Clinical commentary

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Genetic (idiopathic) generalized epilepsy with occipital semiology

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ABSTRACT – Idiopathic photosensitive occipital lobe epilepsy (IPOE) is a syndrome that should be suspected in patients with seizures with occipital semiology, photosensitivity, and normal MRI. It should be distinguished from occipital epilepsy of unknown aetiology (cryptogenic) given the differences in management. We reviewed patients with occipital seizures which were investigated in our epilepsy unit during the last three years. Three patients were identified with features of IPOE and genetic generalized epilepsy (GGE), formerly known as idiopathic generalized epilepsy, and their clinical characteristics were analysed. We propose the term "idiopathic generalized epilepsy with occipital semiology" based on the significance of managing and treating this syndrome as a GGE.

Key words: genetic epilepsy, visual, photosensitivity, light, idiopathic, occipital epilepsy

Differential diagnosis between occipital cryptogenic epilepsy (OCE) and idiopathic photosensitive occipital lobe epilepsy (IPOE) is often difficult. These two epilepsies are usually considered in the presence of spontaneous or light-induced seizures with occipital semiology, with normal neurological examination and normal brain MRI. IPOE was first described in 1995 by Guerrini *et al*. (1995) who reported 10 patients with a pure phenotype and presentation of reflex occipital seizures exclusively. Subsequently, other groups reported similar cases, broadening the clinical spectrum to include also spontaneous occipital seizures, leading to the recognition that IPOE could be a syndrome with no well-defined boundaries. Further support to the existence of a form of genetic generalized epilepsy (GGE) with occipital lobe semiology was presented by Taylor *et al*. (2004) who described three patients with myoclonic juvenile epilepsy, also presenting with visual auras. In addition, these authors described four families whose members suffered from epilepsy with both GGE and IPOE features.

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These descriptions have demonstrated that IPOE and GGE share common clinical features and may form part of the same spectrum, making it critically important to differentiate between IPOE and OCE, given the management implications. In this article, we describe three patients with simultaneous features of IPOE and GGE and propose the term "idiopathic generalized epilepsy with occipital semiology" to emphasize the significance of managing and treating this syndrome as a GGE.

Patient reports

Patient 1

A 24-year-old male was admitted for presurgical evaluation. The father had seizures (syndrome not known) that ceased spontaneously in his thirties. The patient's first generalized tonic-clonic seizure (GTCS) occurred at age 12. He was treated with valproic acid but continued having one seizure a year. At age 19, valproic acid was suspended and replaced by carbamazepine, after which seizure frequency increased to one GTCS every three months. At 23 years of age, the patient began to experience visual episodes consisting of blurring that first initiated in the outer part of the visual field, progressing to complete blindness within 3 to 5 minutes. Generalized tonic-clonic seizures were preceded by these visual symptoms. Although he could not recall a specific trigger for all of his seizures, he referred that at least some of them were triggered by watching television or after sunlight exposure and dark-light transition. Video-EEG showed occipital, bilateral epileptiform activity, with left predominance, which sometimes generalized, reaching 3-Hz generalized spike-wave (GSW) morphology (*figure 1A, B*). EEG also showed a photoparoxysmal response with intermittent photic stimulation (IPS) between 10 and 30 Hz (*figure 1C*). The photoparoxysmal response was more intense and prolonged when the IPS was performed in the morning, immediately after the patient awoke. Given the EEG findings, carbamazepine was withdrawn. Video-EEG performed three days after carbamazepine withdrawal showed remarkable improvement, with just infrequent occipital, bilateral, epileptiform activity observed only after awakening. 3-Tesla MRI and brain PET-CT were both normal. The patient is being treated with levetiracetam, 1,000 mg bid, and is seizure-free.

