Original article

Epileptic Disord 2020; 22 (3): 281-90

Pitfalls in the diagnosis of Jeavons syndrome: a study of 32 cases and review of the literature

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Received May 19, 2019; Accepted February 09, 2020

ABSTRACT – *Aims.* Jeavons syndrome (JS) is mainly characterized by eyelid myoclonia with or without absences. It is thought to be underdiagnosed rather than have a rare prevalence. We aimed to investigate the electroclinical features of JS to determine possible factors influencing the diagnosis.
Methods. We retrospectively identified the medical records of 32 cases (0.55%) from 5,796 patients with epilepsy. The inclusion criteria were: (1) eyelid myoclonia with or without absences; (2) generalized paroxysmal activity on EEG; and (3) discharges triggered by eyelid closure and/or intermittent photic stimulation.
Results. Eighteen (56.2%) of the patients were female. The mean age at seizure onset was 8.7±5.3 years and the mean age at admission to hospital was 17.8±10.7 years. A family history of epilepsy was present in 15 (46.8%) patients. Eyelid myoclonias were noticed in six (18.7%) patients by themselves. Based on the analysis of video-EEG recordings, 26 (81.2%) patients were sensitive to eye closure, 22 (68.7%) had photoparoxysmal responses, and 16 (50%) presented with absence seizures. Ten (31.2%) patients had focal epileptic discharges. Eight (25%) patients were on monotherapy. Seven (21.8%) patients achieved seizure freedom. Three patients underwent ketogenic diet therapy, which was effective in two patients. A vagus nerve stimulator was implanted into three patients, one of whom reported seizure reduction.
Conclusions. Eyelid myoclonias are the main seizure type of JS but are usually overlooked. The time interval between seizure onset and clinical diagnosis suggests that this syndrome continues to be under-recognized. The genetic heterogeneity and phenotypic variability are likely to be more extensive than currently recognized, making the diagnosis more phalangine. [*Published with video sequence*].

Key words: Jeavons syndrome, eyelid myoclonia, absences, genetic generalized epilepsy

VIDEO ONLINE

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doi:10.1684/epd.2020.1162

Eyelid myoclonia with absences (EMA) has been recently recognized as a distinct type of non-motor generalized-onset seizure by the International League Against Epilepsy (ILAE). An epileptic syndrome characterized by EMA with well-defined clinical and electroencephalogram (EEG) features was first described in 1977 by Jeavons, who became the eponym of Jeavons syndrome (JS) (Striano *et al*., 2002). JS is considered as a separate entity among genetic generalized epilepsies (GGE) associated with eyelid myoclonias and brief absences related to generalized paroxysmal activity on EEG triggered by eye closure or intermittent photic stimulation (IPS) (Striano *et al*., 2002, 2009). The hallmark of EMA in this syndrome is the eyelid myoclonia, not the absences (Joshi and Patrick, 2007; Mourente-Diaz *et al*., 2007). Brief absences may or may not follow the eyelid myoclonias (Striano *et al*., 2009).

The onset of JS typically occurs in childhood with female predominance (Joshi and Patrick, 2007; Smith *et al*., 2018). The seizures are often highly resistant to treatment (Panayiotopoulos, 2005; Striano *et al*., 2009). Eyelid myoclonias occur many times per day, mainly after eye closure (Capovilla *et al*., 2009). Patients also commonly experience generalized tonic-clonic seizures (GTCS) and myoclonias of the limbs (Panayiotopoulos, 2005; Smith *et al*., 2018). Evidence from reports of concordant monozygotic twins and family studies has shown that JS has a strong genetic predisposition. Relatives of JS probands have heterogeneous epilepsy phenotypes that are almost exclusively generalized (Sadleir *et al*., 2012).

Although JS is a well-defined distinctive electroclinical syndrome with peculiar manifestations, it has many similar features with other idiopathic generalized epilepsy (IGE) syndromes and is thought to present phenotypic variability that is mores extensive than currently recognized (Ferrie *et al*., 1996). The number of reported cases of JS is very small, even in specialized epilepsy centres (Striano *et al*., 2002; Smith *et al*., 2018). The exact prevalence of JS is not known, but a study with strict selection criteria reported its prevalence as high as 12.9% among patients with IGEs, and 2.7% among all patients with epilepsy (Giannakodimos and Panayiotopoulos *et al*., 1996). Most patients do not become aware of their eyelid myoclonias and the diagnosis is usually established after the occurrence of GTCS or analysis of video-EEG (VEEG) (Wang *et al*., 2014; Topaloglu Tuac *et al*., 2017). Thus, it is not clear whether this is a true rarity or whether cases are under-diagnosed, misdiagnosed or diagnosis is at least delayed (Joshi and Patrick, 2007; Topaloglu Tuac *et al*., 2017; Smith *et al*., 2018). On this basis, we aimed to make a detailed investigation into the clinical and electrophysiologic features of JS in order to determine possible underlying factors influencing the diagnosis.

