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Use of Neurophysiological Methods in Early Diagnosis of Primary Open-Angle Glaucoma

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Abstract.

Glaucoma is a leading cause of irreversible vision loss. The study of structural and neurophysiological processes of the upper divisions of the visual analyzer in patients with primary glaucoma helps in detecting primary structural lesions in this pathology. The investigation of brain evoked potentials provides the most important information about the processes in the visual cortex of the brain, and the study of visual evoked potentials (VEP) provides us with the most valuable information. When performing a comparative evaluation of VEP responses for each eye good correlation between the obtained VEP parameters and the results of Humphrey perimetry is observed. It is well known that in clinical practice there are no specific neurophysiological tests for diagnosing glaucoma. However, neurophysiological examinations detect the changes which are asymptomatic for a remarkably long period of time until the occurrence of clinical manifestations quite often being especially important for early diagnosis of any glaucomatous process. ***The objective*** of the research was to study the appropriateness of using neurophysiological methods for early detection of primary open-angle glaucoma. ***Materials and methods.*** Complex clinical and neurophysiological study of both eyes of 186 patients (358 eyes) with primary open-angle glaucoma (POAG) and those whose diagnosis was still not clarified was performed at the Filatov Institute of Eye Diseases and Tissue Therapy of National Academy of Medical Sciences of Ukraine. The main group included 81 (51.92%) females and 75 (48.08%) males with different stages of the glaucomatous process. The average age of patients was 56.8±4.26 years. Neurophysiological methods - VEPs (both flash and checkerboard type) - were used to diagnose the pathological condition. The study of VEPs was performed using a RETI-scan multifocal ERG system (Roland Consult, Wiesbaden, Germany). ***Results.*** In patients with suspected glaucoma latency values of the N75 and P100 remained within the normal range in 96.1% ($p<0.05$) and 86.2% ($p<0.05$) of cases, respectively. When examining the N75-P100 and P100-N135 peaks an increase in the amplitude above the normal range (according to the standards of the equipment and the laboratory where the research was conducted) was observed in 78.6% ($p<0.05$) and 65.5% ($p<0.05$) of cases, respectively. The threshold for electrically induced phosphenes was within normal limits (65.61±7.32 Hz); the lability of the visual analyzer (phosphene electrical stimulation) increased by 13.63%, $p<0.05$ compared to the control group. In patient with mild glaucoma latency values of the N75 and P100 remained within the normal range in 86.4% ($p<0.05$) і 81.2% ($p<0.05$) of cases, respectively. When examining the N75-P100 and P100-N135 peaks an increase in the amplitude above the normal range was observed in 65.15% ($p<0.05$) and 58.14% ($p<0.05$) of cases, respectively. The threshold for electrically induced phosphenes was within normal limits (71.69±9.08 Hz); the lability of the visual analyzer (phosphene electrical stimulation) reduced by 9.63%, $p<0.05$ compared to the control group. In 78.4% of patients with suspected glaucoma the diagnosis of primary open-angle glaucoma was confirmed by clinical investigations 6 months and 1 year after the examination. Additional neurophysiological methods revealed more pronounced changes in the glaucomatous process in 34.80% of patients with mild glaucoma. They were included to the group of patients with advanced glaucoma. Optimal treatment tactics was applied.

Problem statement and analysis of the recent research

Glaucoma is a leading cause of irreversible vision loss [1, 2, 3]. It is not only one of the most common and serious eye diseases worldwide but one of the most complex in terms of the pathogenesis and diagnostics. Some scientists consider the term "glaucoma" to include a wide range of conditions. They suggest it to be not a specific disease, but a group of diseases having similar signs [4]. Until recently, progressive changes in the optic nerve head and narrowing of the visual field were considered as the main signs of glaucoma. Glaucoma typically results in irreversible bilateral vision loss. It is the second leading cause of blindness worldwide [2]. The systemic influence and local risks have a great influence on the development of the disease, however, the pathophysiology of glaucoma remains insufficiently studied. The only way to overcome this disease is early detection of risk factors for the development of glaucoma as well as timely treatment of the disease [3, 5].

