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Electroretinography and Visual Evoked Potential – Useful Techniques to Investigate Depressive Disorders. Review and Case Report

Elektroretinografia i wzrokowe potencjały wywołane jako pomocne narzędzie w diagnostyce zaburzeń depresyjnych. Przegląd piśmiennictwa i opis przypadku

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Abstract: Aim: To present current knowledge about visual pathway dysfunction observed in patients with depressive disorders, as well as to describe results of pattern electroretinography (PERG) in patient with major depressive disorder (MDD).
Material and Method: Searches concerning examinations: full field electroretinography (ERG), pattern electroretinography and pattern visual evoked potential (PVEP) in depressive disorders were found in the PubMed database. Also, we present PERG results in the patient with major depressive disorder. The electrophysiological measurements were performed according to the guidelines of the International Society for Clinical Electrophysiology of Vision – 2010 update or 2016 update (ISCEV).
Results: The majority of published studies confirm the thesis that visual pathway dysfunction can be detected in patients with depressive disorders. Our pattern electroretinogram results in the patient with MDD revealed ganglion cell dysfuntion.
Conclusion: In depressive disorders visual pathway dysfunction measured by retinal electrophysiological tests, presumably can serve as marker of neurotransmission in central nervous system. We assume ERG, PERG and PVEP examinations might be diagnostic tools and help to monitor therapy in patients with depressive disorders.
Key words: depressive disorder, visual pathway dysfunction, retinal electrophysiological tests.
Abstrakt: Cel pracy: Przedstawienie aktualnej wiedzy o dysfunkcji drogi wzrokowej obserwowanej u pacjentów z zaburzeniami depresyjnymi, jak również omówienie wyników badania elektroretinogramu wywołanego wzorcem (PERG) u pacjenta z dużą depresją.
Materiał i metody: Prace dotyczące badań: elektroretinografii (ERG), elektroretinogramu wywołanego wzorcem oraz wzrokowych potencjałów wywołanych wzorcem (PVEP) u pacjentów z zaburzeniami depresyjnymi pochodzą z bazy PubMed. Prezentujemy również wyniki własne badań PERG u pacjenta z dużą depresją. Badania elektrofizjologiczne przeprowadzone były zgodnie z wytycznymi International Society for Clinical Electrophysiology of Vision (ISCEV) z 2010 r. i 2016 r.
Wyniki: Większość opublikowanych badań potwierdza tezę, iż dysfunkcja drogi wzrokowej może występować u pacjentów z depresją. Nasze wyniki elektroretinogramu stymulowanego wzorcem u pacjenta z dużą depresją wykazały dysfunkcję komórek zwojowych siatkówki.
Wnioski: W zaburzeniach depresyjnych dysfunkcja drogi wzrokowej mierzona za pomocą badań elektrofizjologicznych siatkówki może służyć jako marker neurotransmisji w centralnym układzie nerwowym. Badania ERG, PERG oraz PVEP mogą stać się diagnostycznym narzędziem i pomocą w monitorowaniu terapii u pacjentów z zaburzeniami depresyjnymi.
Słowa kluczowe: zaburzenia depresyjne, dysfunkcja drogi wzrokowej, badania elektrofizjologiczne siatkówki.
The authors declare no conflict of interest/ Autorzy zgłaszają brak konfliktu interesów w związku z publikowaną pracą

Introduction

In mental disorders there can be retinal and optic nerve disturbances.

Retina and optic disc are the only part of the central nervous system that can be seen by ophthalmologists during routine examinations. Retina and brain develop from the same neuroectodermal tissue. For that reason, it has been suggested that changes in retinal function can serve as a biomarker for brain tissue disorders and disease progression (1).

The neurotransmitters are endogenous substances which transmit signal across chemical synapse from neuron to the target cell. It can be another neuron, muscle cell or gland cell.

