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The influence of escitalopram therapy on macular function in patients with major depression – preliminary report

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ABSTRACT

Aim of the study: To analyze macular function after escitalopram treatment in patients with major depression.

Material and methods: In 21 newly diagnosed (42 eyes) patients (mean age: 46.4 ±11.6 years) with major depression (MD), and in 29 (58 eyes) age- and sex-matched healthy controls (mean age: 46.3 ±10.4 years) the following examinations were performed: visual acuity (Snellen Table), intraocular pressure, biomicroscopy of anterior and posterior segment of the eye and macular structure (SD-OCT-Zeiss). In the MD group, before and after 4 weeks of escitalopram treatment, a pattern electroretinogram (PERG) was registered and amplitudes (A) of P50 and N95 waves and peak times (PT) of P50 waves were analyzed. An analysis of the correlation between post-treatment changes of PERG parameters and depression severity (Hamilton Depression Rating Scale – HAMD) was achieved. The results were considered as a statistically significant with $p < 0.05$.

Results: In the MD group and healthy control the clinical results were normal. After treatment in the PERG test, significant shortening of PTP50 mean ($p = 0.03$) was detected. The amplitudes of P50 and N95 waves did not change significantly. Correlations between analyzed PERG parameters and HAMD score before and after treatment were not found ($p > 0.05$) but in MD patients in whom after treatment the change from severe to mild (using scores of HAMD) was achieved, a significant positive correlation ($p = 0.04$) between reduction of HAMD score and shortening of the PTP50 wave was found.

Conclusions: In patients with MD after escitalopram treatment, the improvement of bioelectrical macular function was detected. The PERG has a potential value to be useful, objective test in estimation of the treatment success.

KEY WORDS: escitalopram, major depression, PERG.

INTRODUCTION

Major depression is a chronic, recurrent mental disease with the highest lifetime prevalence among major psychiatric disorders. The World Health Organization expects that, by 2030, MD will become the second most common cause of disability and burden of disease [1]. In the treatment of MD, antidepressant medications remain a mainstay especially for cases with moderate to severe depression, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs). Nowadays, most clinical guidelines recommend the new generation of antidepressants as the first-line treatment for MD [2, 3]. Escitalopram, an S-enantiomer of racemic citalopram, is an SSRI and also has a modulatory effect at an allosteric binding site of the serotonin transporter protein [4, 5]. It has been shown that escitalopram is effective for MD treatment and presents better efficacy and tolerability to other SSRIs and other antidepressants [4-6].

For the evaluation of the therapeutic response to medication in patients with major depression objective biomarkers of depression could be very helpful. One possible candidate in this case might be the pattern electroretinogram (PERG), because this test records the macular photoreceptors' function as well as the retinal ganglion cells' response. The retinal ganglion cells indirectly examine the brain activity because of their anatomical and functional properties [7].

To date, only one study's results have been published in the literature describing the effect of antidepressive therapy

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on ganglion cells function measured by PERG [8]; reduced PERG-contrast gain normalized after antidepressive therapy, suggesting that this test can serve as a state marker of depression. Also there can be found reports of PERG scores in another psychiatric disorder where SSRIs are used – schizophrenia. Bernardin et al. observed a significant increase of the peak time of P50 and N95 waves in schizophrenia patients compared with controls [9]. To confirm the potential value of PERG examination in objective estimation of the therapeutic response to medication, we decided to perform in a newly recognized, untreated group of patients with major depression the ISCEV transient PERG before and after escitalopram treatment.

MATERIAL AND METHODS

Before treatment, in 21 newly, diagnosed (42 eyes) patients (mean age: 46.4 ±11.6 years) with major depression (MD), and in 29 (58 eyes) age- and sex-matched healthy controls (mean of age:46.3 ±10.4 years) the following examinations were performed: the best distance corrected visual acuity (Snellen Table), intraocular pressure, biomicroscopy of anterior and posterior segment of the eye and macular structure (SD-OCT-Zeiss). In the MD group, before and after 4 weeks of escitalopram treatment a pattern electroretinogram (PERG-ISCEV standards) [10] was registered. The amplitudes of P50 and N95 waves, as well as peak time of the P50 wave, were measured. Values of all parameters were compared with age- and sex-matched healthy controls.

