

Idiopathic generalised epilepsies of adult onset: a reappraisal and literature review*

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ABSTRACT – Idiopathic generalised epilepsies are characterised by widespread, symmetric, bilateral spike-and-wave discharges on EEG. Onset typically occurs in children and adolescents, but may also start in adulthood. These forms of adult onset constitute the focus of this review. A critical analysis of the medical literature was conducted through a narrative review search of PubMed and Medline databases. Cases of idiopathic generalised epilepsies with adult onset, in general, are not considered to be independent nosological entities. The “grand mal on awakening” seems to prevail among the idiopathic syndromes of adult onset. The EEG findings that question the diagnosis of late-onset idiopathic generalised epilepsies consist mainly of patterns interpreted as representing focal epileptiform activity. Normal brain MRI and typical EEG abnormalities are essential for diagnosis. For all cases with symptomatology of suspected adult-onset idiopathic generalised epilepsy, it is mandatory to exclude neurological conditions that may be associated with epileptic seizures which appear in this age group. A correct diagnosis of adult-onset idiopathic generalised epilepsy alleviates concern for a symptomatic origin, leading to appropriate antiepileptic treatment.

Key words: idiopathic (genetic) generalised epilepsy, late-onset generalised epilepsy, juvenile myoclonic epilepsy, grand mal seizures on awakening, nosology of the epilepsies

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The main focus of this review concerns adult-onset idiopathic generalised epilepsies (IGE). According to the most recent position paper of the ILAE (Scheffer *et al.*, 2017), which is referred to in this manuscript, it would be more precise to use the term “genetic” rather than “idiopathic” epilepsy, in order to convey the idea that these epilepsies have a “known or presumed genetic defect”. Nonetheless, the same paper stated that the term “IGE” is also acceptable, due to its widespread clinical use, specifically for four epilepsy syndromes: childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and generalised tonic-clonic seizures alone (GTCS). These syndromes are typically diagnosed in childhood and adolescence, with a good prognosis over time, however, there is a need to maintain anticonvulsants for some patients (ILAE, 1989; Loiseau *et al.*, 1991; Wolf, 2005). According to Jallon and Latour (Jallon and Latour, 2005), IGE affects approximately 15-20% of all patients with epilepsy (children and adults). Regarding adult-onset IGE, the specific topic of this review, this is classically viewed as rare. However, a few different studies have demonstrated a non-negligible, variable prevalence of 8.5 to 28%, considering the global population with IGE (Cutting *et al.*, 2001; Marini *et al.*, 2003; Nicolson *et al.*, 2004).

The interest in this topic reflects the need to discuss recent advances in neuroimaging and neurophysiology that might bring new insights to the concept of generalised epilepsies. This literature review aims to highlight the evidence of late-onset IGE by describing clinical and EEG characteristics of adult patients with IGE, regardless of age at onset. Finally, specific aspects of the differential diagnosis of IGE in the adult are discussed.

Material and methods

Literature search

We carried out a literature search respecting the main theme of this study using Pubmed and Medline databases up to October 2017. The search was performed with the following terms: “adult-onset IGE”, “adult-onset genetic epilepsy”, “late-onset IGE”, “late-onset genetic epilepsy”, “generalised absences” (or “petit mal”), “generalised myoclonic seizures”, and “generalised tonic-clonic seizures” (or “grand mal”). Articles written in English, Portuguese, French, and Spanish languages, irrespective of publication date, were included. Cited references within selected articles were also evaluated. From the bulk of titles retrieved ($n=1,069$), we excluded papers according to language criteria and those that did not report

explicitly patients with adult-onset IGE. The flow chart (*figure 1*) indicates the reasons why we eliminated 32 papers. Ultimately, we were left with a selected group of 11 papers in which cases with adult-onset IGE were reported, either presumed on the basis of clinical manifestations and/or confirmed through EEG data, as well as six other references of interest. Data collected from the selected articles were as follows: sample size, clinical type of IGE, age at seizure onset, family history of epilepsy, seizure precipitating factors, diagnostic procedures, EEG findings, antiepileptic therapy, psychiatric comorbidity, and prognosis. The results of the literature review are presented from a descriptive and critical point of view, considering the following aspects: existence of adult-onset IGE, adult-onset IGE clinical characteristics, occurrence in the elderly, and differential diagnosis.