Patient 2

A 28-year-old woman with normal neurological development and no family history of epilepsy. At three years of age, she had episodes of unresponsiveness which were particularly evident when exposed to intermittent lights, television, and computer screens. Two years later, she developed seizures in which she would see coloured spots in the right visual field for one minute that could progress to a GTCS. She reported light exposure and psychological stress as potential triggers. 3-Tesla MRI was normal. Video-EEG showed a photoparoxysmal response with IPS at 18 Hz showing 4-5-Hz GSW discharges. No spontaneous discharges were identified. The GSW had frontal predominance. The patient was first administered ethosuximide which was not effective, and seizures were eventually controlled by valproic acid. Valproic acid was replaced by lamotrigine, with complete seizure control being maintained.

Patient 3

A 33-year-old male with normal neurological development and no family history of epilepsy came to the clinic after suffering a GTCS. He had typical febrile seizures in early childhood. The patient reported that he started to feel discomfort while sitting, exposed to sunlight, and then lost his sight completely for 30-60 seconds. He stood up and then suffered a GTCS. 1.5-Tesla MRI was normal. Twenty-four-hour video-EEG showed 3-Hz GSW with occipital predominance and focal, independent, bilateral, occipital spikes. Background activity was normal. Photoparoxysmal response, consisting of occipital spikes and GSW discharges with occipital predominance, was elicited with IPS at 25 Hz when performed in the afternoon, and between 17 and 30 Hz when performed in the morning after waking the patient. The patient was controlled when valproic acid was initiated.

The clinical and electrographic features of the three patients are summarized in *table 1*.

Discussion

In 1995, Guerrini *et al*. reported 10 patients with a pure phenotype which they called "idiopathic photosensitive occipital lobe epilepsy". These patients suffered seizures with elemental occipital semiology (seeing coloured spots, bright lights, blurred vision or amaurosis), all of which was triggered by photic stimuli, mainly from television, video games, and disco lights. Interictal EEG showed normal background activity, occipital spikes and waves, and a photoparoxysmal response that could be occipital, generalized or both. Ictal EEG was characterized by unilateral occipital activity extending to the contralateral occipital lobe, with occasional propagation to the temporal lobe. These authors considered the possibility that this syndrome belongs to the group of idiopathic epilepsies, based