Written informed consent was obtained from all participants. The study was approved by the local ethics committee of Pomeranian Medical University (PMU) in Szczecin.

Patients with MD were referred from the Department of Psychiatry of PMU with a major depressive episode according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-DSM-IV) and were assessed psychometrically with the Hamilton Depression Rating scale (HAMD) before and after escitalopram treatment (Table I). Patients with other psychiatric disorders, as well as ocular and systemic diseases with a known influence on retinal function, were excluded.

Table I. Gender, age, HAMD score in the study and healthy control groups

	MD patients	Healthy control
Number of patients/eyes	21/42	29/58
Gender m/f	5/16	4/25
Age (years)	46.4 ±11.6	46.3 ±10.4
HAMD score		
before treatment	26.4 ±6.6	2.27 ±1.36
after treatment	15.3 ±4.9	

Statistical analysis

The obtained data of PERG parameters from the MD group before and after escitalopram treatment, and from controls, were analyzed statistically. The assumption of normality was checked using the Shapiro-Wilk test. In reference to normality tests, the norm ranges have been determined based on the values of parameters from the control group. In the case of the normal distribution of the variables, the range of the norm was between –2SD and +2SD, in the absence of normality the range of the norm was between 2.5 and 97.5 percentiles. The values of the PERG parameters before and after treatment and in relation to the control were compared. Depending of the variable distribution, two different tests were used, parametric or nonparametric, Student's t-test, Wilcoxon test) or the Mann-Whitney U test, respectively. An analysis of the correlation (Spearman rank correlation test) between pre- and post treatment changes of PERG parameters and depression severity (measured using the Hamilton Depression Rating Scale – HAMD) was achieved. Results were considered as statistically significant with $p < 0.05$.

RESULTS

In the study group and controls the clinical results were normal and were as follows: the best distance corrected visual acuity – 1.0 (both groups), intraocular pressure (16.7 ±1.2 versus 16.2 ±1.2 mmHg)- between normal limits, biomicroscopy of anterior and posterior segment of the eye – normal, normal macular structure (cube average thickness- 280.4 ±13.5 versus 282.4 ±8.8 μm), retinal nerve fiber layer thickness – 93.6 ±11.1 μm versus 95.0 ±8.2 μm.

There was no statistical difference in age between MD patients and controls ($p > 0.5$; Table II).

Before treatment a significant reduction of mean amplitudes of P50 and N95 waves in comparison to the control group was obtained as well as a non-significant increase of PTP50.

Normal range of PERG parameters is presented in Table III. The Shapiro-Wilk test was used to check normal distribution of particular parameters.

Table IV shows the frequency of abnormal results of PERG parameters before and after escitalopram treatment of MD patients ($n = 42$ eyes) in relations to normal values presented in Table III.

After escitalopram treatment, the most prominent feature was disappearance of prolonged PTP50 seen initially (Figure 1).

In the PERG test, after treatment, significant shortening of PTP50 was achieved ($p = 0.03$). The amplitudes of AP50 and AN95 did not change significantly after treatment ($p = 0.55$, $p = 0.73$, respectively).

Figure 2 shows PERG results of an MD patient with significant shortening of PTP50 after escitalopram treatment in comparison to the peak time of theP50 wave before treatment.

