Original article

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The electroclinical features of idiopathic generalized epilepsy patients presenting with fixation-off sensitivity*

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ABSTRACT – *Aims*. To determine the electroclinical features of fixation-off sensitivity (FOS) in patients with idiopathic generalized epilepsy (IGE).
Methods. We searched the EEG database using the terms "fixation-off sensitivity" and "idiopathic generalized epilepsy" over a four-year period from March 2014 to April 2018 in the Xijing Hospital, Xi'an, China. FOS was evaluated according to the technique proposed by Panayiotopoulos. Photic stimulation procedure and neuropsychological testing were performed during video-EEG monitoring.
Results. FOS was observed in eight patients with several different IGE syndromes, including four with eyelid myoclonia/Jeavons syndrome, two with juvenile myoclonic epilepsy, one with photosensitivity epilepsy, and one with epilepsy with generalized tonic-clonic seizures only. FOS was associated with seizures in five patients manifesting with eyelid myoclonic, myoclonic, and myoclonic-tonic-clonic seizures, and eyelid myoclonic status. FOS coexisted with photosensitivity in six patients as independent EEG features. Neuropsychological testing revealed transitory cognitive impairments associated with FOS.
Conclusion. FOS is associated with several different IGE syndromes and may coexist with photosensitivity in the same patient as independent EEG features. FOS may be associated with both clinical seizures and cognitive impairments. Intermittent photic stimulation and registration of different eye conditions with and without fixation will aid the study of the dynamics of the visual system in epilepsy patients. [*Published with video sequences on www.epilepticdisorders.com*]

Key words: fixation-off sensitivity, idiopathic generalized epilepsy (IGE), higher cortical cognitive function, photosensitivity

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Fixation-off sensitivity (FOS) is a unique EEG term coined by Panayiotopoulos in 1981 to denote a rare pattern of EEG abnormalities in patients with Panayiotopoulos syndrome and occipital childhood epilepsy of Gastaut syndrome. FOS is elicited by suppressing central vision and fixation, and characterized by continuous epileptiform discharges (EDs) that occur after eye closure, persist as long as the eyes are closed, and disappear immediately upon eye opening (Panayiotopoulos, 1981; Panayiotopoulos, 1998). In subsequent studies, Panayiotopoulos also described FOS in idiopathic generalized epilepsies (IGEs) and cryptogenic epilepsies, categorizing three types of epilepsy patients presenting with the EEG abnormality:
– patients with occipital paroxysms;
– patients with cryptogenic generalized epilepsy with a "pure" and distinct clinical form of FOS;
– patients with IGE and photosensitivity (Panayiotopoulos, 2007).
FOS can usually be inhibited by intermittent photic stimulation (IPS), but can also coexist with photosensitivity in some patients with IGE (Agathonikou *et al*., 1998; Koutroumanidis *et al*., 2009; Brigo *et al*., 2013).
Nevertheless, the electroclinical features of FOS in these relevant epilepsy syndromes have not been clearly characterized. The level of impaired consciousness and cognitive function associated with FOS in patients with IGE has been seldom studied so far. Assessment of consciousness and cognitive function during FOS is important and allows a comprehensive evaluation of patients with FOS and photosensitivity to be performed, which may lead to a better understanding of brain areas involved in FOS. In this study, we aimed to characterize the electroclinical features of FOS and further assess the level of impaired consciousness and cortical functions associated with FOS in patients with IGE.

Methods

We retrospectively reviewed consecutive video-EEG reports in our centre during a four-year period from March 2014 to April 2018, and searched the EEG database using the terms "fixation-off sensitivity" and "idiopathic generalized epilepsy". Eight patients with FOS were included in this study. Patients' demographics and clinical data were extracted from the electronic medical records, including clinical notes, video-EEG reports, and neuroimaging studies. The epilepsy syndromes were diagnosed and classified according to ILAE recommendations (Koutroumanidis *et al*., 2017).
The study was approved by the Xijing Hospital Research Ethics Committee and consent was obtained individually from the patients' parents.

Video-EEG recording techniques

A 32-channel scalp EEG was recorded for 24 hours in the EMU according to the international 10-20 system using the Nicolet Voyageur system (USA), Nihon-Kohden Neurofax EEG-1200C system (Japan), and XLTEK Natus system (USA). Hyperventilation and IPS were performed during video-EEG study.
FOS was evaluated according to the technique proposed by Panayiotopoulos (Panayiotopoulos, 1998). Complete darkness was achieved using standard underwater goggles covered completely with black adhesive tape. During video-EEG recording, the patient was asked to perform spontaneous eye opening and closing, and dark underwater goggles covered with opaque tape were used to eliminate central fixation and vision. FOS was diagnosed by the presence of continuous EDs that occurred after eye closure, which persisted for as long as the eyes were closed and disappeared immediately upon eye opening, or consistently occurred in patients wearing underwater goggles covered with opaque black cloth, regardless of eyes opened or closed.
Photic stimulation was performed according to the methodology of the updated European algorithm for visual stimulation (Kasteleijn-Nolst Trenité *et al*., 2012) using the Natus system (REF:580-SSPL01), Nicolet NicLED Photic (REF:224-476300), and Nihon-Kohden (MODEL: LS-703A). Patients were instructed to look at the centre of the strobe lamp, placed 30 cm from their eyes, and to report any symptoms they may experience during IPS. Uninterrupted trains of stimuli of about five seconds were given for each frequency with a five-second resting interval between different frequencies, starting with the eyes open for around five seconds, then eyes closed, and finally with eye closure for around five seconds. An ascending stepwise sequence was performed at strobe frequencies of 1-2-8-10-15-18-20-25-40-50-60 Hz. These ranges were assessed in three distinct eye conditions: eyes open, eyes closed, and eye closure. If a photoparoxysmal response (PPR) was elicited at certain frequencies (lower threshold), the remainder of the series was skipped. A descending sequence in the reverse order was then performed to elicit PPR (upper threshold) and define the range of photosensitivity. Stimulation at any frequency that elicited any PPR was repeated at least once (after an interval of 10-20 seconds) to confirm consistency, and the patient was evaluated for possible symptoms by the technicians and neurophysiologist, which were then compared with the EEG changes and the video, as there may be overlap between the FOS phenomenon and photosensitivity when the IPS was performed with eyes closed and eye closure. Photosensitivity was then categorized into three groups:

