

Juvenile myoclonic epilepsy and idiopathic photosensitive occipital lobe epilepsy: is there overlap?

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Summary

Although epileptic photosensitivity is well known, its genetics and syndromic associations are incompletely understood. Seizures triggered by photic stimulation are usually a manifestation of the idiopathic generalized epilepsies, especially juvenile myoclonic epilepsy (JME), or of the occipital epilepsies. Idiopathic photosensitive occipital epilepsy (IPOE) is a focal epilepsy with colourful elementary visual auras, often with conscious tonic head and eye version; myoclonus is not a feature. All seizures are induced by photic stimuli. We describe four families with phenotypic overlap between JME and IPOE. Families were identified if two or more affected individuals had visual auras and electro-clinical features of an idiopathic epilepsy. Family members underwent detailed electro-clinical assessment. In addition, 40 unrelated JME probands were investigated systematically for unrecognized features of IPOE (visual aura and conscious head version). There were 12 affected individuals in four families; 11 were female. Clinical onset was at 8–21 years of age. Of 10 patients with visual auras, six had conscious head version and five also experienced myoclonic jerks; eight had non-photically induced tonic-clonic seizures (TCS). Of the remaining individuals, one had myoclonic jerks and occipital spikes; the other had TCS without visual aura or myoclonic jerks. Of 10

patients with EEG studies, eight had generalized spike and wave (GSW) and six had occipital spikes. All had photosensitivity with GSW and four had additional occipital spikes. Of the 40 JME probands, six had visual aura and/or conscious head version; five of these were photosensitive. There is overlap between the clusters of clinical features used to diagnose IPOE and JME. Half of the affected individuals in our families with visual aura had myoclonic jerks; the former is characteristic of IPOE and the latter of JME. Importantly, visual aura is not regarded as part of JME, nor myoclonus part of IPOE, but our data emphasize that these symptoms may occur in both disorders. Moreover, two-thirds of individuals with visual aura had spontaneous TCS; the latter feature is not described in IPOE. Additionally, we demonstrate that visual aura and conscious head version are under-recognized features of JME, particularly among photosensitive patients. These findings could be explained by shared genetic determinants underlying IPOE and JME. Understanding the genetic basis of these disorders must account for the striking female predominance, the variable phenotypes associated with photosensitivity and the overlap of clinical features classically regarded as distinguishing focal and generalized syndromes.

Keywords: photosensitive; occipital; myoclonic; epilepsy; genetic

Abbreviations: GSW = general spike and wave; IPOE = idiopathic photosensitive occipital epilepsy; JME = juvenile myoclonic epilepsy; TCS = tonic-clonic seizures

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Introduction

Seizures triggered by environmental flicker may be a manifestation of the partial occipital epilepsies and specific subsyndromes of the idiopathic generalized epilepsies. Although a relatively uncommon feature of epilepsy overall (Quirk *et al.*, 1995), photosensitivity is well known to the public, and is of increasing importance with phenomena such as video game-induced seizures. Photosensitivity is genetically determined and occurs predominantly in females (Waltz and Stephani, 2000). No genes have been identified for photosensitivity. Careful analysis of the associated syndromes is the key to identification of the underlying genes.

Idiopathic photosensitive occipital epilepsy (IPOE) (Guerrini *et al.*, 1995) is a recently described, apparently uncommon, focal epilepsy beginning in late childhood or adolescence. As initially described, seizures are always triggered by environmental photic stimulation such as the television (Guerrini *et al.*, 1995; Yalcin *et al.*, 2000). They begin with colourful elementary visual symptoms with or without blurred vision and the patient may feel 'drawn towards' the photic stimulus. Conscious tonic head and eye version, nausea, vomiting and headache ensue even when the patient is removed from the photic stimulus (Guerrini *et al.*, 1995). Seizures are usually diurnal, last minutes to hours and rarely secondarily generalize (Yalcin *et al.*, 2000). Absence and myoclonic seizures are not described. A history of febrile convulsions or idiopathic generalized epilepsy in relatives may be observed (Guerrini *et al.*, 1995), but little is understood regarding the genetic basis of IPOE. The interictal EEG shows bilateral spontaneous synchronous or asynchronous occipital spikes or spike and wave of negative polarity at the occiput, unilateral occipital spikes and/or generalized spike and wave (GSW) discharges (Guerrini *et al.*, 1995, 1997; Yalcin *et al.*, 2000). Epileptiform activity is not affected by eye opening and may only be obvious with a midline occipital electrode at O_z (Guerrini *et al.*, 1995). Intermittent photic stimulation induces an occipital photoparoxysmal response and may induce generalized discharges with a wide range of flash frequencies (5–40 Hz) (Guerrini *et al.*, 1995). Management includes avoidance of provocative factors such as environmental photic stimulation, and antiepileptic therapy if seizures are frequent. Sodium valproate monotherapy is effective for photosensitive epilepsy (Chadwick, 1987), although specific studies in IPOE have not been reported.

