Доклади на Българската академия на науките
Comptes rendus de l'Académie bulgare des Sciences
Tome 75, No 8, 2022

MEDICINE

Ophthalmology

PATTERN ELECTRORETINOGRAPHY IN PREPERIMETRIC GLAUCOMA

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Received on January 6, 2020
Presented by P. Vassileva, Member of BAS, on January 28, 2020

Abstract

The aim of the study was to explore the informativeness of pattern electroretinography (PERG) as an objective method for detection of early changes in the retinal ganglion cells (RGCs) function in patients with preperimetric glaucoma. A group of 103 people was studied – 56 patients with preperimetric glaucoma and 47 healthy individuals as controls. Full ophthalmological examination, standard automated perimetry (SAP), optical coherent tomography (OCT) and PERG were performed. The main variables that were considered in the results analysis were the latency (L), amplitudes (A) and amplitude ratio (AR), reflecting the configuration of the wave forms. Statistical analysis was performed with IBM SPSS Statistics 23.0 statistical package. The comparative analysis between the PERG components values of patients from both groups demonstrated significant differences in L of P50 and N95 in central stimulation and in N95 in paracentral stimulation. L of the glaucoma patients were longer than those of the controls. In PERG A significant difference was found in component N35-P50 in central stimulation and in AR N35-P50/P50-N95 in paracentral stimulation. The PERG A of glaucoma patients were lower than those of the healthy subjects. These results correlated with the significant differences in the macular RNFL thickness between the two groups. PERG could be used as an objective method for registration of early changes in the RGCs function in glaucoma suspected patients before the presence of any functional changes in SAP and significant structural changes at OCT and also for monitoring the changes in dynamics.

Key words: pattern electroretinography, optical coherent tomography, glaucoma

DOI:10.7546/CRABS.2022.08.15

Introduction. According to European Glaucoma Society (EGS) the open-angle glaucomas are chronic progressive optic neuropathies that have characteristic morphological changes at the optic nerve head and retinal nerve fibre layer (RNFL) in the absence of other ocular disease or congenital anomalies. Progressive retinal ganglion cells (RGCs) death and visual field loss are associated with these changes [1]. The scientists' efforts have been directed towards discovering methods for detection of very early changes in the normal vision function as a result of glaucoma [2]. It is known that the RGCs start to die in the very early stages of glaucoma, although there is evidence to suggest that complete RGCs death takes months or years in the natural history of the disease [3].

Nowadays optical coherence tomography (OCT) has become an important tool for assessing early signs of glaucoma [4, 5]. According to some authors the loss of ganglion cells at the optic nerve may be observable at OCT before functional vision loss is demonstrated on visual field testing [5]. OCT in glaucoma, though, has an important disadvantage – there must be death of a significant amount of ganglion cells to observe thinning of the nerve fibre layers at OCT [6]. Changes at OCT are therefore not so early sign of glaucoma [7].

PERG is an objective, minimally invasive, reproducible method for direct measurement of RGCs function. It is extremely sensitive, allowing us to detect abnormalities prior to RGCs death (particularly in glaucoma suspects) and if we start treatment, it can help preserve the ganglion cells health [8, 9].

Clinical evidence shows that there is a time window to detect RGCs abnormalities via PERG testing while the cells are still viable (i.e., before RGCs apoptosis), making it possible that intervention may slow or abate RGCs death [9]. Therefore PERG has great utility for detecting the earliest signals of glaucoma, even before they are visible at OCT, when it is in a reversible state. It is very important, especially regarding when to start therapy to avoid vision loss from glaucoma progression [10, 11]. The use of anti-glaucoma medication has been shown to improve the PERG signal [12].

Material and methods. This is a prospective observation study with 3-year duration (2016–2019). A group of 103 people was studied. The patients with preperimetric glaucoma were 56 (29 males and 27 females, average age of 47.46 ± 12.2 years) with normal best corrected visual acuity (BCVA) (LogMar score 0.00 ETDRS Early Treatment Diabetic Retinopathy Study) and acceptable refractive errors ± 2 dpt. Controls for the study were 47 healthy individuals with normal BCVA (LogMar score 0.00 ETDRS) and acceptable refractive errors ± 2 dpt and without any known ophthalmological or neurological disease as well as other systemic diseases. The control group included 21 males and 26 females of an average age of 38.57 ± 12.37 years.

People were examined clinically by full ophthalmological examination, Goldmann applanation tonometry, indirect gonioscopy (Goldmann mirror), ultrasound pachimetry (Ocuscan RxP Alcon, USA) Central corneal thickness (CCT) testing,

visual field testing (Humphrey HFA II, Carl Zeiss Meditec) 30-2 Sita Standard program, OCT (Topcon 3D OCT 2000 FA plus, Japan) OCT 3D disc protocol, OCT circle disc protocol and OCT Glaucoma Analysis Macula protocol, fundus photography (Topcon 3D OCT 2000 FA plus, Japan) and funduscopy for C/D ratio detecting (Cap/Disc ratio – the ratio between the capping area and the whole disc area) [1]. Patients were tested electrophysiologically by PERG (NeuroMEP 4, Neurosoft Company). We studied both eyes in all patients in both groups but decided to analyze the right eyes results only, to prevent the results from intereye correlation which doubles the sample size and increases the probability of false positive results. The study met the criteria of standards for good medical practice. It was carried out with the informed consent of all participants in compliance with all ethics standards under Helsinki Declaration (2013).