Materials and methods

The study was performed retrospectively by evaluating the medical records of 5,796 patients who attended the epilepsy centre in Cerrahpasa Medical Faculty, Department of Neurology, between 2002 and 2018. The patients who fulfilled the diagnostic criteria for JS and had regular follow-up for at least one year were included.

The inclusion criteria for the JS study group were as follows:

– eyelid myoclonia with or without absences;
– EEG showing generalized paroxysmal activity;
– and a history of discharges triggered by eyelid closure and / or IPS. Patients with neurological deficits, brain lesions, and abnormal background EEG were excluded from the study.

Demographic and clinical features, especially focusing on seizure history, family history, VEEG recordings, neuroimaging, and cognitive status of all patients were investigated. In the event of missing data, telephone calls were made with the patients or their relatives. The literature between 1989 and 2019 was searched using PubMed as a database using the search terms "JS", "eyelid myoclonia", "eyelid myoclonia with or without absences", "genetic generalized epilepsy", and "idiopathic generalized epilepsy".

Statistical analysis was performed using the NCSS 2007 software package. All data are reported as mean±standard deviation, frequency, and percentages.

Results

Thirty-two patients fulfilled the inclusion criteria for JS and were included in the study. This accounted for 0.55% of the patients with epilepsy in our epilepsy centre. Eighteen (56.2%) of the patients were female. The mean age at seizure onset was 8.7±5.3 (range: 2-20) years, and the mean age at admission to hospital was 17.8±10.7 (range: 7-63) years. The mean follow-up period of the patients was 4.1±2.9 years, with a minimum of one year and a maximum of 12 years. *Table 1* summarizes the main features of the patients with JS. Seven (21.8%) patients had a history of febrile seizures. A family history of epilepsy was present in 15 (46.8%) patients. We also investigated the pedigrees of two families that were under follow-up in our clinic, of which members with JS were included in this study. In the first family, the parents were second-degree relatives and the mother had been diagnosed with IGE.

Table 1. Demographic and clinical features of patients with Jeavons syndrome (*n*=32).

Demographic features	
Sex (females: *n*, %)	18, 56.2%
Febrile convulsion (*n*, %)	7, 21.8%
Family history of epilepsy (*n*, %)	15, 46.8%
Poor school performance (*n*, %)	5, 15.6%
Clinical features	
Age at onset of epilepsy (years)	8.7±5.3
Delay of diagnosis (years)	9.1±5.4
Follow-up time (years)	4.1±2.9
Seizure types	
Absence seizures (*n*, %)	29, 90.6%
GTCS (*n*, %)	25, 78.1%
Limb myoclonia (*n*, %)	14, 43.7%
Atonic seizures (*n*, %)	1, 3.1%
EEG features	
Photoparoxysmal response (*n*, %)	22, 68.7%
Eye closure sensitivity (*n*, %)	26, 81.2%
Focal spikes on EEG (*n*, %)	10, 31.2%
Seizure control	
Seizure freedom (*n*, %)	7, 21.8%

GTCS: generalized tonic-clonic seizure.

The family had five daughters, two of the girls were diagnosed with JS, with a maternal uncle who had a history of febrile seizures. In the second family, there were seven siblings including three girls and four boys. The girls were under follow-up for different kinds of generalized epilepsies. One of the girls had JS and the other two had juvenile myoclonic epilepsy (JME) and IGE. Their paternal aunt and paternal grandmother were also diagnosed with IGE.

Eyelid myoclonias were noticed in only six (18.7%) patients by themselves or by their relatives, and for the remainder were observed during follow-up through analysis of VEEG. The patients had eyelid myoclonias in addition to one or more other types of seizure. Eyelid myoclonia, as the only seizure type, was reported in only one (3.1%) patient. Twenty-nine patients (90.6%) had absence seizures, 25 (78.1%) had GTCS, 14 (43.7%) had myoclonic seizures, one (3.1%) had atonic seizures, and one patient (3.1%) had oral automatisms. Precipitating factors for seizures included sleep deprivation in 14 (43.7%) patients, stress and anxiety in nine (28.1%), infections in eight (25.0%), poor drug compliance in six (18.7%), menstruation in three (9.4%), sunlight in two (6.2%), bathing in two (6.2%), and TV or video-games in two (6.2%) patients.