Juvenile myoclonic epilepsy (JME) is a common subsyndrome of the idiopathic generalized epilepsies. Myoclonic seizures are the hallmark of JME, and generalized tonic-clonic seizures (TCS) usually occur; absence seizures are seen in one-third of patients. The interictal EEG shows generalized polyspike wave discharges on a normal background. Focal features occur in >50% of patients, such as focal slowing, focal onset of generalized discharges, focal sharp waves and frontal or occipital features during the photoparoxysmal response (Grunewald *et al.*, 1992; Grunewald and Panayiotopoulos, 1993; Niedermeyer, 1996). Photic

sensitivity is typically seen in 30% of cases, particularly in female patients (Janz, 1985), although it has been described in up to 90% of cases after prolonged photic stimulation (Appleton *et al.*, 2000). Sodium valproate is first line therapy (Thomas *et al.*, 2002).

IPOE and JME share some characteristics; both are idiopathic, commence in childhood or early adolescence, exhibit photic sensitivity and have generalized activity. The neurobiological relationships between these epilepsy syndromes remain to be fully explored, and family studies provide insights into their inter-relationship. In particular, family studies of IPOE have not been reported. Here, we use the power of family studies to interrogate the relationship between these syndromes under the hypothesis that there may be clinical and genetic overlap. We also systematically questioned 40 unrelated probands with JME, 20 of whom had proven photosensitivity on EEG, to determine if occipital symptoms have been underappreciated in JME.

Methods

Family studies

Recruitment of families

Families were obtained through referral to the First Seizure Clinic of the Austin Health, and the Epilepsy Genetics Clinic of the Royal Children's Hospital, Melbourne, Australia, and the investigators' private practices. Four families were identified where two or more affected individuals had visual auras and electro-clinical features of an idiopathic epilepsy.

Clinical diagnosis

Available living affected family members underwent detailed clinical assessment including a personal interview using a validated seizure questionnaire (Reutens *et al.*, 1992), neurological examination and neuroimaging. A 21-channel EEG, including intermittent photic stimulation and 3 min of hyperventilation, was performed on each person. An additional midline occipital O_z electrode was used in some cases, and two patients underwent long-term video-EEG monitoring. Strenuous efforts were made to obtain previous medical records and EEG recordings. Seizure types were classified according to the international classification of seizures. The diagnosis of JME was in accordance with the ILAE (International League Against Epilepsy) classification of epilepsy syndromes, and the features of IPOE were considered according to Guerrini's description (Commission on Classification and Terminology of the International League Against Epilepsy, 1981; Guerrini *et al.*, 1995).

Unrelated JME probands

Recruitment of 40 JME cases

JME patients were obtained through our epilepsy genetics database and had been referred from the epilepsy clinics at Austin Health and the investigators' private practices. All had primary generalized TCS and myoclonic seizures, and GSW on routine EEG. Twenty unrelated JME cases with photosensitivity as defined by GSW induced by

intermittent photic stimulation were recruited, as well as 20 unrelated cases without photosensitivity on EEG.

Clinical diagnosis

Each patient with JME underwent a personal interview using a structured questionnaire, specifically focusing on clinical photic and pattern sensitivity, photic-induced visual hallucinations, photic-induced seizure patterns and conscious head and eye version. An EEG recording including intermittent photic stimulation, with flash frequencies up to 60 Hz in some cases, was performed.

Results

Families with features of JME and IPOE: (Figs 1–4 and Table 1 for electro-clinical features)

Of the 12 affected individuals in four families, 11 were female. Mean clinical seizure onset was at the age of 11 years (range 8–21 years). Ten patients had visual auras including coloured circles or bright flashes of light, six with conscious head version; five also experienced myoclonic seizures; eight had non-photoc-induced TCS. Of the remaining individuals, one had myoclonic seizures and occipital spikes and the other had TCS without visual aura or myoclonus. Of 10 patients with EEG studies, eight had GSW and six had occipital spikes in the resting record. All had photosensitivity with GSW, and four had photic-induced occipital spikes.

