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Persistence of Photosensitivity

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Summary: *Purpose:* One hundred patients with photosensitive epilepsy were investigated as part of an ongoing follow-up study. Average duration of follow-up was 14 years; mean age at follow-up was 27 years.

Methods: All patients were EEG investigated using a standard technique of intermittent photic stimulation (IPS). The presence of a photoparoxysmal response (PPR) or a degraded PPR indicated the presence of photosensitivity.

Results: Seventy-seven patients became seizure free. Of the untreated patients, photosensitivity disappeared in 14 patients but was present in 32 patients. Of the patients who were treated, 31 showed evidence of PPRs or degraded PPRs, but 23 patients no longer showed evidence of photosensitivity. Thirty-two mothers had 67 children during the follow-up period. Thirteen have so far proved to be sensitive to IPS in the laboratory and four have also had photosensitive seizures induced in the outside environment. Nine of the children have been found not to be photosensitive nor have they had seizures.

Conclusions: This study suggests that photosensitivity persists in at least two thirds of patients with photosensitive epilepsy and that valproate is effective in controlling this photosensitivity. **Key Words:** Photosensitive epilepsy—Photoparoxysmal response—Intermittent photic stimulation—Sodium valproate.

There are remarkably few long-term studies of the course of photosensitivity in patients with photosensitive epilepsy. In 1978 we reported (1) on 167 patients who had been studied over a period of ≤12 years. We studied changes in photosensitivity range, that is, the range of intermittent photic stimulation (IPS) flash rates to which the patient is sensitive (2) and demonstrated that without drug intervention, there was no significant change in sensitivity range over a period of 7–12 years. In 1983 we selected (from our original 1975 cohort) 82 patients and four siblings, of whom 72 had reached the age of 20 years, the rest being between 15 and 19 years old. The mean duration of follow-up was 9.8 years. Of patients, 75% were treated with sodium valproate, and the drug had been withdrawn in 15 patients but had been restarted in eight because of the return of photosensitivity. Photosensitivity was no longer present in 55 patients, but 45 (82%) of these were receiving medication; photosensitivity persisted in 31 patients despite medication in 23 (74%). It was noted that, without change in medication, photosensitivity disappeared as the patients became older, and therefore it was proposed that photosensitivity disappeared spontaneously at ~24 years of age (3).

Our report concerns 91 patients and nine close relatives who have attended for repeated EEG investigations over the period from 1968 through 1993. As far as possible, we have selected patients from our 1986 study, but six were excluded on the grounds of unreliability of attendance, and we have added 16 patients who have regularly attended over 10 years and four siblings of the patients in the 1986 study.

METHODS

A standard technique of IPS (2) was used for all investigations. Silver–silver chloride electrodes were placed according to the International 10-20 system. After a basic EEG recording, including hyperventilation, the responses to IPS were recorded on a 16-channel longitudinal bipolar montage from frontal (F_{p1}, F_{p2}) to occipital poles (O_1, O_2). Photic stimulation was produced by a Grass PS 22 photostimulator fitted with a diffuser and a grid (or quadrille) pattern in which the spacing between lines occupied 20 min visual angle (4). The photostimulator was placed 30 cm from the eyes and subtended a visual angle of 24°. The intensity of the stimulus was 1,363 cd/m^2 (Grass intensity 2), and rates between 1 and 60 flashes per second (fps) were tested by using one flash rate

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at a time. Up to 20 fps alternate flash rates were tested (1, 3, 5, etc.). Above this frequency, steps of 5 fps (25, 30, 35, etc.) were used for routine testing. In patients who were very photosensitive a 2-s timer was used, and stimulation was given in either the eyes-open or eyes-closed condition.

With less marked photosensitivity, the period of stimulation was 10 s, with eye closure occurring after the first 5 s of stimulation. The effect of monocular occlusion was always tested. All patients had corrected visual acuity of 6/9 or better.

The responses to IPS can be divided into three broad categories:

1. A typical photoparoxysmal response (PPR) (4) consists of a spike-and-wave discharge that is generalised (that is, involving both anterior and posterior regions), bilateral, and synchronous (Fig. 1). This discharge was originally defined by Bickford et al. (5) as a photoconvulsive response;
2. Other abnormalities evoked by IPS including degraded spike and wave (Fig. 2) and paroxysmal slow activity involving both anterior and posterior regions; and
3. Spikes time-locked to the flash and confined to occipital regions either occurring in isolation or preceding a PPR (Fig. 3). They are distinguished in structure from photic driving by their negative polarity at the occiput and are increased in amplitude by raising the flash rate or by pattern stimulation rather than diffuse IPS (6).

