6-1-2020

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Epilepsy & Behavior 107 (2020) 107046

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

A study of the significance of photoparoxysmal responses and spontaneous epileptiform discharges in the EEG in childhood epilepsy

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ARTICLE INFO

Article history:
Received 6 February 2020
Revised 14 March 2020
Accepted 15 March 2020
Available online 15 April 2020

Keywords:
Photosensitivity
Intermittent photic stimulation
PPR
Self-limiting
SED
HV

ABSTRACT

Aim: In clinical practice, there is a prevailing notion that photosensitivity mostly occurs in children with epilepsy (CWE) with idiopathic generalized epilepsy. We investigated the distribution of epilepsy types and etiology in photosensitive children and the associations with specific clinical and electroencephalogram (EEG) variables.
Methods: In this retrospective cohort study, clinical data were acquired from all children that showed photosensitivity during systematic intermittent photic stimulation (IPS), over a 10-year interval at a tertiary level Children's Hospital, Winnipeg. Patient demographics, EEG findings, and clinical data and symptoms during IPS were abstracted. Classification of diagnoses using the International League Against Epilepsy (ILAE) 2017 guidelines was done by an expert panel.
Results: Seventy-eight photosensitive children were identified. Forty (51.3%) had generalized epilepsy (idiopathic: 27, structural: 2, other: 11) compared with 19 (24.4%) focal (idiopathic: 1, structural: 2, other: 16), 8 (10.3%) combined focal and generalized (structural: 4, other: 4), and 11 (14.1%) unknown epilepsy (other: 11); (χ^2 (3) = 32.1, p = .000).
Self-sustaining or outlasting photoparoxysmal responses (PPRs) occurred in association with all epilepsy types; however, the EEGs of focal CWE without treatment comprised almost solely of PPRs which outlasted the stimulus (8/10), in contrast to only 8/17 of focal CWE with treatment and to 13/26 of generalized epilepsy without treatment.
Most frequency intervals in individual patients were less under treatment: a decrease in standardized photosensitivity range (SPR) was seen in 5 CWE, an increase in 2, and no change in 1 during treatment. Both CWE with focal and generalized epilepsy showed abnormal activity on EEG during hyperventilation (40% vs 65.7%). Thirteen out of 14 CWE with clinical signs during IPS had independent spontaneous epileptiform discharges (SEDs) in the EEG recording.
Conclusion: Photosensitivity occurs in all types of epilepsy rather than in idiopathic generalized epilepsy alone. Surprisingly, there is a tendency for focal epilepsy to be associated with self-sustaining PPRs, especially when no treatment is used. Treatment tends to make the PPR more self-limiting and decrease the SPR. There is a tendency that clinical signs during IPS occur in EEGs in individuals with SEDs.

1. Introduction

Photosensitivity is characterized by an abnormal response of the electroencephalogram (EEG) during visual stimulation. This phenomenon is called a photoparoxysmal response (PPR). Photoparoxysmal responses can be elicited using intermittent photic stimulation (IPS) during EEG [1]. Photoparoxysmal responses can occur with or without clinical symptoms. When visual stimulation provokes an epileptic seizure, it is called a photic-induced seizure. During IPS, frequencies in the 15–25-Hz range were found to be most likely to trigger seizures [2].

The prevalence of photosensitivity in the general population is believed to be around 1/4000. It is much more common in children with epilepsy (CWE), approximately 2–5% [3]. Photosensitivity is mostly seen in children and adolescents, and a preponderance in the female gender is noted [4]. In clinical practice, a prevailing notion remains that photosensitivity in CWE suggests that the clinical diagnosis is

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https://doi.org/10.1016/j.yebeh.2020.107046

idiopathic generalized epilepsy [5], but photosensitivity may occur in association with different epilepsy syndromes and various seizure types [1]. The study of Kasteleijn-Nolst Trenite et al. found that PPRs are described in association with focal epilepsy and that clinical signs and symptoms during PPRs can be focal [6].

In daily life, several visual phenomena act as triggers that can provoke clinical symptoms of photosensitivity. Most common and best recognized triggers are flickering sunlight, television (TV), video games, and environmental lighting (e.g., stroboscope/disco lights). Increased artificial light stimulation in recent years has significantly increased the likelihood of clinical manifestation of photosensitivity [3,7].

Electroencephalogram responses to photic stimulation can be divided in the following 3 categories: (1) Photomyoclonic responses which result from twitching of orbital and craniofacial musculature in response to light flashes and are a physiologic phenomenon seen in adults; (2) Physiologic responses which are only seen in the posterior electrode chains, for example, photic driving or occipital spikes time-locked to the stimulus; and (3) PPRs, consisting of spikes, spike–waves, or intermittent slow waves, that may or may not outlast the period of IPS and can be focal or generalized [2,8].

Spontaneous epileptiform discharges (SEDs) are reported to occur in up to 65% of CWE with a PPR. Although PPR is usually assumed to indicate a predisposition to generalized seizures and idiopathic generalized epilepsy, the clinical significance of associated SEDs and its association to epilepsy is not known [9]. It is thought that CWE with PPRs without SEDs carry a lower risk for seizures (30%) than CWE with generalized SEDs (~60%) [10]. Hyperventilation (HV) is an additional activation method during EEG, similar to IPS. It mostly provokes generalized epileptiform discharges; however, it can also provoke focal epileptiform discharges in up to 10% of CWE with focal epilepsies [11].

Many studies have shown that there is a relationship between PPRs, visual sensitivity in daily life, and epilepsy; however, it is still unclear to what extent PPRs are related to different types of epilepsy [12,13]. With the new International League Against Epilepsy (ILAE) seizure and epilepsy classification at hand, we investigated the distribution of epilepsy types and etiologies in children that showed photosensitivity during IPS, aged 8 to 207 months, and the associations with specific EEG variables.

Our primary hypothesis is that a substantial part of the PPR positive CWE has focal epilepsy, while CWE with generalized epilepsy types display provocation of epileptiform activity by both IPS and HV. Secondly, we hypothesized that having clinical signs during PPRs is correlated with having SEDs. Furthermore, we explored whether use of antiseizure medications (ASM) in CWE would be related more often with self-limiting PPRs and with smaller photosensitivity ranges.

