Genetic Generalized Epilepsies

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

27.1 Childhood Absence Epilepsy (CAE)

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

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

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

27.1.1 EEG Features

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

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

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

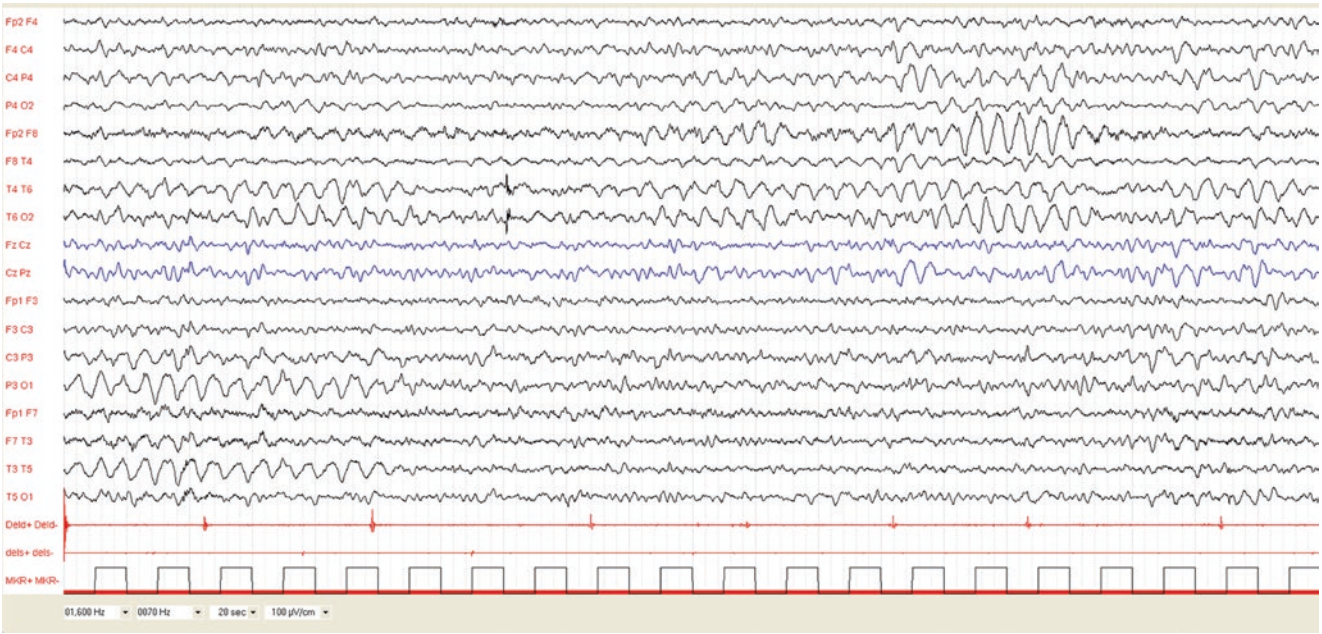

Fig. 27.1 Occurrence of trains of delta activity over the posterior region of both hemispheres, independently, in a 7-year-old girl with CAE