The retinal cells send signals using various excitatory and inhibitory amino acids, catecholamines, peptides and nitric oxide (2) – the same neuropeptides which exist in the brain. Substances involved in retinal neurotransmission are shown in table I (3, 4). Presumably retinal neurotransmitter levels reflect neurotransmitter levels in the brain.

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retinal cells/ komórki siatkówki	substances involved to retinal neurotransmission/ substancje zaangażowane w neuroprzekaźnictwo siatkówki
photorecetors/ fotoreceptory	Amino acid glutamate, Dopamine D2, Melatonin/ Aminokwas glutaminowy, Dopamina D2, Melatonina
bipolar cells/ komórki dwubiegunowe	Amino acid glutamate, Dopamine D1, Glicyne Gamma-Aminobutyric acid (GABA)/ Aminokwas glutaminowy, Dopamina D1, Glicyca Kwas gamma-aminomasłowy (GABA)
horizontal cells/ komórki horyzontalne	Gamma-Aminobutyric acid, Amino acid glutamate/ Kwas gamma-aminomasłowy, aminokwas glutaminowy
amacrine cells/ komórki amakrynowe	Glicyne, Gamma-Aminobutyric acid, Serotonin, Dopamine D1, Acetylcholine, Adenosine, Nitric oxide, Substance P, Somatostatin, Cholecystokinin/ Glicyna, kwas gamma-aminomasłowy, Serotonina, Dopamina D1, Acetylocholina, Adenozyna, tlenek azotu, Substancja P, Somatostatyna, Cholecystokinina
ganglion cells/ komórki zwojowe	Amino acid glutamate,Dopamine D1, Glicyne Gamma-Aminobutyric acid, NMDA glutamate, Acetylocholine/ Aminokwas glutaminowy, Dopamina D1, Glicyna Kwas gamma-aminomasłowy, NMDA glutaminian, Acetylocholina

Tab. I. Retinal cells and substances involved to retinal neurotransmission.
Tab. I. Komórki siatkówki i substancje zaangażowane w neuroprzekaźnictwo siatkówki.

Disturbances due to insufficient secretion of neurotransmitters can be very severe and can cause a negative impact on individual organs. Noticeable symptoms come from the central nervous system – may appear as psychiatric or neurological disorders. For example, low dopamine level is the characteristic feature of Parkinson's disease (5). A decrease in acetylcholine level coexists with Alzheimer's disease (6), whereas GABA (Gamma-Aminobutyric acid) – with epilepsy and anxiety disorder.

Abnormalities in neurotransmitters are also observed in depressive disorder; low levels of serotonin, noradrenaline and dopamine and high levels of melatonin.

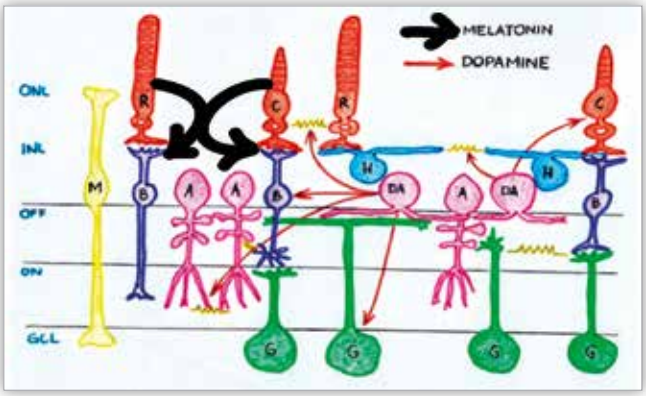

Fig. 1. Neurochemical outputs of the retina.
Ryc. 1. Neuroprzekaźnictwo siatkówki.

Most antidepressant medications alter the levels of one or more of these neuromodulators in a synaptic cleft between neurons in the brain (7).

Depression is one of the most frequent psychiatric disorders. In most countries the number of people who suffer from depression during their lives is 8–18% (8). Depressive disorders are more common to observe in urban than in rural population, more often in women (9). Between 2 and 7% of adults with major depression die by suicide (10).

