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CRITICAL REVIEW AND INVITED COMMENTARY

The electroencephalogram of idiopathic generalized epilepsy

*†Udaya Seneviratne, *Mark Cook, and *‡Wendyl D'Souza

*Department of Medicine, St. Vincent's Hospital, University of Melbourne, Melbourne, Victoria, Australia; †Department of Neuroscience, Monash Medical Centre, Melbourne, Victoria, Australia; and ‡Centre for Molecular, Environmental, Genetic & Analytic Epidemiology, Melbourne School of Population Health, University of Melbourne, Melbourne, Victoria, Australia

Summary

Idiopathic generalized epilepsy (IGE) is classified into several subsyndromes based on clinical and electroencephalography (EEG) features. The EEG signature of IGE is bisynchronous, symmetric, and generalized spike-wave complex; although focal, irregular, and so called "fragments" of discharges are not uncommon. Other characteristic EEG features include polyspikes, polyspike-wave discharges, occipital intermittent rhythmic delta activity, and photoparoxysmal response. Both human and animal data suggest involvement of the thalamus and the cortex in the generation of spike-wave discharges in IGE. Circadian variations of generalized epileptiform discharges are well described, and these can be useful in diagnostic confirmation. Those discharges tend to occur more often after awakening and during cyclic alternating pattern phase-A of non–rapid eye movement sleep. Activation procedures such as hyperventilation, intermittent photic stimulation, eye closure, and fixation-off are useful techniques to increase the yield of both interictal and ictal EEG abnormalities. Although not in routine use, specific triggers such as pattern stimulation and cognitive tasks may also be of value in eliciting rare reflex seizure-related EEG abnormalities. Variations of EEG abnormalities are evident between different electroclinical syndromes. EEG is also affected by certain external as well as internal factors, which should be borne in mind when interpreting EEG studies in IGE.

KEY WORDS: Spike-wave, Polyspike, Photoparoxysmal response, Myoclonus, Absence, Tonic–clonic seizure.

Idiopathic generalized epilepsy (IGE) constitutes 15–20% of all epilepsies in adult and children cohorts (Jallon & Latour, 2005). The diagnosis of IGE and its electroclinical syndromes is based primarily on clinical features including seizure types, age of onset and typical electroencephalography (EEG) characteristics (ILAE, 1989). Although not mandatory for the diagnosis, EEG plays a key role in the dichotomous classification of epilepsies into focal and generalized. In a cohort of first-seizure patients, 92% with a clinical diagnosis of generalized epilepsy demonstrated generalized epileptiform abnormalities on the initial routine study and subsequent sleep-deprived EEG (King et al., 1998). In the same study, supplementation of EEG data to the clinical diagnosis increased the diagnostic yield of an epilepsy syndrome, both focal and generalized, from 47 to 77%.

First described by Gibbs et al. (1935), bilateral, synchronous, and symmetrical generalized spike-wave (GSW) activity is the electrographic hallmark of IGE. These discharges are typically seen on a normal background. Other EEG features of IGE include photoparoxysmal response, occipital intermittent rhythmic delta activity (OIRDA), polyspikes, and polyspike-wave discharges (Markand, 2003a).

This review focuses on the spectrum of EEG abnormalities in IGE. We will be discussing the electrophysiologic basis of the generation of epileptiform discharges, morphology of the spike-wave complex, activation techniques, and factors affecting EEG. The ictal as well as interictal epileptiform abnormalities in different subsyndromes will also be discussed.

Pathophysiology of Spike-Wave Complex and Generalized Seizures

Cellular and network mechanisms of spike-wave paroxysms and generalized seizures are complex. IGE encompasses several subsyndromes with different seizure types. It is unclear whether the same pathophysiologic mechanism is responsible for all the manifestations. The most informative data in this regard comes from animal experiments involving genetic absence epilepsy models to demonstrate the underlying mechanisms of spike-wave complex. More recently, simultaneous recordings of EEG and functional

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Address correspondence to Udaya Seneviratne, Department of Neuroscience, St. Vincent's Hospital, PO Box 2900, Fitzroy, Melbourne, Vic. 3065, Australia. E-mail: udaya.seneviratne@svhm.org.au; wusenevi@optusnet.com.au

magnetic resonance imaging (fMRI) have provided useful insights in humans.

Several theories have evolved to explain the pathophysiology of absence seizures, the electroclinical prototype of generalized epilepsy (Meeren et al., 2005). Historically, the ''centrencephalic theory'' was the first proposed mechanism arguing for the existence of a pacemaker in the brainstem and diencephalon responsible for generalized seizure activity (Penfield & Jasper, 1954). The ''thalamic clock theory'' postulated a pacemaker in the reticular thalamic nucleus (Buzsaki, 1991). Gloor (1968) proposed the ''corticoreticular theory'' describing the genesis of spike-wave discharges in a thalamo-cortical circuitry. The ''cortical theory'' and the ''cortical focus theory'' propose initiation by cortex in the generation of spike-wave discharges, whereas the thalamus is playing a secondary role in the circuitry (Meeren et al., 2005).

The hypothesis of thalamocortical network in the generation of generalized seizures and spike-wave complex has received much emphasis. Gloor (1978) proposed that the same thalamocortical circuit producing sleep spindles would generate GSW discharges in states of cortical hyperexcitability. A more recent report disputed the theory that spike-wave discharges are transformed sleep spindles. Upon reviewing the evidence, the authors concluded that even though the same cortico-thalamo-cortical network underlies both spike-wave discharges and sleep spindles, the ''initiation site'' of the activity is different with spike-wave discharges originating from the cortex and sleep spindles from the thalamus (Leresche et al., 2011).

The thalamus is involved in all of the proposed mechanisms of absence seizures. Animal experiments provide evidence supporting this, where thalamic stimulation has been shown to generate generalized, synchronous, cortical rhythms, and behavioral changes resembling ''petit mal'' and ''grand mal'' attacks in humans (Morison & Dempsey, 1941). Laws et al. reported depth electrode EEG findings in a 14-year-old female adolescent with ''petit mal'' and ''grand mal'' seizures. The typical 3-Hz spike-wave bursts were recorded synchronously from the scalp as well as depth electrodes in the thalamus (Laws et al., 1970). More recently, simultaneous recordings of EEG and fMRI have demonstrated the involvement of the thalamus during GSW activity (Moeller et al., 2011).

Although there is an emerging consensus that both the cortex and the thalamus are involved in the generation of spike-wave complex, their relative importance and the site of initiation remain contentious. Mostly animal and limited human data support the hypothesis that SWDs originate from the cortex. There is robust evidence from in vivo studies involving two rat genetic models of absence epilepsy: the Genetic Absence Epilepsy Rats from Strasbourg (GAERS) and the Wistar Albino Glaxo/Rijswijk (WAG/Rij). Meeren et al. (2002) demonstrated in the WAG/Rij model, a cortical focus within the perioral region of the somatosensory cortex leads the thalamus by a mean time of 8.1 ms during the first 500 ms of an absence seizure. Other researchers have reported concordant findings in the GAERS model (Polack et al., 2007). Using stereoelectroencephalography in humans, Bancaud and Talairach demonstrated that stimulation of the mesial frontal cortex could induce electrographic generalized SWDs as well as clinical absences and generalized tonic–clonic seizures (Bancaud et al., 1974).