2. Methods

A retrospective study was conducted using detailed data of 78 children (0–18 years) with 114 abnormal EEG reports during IPS, found over a 10-year period (January 1st 1989 to December 31st 1998) from the Clinical Neurophysiology Laboratory at the Children's Hospital, Winnipeg, Manitoba.

2.1. Design

In this retrospective cohort study, clinical and EEG data were acquired at the Children's Hospital, Winnipeg, Manitoba. This study was designed to examine the association between PPRs, epilepsy type, and seizures in the pediatric population. All available clinical information was gathered including comorbidities. Clinical symptoms and signs were noted during IPS. The frequency of photic stimulation during PPRs was recorded as well.

2.2. Subjects

Children with epilepsy were considered case subjects if they had at least one EEG with a PPR. In the present study, 78 children with one or more abnormal EEG reports during IPS were included. Those 78 CWE had a total of 208 EEGs, whereof 114 contained a PPR. The age of subjects during the EEGs ranged from 0 to 17 years. Of 16 CWE, visual triggers in daily life were noted. Informed consent was obtained from all CWE. The anonymity of the CWE was guaranteed by changing the names/patient numbers into subject numbers. Patient confidentiality and protection of personal data standards were adhered to during the performance of this study. Ethics approval was obtained from the University of Manitoba Health Research Ethics Committee. Each record obtained was identified by a randomly assigned number to maintain patient confidentiality. There were no unique identifiers that could result in potential identification, and all data were performed in accordance with PHIA (Personal Health Information Act).

2.3. Procedure

For each subject, the EEG records indicating abnormal PPRs and records collected during patient management –and data were abstracted for the following variables: age, sex, indication for performing the EEG, seizure semiology, photic stimulation trains administered, EEG response to photic stimulation, presence or absence of SED, type of SED (focal/regional, generalized), presence of clinical signs and symptoms, previous seizure type associated in accordance with ILAE classification, medication used, and any history of TV/computer/videogame/Pokémon (Japanese cartoon) induced seizures.

Testing was done with stepwise increase of frequencies up to 30 Hz with a strobe light approximately 20–30 cm from the nasion. The laboratory used a Nihon-Kohden photic stimulator for IPS. The CWE were awake, drowsy, or asleep. Sleep deprivation is known to provoke PPR. It has also been shown that PPRs significantly decrease during drowsiness, vanish during deep non-rapid eye movement (REM) sleep, and then reemerge during REM sleep, similar to wakefulness [14]. In a recent study by AD Elmali et al. [15], authors found that by comparing photoparoxysmal activity before and after sleep, 70% of the photosensitive patients were more sensitive to IPS after sleep (increment group). Within this group, 45.7% showed no PPR before sleep. No change group was 23% of the photosensitive patients, and 7% showed decreased activity. Transition periods between sleep and wakefulness are vulnerable to show epileptiform activity in general [15]. Stimulation was performed in a brightly to dimly illuminated room, after at least 2 min following HV. The subject was instructed to look at the light in the waking state. Flash frequencies used were 1, 3, 6, 9, 12, 15, 18, 21, 24, 27, and 30 Hz. The flash duration and flash interval were 5 s. If generalized discharges were evoked, or if the discharges outlasted the stimulus train, the stimulator was turned off, and the next stimulus frequency was introduced on cessation of the activated discharge. If a clinical or electrographic seizure was triggered, then the process of photic stimulation was terminated.

To reclassify epilepsy types according to the latest classification, we created an algorithm based on the classification of the ILAE 2017 (Fig. 1). Diagnosis of epilepsy type was done by a panel of epilepsy experts (CF/DKT), using information from the dataset regarding medical history, seizure semiology, and EEG findings. The expert panel reached consensus in all 78 CWE. Any disagreement throughout the diagnosing process was resolved by discussion between the two experts. Diagnosis of epilepsy consisted of epilepsy type and etiology. Epilepsy type was classified as focal, generalized, combined focal and generalized, or unknown. The etiology was classified as structural, idiopathic, or other etiology. If an anatomical abnormality in the brain was mentioned in the medical history and the