Ninety-six VEEG recordings were reviewed, which revealed 2-6-Hz generalized spike / polyspike-wave discharges with a duration of 0.5-10 seconds with normal background activity (*figure 1*). All patients presented with eyelid myoclonia with or without absences during the VEEG recordings (*video sequence*). Twenty-six (81.2%) patients showed eye closure sensitivity and 16 (50%) patients presented with absence seizures during the VEEG recordings. Twenty-two (68.7%) patients had photoparoxysmal responses, and 19 (59.3%) patients were reactive to hyperventilation. The oldest patient of this study, a 63-year-old male patient, continued to be photosensitive despite his age (Gülen Abanoz *et al*., 2018). Two (6.25%) patients demonstrated a tonic pattern on VEEG, and one (3.1%) had a pattern close to electrical status epilepticus in sleep (ESES). Fifteen (46.8%) patients had predominant frontal epileptiform discharges (ED), three (9.3%) had predominant occipital ED, and five (15.6%) patients had predominant ED both in the frontal and occipital regions. Also, focal ED were found in 10 (31.2%) patients in addition to generalized discharges. The focal ED were investigated and shown to be in bilateral frontal regions in five (15.6%) patients, bilateral occipital regions in one (3.1%), left temporal region in one (3.1%), right occipital region in one (3.1%), and bilateral frontal or occipital regions on different EEG recordings in two (6.2%).

Sleep EEG was performed in 29 (90.6%) patients. The ED identified in the awake recordings had decreased in frequency and duration in 15 (51.7%) patients and increased in seven (24.1%) patients. In 12 (37.5%) patients, the ED increased after awakening. Eyelid myoclonias were observed during sleep in four (13.7%) patients. Cranial magnetic resonance imaging was performed in 14 (43.7%) patients, which revealed non-specific findings. Cognitive functions were found to be within normal limits, except for poor school performance in five (15.6%) patients.

All of the patients were receiving antiepileptic drugs (AEDs). Eight (25%) patients were on monotherapy, and the others were on two or more antiepileptic medications. Only seven (21.8%) patients achieved seizure freedom. Six of the patients who were seizure-free were taking monotherapy (three patients were treated with valproic acid, one patient with levetiracetam, one patient with clobazam, and one patient with topiramate), and the other seizure-free patient was under both valproic acid and clobazam. The mean duration of seizure freedom for these patients was 27.7±19.1 months (range: eight months to five years). Three patients underwent ketogenic diet (KD) therapy, one of whom became seizure-free, one reported 80% seizure reduction, whereas the third patient gained no benefit. The patient with 80% seizure reduction using KD was investigated for the presence of *SLC2A1* gene mutation but this was not found. Also, a vagus nerve stimulator was implanted into three patients and only one reported 60-70% seizure reduction.

