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Brief Communication

Monozygous Twin Brothers Discordant for Photosensitive Epilepsy: First Report of Possible Visual Priming in Humans

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Summary: *Purpose:* The interaction of genetic predisposition and the environment in the development of epilepsy is often discussed, but, aside from some animal reflex epilepsies, little evidence supports such interaction in the development of reflex epilepsy in humans.

Methods: We describe the history of a 16-year-old boy in whom photosensitive epilepsy developed after a period of weekly exposures to high-intensity light flashes.

Results: Both he and his clinically unaffected monozygotic twin were found to be photosensitive.

Conclusions: This case report suggests that some genetic forms of human reflex epilepsy may be elicited by repeated environmental exposure to the appropriate stimulus, similar to some of the stimulus-induced epilepsies seen in animals. **Key Words:** Photosensitive epilepsy—Kindling—Visual priming—Monozygous twins—Discordant twins.

Studies in monozygotic (MZ) twins are a powerful method for determining whether genotype alone is the most important factor in the etiology of a disease. A concordance rate of 65–76% for idiopathic generalized epilepsies (IGEs) has been demonstrated in MZ twin pairs indicating the importance of genetic factors in the etiology of IGEs (1,2). MZ twins discordant for diseases with an important genetic contribution, such as IGE, raise the issue of the potential role of environmental factors in the expression of the epileptic phenotype (3). This issue has been described in several animal models of reflex epilepsy, such as the genetically epilepsy-prone rat (GEPR) (4) and the DBA/J2 mouse (5,6). In these rodents, repeated exposure to specific sensory stimuli, often within a limited age window, resulted in the persistent phenotype of a seizure on exposure to the appropriate stimulus.

Photosensitivity is characterized by a photoparoxysmal response (PPR) in the EEG and is associated with an increased seizure propensity (7). Inheritance is likely to be autosomal dominant (8). The PPR may be elicited by intermittent photic stimulation (IPS) or by pattern or color changes and consists of a localized or generalized spike–wave response. Only a minority of PPR-positive patients without other neurologic symptoms will develop seizures (9).

Photosensitive epilepsy is characterized by seizures elicited by visual stimuli. Eyelid myoclonia is the most frequent clinical manifestation, but generalized myoclonic jerks, absences, generalized tonic–clonic seizures, or even partial seizures may be evoked by visual stimuli. Almost all patients with photosensitive epilepsy have a PPR in the EEG (10). The ability to detect the PPR can be influenced by concomitant use of anticonvulsant medication and is age dependent, usually with maximal expression between ages 7 and 19 years (11). The ability to induce a PPR depends on the stimulation parameters used (12). This may be an important reason for the variations in the prevalence of photosensitivity reported in the literature. We describe monozygous twins concordant for a PPR but discordant for photically induced seizures and link this discordance to repeated exposure to stroboscopic light flashes, which may have served to move a genetic predisposition to a fully expressed phenotype.

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CASE HISTORY

A 16-year-old boy apparently had a generalized tonic–clonic seizure while being exposed to intense, long-lasting visual stimulation by a recreational stroboscope lamp. For some minutes before the seizure, he had felt dizzy, and he had uncontrollable jerky movements. The seizure occurred late one evening during a garage party. He reported having had only one glass of beer, but no other neuroactive products. In the months before the seizure, he had visited ~10 parties at different locations, and the same strong stroboscope lamps had been used for prolonged periods at each party. He often danced in front of the lamps but reported that he had never previously noticed jerks or felt uncomfortable while exposed to the flashes.

After the seizure, he became hypersensitive to visual stimuli. While watching a 50-Hz television or in the presence of flickering neon lights, he had jerks in the shoulders or became nauseated. He was advised to avoid flashing visual stimuli. No medical treatment was started, and for the past 3 years, he has remained free of seizures, with only occasional jerks induced by TV or disco lights.

Photosensitivity was tested during an EEG 6 months after the seizure. Photic stimulation was performed according to a standardized protocol (11) with flash frequencies between 2 and 60 Hz. In the background EEG of the affected twin (Fig.1), sharp activity occurred over the frontal and left temporal regions, increasing at hyperventilation. The stimulation elicited occipital and generalized paroxysmal activity at eye closure and with eyes closed at flash frequencies of 10 Hz and at 30–40 Hz. The frequencies in between were not tested to avoid seizures. The paroxysmal activity at 30 Hz was accompanied by jerks in the shoulders and subjective jerky sensations in the legs.