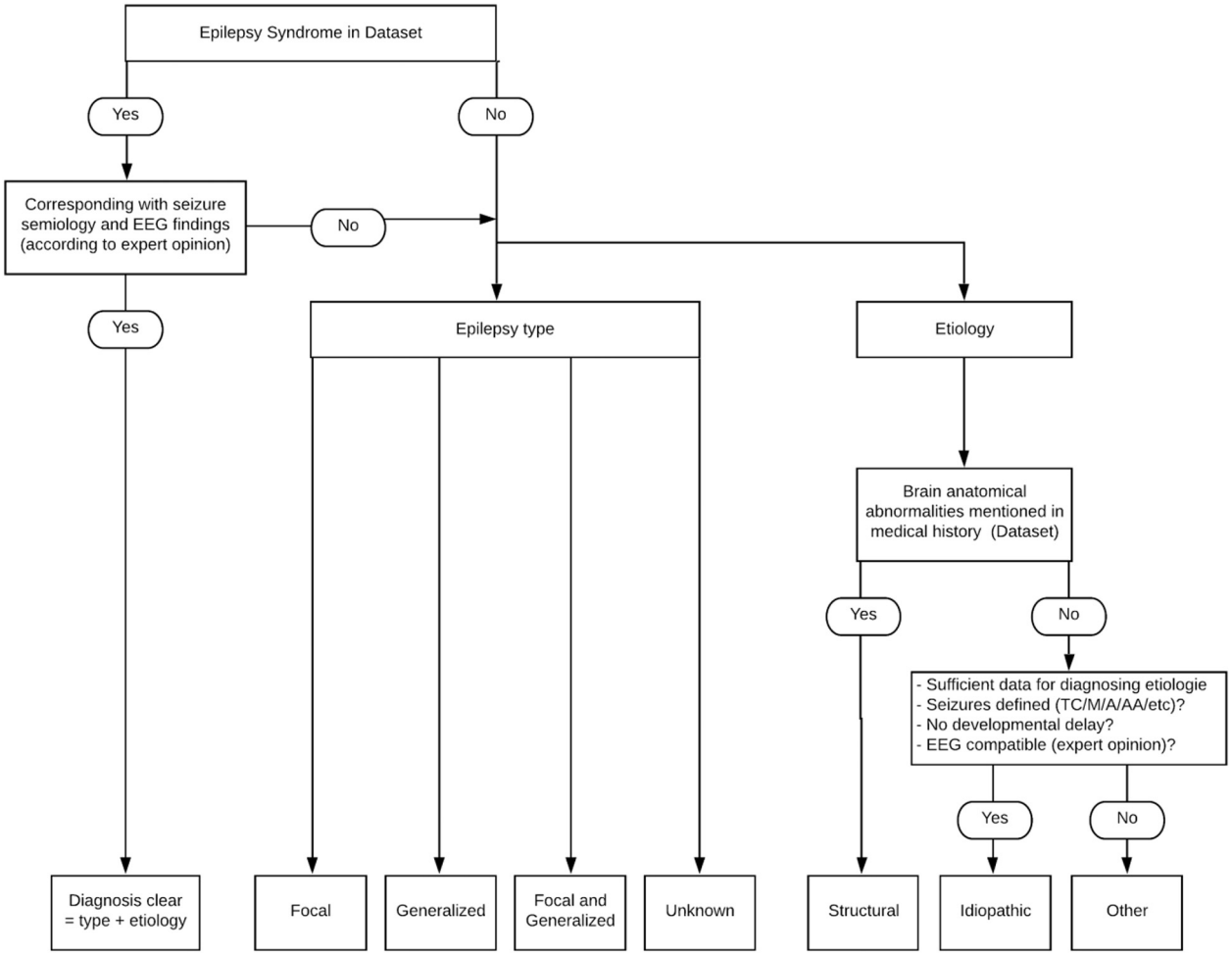

Fig. 1. Algorithm whereby the patients were classified into an epilepsy type (TC = tonic–clonic, M = myoclonic, A = Absence, AA = Atypical absence).

seizures and EEG findings were compatible with this abnormality, the etiology was classified as structural. The etiology was classified as idiopathic/genetic if there was sufficient data compatible with this etiology. From here, we will call this etiology idiopathic. The epilepsy etiology of the remaining CWE was classified as "other".

2.3.1. Epilepsy type and persistency of PPRs

Photoparoxysmal responses, that cease when the IPS pauses or before, can be distinguished from self-sustaining PPRs, which continue after the stimulus ceases. We studied if self-sustaining or self-limiting PPRs occur more often in a specific epilepsy type. We tested this by examining the separate EEGs. We sorted the EEGs by epilepsy types, by PPR (self-sustaining, self-limiting, both, or not specified), and by receiving treatment or not. We also examined if the occurrence of CWE with evidence of self-sustaining PPRs differed between the epilepsy types.

2.3.2. Epilepsy type and IPS frequencies provoking PPRs

We investigated the most provocative IPS frequencies in this population by measuring the median lower and upper limits of IPS frequencies which induced PPRs in all EEGs; the so-called photosensitivity ranges [16]. Furthermore, we compared the median lower and upper limits of flash frequencies which caused PPRs in EEGs of CWE with different epilepsy types.

The ranges in Hz between the upper and the lower limits for each EEG were also transformed into a metric, called the standardized photosensitivity range (SPR). The SPR is defined as the number of frequency steps between the lower and upper limits at which EEG epileptiform activity has occurred [16].

We studied the median SPR ranges in EEGs of CWE receiving treatment compared with EEGs of CWE not receiving treatment. Additionally in individual CWE who switched from not using treatment to receiving treatment, the SPR was compared between their EEG(s) while not using therapy and their EEG(s) while using therapy.

2.3.3. PPR response type on the EEG and flash frequencies

The response to IPS was classified using the following descriptors: generalized spike wave (or polyspike wave complexes) (GSW), generalized spike wave or polyspike wave complexes with temporoparieto-occipital beginning (OGSW), temporoparieto-occipital spike-wave or polyspike wave complexes (OSW), and other atypical responses (OR) [10]. The median lower and upper limits of IPS frequencies which caused PPRs were compared in the different PPR response types on the EEG along with the median SPRs.

2.3.4. Hyperventilation compared with IPS (sorted per epilepsy type)

In our study population in CWE with a PPR documented at least once, we examined the number of CWE with an abnormal response on the EEG during HV classified by epilepsy type. We also studied the number of CWE with a HV-induced seizure during the EEG. We compared these numbers with the number of CWE with clinical symptoms during IPS.

2.3.5. Clinical signs and SEDs

We examined the occurrence of SEDs on the EEGs of CWE with clinical symptoms during IPS. We divided the CWE with clinical symptoms

Table 1
Demographic table of the population. anti seizure drug (ASD) type per patient means a patient used this AED as monotherapy during at least 1 EEG. Combination therapy means a combination of 2 or more AEDs (not further specified which).

Demographic data of 78 patients	
Gender (%)	
○ Male	36 (46.2)
○ Female	42 (53.8)
Age during EEGs (months)	
○ Range	8–207
○ Median	126
○ Mean	122
# EEGs per patient	
○ Range	1–9
○ Median	2
# EEGs	
○ With PPR	114
○ Without PPR	94
N of patients receiving ASD during at least one EEG:	
○ No therapy	52
○ Monotherapy	54
○ Polytherapy	14
N of patients receiving during all EEGs: (1–5)	
○ No therapy	18
○ Monotherapy	13
○ Polytherapy	2
ASD type per patient	
○ Valproic acid	31
○ Carbamazepine	16
○ Phenobarbitone	6
○ Ethosuximide	5
○ Clobazam	3
○ Phenytoin	3
○ Clonazepam	1
○ Combination therapy	13
○ Other	2
○ Not specified	7

during IPS in CWE with at least one EEG with a SED and CWE without any SEDs on their EEG(s).

2.3.6. Clinical signs and persistence of PPRs

Clinical signs were classified in the dataset as absence, atypical absence, or myoclonic. We combined these labels in our results as one, which we labeled nonmotor symptoms. We studied if the PPRs on the EEGs during which CWE showed clinical symptoms evoked by IPS were more often self-sustaining or self-limiting. Furthermore, we examined if self-sustaining PPRs more often evoke clinical symptoms compared with self-limiting PPRs.

Table 2
Demographic table comorbidities: patients might have multiple comorbidities.

