Chromosomal Abnormalities and Cortical Malformations

33

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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

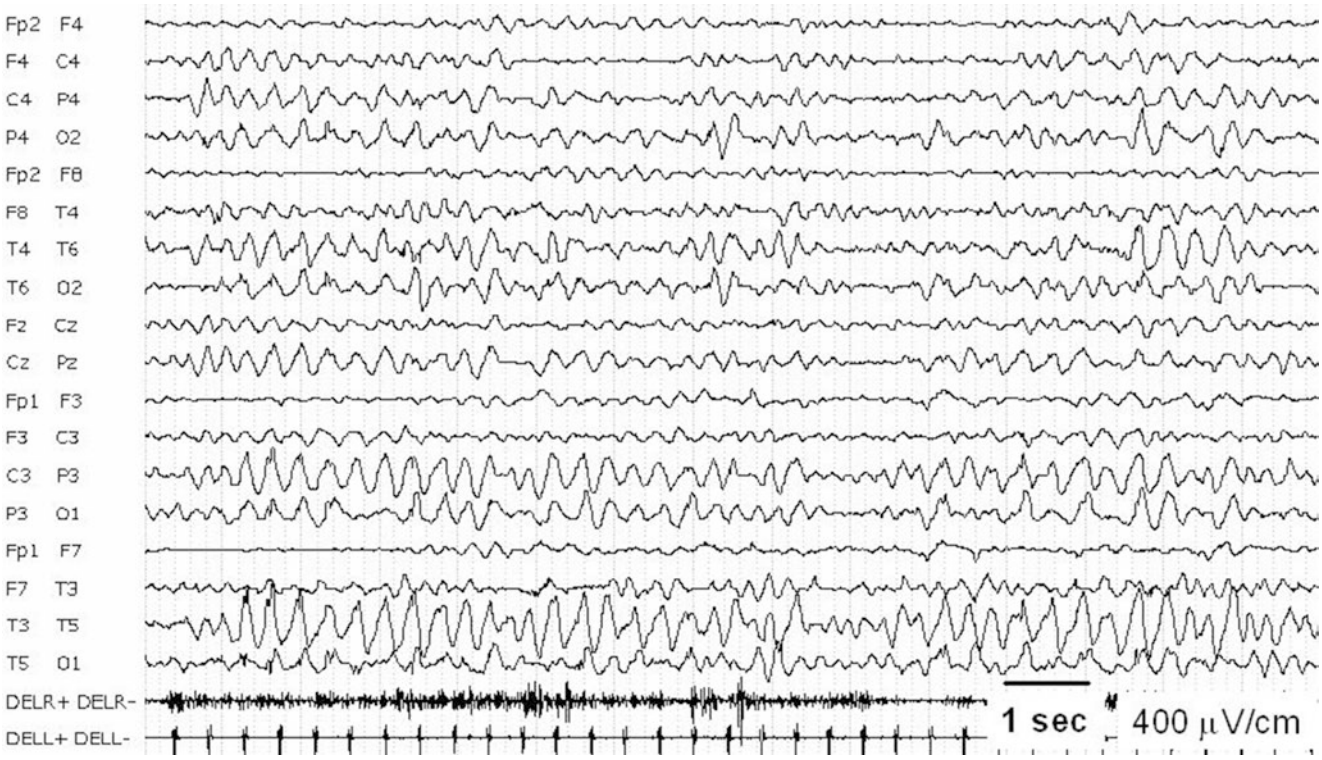

Fig. 33.1 Wakefulness EEG of a 1-year-old female with 4p⁻ syndrome. Long sequences of high-voltage slow waves and spike-and-wave complexes are evident over the parieto-temporo-occipital regions of both hemispheres, prominent on the left one (*R* right, *L* left, *DELT* deltoid muscle)

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

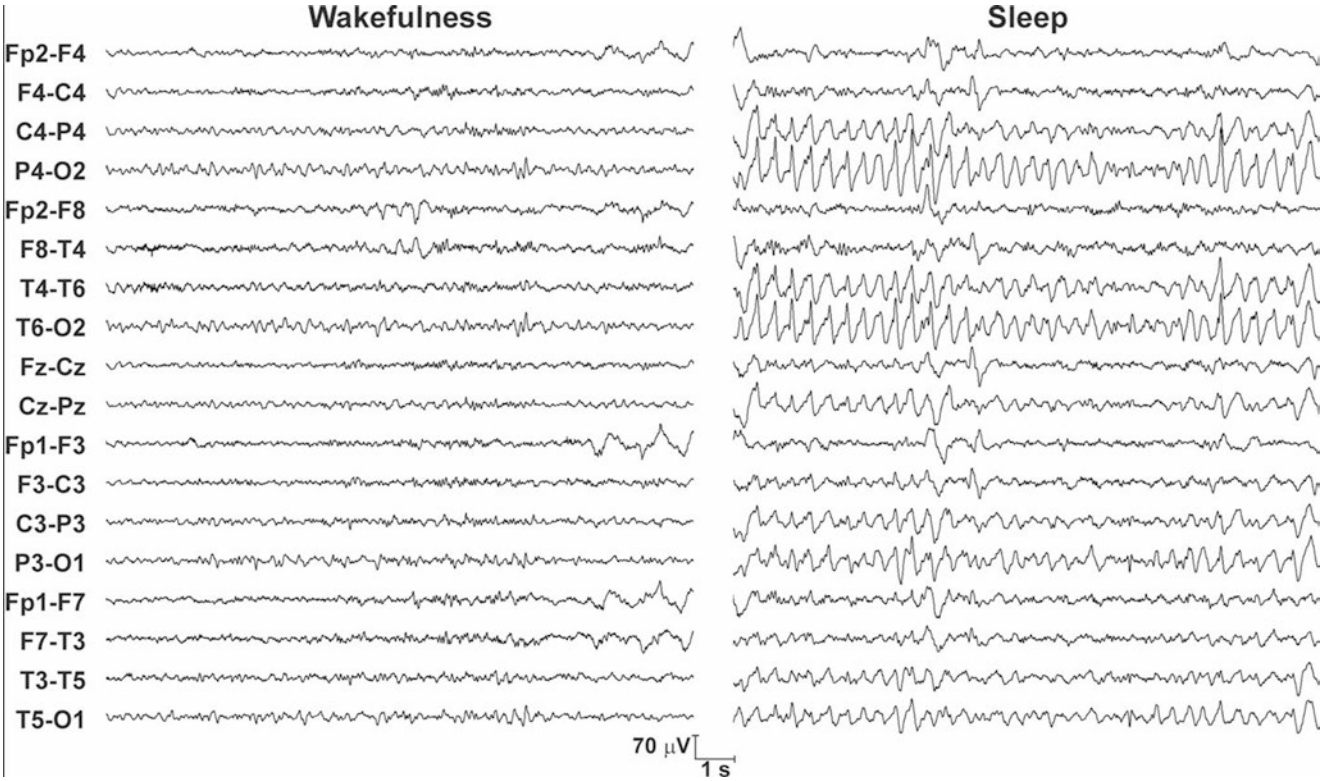

Fig. 33.2 Wakefulness EEG of a 19-year-old male with 6q terminal deletion showing sharp waves over the occipital regions of the right hemisphere (**a**). During non-REM sleep, high-voltage rhythmical delta activity is present over the temporo-parietal regions (**b**)

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

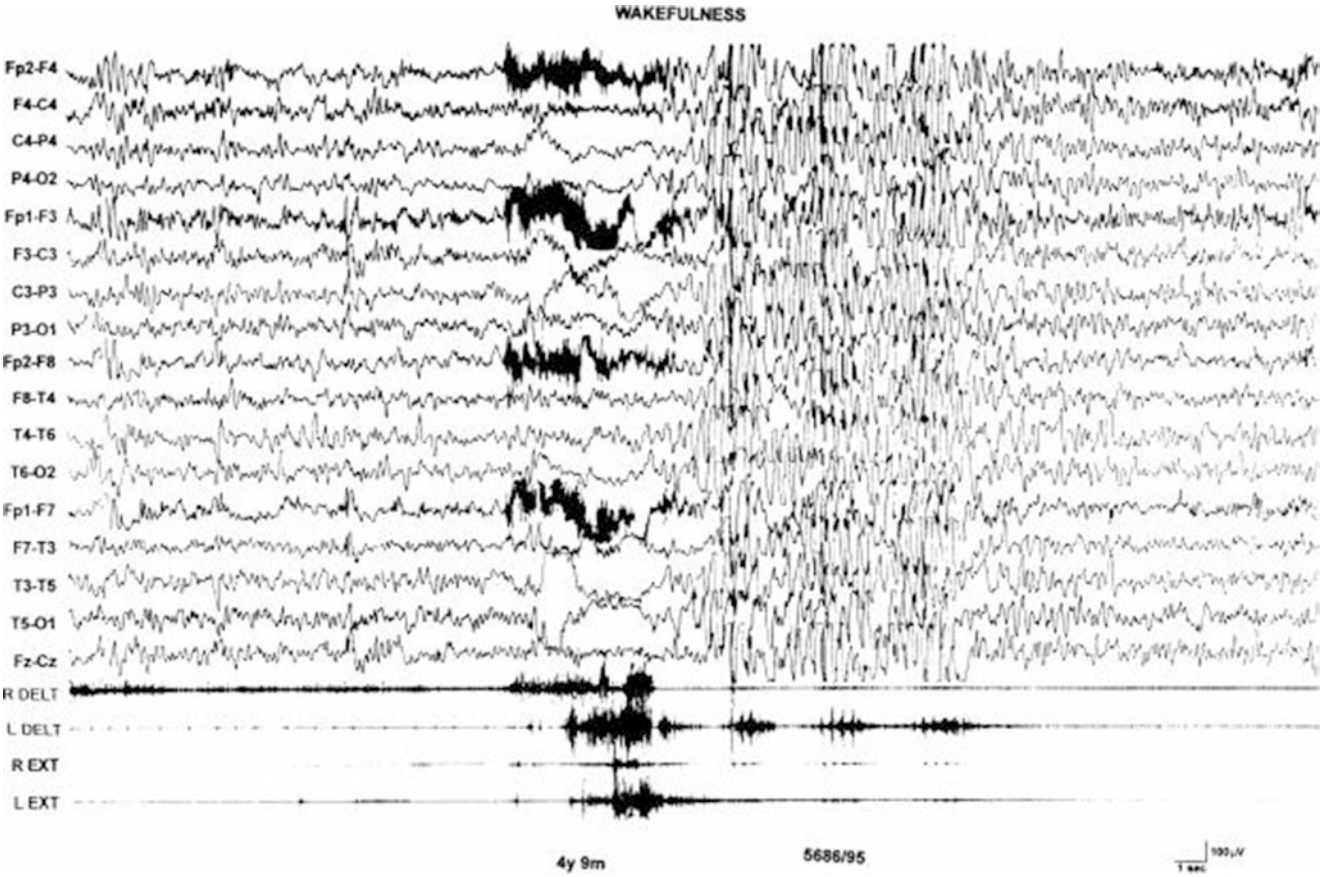

Fig. 33.3 Wakefulness EEG of a 4-year-old female with trisomy 12p syndrome. A myoclonic absence is recorded, characterized by a diffuse spike-and-wave discharge, accompanied by rhythmical myoclonic jerks, prevalent at the left deltoid muscle, superimposed over a tonic contraction (*R* right, *L* left,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

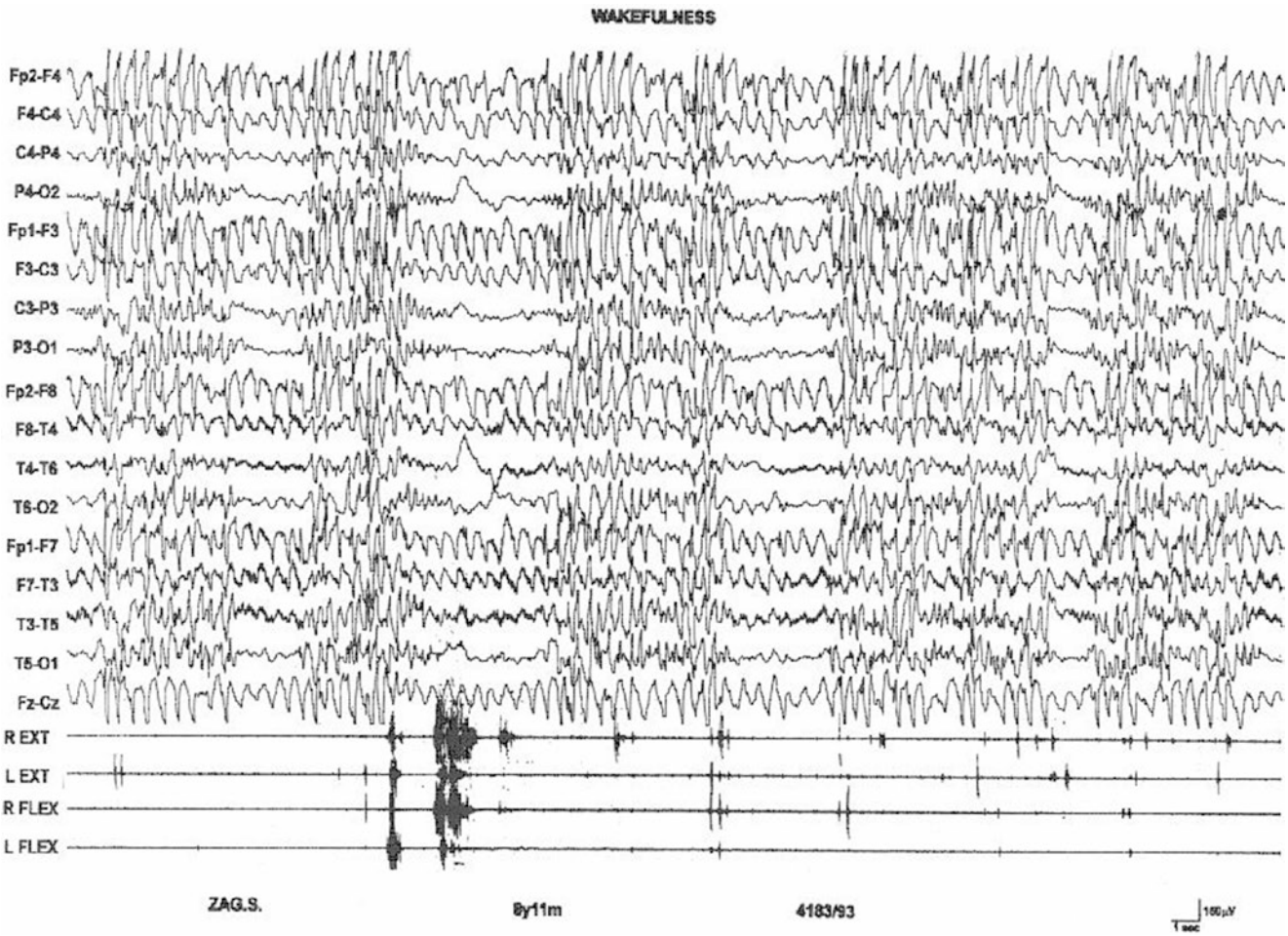

Fig. 33.4 An 8-year-old female with Angelman syndrome. At wakefulness EEG, a slow background activity and quasi-continuous spike-and-wave discharges, better represented over the frontal regions, are present. Surface EMG of forearm extensor and flexor muscles records numerous bilateral, sometimes rhythmical 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].