Classification and terminology: the evolving concept of “generalised epilepsy”

Given the particular topic of this review, it is relevant to briefly consider the evolution of the basic concept of IGE. Concerning the origin of IGE seizures, in the last operational classification of seizures in 2017 (Fisher *et al.*, 2017), what was previously stated was reinforced (Berg *et al.*, 2010), namely, that the biomarker of seizures, the typical spike-and-wave discharges (SWDs), “originate in some defined cortical network and rapidly engage bilaterally distributed networks” where apparently bilateral synchronous SWDs are seen. The same operational classification (Fisher *et al.*, 2017) also added that “classifying a seizure as having apparently generalised onset does not rule out a focal onset obscured by limitations of our current clinical methods”.

In this context, it is relevant to recall the recent neurophysiological evidence obtained from a genetic animal model of absence seizures (WAG/Rij rat) (Meeren *et al.*, 2002), which led to the discovery that typical SWDs originate at a cortical site in the peri-oral region of the somatosensory cortex: “the cortical driver for SWDs”. From this cortical site, SWDs spread with very short time delays to other cortical and subcortical neuronal networks. The characterisation of this “cortical driver area” was confirmed and extended by other experimental findings (Avoli, 2012).

Transposing these animal neurophysiological findings to the human brain is, however, challenging due to the difficulty in measuring, with the required precision, the time course of spread of SWDs in the intact human brain. Nonetheless, studies of patients with IGE absences, using 256-channel scalp EEG recordings (Holmes *et al.*, 2004), support the evidence that

Table 1. Characteristics of included studies.

References	Patients with adult onset (n and/or %)	Age at onset (range or max)	Precipitating factors (no. of patients)	AED regimen (number of patients)	Specific AED	Family history (%)	Seizure type (%)			Epileptic syndrome (%)	EEG main features	Brain imaging	Patients with controlled seizures (%)
							GTCS	Myoclonic seizure	Absence seizure				
Asadi-Pooya <i>et al.</i> , 2012	66; 14.9%	JAE=21y; GTCS=54y	n/a	n/a	n/a	n/a	97	66.7	50	JME=65.2; GTCS only=16.7; Phantom GPSW; 3-Hz GPSW; JAE=3.0; Unidentified=3.0	3-Hz GSW; 3.5-6-Hz GPSW;	n/a	n/a
Cutting <i>et al.</i> , 2001	42; 13.4%	18-55	26	No AEDs=1; Monotherapy=26; 2 or 3 AEDs=15	Valproic acid; topiramate; phenytoin; lamotrigine; acetazolamide; clonazepam	26	97.6	50	38.1	AME=50; GTCS only=7; Unidentified=43	Generalised spike and slow-wave activity ≥3 Hz	n/a	71
Gilliam <i>et al.</i> , 2000	11	25-53	n/a	Monotherapy=9; 2 AEDs=1	Valproic acid; lamotrigine	55	81.8	100	45.5	n/a	GPSW; GSW; PPR	y	83
Hiyoshi and Yagi, 2000	4	81	1	n/a	Valproic acid; phenobarbital	-	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Marini <i>et al.</i> , 2003	34	20-75	25	No AEDs=8; Monotherapy=24	Valproic acid (20 patients); phenytoin; carbamazepine; lamotrigine; topiramate (single cases)	56	73.5	17.6	8.8	Adult-onset absence epilepsy=8.8; AME=17.6; GTCS only=73.5	GSW or GPSW pattern at 2.5 to 5 Hz, with normal background	y	90.6
Michel <i>et al.</i> , 2011	4	35-80	-	Monotherapy	Valproic acid; lamotrigine; levetiracetam	75	100	25	-	GTCS only=3; Unidentified=1	3-4-Hz GSW; polyspikes	y	75

Table 1. Characteristics of included studies (Continued).

