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Suppressive Efficacy by a Commercially Available Blue Lens on PPR in 610 Photosensitive Epilepsy Patients

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Summary: *Purpose:* Photosensitivity can represent a serious problem in epilepsy patients, also because pharmacologic treatment is often ineffective. Nonpharmacologic treatment using blue sunglasses is effective and safe in controlling photosensitivity, but large series of patients have never been studied.

Methods: This multicenter study was conducted in 12 epilepsy centers in northern, central, southern, and insular Italy. A commercially available lens, named Z1, obtained in a previous trial, was used to test consecutively enrolled pediatric and adult epilepsy patients with photosensitivity. Only type 4 photosensitivity (photoparoxysmal response, PPR) was considered in the study. A standardized method was used for photostimulation.

Results: Six hundred ten epilepsy patients were tested. Four hundred (66%) were female patients; 396 (65%) were younger than 14 years. Three hundred eighty-one (62%) subjects were pharmacologically treated at the time of investigation. Z1 lenses made PPR disappear in 463 (75.9%) patients, and PPR was considerably reduced in an additional 109 (17.9%) of them. PPR remained unchanged only in the remaining 38 (6.2%) patients. The response of PPR to Z1 lenses was not significantly influenced by the patients' age, sex, or type of epilepsy. No difference was found between pharmacologically treated and untreated patients.

Conclusions: The Z1 lens is highly effective in controlling PPR in a very large number of photosensitive epilepsy patients irrespective of their epilepsy or antiepileptic drug treatment. The lens might become a valid resource in the daily activity of any clinician who cares for patients with epilepsy. **Key Words:** Photosensitive epilepsy—Photosensitivity—Blue glasses—Nonpharmacologic treatment—Photoparoxysmal response—PPR.

Photosensitivity is detected on EEG recordings in ∼5% of epilepsy patients (1–5), and it represents a serious problem, because up to 75% of them report visually induced seizures in their daily life (4). This problem will become even more important in the near future owing to the diffusion of various precipitating factors at school, work, home, and leisure. Moreover, apart from seizure elicitation, in favorable environmental conditions, photosensitivity can cause a subjective unpleasant sensation and induce a state of anxiety in photosensitive epilepsy patients, who are aware of possible reflex seizures.

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Different types of lenses have been suggested for managing photosensitivity, and evidence now exists that their effectiveness depends on both the lens color and the lens transmittance (6–8). However, many clinicians who carefor patients with epilepsy are uncertain about the use of sunglasses in daily activities and still view them as a remote resort for photosensitive patients with epilepsy. The absence of robust evidence supporting their efficacy figures prominently among the possible reasons for this view. In all articles focusing on this topic, the number of patients was too limited (8–13); moreover, most studies referred to experimental optical filters (8–10). In 1999, Capovilla et al. (14) tested 83 epilepsy patients for photosensitivity suppression during intermittent photic stimulation (IPS) by using different types of lenses. A particular type of

lens, named Z1, was compared with four other types of optical filters and was found to be significantly more effective in abolishing photosensitivity than were all other control lenses (14). The Z1 lens was obtained, in a previous trial (8), by testing many lens combinations of different materials, colors, and shades of dark in 20 photosensitive epilepsy patients. This type of lens is now commercially available in Italy.

The aim of this work is further to assess the efficacy of Z1 lenses during IPS in a very large series of photosensitive epilepsy patients.

METHODS

Study centers

This was a multicenter study. The patients were consecutively recruited in 12 epilepsy centers, distributed in northern, central, and southern regions of Italy. All tests were done for clinical indications.

Patients

Inclusion–exclusion criteria

Only photosensitive epilepsy patients were considered. The patients were enrolled in the study only if they had the classic type 4 photosensitivity (photoparoxysmal response, PPR) in accordance with Waltz's classification (15). The patients could be either taking antiepileptic drugs (AEDs) or not. Patients with febrile convulsions and photosensitivity or nonepileptic subjects with photosensitivity were excluded.

Patient data

Most of the patients (65%) are children (range, 2–77 years; mean, 14.1 years; median, 11.9 years) and have a generalized epilepsy syndrome (68%), with a female predominance (66%). At the test time, 38% of the patients were not taking AEDs. The diagnosis of the type of epilepsy was made by using the 1989 Classification of the International League Against Epilepsy (16). A special group included epileptic encephalopathy, according to the definition of the recently proposed diagnostic scheme for people with epileptic seizures and with epilepsy of the International League Against Epilepsy (17). Table 1 shows the main demographic data of the patients. The 83 patients reported in 1999 (14) are included in the present study.