It was previously shown that although the latter two categories may warn investigators of their approach to a flash rate that will evoke a PPR (4), only PPRs have any clinical predictive value (4,7). However, drug treatment with AEDs may diminish photosensitivity to the point at which these other abnormalities must be considered as indicating latent photosensitivity (4). For this reason, we used both the PPR and degraded PPR as indicating remaining photosensitivity. PPRs are seen in only 0.35% of the 17- to 25-year-old population (8).

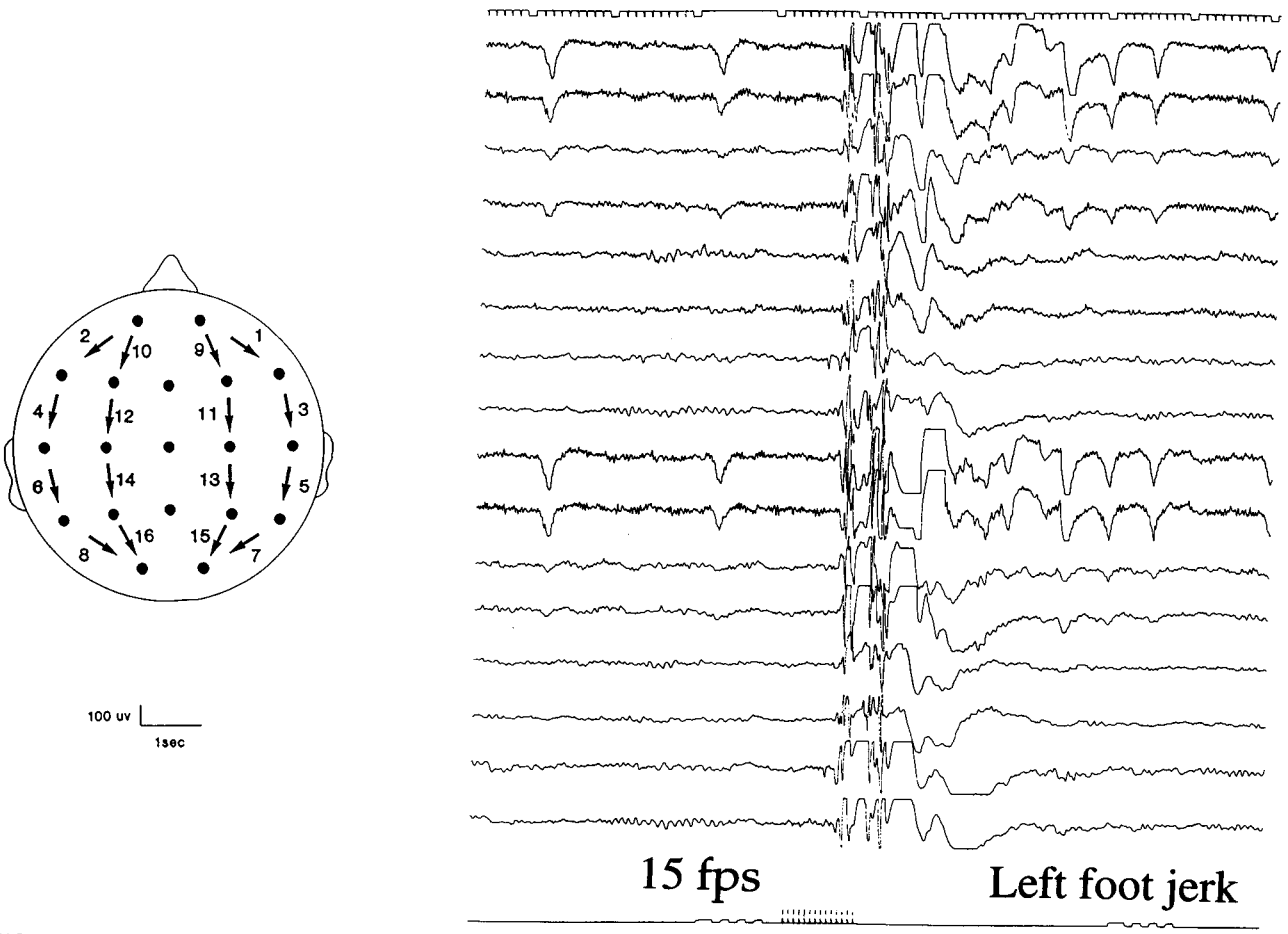

FIG. 1. Photoparoxysmal response occurring after <1-s stimulation at 15 fps. The response can be seen to involve all derivations, being at least as high amplitude frontally as posteriorly, and in this case, involving both polyspikes and spike-and-wave. This particular stimulus also produced a subjective response in the form of a left-foot jerk.

