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Photosensitivity in epileptic syndromes of childhood and adolescence

Yang Lu[1,2], Stephan Waltz[1,3], Katja Stenzel[1,4], Hiltrud Muhle[1], Ulrich Stephani[1]

[1] Neuropaediatric Department of University Hospital of Schleswig-Holstein, Campus Kiel, Germany
[2] The First Affiliated Hospital of Chongqing Medical University, Chongqing, People's Republic of China
[3] Neuropaediatric Department, Children's Hospital Amsterdamer Strasse, Cologne, Germany
[4] Paediatric Department, Ostholstein Kliniken Eutin, Eutin, Germany

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ABSTRACT – *Purpose.* Photosensitivity, a reaction of the brain to external photic stimulation, can be graded from 1 to 4, and is most frequently seen in the first decades of life. This study investigated photosensitivity in children with epilepsy. *Methods.* A retrospective study performed in the neuropaediatric department of the largest paediatric hospital in Kiel, treating patients at all medical care levels. The clinical data and EEG records of 566 patients with the most common epileptic syndromes were analyzed, in particular regarding photosensitivity. Their EEGs included application of intermittent light stimulation using standard techniques at twice the minimum. *Results.* The proportion of photosensitive patients was significantly higher in the paediatric cohort than in adult patients, as published in the literature: 46% of patients with generalized epilepsies showed photosensitivity as compared to 20% with focal epilepsies. Photosensitivity was more common in idiopathic generalized epilepsy (IGE), (epilepsy with *grand mal* on awakening, 74%; juvenile absence epilepsy, 56%; juvenile myoclonic epilepsy, 50%; childhood absence epilepsy, 44%) than in focal types (idiopathic partial – Rolandic epilepsy, 23%; symptomatic/cryptogenic type of epilepsy, 16%), while in patients who experienced occasional seizures (neonatal/febrile seizures), this ranged between 40% and 23%, respectively. The generalized photoparoxysmal response, (PPR), grades 3 and 4 were found significantly more often in patients with IGE (92%) than in patients with focal epilepsies. Finally, the female preponderance was confirmed (37% to 27% of all epilepsies). *Conclusions.* Photosensitivity can be detected both in patients with IGE, with idiopathic and symptomatic/cryptogenic types of focal epilepsies, and with epileptic (occasional) seizures. PPR grades 3 and 4 are the most common in IGE.

Key words: photosensitivity, epileptic syndromes, childhood, adolescence, adulthood, photoparoxysmal response

Correspondence:
U. Stephani, MD PhD
Neuropaediatric Department of University,
Hospital of Schleswig-Holstein,
Campus Kiel, Schwanenweg 20,
D-24105 Kiel, Germany
<stephani@pedneuro.uni-kiel.de>

On electroencephalography (EEG), photosensitivity (photoparoxysmal response, [PPR]) is a common genetic trait in about 8% of healthy children (Doose and Gerken 1973). It is defined as the occurrence of irregular spikes or spikes-and-waves in response to intermittent photic stimulation (IPS), ranging from the localized form of occipital spikes (grade 1) to the

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most generalized form (grade 4) of generalized spikes-and-waves or polyspike waves (Waltz *et al.* 1992, Doose and Waltz 1993).

Many studies on photosensitivity have been performed in children and adolescents, the periods during which the prevalence of photosensitivity is highest (for review see Kasteleijn-Nolst Trenité, 1989). However, studies investigating the distribution of the photoparoxysmal response within the different epileptic syndromes have been confined to adult patients (Wolf and Gooses 1986, Obeid *et al.* 1991, Harding *et al.* 1997). The purpose of this study was to examine the relationship between photosensitivity and the epileptic syndromes in childhood and adolescents, in particular, generalized and focal epilepsies and idiopathic, symptomatic, cryptogenic forms of epileptic syndromes, and epileptic syndromes with occasional seizures such as neonatal and febrile seizures. Furthermore, the grades of the PPR in different epileptic syndromes were analyzed.