Conversely, some animal studies have demonstrated initiation of spike-wave activity in the thalamus (Seidenbecher et al., 1998; Inoue et al., 1993). Other researchers have interpreted these findings as a misrepresentation due to cortical recordings being done at distant sites from the typical facial focus in the somatosensory cortex (Meeren et al., 2005). Studies involving feline generalized penicillin epilepsy (FGPE) model (Avoli & Gloor, 1982) as well as GAERS model (Danober et al., 1998) have demonstrated that both thalamus and cortex with their interconnections are needed to generate spike-wave complexes. On the basis of this wide-ranging evidence, the emerging consensus is that although some forms of spike-wave activity can originate from cortex or thalamus, an intact thalamocortical circuitry is required for the generation of typical spike-wave discharges (Blumenfeld, 2005a). According to the cortical focus theory, it is postulated that spike-wave activity is rapidly synchronized by propagating via cortico-cortical networks from the focal cortical site of origin and the thalamocortical loop functions as an oscillatory network with the two structures driving each other resulting in amplification and sustenance of the discharges (Meeren et al., 2005).

There is evidence for selective involvement of certain thalamocortical networks during GSW discharges. Electrical field mapping of GSW activity has demonstrated the field maximum over the frontal regions (Rodin & Ancheta, 1987). In absence seizures the ictal onset is characterized by activation of dorsolateral frontal or orbital frontal regions based on EEG source analysis (Holmes et al., 2004a). A recent EEG–fMRI study has demonstrated activation of thalamus, frontomesial cortex, and cerebellum related to GSW discharges (Moeller et al., 2011).

At cellular level, ion channels and receptors play a key role in the interplay between excitatory and inhibitory neurons involved in the generation of the spike-wave complex (Blumenfeld, 2005a). It is conceivable that genetic mutations affecting various ion channels and receptors form the foundation to understand the cellular mechanisms of GSW discharges. The spectrum of inherited epilepsies due to such mutations ranges from monogenic epilepsies to those with complex inheritance. Mutations involving sodium channels (SCN1B, SCN1A), chloride channels (CLCN2), calcium channels (CACNA1H), and γ-aminobutyric acid $(GABA)_A$ receptors (GABRG2, GABRA1, GABRD) have been described in IGE (Reid et al., 2009). In the GAERS model, *N*-methyl-D-aspartate (NMDA)–dependent mechanisms

have been demonstrated in the cerebral cortex (Pumain et al., 1992).

The Morphology and Topography of the Spike-Wave Complex

Gibbs et al. (1935) provided the first classic description of the spike-wave discharge. In a meticulous morphologic analysis of EEGs from 200 patients with "centrencephalic epilepsy," Weir (1965) found that the spike of spike-wave complex consisted of three components: spike 1, positive transient, and spike 2. The first component, spike 1, is negative in polarity, small in amplitude (25–50 μV), and short in duration (about 10 ms). It is followed by a positive transient lasting 100–150 ms, which continues into spike 2, the main negative component of this complex lasting 30–60 ms. The amplitude is maximum over the frontal regions and tends to wax and wane in a sequence with the maximum at the onset of the spike-wave rhythm. This spike complex is followed by a dome-shaped surface negative wave lasting 150–200 ms (Weir, 1965) (Fig. 1).

Computer-generated, three-dimensional, field potential maps were used to study the topographic evolution of spike-wave complexes. It was found that spikes had the highest amplitude at anterior and midline electrodes over the frontal region. The pattern of distribution revealed that spike and trough were often seen over the anterior and central regions, whereas waves were usually centrally distributed (Lemieux & Blume, 1986). In a computer-aided analysis of the electrical fields of spike-wave complexes during absence seizures, the field maxima was consistently found at Fz electrode spreading laterally to F3, F4 and posteriorly to Cz electrodes. The negative spike (spike 2 of Weir) originated from the frontal region involving FP1, F3 or FP2, F4 electrodes and spreading within 5 ms to the midline and the opposite hemisphere. The negative slow wave was seen to originate frontally as well as posteriorly (Rodin & Ancheta, 1987).

To fulfill diagnostic criteria in IGE, the epileptiform discharges need to occur on normal background activity, whereas in symptomatic generalized epilepsies the background is typically disorganized and slow (Markand, 2003a).

Bisynchronous, symmetrical, generalized, regular spike-wave discharges and polyspike-wave discharges are the typical findings in IGE. However, some atypical features are often encountered. This includes focalities, asymmetries, and "irregular" spike-wave activity defined as generalized paroxysms of spikes or spike-wave discharges with an irregular frequency of 3–5 Hz (Markand, 2003a) (Fig. 2).

Provoking and Confounding Factors Affecting the EEG

Arousal, sleep, and sleep deprivation

Circadian variations of seizure occurrence have been known since the early 20th century. Generalized spike-wave

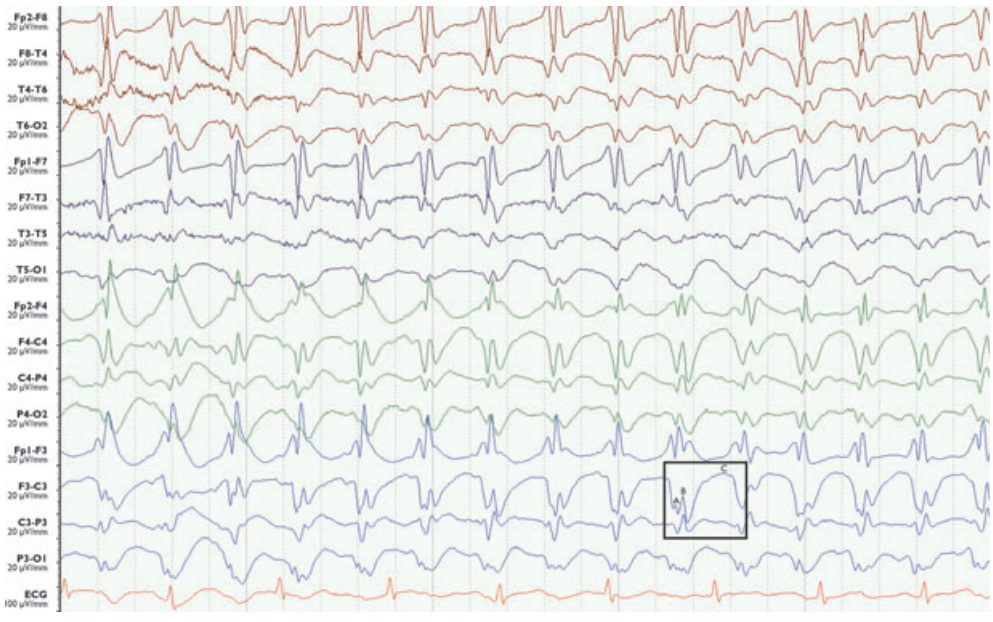

Figure 1.
Ictal electroencephalography of a typical absence seizure from a 13-year-old girl diagnosed with childhood absence epilepsy. Note the spike-wave morphology is best defined and of highest amplitude over the frontocentral regions. Inbox shows a spike-wave complex with typical morphology. A, spike 1 of Weir; B, spike 2; C, slow wave. Note spike 2 is more prominent and spike 1 is only rarely seen in the rest. High frequency filter = 70 Hz, low frequency filter = 0.5 Hz, sensitivity = 20 μV/mm, paper speed = 5 s/page.
Epilepsia © ILAE