Comorbidities in the population (total N = 36)	
Psychiatric/behavioral problems (N = 21)	
○ Behavior problems	14
○ Autism	2
○ School difficulties	6
○ Obsessive compulsiveness	1
Developmental delay (N = 22)	
○ Mental retardation	3
○ Speech delay	8
○ Motor delay	5
○ Not specified	6
Neurological disorders (N = 9)	
○ Cerebral atrophy	1
○ Cerebral palsy	3
○ Hydrocephalus/meningitis	1
○ Microcephaly	2
○ Neuronal ceroid lipofuscinosis	1
○ Porencephalic cyst	1
○ Tuberous sclerosis	1
○ Ventriculomegaly	2
○ Spina bifida/VP shunt	1

Table 3
Number of patients per epilepsy type with a subdivision of the etiologies.

Epilepsy type	Patients (%)
Focal	19 (24.4)
• Idiopathic	1 (1.3)
• Other	16 (20.5)
• Structural	2 (2.6)
Generalized	40 (51.3)
• Idiopathic	27 (34.6)
• Other	11 (14.1)
• Structural	2 (2.6)
Focal and generalized	8 (10.3)
• Other	4 (5.1)
• Structural	4 (5.1)
Unknown	11 (14.1)
• Other	11 (14.1)
Total	78 (100)

2.4. Analysis

The analysis of the data was executed using Statistical Product and Service Solutions (SPSS) statistics data editor 25.0.0.2. A one-sample chi-square test was conducted to demonstrate if the epilepsy types were equally frequent in CWE with PPRs. The Pearson chi-square independence test was conducted to compare the number of CWE with a self-sustaining PPR in the various groups with epilepsy, to compare the number of self-sustaining PPRs in CWE receiving treatment versus CWE receiving no treatment, to compare the number of abnormal EEGs during HV between the different epilepsy types, and to compare the number of CWE with EEGs comprising of SEDs between the group of CWE with and without clinical symptoms during PPRs.

An independent samples median test was used to compare the median SPR in EEGs while CWE were using treatment compared with EEGs while CWE were not using treatment. The P-values of $<.05$ were considered statistically significant.

3. Results

Table 1 presents demographic and clinical characteristics of 78 CWE (53.8% female) with a PPR. Most CWE had up to 3 EEGs (median: 2). Out of 208 EEG recordings from 78 CWE, 114 showed PPRs, and 94 did not. The median age of the subjects during the EEGs was 126 months (range: 8–207). Children with epilepsy received different ASM and at times switched to a new ASM in subsequent EEGs. The different types of treatment are shown in Table 1. The comorbidities of the CWE are presented in Table 2. Children with epilepsy might have multiple comorbidities. Approximately half of the CWE had comorbidities (N = 36; 46.2%). The comorbidities consisted of psychiatric/behavioral problems (N = 21; 26.9% of all CWE), developmental delay (N = 22; 28.2%), neurological disorders (N = 9; 11.5%), and other comorbidities. The other comorbidities included asthma, carnitine deficiency, diabetes, cleft palate, leukemia, short stature, vitiligo, ventricular septum defect/bicuspid aortic valve, and deafness.

Table 4a
Number of patients with at least 1 EEG with an outlasting PPR per epilepsy type (statistical analysis with the Pearson chi-square).

Patients with evidence of outlasting PPRs	Focal	Generalized	Focal and generalized	Unknown	Pearson chi-square
Yes	12	30	8	9	$\chi^2(3) = 4.4$, p = .2
No	7	10	0	2	
Total	19	40	8	11	

Table 4b
Number of EEGs without/with therapy per epilepsy type with: PPRs which outlasted the stimulus, PPRs which were self-limiting, both outlasting and self-limiting PPRs, or not specified. In 5 EEGs, it was unknown if the patients used treatment or not. (Focal other = 2, generalized idiopathic = 2, combined focal and generalized = 1). N = no therapy, T = therapy.

Epilepsy type	Number of EEG's (no therapy/therapy)	Outlasted (N/T)	Self-limited (N/T)	Both (N/T)	Not specified (N/T)
Focal	10/17	8/8	0/4	0/2	2/3
• Idiopathic	1/0	1/0	0/0	0/0	0/0
• Other	9/14	7/7	0/4	0/0	2/3
• Structural	0/3	0/1	0/0	0/2	0/0
Generalized	26/34	13/14	6/10	3/5	4/5
• Idiopathic	17/21	7/9	5/5	2/4	3/3
• Other	7/13	5/5	1/5	0/1	1/2
• Structural	2/0	1/0	0/0	1/0	0/0
Focal and generalized	3/7	1/3	1/2	0/0	1/2
• Other	1/3	1/1	0/0	0/0	0/2
• Structural	2/4	0/2	1/2	0/0	1/0
Unknown	8/4	5/1	1/1	1/2	1/0
• Other	8/4	5/1	1/1	1/2	1/0
Total	47/62	27/26	8/17	4/9	8/10

3.1. Epilepsy diagnoses

More CWE had generalized epilepsy (51.3%) compared with focal (24.4%), combined focal and generalized (10.3%), and unknown epilepsy (14.1%); (χ^2 (3) = 32.1, p = .000). The types of epilepsies with a subdivision of their etiologies are shown in Table 3.

3.2. Epilepsy type and persistency of PPRs

Self-sustaining PPRs occur in all epilepsy types. The number of CWE with evidence of self-sustaining PPRs across various epilepsy types is presented in Table 4a. In the whole study population, there is no significant difference in the number of CWE with evidence of self-sustaining PPRs in the different groups of epilepsy type (χ^2 (3) = 4.4, p = .2).

The PPRs on the EEGs from CWE not receiving any treatment were examined to see if they outlasted the stimulus or not compared with those receiving treatment. The EEGs of patients with focal epilepsy without treatment comprised solely of PPRs which outlasted the stimulus, except for 2 PPRs which were not specified (N = 8/10; 80%). Out of these 8 PPRs, 4 showed generalized spike–waves, 1 showed occipital spike–waves, 1 showed another response, and in 2 were not specified. In contrast, in patients with generalized epilepsy without treatment, 13 out of 26 (50%) contained solely self-sustaining PPRs, and 6 out of 26 (23.1%) of the EEGs contained solely self-limiting PPRs. The percentage of EEGs with only self-limiting PPRs was similar for the group with focal epilepsy (N = 4/17; 23.5%) and the group with generalized epilepsy (N = 10/34; 29.4%) in those receiving treatment (Table 4b). The EEGs in CWE receiving treatment comprised more often solely of self-limiting PPRs compared with CWE not receiving treatment (17/62 vs 8/47; 27.4% vs 17.0%). However, this finding was not significant (χ^2 (1) = 2.4, p = .1). In patients with focal epilepsy exclusively, this was significant (χ^2 (1) = 4.0, p = .04).