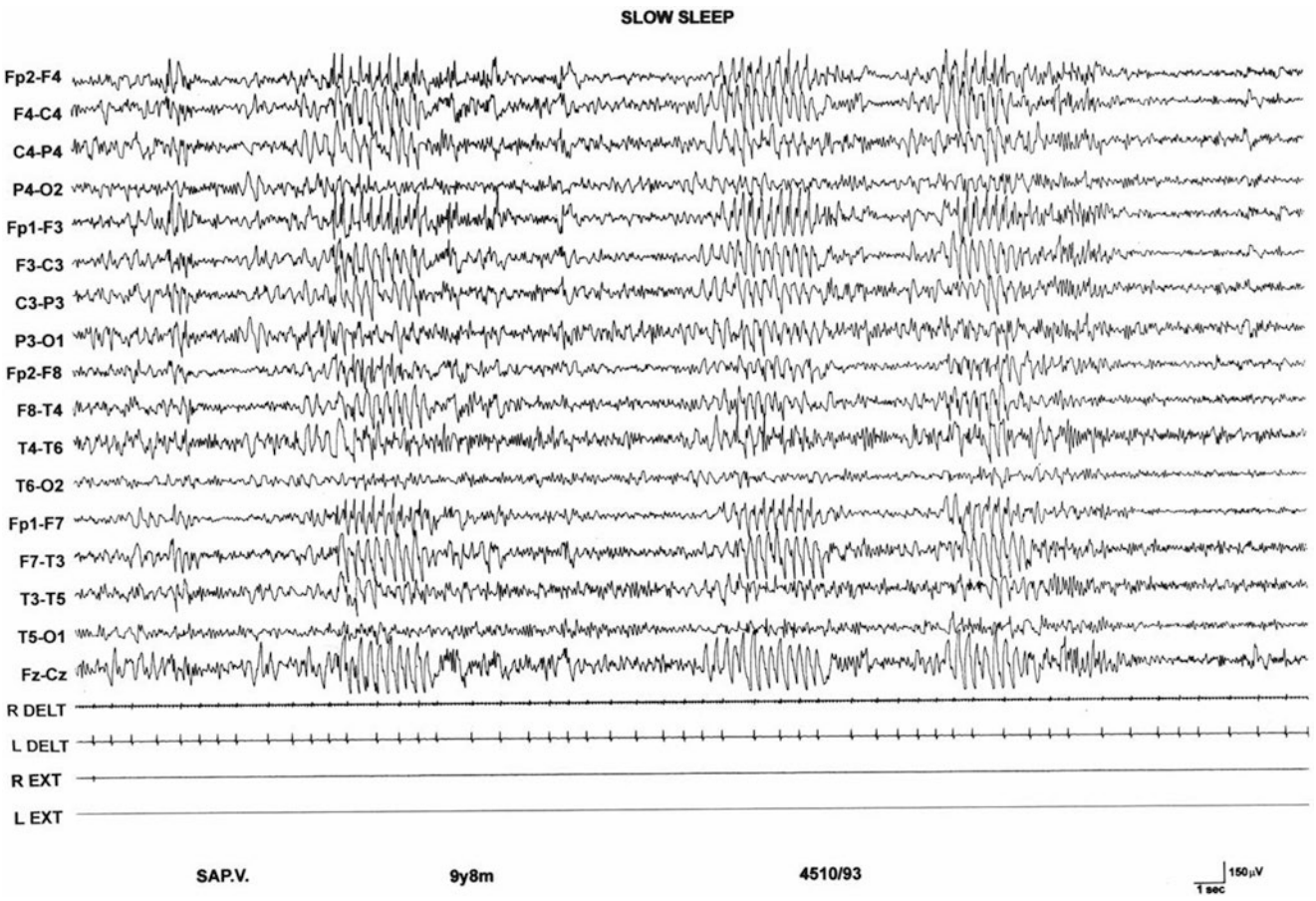

Fig. 33.5 A 9-year-old female with Angelman syndrome. Sleep EEG shows diffuse spike-and-wave discharges, prevalent over the anterior regions of both hemispheres and the vertex. Spindles are bilaterally and symmetrically represented. There are no myoclonic jerks at surface EMG of forearm muscles (*R*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

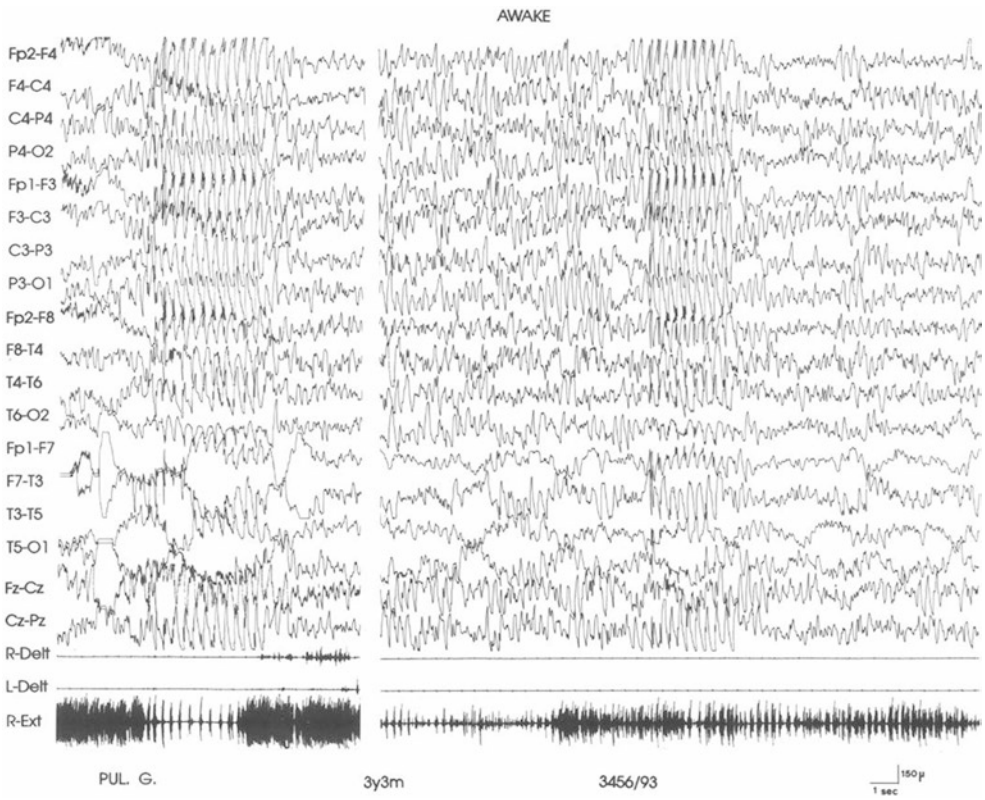

Fig. 33.6 A 3-year-old male with Angelman syndrome. On the left side, a short generalized discharge of spike-and-wave complexes is evident, and it is timely correlated with rhythmical losses of muscle tone, determining an absence with myoclonus. On the right side, EEG shows spike-and-wave complexes over 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)

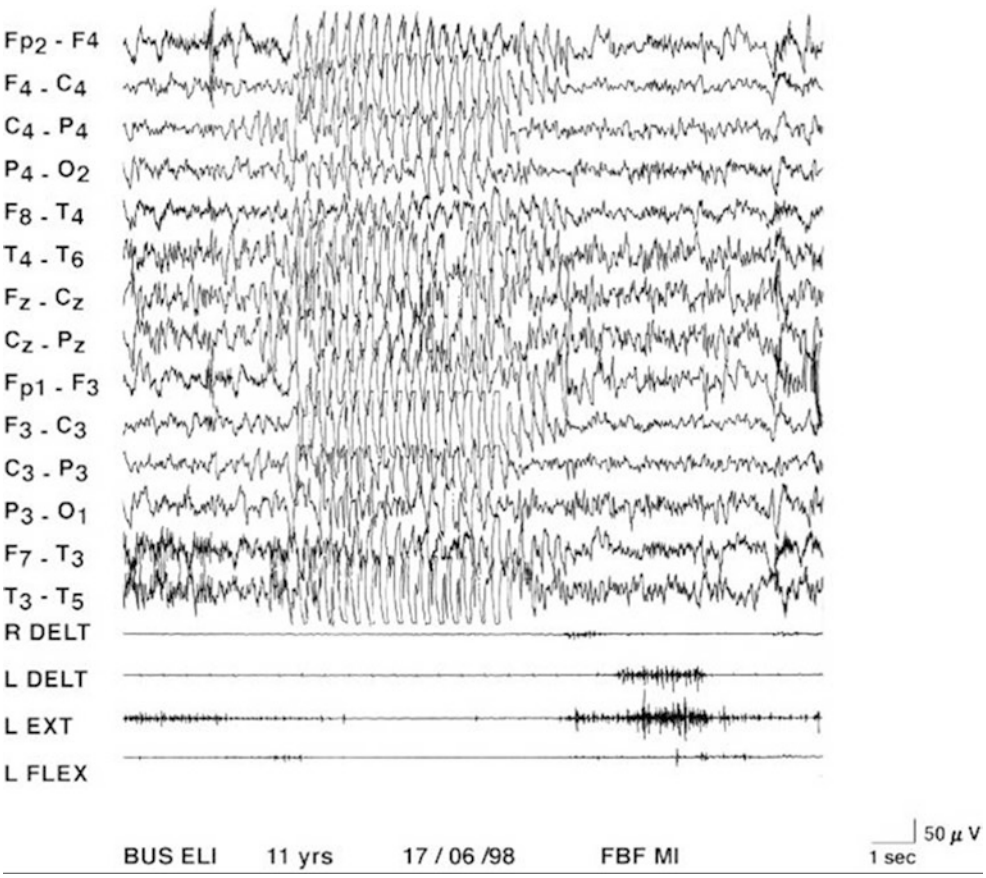

Fig. 33.7 An 11-year-old female with Angelman syndrome. Ictal EEG disclosing an atypical absence, correlated with an interruption of the motor activity at surface EMG of deltoid and forearm extensor muscles (*R* right, *L* left, *DELT* deltoid muscle, *EXT* forearm extensor muscle, *FLEX* forearm flexor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

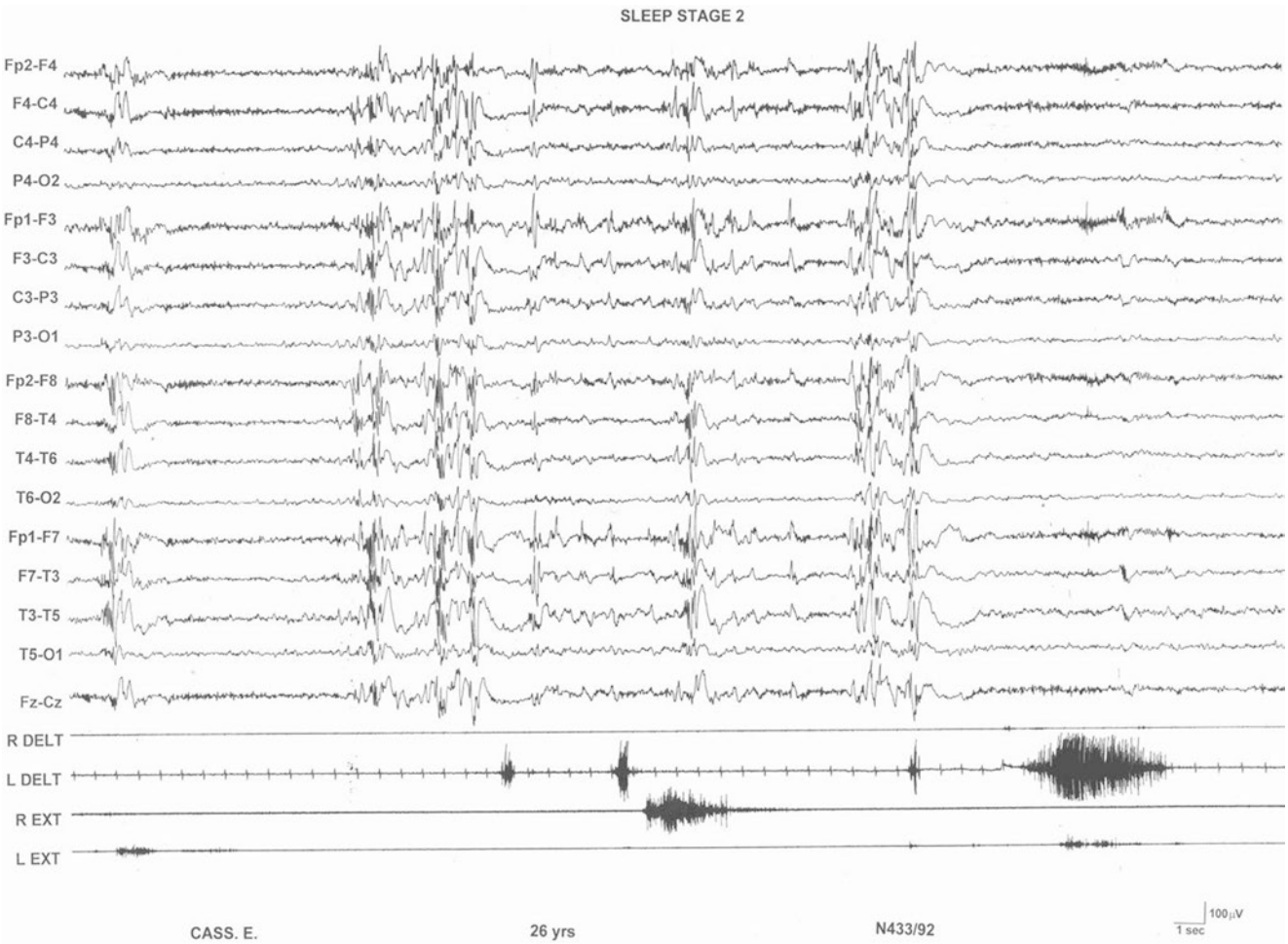

Fig. 33.8 A 26-year-old female with inv. dup (15) syndrome. Sleep EEG shows numerous short fast polyspike discharges, without clinical correlation, as in the typical Lennox-Gastaut syndrome (*R* right, *L* left, *DELT* deltoid muscle, *EXT* forearm extensor muscle)