References	Patients with adult onset (n and/or %)	Age at onset (range or max)	Precipitating factors (no. of patients)	AED regimen (number of patients)	Specific AED	Family history (%)	Seizure type (%)		Epileptic syndrome (%)	EEG main features	Brain imaging	Patients with controlled seizures (%)
							GTCS	Absence seizure				
Mory et al., 2002	2	21-22	1	Monotherapy	Valproic acid	50	-	100	JME=2	n/a	y	n/a
Nicolson et al., 2004	72	27	n/a	No AEDs=5; Monotherapy=50; 2 AEDs=6	Valproic acid; lamotrigine (others not specified)	27.8	94.4	41.7	Absence epilepsys=9.7; Myoclonic epilepsys=41.7; GTCS only=48.6	GSW; PPR	n/a	94.4
Panayiotopoulos et al., 1997	136 (data only from 13 patients with absences)	16-56	4/13	No AEDs=5; Monotherapy=7; 2 AEDs=1	Valproic acid; phenytoin; lamotrigine	23.0	n/a	n/a	Phantom absences and GTCS=9.6; Others not specified	GSW; GPSW at 3-4 Hz	y	46
Reichsoellner et al., 2010	80 (28 >30y)	34	49/180 (15-30y); 18/28 (>30y)	n/a	Valproic acid	35.0 (15-30y) and 14 (>30y)	65 (15-30y); 85.7 (>30y)	25 (15-30y); 7.1 (>30y)	GTCS only=53.3 (15-30y) and 75 (>30y); JME=30 (15-30y) and 10.7 (>30y); JAE=12.8 (15-30y) and 3.6 (>30y)	GSW; GPSW; local or diffuse slowing	y	92
Yenjun et al., 2003	29	20-75	n/a	n/a	n/a	n/a	n/a	n/a	GTCS only=69; AME=24; AAE=7	GSW; GPSW; GSW with frontal predominance; hyperventilation activation of GSW; PPR; paroxysmal slow or fast activity	y	n/a

AED: antiepileptic drug; AME: adult myoclonic epilepsy; GSW: generalized spike-waves; GPSW: generalized polyspike-waves; GTCS: generalised tonic-clonic seizures; JAE: juvenile absence epilepsy; JME: juvenile myoclonic epilepsy; n/a: information not available; PPR: photoparoxysmal response; y: yes.