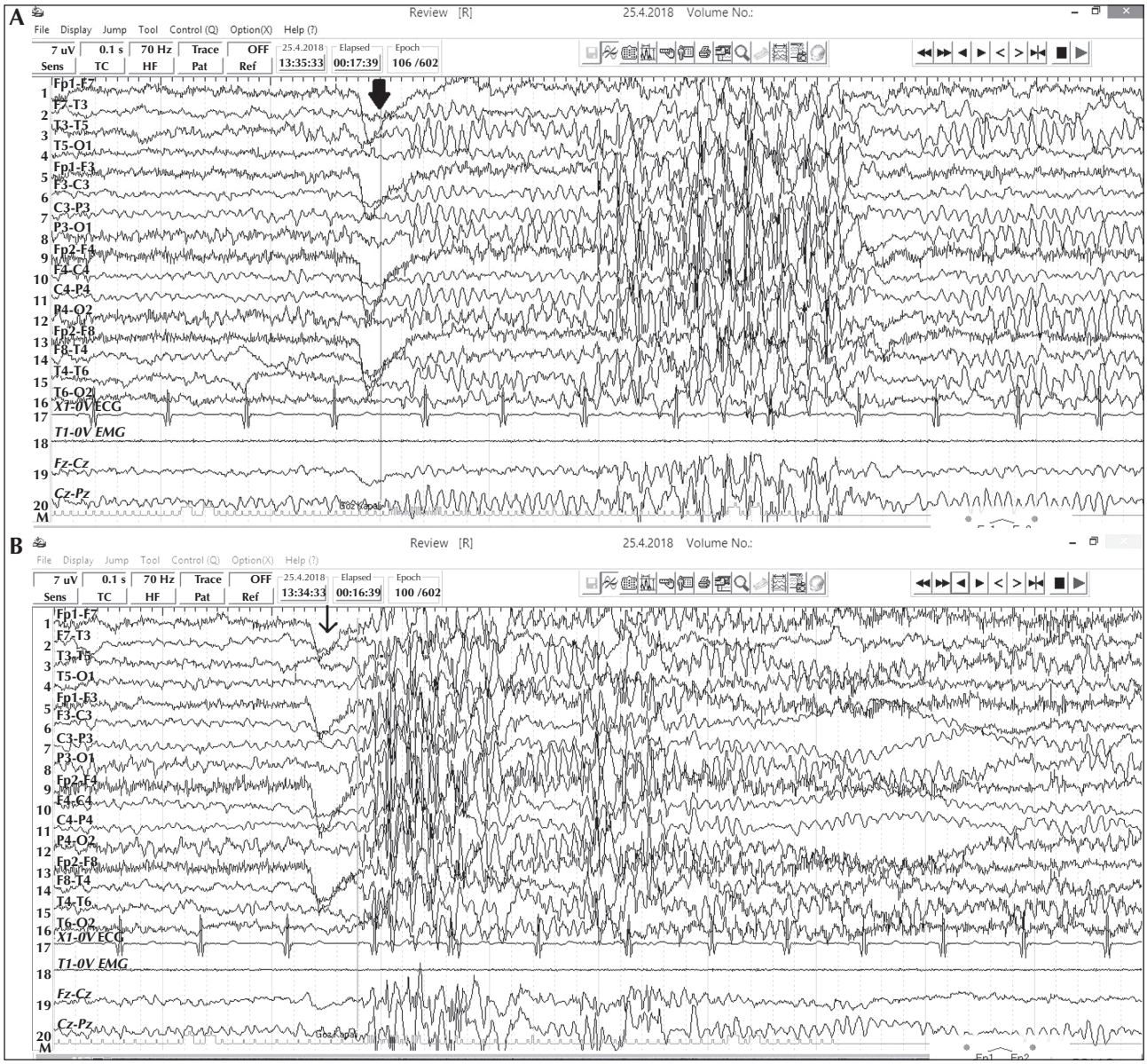

Figure 1. (A) Longitudinal bipolar EEG montage during IPS showing the induction of generalized spike-wave and polyspike-wave discharges, two seconds after eye closure (thick arrow); the discharges are associated with eyelid myoclonia. (B) The discharges appear immediately after eye closure (thin arrow) without a latent period on the same EEG (low-frequency filter: 0.3 Hz; high-frequency filter: 70 Hz; notch filter: 50 Hz).

Discussion

Among the GGEs, JS deserves to be a distinct epilepsy type based on specific seizure features, electroclinical findings, and resistance to treatment. Most studies indicate that there is an under-recognition, misdiagnosis or at least a delay in the diagnosis due to different causes, which makes estimating the exact prevalence very hard (Striano *et al.*, 2002; Wang *et al*., 2014; Smith *et al*., 2018). *Table 2* summarizes the main features reported in the studies reviewed. We found that 0.55% of the patients with epilepsy in our department had a diagnosis of JS. This is exactly the same as the prevalence reported by Caraballo *et al*. (2009) (0.56%), but lower than that reported by Giannakodimos and Panayiotopoulos (1996) at 2.7%. JS is known to be observed in females more frequently, as with other photosensitive epilepsies (Striano *et al*., 2002; Viravan *et al*., 2011; Smith *et al*., 2018). However, in contrast to other studies, we found the sex ratio to be almost equal, which is similar to the study performed with 50 Chinese patients diagnosed with JS (Wang *et al*., 2014).

Table 2. The main features of the studies included in the references.