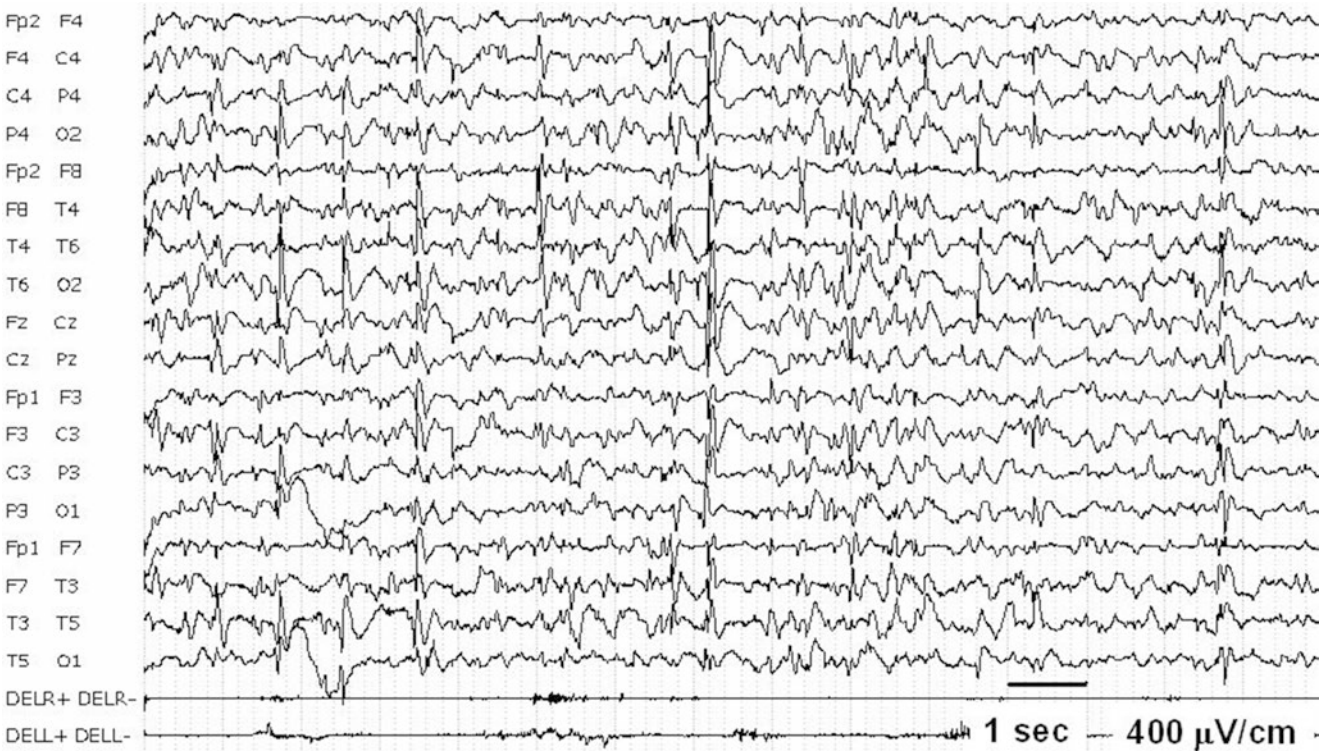

Fig. 33.9 A 2-year-old male with inv. dup (15) syndrome. Wakefulness interictal EEG is characterized by numerous high-voltage, multifocal or diffuse spikes and slow spike-and-wave complexes (*R* right, *L* left, *DELT* deltoid muscle)

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,

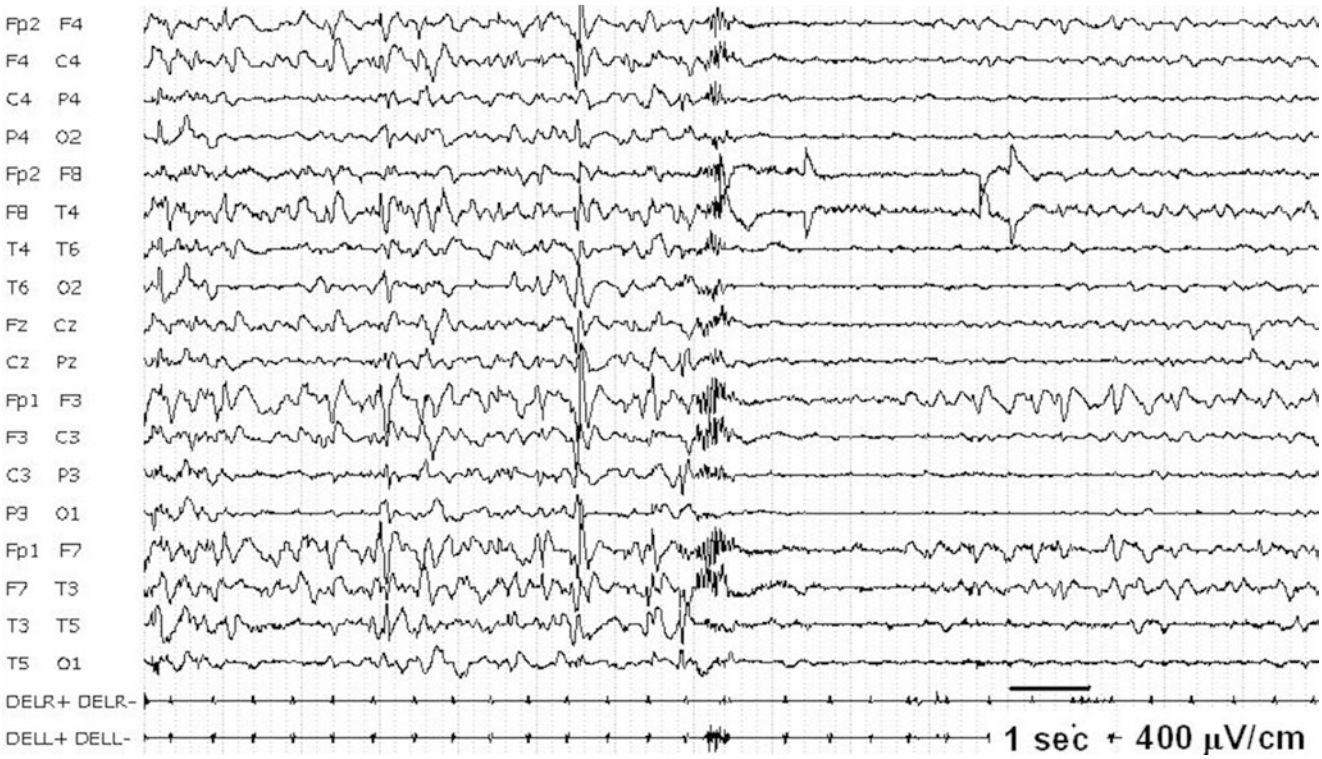

Fig. 33.10 The same patient of Fig. 33.9, at 3 years of age. EEG recording of a short tonic seizure, characterized by a short sequence of diffuse fast activity, followed by diffuse desynchronization. At surface EMG of deltoid muscles, a short tonic contraction, more intense on the left side, is evident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

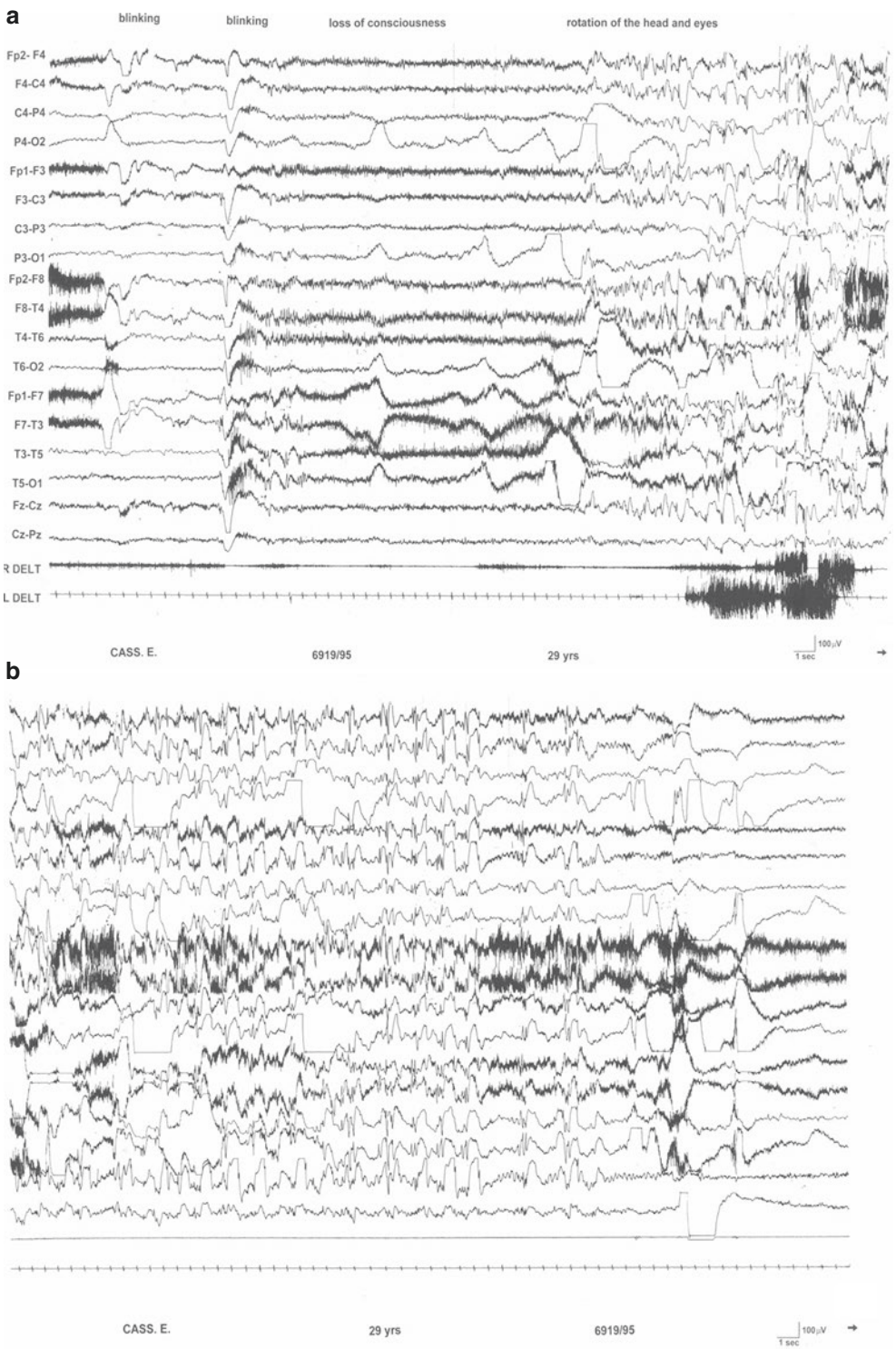

Fig. 33.11 (**a**, **b**) A 29-year-old female with inv. dup (15) syndrome. Ictal EEG is characterized by repetitive artifacts correlated with eye blinking, followed by diffuse desynchronization, and diffuse spikes (**a**) and spike-and-wave complexes (**b**). The patient presents loss of consciousness, 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].

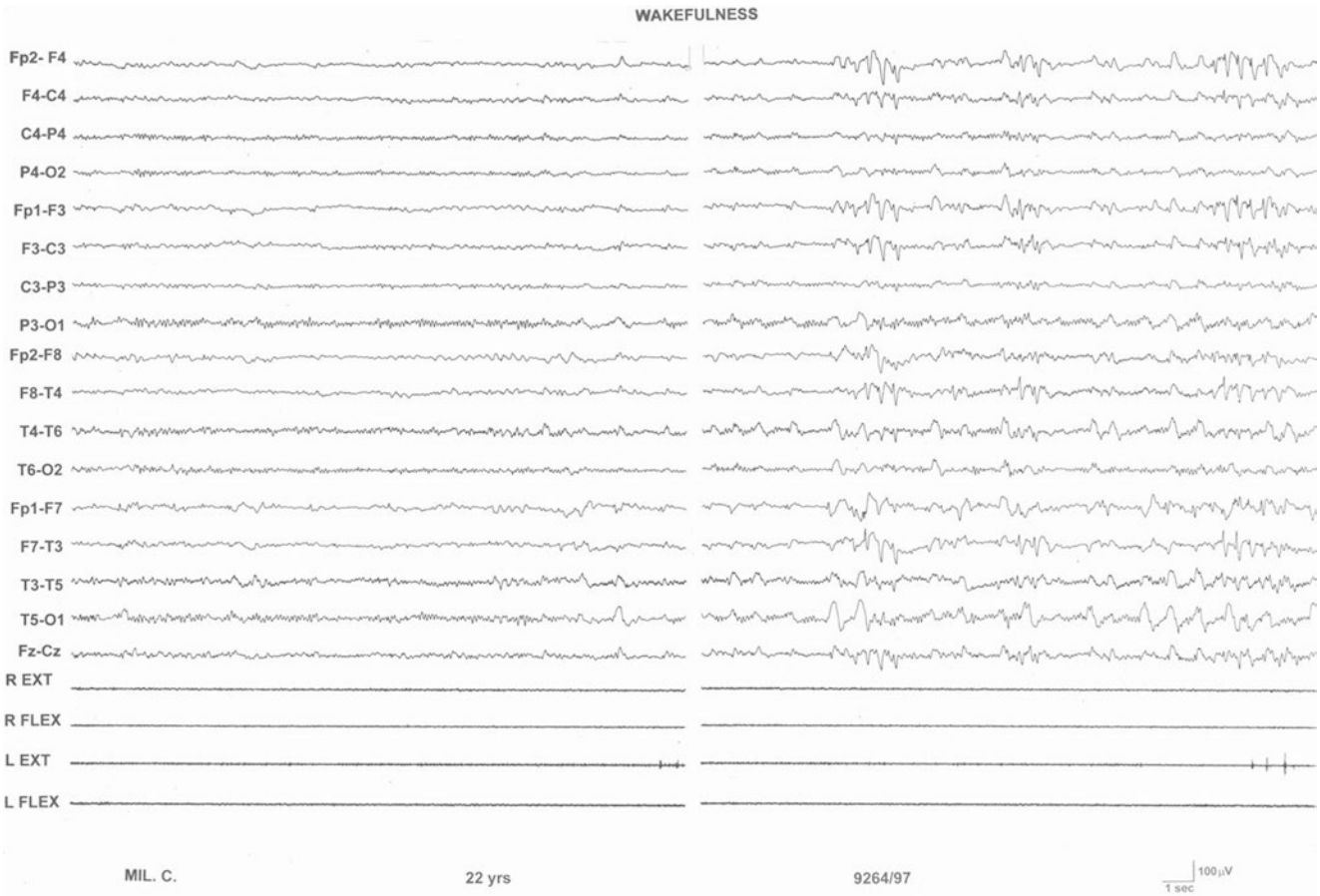

Fig. 33.12 A 22-year-old male with ring chromosome 20 syndrome. On the left side, wakefulness interictal EEG shows theta waves over the left temporal regions; on the right side, diffuse, repetitive sequences of theta waves and spike-and-wave complexes, prominent over the frontal regions of both hemispheres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

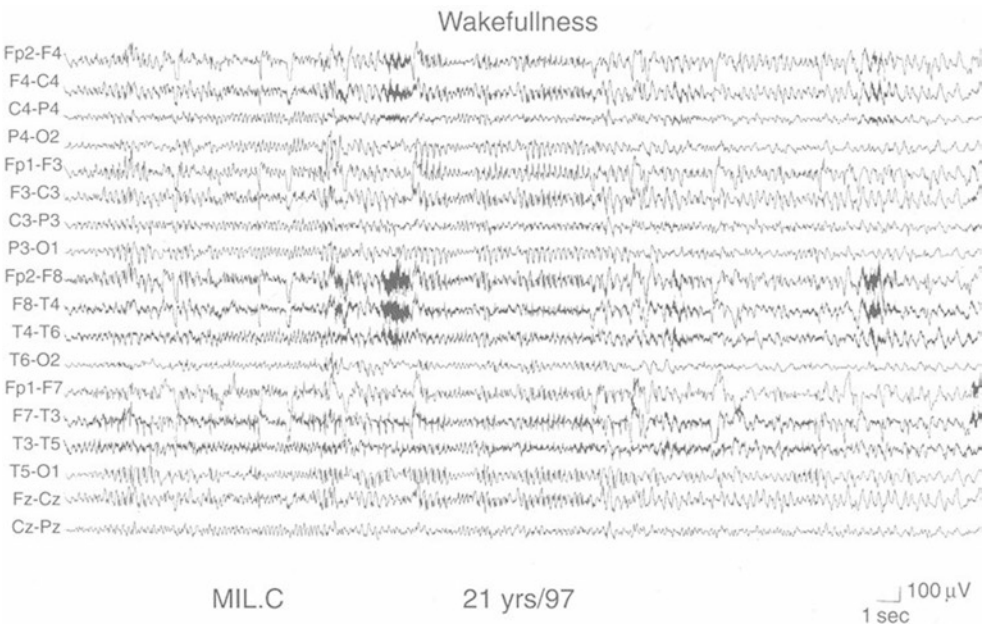

Fig. 33.13 The same patient of Fig. 33.12 at age 21 years. Ictal EEG, during nonconvulsive status epilepticus, characterized by sequences of slow waves intermixed with spikes; the frequency of the spike-and-wave complexes changes during the recording

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).

