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Pattern electroretinography in individuals with major depression

Wojciech Lubiński[1], Hanna Grabek-Kujawa[1], Jerzy Samochowiec[2], Jolanta Kucharska-Mazur[2], Ewa Dańczura[2], Maciej Mularczyk[3]

[1]2nd Department of Ophthalmology, Pomeranian Medical University, Szczecin, Poland
[2]Department of Psychiatry, Pomeranian Medical University, Szczecin, Poland
[3]Chair and Department of Human and Clinical Anatomy, Pomeranian Medical University, Szczecin, Poland

ABSTRACT

Aim of the study: Investigation of pattern electroretinography in individuals with major depression (MD).

Material and methods: In 25 untreated individuals with MD (mean age 46.8 years) and in 25 of age- and sex-matched healthy controls (mean age 46.9 years) the following examinations were performed: visual acuity (Snellen), intraocular pressure, biomicroscopy of anterior and posterior segment of eye, macular structure (SD-OCT-Zeiss) and pattern electroretinogram (PERG-ISCEV standards). An analysis of correlation between the parameters of PERG and depression severity (the Hamilton Scale) was performed. To estimate the diagnostic power of the PERG test a receiver operating characteristics (ROC) curve was used. Obtained data were used to analyze the significance level $p < 0.05$.

Results: In both groups the clinical results and macular structure were normal. In the PERG test in the MD group a significant decrease of amplitudes of P50 (AP50) and N95 (AN95) waves ($p < 0.001$) was detected. The most frequent abnormality was the reduction of AN95 (32.0%). The Hamilton Scale correlated negatively and significantly with AN95 ($p = 0.036$). The analysis of ROC curve revealed that in the case of AP50 the cut-off point was 6.75 with sensitivity 0.960 and specificity 0.840. The area under the curve (AUC) was 0.931 ($p < 0.001$). In the case of AN95, the cut-off point was 9.0, with sensitivity 0.920 and specificity 0.920. The AUC was 0.923 ($p < 0.001$).

Conclusions: In major depression, a dysfunction of the ganglion cells in the macular region is present with the ability to be registered by PERG recording. The abnormalities in function of the ganglion cells detected in PERG examination have the potential to be an objective marker of MD.

KEY WORDS: depression, PERG, major depressive disorder, retinal function.

INTRODUCTION

The diagnosis of mental illness is often a longstanding process and its categorization is complex. That is why a search for objective biomarkers of mental illness is crucial to facilitate an accurate clinical assessment [1].

Major depression (MD) is one of the most severe mental illnesses and the fourth leading cause of disability recognized by the World Health Organization [2]. The pathophysiology of MD is multifactorial [3] and the precise mechanisms of MD development are unclear [4, 5].

There is evidence that the dysfunction of the dopaminergic system is significant in this mental illness [3, 6] and other diseases [7] and, in the case of MD, is responsible for anhedonia and loss of motivation. The retina is a neurosensory extension of the central nervous system (CNS), derives from the neuroblast cells and is important for the studies on brain abnormalities in mental illness [8]. Electrophysiological responses from the retina might be a candidate for a biomarker of different psychiatric diseases [7], such as Alzheimer's disease, schizophrenia and disorders: substance use, panic, eating, attention deficit, hyperactivity as well as depressive disorders (seasonal affective, major depression). The retinal ganglion cells are particularly interesting for indirect examination of brain activity because of their similar anatomical and functional characteristics to the cortical neurons [9]. The bioelectrical function of these cells can be measured using pattern electroretinography (PERG) [10], while their structure can be measured by optical coherent tomography (OCT). In the available literature, only a few study results have described changes in PERG recordings [11-15] and OCT [16] in individuals with MD. That is why we decided to analyze the retinal function and thickness in a newly diagnosed, untreated group of individuals with major depression.