The unaffected twin lived within the same family but had different friends and, in contrast to his brother, did

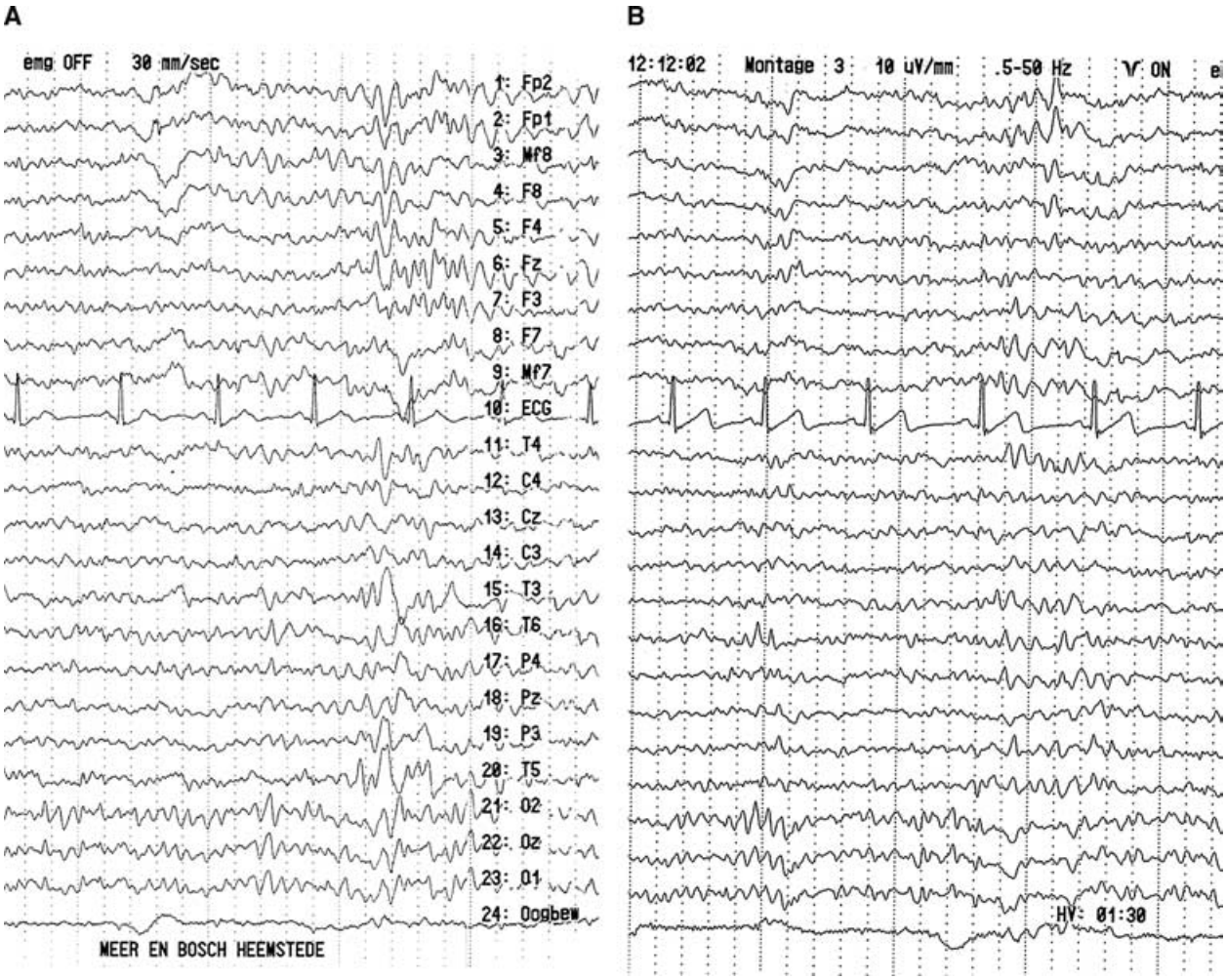

FIG. 1. Samples of EEG recordings: **(A)** and **(C)** of the affected monozygotic twin, and **(B)** and **(D)** of the unaffected twin. **A, B:** EEG activity during hyperventilation with **(A)** left frontotemporal slowing in the affected twin and **(B)** right frontotemporal slowing in the unaffected twin. **C, D:** Photic stimulation at 30 Hz with closed eyes; note identical generalized photoparoxysmal response in both twins. Recordings **A**/**B** and **C**/**D** have identical montage and filter settings.