Table 1. Clinical characteristics of IGE patients presenting with FOS.

Pts/sex	GTCS onset/age (yrs)	MRI/ND/IQ	FH	Seizure type	No. of GTCS	PPR	AED	Precipitating factors for seizures	Epilepsy syndrome	GTCS freedom period (yrs)	Non-epileptic event
1/M	8/10	N/N/N	+	GTCS	3	+C	VPA	Emotional stress Sleep deprivation	EGTCS-a	2	-
2/M	14/18	N/N/N	+	GTCS	4	+C	OXZ/ LEV	Television Sleep deprivation	Reflex epilepsy Photosensitivity	2	EM without ED
3/M	12/15	N/N/N	-	Myoclonic M-GTCS	3	±P	VPA	Brief sleep	JME	-	-
4/F	8/13	N/N/N	+	EMA GTCS	1	±P	LEV	Sleep deprivation Brief sleep	EMA/JS	-	-
5/M	14/22	N/N/N	-	EMA GTCS	2	-	VPA	Flashing disco light Emotional stress Sleep deprivation	EMA/JS	2	EM without ED
6/F	11/16	N/N/N	-	EMA Myoclonic GTCS	25	±P	LTG	Menstruation	EMA/JS	-	-
7/M	13/16	N/N/N	-	Myoclonic Absence GTCS	6	±P	VPA	Sleep deprivation Fatigue	JME	-	-
8/F	15/24	N/N/N	-	M-GTCS EMA status Myoclonic	20	-	VPA	Sleep deprivation Brief sleep	EMA/JS	-	EM without ED

IGE: idiopathic generalized epilepsy; FOS: fixation-off sensitivity; ND: neuropsychology development; IQ: intelligence quotient; FH: family history; PPR: photoparoxysmal response; AED: antiepileptic drug; N: normal; C: confirmatory; P: probable; M-GTCS: myoclonic-generalized tonic colonic seizure; VPA: sodium valproate; OXZ: oxcarbazepine; EGTCS-a: epilepsy with GTCS alone; LEV: levetiracetam; JME: juvenile myoclonic epilepsy; EMA/JS: eyelid myoclonia with or without absences/Jeavons syndrome; ED: epileptic discharge.