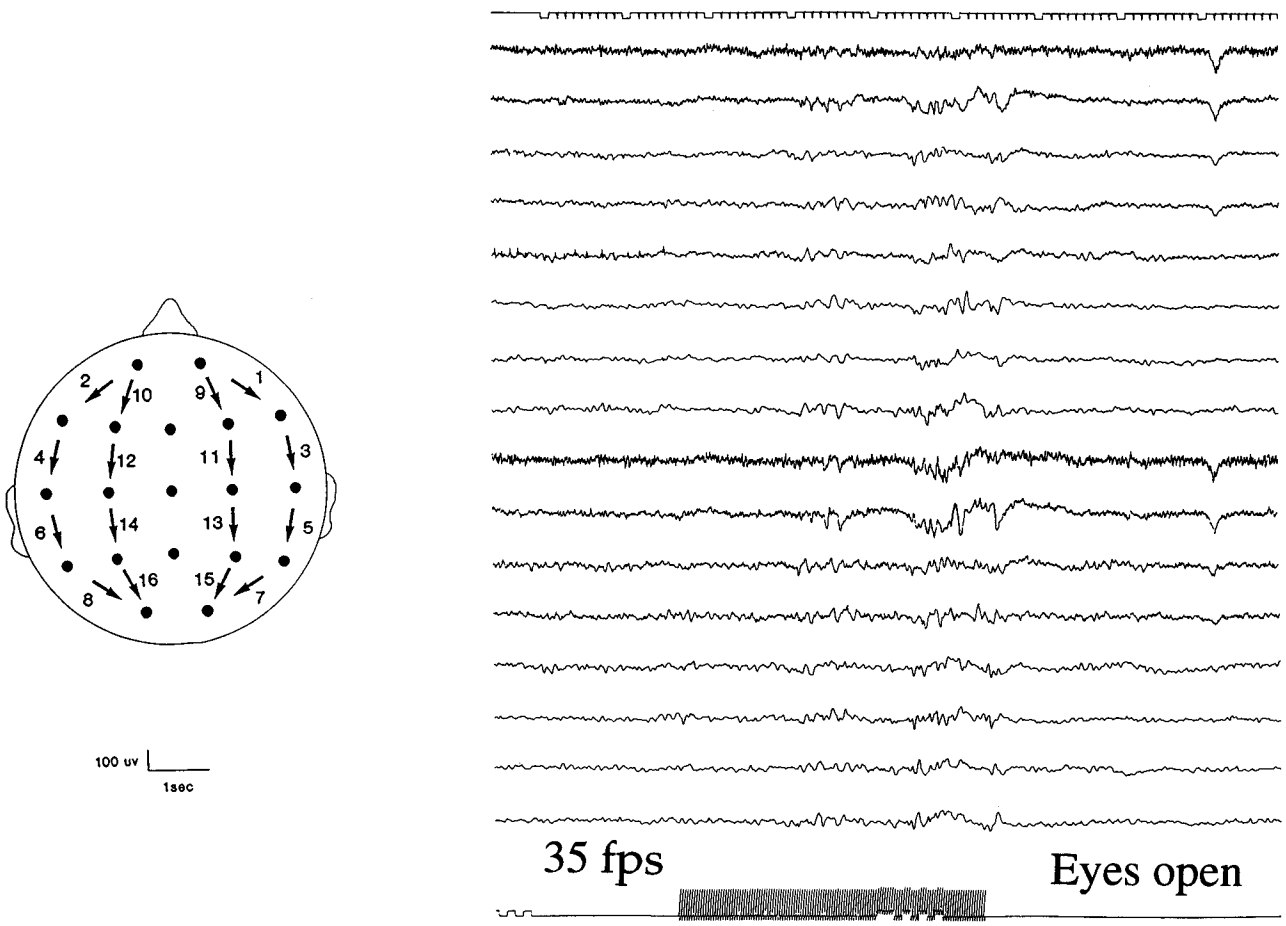

FIG. 2. Occipital spikes occurring only in posterior derivations and surface negative at the occiput. The responses seen to occur at the same rate as the flash are of slightly higher amplitude at the right occiput compared with the left and disappear when the eyes are closed.