Author, year	Number of patients	Sex (F:M)	Mean age (years)	Outcome
Capovilla *et al.*, 2009	18	10:8	24,3	Patients with eyelid fluttering, typical EEG pattern of EMA patients and impaired intellectual function can constitute a homogeneous subgroup of patients with EMA.
Caraballo *et al.*, 2009	63	38:25	7,5	EMA associated with infrequent GTCS should be recognized as JS. Early-onset EMA refractory to AED and intellectual disability may be a variant of JS. EMA with GTCS and/or massive myoclonias or GTCS induced by IPS may be a subgroup of patients with IGE.
Destina Yalçın *et al.*, 2006	4	4:0	15	Four patients whose diagnosis are compatible with either EMA or JME were reported, supporting that these are dynamic syndromes that tend to evolve into one another.
Dragoumi *et al.*, 2018	2	2:0	13,5	Two cases presented with EMA but demonstrated prominent myoclonic seizures, atonic components and cognitive impairment suggesting an atypical JS variant or an overlap GGE phenotype.
Ferrie *et al.*, 1996	9	5:4	13.2	Patients with EMA have wide phenotypic expression of EMA and include: typical cases, possible atypical cases or cryptogenic/symptomatic epilepsies.
Fournier-Goodnight *et al.*, 2015	6	4:2	11	Overall, cognitive ability of patients with JS ranged from low average to borderline impaired; no participants could be accurately described as impaired or having intellectual disability.
Galizia *et al.*, 2015	635	-	-	*CHD2* mutation is the first identified cause of EMA.
Galli *et al.*, 2018	108	56:52	7.5	In the follow-up of 108 patients diagnosed with childhood absence epilepsy, five of them evolved to EMA.
Giannakodimos *et al.*, 1996	11	11:0	30.9	The clinical and EEG features of EMA were identified in 11 patients.
Giuliano *et al.*, 2019a	51	40:11	30.8	Family history indicates better outcome, and photosensitivity and eye closure sensitivity are associated with the persistence of seizures in patients with EMA.
Giuliano *et al.*, 2019b	10	7:3	23.1	Abnormal occipital and frontal cortex activities seem to be related with visual sensitivity and eyelid myoclonia in patients with EMA.
Harding *et al.*,1997	100	72:28	27	Photosensitivity persists in at least two thirds of patients with photosensitive epilepsy.
Joshi *et al.*, 2007	71	42:29	8.6	The diagnosis of EMA can be made with clinical history and routine EEG.
Liu *et al.*, 2008	4	2:2	10.25	Activation in the thalamus may be associated with generalized spike waves in EMA.

Table 2. The main features of the studies included in the references (*continued*).

Author, year	Number of patients	Sex (F:M)	Mean age (years)	Outcome
Nar Senol *et al.*, 2015	61	45:16	27.4	EMA meets the criteria for an epileptic syndrome but eyelid myoclonia can be seen in symptomatic epilepsies.
Sadleir *et al.*, 2012	18	12:6	4	Family history was found in 83% of patients with JS suggesting a complex inheritance with shared genetic determinants.
Smith *et al.*, 2018	30	24:6	7.3	GTCS and seizure types other than absence seizures may be predictors of drug-resistant epilepsy in patients with JS.
Smith *et al.*, 1996	11	8:3	30.8	The combination of brief absences, eyelid myoclonia and eyeball retropulsion and normal neurological examination is sufficient to indicate that EMA is a discrete syndrome of IGE.
Striano *et al.*, 2002	35	22:13	6.5	EMA was thought to be underdiagnosed and 7.46% of patients with IGE were classified as EMA.
Topaloglu Tuac *et al.*, 2017	12	8:4	13.5	JS can be misdiagnosed or overlooked. Focal or asymmetric findings on EEG are not uncommon.
Viravan *et al.*, 2011	12	11:1	4.9	The occipital cortex may initiate the generalized epilepsy network of the JS.
Vaudano *et al.*, 2014	15	13:2	25.4	Eye closure sensitivity in patients with EMA involves a circuit of the visual cortex, the thalamic pulvinar and the frontal lobe networks for the control of eye closure and gaze.
Wang *et al.*, 2014	50	25:25	8 / 5.8	There may be two subtypes of JS: a predominantly male group with frontal predominant ED, eyelid myoclonia and eyes that roll upwards; and a predominantly female group with only occipital predominant ED and eyelid myoclonia.
Yeni *et al.*, 2011	2	0:2	11	A patient with JS and his twin brother with photosensitive epilepsy were reported.
Zaiwalla *et al.*, 1996	6	1:5	11.5	EMA is a distinct but uncommon epilepsy syndrome which overlaps with other types of IGE.

EMA: eyelid myoclonia with absence; GTCS: generalized tonic-clonic seizure; JS: Jeavons syndrome; AED: antiepileptic drug; IGE: idiopathic generalized epilepsy; JME: juvenile myoclonic epilepsy; GGE: genetic generalized epilepsy.