Methods and material

Patients

This is a retrospective study performed in the neuropaediatric department of the largest paediatric hospital in Kiel, treating patients at all medical care levels. We analyzed the clinical charts and EEGs involving photostimulation of all 1241 patients who were treated from 1975 to 2002 (*table 1* with age distribution), and met the following criteria: 1) at least two EEGs with intermittent photic stimulation (IPS) were performed in individuals aging from five to 15 years; 2) patients were clearly classified as suffering from one of the more common epileptic syndromes, including occasional seizures (*i.e.* neonatal seizures and febrile seizures), West syndrome, Lennox-Gastaut syndrome, myoclonic-astatic epilepsy, childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, *grand mal* on awakening, Rolandic epilepsy, or epilepsy with complex-focal seizure; 3) the definition of epilepsy syndrome was consistent with the revised classification of epilepsy, epileptic syndrome, proposed by the International League Against Epilepsy (1989). The charts of the patients were analysed carefully in order to rule out the possibility of their being wrongly diagnosed with epilepsy. In particular, the group with "occasional seizures" referred to those patients who had experienced neonatal seizures and febrile seizures, without being associated with other epileptic seizures. Neonatal seizures were considered as all types of seizure within a postnatal period of four weeks. Febrile seizures were defined as fever-induced seizures at the age of six weeks to five years. The percentage of the photosensitivity rate in those children without a definite diagnosis of an epileptic syndrome was not determined in this study.

In some patients (e.g. those with absence seizures and febrile seizures), repeated EEGs had been performed in the Kiel neuropaediatric department for scientific studies. Because of the huge amount of data available, only every third patient with childhood absence epilepsy, with Rolandic epilepsy, and with febrile seizures was randomly selected for further analysis, which resulted in a cohort of 566 patients, with 122, 103, and 117 patients being diagnosed respectively *(table 2)*.

Electroencephalographic assessment of the PPR

IPS stimulation had been carried out with standard photostimulators (Knott or Grass PS22 stimulator) in a dim room; lamp distance was approximately 25 cm (Waltz *et al.* 1992, Doose *et al.* 1969). For 30 sec, the flash frequency was slowly increased up to 20/sec, and for the next 30 sec reduced to 4/sec. Thereafter, flash frequencies of 5, 10, 12, 15, 20, and 25/sec (in a few patients examined with a new device, up to 50/sec) were used for 20 sec each and irregular frequencies for a period of 30 sec. During each 30-sec period the effect of three eye conditions (eye closure, eyes closed, and eyes open) was tested once. The quantitative expression of the age-dependent PPR was graded on a scale of 1 to 4, ranging from solely occipital-spikes within the occipital alpha rhythm (grade 1), parieto-occipital spikes followed by biphasic slow waves (grade 2), parieto-occipital spikes followed by biphasic slow waves and spreading to the frontal region (grade 3), to generalized spikes-and-waves and polyspike waves discharges (grade 4) (Waltz *et al.* 1992). The EEG recordings of the patients were re-analysed and only patients with unambiguous findings were included.

Table 1. Number of EEGs with photic stimulation in relation to photosensitive patients in different age groups.

Age group	EEGs with photostimulation	PS+ -EEGs		Investigated patients	Patients with PPR	
		Nr.	%		Nr.	%
1-3 years	209	8	4	146	6	4
4-6 years	694	116	17	430	70	16
7-9 years	520	116	22	338	83	25
10-12 years	261	68	26	186	52	28
13-15yars	195	70	36	124	41	33
> 15 years	18	4	22	17	4	24
	1 897	382		1 241	256	

Table 2. The classification and clinical data of epileptic patients and epileptic syndromes.