CORRESPONDING AUTHOR
Prof. Wojciech Lubiński, 2nd Department of Ophthalmology, Pomeranian Medical University, 72 Powstańców Wlkp. St., 70-111 Szczecin, Poland, e-mail: okulistyka@spsk2-szczecin.pl; lubinski@pro.onet.pl

MATERIAL AND METHODS

In the untreated, newly diagnosed 25 individuals (50 eyes) with MD (mean age: 46.8 years, age range: 20-64 years) and in 25 (50 eyes) age-, sex-, refractive error-matched healthy controls (mean age: 46.9, age range: 22-65 years), the following examinations were performed: best corrected distance visual acuity (Snellen table), intraocular pressure (Pascal tonometer), biomicroscopy of anterior and posterior segments of the eye, macular structure (thickness: ILM-RPE average cube, average retinal nerve fiber layer and average ganglion cell layer (GCL) + inner plexiform layer (IPL – Cirrus HD OCT, Model 5000-Zeiss) and pattern electroretinogram (PERG-ISCEV standards) [10] (RetiPort Roland Consult GmbH, Germany). Monocular stimulation was used without dilation of the pupils. Central fixation was applied and appropriate refraction correction was provided to the distance between the patient's eye and the stimulus display. The patient was monitored with a TV camera and when frequent blinking or fixation losses were observed, the test was interrupted. An alternating black and white checkerboard pattern was presented on a 21″ CRT monitor with a frame rate of 70 fps. The stimulus parameters were as follows: mean width and height of the stimulus field was 15.4°, with the aspect ratio between both dimensions (i.e. screen proportion H/V) equal to 4:3; check size was equal to 0.8°; luminance for the white elements was 120 cd/m^2, mean luminance of the stimulus screen: 61 cd/m^2 and the Michelson contrast was set to 97%; temporal frequency was equal to 4.0 rps (2.0 Hz). Thread DTL-like recording electrodes (Roland Consult) were used. As a reference, a gold disc (Grass, USA) surface electrode was placed at the ipsilateral outer canthus. A separate ground electrode (gold disc, Grass) was located on the forehead at Fpz. The parameters of the recording channel were as follows: amplifiers sensitivity 20 μV/div, filter frequency bandwidth 1-100 Hz. The analysis period (sweep time) was equal to 250 ms. The artefact rejection threshold was set to 95% for the amplifier range ±100 μV and 200 sweeps were averaged. For each eye, two consecutive PERG waveforms were recorded and off-line averaged for further analysis. According to the standard, AP50 and AN95 and peak time of P50 were analyzed. Values of all parameters were compared with the age-, sex-, refractive error-matched healthy controls. The PERG tests were performed by experienced staff. The analysis of the PERG waveforms was unblinded.

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

Trait	MD individuals	Healthy controls
Number of subjects	25	25
Gender M/F	6/19	6/19
Age (years)	46.8 ±11.5	46.9 ±11.4
HAMD	25.4 ±6.8	2.27 ±1.36

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

The individuals with MD were referred from the Department of Psychiatry of the PMU with major depressive episodes according to DSM-V (Diagnostic and Statistical Manual of Mental Disorders-DSM-V) [17] and were assessed psychometrically with the Hamilton Depression Rating Scale (HAMD) [18, 19] (Table I). Individuals with MD and other psychiatric disorders, as well as ocular and systemic diseases with known influence on the retinal function, were excluded. MD individuals with poor focusing ability were also excluded. The subjects from MD and control groups did not routinely use any drugs including hypnotics and sedatives. In particular, they did not use other drugs at least three days before ophthalmological examinations. In the group with MD, five individuals smoked cigarettes, which did not have a significant influence on the obtained results.

Statistical analysis

The average value of the PERG parameters from the right and left eye from the MD and the control group were taken for further statistical analysis. The assumption of normality was checked using the Shapiro-Wilk test. With reference to the normality tests, the normal ranges were determined based on the values of parameters from the control group. In the case of normal distribution of the variables, the normal range was between –2 SD and +2 SD; in the absence of normality, the normal range was between 2.5 and 97.5 percentiles. The values of parameters between the two groups were compared. To compare the parameters between the groups, the *t*-test was used in the case of normal distribution of variables or the non-parametric Mann-Whitney *U* test in the case of non-normal distribution. An analysis of the correlation (Spearman's rank correlation test) between the parameters of PERG and the depression severity scale (Hamilton's scale) was performed. To estimate the diagnostic power of the PERG test, the receiver operating characteristics (ROC) curves were used. The results were considered as statistically significant with $p < 0.05$.