The study of structural and neurophysiological processes of the upper divisions of the visual analyzer in patients with primary glaucoma helps in diagnosing primary structural lesions in this pathology. A number of studies indicated structural brain abnormalities in patients with primary glaucoma. Microscopically, marked atrophy with significant loss of axons was observed in the optic nerve. Macroscopically, the lateral geniculate nucleus (LGN) reduced in size indicating significant loss of neurons due to LGN degenerative changes. In the visual cortex of the brain in patients with primary glaucoma a reduction the thickness of the cellular layer was observed. Marked cortical degeneration was observed at the level of the calcarine sulcus [5, 6].

Recently, much attention has been paid to the study of the retina in patients with primary open-angle glaucoma. Accelerated death of ganglion cells and their axons which comprise the optic nerve as well as their involvement in the pathological process of neuroglia which provides nutrition for the optic nerve are considered as the main components of the glaucomatous process [4, 7, 9]. The latest methods of clinical investigations including scanning laser polarimetry and optical coherence tomography (OCT) measure structural changes in different functional levels of the retina and the optic nerve [10].

VEPs are not a specific method for studying the glaucomatous process; however they allow us to study the processes in the visual cortex of the brain and at different morphofunctional levels of the retina as well as to detect any pathological changes in the preclinical stage of the disease that is very important for studying the pathogenesis and early diagnostics [6]. Foreign and Ukrainian ophthalmologists pay insufficient attention to diagnostics of pathological changes in the retina during the clinical course of the disease in patients with different stages of primary open-angle glaucoma [5, 7, 9].

The objective of the research was to study the appropriateness of using neurophysiological methods for early detection of primary open-angle glaucoma.

Materials and methods

Complex clinical and neurophysiological study of both eyes of 186 patients (358 eyes) with primary open-angle glaucoma (POAG) and those whose diagnosis was still not clarified was performed at the Filatov Institute of Eye Diseases and Tissue Therapy of National Academy of Medical Sciences of Ukraine. The main group included 81 (51.92%) females and 75 (48.08%) males with different stages of the glaucomatous process. The average age of patients was 56.8±4.26 years.

All patients underwent visometry, tonometry, tonography, refractometry, biomicroscopy, direct and indirect ophthalmoscopy, computer perimetry with the Humphrey Field Analyzer (HFA; Carl-Zeiss Meditec, Dublin, CA, USA), and OCT with the use of SOCT Copernicus (Optopol, Zawiercie, Poland). The lability and the threshold for electrically induced phosphenes were also determined in all patients.

Neurophysiological methods - VEPs (both flash and checkerboard type) - were used to diagnose the pathological condition. When determining the peak amplitudes and latencies obtained from all leads interocular difference in these data was analyzed. The study of VEPs was performed using a RETI-scan multifocal ERG system (Roland Consult, Wiesbaden, Germany). To characterize the pathological process there were considered changes in the latency of VEPs elicited by checkerboard stimuli, changes in the latency of the N75, P100 and N135 peaks, changes in the amplitude of the N75-P100, P100-N75, VEPs elicited by a flash, changes in the peak latencies of N1, P1 as well as the P1-N1 amplitude. The above-mentioned parameters are important for evaluating VEP dynamics as well as for evaluating the degree of progression of the pathological process.

The main group included 158 (298 eyes) patients being divided into 4 subgroups: subgroup I included 42 (84 eyes) patients with pre-glaucoma; subgroup II included 48 (96 eyes) patients with mild glaucoma; subgroup III comprised 36 (65 eyes) patients with advanced glaucoma; subgroup IV included 30 (53 eyes) patients with severe glaucoma.

Subgroup I included patients with suspected glaucoma. The results of reoophthalmography, OCT, tonometry, tonography (difference in interocular or daily tonometry was 3-4 mm higher) in this group of patients differed from normal values by one or several indicators.

Patients with end-stage POAG and high-degree emmetropia were excluded from the study.

The control group included 30 patients with mild-degree and moderate-degree emmetropia without POAG and was compared with the main group by gender, age, and other somatic diseases (Table 1).

