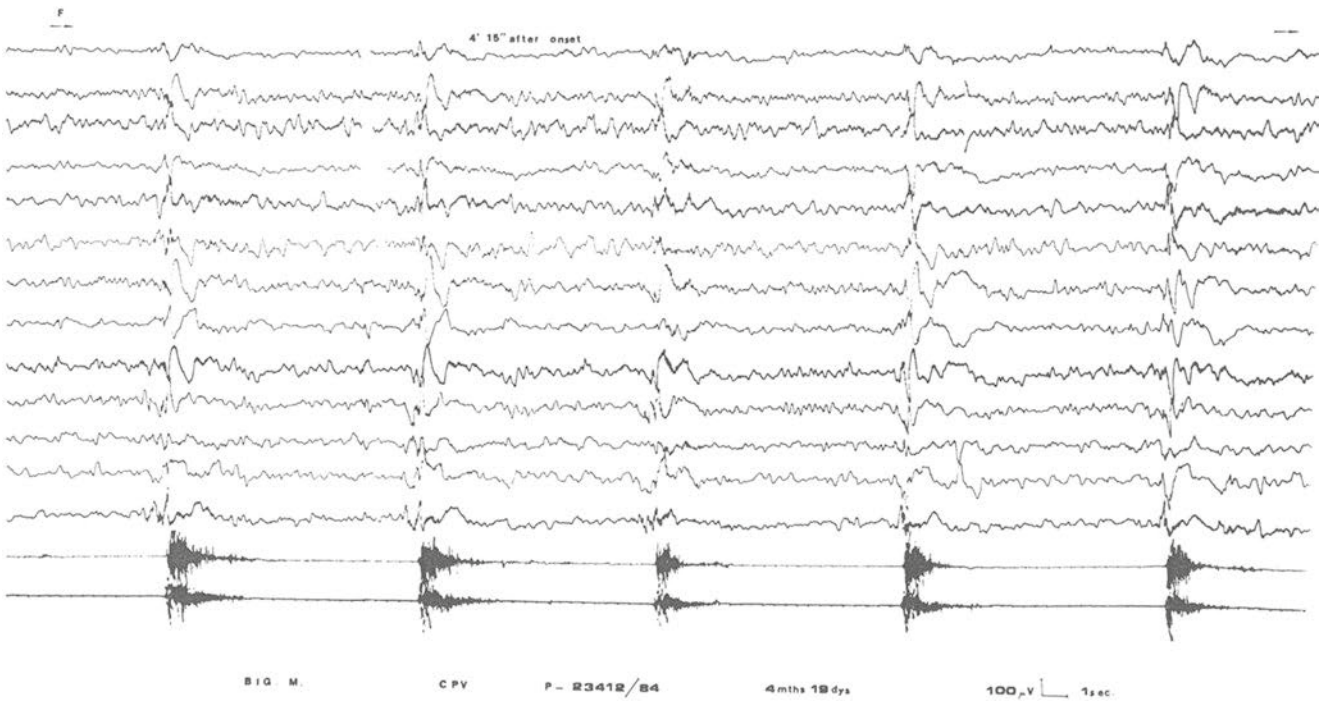

Fig. 33.22 Male at 4 months of age with tuberous sclerosis. Ictal EEG shows a long series of spasms which interrupts hypsarrhythmia. Spasms are characterized by repetitive synchronous and symmetrical muscle contractions, corresponding to high-voltage diffuse slow complexes at the EEG

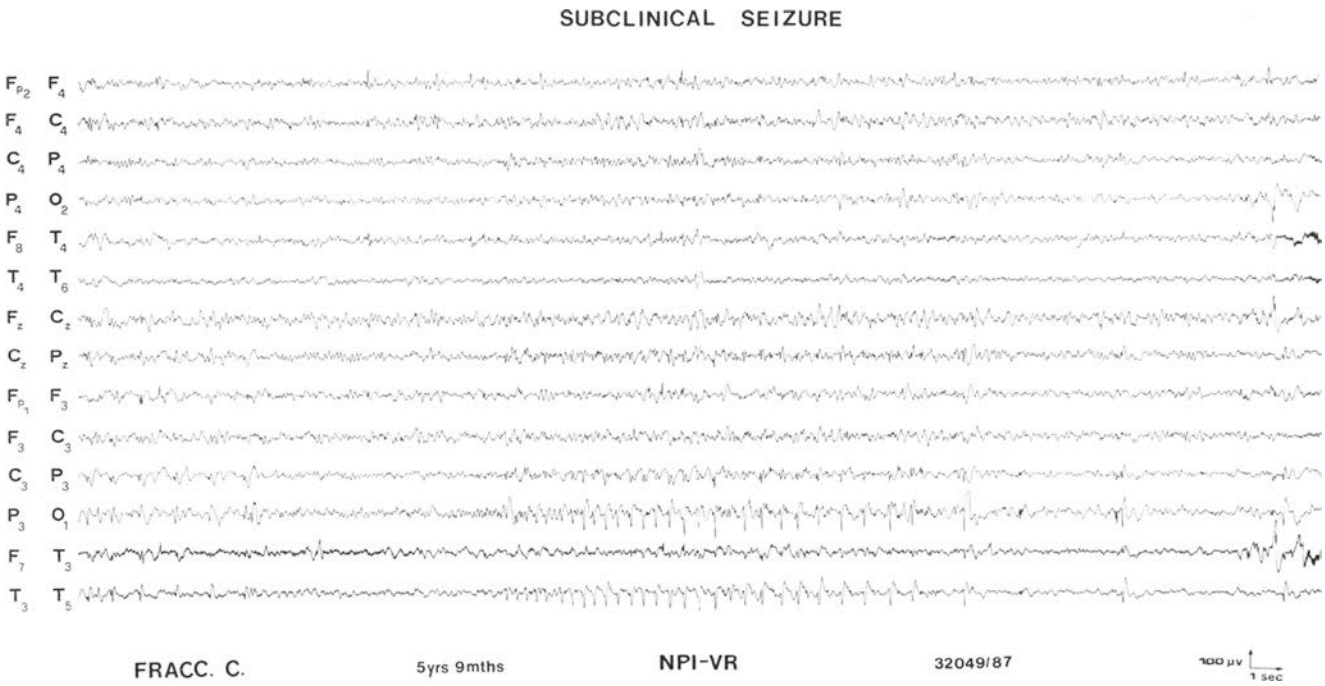

Fig. 33.23 A 5-year-old female with tuberous sclerosis. A subclinical focal seizure, characterized by rhythmical spikes, is recorded over the left temporo-occipital regions

Multimodality imaging, including MRI scans, positron emission tomography, and magnetoencephalography, has been used to localize epileptogenic tubers and peritubular regions. Surgical resection of epileptogenic foci has yielded excellent results: seizures have been stopped in 57% of drug-resistant patients. If antiepileptic drugs fail and no clear epileptogenic tuber is identified, alternative therapies, such as ketogenic diet, and vagus nerve stimulation can be considered [125].

There is now also particular interest in the potential role of mTOR inhibitors in treating seizures, neurodevelopmental disabilities, and other extra-neurological manifestations of TSC. Although no mTOR inhibitors are currently indicated specifically for the treatment of seizures associated with TSC, the results of some studies suggest that sirolimus and everolimus may be effective [127].

33.2.2 Focal Cortical Dysplasias Type II

The new classification supports the classification of focal cortical dysplasias (FCDs) type II as a malformation due to abnormal proliferation. FCDs type II are malformations presenting with disrupted cortical lamination and specific cytologic abnormalities, which differentiate FCDs type IIa (dysmorphic neurons without balloon cells) and FCDs type IIb (dysmorphic neurons and balloon cells).

FCDs type IIa are rarely detected at MRI. FCDs type IIb are often characterized by hypo-, de-, or dysmyelination (blurring) in the subcortical white matter. The white matter signal alterations frequently taper from a gyrus or a sulcus toward the ventricle, reflecting the involvement of radial glial-neuronal units. This is named "transmantle sign" and is almost exclusively found in FCD type IIb [128].

Using WES in blood, saliva and brain biopsy specimens from FCD type II patients, somatic mutations of mTOR, and other five genes involved in mTOR pathways (PIK3CA, PIK3R2, AKT3, TSC1, and TSC2) were identified. In addition to somatic mutations, also germline mutations of DEP domain containing 5 (DEPDC5), nitrogen permease regulator-like 3 (NPRL3), and TSC1 genes have been associated with FCDs type II [129].

Interictal EEG—In FCDs type IIb, stereo-EEG, subdural and epidural, and sometimes surface recordings are characterized by total absence of background activity and a distinctive pattern of repetitive, high amplitude, fast spikes, followed by high amplitude slow waves, interspersed with relatively flat periods. Sometimes, also repetitive bursts of low-amplitude high-frequency oscillations intermixed with flat periods can be recorded. During sleep, fast spikes become more evident, activated in frequency, and spread into contiguous nonlesional areas. During REM sleep, these paroxysms are markedly reduced [128].

Seizures and ictal EEG—Seizure presentation is age and location related. In a recent study, six different ictal patterns were described in FCDs. In FCDs type II, the most prevalent resulted pattern 3 (burst of polyspikes followed by low-voltage fast activity, LVFA), pattern 1 (LVFA), and pattern 2

(preictal spiking followed by LVFA). Better postsurgical outcome is associated with patterns including LVFA [130].

Seizures are often drug-resistant. Pathogenic mutations of mTOR genes open the way to new treatment options with mTOR inhibitors. The ketogenic diet can be effective. Surgery and neurostimulation techniques, such as vagus nerve stimulation, have demonstrated variable clinical outcomes [131].

33.2.3 Hemimegalencephaly

Hemimegalencephaly (HME) is a rare cortical malformation characterized by the enlargement of one cerebral hemisphere, associated with developmental delay, contralateral hemiplegia, and severe epilepsy with onset in the first months of life. It can be isolated or syndromic, in Proteus syndrome, neurofibromatosis, hypomelanosis of Ito, Klippel-Weber-Trenaunay syndrome, TSC, and linear sebaceous nevus syndrome.

An abnormal gyral pattern (pachygyria, polygyria, or polymicrogyria), as well as increased thickness of the cortex of the enlarged hemisphere are present at neuropathology or neuroimaging.

The similarities in neuropathology between HME, FCD type II, and TSC strongly suggest a pathogenic link between these malformations, leading to the introduction of the common term of "mTORopathies."

De novo somatic mutations in PIK3CA, AKT3, and MTOR, encoding regulators of the mTOR signaling pathway, have been reported, and recent studies reported pathogenic germline and mosaic mutations in multiple phosphatidylinositol 3-kinase (PI3K)-AKT3-mTOR signaling genes (i.e., DEPDC5, PIK3CA, mTOR, and TSC2) [132].

Interictal EEG—Three different EEG patterns have been described: (1) triphasic complexes of very large voltage characterized by a small negative wave, followed by a large amplitude, positive slow spike, and a very slow wave, which formed a "plateau," often associated with a monomorphic, sharp theta activity; (2) an asymmetrical suppression-burst pattern, with bursts of "alpha-like" activity interrupted by hypoactive phases on the affected hemisphere and high-voltage bursts of polymorphous polyspikes on the unaffected side; and (3) a large amplitude asymmetrical "alpha-like" activity, at 7–12 Hz, scarcely modified by waking state. "Alpha-like" pattern was associated with a relatively favorable outcome than triphasic complexes; prognostic significance of the suppression-burst was less clear [133].

Seizures and ictal EEG—Seizures have a very early onset, also in neonatal age. Semiology is characterized by repeated tonic seizures in series, usually asymmetric because of a greater involvement of the side contralateral to the brain malformation, associated with homolateral eye deviation; they can be preceded by short, clonic, unilateral jerks. Also atonic seizures, spasms, and myoclonic jerks can be observed. In one case, ictal EEG was characterized by focal theta activity followed by isolated periodic high-voltage diffuse triphasic delta wave complexes. In a neonate, epileptic negative myoclonus has been recorded. In the evolution, epilepsy can assume a picture resembling Ohtahara syndrome before, usually after the third month of life, then can present electroclinical features typical of West and Lennox-Gastaut syndrome, finally a focal epilepsy or epilepsia partialis continua is evident.

Seizures are almost invariably resistant to antiepileptic drugs, and early surgery is needed to remove or functionally disconnect the epileptogenic area within the affected hemisphere, in order to control seizures, protect the healthy hemisphere from damage, and prevent cognitive impairment [132, 134–136].

33.2.4 Lissencephaly

Classical lissencephaly (LIS) represents a very severe neurodevelopmental disorders due to a rare abnormality of neuronal migration occurring between the 12th and 16th week of pregnancy, determining a smooth and thickened cortex constituted by four layers instead of six layers (agyria-pachygyria, Fig. 33.24). Miller-Dieker syndrome (MDS) is a LIS accompanied by profound ID, often by the absence of

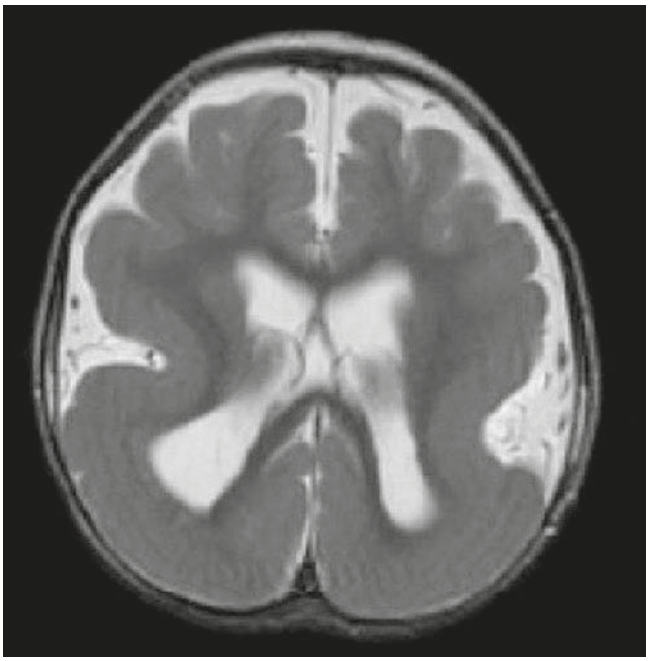

Fig. 33.24 Brain MRI of a 4-year-old male with lissencephaly (TUBA1A mutation). The typical posterior-to-anterior gradient of agyria-pachygyria

psychomotor milestones, and facial dysmorphisms such as bitemporal narrowing, short nose, prominent upper lip, and jaw hypoplasia [137].

In the 17p13.3 region, the LIS1 (PAFAH1B1) gene has been identified, and it codifies for an enzyme regulating the platelet-activating factor (PAF). LIS1 gene plays an important role in stabilizing neuronal microtubules which intervene in the CNS development. Approximately 65% of patients with LIS present a LIS1 mutation (deletion of the entire gene in 40% of cases, intragenic mutation in 25% of cases). Missense mutations are correlated with a milder phenotype than truncating mutations or deletions. Mutations of the doublecortin gene (DCX or XLIS) determine LIS in males and subcortical band heterotopia (SBH) in females. Lissencephaly is prevalently posterior in patients with LIS1 mutations, anterior in those with DCX mutations. MDS is caused by large deletions of LIS1 gene, and sometimes of two other genes, CRK and YWHAE, in approximately 92% of cases [137–139].

Another form of lissencephaly in males is X-linked lissencephaly with corpus callosum agenesis and ambiguous genitalia (XLAG). The anatomoclinical picture is characterized by agyria-pachygyria with posterior-to-anterior gradient, mild thickening of the cerebral cortex (6–7 mm versus 15–20 mm observed in LIS or DCX-associated lissencephaly), the absence of the corpus callosum, poorly delineated and capitate basal ganglia, postnatal microcephaly, early onset epilepsy, hypothalamic dysfunction, chronic diarrhea, and ambiguous genitalia. XLAG has been associated with mutations of the aristaless-related homeobox (ARX) gene [137].

Autosomal recessive lissencephaly with abnormalities of the cerebellum, hippocampus, and brainstem represents a further subtype, due to mutations of reelin (RELN) gene mapping in the 7q22 region and codifying for a protein which controls cell interactions and positioning during CNS development [137].

Finally, mutations of the tubulin α -1A (TUBA1A) gene have been found in patients with lissencephaly (posterior-to-anterior gradient), associated to other abnormalities of hippocampus, corpus callosum, internal capsula, and brainstem [137, 140–142].

Interictal EEG—In LIS, a characteristic EEG pattern, with unusually diffuse high-voltage fast rhythms, has been described from the first year of age. This activity can be alternated with theta e delta rhythms (Fig. 33.25) [143]. The EEG may not show typical hypsarrhythmia [137].

More recently, three distinct EEG patterns have been described in LIS patients: (1) diffuse bi-hemispheric

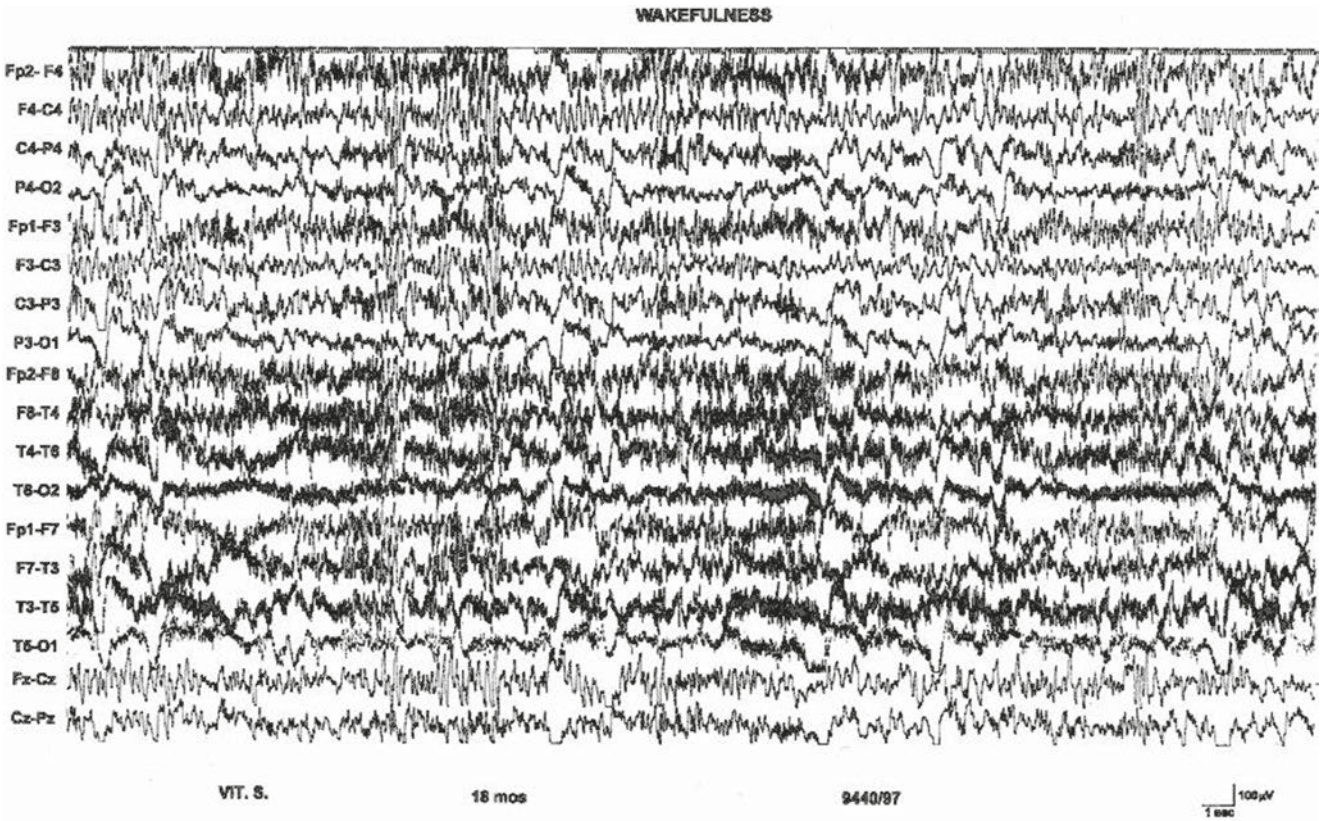

Fig. 33.25 Male at 18 months of age with isolated lissencephaly. Wakefulness EEG reveals a diffuse high-voltage theta activity, prominent over the anterior regions

distribution of high-voltage 8 Hz alpha with intermingled 14–16 Hz beta activity; (2) diffuse bi-hemispheric distribution of high-voltage rather sharp 1.5–2.5 Hz slow waves, with amplitude fluctuations of cortical activity; and (3) very high-voltage generalized 1–1.5 Hz sharp waves [144].

Seizures and ictal EEG—In LIS, seizures, present in more than 90% of cases, usually start before 6 months of age and are polymorphous: more often spasms, but also tonic-clonic, myoclonic, focal, tonic, or atonic seizures and atypical absences (Figs. 33.26, 33.27, and 33.28) [137, 145, 146].

In XLAG tonic, multifocal myoclonic and generalized tonic-clonic seizures have been reported with a very early onset [147].

In patients with TUBA1A mutations, epilepsy presents with infantile spasms or astatic-myoclonic seizures early on, evolving to atypical absences, myoclonic and atonic drop seizures, focal seizures, and tonic and tonic-clonic seizures in later childhood [142].

Outcome is very poor regarding epilepsy which is almost intractable, since reduction of seizures can be obtained with old and new antiepileptic drugs (phenobarbital, valproate, lamotrigine) and with corticosteroids [146]. Death occurs in the majority of cases before adult age.