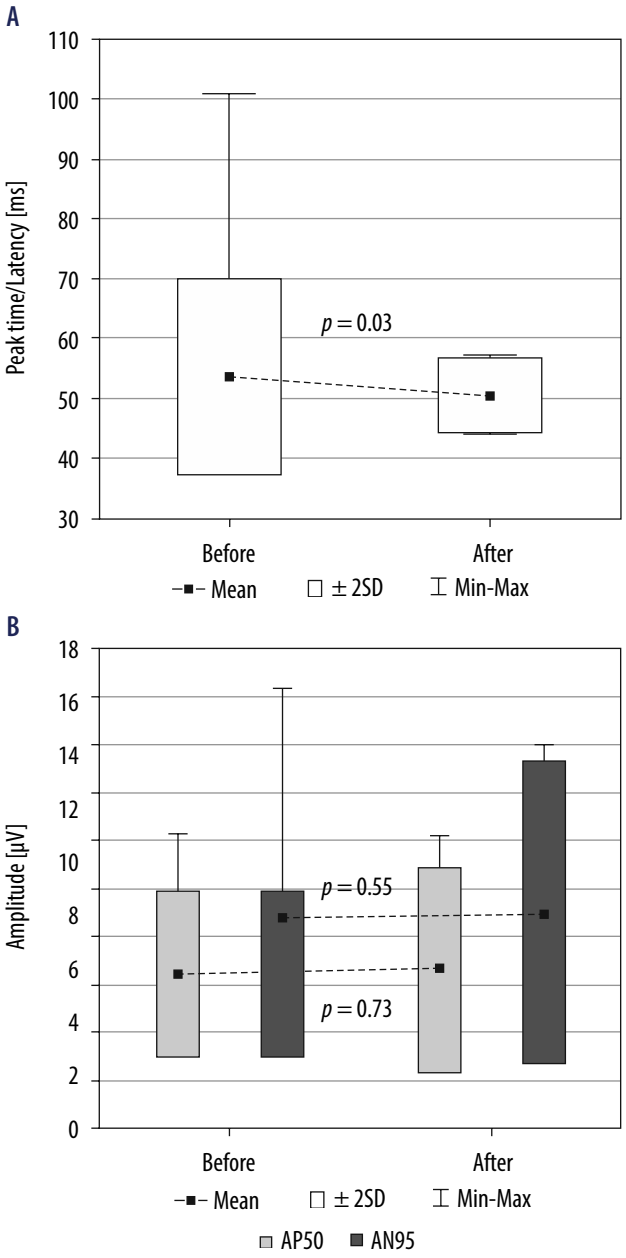


Figure 1 shows comparisons of means from both eyes of PERG parameters (AP50, ITP50, AN95) of MD patients before and after treatment

In the MD group after treatment a significant reduction of HAMD score was detected in comparison to the initial value (26.4 ±6.6 versus 15.3 ±4.9; $p = 0.0001$*).

Correlation analysis of PERG parameters and HAMD score before and after treatment and after treatment ($n = 21$ patients) is shown in Table V.

Correlations between analyzed PERG parameters and HAMD score before treatment and after treatment were not found (Spearman rank test; $p > 0.05$).

After escitalopram treatment, in four MD patients improvement from severe to mild depression and in one patient from severe to normal was achieved. In these patients a statistically significant positive correlation between reduction of HAMD score and PTP50 was observed ($p = 0.04$).

Table II. Means values of PERG parameters in patients with MD ($n = 42$ eyes) before treatment in comparison to control group ($n = 58$ eyes)

Parameter	MD		Control		*p*
	Mean	SD	Mean	SD	
AP50 (µV)	4.3	1.8	9.1	3.1	0.00
PTP50 (ms)	53.6	3.5	51.8	2.8	0.10
AN95 (µV)	6.4	3.0	12.3	3.4	0.00

Table III. Normal values of PERG parameters ($n = 29$ patients, 58 eyes)

Parameter	*p*	Limit of normal
AP50 (µV)	0.994	2.9 (–2SD)
PTP50 (ms)	0.715	57.3 (+2SD)
AN95 (µV)	0.940	(–2SD)

A – amplitude; PT – peak time

Table IV. Abnormal PERG parameters (reduced A or PT increase) before and after escitalopram treatment of MD patients ($n = 42$ eyes)

Parameter	Before treatment		After treatment	
	n	%	*n*	%
AP50	9	21.4	9	21.4
PTP50	4	9.5	0	0
AN95	17	40.4	15	35.7

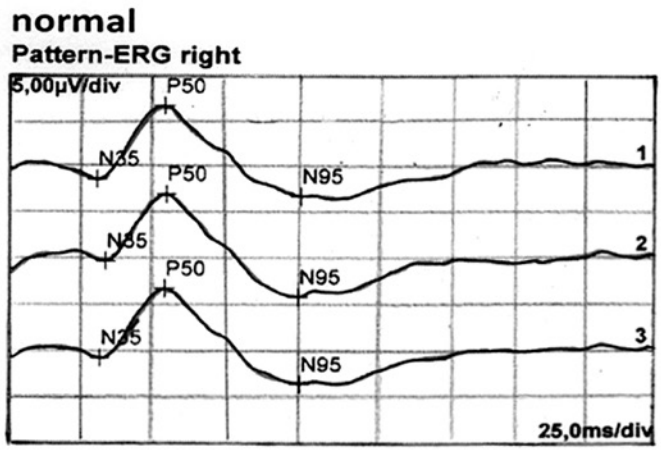
n *– number of eyes*

Table V. Correlation of PERG AP50, AN95 and PTP50 and HAMD score before and after escitalopram treatment