RESULTS

In the MD group and the healthy control, the clinical results were as follows: best corrected distance visual acuity – 1.0 (both groups), intraocular pressure (16.4 ±1.3 vs. 16.2 ±1.2 mmHg, $p = 0.51$) – within normal limits, biomicroscopy of anterior and posterior segment of the eye – normal, normal macular structure (cube average thickness – 275.2 ±12.6 vs. 280.3 ±9.2 μm, $p = 0.78$; average retinal nerve fiber layer thickness – 92.6 ±10.4 vs. 94.0 ±7.9 μm, $p = 0.73$; average ganglion cell layer (GCL) + inner plexiform layer (IPL) thickness – 81.13 ±7.35 vs. 81.57 ±5.00 μm, $p = 0.70$.

There was no statistically significant difference in age between the two groups ($p = 0.75$; Student's *t*-test). In the MD group, the mean HAMD score was 25.40. There was a significant difference in the psychometric measure between the MD and the control group ($p < 0.05$) (Table I).

Table II. Descriptive statistics of PERG parameters and result of the comparison between the two groups

Parameter	Group	*n*	Mean	SD	Median	Min	Max	*p*-value
AP50	MD	25	4.44	1.57	4.49	1.22	8.22	0.000*
	Control	25	9.08	3.01	8.80	2.70	15.50	
PTP50	MD	25	52.42	3.61	52.80	45.50	58.40	0.40*
	Control	25	51.65	2.80	52.00	46.00	57.70	
AN95	MD	25	6.63	2.53	6.06	2.05	14.00	0.000*
	Control	25	12.37	3.23	12.50	5.53	19.50	

A – amplitude; PT – peak time

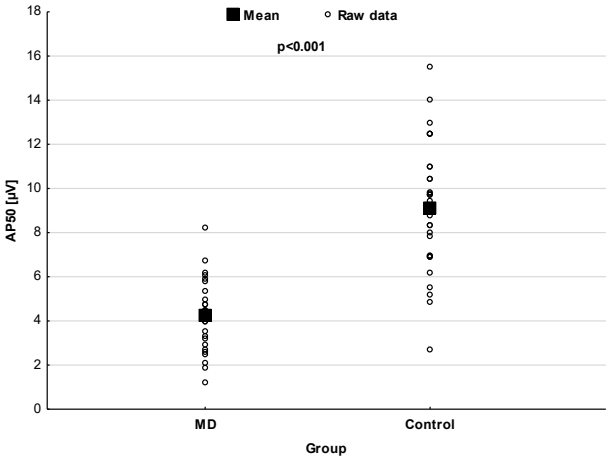

Figure 1. Values of AP50 in the two groups. The difference was statistically significant ($p < 0.001$; Student's *t*-test)

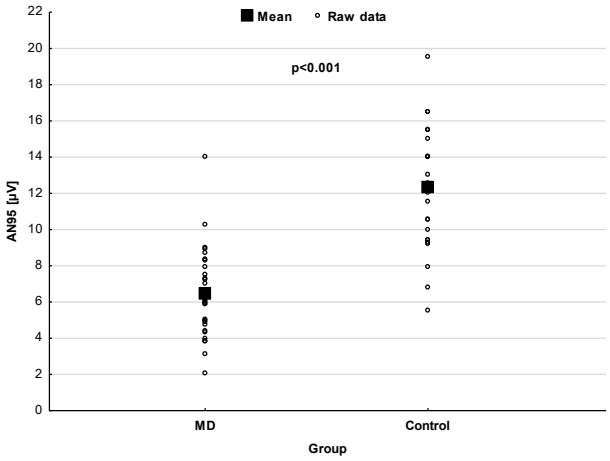

Figure 2. Values of AN95 in the two groups. The difference was statistically significant ($p < 0.001$; Student's *t*-test)

Table II presents comparisons of PERG parameters such as AP50, PTP50 and AN95 between the MD and the control group. In the MD group (Figures 1, 2), a significant decrease of P50 and N95 amplitudes ($p < 0.001$) was detected. A significant difference of PTP50 between the MD and the control group was not obtained ($p = 0.40$). Figure 3 presents abnormal PERG (reduced amplitudes of P50, N95 waves) of the MD individuals in comparison to the normal PERG recording.