Perinatal and developmental history, intellect, neurological examination, medical history and neuroimaging were unremarkable in all family members unless otherwise stated. None of the families studied had individuals with a history of febrile convulsions.

Family A (Fig. 1)

The proband (A-IV-3) is a 12-year-old girl who at 8 years of age, while watching TV, felt as if she were ‘pulled’ towards the

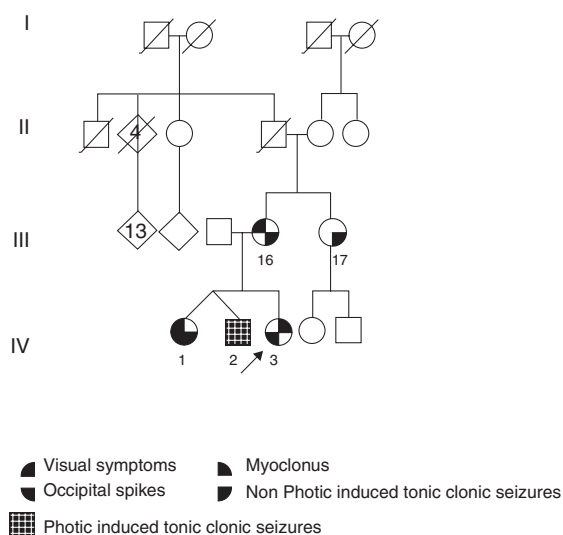


Fig. 1 Family A showing overlap in features of IPOE and JME.

screen, became unresponsive, stood motionless for 1 min then fell to the floor and vomited. She had eight similar seizures sometimes followed by a TCS. All events were triggered by watching the TV or computer or looking at leaves blowing in the trees on a windy day. All seizures were preceded by a ‘stomach ache’ or a ‘tinge of a headache’. She was seizure free on sodium valproate. She also described weekly arm and leg jerks both on awakening and sporadically during the day when relaxing, causing her to spill drinks; they were not triggered by photic stimuli.

Her 15-year-old sister (A-IV-1) experienced three episodes over months of complete visual loss while watching TV at 6 years of age. The episodes lasted up to 2 min; she remained alert, commented she was unable to see and slept. At 14 years of age while watching TV, she had two TCS not preceded by aura. Currently, she has monthly TCS precipitated by TV, stress or sleep deprivation.

Her 15 year-old brother (A-IV-2) reported two episodes commencing at the age of 15 years where he had TCS precipitated by playing video games on the television in the evening. He did not experience conscious head version, visual hallucinations or myoclonic jerks, and was diagnosed with idiopathic generalized epilepsy unspecified.

Their 43-year-old mother (A-III-16) had seizures beginning at 5 years of age. Her first and only seizure with visual aura occurred in front of the TV. She saw bright lights for 1 min, walked around disoriented and nauseated, followed by a TCS. She then avoided TV until 12 years of age. In the interim, she had a few TCS not preceded by visual symptoms, although some were precipitated by looking at reflected sunlight at the beach. As a teenager, she had frequent diurnal TCS precipitated by sleep deprivation, medication non-compliance or stress. She was treated initially with phenytoin and carbamazepine without control. Sodium valproate was effective. Currently, she has a single TCS from sleep every few years. Recordings of her childhood EEGs were unavailable for review. An EEG at 41 years of age was normal.

The proband’s maternal aunt (A-III-17), a 51-year-old woman, had a nocturnal TCS at 21 years of age associated with stress. Every 6 months since, she had episodes where she went ‘into a trance for a few seconds’, apparently stared, stopped talking, had a ‘dizzy feeling’ and had to sit down. In the mornings prior to these episodes, she ‘felt funny’. She has only had one other TCS and denied myoclonic seizures or visual symptoms. An EEG at 21 years of age showed epileptiform activity of unknown type as the EEG was unavailable for review. She is on phenytoin.