Depression is a heterogeneous disorder. A number of classification systems have been used.

DSM (Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Association), recognizes five subtypes of major depression disorder (MDD), called specifiers: melancholic depression, catatonic depression, atypical depression, seasonal affective disorder (SAD) and postpartum depression. ICD–10 (International Statistical Classification of Diseases and Related Health Problems) also provides specifiers for psychotic and somatic symptoms (11).

The aim of this study is to present current knowledge about retinal and visual pathway dysfunctions observed in electrophysiological measurements in patients with depression and to describe retinal abnormalities in patient with newly diagnosed major depressive disorder.

Material and method

PubMed searches concerned full field electroretinography (ERG), pattern electroretinography (PERG) and pattern visual evoked potentials (PVEP) in patients with depression. The ERG, PERG and VEP were performed according to the guidelines of the International Society for Clinical Electrophysiology of Vision – 2010 or 2016 update (ISCEV)

Also, we described a case – pattern electroretinography results in a patient with newly diagnosed major depressive disorder before and after 3 weeks of antidepressant treatment with escitalopram, a selective serotonin reuptake inhibitor.

Results and discussion

ERG changes in SAD

Up to date, only four published studies concerned ERG changes in SAD.

In a pilot study performed by Hebert et al. 2002 (12), 12 patients with subsyndromal seasonal affective disorder (S-SAD) and 9 patients from control group were examined. In this study retinal sensitivity was estimated with scotopic luminance response function. Electroretinograms were analyzed once in winter and once in summer. To better analyze the dynamics of retinal response, the b-wave amplitude obtained at various intensities was plotted against flash luminance to generate a luminance-response function curve. A difference in retinal sensitivity between the two groups appeared only in winter, with lower retinal sensitivity found in the S-SAD group. The causes of these anomalies are still unknown, but it has been

suggested that they could be related to changes in retinal and cerebral neurotransmitter levels. The authors consider that serotonin would be a good candidate, since it is the precursor of melatonin and a dysregulation in serotoninergic transmission has been postulated in SAD. Serotonin could have an impact on both mood and retinal sensitivity. Serotonin is present in amacrine cells, but little is known about the physiological role of retinal serotonergic circuity. There is a hypothesis that ganglion cells express a serotonin receptor which could affect plasticity during the development of retinal neural network and modulate ganglion cell's response to visual stimulation (3).

The next study described by the same author in 2004 (13) concerned 27 depressed patients with a seasonal pattern diagnosed according to the DSM III R and 23 normal control patients. The electroretinogram was used to assess the retinal sensitivity of the rod system. ERG testing was performed in dark-adapted, dilated eyes in winter between 10:00 a.m. and 3:00 p.m. Rod system sensitivity was significantly lower in SAD patients compared with normal control group.

The result presented in the studies mentioned above suggest that SAD patients may represent lower rod system sensitivity, but only in wintertime. In this study authors postulate that a possible explanation for changes in sensitivity could be a dysregulation of levels of retinal neurotransmitters such as melatonin and dopamine. It is known that the daily synthesis and release of retinal dopamine and melatonin shows a 24-hour rhythm: dopamine appears in retina triggered by light, while melatonin is produced by photoreceptors in darkness. Many patients with SAD have a delay in their circadian rhythm – they have high level of melatonin and low dopamine level. Authors emphasize that brain neurotransmitter dysregulation is the one hypothesis that can explain both the mood disorder and the change in retinal sensitivity.