From 50 eyes of 25 healthy controls, the range of normal values for measurable PERG parameters was obtained (Table III).

On the basis of the normal PERG values, the percentage of abnormal results of the analyzed PERG parameters in the MD group was estimated (Table IV).

The most frequent abnormality in PERG examination in the group of MD individuals was the reduction of AN95 (32.0%).

The Hamilton Depression Rating Scale score was negatively and significantly correlated only with the AN95 wave ($p = 0.036$), Table V, Figure 4.

Correlations between AP50 and AN95 waves and the severity of depression were also analyzed, adopting a two-degree division of MD [20]: mild and moderate (HAMD score 8-23; 10 eyes), severe (score ≥ 24; 15 eyes). No statistically significant correlation was found ($p > 0.05$) (Table VI).

ROC analyses for AP50 and AN95 were performed to assess the accuracy of the electrophysiological examination of the retinal function with reference to depression. In the case of AP50, the cut-off point was 6.75, with sensitivity 0.960 and specificity 0.840. The area under the curve (AUC) was 0.931 ($p < 0.001$). In the case of AN95, the cut-off point was 9, with sensitivity 0.920 and specificity 0.920. The area under the curve (AUC) was 0.923 ($p < 0.001$) (Figures 5, 6).

DISCUSSION

There were several reasons why we decided to perform the PERG test in newly diagnosed, untreated MD individuals. Only 3 PERG studies with a small sample size in individuals with MD are described in the literature. The study by Bubl *et al.* [11,13] indicated a reduction of contrast gain in MD individuals. The decrease in retinal contrast gain was correlated with the reduction of visual evoked potential amplitude [15]. In contrast, Fam *et al.* did not find an anomaly in the PERG recordings in MD individuals. It was also suggested that the PERG test might predict the state of illness and may be a valuable tool for monitoring the progression of illness and treatment success [13]. In the above-mentioned studies the steady-state PERG recordings were performed which were linked mainly to the function of the ganglion cells. In our study, transient PERGs (ISCEV standards) [10] were recorded and made it possible to