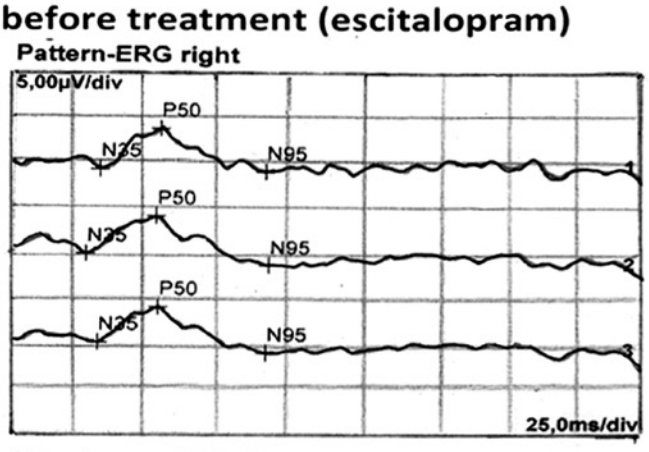
HAMD score before treatment	Spearman R	*p*
AP50	–0.24	0.3
PTP50	0.01	0.9
AN95	–0.36	0.1
HAMD score after treatment	**Spearman R**	***p***
AP50	0.09	0.7
PTP50	0.10	0.7
AN95	–0.02	0.9

DISCUSSION

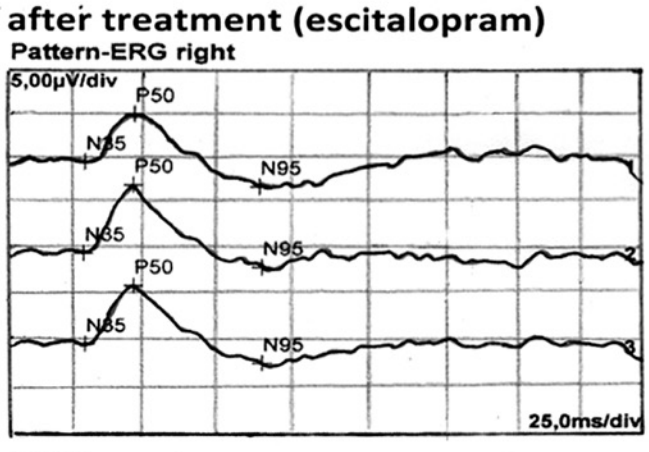
Our study results suggest that in patients with MD treated with escitalopram, the improvement of macular cone system function can be registered and manifested by significant shortening of the PTP50 wave (Figures 1, 2). The amplitudes of P50 and N95 waves did not change significantly and indicate that ganglion cells function remains abnormal. In the monoamine deficiency hypothesis, MD pathophysiology is connected with a deficit in neurotransmission of serotonin, norepinephrine and dopamine [12-14]. Serotonin is detected in the mammalian retina and is involved in retinal neuro-



Channel	N35 [ms]	P50 [ms]	N95 [ms]	AP50	AN95
1 right	30,8	54,3	101,3	8µV	9,8µV
2 right	33,8	54,8	100,3	7,3µV	11,1µV
3 P-ERG righ	31,8	54,3	100,8	7,6µV	10,4µV



Channel	N35 [ms]	P50 [ms]	N95 [ms]	AP50	AN95
1 right	34,7	58,7	100,3	4,56µV	4,77µV
2 right	29,4	57,2	101,8	4,23µV	5,46µV
3 P-ERG righ	34,2	58,2	100,8	3,98µV	5,06µV



Normals	-	-	-		
Channel	N35 [ms]	P50 [ms]	N95 [ms]	AP50	AN95
1 right	30,3	49,9	98,8	5,33µV	8,05µV
2 right	29,8	49,4	99,8	7,48µV	9,03µV
3 P-ERG righ	30,3	49,4	99,8	6,41µV	8,53µV