33.2.5 Subcortical Band Heterotopia (Double Cortex)

Subcortical band heterotopia (SBH) or double cortex is characterized by simplified cortical gyri and, often, by thickening

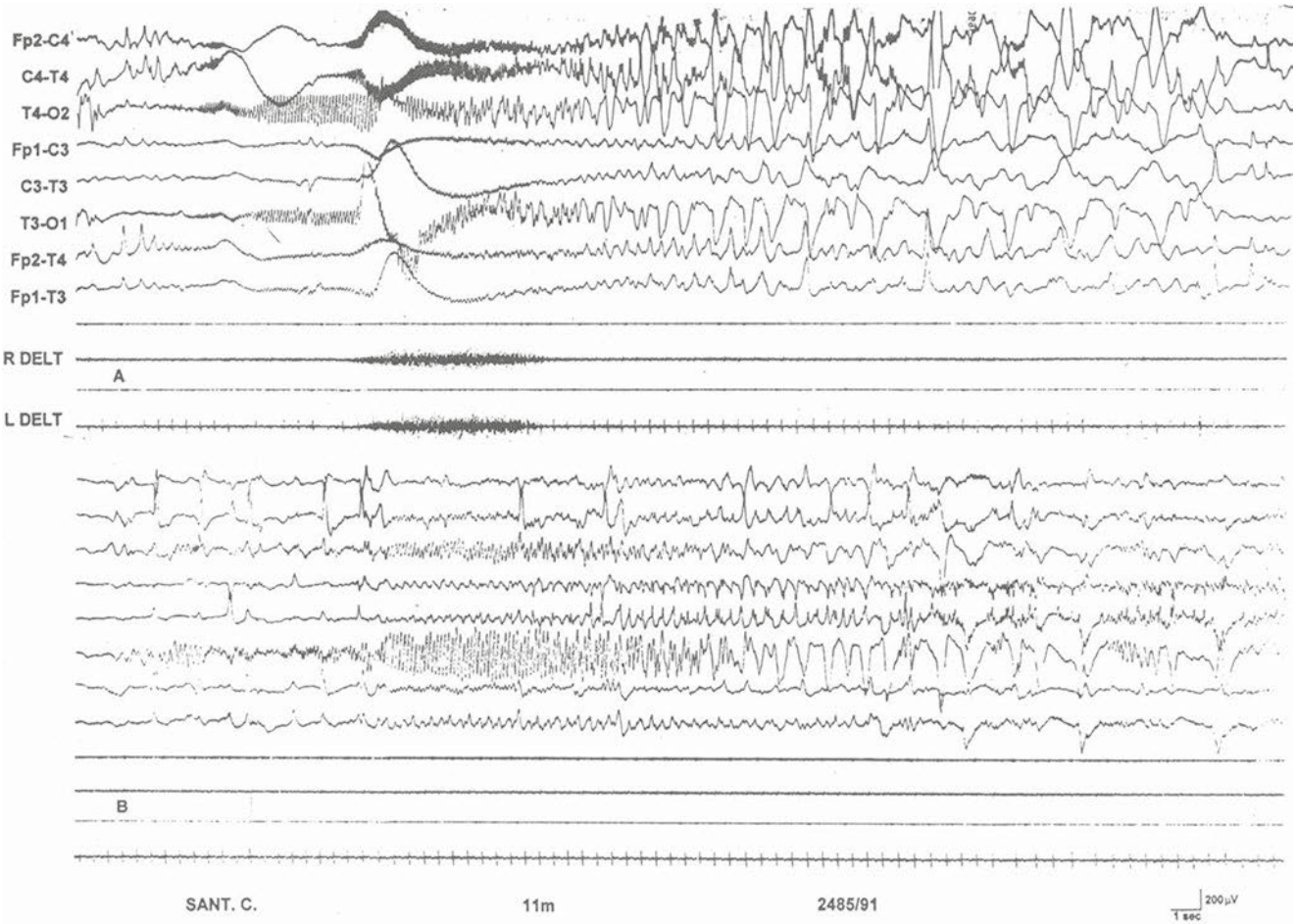

Fig. 33.26 Female at 11 months of age with lissencephaly and cerebellar hypoplasia. On the top, ictal recruiting activity starting from the right posterior regions, rapidly spreading to the contralateral hemisphere, followed by spike and spike-and-wave activity. At surface EMG of deltoid muscles, a short tonic contraction is evident. On the bottom, after the end of the seizure, a second seizure starts from the left hemisphere and promptly diffuses to the contralateral hemisphere, apparently without motor manifestations (*R* right, *L* left, *DELT* deltoid muscle)

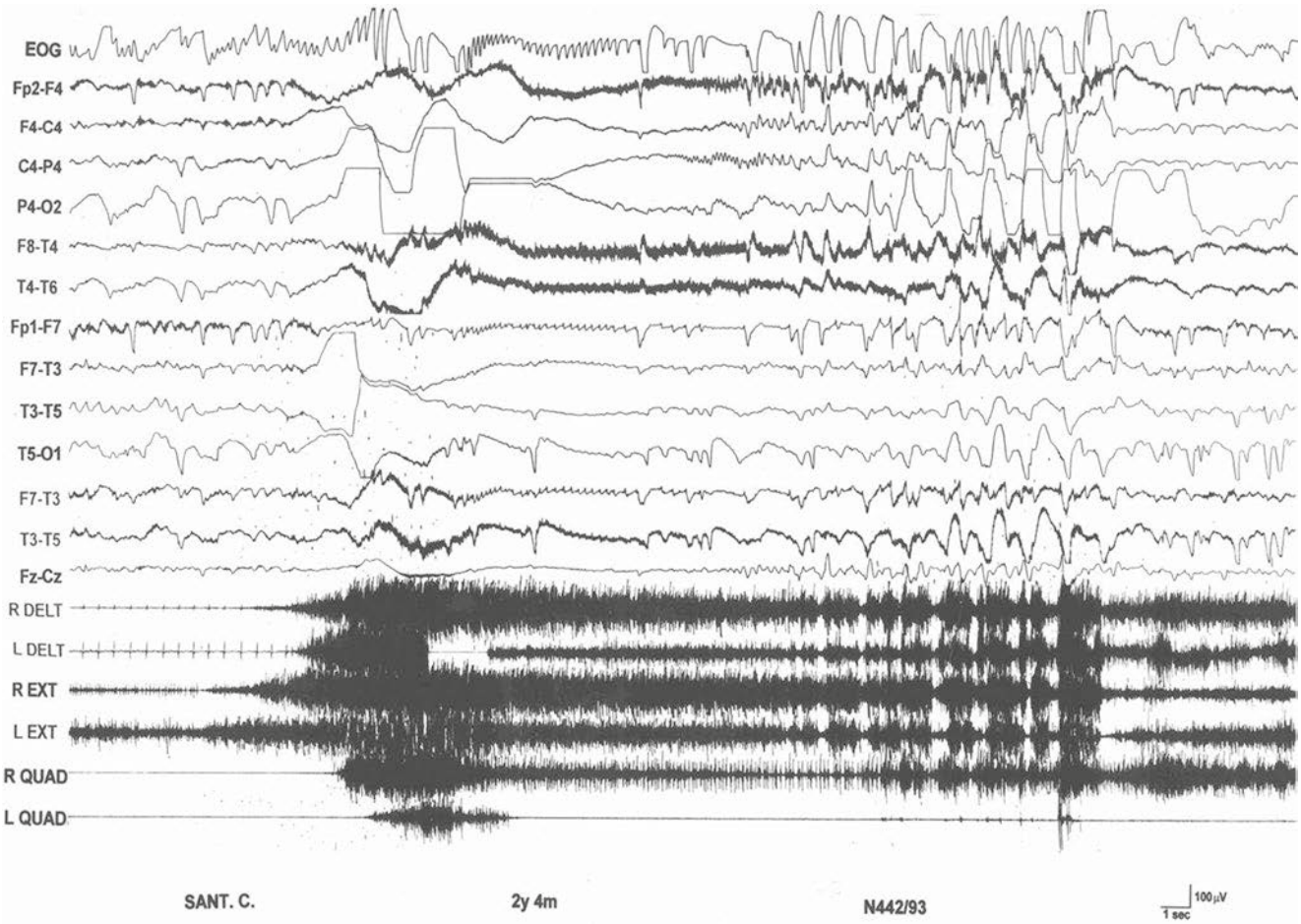

Fig. 33.27 The same patient of Fig. 33.26. EEG shows a tonic seizure with diffuse desynchronization. The appearance of the spike-and-slow wave complexes is correlated with shorter rhythmical tonic contractions (*R* right, *L* left, *DELT* deltoid muscle, *EXT* forearm extensor muscles, *QUAD* quadriceps femoris muscle)

of the cortex. A thin band of white matter divides the cortex from another band of gray matter (heterotopia) of variable thickness and extension (Fig. 33.29).

Mutations of doublecortin (DCX) gene, localized in the Xq22.3–q24 region, are responsible for SBH. These mutations have been reported in all familial cases and in 38–91% of sporadic cases. All the females with DCX gene mutations present a prevalently anterior double cortex; on the other hand, one quarter of those with an anterior pattern of double cortex and all those with a posteriorly predominant or unilateral double cortex do not have DCX mutations. In these cases, an intragenic deletion is found by means of MLPA assay, or the involvement of other genes, or a mosaic condition can be suspected. Rare reports of males with SBH, determined by DCX or LIS1 mutations, have been described.

The main clinical features of females with SBH are ID and epilepsy (in approximately 95% of cases).

ID degree appears correlated with the thickness of the subcortical band and with the coexistence of an overlying cortical pachygyria. The subjects with pachygyria and with larger ventricle dilation present an earlier onset of seizures [137, 145].

Interictal EEG—During wakefulness, frequent multifocal paroxysmal abnormalities are evident; during sleep, spike-and-wave or polyspike-and-wave complexes or sequences of fast paroxysmal activity, prominent over the frontal regions, are recorded (Figs. 33.30 and 33.31).

Seizures and ictal EEG—The typical pattern of Lennox-Gastaut syndrome, with tonic, atonic, generalized tonic-clonic, and atypical absence seizures is present. Using depth electrodes, the epileptiform activity may originate directly from

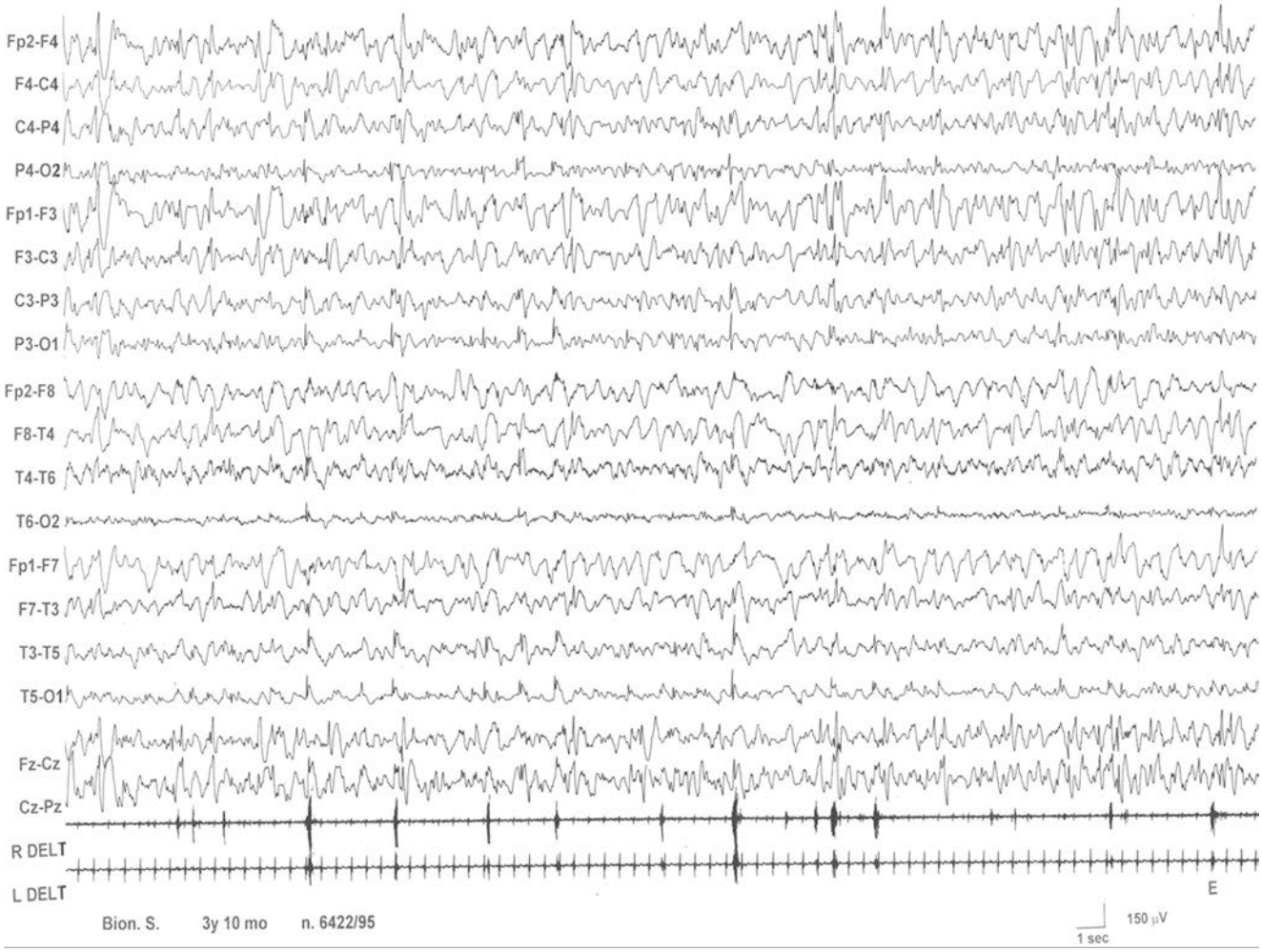

Fig. 33.28 A 3-year-old male with classical lissencephaly. EEG shows numerous diffuse spike-and-wave complexes, prominent over the anterior regions, often correlated with myoclonic jerks at surface EMG of deltoid muscles (*R* right, *L* left, *DELT* deltoid muscle)

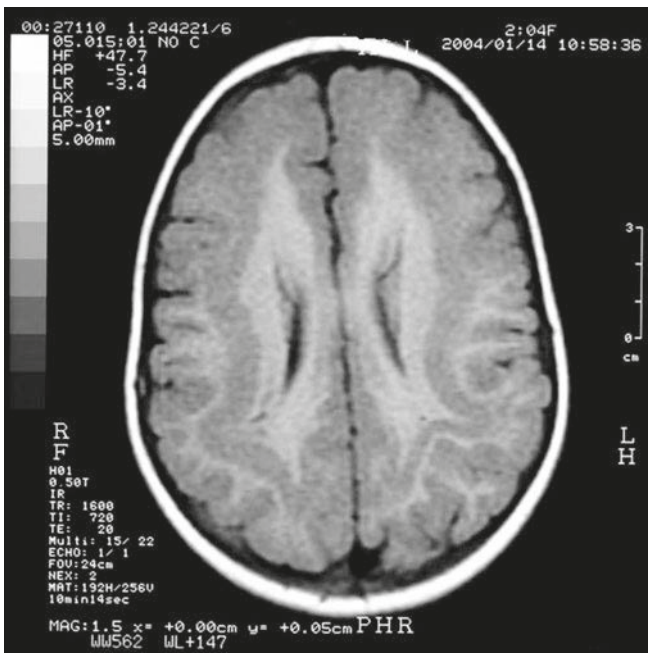

Fig. 33.29 Brain MRI of a 2-year-old female with subcortical band heterotopia (double cortex)

the heterotopic neurons. Approximately 65% of patients with SBH have intractable seizures. Callosotomy has been helpful in controlling atonic seizures in a few cases [137, 145].

33.2.6 Bilateral Periventricular Nodular Heterotopia

Bilateral periventricular nodular heterotopia (PNH) is characterized by subependymal gray matter nodules, confluent and symmetric, along the lateral ventricles (Fig. 33.32). PNH has an X-linked inheritance in females, with a high rate of lethality in males. Almost all familial cases, and 26% of sporadic cases are associated with filamin (FLNA) gene mutations (splicing or nonsense mutations, intragenic deletions), mapping in the Xq28 region. FLNA gene promotes orthogonal ramification of actin filaments and links them to membrane glycoproteins, influencing neuronal migration.

Females with FLNA mutations have a normal or borderline intellectual functioning and an epilepsy of variable severity.

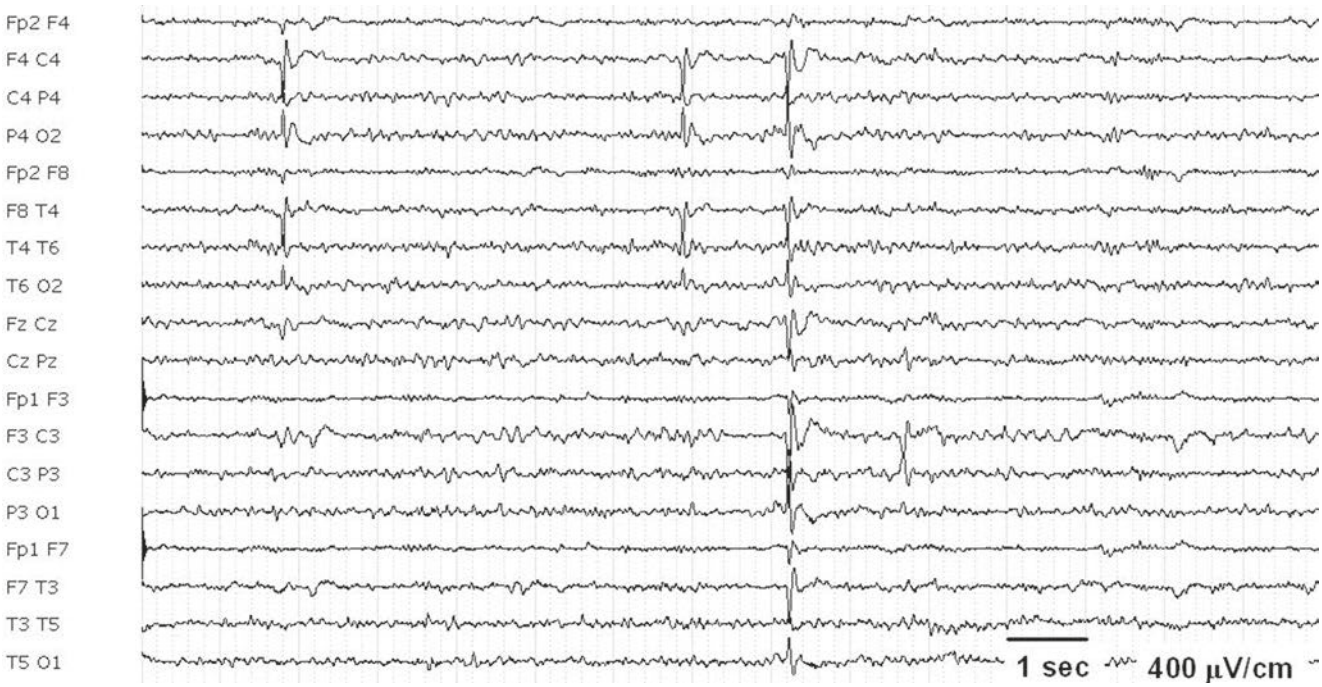

Fig. 33.30 Wakefulness EEG of a 3-year-old female with subcortical band heterotopia. High-voltage spikes are diffuse or asynchronously localized over the centrotemporal regions of both hemispheres, with right prevalence

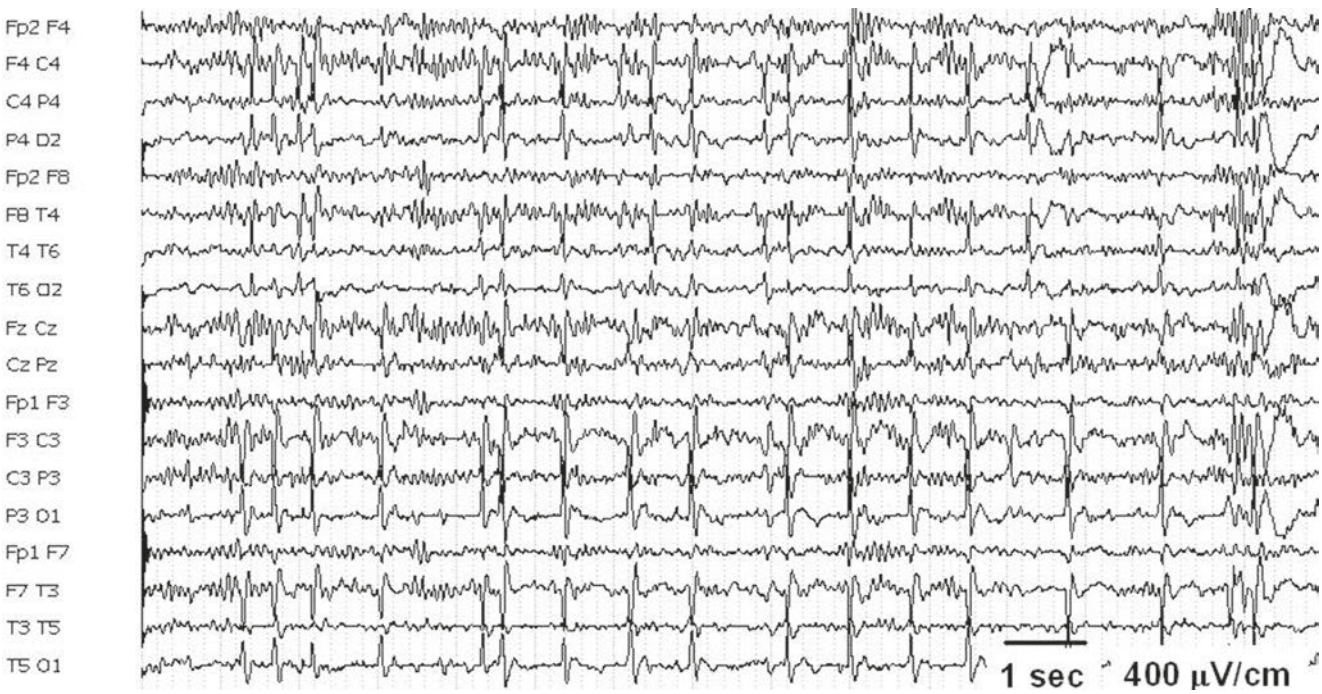

Fig. 33.31 Sleep EEG of the same patient of Fig. 33.30, at 3 years of age. Epileptiform abnormalities are diffuse and quasi-continuous over both hemispheres. Diffuse fast activity, more represented over the fronto-central regions and vertex, is evident

A rare form of autosomal recessive PNH associated with microcephaly and severe ID has been reported in two siblings, and it was due to a mutation of ADP-ribosylation factor guanine nucleotide-exchange factor-2 (ARFGEF2) gene.

Many other sporadic cases of PNH have been reported in association with more complex malformative syndrome, chromosomal abnormalities, or copy number variants [126, 137].