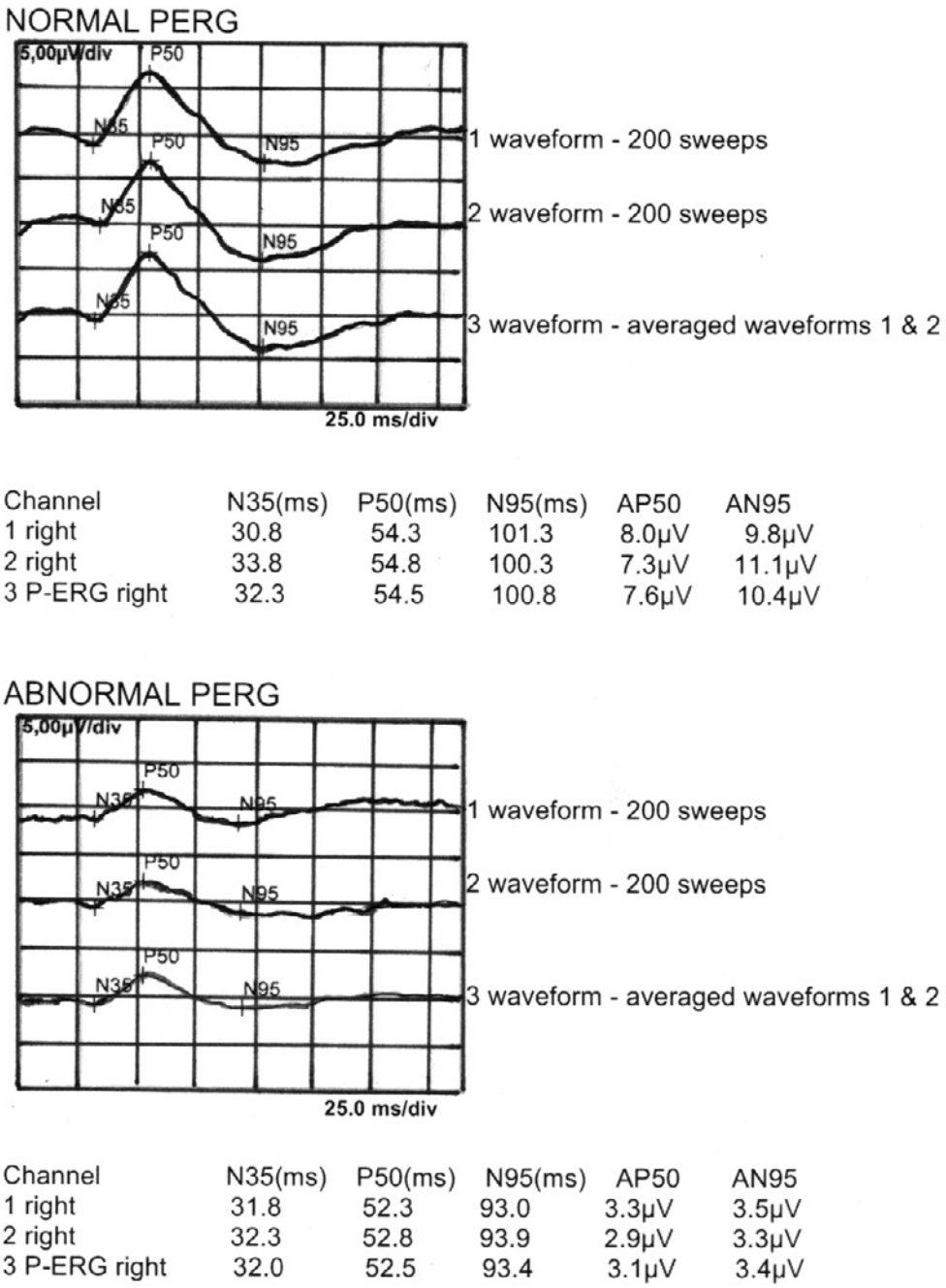

Figure 3. Example of PERG recording from right eye of 20-year-old newly diagnosed MD male with reduced AP50 and AN95 (below) in comparison to normal PERG from age- and sex-matched control (above)

measure not only the function of the ganglion cells (N95 wave) in the macular region but also, in part, the macular photoreceptors (P50 wave). We did not perform measurements of the contrast gain in the PERGs. We wanted to check whether standard ISCEV PERG recordings are useful in detection of central macular dysfunction of the retina in individuals with MD.

Our study results strongly suggest that in individuals with diagnosed and untreated major depression, mainly retinal ganglion cell dysfunction is present without other signs of ocular pathology and can be registered by ISCEV PERG recordings (Table II, Figures 1-3). Significant reduction of AP50 suggested possible functional abnormalities also in the macular photoreceptors. When separated eyes of MD individuals were compared to age- and sex-matched normal values (Table III) of PERG examination, significant abnormalities in all measurable parameters were detected. The most frequent feature in PERG recording was the reduction of AN95 (Table IV). There was a significant correlation between AN95 and the Hamilton's Scale score (Table V, Figure 4).

In our study, the lack of correlation between AP50 and AN95 waves, mild and moderate as well as severe depression suggested that ISCEV standard PERG, opposite to the PERG

Table III. Results of the Shapiro-Wilk test and normal range for PERG parameters based on healthy eyes of the control group (n= 50)

Parameter	W test	*p*-value	Range of norm
AP50	0.98	0.47	2.94-15.33*
PTP50	0.97	0.16	46.19-57.34*
AN95	0.98	0.67	5.43-19.23*

Table IV. Frequency of abnormal PERG parameters in eyes of individuals with MD

Parameter	*n*	%
AP50	5	20.0
ITP50	2	8.0
AN95	8	32.0

Table V. Results of the correlation between PERG parameters and the values of the Hamilton Depression Rating Scale (n = 25)