Optic nerve disorders, macular dystrophy, hypertensive retinopathy, acute and chronic disorders of cerebral circulation, clouding of the optic media, diabetes mellitus, brain injury were not observed among patients of the main and control groups.

VEP test results were compared with the results obtained in the control group, literature data [11] and the standards of the equipment and the laboratory where the research was conducted as in clinical practice there are no recognized data standards.

The obtained data were processed using Statistica 10 software, the average values of standard deviation, reliability of the differences – $p > 0.05$ (paired test with bilateral distribution), the Mann-Whitney U test, the chi-square coefficient and the Spearman's correlation coefficient.

Results and discussion

156 (298 eyes) patients of the main group and 30 (60 eyes) patients of the control one underwent clinical examinations as well as neurophysiological ones (VEPs; both flash and checkerboard type).

There was no statistically significant difference in gender, age and other somatic diseases between patients of both groups (Table 1).

Table 1

General characteristics of patients of both groups

Parameters	Main group,% (n)	Control group,% (n)
Age	56.8±4.26	53.4±5.82*
Gender - females - males	 51.92 48.08	 53.6* 46.4*
Angiopathy	68.20%	70.40%*
Mild hyperopia	17.70%	19.60%*
Moderate hyperopia	12.30%	14.60%*

Moderate myopia	8.90%	9.30%*
Mild myopia	12.80%	11.10%*
Presbyopia	48.30%	45.40%*

Notes:
n – number of eyes;
*p – statistically significant difference between the main group and the control one, p>0.05.

Clinical characteristics of patients of both groups which are criteria for the diagnosis and clinical course of the disease are presented in Table 2. In patients with advanced glaucoma and those with severe glaucoma there was a statistically significant difference in the width of the optic disk excavation, intraocular pressure (IOP) and perimetric parameters. Statistically significant difference in perimetric parameters was observed only between patients with mild glaucoma and those with advanced glaucoma as well as between patients with mild glaucoma and those of the control group. There was no statistically significant difference in any parameters between patients with pre-glaucoma and those with mild glaucoma as well as between patients with pre-glaucoma and those of the control group.

Table 2

Characteristics of functional state of visual analyzer in patients with different stages of primary open-angle glaucoma

Parameters	Pre-glaucoma	Mild glaucoma	Advanced glaucoma	Severe glaucoma	Control group
Uncorrected visual acuity	0.61± 0.34	0.55±0.35	0.44±0.36	0.37±0.39 ***	0.65±0.23
Corrected visual acuity	0.89±0.10	0.76±0.22	0.60±0.12	0.45±0.37 ***	0.86 ± 0.12
IOP, mm Hg	20.34±2.69	20.72±2.58	23.12±2.65***	26.0±2.82***	18.06±1.41
Width of the optic disk excavation, min, mm	0.42±0.08	0.45±0.05	0.55±0.07 ***	0.71±0.06 ***	0.43±0.03
Retinal sensitivity, MD, dB	0.18±1.21	1.96±2.61* ***	7.63±3.68** ***	21.2±4.27 ***	0.32±1.08
Visual Field Index, %	0.99±0.01	0.93±0.03* ***	0.81±0.09** ***	0.34±0.17 ***	0.98±0.02
Lability of the visual analyzer (phosphene electrical stimulation), Hz	40.01±3.89 ***	31.82±1.65* ***	27.41±1.41 ** ***	20.52±0.75 ***	35.21±0.75

Notes:
n – number of eyes;
*p – statistically significant difference between patients with mild glaucoma and those with advanced glaucoma, p>0.05;
**p - statistically significant difference between patients with advanced glaucoma and those with severe glaucoma, p<0.05;
***p - statistically significant difference between patients of the main group and those of the control one, p<0.05.

The analysis of data obtained from patients with different stages of the glaucomatous process was made using the chi-square coefficient.