Epileptic syndrome	Gender		Age of onset	
	Male	Female	Mean	Range
Occasional seizures				
Neonatal seizures (n = 15)	7 (47%)	8 (53%)	4 days	1 day to 14 days
Febrile seizures (n = 117)	71(61%)	46 (39%)	2.2 years	1.5 months to 6 years
Epilepsies				
Generalized epilepsy				
Symptomatic/ cryptogenic				
West syndrome (n = 17)	13 (76%)	4 (24%)	8months	1.5 months to 12 months
Lennox-Gastaut syndrome (n = 7)	5 (71%)	2 (29%)	2 years	2 months to 7 years
Idiopathic				
Myoclonic-astatic epilepsy (n = 11)	7 (64%)	4 (36%)	3.4 years	7 months to 8 years
Childhood absence epilepsy (n = 122)	54 (44%)	68 (56%)	5.5 years	3 years to 9 years
Juvenile absence epilepsy (n = 25)	10 (40%)	15 (60%)	11 years	10 years to 15 years
Juvenile myoclonic epilepsy (n = 12)	6 (50%)	6 (50%)	13 years	11 years to 15 years
Grand mal on awakening (n = 31)	17(55%)	14 (45%)	9.6 years	4 years to 15 years
Focal epilepsy				
Idiopathic				
Rolandic epilepsy (n = 103)	63(61%)	40 (39%)	6 years	2 days to 13 years
Symptomatic/ cryptogenic				
Complex focal seizures (n = 106)	69 (65%)	37 (35%)	6 years	1 day to 14 years
Total (n = 566)	322(57%)	244 (43%)	5.3 years	1 day to 15 years

Statistic analysis

Chi-squared tests and Fisher's exact tests were performed. A P-value less than 5% was considered as significant.

Results

Patients

Our cohort contained 566 patients, comprising 322 males and 244 females. Eleven epileptic syndromes were classified into two groups; occasional seizures and epilepsies. *Table 2* lists the distribution of the different epileptic syndromes and age-at-onset in the male and female patients. IPS was performed twice in 100%, three times in 67% and four times or more in 33% of the patients.

Photosensitivity

Photosensitivity in different epileptic syndromes

Thirty-one percent of the total 566 patients had a PPR *(table 3)*. The frequency of the PPR in generalized epilepsy (46%) was significantly higher than in focal epilepsy (20%). Of the patients with idiopathic generalized epilepsy (IGE), 49% showed photosensitivity. This was significantly different from the rate of 23% photosensitivity in patients with idiopathic focal Rolandic epilepsy ($p < 0.0001$). The patients with generalized or focal symptomatic/cryptogenic epilepsies had similarly low PPR rates (17% to 16%).

The highest rate of PPR was 74% in patients with *grand mal* on awakening (IGE), followed by patients with juvenile absence epilepsy (56%), patients with juvenile myoclonic epilepsy (50%), and patients with childhood absence epilepsy (44%). A statistically significant difference was observed between the patients with *grand mal* on awakening and those with childhood absence epilepsy ($p < 0.015$).

Photosensitivity was found in 20% of all patients with focal epilepsies, (23% of patients with Rolandic epilepsies). There was no significant difference between the occurrence of the PPR in Rolandic epilepsy as compared to symptomatic/cryptogenic epilepsies with complex-focal seizures (16%).

Twenty-five percent of patients with occasional seizures (neonatal seizures and febrile seizures) were photosensitive. The PPR rate was higher in patients with neonatal seizures (40%), but the difference, compared to patients with febrile seizures (23%), was not significant.

Photosensitivity in male and female patients

Overall, the PPR rate was significantly higher in females (37%) than in males (27%) *(table 3)*. The incidence of the the PPR in female patients with *grand mal* on awakening was much higher than that found in male patients (93% *versus* 59%, $p < 0.001$). In the subgroup of juvenile

Table 3. Photosensitivity in the epileptic syndromes and the respective sex distribution.