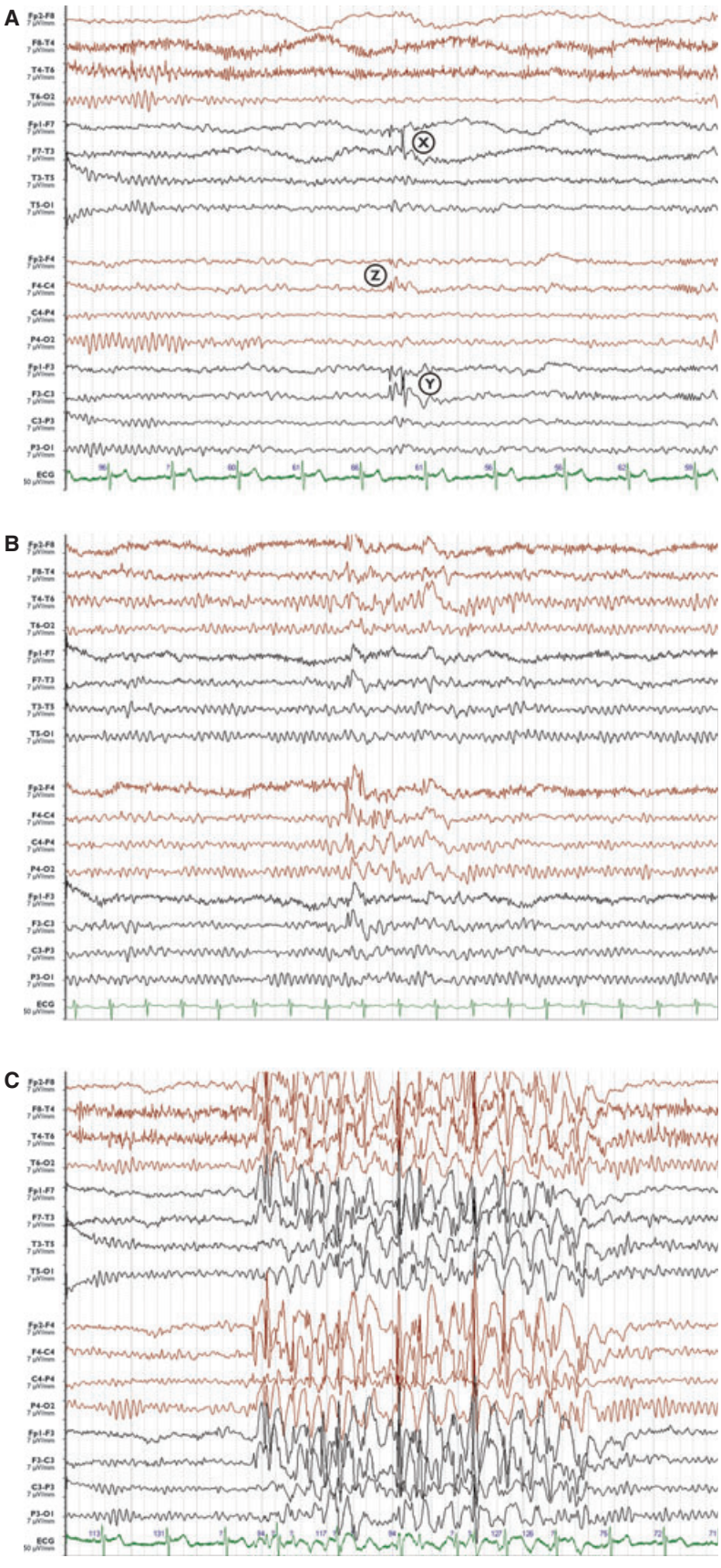

Figure 2.
Atypical electroencephalographic features of idiopathic generalized epilepsy. The electroencephalograph of a 23-year-old man diagnosed with idiopathic generalized epilepsy since age 16. (**A**) Focal discharges. Note focal spike-wave discharges over the left frontal region (X, Y). However, careful observation reveals subtle, low-amplitude activity over the right frontal region as well (Z). (**B**) Asymmetry and irregular discharges. Another segment of the electroencephalograph from the same patient demonstrates irregular discharges of higher amplitude over the right hemisphere with frontal maxima. (**C**) This electroencephalograph segment from the same subject shows more typical, generalized, spike-wave discharges.
Epilepsia © ILAE

activity is seen more often in sleep, but is less frequent in rapid eye movement (REM) sleep compared to non-REM sleep (Martins da Silva et al., 1984).

A more recent study conducted in a controlled laboratory environment using a ''forced desynchrony protocol'' (schedule of evenly distributed sleep/wake cycles) found a 14-fold higher number of generalized spike-wave discharges in non-REM sleep compared to wakefulness. Few discharges were seen in REM sleep. The researchers also noted some suggestion of a circadian variation of discharges independent of sleep–wake effect (Pavlova et al., 2009).

A significant increase in spike-wave discharge density in all states of vigilance is seen after sleep deprivation in patients with IGE (Halasz et al., 2002). In a cohort of patients who presented with the first seizure, generalized epileptiform discharges were seen in the first EEG of 68% of patients clinically diagnosed with generalized epilepsy, which increased by 75% following the addition of a sleep-deprived EEG, giving an overall yield of 92% (King et al., 1998).

The spike-wave complex seems to undergo morphologic changes during sleep. In non-REM sleep generalized spike-wave discharges occur in isolation or in shorter bursts with a slower (<3 Hz) frequency. In stage III and stage IV non-REM sleep, polyspikes and irregular spike-wave discharges occur at a slower frequency (<3 Hz). During that period the wave becomes longer in duration and distorted in morphology. In REM sleep, the discharges are rare yet similar in morphology to those in the waking state (Sato et al., 1973).

Timing and the duration of recording

In patients presenting with the first seizure, the EEG done within 24 h was found to have a higher yield of epileptiform abnormalities compared to late recordings (51% vs. 34%) (King et al., 1998). However, there are no other concordant studies with similar findings in the literature.

Given the paroxysmal nature of interictal epileptiform discharges, it is likely that the length of EEG recording could affect the yield. The mean time to the first generalized discharge was found to be 22 min, compared to 56 min for the first focal discharge (temporal) in sleep-deprived EEG of adult patients (age range 18–92). In the cohort, 70% of EEGs were done while the subject was on AEDs (Losey & Uber-Zak, 2008).

Hyperventilation

Historically, hyperventilation was the first activation method used in EEG. Hyperventilation was found to be more effective in activating seizures and interictal abnormalities in children with absence seizures (Dalby, 1969). Wirrell et al. (1996) found hyperventilation induced absence seizures in 67% of their patients. On the contrary, another series reported hyperventilation-induced seizures in only 0.46% and interictal epileptiform discharges in 4.4% (Holmes et al., 2004b). It should be noted that the study by Wirrell et al. involved children (mean age 9.3 years) with juvenile absence epilepsy and childhood absence epilepsy, whereas the other study had a mix of focal (88.7%) and generalized (11.3%) epilepsies in patients aged 10–64 years. In the latter study, among those diagnosed with generalized epilepsy only 50% had absence seizures. Therefore, the discrepancy in the yield could be due to the differences in activation by hyperventilation in generalized and focal epilepsies as well as IGE syndromes with and without absence seizures. Another potential factor for conflicting results could be methodologic differences, in particular lack of a universal protocol. The degree of hypocapnia and the decrease in cerebral blood flow appear to be crucial in inducing hyperventilation-related electrophysiologic abnormalities (Wirrell et al.,1996).

