■ Original article

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Characteristics of visual sensitivity in familial cortical myoclonic tremor and epilepsy

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ABSTRACT

Objective. The aim of the study was to describe the electroclinical features of visual sensitivity in patients with familial cortical myoclonic tremor and epilepsy.

Methods. We searched the EEG database using the terms "familial cortical myoclonic tremor and epilepsy" and "visual sensitivity" over a seven-year period from March 2013 to April 2020 in the Xijing hospital, Xi'an, China. The inclusion criteria were demonstrable electroclinical visual sensitivity in the form of eye-opening sensitivity, eye-closure sensitivity, eyes-closed sensitivity and photosensitivity. Clinical, EEG and imaging records of patients were screened, and subsequently, detailed analysis of their data was undertaken.

Results. We enrolled six patients with visual sensitivity, five of whom suffered with rare generalized tonic-clonic seizures. Neuroimaging was negative in all cases. All patients demonstrated photosensitivity; eye-opening sensitivity associated with cortical myoclonic in one patient, eyes-closed sensitivity associated with cortical myoclonic tremor status in three patients, and eye-closure sensitivity in two patients. At the last follow-up visit, cortical myoclonic tremor and epilepsy in all patients was well controlled wit h first-line treatment.

Significance. Visual sensitivity is therefore likely to be an important reflex trait in some patients with familial cortical myoclonic tremor and epilepsy, and should be routinely evaluated in order to better define the electroclinical features in FCMTE syndrome. [*Published with video sequences*].

Key words: familial cortical myoclonic tremor and epilepsy; visual sensitivity; eye sensitivity

VIDEOS ONLINE

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Familial cortical myoclonic tremor and epilepsy (FCMTE) is characterised by cortical myoclonic tremor and overt myoclonic and later generalised tonic-clonic seizures (GTCS) [1]. The onset of symptoms usually occurs in the second to third decade of life, with rare generalized tonic-clonic seizures that appear later than cortical myoclonic tremor [1, 2]. Emotional stress, fatigue, sleep deprivation and photic stimulation are notable triggers for cortical myoclonic tremor (CMT).

Aside from photosensitivity, little is known about other visual sensitivities in FCMTE. Only one study has reported a patient with cortical myoclonic tremor induced by fixation-off sensitivity [3]. Assessment of visual sensitivity in patients with FCMTE is important, which may lead to a better understanding of the brain areas involved in generating cortical myoclonic tremor. However, the electroclinical features of visual sensitivity in this syndrome have not been clearly characterized.

Based on these conditions, this study aimed to characterize the electroclinical features of visual sensitivity and further assess the underlying brain network in patients with FCMTE.

Methods

Standard protocol for approval, registration, and patient consent

Ethical permission for scanning the patients was obtained from the Xijing Hospital Research Ethics Committee and individually from the patients.

Patients

We retrospectively reviewed the consecutive video-EEG reports in our centre over a seven-year period from March 2013 to April 2020, and searched the EEG database using the terms "visual sensitivity" and "cortical myoclonic tremor and epilepsy". We included patients with video-EEG documented clinical seizures with FCMTE, excluding cases with CMTE but without family history. Patients with progressive myoclonus epilepsies who presented with action myoclonus, visual seizures and progressive mental and motor deterioration were also excluded. Six patients diagnosed with FCMTE 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.

Video-EEG examination with photic stimulation

Twenty-four-hour video-EEG monitoring was performed for all patients. Video-EEG was performed in an illuminated room using a 32-channel digital video-EEG system (Bio-logic; American) with scalp electrodes placed according to the international standard 10-20 system. The sampling rate was 500 Hz with a band pass filter (high-pass cut-off frequency at 0.3 Hz and low-pass cut-off frequency at 70 Hz). Electromyography electrodes were placed over both deltoid muscles. Three technicians and one physician reviewed and analysed the EEG and determined the onset and offset of interictal or ictal epileptiform discharges (EDs). We analysed interictal EDs during both asleep and awake stages. The ictal EEG features of patients with FCMTE were analysed during the video monitoring.