Epileptic syndrome	Photo-sensitivity	Male		Female	
	Nr. (%)	Nr.	Nr. (%) of PPR	Nr.	Nr. (%) of PPR
OCCASIONAL SEIZURES					
Neonatal seizures (n = 15)	6 (40)	7	3 (43)	8	3 (37)
Febrile seizures (n = 117)	27 (23)	71	17 (24)	46	10 (22)
Total (n = 132)	33 (25)	78	20 (26)	54	13 (24)
EPILEPSIES					
Generalized epilepsy					
Symptomatic/ cryptogenic					
West syndrome (n = 17)	3 (18)	13	1 (8)	4	2 (50)
Lennox-Gastaut syndrome (n = 7)	1 (14)	5	1 (20)	2	0 (0)
Total (n = 24)	4 (17)	18	2 (11)	6	2 (33)
Idiopathic					
Myoclonic-astatic epilepsy (n = 11)	2 (18)	7	2 (29)	4	0 (0)
Childhood absence epilepsy (n = 122)	54 (44)*	54	21 (39)	68	33 (49)
Juvenile absence epilepsy (n = 25)	14 (56)	10	8 (80)$^{+}$	15	6 (40)$^{+}$
Juvenile myoclonic epilepsy (n = 12)	6 (50)	6	2 (33)	6	4 (67)
Grand mal on awakening (n = 31)	23 (74)*	17	10 (59)$^{++}$	14	13 (93)$^{++}$
Total (n = 201)	99 (49)**	94	43 (46)	107	56 (52)
Total (generalized epilepsies, n = 225)	103 (46)***	112	45 (40)	113	58 (51)
Focal epilepsy					
Idiopathic					
Rolandic epilepsy (n = 103)	24 (23)**	63	12 (19)	40	12 (30)
Symptomatic/ cryptogenic					
Complex focal seizures (n = 106)	17 (16)	69	11 (16)	37	6 (16)
Total (focal epilepsies, n = 209)	41 (20)***	132	23 (17)	77	18 (23)
Total (n = 566)	177	322	88 (27)$^{+++}$	244	89 (37)$^{+++}$

* $p < 0.015$ between *grand mal* on awakening and childhood absence epilepsy; ** $p < 0.0001$ between idiopathic generalized epilepsy and idiopathic focal Rolandic epilepsy; *** $p < 0.0001$ between generalized epilepsies and focal epilepsies; $^{+}$ shows the PPR incidence higher in males with juvenile absence epilepsy than in females, $p < 0.0001$; $^{++}$ shows the PPR incidence in female patients with *grand mal* on awakening higher than that of male patients, $p < 0.0001$; $^{+++}$ overall the PPR rate significantly higher in females than in males, $p = 0.002$.

absence epilepsy, the incidence of the PPR was higher in males than in females (80% *versus* 40%, $p < 0.001$).

Photosensitivity in individual age groups

The finding of a PPR was an age-related trait in our selected cohort *(table 1)*. The incidence of PPR was low (4%) in children 1-3 years of age, and increased gradually with increasing age until the maximal PPR penetrance appeared in EEGs in 13-15-year-old patients (33%). Thereafter, the incidence of the PPR decreased by 24% in patients older than 15 years of age. However, photostimulation was performed most frequently in patients 4-6 years of age.

Effect of medication on photosensitivity

The incidence of the PPR in 355 patients who had received at least one IPS without drug therapy was 51%. IPS was performed in another 211 patients during drug treatment; the PPR rate was 59%. The difference in the frequency of the PPR in patients with and without medication was not significant.

Of the patients with classical IGE syndromes (childhood and juvenile absence epilepsies, juvenile myoclonic epilepsy, *grand mal* on awakening), 49 (44%) of a total of 111 patients on valproic acid (VPA) were photosensitive as compared to 48 (60%) of 79 patients not receiving VPA therapy *(table 4A)*. Of the patients with mixed non-IGE-syndromes (neonatal seizures, febrile seizures, West-syndrome, Lennox-Gastaut syndrome, myoclonic astatic epilepsy, Rolandic epilepsy, symptomatic/cryptogenic focal epilepsy) 4 (18%) of 22 patients receiving VPA were photopositive as compared to 75 (21%) of 354 patients not receiving VPA *(table 4B)*.

Table 4. The PPR in patients with and without VPA.

