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Diagnostic applications of the “pattern” electroretinography and visual evoked potentials in the evaluation of disorders of visual pathway function in Parkinson’s disease

Dijagnostička primena *pattern* elektroretinografije i vizuelnih evociranih potencijala u evaluaciji poremećaja funkcije vizuelnih puteva kod Parkinsonove bolesti

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Abstract

Background/Aim. In spite of continuous research efforts, specific laboratory, neuropsychological or neurophysiological tests for diagnosing Parkinson’s disease (PD) have not been established. The aim of the study was to determine the nature and extent of visual pathway disorders on “pattern” electroretinography (PERG) and visual evoked potentials (VEPs) in certain stages of PD. **Methods.** The study was carried out in a group of 60 persons of both sexes who were suffering from idiopathic PD at the I–IV stage of the disease according to the Hoehn and Yahr scale, and 30 healthy persons in the control group. The battery of noninvasive neurophysiological tests was used to estimate the functional status of the visual pathway − PERG and VEPs. **Results.** In the early phase of PD, there was a linear increase in the latency of the wave N50 of the PERG and the wave P100 of the VEPs, with a significant extension of the latency of the N50 and P100 waves in subsequent stages of PD. Diagnostic application of the PERG and VEPs enabled the confirmation of a disorder in the visual pathway function in PD. **Conclusion.** Applied neurophysiological techniques may record early changes in the function of retinal structures and the optic nerve in PD, which might be significant from both the diagnostic and therapeutic aspects.

Key words:
diagnosis; electroretinography; evoked potentials, visual; parkinson’s disease.

Apstrakt

Uvod/Cilj. Uprkos neprekidnim istraživačkim naporima, specifični laboratorijski, neuropsihološki ili neurofiziološki testovi za dijagnozu Parkinsonove bolesti (PB) nisu utvrđeni. Cilj rada bio je da se utvrdi priroda i obim poremećaja vidnog puta na *pattern* elektroretinogramu (PERG) i vizuelni evocirani potencijali (VEP) u određenim fazama PB. **Metode.** Ispitivanje je sprovedeno u grupi od 60 osoba oba pola, obolelih od idiopatske PB, u I–IV fazi bolesti prema skali Henove i Jara i 30 zdravih osoba u kontrolnoj grupi. Baterija neinvazivnih neurofizioloških testova upotrebljena je za procenu funkcionalnog statusa vizuelnog puta − PERG i VEP. **Rezultati.** U ranoj fazi PB došlo je do lineranog povećanja latence talasa N50 PERG i talasa P100 VEP, sa značajnim produženjem latencije talasa N50 i P100 u odmaklim fazama PB. Dijagnostička primena PERG i VEP omogućila je potvrđivanje poremećaja funkcije vizuelnog puta kod PB. **Zaključak.** Primenjene neurofiziološke metode mogu registrovati rane promene u funkciji retinalnih struktura i optičkog nerva u PB, koje mogu biti značajne i sa dijagnostičkog i sa terapijskog aspekta.

Ključne reči:
dijagnoza; elektroretinografija; evocirani potencijali, vizuelni; parkinsonova bolest.

Introduction

The diagnosis of Parkinson's disease (PD) is based on the clinical recognition of relevant symptoms and signs, as well as on a relatively good therapeutic response after the administration of levodopa. In spite of continuous research efforts, specific laboratory, neuropsychological or neurophysiological tests for the diagnosis of this disease have not been established [1].

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Neurophysiological methods have been used to identify subclinical bradykinesia and rigidity, as well as the differential diagnosis of an isolated static tremor. Certain results were obtained by examining the motion time in the paradigm of the reaction time, the quantification of the tremors, and the electromyographic response of the long latency. Early diagnosis of PD would allow not only differentiation of this disease from other parkinsonian syndromes, but also an adequate treatment and rehabilitation procedures.

The aims of the paper are to determine the nature and extent of visual pathway disorders on "pattern" electroretinogram (PERG) and visual evoked potentials (VEPs) in certain stages of PD, as well as to determine the diagnostic sensitivity of applied neurophysiological methods in PD.

Methods

Study design and ethical standards

The cross-sectional study was carried out at the Clinic of Neurology, University Clinical Center in Niš, during the period from 2017 to 2018. The study was carried out strictly in accordance with the principles of the Declaration of Helsinki as revised in 2000, ensuring full patient anonymity. Prior to the start of the study, the consent of the Ethics Committee of the institution was obtained.

