Original article

Colour vision in juvenile myoclonic epilepsy

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ABSTRACT – *Aims.* To determine the integrity of colour perception, related to photic sensitivity, in patients with juvenile myoclonic epilepsy.
Methods. Twenty-four patients with photoparoxysmal response, 27 patients without photoparoxysmal response, and 32 healthy individuals were investigated using the Farnsworth Munsell-100 Hue test to calculate error scores for total colour, blue/yellow, and red/green.
Results. No significant differences were observed regarding blue/yellow, red/green or total error score between juvenile myoclonic epilepsy patients with or without photoparoxysmal response. However, the data for all three scores were significantly higher in both patient groups compared to the healthy control group. In both patient groups, the blue/yellow error score was significantly higher than the red/green error score.
Conclusions. We were unable to identify a relationship between photoparoxysmal response and colour vision in patients with juvenile myoclonic epilepsy. We believe that the underlying reason why juvenile myoclonic epilepsy patients had significantly higher blue/yellow, red/green, and total error score compared to the healthy control group may be due to GABA dysfunction, which is considered to play a role in the pathophysiology of this disease as well as the physiology of colour vision.

Key words: colour perception, photic sensitivity, juvenile myoclonic epilepsy, photoparoxysmal response, GABA

Juvenile myoclonic epilepsy (JME) is an idiopathic generalized epilepsy (IGE) syndrome that begins during puberty. It accounts for 20-27% of all IGEs, and about 5-11% of all epilepsies (Loddenkemper and Serratosa, 2006). Recent studies have shown that JME is a heterogeneous disease with a complex inheritance associated with various mutations (Sapio *et al.*, 2015). Although the pathogenesis of JME has not been fully elucidated, new perspectives are developing based on EEG, new MR techniques, and nuclear medicine studies, such as SPECT and PET. Although this syndrome is accepted as a generalized epilepsy syndrome, some clinical and EEG features support local hyperexcitability of the cortex. The hyperexcitability of the motor system resulting from the degradation of cortical inhibitor pathways is responsible for the pathogenesis of JME (Zifkin *et al.*, 2005).

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JME patients are among those with the highest photoparoxysmal response (PPR) of all epilepsy patients (approximately 30%) (Verrotti *et al.*, 2012). PPR is defined as an abnormal EEG response, also called "photosensitivity", produced by intermittent photic stimulation (IPS). The pathophysiology of this phenomenon is thought to involve altered excitability of the visual pathways and regions of the occipital cortex in response to underlying genetic factors and flickering light (Verrotti *et al.*, 2012; Strigaro *et al.*, 2013). Also, it has been suggested that patients with PPR may have occipital hyperexcitability (Brigo *et al.*, 2013). The PPR can be seen on EEG as spikes, or spike-and-wave or intermittent slow waves. PPR are divided into four subgroups according to the abnormal response to IPS:
– spikes within an occipital rhythm;
– parieto-occipital spikes with a biphasic slow wave;
– parieto-occipital spikes with a biphasic slow wave and spread to the frontal region;
– generalized spikes and waves or polyspikes and waves (Waltz *et al.*, 1992; Doose and Waltz, 1993; Verrotti *et al.*, 2012).
Although a relationship between visual system abnormality and PPR could not be established (Kasteleijn-Nolst Trenité, 1989), some recent studies have shown that PPR also characterizes some abnormalities in the visual system, such as altered visual contrast control and increased sensitivity to certain wavelengths. Some ocular abnormalities are also known to accompany PPR (Takahashi *et al.*, 1999; Porciatti *et al.*, 2000; Anyanwu and Ehiri, 2004).
We used the Farnsworth Munsell-100 Hue (FM-100 Hue) test, which discriminates between colours with high sensitivity, with the aim of revealing a possible alteration of colour perception responsible for photic sensitivity in patients with JME. In this respect, we aimed to reveal a possible relationship between photic sensitivity and colour vision function.

Materials and methods

The present study was designed as a prospective controlled study and conducted at our outpatient department. The study was approved by the Antalya Education and Research Hospital Ethics Committee.