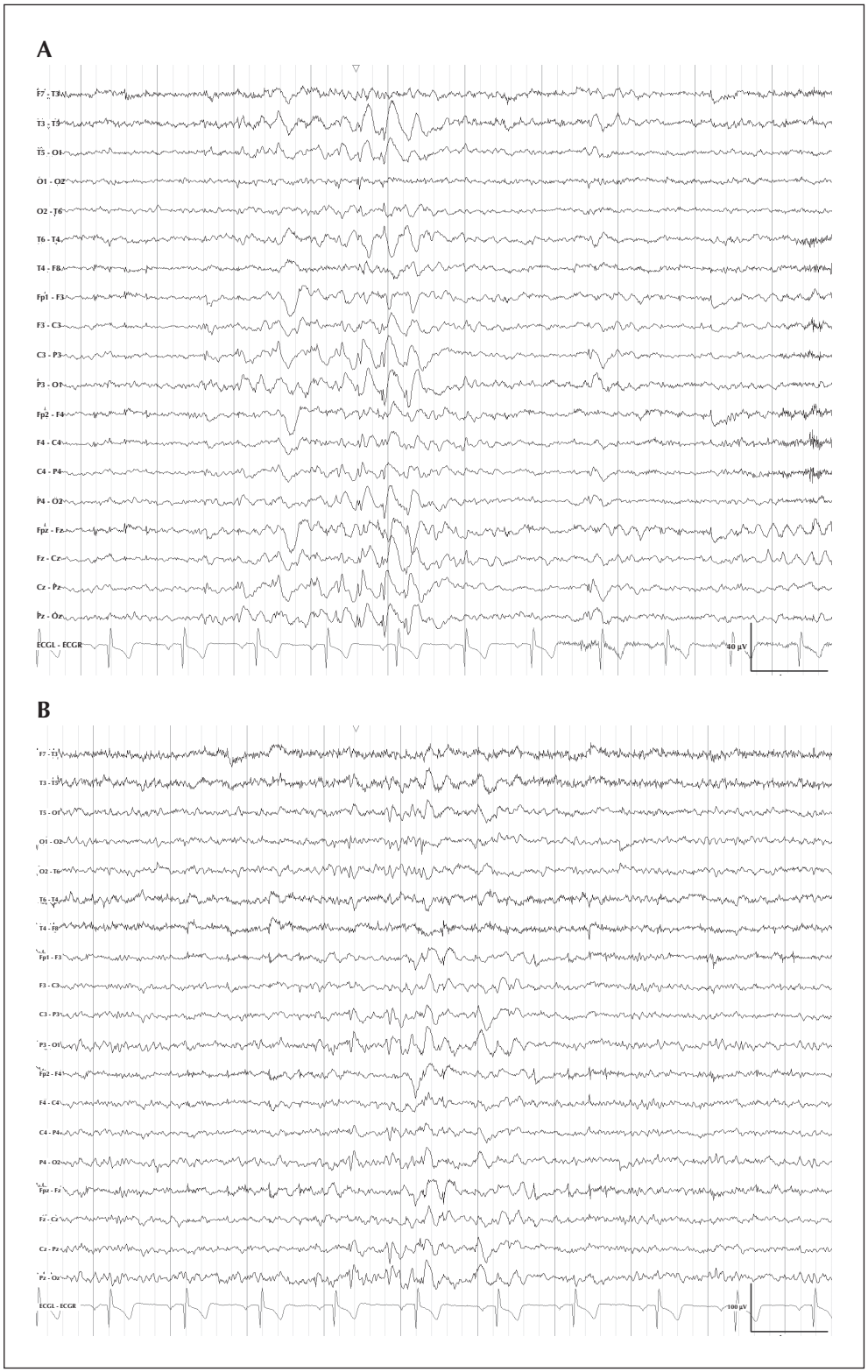

Figure 1. EEG of Patient 1 showing (A) 3-Hz generalized spike-wave (GSW) complexes and focal occipital, bilateral epileptiform activity; (B) focal, occipital, bilateral epileptiform activity, with left predominance.