Study subjects

The study group consisted of 60 patients of both sexes who came for regular neurological examinations for two years. They were suffering from idiopathic PD at the I–IV stage of the disease according to the Hoehn and Yahr scale. Computerized brain tomography excluded other possible etiological factors for the development of Parkinsonism (vascular lesions, expansive intracranial processes). The control group included 30 healthy subjects of both sexes and the appropriate lifespan. This group was formed by patients who underwent a neurological examination due to headache or dizziness but did not confirm the diagnosis of any neurological disease. All patients and subjects in the control group had previously undergone an ophthalmic examination to rule out any ocular disease.

Electrophysiological procedures

In this study, a battery of noninvasive neurophysiological tests was used to estimate the functional status of the visual pathway as a whole. These are PERG and VEP. Using these methods, detection of neuroelectric signals at different levels of the optical pathway, from the retina to the primary cortical optic center in the occipital lobe, was performed.

For the registration of PERG, a surface disk of electrodes placed below the lower eyelid is used. A "pattern" is triggered by a stimulus that is similar to the stimulus for the registration of VEP. The respondent is 1.25 m away from the monitor with a structured "pattern" stimulus, which looks at an angle of 13.91. This registered PERG has a three-phase format: positive, negative (N50), and positive wave. Values of latency and amplitude of PERG waves depend on the angle of stimulation, stimulus intensity, and type of electrodes for registration. The latency of the N50 wave is 40–50 ms in healthy persons.

VEP is a neurophysiological method for examining the function of the optical pathway from the ganglion layer of the retina to the visual cortex. VEP is registered using the "pattern" stimulus that represents a structured light stimulus according to the type of "chessboard". The form of evoked response depends, first of all, on the frequency of the stimulus. If the stimulus frequency is less than 5 stimuli per second, the V-shaped three-phase response, consisting of the first negative component N75, the positive component P100, and the negative component N145, is registered. Pattern VEP is stable and has a wide clinical application. The wave P100 comes from central neural elements of the field of vision, and its latency can be distinguished between the left and right eye. It has been accepted that the physiological interocular difference is up to 8 ms. The following equipment is required for VEP registration: a "pattern" monitor structured stimulation, in the form of a chess field with a series of white and black squares, size 32 min alternating signals, recording electrodes, an amplification system, and a computer for stimulating, with a response reading system. The square and the intensity of contrast are the most important variables when using the "pattern" stimulus. VEP recording is performed in a dark room. The patient is seated comfortably on the chair and looks at the center of the monitor screen, where at a certain frequency, a stimulus in the form of a chess field appears. The respondent is 1 m away from the monitor with a structured "pattern" stimulus, which looks at an angle of 17.34°. VEP registration is monocular, with a frequency of 1 to 2 stimuli per second. The frequency range is 30 and 300 Hz, the analysis time is 300 ms, and the 256 stimulus is copied, which is a sufficient number to obtain a reproducible response. During the recording, complete cooperation of a relaxed patient is required, as even the smallest movements cause artifacts. Patients with refractive anomalies wear glasses with appropriate diopter. Electrode position is determined by a 10–20 international electroencephalography (EEG) system. In the clinical practice for registration of VEP, three channels and the following assembly of electrodes are most commonly used: 1st channel: active Oz (5 cm above the inion) – reference Fz; 2nd channel: active electrode O1 (5 cm left of the inion) – reference Fz; 3rd channel: active electrode O2 (5 cm right of the inion) – reference Fz.

Statistics

Statistical analysis of the results obtained in this study was carried out using the standard Microsoft Excel program by analyzing the following statistical parameters: the arithmetic mean, the standard deviation, the variation of the results (minimum and maximum values), the coefficient of variation (CV), with the determination of the confidence interval, or the reliability limit of the estimated statistical parameters. The estimation of the statistical significance of the difference in the results was made using Student's *t*-test and

calculating the linear correlation coefficient. An analysis of the data necessary for assessing the reliability and accuracy of the tested method was performed using a linear logic regression model. The results obtained are presented in tabular and graphical form.

Results

This study included a group of 60 patients with PD (39 males and 21 females). There were more males than females, as men were more likely to suffer from PD (Table 1). In the control group, there were 30 healthy subjects (13 men and 17 women). The majority of patients belonged to the age group of 69 to 73 years (14 men) and from 59 to 63 years (9 women). The study included parkinsonian patients and healthy subjects of the control group approximately equivalent to the age structure. Based on the value of CV, it was found that the experimental group of parkinsonian patients and the control group of healthy subjects showed satisfactory homogeneity in relation to the age of the subjects. The average age of parkinsonian male patients was 66.1 years, and women with PD were 62.3 years old (Table 2). The average age of the males in the control group was 66.9 years, and the female age was 68.1 years.