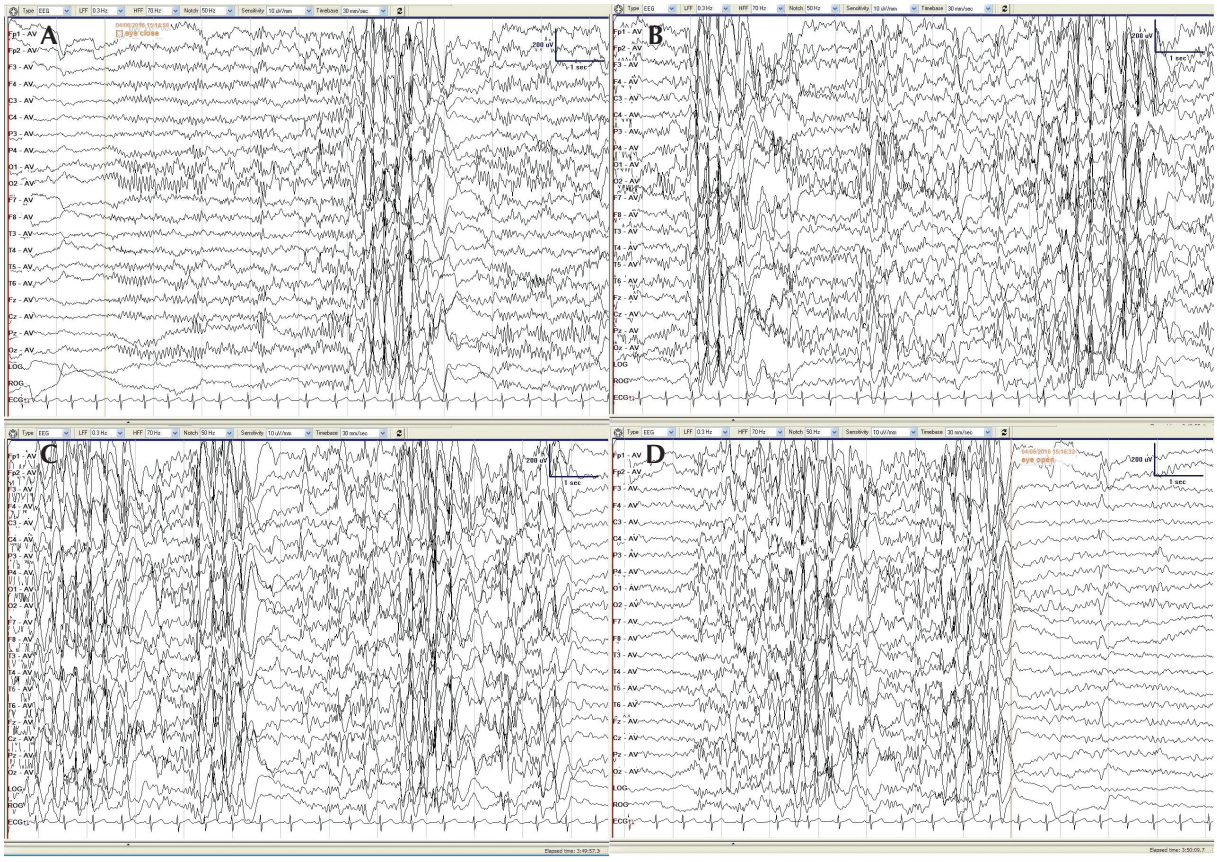

Figure 1. (A-D) Consecutive EEG images from Patient 1 showing continuous high-voltage 3-4-Hz generalized spike-wave activity mixed with fast rhythms with an anterior predominance, which was induced by eyes closing and blocked by eyes opening.

– definitive (IPS-related ED occurring during all three eye conditions);
– probable (IPS-related ED occurring during eyes closed and eye closure);
– and possible (IPS-related ED occurring only during eye closure.

Neuropsychological evaluation

Neuropsychological evaluation, including reaction times to auditory stimuli, word repetition, and backward counting, was preformed to evaluate the transient cognitive effects during FOS. For comparison, performance during eyes open was used as a normal baseline. The patient was then asked to open and close his/her eyes in order to elicit FOS. Reaction times to calling patients' name, repeating commands and sentences, and time for backward mathematical calculations were assessed as transient cognitive impairments during FOS (Beniczky *et al*., 2016).

Results

Demographics and clinical features

FOS was observed in eight patients (five males and three females) with IGE. Although it was difficult to determine the age at epilepsy onset in patients with juvenile myoclonic epilepsy (JME) and eyelid myoclonia (EMA), the mean age at generalized tonic-clonic seizure (GTCS) onset was 12.5 years (range: 8-14 years; median: 13 years) (*table 1*). All the patients were admitted to the hospital after suffering GTCS. Sleep deprivation, fatigue, and brief sleep, particularly interrupted by compulsory early awakening, were the most common precipitants of myoclonic seizures and GTCSs in our patients. Other seizure precipitating factors included stress, being emotional, watching television, and menstruation. The frequency of GTCS appeared to be fairly variable among the eight patients. Three patients (Patient 1, 2 and 5) reported GTCS

freedom for two years, though EMA persisted. The frequency of GTCSs in the remaining five patients ranged from annually to monthly.

EEG features

Several EEG patterns were observed.

– During eyes opening, normal EEG activity was demonstrated in seven patients, while rare EDs were found in only one patient with JME.

– With the elimination of central visual fixation, FOS manifesting polyspikes intermixed with rare slow waves, more prominent over the frontal and parietal-occipital regions, were observed in all eight patients and persisted for as long as the eye were closed and disappeared when eyes were open (*figures 1, 2, 3*).

– FOS occurred consistently in all patients wearing underwater goggles covered with opaque black cloth, regardless of eyes opened or closed (*figure 4*).

– During sleep stage, FOS disappeared in all the patients; three patients had focal spike and waves in the parietal-occipital lobe, two patients had briefly attenuated generalized EDs, while the remaining three patients had normal EEG.

Photosensitivity

Photosensitivity was observed in six patients without overt ictal symptoms during video-EEG recording. PPR was elicited during IPS at frequencies ranging from 10 to 20 Hz. The complete inhibition of FOS by IPS was found at a frequency lower than 15 Hz in the eyes closed condition in five patients *(figures 5, 6)*. With eyes open, only two patients (Patient 1 and 2) presented with definitive PPR at a frequency of 10-20 Hz, and the remaining patients only showed EDs with eyes closed and eye closure (it is possible that there was overlap between FOS and PPR). The EEG was normal during IPS in two adult patients (Patients 5 and 8), however, GTCS were triggered by flashing lights in one of them, suggesting that photosensitivity may develop over time and vary at different ages in the same patient.