	AP50	PTP50	AN95
Hamilton scale	–0.11	0.03	–0.35
p-value	0.59	0.90	0.036

Table VI. Correlation between the AP50 and AN95 waves and severity of depression (n = 25)

Parameter	Spearman's R	*p*-value
AP50	–0.05	0.78
AN95	–0.10	0.62

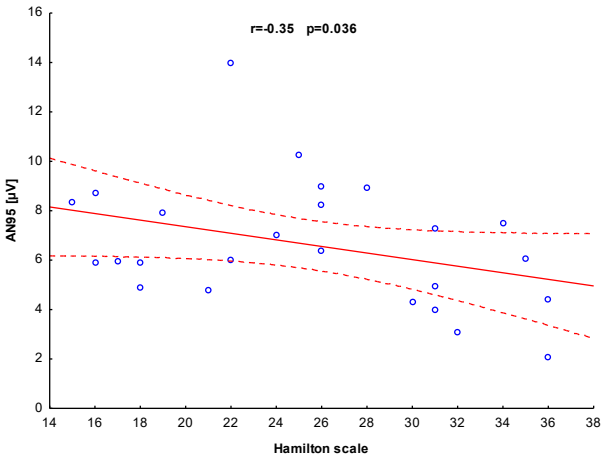

Figure 4. Scatterplot of AN95 and Hamilton's scale

contrast gain [13], is not useful in estimating MD severity using the above-mentioned division (Table VI). This is a limitation of ISCEV standard PERG in comparison with low contrast PERG in evaluation of ganglion cell function in MD illness.

ROC curve analysis revealed high sensitivity and specificity of AN95 and AP50 waves to detect MD in patients (Figures 5, 6). The ROC curves, for both PERG amplitudes, indicated a high predictive ability of the electrophysiological examination to discriminate ganglion cell dysfunction in depression from a healthy one. According to the classification suggested by Hosmer *et al.* [21], the obtained results were outstanding. Nevertheless, comparable studies using similar parameter evaluation methods are needed. In the available literature, the ROC curve was used for estimation of sensitivity and specificity of PERG contrast gain [11] and was equal to 77.5% and 92.5%, respectively. It is not possible to compare it precisely with our ROC curve results due to the difference in PERG methodology used.

Previous study results revealed that PERG contrast gain is a good indicator of dopamine neurotransmission in MD [11-13] and also another psychiatric disease, Parkinson's disease [22]. Our results in the present study strongly suggested that not only the PERG contrast gain but also the ISCEV standard PERG obtained with high contrast (97%) can register retinal dysfunction due to the monoamine neurotransmission abnormalities in individuals with MD. In our study, the obtained significant reduction of N95 wave amplitudes was a marker of abnormal retinal ganglion cell function. The reduction of P50 wave amplitude may also indicate macular photoreceptor dysfunction [23] induced probably by abnormal activation of D2 receptors by dopamine. It is known from other study results that in the photoreceptors dopamine acting via D2 dopamine, the receptors decrease the cAMP concentration, suppress melatonin synthesis and regulate the conductivity of gap junctions between the rods and the cones, depending on the phase of the light cycle [24].

In the past, in individuals with MD, retinal function was also analyzed using full field electroretinography (ERG) and the results are inconclusive. In some studies, in the ERG test significant differences between the MD individuals and healthy subjects were not observed [12, 14, 25]. In contrast, in the largest study (n = 200) Hébert *et al.* [26] observed a prolonged cone b-wave and reduced rod/cone a-waves in medicated and unmedicated MD individuals compared with the controls.

More conclusive results were obtained in seasonal affective disorder. In this case, the ERG was useful in estimation of the state of the disease and also in prediction of treatment effectiveness [27].

In our study with MD individuals, the retinal structure (RNFL and GCL + IPL thickness) was also examined by the OCT test and compared with the controls.

We did not find significant changes in GCL + IPL and RNFL thickness in the MD group. This can be expected, because our study group consisted of individuals with early MD stages at which, due to neurotransmitter deficiency, ganglion cell dysfunction was detected without the presence of structural changes.