Family B (Fig. 2)

The proband B-IV-16, a 14-year-old girl, was the sixth child of consanguineous Lebanese parents. At 12 years of age, she went up to the TV to turn it off when she felt it was ‘too powerful’ for her. Subsequently she saw colourful moving balls, the colour green, then ‘a coloured reflection of the sun’. She sat down, conscious head version to the right followed and 2 min later she

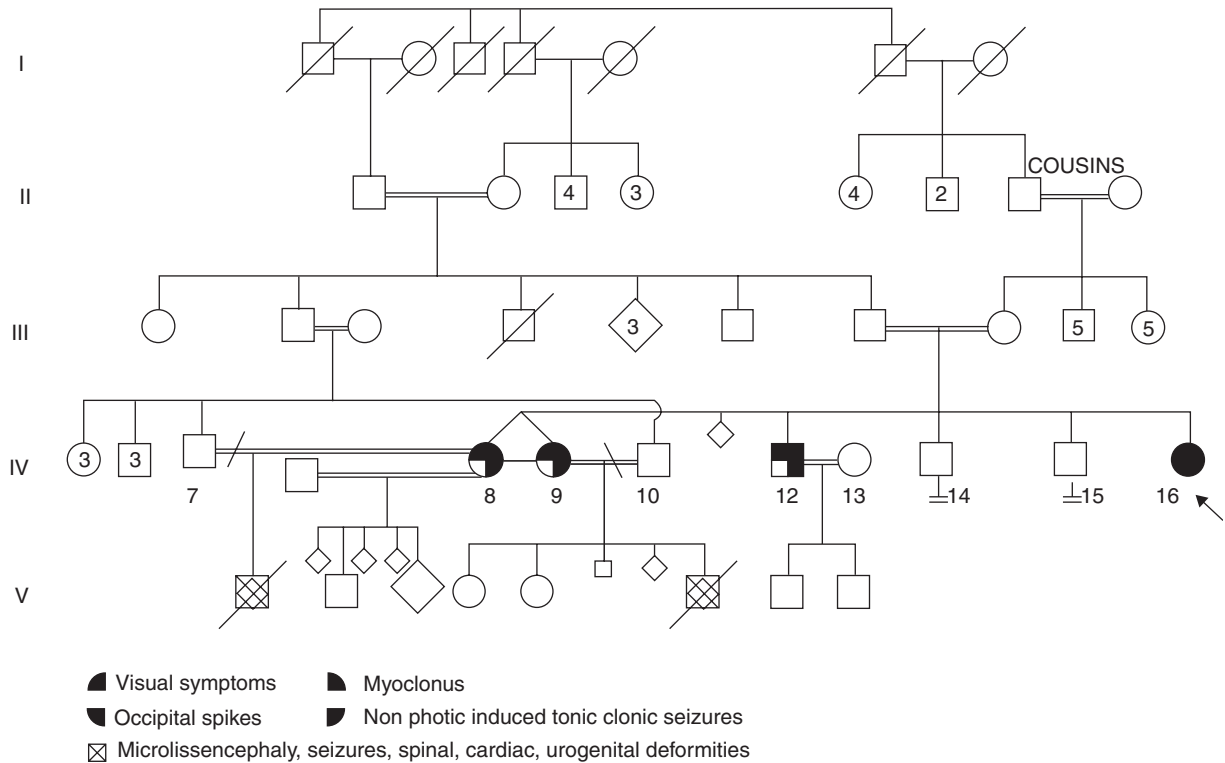


Fig. 2 Family B showing overlap in features of IPOE and JME.

lost awareness, followed by a TCS. In retrospect, she had had a similar episode without secondary generalization at 10 years of age. From 13 years of age, she developed daily myoclonic seizures exacerbated by stress, waking early and sitting too close to the TV. TCS in sleep have occurred. Sodium valproate provided seizure control.

Her 30-year-old brother, B-IV-12, had seizure onset at 11 years with TCS, myoclonic and absence seizures. He experienced generalized TCS on awakening, every few months until 26 years of age. TCS triggered by watching TV commenced with seeing ‘stars and circles’ followed by frightening conscious head and eye deviation, loss of awareness and a subsequent convulsion. He has weekly myoclonic seizures on awakening and triggered by playing soccer, sitting close to the TV or driving through tree-lined streets on sunny days. He also has brief absence seizures which last seconds and terminate with a myoclonic jerk. He is on sodium valproate.

