■ Clinical commentary

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Flashing lights and epileptic spasms: should we be routinely performing intermittent photic stimulation in infants?

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ABSTRACT

Abnormal cortical excitation in response to photic stimulation (photosensitivity) has historically been associated with generalized epilepsies, in patients outside of infancy. At our tertiary centre, we encountered a patient with infantile spasms secondary to a mutation in *ALG13* (c320A>G) who had photic stimulation-induced epileptic spasms over a broad range of frequencies on multiple EEGs, which were worse without treatment and decreased as treatment was escalated. This is the first reported case of epileptic spasms triggered by photic stimulation and it is unclear whether the phenomenon is unique to this patient, to those with this mutation or whether it is present in a broader group of patients with infantile spasms.

Key words: *ALG13*, epileptic spasms, photosensitivity

VIDEO ONLINE

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Photosensitivity, an abnormal cortical response to light, is a strongly genetically determined trait which occurs in a small proportion (~1%) of the normal population [1,2]. However, it is much more commonly associated with epilepsy [3] and testing for its presence is a standard part of a routine EEG. When an abnormal cortical response is triggered, it is known as a photoparoxysmal response (PPR); when the abnormal cortical response also results in clinical ictal phenomena, it is labelled a photoconvulsive response (PCR). Photosensitivity has not been extensively studied in children <three years old, but it is felt to be rare (~1% of patients tested) [3]. In all age groups, photosensitivity is typically linked to generalized epilepsies, from idiopathic generalized epilepsy (IGE) such as childhood absence epilepsy (CAE) and juvenile myoclonic epilepsy (JME) to eyelid myoclonia with absence seizures (EMA), to Dravet syndrome and even to neurodegenerative diseases such as the progressive myoclonic epilepsies [2-5]. However, while the trait of photosensitivity is found within the epilepsy spectrum, from the relatively benign (CAE) to the severe (neuronal ceroid lipofuscinoses [NCL]), there are no accepted guidelines on what age testing for this should start [6].

At our tertiary centre, intermittent photic stimulation (IPS: flashing lights at various frequencies during an EEG) is initiated after the age of one due to difficulties in cooperation with younger patients as well as a consensus that generalized epilepsy tends to present later in life. However, the idea that infants are unlikely to manifest with generalized epilepsy is evolving and seizure onset in infants has been recognized to be generalized, focal or "unknown" [7].

Here, we present the case of a patient with infantile spasms (IS) associated with a mutation in the asparagine-linked glycosylation 13 gene (*ALG13)* (c.320A>G (p.Asn107Ser)), an X-linked dominant mutation which results in severe developmental delay and epileptic encephalopathy [8, 9]. On multiple EEGs recorded between the ages of 13 to 18 months, the patient had reproducible PCR (epileptic spasms) or PPR triggered by photic stimulation.

Case study

Our patient was born to a mother with two previous children from different fathers who also had a single spontaneous miscarriage. During the pregnancy, there was exposure to daily cannabis and tobacco as well as occasional cocaine use during the first trimester. The pregnancy was otherwise uncomplicated, and the patient was born at full term, via planned C-section, 2,902 g, without complications.

There is a family history of epilepsy with a maternal aunt diagnosed with childhood epilepsy which resolved in adulthood. At age 13, the patient's mother began having nocturnal events triggered by "stress" that have been controlled with daily cannabis smoking.

At approximately four months of age, parents recognized abnormal movements: eye rolling, hip flexion and shrugging of her arms/shoulders. Over the next two months, these increased in frequency and began to cluster, typically occurring after waking up. At six and a half months of age, the diagnosis of IS was confirmed on EEG, and she was started on oral prednisolone.