IGE syndromes in patients with FOS

Patients 3 and 7 presented with JME, manifesting with occasional myoclonic seizures involving the jaw and arms; Patients 4, 6 and 8 presented with EMA with eyelid fluttering and myoclonic seizures immediately after eyes closed. Three patients (Patients 2, 5, and 8) presented with eyelid myoclonus when eyes were closed,

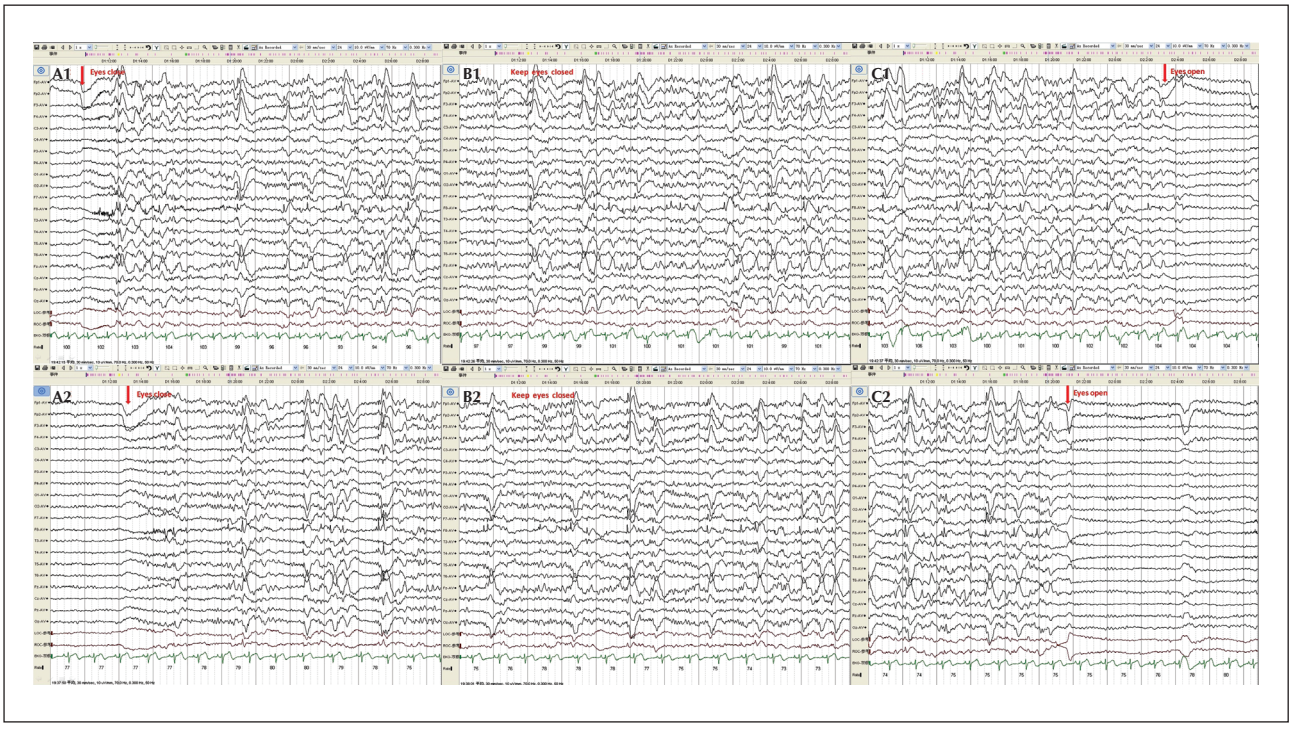

Figure 2. Patient 2 presented with two episodes of eye closing-induced high-voltage spike-wave activity mixed with fast rhythms and slow wave with anterior predominance, which was blocked by eyes opening.