Interictal EEG—Background activity is usually normal, and sleep physiological elements are preserved. Photic

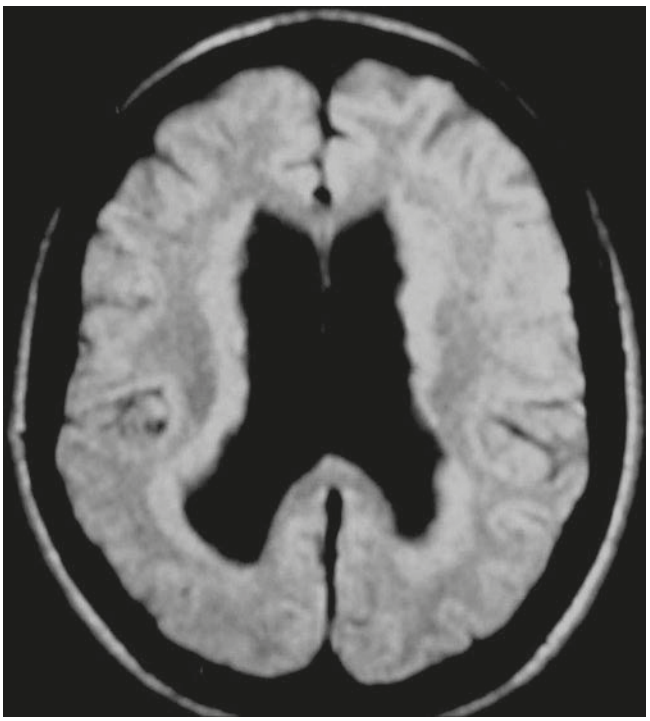

Fig. 33.32 Brain MRI of a 30-year-old female with bilateral periventricular nodular heterotopia

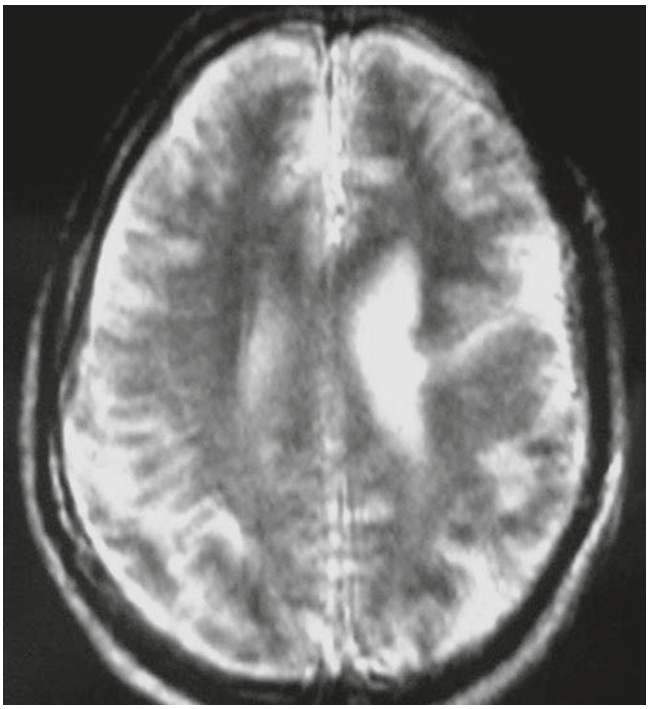

Fig. 33.33 Brain MRI of an 8-year-old male with polymicrogyria and schizencephaly at the left frontal cortex

driving at the intermittent photic stimulation is bilateral and symmetric in patients with bilateral PNH but asymmetrically represented over the affected hemisphere.

In the majority of cases, paroxysmal abnormalities are focal. Bilateral asynchronous abnormalities over the temporal regions are present in patients with symmetrical or asymmetrical PNH. In patients with unilateral PNH, abnormalities can be concordant with neuroimaging, but they are frequently multifocal. During NREM sleep, paroxysms tend to diffuse and to present as polyspike discharges [148].

Seizures and ictal EEG—About 88% of patients with PNH present epilepsy with a variable onset age (from infancy to adult age).

Three different ictal patterns have been proposed: (1) a spike-and-slow wave burst rapidly followed by a discharge of fast spikes which diffuse to the ipsilateral or contralateral hemisphere; (2) a tonic seizure correlated with fast spikes, rapidly involving the entire hemisphere where PNH is located; and(3) recruiting theta rhythms rapidly diffusing to the affected hemisphere.

Different asynchronous seizures can start from both hemispheres in cases of asymmetrical PNH.

Seizures are frequently drug-resistant. Outcome is worse when PNH is asymmetrical or unilateral, with or without extension to the overlying cortex [137, 148].

33.2.7 Schizencephaly

Schizencephaly is characterized by a unilateral or bilateral cerebral cleft, which can result in a communication between ventricle and subarachnoid spaces. The walls of the fissure are separated (open-lip schizencephaly) or appose each other (closed-lip schizencephaly) (Fig. 33.33). Schizencephaly may have different localizations but generally is found at the perisylvian region, and its edges are often covered by polymicrogyric cortex.

Schizencephaly has been correlated with different environmental factors, such as prenatal cytomegalovirus infection, but in some cases, mutations of the homeobox gene EMX2, mapping on 10q26.1 region, have been found.

The clinical phenotype is very heterogeneous. Patients with bilateral schizencephaly may present microcephaly, severe psychomotor delay, and spastic quadriplegia; those with unilateral schizencephaly tend to show milder neurological signs [137, 149].

Interictal EEG—Focal epileptiform abnormalities correlated with the localization of the schizencephaly are present; they increase in frequency and tend to diffuse during drowsiness and sleep (Fig. 33.34) [137, 150]. The frequency of EEG abnormalities is not different in patients with unilateral and bilateral schizencephaly [149].

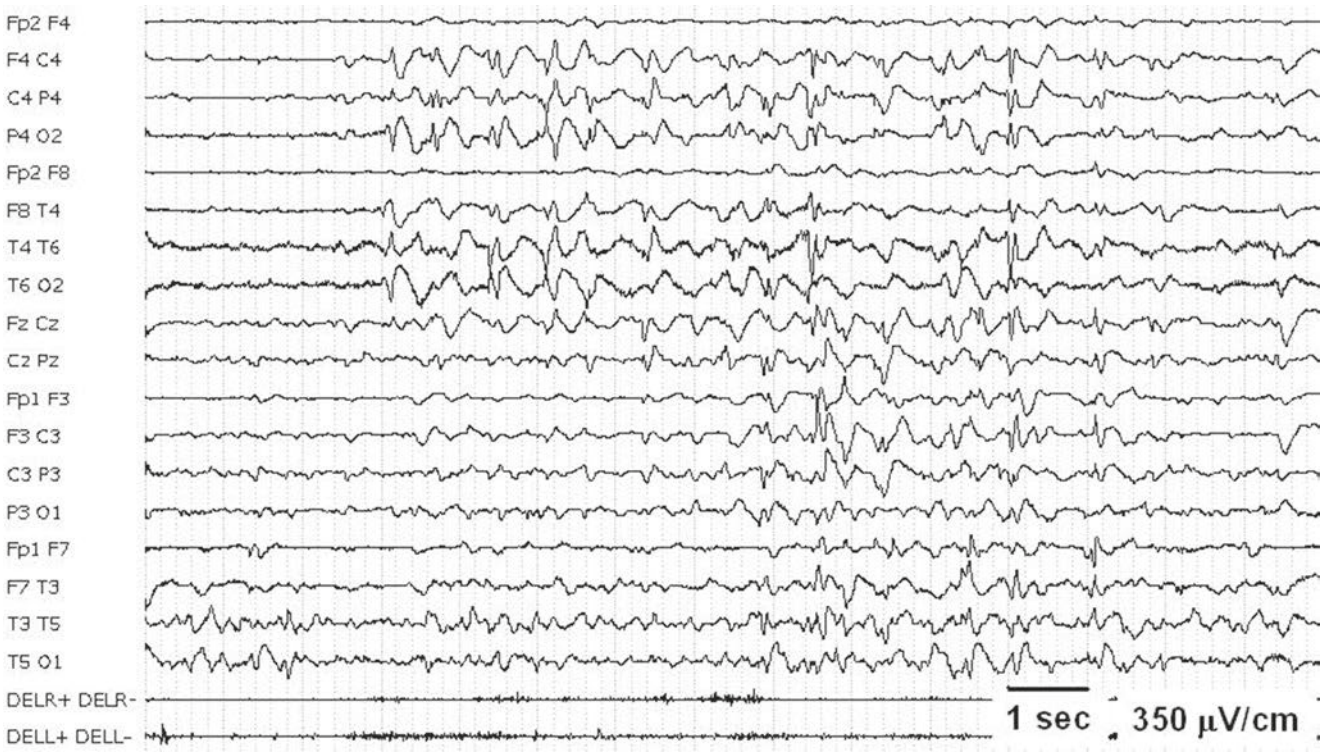

Fig. 33.34 A 1-year-old male with schizencephaly. Wakefulness EEG reveals high-voltage spike-and-slow-wave complexes, mostly localized over the right posterior regions and diffused contralaterally (*R* right, *L* left, *DELT* deltoid muscle)

Seizures and ictal EEG—Epilepsy is present in 36–65% of patients. Seizures start before 3 years of age and are drug-resistant in 9–38% of cases. Seizures are mostly focal, and their semiology strictly depends on the schizencephaly localization. Infantile spasms and myoclonic, tonic, and atonic seizures are rarely observed (Fig. 33.35). A young boy with unilateral schizencephaly and epilepsia partialis continua presented a normal scalp electroencephalogram (EEG) but an abnormal intracranial EEG, with synchronized periodic lateralized epileptiform discharges [151]. The extent of the cortical malformation in patients with schizencephaly does not correlate statistically with the severity of the clinical and EEG features of epilepsy, but in some series, seizures were more frequent in unilateral schizencephaly, with an onset ranging from 21 months to 21 years of age. It has been hypothesized that reorganization of cortical and subcortical circuits, together with the frequent presence of genesi of the corpus callosum, could prevent the occurrence and the diffusion of epileptic discharges. Surgery can be proposed in unilateral forms and callosotomy in bilateral ones complicated by tonic or atonic seizures [137, 149, 150].

33.2.8 Polymicrogyria

This term defines a disorder of the cortical organization with an increased number of small and prominent gyri divided by shallow and large sulci, determining a knobbly aspect of the cortical surface. Two histological types of polymicrogyria (PMG) are recognized: the unlayered form, in which the molecular layer is continuous and does not follow the profile of gyri, and the underlying neurons are radially distributed, without a laminar organization; the four-layered form, with an intracortical laminar necrotic layer, consequent late disorder of migration, and cortical disorganization.

PMG can be focal, unilateral, bilateral, symmetric or asymmetric, and isolated or associated with other cortical malformations, such as schizencephaly.

Clinical spectrum is wide, including normal neurological development, mild and selective cognitive dysfunctions with and without epilepsy, and severe and drug-resistant epileptic encephalopathies.

Specific PMG syndromes have been described: bilateral perisylvian PMG, bilateral parasagittal parieto-occipital

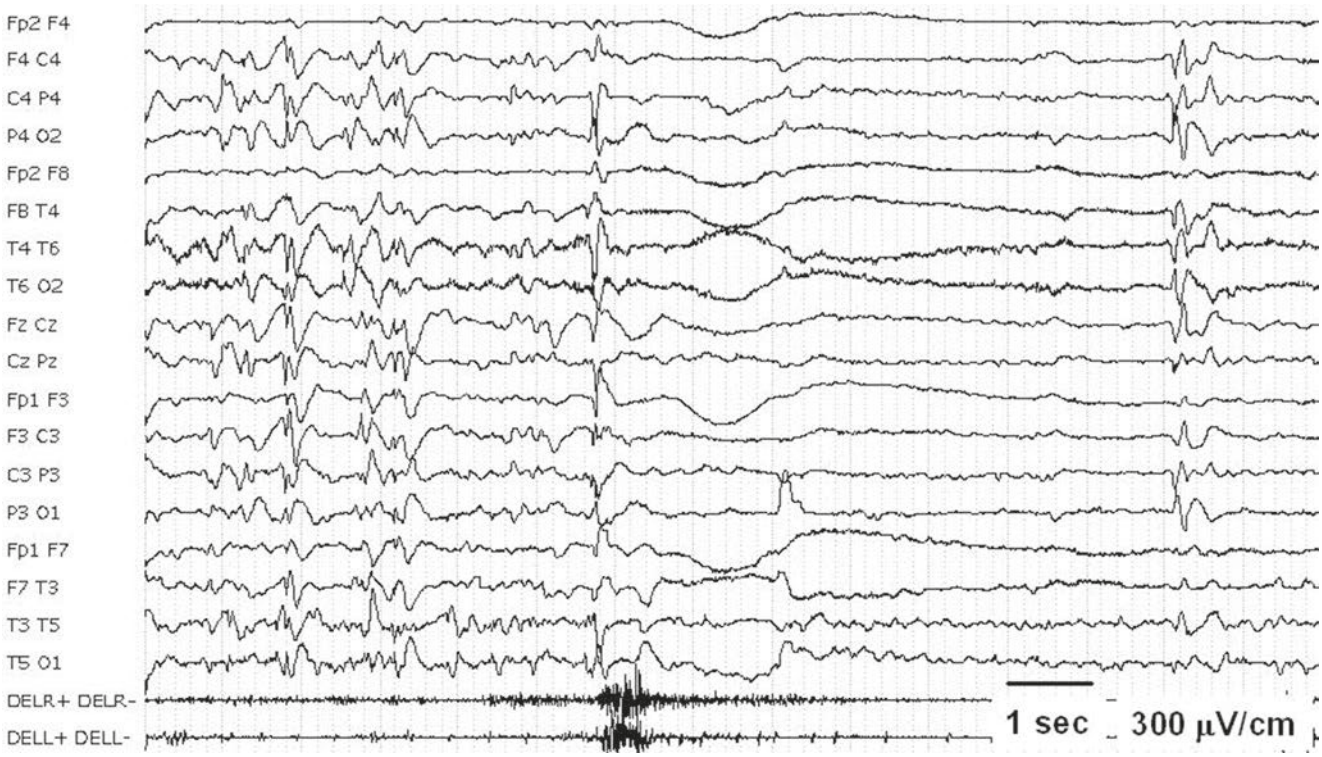

Fig. 33.35 The same child of Fig. 33.34. EEG recording of a seizure characterized by a diffuse slow complex and subsequent desynchronization; at surface EMG of deltoid muscles, a short tonic contraction is present (*R* right, *L* left, *DELT* deltoid muscle)

PMG, frontal and fronto-parietal PMG, unilateral or multilobar PMG, and bilateral generalized PMG.

Bilateral perisylvian PMG has been observed in sporadic and familial cases, associated with a missense mutation of SRPX2 gene (Xq22), with chromosome 22q11.2 deletion, with twin pregnancies complicated by twin-twin transfusion syndrome [137], with severe neonatal encephalopathy and mutation of MECP2 gene [152], with MELAS syndrome due to A3243G mitochondrial mutation [153]. The clinical picture in bilateral perisylvian PMG is characterized by facio-pharyngo-glosso-masticatory diplegia, ID, spastic quadriplegia, and epilepsy [137].

Bilateral parasagittal parieto-occipital PMG involves the mesial regions of the parietal and occipital lobes. Only sporadic cases with normal or mildly impaired cognitive level and mostly drug-resistant focal seizures beginning between 20 months and 15 years of age have been described [137, 154].

Frontal PMG has been reported in children with ID, spastic quadriplegia, and epilepsy. The majority of cases are sporadic, but its presence in probands born from consanguineous parents or in sibs suggests an autosomal recessive inheritance. Frontoparietal PMG (Fig. 33.36) is a recessive disorder described in familial cases and associated with mutations of the G protein-coupled receptor 56 (GPR56) gene, mapping on 16q13 region and involved in the regulation of the cortical pattern. Recently, frontoparietal PMG has been reclassified as a cobblestone malformation, associated with N-glycosylation defect [137, 155].

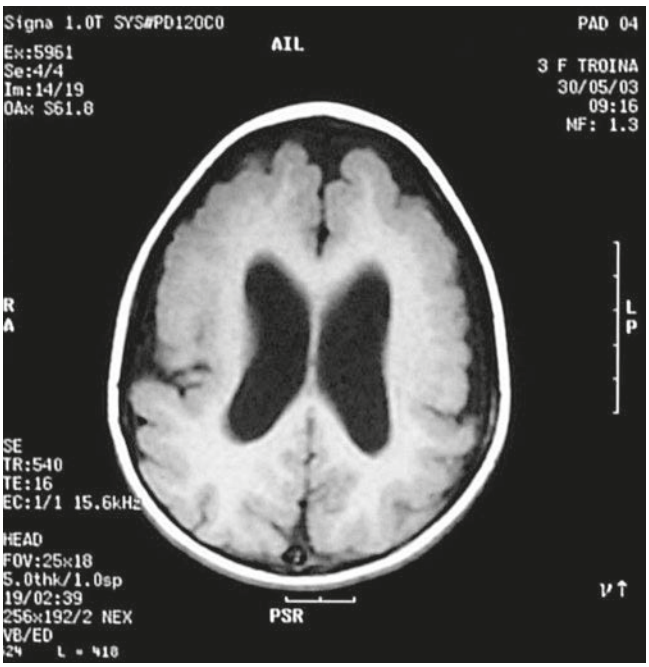

Fig. 33.36 Brain MRI of a 3-year-old female with frontoparietal polymicrogyria

Unilateral PMG has been found in association with mutations of PAX6 (paired-box transcription factor) gene, mapping on 11p13 region. This disorder is very often characterized by hemiparesis, ID, and focal seizures [137, 156, 157].

Multilobar PMG can present with status epilepticus during sleep (ESES), accompanied by focal seizures and, sometimes, atonic seizures [137, 158].

Bilateral generalized PMG entirely affects both hemispheres but is prominent at the perisylvian regions. Patients show cognitive and motor delay and epilepsy with a variable outcome [159].

Recently, TUBB2B mutations have been found in association with PMG, with different localizations (anterior asymmetric and involving perisylvian regions, diffuse and bilateral) and with other malformative features (dysmorphism of basal ganglia, hypoplasia of the internal capsula, corpus callosum agenesis) [137].

PMG, isolated or complicated by other malformations, has been associated with some pathogenic copy number variants, such as 1p36.3, 2p16–p23, 4q21–q22, 6q26–q27, and 21q2 [137].

Interictal EEG—In the bilateral perisylvian PMG, interictal EEG can be normal. In cases with focal seizures, multifocal spikes are recorded; in patients with generalized seizures, frequent slow waves are evident, bilaterally, but prominent over the centro-temporal regions, with intermingled bilateral or unilateral spikes or sharp waves or diffuse spike-and-wave complexes.

In the bilateral parasagittal parieto-occipital PMG, interictal EEG can be also normal. However, in the majority of cases, focal or bilateral paroxysmal abnormalities, localized over the parieto-occipital, parieto-temporal, or centro-parietal regions, are evident. More rarely, diffuse paroxysms are recorded [154].

In the frontal PMG, frontal slow and sharp waves or diffuse paroxysms are observed [160].

Interictal EEG reports regarding the frontoparietal PMG are sporadic. Bilateral, synchronous and asyncronous sharp waves, spikes and polyspikes are present (Figs. 33.37 and 33.38) [155].

In the unilateral PMG, epileptiform abnormalities are localized over the affected hemisphere. Patients without seizures and with normal interictal EEG have been reported [156, 157, 161]. In a series of cases with hemispheric PMG, focal electrical status has been described, presenting with continuous epileptiform abnormalities over a focal area on awakeness, which become bilateral and synchronous during sleep [162]. In another more recent review of cases with unilateral PMG, a typical ESES was constantly recorded [161].

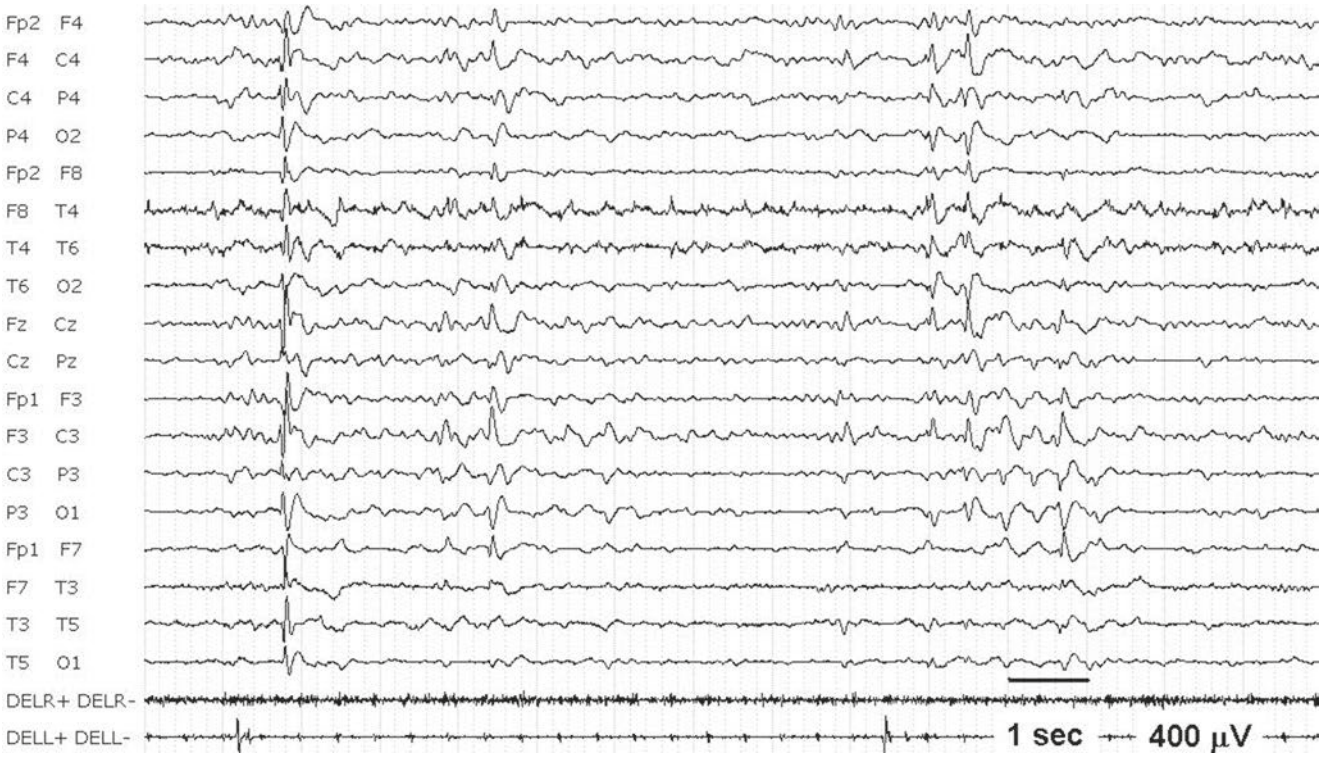

Fig. 33.37 The same child of Fig. 33.36. At age 8, wakefulness EEG in veglia shows high-voltage spikes and spike-and-slow wave complexes, asynchronously localized over the fronto-centro-parietal regions of both hemispheres; a bisynchronous discharge is also evident (*R* right, *L* left, *DELT* deltoid muscle)

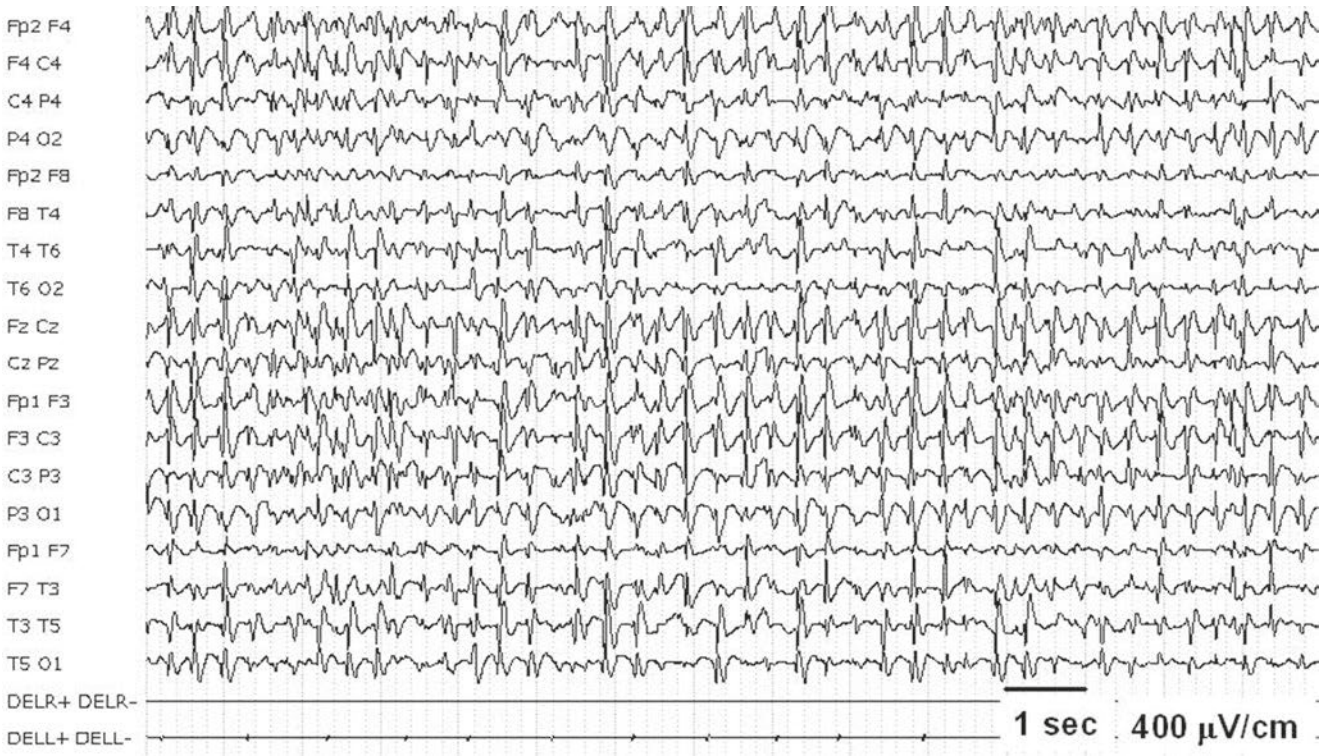

Fig. 33.38 The same child of Fig. 33.37 at age 8. Sleep EEG discloses a diffuse continuous spike-and-wave pattern (*R* right, *L* left, *DELT* deltoid muscle)

In the multilobar PMG, ESES is frequently observed between 2 and 10 years of age. All patients present also focal or multifocal spikes during wakefulness, prominent over the centro-parietal regions of the hemisphere from which start focal seizures [158].