In patients with suspected glaucoma latency values of the N75 and P100 remained within the normal range in 96.1% ($p<0.05$) and 86.2% ($p<0.05$) of cases, respectively. When examining the N75-P100 and P100-N135 peaks an increase in the amplitude above the normal range (according to the standards of the equipment and the laboratory where the research was conducted) was observed in 78.6% ($p<0.05$) and 65.5% ($p<0.05$) of cases, respectively. In patients with pre-glaucoma statistically significant increase in the N75-P100 amplitude of VEP response to 60 arcsec by 140.6% as well as an increase in the amplitude of VEP response to 15 arcsec by 101.2%, $p<0.05$ was observed compared to the control group. There was no statistically significant difference in latency values of the N75, P100, N135 peaks compared to the control group. The threshold for electrically induced phosphenes was within normal limits (65.61±7.32 Hz); the lability of the visual analyzer (phosphene electrical stimulation) increased by 13.63%, $p<0.05$ compared to the control group.

In patients with mild glaucoma latency values of the N75 and P100 remained within the normal range in 86.4% ($p<0.05$) and 81.2% ($p<0.05$) of cases, respectively. When examining the N75-P100 and P100-N135 peaks an increase in the amplitude above the normal range was observed in 65.15% ($p<0.05$) and 58.14% ($p<0.05$) of cases, respectively. In patients with mild glaucoma increased N75-P100 amplitude of VEP response to 60 arcsec by 180% as well as an increased amplitude of VEP response to 15 arcsec by 166.87%, $p<0.05$ was observed compared to the control group. There was no statistically significant difference in latency values of the N75, P100, N135 peaks compared to the control group. The threshold for electrically induced phosphenes was within normal limits (71.69±9.08 Hz); the lability of the visual analyzer (phosphene electrical stimulation) reduced by 9.63%, $p<0.05$ compared to the control group.

The Mann-Whitney U test revealed that there was a statistically significant difference in latency values of the P100 ($Z = 2.33$; p-value = 0.028), amplitude of the P100-N135 peaks ($Z = 3.50$ p-value = 0.00046), amplitude of the N75-P100 peaks ($Z = 2.04$; p-value = 0.04) between patients with mild glaucoma and those with advanced glaucoma.

In 78.4% of patients with suspected glaucoma the diagnosis of primary open-angle glaucoma was confirmed by clinical investigations 6 months and 1 year after the examination. Additional neurophysiological methods revealed more pronounced changes in the glaucomatous process in 34.80% of patients with mild glaucoma. They were included to the group of patients with advanced glaucoma. Optimal treatment tactics was applied.

Considering all the above-mentioned data including changes in the characteristics of VEPs elicited by checkerboard stimuli in the early stages of the pathological process, normal values for flash VEPs and the threshold for electrically induced phosphenes in patients with pre-glaucoma, mild and advanced glaucoma as well as structural characteristics of formation of VEP responses to checkerboard and flash stimuli [11] we can conclude that changes in VEP response to pattern in patients with primary open-angle glaucoma conform to the pathological processes occurring in the retinal ganglion cells. With the progression of the pathological process there is an increase in abnormalities in the retinal ganglion cells indicating the pathogenic nature of these changes.

Conclusions

1. Neurophysiological methods – visual evoked potentials – were firstly used in clinical practice for complex examination of patients and early diagnosis of the glaucomatous process.

2. Neurophysiological criteria for early diagnosis of pre-glaucoma and mild primary open-angle glaucoma in the preclinical stage of the disease and further dynamic observation were firstly studied and determined.

3. The complex of neurophysiological parameters used for early detection of suspected glaucoma was firstly formulated including statistically significant increase in the amplitude of the

N75-P100 peaks, preservation of bioelectrical activity of the cerebral cortex when analyzing latency values of pattern VEPs, statistically significant increase in the lability of the visual analyzer (phosphene electrical stimulation), preservation of the threshold for electrically induced phosphenes.

4. The use of neurophysiological methods - pattern VEPs – is important for early detection of the disease, clarification of the diagnosis and formation of groups including people being at risk of the development of glaucoma for dispensary observation of these patients.

Prospects for further research

Prospects for further research include the study of correlation between clinical and neurophysiological parameters when using VEPs to determine criteria for progression of the pathological process in patients with primary open-angle glaucoma.

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