Visual sensitivity

We diagnosed patients with visual sensitivity on the basis of:
Eye-open sensitivity presenting with paroxysmal EDs associated with or without clinical seizures occurring during the state of eye opening, and disappearing after eyes closed.

- Eye-closure sensitivity presenting with paroxysmal EDs associated with or without clinical seizures occurring within 1–3 seconds after closing the eyes. These are usually brief EEG paroxysms lasting for 1–4 seconds and do not persist in the remaining period when the eyes are closed.
- Eyes-closed sensitivity 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.
- Photosensitivity that was diagnosed by the appearance of photoparoxysmal response (PPR) with or without clinical seizures elicited at certain frequencies.
- Symptoms known to be triggered by environmental sources of light that were identified in the patients.

Patients who fulfilled at least one of the above criteria were diagnosed with abnormal visual sensitivity.

Results

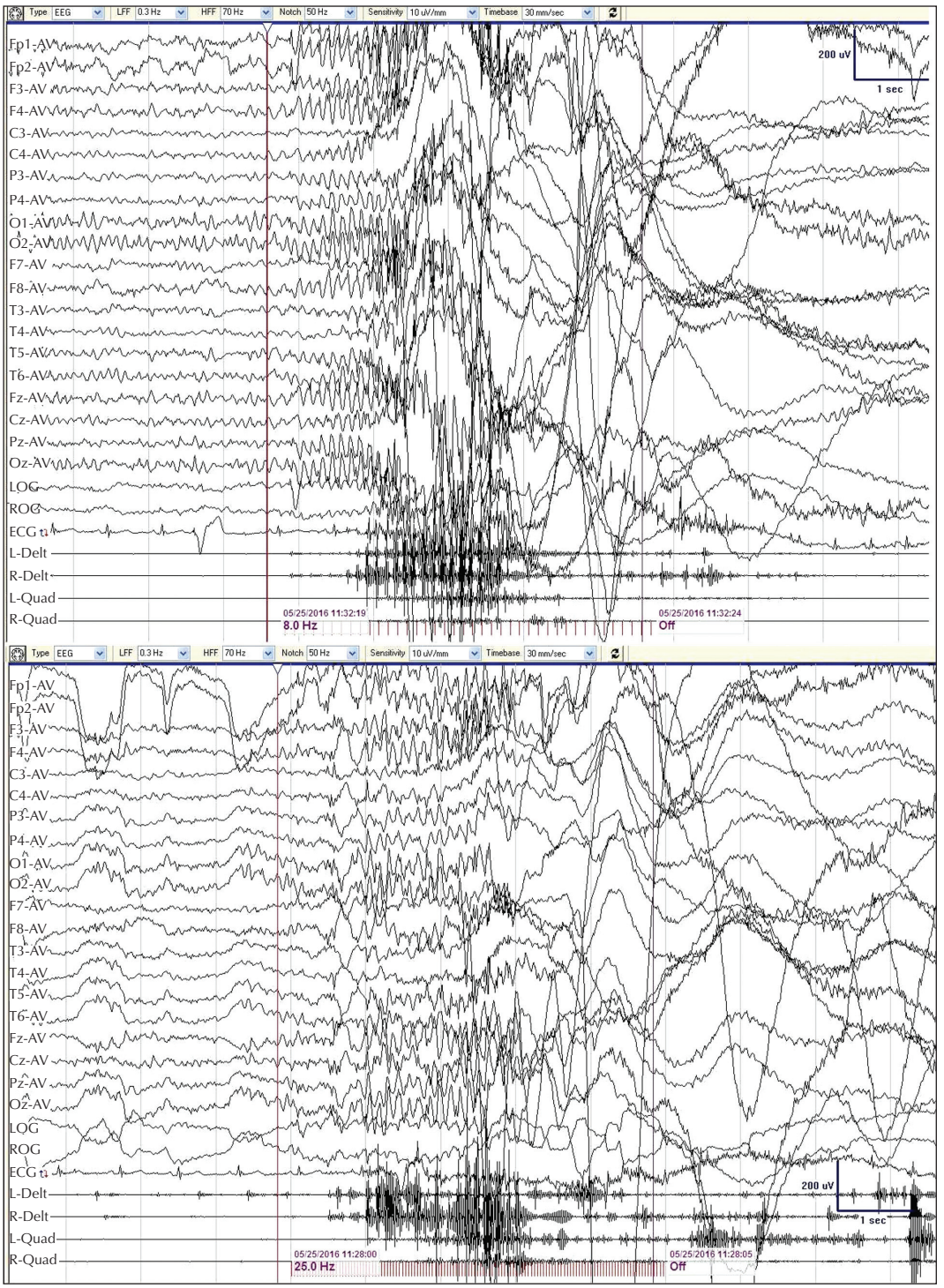
Demographics and clinical features

We enrolled six patients diagnosed with FCMTE, five of whom were women (83%), and all of whom presented with photosensitivity (*figure 1*). *Table 1* details the main clinical characteristics of this case series. Although it was difficult to determine the precise onset age of CMT, all patients began to have the disease after adulthood, usually after the second decade of life. Four of them suffered with rare generalized tonic-clonic seizures (range: 0-6 times), and the mean age at onset of generalized tonic-clonic seizure (GTCS) was 51.6 years (range: 45-63 years). The average duration of delayed diagnosis was 25.3 years (range: 8-47years). Neuroimaging was negative in all cases. Four patients experienced CMT triggered by environmental light stimulation. Different eye states (including eyes closed, eyes opening and eye closure), sleep deprivation, stress, being emotional, and light stimulation were the most common precipitants of CMT and GTCSs in our patients. The clinical follow-up ranged from 1 to 6 years (mean: 2.8 years), and there was no significant progression over time. At the last follow-up visit, CMT and GTCS were well controlled with VPA or LEV in all patients, and some of them even achieved seizure freedom. However, Patient 6 died of lung cancer at the age of 69.