She responded well to her initial oral prednisolone treatment, with clinical and electrographic resolution within one month. However, ~six months after stopping medication, there was recurrence of spasms and hypsarrhythmia on her EEG. Clinically, her spontaneous spasms involved flexion and extension of her limbs (right-sided, left-sided or bilateral) and trunk, which correlated electrographically with a diffuse high-amplitude sharp wave followed by decremental responses: low-amplitude, fast activity followed by attenuation. Her parents were reticent to begin steroid treatment a second time and alternative treatments (CBD oil, topiramate and vigabatrin) were utilized over the next four months with limited success. With the reintroduction of prednisolone and up-titration of vigabatrin, there were clinical and electrographic improvements, as the spasm frequency and her BASED score [10] both decreased (*table 1*). Despite relative improvements in amplitude and discharge abundance, interictally, her background EEG from the ages of 13 to 18 months continued to meet the definition of typical hypsarrhythmia, with multifocal independent epileptiform discharges and diffuse background slowing >200 µV (BASED 4) or >300 µV (BASED 5) [10].

The patient had 11 EEGs following her diagnosis of IS; six after the age of one which included IPS. In five of those EEGs, there was either PPR or PCR (*figure 1*), with spasms reproducibly triggered by photic stimulation during wakefulness (*video 1*). The spasms occurred at the onset (within 1-2 seconds) of the IPS trains, independent of their frequency. During the two EEGs in which the IPS was performed during sleep, there were only PPR (*figure 1C*). However, at 16 months of age, spasms were recorded during a brief awakening during the IPS (*table 1*). This mirrors the clinical phenotype whereby spasms do not typically occur during sleep [10].

The frequencies which resulted in photic-induced spasms included 1, 2, 6, 7, 9, 10, 11, 13, 14, 15, 16, 17, 18, 20, 23, 25, 30 Hz. Coloured filters were utilized in the last two EEGs and the response was blocked by blue filters (*figure 2*).

At around the time of her epilepsy diagnosis, she began to show clear evidence of global developmental delay and regression, and at two years of age, she remains significantly delayed with the approximate developmental level of a six-month-old infant. She is making gains, learning to roll over and to maintain her head upright while lying prone, but is unable to sit and is non-ambulatory. She also has visual impairments, with inconsistent visual fixing/following/tracking. While her development remains markedly abnormal, her appearance was and is unremarkable, without any distinctive features or malformations.

As part of her work-up for IS, a comprehensive epilepsy panel was tested by Blueprint Genetics (Seattle, WA, USA, www.blueprintgenetics.com). This revealed that the patient had a known pathogenic variant in the *ALG13* gene, c320A>G, (p.Asn107Ser), an X-linked dominant developmental and epileptic encephalopathy gene.

Discussion

IS is the most common epileptic syndrome in infancy (for a review see [11]), with peak onset at between four and eight months and an EEG pattern known as hypsarrhythmia: disorganized, high-amplitude waveforms intermixed with multi-focal spikes and a chaotic pattern of brain waves. IS have a myriad of causes (structural-genetic, structural-acquired, genetic, infectious, metabolic) [12] and, as such, both focal and (apparently) generalized clinical and EEG findings can be present. This uncertainty was recognized in the most recent ILAE classification of seizures, in which epileptic spasms are categorized as "unknown onset" [6].

While there have been reports of photosensitive myoclonic seizures in infants and young children with trisomy 13 [13] and benign myoclonic epilepsy of infancy [14], this is the first report of IS reproducibly triggered by IPS. The PPR in the different conditions mirrors the ictal and PCR semiology, with diffuse/generalized discharges occurring in trisomy 13 and BMEI, and multifocal (albeit posterior dominant) discharges in our patient. Given the predominance of photosensitivity in patients with IGE, perhaps it is unsurprising that this occurred in a patient with a genetic aetiology for her epilepsy. *ALG13* mutations have been increasingly reported in the literature, associated with a phenotype of developmental and epileptic encephalopathies. p.(Asn107Ser) (c.320A>G), the particular mutation of our patient has now been reported 37 times, and in all cases, the patients with this mutation have a drug-resistant epilepsy, typically with epileptic spasms and hypsarrhythmia as well as developmental delay, regression and visual impairment [8, 9].

Visual impairment is also associated with prominent photosensitivity at low frequencies in NCL2 [5], in which retinal impairment is initially associated with marked occipital hyperactivity and excessive photosensitivity before progressive degeneration of the visual cortex results in the loss of PPR. While it is tempting to envisage similar links between visual impairment, cortical occipital hyperactivity and PPR in our patient, clinically, she shows no evidence of progressive global deterioration or worsening visual function.

