Impaired Visual Habituation in Idiopathic Generalized Epilepsy with Photosensitivity Patients

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ABSTRACT

Introduction: In this study, our goal was to analyze further the cortical excitability levels in idiopathic generalized epilepsy (IGE) patients with and without photosensitivity.

Methods: Forty-two patients (16 men and 26 women; mean age 30±8 years; range: 18–43 years) with IGE and thirty healthy age-matched control subjects (15 men and 15 women; mean age 35±3 years; range: 20–45 years) were enrolled for the investigation. We investigated the following two groups: 18 subjects with IGE with photosensitivity (IGE+PS), and 24 patients with IGE without photosensitivity (IGE-PS). Pattern reversal and potential inter-peak amplitudes, N75-P100 and P100-N145, as well as the corresponding latencies (N75, P100, and N145) for one hundred responses were measured 6 times. A linear regression slope was used for N75-P100 and P100-N145.

Results: Statistical analysis showed difference between groups where the IGE+PS had reduced N75-P100 compared to IGE-PS and controls. In IGE+PS group, the amplitude of N75-P100 was drastically reduced receiving antiepileptic therapy compared to those not receiving any anti-epileptic treatment ($p=0.035$).

Conclusion: These results show that the IGE+PS group has a different photoparoxysmal response phenotype driven by an unknown and distinct molecular mechanism. Pre-activation cortical excitability may be increased in IGE+PS patients compared to the IGE-PS or in healthy group. PR-VEP habituation may project the pathophysiological mechanisms underlying photosensitivity and it may be potential biomarker in patients with IGE+PS.

Keywords: Photosensitivity, epilepsy, pattern-reversal VEP

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INTRODUCTION

Photosensitivity (PS), known as visual sensitivity, is an abnormal susceptibility against visual/light stimulus in the brain. Photoparoxysmal response (PPR), which can be identified by electroencephalogram (EEG) in non-epileptics, is defined as a response consisting of paroxysmal, focal, or frequently against an intermittent light stimulus (ILS) (1). It is most commonly observed in adolescents and women. Its prevalence is lower in general population (1/4000). Although reported at different rates, its incidence rate varies between 1 and 10% (2).

Photosensitivity (PS) has been associated with multiple seizure types. Eyelid myoclonus, generalized myoclonic splashes, focal seizures and more rarely, tonic-verse seizures and focal asymmetric myoclonic seizures may be triggered by photic stimulation (3). However, the most common association with PS is IGE, including childhood absence epilepsy (CAE) and juvenile myoclonic epilepsy (JME) (4).

IGE accounts for 20 to 40% of all epileptic seizures (1). The international classification system has categorized four main IGE groups: CAE, JAE, JME, and IGE with tonic-clonic seizures alone (GTCA) (5–7).

The response decreases because of repeated stimulus during the habituation. Such reduced response is a result from the decreased glutamate-mediated strength of synaptic associations between postsynaptic and presynaptic neurons. As the number of Ca^{2+} channels decreases, the synaptic strength decreases and therefore extrasensory perception (ESP) level reduction is observed (8).

During repeated stimulation, the VEP adapts and progressively reduces in amplitude. The adaptation/habituation process serves to protect from neuronal stress and metabolite accumulation (9, 10).

In the present study, we aimed to verify PS and evaluate the visual habituation in IPE + PS and IGE-PS.

METHODS

Participants

Patients diagnosed with IGE checked into our polyclinic between April 2014 and July 2017 were consented and enrolled in our study. The patients answered questions about their seizures and IGE was diagnosed based on the ILAE (11).

Forty-two patients (16 men and 26 women; mean: 30 ± 8 years of age; range: 18–43 years) with IGE and thirty healthy age-matched control subjects (15 men and 15 women; mean: 35 ± 3 years of age; range: 20–45 years) were enrolled for the investigation.

We evaluated the following two groups: 18 subjects with IGE+PS and 24 patients with IGE-PS.

Clinical demographics including age, gender, the age of onset, family history, incidence, febrile convulsion (FC) presence, anti-epileptic drug usage and EEG results were evaluated. Patients with normal cognitive exams and normal cerebral MRIs results were included. Volunteers with mental retardation, any systemic disorder, migraine, and patients using drugs other than antiepileptics were excluded. In addition, a control group with no history of seizures, migraine, alcoholism, and no drug use was included.