Occipital spikes induced by IPS are rarely seen in the normal population. It is likely that they represent hyperexcitability of the visual cortex and, in the absence of a lowered convulsive threshold, do not appear to have behavioural significance.

Material

One hundred patients and siblings had shown a PPR when exposed to IPS according to our standard clinical criteria (2). They were divided into four groups:

Group 1: 32 patients had seizures only when exposed to visual stimuli in everyday life (i.e., television or sunlight).

Group 2: 39 patients had seizures with visual stimuli but also had "spontaneous" seizures.

Group 3: 20 patients had spontaneous seizures but had not had seizures to known visual stimuli in the environment but had PPR on IPS in the laboratory.

Group 4: Nine siblings or parents of photosensitive patients had no history of seizures but demonstrated PPR on IPS in the laboratory.

The age of onset of photosensitive epilepsy in Group 1 ranged from 7 to 17 years (mean, 11.8 ± 2.9 years). Mean age of onset in Group 2 was 11.5 years (SD, 4.2 years) with a range of 2–21 years, and in Group 3, mean onset age was 12.2 years (SD, 3.6 years; range, 6–20 years). The clinical data on the patients are summarised in Table 1.

Eight female and six male patients had shown impulsive attraction to the television screen (4), and one male patient had shown self-induction by using hand waving in sunlight. Seven of these patients were purely photosensitive (Group 1), and there were eight in Group 2.

Seventy-five patients and two nonepileptic siblings were treated with valproate (VPA) mono-therapy, four received VPA in combination with other antiepileptic drugs (AEDs), and six were treated with drugs other than VPA.

Drug therapy was withdrawn either temporarily or permanently in 33 patients; in 12 of them, withdrawal was related to proposed pregnancy. Thirteen never received any AED.