In the bilateral generalized PMG, interictal EEG shows focal, multifocal (ventral, temporal, frontal), or diffuse epileptiform abnormalities [159].

Seizures and ictal EEG—In the bilateral perisylvian PMG, seizures start between 4 and 12 years of age and are drug-resistant in approximately 65% of cases. Atypical absence, tonic, atonic, or tonic-clonic seizures are frequent, also in the framework of a Lennox-Gastaut syndrome. Focal seizures are rare [137].

In the bilateral parasagittal parieto-occipital PMG, focal seizures with a possible apparently generalized or parieto-occipital onset are recorded [137, 154].

In the frontal and frontoparietal PMG, epilepsy is almost always present, polymorphous, with focal (with or without unawareness), generalized tonic-clonic seizures, or atypical absences. Outcome is variable [137, 154, 160].

In the unilateral PMG, focal, generalized tonic-clonic seizures, atypical absences, and negative and positive myoclonus are most commonly reported, between 9 months and 9 years of age [137, 156, 157, 161].

In the multilobar PMG, epilepsy starts between 14 months and 5 years of age, with sporadic focal motor seizures and atypical absences. ESES appears at the same time with atonic seizures. They are of variable intensity and duration and if very fast can determine an abrupt fall. At video EEG, the atonic event is correlated with a diffuse spike-and-wave complex. Focal motor seizures can occur with unilateral clonic jerks of the face. Seizure outcome is good with remission before adolescence, but neuropsychological impairment, typical of ESES, may persist [137, 158, 163].

In the bilateral generalized PMG, generalized, febrile, myoclonic, or atonic seizures occur also from the neonatal period [159].

Recently, a series of 58 cases with different types of PMG was retrospectively studied, and the results suggested that also PMG-related drug-resistant epilepsy warrants a comprehensive presurgical evaluation, including SEEG investigations, given that the epileptic zone may only partially overlap with the PMG or include solely remote cortical areas. Indeed, seizure freedom was reached in 72% of patients with PMG (mostly unilateral) who underwent corticectomy or hemispherotomy. These data support that surgery may play a role in the treatment of PMG whatever it is its extent [164].

33.2.9 Focal Cortical Dysplasia Types I and III

FCD types I and III are classified as secondary to abnormal postmigrational development because evidence suggests that they can result from injury to the cortex during later stages of cortical development.

FCD type I presents with abnormal cortical layering and is subdivided into three subtypes: (1) FCD type Ia, with abnormal radial cortical lamination; (2) FCD type Ib, with abnormal tangential cortical lamination; and (3) FCD type Ic, with abnormal radial and tangential cortical lamination. Prenatal and perinatal insults are frequently associated in children with FCD type I.

FCDs type III are characterized by cortical lamination abnormalities associated with a main lesion, usually close to or affecting the same cortical region. Four subtypes of FCD type III are now recognized: (1) cortical lamination abnormalities in the temporal lobe associated with hippocampal sclerosis (FCD type IIIa); (2) cortical lamination abnormalities adjacent to a glial or glioneuronal tumor (FCD type IIIb); (3) cortical lamination abnormalities adjacent to vascular malformation (FCD type IIIc); and (4) cortical lamination abnormalities adjacent to any other lesion acquired during early life (FCD type IIId) [126, 128].

Interictal EEG—Comparing scalp EEG in patients with FCD types I and II, no statistical differences for asymmetry of alpha rhythm and sleep spindles, intermittent slowing, and type and extent of interictal pattern were found; continuous irregular slowing was more frequently observed in FCD type I [165].

In a young girl with FCD type 1b, who underwent surgery, interictal pattern at electrocorticography disclosed multifocal 2 Hz spike-and-waves asynchronous over the right and left hemispheres, with sporadic spreading to the cortical surface, and especially to frontopolar electrodes [166].

The interictal EEG in FCDs type III involving the temporal regions are similar to those observed in extratemporal areas. Isolated spikes, a repetitive intermittent or almost continuous spike activity, and a paroxysmal fast pattern were frequently recorded during wakefulness and non-REM sleep in patients with FCD and hippocampal sclerosis [167].

Seizures and ictal EEG—In FCD type I, the most prevalent seizure-onset patterns at stereoelectroencephalography were slow wave or baseline shift followed by LVFA and LVFA [130]. In a study carried out on 215 consecutive patients with FCDs type I, two subgroups were distinguished: isolated FCDs, characterized by more frequent seizures, negative MRI, multilobar involvement, and worse postsurgical seizure control, and FCDs associated with hippocampal sclerosis and tumors, with a clinical picture similar to that of patients with HS or with tumors alone [168].

A study correlated ictal onset patterns in temporal lobe epilepsy patients with FCD associated with hippocampal sclerosis (type IIIa), and invasive EEG recordings showed that about 40% of seizures arose from the amygdala/hippocampus complex, 35% from the temporal neocortex with the FCD, 22% were simultaneously recorded from both areas, and 2% from the contralateral hemisphere [167].

Although literature data on surgery outcome of patients with FCD IIIa are controversial, some evidences demonstrate that these patients may have a favorable evolution when both pathologies (FCD and hippocampal sclerosis) are removed [167].

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Questionario di autovalutazione

1. Nella Sindrome di Ohtahara il pattern EEG più tipico è rappresentato da:
   a. ipsaritmia
   b. low-voltage diffuso
   c. pattern di tipo suppression-burst
   d. complessi onda puntuta-onda lenta diffusi

2 Nella Sindrome di West, l'EEG critico (spasmo in flessione) è tipicamente caratterizzato da:
   a. ipsaritmia
   b. scarica diffusa di polipunta-onda
   c. depressione del tracciato
   d. ampia onda lenta diffusa seguita da tracciato ipovoltato

3 Le crisi di assenza atipiche nella Sindrome di Lennox-Gastaut si associano a:
   a. scariche di polipunta-onda diffuse
   b. scariche di complessi punta-onda a 3-5 Hz
   c. scariche di complessi punta-onda di frequenza <3 Hz
   d. scariche periodiche a breve intervallo

4. Le crisi toniche della S. di Lennox-Gastaut a quale pattern EEG si associano?
   a. ritmi rapidi diffusi a 10-15 Hz
   b. scariche diffuse di complessi punta-onda a 2-2.5 Hz
   c. scariche diffuse di polipunte-onda
   d. depressione del tracciato

5. L'EEG di sonno nella Sindrome di Landau-Kleffner è caratterizzato da:
   a. attività epilettica subcontinua diffusa in sonno NREM e REM
   b. attività focale centro-temporale in sonno NREM
   c. attività epilettiforme continua e/o subcontinua, > regioni temporali, in sonno NREM
   d. attività epilettiforme in temporale sinistra subcontinua in stadio I-I NREM

6. Nell'Epilessia con mioclonie palpebrali ed assenze l'EEG critico è caratterizzato da:
   a. scariche generalizzate di polipunta-onda a 3-6 Hz che compaiono immediatamente dopo la chiusura degli occhi
   b. scariche generalizzate di polipunta-onda a 3-3.5 Hz
   c. scariche di polipunta-onda in ambito medio-anteriore sia ad occhi aperti che chiusi
   d. scariche diffuse di polipunta-onda frammiste ad attività rapida

7. **Nella Epilessia Benigna con Punte Centro-Temporali l'EEG intercritico in veglia è caratterizzato da:**
   a. anomalie epilettiformi interictali (sporadiche o in sequenze) in sede centro-temporale
   b. assenza di anomalie
   c. scariche di polipunte diffuse
   d. brevi scariche parossistche di morfologia variabile

8. **Nella Sindrome di Panayiotopoulos l'EEG intercritico in veglia è:**
   a. negativo
   b. caratterizzato dalla presenza di anomalie epilettiformi solo in sede occipitale
   c. caratterizzato da punte focali sia in sede occipitale che frontale
   d. caratterizzato da multifocalità

9. **Nell'Epilessia Mioclonica Giovanile la stimolazione luminosa intermittente provoca la comparsa di scariche diffuse di complessi polipunta-onda in circa il:**
   a. 30% dei casi
   b. 50% dei casi
   c. 90% dei casi
   d. 10% dei casi

10. **Nella Sindrome di Angelman il tracciato intercritico in veglia è in genere rappresentato da:**
    a. rallentamento dell'attività di fondo
    b. rallentamento dell'attività di fondo associato a complessi punta-onda prevalenti in regione frontale o occipitale
    c. scariche di punta-onda lente diffuse
    d. scariche di punta-onda lente intervallate a periodi di depressione dell'attività bioelettrica corticale

Clicca qui per consultare le risposte

ITALEPT Levetiracetam

RIASSUNTO DELLE CARATTERISTICHE DEL PRODOTTO

1. DENOMINAZIONE DEL MEDICINALE

ITALEPT 500 mg compresse rivestite con film.
ITALEPT 1000 mg compresse rivestite con film.

2. COMPOSIZIONE QUALITATIVA E QUANTITATIVA

Ogni compressa rivestita con film contiene 500 mg di levetiracetam. Ogni compressa rivestita con film contiene 1000 mg di levetiracetam.
Per l'elenco completo degli eccipienti, vedere paragrafo 6.1.

3. FORMA FARMACEUTICA

Compressa rivestita con film.
Compressa gialla, di forma oblunga, con linea di incisione, di circa 18 mm di lunghezza, con la scritta "500" impressa su un lato e una linea di incisione centrale. La compressa può essere divisa in due metà uguali.
Compressa bianca, di forma oblunga, con linea di incisione, di circa 22 mm di lunghezza, con la scritta "1000" impressa su un lato e linea di incisione centrale. La compressa può essere divisa in due metà uguali.

4. INFORMAZIONI CLINICHE

4.1 Indicazioni terapeutiche

ITALEPT è indicato come monoterapia nel trattamento delle crisi convulsive ad esordio parziale con o senza generalizzazione secondaria in adulti ed adolescenti a partire dai 16 anni di età con epilessia di nuova diagnosi. ITALEPT è indicato quale terapia aggiuntiva:

- nel trattamento delle crisi convulsive ad esordio parziale con o senza secondaria generalizzazione in adulti, adolescenti, bambini e infanti a partire da 1 mese di età con epilessia;
- nel trattamento delle crisi miocloniche in adulti ed adolescenti a partire da 12 anni di età con epilessia mioclonica giovanile;
- nel trattamento delle crisi convulsive tonico-cloniche generalizzate primarie in adulti ed adolescenti a partire da 12 anni di età con epilessia idiopatica generalizzata.

4.2 Posologia e modo di somministrazione

Posologia

Monoterapia per adulti e adolescenti a partire da 16 anni di età La dose iniziale raccomandata è 250 mg due volte al giorno, da aumentare fino a una dose terapeutica iniziale di 500 mg due volte al giorno dopo due settimane. La dose può essere ulteriormente aumentata di 250 mg due volte al giorno ogni due settimane sulla base della risposta clinica. La dose massima è di 1500 mg due volte al giorno.

Terapia aggiuntiva per adulti (≥ 18 anni) ed adolescenti (da 12 a 17 anni) del peso di 50 kg o superiore

La dose terapeutica iniziale è 500 mg due volte al giorno. Questa dose può essere iniziata dal primo giorno di trattamento. Sulla base della risposta clinica e della tollerabilità, la dose giornaliera può essere aumentata fino ad un massimo di 1500 mg due volte al giorno. Gli aggiustamenti posologici possono essere fatti con aumenti o diminuzioni di 500 mg due volte al giorno ogni 2-4 settimane.

Interruzione del trattamento

In accordo con la pratica clinica corrente, se si deve interrompere il trattamento con ITALEPT si raccomanda una sospensione graduale (ad es. negli adulti e negli adolescenti di peso superiore a 50 kg: diminuzione di 500 mg due volte al giorno ad intervalli di tempo compresi tra due e quattro settimane; negli infanti di età superiore ai 6 mesi, nei bambini e negli adolescenti di peso inferiore a 50 kg: la diminuzione della dose non deve superare i 10 mg/kg due volte al giorno ogni due settimane; negli infanti (di età inferiore a 6 mesi): la diminuzione della dose non deve superare i 7 mg/kg due volte al giorno ogni due settimane).

Popolazioni speciali

Anziani (da 65 anni in poi) Si raccomanda un aggiustamento della posologia nei pazienti anziani con funzionalità renale compromessa (vedere più avanti "*Compromissione renale*).

Compromissione renale La dose giornaliera deve essere personalizzata in base alla funzionalità renale.
Per i pazienti adulti, fare riferimento alla tabella seguente e modificare la dose come indicato. Per utilizzare questa tabella posologica è necessario valutare la clearance della creatinina del paziente (CLcr) in ml/min. La CLcr in ml/min può essere calcolata dalla determinazione della creatinina sierica (mg/dl) utilizzando, per adulti e adolescenti di peso superiore o uguale a 50 kg, la seguente formula:

$$\text{CLcr (ml/min)} = \frac{[140 - \text{età (anni)}] \times \text{peso (kg)}}{72 \times \text{creatinina sierica (mg/dl)}} \quad (\times 0{,}85 \text{ nelle donne})$$

Inoltre, la CLcr viene aggiustata secondo l'area della superficie corporea (BSA) come segue:

$$\text{CLcr (ml/min/1,73 m}^2\text{)} = \frac{\text{CLcr (ml/min)}}{\text{BSA del soggetto (m}^2\text{)}} \times 1{,}73$$

Aggiustamento posologico per pazienti adulti ed adolescenti di peso superiore a 50 kg con funzionalità renale alterata:

Gruppo	Clearance della creatinina (ml/min/ 1,73 m²)	Dose e numero di somministrazioni
Normale	>80	500-1500 mg due volte al giorno
Lieve	50-79	500-1000 mg due volte al giorno
Moderata	30-49	250-750 mg due volte al giorno
Severa	<30	250-500 mg due volte al giorno
Pazienti con malattia renale allo stadio finale sottoposti a dialisi[1]	-	500-1000 mg una volta al giorno[2]

[1] Una dose di carico pari a 750 mg è raccomandata nel primo giorno di trattamento con levetiracetam.
[2] Dopo la dialisi si raccomanda una dose supplementare compresa tra 250 e 500 mg.

Per bambini con ridotta funzionalità renale, la dose di levetiracetam deve essere adattata sulla base della funzionalità renale, perché la clearance del levetiracetam è correlata alla funzionalità renale. Questa raccomandazione si basa su uno studio condotto su pazienti adulti con ridotta funzionalità renale. Nei giovani adolescenti, nei bambini e negli infanti, la CLcr, in ml/min/1,73 m², può essere stimata dalla determinazione della creatinina sierica (in mg/dl) utilizzando la seguente formula (formula di Schwartz):

$$\text{CLcr (ml/min/1,73 m}^2\text{)} = \frac{\text{Altezza (cm)} \times \text{ks}}{\text{Creatinina sierica (mg/dl)}}$$

ks= 0,45 negli infanti nati a termine, di età fino a 1 anno; ks= 0,55 nei bambini di età inferiore a 13 anni e nelle femmine adolescenti; ks= 0,7 nei maschi adolescenti.

Aggiustamento posologico per infanti, bambini e adolescenti di peso inferiore a 50 kg con funzionalità renale alterata:

Gruppo	Clearance della creatinina (ml/min/ 1,73 m²)	Dose e frequenza[1]	
		Infanti da 1 mese a meno di 6 mesi	Infanti da 6 a 23 mesi, bambini e adolescenti di peso inferiore ai 50 kg
Normale	>80	7-21 mg/ kg (0,07-0,21 ml/kg) due volte al giorno	10-30 mg/ kg (0,10-0,30 ml/kg) due volte al giorno
Lieve	50-79	7-14 mg/ kg (0,07-0,14 ml/kg) due volte al giorno	10-20 mg/ kg (0,10-0,20 ml/kg) due volte al giorno
Moderata	30-49	3,5-10,5 mg/ kg (0,035-0,105 ml/ kg) due volte al giorno	5-15 mg/ kg (0,05-0,15 ml/kg) due volte al giorno
Severa	<30	3,5-7 mg/ kg (0,035-0,07 ml/kg) due volte al giorno	5-10 mg/ kg (0,05-0,10 ml/kg) due volte al giorno
Pazienti con malattia renale allo stadio finale sottoposti a dialisi	--	7-14 mg/ kg (0,07-0,14 ml/kg) una volta al giorno[2] [4]	10-20 mg/ kg (0,10-0,20 ml/kg) una volta al giorno[3] [5]

[1] Utilizzare ITALEPT soluzione orale per dosi inferiori a 250 mg, per dosi non multiple di 250 mg quando non è possibile ottenere la dose raccomandata assumendo un numero multiplo di compresse, e per i pazienti incapaci di deglutire le compresse.
[2] Si raccomanda una dose di carico di 10,5 mg/kg il primo giorno di trattamento con levetiracetam.
[3] Si raccomanda una dose di carico di 15 mg/kg il primo giorno di trattamento con levetiracetam.
[4] Dopo la dialisi, si raccomanda una dose supplementare di 3,5-7 mg/kg.
[5] Dopo la dialisi, si raccomanda una dose supplementare di 5-10 mg/kg.

Compromissione epatica
Non è necessario alcun adeguamento posologico nei pazienti con compromissione epatica di grado da lieve a moderato. In pazienti con compromissione epatica severa, la clearance della creatinina può far sottostimare il grado di insufficienza renale. Pertanto, quando la clearance della creatinina è <60 ml/min/1,73 m², si raccomanda una riduzione del 50% della dose di mantenimento giornaliera.
Popolazione pediatrica
Il medico deve prescrivere la forma farmaceutica, la presentazione e il dosaggio più appropriati in base all'età, al peso e alla dose. La formulazione in compresse non è adatta all'uso nella prima infanzia e nei bambini di età inferiore a 6 anni.
ITALEPT soluzione orale è la formulazione più indicata per questa popolazione di pazienti. Inoltre, i dosaggi disponibili per le compresse non sono indicati per il trattamento iniziale dei bambini di peso inferiore a 25 kg, dei pazienti incapaci di deglutire le compresse o per la somministrazione di dosi inferiori a 250 mg. In tutti questi casi deve essere utilizzato ITALEPT soluzione orale.
Monoterapia Non sono state ancora stabilite la sicurezza e l'efficacia di ITALEPT somministrato in monoterapia nei bambini e negli adolescenti di età inferiore a 16 anni. Non vi sono dati disponibili.
Terapia aggiuntiva per bambini piccoli da 6 a 23 mesi di età, bambini (da 2 a 11 anni) e adolescenti (da 12 a 17 anni) di peso inferiore a 50 kg ITALEPT soluzione orale è la formulazione più indicata nella prima infanzia e nei bambini di età inferiore a 6 anni. Per i bambini dai 6 anni in su, ITALEPT soluzione orale deve essere utilizzato per dosi inferiori ai 250 mg, per dosi non multiple di 250 mg quando la dose raccomandata non è raggiungibile con più compresse, e per i pazienti incapaci di deglutire le compresse. Deve essere utilizzata la più bassa dose efficace. La dose iniziale per un bambino o un adolescente di 25 kg deve essere 250 mg due volte al giorno, con una dose massima di 750 mg due volte al giorno. La dose in bambini di 50 kg o più è uguale a quella degli adulti.
Terapia aggiuntiva per lattanti da 1 mese a meno di 6 mesi di età La soluzione orale è la formulazione da utilizzare negli infanti.
Modo di somministrazione
Le compresse rivestite con film devono essere somministrate per via orale, deglutite con una sufficiente quantità di liquido e possono essere assunte con o senza cibo. La dose giornaliera va ripartita in due somministrazioni uguali.