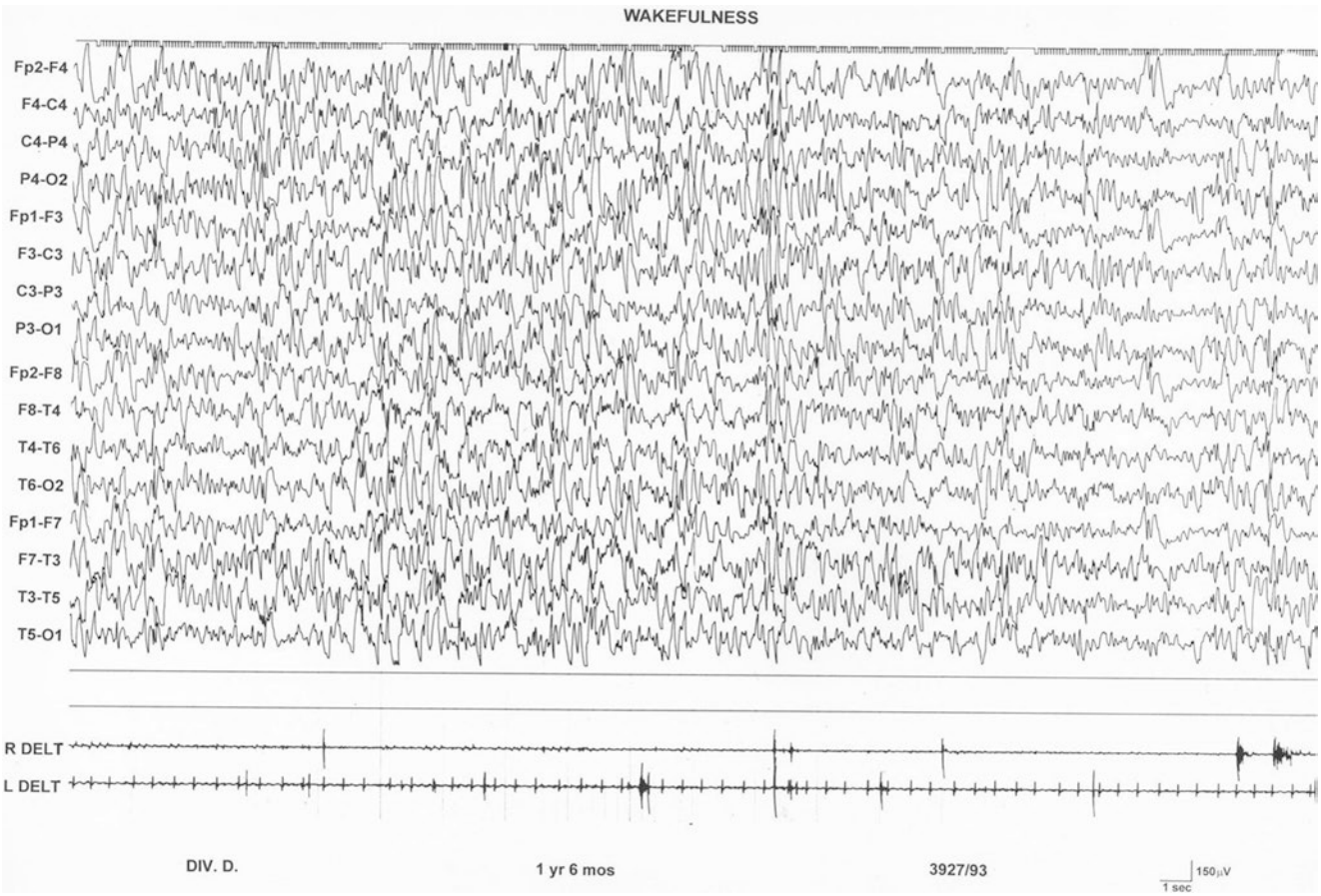

Fig. 33.14 A 1-year-old male with Down syndrome. Interictal EEG shows a hypsarrhythmic pattern (*R* right, *L* left, *DELT* deltoid muscle)

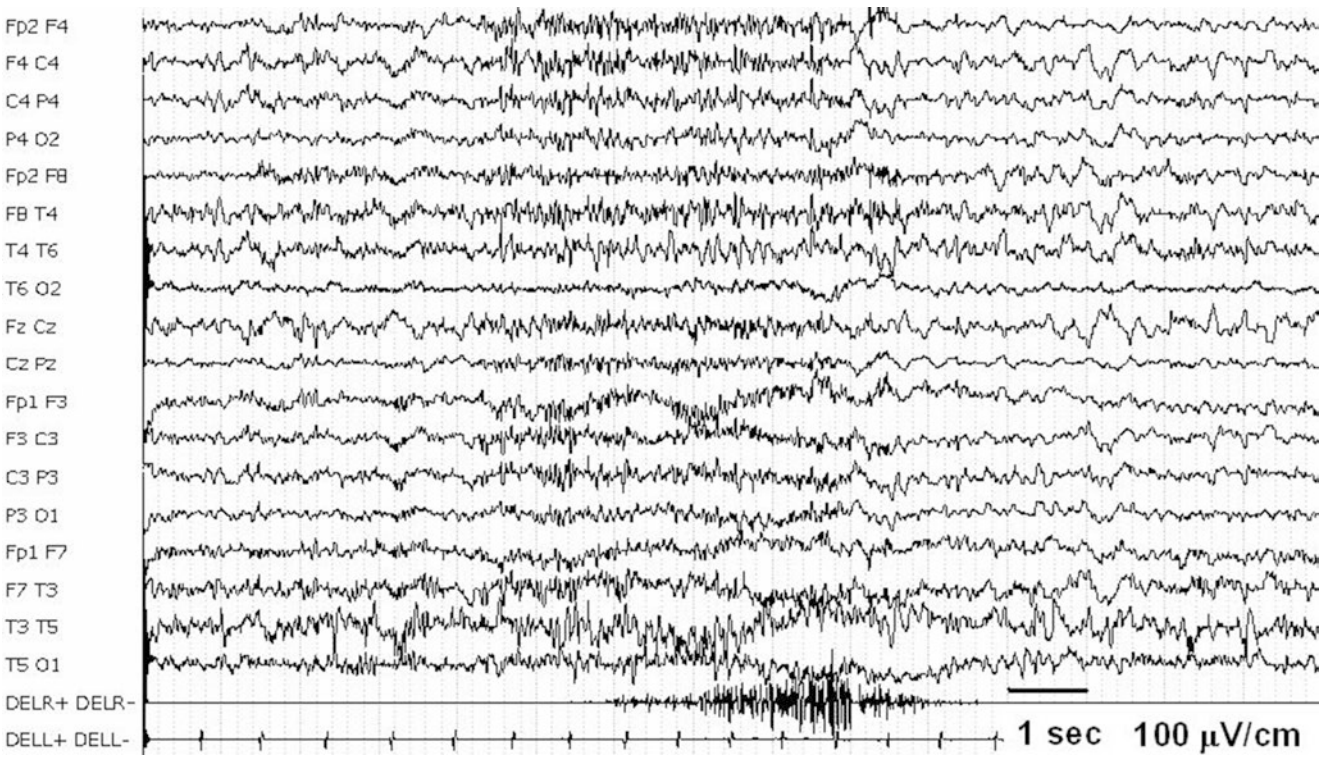

Fig. 33.15 A 43-year-old female with Down syndrome. Ictal EEG during sleep. The seizure is characterized by a diffuse fast activity discharge. At surface EMG of deltoid muscles, an asymmetrical tonic contraction, prevalent on the right side, is present (*R* right, *L* left, *DELT* deltoid muscle)

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].

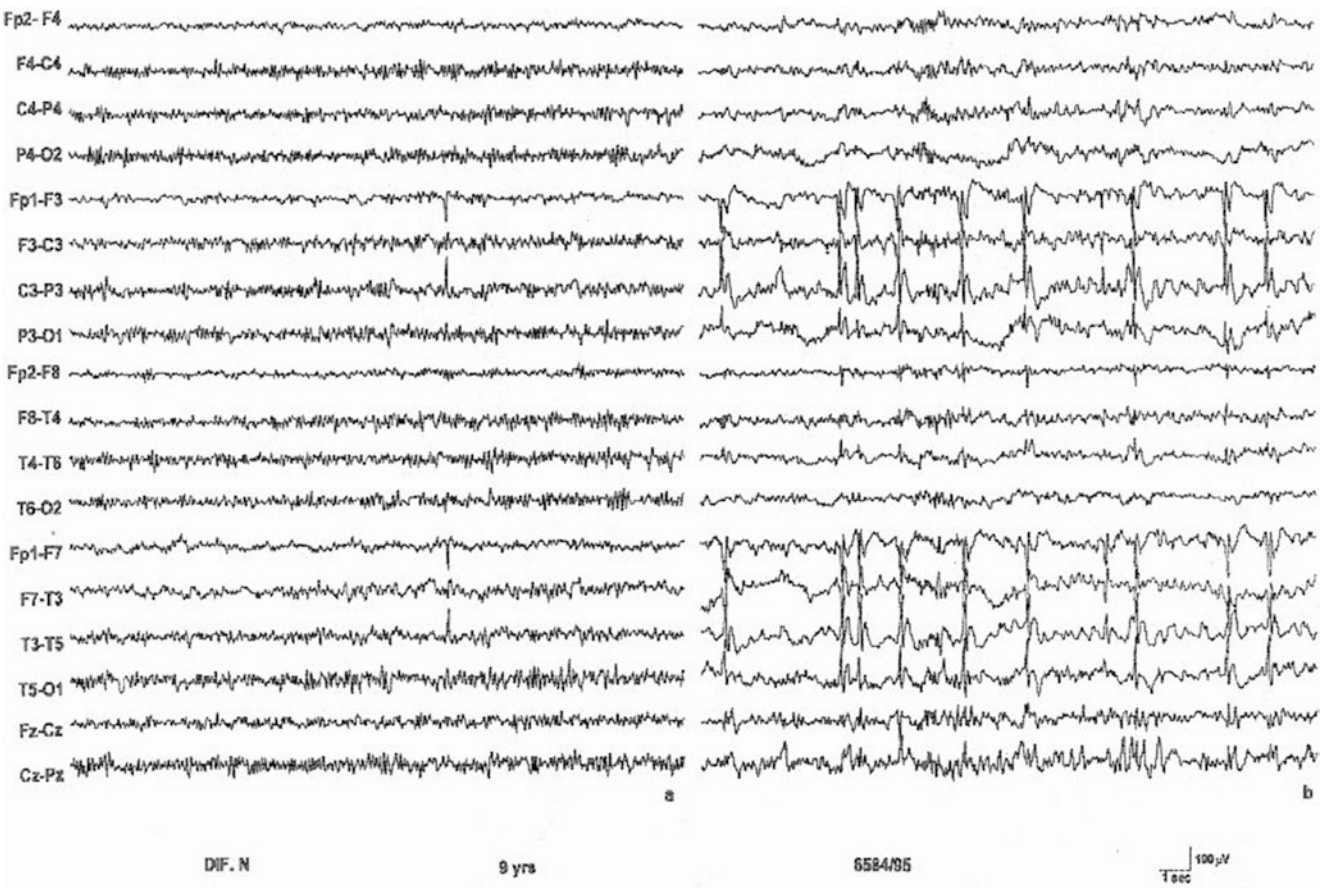

Fig. 33.16 A 9-year-old male with fragile X syndrome. On the left side, wakefulness EEG shows a single high-voltage spike localized over the right centro-temporal regions; on the right side, during sleep, there is a marked activation of paroxysmal abnormalities over the same regions

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].

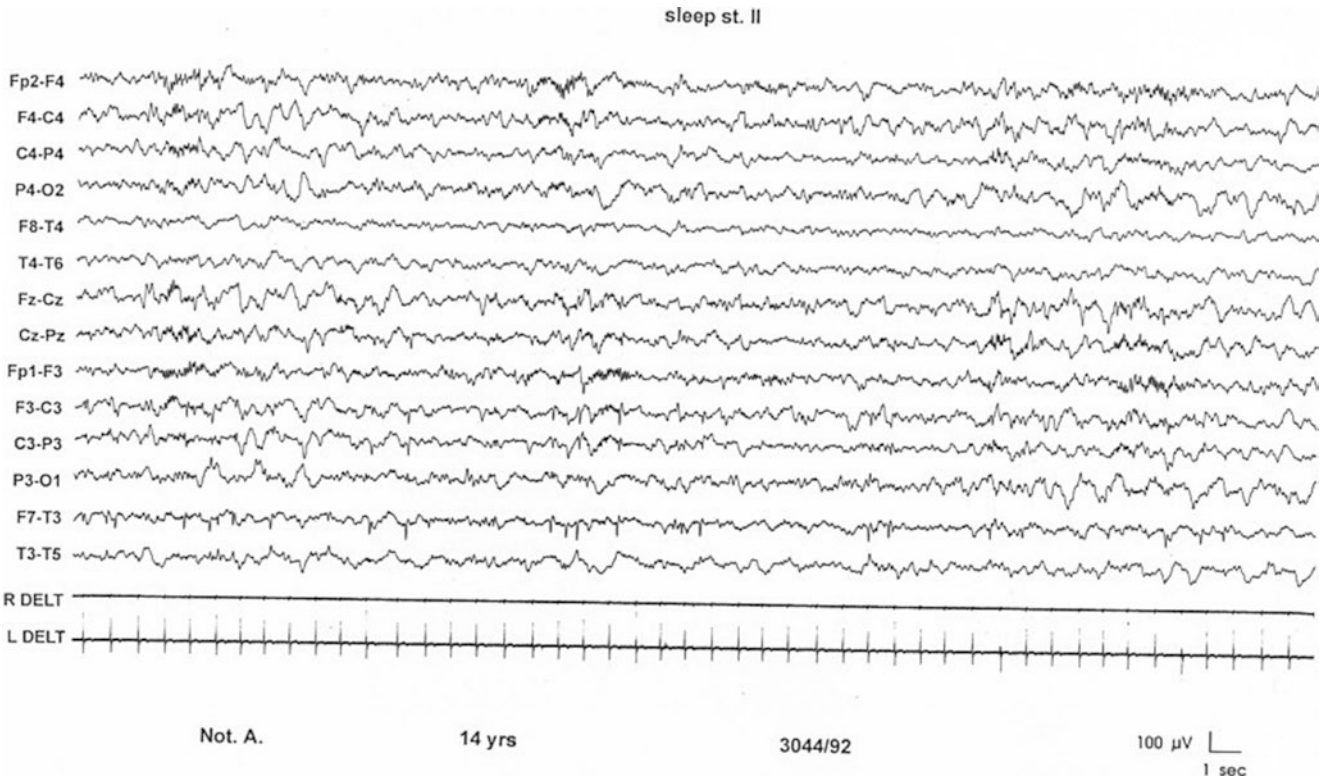

Fig. 33.17 A 14-year-old male with Klinefelter syndrome. During sleep EEG, focal spikes are recorded over the left fronto-centro-temporal regions and vertex (*R* right, *L* left, *DELT* deltoid muscle)