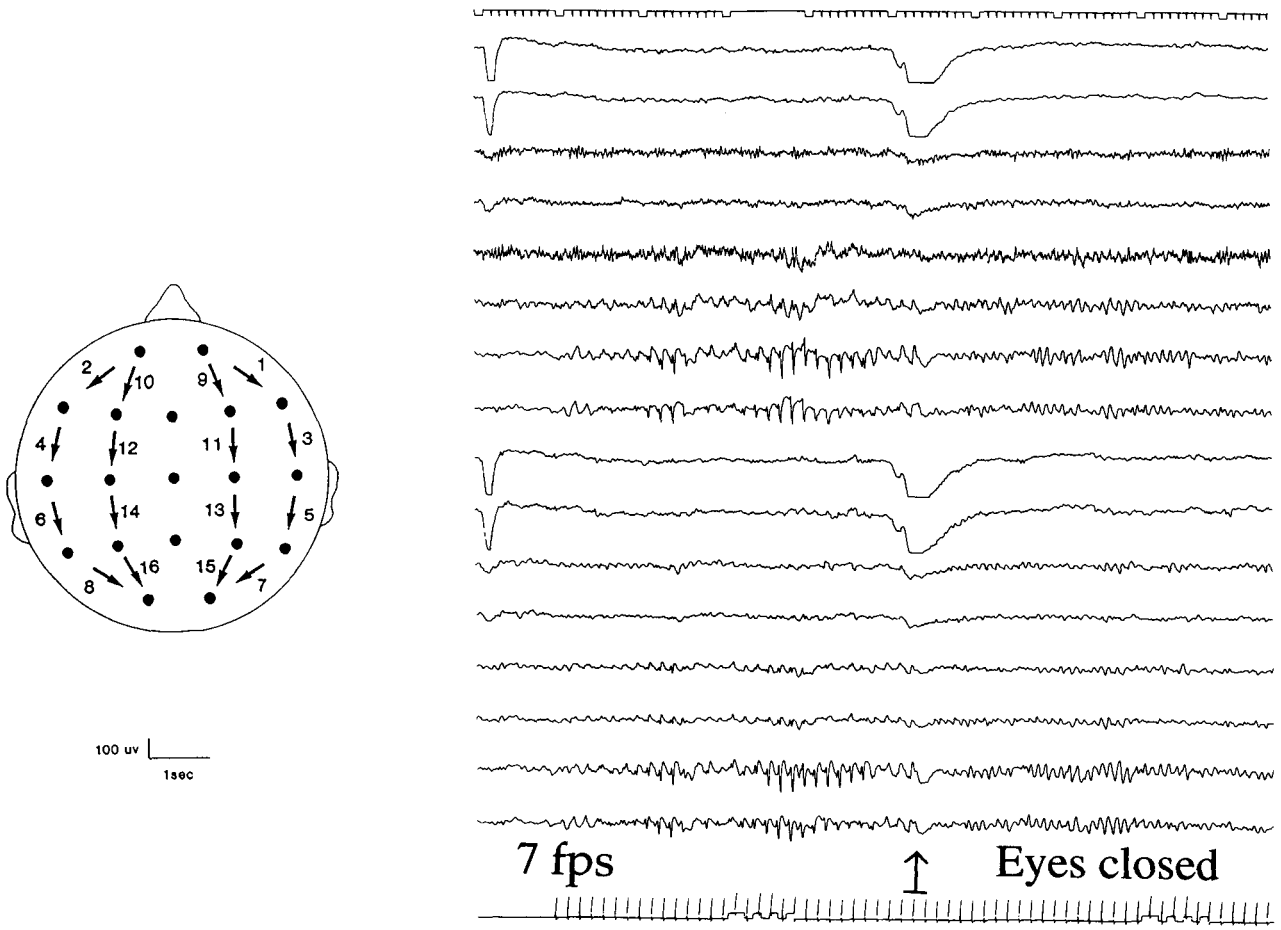

FIG. 3. Degraded photoparoxysmal response. Some sharpish components are present, and the response clearly involves both anterior and posterior derivations but certainly does not show spike-and-wave responses as are normally seen in a photoparoxysmal response. Such degraded responses are often seen at the limits of the patient's sensitivity range (4) or in patients who have been successfully treated with valproic acid.

Subjects not receiving drug therapy were advised about precautions to be taken when viewing television or when exposed to flicker in everyday life (2). Protection from the effect of flicker can usually be obtained by firmly covering one eye with the palm of the hand. Remote control of television sets has reduced the risk of seizures from close viewing or directly adjusting the controls, but the use of television sets for computers or for video games has led to an increase of close viewing. Smaller television screens are less provocative of seizures than large ones (9). In addition, polarised spectacles reduce risk from reflected sunlight.

Family history

Of the 41 purely photosensitive cases (Groups 1 and 4), there was a family history of photosensitivity in 21 (51%) and of epilepsy without photosensitivity in four (10%). Of the other 59 patients (Groups 2 and 3), a family history of photosensitivity occurred

TABLE 1. *Clinical data on patients in the four photosensitivity groups*

Group	Total	Male	Female	Tonic–clonic	Myoclonic	Absence	Other
1	32	16	25	25	0	0	7
2	39	10	29	19	7	7	6
3	20	0	20	4	8	5	3
4	9	2	7	0	0	0	0
Total	100	28	72	48	15	12	16

"Other" seizures include rare partial seizures or multiple types of seizure with no predominant pattern, or seizures difficult to classify. The 15 patients with myoclonic seizures all have juvenile myoclonic epilepsy.

TABLE 2. *Clinical response to medication*

Medication	No seizures	Seizures continued	Total
VPA monotherapy	48	9	57
Other AED ± VPA	5	2	7
None	24	3	27
Total	77	14	91

Two patients in Group 4 received VPA prophylactically.
VPA, valproate; AED, antiepileptic drugs.

in only nine (15%) and of epilepsy without photosensitivity in eight (14%).

RESULTS

The mean duration of follow-up was 14 ± 5 years (range, 4–29 years). The mean age at follow-up was 27 ± 7 years (range, 17–65 years). A total of 1,273 EEG recordings was made on the 100 cases. The number of EEGs recorded range from two to 37 for any individual.

Clinical

Control of seizures is defined as a minimum of 2 years without any attack. Of the original 91 patients who had seizures, 77 became seizure free. Of the remaining 14, two had a history of impulsive attraction to television and one a history of self-induction by using sunlight as a source. Two patients had stopped taking VPA of their own accord, and noncompliance is suspected in three more. One patient had a seizure during pattern testing without IPS. Three of these 14 patients have normal EEGs but only a rare seizure. One still has eyelid myoclonia with absences. One was reported by another hospital to have had a seizure, having failed to attend our follow-up. In addition to these 14 patients, five female patients had a seizure after temporary withdrawal of VPA but subsequently became seizure free for periods >2 years on return to medication. Freedom from seizures for a period >2 years occurred in 85% of patients. Of the 24 patients seizure free without medication, VPA had been successfully discontinued in 15. These findings are summarised in Table 2.