4.3 Controindicazioni
Ipersensibilità al principio attivo o ad altri derivati pirrolidonici o ad uno qualsiasi degli eccipienti elencati al paragrafo 6.1.

4.4 Avvertenze speciali e precauzioni di impiego
Compromissione renale
La somministrazione di ITALEPT in pazienti con compromissione renale può richiedere un aggiustamento posologico. In pazienti con funzionalità epatica gravemente compromessa si raccomanda di valutare la funzionalità renale prima di stabilire la posologia (vedere paragrafo 4.2).
Suicidio
Casi di suicidio, tentato suicidio, idea e comportamento suicida sono stati riportati in pazienti trattati con antiepilettici (incluso levetiracetam). Una meta-analisi di studi randomizzati e controllati con placebo, condotti con medicinali antiepilettici, ha mostrato un lieve incremento del rischio di idea e comportamento suicida. Il meccanismo di tale rischio non è noto.
Di conseguenza, i pazienti devono essere monitorati per quanto riguarda la comparsa di segni di depressione e/o idea e comportamento suicida, e deve essere preso in considerazione un trattamento appropriato. I pazienti (e coloro che se ne prendono cura) devono essere avvisati che, nel caso in cui compaiano segni di depressione e/o idea o comportamento suicida, è necessario consultare un medico.
Popolazione pediatrica
La formulazione in compresse non è adatta all'uso nella prima infanzia e nei bambini di età inferiore a 6 anni. Dai dati disponibili nei bambini non si evince un'influenza sulla crescita e sulla pubertà. Tuttavia, non sono noti gli effetti a lungo termine sull'apprendimento, l'intelligenza, la crescita, la funzione endocrina, la pubertà e sul potenziale riproduttivo nei bambini.

4.5 Interazioni con altri medicinali ed altre forme di interazione
Medicinali antiepilettici
I dati provenienti da studi clinici pre-marketing, condotti negli adulti, indicano che levetiracetam non influenza le concentrazioni sieriche degli antiepilettici esistenti (fenitoina, carbamazepina, acido valproico, fenobarbital, lamotrigina, gabapentin e primidone) e che questi antiepilettici non influenzano la farmacocinetica di levetiracetam.
Come negli adulti, nei pazienti pediatrici cui sono state somministrate dosi fino a 60 mg/kg/die di levetiracetam, non c'è evidenza di interazioni clinicamente significative con altri medicinali. Una valutazione retrospettiva di interazioni farmacocinetiche, in bambini e adolescenti affetti da epilessia (da 4 a 17 anni) ha confermato che la terapia aggiuntiva con levetiracetam somministrato per via orale non influenzava le concentrazioni sieriche allo stato stazionario di carbamazepina e valproato somministrati contemporaneamente. Tuttavia, i dati hanno suggerito una clearance del levetiracetam del 20% più elevata nei bambini che assumono medicinali antiepilettici con un effetto di induzione enzimatica. Non è richiesto un aggiustamento della dose.
Probenecid
Il probenecid (500 mg quattro volte al giorno), un agente bloccante della secrezione tubulare renale, ha mostrato di inibire la clearance renale del metabolita primario, ma non di levetiracetam. Tuttavia, la concentrazione di questo metabolita rimane bassa.

Metotrexato
È stato riportato che la somministrazione concomitante di levetiracetam e metotrexato diminuisce la clearance del metotressato, con conseguente concentrazione ematica di metotrexato aumentata/prolungata fino a livelli potenzialmente tossici. I livelli ematici di metotrexato e levetiracetam devono essere attentamente monitorati nei pazienti trattati in concomitanza con i due farmaci.
Contraccettivi orali e altre interazioni farmacocinetiche
Levetiracetam 1000 mg al giorno non ha influenzato la farmacocinetica dei contraccettivi orali (etinilestradiolo e levonorgestrel); i parametri endocrini (ormone luteinizzante e progesterone) non sono stati modificati. Levetiracetam 2000 mg al giorno non ha influenzato la farmacocinetica di digossina e warfarin; i tempi di protrombina non sono stati modificati. La somministrazione concomitante di digossina, contraccettivi orali e warfarin non ha influenzato la farmacocinetica di levetiracetam.
Lassativi
Sono stati riportati casi isolati di diminuita efficacia di levetiracetam quando il lassativo osmotico macrogol è stato somministrato in concomitanza con levetiracetam per via orale. Pertanto, macrogol non deve essere assunto per via orale da un'ora prima ad un'ora dopo l'assunzione di levetiracetam.
Cibo e alcool
L'entità dell'assorbimento di levetiracetam non è stata modificata dal cibo, ma la velocità di assorbimento era lievemente ridotta. Non sono disponibili dati sulle interazioni di levetiracetam con l'alcool.

4.6 Fertilità, gravidanza e allattamento

Gravidanza
Dati post-marketing di diversi registri prospettici di gravidanza hanno documentato i risultati della esposizione a levetiracetam in monoterapia in più di 1000 donne durante il primo trimestre di gravidanza. Nel complesso, questi dati non suggeriscono un sostanziale aumento del rischio di malformazioni congenite maggiori, sebbene un rischio teratogeno non possa essere completamente escluso. La terapia con più farmaci antiepilettici è associata ad un più alto rischio di malformazioni congenite rispetto alla monoterapia e, pertanto, la monoterapia deve essere presa in considerazione. Gli studi sugli animali hanno mostrato una tossicità riproduttiva (vedere paragrafo 5.3). ITALEPT non è raccomandato durante la gravidanza e nelle donne in età fertile che non utilizzano metodi contraccettivi, a meno che non sia clinicamente necessario. Le alterazioni fisiologiche durante la gravidanza possono influenzare le concentrazioni di levetiracetam. Durante la gravidanza, è stata osservata una riduzione delle concentrazioni plasmatiche di levetiracetam. Questa riduzione è più pronunciata durante il terzo trimestre (fino al 60% della concentrazione basale prima della gravidanza). Le donne in gravidanza trattate con levetiracetam devono essere accuratamente seguite dal punto di vista clinico. L'interruzione dei trattamenti antiepilettici può comportare una esacerbazione della malattia che può essere nociva per la madre e per il feto.
Allattamento
Levetiracetam è escreto nel latte materno. Pertanto, l'allattamento con latte materno non è raccomandato. Tuttavia, se il trattamento con levetiracetam è necessario durante l'allattamento, deve essere valutato il rapporto rischio/beneficio del trattamento, tenendo in considerazione l'importanza dell'allattamento con latte materno.
Fertilità
Non è stato rilevato alcun impatto sulla fertilità negli studi sugli animali (vedere paragrafo 5.3). Non sono disponibili dati clinici; il rischio potenziale nell'uomo è sconosciuto.

4.7 Effetti sulla capacità di guidare veicoli e sull'uso di macchinari

Levetiracetam ha una bassa o moderata influenza sulla capacità di guidare veicoli e sull'uso di macchinari. Data la possibile differente sensibilità individuale, alcuni pazienti possono manifestare sonnolenza o altri sintomi legati all'azione sul sistema nervoso centrale, specialmente all'inizio del trattamento o in seguito ad un incremento della dose. Si raccomanda pertanto cautela nei pazienti che sono impegnati in attività che richiedono elevata concentrazione, quali guidare autoveicoli o azionare macchinari. I pazienti devono essere avvertiti di non guidare o utilizzare macchinari finché non sia stato accertato che la loro abilità ad eseguire queste attività non sia compromessa.

4.8 Effetti indesiderati

Riassunto del profilo di sicurezza
Il profilo delle reazioni avverse di seguito presentato si basa sull'analisi degli studi clinici controllati verso placebo aggregati, relativi a tutte le indicazioni studiate, per un totale di 3.416 pazienti trattati con levetiracetam. Questi dati sono integrati con l'uso di levetiracetam in corrispondenti studi di estensione in aperto, così come dall'esperienza post-marketing.
Le reazioni avverse più frequentemente riportate sono state rinofaringite, sonnolenza, cefalea, affaticamento e capogiro. Il profilo di sicurezza del levetiracetam è generalmente simile nell'ambito dei diversi gruppi di età (pazienti adulti e pediatrici) e delle indicazioni approvate nel trattamento dell'epilessia.
Tabella delle reazioni avverse
Le reazioni avverse segnalate nel corso di studi clinici (adulti, adolescenti, bambini ed infanti di età superiore ad 1 mese) e nell'esperienza post-marketing sono elencate nella tabella seguente secondo la classificazione per sistemi e organi e per frequenza. Le reazioni avverse sono presentate in ordine decrescente di gravità e la loro frequenza è definita come segue: molto comune (≥1/10), comune (≥1/100, <1/10), non comune (≥1/1000, <1/100), raro (≥1/10.000, <1/1000) e molto raro (<1/10.000).

Classificazione per sistemi e organi (MedDRA)	Categoria di frequenza			
	Molto comune	Comune	Non comune	Raro
Infezioni ed infestazioni	Rinofaringite			Infezione
Patologie del sistema emolinfopoietico			Trombocitopenia, leucopenia	Pancitopenia, neutropenia, agranulocitosi
Disturbi del sistema immunitario				Reazione a farmaco con eosinofilia e sintomi sistemici (DRESS), ipersensibilità (incluso angioedema e anafilassi)
Disturbi del metabolismo e della nutrizione		Anoressia	Perdita di peso, aumento di peso	Iponatriemia
Disturbi psichiatrici		Depressione, ostilità/aggressività, ansia, insonnia, nervosismo/irritabilità	Tentato suicidio, idea suicida, disturbo psicotico, comportamento anormale, allucinazioni, collera, stato confusionale, attacco di panico, labilità affettiva/sbalzi d'umore, agitazione	Suicidio riuscito, disturbo della personalità, pensiero anormale

Classificazione per sistemi e organi (MedDRA)	Categoria di frequenza			
	Molto comune	Comune	Non comune	Raro
Patologie del sistema nervoso	Sonnolenza, cefalea	Convulsione, disturbo dell'equilibrio, capogiro, letargia, tremore	Amnesia, compromissione della memoria, coordinazione anormale/atassia, parestesia, alterazione dell'attenzione	Coreoatetosi, discinesia, ipercinesia
Patologie dell'occhio			Diplopia, visione offuscata	
Patologie dell'orecchio e del labirinto		Vertigine		
Patologie respiratorie, toraciche e mediastiniche		Tosse		
Patologie gastrointestinali		Dolore addominale, diarrea, dispepsia, vomito, nausea		Pancreatite
Patologie epatobiliari			Test della funzionalità epatica anormali	Insufficienza epatica, epatite
Patologie della cute e del tessuto sottocutaneo		Rash	Alopecia, eczema, prurito	Necrolisi epidermica tossica, sindrome di Stevens-Johnson, eritema multiforme
Patologie del sistema muscolo-scheletrico e del tessuto connettivo			Debolezza muscolare, mialgia	
Patologie sistemiche e condizioni relative alla sede di somministrazione		Astenia/ affaticamento		
Traumatismo, avvelenamento e complicazioni da procedura			Traumatismo	

Descrizione di determinate reazioni avverse

Il rischio di anoressia è più elevato quando assieme al levetiracetam viene somministrato il topiramato. In numerosi casi di alopecia, è stata osservata guarigione dopo la sospensione del trattamento con levetiracetam.

In alcuni dei casi di pancitopenia è stata identificata soppressione del midollo osseo.

Popolazione pediatrica

In pazienti di età compresa tra 1 mese e meno di 4 anni, un totale di 190 pazienti è stato trattato con levetiracetam in studi controllati con placebo ed in studi di estensione in aperto. Sessanta (60) di questi pazienti sono stati trattati con levetiracetam in studi controllati con placebo. In pazienti di età compresa tra 4 e 16 anni, un totale di 645 pazienti è stato trattato con levetiracetam in studi controllati con placebo ed in studi di estensione in aperto. 233 di questi pazienti sono stati trattati con levetiracetam in studi controllati con placebo. In entrambi questi intervalli di età pediatrica, questi dati sono integrati con l'esperienza post-marketing relativa all'uso di levetiracetam.

Inoltre, 101 bambini di età inferiore a 12 mesi sono stati esposti in uno studio di sicurezza post-autorizzazione. Non sono stati identificati nuovi problemi di sicurezza per levetiracetam in infanti di età inferiore a 12 mesi con epilessia.

Il profilo delle reazioni avverse del levetiracetam è generalmente simile nell'ambito dei diversi gruppi di età e delle indicazioni approvate nel trattamento dell'epilessia. Negli studi clinici controllati con placebo, i risultati sulla sicurezza nei pazienti pediatrici sono stati coerenti con il profilo di sicurezza di levetiracetam negli adulti, ad eccezione delle reazioni avverse comportamentali e psichiatriche che sono state più comuni nei bambini rispetto che negli adulti. Nei bambini e negli adolescenti di età compresa tra 4 e 16 anni, sono stati riportati più frequentemente che in altri gruppi di età o nel profilo di sicurezza complessivo vomito (molto comune, 11,2%), agitazione (comune, 3,4%), sbalzi d'umore (comune, 2,1%), labilità affettiva (comune, 1,7%), aggressività (comune, 8,2%), comportamento anormale (comune, 5,6%) e letargia (comune, 3,9%). In infanti e bambini di età compresa tra 1 mese e meno di 4 anni, sono state riportate più frequentemente che in altri gruppi di età o nel profilo di sicurezza complessivo irritabilità (molto comune, 11,7%) e coordinazione anormale (comune, 3,3%). Uno studio di sicurezza sui pazienti pediatrici, condotto secondo un disegno di non inferiorità, in doppio cieco e controllato con placebo, ha valutato gli effetti cognitivi e neuro-psicologici di levetiracetam in bambini da 4 a 16 anni di età con crisi convulsive a esordio parziale. Il levetiracetam si è dimostrato non differente (non inferiore) rispetto al placebo per quanto riguarda la modifica rispetto al basale nel punteggio ottenuto ai test "Attenzione e Memoria" della scala di Leiter-R (*Memory Screen Composite score*) nella popolazione per protocol. I risultati correlati alle funzioni comportamentali ed emozionali hanno indicato un peggioramento, nei pazienti trattati con levetiracetam, del comportamento aggressivo misurato in maniera standardizzata e sistematica, con l'utilizzo di uno strumento validato (*CBCL-Achenbach Child Behavior Checklist*).

Tuttavia, i soggetti che hanno assunto levetiracetam nello studio in aperto di follow-up a lungo termine non hanno manifestato, in media, un peggioramento delle loro funzioni comportamentali ed emozionali; in particolare, le valutazioni dell'aggressività nei comportamenti non sono peggiorate rispetto al basale.

Segnalazione delle reazioni avverse sospette

La segnalazione delle reazioni avverse sospette che si verificano dopo l'autorizzazione del medicinale è importante, in quanto permette un monitoraggio continuo del rapporto beneficio/rischio del medicinale. Agli operatori sanitari è richiesto di segnalare qualsiasi reazione avversa sospetta tramite il sistema nazionale di segnalazione dell'Agenzia Italiana del Farmaco, Sito web: http://www.agenziafarmaco.gov.it/it/responsabili.

4.9 Sovradosaggio

Sintomi

Sonnolenza, agitazione, aggressività, ridotto livello di coscienza,

depressione respiratoria e coma sono stati osservati con sovradosaggi di levetiracetam.

Trattamento del sovradosaggio

Dopo un sovradosaggio acuto, lo stomaco può essere svuotato mediante lavanda gastrica o induzione del vomito. Non esiste un antidoto specifico per levetiracetam. Il trattamento del sovradosaggio dovrà essere sintomatico e può includere l'emodialisi. L'efficienza di estrazione mediante dialisi è del 60% per levetiracetam e del 74% per il metabolita primario.

5. PROPRIETÀ FARMACOLOGICHE

5.1 Proprietà farmacodinamiche

Categoria farmacoterapeutica: antiepilettici, altri antiepilettici. Codice ATC: N03AX14.

Il principio attivo, levetiracetam, è un derivato pirrolidonico (S-enantiomero dell'α-etil- 2-oxo-1-pirrolidin acetamide), non correlato chimicamente con sostanze ad attività antiepilettica esistenti.

Meccanismo d'azione

Il meccanismo d'azione di levetiracetam non è stato ancora del tutto spiegato. Esperimenti *in vitro* ed *in vivo* suggeriscono che levetiracetam non altera le caratteristiche cellulari di base e la normale neurotrasmissione.

Studi *in vitro* dimostrano che levetiracetam agisce sui livelli intraneuronali di Ca^{2+} attraverso la parziale inibizione delle correnti di Ca^{2+} di tipo N e riducendo il rilascio di Ca^{2+} dai depositi intraneuronali. Inoltre, il farmaco inverte parzialmente la riduzione, indotta da zinco e β-carboline, delle correnti indotte da GABA e glicina. Studi *in vitro* hanno inoltre evidenziato che levetiracetam si lega ad uno specifico sito nel tessuto cerebrale dei roditori. Questo sito di legame è la proteina 2A della vescicola sinaptica, che si ritiene sia coinvolta nella fusione della vescicola e nell'esocitosi del neurotrasmettitore. Levetiracetam e i relativi analoghi mostrano un grado di affinità per il legame alla proteina 2A della vescicola sinaptica che è correlato con la potenza della loro protezione antiepilettica nel modello audiogenico di epilessia nel topo. Questa scoperta suggerisce che l'interazione tra levetiracetam e la proteina 2A della vescicola sinaptica sembra aver parte nel meccanismo d'azione antiepilettica del medicinale.

Effetti farmacodinamici

Il levetiracetam induce un'azione di protezione nei confronti delle crisi epilettiche in un ampio spettro di modelli animali di epilessia parziale e generalizzata primaria, senza avere un effetto pro-convulsivante. Il metabolita primario è inattivo. Nell'uomo, un'attività in condizioni di epilessia sia parziale che generalizzata (scarica epilettiforme/risposta fotoparossistica) ha confermato l'ampio spettro del profilo farmacologico del levetiracetam.

Efficacia e sicurezza clinica

Terapia aggiuntiva nel trattamento delle crisi parziali con o senza generalizzazione secondaria in adulti, adolescenti, bambini ed infanti a partire da 1 mese di età con epilessia Negli adulti, l'efficacia di levetiracetam è stata dimostrata in 3 studi in doppio cieco, controllati con placebo, con dosi di 1000 mg, 2000 mg o 3000 mg/die, suddivise in 2 somministrazioni, per una durata di trattamento fino a 18 settimane. In una analisi globale, la percentuale di pazienti che ha ottenuto una riduzione della frequenza delle crisi parziali per settimana, nel periodo di trattamento a dose stabile (12/14 settimane), uguale o superiore al 50% rispetto al basale, è stata del 27,7%, 31,6% e 41,3% dei pazienti trattati rispettivamente con 1000, 2000 o 3000 mg di levetiracetam e del 12,6% per i pazienti trattati con placebo.

Popolazione pediatrica L'efficacia di levetiracetam nei pazienti pediatrici (dai 4 ai 16 anni di età) è stata dimostrata in uno studio in doppio cieco, controllato con placebo, che ha incluso 198 pazienti ed ha avuto una durata di trattamento di 14 settimane. In questo studio, i pazienti hanno assunto levetiracetam alla dose fissa di 60 mg/kg/die (con due somministrazioni giornaliere).

Il 44,6% dei pazienti trattati con levetiracetam e il 19,6% dei pazienti trattati con placebo ha avuto, rispetto al basale, una riduzione della frequenza delle crisi convulsive a esordio parziale per settimana uguale o superiore al 50%.

Con il trattamento continuato a lungo termine, l'11,4% dei pazienti è rimasto libero da crisi per almeno 6 mesi e il 7,2% è rimasto libero da crisi per almeno 1 anno.

Nei pazienti pediatrici (da 1 mese a meno di 4 anni di età), l'efficacia di levetiracetam è stata dimostrata in uno studio in doppio cieco, controllato con placebo, che ha incluso 116 pazienti e ha avuto una durata di trattamento di 5 giorni. In questo studio è stata prescritta ai pazienti una dose giornaliera di 20 mg/kg, 25 mg/kg, 40 mg/kg o 50 mg/kg di soluzione orale, basandosi sullo schema di titolazione della dose riferito alla loro età. Nello studio sono state utilizzate le seguenti dosi: 20 mg/kg/die, titolata a 40 mg/kg/die, per infanti da un mese a meno di sei mesi di età; 25 mg/kg/die, titolata a 50 mg/kg/die, per infanti e bambini da 6 mesi a meno di 4 anni di età. La dose totale giornaliera è stata suddivisa in due somministrazioni al giorno. Il principale parametro dell'efficacia del trattamento è stato il tasso di pazienti responsivi (percentuale di pazienti con una riduzione della frequenza media giornaliera delle crisi convulsive a esordio parziale $\geq$50% rispetto ai valori basali), valutato da un esaminatore unico in cieco utilizzando un video EEG per un periodo di 48 ore. L'analisi dell'efficacia è stata effettuata su 109 pazienti che erano stati sottoposti a video EEG per almeno 24 ore, sia durante il periodo basale che durante il periodo di valutazione. Il 43,6% dei pazienti trattati con levetiracetam e il 19,6% dei pazienti trattati con placebo sono stati considerati responsivi. I risultati sono coerenti nei diversi gruppi di età. Nel trattamento continuato a lungo termine, l'8,6% dei pazienti è rimasto libero da crisi per almeno 6 mesi e il 7,8% è stato libero da crisi per almeno 1 anno. 35 infanti di età inferiore ad 1 anno, dei quali solo 13 di età inferiore ai 6 mesi, con crisi ad esordio parziale sono stati esposti in studi clinici controllati con placebo.

Monoterapia nel trattamento delle crisi convulsive ad esordio parziale con o senza generalizzazione secondaria in pazienti a partire da 16 anni di età con epilessia di nuova diagnosi L'efficacia del levetiracetam in monoterapia è stata dimostrata in uno studio comparativo di non inferiorità in doppio cieco, a gruppi paralleli, verso carbamazepina a rilascio controllato (CR), in 576 pazienti di 16 anni di età o più, con epilessia di nuova o recente diagnosi. I pazienti dovevano presentare solo crisi parziali non provocate oppure crisi tonico-cloniche generalizzate. I pazienti sono stati randomizzati a carbamazepina CR 400-1200 mg/die o levetiracetam 1000-3000 mg/die e il trattamento ha avuto una durata fino a 121 settimane in base alla risposta.

La libertà dalle crisi per un periodo di 6 mesi è stata ottenuta nel 73,0% dei pazienti trattati con levetiracetam e nel 72,8% dei pazienti trattati con carbamazepina CR; la differenza assoluta corretta tra i trattamenti è stata dello 0,2% (IC 95%:-7,8 8,2). Più della metà dei soggetti è rimasta libera da crisi per 12 mesi (56,6% e 58,5% dei soggetti trattati rispettivamente con levetiracetam e carbamazepina CR).