A) Idiopathic generalised epilepsies (IGE)				
Epileptic syndrome	**With VPA**		**Without VPA**	
	Nr.	**Nr. (%) of PPR**	**Nr.**	**Nr. (%) of PPR**
Childhood absence epilepsy (n = 122)	84	33 (39%)	38	21 (55%)
Juvenile absence epilepsy (n = 25)	18	11 (61%)	7	3 (43%)
Juvenile myoclonic epilepsy (n = 12)	7	4 (57%)	5	2 (40%)
Grand mal on awakening (n = 31)	2	1 (50%)	29	22 (76%)
Total (n = 190)	111	49 (44%)	79	48 (60%)
B) Mixed non-IGE syndromes				
Epileptic syndrome	**With VPA**		**Without VPA**	
	Nr.	**Nr. (%) of PPR**	**Nr.**	**Nr. (%) of PPR**
Neonatal seizures (n = 15)	0	0 (0%)	15	6 (40%)
Febrile seizures (n = 117)	2	1(50%)	115	25 (22%)
West syndrome (n = 17)	0	0 (0%)	17	3 (18%)
Lennox-Gastaut syndrome (n = 7)	2	0 (0%)	5	1 (20%)
Myoclonic-astatic epilepsy (n = 11)	5	1 (20%)	6	1 (17%)
Rolandic epilepsy (n = 103)	4	1 (25%)	99	23 (23%)
Complex focal seizures (n = 106)	9	1 (11%)	97	16 (16%)
Total (n = 566)	22	4 (18%)	354	75 (21%)

Different grades of photosensitivity

In a total of 177 patients with a PPR, 82% showed a generalized PPR grade 3 and 4 reaction, and 18% individuals demonstrated a PPR grade 1 and 2 reaction *(figure 1)*.

Grade 3 and 4 reactions were found in 92% of photosensitive patients with IGE, in 100% of such patients with symptomatic/cryptogenic generalized epilepsies, in 71% each with idiopathic and symptomatic/cryptogenic partial epilepsies, and 67% and 63% with neonatal seizures and febrile seizures, respectively.

Grade 4 reaction was found significantly more often in IGE (59%) than in idiopathic focal Rolandic epilepsy (38%).

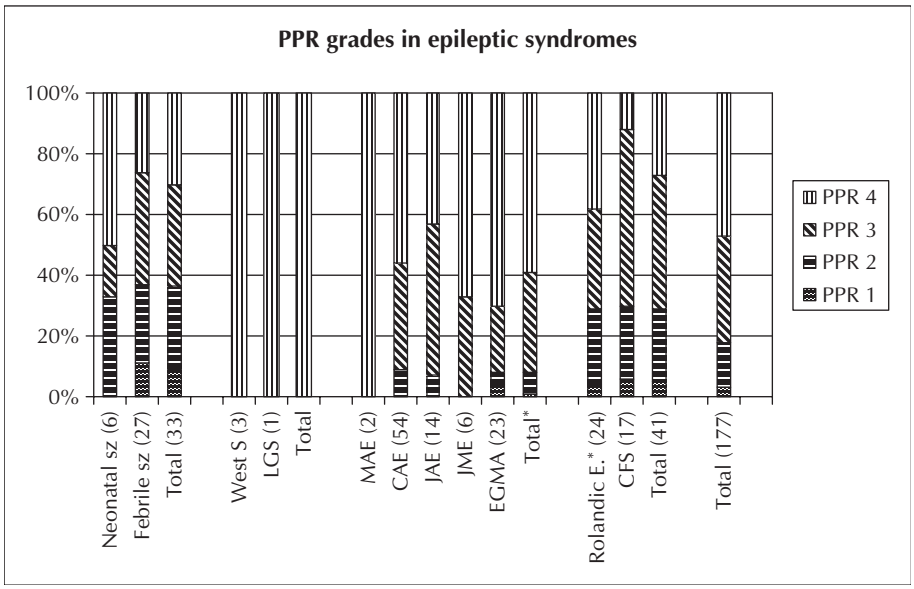

Figure 1. PPR grades in epileptic syndromes.
(Nr): absolute numbers of patients; sz: seizures; Total: summarizes the left sided bars of each Total; West S: West syndrome; LGS: Lennox-Gastaut-syndrome; MAE: myoclonic astatic epilepsy; CAE: childhood absence epilepsy; JAE: juvenile absence epilepsy; JME: juvenile myoclonic epilepsy; EGMA: epilepsy with *grand mal* on awakening; Rolandic E.: Rolandic epilepsy; CFS: complex focal seizures. PPR 1-4: PPR grades 1-4. * Shows that the PPR grade 4 reaction is significantly higher in patients with idiopathic generalized epilepsy than with idiopathic focal Rolandic epilepsy, $p < 0.001$.