Fourteen patients had shown impulsive attraction to the television screen, and this disappeared in 11. Two of them continued to have seizures despite medication with VPA, as did the one patient with self-induced epilepsy, although he no longer has self-induced attacks. Ten patients were seizure-free with VPA, as were two for whom VPA had been discontinued. Despite control of seizures, some EEG abnormality on IPS was still present in 12 of the 15 patients.

Pregnancy

Thirty-two mothers had a total of 67 children, 21 of whom were born to mothers treated with VPA. Two mothers received other AEDs during pregnancy, and 44 babies were born to mothers not receiving AEDs during pregnancy. Thirteen children of the 32 mothers have proved to be photosensitive (seven in one family), but many are still too young for photosensitivity to have become manifest.

No baby has been born with spina bifida.

Photosensitivity on IPS

We have divided the responses into four broad categories.

1. No abnormality occurs on IPS.
2. There are no PPRs, but occipital spikes occur with IPS and without any subjective sensation.
3. PPRs to IPS are still present either in eyes-open, eyes-closed, or eye-closure conditions.
4. Degraded PPRs are seen in response to a number of flash rates.

Categories 1 and 2 are regarded as no longer photosensitive, whereas categories 3 and 4 are regarded as showing evidence of photosensitivity.

Persistence of photosensitivity

Fourteen patients who were not receiving medication are no longer photosensitive (age range, 16–32 years; mean, 23.5 ± 10.6 years). Abnormality was still present in 32 patients not receiving medication (age range, 19–65 years; mean age, 27.7 ± 10.6 years). Evidence of photosensitivity was still present in 31 patients receiving medication (30 with VPA only), their age range being 17–36 years (mean age, 26.5 ± 4.5 years) but was not present in 23 patients. Thus 63 patients still showed evidence of photosensitivity at a mean age of 27.3 ± 8.1 years (range, 17–65 years). Only three patients are older than 40 years. The details are shown in Table 3.

Table 4 shows the relation of persistence of abnormality on photic stimulation to the family history of epilepsy or a family history of photosensitivity. We

TABLE 3. *Final assessment*

	Not photosensitive	Photosensitive	Total
Not receiving AEDs			
Groups 1 + 4	7 (26%)	20 (74%)	27
Groups 2 + 3	7 (37%)	12 (63%)	19
Total	14 (30%)	32 (70%)	46
Receiving AEDs			
Groups 1 + 4	3 (20%)[a]	12 (80%)	15
Groups 2 + 3	20 (51%)[a]	19 (49%)	39
Total	23 (43%)	31 (57%)	54

AEDs, antiepileptic drugs.
Groups 1 and 4 were combined as demonstrating pure photosensitivity. Groups 2 and 3 were combined because both demonstrated epilepsy with photosensitivity.
[a] Excluded from assessment of prognosis.

TABLE 4. *Persistence of IPS abnormality and family history*

	Abnormality on IPS	No abnormality	Total
Family history of epilepsy	9	0	9
Family history of photosensitivity	23	5	28
No family history of either	31	9	40
Total	63	14	77

IPS, intermittent photic stimulation.

excluded two patients with a family history of photosensitivity and three with a family history of epilepsy, all of whom are receiving drugs and show no abnormality on IPS.

DISCUSSION

Regesta and Tanganelli (10) studied eight cases of pure photosensitive epilepsy, 32 cases in Group 2, and 13 in Group 3, for a period of 6–14 years, by using our method of IPS. Five patients in Group 1 did not receive AEDs, the others being treated with VPA with or without other AEDs. The clinical characteristics of the 53 patients were very similar to ours except for there being slightly more patients with tonic–clonic seizures and different sex ratios in both the groups and in total (their male-to-female ratio was 1:6.5 compared with ours of 1:2.6).