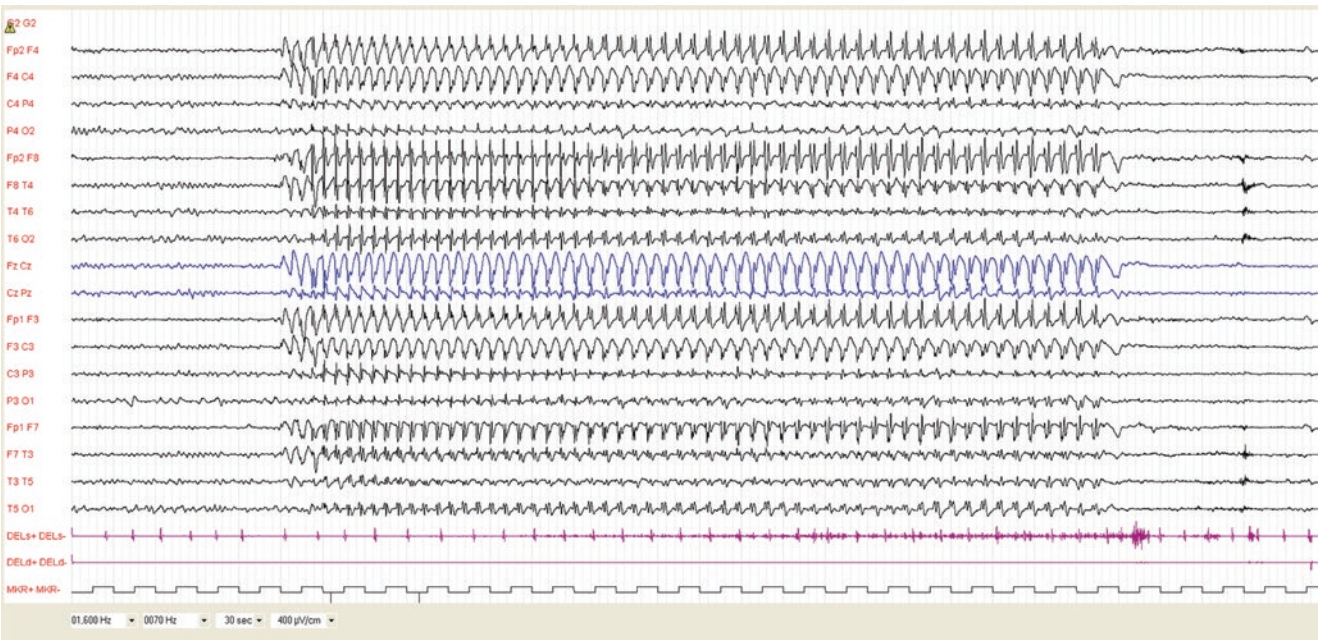

Fig. 27.2 Ictal recording of a typical absence seizure in a 5-year-old boy: 3 Hz spike and wave discharge lasts up to 20 s. Note the abrupt onset and end of the discharge. The boy does not answer to the acoustic stimulus (MRK) produced by the technician

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

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

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

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

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

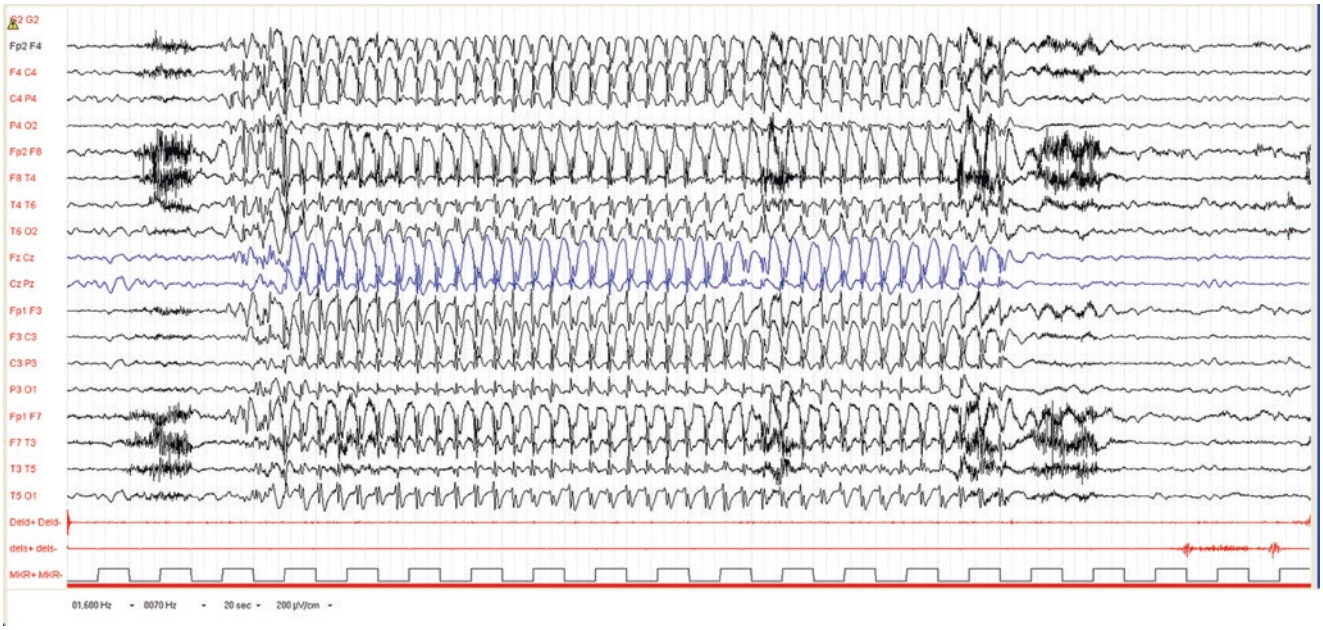

Fig. 27.3 Typical absence in an 8-year-old girl with CAE: the 3 Hz spike and wave discharge is preceded by bilateral spikes over the frontal regions