In uno studio che rifletteva la pratica clinica, il trattamento antiepilettico concomitante ha potuto essere sospeso in un numero limitato di pazienti che avevano risposto alla terapia aggiuntiva con levetiracetam (36 pazienti adulti su 69).

Terapia aggiuntiva nel trattamento delle crisi miocloniche in adulti ed adolescenti a partire da 12 anni di età con epilessia mioclonica giovanile L'efficacia del levetiracetam è stata dimostrata in uno studio in doppio cieco, controllato con placebo, della durata di 16 settimane, in pazienti a partire dai 12 anni di età e oltre, affetti da epilessia generalizzata idiopatica con crisi miocloniche in differenti sindromi. La maggioranza dei pazienti presentava epilessia mioclonica giovanile.

In questo studio, la dose di levetiracetam è stata di 3000 mg/die, somministrata in due dosi separate.

Il 58,3% dei pazienti trattati con levetiracetam e il 23,3% dei pazienti trattati con placebo ha avuto almeno una riduzione del 50% dei giorni con crisi miocloniche per settimana. A seguito del trattamento continuato a lungo termine, il 28,6% dei pazienti è rimasto libero da crisi miocloniche per almeno 6 mesi ed il 21,0% dei pazienti è rimasto libero da crisi miocloniche per almeno 1 anno.

Terapia aggiuntiva nel trattamento delle crisi tonico-cloniche generalizzate primarie in adulti e adolescenti a partire da 12 anni di età con epilessia generalizzata idiopatica L'efficacia del levetiracetam è stata dimostrata in uno studio di 24 settimane in doppio cieco, controllato con placebo, che ha incluso adulti, adolescenti e un numero limitato di bambini affetti da epilessia generalizzata idiopatica con crisi tonico-cloniche generalizzate primarie (PGTC) in differenti sindromi (epilessia mioclonica giovanile, epilessia giovanile da assenza, epilessia infantile da assenza oppure epilessia con crisi da grande male al risveglio). In questo studio, la dose di levetiracetam è stata di 3000 mg/die per adulti e adolescenti oppure di 60 mg/kg/die per i bambini, somministrata in due dosi separate.

Il 72,2% dei pazienti trattati con levetiracetam e il 45,2% dei pazienti trattati con placebo ha avuto una riduzione della frequenza delle crisi PGTC per settimana uguale o superiore al 50%. A

seguito del trattamento continuato a lungo termine, il 47,4% dei pazienti è rimasto libero da crisi tonico-cloniche per almeno 6 mesi e il 31,5% è stato libero da crisi tonico-cloniche per almeno 1 anno.

5.2 Proprietà farmacocinetiche

Levetiracetam è un composto estremamente solubile e permeabile. Il profilo farmacocinetico è lineare, con una scarsa variabilità intra- ed inter-individuale. Non c'è modificazione della clearance dopo somministrazioni ripetute. Non c'è evidenza di alcuna rilevante variabilità circadiana e per sesso e razza. Il profilo farmacocinetico è comparabile nei volontari sani e nei pazienti con epilessia. Dato il suo completo e lineare assorbimento, i livelli plasmatici di levetiracetam possono essere predetti dalla dose orale espressa come mg/kg di peso corporeo. Perciò non c'è bisogno di monitorare i livelli plasmatici di levetiracetam. È stata evidenziata negli adulti e nei bambini una significativa correlazione tra le concentrazioni nella saliva e nel plasma (il rapporto delle concentrazioni saliva/plasma variava in un intervallo da 1 a 1,7 per la formulazione orale in compresse e, dopo 4 ore dall'assunzione, per la formulazione orale in soluzione).

Adulti e adolescenti

Assorbimento

Levetiracetam è assorbito rapidamente dopo somministrazione orale. La biodisponibilità orale assoluta è prossima al 100%. Le concentrazioni al picco plasmatico (C_{max}) sono raggiunte 1,3 ore dopo l'assunzione. Lo stato stazionario è raggiunto dopo due giorni di somministrazione di due dosi quotidiane. Le concentrazioni al picco plasmatico (C_{max}) sono tipicamente di 31 e 43 µg/ml in seguito, rispettivamente, ad una singola dose di 1000 mg e a una dose di 1000 mg ripetuta due volte al giorno. L'entità di assorbimento non è dose dipendente e non è influenzata dal cibo.

Distribuzione

Non sono disponibili dati sulla distribuzione tissutale nell'uomo. Né levetiracetam né il suo metabolita primario si legano significativamente alle proteine plasmatiche (<10%). Il volume di distribuzione di levetiracetam va approssimativamente da 0,5 a 0,7 l/kg, ed è un valore prossimo al volume totale corporeo di acqua.

Biotrasformazione

Levetiracetam non è ampiamente metabolizzato nell'uomo. La principale via metabolica (24% della dose) è l'idrolisi enzimatica del gruppo acetamide. La produzione del metabolita primario, ucb L057, non è supportata dalle isoforme del citocromo P450 epatico. L'idrolisi del gruppo acetamide è stata misurabile in numerosi tessuti, comprese le cellule ematiche. Il metabolita ucb L057 è farmacologicamente inattivo.

Sono stati inoltre identificati due metaboliti minori. Uno è stato ottenuto dall'idrossilazione dell'anello pirrolidonico (1,6% della dose) e l'altro dall'apertura dell'anello pirrolidonico (0,9% della dose). Altri componenti non noti erano responsabili soltanto dello 0,6% della dose. *In vivo* non sono state evidenziate interconversioni enantiomeriche né per levetiracetam né per il suo metabolita primario. *In vitro*, levetiracetam ed il suo metabolita primario hanno mostrato di non inibire le attività delle principali isoforme del citocromo P450 epatico umano (CYP3A4, 2A6, 2C9, 2C19, 2D6, 2E1 e 1A2), della glucuronil transferasi (UGT1A1 e UGT1A6) e dell'epossido idrossilasi. Inoltre, levetiracetam non influenza la glucuronazione *in vitro* dell'acido valproico. In colture di epatociti umani, levetiracetam ha avuto un effetto minimo o nullo su CYP1A2, SULT1E1 o UGT1A1. Levetiracetam ha causato una moderata induzione del CYP2B6 e del CYP3A4 I dati *in vitro* ed i dati *in vivo* relativi alla interazione con contraccettivi orali, digossina e warfarin indicano che non è attesa alcuna significativa induzione enzimatica *in vivo*. Quindi, l'interazione di ITALEPT con altre sostanze, o viceversa, è improbabile.

Eliminazione

L'emivita plasmatica negli adulti è di 7±1 ore e non si modifica in relazione alla dose, alla via di somministrazione o alla somministrazione ripetuta. La clearance totale corporea media è di 0,96 ml/min/kg. La principale via di escrezione è la via urinaria, responsabile in media dell'eliminazione del 95% della dose somministrata (approssimativamente il 93% della dose è stato escreto entro 48 ore). L'eliminazione fecale rappresenta solo lo 0,3% della dose. L'escrezione cumulativa urinaria di levetiracetam e del suo metabolita primario è responsabile rispettivamente dell'eliminazione del 66% e del 24% della dose, nell'arco delle prime 48 ore. La clearance renale di levetiracetam e di ucb L057 è rispettivamente di 0,6 e 4,2 ml/min/kg, indicando che il levetiracetam è escreto mediante filtrazione glomerulare con successivo riassorbimento tubulare e che il metabolita primario è escreto anche mediante secrezione tubulare attiva oltre che con filtrazione glomerulare. L'eliminazione di levetiracetam è correlata alla clearance della creatinina.

Anziani

Nell'anziano, l'emivita è aumentata di circa il 40% (da 10 a 11 ore). Ciò è dovuto alla riduzione della funzionalità renale in questa popolazione (vedere paragrafo 4.2).

Compromissione renale

La clearance corporea apparente sia di levetiracetam sia del suo metabolita primario è correlata alla clearance della creatinina. Nei pazienti con insufficienza renale di grado moderato e grave si raccomanda pertanto di aggiustare la dose giornaliera di mantenimento di ITALEPT, basandosi sulla clearance della creatinina (vedere paragrafo 4.2).

Nei soggetti adulti affetti da anuria con malattia renale allo stadio terminale, l'emivita è risultata approssimativamente pari a 25 e 3,1 ore, rispettivamente nei periodi tra le dialisi e durante la dialisi.

La frazione del levetiracetam rimossa era del 51% nel corso di una tipica seduta di dialisi di 4 ore.

Compromissione epatica

In soggetti con insufficienza epatica lieve e moderata non è stata rilevata alcuna modificazione significativa della clearance del levetiracetam. Nella maggioranza dei soggetti con compromissione epatica grave, la clearance del levetiracetam è stata ridotta di oltre il 50% a causa della compromissione renale concomitante (vedere paragrafo 4.2).

Popolazione pediatrica

Bambini (dai 4 ai 12 anni)

In seguito ad una singola somministrazione orale (20 mg/kg) in bambini (da 6 a 12 anni) con epilessia, l'emivita di levetiracetam è risultata di 6,0 ore. La clearance apparente corretta in funzione del peso corporeo è risultata approssimativamente più alta del 30% rispetto agli adulti con epilessia.

In seguito a somministrazione orale per dosi ripetute (da 20 a 60 mg/kg/die) in bambini epilettici (da 4 a 12 anni), il levetiracetam è stato rapidamente assorbito. Il picco di concentrazione plasmatica è stato osservato a 0,5 - 1,0 ora dalla somministrazione. Sono stati osservati aumenti lineari e proporzionali alla dose per il picco delle concentrazioni plasmatiche e per l'area sotto la curva. L'emivita di eliminazione è risultata pari a circa 5 ore. La clearance corporea apparente è stata di 1,1 ml/min/kg.

Infanti e bambini (da 1 mese a 4 anni)

A seguito di somministrazione di una dose singola (20 mg/kg) di soluzione orale 100 mg/ml in bambini epilettici (da 1 mese a 4 anni), il levetiracetam è stato rapidamente assorbito e le concentrazioni plasmatiche di picco sono state osservate circa 1 ora dopo la somministrazione. I risultati farmacocinetici hanno indicato che l'emivita è più breve (5,3 ore) che negli adulti (7,2 ore) e la clearance apparente è risultata più veloce (1,5 ml/min/kg) rispetto agli adulti (0,96 ml/min/kg). Nelle analisi farmacocinetiche di popolazione condotte in pazienti da 1 mese a 16 anni di età, il peso corporeo era significativamente correlato alla clearance apparente (la clearance aumentava all'aumentare del peso corporeo) ed al volume di distribuzione apparente. Anche l'età ha influenzato entrambi i parametri. Questo effetto è risultato marcato per i bambini più piccoli e attenuato con l'aumentare dell'età, per poi diventare trascurabile intorno ai 4 anni di età. In entrambe le analisi farmacocinetiche di popolazione, vi è stato un aumento del 20% circa della clearance apparente del levetiracetam quando somministrato assieme a un farmaco antiepilettico induttore enzimatico.

5.3 Dati preclinici di sicurezza

I dati non-clinici non rivelano rischi particolari per l'uomo sulla base di studi convenzionali di sicurezza farmacologica, genotossicità e potenziale cancerogeno.

Gli effetti indesiderati non osservati negli studi clinici, ma visti nel ratto e in minore entità nel topo, a livelli di esposizione simili ai livelli di esposizione nell'uomo e con possibile rilevanza per l'uso clinico, sono state variazioni epatiche come indice di una risposta adattativa, quali aumento ponderale ed ipertrofia centro lobulare, infiltrazione adiposa ed innalzamento degli enzimi epatici nel plasma.

Nel ratto non si sono osservate reazioni avverse sulla fertilità maschile e femminile o sulla capacità riproduttiva a dosi fino a 1800 mg/kg/die (6 volte la dose massima giornaliera raccomandata nell'uomo -MRHD, *Maximum Recommended Human Daily*

Dose- in base ai mg/m^2 o in base all'esposizione), sia nella generazione parentale che nella generazione F1.
Due studi sullo sviluppo embriofetale (EFD: *Embryo-Fetal Development*) sono stati condotti nel ratto a 400, 1200 e 3600 mg/kg/die. A 3600 mg/kg/die, in uno solo dei 2 studi EFD si è registrato un lieve calo di peso fetale associato ad un aumento marginale delle alterazioni scheletriche/anomalie minori. Non si è verificato alcun effetto sulla mortalità embrionale, né vi è stato un aumento dell'incidenza di malformazioni. Il NOAEL (*No Observed Adverse Effect Level*) è stato di 3600 mg/kg/die per le femmine di ratto gravide (12 volte la MRHD in base ai mg/m^2) e 1200 mg/kg/die per i feti.
Quattro studi sullo sviluppo embrio-fetale sono stati condotti sul coniglio utilizzando dosi di 200, 600, 800, 1200 e 1800 mg/kg/die. La dose di 1800 mg/kg/die ha indotto una marcata tossicità materna e una diminuzione del peso fetale, in associazione con una maggiore incidenza di feti con anomalie cardiovascolari/scheletriche. Il NOAEL è stato <200 mg/kg/die per le madri e di 200 mg/kg/die per i feti (equivalente alla MRHD in base ai mg/m^2). Uno studio sullo sviluppo peri- e post-natale è stato condotto sul ratto con dosi di levetiracetam di 70, 350 e 1800 mg/kg/die. Il NOAEL è stato ≥1800 mg/kg/die per le femmine F0 e per la generazione F1 per quanto riguarda la sopravvivenza, l'accrescimento e lo sviluppo fino allo svezzamento (6 volte la MRHD in base ai mg/m^2). Studi nel ratto e nel cane, nell'animale neonato e giovane, hanno dimostrato che non si manifestano effetti indesiderati in alcuno degli endpoint standard di sviluppo o di maturazione a dosi fino a 1800 mg/kg/die (6-17 volte la MRHD in base ai mg/m^2).

6. INFORMAZIONI FARMACEUTICHE

6.1 Elenco degli eccipienti

Nucleo della compressa:
amido di mais
povidone K 30
talco
diossido di silicio colloidale
magnesio stearato (E572).
Compresse rivestite con film da 500 mg
Film di rivestimento:
polivinil alcol, parz. idrolizzato
titanio diossido (E171)
macrogol 3350
talco
ferro ossido giallo (E172)
Compresse rivestite con film da 1000 mg
Film di rivestimento:
polivinil alcol, parz. idrolizzato
titanio diossido (E171)
macrogol 3350
talco.

6.2 Incompatibilità

Non pertinente.

6.3 Periodo di validità

3 anni.

6.4 Precauzioni particolari per la conservazione

Compresse rivestite con film da 500 mg
Questo medicinale non richiede alcuna condizione particolare di conservazione.
Compresse rivestite con film da 1000 mg
Non conservare a temperatura superiore a 30°C.

6.5 Natura e contenuto del contenitore

Blister in alluminio/PVC con:
Compresse rivestite con film da 500 mg 60 compresse rivestite con film.
Compresse rivestite con film da 1000 mg 30 compresse rivestite con film.
È possibile che non tutte le confezioni siano commercializzate.

6.6 Precauzioni particolari per lo smaltimento e la manipolazione

Il medicinale non utilizzato ed i rifiuti derivati da tale medicinale devono essere smaltiti in conformità
alla normativa locale vigente.

7. TITOLARE DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO

So.Se.PHARM S.r.l. - Via dei Castelli Romani, 22- 00071 Pomezia (Roma) Italia. Concessionario per la vendita: Istituto Luso Farmaco D'Italia SpA – Milanofiori - Strada 6 - Edificio L - Rozzano (MI).

8. NUMERO(I) DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO

AIC 040273017 - "500 mg compresse rivestite con film" 60 compresse in blister PVC/Al.
AIC 040273029 - "1000 mg compresse rivestite con film" 30 compresse in blister PVC/Al.

9. DATA DELLA PRIMA AUTORIZZAZIONE/RINNOVO DELL'AUTORIZZAZIONE

Prima Autorizzazione: 19 Luglio 2012.
Rinnovo: 19 luglio 2016.

10. DATA DI REVISIONE DEL TESTO

14 Settembre 2016.

ITALEPT 500 mg 60 compresse rivestite con film
Prezzo SSN € 37,67* Classe A - Ricetta ripetibile.
ITALEPT 1000 mg 30 compresse rivestite con film
Prezzo SSN € 36,16* Classe A - Ricetta ripetibile.

**Prezzo comprensivo delle riduzioni temporanee di cui alle determinazioni AIFA, 3 luglio 2006 e 27 settembre 2006.*

ITALEPT Levetiracetam

RIASSUNTO DELLE CARATTERISTICHE DEL PRODOTTO

1. DENOMINAZIONE DEL MEDICINALE

ITALEPT 100 mg/ml soluzione orale.

2. COMPOSIZIONE QUALITATIVA E QUANTITATIVA

Ogni ml contiene 100 mg di levetiracetam.
Eccipienti con effetti noti:
Ogni ml contiene 2,7 mg di metile paraidrossibenzoato (E218), 0,3 mg di propile paraidrossibenzoato (E216) e 300 mg di maltitolo liquido.
Per l'elenco completo degli eccipienti, vedere paragrafo 6.1.

3. FORMA FARMACEUTICA

Soluzione orale. Liquido limpido.

4. INFORMAZIONI CLINICHE

4.1 Indicazioni terapeutiche

ITALEPT è indicato come monoterapia nel trattamento delle crisi convulsive ad esordio parziale con o senza generalizzazione secondaria in adulti ed adolescenti a partire dai 16 anni di età con epilessia di nuova diagnosi. ITALEPT è indicato quale terapia aggiuntiva:

- nel trattamento delle crisi convulsive ad esordio parziale con o senza secondaria generalizzazione in adulti, adolescenti, bambini e infanti a partire da 1 mese di età con epilessia;
- nel trattamento delle crisi miocloniche in adulti ed adolescenti a partire da 12 anni di età con epilessia mioclonica giovanile;
- nel trattamento delle crisi convulsive tonico-cloniche generalizzate primarie in adulti ed adolescenti a partire da 12 anni di età con epilessia idiopatica generalizzata.

4.2 Posologia e modo di somministrazione

Posologia

Monoterapia per adulti e adolescenti a partire da 16 anni di età La dose iniziale raccomandata è 250 mg due volte al giorno, da aumentare fino a una dose terapeutica iniziale di 500 mg due volte al giorno dopo due settimane. La dose può essere ulteriormente aumentata di 250 mg due volte al giorno ogni due settimane sulla base della risposta clinica. La dose massima è di 1500 mg due volte al giorno.

Terapia aggiuntiva per adulti (≥18 anni) ed adolescenti (da 12 a 17 anni) del peso di 50 kg o superiore La dose terapeutica iniziale è 500 mg due volte al giorno. Questa dose può essere iniziata dal primo giorno di trattamento. Sulla base della risposta clinica e della tollerabilità, la dose giornaliera può essere aumentata fino ad un massimo di 1500 mg due volte al giorno. Gli aggiustamenti posologici possono essere fatti con aumenti o diminuzioni di 500 mg due volte al giorno ogni 2 - 4 settimane.

Interruzione del trattamento

In accordo con la pratica clinica corrente, se si deve interrompere il trattamento con ITALEPT si raccomanda una sospensione graduale (ad es. negli adulti e negli adolescenti di peso superiore a 50 kg: diminuzione di 500 mg due volte al giorno ad intervalli di tempo compresi tra due e quattro settimane; negli infanti di età superiore ai 6 mesi, nei bambini e negli adolescenti di peso inferiore a 50 kg: la diminuzione della dose non deve superare i 10 mg/kg due volte al giorno ogni due settimane; negli infanti (di età inferiore a 6 mesi): la diminuzione della dose non deve superare i 7 mg/kg due volte al giorno ogni due settimane).

Popolazioni speciali

Anziani (da 65 anni in poi) Si raccomanda un aggiustamento della posologia nei pazienti anziani con funzionalità renale compromessa (vedere più avanti "*Compromissione renale*).

Compromissione renale La dose giornaliera deve essere personalizzata in base alla funzionalità renale.
Per i pazienti adulti, fare riferimento alla tabella seguente e modificare la dose come indicato. Per utilizzare questa tabella posologica è necessario valutare la clearance della creatinina del paziente (CLcr) in ml/min. La CLcr in ml/min può essere calcolata dalla determinazione della creatinina sierica (mg/dl) utilizzando, per adulti e adolescenti di peso superiore o uguale a 50 kg, la seguente formula:

$$\text{CLcr (ml/min)} = \frac{[140\text{-età (anni)}] \times \text{peso (kg)}}{72 \times \text{creatinina sierica (mg/dl)}} \quad (\times 0{,}85 \text{ nelle donne})$$

Inoltre, la CLcr viene aggiustata secondo l'area della superficie corporea (BSA) come segue:

$$\text{CLcr (ml/min/1,73 m}^2) = \frac{\text{CLcr (ml/min)}}{\text{BSA del soggetto (m}^2)} \times 1{,}73$$

Aggiustamento posologico per pazienti adulti ed adolescenti di peso superiore a 50 kg con funzionalità renale alterata:

Gruppo	Clearance della creatinina (ml/min/1,73 m²)	Dose e numero di somministrazioni
Normale	>80	500-1500 mg due volte al giorno
Lieve	50-79	500-1000 mg due volte al giorno
Moderata	30-49	250-750 mg due volte al giorno
Severa	<30	250-500 mg due volte al giorno
Pazienti con malattia renale allo stadio finale sottoposti a dialisi[1]	-	500-1000 mg una volta al giorno[2]

[1] Una dose di carico pari a 750 mg è raccomandata nel primo giorno di trattamento con levetiracetam.
[2] Dopo la dialisi si raccomanda una dose supplementare compresa tra 250 e 500 mg.

Per bambini con ridotta funzionalità renale, la dose di levetiracetam deve essere adattata sulla base della funzionalità renale, perché la clearance del levetiracetam è correlata alla funzionalità renale. Questa raccomandazione si basa su uno studio condotto su pazienti adulti con ridotta funzionalità renale.
Nei giovani adolescenti, nei bambini e negli infanti, la CLcr, in ml/min/1,73 m², può essere stimata dalla determinazione della creatinina sierica (in mg/dl) utilizzando la seguente formula (formula di Schwartz):

$$\text{CLcr (ml/min/1,73 m}^2) = \frac{\text{Altezza (cm)} \times \text{ks}}{\text{Creatinina sierica (mg/dl)}}$$

ks= 0,45 negli infanti nati a termine, di età fino a 1 anno; ks= 0,55 nei bambini di età inferiore a 13 anni e nelle femmine adolescenti; ks= 0,7 nei maschi adolescenti.