In our study, all parkinsonian subjects were classified into groups according to the stage of the disease, using the Hoehn and Yahr scale (Table 2). The majority of parkinsonian males (13) were of the average age of 70.7 years and belonged to the third stage of PD. The highest number of parkinsonian women (7) was 65.1 years old and belonged to the IV stage of PD.

In Table 3, we compared the parameters of the N50 wave of PERG and the P100 wave of VEPs registered on the right and left eye in parkinsonian patients and the control group of healthy persons.

Table 1

The age and gender structure of parkinsonian patients

Age (years)	Parkinsonian patients, n (%)			Control group, n (%)		
	male	female	total	male	female	total
34–38	2 (5.1)	0 (0.0)	2 (3.3)	1 (7.7)	0 (0.0)	1 (3.3)
39–43	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
44–48	0 (0.0)	3 (14.3)	3 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
49–53	1 (2.6)	0 (0.0)	1 (1.7)	2 (15.4)	2 (11.8)	4 (13.3)
54–58	5 (12.8)	1 (4.8)	6 (10.0)	2 (15.4)	1 (5.9)	3 (10.0)
59–63	2 (5.1)	9 (42.9)	11 (18.3)	0 (0.0)	0 (0.0)	0 (0.0)
64–68	9 (23.1)	3 (14.3)	12 (20.0)	1 (7.7)	6 (35.3)	7 (23.3)
69–73	14 (35.9)	3 (14.3)	17 (28.3)	1 (7.7)	2 (11.8)	3 (10.0)
74–78	5 (12.8)	2 (9.5)	7 (11.7)	2 (15.4)	5 (29.4)	7 (23.3)
79–83	1 (2.6)	0 (0.0)	1 (1.7)	4 (30.8)	1 (5.9)	5 (16.7)
Total	39 (100.0)	21 (100.0)	60 (100.0)	13 (100.0)	17 (100.0)	30 (100.0)

Table 2

The age and gender structure of parkinsonian patients in relation to the stage of Parkinson's disease (PD)

Stage of PD (H&Y)	Male		Female	
	n (%)	age (years)	n (%)	age (years)
1	12 (20.0)	59.8	5 (23.8)	56.2
2	10 (16.7)	66.6	5 (23.8)	64.0
3	13 (21.7)	70.7	4 (19.0)	63.0
4	4 (6.7)	68.5	7 (33.3)	65.1
Total	39 (65.0)	66.1	21 (35.0)	62.3

H&Y – Stage of PD according to the modified Hoehn and Yahr scale.

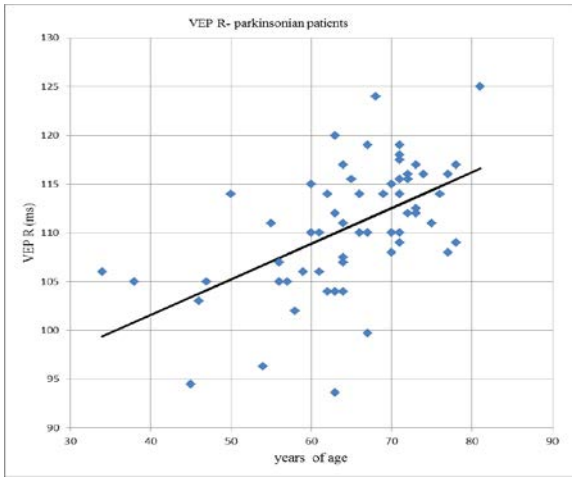
Table 3

Parameters of PERG (N50 wave) and VEP (P100 wave) for parkinsonian patients and the control group (healthy subjects)