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

27.2 Juvenile Absence Epilepsy (JAE)

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

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

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

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

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

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

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

27.2.1 EEG Features

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

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

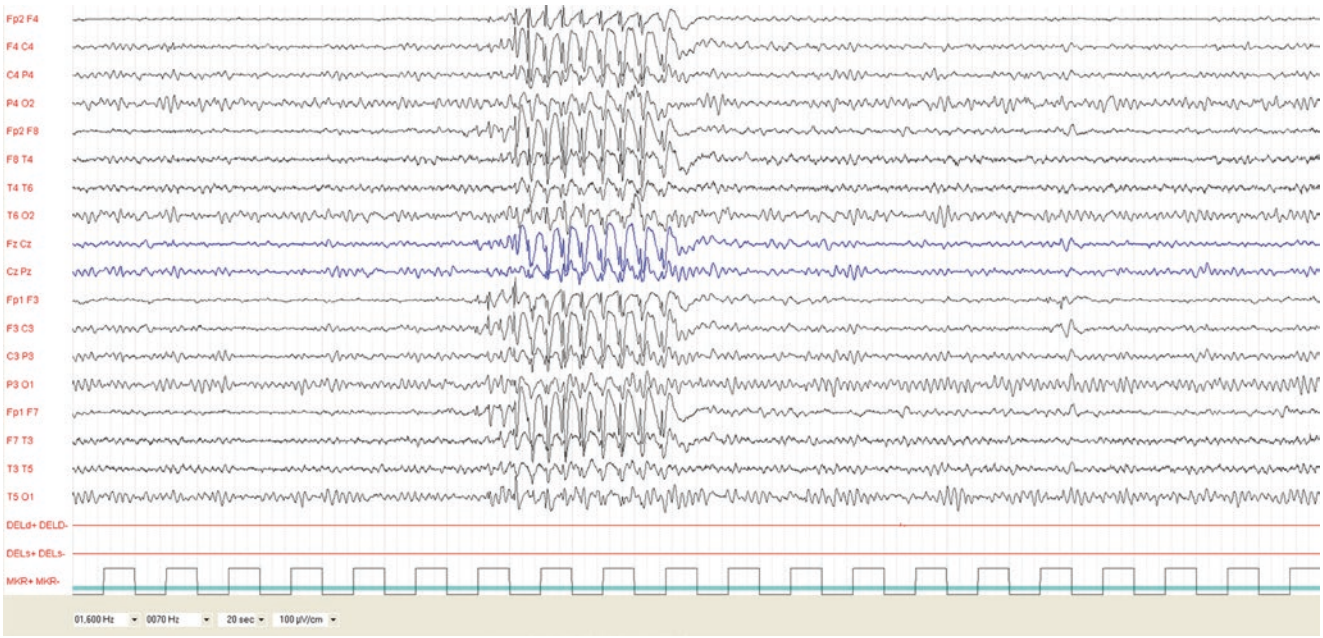

Fig. 27.4 Ictal discharge occurring during HV in an 18-year-old boy with JAE; note that absences are usually shorter than in CAE. At the onset of the ictal discharge, polyspikes followed by 3 Hz spike and waves