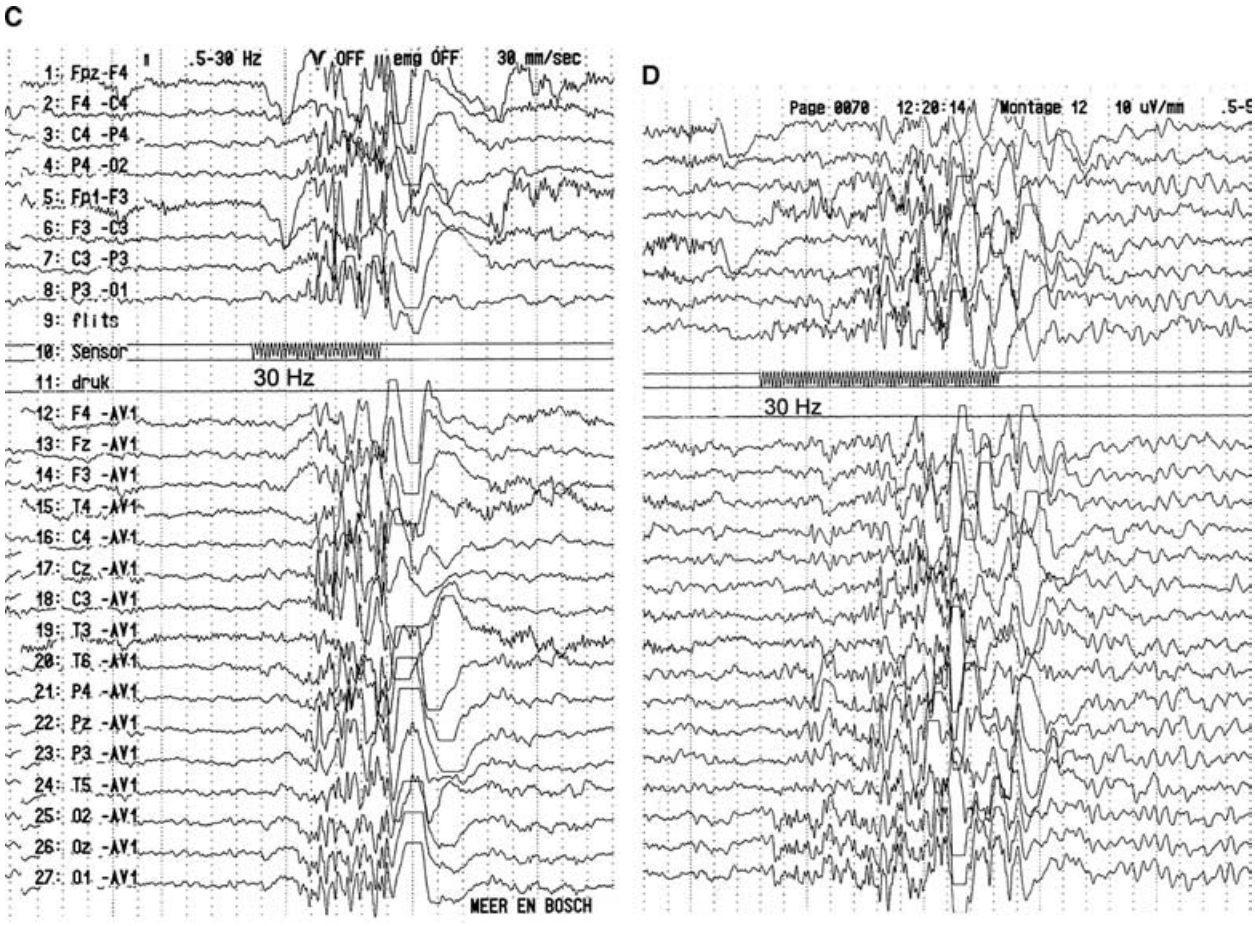

FIG. 1. (Continued).

not attend parties with stroboscope lights, nor did he report having been exposed to any other strong, flashing stimuli. Other than this, we could not detect significant differences in life habits or exposure between the two twins, based on an extensive history taken from the twins as well as their parents. His EEG, recorded on the same day as his brother's, demonstrated paroxysmal sharp activity with right frontotemporal predominance. On photic stimulation, he had occipital and generalized photoparoxysmal activity between 10 and 40 Hz, without subjective or objective clinical signs accompanying the EEG paroxysms. During the same follow-up period of 3 years, he had still been free of symptoms when exposed to flashes, contrary to his affected brother.

Both brothers were healthy, with a history of mild asthmatic bronchitis in early childhood. They had never had seizures or febrile convulsions, nor had absences or myoclonic jerks ever been noticed. Both brothers were doing well in the same class in high school. The parents had no seizure history, but an uncle of the father reportedly had epilepsy in his youth. The father's EEG demonstrated occipital spikes during photic stimulation with eyes closed at a frequency of 20 Hz. The mother had a normal EEG and no PPR. Eleven informative polymorphic DNA markers in the twins were found to be identical, confirming that they were monozygous with >99% certainty.