Patients

The study group consisted of 51 JME patients (24 with and 27 without PPR) and 32 age/sex-matched healthy individuals. Data on seizure frequency and type, disease duration, antiepileptic drugs and doses, and neuroimaging findings of patients were obtained. All patients were diagnosed with JME according to the recommendations issued by the International League Against Epilepsy (ILAE) Classification and Terminology Committee in 2010, based on seizure type, dominant seizure type, age at onset of seizures, EEG characteristics, and the "Diagnostic criteria for JME Class II" (see below) (Berg *et al.*, 2010; Kasteleijn-Nolst Trenité *et al.*, 2013).

Diagnostic criteria for JME Class II
– Myoclonic jerks predominantly occurring on awakening.
– Myoclonic jerks facilitated by sleep deprivation and stress and provoked by visual stimuli and praxis or generalized tonic-clonic seizures preceded by myoclonic jerks.
– EEG showing a normal background and at least one interictal generalized spike or polyspike and waves with some asymmetry with or without myoclonic jerks.
– No intellectual disability or deterioration.
– Age at onset of between 6 and 25 years.
Each patient and healthy control underwent a complete ophthalmologic examination by the same physician who was uninformed of the EEG findings of the patients. Also, all patients underwent a best corrected visual acuity test, half-lamp biomicroscopy, intraocular pressure measurement, gonioscopy, dilate funduscopic examination, and refraction. Gonioscopy is the examination of the angle of the anterior chamber, and is used to identify eyes at risk of closure and detect angle abnormalities that could have diagnostic and therapeutic implications. It is a clinical technique used to examine structures within the anterior chamber angle and constitutes an essential diagnostic tool in everyday ophthalmic practice.

Inclusion criteria

– Volunteer patients diagnosed with JME according to the ILAE.
– Normal ophthalmologic and Standard Pseudoisochromatic Plates 2 (SPP2) examination.

Exclusion criteria

– Other types of epilepsy other than JME.
– Not volunteering.
– Intellectual disability, psychiatric or systemic disease, or drug or substance use that may lead to deterioration of cognitive functions.
– Abnormal SPP2 or ophthalmologic examination, ocular pathology (strabismus, nystagmus, and retinal pathology), or ocular surgery history.
– A systemic disease that may affect the visual system, such as diabetes mellitus or hypertension.

EEG analysis

Photic stimulation was performed according to the "Updated European algorithm for visual stimulation

Table 1A. Demographic data of patients and the control group.

		Photosensitive JME group		Non-photosensitive JME group		All patients		Healthy control group		*p* value
		n (mean)	% (SS)	*n* (mean)	% (SS)	*n* (mean)	% (SS)	*n* (mean)	% (SS)	
Sex	**Female**	17	70.8	19	70.4	36	70.6	21	65.6	**0.948**
	Male	7	29.2	8	29.6	15	29.4	11	34.4	
Total		24	47	27	53	51		32		
Age (year)		28.6	9.1	24.96	6.7	26.7	8.06	25.9	5.4	**0.252**

in the EEG laboratory" (Kasteleijn-Nolst Trenité *et al.*, 2012). All patients received standard 30-minute EEG recording, including four minutes of hyperventilation and five minutes of IPS using a Nihon Kohden/LS-703A Model stimulator with electrodes placed according to the international 10-20 system. IPS was performed under dim light conditions, with the patient in a vertical position, with simultaneous video recording. A circular reflector lamp was placed 30 cm away from the patient's nasion, and flashes with 0.7 Joules were produced. For IPS, the eyes were kept open for the first five seconds and then closed for at least seven seconds, before switching to the next frequency. The frequencies used for IPS were 1, 2, 4, 8, 10, 12, 15, 18, 20, 25, 40, 50, 60 Hz, and the filters were 0.5 and 70 Hz. The interictal EEG findings for each patient were evaluated by the same neurologist experienced in EEG photoparoxysms.

The Farnsworth Munsell-100 Hue test (FM-100 Hue)

The SPP2 test was used as the first colour vision examination to exclude congenital colour vision defects in

Table 1B. Correlation between duration of epilepsy and FM-100 Hue test score.