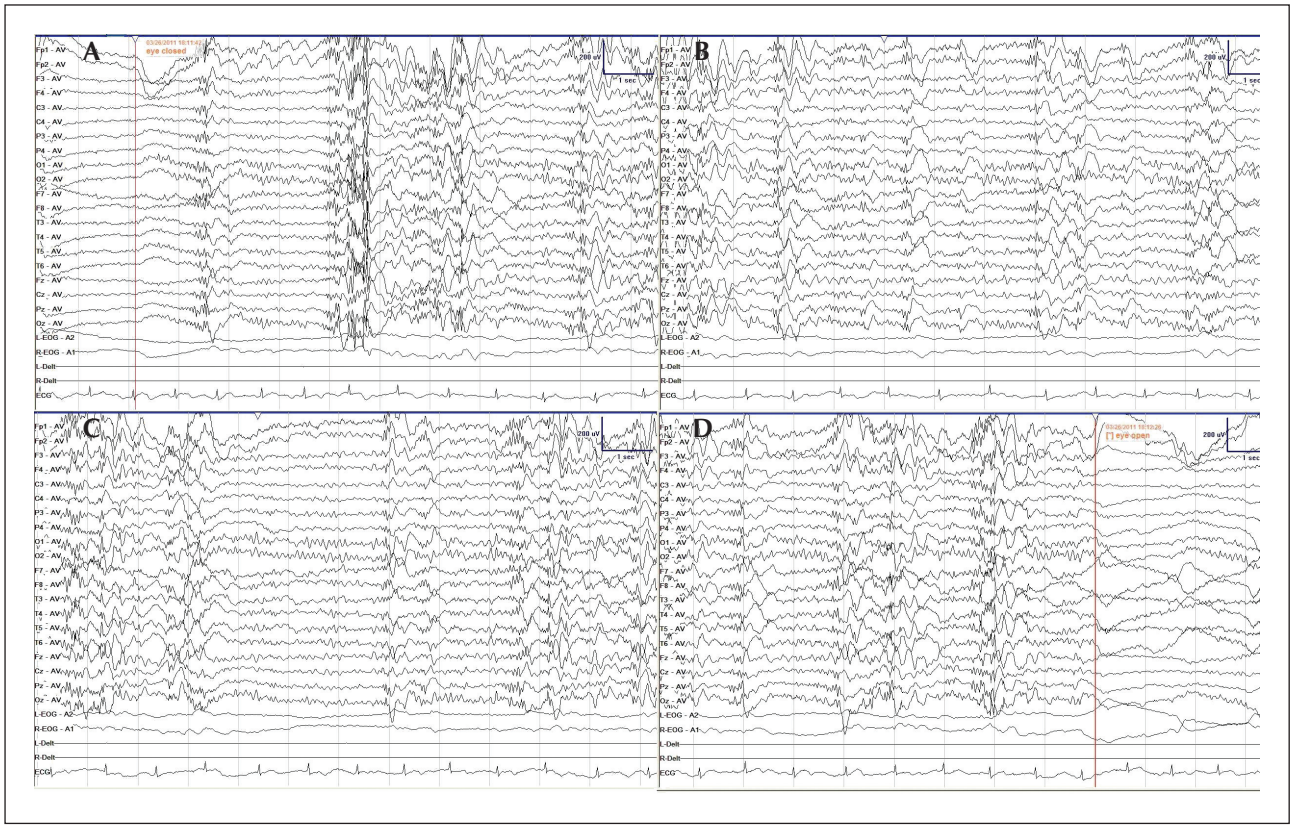

Figure 3. (A-D) Consecutive EEG images from Patient 8 showing continuous irregular generalized bursts of polyspike-wave activity mixed with theta and alpha waves when eyes were closed; the epileptic discharge was blocked upon eye opening.

regardless of epileptic EEG discharges. To some extent, such paroxysmal clinical phenomena resemble epileptic eyelid myoclonus. No overt seizure related to FOS was found in Patient 1. Patient 8 underwent a sleep-deprived video-EEG and experienced prolonged mild eyelid myoclonic status with eyes closed, lasting for more than 12 hours. This led to insomnia during the whole night and evolved into a myoclonic GTCS (*video sequence 1*). Two days later, a repeat 24-hour video-EEG without sleep deprivation was performed, and the result appeared to be normal.

Neuropsychological outcomes

A complete loss of consciousness did not occur during FOS in our case series, and patients were fully aware of themselves and their environment. All of them demonstrated normal performance with eyes open, as they promptly answered simple questions and recited number sequences correctly. During eyes closed, performance in response to auditory calling and short word repetition showed no difference compared with eyes open in six patients. However, when patients were asked to perform a more difficult task, "forward and backward counting" with eyes closed, seven of them showed mild transitory impairment and recited incorrect numbers with a clearly slow reaction (a transient pause and reduced fluency) during consecutive counting (*video sequence 2*). These performances indicated that their higher cortical cognitive function (calculation) was impaired by the EDs related to FOS (*video sequences 3, 4*). Cognitive function was completely affected in the last patient with eyelid myoclonic status during the video-EEG recording, and the tasks could not be performed by the patient (*video sequence 1*).

Discussion

We report a series of eight patients with IGE presenting with unique electroclinical features associated with FOS, including eyelid myoclonic, myoclonic, and myoclonic-tonic-clonic seizures, eyelid myoclonic status, and transient impairment of higher cortical function. Notably, one patient experienced prolonged episodes of EMA and status myoclonus induced by sleep deprivation in the eyes closed condition, and eventually proceeded to a myoclonic GTCS, as FOS phenomenon can be readily induced by