Aggiustamento posologico per infanti, bambini e adolescenti di peso inferiore a 50 kg con funzionalità renale alterata:

Gruppo	Clearance della creatinina (ml/min/ 1,73 m²)	Dose e frequenza[1]	
		Infanti da 1 mese a meno di 6 mesi	Infanti da 6 a 23 mesi, bambini e adolescenti di peso inferiore ai 50 kg
Normale	>80	7-21 mg/ kg (0,07-0,21 ml/kg) due volte al giorno	10-30 mg/ kg (0,10-0,30 ml/kg) due volte al giorno
Lieve	50-79	7-14 mg/ kg (0,07-0,14 ml/kg) due volte al giorno	10-20 mg/ kg (0,10-0,20 ml/kg) due volte al giorno
Moderata	30-49	3,5-10,5 mg/kg (0,035-0,105 ml/ kg) due volte al giorno	5-15 mg/ kg (0,05-0,15 ml/kg) due volte al giorno
Severa	<30	3,5-7 mg/ kg (0,035-0,07 ml/kg) due volte al giorno	5-10 mg/kg (0,05-0,10 ml/kg) due volte al giorno
Pazienti con malattia renale allo stadio finale sottoposti a dialisi	--	7-14 mg/ kg (0,07-0,14 ml/kg) una volta al giorno[2] [4]	10-20 mg/ kg (0,10-0,20 ml/kg) una volta al giorno[3] [5]

[1] Utilizzare ITALEPT soluzione orale per dosi inferiori a 250 mg, per dosi non multiple di 250 mg quando non è possibile ottenere la dose raccomandata assumendo un numero multiplo di compresse, e per i pazienti incapaci di deglutire le compresse.
[2] Si raccomanda una dose di carico di 10,5 mg/kg il primo giorno di trattamento con levetiracetam.
[3] Si raccomanda una dose di carico di 15 mg/kg (0,15 ml/kg) il primo giorno di trattamento con levetiracetam.
[4] Dopo la dialisi, si raccomanda una dose supplementare di 3,5-7 mg/kg (0,035-0,07 ml/kg).
[5] Dopo la dialisi, si raccomanda una dose supplementare di 5-10 mg/kg (0,05-0,10 ml/kg).

Compromissione epatica
Non è necessario alcun adeguamento posologico nei pazienti con compromissione epatica di grado da lieve a moderato. In pazienti con compromissione epatica severa, la clearance della creatinina può far sottostimare il grado di insufficienza renale. Pertanto, quando la clearance della creatinina è <60 ml/min/1,73 m², si raccomanda una riduzione del 50% della dose di mantenimento giornaliera.
Popolazione pediatrica
Il medico deve prescrivere la forma farmaceutica, la presentazione e il dosaggio più appropriati in base all'età, al peso e alla dose.
ITALEPT soluzione orale è la formulazione più indicata nella prima infanzia e nei bambini di età inferiore ai 6 anni. Inoltre, i dosaggi disponibili per le compresse non sono indicati per il trattamento iniziale dei bambini di peso inferiore a 25 kg, dei pazienti incapaci di deglutire le compresse o per la somministrazione di dosi inferiori a 250 mg. In tutti questi casi deve essere utilizzato ITALEPT soluzione orale.
Monoterapia Non sono state ancora stabilite la sicurezza e l'efficacia di ITALEPT somministrato in monoterapia nei bambini e negli adolescenti di età inferiore a 16 anni.
Non vi sono dati disponibili.
Terapia aggiuntiva per bambini piccoli da 6 a 23 mesi di età, bambini (da 2 a 11 anni) e adolescenti (da 12 a 17 anni) di peso inferiore a 50 kg La dose terapeutica iniziale è di 10 mg/kg due volte al giorno.
Sulla base della risposta clinica e della tollerabilità, la dose può essere aumentata fino a 30 mg/kg due volte al giorno.
Gli aggiustamenti posologici non devono superare aumenti o diminuzioni di 10 mg/kg due volte al giorno ogni due settimane. Deve essere usata la dose efficace più bassa. La dose in bambini di 50 kg o più è uguale a quella degli adulti.

Dose raccomandata nella prima infanzia a partire da 6 mesi di età, nei bambini e negli adolescenti:

Peso	Dose iniziale: 10 mg/kg due volte al giorno	Dose massima: 30 mg/kg due volte al giorno
6 kg[1]	60 mg (0,6 ml) due volte al giorno	180 mg (1,8 ml) due volte al giorno
10 kg[1]	100 mg (1 ml) due volte al giorno	300 mg (3 ml) due volte al giorno
15 kg[1]	150 mg (1,5 ml) due volte al giorno	450 mg (4,5 ml) due volte al giorno
20 kg[1]	200 mg (2 ml) due volte al giorno	600 mg (6 ml) due volte al giorno
25 kg	250 mg due volte al giorno	750 mg due volte al giorno
Da 50 kg[2]	500 mg due volte al giorno	1500 mg due volte al giorno

[1] I bambini dal peso di 25 kg o inferiore devono preferibilmente iniziare il trattamento con ITALEPT 100 mg/ml soluzione orale.
[2] La dose in bambini e adolescenti dal peso di 50 kg o superiore è uguale a quella degli adulti.

Terapia aggiuntiva per infanti da 1 mese a meno di 6 mesi di età La dose terapeutica iniziale è di 7 mg/kg due volte al giorno. Sulla base della risposta clinica e della tollerabilità, la dose può essere aumentata fino a 21 mg/kg due volte al giorno. Gli aggiustamenti posologici non devono superare aumenti o diminuzioni di 7 mg/kg due volte al giorno ogni due settimane. Deve essere usata la dose efficace più bassa. Gli infanti devono iniziare il trattamento con ITALEPT 100 mg/ml soluzione orale.

Dose raccomandata per infanti di età compresa tra 1 mese e meno di 6 mesi:

Peso	Dose iniziale: 7 mg/kg due volte al giorno	Dose massima: 21 mg/kg due volte al giorno
4 kg	28 mg (0,3 ml) due volte al giorno	84 mg (0,85 ml) due volte al giorno
5 kg	35 mg (0,35 ml) due volte al giorno	105 mg (1,05 ml) due volte al giorno
7 kg	49 mg (0,5 ml) due volte al giorno	147 mg (1,5 ml) due volte al giorno

È disponibile una presentazione:
- Un flacone da 300 ml con siringa graduata da 10 ml per uso orale (contenente fino a 1000 mg di levetiracetam), con una tacca graduata ogni 0,25 ml (corrispondente a 25 mg).

Questa presentazione deve essere prescritta ai bambini di età pari o superiore ai 4 anni, agli adolescenti e agli adulti.
Modo di somministrazione
La soluzione orale può essere diluita in un bicchiere d'acqua o nel biberon e può essere assunta con o senza cibo. Con ITALEPT vengono forniti una siringa graduata per somministrazione orale, un adattatore per la siringa e le istruzioni per l'uso nel foglio illustrativo.
La dose giornaliera va ripartita in due somministrazioni uguali.

4.3 Controindicazioni
Ipersensibilità al principio attivo o ad altri derivati pirrolidonici o ad uno qualsiasi degli eccipienti elencati al paragrafo 6.1.

4.4 Avvertenze speciali e precauzioni di impiego
Compromissione renale
La somministrazione di ITALEPT in pazienti con compromissione renale può richiedere un aggiustamento posologico. In pazienti con funzionalità epatica gravemente compromessa si racco-

manda di valutare la funzionalità renale prima di stabilire la posologia (vedere paragrafo 4.2).

Suicidio

Casi di suicidio, tentato suicidio, idea e comportamento suicida sono stati riportati in pazienti trattati con antiepilettici (incluso levetiracetam). Una meta-analisi di studi randomizzati e controllati con placebo, condotti con medicinali antiepilettici, ha mostrato un lieve incremento del rischio di idea e comportamento suicida. Il meccanismo di tale rischio non è noto.

Di conseguenza, i pazienti devono essere monitorati per quanto riguarda la comparsa di segni di depressione e/o idea e comportamento suicida, e deve essere preso in considerazione un trattamento appropriato. I pazienti (e coloro che se ne prendono cura) devono essere avvisati che, nel caso in cui compaiano segni di depressione e/o idea o comportamento suicida, è necessario consultare un medico.

Popolazione pediatrica

Dai dati disponibili nei bambini non si evince un'influenza sulla crescita e sulla pubertà. Tuttavia, non sono noti gli effetti a lungo termine sull'apprendimento, l'intelligenza, la crescita, la funzione endocrina, la pubertà e sul potenziale riproduttivo nei bambini.

Eccipienti

ITALEPT 100 mg/ml soluzione orale contiene metil paraidrossibenzoato (E218) e propil paraidrossibenzoato (E216), che possono causare reazioni allergiche (anche ritardate). Il prodotto contiene inoltre maltitolo liquido; i pazienti affetti da rari problemi ereditari di intolleranza al fruttosio non devono assumere questo medicinale.

4.5 Interazioni con altri medicinali ed altre forme di interazione

Medicinali antiepilettici

I dati provenienti da studi clinici pre-marketing, condotti negli adulti, indicano che levetiracetam non influenza le concentrazioni sieriche degli antiepilettici esistenti (fenitoina, carbamazepina, acido valproico, fenobarbital, lamotrigina, gabapentin e primidone) e che questi antiepilettici non influenzano la farmacocinetica di levetiracetam.

Come negli adulti, nei pazienti pediatrici cui sono state somministrate dosi fino a 60 mg/kg/die di levetiracetam, non c'è evidenza di interazioni clinicamente significative con altri medicinali.

Una valutazione retrospettiva di interazioni farmacocinetiche, in bambini e adolescenti affetti da epilessia (da 4 a 17 anni) ha confermato che la terapia aggiuntiva con levetiracetam somministrato per via orale non influenzava le concentrazioni sieriche allo stato stazionario di carbamazepina e valproato somministrati contemporaneamente.

Tuttavia, i dati hanno suggerito una clearance del levetiracetam del 20% più elevata nei bambini che assumono medicinali antiepilettici con un effetto di induzione enzimatica. Non è richiesto un aggiustamento della dose.

Probenecid

Il probenecid (500 mg quattro volte al giorno), un agente bloccante della secrezione tubulare renale, ha mostrato di inibire la clearance renale del metabolita primario, ma non di levetiracetam. Tuttavia, la concentrazione di questo metabolita rimane bassa.

Metotrexato

È stato riportato che la somministrazione concomitante di levetiracetam e metotrexato diminuisce la clearance del metotrexato, con conseguente concentrazione ematica di metotrexato aumentata/prolungata fino a livelli potenzialmente tossici. I livelli ematici di metotrexato e levetiracetam devono essere attentamente monitorati nei pazienti trattati in concomitanza con i due farmaci.

Contraccettivi orali e altre interazioni farmacocinetiche

Levetiracetam 1000 mg al giorno non ha influenzato la farmacocinetica dei contraccettivi orali (etinilestradiolo e levonorgestrel); i parametri endocrini (ormone luteinizzante e progesterone) non sono stati modificati. Levetiracetam 2000 mg al giorno non ha influenzato la farmacocinetica di digossina e warfarin; i tempi di protrombina non sono stati modificati.

La somministrazione concomitante di digossina, contraccettivi orali e warfarin non ha influenzato la farmacocinetica di levetiracetam.

Lassativi

Sono stati riportati casi isolati di diminuita efficacia di levetiracetam quando il lassativo osmotico macrogol è stato somministrato in concomitanza con levetiracetam per via orale. Pertanto, macrogol non deve essere assunto per via orale da un'ora prima ad un'ora dopo l'assunzione di levetiracetam.

Cibo e alcool

L'entità dell'assorbimento di levetiracetam non è stata modificata dal cibo, ma la velocità di assorbimento era lievemente ridotta. Non sono disponibili dati sulle interazioni di levetiracetam con l'alcool.

4.6 Fertilità, gravidanza e allattamento

Gravidanza

Dati post-marketing di diversi registri prospettici di gravidanza hanno documentato i risultati della esposizione a levetiracetam in monoterapia in più di 1.000 donne durante il primo trimestre di gravidanza. Nel complesso, questi dati non suggeriscono un sostanziale aumento del rischio di malformazioni congenite maggiori, sebbene un rischio teratogeno non possa essere completamente escluso. La terapia con più farmaci antiepilettici è associata ad un più alto rischio di malformazioni congenite rispetto alla monoterapia e pertanto la monoterapia deve essere presa in considerazione.

Gli studi sugli animali hanno mostrato una tossicità riproduttiva (vedere paragrafo 5.3). ITALEPT non è raccomandato durante la gravidanza e nelle donne in età fertile che non utilizzano metodi contraccettivi, a meno che non sia strettamente necessario.

Le alterazioni fisiologiche durante la gravidanza possono influenzare le concentrazioni di levetiracetam. Durante la gravidanza, è stata osservata una riduzione delle concentrazioni plasmatiche di levetiracetam. Questa riduzione è più pronunciata durante il terzo trimestre (fino al 60% della concentrazione basale prima della gravidanza).

Le donne in gravidanza trattate con levetiracetam devono essere accuratamente seguite dal punto di vista clinico.

L'interruzione dei trattamenti antiepilettici può comportare una esacerbazione della malattia che può essere nociva per la madre e per il feto.

Allattamento

Levetiracetam è escreto nel latte materno. Pertanto, l'allattamento con latte materno non è raccomandato. Tuttavia, se il trattamento con levetiracetam è necessario durante l'allattamento, deve essere valutato il rapporto rischio/beneficio del trattamento, tenendo in considerazione l'importanza dell'allattamento con latte materno.

Fertilità

Non è stato rilevato alcun impatto sulla fertilità negli studi sugli animali (vedere paragrafo 5.3). Non sono disponibili dati clinici; il rischio potenziale nell'uomo è sconosciuto.

4.7 Effetti sulla capacità di guidare veicoli e sull'uso di macchinari

Levetiracetam ha una bassa o moderata influenza sulla capacità di guidare veicoli e sull'uso di macchinari. Data la possibile differente sensibilità individuale, alcuni pazienti possono manifestare sonnolenza o altri sintomi legati all'azione sul sistema nervoso centrale, specialmente all'inizio del trattamento o in seguito ad un incremento della dose.

Si raccomanda pertanto cautela nei pazienti che sono impegnati in attività che richiedono elevata concentrazione, quali guidare autoveicoli o azionare macchinari.

I pazienti devono essere avvertiti di non guidare o utilizzare macchinari finché non sia stato accertato che la loro abilità ad eseguire queste attività non sia compromessa.

4.8 Effetti indesiderati

Riassunto del profilo di sicurezza

Le reazioni avverse più frequentemente riportate sono state rinofaringite, sonnolenza, cefalea, affaticamento e capogiro. Il profilo delle reazioni avverse di seguito presentato si basa sull'analisi degli studi clinici controllati verso placebo aggregati, relativi a tutte le indicazioni studiate, per un totale di 3.416 pazienti trattati con levetiracetam.

Questi dati sono integrati con l'uso di levetiracetam in corrispondenti studi di estensione in aperto, così come dall'esperienza post-marketing. Il profilo di sicurezza del levetiracetam è ge-

neralmente simile nell'ambito dei diversi gruppi di età (pazienti adulti e pediatrici) e delle indicazioni approvate nel trattamento dell'epilessia.

Tabella delle reazioni avverse

Le reazioni avverse segnalate nel corso di studi clinici (adulti, adolescenti, bambini ed infanti di età superiore ad 1 mese) e nell'esperienza post-marketing sono elencate nella tabella seguente secondo la classificazione per sistemi e organi e per frequenza.

Le reazioni avverse sono presentate in ordine decrescente di gravità e la loro frequenza è definita come segue: molto comune (≥1/10), comune (≥1/100, <1/10), non comune (≥1/1000, <1/100), raro (≥1/10.000, <1/1000) e molto raro (<1/10.000).

Classificazione per sistemi e organi (MedDRA)	Categoria di frequenza			
	Molto comune	Comune	Non comune	Raro
Infezioni ed infestazioni	Rinofaringite			Infezione
Patologie del sistema emolinfopoietico			Trombocitopenia, leucopenia	Pancitopenia, neutropenia, agranulocitosi
Disturbi del sistema immunitario				Reazione a farmaco con eosinofilia e sintomi sistemici (DRESS), ipersensibilità (incluso angioedema e anafilassi)
Disturbi del metabolismo e della nutrizione		Anoressia	Perdita di peso, aumento di peso	Iponatriemia
Disturbi psichiatrici		Depressione, ostilità/aggressività, ansia, insonnia, nervosismo/irritabilità	Tentato suicidio, idea suicida, disturbo psicotico, comportamento anormale, allucinazioni, collera, stato confusionale, attacco di panico, labilità affettiva/sbalzi d'umore, agitazione	Suicidio riuscito, disturbo della personalità, pensiero anormale
Patologie del sistema nervoso	Sonnolenza, cefalea	Convulsione, disturbo dell'equilibrio, capogiro, letargia, tremore	Amnesia, compromissione della memoria, coordinazione anormale/atassia, parestesia, alterazione dell'attenzione	Coreoatetosi, discinesia, ipercinesia
Patologie dell'occhio			Diplopia, visione offuscata	
Patologie dell'orecchio e del labirinto		Vertigine		
Patologie respiratorie, toraciche e mediastiniche		Tosse		
Patologie gastrointestinali		Dolore addominale, diarrea, dispepsia, vomito, nausea		Pancreatite
Patologie epatobiliari			Test della funzionalità epatica anormali	Insufficienza epatica, epatite
Patologie della cute e del tessuto sottocutaneo		Rash	Alopecia, eczema, prurito	Necrolisi epidermica tossica, sindrome di Stevens-Johnson, eritema multiforme
Patologie del sistema muscolo-scheletrico e del tessuto connettivo			Debolezza muscolare, mialgia	
Patologie sistemiche e condizioni relative alla sede di somministrazione		Astenia/ affaticamento		
Traumatismo, avvelenamento e complicazioni da procedura			Traumatismo	

Descrizione di determinate reazioni avverse
Il rischio di anoressia è più elevato quando assieme al levetiracetam viene somministrato il topiramato. In numerosi casi di alopecia, è stata osservata guarigione dopo la sospensione del trattamento con levetiracetam. In alcuni dei casi di pancitopenia è stata identificata soppressione del midollo osseo.
Popolazione pediatrica
In pazienti di età compresa tra 1 mese e meno di 4 anni, un totale di 190 pazienti è stato trattato con levetiracetam in studi controllati con placebo ed in studi di estensione in aperto. Sessanta (60) di questi pazienti sono stati trattati con levetiracetam in studi controllati con placebo. In pazienti di età compresa tra 4 e 16 anni, un totale di 645 pazienti è stato trattato con levetiracetam in studi controllati con placebo ed in studi di estensione in aperto. 233 di questi pazienti sono stati trattati con levetiracetam in studi controllati con placebo. In entrambi questi intervalli di età pediatrica, questi dati sono integrati con l'esperienza post-marketing relativa all'uso di levetiracetam.
Inoltre, 101 bambini di età inferiore a 12 mesi sono stati esposti in uno studio di sicurezza post-autorizzazione. Non sono stati identificati nuovi problemi di sicurezza per levetiracetam in infanti di età inferiore a 12 mesi con epilessia. Il profilo delle reazioni avverse del levetiracetam è generalmente simile nell'ambito dei diversi gruppi di età e delle indicazioni approvate nel trattamento dell'epilessia. Negli studi clinici controllati con placebo, i risultati sulla sicurezza nei pazienti pediatrici sono stati coerenti con il profilo di sicurezza di levetiracetam negli adulti, ad eccezione delle reazioni avverse comportamentali e psichiatriche che sono state più comuni nei bambini rispetto che negli adulti. Nei bambini e negli adolescenti di età compresa tra 4 e 16 anni, sono stati riportati più frequentemente che in altri gruppi di età o nel profilo di sicurezza complessivo vomito (molto comune, 11,2%), agitazione (comune, 3,4%), sbalzi d'umore (comune, 2,1%), labilità affettiva (comune, 1,7%), aggressività (comune, 8,2%), comportamento anormale (comune, 5,6%) e letargia (comune, 3,9%). In infanti e bambini di età compresa tra 1 mese e meno di 4 anni, sono state riportate più frequentemente che in altri gruppi di età o nel profilo di sicurezza complessivo irritabilità (molto comune, 11,7%) e coordinazione anormale (comune, 3,3%).
Uno studio di sicurezza sui pazienti pediatrici, condotto secondo un disegno di non inferiorità, in doppio cieco e controllato con placebo, ha valutato gli effetti cognitivi e neuro-psicologici di levetiracetam in bambini da 4 a 16 anni di età con crisi convulsive a esordio parziale. Il levetiracetam si è dimostrato non differente (non inferiore) rispetto al placebo per quanto riguarda la modifica rispetto al basale nel punteggio ottenuto ai test "Attenzione e Memoria" della scala di Leiter-R (*Memory Screen Composite score*) nella popolazione per-protocol. I risultati correlati alle funzioni comportamentali ed emozionali hanno indicato un peggioramento, nei pazienti trattati con levetiracetam, del comportamento aggressivo misurato in maniera standardizzata e sistematica, con l'utilizzo di uno strumento validato (*CBCL – Achenbach Child Behavior Checklist*).
Tuttavia, i soggetti che hanno assunto levetiracetam nello studio in aperto di follow-up a lungo termine non hanno manifestato, in media, un peggioramento delle loro funzioni comportamentali ed emozionali; in particolare, le valutazioni dell'aggressività nei comportamenti non sono peggiorate rispetto al basale.
Segnalazione delle reazioni avverse sospette
La segnalazione delle reazioni avverse sospette che si verificano dopo l'autorizzazione del medicinale è importante, in quanto permette un monitoraggio continuo del rapporto beneficio/rischio del medicinale. Agli operatori sanitari è richiesto di segnalare qualsiasi reazione avversa sospetta tramite il sistema nazionale di segnalazione dell'Agenzia Italiana del Farmaco, Sito web: http://www.agenziafarmaco.gov.it/it/responsabili.

4.9 Sovradosaggio
Sintomi
Sonnolenza, agitazione, aggressività, ridotto livello di coscienza, depressione respiratoria e coma sono stati osservati con sovradosaggi di levetiracetam.
Trattamento del sovradosaggio
Dopo un sovradosaggio acuto, lo stomaco può essere svuotato mediante lavanda gastrica o induzione del vomito. Non esiste un antidoto specifico per levetiracetam. Il trattamento del sovradosaggio dovrà essere sintomatico e può includere l'emodialisi. L'efficienza di estrazione mediante dialisi è del 60% per levetiracetam e del 74% per il metabolita primario.