Lavoie et al. in 2009 (14) showed the results of ERG examinations in twenty-two patients with SAD and in 16 healthy controls. The patients were selected according to the DSM-IV criteria. All the participants were examined 3 times in the fall/winter season; the first time before the light therapy (LT), the second time after 2 weeks of LT and the third time after 4 weeks of LT (LT was self-administered at home using a commercial fluorescent lamp 5000 lux for 30 min). The patients were also examined once in the summer season Photopic and scotopic ERGs were conducted in all the participants at 11:00 AM in both seasons. The depressed patients demonstrated cone system changes; lower b-wave amplitude in winter before the light therapy, but not different in summer and after 4 weeks of LT, b-wave implicit time changed marginally during the treatment and was longer in patients during the depressive episode only. Changes in rod system concerned different responses according to the intensity of stimulation.

The patients also underwent examinations of salivary melatonin, but the mean melatonin concentrations in patients with SAD were not significantly different than those observed in healthy controls.

Authors postulate that reduced ERG functioning appears to be a marker for SAD, with retinal anomalies observed only during the fall/winter depressive episode and with normalization of retinal parameters following the treatment with LT. They believe that retina represents a good model to investigate neurotransmission in brain.

In another study presented by Gagne et al. in 2010 (15), 12 SAD patients and 11 healthy controls took part in the trial. They were exposed to three light conditions for 60 min (5 lux, 100 lux and 10,000 lux) on different days, within a 1-week period, during fall/winter season and spring/summer season. ERG changes in cone system were observed. Compared with the 100 lux and 1000 lux conditions, the 5 lux exposure caused a significant decrease in b-wave amplitude in both depressed and healthy groups regardless of season. In winter, the a-wave amplitude in SAD was significantly lower than that observed in healthy controls, but not during summer. Changes in rod system were also observed. SAD patients showed lower b-wave amplitude in 10,000 lux and in 5 lux conditions when compared to healthy controls. Groups showed similar amplitudes in 100 lux conditions. Authors suggested that the described ERG abnormalities might be related to the abnormal dopaminergic transmission. They postulated that retinal response modulation may represent an interesting biomarker of the disease for future research.

In summary, ERG changes in cone and rod system are observed in patients with SAD. These findings may be related to common neurotransmitter dysfunctions in the central nervous system and retina.

ERG changes in MDD

The study presented by Fornaro et al. in 2011 (16) included 20 patients with a diagnosis of MDD and current major depressive episode without a seasonal pattern (according to DSM IV) and 20 matched control subjects. All the patients were monitored by standard ERG recording before and after 12 weeks of treatment with duloxetine 60mg/day (serotonin-norepinephrine reuptake inhibitor). The authors observed that some MDD patients responding to duloxetine had statistically higher baseline values of rod b-wave amplitude compared to those not respondent and the control group. The authors speculated that such a change in the rod b-wave amplitude might reflect a dysregulation in the neurotransmitter balance associated with a hypo-dopaminergic state, which would then be normalized by the drug. The ERG b-wave amplitude reflected the levels of retinal dopaminergic activity and the related changes in photoreceptor and bipolar cell function. The authors suggested that ERG might serve as a potential technique to predict and monitor the pharmacotherapy response in MDD patients.

PERG changes in MDD

Studies reporting PERG anomalies in MDD patients were described twice by Bubl et al.

Several PERG modifications are used for research: transient PERG with the measurement of the N95 wave amplitude and implicit time, steady-state PERG with amplitude and phase of response, and PERG-based contrast gain with PERG amplitude versus contrast.

In the study from 2010, Bubl (17) found a strong and significant correlation between PERG–based contrast gain and severity of depression. The study included 40 patients with a diagnosis of major depression (20 with and 20 without medication) and 40 matched healthy subjects. Five series of reversing checkerboard at 12 reversals per second were used (contrast level: 3.2%, 7.3%, 16.2%, 36%, 80%). The unmedicated and medicated

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depressed patients displayed dramatically lower retinal contrast gain than healthy controls.

The contrast gains were slightly steeper in the medicated patients. The authors found no specific effect of different psychotropic substances on the PERG recording.

Two years later, Bulb et al. (18) conducted a second study in those 40 depressed patients after a successful antidepressant therapy. The authors observed a normalization of contrast gain in remitted patients. The results suggest ganglion cells dysfunction.