Photic stimulation

Photic stimulation is mostly useful in inducing generalized epileptiform discharges and rarely focal discharges. Photic driving is a normal physiologic response, whereas photoparoxysmal response (PPR) is an abnormal finding with intermittent photic stimulation (IPS). PPR is classified into three grades: posterior stimulus dependent response, posterior stimulus independent response, and generalized PPR either limited to the stimulus train or self-sustained (Kasteleijn-Nolst Trenite et al., 2001). The likelihood of having epilepsy in those with generalized PPR is 80–90%, based on a study from a tertiary center (Jayakar & Chiappa, 1990). This high value could be an overestimate due to selection bias. In a retrospective study, prolonged self-sustained PPR was associated with a significantly higher incidence of seizures compared to self-limited response, whereas both groups had a significantly higher incidence of seizures than age- and sex-matched controls (Puglia et al., 1992). However, the influence of antiepileptic drugs, age, epilepsy syndrome, and state were not taken into account in the analysis. Even though there appears to be a clear relationship between PPR and epilepsy, its strength and degree cannot be ascertained due to the lack of population-based data.

Photosensitivity is influenced by several confounding factors such as syndrome, age, gender, ethnicity, antiepileptic drug (AED) therapy, genetics, state of vigilance, sleep deprivation, and stimulation technique. PPR is most often seen in IGE (Kasteleijn-Nolst Trenite et al., 2001), and this association is most robust in juvenile myoclonic epilepsy (JME) (30.5%), followed by childhood absence epilepsy (CAE) (18%) and juvenile absence epilepsy (JAE) (7.5%) (Wolf & Goosses, 1986). PPR is more often seen in the younger age group, and the onset of photosensitivity is usually between 8 and 19 years (Harding & Jeavons, 1994). In 30%, PPR disappears without treatment at ages between 16 and 32 (mean 23.5) (Harding et al., 1997). Photosensitivity is more common in female patients (Kasteleijn-Nolst Trenité, 1989; Harding & Jeavons, 1994). The prevalence of

PPR was found to be significantly higher in the ethnic white population compared to black Africans (2.5% vs. 0.9%), reflecting ethnic differences (De Graaf et al., 1980). Sodium valproate therapy abolishes or improves photosensitivity in most patients (Harding & Jeavons, 1994). There is a genetic basis for PPR. A retrospective study on a proband with electrographic photosensitivity found positive PPR among 40% siblings and 15% parents (Waltz et al., 1992). Monozygotic twins demonstrate almost 100% concordance for PPR (Harding & Jeavons, 1994). Photosensitivity is markedly reduced in drowsiness as well as non-REM sleep and increased in REM sleep (Hishikawa et al., 1967). Sleep deprivation is a very potent trigger for PPR (Scollo-Lavizzari & Scollo-Lavizzari, 1974). There are many variables in the photic stimulation technique affecting the outcome (Harding & Jeavons, 1994), which highlight the difficulty in comparing different studies. It should also be noted that PPR could be seen in 0.5–5% individuals without a history of epilepsy (Kasteleijn-Nolst Trenite et al., 2001).

Fixation

Fixation-off sensitivity (FOS) is a rare EEG phenomenon characterized by occipital or generalized epileptiform discharges induced by elimination of central vision and fixation which is distinct from photosensitivity (Panayiotopoulos, 2005a). In the routine EEG, FOS manifests with epileptiform discharges that occur as long as the eyes remain closed and disappears as soon as they are opened. This could be confirmed by elimination of central vision and fixation with spherical lenses, underwater goggles covered with semitransparent tape, Frenzel lenses, or Ganzfeld stimulation technique (Koutroumanidis et al., 2009). This phenomenon should be differentiated from eye closure–related paroxysms characterized by epileptiform discharges appearing within 1–3 s of eye closure and lasting 1–4 s but not for the entire duration of eyes-closed period. Eye-closure sensitivity is usually related to photosensitivity (Panayiotopoulos, 2005a,b). First described by Panayiotopoulos in childhood occipital epilepsies, FOS was later found to occur in several other epilepsy syndromes including IGE (Koutroumanidis et al., 2009). FOS can coexist with photosensitivity in some patients (Agathonikou et al., 1998).

Reflex triggers

Some patients with IGE develop reflex seizures on exposure to specific stimuli. Although not tested routinely, there may be merit in recording the EEG with such stimuli as activating procedures in select patients.

Reflex seizures of the visual system are complex and could be seen in IGE as well as symptomatic generalized and occipital epilepsies (Zifkin & Kasteleijn-Nolst Trenite, 2000). Usual environmental triggers include flickering lights, television, and electronic screen games. Both photosensitivity and pattern sensitivity are linked to television- and video game–induced seizures. Pattern sensitivity is elicited by asking the subject to visually scan a pattern (usually a series of parallel black lines or stripes), which would trigger epileptiform paroxysms in the EEG (Radhakrishnan et al., 2005). In those with electrographic pattern sensitivity, ~90% demonstrate photoparoxysmal response as well (Radhakrishnan et al., 2005).

Reflex seizures due to nonverbal cognitive stimuli are induced by both thinking and praxis. Sensitivity to verbal cognitive stimuli includes reading, talking, and writing (Ferlazzo et al., 2005). Thinking-induced (noogenic) seizures are often caused by mental arithmetic and decision-making, whereas praxis-induced seizures are characterized by cognitive tasks in association with planned motor activity (usually involving hands) such as written calculations and spatial construction (Ferlazzo et al., 2005). This phenomenon can be tested by getting the subject to perform specific cognitive tasks during EEG recording.

Interictal versus Ictal Abnormalities: The Conundrum of Responsiveness

Interictal EEG abnormalities refer to ''epileptiform patterns occurring singly or in bursts lasting at most a few seconds'' as opposed to ictal abnormalities characterized by ''repetitive EEG discharges with relatively abrupt onset and termination and characteristic pattern of evolution lasting at least several seconds'' (Chatrian et al., 1974). When the EEG seizure pattern is not accompanied by clinical manifestations, it is classified as subclinical seizure activity (Chatrian et al., 1974). However, the distinction between interictal and ictal epileptiform activity becomes murky in IGE, in which the generalized epileptiform discharges are usually monomorphic. Hence the duration of epileptiform discharges that distinguishes interictal from subclinical ictal activity is debatable. Even more debatable is how to measure the impairment of consciousness defining clinical seizure activity in conjunction with electrographic changes.

Several researchers have attempted to study cognitive functions during generalized spike-wave discharges. Many testing paradigms ranging from repetitive motor tasks to higher function testing have been used to evaluate different domains of cognitive function during spike-wave activity (Blumenfeld, 2005b). Using reaction time as a measure of responsiveness, Porter et al. (1973) demonstrated that 56% of the responses were abnormal at the onset of spike-wave paroxysms of absence seizures, increasing to 80% at 0.5 s after the onset indicating impaired responsiveness. They did not find the duration of the paroxysm as a significant factor deciding responsiveness. Holmes et al. (1987) employed the operational definition of GSW or polyspike-wave activity lasting 3 s or more as an absence seizure, whereas a more recent study used 2 s as the cutoff (Sadleir et al., 2009).

Focal EEG Features in IGE

Even though the typical electrographic signature of IGE is generalized discharges, the existence of focal EEG features has been reported. In a large cohort of IGE patients, EEG focalities were found in 56% and localized to temporal regions in most (Lombroso, 1997). In a series of IGE patients studied with video-EEG, focal interictal epileptiform discharges and semiologic features of focal seizure onset were observed in 35%. However, no seizures with focal EEG onset were seen (Leutmezer et al., 2002). Other studies have reported EEG focalities in 30–55% of patients with JME (Panayiotopoulos et al., 1994). The reported frequency of focal or lateralized EEG abnormalities in patients with absence seizures ranges from 16–35% (Matur et al., 2009; Vierck et al., 2010). Based on the results of these studies, it appears that focal interictal EEG abnormalities are found among one third of patients with IGE. However, it should be noted that patient populations of these studies are heterogeneous and that the influence of potential confounding factors such as age, arousal state, and AED therapy are not specified.