Interictal and ictal video-EEG findings

- ***Interictal EEG***

EEG background was normal during the course of the disease in all of the six patients with alpha rhythm, ranging from 8 to 11 Hz. EEG features are summarized



■ **Figure 1.** Patient 5 was a 50-year-old female at the time of EEG monitoring. During IPS procedures, the patient presented with a photoparoxysmal convulsion in response to IPS at 8 Hz and 25 Hz (purple bar indicates the IPS sequence). EDs with 6-8-Hz sharp waves, associated with cortical myoclonic tremor, were promptly induced by IPS.

▼ **Table 1.** Demographic and electroclinical characteristics of FCMTE patients.

Pt/sex	Family history	Seizure symptom	CMT /GTCS onset/ current age	No. GTCS	Other symptoms	Precipitating factors of CMT	MRI	AED	Outcome
1/F	Y	CMT	30s/-/45	0		Eyes closed Emotional/stress	N	VPA	Well controlled
2/F	Y	CMT/GTCS	20s/55/69	6		At rest, Eyes closed Emotional/stress	N	VPA	Seizure-free >3 years
3/F	Y	CMT/GTCS	40s/45/49	3		Light stimulation Snow	N	LEV	Seizure-free >2 years
4/F	Y	CMT/GTCS	20s/63/65	1	Visional hallucination before GTCS	Emotional/stress Sleep deprivation	N	VPA	Seizure-free >2 years
5/F	Y	CMT/GTCS	40s/45/53	4		Eyes closed Light stimulation Emotional/ stress	N	VPA	Well controlled
6/M	Y	CMT/GTCS	30s/50/69	5		Light stimulation Ripples of water Eye opening	N	VPA	Well controlled Died of lung cancer

AED: antiepileptic drug; CMT: cortical myoclonic tremor; GTCS: generalized tonic-clonic seizure; MRI: magnetic resonance imaging; N: normal; VPA: valproate acid; LEV: levetiracetam; Y: yes.

in *table 2*. Five patients presented with seizures only during wakefulness, and showed generalized discharges with parietal-occipital and frontal predominance. Patient 1 presented with both focal spike-waves in the parietal-occipital region and generalized discharges, with seizures occurring during both wakefulness and sleep.