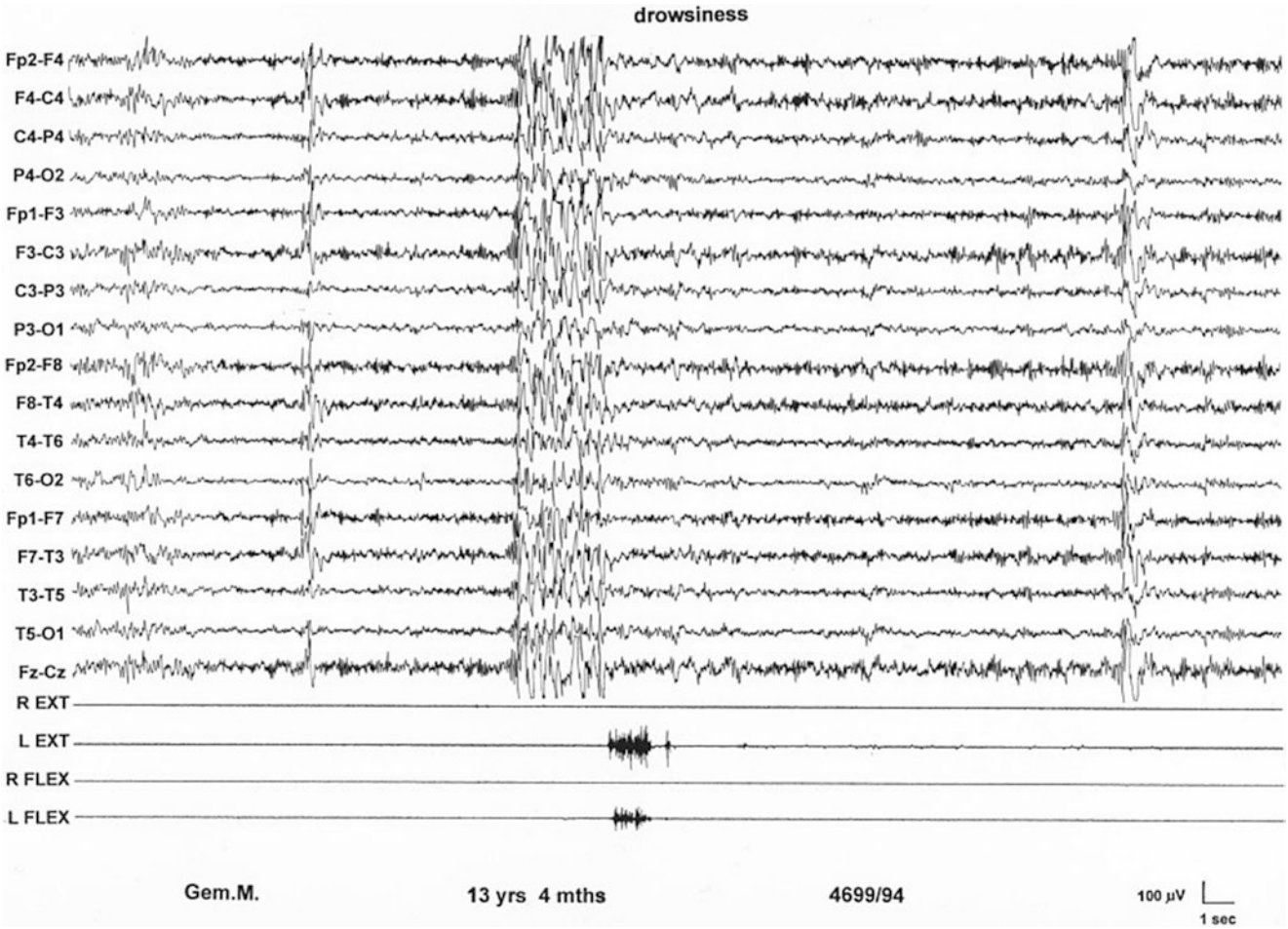

Fig. 33.18 A 13-year-old male with Klinefelter syndrome. EEG during drowsiness presents numerous diffuse spikes and spike-and-waves (*R* right, *L* left, *EXT* forearm extensor muscles, *FLEX* forearm flexor muscles)

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].

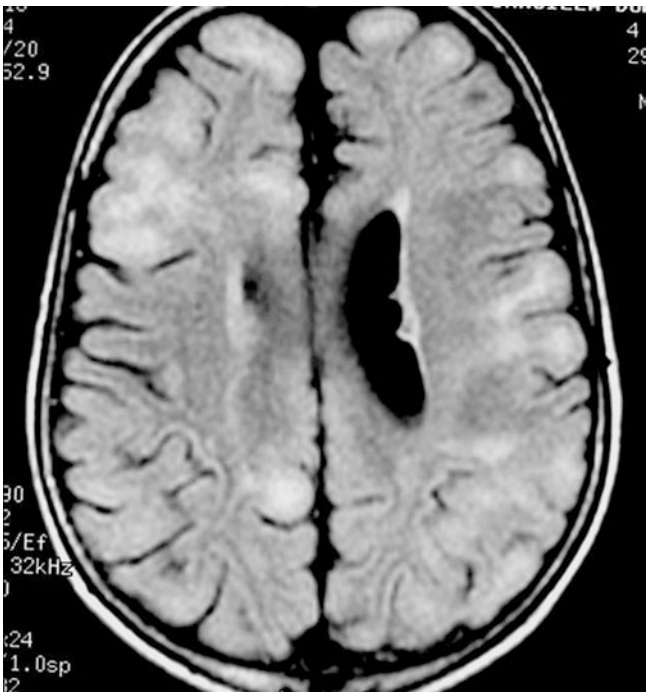

Fig. 33.19 Brain MRI of a 4-year-old male with tuberous sclerosis. Numerous cortical tubers are present over both hemispheres

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

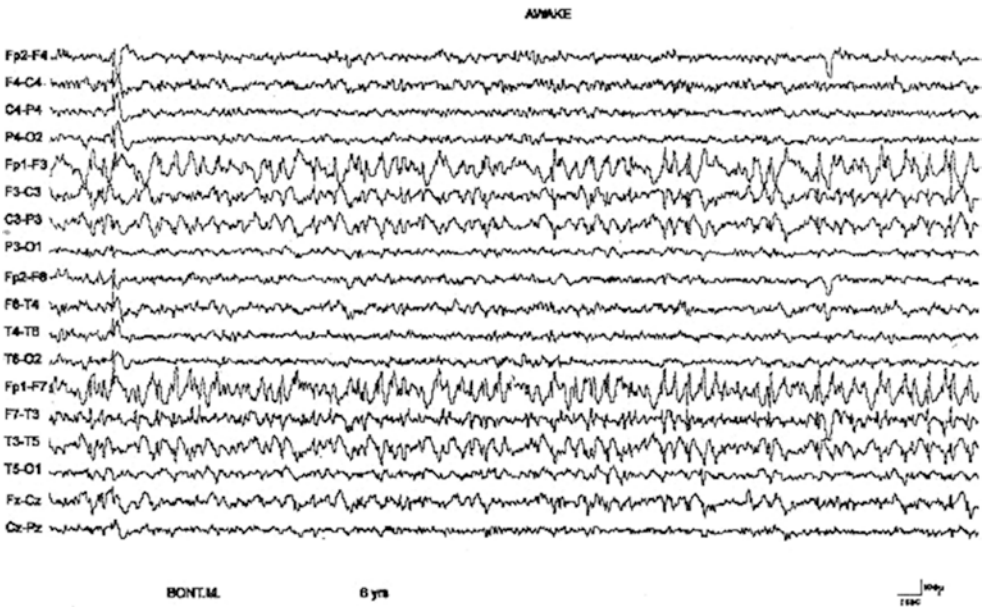

Fig. 33.20 A 6-year-old male with tuberous sclerosis. Wakefulness EEG shows quasi-continuous sharp waves and spikes over the left fronto-central-temporal (correlated with the localization of a large cortical tuber)

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].

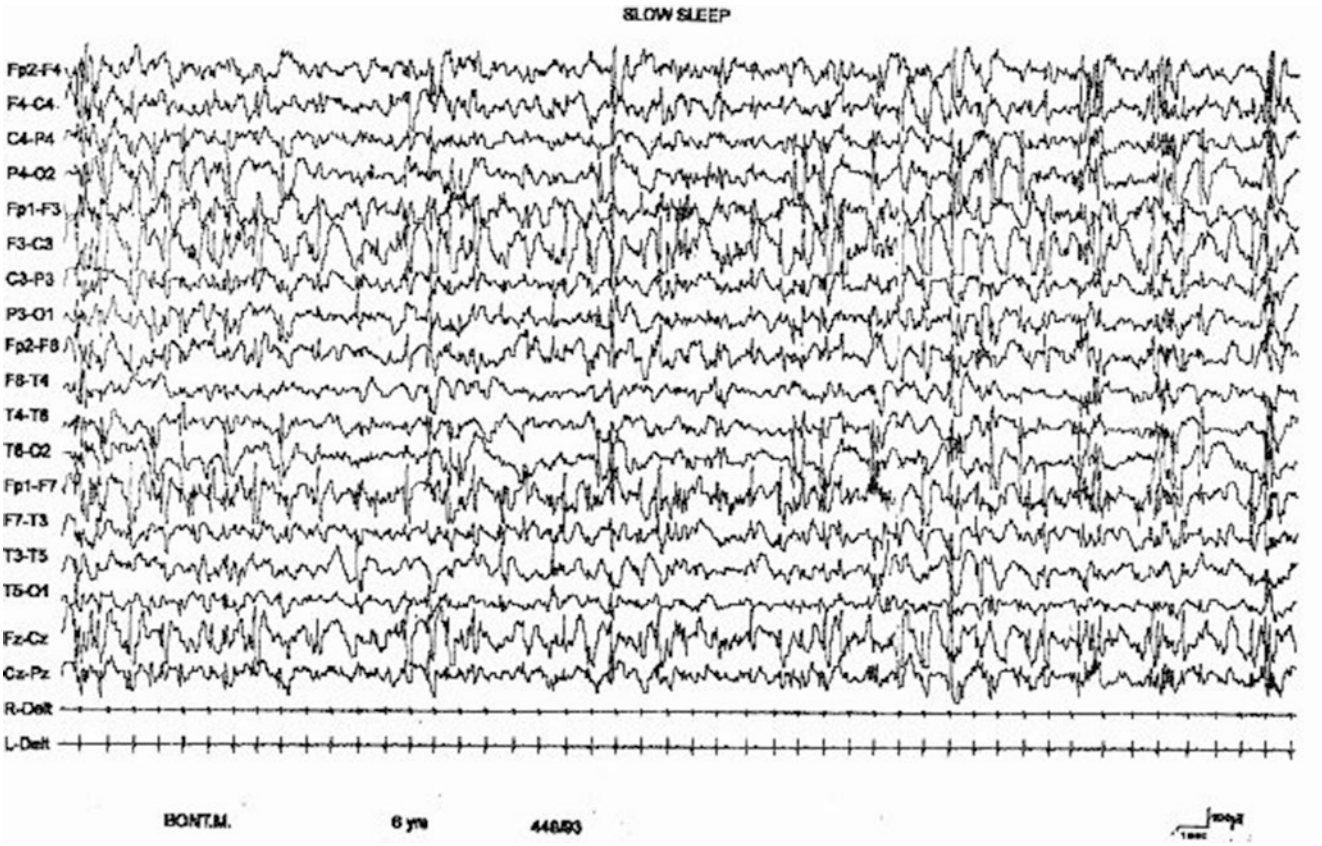

Fig. 33.21 The same subject of Fig. 33.20. During sleep, paroxysmal abnormalities become quasi- continuous over both hemispheres (*R* right, *L* left, *DELT* deltoid muscle)

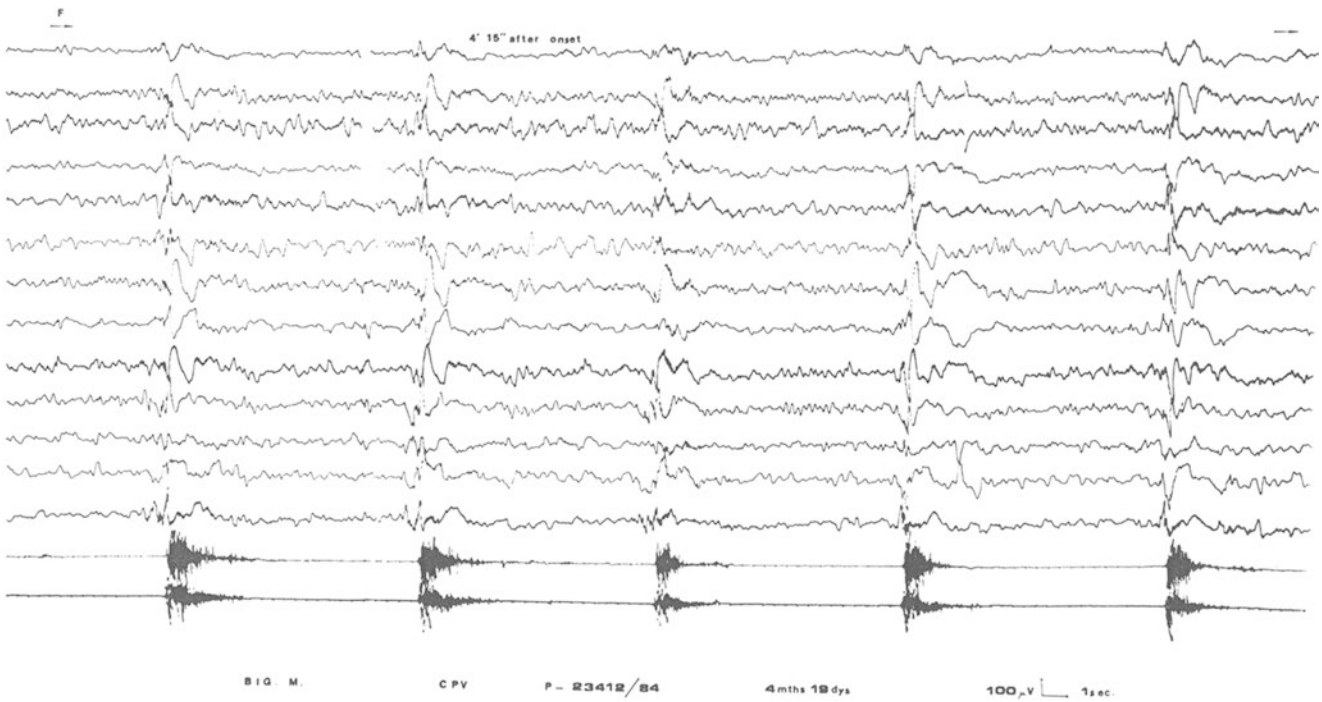

Fig. 33.22 Male at 4 months of age with tuberous sclerosis. Ictal EEG shows a long series of spasms which interrupts hypsarrhythmia. Spasms are characterized by repetitive synchronous and symmetrical muscle contractions, corresponding to high-voltage diffuse slow complexes at the EEG