The proband’s monozygotic twin sisters aged 32 years had seizures from 13 and 14 years of age, respectively. Twin 1’s (B-IV-8) first seizure was precipitated by watching TV. She complained of headache, saw colours, followed by conscious head version to the right and left, then right hemiclonic activity followed by secondary generalization. Other generalized TCS occurred on awakening, and in the shower. Her last TCS was at 26 years of age. Myoclonic seizures have continued frequently since 13 years, they are present on awakening and also precipitated by watching TV, stress and sleep deprivation. She has not had absence seizures. She is on sodium valproate.

Twin 2 (B-IV-9) had generalized TCS often whilst watching TV from 14 years of age. Initially she saw ‘coloured circles and stars’ followed by conscious head version, myoclonic jerks then a secondarily generalized convulsion. Her last TCS was at 30 years of age while watching TV. She also has frequent myoclonic seizures on awakening. She is on sodium valproate and clonazepam.

The twin sisters married brothers who were their first cousins. Twin 1 had three miscarriages in the first trimester (fetal sex unknown). She had a son who died at 4 years of age with seizures secondary to microlissencephaly, and spinal, cardiac and urogenital deformities (described by Gardner *et al.*, 2001). Twin 2 also had a son who died at 3 years of age with the same abnormalities, as well as two miscarriages; one was a male at 15 weeks gestation with an Arnold–Chiari malformation. Mutation of the *ARX* gene was not detected in twins 1 and 2. All family members were of consanguineous unions, and other distant relatives have also had multiple miscarriages.

Family C (Fig. 3)

The 18-year-old proband (C-IV-2) developed seizures at 11 years of age. Her first convulsion occurred while watching TV when unwell. No visual symptoms were reported. Some months previously, weekly staring attacks of 30 s duration were noted. Five further TCS occurred, one while reading out loud in class preceded by 2 min of seeing blotches covering words on the page, and one while watching a video, starting

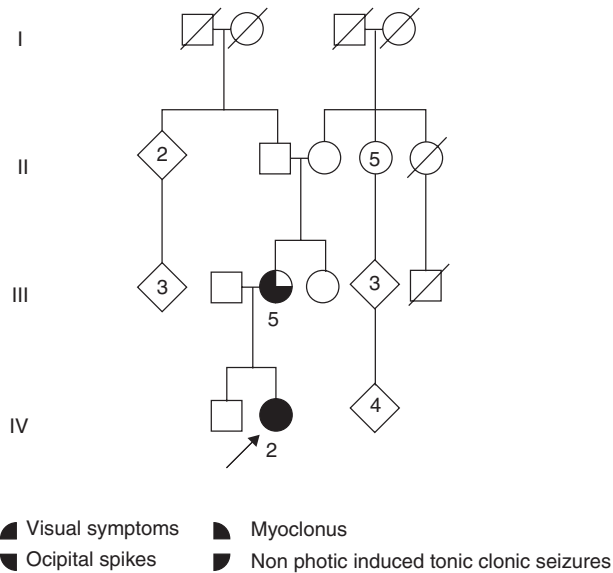


Fig. 3 Family C showing overlap in features of IPOE and JME.

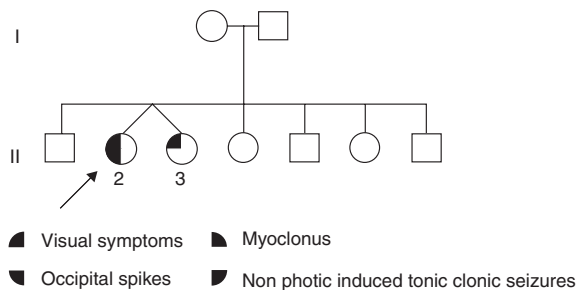


Fig. 4 Family D showing overlap in features of IPOE and JME.

with partial loss of awareness in which she could not understand what was being said for 2 min. Over the years, she experienced isolated events of ‘flashes of light’ in the corners of her eyes. She has myoclonic seizures on awakening with sleep deprivation, and takes lamotrigine.

Her 47-year-old mother (C-III-5) had TCS predominantly in the morning with sleep deprivation from age 24 years. Seizures were not controlled with carbamazepine or phenytoin. Valproate produced seizure freedom from the ages of 35–45 years. During this period, she experienced ‘sparkles’ in the corners of her eyes lasting 30 s. Recently, during a period of stress, she had an early morning TCS.