• ***Visual sensitivity and ictal EEG***

Table 2 summarizes the EEG features of the six patients during EEG monitoring. All six patients presented with visual sensitivity. Patient 6 presented with eye-open sensitivity. The EEG showed eye opening-related paroxysmal slow waves mixed with spike waves, mainly in the occipital region, and eye opening was always associated with myoclonic seizures; eyes closed was associated with EDs and disappearance of seizures (*video sequence 1*). Two patients presented with eye-closure sensitivity, with spontaneous EEG showing paroxysmal generalized slow-waves mixed with spike-wave discharges without clinical seizures. Three patients presented with eyes-closed sensitivity associated with cortical myoclonic tremor status (Patients 1, 2 and 5), and the EDs were mainly located on parietal, occipital and frontal regions (*figure 2*). During wakefulness, Patient 1 presented with myoclonic jerks involving both the upper and lower limbs triggered by eye closure. Ictal EEG showed focal pseudo-periodic spike-wave activity during the eyes closed state, prevalent over the central-parietal-occipital region, and paroxysmal arrhythmic generalized spike-wave activity mainly on the frontal region associated with pseudo-rhythmic myoclonic activity (*video sequence 2*). During sleep, VEEG monitoring documented spike-wave discharges on the middle line of the central-parietal region associated with myoclonic activity only on quadricep muscles. Patient 2 presented with continuous, arrhythmic, mainly distal twitches in the hands after eyes closed and at rest, and EEG showed diffuse 8-10-Hz spike-waves with fast waves (*figure 3 and video sequence 3*). Patient 5 presented with continuous distal arrhythmic twitches in the hands and eyelids, and EEG showed diffuse 4-6-Hz slow waves mixed with spike-waves on the occipital region, and paroxysmal generalized spike-waves, mainly frontal and predominant during the eyes closed state (*video sequence 4*). While eye opening could reduce CMT or make it disappear, the CMT would reappear whenever the eyes were closed again.

In addition, consciousness was well preserved in four patients during seizures, even with CMT status in the eyes closed state. All patients presented with photosensitivity to a boarder frequency band, ranging from 5 to 60 Hz. Three of them presented with intermittent photic stimulation (IPS)-induced myoclonic seizures, while the other two patients only presented with photoparoxysmal responses without obvious clinical seizures.

Treatment and outcome

After correct diagnosis, all patients were prescribed first-line treatment and CMT was well controlled by drugs; five patients were treated with VPA and one with LEV. At the last follow-up visit, seizures were all well controlled. Three patients achieved seizure freedom for >two years, and two of them reported that they only had rare seizures when they felt mentally stressed or sleep deprived. Only Patient 6 died, of lung cancer at the age of 69.