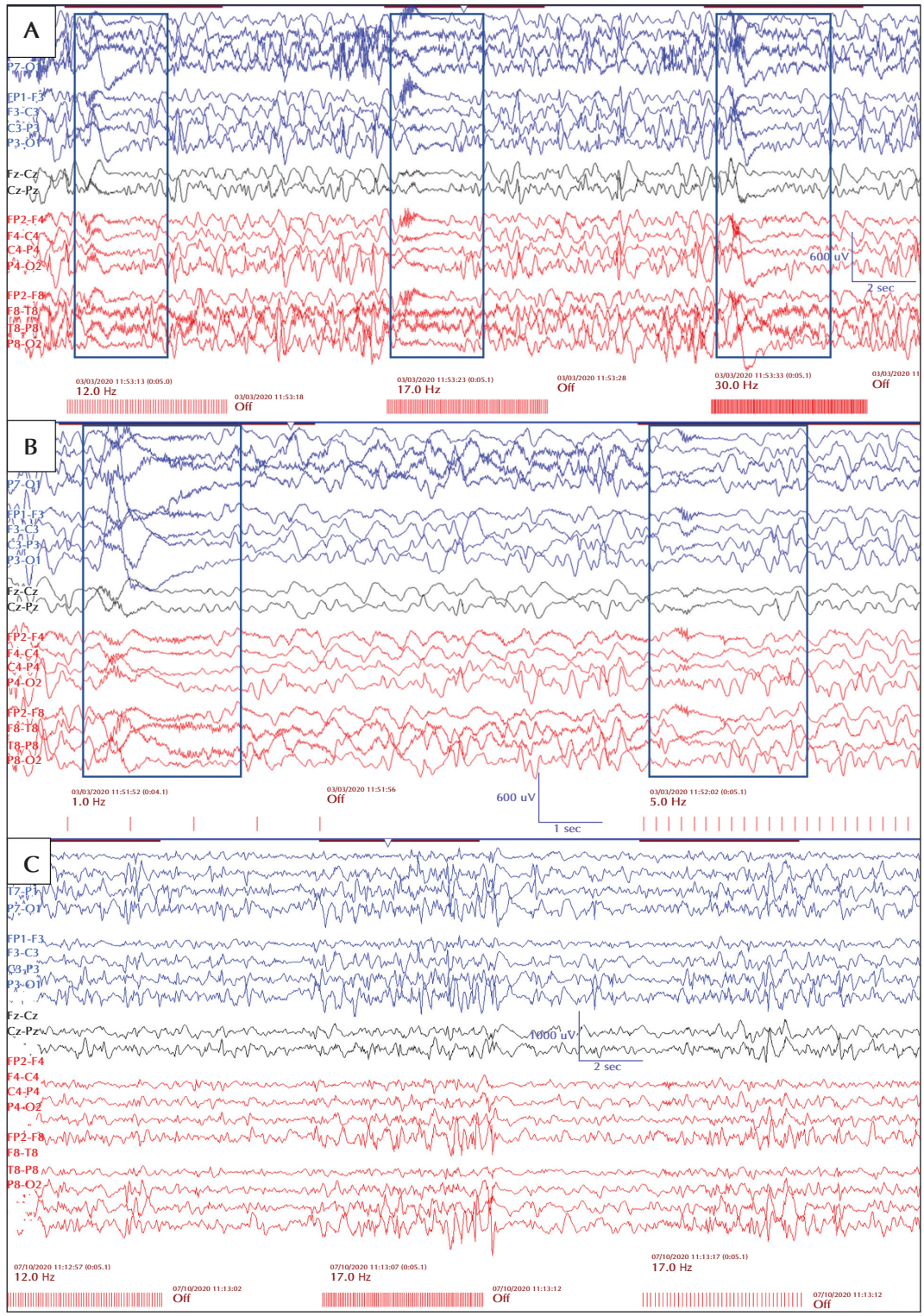
Therefore, as intriguing as the link between visual impairment and photosensitivity is, the fact that the PPR worsened without treatment and disappeared with treatment escalation (*table 1*) is more in keeping with the PPR in IGEs. In IGEs, the abnormal photic responses are thought to be a marker of an abnormally excitable cortex [15] and represent an increased risk of seizures. Concomitantly, as epilepsy management improves, the PPR decreases. This finding is reproducible enough to be utilized in clinical trials, where the PPR induced by IPS is used to track medication efficacy [16].