Family D (Fig. 4)

The proband is a 25-year-old computer operator (D-II-2), the first of monozygotic twins, who had seizures from 7.5 years of age precipitated by watching TV, video games, computer screens or the sunlight flickering through the trees. Seizures commenced with the feeling that her eyes were ‘glued’ to the screen and she became oblivious to her surroundings. The screen would then seem to spin, blur and the picture would

move off the screen, and then she felt her ‘neck and head turn’ to the left which she could not stop. Secondary generalization occurred. She refused anticonvulsants and avoided precipitants, and had two focal seizures per year. She was seizure free from 18 years of age.

Her identical twin sister (D-II-3) began having seizures at 8 years of age, always triggered by using the computer. Her seizures consisted of initial blurred vision, followed by colour change and a feeling of being ‘drawn’ into the computer with loss of awareness. Seizures stopped at 15 years of age without anticonvulsants. Neither twin had myoclonic seizures.

Occipital symptoms in sporadic JME

Forty unrelated patients with JME were analysed. Of 20 patients with a photoparoxysmal response on EEG, 13 reported clinical photosensitivity manifesting as myoclonic seizures or generalized TCS on exposure to light stimulation in everyday life. Three had associated visual symptoms such as flashes of colour or hallucinations lasting up to 1 min; in addition, two had associated conscious head version. Two other patients had isolated conscious head version. Of the 20 patients without photosensitivity on EEG, four had environmentally triggered myoclonic seizures or primary TCS, one had associated visual symptoms lasting 2 min, and none reported conscious head version.

Discussion

We describe four families with electro-clinical overlap between the classical features of two idiopathic epilepsy syndromes previously considered unrelated, JME and IPOE. We found that some patients with IPOE had myoclonic seizures and TCS without photic stimulation, features not included in the initial description of the syndrome. Initial recognition of this disorder was probably based on a select collection of ‘pure’ cases. Indeed, according to Panayiotopoulos (2002), other seizure types such as absence and myoclonic seizures as well as generalized TCS in sleep have been observed in this syndrome. Conversely, we found that family members previously regarded as ‘pure’ JME patients had prolonged visual auras and conscious head version previously not recognized. These findings call into question the neurobiological relationship of these idiopathic disorders and the overlap of generalized and focal epilepsies.

We investigated these findings further by examining 40 unrelated probands with JME for the presence of unreported visual aura and conscious head version. Twenty-five percent of 20 unrelated photosensitive JME patients had prolonged visual hallucinations and/or conscious head version. Visual symptoms among patients with JME may be more common than previously realized; visual auras may not be volunteered or may be misinterpreted as part of the photic stimulus. Similarly, conscious head version may not be described or may be discounted by the clinician once the history of TCS and myoclonic seizures is obtained in the setting of an EEG with GSW. The

Table 1 Electroclinical features of patients

Pedigree, references	A-IV-3	A-IV-1	A-IV-2	A-III-16	A-III-17	B-IV-16	B-IV-8	B-IV-9	B-IV-12	C-IV-2	C-III-5	D-II-2	D-II-3
Age of onset (years)	8	6	15	5	21	10	13	14	11	11	17	7	8
Age at study (years)	12	15	15	43	51	14	32	32	30	18	47	25	25
Gender	Female	Female	Male	Female	Female	Female	Female	Female	Male	Female	Female	Female	Female
Environmental photosensitivity	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Visual symptoms	No	Blind	No	Bright lights	No	Colour change, coloured reflection of sun	Colours, stars	Coloured circles, moving around, stars	Circles, stars	Blotches, flashes of light	Flashes of light in corner of eyes	TV screen spins, blur, then picture moves off the screen	Blurred vision, followed by colour change
Duration of visual Sx	N/A	2 min	N/A	1 min	N/A	1 min	Few seconds	1–2 min	1 min	2 min	30 s	20 s	20 s
Conscious tonic head version	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Ictal nausea	Yes	No	No	Yes	No	Yes	No	Yes	No	No	–	No	No
Myoclonus	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Yes	No	No	No
Absence	No	No	No	No	Yes	No	No	No	Yes	Yes	No	No	No
Spontaneous TCS	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
EEG													
Interictal focal spikes	O2,O1	T5,T6,O1	–	N/A	N/A	Yes	P3,P4,T5	T5,P3	No	O1,O2,T6	T5,O1,O2	T6	T3,T6,O2,Oz
Interictal GSW	4–5 Hz	5 Hz PSW	4–5 Hz	–	–	5–6 Hz	3–4 Hz	3–4 Hz	PSW	4–5 Hz PSW	4–5 Hz PSW	No	No
Photoc occipital SW	Yes	Yes	No	–	–	No	No	No	No	Yes	No	No	Yes
Photoc GSW or PSW	Yes	Yes	No	–	–	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ictal EEG	4–5 Hz	PSW	–	–	–	4 Hz PSW	4 Hz PSW	3–4 Hz PSW	4–5 Hz PSW	4–5 Hz	4–5 Hz	4 Hz	4–5 Hz PSW
Flash frequency (Hz)	9,17	5,17,20	–	–	–	–	20	15,20	–	15	9,12	16	16