PVEP changes in MDD

In 2015, Bulb (19) decided to analyze PVEP test in a group of 40 patients with depression and 28 healthy controls. The patients were diagnosed according to DSM IV. At the time of the study they were taking various antidepressants. The depressed group displayed a reduced PVEP amplitude of P100 wave (about 25%) compared to the control group. Differences in latency of P100 between the groups were not described.

In patients with major depressive disorders, PVEP components could be functional markers of dysfunctions in the dopaminergic transmission (20). This is consistent with the distribution of dopaminergic signaling pathways in retinal ganglion cells and also in the occipital cortex. On the basis of these results, the authors suggested that PVEP might be used as a marker of disease state.

Fotiou et al. in 2003 (21) showed results of the PVEP examinations in fifty patients suffering from MDD according to DSM-IV criteria and depression according to ICD-10 criteria (World Health Organization, 1993) and in 20 controls. The depressed patients were divided in two subtypes of depression: melancholic and atypical type. The comparison between these two subgroups showed that N80 and P100 latencies were significantly shorter in the atypical and significantly longer in the melancholic patients, especially in the dominant right eye. The results of this study suggest that visual evoked potentials could be helpful in the differentiation of subtypes of depression.

Analysis of the data from the literature concerning ERG, PERG and PVEP in MDD strongly suggests that the retinal dysfunction is present. ERG, PERG, PVEP recordings could be functional markers of specific neurotransmitter levels in retina and indirect in brain.

Case report

Encouraged by the literature data, we decided to perform PERG test, optical coherence tomography (OCT) of the macula and optic nerve head and routine eye examination in a male patient, aged 20 with newly diagnosed major depressive disorder.

The initial routine eye examinations results were normal. The best corrected visual acuity was equal 1.0 in the right eye and 0.9 in the left eye on a snellen chart. The intraocular pressure, the anterior and the posterior segment of the eye, macular and optic nerve head structure were within normal limits.

In figure 2 we present normal OCT of the macula and optic nerve head in our patient with depression.

However, we observed abnormal PERG recording in comparison with normal values from our lab. Table II presents transient PERG examinations. Tab. IIa shows an example of normal PERG examination in the healthy patient. Tab. IIb shows an example of abnormal PERG examination in the patient with newly diagnosed depression – reduced amplitudes of P50- and N95-waves in both eyes. Implicit time (IT) of P50 and N95 were normal. These results suggest that patient with depression could have