Interictal EEG Abnormalities in Electroclinical Syndromes of IGE

The classification of IGE has been a focus of discussion and debate. While acknowledging the current changes taking place in the classification of epilepsies, in this review we use the 1989 International League Against Epilepsy (ILAE) classification (ILAE, 1989) and subsequent revision published in 2001 (Engel, 2001) for the purpose of describing EEG abnormalities in different electroclinical syndromes.

EEG abnormalities in IGE are affected by several internal and external factors including age, gender, state of vigilance, activation procedures, syndrome, and AED therapy to varying degrees (Table 1). A greater than75% reduction in the number of spike-wave discharges was prospectively recorded following sodium valproate therapy in 44% and 57% of patients, respectively (Villarreal et al., 1978; Bruni et al., 1980), whereas another study reported 100% improvement in 24% cases (Maheshwari & Jeavons, 1975). However, these results should be interpreted with caution as they were not based on 24-h recordings and thus missed the effect of circadian variations.

Interictal EEG in Childhood Absence Epilepsy (CAE)

CAE occurs in school age children and the EEG is characterized by bilateral, synchronous, symmetrical 3-Hz spike-wave discharges on a normal background (ILAE, 1989). Although the classic frequency is 3 Hz, variations with lower and higher frequencies are sometimes encountered (Sadleir et al., 2009). Fragments of generalized spike-wave discharges defined as brief (<2 s) epileptiform discharges with the morphology of GSW, which may not necessarily be generalized and not associated with clinical symptoms, are seen in 92% of cases (Sadleir et al., 2006). These discharges are more often seen in drowsiness and sleep. In the same study, interictal polyspikes were witnessed in 40%, which were confined to drowsiness and sleep. Another study found polyspike-wave discharges in 26% (Vierck et al., 2010).

Wolf & Goosses (1986) reported PPR in 18% of CAE patients, whereas it was found to be 44% in another study (Lu et al., 2008). This discrepancy could be due to population differences (mean age 16.8 vs. 5.5 years), AED therapy, sleep deprivation, IPS technique, and the classification of PPR.

Occipital intermittent rhythmic delta activity (OIRDA) (also described as rhythmic posterior bilateral delta activity) is another interictal abnormality described in CAE. It is characterized by symmetrical or asymmetrical bursts of rhythmic, sinusoidal, 3-Hz, delta activity over the occipital region, which is attenuated by eye opening and deep stages of sleep while enhanced by hyperventilation and drowsiness (Riviello & Foley, 1992). Sadleir et al. (2006) reported posterior bilateral delta activity in 32% of CAE subjects of which in 40% there was a notched appearance. In a series of 54 children with OIRDA in the EEG, epilepsy was diagnosed in 81%, of which 83% had generalized epilepsy, although syndromic classification was not provided (Riviello & Foley, 1992). OIRDA is not specific to CAE. Studies indicate that it is an EEG abnormality seen in children, associated more commonly with seizures (generalized epilepsy being the most frequent etiology) and occasionally with encephalopathies (Riviello & Foley, 1992).

Interictal EEG in Juvenile Absence Epilepsy (JAE)

JAE presents around puberty (10–17 years) with less frequent absence seizures compared to CAE. Generalized tonic–clonic seizures (GTCS) more often precede absences, and myoclonus occurs more commonly than in CAE (ILAE, 1989; Wolf, 1992). The morphology of spike-wave discharges in JAE is no different from that in CAE. However, the frequency of spike-wave discharges in JAE may be faster (3.5–4 Hz) than in CAE (ILAE, 1989; Wolf, 1992). PPR is less frequent than in CAE (7.5% vs. 18%) (Wolf & Goosses, 1986). However, different results have been reported by other authors: 18% in both syndromes (Waltz et al., 1990) and more often in JAE than CAE (56% vs. 44%) (Lu et al., 2008). These observed discrepancies may be due to population and methodologic differences between the studies. As in CAE, polyspikes are seen only during drowsiness and sleep (Sadleir et al., 2009).

Table 1. Variables affecting the interictal electroencephalographic characteristics

Characteristic	Feature	Variable	Description	References
GSW discharges	Density	State	NREM sleep > awake > REM sleep	Martins da Silva et al. (1984); Kellaway et al. (1980); Pavlova et al. (2009)
		Sleep deprivation	Increased in awake and NREM sleep following sleep deprivation	Halasz et al. (2002)
		Postictal <24 h	Increased	King et al. (1998)
		HV	Increased	Dalby (1969)
		Circadian rhythm	Increased on awakening	Fittipaldi et al. (2001)
		Drug therapy	Reduced by valproate	Maheshwari & Jeavons (1975); Villarreal et al. (1978); Bruni et al. (1980)
	Morphology and frequency	State	NREM sleep: isolated complexes or short bursts of <3 Hz, irregular GSW discharges, slow wave longer and distorted REM sleep and wake: isolated complexes rare, long bursts, regular GSW discharges, well rounded slow wave	Sato et al. (1973)
		Syndrome	CAE: 3 Hz; JAE: 3.5–4 Hz; JME: >3.5 Hz; MAE: 2–3 Hz; POMA: 4–7 Hz	Delgado-Escueta & Enrile-Bacsal (1984); Panayiotopoulos (2005a,b); Doose (1992); Wolf (1992); Sadleir et al. (2006, 2009)
PS and PSW	Density	State and syndrome	CAE and JAE: only during drowsiness and sleep; JME: during all states	Bartolomei et al. (1997); Sadleir et al. (2006, 2009); Vierck et al. (2010)
PPR	Frequency and density	Gender	Female > male	Kasteleijn-Nolst Trenite (1989); Harding & Jeavons (1994)
		Age	Onset 8–19 years; more common in young	Klass (1964); Harding & Jeavons (1994)
		Ethnicity	White > black	De Graaf et al. (1980)
		Drug therapy	Reduced by valproate	Harding & Jeavons (1994)
		Syndrome	JME > CAE > JAE	Wolf & Goosses (1986)
		State	Reduced in drowsiness and NREM sleep	Rodin et al. (1955); Hishikawa et al. (1967)
		Sleep deprivation	Increased after sleep deprivation	Scollo-Lavizzari & Scollo-Lavizzari (1974)
		IPS technique	Vary depending on type of stroboscope, frequency of stimulation, duration of IPS, light intensity, distance from subject, diffusion of light, eyes open or closed, mono- or bi-ocular stimulation, background illumination, color of light, direction of gaze, angle of illumination	Harding & Jeavons (1994)

CAE, childhood absence epilepsy; GSW, generalized spike-wave; HV, hyperventilation; IPS, intermittent photic stimulation; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; MAE, myoclonic astatic epilepsy; NREM, non–rapid eye movement; POMA, perioral myoclonia with absences; PPR, photoparoxysmal response; PS, polyspike; PSW, polyspike-wave.

Interictal EEG in Juvenile Myoclonic Epilepsy (JME)

JME appears at around puberty (ages 12–18) and the phenotypic hallmark is myoclonic jerks predominantly in the arms. Most patients experience GTCS but absence seizures are less common (ILAE, 1989). Seizures, in particular myoclonus, usually occur shortly after awakening and are often provoked by sleep deprivation and alcohol (Delgado-Escueta & Enrile-Bacsal, 1984).