Method of photostimulation

Photostimulation was performed in a darkened room at frequencies between 3 and 50 Hz. The photic stimulator used always had a minimum strobe light of 0.64 joule/flash and a flash duration of 1 ms, set 30 cm from the nasion. Patients were asked to stare at the photic stimulator. The stimulus was given for 5 s at the patient's eye closing and interrupted if PPR occurred. Each patient was tested, during the same EEG session, without and with the use of Z1 lenses. The interval between each photostimulation was 30 s. Scalp silver–silver chloride electrodes were placed by using the international 10-20 system. Additional electrodes were used for polygraphic parameters, in particular for muscular polygraphy. All examinations were recorded on split-screen video-EEG. The lens used, named Z1, is a blue lens of an ultraviolet material with an 80% luminance cut. Lens spectroscopy is shown in Fig. 1. The manufacturer of the lens is Zeiss.

Response evaluation

EEG recordings were always evaluated by one of the authors, each of them an expert electroencephalographer of the epilepsy centers participating to the study. The response to the lenses was classified into three main groups: (a) PPR disappearance, (b) PPR persistence, or (c) PPR attenuation when one of the following four modifications of photosensitive response occurred: latency extension > 2 s between stimulus and PPR appearance; decrease in PPR duration; disappearance of clinical signs correlated to the PPR; and, in accordance with Waltz's classification (15), change to a less severe degree of photosensitivity (i.e., change to type I–III).

Statistical analysis

Fisher's exact test was used to compare proportions. Multivariate regression analysiswas performed to assess the potential influences of baseline differences among the groups on the lens efficacy. Two-tailed p values of <0.05 were considered to indicate statistical significance.

RESULTS

We tested 610 patients. Z1 lenses made PPR disappear in 463 (75.9%) patients, whereas PPR was reduced in additional 109 (17.9%) of them. No differences were found in the effectiveness of the lens depending on the frequency

TABLE 1. *Demographic data of the 610 epileptic patients with PPR*

Sex		Type of epilepsy				AEDs		Patient's age at examination	
Male	Female	G	F	EE	U	Yes	No	<14 yr	>14 yr
210 (34)	400 (66)	414 (68)	124 (20)	50 (8)	22 (4)	381 (62)	229 (38)	396 (65)	214 (35)

Values expressed as number (%).
AED, antiepileptic drug; EE, epileptic encephalopathy; F, focal; G, generalized; U, unclassified.

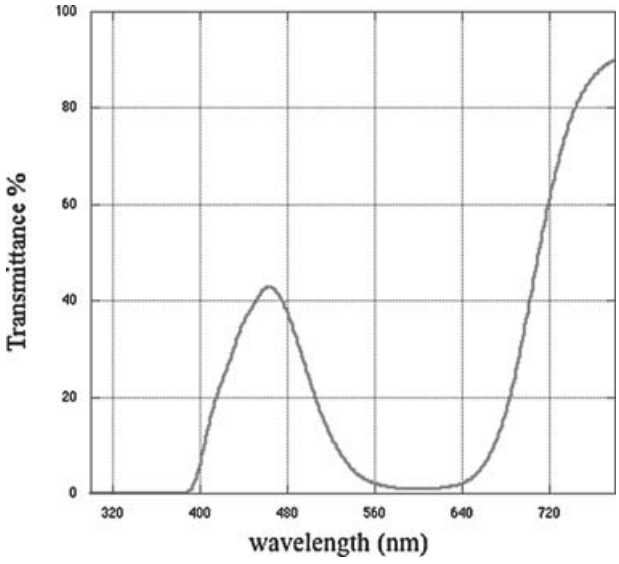

FIG. 1. Spectroscopy of the Z1 lens.

that had been used. The results shown in Table 2 are relative to the frequency of 15 Hz. PPR remained unchanged only in the remaining 38 (6.2%) patients. The type of PPR response to Z1 lenses was not significantly influenced by the patients' age, sex, or type of epilepsy (Table 2). Z1 lenses also were effective in the subgroup of 50 patients with epileptic encephalopathy, as a PPR disappearance occurred in 68% and a reduction in 16% of them. Although the overall efficacy was less than that observed in all other patient groups, this difference was not statistically significant. The lens efficacy was not different between pharmacologically treated and untreated patients. No differences were noted regarding the severity of photosensitivity.

DISCUSSION

The results of this multicenter study illustrate the undoubted efficacy of these commercially available Z1 lenses, as they are highly effective in completely controlling PPR in >75% and reducing it in an additional 17% of our photosensitive epilepsy patients. The very large number of patients is justified by the awareness of the remarkable variability in photosensitivity related to ethnic, seasonal, or geographical factors (18,19).

TABLE 2. *Effectiveness of Z1 in controlling PPR*

	Disappearance	Reduction	Persistence
Whole group, n (%)	463 (75.9)	109 (17.9)	38 (6.2)
Sex			
Male	157 (74.8)	39 (18.6)	14 (6.6)
Female	306 (76.5)	70 (17.5)	24 (6)
Age at evaluation			
<14 yr	308 (77.7)	66 (16.7)	22 (5.6)
≥14 yr	155 (72.5)	43 (20.1)	16 (7.4)
Therapy			
Yes	288 (75.6)	73 (19.1)	20 (5.3)
No	175 (76.4)	36 (15.8)	18 (7.8)
Type of epilepsy			
Generalized	312 (75.3)	80 (19.3)	22 (5.4)
Focal	103 (83.1)	15 (12.1)	6 (4.8)
EE	34 (68)	8 (16)	8 (16)
Unclassified	14 (63.7)	6 (27.3)	2 (9)