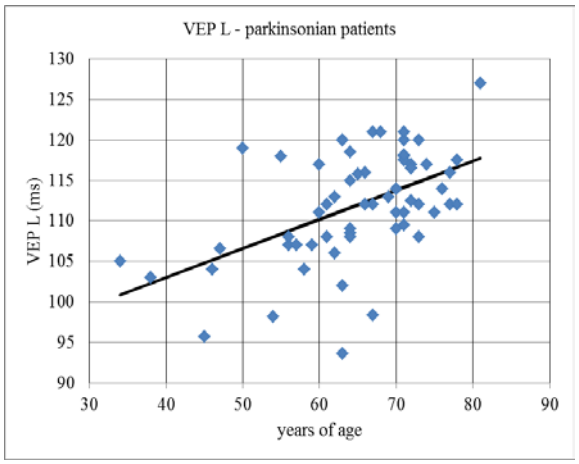
Study groups	PERG R	PERG L	VEP R	VEP L
PD patients				
mean	59.822	60.565	110.635	111.917
SD	4.963	5.263	6.507	6.801
Control group				
mean	52.440	52.480	104.083	104.150
SD	1.982	2.037	3.637	3.697

PERG – "pattern" electroretinograms; VEP – visual evoked potentials; PERG R – right-hand N50 wave of PERG; PERG L – left-hand N50 wave of PERG; VEP R – right-hand P100 wave of VEP; VEP L – left-hand P100 wave of VEP; PD – Parkinson's disease; SD – standard deviation.

Figures 1a, 1b, 2, 3a, 3b, and 3c show the regression lines for VEP parameters depending on the age and the stage of PD, as well as the regression lines for PERG parameters depending on the age and the stage of PD.



a)



b)

Fig. 1 – a) P100 wave latency of right-hand visual evoked potentials (VEP R) depending on the age of parkinsonian patients. Dots represent individual values [$p < 0.0001$ ($p = 1.13026435E-53$); $r = 0.545$]; b) P100 wave latency of left-hand visual evoked potentials (VEP L) depending on the age of parkinsonian patients. Dots represent individual values [$p < 0.0001$ ($p = 1.25723673E-58$); $r = 0.511$].

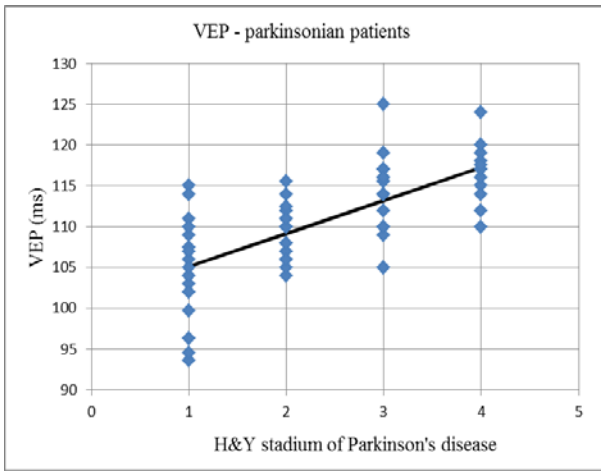


Fig. 2 – P100 wave latency of visual evoked potentials (VEPs) depending on the Hoehn and Yahr (H&Y) stadium of Parkinson's disease. Dots represent individual values [$p < 0.0001$ ($p = 3.5693995E-128$); $r = 0.678$].