Grade 1 and 2 reactions were seen in 8% of patients with IGE with a PPR, in 29% of patients each with idiopathic and symptomatic/cryptogenic partial epilepsies and a PPR, and in 33% and 37% with neonatal and febrile seizures, respectively.

Photosensitive seizures

Of 177 photosensitive patients, eight had photosensitive seizures (PSS), and all suffered from IGE. Among them, three photosensitive patients with childhood absence epilepsy had absence seizures during IPS; three photosensitive patients with *grand mal* on awakening showed tonic-clonic seizures during IPS; and myoclonic seizures were provoked by IPS in another two photosensitive patients with juvenile myoclonic epilepsy.

Discussion

Photosensitivity

According to published reports, a PPR can be elicited in about 1.6% of healthy adults and patients with neurological-psychiatric disorders in general, but in 7.4%-9.9% of adult patients with epilepsy (Buchthal and Lennox 1953, Gastaut *et al.* 1958, Rabending and Klepel 1978, Obeid *et al.* 1991, Wolf and Gooses 1986). Higher rates of photosensitivity have been reported in children. Of a total of 662 healthy children and adolescents, 7.6% showed photosensitivity, with the maximal PPR penetrance in the age range of 5-15 years (Doose and Gerken, 1973). A similar rate for the PPR, 8.3%, was also reported in healthy children younger than five years of age (Eeg-Oloffson *et al.* 1971). Within a mainly adult population, Klepel found the highest PPR rate in patients with neurological-psychiatric disorders in the age range of 10-20 years (Klepel and Rabending 1989).

In the present study, 31% of patients with epilepsy had a PPR. This high rate of PPR might be explained by the following:

– repeated IPS procedures might result in higher PPR rates than fewer or single investigations (33% of all the analyzed patients had received four or more EEGs with IPS). Therefore, those studies which deal only with routine clinical aspects probably overlook the higher rate of PPR;

– a PPR may be missed in a given individual if photic stimulation is performed before age-related appearance of the PPR or after remission of the electroencephalographic trait (Harding *et al.* 1997). We selected patients, who had been investigated at least twice at the age of maximum penetrance of the photoparoxysmal response (three times between the age of four and 18 years as a rule, in the unselected patient cohort) (Doose and Waltz 1993). It is reasonable to admit that investigations involving patients, who had only been investigated at a younger or older age (Wolf and Gooses 1986) will report a lower rate of photosensitivity;

– some older PPR studies do not consider grade 1 and 2 PPR (Wolf and Gooses 1986, Kasteleijn-Nolst Trenité 1989). This might be a selection bias in other studies.

Photosensitivity in different epileptic syndromes - comparison of adult and children groups

As was already shown in previous investigations (Wolf and Gooses 1986, Stephani *et al.* 2004), the present study confirms that PPR rates are significantly higher in patients with generalized epilepsy than in patients with focal epilepsies. Moreover, the present study shows that generalized types of PPR are more prevalent in generalized epilepsies than in symptomatic/cryptogenic focal epilepsies.

The distribution of the photosensitivity rate among the different syndromes of IGE was somewhat different from the data reported by Wolf and Gooses (1986) and Waltz *et al.* (1990) in adults. The rate of photosensitivity in absence epilepsies is higher than previously reported. Thus, investigation of patients in childhood shows that a PPR occurs more frequently in childhood absence epilepsies (*e.g.* pycnolepsy) than in adult patients (*e.g.* spaniolepsy). In the studies of Wolf and Gooses (1986) and Waltz *et al.* (1990), the epileptic syndrome with the highest rate of photosensitivity was JME (Waltz 2000, Appleton *et al.* 2000), whereas in the present study the highest rate of photosensitivity was found in epilepsy with *grand mal* on awakening. However, our study included only a small number of patients with JME. Furthermore, some of our young patients with *grand mal* on awakening only, may have developed JME later in life.