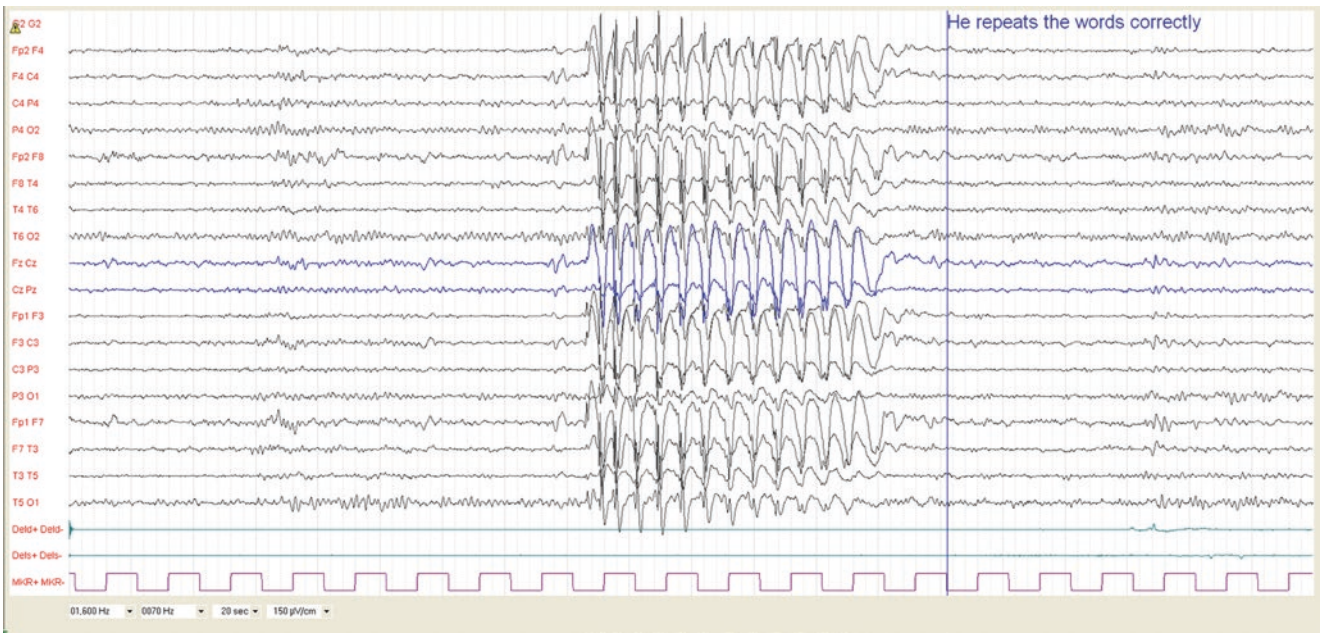

Fig. 27.5 Awareness can be preserved during absences in JAE, like in this 16 year old boy with 3 Hz ictal discharge with frontal predominance