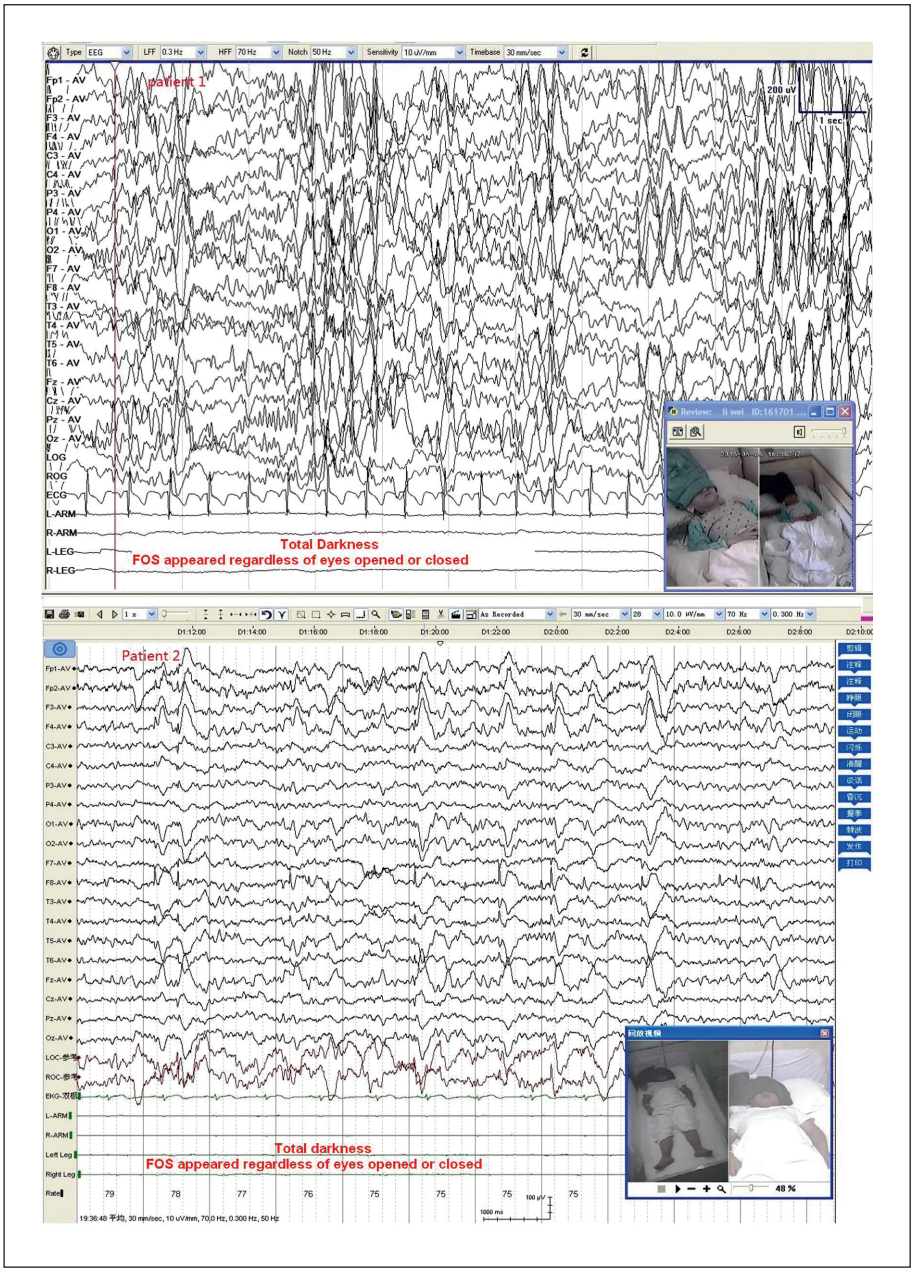

Figure 4. FOS consistently occurred while wearing underwater goggles covered with opaque black cloth in both patients, regardless of eyes open or closed.

sleep-deprivation. Our results demonstrate that the FOS phenomenon is frequently associated with seizures, in contrast to previous findings that FOS is of relatively low epileptogenicity (Brigo *et al.*, 2013). Moreover, video-EEG recordings allowed us to differentiate FOS, in our cases, from eye closure sensitivity in which the EDs last only for 3-5 seconds once the eyes are closed (Viravan *et al.*, 2011; Wang *et al.*, 2014).

Interestingly, the opposite reflex EEG phenomenon of fixation-off sensitivity and photosensitivity co-existed in the same patient in our cases, which was described previously in idiopathic occipital epilepsy and generalized epilepsy patients (Koutroumanidis *et al.*, 2009; Brigo *et al.*, 2013). In line with the previous findings, the EEG features of PPR in our case series were characterized as irregular generalized spike waves with frontal and paracentral predominance, which is similar to the EEG pattern of the FOS phenomenon (Zifkin and Kasteleijn-Nolst Trenite, 2000; Fisher *et al.*, 2005; Koutroumanidis *et al.*, 2009; Italiano *et al.*, 2014; Poleon