		TES	B/Y	R/G
Duration of epilepsy in photosensitive JME group	r	0.057	0.122	0.056
	p	0.779	0.544	0.783
Duration of epilepsy in non-photosensitive JME group	r	0.114	0.077	0.094
	p	0.594	0.720	0.663

TES: total error score; B/Y: blue/yellow error score; R/G: red/green error score.

patients and the control group. The FM-100 Hue test was then applied to the patients and control group, for whom the SPP2 test was error-free. The total error score (TES) as well as blue/yellow (B/Y) and red/green (R/G) error scores were calculated. The tests were performed on a black background, in front of a window, in daylight (between 12:00 pm and 2:00 pm), during summer and only on sunny days. In addition, the test was conducted in a quiet environment and without time constraints. TES and R/G and B/Y error scores were calculated using Microsoft Excel software according to the sequences performed by the patient and the control group, and the results were compared. The test practitioner, a physiologist, was blinded to the participants (patient or control group).

Statistical analysis

Data obtained from the study were evaluated using PASW 18 (SPSS/IBM, Chicago, IL, USA) software and $p < 0.05$ was considered statistically significant. Categorical measurements were recorded as number and percentage, while continuous measurements were mean and standard deviation. The Shapiro Wilk test was used to demonstrate whether continuous variables showed a normal distribution. Statistical analysis of the clinical data between the two groups were performed using unpaired t-tests for parametric data, the Mann-Whitney U test for non-parametric data, and the chi-square/Fisher exact test for categorical variables.

Results

One of the 52 JME patients, who had congenital R/G vision impairment based on the SPP2 examination, was excluded from the study. Of the 51 JME patients

Table 2. Correlation between photosensitivity and FM-100 Hue test score.

	Photosensitive JME group (*n=24*)	Non-photosensitive JME group (*n=27*)	*p* value
TES	140.00	138.37	**0.439**
B/Y	77.38	73.89	**0.380**
R/G	61.04	58.41	**0.274**

TES: total error score; B/Y: blue/yellow error score; R/G: red/green error score.

Table 3. Comparison of FM-100 Hue test scores between the JME patient group and control group.

	Total patients (*n=51*)	Control group (*n=32*)	*p* value
TES	139.1373	48.5000	**<0.001**
B/Y	75.5294	24.7500	**<0.001**
R/G	59.6471	22.5938	**<0.001**

TES: total error score; B/Y: blue/yellow error score; R/G: red/green error score.

included in the study, 36 (70.6%) were female and 15 (29.4%) were male, and the mean age was 26.7. The control group (*n=32*) consisted of 21 (65.6%) female and 11 (34.4%) male participants, and the mean age was 25.9. Patients were divided into two groups according to the presence of photosensitivity on EEG. Thus, three groups were formed: the photosensitive JME group, the non-photosensitive JME group, and the healthy control group. In the photosensitive group, there were 17 (70.8%) females and seven (29.2%) males and the mean age was 28.6. In the non-photosensitive JME group, there were 19 (70.4%) females and eight (29.6%) males and the mean age was 24.96. There was no statistically significant difference in mean age or gender ratio between the photosensitive or non-photosensitive group and the control group (*table 1A*).

No significant difference in duration of epilepsy (*table 1B*) or total, B/Y or R/G error scores based on the FM-100 Hue test (*table 2*) was identified in patients with or without photosensitivity. However, total, B/Y, and R/G error scores were significantly higher in JME patients (independent of photosensitivity) than in the control group (*table 3*). Moreover, in the patient group, B/Y visual impairment was found to be significantly worse than R/G visual impairment (*table 4*).

In the patient group, the most frequently used antiepileptic drugs (AEDs) were valproic acid (VPA) (mostly used alone), levetiracetam (LEV), lamotrigine (LTG), as well as polytherapy (*figure 1*). No significant difference in TES or B/Y and R/G error scores was identified according to the type of monotherapy used by the patients (*table 5*). Moreover, no differences in visual error scores were identified between patients receiving polytherapy and monotherapy, when analysed for each AED collectively (*table 6*) or separately (*table 7*).