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

27.3 Juvenile Myoclonic Epilepsy (JME) (Janz Syndrome)

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

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

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

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

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

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

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

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

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

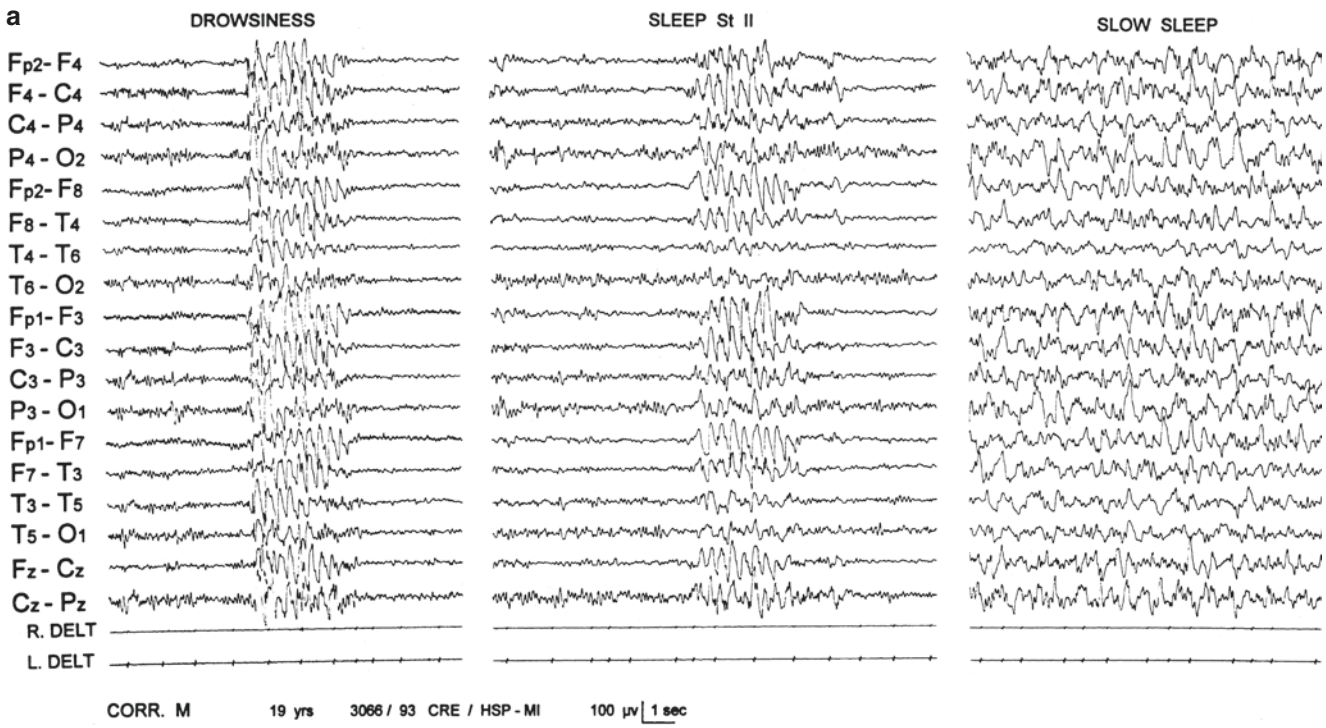

Fig. 27.6 A 19-year-old patient with JME. EEG recording after sleep deprivation. Panel (**a**): during drowsiness and sleep stage 2, sharp and slow wave discharges without clinical correlate. During slow sleep, rare slow abnormalities intermingled with slow background activity. Panel (**b**): 15 min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