Generalized polyspikes and polyspike-wave discharges are the electrographic signatures of JME, which can sometimes be fragmented and confined to frontal regions (Delgado-Escueta & Enrile-Bacsal, 1984; Hrachovy & Frost, 2006). Those bursts appear at a frequency of 3.5–6 Hz (Delgado-Escueta & Enrile-Bacsal, 1984). Generalized ''fast'' spike-wave activity (>3.5 Hz) is also often seen, although classic 2.5–3.5 Hz GSW discharges are less common (Delgado-Escueta & Enrile-Bacsal, 1984; Montalenti et al., 2001; Hrachovy & Frost, 2006). The interictal EEG appears as an irregular mix of 3–6 Hz spike/polyspike-waves with intradischarge fragmentations (Panayiotopoulos, 2005a,b). Focal EEG abnormalities are not uncommon (Panayiotopoulos et al., 1994).

Janz (1985) in his original work on JME noted that seizures tended to occur soon after waking and sleep

deprivation was a potent trigger. Subsequent EEG studies have shed more light on the relationship between JME and the sleep–wake cycle. In a series of 24-h ambulatory EEG recordings from 1,000 patients with epilepsy, epileptiform discharges on awakening were found in 4.6%, all of whom were diagnosed with IGE. Most notably, in JME the discharges appeared between 20 and 50 min after awakening (Fittipaldi et al., 2001). In another study on JME, it was shown that routine EEG (without prior sleep deprivation) done in the morning had a significantly higher pickup rate of epileptiform abnormalities compared to those done in the afternoon (Labate et al., 2007). Sleep-EEG showed generalized epileptiform discharges in all JME patients in another series (Dhanuka et al., 2001).

Studies on sleep microstructure in non-REM sleep and epileptiform discharges (ED) in JME highlight the importance of arousals in the generation of ED. The cyclic alternating pattern (CAP) is characterized by periodic EEG desynchronization pattern in non-REM sleep related to fluctuations in the level of arousal, which is further subdivided into two phases with greater (phase A) and lesser (phase B) arousal (Terzano et al., 1985). During non-REM sleep, JME patients express the maximum rate of ED in CAP phase A and the minimum during phase B, whereas it is intermediate during non-CAP periods (Gigli et al., 1992). Another study has demonstrated a bidirectional relationship between ED and sleep instability in JME. Most of ED is seen during CAP periods, whereas the discharges in turn seem to increase CAP rate indicating increased sleep instability (Bonakis & Koutroumanidis, 2009).

Interictal polyspikes are seen in 50% of patients. The discharges appear in all three states (wake, drowsy, sleep) in contrast to CAE and JAE where polyspikes are not seen during wakefulness (Sadleir et al., 2009).

Hyperventilation appears to be a strong provoking factor for ED and abnormalities were found during hyperventilation in all JME patients in a series (Panayiotopoulos et al., 1994). However, those abnormalities were found to be only 30.2% in a different study (Montalenti et al., 2001). The latter was conducted on drug-naive patients, but the technique of hyperventilation is not detailed in the article, which could account for this discrepancy.

PPR is demonstrated in approximately one third of patients (Wolf & Goosses, 1986; Montalenti et al., 2001). FOS as well as eye-closure sensitivity has been reported in JME (Panayiotopoulos et al., 1994).

Interictal EEG in Epilepsy with Grand Mal Seizures on Awakening (EGMA)

EGMA is defined as an epilepsy syndrome with the onset during the second decade characterized by GTCS occurring in two phases: exclusively or predominantly after awakening (irrespective of time) and in the evening hours of relaxation (ILAE, 1989; Janz, 2000). However, some authors have queried a possible overlap with JME based on genetic linkage studies (Greenberg et al., 1995). This syndrome was subsequently expanded as ‘‘epilepsy with generalized tonic-clonic seizures only’’ in the revision to the 1989 classification published in 2001 (Engel, 2001). Early studies found GSW discharges in 41% of patients and rare (2.6%) focal abnormalities (Janz, 2000), whereas higher figures (GSW in 89% and focal in 3%) were reported later (Unterberger et al., 2001). Another group found GSW discharges in the first EEG of 89% increasing to 100% with the second EEG following sleep deprivation. They also reported polyspikes in 33% and PPR in 28% (Koutroumanidis et al., 2008). In the last study, prolonged EEG recordings with multiple sessions of hyperventilation were done following sleep deprivation, which may account for the higher yield.

Interictal EEG in Epilepsy with Myoclonic Absences (EMA)

EMA is a rare IGE syndrome of childhood with a mean age of onset 7 years and male preponderance (ILAE, 1989). Patients classically present with frequent absences accompanied by bilateral rhythmic myoclonic jerks involving shoulders, arms, and legs. Myoclonia is often associated with underlying progressive tonic contraction of the muscles causing progressive elevation of upper limbs. Myoclonic absences typically have an abrupt onset and offset lasting 10–60 s. In two-thirds of patients other seizure types such as GTCS and typical absences are observed (Bureau & Tassinari, 2005). The idiopathic group needs to be differentiated from symptomatic cases (Engel, 2001).

The interictal EEG shows GSW discharges in one third of cases. Focal abnormalities are rare. Myoclonic absences are often provoked by hyperventilation, drowsiness and awakening from light sleep. IPS triggers myoclonic absences in 14%, although PPR is not reported (Bureau & Tassinari, 2005).

Interictal EEG in Epilepsy with Myoclonic-Astatic Seizures (Doose Syndrome)

Although initially considered to be a symptomatic generalized epilepsy (ILAE, 1989), this was later reclassified as an IGE syndrome by the ILAE task force (Engel, 2001), in keeping with the view of Doose who published the first descriptions of the syndrome (Doose, 1992). However, care should be taken to differentiate the idiopathic group from symptomatic cases and epileptic encephalopathies. In this article, we confine our discussion to idiopathic myoclonic-astatic epilepsy.

This condition has an onset between 7 months and 6 years in children with previously normal development.

Myoclonic–astatic (or atonic) seizure is the semiologic signature of the syndrome, although multiple seizure types such as myoclonic, atonic, tonic, absence, GTCS, and status epilepticus are also seen (Doose, 1992).

At the onset, the interictal EEG may be normal or show rhythmic theta activity over the parietal region as well as rhythmic 4-Hz delta activity over the occipital region attenuating on eye opening. GSW of 2–3 Hz appears subsequently. These discharges are usually irregular in shape or interrupted by high amplitude slow waves when discharges occur in rhythmic clusters. Focalities (pseudofoci) are often seen, which usually keep changing laterality from side to side. Bursts of polyspike-wave complexes are typically seen in patients with myoclonic seizures. PPR is common particularly between 5 and 15 years of age (Doose, 1992).

IGE Subgroups Not Recognized by ILAE

Several authors have reported groups of IGE patient with specific characteristics, some of which may fit into distinct subsyndromes although not yet included in the ILAE classification. These groups include perioral myoclonia with absences, IGE with phantom absences, eyelid myoclonia with absences (Jeavons syndrome), and adult-onset IGE.

Perioral myoclonia with absences is a rare condition characterized by brief typical absences accompanied with perioral rhythmic myoclonic movements and rarely jaw jerking due to masticatory muscle involvement lasting 2–9 s (mean 4). The age of onset is 2–13 years and all patients experience infrequent GTCS as well. Absence status epilepticus is common. The interictal EEG shows brief 4–7 Hz spike-wave and polyspike-wave discharges, usually asymmetrical, as well as focal discharges (Panayiotopoulos, 2005a,b).

