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COMBINED ELECTROPHYSIOLOGICAL METHOD FOR EARLY DIAGNOSTICS OF FUNCTIONAL CHANGES IN THE VISUAL ANALYZER IN PATIENTS WITH DIABETES MELLITUS WITHOUT DIABETIC RETINOPATHY

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Abstract

The aim of the study is to explore objectively the function of the visual analyzer by simultaneously performed pattern electroretinography (PERG) and visual evoked potentials (PVEPs) in patients with diabetes mellitus (DM) without diabetic retinopathy, detected with the specialized ophthalmological exams. A group of 112 people (224 eyes) were studied. The control group consisted of 47 healthy controls (94 eyes). The patients with DM were 65 (130 eyes). Two types of objective electrophysiological (EF) methods were performed - PERG and PVEPs. The main variables that were considered in the results analysis were the latency and amplitudes, reflecting the configuration of the wave forms. The comparative analysis of components of the two EF studies between patients with DM without DR and controls demonstrated significant differences. The two groups statistically differed in P50 amplitude and latency of PERG. PVEPs had also statistically significant prolonged latencies and lower amplitudes in the diabetic group. EF studies could be used as an objective method for registration of early changes in the visual analyzer's function associated with DM. Also, to monitor the dynamics of changes as they are non-invasive, harmless, faster and

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less expensive than fluorescein angiography (FA), optical coherent tomography (OCT) and angio-OCT.

Key words: pattern electroretinography, visual evoked potentials, diabetes mellitus

Introduction. According to the latest definition of the International Expert Committee diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia which is a result of impaired insulin secretion, decreased insulin action, or both. According to the World Health Organization (WHO) by 2014 at least 422 million people worldwide (8.5% of the adult population) suffer from DM. This number is expected to increase, by 2030 their number will reach 522 million [1].

Usually we speak about diabetic changes in vision when we can detect ophthalmoscopic or angiofluorographic visible changes in the retina so-called diabetic retinopathy (DR). It is a manifestation of microangiopathy. But from a functional point of view, the retina is a vascularized neuronal tissue. In addition, in order to have a clear image, it is necessary for the entire visual path to the cortex to function properly. This is the reason why the modern concept of retinopathy involves retinal neurodegeneration and microvascular complications [2].

Many studies have demonstrated the role of electrophysiological (EF) methods for early detection and monitoring the functional changes in the visual analyzer (VA) in diabetic patients. Electroretinography (ERG) and visual evoked potentials (VEPs) are used for objective studying the VA function. ERG is used to diagnose and monitor a number of retinal diseases, and VEPs depend on the functional integrity of the entire visual pathway from the retina through the optic nerve, the optic tract, the optical radiation to the visual cortex [3].

The aim of the study is to explore objectively the VA function by simultaneously performed pattern electroretinography (PERG) and visual evoked potentials (PVEPs) in patients with diabetes mellitus (DM) without diabetic retinopathy, detected with the specialized ophthalmological exams.

Material and methods. A group of 112 people (224 eyes) was studied. The patients with DM were 65 (130 eyes) with an average age of 41.5 years (from 28 to 54) – 30 males and 35 females. In this group, 31 patients had type 1 DM and 34 – type 2 DM. The mean duration of DM was 7.4 years (from 3 to 12). All diabetic patients were in normoglycemic condition and had not DR, detected with the specialized ophthalmological exams. They had normal best corrected visual acuity.

Controls for the EF studies were 47 healthy individuals (94 eyes) with normal best corrected visual acuity and without any known ophthalmic or neurological disease as well as other systemic diseases. The control group included individuals of an average age of 38.57 years (from 27 to 51 years) – 21 males and 26 females.

The patients were examined clinically by full ophthalmologic examination,

FA, electrophysiologically by PERG and PVEPs. Laboratory tests for blood sugar level, HgA1c and lipid levels were performed additionally.

Inclusion criteria: Patients with type 1 and type 2 diabetes without DR, detected with the specialized ophthalmological exams with normal best corrected visual acuity.

Exclusion criteria: Glaucoma, senile macular degeneration, advanced cataract, vascular eye diseases, optic neuritis, amblyopia. Multiple sclerosis, Parkinson's disease, epilepsy, dementia, and brain tumour were excluded by the neurologists.

Methodology of electrophysiological studies. All studies of PERG and PVEPs were performed in a specially equipped certified electrophysiological laboratory (light and sound insulated). Standardized four channels equipment "Neuro-MEP 4" produced by Neurosoft Company, was used. The investigation was performed with a three-channel recording with equipment adjustments according to the latest published ISCEV standards for PERG (2013) and PVEPs (2010) [4, 5]. The main variables that were considered in the analysis of PERG and PVEPs in the present study were latency (L) and amplitudes (A), reflecting the configuration of the wave forms.