Discussion

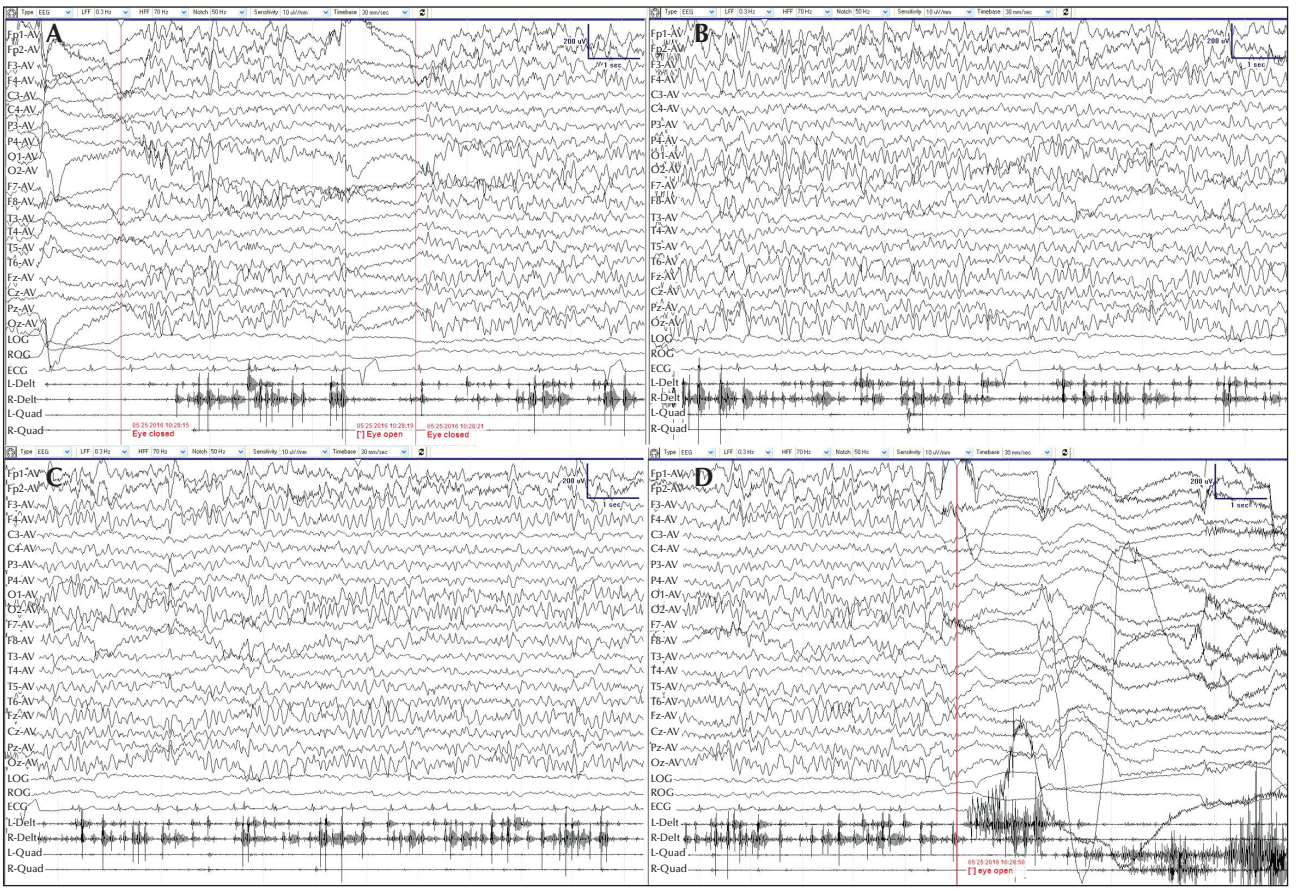
We report a series of six patients with FCMTE presenting with abnormal visual sensitivity, including eyes-opening sensitivity, eye-closure sensitivity, eyes-closed sensitivity and photosensitivity. Photic stimulation is a recognized trigger for seizures in FCMTE, but the frequency band has not been specified in previous studies. In line with the previous findings, photosensitivity was also identified in our six patients, and four patients were responsive to a similar band to that of IGE patients with a frequency ranging from 8 to 30 Hz [2, 4]. The other two patients presented with sensitivity to a broader band involving lower and higher frequency ranging from 5 to 60 Hz. In IGE patients, sensitivity to IPS tends to disappear over time, but in patients with FCMTE, the phenomenon of photosensitivity tends to persist into elderly life. Three of our patients were over 60 years old and still presented with photosensitivity. Therefore, the reflex epileptic traits in the two different syndromes appear to evolve differently over time.

To our knowledge, abnormal eye state-related seizures in FCMTE have been rarely reported before. However, seizures and abnormal EDs triggered by different eye states are already well known in idiopathic generalized epilepsy syndromes, such as Jeavons syndrome and generalized epilepsy with fixation-off sensitivity [5,6]. In our study, we found eye-open sensitivity in one male patient, and eye-closure and eyes-closed sensitivity in two and three female patients, respectively. Notably, three patients experienced prolonged episodes of CMT status in the eyes-closed state, similar to previously reported cases presenting with evolution from visually induced CMT to GTCS [7]. Our results demonstrate that CMT is a kind of visual-sensitive seizure. Eye sensitivity was ignored by the patients for a long time, and was noted only upon

▼ **Table 2.** EEG features of six patients during EEG monitoring.