EEG recording

All patients received routine an awaking EEG recording regardless of seizure history. Scalp EEG recordings were performed using electrodes placed based on the international 10-20 system. Intermittent photic stimulation (IPS) was conducted according to internationally recommended guidelines. The EEGs were independently analyzed by two experienced epileptologists that assessed the presence of epileptiform abnormalities and the type of PPR to IPS.

PPR was divided into 4 subgroups based on given response to IPS including: 1) spike wave with normal rhythm in the occipital region, 2) parietooccipital spike (biphasic slow wave (BSW)), 3) parietooccipital spike BSW spreading in the front of the brain and 4) generalized spike-wave or multiple spikes (12, 13).

The standard protocol for IPS is initiated with five seconds of eyes opened followed by closed eyes for the same time. Stimulation using 5-10-15-20-25-30-35 Hertz were set 30 centimeters from an ambient lit room.

According to the EEG results, patients were classified as photosensitive or non-photosensitive idiopathic generalized epilepsy.

Visual habituation

Visual habituation was performed has been well characterized and a protocol was followed as previously described.

Habituation was given as the linear regression slope of N75, P100 and P100 N145 peak amplitudes. A negative slope was indicative of adaptation/habituation while a negative slope showed lack of habituation. The slope of the latencies were also recorded and measured.

Ethics approval participate

Approval for the investigation was granted by the local ethics committee, and consent was obtained by all participants.

Statistical analysis

A non-normal distribution was analyzed statistically using preliminary descriptive analysis. Following log transformation, normal distribution was reached for all data (Kolmogorov- Smirnov test, $p > 0.2$).

A general linear model approach was used to analyze the “between-factor” × “within-factors” effect. The between-subject factor was “group”, while the within-subject factor was “blocks” (1 to block 6). Univariate results were measured when the Wilks’ Lambda multivariate significance criterion was reached. The homogeneity of covariance was examined with Mauchley Sphericity Test. Group analysis was performed with a

one-way ANOVA. Post hoc tests were performed to define variables after Bonferroni’s confidence interval adjustment for multiple comparisons. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Out of the 42 IGE patients, 24 were IGE-PS and 18 were IGE+PS. For IGE+PS group, 7 were male and 11 were female (mean: 26.2±3.2 years of age). For IGE-PS group, 9 were male, and 15 were female (mean: 33.8±4.6 years of age). The control group consisted of 30 healthy individual including 15 female and 15 male (mean: 35.3±3.7 years of age). No stastical significant difference was determined for age or gender between groups ($p > 0.05$). Seven patients were diagnosed as JME and 17 were diagnosed as GTCA in IGE-PS group. Similarly, 9 patients were diagnosed as JME and 9 were diagnosed as GTCA in IGE+PS group (Table 1). Of the 42 patients, 12 were treated with levetiracetam (LEV), 3 were treated with valproic acid (VPA), and 2 were treated with lamotrigine (LTG) monotherapies. Five patients were treated with LEV+LTG combination and 2 patients were treated with VPA+LEV combination. Seven patients from the IGE+PS group and 9 patients from IGE-PS group did not receive any anti-epileptic therapy (Table 2).

N75, P100, and N145 latencies were not found to be significantly different between groups ($p>0.05$) (Table 3).

There were no differences in the mean N75-P100 and P100-N145 peak-to-peak amplitudes between patients that took anti-epileptic drugs and the 16 non-medicated patients in the first block.

Univariate analysis showed significant findings between groups in the singularly for the first block only ($F_{2,59}=3.485$, $p<0.02$) (Table 4). In IGE+PS group, the amplitude of N75-P100 was significantly lower in cases receiving anti-epileptic therapy compared to those not receiving any anti-epileptic treatment ($p=0.035$).

The P100-N145 slope was not different statistically between the groups (Table 5).

However, the three groups had statistical differences for the N75–P100 amplitude slope index ($F_{2,59}=7.581$, $p<0.002$) with IGE+PS presenting higher slope values than IGE-PS and control (Table 4).

Table 1. Clinical data of patients with IGE+PS and IGE-PS

	IGE+PS (n=18)	IGE-PS (n=24)
Mean age	26.2±3.2	33.8±4.6
Gender (F/M)	11/7	15/9
Diagnosis	9 JME/9 GTCA	7 JME/17 GTCA
Antiepileptic drugs		
None	7	9
One	8	11
Two	3	4
PPR		
I and II type	10	-
III and IV type	8	-

JME: juvenile myoclonic epilepsy; GTCA: idiopathic generalized epilepsy with tonic-clonic seizures alone; PPR: photoparoxysmal response.