Inclusion criteria. Glaucoma suspected patients with normal BCVA (LogMar score 0.00 ETDRS) and acceptable refractive errors up to 2 dpt. As patients with preperimetric glaucoma we considered those who had minimal structural defects in any of the OCT protocols (insignificantly thinner average total peripapillar or macular RNFL or insignificantly thinner sup. RNFL or inf. RNFL or impaired "ISNT" (Inferior – Superior – Nasal – Temporal) rule (the neuroretinal rim is usually widest in the inferior disc pole, followed by the superior disc pole, the nasal disc region and finally the temporal sector [1], or patients had asymmetry of the disc cupping between both eyes, along with at least two other risk factors for developing glaucoma such as ocular hypertension, family history, thin corneas. The patients did not have any visual field defects in perimetry according to the Ocular Hypertension Treatment Study (OHTS) criteria [13]. None of the patients instilled drops in the eyes before and during the examinations.

Exclusion criteria. Senile macular degeneration, advanced cataract, vascular eye diseases, optic neuritis, refractive errors more than 2 dpt., amblyopia, multiple sclerosis, Parkinson's disease, epilepsy, dementia, brain tumour and diabetes mellitus were excluded.

Method of PERG. All studies of PERG were performed with a standardized four channels equipment "Neuro-MEP 4" produced by Neurosoft Company. The study was performed with a three-channel recording with equipment adjustments according to the latest published ISCEV standards for PERG (2013) [14]. One of the channels recorded simultaneously visual evoked potentials. The main variables that were considered in the results analysis in the present study were latency (L), amplitudes (A) and amplitude ratio (AR) , 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, 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. The study was binocular as it is considered to be more stable. A standardized silver fibre active electrode (Cornea) was used. It was placed in contact with the globe after local topical anesthesia. The reference electrode (A) was placed on the ear, and the ground electrode on the right wrist. At least three of each stimulus were carried out to confirm the reproducibility of the obtained curves. The results analysis was based on the L, A and AR of components N35, P50 and N95.

Statistical analysis was performed with IBM SPSS Statistics 23.0 statistical package. Descriptive statistical analysis was used, based on the calculation of the median and percentiles from the observed sample distribution with 95% reference interval as a limit of normal. The RefVal program was used for calculating the laboratory normal ranges. Variation and comparative analyses were also performed.

Results. Both groups were subjected to a variation analysis to determine the reference values of all studied parameters and their variability.

We performed a comparative analysis between all the studied values of right eyes of patients with preperimetric glaucoma and controls. The examination of the known obscuration factors sex and age showed no significant difference between the study groups.

Table 1 presents the mean age and the mean values and standard deviation (SD) of the studied parameters in both groups as well as the values with significant differences ($p < 0.05$) between both groups.

As we can see in Table 1 the glaucoma suspected patients had significantly thinner corneas, the difference between the C/D ratios in both group is also significant, as well as the mean macular RNFL thickness and the mean total peripapilar RNFL (ppRNFL) thickness. That was the reason why we diagnosed those patients with preperimetric glaucoma.

The comparative analysis between the PERG components values of the right eyes of patients from both groups demonstrated significant differences in the latencies of components P50 and N95 at central stimulation (15°) and in component N95 at paracentral stimulation (30°). The latencies of the glaucoma patients were longer than those of the controls (Table 2). Our conclusion was that the central stimulation was more sensitive, with a higher number of significantly different values between the two groups.

These results correlated with the significant differences in the macular RNFL thickness between the two groups.

When we compared the PERG amplitudes in both groups we found statistically significant difference in component N35-P50 at central stimulation and in the amplitude ratio N35-P50/P50-N95 at paracentral stimulation. The PERG amplitudes of glaucoma patients were lower than those of the healthy subjects (Table 2).