DISCUSSION

This report describes the case of an MZ twin pair that carried the trait for PPR, but only in the brother who had been exposed to repeated visual stimuli did photosensitive epilepsy and symptoms develop. This observation raises the question about the interaction between genetic predisposition and environmental factors in inducing the photosensitive epilepsy phenotype. Our observations should not be misinterpreted to mean that prior exposure to flashing lights created the clinical photosensitivity or epileptic condition de novo. Rather, based on the sensitivity of the unaffected twin, we hypothesize that the clinical expression of the seizures represents a preexisting tendency that was enhanced or provoked by repeated exposure to appropriate stimulation, a sort of visual-priming phenomenon. It may be worthwhile to investigate clinically discordant MZ twin pairs more systematically for variation in environmental factors that may play a role in epileptogenesis.

An analogy exists between this case history and genetically epilepsy-prone rodents. Certain mouse and rat

models develop seizures after sensory priming. Inbred substrains of the GEPR rat (GEPR-3 and GEPR-9) developed running seizures after priming by a variable number of audiogenic stimulations (4,6). It was suggested that repeated exposure to a stimulus that results in a convulsion appears to facilitate the occurrence of the next stimulus-induced convulsion (13). Young rats have longer latency and need more stimulation before generalized running seizures occur, indicating an age-related effect (6,13). Once the rodent has been primed, it remains seizure prone for the rest of its life. The DBA/J2 mouse model also develops audiogenic seizures after acoustic priming. In contrast with the GEPRs, an age window exists in which audiogenic priming has maximal effect. After this period, it is difficult to induce seizures in this mouse model (5).

Photosensitivity in humans is most likely to be prominent at an early age. Age at onset of photosensitive epilepsy is 7–19 years. Photosensitivity gradually declines in adulthood (15), but completely disappears only in about one in four patients before age 30 years (11). Many examples are known of photosensitive patients with visually induced seizures. The Pokemon observation demonstrated that low-intensity red/blue flicker may induce seizures in visually sensitive children (16). About 10% of these patients had later recurrences (17). The Pokemon video is considered to have been the appropriate stimulus to unveil a preexisting visual sensitivity in the children. It is unknown whether the event has contributed to a subsequently increased seizure propensity in some of these children.

Discordance in MZ twins might be explained by other mechanism like an early postzygotic de novo mutation in only one of the twins. Examples of this are MZ twin pairs discordant for trisomy 21 (18) or Turner syndrome (XO) (19). However, such mutations are very rare and cannot explain the large proportion of MZ twin pairs who are discordant for idiopathic epilepsy. Twins also may differ with respect to extent and degree of genomic imprinting of nuclear genes, degree of heteroplasmy for mitochondrial DNA, or X chromosome inactivation pattern (in women). These possible factors could not be investigated in our twins because no genes involved in idiopathic photosensitivity have yet been identified. Other environmental factors that may explain the discordance in these twins cannot be excluded either. We suggest, however, that the observations in our case report represent a process of visual priming. The MZ twin brother with comparable photosensitivity but without clinical symptoms had not been exposed to repetitive stroboscope flashes that may have primed the affected boy and resulted in increased sensitivity to visual stimuli.

The process of visual priming in humans has not been described before. In a study of 100 photosensitive patients, no apparent difference was found in the range of flash sequences eliciting generalized PPRs before and after extensive visual stimulation (Kasteleijn–Nolst Trenité, personal communication). Patients with visual autoinduction may gradually lose it in adulthood, even though the compulsory behavior may induce tens to hundreds of EEG paroxysms per day (15). These observations make the existence of visual priming in humans less likely. Priming also does not appear to play a role in the photosensitive *Papio papio* baboon (Naquet, personal communication). No evidence exists that individual baboons without predisposition can be made photosensitive by repeated and prolonged exposure to flashing lights (20).

However, modern technology frequently exposes humans to intermittent visual stimuli. It is often unclear or unknown whether patients with photosensitive seizures have been exposed to multiple stimulations before the onset of seizures. It is open to discussion whether repetitive subthreshold stimuli lead to an increased propensity to seizures in photosensitive humans, but the parallels between this case report and some animal models is striking. However, we cannot exclude prior visual stimulation being necessary for the development of seizures in other patients with photosensitive epilepsy, nor can we determine whether our report represents an isolated case. It would be almost impossible to replicate the genetic and environmental conditions of this case in a larger population study.

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