Table 2. The main patient clinical features

Patient no	Age	Sex	Syndromic diagnosis	Current treatment	Photosensitivity
1	26	F	JME	LEV	Yes
2	18	M	GTCA	None	Yes
3	22	M	GTCA	None	No
4	32	F	JME	LEV	No
5	31	F	JME	LEV	No
6	43	M	GTCA	None	No
7	25	F	GTCA	LTG	Yes
8	21	F	GTCA	None	No
9	31	F	GTCA	LEV+LTG	No
10	23	M	JME	VPA	Yes
11	28	M	GTCA	LEV	No
12	30	F	GTCA	LEV+LTG	No
13	19	F	GTCA	None	Yes
14	22	F	JME	LEV	No
15	32	F	JME	VPA+LEV	Yes
16	27	M	GTCA	VPA	Yes
17	23	M	GTCA	LEV	Yes
18	24	F	GTCA	None	No
19	31	F	GTCA	LEV+LTG	No
20	40	M	JME	LEV	Yes
21	24	F	GTCA	None	Yes
22	25	F	JME	None	Yes
23	22	F	JME	LEV	No
24	18	F	JME	LEV+LTG	No
25	26	F	GTCA	LEV	Yes
26	19	M	GTCA	None	No
27	33	M	GTCA	LEV	No
28	20	M	GTCA	None	No
29	28	F	JME	LTG	No
30	19	M	JME	VPA	Yes
31	27	F	GTCA	LEV+LTG	Yes
32	25	F	GTCA	None	No
33	23	F	JME	LEV	No
34	32	F	JME	None	Yes
35	21	F	GTCA	LEV	No
36	18	F	GTCA	None	No
37	26	F	JME	None	Yes
38	28	M	GTCA	LEV	No
39	24	F	JME	LEV	No
40	27	M	GTCA	None	No
41	24	F	GTCA	None	Yes
42	31	M	JME	VPA+LEV	Yes

JME, juvenile myoclonic epilepsy; GTCA, idiopathic generalized epilepsy with tonic-clonic seizures alone; LEV, levetiracetam; LTG, lamotrigine; VPA, valproic acid.

Table 3. Latencies (in milliseconds) of VEPs in control (C), IGE+PS, and IGE-PS

VEP latencies (ms)	IGE+PS (n=18)	IGE-PS (n=24)	C (n=30)
N75	72.8±3.7	73.6±6.4	73.8±5.8
P100	106.4±6.2	105.8±5.7	104.7±7.2
N145	144.6±9.8	145.3±10.5	144.9±11.3

Table 4. N75-P100 PRVEP component amplitude (μv) and habituation slope index for IGE+PS, IGE-PS, and C subjects

N75-P100 PR-VEP amplitude	IGE+PS (n=18)	IGE-PS (n=24)	C (n=30)
Age (mean)	26.2±3.24	33.8±4.60	35.3±3.72
1st amplitude block (μv)	6.96±2.6	9.48±3.2	9.84±1.4
2nd amplitude block (μv)	7.99±2.4	9.49±2.7	9.81±2.3
3rd amplitude block (μv)	7.09±3.1	9.51±3.5	9.59±2.6
4th amplitude block (μv)	7.12±1.9	9.54±2.3	9.17±1.8
5th amplitude block (μv)	7.17±2.3	9.53±1.9	9.07±2.7
6th amplitude block (μv)	7.23±1.7	8.59±1.3	8.97. ±1.8
Slope index	+0.0047±0.11	+0.032±0.35	-0.45±0.25

IGE+PS, IGE with photosensitivity; IGE-PS, IGE without photosensitivity; C, control.

Table 5. P100-N145 PRVEP component amplitude (μv) and habituation slope index IGE+PS, IGE-PS, and C subjects

P100-N145 PR-VEP amplitude	IGE+PS (n=18)	IGE-PS (n=24)	C (n=30)
Age (mean)	26.2±3.24	33.8±4.60	35.3±3.72
1st amplitude block(μv)	8.47±2.1	9.26±3.4	9.57±2.7
2nd amplitude block(μv)	8.41±3.2	9.13±2.7	9.21±2.4
3rd amplitude block(μv)	8.25±2.8	9.04±2.8	9.07±2.9
4th amplitude block(μv)	8.27±1.6	8.87±3.2	9.11±1.8
5th amplitude block(μv)	8.11±2.9	8.67±2.5	8.96±2.3
6th amplitude block(μv)	8.09±1.8	8.49±2.1	8.57±1.9
Slope index (p value)	-0.085±0.37	-0.065±0.55	-0.40±0.65

IGE+PS, IGE with photosensitivity; IGE-PS, IGE without photosensitivity; C, control.