Pt/sex	Age at EEG	Interictal EEG	CMT characteristics			Precipitating factors of CMT	Visual sensitivity		
							IPS-induced		Eye sensitivity
			Ictal EEG	Location	period		IPS	Frequency	
1/F	42	Spike-waves in parietal-central region	Spike wave and spike-wave complex	Parietal-occipital	Wakefulness and sleep	Eyes closed	PCR	8-60	Eyes closed
			Paroxysmal arrhythmic generalized spike-wave	Generalized with frontal predominance	Wakefulness				
2/F	67	Diffused low-amplitude fast wave mixed with spike wave	Diffuse 8-10-Hz spike-wave with fast wave	Parietal-occipital frontal predominance	Wakefulness	Resting	PPR	8-18	Eyes closed
3/F	48	Paroxysmal generalized arrhythmic spike-wave mixed with slow waves / diffuse low-amplitude fast waves	Paroxysmal arrhythmic spike-wave	Parietal-occipital predominance	wakefulness	Light stimulation	PCR	8-25	Eye closure
4/F/	63	Low-amplitude waves with paroxysmal generalized arrhythmic spike-wave mixed with slow wave	Same as interictal EEG	Generalized with frontal predominance	Wakefulness	Sleep deprivation	PPR	8-25	Eye closure
5/F/	50	Paroxysmal generalized arrhythmic spike-waves mixed with slow waves	Generalized 4-6-Hz slow wave mixed with spike-wave	Generalized with frontal and occipital predominance	Wakefulness	Eyes closed	PCR	8-25	Eyes closed
6/M/	63	Spike-waves in temporal and parietal-occipital region	Paroxysmal slow wave with spike-wave mainly in the occipital region	Parietal-occipital predominance	Wakefulness	Eyes open	PCR	5-19	Eye opening

IPS: intermittent photic stimulation; CMT: cortical myoclonic tremor; PCR: photoparoxysmal convulsion response; PPR: photoparoxysmal response.