T a b l e 1

Mean age and the mean values and SD of the studied parameters in both groups. Comparative analysis between the study parameters

	Controls ($n = 47$)		Patients ($n = 56$)		T-Test
	$\overline{X}$	SD	$\overline{X}$	SD	P
Age	38.57	12.37	47.46	12.23	0.52
IOP	15.02	2.34	23.38	1.98	0.06
CCT	572.87	27.39	520.11	14.76	< 0.001
Mean total macular RNFL	34.89	1.92	32.88	4.40	0.003
Mean sup. macular RNFL	34.15	1.78	33.11	4.88	0.002
Mean inf. macular RNFL	34.91	1.99	33.5	5.86	0.001
Mean total disc RNFL	101.49	6.73	92.11	11.02	< 0.001
Mean sup. disc RNFL	102.66	11.02	107.5	2.92	0.13
Mean inf. disc RNFL	118.83	13.47	108.04	17.58	0.35
C/D	0.02	0.05	0.34	0.15	< 0.001

IOP – intraocular pressure
inf ppRNFL – inferior peripapilar retinal nerve fiber layer thickness from 3D disc protocol on OCT
mRNFL – macular RNFL thickness from OCT Glaucoma Analysis Macula protocol
C/D – cap/disc ratio
CCT – central corneal thickness
ppRNFL – peripapilar retinal nerve fiber layer thickness from 3D disc protocol on OCT
sup ppRNFL – superior peripapilar retinal nerve fiber layer thickness from 3D disc protocol on OCT

T a b l e 2

Comparative analysis of PERG components between glaucoma suspected patients and controls

		Controls ($n = 47$)		Patients ($n = 56$)		T-Test
Component	Stimulus	$\overline{X}$	SD	$\overline{X}$	SD	P
Amplitude						
N35-P50	15°	1.96	0.74	2.35	2.26	0.008
P50-N95	15°	4.07	1.55	3.44	1.60	0.58
N35-P50	30°	2.29	0.88	2.50	1.08	0.23
P50-N95	30°	4.54	1.65	3.99	1.67	0.84
Amplitude ratio						
N35-P50/P50-N95	15°	0.52	0.23	0.56	0.27	0.26
N35-P50/P50-N95	30°	0.55	0.25	0.87	0.96	0.018
Latency						
N35	15°	30.35	4.85	32.12	5.25	0.91
P50	15°	52.80	4.24	56.41	7.43	0.004
N95	15°	97.61	3.77	100.72	9.01	< 0.001
N35	30°	28.05	4.07	29.24	4.86	0.37
P50	30°	52.22	5.30	52.45	4.28	0.68
N95	30°	95.19	4.67	94.11	11.80	< 0.001

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

Discussion. It is considered that component N95 reflects the activity of the RGCs and component P50 reflects the activity of the RGCs and a little more distal, but it has not been established exactly where [15]. The amplitude changes compared to controls suggest neuronal dysfunction, despite the absence of signs of functional changes in the visual field tests. The prolonged PERG latency in the glaucoma patients group demonstrates neuronal conduction delay.

Our results demonstrate that PERG is a sensitive method for detecting early functional changes in RGCs before the functional changes in the visual field tests and before the significant RNFL thinning. We found more changes in PERG latency which means RGCs dysfunction. The reduction in amplitude which indicates cells death was in component N35-P50 only. Therefore, with PERG we detect changes in a reversible stage, and with appropriate treatment, we can expect improvement. Similar results were obtained by other investigators [16]. They studied patients with early glaucoma and glaucoma suspected patients and found PERG latency elongation in both groups compared to the healthy control group and amplitude reduction in the early glaucoma group only. Preiser et al. [17] found that the amplitude ratio was more informative investigating patients with preperimetric glaucoma. In our study we also found significant difference in amplitude ratio N35-P50/P50-N95 in paracentral stimulation. Sehi et al. [18] examined RGCs function measured by using the PERG A in glaucoma patients and glaucoma suspects and found that the A was reduced in the glaucoma patients group only. Ventura et al. [7] found reduction of PERG A in 52% of glaucoma suspects and in 69% of early glaucoma patients.

Banitt et al. [10] studied 107 adults at risk of glaucoma and compared PERG amplitudes and OCT results over a 4-year period in order to determine the time lag between the loss of RGCs function and loss of RNFL thickness. They found that the RNFL thickness did not decrease until the PERG amplitude had lost at least 50% of its normal value for age. The authors concluded that PERG signal was reduced by 10% for about 8 years before there was an observable reduction of the same amount in the RNFL thickness at OCT. In another published study Bode et al. [19] found that PERG changes occur 4 years before the visual field changes in glaucoma suspects.

PERG and perimetry measure different aspects of the visual function. This is the reason why their results often dissociate, particularly in the early stages of the disease. PERG is a direct and objective measurement of the electrical activity of the RGCs population of the central retina in response to a suprathreshold stimulus. Perimetry is a subjective response to focal threshold stimuli covering central and more peripheral retinal regions, which depends on RGCs function, as well as on other postretinal factors, which may exacerbate or mask the reduction of sensitivity due to RGCs loss [19].

Therefore OCT and visual field testing are useful for detecting progression of change over time. PERG improves the ophthalmologist's ability to recognize early function loss associated with abnormalities in the RGCs in glaucoma suspects.

Conclusion. PERG testing represents a powerful tool to aid clinical decision making, especially regarding when to start therapy to avoid vision loss from glaucoma progression. Unfortunately this test is currently underutilized in the clinical practice, despite providing an objective measurement of the RGCs function and its usefulness in early detecting, monitoring the disease's progression, or the response to treatment.

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