In the past, in individuals with MD, the retinal structure using the OCT test was investigated in four case control stud-

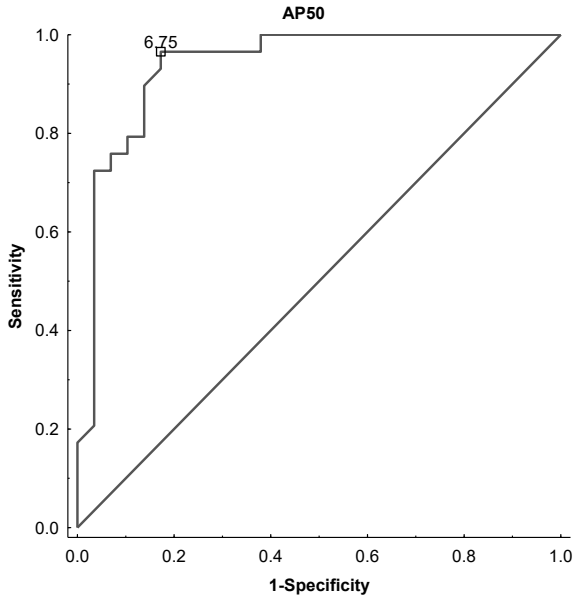

Figure 5. ROC curve of AP50 in reference to depression as a dependent variable. The cut-off point was 6.75 with sensitivity of 0.960 and specificity of 0.840. The area under the curve (AUC) was 0.931 ($p < 0.001$)

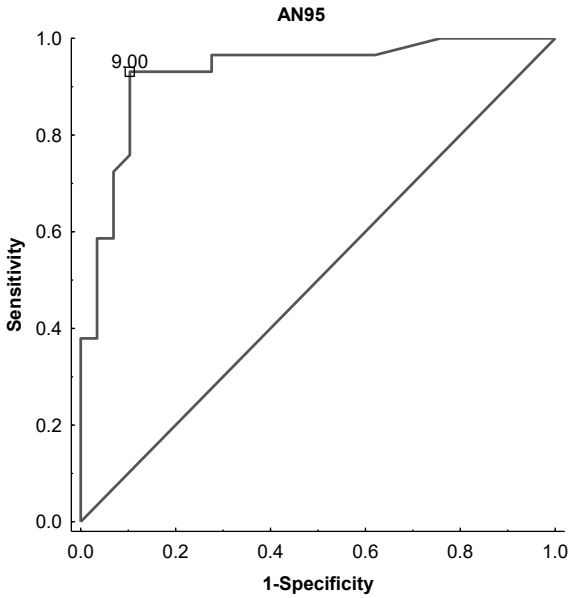

Figure 6. ROC curve of AN95 in reference to depression as a dependent variable. The cut-off point was 9.0 with sensitivity of 0.920 and specificity of 0.920. The area under the curve (AUC) was 0.923 ($p < 0.001$)

ies with mixed results [28-31]. Kalenderoglu *et al.* [28] found significantly reduced GCL, IPL, global and temporal superior RNFL thickness in the recurrent MD individuals compared to the first episode individuals, and in all the MD individuals compared with the controls. This decrease was more severe in individuals with more severe illness. However, other research groups [29-31], comparing MD individuals with healthy controls, found no statistically significant differences in the OCT measures.

LIMITATION

Limitations of the present study are the small number of cases, unblinded examination of the MD individuals as well as possible undetected poor focusing of the fixation point during the PERG test providing abnormal results. In addition, due to technical reasons, we were not able to calculate photoreceptor layer thickness in OCT examination automatically using available HD-OCT equipment and compare the results with the P50 wave in the PERG test from the MD group.

CONCLUSIONS

In conclusion, the present study results are additional evidence that in patients with MD, normal routine ophthalmological examinations and retinal thickness, dysfunction of mainly ganglion cells in the macular region is present based on ISCEV standard PERG. The abnormalities in ganglion cell function detected in PERG recording has the potential to be an objective marker of MD. Future studies using the same methodology with a larger sample size are necessary to confirm this conclusion.

DISCLOSURE

The authors declare no conflict of interest.

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