3.3. Epilepsy type and IPS frequencies provoking PPRs

The median lower and upper limits of IPS frequencies which induced PPRs in all EEGs were, respectively, 12 and 18 Hz, with a range of 1–30 Hz. Fig. 2 and Table 5 show all IPS frequencies which induced PPRs per patient categorized per epilepsy type. Fig. 3 (supplements) shows the effect of ASM on PPRs in ascending age (in months). There was no clear difference in frequencies between those with and without medication (p = .42) (Table 9, supplements): the median SPR was 3 in EEGs without treatment compared with 2 in EEGs with treatment. Examining the influence of treatment on the SPR in individual CWE, by comparing prior EEG(s) without use of ASM with subsequent EEG(s) with treatment, was possible in 8 CWE: a decrease in SPR was seen in 5 CWE, an increase in 2, and no change in 1 (Table 10, supplements).

3.4. PPR type and photosensitivity range

The median upper and lower limits of frequencies causing PPRs during IPS did not differ much between PPRs with GSWs and OSWs, respectively: 12–18, 15–21. The median SPR was 2 in EEGs with GSWs, 3 in EEGs with OSWs, and 2 in CWE with other responses (Table 11, supplements).

3.5. Comparison of hyperventilation with IPS per epilepsy type

Of 15 children with focal epilepsy who were examined with HV, 6 (40.0%) showed an abnormal response during HV. In the generalized group, 23 of 35 children showed abnormal responses on the EEG (65.7%). In those with combined focal and generalized epilepsy, 100% (4/4) showed abnormal responses, and in the group with unknown epilepsy, this was 4 out of 11 CWE (36.4%); (χ^2 (3) = 8.1, p = .04). The manifestation of clinical symptoms during IPS in at least one EEG occurred in 19.2% CWE and during HV in 20.0% (Table 6).

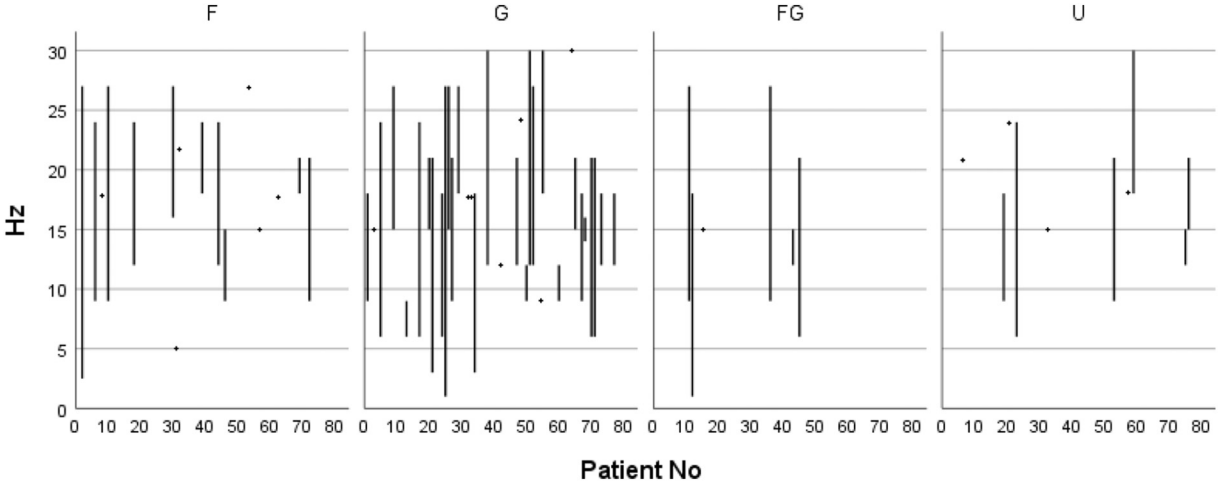

Fig. 2. Upper/lower limit of IPS frequencies causing PPR (Hz), the photosensitivity range, per patient categorized per epilepsy type (focal (F), generalized (G), combined focal and generalized (FG), unknown (U)). Photic stimulation was not performed at frequencies above 30 Hz.

Table 5
Median lower and upper limits of IPS frequencies which caused PPRs in EEGs of all patients.

Epilepsy type	Number of EEGs	Median lower limit (range)	Median upper limit (range)	Median SPR (range)
Focal	22	15.5 (2.5–27)	21 (5–27)	2 (1–7)
• Idiopathic	1	9 (9–9)	27 (27–27)	7 (7–7)
• Other	18	17 (2.5–27)	21 (5–27)	2 (1–7)
• Structural	3	12 (9–18)	24 (18–24)	5 (1–6)
Generalized	48	12 (1–30)	18 (9–30)	2.5 (1–10)
• Idiopathic	31	12 (1–30)	21 (9–30)	3 (1–10)
• Other	16	12 (6–30)	18 (9–30)	2 (1–7)
• Structural	1	9 (9–9)	18 (18–18)	4 (4–4)
Focal and generalized	9	9 (1–27)	15 (3.5–27)	2.0 (1–7)
• Other	4	10.5 (6–27)	18 (9–27)	1.5 (1–6)
• Structural	5	9 (1–15)	15 (3.5–27.0)	2 (1–7)
Unknown	10	15 (6–24)	21 (15–30)	2.5 (1–7)
• Other		15 (6–24)	21 (15–30)	2.5 (1–7)
Total	89	12 (1–30)	18 (3.5–30)	2 (1–10)

3.6. Clinical signs and spontaneous epileptic discharges

Of the 114 EEGs with PPRs, 81.6% also comprised of SEDs. Spontaneous epileptiform discharges observed on the EEGs were generalized in 23.7%, focal in 4.4%, regional in 10.5%, multiregional in 4.4%, and a combination of the above in 39.5%. Of 14 CWE with clinical signs during IPS, 13 had SEDs on their EEGs, whereas 1 did not (χ^2 (1) = 0.7, p = .4) (Table 7).