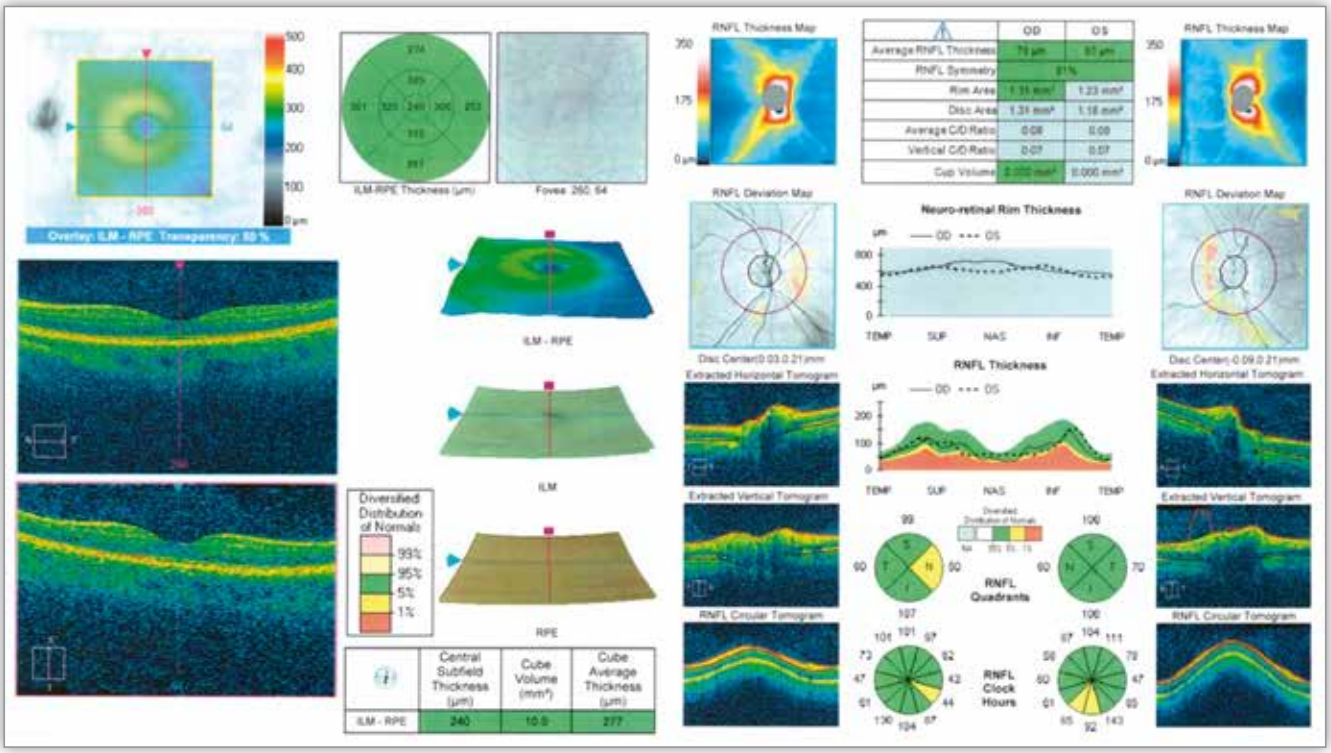
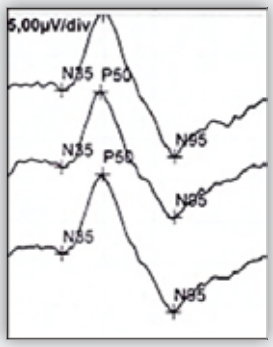
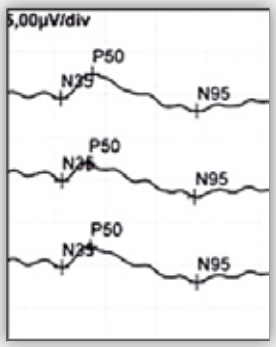
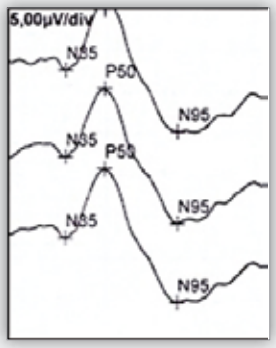
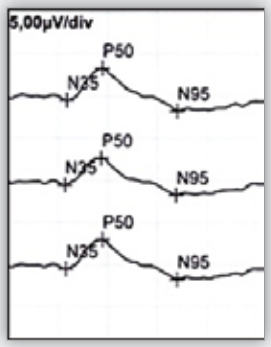
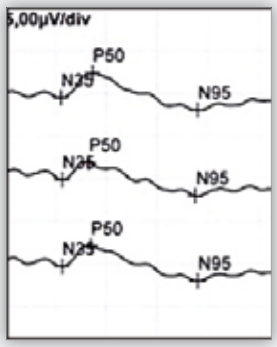
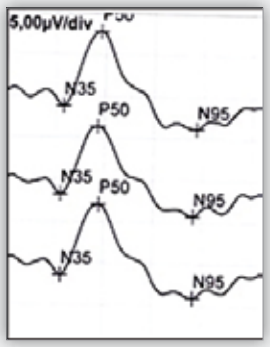
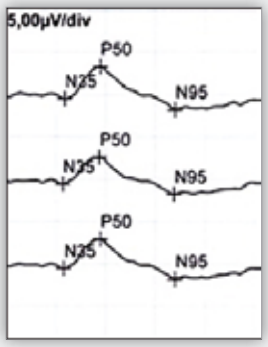
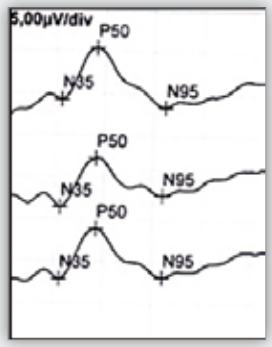