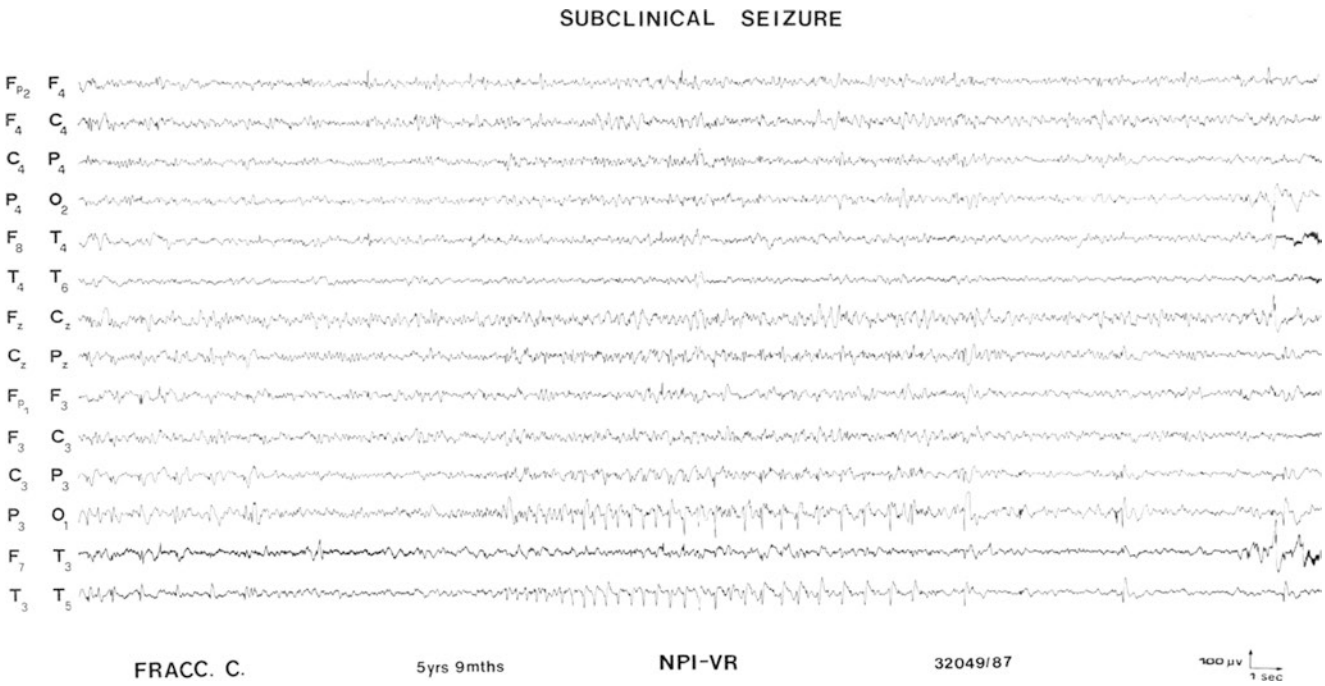

Fig. 33.23 A 5-year-old female with tuberous sclerosis. A subclinical focal seizure, characterized by rhythmical spikes, is recorded over the left temporo-occipital regions

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

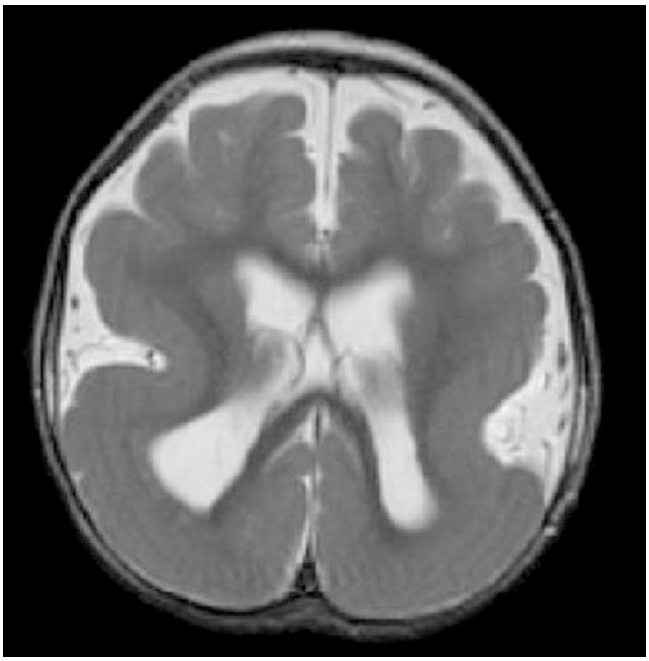

Fig. 33.24 Brain MRI of a 4-year-old male with lissencephaly (TUBA1A mutation). The typical posterior-to-anterior gradient of agyria-pachygyria

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

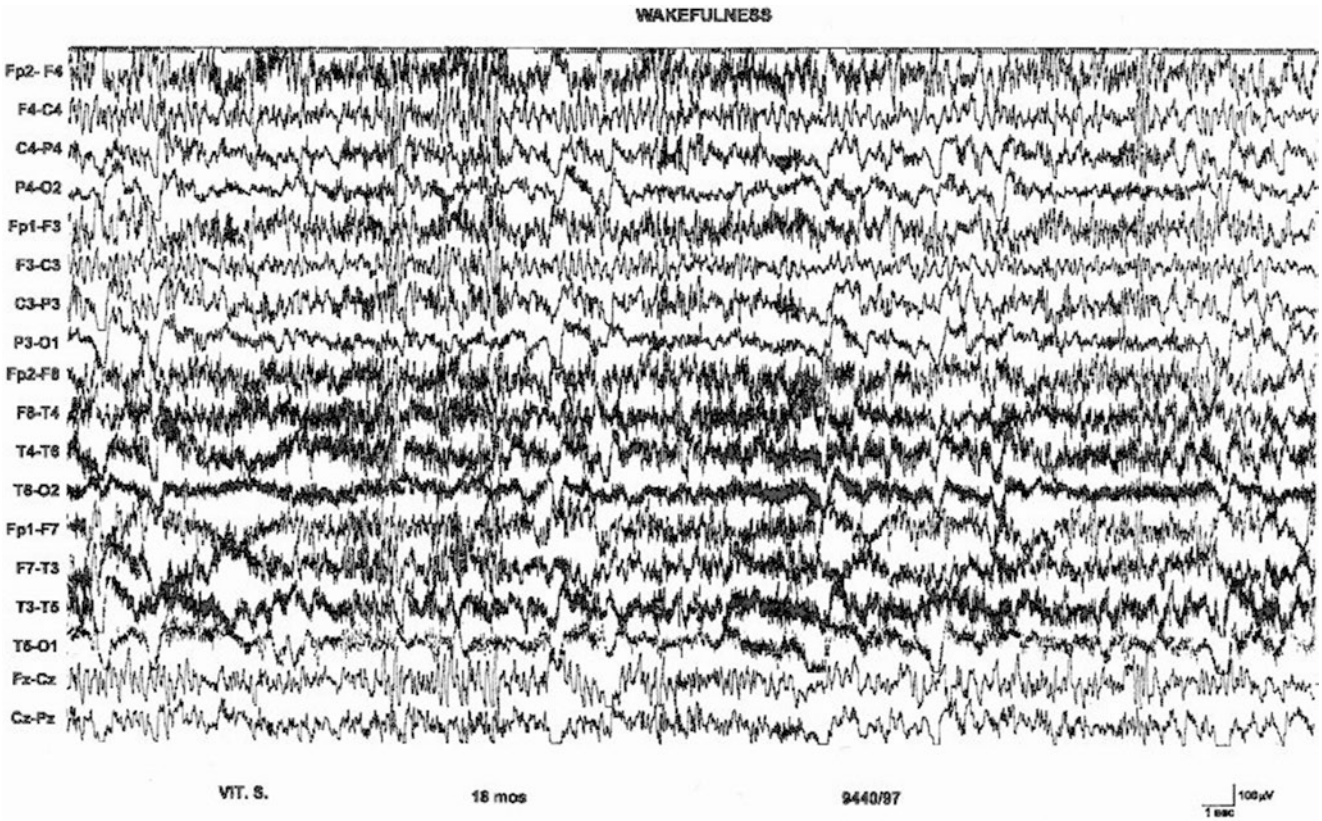

Fig. 33.25 Male at 18 months of age with isolated lissencephaly. Wakefulness EEG reveals a diffuse high-voltage theta activity, prominent over the anterior regions

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

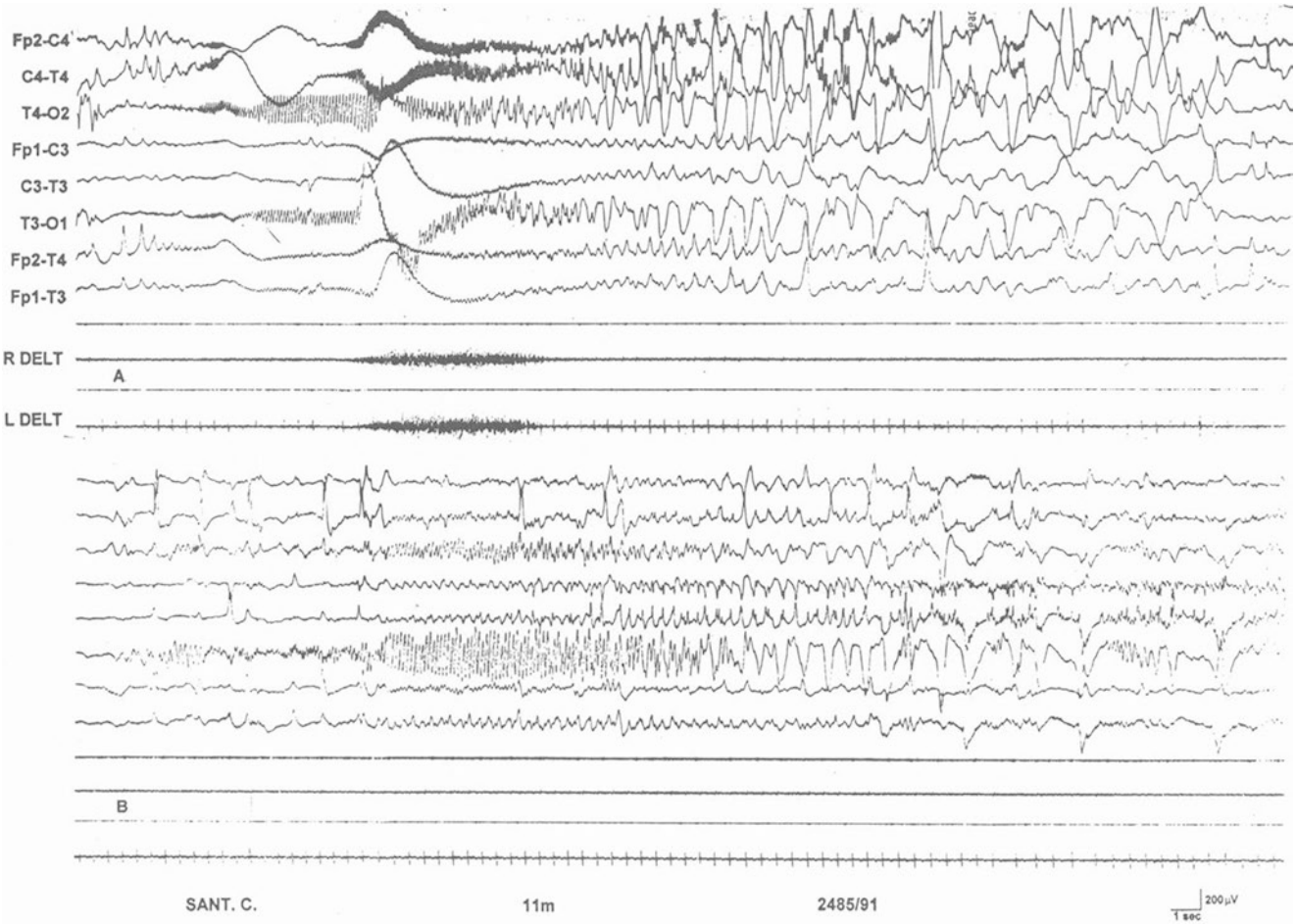

Fig. 33.26 Female at 11 months of age with lissencephaly and cerebellar hypoplasia. On the top, ictal recruiting activity starting from the right posterior regions, rapidly spreading to the contralateral hemisphere, followed by spike and spike-and-wave activity. At surface EMG of deltoid muscles, a short 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)

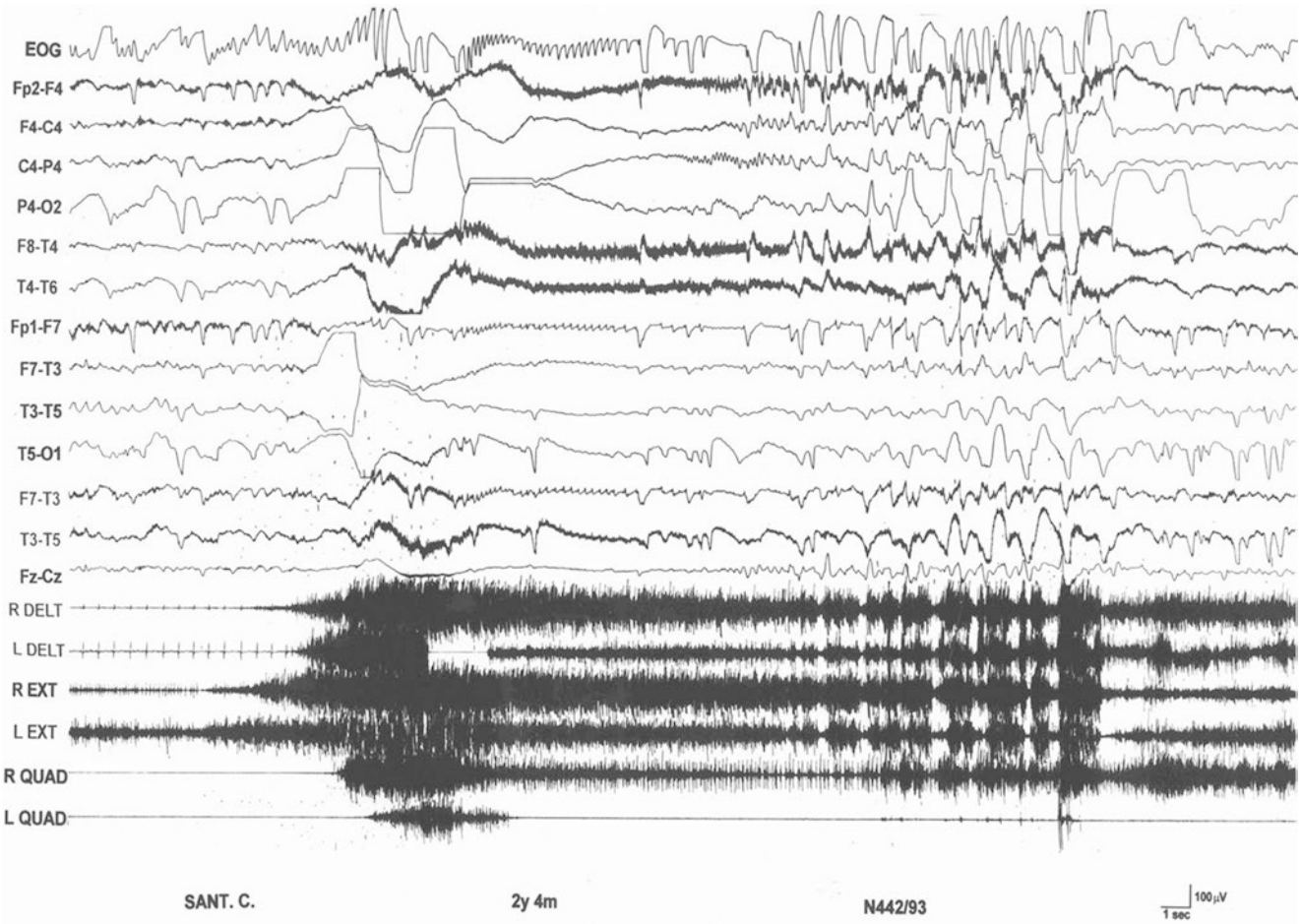

Fig. 33.27 The same patient of Fig. 33.26. EEG shows a tonic seizure with diffuse desynchronization. The appearance of the spike-and-slow wave complexes is correlated with shorter rhythmical tonic contractions (*R* right, *L* left, *DELT* deltoid muscle, *EXT* forearm extensor muscles, *QUAD* quadriceps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