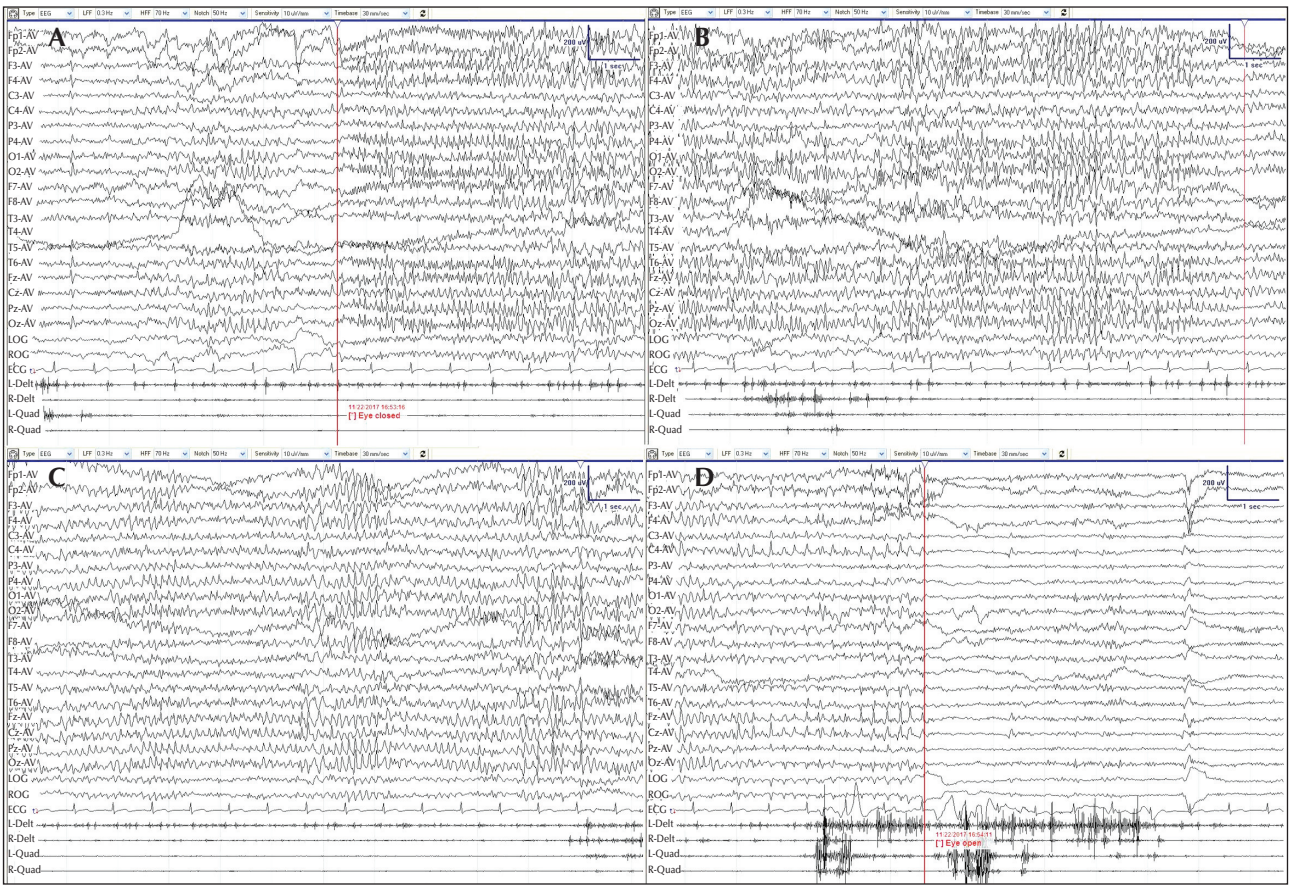


■ **Figure 2.** Patient 5 was a 50-year-old female at the time of EEG monitoring. Consecutive EEG images (A-D) show eyes-closed-induced continuous EDs, mainly on frontal and occipital regions, accompanied by continuous cortical myoclonic tremor involv ed in the bilateral upper limbs, with a diamond-shaped configuration on deltoid muscles, bilaterally. The EDs and associated seizures disappear immediately upon eye opening.

review of the video-EEG recordings. The reason why eye sensitivity is rarely reported in FCMTE syndrome might be due to the lack of detailed medical history investigation and long-term video-EEG monitoring. If not carefully investigated, the unique features can be under-estimated.

Video-EEG recordings allowed us to identify abnormal EDs induced by eye sensitivity in patients with FCMTE. All of the patients also presented with generalized EDs with predominance in parietal-occipital and frontal lobes, and two patients also presented with focal ED in the parietal-occipital region. An interesting finding was that all the patients but one in the study were female. These results are similar to those for Jeavons syndrome, with female predominance, photosensitivity and eye-closure sensitivity [8]. Another interesting finding was the contrasting reflex EEG phenomena of eye sensitivity in female and male patients in our study, with one male patient presenting with eye-open sensitivity, and other female patients presenting with eye-closure and eyes-closed sensitivity. However, further studies using a larger sample are needed to draw any definitive conclusions regarding this difference in gender distribution and differences in clinical and EEG presentation in FCMTE syndrome.

The pathophysiology of this syndrome remains largely speculative. As reported before, increased cortical hyperexcitability has been mentioned [1, 7]. In line with the previous findings, in our study, both EEG with EDs and time-locked seizures with burst EMG suggest cortical hyperexcitability, and the jerks associated with EDs indicate epileptic events. Given the preserved consciousness during CMT status induced by eyes closed 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 consciousness.



■ **Figure 3.** Patient 2 was a 67-year-old female at the time of EEG monitoring. Consecutive EEG images (A-D) show continuous diffuse 8-10-Hz spike-waves mixed with fast wave activity when eyes were closed; the ED was blocked upon eye opening.

Valproate and levetiracetam were the first-line treatments for our patients with FCMTE, obtaining the greatest benefit against cortical myoclonus tremors and GTCS. Valproate has been recognized as the best treatment for photosensitive epilepsy, especially in IGE patients with generalized EDs, and levetiracetam appears to be an alternative therapeutic option [9, 10]. Furthermore, EEG with the characteristic eye sensitivity-related generalized or diffused EDs also make valproate the first choice, as valproate is the most common therapeutic option that has been successfully used by epileptologists for the treatment of eye-sensitivity epilepsy [11]. Three of our patients had been misdiagnosed with essential tremor or Parkinson's disease, and treated with L-dop/carbidopa without any benefits. However, after switching to valproate, seizures were well controlled, indicating that cortical tremor is not responsive to alcohol or l-dopa/carbidopa. The outcomes of all of the five patients were good, with three patients being seizure-free and two patients suffering from rare seizures only when feeling mentally stressed or sleep deprived.