This different sex distribution may be due to the different genetic backgrounds of different populations.

In our study, there was a nine-year time interval between the onset of seizures and admission to hospital. Eyelid myoclonias are defined as the first seizure type in JS, but they may be misinterpreted as behavioural problems and overlooked until the patients experience other types of seizures or a VEEG is performed (Joshi and Patrick, 2007; Wang *et al*., 2014; Smith *et al*., 2018). We found that only 18.7% of our patients were aware of their eyelid myoclonias. Topalogle Tuac *et al*. reported that seven of 12 patients with JS were admitted to hospital due to GTCS, although five of them had noticed their eyelid myoclonias with or without absences, which was not stated as an indication for admission (Topaloglu Tuac *et al*., 2017). Nar Senol *et al*. reported that there was a ten-year delay of diagnosis in patients with eyelid myoclonias with or without absences associated with upward rolling of the eyeballs, but a five-year delay for patients with eyelid myoclonias including massive myoclonias, absences, and GTCS (Nar Senol *et al*., 2015). In JS, absence seizures are inconsistent and very short in duration (Striano *et al*., 2002). Independent absences or absences with severe impairment of consciousness do not support the diagnosis (Ferrie *et al*., 1996). These become less frequent and more subtle with age, and are therefore easily neglected. The time interval between seizure onset and clinical diagnosis suggests that this syndrome continues to be under-recognized (Smith *et al*., 2018).

The clear boundary between JS and other IGE forms is still controversial (Ferrie *et al*., 1996). A family history of epilepsy in JS is reported at rates between 33% and 83% in different studies, and it is thought to be associated with a better outcome (Sadleir *et al*., 2012; Smith *et al*., 2018; Giuliano *et al*., 2019a). We found that a family history of epilepsy was present in 46.8% of our patient group, and the pedigrees of two families had an extensive spectrum of IGE types. A study investigating the families of 18 probands with JS suggested that there was a complex inheritance with shared genetic determinants overlapping with both classic GGEs and genetic epilepsy with febrile seizures plus (Sadleir *et al*., 2012). Yeni *et al*. reported an 11-year-old male patient with a diagnosis of JS whose twin brother was diagnosed with a photosensitive epilepsy, supporting the idea of a shared genetic basis with heterogenous phenotypic expression (Yeni *et al*., 2011). The *CHD2* mutation on chromosome 15q26.1 region was the first identified cause of this distinct epilepsy syndrome (Galizia *et al*., 2015). One of the unique *CHD2* variants was shown to have arisen as a *de novo* mutation which may explain the phenotypic variability that leads to the unusual presentation of patients, causing the under-diagnosis of JS.

In JS, seizure types other than EMA are also present. GTCS are thought to occur in more than half of the patients and are probably inevitable in the long term (Striano *et al*., 2002; Panayiotopoulos, 2005). Myoclonic seizures of the limbs are seen more rarely (Panayiotopoulos, 2005). In our study, GTCS and myoclonic seizures were detected more frequently compared with other studies. We also described patients with atypical features, one (3.1%) with atonic seizures, one (3.1%) with oral automatisms, one (3.1%) with an EEG pattern close to ESES, and two (6.2%) with tonic patterns on VEEG. Automatisms and tonic or atonic seizures were reported not to be compatible with JS (Ferrie *et al*., 1996; Giannakodimos and Panayiotopoulos, 1996). Oral automatisms and the ESES pattern on EEG in JS have not been reported previously. Based on a study with 30 JS patients, one (3.3%) of these patients had tonic seizures and four (13.3%) other patients had atonic seizures (Smith *et al*., 2018). However, the patients in our study were diagnosed with JS based on normal neurological examination and neuroimaging, in addition to electroclinical findings consistent with JS. These unusual findings could be due to genetic heterogeneity and might enlarge the spectrum of seizure types associated with JS. For JS, it is known that seizures persist into adulthood, but it is not clear if the clinical characteristics of the seizures remain the same or evolve with age (Smith *et al*., 1996). Galli *et al*. reported that 4.6% of patients with childhood absence epilepsy progressed to JS (Galli *et al*., 2018). Destina Yalçin *et al*. reported four female patients showing the characteristics of both JS and JME (Destina Yalçin *et al*., 2006). Moutaouakil *et al*. reported a male patient who was diagnosed with benign myoclonic epilepsy of infancy when he was aged five months, which evolved to JS when he was aged ten years (Moutaouakil *et al*., 2010). These findings suggest that there is an overlap among the types of IGE, and that these epileptic syndromes are not static, but rather dynamic syndromes that evolve into one another over time with a possible continuum mediated by a common genetic abnormality. Thus, it seems more logical to consider JS as a system epilepsy with a high susceptibility to changes in the brain network (Wang *et al*., 2014; Nar Senol *et al*., 2015; Takahashi *et al*., 2015).