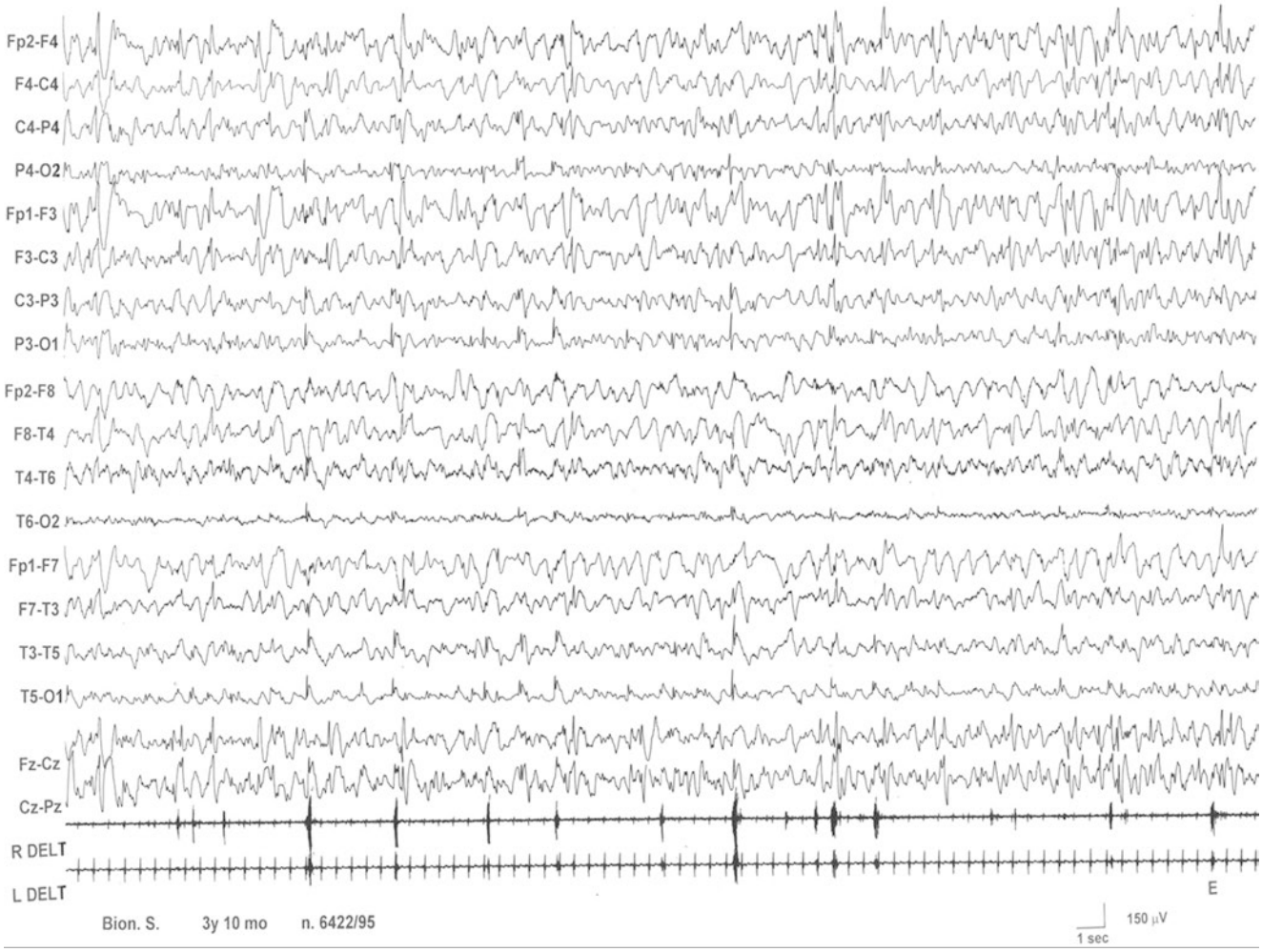

Fig. 33.28 A 3-year-old male with classical lissencephaly. EEG shows numerous diffuse spike-and-wave complexes, prominent over the anterior regions, often correlated with myoclonic jerks at surface EMG of deltoid muscles (*R* right, *L* left, *DELT* deltoid muscle)

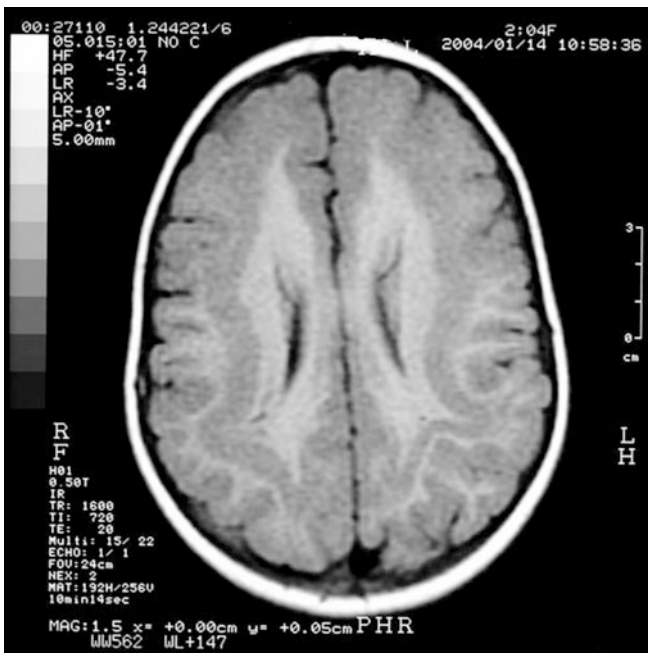

Fig. 33.29 Brain MRI of a 2-year-old female with subcortical band heterotopia (double cortex)

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.

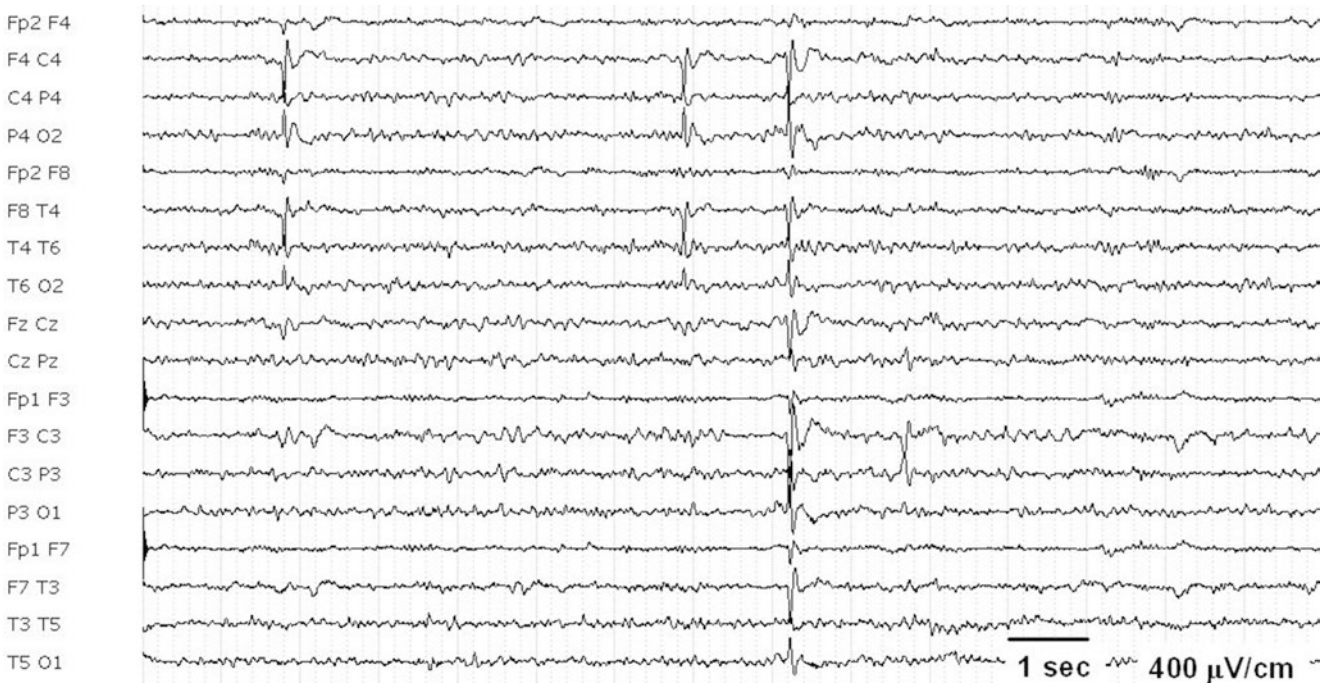

Fig. 33.30 Wakefulness EEG of a 3-year-old female with subcortical band heterotopia. High-voltage spikes are diffuse or asynchronously localized over the centrotemporal regions of both hemispheres, with right prevalence

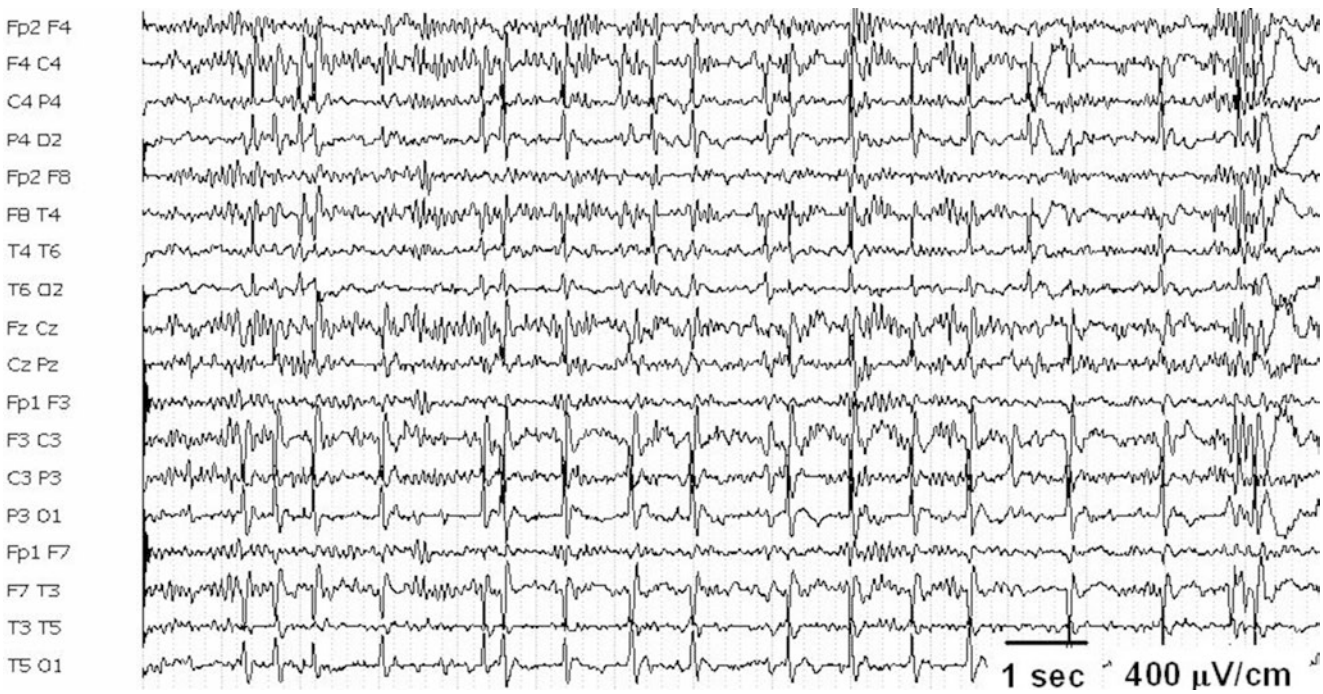

Fig. 33.31 Sleep EEG of the same patient of Fig. 33.30, at 3 years of age. Epileptiform abnormalities are diffuse and quasi-continuous over both hemispheres. Diffuse fast activity, more represented over the fronto-central regions and vertex, is evident

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

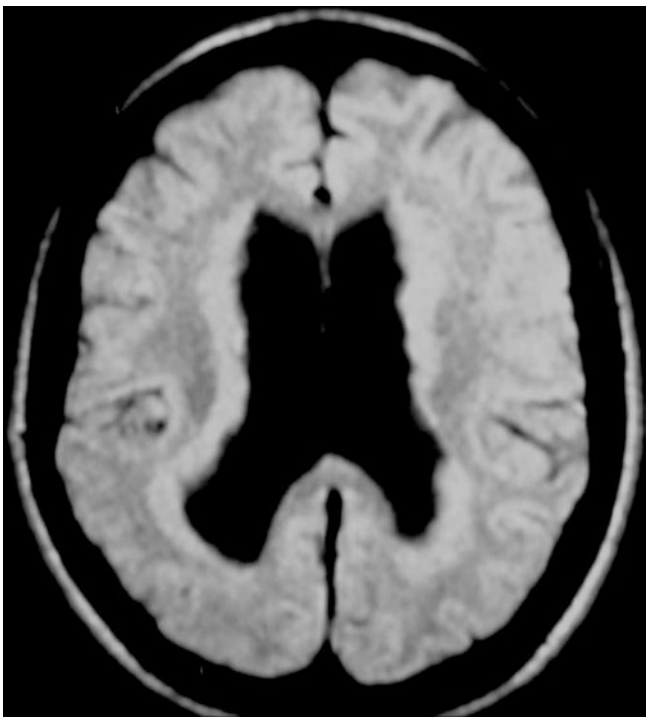

Fig. 33.32 Brain MRI of a 30-year-old female with bilateral periventricular nodular heterotopia

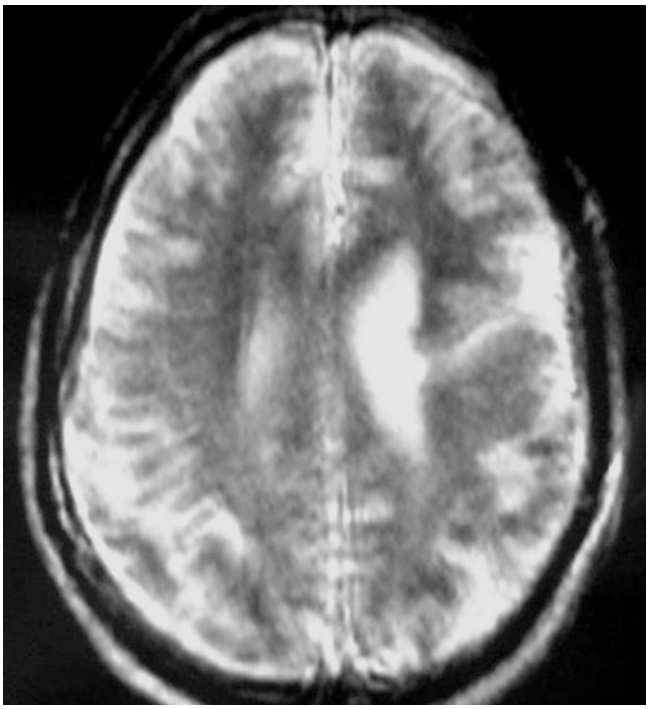

Fig. 33.33 Brain MRI of an 8-year-old male with polymicrogyria and schizencephaly at the left frontal cortex

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].