However, the conclusions drawn from our study are limited by its retrospective design and the small number of cases, moreover, there is also a recruitment bias due to the fact that photosensitivity is more common in women. The genetic cause of FCMTE has long remained elusive, however, we were unable to attain data on whole-genome sequencing for each family group due to the cost of this procedure. It is possible that distinct phenotypic traits in our patients might reflect different genetic mutations. Another limitation is the EMG channels which were only placed on proximal muscles (deltoid and quadriceps), and not on distal muscles, regarding the myoclonic tremor. Future multicentre and well-designed studies are therefore warranted to further define sensitive visual features and delineate the potential pathogenicity of FCMTE.

Conclusions

Visual sensitivity associated with well-characterized clinical-EEG features is a core feature in some patients with FCMTE syndrome. Therefore, standard IPS and different eye state procedures should be routinely implemented for patients with FCMTE in order to better define the electroclinical features. Moreover, further investigation is recommended to better understand the underlying pathological mechanisms of visual sensitivity. ■

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

Acknowledgements and disclosures.
We are grateful to all the parents for their cooperation in this study.
None of the authors have any conflict of interest to declare.

Ethical statement.
The study was approved by Xijing Hospital Research Ethics Committee. All authors report that they have conformed to the principles of ethics in publishing and ethical guidelines for journal publication, and written informed consent was obtained from the parents regarding publication of this report.

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Legend for video sequences

Video sequence 1

Patient 6 was a 63-year-old male at the time of EEG monitoring. During wakefulness, the EEG showed eye-opening-related paroxysmal slow waves mixed with spike-waves, mainly in the occipital region, and eye opening was always associated with cortical myoclonic seizures. In contrast, eyes closed made the EDs and seizures disappear (note: the two channels, Fp2 and F4, are artifacts).

Video sequence 2

Patient 1 was a 42-year-old female at the time of EEG monitoring. During wakefulness, the patient presented with myoclonic jerks involving both the upper and lower limbs, triggered by eyes closed. The ictal EEG showed focal pseudo-periodic spike-wave activity during the eyes closed state, prevalent over the central-parietal-occipital region, as well as paroxysmal arrhythmic generalized spike-wave activity mainly on the frontal region associated with pseudo-rhythmic myoclonic activity. EDs with seizures disappeared upon eye opening.

Video sequence 3

Patient 2 was a 67-year-old female at the time of EEG monitoring. During wakefulness, the patient presented with continuous, arrhythmic, mainly distal twitches in the hands at rest, with diffuse 8-10-Hz spike-waves with fast waves on EEG.

Video sequence 4

Patient 5 was a 50-year-old female at the time of EEG monitoring. During wakefulness, the patient presented with continuous distal arrhythmic twitches in the hands and eyelids. The EEG revealed diffuse 4-6-Hz slow-waves mixed with spike-waves on the occipital region, and paroxysmal generalized spike-waves mainly with frontal predominance during the eyes closed state. EDs with CMT disappeared upon eye opening.

Key words for video research on www.epilepticdisorders.com

Phenomenology: not applicable
Localization: unknown
Syndrome: not applicable
Aetiology: genetic disorder

TEST YOURSELF

(1) What kind of tests should be performed during standard clinical EEG recordings to investigate visual sensitivity?

A. Intermittent photic stimulation (for photosensitivity)
B. Eye-opening and eye-closing test (for eye-opening/closure and eyes closed sensitivity)
C. Pattern test (for pattern sensitivity)
D. Hyperventilation

(2) Which of the following are correct regarding the treatment for patients with familial cortical myoclonic tremor and epilepsy:

A. Valproate, levetiracetam, and benzodiazepines are the first-line treatment.
B. Valproate is the drug most often reported to be effective for FCMTE with visual sensitivity.
C. For elderly FCMTE patients with comorbidity, drug-drug interactions should be considered.
D. Carbamazepine and gabapentin may worsen tremor/myoclonus.

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".