Until now, the management of photosensitivity in epilepsy patients has been based on three main basic principles (20). The first is avoidance of provocative stimuli, the second is drug therapy, and the third is based on a specific counseling or technologies to obtain attenuation of the stimuli. Of course, avoidance of provocative stimuli is the most effective method for seizure prevention in these patients (21). Nonetheless, in the modern way of life, it is impossible to avoid any provocative stimuli without causing important restrictions in the patient's daily activities and personal autonomy. The second option, drug therapy, is not always effective. In the largest series of patients so far studied (22), photosensitivity was abolished by sodium valproate (VPA) in 61% of cases, which is much less than that obtained with our special lenses. Moreover, AEDs can have undesirable side effect and, not less important, relevant costs. In Italy, the cost of 1-year therapy with a potentially effective dosage of VPA (1,000 mg/daily) is 159.68 Euro. We must also add the costs of laboratory tests for patient monitoring. By comparison, in Italy, the cost of the lenses is 90 Euro (none of the authors has any economic interest in their sale).

The third option, the reduction of the stimulus, can be obtained in different ways (20,21). First, we can directly act on the source of the stimulus. Because television is one of most provocative factors in seizure induction, clinicians should recommend television screens with 100-Hz (or 120 for the United States) frequency because they have a less provocative effect in seizure induction than the 50-Hz (or 60 for the United States) screens (23). Moreover, some authors (24,25) recently proposed the use of particular filters for television to reduce the epileptogenic effect of video images and, in Japan and the United Kingdom, specific broadcasting guidelines for TV programs have been successfully adopted (26). Moreover, protective advice can be given to the patients to prevent TV-induced seizures, such as the use of remote control, distance from the TV screen, etc. For these reasons, we do not advise our patients on wearing Z1 lenses while they watch television. In these photosensitive patients, different situations must be considered. A first group of patients has so-called "pure photosensitive epilepsy," in which the seizures are always determined by visual stimuli, and spontaneous attacks do not occur. In this group, in our opinion, the use of protective lenses might be preferred to the AED treatment, at least as a first option. A second group of patients has both spontaneous and photo-induced epileptic seizures. Of course, these patients should be treated with AEDs, because stimulus avoidance or suppression is not sufficient for seizure

control. We have now demonstrated, however, that even these patients may benefit from glasses, as AED therapy alone is often ineffective in controlling PPR, and reflex seizures can occur. It is important to underline that the Z1 lens was also effective in the subgroup of progressive myoclonic epilepsies and severe myoclonic epilepsies, two conditions in which AEDs usually fail to control photosensitivity, and visual reflex seizures are, as a rule, a relevant problem. In a third group of photosensitive epilepsy patients, PPR causes a subjective unpleasant sensation, because of the PPR per se or related to the awareness of possible seizures. This fact is very important for the quality of life of the patients, because it can cause a state of anxiety. Also in this group, even if seizures do not recur, the lens might be used and AED treatment not modified. Last, photosensitivity is occasionally a simple EEG sign without any clinical relevance.

In the literature, the use of protective lenses has been rarely mentioned, and it was often limited to single or very few patients. Furthermore, even if the greater effectiveness of blue color has been repeatedly claimed, a great variability among different blue lenses exists (14), so a generic prescription of blue lenses might be ineffective for optimal photosensitive control. Using a colorimeter examination, some authors (27) found that many photosensitive patients reported beneficial effects with lenses of purple or rose color. However, the design of their study was different from that of the present study, and the patients were not always tested with and without the lenses. Recently, Kepecs et al. (13) reported that blue cross-polarized lenses can have potential additional benefits for photosensitive patients. It remains unclear how the lenses work, but the mechanism of action of many AEDs is also doubtful. Based on previous studies (10), it is reasonable to speculate that the effectiveness of the Z1 lens could be related to its capacity to cut the light frequencies between 550 and 700 nanometers (Fig. 1), which seem to play a major excitatory role in the genesis of PPR. It is also possible, as suggested by Takahashi et al. (28), that some of our patients have a quantity-of-light–dependent PPR. In these cases, the decrease of luminance can play an important role in PPR suppression.

In many of our photosensitive epilepsy patients, pharmacologic treatment was avoided by using the blue sunglasses, and, when prescribed, sunglasses were always well tolerated by the patients. In a subgroup of our patients, we evaluated the tolerability of the lenses. Most (∼80%) of them tolerated the lenses very well during daily life. Of course, we are aware that, in some conditions such as in the darkness, the lenses can prevent optimal vision. In these situations, the patient is free to take off his lenses to obtain a better vision.

In conclusion, the results of our multicenter study give good evidence that the Z1 lens has great effectiveness in controlling photosensitivity. In our opinion, Z1 lens might become a valid resource in the daily activity of clinicians worldwide who carefor patients with epilepsy.

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