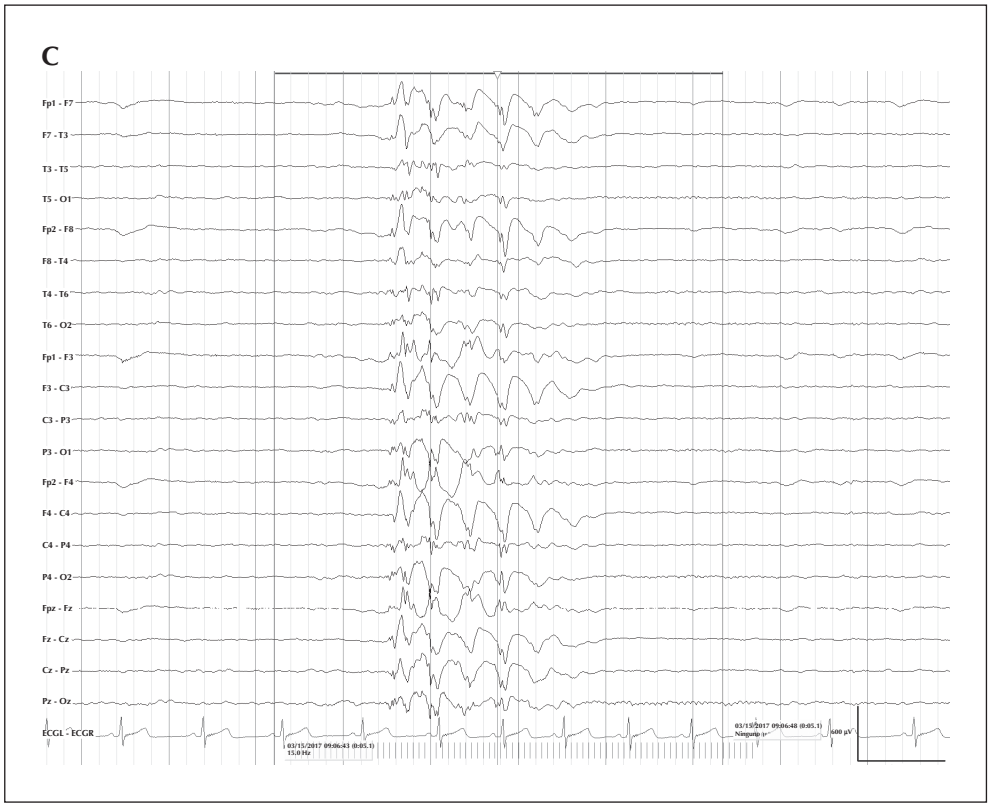

Figure 1. (*Continued*) (C) a generalized photoparoxysmal response with intermittent photic stimulation (IPS) at 15 Hz.

on the history of febrile seizures or Rolandic seizures in some of their patients and the generalized epileptiform activity shown on the EEG (Guerrini *et al*., 1995). Other groups (Yalçin *et al*., 2000) have subsequently reported patients with similar features, further supporting the original description (Guerrini *et al*., 1997) and the description of adult-onset IPOE (Koutroumanidis *et al*., 2015).

IPOE is a syndrome with no well-defined boundaries. Some patients only have seizures with extreme light exposure and a combination of important triggers (sleep deprivation, alcohol or drugs use, fever

Table 1. Clinical and electrographic features of the three patients.

	Occipital semiology	Absences	Myoclonus	GTCS	GSW
Patient 1	Peripheral blurring, blindness	No	No	Yes	3 Hz
Patient 2	Coloured spots	Yes	No	Yes	4-5 Hz
Patient 3	Blindness	No	No	Yes	3 Hz

	PPR and IPS	Remission of seizures	Worsening with sodium channel blockers
Patient 1	Generalized; IPS: 10-30 Hz	Levetiracetam	Worsening with CBZ
Patient 2	Generalized; IPS: 18 Hz	Valproic acid	Not known
Patient 3	Occipital and generalized; IPS: 17-30 Hz	Valproic acid	Not known

GTCS: generalized tonic-clonic seizure; GSW: generalized spike wave; PPR: photoparoxysmal response; IPS: intermittent photic stimulation.

or high psychological stress). Patients with a lower threshold have seizures triggered by smoother photic environmental stimuli, while others may even have spontaneous occipital or generalized seizures (Taylor *et al*., 2004; Politi-Elishkevich *et al*., 2014).

Taylor *et al*. analysed in depth the probable relationship between IPOE and GGE (Taylor *et al*., 2004). The authors described four families in which patients with IPOE and juvenile myoclonic epilepsy (JME) coexisted. They reported 12 patients who suffered from a combination of visual aura, myoclonus, absences or GTCS. They also observed that visual aura and/or head version was present in 10% of patients with JME (in 25% of patients with photosensitive JME). The authors proposed that the coexistence of focal and generalized discharges can be explained by thalamocortical synchronization with focal discharges and focal seizures activating the same system, but only in restricted posterior thalamocortical circuits.

A similar case was described by Bonini *et al*. (2014), who reported a family in which the proband showed electroclinical features of IPOE in childhood, which subsequently evolved into absences and a single GTCS in adolescence. His mother had features suggestive of JME. This association between IPOE and GGE was also found in our second patient, who first had absences and then developed visual auras. On the other hand, there are symptomatic or probably symptomatic focal epilepsies with reflex seizures triggered by photic stimuli, with or without spontaneous seizures. This has been reported in patients with cerebral palsy, vascular malformations, ischaemic brain damage or other causes of focal pathology involving the occipital cortex (Guerrini *et al*., 1994; Guerrini and Genton, 2004).