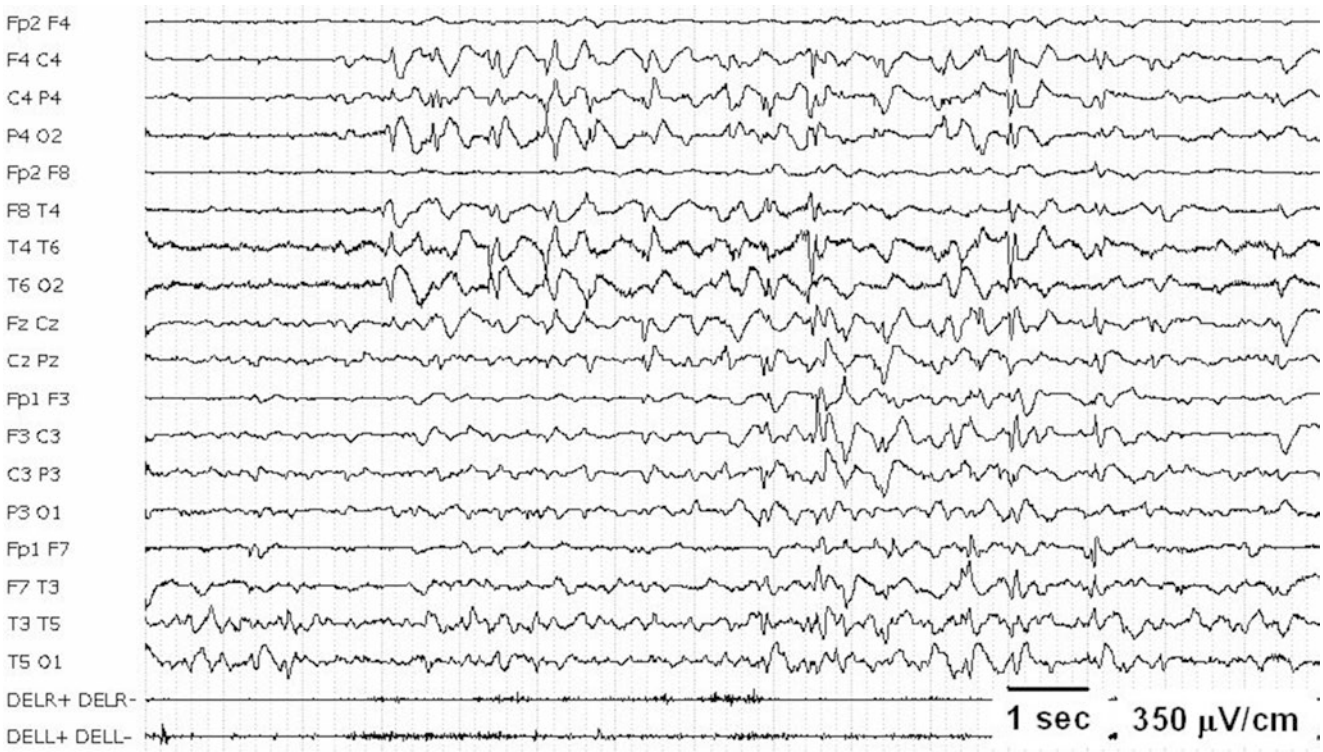

Fig. 33.34 A 1-year-old male with schizencephaly. Wakefulness EEG reveals high-voltage spike-and-slow-wave complexes, mostly localized over the right posterior regions and diffused contralaterally (*R* right, *L* left, *DELT* deltoid muscle)

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

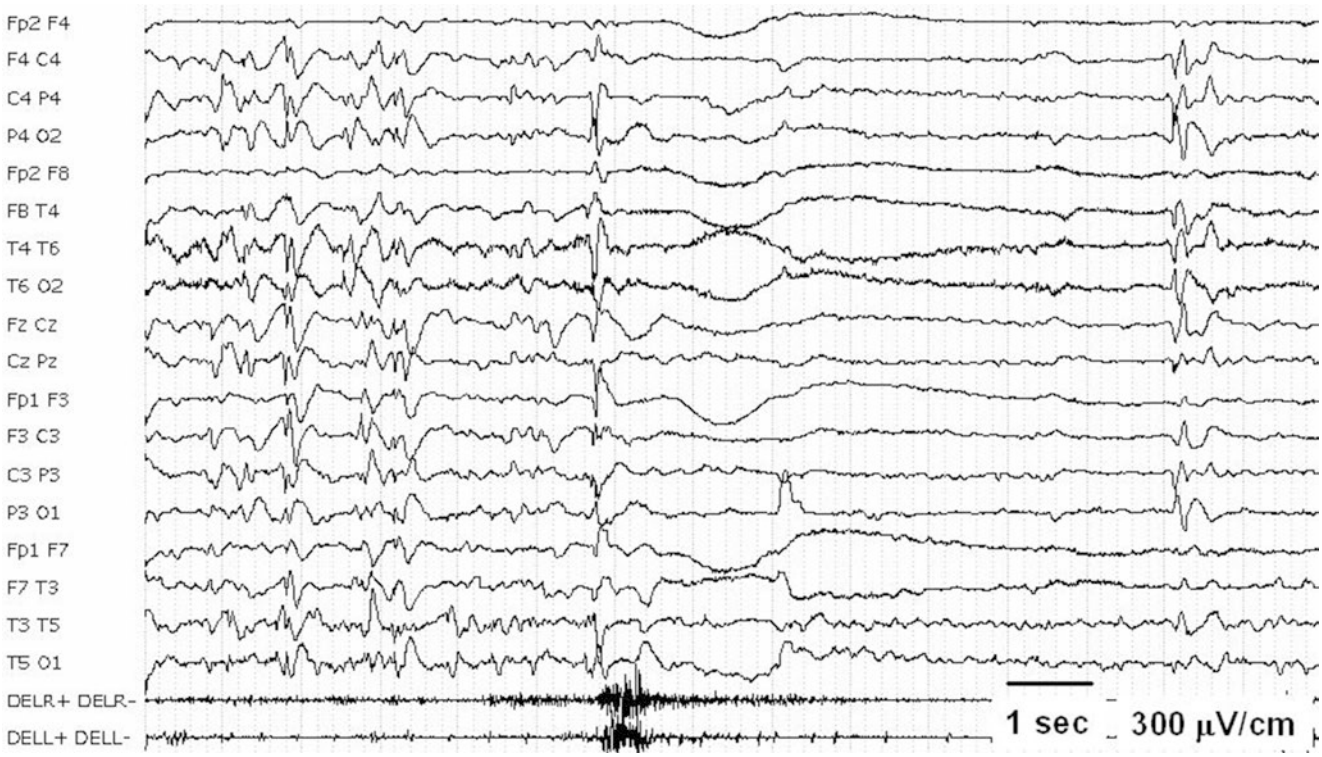

Fig. 33.35 The same child of Fig. 33.34. EEG recording of a seizure characterized by a diffuse slow complex and subsequent desynchronization; at surface EMG of deltoid muscles, a short tonic contraction is present (*R* right, *L* left, *DELT* deltoid muscle)

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].

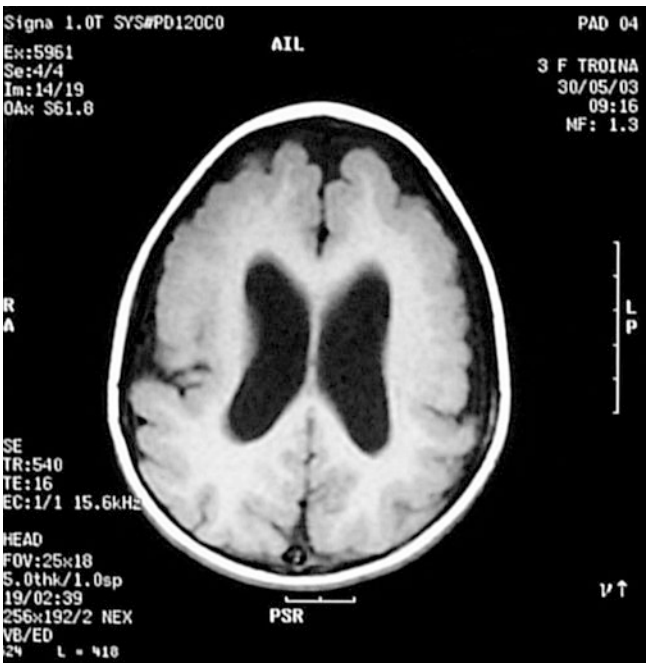

Fig. 33.36 Brain MRI of a 3-year-old female with frontoparietal polymicrogyria

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].

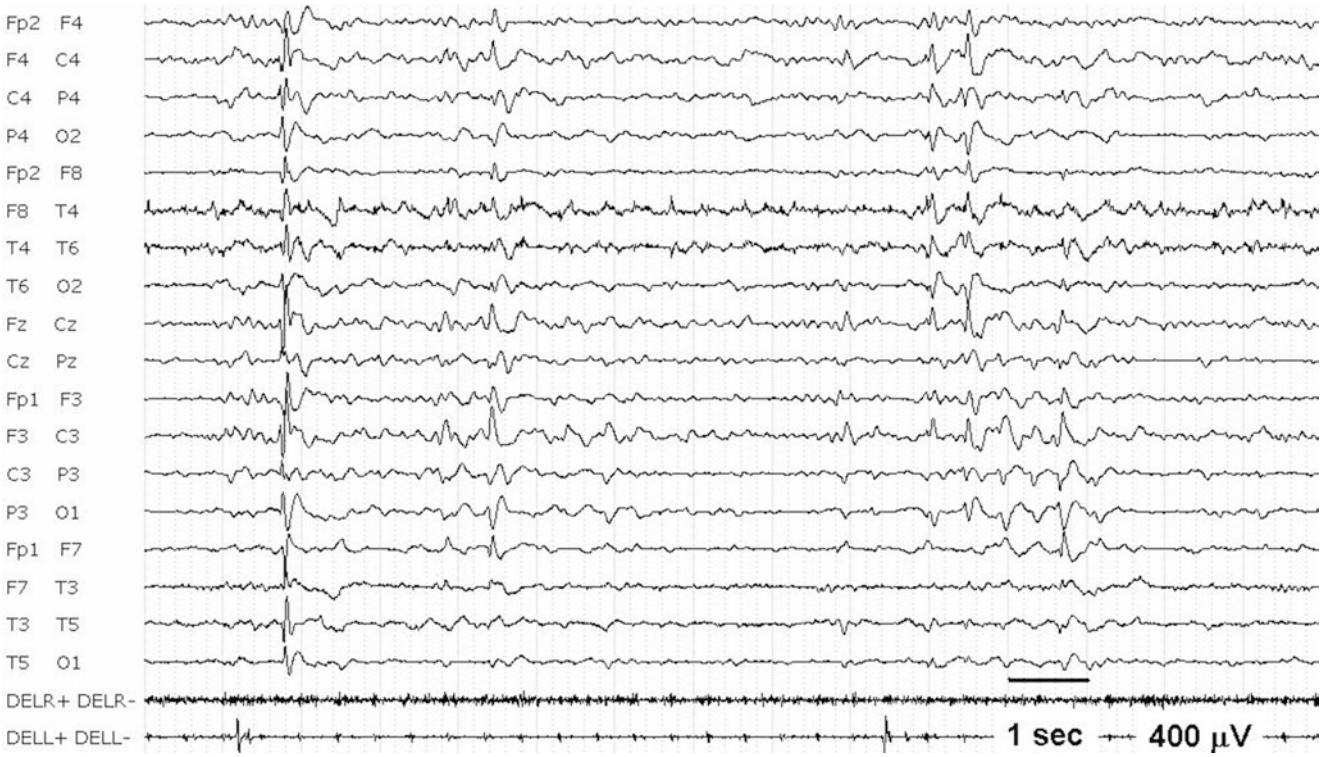

Fig. 33.37 The same child of Fig. 33.36. At age 8, wakefulness EEG in veglia shows high-voltage spikes and spike-and-slow wave complexes, asynchronously localized over the fronto-centro-parietal regions of both hemispheres; a bisynchronous discharge is also evident (*R* right, *L* left, *DELT* deltoid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

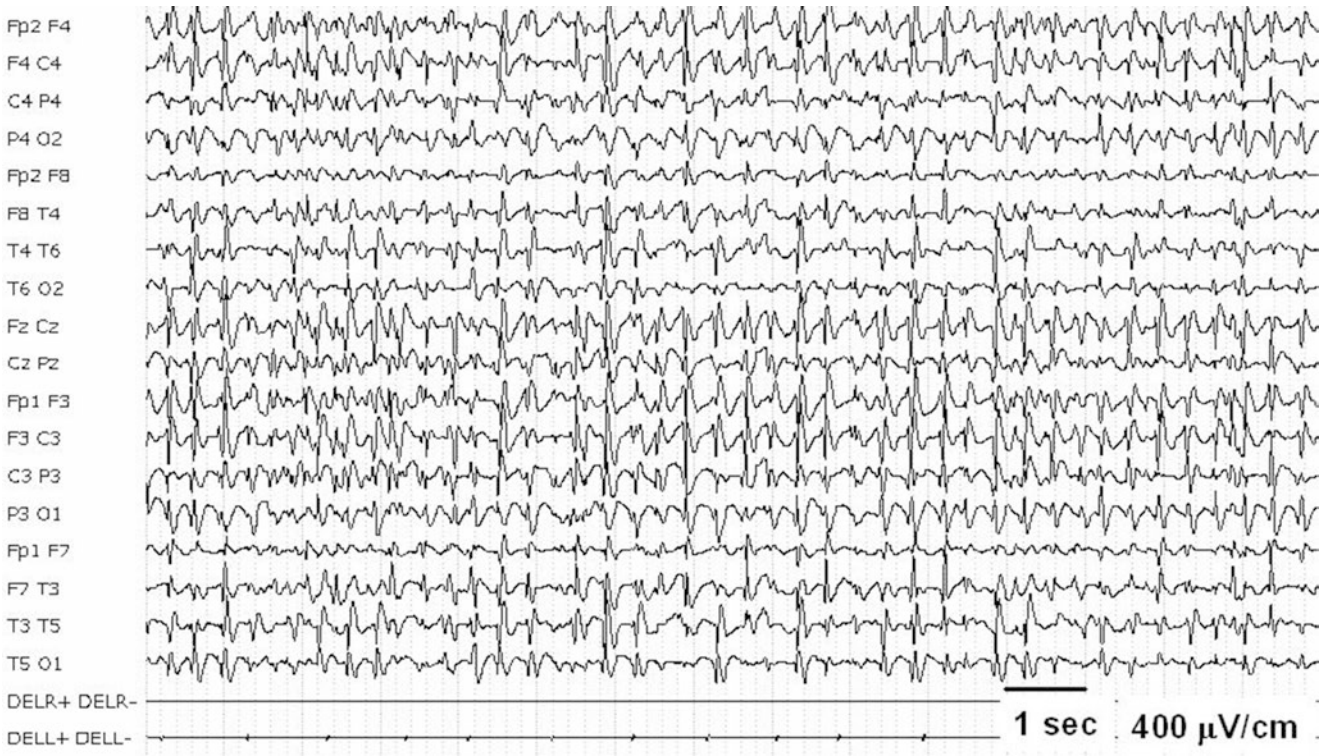

Fig. 33.38 The same child of Fig. 33.37 at age 8. Sleep EEG discloses a diffuse continuous spike-and-wave pattern (*R* right, *L* left, *DELT* deltoid muscle)

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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