The SEDs on the EEGs of those 13 CWE were generalized in 5, multiregional in 1, and a combination in 7 CWE.

3.7. Clinical signs and persistence of PPRs

Fourteen CWE showed clinical signs evoked by IPS during 16 out of 114 EEGs with PPRs: nonmotor symptoms during 13 EEGs from 11 different CWE and myoclonic symptoms during 3 EEGs from 3 CWE (Table 12, supplements). During 5 of those 16 EEGs, the PPRs outlasted the stimulus compared with 3 EEGs where the PPRs were self-limiting.

Out of the 114 EEGs with PPRs, 54 EEGs showed consistently outlasting PPRs with clinical signs during 5 (9.3%) of these 54 PPRs. However, in the 26 EEGs with exclusively self-limiting PPRs, clinical signs were noticed during 3 PPRs only (11.5%) (Table 8).

4. Discussion

Previous studies showed various outcomes as regards to the percentage of focal epilepsies in CWE with photosensitivity. There are few studies that compare HV and photosensitivity. These studies only researched the percentages of CWE with activation during HV and during photic stimulation [17,18]. The present study examined PPRs in a population of children from a single center with a relatively high percentage of comorbidity (46.2%) [19,20].

In this study population with a PPR, we examined the distribution of epilepsy types, whether PPRs outlasted the stimulus or not and IPS frequencies in CWE with and without therapy, the association between photosensitivity and HV, and the percentage of SEDs comparing CWE with and without clinical symptoms during IPS.

Table 7
Number of patients with or without clinical symptoms during IPS divided in patients with SEDs on their EEG and patients without SEDs on the EEG.

Spontaneous epileptic discharge	Clinical symptoms during IPS per patient	No clinical symptoms during IPS per patient	Total
No	1	10	11
Yes	13	54	67
Total	14	64	78

Photoparoxysmal responses are not only seen in children with idiopathic generalized epilepsy but also quite often in those with focal epilepsies or a combination of focal and generalized epilepsies and in epilepsies with a structural etiology. Previous studies have reported different proportions of occurrence of focal epilepsy and photosensitivity: Harding and Jeavons found focal seizures in only 2.8% [21]. In a study by Kasteleijn-Nolst Trenite, 29% reported a history of focal seizure [5]. Hennessy and Binnie found focal seizures in 65% of CWE [22]. Our study found generalized epilepsy in 51.3%, focal epilepsy in 24.4%, and combined focal and generalized epilepsy in 10.3%. This result corresponds with our hypothesis. Our findings are most consistent with the study of Kasteleijn-Nolst Trenite [5].

Further, we hypothesized that the PPRs in CWE receiving treatment would be more often self-limiting compared with CWE not receiving treatment. There are few studies that have examined this hypothesis. In the study of Koutroumanidis et al., all CWE with self-sustaining PPRs (N = 2/15) did not receive treatment, whereas all CWE receiving treatment (N = 4/15) had self-limiting PPRs [23]. In our study, PPRs in CWE receiving treatment were more often self-limiting compared with CWE not receiving treatment, although this difference was not significant. An explanation for this nonsignificant outcome could be that CWE using treatment had more severe epilepsy compared with CWE not receiving treatment.

A remarkable outcome was that all PPRs from children with focal epilepsy without treatment outlasted the stimulus, in contrast to the group with generalized epilepsy in which 23.1% of PPRs were self-limiting. An explanation for this outcome might be that focal PPRs may not be considered a proper PPR. Self-limiting occipital spikes which are not in a synchronous frequency as the IPS might be confused with the physiological response "photic driving" [2,8].

Our study found frequencies of 12–18 Hz to be most provocative for inducing clinical signs during IPS, with a range of 1–30 Hz. These results are partly consistent with the existing literature which reports frequencies of 15–25 Hz to be most provocative, with a range of 1–65 Hz [2]. Our IPS frequency range differs from the IPS frequency range in the literature because of the type of Nihon-Kohden stimulator, which only achieves frequencies to 30 Hz. As predicted, most frequency intervals in individual CWE decreased while on ASM compared with those not on ASM. However, the SPR range was not smaller in those receiving treatment. A new study [24] found that antiepileptic drugs (AEDs)

Table 6
Comparison of hyperventilation with intermittent photic stimulation: 1. Number of patients with normal/abnormal activity on their EEG during hyperventilation, 2. Number of patients with a clinical seizure during hyperventilation (HVA seizure = hyperventilation associated seizure).

	Focal	Generalized	Focal + generalized	Unknown	Total
N of patients with hyperventilation examined during all EEGs total (%)	15 (100)	35 (100)	4 (100)	11 (100)	65 (100)
• Normal	9 (60.0)	10 (28.6)	–	6 (54.5)	25 (38.5)
• Abnormal	6 (40.0)	23 (65.7)	4 (100)	4 (36.4)	37 (56.9)
• ?	–	2 (5.7)	–	1 (9.1)	3 (4.6)
Patients with HVA seizure (%)					
• Yes	2 (13.3)	9 (25.7)	–	2 (18.2)	13 (20.0)
• No	13 (86.7)	26 (74.3)	4 (100)	9 (81.8)	52 (80.0)

Table 8
Number of EEGs in patients with clinical symptoms during IPS with: PPRs which outlasted the stimulus, PPRs which were self-limiting, both outlasting and self-limiting PPRs, or not specified.

	Outlasting	Self-limiting	Both	Not specified	Total
N of EEGs with PPRs	54	26	16	18	114
Clinical symptoms during IPS (%)					
• No	49 (90.7)	23 (88.5)	14 (87.5)	12 (66.7)	98 (86.0)
• Yes	5 (9.3)	3 (11.5)	2 (12.5)	6 (33.3)	16 (14.0)
○ Nonmotor	5	2	1	5	13
○ Myoclonic	0	1	1	1	3

lower the upper limit of photosensitivity substantially, whereas the lower limit only changes minimally.