The clinical distinction between IPOE and symptomatic/cryptogenic occipital epilepsy may not be straightforward in the first place, since photosensitivity can be found in one third of both groups (Adcock and Panayiotopoulos, 2012). According to this review and other articles (Koutroumanidis *et al*., 2015), most patients have a narrow photosensitivity range, but the spectrum of frequencies at which PPR is obtained is relatively broad and variable. In the first IPOE description, the photosensitivity range was between 5 and 40 Hz (Guerrini *et al*., 1995). Other studies show a photosensitivity range of between 8 and 30 Hz (Koutromanidis *et al*., 2015). Further research to identify differences between IPOE and OCE photoparoxysmal responses would be of clinical interest.

It is important to differentiate a focal cryptogenic occipital epilepsy from an IPOE. Treating an IPOE as a focal epilepsy could have negative consequences for patients, a situation reflected by our first patient, who was referred for presurgical evaluation under the assumption that he had a focal epilepsy. However, EEG features and clinical information suggested a phenotype consistent with GGE. Withdrawal of carbamazepine and substitution by levetiracetam led to a striking improvement in the EEG and complete seizure control. In our third patient, the first EEG showed left occipital epileptiform activity which could have led to an incorrect diagnosis of focal occipital cryptogenic epilepsy. However, the presence of GSW complexes and the striking morning photosensitivity allowed us to diagnose IPOE and avoid sodium channel blockers.

Considering these patients and similar cases reported in the literature, we suggest that a diagnosis of IPOE should be considered when the following electroclinical features are present. First, seizures with occipital lobe semiology, consisting predominantly of visual auras, with or without secondary generalization. Second, EEG showing generalized 3-Hz spike-wave complexes, either spontaneous or during photic stimulation, which may be associated with independent focal spikes in the occipital regions, similar to fragmented focal spikes that are recorded in patients with JME (Lancman *et al*., 1994; Thomas *et al*., 2006). Similar to other cases of GGE, epileptiform discharges might be easier to identify when the EEG is performed within the first hours of the morning, when the patient has just awakened (Labate *et al*., 2007). In addition, EEG should show normal background. Third, the presence of clinical or electrographic photosensitivity; photic stimulation can trigger seizures or EEG photoparoxysmal responses. Finally, fourth, normal neurological examination and brain MRI, and in selected cases, exclusion of other causes of occipital lobe epilepsy such as celiac disease, Lafora disease, mitochondrial disorders and ulegyria (Gil-Nagel *et al*., 2005). An additional finding that could support a GGE phenotype is paradoxical seizure worsening when sodium channel blockers are administered (Perucca *et al*., 1998).

In addition, we believe the syndrome described first by Guerrini *et al*., with reflex occipital seizures exclusively, has been clearly documented and allows patients with homogeneous features to be identified, which can be extremely important for clinical and research purposes. For example, identification of this syndrome may facilitate linkage studies or the creation of comparison groups, and may provide precise information about pharmacological response and prognosis.

Conclusion

Distinction between OCE and IPOE must be made. In this article, we have attempted to organize and systematize the clinical picture that should lead to a diagnosis of IPOE.

We believe that the term "idiopathic photosensitive occipital epilepsy" could lead to misunderstanding as it could be considered as a focal epilepsy, with

possible negative implications. Accordingly, we suggest the term "idiopathic generalized epilepsy with occipital semiology" in an attempt to highlight the visual semiology and the clinical overlap with GGE. Because the term "idiopathic" has been extensively used and is in fact a component of the term "IPOE", we propose to retain it as part of our suggested terminology. However, according to the new ILAE classification (Scheffer *et al*., 2017), the term "idiopathic" should be replaced by "genetic". Because of this, following the new terminology recommendations, "genetic generalized epilepsy with occipital semiology" might be a more appropriate option. □

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