Our patient had robust PCR at 13 months of age, implying that the response was also present earlier. Clinically, this raises the argument that IPS should become part of routine EEGs in infants younger than one year of age, at least in those with a possible genetic epilepsy. The reproducible nature of photic

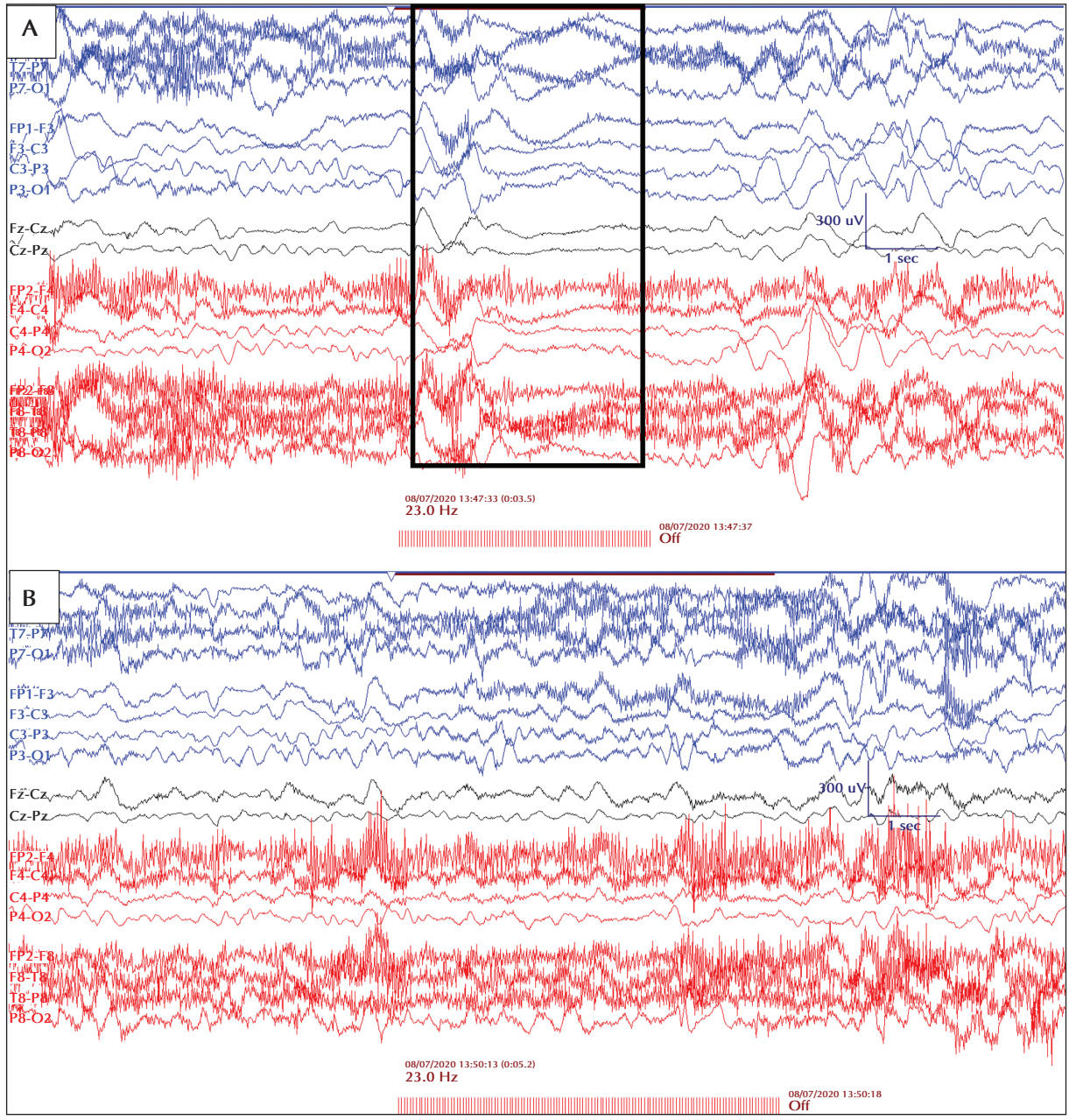
▼ **Table 1.** Age, treatment regimen, EEG characteristics and IPS and photosensitivity documented during the 11 EEGs recorded for the patient.