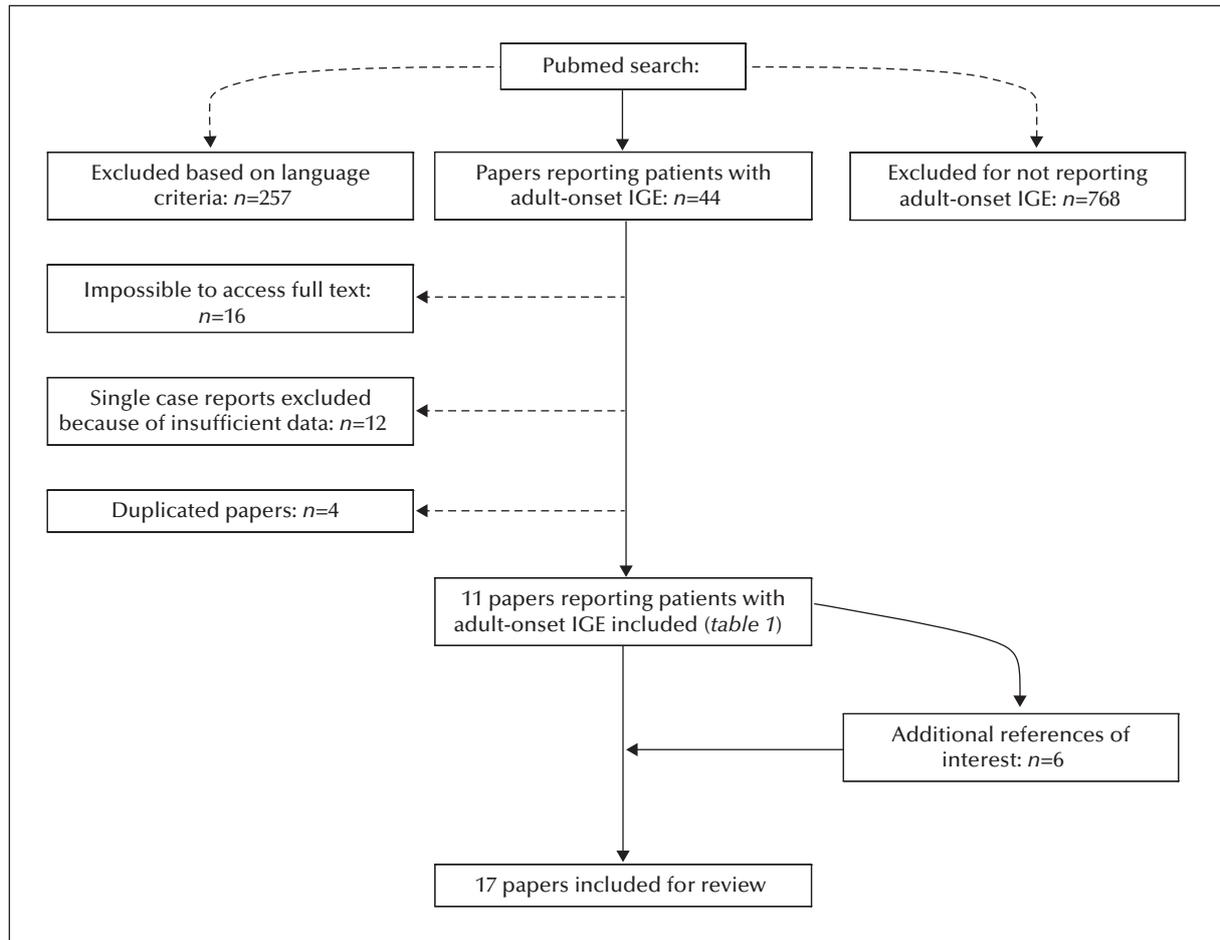


Figure 1. Flow of information regarding literature review.

the onset of seizures is associated with activation of selective cortical networks involving orbital frontal and mesial frontal regions. Magnetoencephalography (MEG) recordings in CAE (Westmijse *et al.*, 2009) also demonstrated a local cortical onset for SWDs in frontal regions. Furthermore, MEG used in cases of childhood absence seizures (Tenney *et al.*, 2013) showed evidence that focal brain areas are responsible for the generation of SWDs. Due to the limited spatial and time resolution, SWDs initially appear generalised on conventional 10-20 scalp EEG recordings.

It is worth highlighting the fact that this “cortical driver” in humans, situated in the frontal cortex, may be one of the reasons why IGE seizures can be confused with complex partial seizures with focal frontal onset, which may lead to a different therapeutic strategy. We may therefore consider that the concept of “apparently generalised onset” of SWDs emanates from the insufficient spatial and time resolution of scalp EEG recordings that are necessary to detect very fast propagation of SWDs in the human brain.

Does adult-onset IGE exist?

There are few papers reporting adult-onset IGE. The process that we used to select relevant articles that comply with our criteria is indicated in the flow diagram displayed in *figure 1*. In 1981, Gastaut already admitted that roughly one third of IGE cases start after the age of 18 years, noting, however, that their onset is rare over the age of 65 (Gastaut, 1981). To analyse this question systematically, it becomes necessary to examine large-scale statistical data. Results of main cohort studies regarding adult-onset IGE are presented at a glance in *table 1*. A large sample of 2,190 patients with IGE was studied according to age distribution at seizure onset (Asadi-Pooya *et al.*, 2012); the peak of age at onset displayed a bimodal distribution with a small peak at two years and a large peak at 15 years of age. Remarkably, in only 14.9% of this cohort of 66 patients was the age at onset 18 years or more. These data indicate that the diagnosis of IGE should also be considered in adults with

new-onset epilepsy. An important question, however, is what are the clinical characteristics of IGE with adult onset.