SW = spike and wave; PSW = polyspike and wave; GSW = generalized spike and wave; N/A = not applicable; TCS = tonic-clonic seizure.

presence of visual aura and clinical photosensitivity in some of the 'non-photosensitive' group of JME probands is explained by state-dependent photosensitivity only elicited under conditions of stress, such as sleep deprivation or modified by anticonvulsants, which was absent on a routine EEG.

The observation of focal and generalized epileptiform discharges as well as the co-occurrence of focal and generalized seizure types within the one syndrome is not novel and may be explained physiologically by the thalamocortical system.

Previous clinical and EEG studies show a relationship between generalized and focal spike-wave discharges in some situations. In focal occipital epilepsies (Ricci and Vigeveno, 1993) and idiopathic generalized epilepsies (Obeid and Panayiotopoulos, 1988; Ricci and Vigeveno, 1993; Niedermeyer, 1996), focal occipital epileptiform discharges and/or GSW may be seen during the resting EEG and during photic stimulation. Focal cortical activation of generalized seizures is observed in reading epilepsy (Radhakrishnan *et al.*, 1995) and can be evoked by calculation (Goossens *et al.*, 1990) and eye closure (Vignaendra *et al.*, 1976). Focal cortical activation of focal occipital seizures (Naquet *et al.*, 1960) can be seen in patients with idiopathic generalized epilepsy during photic stimulation. Photic stimulation is a recognized cortical precipitant of GSW (Niedermeyer, 1996) and focal occipital spike and slow wave (Ricci and Vigeveno, 1993). In addition, a posterior seizure precipitated by photic stimulation can precipitate bursts of GSW (Naquet *et al.*, 1960). The posterior response was noted by Gastaut *et al.* (1959) in 15% of generalized epilepsies and may have a genetic origin (Jeavons and Harding, 1975).

Experimental observations, supported by limited clinical studies, show that GSW discharges are due to bilateral synchronous thalamocortical oscillations (Williams, 1953; Pollen, 1964; Niedermeyer *et al.*, 1969; Rossi *et al.*, 1969; Steriade and Llinas, 1988). The thalamocortical system is thought to be involved in the synchronization and propagation not only of generalized seizures but also of partial seizures (Williams, 1953; Niedermeyer *et al.*, 1969; Rossi *et al.*, 1969; Gutnick and Prince, 1972; Steriade and Llinas, 1988). Within the thalamocortical loop, there is evidence that either the thalamus (Williams, 1953; Quesney *et al.*, 1977; Hosford, 1995) or the cortex (Niedermeyer *et al.*, 1969; Gloor *et al.*, 1977; Quesney *et al.*, 1977; Steriade and Contreras, 1998) can initiate the ictal discharge, but evidence from thalamectomized animals suggests that even though cortically generated seizures may ultimately spread to the thalamus, the minimal substrate of such seizures is the neocortex (Steriade and Contreras, 1998). In addition, during cortically generated generalized EEG seizures in cats, thalamocortical neurons are powerfully inhibited (due to the prevalent excitation of thalamic GABAergic reticular cells) and do not fire any action potentials (Steriade and Contreras, 1995).

Studies in the photosensitive baboon, *Papio papio*, show that photosensitive discharges involve a focal (fronto-rolandic) cortical area initially before spreading secondarily to deeper subcortical structures prior to generalizing (Fischer-Williams

et al., 1968). During the photoparoxysmal discharges, motor cortical neurons are progressively activated (Silva-Barrat *et al.*, 1986) followed by activation of subcortical structures especially the reticular formation (which can perpetuate cortical activation), followed by thalamic activation (Menini *et al.*, 1981). This evidence of cortical-thalamic spread sheds light on the physiology of generalized discharges in the idiopathic generalized epilepsies (Naquet and Menini, 1978), the *P. papio* baboon being a good model of human generalized reflex epilepsy (Menini and Silva-Barrat, 1998).