They reported complete remission of photosensitive seizures in all patients in Group 1 and in 75% of those in Group 2. Photosensitivity, as defined by a PPR, also disappeared in all Group 1 even after discontinuation of medication. However, Groups 2 and 3 did not respond as well as Group 1, and the prognosis was similar to that of nonphotosensitive patients with epilepsy. The mean age of disappearance of photosensitivity in Group 1 was 22 years. However, their findings in Groups 2 and 3 are complicated by the fact that AEDs were continued. Ten showed no photosensitivity at a mean age of 24.5 ± 4.0 years. In 10 other patients receiving VPA, slight abnormality disappeared at a mean age of 22.9 ± 2.5 years, although there had been no alteration in dosage of VPA. Because the findings in this study correlated well with those of our 1986 study (3), we surmised that photosensitivity would disappear at ~24 years of age.

Kasteleijn-Nolst Trenité (11) found that of 64 patients followed up for between 1 and 13 years, 22 showed no photosensitivity, although 16 were receiving AEDs. The age range at follow-up was 9–71 years (mean, 25.6 years).

So et al. (12) reported an interesting study of seizure-free patients who showed a PPR on IPS and found that the mere presence of a PPR did not alter the probability of developing seizures because none of 33 individuals developed seizures over the subsequent 6- to 12-year period. However, all their patients were older than 17 years when a PPR was initially demonstrated, and it is known that photosensitive epilepsy is most likely to occur around puberty (4).

In our previous article on prognosis (3), we considered the age of the patients at which photosensitivity disappeared, as this appeared to be the critical question in predicting the outcome. We now consider that the probability of photosensitivity being still present is a better indicator of prognosis for the young patient because most patients retain their photosensitivity.

In our present study, photosensitivity as evidenced by a PPR or degraded PPR disappeared in 14 untreated patients at ages between 16 and 32 years (mean, 23.5 ± 5.7 years) but is still present in 32 untreated patients at ages between 19 and 65 years (mean, 27.7 ± 10.6 years). It is also present in 31 treated patients aged 17 to 36 years (mean, 26.9 ± 4.5 years). Photosensitivity disappeared in 23 patients on medication (17 receiving monotherapy with VPA and six with combined AEDs). We have never attempted to discontinue drugs in these 23 patients, mainly because of the risk of a withdrawal seizure, which could result in the loss of the patient's driving licence. Because we know that VPA can inhibit all abnormal responses to IPS, these 23 patients must be excluded from an assessment of prognosis. If, however, it was assumed that all the patients receiving medication are still photosensitive but that their photosensitivity is controlled and no longer apparent, then in only 14% of patients has photosensitivity disappeared.

It is not possible to relate our findings on PPRs to prolonged or self-limited PPRs and prognosis (13). As we previously indicated (4), such concepts are dependent on the aggressiveness of photic stimulation. Our standard techniques established over many years (2) are designed to evoke abnormality without risk of seizure to the patient. This care is particularly relevant to long-term, frequent, follow-up studies in which the confidence and level of apprehension of the patient is critical. Other authors (12) commented on this risk and the relation of so-called persistence to the length of stimulation.

It is clear, therefore, that there is no particular age at which photosensitivity disappears. However, from these new results, 30% of patients not receiving AED treatment were no longer photosensitive, but in the remaining 70% of untreated patients, photosensitivity appears to persist to *any* age. If we include the 31 treated patients who still show evidence of photosen-

sitivity, <20% of patients lose their sensitivity to IPS. In our previous publication, we were misled over the disappearance of photosensitivity, because those in whom it disappeared lost their photosensitivity at ~24 years of age. In the patients who are receiving VPA, it is not possible to state the percentage in whom photosensitivity has disappeared, but it is clear that 43% no longer show evidence of photosensitivity, although whether this is related to the effect of the AED or the natural disappearance of photosensitivity cannot be deduced.

Because there is evidence of a possible causal connection between valproate and spina bifida (14–16), all females of child-bearing age were informed of the possible risk of spina bifida and were advised that if they intended to start a family, they should stop taking VPA and wait a month before attempting to conceive. They were further advised to attend for clinical and EEG review after stopping medication and to restart medication 2 weeks before expected parturition.

Thirteen children of the resulting pregnancies have been shown to be photosensitive to IPS in the laboratory, and four of these have also had seizures induced in the outside environment. Nine children have been tested and found to be not photosensitive nor have they had seizures. The findings contrast with the results of So et al (12) but confirm the findings of Waltz et al. (7) of a genetic factor increasing the probability of seizures in siblings with PPRs.

This study indicates that there is a 14–37% probability that photosensitivity will disappear spontaneously, but there is no way of identifying which individuals will have such a remission. Our experience also reaffirms the efficacy of VPA in controlling photosensitivity.

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