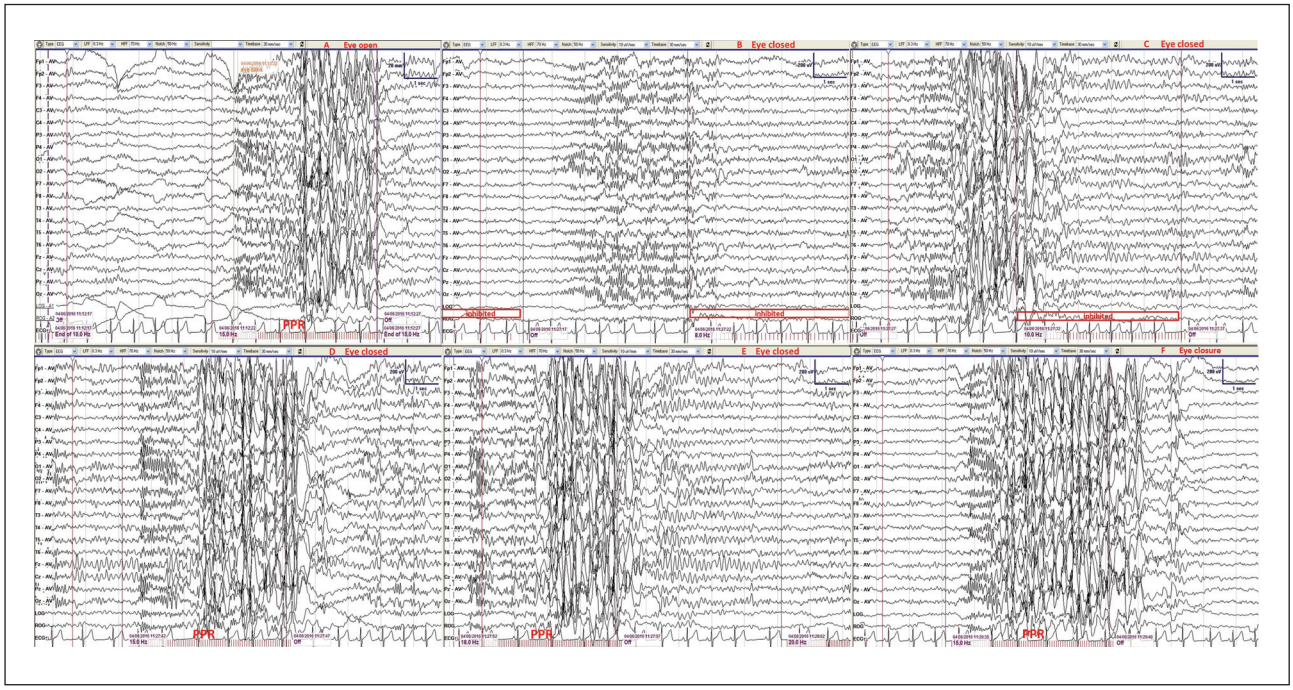

Figure 5. Photoparoxysmal response to IPS in Patient 1. (A) At 15 Hz when eyes were open. The epileptic discharges were promptly inhibited by IPS when eyes were closed (B, C), but IPS still provoked generalized PPR with 15 Hz and 18-Hz IPS (D, E). F) Generalized PPR at 15 Hz upon eye closure.

and Szaflarski, 2017). The underlying pathophysiology of FOS and PPR remains poorly understood. It has been hypothesized that patients with both FOS and photosensitivity might have more "complete" occipital hyperexcitability involving both magnocellular (mainly for photosensitivity) and parvocellular (mainly for FOS) visual pathways, as both pathways participate in the generation of PPR and FOS (Agathonikou *et al.*, 1998; Koutroumanidis *et al.*, 2009; Brigo *et al.*, 2013). Recent studies have identified *CHD2* as a photosensitive epilepsy gene in photosensitive IGE patients, especially those with EMA epilepsy syndrome. Another study has also shown that *CHD2* gene mutation is related to the FOS phenomenon in "myoclonic epilepsy" with visual-sensitive seizures (Galizia *et al.*, 2015). Thus, the two reflex EEG phenomena may share similar pathophysiological mechanisms or a genetic basis, which might explain their occasional coexistence (Caputo *et al.*, 2018). The FOS phenomenon in our patients tended to be persistent into adult life despite the treatment with antiepileptic drugs (AEDs). Therefore, FOS may not be self-limiting. In contrast, PPR tends to disappear over time, likely reflecting more the natural evolution of PPR rather than the treatment with AEDs. Therefore, the two reflex epileptic EEG traits appear to be independent and evolve differently over time.

To our knowledge, cognitive impairment during FOS has not been reported previously in patients with IGE. In our case series, a complete loss of consciousness was not observed during FOS. Nevertheless, neuropsychological testing demonstrated transient cognitive impairments during FOS, manifesting prolonged generalized spike-wave discharges in our patients who had a normal baseline of cognitive function. Functional MRI studies have revealed that prefrontal and parietal cortices play an important role in cognitive function (Smith and Jonides, 1999; Diwadkar *et al.*, 2000). Different frontal regions were activated for memory storage and executive function (Smith and Jonides, 1999). Several recent studies showed that EDs interfered with temporal and frontal connectivity, which might account for the cognitive deficits in patients with epilepsy (Dinkelacker *et al.*, 2016a; Dinkelacker *et al.*, 2016b). Therefore, the frontally predominant EDs related to FOS might have interfered with the functional connectivity in the frontal lobe, causing the transitory cognitive impairment in our patients.

Given the preserved consciousness during FOS in our patients, we speculate that the generalized spike-wave discharges may be generated in a frontal-parietal-occipital network without involving the thalamus, as the thalamus is important for maintaining