Discussion

Although routine MR images of IGE patients have shown normal results, some studies have shown that various cortical and subcortical dystrophic neurons and various microscopic structural anomalies are present in these patients, which is defined as "microdysgenesis" (Meencke and Janz, 1984). Recently, this microdysgenesis in patients with JME has also been shown by voxel-based MRI (Woermann *et al.*, 1999), and it is suggested that these structural abnormalities may be based on *EFHC1* mutation in patients with JME (Suzuki *et al.*, 2004). In addition, Anyanwu and Ehiri's study showed that ocular anomalies may be detected in patients with photosensitive epilepsy and that these abnormalities may affect visual acuity (Anyanwu and Ehiri, 2004). In the study conducted by Gomceli *et al.* (2016) on JME patients, the thickness of the peripapillary retinal nerve fibre layer of the superior quadrants for both eyes and choroid layer of the left eye was significantly greater, while the macular layer was significantly thinner in patients with photosensitivity compared to patients without photosensitivity. The choroidal layer provides

Table 4. Comparison of B/Y and R/G error scores in the JME patient group.

	JME patient group (*n=51*)					*p* value
	Mean	Standard deviation	Median	Minimum	Maximum	
B/Y	75.53	62.45	66.00	2.00	367.00	**<0.001**
R/G	59.65	51.04	48.00	0.00	282.00	

B/Y: blue/yellow error score; R/G: red/green error score.

Table 5. Comparison of FM 100 Hue test scores in patients on monotherapy.

VPA/LTG/LEV monotherapy			
	TES	**B/Y**	**R/G**
p value	0.755	0.742	0.607

TES: total error score; B/Y: blue/yellow error score; R/G: red/green error score.

Table 6. Comparison of FM-100 Hue test scores between patients taking polytherapy and monotherapy.

	Monotherapy (total)	Polytherapy (total)	p value
n (%)	42 (78.8)	9 (17.6)	
TES	128.4	188.8	**0.369**
B/Y	68.3	109.2	**0.267**
R/G	56	76.2	**0.493**

TES: total error score; B/Y: blue/yellow error score; R/G: red/green error score.

metabolic support to the retina in the eye and is a vascular structure that provides blood flow to the external retinal layer. The changes in choroidal thickness and resulting metabolism and vascularisation may be related to photosensitivity, and these microstructural differences in the optic nerve may be the cause or the symptom of photosensitivity (Gomceli *et al.*, 2016).

In this study, we investigated the relationship between photosensitivity and colour vision in JME patients in order to shed light on the pathophysiology of photosensitivity, which still remains unclear.

In the present study, we used the FM-100 Hue test, which is a very sensitive and widely used method to measure colour vision (Kinnear and Sahraie, 2002). We found no significant difference in total, B/Y or R/G

visual acuity scores among JME patients with and without photosensitivity. However, when patients were compared with the healthy control group, the error scores were significantly higher in the patient group in all three categories, with the highest score for B/Y visual acuity. In the literature, colour vision function in epileptic patients taking AEDs was evaluated using the FM-100 Hue test and some abnormalities were detected (Tomson *et al.*, 1988; Bayer, 1991; Bayer *et al.*, 1995a, 1995b; Paulus *et al.*, 1996). Colour vision functions of epileptic patients were compared with control group using the FM-100 Hue test before patients started medication and one year after carbamazepine (CBZ) or VPA were initiated. In both groups of patients, significant deterioration in error scores for colour vision was observed compared to the control group one year after the drugs were started. The reason for this disturbance is thought to be due to inhibition of voltage-gated sodium channel blockade by CBZ and voltage-gated sodium channel blockage and inhibition of T-type calcium channel or GABA receptor channels by VPA. It has been noted that these AEDs have an adverse effect on glutamate and other neurotransmitters in the retina, however, it is still unclear whether this adverse effect also occurs on photo- and bipolar receptors (Verrotti *et al.*, 2004). Steinhoff *et al.* (1997) compared epilepsy patients receiving CBZ, VPA and a combination of CBZ, vigabatrin (VGB), gabapentin and topiramate treatments. VPA and VGB significantly impaired vision function in patients with both monotherapy and polytherapy compared to patients with other AEDs. It was speculated that this disturbance is associated with an increase in GABA in the brain caused by VPA and VGB. In another study, VGB, CBZ and placebo were compared in healthy volunteers. Deficits were detected in both areas (B/Y and R/G) in volunteers who were given CBZ and in the blue colour vision area in volunteers given VGB. It was reported that CBZ caused deterioration in both groups due to non-specific synaptic inhibition, and VGB caused deterioration due to GABAergic inhibition. It has also been suggested that the blue colour vision defect is a consequence of retinal damage