Clinical characteristics of adult-onset IGE

The diagnosis of IGE can be more challenging when this condition starts in adulthood. Two elderly patients with JME were described by Gram *et al.* (Gram *et al.*, 1998); the syndrome actually started during adulthood in only one patient and the other remained misdiagnosed from adolescence.

A detailed study (Cutting *et al.*, 2001) of 313 IGE patients identified 42 cases (13.4%) with adult onset (18 years or older), with an average age at onset of 23.8 years (range: 18 to 55 years). Concerning the diagnosis of the epileptic syndrome, 21 (50%) had myoclonic seizures, three (7%) had GTCS on awakening (GTCS-A), and the remaining had an IGE that did not fit with any of these categories. With respect to therapy, 30 patients (71%) were well controlled, some of them on monotherapy. More than one third presented psychiatric symptomatology (most commonly depression and anxiety); some needed psychotropic drugs, and about half had good seizure control. Nonetheless, in a few patients, poor seizure control was associated with psychological and cognitive disturbances. About two thirds ($n=26$) reported precipitating factors for the first seizure, with sleep deprivation being the most frequent. The conclusion of this study was that adult-onset IGE exists and carries a good prognosis.

A study designed to analyse the clinical features and family history of IGE with pure grand mal, which divided patients into those that had seizures occurring exclusively on awakening or randomly, disclosed cases of adult onset in both groups (Unterberger *et al.*, 2001).

Another study addressed the question whether IGE of adult onset should be considered as a separate nosological entity (Reichsoellner *et al.*, 2010), in which the authors investigated a relatively large cohort of 798 patients with 492 diagnosed with IGE. Seizure onset after the age of 30 years (named Group 3) was revealed in only 28 (5.7%) patients, while seizure onset occurring within the age range of between 15 and 30 (Group 2) was identified in 80 (16.3%) patients (in this study, patients younger than 15 constituted Group 1). The authors reported some differences concerning syndromes in the different age groups. Using their nomenclature, "epilepsy with grand mal on awakening" was diagnosed in 75% of Group 3 and 53.3% of Group 2, JME in 10.7% of Group 3 and 30% of Group 2, JAE in 3.6% of Group 3 and 12.8% of Group 2, and CAE in 10.7% of Group 3 and 3.9% of Group 2.

Based on a study with a large sample of 2,190 patients (Asadi-Pooya *et al.*, 2012), already mentioned, the most frequent syndrome (65.2% cases) in the group of 18 years or older was reported to be JME, followed, at a considerable distance, by GTCS (16.7%).

A few distinct syndromes that start in adulthood have been described. In 1977, a prolonged confusional state in late life due to idiopathic late-onset *petit mal* status (Ellis and Lee, 1977; Pro *et al.*, 2011) was described. In 1994, a specific type of myoclonic epilepsy with cognitive impairment associated, but not exclusively, with elderly Down syndrome patients, and called "senile myoclonic epilepsy" (Genton and Paglia, 1994; Simone *et al.*, 2010), was reported. In 2000, another syndrome displaying mainly myoclonic jerks, but also absence seizures and GTCS, called "adult myoclonic epilepsy", in which the EEG showed generalised epileptiform abnormalities but neuroimaging was unremarkable, was also described (Gilliam *et al.*, 2000).

IGE in the elderly, not exclusively of adult onset

In contrast to previous reports, the study of Michel *et al.* (2011), carried out in a geriatric hospital, aimed to characterise IGE electroclinically in an elderly population, regardless of whether onset occurred at adult age or not. The authors reported 10 cases of IGE from a population of 1,181 geriatric patients (mean age: 79.4; range: 70 to 94); seizures (GTCS) began late in life (at 61 and 80 years) in only two patients. An observation relevant to the topic of this review is that, in several patients, although IGE manifested with early onset, this condition presented a relatively long quiescent period followed by a relapse later in life. The more frequent corresponding clinical manifestations in the elderly patients were absence status, myoclonic status, and repeated GTCS. These results are in line with another report (Hiyoshi and Yagi, 2000) which also described IGE in an elderly population (older than 60 years) as either early onset, which the authors referred to as "persistent cases" (13%), or truly late onset (2%). From this study, also, it appears that IGE is more common in the elderly than previously considered.