DISCUSSION

IGEs are characterized by seizures in an age-related onset in which little clinical and laboratory evidence has been found to determine the etiological cause. With the advanced imaging techniques developed in recent years, the biochemical mechanisms underlying this type of epilepsy and its neuroanatomical bases have been studied (14).

Based on the various mutations identified by genetic studies, it is accepted that both the ion channels and the non-ionic mechanisms are responsible directly for the etiology of IGE. In one of these mechanisms, GABA, has a defined role. As a result of GABA mutations, the transmembrane chloride gradient required for inhibition is thought to cause membrane depolarization and hyper-excitability. In the literature, structural and functional studies on photosensitivity epilepsy demonstrated the role of the visual cortex and frontal lobes (15, 16).

Diminished association between the prefrontal and frontopolar regions may form the basis of motor seizures in the JME (16).

After 100 stimuli in the first block, the N75-P100 inter-peak amplitude was significantly lower in photosensitized patients than the other two groups. The amplitude of N75-P100 was significantly lower in patients receiving anti-epileptic therapy. In the studies of PS in epilepsy patients, Martinovic et al. found that there was no difference in N75-P100 amplitudes, but Genç et al. and Faugh and Lee reported increased N75-P100 amplitudes. In a study by Brazzo et al., N75-P100 amplitudes significantly increased during the first block independently of anti-epileptic treatment (17–20).

This finding was consistent with our study, but the amplitude was significantly lower in patients that received anti-epileptic treatment.

When viewed from the pathological aspect, decreased amplitude during the first block may be electrophysiological confirmation for augmented inhibition of the epileptic cortex at the synaptic/non-synaptic region.

Previous studies have shown that valproic acid increases GABAergic neurotransmission by acting on GABA receptors and that cortical excitability both in motor and visual cortex decreases with treatment (21, 22).

Of the patients with IGE+PS in our study, seven were using LEV, three were using VPA, and one for each was using LTG monotherapy, VPA+LEV, and LEV+LTG polytherapy, respectively. This finding suggests that LEV therapy, as well as VPA therapy, decreases the increased cortical excitability in visual cortex.

LEV has been shown to block neurotransmitter binding to synaptic vesicle glycoprotein 2a (SV2a) and inhibits the presynaptic calcium channels. Thus, it is thought that it inhibits the impulse transmission in the synaptic range (23). Our second important finding is increased slope index of N75-P100 after consecutive blocks in IGE+PS patients. This result was consistent with other studies in the literature (20, 24).

GABAergic networks are known to act as primer inhibitor mechanisms in the visual cortex. In patients with PS epilepsy, it can be said that cortical hyperexcitability may be responsible for the impairment of intracortical inhibitor processes and GABA dysfunction (25, 26).

The present study, like the other studies, suggests that the underlying mechanism of photosensitivity is hyper-excitability in the primary visual cortex. In this context, the N75-P100 slope index used in our study showed decreased amplitude in the first block as well as the habituation deficit in the sixth block. Therefore, these findings may be an indicator of the cortical processes. In addition, these findings suggest that the reduction of cortical excitability due to antiepileptic treatment in these patients (as opposed to epileptic patients without photosensitivity) is compensated by a primary hypercorticality of the primary visual cortex.

One of the most important results of the present study is the significantly reduced first block N75-P100 amplitude, especially in patients receiving antiepileptic therapy. This finding was different from the other studies.

In PS patients group, there were patients receiving LEV therapy other than VPA therapy. Therefore, it is possible that Ca^{2+} and other ion channels, as well as GABA, are involved in the pathogenesis of this disease.

Collectively, our results provide a role for PS in the association with balance instability and cortical processes. PS may be a direct manifestation of particular mechanisms whereby PR-VEP habituation is one of the intermediate phenotypes. It is promising because it is a simple and reliable method for preclinical and clinical application in photosensitized patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Eskisehir Osmangazi University Faculty of Medicine.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

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Author Contributions: Concept - DİA; Design - DİA; Supervision - DİA, OOE; Resource - DİA, OOE; Materials - DİA, OOE; Data Collection and/ or Processing - DİA, OOE; Analysis and/or Interpretation - DİA, OOE; Literature Search - DİA, OOE; Writing - DİA; Critical Reviews -DİA, OOE.

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