Table 7. Comparison of FM-100 Hue test scores between patients taking polytherapy and VPA, LTG and LEV monotherapy.

	VPA monotherapy	LEV monotherapy	LTG monotherapy	Polytherapy	p (VPA)	p (LTG)	p (LEV)
n (%)	23 (45.1)	9 (17.6)	8 (15.6)	9 (17.6)			
TES	120.5	132	142.5	188.8	**0.317**	**0.507**	**0.465**
B/Y	63.6	71.4	76.75	109.2	**0.225**	**0.396**	**0.364**
R/G	50.65	59.2	64.1	76.2	**0.392**	**0.692**	**0.630**

TES: total error score; B/Y: blue/yellow error score; R/G: red/green error score; VPA: valproic acid; LEV: levetiracetam; LTG: lamotrigine.
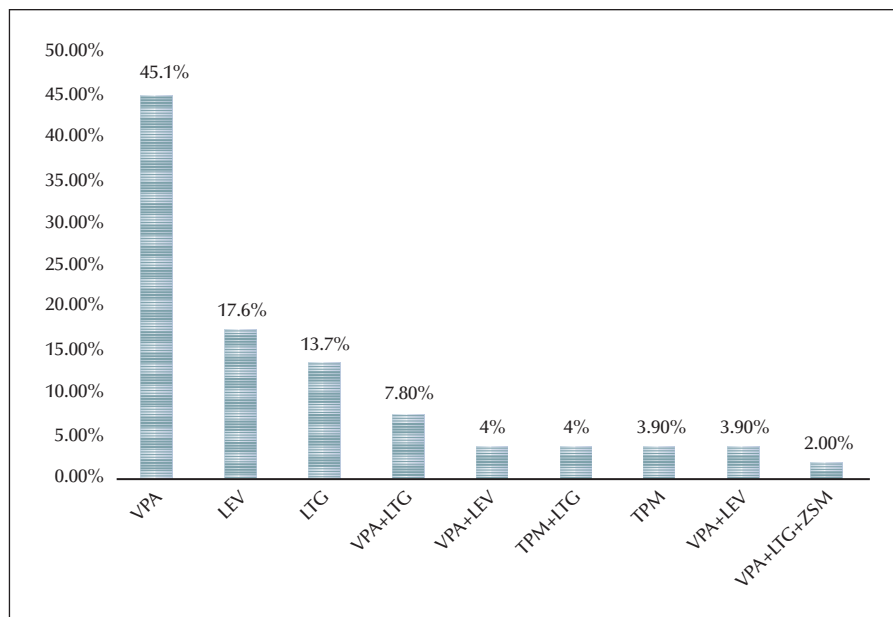
Figure 1. Usage of AEDs.

and thus the GABAergic inhibition effect of VGB also occurs at the retina level (Mecarelli *et al.*, 2001).

In our study, we firstly compared between monotherapy patients as the influence on this group may be due to medication usage. We then compared patients who were taking each drug as monotherapy with patients who received polytherapy, and finally all patients who received monotherapy and all patients who received polytherapy. However, no significant difference was found based on any of the comparisons. Therefore, no significant association was identified between type of AED, or mono- or polytherapy, and error score for colour vision. In the literature, no such side effects are reported following the use of LEV (Krakow *et al.*, 2001). In our study, 17.4% of the patients were taking LEV monotherapy and their colour error scores were high. For this reason, we believe that this disturbance was not a side effect of the drug. As the JME patient group was not specifically assessed in the above-mentioned studies, this may account for the different results of our study.