A notable outcome of this study was that of 16 EEGs with clinical signs during IPS, only 5 PPRs outlasted the stimulus, whereas 3 were self-limiting. Thus, PPRs did not need to be self-sustaining to produce symptoms. Photoparoxysmal responses, which stop instantly when the IPS pauses, can be distinguished from self-sustained PPRs, which outlast the stimulus train [5]. Older studies showed that self-sustained PPRs are highly associated with a history of epilepsy. Some studies from the past did not consider self-limited abnormal activity during IPS to be a PPR. They reported that only prolonged PPRs have a strong correlation to epilepsy and that self-limiting PPRs are not associated with an increased incidence of seizures [12,25,26]. Recent studies, however, found that self-limiting PPRs are also highly associated with epilepsy and epileptic seizures [12,26].

Other studies only examined the number of CWE with a positive reaction to HV and with a positive reaction to IPS. However, these studies did not examine the overlap between the two groups [17,18]. Both IPS and HV are activation methods. It is thought that there is an association between the presence of PPRs and the presence of epileptiform abnormalities during HV. Nonetheless, only 56.9% of our CWE with a PPR showed abnormal responses in the EEG during HV. The percentages of clinical signs during IPS and HV were somewhat similar and did overlap partly. Activation by HV can be seen in several epilepsy types; however, they are classically seen as an indicator for idiopathic generalized epilepsy [27]. Nonetheless, in our study, 40% of CWE with focal epilepsy had an abnormal response during HV. Therefore, we reject our hypothesis which states that in our population of CWE with PPRs, only the group with generalized epilepsy would have a substantial percentage of CWE with abnormal activity on the EEG during HV.

Children with epilepsy often showed SEDs on their EEGs (81.6%) compared with other studies. In the study by Hennessy and Binnie [22], 70% of photosensitive patients had SEDs on their EEG, and Gilliam and Chiappa [9] found that 60% had SEDs. An explanation could be that our population consisted of many CWE with comorbidities, which could have influenced the activity on the EEG. An alternative possibility could be the difference in mean age between our population (10.2 years) and the population of Hennessy and Binnie (16 year) and Gilliam and Chiappa (22.5 years). Except for one patient, all CWE with clinical signs during IPS had indeed independent SEDs. This is in line with the study of Gilliam and Chiappa which showed that the presence of SED was significantly associated with a history of seizures ($p < .0001$), compared with CWE who had a PPR but no SEDs [9].

A major strength of this study was the systematic examination of IPS in an unselected group of children admitted to the EEG department. Another strength was the population of the dataset which consisted of CWE and photosensitivity from a single center included regardless of their comorbidity.

As mentioned above, during the examinations of photosensitivity in the CWE of this study, the laboratory used a Nihon-Kohden photic stimulator for IPS. This photic stimulator can reach up to only 30 Hz and delivers relative low intensity flashes. Yet, it is a type of stimulator that is still often used [28].

Furthermore, classification of epilepsy type was done using detailed patient information, gathered by JB. In some CWE, this information was however limited. This made it more difficult to diagnose these CWE. If there was too little information, CWE got the diagnosis of unknown. Therefore, the percentage of especially focal epilepsy might be an underestimate.

Additionally, structural epilepsy might be underestimated because some structural abnormalities might have not been known yet: the magnetic resonance imaging (MRI) used in the nineties is different and less sensitive than the MRI in 2019.

Moreover, our data were documented per EEG instead of per patient. If a PPR was observed on an EEG, this EEG was included in the dataset. Of the included CWE, all documented EEGs without PPRs, were also reported in the dataset. Therefore, if a certain therapy worked and CWE did not return for another reason, there would not be a control EEG. This causes selection bias based on clinical practice.

Lastly, this study had some missing data in some of the variables. The missing data could potentially impact the findings of this study.

4.1. Conclusion

The more knowledge we acquire of epilepsy and photosensitivity, the more we can use it in the classification of epilepsy and the more we can help photosensitive CWE clinically. Photosensitivity occurs in all types of epilepsy, not only in idiopathic generalized epilepsy as often thought in clinical practice but often also in abnormal activity on the EEG during HV. There is a tendency that focal epilepsy is associated with self-sustaining PPRs. Treatment tends to decrease the persistency and the IPS frequency interval of PPRs. There is a tendency that clinical symptoms during IPS occur in EEGs with SEDs.

Contributors

O.A. van Win, B.Sc.: did analysis of the data, wrote multiple drafts and the final manuscript.

J. W. Barnes, M.D., FRCPC: abstracted data and wrote an initial draft and presented the data at AES conference.

Asuri N. Prasad, MBBS, M.D., FRCPC, FRCPEdin, FAES: developed the research proposal, supervised and mentored Jeff Barnes in the conduct of the study, revised the initial draft, made editorial revisions in the final manuscript.

C.H. Ferrier, MD and D.G.A. Kasteleijn-Nolst Trenite, M.D.: supervised and mentored O. van Win in the conduct of the study and revised multiple drafts and the final manuscript.

Declaration of competing interest

The authors have no conflict of interests.

Acknowledgments

The authors acknowledge the contributions of Dr. Fran Booth and Jill Patrick, EEG technologist in the development of the initial research proposal, for advice and assistance to Jeff Barnes during the conduct of the study. We further thank the Children's Hospital Foundation of Manitoba as well as the Health Sciences Centre Foundation Medical Staff Council Fellowship Committee who financially supported this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2020.107046.

References

[1] Poleon S, Szaflarski JP. Photosensitivity in generalized epilepsies. Epilepsy Behav 2017;68:225–33. https://doi.org/10.1016/j.yebeh.2016.10.040.

[2] Fisher RS, Harding G, Erba G, Barkley GL, Wilkins A. Photic- and pattern-induced seizures: a review for the Epilepsy Foundation of America Working Group. Epilepsia 2005;46:1426–41. https://doi.org/10.1111/j.1528-1167.2005.31405.x.

[3] Okudan ZV, Özkara Ç. Reflex epilepsy: triggers and management strategies. Neuropsychiatr Dis Treat 2018;14:327–37. https://doi.org/10.2147/NDT.S107669.

[4] Martins da Silva A, Leal B. Photosensitivity and epilepsy: current concepts and perspectives—a narrative review. Seizure 2017;50:209–18. https://doi.org/10.1016/j.seizure.2017.04.001.