Specific aspects of the clinical diagnosis of adult-onset IGE

In general, IGE incorporates a triad of seizure types, namely absences, myoclonus, tonic-clonic seizures, or combinations of these (ILAE, 1989). Absences in adulthood, particularly, can be somewhat different from their childhood counterparts. The so called "phantom absences" are characterised by a very mild ictal impairment of cognition, associated with

brief (3-4-second) generalised 3-4-Hz spike/multiple spike-and-slow-wave discharge (Panayiotopoulos *et al.*, 1997). The EEG is the only known biological marker for IGE and is an important tool for differential diagnosis. The majority of patients, either children or adults, with a clinical diagnosis of IGE appear to have generalised epileptiform abnormalities based on initial routine EEG and subsequent sleep-deprived studies (King *et al.*, 1998).

Some signs support a diagnosis of IGE; these include typical GTCS, absences, or myoclonic seizures. A family history of epilepsy can be relevant and normal brain MRI is essential for diagnosis. Findings of generalised SWDs and/or polyspikes on the EEG are essential in order to establish diagnosis (Panayiotopoulos *et al.*, 2005). In the context of this review, a question that needs to be addressed is whether this also applies to IGE in the adult. The evidence from several studies indicates that this is the case. For example, in the study of Michel *et al.* (2011), four out of 10 patients with adult-onset IGE were reported to show “interictal generalised spikes or polyspike-and-wave discharges of around 3 Hz”. Their presence in elderly patients with seizures can contribute, together with the clinical data, to support a diagnosis of IGE (Michel *et al.*, 2011). Thus, IGEs that occur at different ages at onset seem to share common EEG diagnostic signatures.

This conclusion is also supported by other data from a study by Yenjun *et al.* (2003) which was aimed at determining whether IGE with adult-onset should be considered a distinct syndrome, or rather a part of a continuum covering a wide range of onset ages. By comparing two groups of patients, one with ages at onset between 11 and 20 years (56 patients) and the other with adult onset beyond 20 years (29 patients), no differences in morphology, amplitude, duration, frequency, occurrence, or activation of the generalised SWD EEG pattern were identified. Similarly, adult-onset IGE has also been shown to share an array of symptoms with early-onset IGE, including EEG features and prognosis (Nicolson *et al.*, 2004). These findings support the concept that adolescent and adult-onset IGE share common genetic determinants, and draw attention to the strong possibility that the emergence of symptomatology in adults depends on modifying or acquired precipitating factors (King *et al.*, 1998). The precipitating factors for a first seizure in a group of patients with adult-onset IGE have been previously documented (Cutting *et al.*, 2001): “sleep deprivation” reported in 33%, “increased stress” in 19%, and “consumption of two or more alcoholic drinks” also in 19%. However, many cases showed no precipitating factors. In this series, GTCS was the first seizure in the vast majority (79%) of patients, followed by myoclonic jerks, or myoclonic jerks followed by GTCS (12%); in 10%, the nature of the first seizure could not be

ascertained. Of note, more than 25% of the patients experienced a first seizure within 90 minutes after awakening.

A practical aspect worth emphasising is that, in order to detect a typical EEG abnormality in adult-onset IGE patients, several EEG examinations may be needed (Westmijse *et al.*, 2009). An efficient diagnostic procedure should take into account the fact that after a first epileptic seizure in adults, the standard EEG may not display abnormalities, and brain MRI is negative. In such cases, a sleep-deprived EEG should be carried out in order to characterise the epileptic syndrome (Michel *et al.*, 2011).