The patients were in a sitting position. The distance to the monitor was 100 cm. The patients were examined with the appropriate optical correction for that distance if it was necessary. The study was performed under mesopic conditions, identical in all patients, without mydriasis We used a classic cathode stimulator with a contrast-reversing pattern from black to white and vice versa with an equal number of black and white squares in a checkboard, with standard individual width of 1° for a stimulating field of 30° for paracentral stimulation and 0.25° for a stimulating field of 15° for central stimulation (Fig. 1).

Method of PERG. The study was binocular. The active electrode (Corn) was placed in contact with the bulbus after local topical anesthesia. The reference electrode (A) was placed on the ear, and the ground electrode on the right wrist. The generated signal was passing through a standardized amplifier then it was digitalized and saved. At least two of each stimulus were made to confirm the reproducibility of the obtained curves (Fig. 1). The results analysis was based on the latency and amplitudes of components N35, P50 and N95.

Method of PVEPs. The PVEPs study was performed binocularly, simultaneously with PERG, using one channel for recording PVEPs by an active electrode placed on the scalp at a standard location according to the International System 10/20 – above the visual cortex at Oz and reference electrode at Fz mid-frontal (Fig. 1). We analyzed the latency and amplitudes of components P50, N75, P100, N145 and P200.

Results. Both groups were subjected to a variation analysis to determine the reference values of the components of PERG and PVEPs and their variability. In the comparative analysis between patients with DM without DR and controls

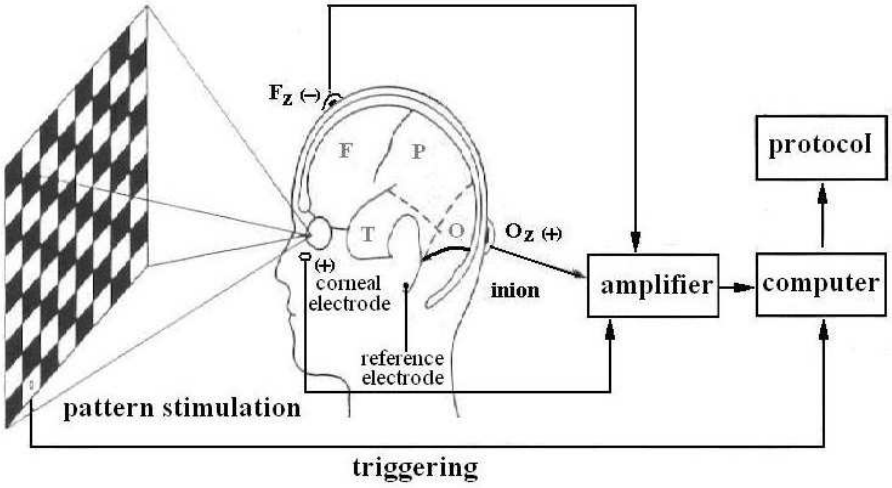

Fig. 1. Block-scheme of methods of stimulation, conduction and averaging

the following was observed:

A statistically significant difference in the PERG latency was found for component P50 at 50% of the electrode positions. The latencies of the diabetic patients were longer than those of the controls. Significant differences were found for amplitude component P50-N95 for all electrode positions. This is the amplitude that is typically measured in this study and is considered to be most informative. Significant differences also occurred in amplitude component N35–P50 at 50% of the electrode positions. The amplitudes of the diabetic patients were lower than those of the healthy subjects (Table 1).

We compared the components of PVEPs between the two groups and obtained the following results: Significant differences were found in the latency of all components at all electrode positions (except component N145) at 15°. At 30° the latency components P50 and P200 significantly differed from the controls. The amplitude analysis demonstrated significant difference in component N75–P100 at 15° (Table 2).

We compared the components of EF studies according to the type of DM and found significant differences in the latency and amplitudes between the groups with type 1 and type 2 DM. The latency of type 2 diabetic patients was statistically longer. The diabetic patients with type 2 DM had significantly reduced amplitudes also.

Discussion. The most important observation was that the group with DM without DR statistically differed from controls by P50 component amplitude of PERG- lower in diabetic patients. In 50% of the electrode positions a statistically significant difference in the latency was found in component P50 also. It is considered that P50 reflects the activity of the retinal ganglion cells and a lit-

Table 1

Comparative analysis between patients with DM without DR and controls according to the components of PERG

				Controls ($n = 47$)		DM without DR ($n = 65$)		P
Electrode position	Component	Side of stimulation	Stimulus	$\bar{X}$	SD	$\bar{X}$	SD	
L								
LCorn-A	P50	both	15°	52.76	4.57	57.08	13.38	0.133
RCorn-A	P50	both	15°	52.73	3.84	59.18	12.25	0.002
LCorn-A	P50	both	30°	50.37	3.91	54.67	7.78	0.008
RCorn-A	P50	both	30°	51.53	3.83	53.98	8.17	0.090
A								
LCorn-A	N35-P50	both	15°	2.02	0.86	1.72	0.72	0.151
	P50-N95			4.09	1.95	3.09	1.45	0.005
RCorn-A	N35-P50	both	15°	1.96	0.55	1.56	0.81	0.005
	P50-N95			4.13	1.65	3.19	1.60	0.026
LCorn-A	N35-P50	both	30°	2.20	0.94	1.69	0.82	0.033
	P50-N95			4.45	1.87	3.42	1.56	0.005
RCorn-A	N35-P50	both	30°	2.20	0.65	1.93	0.92	0.099
	P50-N95			4.54	1.59	3.52	1.72	0.005