Age (month)	Hyps	BASED	Spasms	Treatment	IPS	PPR	PCR (spasms)
6.5	Yes	5	Yes	None	No	-	-
7	Yes	5	Yes	Prednisolone	No	–	-
7.5	No	3	No	Prednisolone	No	-	-
8	No	2	No	Prednisolone weaning	No	-	-
9	No	3	No	None	No	-	-
13	Yes	5	Yes	CBD oil	Yes	Yes	Yes (21 frequencies)
16	Yes	5	Yes	CBD, vigabatrin	Yes (asleep)	Yes	Yes (when awake)
17	Yes	5	Yes	CBD, vigabatrin, topiramate	Yes (asleep)	Yes	No
17.5	Yes	5	Yes	Prednisolone, vigabatrin	Yes	Yes	Yes (11 frequencies)
18	Yes	4	Yes	Prednisolone increased, vigabatrin	Yes	Yes	Yes (15 frequencies)
18.5	Yes	4	Yes	Prednisolone increased, vigabatrin increased	Yes	No	No

Hyps: hypsarrhythmia; IPS: intermittent photic stimulation; PPR: photoparoxysmal response; PCR: photo convulsive response. Using the BASED grading scale for children with IS, a score of 4-5 = hypsarrhythmia, 2-3 = abnormal but not hypsarrhythmia, 1 = normal [9].



■ **Figure 1.** Representative EEGs of intermittent photic stimulation triggering paroxysmal photic convulsions (electroclinical epileptic spasms demarcated by boxes) and paroxysmal photic responses. (A) Spasms triggered by 12, 17 and 30-Hz stimulation. (B) Spasms triggered at 1 and 5-Hz stimulation. (C) IPS performed while the patient was asleep showing PPR at 12, 17 and 8 Hz without clinical spasms.



■ **Figure 2.** (A) Spasms triggered by 23-Hz IPS stimulation; the box demarcates the spasm. (B) During the same routine EEG, the PCR at 23 Hz is blocked by a blue light filter.

stimulation, in a population with photosensitivity, could increase the reliability of routine EEGs as both a diagnostic tool and as a measure of response to treatment.

Furthermore, EEGs are currently non-diagnostic in the aetiology of IS. However, this could change if an association between PPR and genetic aetiologies of infantile epilepsy is found. Certainly, one should be cautious when making extrapolations based on a single patient and it is possible that the presence of PPR in our patient may be limited to her alone or even to others with her *ALG13*, c320A>G, mutation. However, there is currently no evidence for or against the presence of photosensitivity in patients with IS, and until that evidence accumulates, we feel that making IPS part of routine EEG for all IS patients is warranted. ■

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Disclosures.
There are no relevant financial disclosures or conflicts of interest.

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Legend for video sequence

Intermittent photic stimulation recorded when the patient was 13 months old. Photoconvulsive responses (clinical epileptic spasms) are triggered over a range of stimulation frequencies.

Key words for video research on www.epilepticdisorders.com

Phenomenology: spasms (epileptic), photosensitive
Localisation: generalized, unknown
Syndrome: West syndrome
Aetiology: ALG13 mutation

TEST YOURSELF

(1) What is an abnormal response to photic stimulation called and how is it tested for on EEG?

(2) What is *ALG13*?

(3) When is the peak onset of infantile spasms?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.