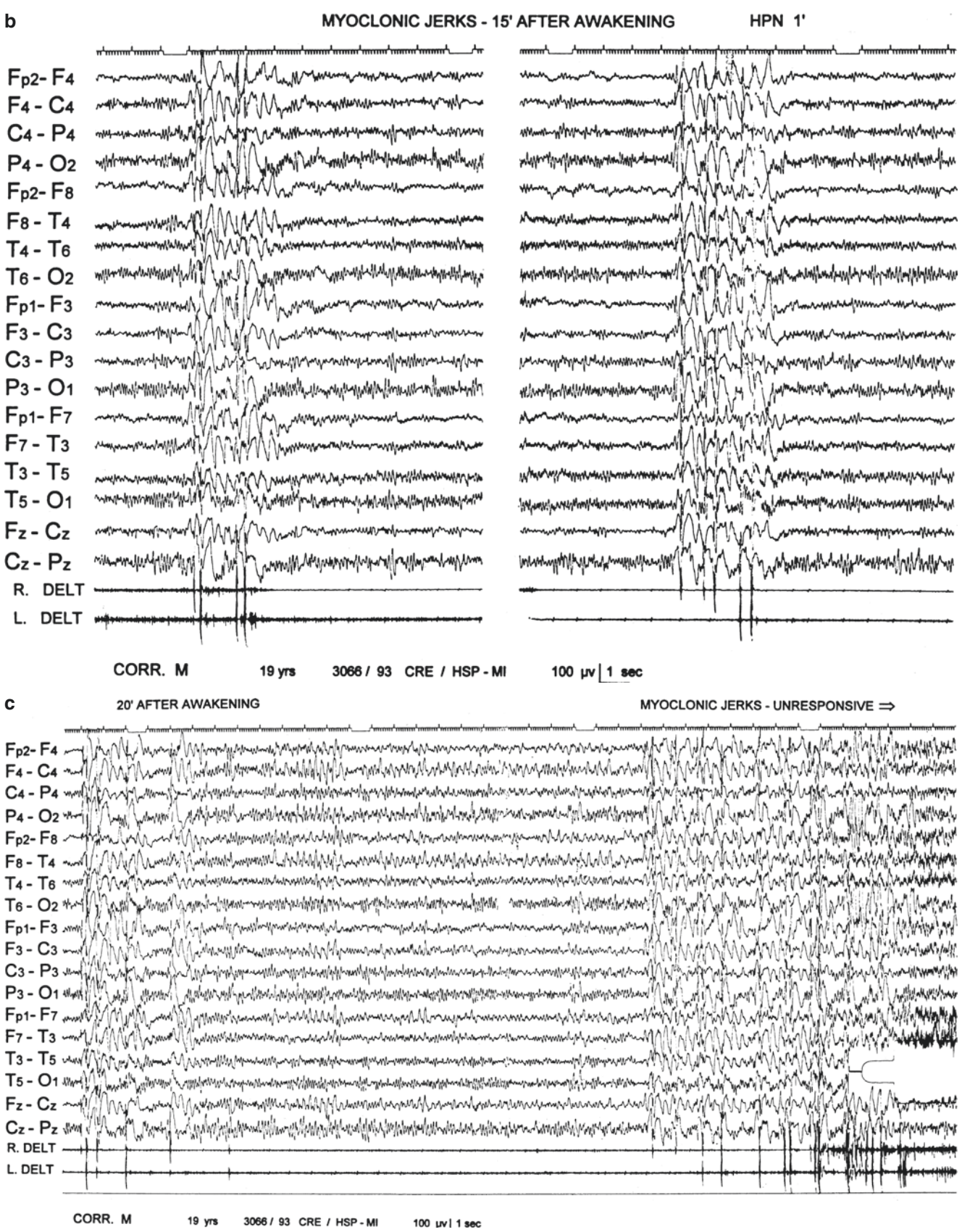

Fig. 27.6 (continued)

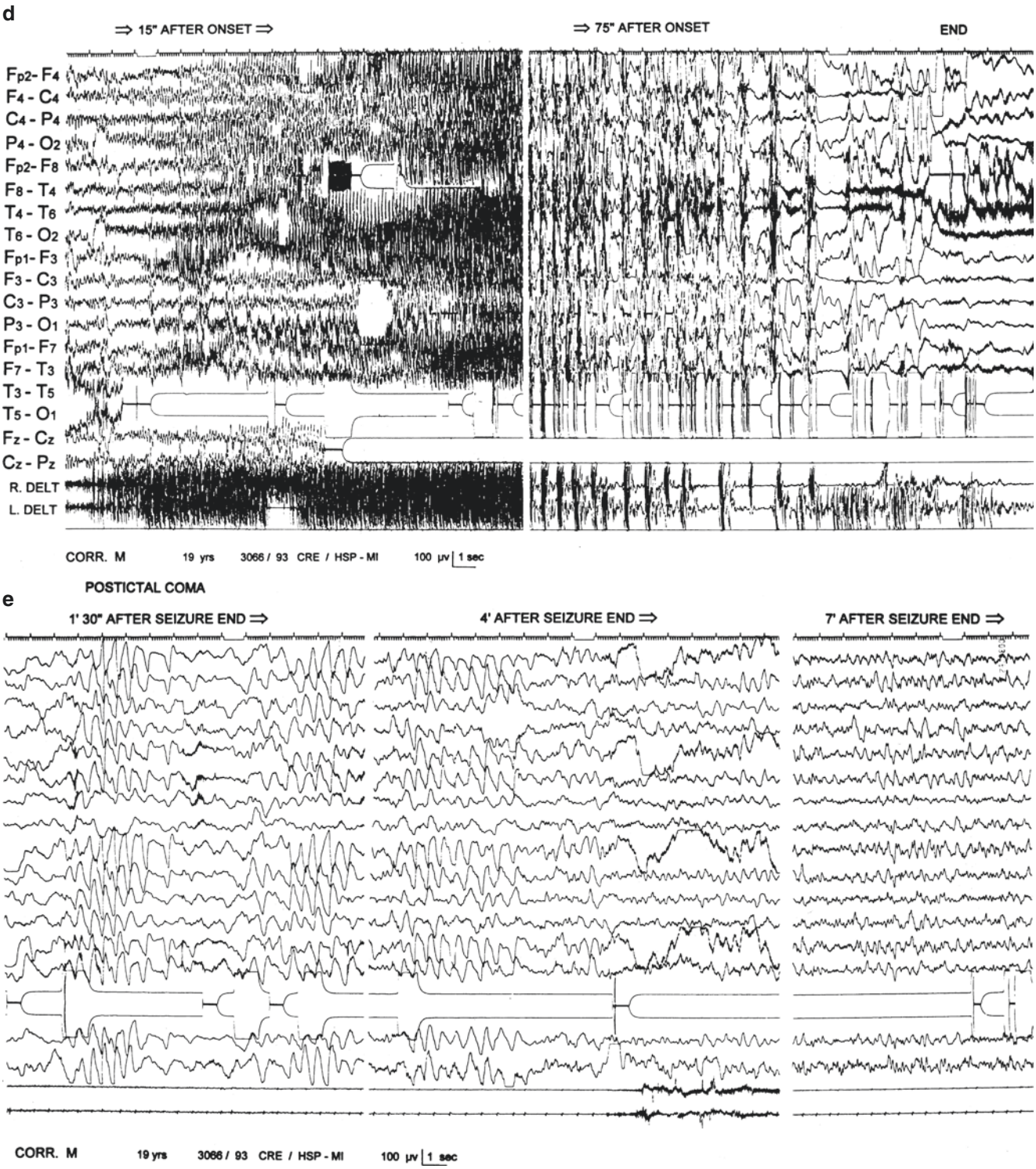

Fig. 27.6 (continued)