Photosensitivity is accepted as the main feature of JS (Gülen Abanoz *et al*., 2018). It was present in 68.7% of our patients. Photoparoxysmal discharges are reported in all untreated young patients, but may be absent or reduced due to aging or the effect of antiepileptic therapy (Joshi and Patrick, 2007; Striano *et al*., 2009; Nar Senol *et al*., 2015). Therefore, in our study, we might have had a higher ratio of photosensitive patients if they were younger and not taking medication. The eldest patient of our study, despite being

aged 63 years and seizure-free on antiepileptic treatment, had ongoing photosensitivity (Gülen Abanoz *et al*., 2018). This unusual presentation is thought to be due to genetic heterogeneity and the complexity of photosensitivity.

Although JS is a type of generalized epilepsy, focal abnormalities were observed in 31.2% of our patients, which is very similar to the findings of Viravan *et al*. who reported their presence in four of 12 patients, but much lower than that from another study, noted in eight of 12 patients (Viravan *et al*., 2011; Topaloglu Tuac *et al*., 2017). In addition to this, 6.2% of the patients in our study had focal ED in the frontal or occipital regions based on their different EEG recordings. An EEG-functional magnetic resonance imaging (fMRI) study revealed that the patterns of activation and deactivation were bilaterally symmetrical in JS, in support of JS being categorised as an IGE (Liu *et al*., 2008). The occipital cortex seems to have a role in the pathophysiology of JS based on eye closure-induced seizures and photosensitivity. Giráldez and Serratosa (2015) reported a patient diagnosed with JS who presented with IPS-induced focal seizures originating from the occipital lobe. Another study demonstrated a significant reduction in physiological alpha activity over the occipital lobe in patients with JS, and noted that lower alpha activity could be found in activated areas (Giuliano *et al*., 2019b). On the other hand, stimulation of the frontal eye field located in the frontal cortex induced vertical upward eye movements, and if the stimulus was prolonged, retropulsion of the head occurred, which is consistent with the features of seizures in JS (Kaiboriboon *et al*., 2012). A study conducted in 50 patients with JS reported that upward rolling of the eyes was observed in 14 of 32 patients with predominant frontal ED, but was seen in only one of 18 patients with predominant occipital ED (Wang *et al*., 2014). Eye closure sensitivity was shown to involve a circuit of the visual cortex, the thalamic pulvinar, and frontal lobe networks, and the abnormal excitation of the occipital lobes was shown to be influenced by the altered brain activity of the systems controlling eye movements and eye closure (Vaudano *et al*., 2014). The frontal cortex or the occipital cortex are thought to be triggering areas in the neural network of JS. The ED originating from one of these areas spread to other brain regions through either the transcortical or thalamocortical pathways to project the generalized discharges. This also supports the idea of frontal lobe or occipital lobe- originated system epilepsies, which is compatible with the notion of a continuum, rather than a distinction between focal and generalized epilepsies (Wang *et al*., 2014; Nar Senol *et al*., 2015; Takahashi *et al*., 2015).

Sleep is thought to have a facilitating effect for both clinical seizures and interictal ED for patients with epilepsy (Kotagal and Yardi, 2008). Although in JS, it is expected that the ED become briefer and fragmented in sleep, Wang *et al*. reported that the sleep EEG of patients with JS demonstrated a large number of ED and the frequency, amplitude, and duration of the ED were amplified without any seizures (Wang *et al*., 2014). Another study found that sleep increased the ED in four patients, reduced them in two, and had no effect in one patient. They also noted that the discharges were shorter during sleep and unaccompanied by discernible clinical manifestations (Giannkodimos and Panayiotopoulos, 1996). Inconsistent with these findings, we demonstrated that during sleep EEG, the ED were reduced in nearly half of our patients and were increased in nearly a quarter. We also found that four (13.7%) patients had eyelid myoclonias in sleep; to the best of our knowledge, this has not previously been reported in the literature.