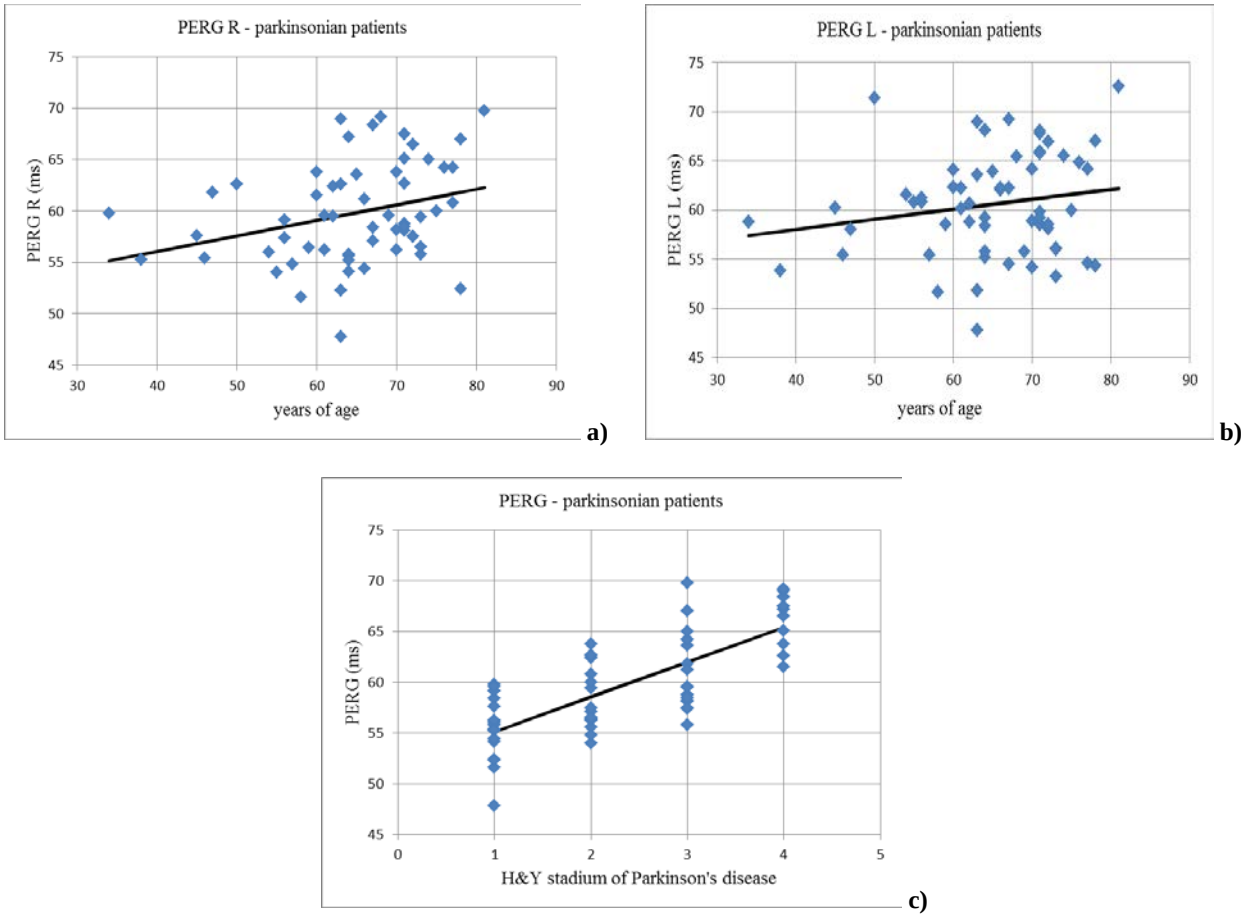


Fig. 3 – a) N50 wave latency of right-hand "pattern" electroretinograms (PERG R) depending on the age of parkinsonian patients. Dots represent individual values [$p < 0.0005$ ($p = 0.000309$); $r = 0.296$]; b) N50 wave latency of left-hand "pattern" electroretinograms (PERG L) depending on the age of parkinsonian patients. Dots represent individual values [$p < 0.005$ ($p = 0.001907$); $r = 0.188$]; c) N50 wave latency of "pattern" electroretinograms (PERG) depending on the Hoehn and Yahr (H&Y) stadium of Parkinson's disease. Dots represent individual values [$p < 0.0001$ ($p = 2.5692374E-110$); $r = 0.752$].

Discussion

In addition to significant movement problems, changes in visual acuity, contrast sensitivity, color discrimination, eye bulb movements, perception of motion, and speed of visual processing, have been described in patients with PD, especially for rapidly changing stimuli. Visual-spatial orientation disorders and visual hallucinations may also occur. Such a wide variety of visual problems can have a significant impact on the quality of life of parkinsonian patients [1]. The retina is the most distal site of visual dysfunction in PD, as demonstrated by electroretinography and optical coherence tomography studies to date. One of the most commonly studied neurotransmitters at the retinal level is dopamine, localized in amacrine cells and intersynaptic layers. Ganglion cells also include glycine and gamma-aminobutyric acid (GABA), responsible for transmission inhibitors.

Clinical electroretinography allows the detection of functional abnormalities of the retina before the onset of morphological changes. The PERG represents the focused and summarized electric potential of the macula. It is believed that the PERG generator in the retina is most likely in ganglion cells. Particularly sensitive to "pattern" stimulation are ganglion fibers that originate from the macula, and most of the PERG response is the electrical activity of that part.

VEP represents a neurophysiological method for examining the function of the optical pathway from the ganglion layer of the retina to the visual cortex. VEP represents the difference in electrical potential that is recorded on the head as a response to visual stimuli.

These methods have been used to detect impaired function of the retinal nerve fiber layer in parkinsonian patients [2].

Two years ago, the study performed by Živković et al. [3] analyzed changes in the thickness of the macular ganglion cell layer and the thickness of the inner plexiform layer in patients with PD. It was concluded that PD is accompanied by thinning of these macular complexes even in the earliest stages of the disease.