Fig. 2. Normal macular and optic nerve structure (OCT) in the patient with MDD, male, aged 20.
Ryc. 2. Prawidłowa struktura plamki i tarczy nerwu wzrokowego (OCT) u pacjenta z depresją dużą, mężczyzna, 20 lat.

a) normal PERG, healthy patient, male, age 21/ prawidłowy PERG, zdrowy pacjent, mężczyzna, 21 lat	b) PERG in a patient with major depressive disorder before antidepressant treatment, male, age 20/ PERG u pacjenta z dużą depresją przed leczeniem antydepresyjnym, mężczyzna, 20 lat
 25.0ms/div right eye/ prawe oko A P50 -9.57μV, A N95 -16.6μV	 25.0ms/div right eye/ prawe oko A P50 -2.39μV, A N95 -4.08μV
 25.0ms/div left eye/ lewe oko A P50 -8.40μV, A N95 -16.1μV	 25.0ms/div left eye/ lewe oko A P50 -3.48μV, A N95 -4.72μV

Tab. II. Transient PERG.
Tab. II. PERG typu przejściowego.

a) PERG in a patient with major depressive disorder before antidepressant treatment, male, age 20/ PERG u pacjenta z dużą depresją przed leczeniem antydepresyjnym, mężczyzna, 20 lat	b) PERG in a patient with major depressive disorder after 3 weeks of antidepressant treatment (escitalopram), male, age 20/ PERG u pacjenta z dużą depresją po 3 tygodniach leczenia antydepresyjnego (escitalopram), mężczyzna, 20 lat
 25.0ms/div right eye/ prawe oko A P50 -2.39μV, A N95 -4.08μV	 25.0ms/div right eye/ prawe oko A P50 -8.53μV, A N95 -11.1μV
 25.0ms/div left eye/ lewe oko A P50 -3.48μV, A N95 -4.72μV	 25.0ms/div left eye/ lewe oko A P50 -6.05μV, A N95- 5.74μV

Tab. III. Transient PERG.
Tab. III. PERG typu przejściowego.

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ganglion cells dysfunction, because PERG provides information about macular and retinal ganglion cells function.

Few days after first PERG examination the patient had received antidepressant treatment with escitalopram, a selective serotonin reuptake inhibitor. The second PERG test was performed when depressive symptoms slightly decreased and it was after 3 weeks of taking escitalopram. What is interesting after pharmacoteraphy PERG parameters normalized. In table III we present PERG examinations in our patient before and after 3 weeks of antidepressant treatment. Tab IIIa shows an example of abnormal PERG examination before treatment – reduced amplitudes of P50- and N95--waves in the right and left. Tab IIIb shows an example of PERG examination after 3 weeks of treatment – increased amplitudes of P50- and N95-waves in the right and left eye.

Our results in the patient with newly diagnosed depression revealed ganglion cell dysfuntion, probably as a consequence of abnormal dopamine, serotonin and/or melatonin neurotransmission. This case implies also that retinal ganglion cells function can be presumably enhanced after antidepressant pharmacoteraphy.

Conclusion

In depressive disorders visual pathway dysfunction measured by retinal electrophysiological tests are recorded. We believe that these measurements might serve as a helpful tool to investigate pathophysiology of depression and probably help to monitor pharmacotherapy. The investigations of the visual pathway function in depressive disorders will be continued in our department.

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