[5] Kasteleijn-Nolst Trenité D. Photosensitivity in epilepsy. Electrophysiological and clinical correlates. Acta Neurol Scand Suppl 1989;125:3–149.

[6] Kasteleijn-Nolst Trenite D, Genton P, Brandt C, Reed RC. The "photosensitivity model" is (also) a model for focal (partial) seizures. Epilepsy Res 2017;133:113–20. https://doi.org/10.1016/j.eplepsyres.2016.11.012.

[7] Covanis A. Photosensitivity in idiopathic generalized epilepsies. Epilepsia 2005;46:67–72. https://doi.org/10.1111/j.1528-1167.2005.00315.x.

[8] Lazarev VV, Simpson DM, Schubsky BM, deAzevedo LC. Photic driving in the electroencephalogram of children and adolescents: harmonic structure and relation to the resting state. Braz J Med Biol Res 2001;34:1573–84. https://doi.org/10.1590/S0100-879X2001001200010.

[9] Gilliam FG, Chiappa KH. Significance of spontaneous epileptiform abnormalities associated with a photoparoxysmal response. Neurology 1995;45:453–6. https://doi.org/10.1212/WNL.45.3.453.

[10] Kasteleijn-Nolst Trenité DGA, Guerrini R, Binnie CD, Genton P. Visual sensitivity and epilepsy: a proposed terminology and classification for clinical and EEG phenomenology. Epilepsia 2001;42:692–701. https://doi.org/10.1046/j.1528-1157.2001.30600.x.

[11] Sundaram M, Sadler RM, Young GB, Pillay N. EEG in epilepsy: current perspectives. Can J Neurol Sci 1999;26:255–62. https://doi.org/10.1017/S0317167100000342.

[12] Nagarajan L, Kulkarni A, Palumbo-Clark L, Gregory PB, Walsh PJ, Gubbay SS, et al. Photoparoxysmal responses in children: their characteristics and clinical correlates. Pediatr Neurol 2003;29:222–6. https://doi.org/10.1016/S0887-8994(03)00207-8.

[13] Verrotti A, Trotta D, Salladini C, di Corcia G, Chiarelli F. Photosensitivity and epilepsy. J Child Neurol 2004;19:571–8. https://doi.org/10.1136/jnnp.43.9.855-a.

[14] Scollo-Lavizzari G, Scollo-Lavizzari GR. Sleep, sleep deprivation, photosensitivity and epilepsy. Eur Neurol 1974;11:1–21. https://doi.org/10.1159/000114301.

[15] Elmalı AD, Kurucu H, Ertürk Çetin Ö, Çokar Ö, Matur Z, Dervent A, et al. Augmentation de la photosensibilité après un court sommeil chez des patients privés de sommeil. Neurophysiol Clin 2017;47:239–45. https://doi.org/10.1016/j.neucli.2017.01.011.

[16] Gurrell R, Gorman D, Whitlock M, Ogden A, Reynolds DS, DiVentura B, et al. Photosensitive epilepsy: robust clinical efficacy of a selective GABA potentiator. Neurology 2019;92:e1786–95. https://doi.org/10.1212/WNL.0000000000007271.

[17] Dziadkowiak E, Podemski R. Impact of hyperventilation and sleep deprivation upon visual evoked potentials in patients with epilepsy. Neurol India 2019;67:1027–32. https://doi.org/10.4103/0028-3886.266246.

[18] Mullins GM, O'Sullivan SS, Neligan A, McCarthy A, McNamara B, Galvin RJ, et al. A study of idiopathic generalised epilepsy in an Irish population. Seizure 2007;16:204–10. https://doi.org/10.1016/j.seizure.2006.12.007.

[19] Linehan C, Tellez-Zenteno JF, Burneo JG, Berg AT. Future directions for epidemiology in epilepsy. Epilepsy Behav 2011;22:112–7. https://doi.org/10.1016/j.yebeh.2011.06.006.

[20] Kozyrskyj AL, Prasad AN. The burden of seizures in Manitoba children: a population-based study. Can J Neurol Sci 2004;31:48–52. https://doi.org/10.1017/S0317167100002821.

[21] Harding GFA, Jeavons PM. Photosensitive epilepsy. Wiley; 1994.

[22] Hennessy MJ, Binnie CD. Photogenic partial seizures. Epilepsia 2000;41:59–64. https://doi.org/10.1111/j.1528-1157.2000.tb01506.x.

[23] Koutroumanidis M, Tsirka V, Panayiotopoulos C. Adult-onset photosensitivity: clinical significance and epilepsy syndromes including idiopathic (possibly genetic) photosensitive occipital epilepsy. Epileptic Disord 2015;17:275–86. https://doi.org/10.1684/epd.2015.0765.

[24] Reed RC, Kasteleijn-Nolst Trenité DGA, West Virginia University, Morgantown, WV1, Utrecht University, The Netherlands2 and Sapienza University, Rome I. Antiepileptic drugs (AEDs) reduce the upper photosensitivity threshold-limit more than the lower threshold in the "photosensitivity model of epilepsy" 2018.

[25] Puglia JF, Brenner RP, Soso MJ. Relationship between prolonged and self-limited photoparoxysmal responses and seizure incidence: study and review. J Clin Neurophysiol 1992;9:137–44. https://doi.org/10.1097/00004691-199201000-00015.

[26] Jayakar P, Chiappa KH. Clinical correlations of photoparoxysmal responses. Electroencephalogr Clin Neurophysiol 1990;75:251–4. https://doi.org/10.1016/0013-4694(90)90178-M.

[27] Guaranha MSB, Garzon E, Buchpiguel CA, Tazima S, Yacubian EMT, Sakamoto AC. Hyperventilation revisited: physiological effects and efficacy on focal seizure activation in the era of video-EEG monitoring. Epilepsia 2005;46:69–75. https://doi.org/10.1111/j.0013-9580.2005.11104.x.

[28] Specchio N, Kasteleijn-Nolst Trenité DGA, Piccioli M, Specchio LM, Trivisano M, Fusco L, et al. Diagnosing photosensitive epilepsy: fancy new versus old fashioned techniques in patients with different epileptic syndromes. Brain Dev 2011;33:294–300. https://doi.org/10.1016/j.braindev.2010.06.001.