In recent years, the results of studies examining visual pathway disorders in parkinsonian patients have been published. The latencies of the VEP and PERG parameters were taken into account. However, the results of a study by Langheinrich et al. [4] also show a significant reduction in PERG amplitude.

Garcia-Martin et al. [5] examined the VEP and PERG parameters as well as the thickness of the foveal and macular region of the retina in parkinsonian patients and found that the symptoms of the disease were more severe in patients with more severe retinal damage.

The results of a study by Liu et al. [6] also show that visual pathways in the brainstem can be disturbed in parkinsonian patients.

A study by Hasanov et al. [7] examining pattern VEP and thickness of the retinal nerve layers revealed that electrophysiological and morphological changes are present at different levels of the visual pathway in the early stages of PD.

The results of our study indicate a median, positive linear relationship between the P100 wave latency values of VEP waves in Parkinson's patients and their lifespan (Figures 1a and 1b).

It can be assumed that the aging of parkinsonian patients further affects the already existing neurodegenerative process and further loss of dopaminergic receptors, both in brain structures and in the corresponding retinal layers.

This neurodegenerative process affects the significant prolongation of the latency of the N50 PERG wave and the P100 VEP wave in parkinsonian patients, which increases with age.

A weak positive linear relationship between the N50 PERG wave latency and the lifespan of parkinsonian patients was also recorded (Figures 3a and 3b).

By comparing the registered N50 PERG wave latencies and P100 VEPs in parkinsonian patients and healthy subjects of the control age-matched group, their significant prolongation was observed in the patients (Table 3).

This finding indicates the presence of a significant neurodegenerative process in the retinal structures of parkinsonian patients relative to healthy subjects. Degenerative changes of retinal structures with consequent disruption of dopaminergic neurotransmission significantly affect the function of visual pathways of parkinsonian patients. The greatest number of the patients was in the first three stages of PD, and that is the period when the dynamics and development of the neurodegenerative process can be monitored (Table 2).

By comparing the P100 wave latency values of VEP (Figures 1a and 1b) and N50 PERG (Figures 3a and 3b), it was observed that the P100 wave latency correlated significantly more positively with the patient's age than the N50 wave latency. A possible reason may be the location, and the length of the visual path, which is examined by the specified parameters. Specifically, the N50 wave of PERG is the response of retinal structures to the applied light stimulus, and the P100 wave of VEP is the response transmitted along the entire visual path to the primary cortical optic areas. The longer the impulse transmission path, the more pronounced are the consequences of the neurodegenerative process present.

In our study, it was observed that the latency values of P100 waves of VEP and N50 waves of PERG show a median or strong correlation with the stage of PD (Figures 2 and 3c). In this way, it was also found that the severity of the neurodegenerative process in the visual system more significantly depends on the stage of PD than on the age of the patient, as expected.

The results of our study are consistent with the results of the earlier conducted study [8], where bioelectric retinal dysfunction was observed in patients in the early stages of PD during the PERG test, possibly as a result of retinal dopamine deficiency. This finding indicates that PERG may be a useful test for understanding the causes of nonspecific visual disturbances that occur in parkinsonian patients. It can be concluded that PERG is useful for assessing retinal dopaminergic function as well as for monitoring the therapeutic action of dopaminergic drugs. Meta-analysis performed by He et al. [9] as well as the study made by Miri et al. [10] showed that P100 VEP wave latencies are longer in parkinsonian patients compared to healthy subjects.

These findings, as well as the results of our study, suggest that electrophysiological changes and functional deficits of visual pathways in parkinsonian patients may be important for understanding the pathophysiology of visual disorders in PD. Based on the previous presentation, it can be concluded that VEP and PERG may be sensitive parameters for the prognosis and assessment of the severity of PD. However, it is well known that VEP and PERG are not specific electrophysiological tests for a particular disease. This fact limits, to some extent, their diagnostic applicability. However, it is hypothesized that with careful selection of patients with an accurate exclusion of other diseases that may affect visual function, the results of future electrophysiological studies may significantly contribute to the differential diagnosis and treatment approach planning for parkinsonian patients. In this regard, future studies of VEP and PERG parameters in parkinsonian patients are needed.

Conclusion

Diagnostic application of the PERG and VEPs enabled the confirmation of a disorder in the visual pathway function in PD. Applied neurophysiological techniques may record early changes in the function of retinal structures and the optic nerve in PD, which might be significant both from the diagnostic and therapeutic aspects.

Conflict of interest

No conflict of interest exists for any of the authors listed in the article.

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