IGE with phantom absences was proposed as a distinct syndrome by Panayiotopoulos to identify a group of IGE patients presenting with the first GTCS in adulthood and prior absences which were inconspicuous. Absence status epilepticus is common among these patients. Interictal EEG abnormalities are seen in 50% characterized by brief, 3–4 Hz GSW discharges, polyspikes, as well as focal discharges occurring independently or in association with generalized discharges (Panayiotopoulos, 2005a,b). Polyspikes are more common compared with IGE with GTCS only (80% vs. 33%) and PPR is seen in 13.5% (Koutroumanidis et al., 2008).

The semiologic hallmark of Jeavons syndrome is eyelid myoclonia with or without absences in association with seizures and/or EEG paroxysms triggered by eye closure as well as photosensitivity, typically presenting in childhood (Jeavons, 1977; Panayiotopoulos, 2005a,b). The EEG classically shows brief paroxysms of high amplitude 3–6 Hz GSW and polyspike-wave discharges related to eye closure in an illuminated environment and abolished in darkness (Panayiotopoulos, 2005a,b). These discharges are often accompanied by eyelid myoclonia. Hyperventilation often triggers typical discharges (Panayiotopoulos, 2005a,b). PPR is seen in all young patients, which decreases with age and AED therapy (Panayiotopoulos, 2005a,b). Photosensitivity and FOS may coexist in some patients (Ogura et al., 2005).

Adult-onset IGE, arbitrarily defined as seizure onset over the age 18–20 years, has been described as a separate entity. Paroxysmal slow activity and frontal predominance of GSW discharges were found more commonly in classic IGE in comparison to adult-onset IGE, which, however, did not reach significance with statistical correction (Yenjun et al., 2003). Overall, there does not appear to be any difference in EEG characteristics between the two groups (Yenjun et al., 2003). Apart from the age of onset, there are no significant differences from classical IGE to recognize this entity as a distinct syndrome (Reichsoellner et al., 2010).

Caveats and Pitfalls in the Recognition of Interictal Discharges

Focal versus generalized epilepsies

Interictal discharges of IGE need to be differentiated from those of focal epilepsies. This distinction depends primarily on the distribution and morphology of discharges along with the response to provoking stimuli. In focal epilepsies, interictal discharges usually demonstrate a typical field depending on the dipole orientation of the source. Spikes, sharp waves, spike-wave complexes, sharp-and-slow-wave complexes, polyspikes, polyspike-wave complexes, and paroxysmal fast activity have been reported as interictal abnormalities in focal epilepsies (Westmoreland, 1998; Noachtar et al., 2008). The amplitude ratio of slow wave and spike (slow wave/spike amplitude) appear to be helpful in this distinction. In IGE this ratio is >1, which increases significantly during sleep as opposed to focal epilepsies where the ratio is <1, which does not change in sleep (Terney et al., 2010).

Secondary bilateral synchrony is an EEG phenomenon of focal epilepsy that could be mistaken for IGE paroxysms. It is described as bilaterally synchronous, generalized epileptiform paroxysms driven by preceding focal discharges. Secondary bilateral synchrony is distinguished from GSW discharges of IGE by the presence of focal triggering spikes with a different morphology and at least 2-s of lead-in time (Blume & Pillay, 1985).

Despite having classic differences, distinguishing generalized from focal epileptiform discharges is not always straightforward. Focal discharges seen in IGE, as highlighted in a previous section, could be misleading at times. Some form of focal onset is seen in the EEG of absence seizures in 50% (Sadleir et al., 2006), which may cast some doubt about the diagnosis. Patients with focal epilepsy due to parasagittal lesions are known to demonstrate bilaterally

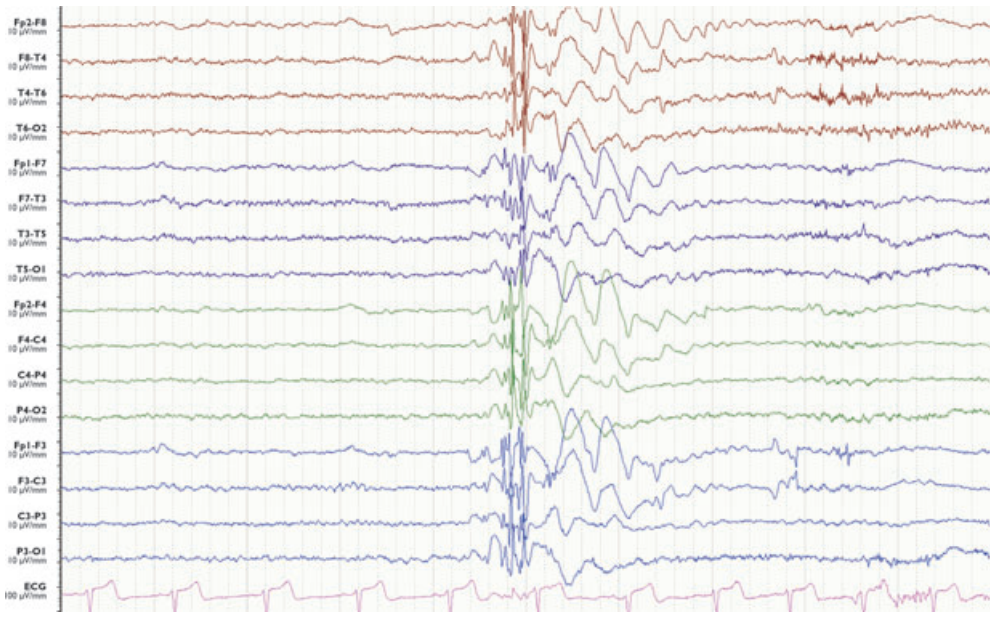

Figure 3.
Ictal electroencephalography of a myoclonic seizure in a 15-year-old boy diagnosed with juvenile myoclonic epilepsy. Note high amplitude, generalized polyspikes with frontocentral accentuation followed by 2.5 Hz slow waves.
Epilepsia © ILAE

synchronous SWD in the EEG due to secondary bilateral synchrony (Tukel & Jasper, 1952). Given these potential pitfalls, one has to carefully evaluate all the data including clinical details, neuroimaging, and EEG in arriving at the final diagnosis.

Symptomatic generalized epilepsies (SGE)

Slow spike-wave discharge is the typical EEG feature of SGE. Compared to classic spike-wave discharge in IGE, it occurs at a slower frequency (1.5–2.5 Hz) and shows irregularities in frequency, amplitude, morphology, as well as distribution within and between paroxysms. Other interictal electrographic features include background slowing, coexistent focal/multifocal discharges, and generalized paroxysmal fast activity (Markand, 2003a,b).

Benign variants

Epileptiform discharges should be differentiated from various normal, nonepileptiform variants such as ''phantom spike and wave'' discharges and ''small sharp spikes,'' the discussion of which is beyond the scope of this article.

Ictal EEG of Myoclonic Seizures

The classic phenotype of myoclonic seizures is seen in JME, which is electrographically characterized by high amplitude, generalized, polyspike activity with frontocentral accentuation occurring at a frequency of 10–16 Hz (Delgado-Escueta & Enrile-Bacsal, 1984; Janz, 1985). The EEG activity may outlast the clinical seizure by several seconds (Janz, 1985; Hrachovy & Frost, 2006). Ictal discharges are sometimes preceded by irregular 2–5 Hz GSW complexes and followed by irregular 1–3 Hz slow waves (Delgado-Escueta & Enrile-Bacsal, 1984; Janz, 1985; Hrachovy & Frost, 2006) (Fig. 3).