Seizures other than eyelid myoclonias are usually controlled with AEDs. Mild eyelid movements without apparent absences, photosensitivity or EEG discharges continue with a tick-like behaviour, making it a lifelong disorder (Panayiotopoulos, 2005; Covanis, 2010). The cognitive status of these patients is usually normal except for slight deficits in rare cases (Striano *et al*., 2009; Wang *et al*, 2014). However, Capovilla *et al*. found that 18 of the 153 patients presenting with eyelid myoclonia and unremarkable neuroradiological findings showed impairment of intellectual functions varying from borderline level to moderate intellectual disability which may be an atypical form of patients presenting with eyelid myoclonia (Capovilla *et al*., 2009). Fournier-Goodnight *et al*. reported that none of these patients could be described as being impaired or having intellectual disability based on some high-order tasks (Fournier-Goodnight *et al*., 2015). There is also no evidence of cognitive deterioration with ongoing seizures (Zaiwalla, 1996). Accordingly, if patients with JS are resistant to treatment, patients can be kept on a single moderate dose of AED to protect them against GTCS. We found that 21.8% of our patients were seizure-free with a mean duration of 27.7 months. Similar to our results, Joshi *et al*. reported that 28% of patients with JS became seizure-free (Joshi and Patrick, 2007). By contrast, another study stated that for 80% of their patients, multiple AEDs were unsuccessful due to adverse effects and ineffectiveness of treatment (Smith *et al*., 2018). AED therapy may also change or suppress seizure semiology, which is another factor for misdiagnosis (Striano *et al*., 2002; Nar Senol *et al*., 2015). The treatment options of KD therapy or vagus nerve stimulation (VNS) for JS were mentioned in only one study in which three of four patients with VNS and two of three patients taking KD therapy reported a reduction in their seizures (Smith *et al*., 2018). Although the information gained from only two studies provides little

evidence supporting the effect of VNS or KD therapy in patients with JS, we believe that these types of treatment could be used more commonly for drug-resistant seizures based on further research.

JS is a relatively homogeneous epileptic syndrome without a clear-cut boundary separating it from other IGE types. There are some challenges in the diagnosis and its classification still seems to be a debatable issue for the ILAE. The genetic heterogeneity and phenotypic variability may lead to an underestimation of the clinical presentations, which makes the diagnosis more difficult. Eyelid myoclonias are the main seizure type, but are usually misinterpreted or overlooked until other types of seizures develop or a VEEG is performed. Photosensitivity can be reduced or may even completely disappear with age or AED therapy. Age or AED therapy can also make both absence seizures and other types of seizures more subtle. Thus, if the diagnosis is not made in the early period, it can easily be neglected. Also, focal abnormalities are not very rare in this generalized type of epilepsy, which may also misdirect the management. These findings suggest that the estimation of the true prevalence of JS is not easy to establish and is probably much higher than reported in the literature. The diagnosis may be difficult or confusing, especially for adult patients. For adult patients on appropriate treatment with electroclinical features compatible with JS, the lack of some features should not directly exclude the diagnosis, instead these patients should be monitored under close follow-up until such features are demonstrated. Future clinical and genetic research will help to better clarify this distinct, but uncommon, epilepsy syndrome. □

Legend for video sequence

Sample from a VEEG of a patient with JS. The discharges occur after eye closure during IPS and show a strong association with eyelid myoclonia. They are brief and do not persist during the remaining period when the eyes are closed.

Key words for video research on www.epilepticdisorders.com
Phenomenology: eyelid myoclonia
Localisation: generalized
Syndrome: Jeavons syndrome
Aetiology: genetic

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

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

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TEST YOURSELF

(1) What is the main seizure type in JS?
A. Eyelid myoclonia
B. Absence seizures
C. GTCS
D. Myoclonic seizures
E. Atonic seizures

(2) Which of the following is one of the EEG features of patients with JS?
A. Normal background activity
B. Generalized spike / polyspike wave discharges
C. Eye closure sensitivity
D. Photoparoxysmal discharges
E. All of them

(3) Why is there an under-recognition or a delay in the diagnosis of JS?
A. Eyelid myoclonias can be misinterpreted as behavioural problems or can be overlooked until the patients experience other types of seizure or a VEEG is performed.
B. The absence seizures of JS are inconsistent and very short in duration. Also, they become less frequent and more subtle with age, and can therefore easily be neglected.
C. Photosensitivity can decrease or even completely disappear with age or antiepileptic therapy.
D. Genetic heterogeneity and phenotypic variability may lead to underestimation of the clinical presentation, making the diagnosis even more challenging.
E. All of them

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".