Figure 2. PERG recording of right eye in patient with severe depression in whom after escitalopram treatment significant shortening of P50 wave (from 58.2 to 49.4 ms) to a normal value was detected

transmission. Anatomical studies demonstrated that mammalian retinas receive inputs from the brain via retinopetal axons emerging from the optic nerve [15]. This chemical messenger is targeted by a broad range of antidepressant drugs such as escitalopram mediating the serotoninergic neurotransmission. Tryptophan hydroxylase 1 (Tph1) is responsible for serotonin synthesis in the retina [16].The levels of endogenous serotonin in mammalian retinas are relatively low, approximately 10% of the levels of an amacrine cell neurotransmitter, dopamine. Low levels of endogenous serotonin suggest that this neurotransmitter is used by a sparse population of retinopetal axons rather than amacrine cells. Since serotonin receptors are detected not only in the ganglion cells but also in cone photoreceptors (5-HT2A receptor) in mammalian retinas [17], it may be possible that stimulation of the serotoninergic pathway can impact the PERG recording, as was shown in escitalopram responder MD patients in our study. It is commonly know that a change of the PTP50 wave in PERG examination is associated with dysfunction of the outer retinal layer (cone photoreceptors, bipolar cells) of the macular region [18]. It is also known that the electroretinographic photopic b-wave originates from bipolar cells but after cone photoreceptor stimulation. We think that in the present study the prolonged PTP50 albeit not significant in MD patients in comparison to controls is a result of the reduced level of serotonin in the brain (Table II). It was demonstrated previously that patients with depressive symptoms have increased photopic b-wave implicit time [19]. From another study it is known that Tph2 knockin (Tph2-K1) mice have reduction of 80% in brain serotonin and express depression-related behavioral abnormalities [20] and are characterized by an increase of photopic ERG b-wave implicit time [21]. The genetic mutation of Tph2-K1 mice does not affect the serotonin content in the retina. It suggests that a decrease in brain serotonin might be sufficient to modify the photopic b-wave implicit time via retinopetal axons. A longer photopic b-wave implicit time was also observed during depressive episodes in seasonal affective disorder [22]. Consequently, increase of serotonin level in the brain after escitalopram treatment was a cause of shortening of the PTP50 wave in PERG examination, which was shown for the first time in our study (Table IV, Figures 1, 2). It remains unsolved why the increase of serotonin level in the brain after treatment did not change reduced amplitudes of P50 and N95 waves seen initially which are mainly of ganglion cell origin. One possible explanation is the fact that although retinopetal axons terminate in the inner retina, their targets are often in the outer retina where serotonin receptors are located (photoreceptor terminals). Additionally, the probable lack of the increase of retinal serotonin after escitalopram treatment might also be responsible for unchanged retinal ganglion cell function.

After escitalopram application in all patients a decrease of HAMD score was noted and indicates efficacy of this drug in MD treatment. In the whole group HAMD score improvement was not correlated with PERG parameters (Table V). When patients were analyzed separately, in 5 MD patients in whom improvement from severe to mild depression or normal was detected, a statistically significant positive correlation between reduction of HAMD score and PTP50 was observed ($p = 0.04$). The data we obtained are in line with previous observations [9] that PERG can be an important method for assessing responses to treatment in major depression. There are not enough data to say why PTP50 is an indicator of improvement. According to observations by Bulb *et al.* [28], higher sensitivity of depressive symptoms correlates with higher VEP amplitude, but the PERG signal is more sensitive. As the PERG study on depression is a new area, there is no information on PTP50 as an indicator of the severity of depression. It is worth noting that the observations we have made concern a small group.

In conclusion, our study results suggest that in patients with major depression, the improvement of bioelectrical macular cone system function was detected after escitalopram treatment. The ISCEV PERG has a potential value to be useful, objective test in estimation of the treatment success. Investigations on a larger group of patients are necessary to confirm our promising initial results. Additional studies are also necessary to clarify the interaction between neurotransmitters in the retina and in the brain and how they relate to the pathogenesis of MD.

DISCLOSURE

The authors declare no conflict of interest.

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