Differential diagnosis of adult-onset IGE

In adult patients presenting with IGE, special attention should be paid to certain aspects regarding the differential diagnosis. This issue was examined in 41 adults with a diagnosis of “complex partial epilepsy”, according to the old terminology, who had EEG findings that made this diagnosis questionable (Mory *et al.*, 2002). These consisted mainly of patterns that were interpreted as representing focal epileptiform activity, as already stressed (Panayiotopoulos *et al.*, 1991). It should be mentioned that these patients were clinically re-evaluated in adult life, but the onset of seizures occurred in childhood or adolescence (age range: 5-22 years). In the same study, the re-evaluation led to the diagnosis of IGE in 25 of the patients: 22 (88%) with JME, one with juvenile absences, one with peri-oral myoclonia with absences (Panayiotopoulos, 1994), and another with eyelid myoclonia with typical absences. The reasons for missing the diagnosis of IGE in these cases included the rarity and short duration of the absences as well as the existence of focal abnormalities on the EEG. Other reasons were the lack of properly reported absence seizures antedating myoclonic jerks by many years, myoclonic jerks reported as unilateral, GTCS occurring during sleep, and focal EEG abnormalities with SWDs, particularly when limited to the frontal regions. However, it should be stressed that “focality” does not exclude this diagnosis. Studies of source analysis of SWDs in IGE, using conventional EEG, have already highlighted the importance of the frontopolar cortex as the generator of absence seizures (Rodin *et al.*, 1994). Holmes *et al.* (2004) improved spatial resolution through dense array studies (256-channel scalp EEG) using source analysis with equivalent dipole (BESA) and smoothed linear inverse (LORETA) methods and achieved the same conclusion, showing that absences involve a more restricted network, constituted by dorsolateral, orbital or mesial frontal cortices (Holmes *et al.*, 2004). Source analysis based on MEG combined with EEG studies confirmed this finding,

showing the involvement of frontal, perinsular, and thalamic areas in IGE (Stefan *et al.*, 2009). In addition, brain imaging techniques have allowed us to obtain a more complete delineation of the networks involved in IGE (Duncan, 2005). The use of EEG combined with fMRI proved that SWDs are always associated with activation of the thalamus and specific cortical areas, in which cortical activation appears to precede the thalamic activation with a concomitant deactivation of default mode network (Seneviratne *et al.*, 2014).

From a practical point of view, the correct differential diagnosis leading to IGE is achieved mainly on the basis of repeated EEG examinations, EEG plus a history of myoclonus (bilateral or unilateral), or EEG combined with a family history of myoclonus.

In addition, it is also relevant to note that frontal seizures may have components that can appear similar to absences, especially if they are very short and lack associated postictal confusion (Trinka, 2005). Thus, these are important elements to consider in the differential diagnosis of adult IGE, which is clinically very relevant since this may entail consequences for therapy. Indeed, in cases where a diagnosis of JME is not properly recognised, on the assumption that these patients have “complex partial seizures”, their treatment could involve inadequate antiepileptic drugs, such as carbamazepine or phenytoin, which can aggravate absences and myoclonus.

Conclusion

Idiopathic generalised epilepsies may start in adulthood, particularly in the second and third decades of life, but also in the elderly. However, adult-onset IGE does not appear to be an independent nosological entity. Adult-onset IGE must not be overlooked, since its correct diagnosis alleviates concern for a symptomatic origin and may avoid unnecessary investigations. Additionally, it points to appropriate treatment. Indeed, most adult patients with IGE have a good prognosis if treated adequately. Comorbidity with psychiatric conditions (mainly depression and anxiety) may occur, although with a frequency similar to that found in the general epilepsy population. Differential diagnosis, specifically regarding cases in which the EEG presents focal frontal abnormalities, should be carried out considering the necessity for repeated EEG examinations, particularly with sleep deprivation. □

Supplementary data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.

None of the authors have any conflicts of interest to declare.

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TEST YOURSELF



- (1) Are spike-and-wave discharges, typical of IGE, truly generalised from onset?
- (2) Does the symptomatology of IGEs of adult onset differ from that of typical IGEs of childhood?
- (3) Given the rarity of the condition, what are the concerns one should have when diagnosing IGE in adulthood?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".