$\bar{X}$ – mean, SD – standard deviation

tle more distal, but it has not been established exactly where [6]. P50 changes compared to controls suggest initial neuronal dysfunction, despite the absence of signs of vascular damage in the retina. The prolonged latency in diabetic patients demonstrates neuronal conduction delay. In the available literature a few studies have been performed, which prove the early EF changes in patients with DM without DR. Changes in PERG amplitude and latency have been identified by several authors [7,8]. Changes in ERG in diabetic patients without DR, similar to ours, have been identified by other investigators using different ERG techniques [9,10]. But there has been opposite opinion also, that PERG changes occur only in patients with DM with signs of DR [11,12]. The authors believe that PERG could be used as a screening for DR progression. Very few authors in the available literature have performed both studies of the same patients. Some of them have concluded that changes in PERG are observed at the beginning of DM without presence of DR, and that changes in PVEPs occur earlier than those in PERG in both types of diabetes [13]. Other researchers have also performed PERG and PVEPs and have found changes in patients without DR and normal visual acuity only in PVEPs – reduced amplitude and delayed latency of P100 component [14].

Table 2

Comparative analysis between patients with DM without DR and controls according to the components of PVEPs

				Controls ($n = 47$)		DM without DR ($n = 65$)		P
Electrode position	Component	Side of stimulation	Stimulus	$\bar{X}$	SD	$\bar{X}$	SD	
L								
Oz-Fz	P50	both	15°	54.39	4.41	59.47	8.87	0.002
	N75			79.33	4.02	82.49	6.02	0.008
	P100			103.59	4.66	108.72	10.50	0.009
	N145			146.97	11.34	150.54	16.96	0.216
	P200			209.62	12.74	225.28	21.21	< 0.001
Oz-Fz	P50	both	30°	50.36	6.95	53.70	6.49	0.020
	N75			74.50	4.35	74.96	4.87	0.730
	P100			100.03	5.06	101.19	6.60	0.718
	N145			139.09	12.14	140.46	15.66	0.959
	P200			209.82	19.91	221.68	22.12	0.010
A								
Oz-Fz	P50-N75	both	15°	7.93	4.49	6.47	4.35	0.078
	N75-P100			15.71	6.81	12.76	5.86	0.032
	P100-N145			12.43	5.49	10.69	4.81	0.106
	N145-P200			6.93	3.26	6.18	3.41	0.182

In our PVEPs studies, we found statistically significant differences in the latency of all components (except N145) in all electrode positions at 15°. At 30° – for components P50 and P200 only. Significant difference in the amplitudes was found for component N75-P100 at 15°.

Our conclusion was that the central electrode positions were more sensitive, with a higher number of significantly different values between the two groups. Such a result has also been found by other authors in PVEPs [15]. In the recent years, it has been suggested that the peripheral stimulation test is more sensitive [16]. Progressive VEPs delay, as well as reduced amplitudes, which mainly demonstrate changes in the visual pathway, have been described by other authors also [17,18]. Other investigators have not detected changes in VEPs in diabetic patients without DR but only in those with DR [19].

We assume that hyperglycemia and the activation of the alternative polyol pathway of glucose metabolism lead to structural changes in neurons – neuronal degeneration, impaired axonal transport followed by nerve dysfunction. The products of glycation around the neurons lead to segmental demyelination, disturbed

axonal transport and delayed neuronal conduction. Vascular changes in vasa nervorum further increase the oxidative stress on the nerve cells. EF studies detect subclinical affection of the visual pathway.

In the diabetic patients group the asymmetrical involvement of the two eyes was observed – in some of the electrode positions in one eye there was a significant difference with controls while the difference in the fellow eye was much smaller or sometimes non-significant.

Conclusion. The comparative analysis of the components of the two EF studies between patients with DM without DR and controls demonstrated significant differences, indicating that they could be used as an early detector of VA function changes associated with DM. Our data demonstrate objectively that the neurodegenerative changes occur very early in diabetic patients before any signs of DR. Therefore the functional changes in VA in diabetic patients develop before the structural damage.

We believe that additionally to the detecting of early changes, EF methods could also be used for monitoring the dynamics of changes in VA function in DM [12]. They are non-invasive, harmless, faster and less expensive than FA, OCT and anglo-OCT, repeatable and objective. The biggest disadvantage of these methods is their limited use in clinical practice due to the lack of equipment and the insufficient training of young doctors for their effectiveness in practice for diagnosing and monitoring the VA function in a number of ophthalmic and neurological diseases.

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