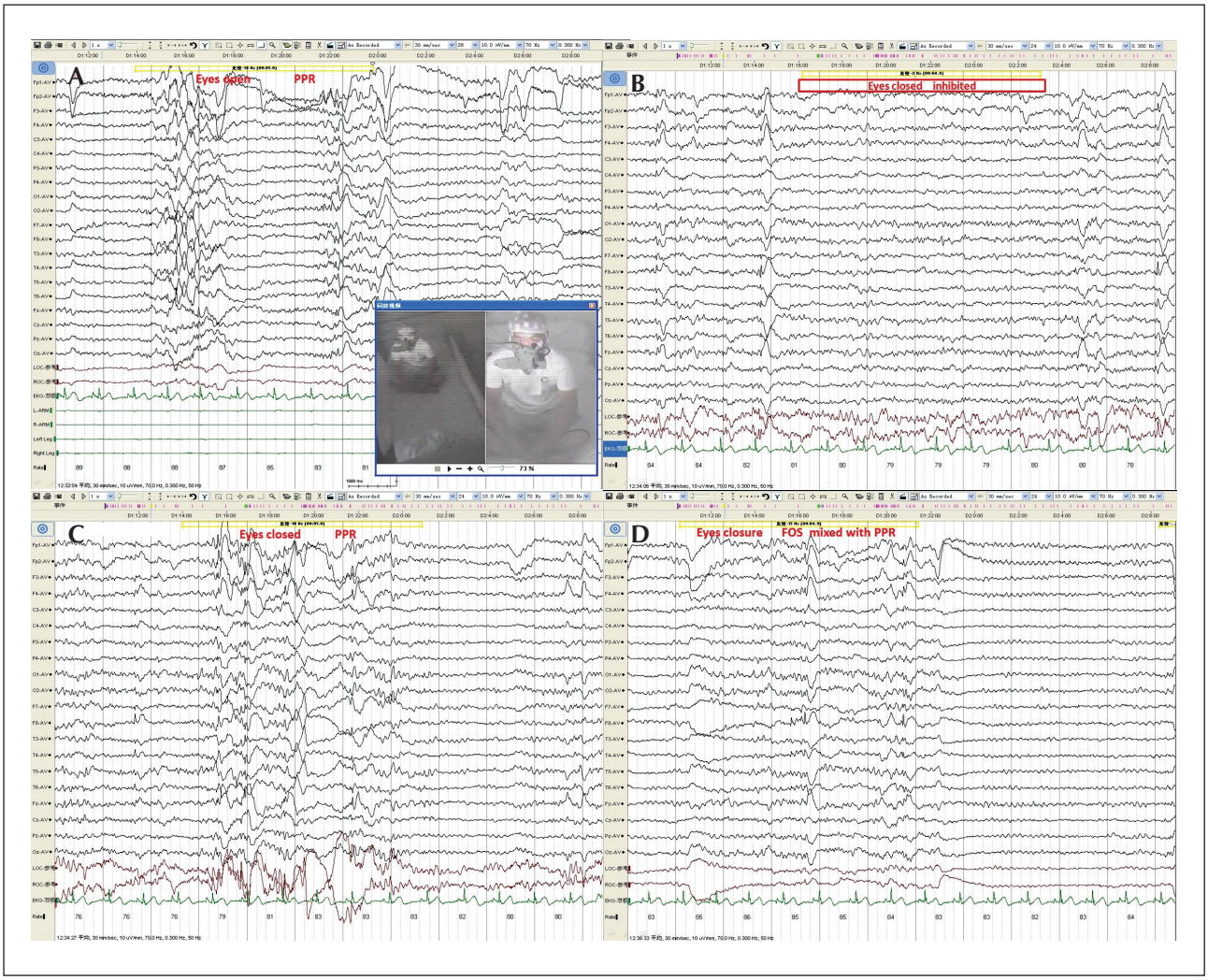

Figure 6. Photoparoxysmal response to IPS in Patient 2 (yellow bar indicates the IPS sequence). (A) At 18 Hz when eyes were open. The epileptic discharges were promptly inhibited by IPS when eyes were closed (B), but IPS still provoked generalized PPR at 10 Hz (C). D) Epileptic discharge occurred at each IPS sequence upon eye closure.

consciousness. Similar to the term "focal cognitive seizure" proposed in the ILAE seizure classification (Fisher *et al.*, 2017), our findings suggest that there might be a new seizure type, generalized cognitive seizure, in patients with IGE presenting FOS, possibly an absence seizure variant. Given that FOS is a well-defined EEG pattern associated with several epilepsy syndromes and may be associated with cognitive impairment, FOS may reflect a unique class of reflex epilepsy syndrome, or "FOS epilepsy" as proposed previously (Koutroumanidis *et al.*, 2009). The conclusions drawn from our study are, however, limited by its retrospective design and the small number of cases, owing to the fact that the FOS phenomenon is rarely observed in a tertiary epilepsy centre. Future multicentre studies are warranted to further define the electroclinical features and delineate the pathophysiology of FOS.

Conclusion

Our study demonstrates that fixation-off sensitivity is associated with clinical seizures and transitory cognitive impairment in several different IGE syndromes. Meanwhile, FOS and PPR may coexist in the same patient and evolve independently over time, and they may share similar pathophysiological mechanisms or a genetic basis, which might explain their occasional coexistence. IPS and registration of different

eye conditions with and without fixation will aid the study of the dynamics of the visual system in epilepsy patients. Neuropsychological testing should be considered in order to assess the cognitive impairments associated with FOS, as these might be too subtle to observe clinically. □

Legends for video sequences

Video 1

Patient 8 is a 24-year-old female. She experiences a prolonged episode of mild eyelid myoclonic status and myoclonic seizures involving the arms, persisting with eyes closed (lasting for more than 12 hours and leading to insomnia over the entire night), which later proceeds to an M-GTCS; she is unable to recite a sequence of numbers.

Video 2

Patient 1 is a 10-year-old boy reciting a sequence of ascending numbers. He could finish the task without hesitation and correctly with eyes open. However, with eyes closed, his performance shows a transitory impairment and he recites incorrect numbers with a clearly slow reaction (with a transient pause and reduced fluency).

Video 3

Patient 1 is a 10-year-old boy reciting a sequence of ascending numbers. He hesitates after reciting the number eight and 10, and follows the number 29 with the number 21. However, he is able to continue reciting the remaining sequence of numbers correctly. Note that the duration of the responsible generalized spike-wave discharge (GSWD) is less than two seconds.

Video 4

Patient 2 is an 18-year-old university student reciting a sequence of numbers in descending order. He hesitates when reciting the numbers 145, 142 and 140, and there is a long pause between the number 140 and 141. He follows the number 135 with the number 133 and pauses for a while, then repeats the number 133 again. However, he was able to continue reciting the remaining sequence of numbers correctly.

Key words for video research on www.epilepticdisorders.com

Phenomenology: fixation-off sensitivity
Localisation: unknown
Syndrome: idiopathic generalized epilepsy
Aetiology: unknown

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

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