5. PROPRIETÀ FARMACOLOGICHE

5.1 Proprietà farmacodinamiche
Categoria farmacoterapeutica: antiepilettici, altri antiepilettici, codice ATC: N03AX14.
Il principio attivo, levetiracetam, è un derivato pirrolidonico (S-enantiomero dell'α-etil- 2-oxo-1-pirrolidin acetamide), non correlato chimicamente con sostanze ad attività antiepilettica esistenti.
Meccanismo d'azione
Il meccanismo d'azione di levetiracetam non è stato ancora del tutto spiegato. Esperimenti *in vitro* ed *in vivo* suggeriscono che levetiracetam non altera le caratteristiche cellulari di base e la normale neurotrasmissione.
Studi *in vitro* dimostrano che levetiracetam agisce sui livelli intraneuronali di Ca^{2+} attraverso la parziale inibizione delle correnti di Ca^{2+} di tipo N e riducendo il rilascio di Ca^{2+} dai depositi intraneuronali. Inoltre, il farmaco inverte parzialmente la riduzione, indotta da zinco e β-carboline, delle correnti indotte da GABA e glicina. Studi *in vitro* hanno inoltre evidenziato che levetiracetam si lega ad uno specifico sito nel tessuto cerebrale dei roditori.
Questo sito di legame è la proteina 2A della vescicola sinaptica, che si ritiene sia coinvolta nella fusione della vescicola e nell'esocitosi del neurotrasmettitore. Levetiracetam e i relativi analoghi mostrano un grado di affinità per il legame alla proteina 2A della vescicola sinaptica che è correlato con la potenza della loro protezione antiepilettica nel modello audiogenico di epilessia nel topo. Questa scoperta suggerisce che l'interazione tra levetiracetam e la proteina 2A della vescicola sinaptica sembra aver parte nel meccanismo d'azione antiepilettica del medicinale.
Effetti farmacodinamici
Il levetiracetam induce un'azione di protezione nei confronti delle crisi epilettiche in un ampio spettro di modelli animali di epilessia parziale e generalizzata primaria, senza avere un effetto pro-convulsivante. Il metabolita primario è inattivo. Nell'uomo, un'attività in condizioni di epilessia sia parziale che generalizzata (scarica epilettiforme/risposta fotoparossistica) ha confermato l'ampio spettro del profilo farmacologico del levetiracetam.
Efficacia e sicurezza clinica
Terapia aggiuntiva nel trattamento delle crisi parziali con o senza generalizzazione secondaria in adulti, adolescenti, bambini ed infanti a partire da 1 mese di età con epilessia
Negli adulti, l'efficacia di levetiracetam è stata dimostrata in 3 studi in doppio cieco, controllati con placebo, con dosi di 1000 mg, 2000 mg o 3000 mg/die, suddivise in 2 somministrazioni, per una durata di trattamento fino a 18 settimane. In una analisi globale, la percentuale di pazienti che ha ottenuto una riduzione della frequenza delle crisi parziali per settimana, nel periodo di trattamento a dose stabile (12/14 settimane), uguale o superiore al 50% rispetto al basale, è stata del 27,7%, 31,6% e 41,3% dei pazienti trattati rispettivamente con 1000, 2000 o 3000 mg di levetiracetam e del 12,6% per i pazienti trattati con placebo.
Popolazione pediatrica L'efficacia di levetiracetam nei pazienti pediatrici (dai 4 ai 16 anni di età) è stata dimostrata in uno studio in doppio cieco, controllato con placebo, che ha incluso 198 pazienti ed ha avuto una durata di trattamento di 14 settimane. In questo studio, i pazienti hanno assunto levetiracetam alla dose fissa di 60 mg/kg/die (con due somministrazioni giornaliere).
Il 44,6% dei pazienti trattati con levetiracetam e il 19,6% dei pazienti trattati con placebo ha avuto, rispetto al basale, una riduzione della frequenza delle crisi convulsive a esordio parziale per settimana uguale o superiore al 50%. Con il trattamento continuato a lungo termine, l'11,4% dei pazienti è rimasto libero da crisi per almeno 6 mesi e il 7,2% è rimasto libero da crisi per almeno 1 anno.
Nei pazienti pediatrici (da 1 mese a meno di 4 anni di età), l'efficacia di levetiracetam è stata dimostrata in uno studio in doppio cieco, controllato con placebo, che ha incluso 116 pazienti e ha avuto una durata di trattamento di 5 giorni. In questo studio è stata prescritta ai pazienti una dose giornaliera di 20 mg/kg,

25 mg/kg, 40 mg/kg o 50 mg/kg di soluzione orale, basandosi sullo schema di titolazione della dose riferito alla loro età. Nello studio sono state utilizzate le seguenti dosi: 20 mg/kg/die, titolata a 40 mg/kg/die, per infanti da un mese a meno di sei mesi di età; 25 mg/kg/die, titolata a 50 mg/kg/die, per infanti e bambini da 6 mesi a meno di 4 anni di età. La dose totale giornaliera è stata suddivisa in due somministrazioni al giorno.
Il principale parametro dell'efficacia del trattamento è stato il tasso di pazienti responsivi (percentuale di pazienti con una riduzione della frequenza media giornaliera delle crisi convulsive a esordio parziale ≥50% rispetto ai valori basali), valutato da un esaminatore unico in cieco utilizzando un video EEG per un periodo di 48 ore. L'analisi dell'efficacia è stata effettuata su 109 pazienti che erano stati sottoposti a video EEG per almeno 24 ore, sia durante il periodo basale che durante il periodo di valutazione. Il 43,6% dei pazienti trattati con levetiracetam e il 19,6% dei pazienti trattati con placebo sono stati considerati responsivi. I risultati sono coerenti nei diversi gruppi di età. Nel trattamento continuato a lungo termine, l'8,6% dei pazienti è rimasto libero da crisi per almeno 6 mesi e il 7,8% è stato libero da crisi per almeno 1 anno.
35 infanti di età inferiore ad 1 anno, dei quali solo 13 di età inferiore ai 6 mesi, con crisi ad esordio parziale sono stati esposti in studi clinici controllati con placebo.
Monoterapia nel trattamento delle crisi convulsive ad esordio parziale con o senza generalizzazione secondaria in pazienti a partire da 16 anni di età con epilessia di nuova diagnosi
L'efficacia del levetiracetam in monoterapia è stata dimostrata in uno studio comparativo di non inferiorità in doppio cieco, a gruppi paralleli, verso carbamazepina a rilascio controllato (CR), in 576 pazienti di 16 anni di età o più, con epilessia di nuova o recente diagnosi. I pazienti dovevano presentare solo crisi parziali non provocate oppure crisi tonico-cloniche generalizzate. I pazienti sono stati randomizzati a carbamazepina CR 400-1200 mg/die o levetiracetam 1000-3000 mg/die e il trattamento ha avuto una durata fino a 121 settimane in base alla risposta.
La libertà dalle crisi per un periodo di 6 mesi è stata ottenuta nel 73,0% dei pazienti trattati con levetiracetam e nel 72,8% dei pazienti trattati con carbamazepina CR; la differenza assoluta corretta tra i trattamenti è stata dello 0,2% (IC 95%:-7,8 8,2). Più della metà dei soggetti è rimasta libera da crisi per 12 mesi (56,6% e 58,5% dei soggetti trattati rispettivamente con levetiracetam e carbamazepina CR).
In uno studio che rifletteva la pratica clinica, il trattamento antiepilettico concomitante ha potuto essere sospeso in un numero limitato di pazienti che avevano risposto alla terapia aggiuntiva con levetiracetam (36 pazienti adulti su 69).
Terapia aggiuntiva nel trattamento delle crisi miocloniche in adulti ed adolescenti a partire da 12 anni di età con epilessia mioclonica giovanile L'efficacia del levetiracetam è stata dimostrata in uno studio in doppio cieco, controllato con placebo, della durata di 16 settimane, in pazienti a partire dai 12 anni di età e oltre, affetti da epilessia generalizzata idiopatica con crisi miocloniche in differenti sindromi. La maggioranza dei pazienti presentava epilessia mioclonica giovanile.
In questo studio, la dose di levetiracetam è stata di 3000 mg/die, somministrata in due dosi separate.
Il 58,3% dei pazienti trattati con levetiracetam e il 23,3% dei pazienti trattati con placebo ha avuto almeno una riduzione del 50% dei giorni con crisi miocloniche per settimana.
A seguito del trattamento continuato a lungo termine, il 28,6% dei pazienti è rimasto libero da crisi miocloniche per almeno 6 mesi ed il 21,0% dei pazienti è rimasto libero da crisi miocloniche per almeno 1 anno.
Terapia aggiuntiva nel trattamento delle crisi tonico-cloniche generalizzate primarie in adulti e adolescenti a partire da 12 anni di età con epilessia generalizzata idiopatica L'efficacia del levetiracetam è stata dimostrata in uno studio di 24 settimane in doppio cieco, controllato con placebo, che ha incluso adulti, adolescenti e un numero limitato di bambini affetti da epilessia generalizzata idiopatica con crisi tonico-cloniche generalizzate primarie (PGTC) in differenti sindromi (epilessia mioclonica giovanile, epilessia giovanile da assenza, epilessia infantile da assenza oppure epilessia con crisi da grande male al risveglio). In questo studio, la dose di levetiracetam è stata di 3000 mg/die per adulti e adolescenti oppure di 60 mg/kg/die per i bambini, somministrata in due dosi separate.
Il 72,2% dei pazienti trattati con levetiracetam e il 45,2% dei pazienti trattati con placebo ha avuto una riduzione della frequenza delle crisi PGTC per settimana uguale o superiore al 50%. A seguito del trattamento continuato a lungo termine, il 47,4% dei pazienti è rimasto libero da crisi tonico-cloniche per almeno 6 mesi e il 31,5% è stato libero da crisi tonico-cloniche per almeno 1 anno.

5.2 Proprietà farmacocinetiche

Levetiracetam è un composto estremamente solubile e permeabile. Il profilo farmacocinetico è lineare, con una scarsa variabilità intra- ed inter-individuale. Non c'è modificazione della clearance dopo somministrazioni ripetute. Non c'è evidenza di alcuna rilevante variabilità circadiana e per sesso e razza. Il profilo farmacocinetico è comparabile nei volontari sani e nei pazienti con epilessia.
Dato il suo completo e lineare assorbimento, i livelli plasmatici di levetiracetam possono essere predetti dalla dose orale espressa come mg/kg di peso corporeo. Perciò non c'è bisogno di monitorare i livelli plasmatici di levetiracetam.
È stata evidenziata negli adulti e nei bambini una significativa correlazione tra le concentrazioni nella saliva e nel plasma (il rapporto delle concentrazioni saliva/plasma variava in un intervallo da 1 a 1,7 per la formulazione orale in compresse e, dopo 4 ore dall'assunzione, per la formulazione orale in soluzione).
Adulti e adolescenti
Assorbimento
Levetiracetam è assorbito rapidamente dopo somministrazione orale. La biodisponibilità orale assoluta è prossima al 100%.
Le concentrazioni al picco plasmatico (C_{max}) sono raggiunte 1,3 ore dopo l'assunzione. Lo stato stazionario è raggiunto dopo due giorni di somministrazione di due dosi quotidiane.
Le concentrazioni al picco plasmatico (C_{max}) sono tipicamente di 31 e 43 µg/ml in seguito, rispettivamente, ad una singola dose di 1000 mg e a una dose di 1000 mg ripetuta due volte al giorno.
L'entità di assorbimento non è dose dipendente e non è influenzata dal cibo.
Distribuzione
Non sono disponibili dati sulla distribuzione tissutale nell'uomo.
Né levetiracetam né il suo metabolita primario si legano significativamente alle proteine plasmatiche (<10%). Il volume di distribuzione di levetiracetam va approssimativamente da 0,5 a 0,7 l/kg, ed è un valore prossimo al volume totale corporeo di acqua.
Biotrasformazione
Levetiracetam non è ampiamente metabolizzato nell'uomo. La principale via metabolica (24% della dose) è l'idrolisi enzimatica del gruppo acetamide. La produzione del metabolita primario, ucb L057, non è supportata dalle isoforme del citocromo P450 epatico.
L'idrolisi del gruppo acetamide è stata misurabile in numerosi tessuti, comprese le cellule ematiche. Il metabolita ucb L057 è farmacologicamente inattivo.
Sono stati inoltre identificati due metaboliti minori. Uno è stato ottenuto dall'idrossilazione dell'anello pirrolidonico (1,6% della dose) e l'altro dall'apertura dell'anello pirrolidonico (0,9% della dose). Altri componenti non noti erano responsabili soltanto dello 0,6% della dose.
In vivo non sono state evidenziate interconversioni enantiomeriche né per levetiracetam né per il suo metabolita primario.
In vitro, levetiracetam ed il suo metabolita primario hanno mostrato di non inibire le attività delle principali isoforme del citocromo P450 epatico umano (CYP3A4, 2A6, 2C9, 2C19, 2D6, 2E1 e 1A2), della glucuronil transferasi (UGT1A1 e UGT1A6) e dell'epossido idrossilasi. Inoltre, levetiracetam non influenza la glucuronazione *in vitro* dell'acido valproico.
In colture di epatociti umani, levetiracetam ha avuto un effetto minimo o nullo su CYP1A2, SULT1E1 o UGT1A1. Levetiracetam ha causato una moderata induzione del CYP2B6 e del CYP3A4.
I dati *in vitro* ed i dati *in vivo* relativi alla interazione con contraccettivi orali, digossina e warfarin indicano che non è attesa alcu-

na significativa induzione enzimatica *in vivo*. Quindi, l'interazione di ITALEPT con altre sostanze, o *viceversa*, è improbabile.

Eliminazione

L'emivita plasmatica negli adulti è di 7±1 ore e non si modifica in relazione alla dose, alla via di somministrazione o alla somministrazione ripetuta. La clearance totale corporea media è di 0,96 ml/min/kg.

La principale via di escrezione è la via urinaria, responsabile in media dell'eliminazione del 95% della dose somministrata (approssimativamente il 93% della dose è stato escreto entro 48 ore). L'eliminazione fecale rappresenta solo lo 0,3% della dose.

L'escrezione cumulativa urinaria di levetiracetam e del suo metabolita primario è responsabile rispettivamente dell'eliminazione del 66% e del 24% della dose, nell'arco delle prime 48 ore.

La clearance renale di levetiracetam e di ucb L057 è rispettivamente di 0,6 e 4,2 ml/min/kg, indicando che il levetiracetam è escreto mediante filtrazione glomerulare con successivo riassorbimento tubulare e che il metabolita primario è escreto anche mediante secrezione tubulare attiva oltre che con filtrazione glomerulare.

L'eliminazione di levetiracetam è correlata alla clearance della creatinina.

Anziani

Nell'anziano, l'emivita è aumentata di circa il 40% (da 10 a 11 ore). Ciò è dovuto alla riduzione della funzionalità renale in questa popolazione (vedere paragrafo 4.2).

Compromissione renale

La clearance corporea apparente sia di levetiracetam sia del suo metabolita primario è correlata alla clearance della creatinina. Nei pazienti con insufficienza renale di grado moderato e grave si raccomanda pertanto di aggiustare la dose giornaliera di mantenimento di ITALEPT, basandosi sulla clearance della creatinina (vedere paragrafo 4.2).

Nei soggetti adulti affetti da anuria con malattia renale allo stadio terminale, l'emivita è risultata approssimativamente pari a 25 e 3,1 ore, rispettivamente nei periodi tra le dialisi e durante la dialisi.

La frazione del levetiracetam rimossa era del 51% nel corso di una tipica seduta di dialisi di 4 ore.

Compromissione epatica

In soggetti con insufficienza epatica lieve e moderata non è stata rilevata alcuna modificazione significativa della clearance del levetiracetam. Nella maggioranza dei soggetti con compromissione epatica grave, la clearance del levetiracetam è stata ridotta di oltre il 50% a causa della compromissione renale concomitante (vedere paragrafo 4.2).

Popolazione pediatrica

Bambini (dai 4 ai 12 anni)

In seguito ad una singola somministrazione orale (20 mg/kg) in bambini (da 6 a 12 anni) con epilessia, l'emivita di levetiracetam è risultata di 6,0 ore.

La clearance apparente corretta in funzione del peso corporeo è risultata approssimativamente più alta del 30% rispetto agli adulti con epilessia.

In seguito a somministrazione orale per dosi ripetute (da 20 a 60 mg/kg/die) in bambini epilettici (da 4 a 12 anni), il levetiracetam è stato rapidamente assorbito. Il picco di concentrazione plasmatica è stato osservato a 0,5-1,0 ora dalla somministrazione. Sono stati osservati aumenti lineari e proporzionali alla dose per il picco delle concentrazioni plasmatiche e per l'area sotto la curva. L'emivita di eliminazione è risultata pari a circa 5 ore. La clearance corporea apparente è stata di 1,1 ml/min/kg.

Infanti e bambini (da 1 mese a 4 anni)

A seguito di somministrazione di una dose singola (20 mg/kg) di soluzione orale 100 mg/ml in bambini epilettici (da 1 mese a 4 anni), il levetiracetam è stato rapidamente assorbito e le concentrazioni plasmatiche di picco sono state osservate circa 1 ora dopo la somministrazione. I risultati farmacocinetici hanno indicato che l'emivita è più breve (5,3 ore) che negli adulti (7,2 ore) e la clearance apparente è risultata più veloce (1,5 ml/min/kg) rispetto agli adulti (0,96 ml/min/kg).

Nelle analisi farmacocinetiche di popolazione condotte in pazienti da 1 mese a 16 anni di età, il peso corporeo era significativamente correlato alla clearance apparente (la clearance aumentava all'aumentare del peso corporeo) ed al volume di distribuzione apparente. Anche l'età ha influenzato entrambi i parametri. Questo effetto è risultato marcato per i bambini più piccoli e attenuato con l'aumentare dell'età, per poi diventare trascurabile intorno ai 4 anni di età.

In entrambe le analisi farmacocinetiche di popolazione, vi è stato un aumento del 20% circa della clearance apparente del levetiracetam quando somministrato assieme a un farmaco antiepilettico induttore enzimatico.

5.3 Dati preclinici di sicurezza

I dati non-clinici non rivelano rischi particolari per l'uomo sulla base di studi convenzionali di sicurezza farmacologica, genotossicità e potenziale cancerogeno.

Gli effetti indesiderati non osservati negli studi clinici, ma visti nel ratto e in minore entità nel topo, a livelli di esposizione simili ai livelli di esposizione nell'uomo e con possibile rilevanza per l'uso clinico, sono state variazioni epatiche come indice di una risposta adattativa, quali aumento ponderale ed ipertrofia centrolobulare, infiltrazione adiposa ed innalzamento degli enzimi epatici nel plasma.

Nel ratto non si sono osservate reazioni avverse sulla fertilità maschile e femminile o sulla capacità riproduttiva a dosi fino a 1800 mg/kg/die (6 volte la dose massima giornaliera raccomandata nell'uomo -MRHD, *Maximum Recommended Human Daily Dose*- in base ai mg/m^2 o in base all'esposizione), sia nella generazione parentale che nella generazione F1.

Due studi sullo sviluppo embrio-fetale (EFD: *Embryo-Fetal Development*) sono stati condotti nel ratto a 400, 1200 e 3600 mg/kg/die. A 3600 mg/kg/die, in uno solo dei 2 studi EFD si è registrato un lieve calo di peso fetale associato ad un aumento marginale delle alterazioni scheletriche/anomalie minori. Non si è verificato alcun effetto sulla mortalità embrionale, né vi è stato un aumento dell'incidenza di malformazioni. Il NOAEL (*No Observed Adverse Effect Level*) è stato di 3600 mg/kg/die per le femmine di ratto gravide (12 volte la MRHD in base ai mg/m^2) e 1200 mg/kg/die per i feti.

Quattro studi sullo sviluppo embrio-fetale sono stati condotti sul coniglio utilizzando dosi di 200, 600, 800, 1200 e 1800 mg/kg/die. La dose di 1800 mg/kg/die ha indotto una marcata tossicità materna e una diminuzione del peso fetale, in associazione con una maggiore incidenza di feti con anomalie cardiovascolari/scheletriche. Il NOAEL è stato <200 mg/kg/die per le madri e di 200 mg/kg/die per i feti (equivalente alla MRHD in base ai mg/m^2).

Uno studio sullo sviluppo peri- e post-natale è stato condotto sul ratto con dosi di levetiracetam di 70, 350 e 1800 mg/kg/die. Il NOAEL è stato ≥1800 mg/kg/die per le femmine F0 e per la generazione F1 per quanto riguarda la sopravvivenza, l'accrescimento e lo sviluppo fino allo svezzamento (6 volte la MRHD in base ai mg/m^2).

Studi nel ratto e nel cane, nell'animale neonato e giovane, hanno dimostrato che non si manifestano effetti indesiderati in alcuno degli endpoint standard di sviluppo o di maturazione a dosi fino a 1800 mg/kg/die (6-17 volte la MRHD in base ai mg/m^2).

6. INFORMAZIONI FARMACEUTICHE

6.1 Elenco degli eccipienti

Sodio citrato diidrato
Acido citrico monoidrato
Metil paraidrossibenzoato (E218)
Propil paraidrossibenzoato (E216)
Ammonio glicirrizinato
Glicerolo (E422)
Maltitolo liquido (E965)
Acesulfame potassio (E950)
Aroma di pompelmo
Acqua purificata

6.2 Incompatibilità

Non pertinente.

6.3 Periodo di validità

3 anni.

Dopo la prima apertura: 7 mesi.

6.4 Precauzioni particolari per la conservazione

Conservare nella confezione originale per proteggere il medicinale dalla luce.
Conservare il flacone in posizione verticale.

6.5 Natura e contenuto del contenitore

300 ml di soluzione in un flacone di vetro ambrato (tipo III) con chiusura a prova di bambino (polipropilene), in una scatola di cartone contenente anche una siringa da 10 ml per uso orale, con tacca graduata ogni 0,25 ml (polipropilene, polietilene), e un adattatore per la siringa (polietilene).

6.6 Precauzioni particolari per lo smaltimento e la manipolazione

Il medicinale non utilizzato ed i rifiuti derivati da tale medicinale devono essere smaltiti in conformità
alla normativa locale vigente.

7. TITOLARE DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO

So.Se.PHARM S.r.l. - Via dei Castelli Romani, 22-00071 Pomezia (Roma) Italia. Concessionario per la vendita: Istituto Luso Farmaco D'Italia SpA – Milanofiori - Strada 6 - Edificio L - Rozzano (MI).

8. NUMERO(I) DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO

AIC 040273031 - "100 mg/ml soluzione orale" 1 flacone da 300 ml + 1 siringa orale da 10 ml.

9. DATA DELLA PRIMA AUTORIZZAZIONE/RINNOVO DELL'AUTORIZZAZIONE

Prima Autorizzazione: 19 Luglio 2012.
Rinnovo: 19 Luglio 2016.

10 DATA DI REVISIONE DEL TESTO

14 Settembre 2016.

ITALEPT 100 mg/ml soluzione orale
Prezzo SSN € 37,97* Classe A - Ricetta ripetibile.

**Prezzo comprensivo delle riduzioni temporanee di cui alle determinazioni AIFA, 3 luglio 2006 e 27 settembre 2006.*

Depositato in AIFA in data 02/11/2020 - Cod. ITAL 20-10