Thus, in the families described here, the generalized clinical and EEG phenomena are likely to be due to bilateral paroxysmal thalamocortical discharges. The focal discharges and focal seizures may activate the same system, but only in restricted posterior thalamocortical circuits. This could explain the finding of focal occipital seizures, ictal head turning and subsequent generalized phenomena seen in our patients.

Autosomal dominant (Davidson and Watson, 1956; Herrlin, 1960; Watson and Marcus, 1962; Jeavons and Harding, 1975; Waltz and Doose, 1992; Doose and Waltz, 1993; Harding and Jeavons, 1994), autosomal dominant with age-dependent penetrance (Doose and Waltz, 1993; Waltz and Stephani, 2000) and polygenic (Doose and Gerken, 1973; Doose *et al.*, 1969a) modes of inheritance have been proposed for the trait of photosensitivity. Whilst rare dominant families appear to exist (Herrick *et al.*, 1975; Jeavons and Harding, 1975), the literature suggesting that this is the usual mode of inheritance of photosensitivity is flawed by ascertainment bias. For example, by examining siblings in families with both a photosensitive proband and a photosensitive parent, a dominant mode of inheritance has been claimed (Waltz and Stephani, 2000). Our interpretation of the literature concurs with a polygenic basis, as suggested by Doose *et al.* (Doose and Gerken, 1973; Doose *et al.*, 1969a, b, c)

The majority of our subjects were photosensitive and female. The trait of photosensitivity has been shown by some to be equally common among male and female family members (Davidson and Watson, 1956), yet others show conflicting results with a prominent female bias (Doose *et al.*, 1969a; Doose and Gerken, 1973). Harding and Jeavons (1994) noted that among their large cohort of patients with photosensitivity, the subgroup with the highest female to male bias was that comprising patients who had seizures evoked by flickering or bright light (but not the TV) in addition to spontaneous myoclonic seizures. This may well be in accord with our patients discussed here. Despite considerable interest in the search for photosensitivity genes, and a complex rearrangement of chromosome 2 described in a patient with refractory myoclonic photosensitive epilepsy (Van Esch *et al.*, 2002), no genes for the trait of photosensitivity have been found to date.

JME has a genetic aetiology with a polygenic basis. A positive family history of seizure disorders occurs in 30–50% of JME cases (Janz, 1985; Delgado-Escueta *et al.*, 1989). Phenotypic heterogeneity is typically seen, with affected family members having a variety of idiopathic generalized epilepsy subsyndromes (Bianchi *et al.*, 2003; Marini *et al.*, 2004).

Although one gene for JME has been determined in a single kindred with a rare form of autosomal dominant JME (*GABRA1* that encodes the $\alpha 1$ subunit of the GABA_A receptor) (Cossette *et al.*, 2002), *BRD2* is postulated as a possible susceptibility gene (Pal *et al.*, 2003), and mutations in *CLCN2* are associated with JME (Haug *et al.*, 2003), no genes have been identified definitively for the common form of JME with a polygenic basis.

The electro-clinical overlap between IPOE and JME is intriguing from a genetic standpoint. Both disorders are likely to follow polygenic inheritance, and our findings suggest that they may have some shared genetic determinants in the families discussed here. Perhaps each condition arises from a number of epilepsy genes and various combinations result in subtle phenotypic differences probably influenced by environmental factors such as photic stimulation. These families may be a key to the elusive photosensitivity genes and may present a more genetically homogeneous population in which to perform successful linkage studies.

Our study of four families emphasizes the electro-clinical overlap between JME and IPOE, further reinforced by the finding of focal symptoms in an unrelated cohort of JME patients. In patients with either of these syndromes, it is crucial that the clinician ask specifically about visual auras, conscious head version, myoclonic seizures and photic sensitivity. Furthermore, the electrographic findings in both syndromes include GSW or occipital spikes. This overlap may be due to shared genetic determinants. Finally, these observations have practical management implications. Focal features such as visual aura and conscious head version in JME might lead to a misdiagnosis of focal epilepsy. Indeed, a number of individuals in the four families were treated unsuccessfully with carbamazepine and phenytoin on this basis, yet later responded well to valproate. Had these features been recognized as part of the spectrum of JME, this would have led to initial successful treatment with valproate.

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