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

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

27.3.1 Neurophysiology

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

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

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

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

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

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

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

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

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

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

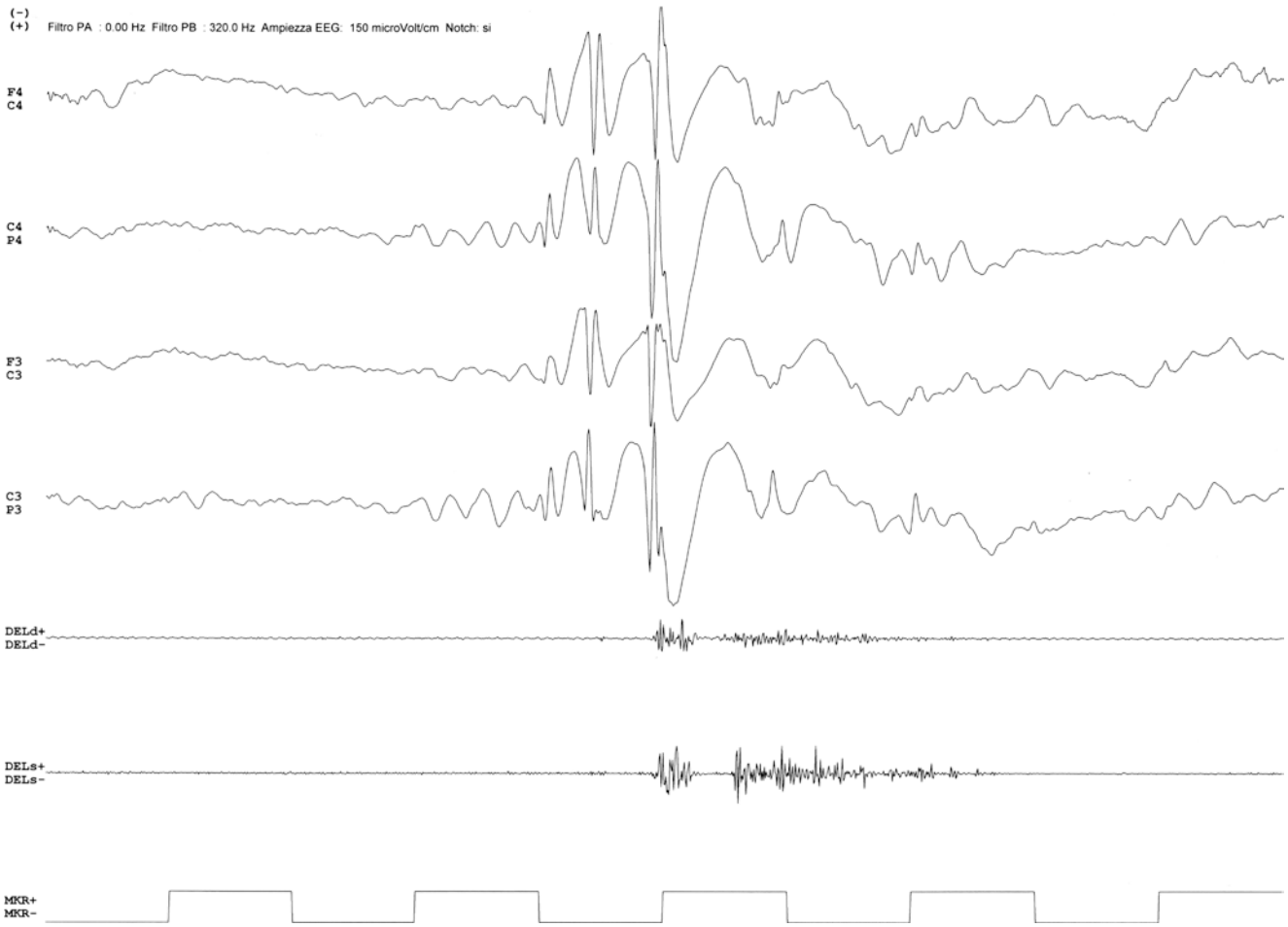

Fig. 27.7 Polyspike-wave discharges have a prominent amplitude on bilateral frontal regions. The polyspike component is related to the occurrence of myoclonic jerks