In our investigation, a PPR was found in 20% of patients with focal epilepsy; this is much higher than in other reports; 2.7% in the study by Wolf; 0.6% in Obeid's studies. The reason for the great difference might not just be the age of patients. The investigations of Wolf and Gooses (1986) and Obeid *et al.* (1991), did not include patients with Rolandic epilepsy, who, in our study, showed the highest rate of photosensitivity among the focal epilepsies.

Our study, including nongeneralized grades of photosensitivity as proposed by current classification systems (Waltz *et al.* 1992, Kasteleijn-Nolst Trenité *et al.* 2001) shows a high proportion of grade 1 and grade 2 PPR in focal epilepsy. Thus, previous studies that excluded nongeneralized grades of PPR may have underestimated the rate of the PPR in focal epilepsies. However, the higher rate of photosensitivity in focal epilepsies is restricted to photosensitivity as an electroencephalographic trait. The presence of a PPR in focal epilepsies may represent a contributing factor in the multifactorial pathogenesis of epilepsy in such children (Andermann and Straszak 1982, Doose et Waltz 1993). None of the patients with focal epilepsy in this study showed photosensitive seizures.

Some patients with occasional seizures (neonatal and febrile seizures) are also photosensitive. Indeed, the PPR rate reached 42% in young patients with febrile seizures

(Doose *et al.* 1983). In our investigation however, the PPR rate in patients with febrile seizures is somewhat lower, at only 23%.

Photosensitivity in male and female patients

It is generally accepted that the PPR rate is higher in females than in males (Newmark and Penry 1979, Klepel and Rabending 1989, Wolf and Gooses 1986). In line with those findings, the overall incidence of a PPR was also higher in females than in males in the present study.

In patients with IGE, the PPR in females is predominant, except for in the group of juvenile absence epilepsy. However, this group comprised only 25 patients. Therefore, it is hard to draw any conclusions from this finding.

VPA effect on photosensitivity

The expected decline of the PPR rates in patients taking VPA was moderate in both IGE syndromes and mixed non-IGE syndromes. The PPR was lower in patients receiving VPA than in those not receiving VPA (44 to 60% in patients with IGE and 18 to 21% in non-IGE patients). Those patients who received VPA belong mainly to the IGE group, which shows higher PPR rates than other types of epileptic syndromes. In addition, a prospective comparison before and after VPA was administered was not performed in this study. Therefore, we cannot make conclusions about the extent of the effect of VPA on the PPR.

Photosensitive seizures

Patients with PSS mainly display generalized seizures, such as myoclonic, tonic-clonic seizure, or absence seizures: photosensitive focal seizures occurring only rarely (Kasteleijn-Nolst Trenité 1989 and 1994, Newmark and Penry 1979), with myoclonic seizures being the most frequent PSS (Kruse 1991). However, photosensitive partial seizures with secondary generalization have been observed in a small cohort (Kosaburo *et al.* 1994). The aim of the present study was to investigate the EEG-trait of photosensitivity.

The rate of photosensitive seizures may be underestimated in the present study for several reasons: we did not analyze video documentation of photic stimulation. Short seizures may therefore have been missed by our technicians. Furthermore, in our laboratory, technicians have to stop IPS when generalised spikes and waves occur twice (PPR grade 3 and 4) during the photic stimulation.

In conclusion, this study shows high rates of the PPR in young patients investigated at least twice for photosensitivity with generalized epilepsies, focal epilepsies, and neonatal and febrile seizures. PPR grade 3 and 4 reactions were predominant. Grade 4 PPR is found more often in IGE than in Rolandic epilepsy. The greatest penetrance of the PPR is seen in the 13-15 year age group. □

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