In epilepsy with myoclonic-astatic seizures, myoclonic jerks are associated with fast (>2.5–3 Hz), generalized, polyspike-wave discharges or spike-wave complexes with simultaneous activation of both flexor and extensor muscles of the body on polygraphic recordings (Oguni et al., 2001; Panayiotopoulos, 2005a,b). Positive-negative-deep positive spike followed by large negative slow wave is the signature of atonic seizures (Oguni et al., 2001). The negative slow wave corresponds with the loss of muscle tone, and the degree of atonia seems to correlate with the amplitude of the second positive component of the spike-wave complex (Oguni et al., 2001).

Ictal EEG of Absence Seizures in CAE, JAE, and JME

Typical absence seizures are seen in several IGE syndromes, which are electrographically characterized by bilateral, symmetrical, and synchronous 3-Hz spike-wave discharges on a normal background (ILAE, 1989; Drury & Henry, 1993) (Fig. 1). This is best described as a monomorphic ictal rhythm. Certain differences between syndromes have been described.

Sadleir et al. defined discharges lasting longer than 2 s or shorter than 2 s if accompanied by clinical correlates as ictal EEG in absence seizures. In their cohort of CAE, the initial ictal discharge was nongeneralized in 50% of seizures, which would last an average of 0.5 s before generalization. In 50% of seizures the initial generalized discharge had typical spike-wave morphology, whereas in others it consisted of single spike, polyspikes, or atypical, irregular GSW discharges becoming typical GSW discharges after an average of 0.7 s. Seizures without regular GSW were rare. The spike-wave complex consisted of one or two spikes per wave in the majority. However, those with a PPR often tended to have three or more spikes per wave. The initial frequency of GSW discharges ranged from 2.5 to 5 Hz (median 3 Hz). The offset showed irregular and nongeneralized discharges in 42% of seizures. Hyperventilation and IPS induced absence seizures in 83% and 21%, respectively. The average seizure duration was 9.4 s (Sadleir et al., 2006). They were also able to demonstrate that EEG features of absence seizures were affected by several factors including age, epilepsy syndrome and the state of alertness (Sadleir et al., 2009) (Table 1).

Frequency of GSW discharges

The median initial frequency (in the first second) of GSW is the highest for absence seizures in JME at 3.5 Hz followed by JAE (3.25 Hz) and CAE (3 Hz) (Sadleir et al., 2009). In all syndromes the initial frequency of the paroxysm tends to be faster and then becomes more regular and slower by 0.4–0.6 Hz. In the terminal phase it slows down again in CAE and JAE (Panayiotopoulos et al., 1989).

Epileptiform discharge morphology and duration

The morphology of discharges during absence seizures in JME resembles compressed ''W''s due to multiple spikes preceding or overlapping the slow waves (Panayiotopoulos et al., 1989). The electrographic seizure duration is shorter in JME compared to CAE and JAE (Panayiotopoulos et al., 1989; Sadleir et al., 2008). In general, seizures tend to be shorter during sleep and IPS, whereas longer during hyperventilation (Sadleir et al., 2008).

A significantly greater number of spikes per wave is seen in JME and JAE than CAE. More spikes are seen in IPS-induced absence seizures compared with hyperventilation or state of arousal. However, the number of spikes does not seem to depend on age, seizure duration, presence of clinical signs, or the level of arousal. There appear to be significant variations in the number of spikes between different individuals, raising the possibility of influence by individual-specific intrinsic factors (Sadleir et al., 2009).

Organization of discharges

Epileptiform discharges in absence seizures are usually well organized in the form of a regular, rhythmic, ictal pattern. Sometimes they could be disorganized, which is defined as disruption of the regular rhythmic ictal discharges by slow waves or complexes of different frequency and/or morphology or brief (<1 s), transient interruptions of seizure discharges (Sadleir et al., 2009). JME is more likely to show disorganized ictal discharges, followed by JAE and CAE (Panayiotopoulos et al., 1989; Sadleir et al., 2009). Hyperventilation produces more organized discharges compared with IPS (Sadleir et al., 2009). The level of arousal also has an influence, and organized discharges are more common in the awake state, followed by drowsiness and sleep. With advancing age, the discharges become organized more often; this is not influenced by seizure duration (Sadleir et al., 2009).

Ictal EEG of Absence Seizures in Other IGE Syndromes

In EMA the ictal EEG shows regular, rhythmic, bisynchronous, 3 Hz spike-wave discharges usually with abrupt onset and offset. Sometimes there are admixed polyspikes. Polygraphic recording demonstrates that each spike is followed by rhythmic myoclonus on the electromyographic channel, subsequently superimposing on progressive tonic contraction predominantly involving the shoulder and deltoid muscles (Bureau & Tassinari, 2005).

In perioral myoclonia with absences, the ictal EEG shows 3–4 Hz generalized spike-wave and polyspike wave discharges, which are often irregular and disorganized (Panayiotopoulos, 2005a,b). The ictal EEG of phantom absences is characterized by brief (<5 s), 3–4 Hz, generalized spike/polyspike-wave discharges that are occasionally disorganized (Panayiotopoulos, 2005a,b).

Ictal EEG of GTCS in IGE

Studying the ictal EEG of GTCS is made difficult by high-frequency muscle artifact, unless the patient is paralyzed with muscle relaxants as may happen in the intensive care setting. The use of appropriate high-frequency digital filters to remove muscle artifact can help visualize underlying EEG rhythms at seizure onset in routine recordings.

The ictal onset is often marked by bursts of generalized polyspike-wave discharges associated with myoclonic jerks semiologically. This is followed by generalized voltage attenuation with or without superimposition of low voltage, 20–40 Hz fast activity in all leads lasting a few seconds. The attenuation marks the beginning of tonic phase clinically. The next electrographic phase is characterized by generalized, rhythmic activity of alpha frequency (10–12 Hz), which progressively increases in amplitude (epileptic recruiting rhythm). Semiologically, tonic phase continues with this activity. This is followed by gradual slowing of frequency from theta to delta range with associated gradual increment in amplitude. When the frequency slows down to 4 Hz, it

becomes admixed with repetitive polyspike-wave complexes corresponding to clonic and myoclonic activity semiologically. These bursts become intermittent with background suppression in between as the seizure activity progresses. When the clonic activity ceases, the EEG shows generalized voltage suppression for a variable period. Cerebral activity gradually returns, which is initially characterized by irregular, generalized, delta activity gradually progressing to theta and then alpha range signifying the restoration of normal background rhythm (Hrachovy & Frost, 2006) (Fig. S1).

Gaps in Current Knowledge and Future Directions

As highlighted in this review, there are several confounding variables, particularly circadian and AED treatment, affecting the EEG features of IGE. In addition, among published studies, there is no uniformity in recording the EEG with respect to duration and provoking stimuli (sleep deprivation, IPS, hyperventilation, fixation-off ,and reflex triggers) (Table S1). These differences need consideration when interpreting and comparing different studies. Future studies using a prospective design in untreated populations with standardized methods would greatly improve our diagnostic, phenotypic, and prognostic understanding of IGE.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Ictal electroencephalography of a generalized tonic–clonic seizure in a 26-year-old man diagnosed with juvenile myoclonic epilepsy.

Table S1. Characteristic features of electroencephalographic studies in idiopathic generalized epilepsy (with additional references).

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