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

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

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

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

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

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

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

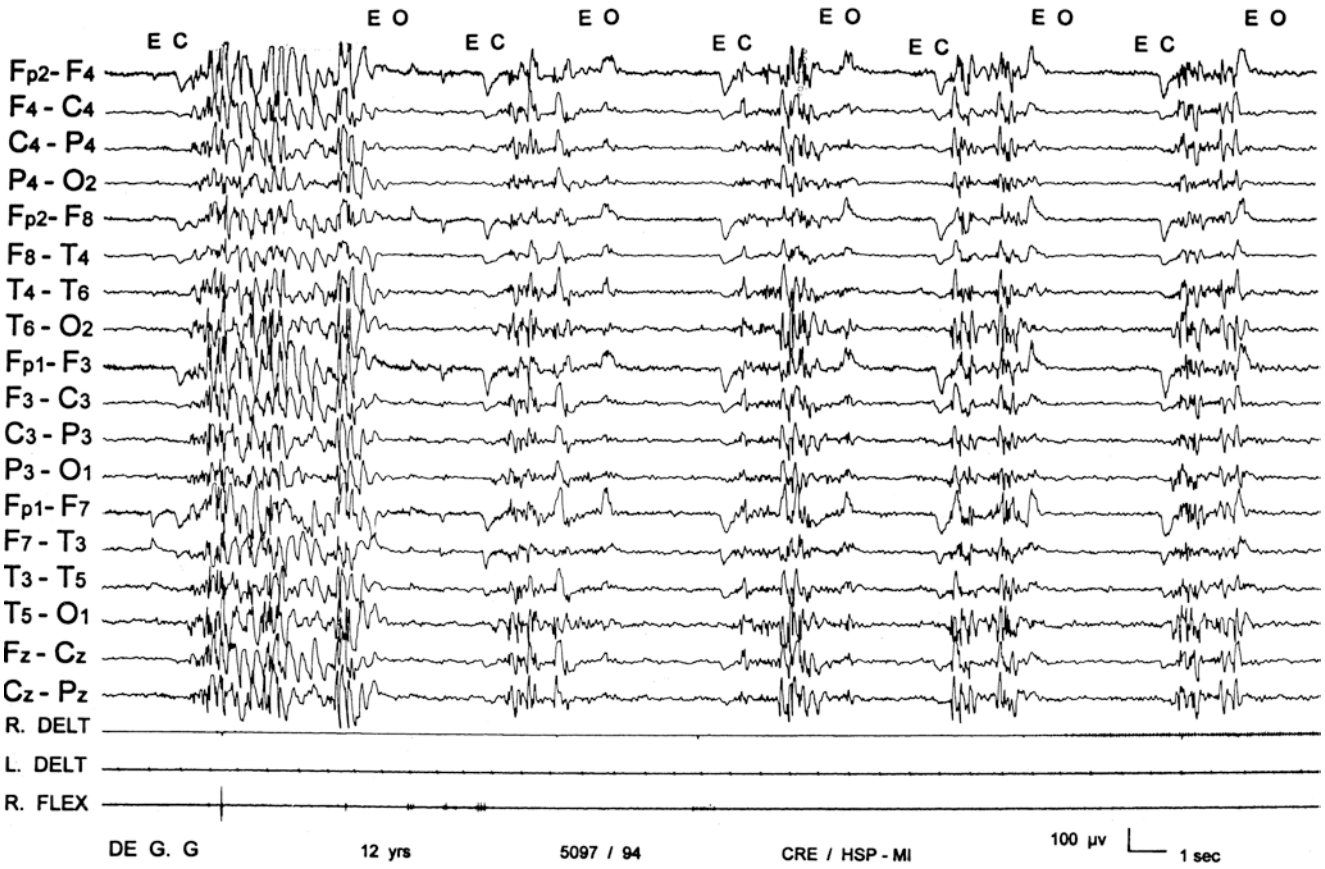

Fig. 27.8 Eyelid myoclonia without absence in a 12-year-old girl. Note that the discharge is characterized by polyspikes occurring at eye closure (EC), which disappear at eye opening (EO)

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

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

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

27.6 Lifestyle and Drugs Can Influence EEG in GGE

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

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

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

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

27.7 Conclusion

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

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