The significant difference between the patients and control group raises the question "could colour vision impairment be due to the pathophysiology of JME?". Koepp *et al.* (1997) investigated the distribution of C-11-labelled FMZ in the brain by PET and demonstrated increased cerebral cortex cBZ/GABA binding in patients with IGE and JME. This increase was linked to a presence of cortical hyperexcitability status and microdysgenesis in IGE patients. In another study, a total of 15 IGE patients (two of them with JME) were evaluated by magnetic resonance-spectroscopy (MR-S) and an increased level of GABA was detected in

the occipital lobe (Simister *et al.*, 2003). Hattingen *et al.* (2014) also found that GABA and precursor glutamine concentration increased in the frontal lobe and that GABA and N-acetyl-aspartate (NAA) concentration decreased in the thalamus in JME patients evaluated by MR-S. This result suggests the presence of a neurotransmission defect in this brain region. The fact that NAA is reduced in the grey matter of the thalamus supports the presence of a defect of GABAergic neurons. Finally, increased GABA and its precursor glutamine in the frontal lobe supports the congenital malformation of the thalamo-frontal neuronal network and the increase in GABAergic neuron density due to the number or structure of the receptors during corticogenesis. In the study of Cossette *et al.*, mutations in the *GABRA1* gene, encoding the subunit of the $GABA_A$ receptor, have been demonstrated in JME (Cossette *et al.*, 2002; Cossette, 2010). Recently, new electrophysiologic findings have been detected by transcranial magnetic stimulation (TMS) in JME patients. These findings are believed to be due to a defective GABA-A mechanism as well as defective intracortical inhibition, resulting in a conserved GABA-B mechanism (Serafini *et al.*, 2013). In conclusion, all these studies refer to a dysfunction in GABAergic mechanism in JME patients. GABA is also the major neurotransmitter inhibitor in the retina and GABAergic transmission is involved in colour coding (Kupenova *et al.*, 2010). This neurotransmitter, also acting as a major inhibitor in the central nervous system, plays an important role in retinal signal processing by being released from horizontal cells in the outer layer of the retina by a calcium-independent mechanism (Xu and Yang, 2000).

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This neurotransmitter has also been shown to regulate communication between horizontal cells and cone and bipolar cells (Xu and Yang, 2000). Recent studies support that mammalian horizontal cells are GABAergic (Vardi and Sterling, 1994). GABA and some other neurotransmitters have also been shown to be present in different types of amacrine cells in the retina and that interplexiform cells contain dopamine or GABA (Ryan and Hendrickson, 1987; O'Malley and Masland, 1989). GABA$_A$ and GABA$_C$ receptors are not localized to a particular synaptic region, suggesting that GABA may play a role in different pathways in the retina (Kupenova *et al.*, 2010).

Therefore, GABAergic mechanisms appear to be a common pathway in both JME pathophysiology and colour vision physiology. Even though a dysfunctional GABAergic mechanism may play a significant role in the pathophysiology of JME in particular, rather than other epilepsy groups, more robust results are required based on a comparison between patients with JME and other epilepsy groups in future studies.

Conclusion

In the present study, although we were unable to demonstrate a correlation between photosensitivity and colour vision in JME patients, the error score for colour vision in JME patients was significantly higher than in the healthy control group. We hypothesise that the underlying cause of colour vision defects in JME patients may be due to the pathophysiology of the disease itself. Consequently, we believe that GABA dysfunction, which we consider to be involved in the pathophysiology of JME, also has an effect in the retina. ☐

Disclosures.
None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) What is the general perspective regarding the underlying cause of PPR pathophysiology?

(2) Although JME is classified as an IGE, which findings indicate that it also exhibits focal abnormalities?

(3) What mechanism may underlie the pathophysiology of both JME and dysfunctional colour vision?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".