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Pattern electroretinogram (PERG) in the early diagnosis of optic nerve dysfunction in the course of Graves' orbitopathy

Elektroretinogram generowany wzorcem (PERG) we wczesnej diagnostyce dysfunkcji nerwu wzrokowego w przebiegu orbitopatii Gravesa

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Streszczenie: Cel: ocena przydatności elektroretinogramu generowanego wzorcem w diagnostyce wczesnych zmian funkcji narządu wzroku u pacjentów z orbitopatią Gravesa bez perymetrycznych objawów neuropatii nerwu wzrokowego.
Materiał i metody: badaniem objęto 19 oczu dziesięciorga pacjentów w średnim wieku 36 ± 6 lat (7 K, 3 M) z orbitopatią Gravesa w stadium zaawansowania od 1 do 4 NOSPECS. Grupę kontrolną stanowiło 22 oczu (11 pacjentów). Elektroretinogram generowany wzorcem oznaczano za pomocą systemu PRIMUS 2,5 (Tomey), używając zestawu elektrod typu TE-1000. Rozdzielczość czasowa pattern elektroretinogramu wynosiła 2 Hz, a wielkość pola szachownicy 1°.
Test t-Studenta został użyty do analizy statystycznej średniej i odchyleń standardowych. Dla wszystkich analizowanych parametrów za znamienny statycznie wynik przyjmowano $p < 0,05$. Punkt odcięcia, czułość i specyficzność parametrów elektroretinogramu generowanego wzorcem były oceniane za pomocą krzywych ROC, które wykonano, używając programu Medcalc ®.
Wyniki: u pacjentów z orbitopatią Gravesa stwierdzono znamiennie obniżoną amplitudę fali P50 (2,04 ± 0,99 względem 2.69 ± 0.88 w grupie kontrolnej). Analiza krzywych ROC wykazała wysoką czułość amplitudy fali P50 oraz amplitudy fali N95-50 w rozróżnieniu między grupą pacjentów z orbitopatią Gravesa a grupą kontrolną (kolejno 78,9%, 81,8%). Swoistość amplitudy fali P50 była dość wysoka (63,6%), natomiast amplitudy fali N95-P50 niska (47,4%).
Wnioski: obniżenie amplitudy fali P50 może być markerem wczesnej dysfunkcji niedokrwiennej nerwu wzrokowego u pacjentów z orbitopatią Gravesa. Ocena amplitudy fali PERG P50 oraz N95-P50 u pacjentów z orbitopatią Gravesa może stanowić czuły test skryningowy neuropatii nerwu wzrokowego.

Słowa kluczowe: elektroretinogram generowany wzorcem – PERG, neuropatia nerwu wzrokowego – DON – w przypadku dysfunkcji tarczycy, orbitopatia Gravesa – GO.

Summary: Purpose: The present study was design to evaluate the pattern electroretinogram in the diagnosis of early changes in visual function of patients with Graves' orbitopathy without perimetrical signs of optic nerve neuropathy.
Material and methods: 19 eyes from ten patients, mean age 36 ± 6.8 SD, comprising (7 F and 3 M) with GO, affected by (1–4) NOSPECS severity class were enrolled in the study. 22 eyes from eleven healthy volunteers served as a control.
The pattern electroretinogram was recorded with TE-1000 headset electrode using PRIMUS 2,5 (Tomey). The temporal frequency of PERG was 2 Hz and the check size was 1°. Student's t-test was used for the statistical analysis of mean and standard deviations. Statistical significance was assumed at $p < 0.05$ for all analyses. Cut-off points, sensitivity and specificity of the pattern elektroretinogram parameters assessed by receiver operating characteristic curves were performed by Medcalc ®.
Results: In patients with Graves' orbitopathy a significantly decreased P50 amplitude was found (2.04 ± 0.99 vs. 2.69 ± 0.88 in healthy controls). Receiver operating characteristic curves analysis revealed a high sensitivity of P50 amplitude and N95-P50 amplitude for discrimination between Graves' orbitopathy and healthy group (78.9% and 81.8%, respectively). The specificity of P50 amplitude was fairly high (63.6%) while N95-P50 amplitude was rather low (47.4%).
Conclusions: The reduction of the P50 amplitude could be a marker of an early ischemic optic nerve dysfunction in patients with Graves' orbitopathy. The evaluation of the pattern electroretinogram P50 and N95-P50 amplitude might be a fairly sensitive test for screening dysthyroid optic neuropathy.

Key words: pattern electroretinogram – PERG, dysthyroid optic neuropathy – DON, Graves' orbitopathy – GO.

Introduction

Dysthyroid optic neuropathy (DON) in patients with Graves' orbitopathy (GO) can essentially be referred to as processes of ischemic type of the optic nerve, secondary to direct compression on the optic nerve vascular system and to vessel inflammatory occlusions (1, 2).

The pattern electroretinogram (PERG) may be altered in dysfunction confined to the macula or to the retinal ganglion cells (RGC), which do not significantly affect the conventional full-field ERG (3). In agreement with that, the PERG may be affected due to retrograde axonal degeneration in the prolong congestive mechanism of DON (2).

Previously it was observed that the electrophysiological tests were useful to detect small changes in the visual function of patients affected by initial stages of GO (2, 4, 5). In our recent study we demonstrated the role of pattern visual evoked potentials in the early diagnosis of optic neuropathy in the GO without evident DON (5).

Recently it was found that the very early glaucomatous damage can affect the PERG, even before the visual field shows a loss (6).

The present study was design to evaluate the PERG in the diagnosis of early changes in visual function of patients with Graves' orbitopathy without perimetrical signs of optic nerve neuropathy.

Patients and methods

Ten patients (19 eyes), mean age 36 $\pm$ 6.8 SD, range 24 – 55 years, comprising 7 females and 3 males with Graves's orbitopathy, affected by 1–4 NOSPECS severity class according to EUGOGO were enrolled in the study.

Exclusion criteria were: NOSPECS class 6 with evident optic neuropathy, best corrected visual acuity below 0.9, keratopathy that could influence on visual acuity, colour test impairment, RAPD (relative afferent papillary reflex) or visual field loss (MD $>$ 2dB). Treatment with drug alternating electrophysiological findings previous radiotherapy and age over 60 years, other visual diseases. Since a different thyroid state can influence on PERG recordings only euthyroid patients were enrolled in the study (7).

The ocular examination included determination of best corrected visual acuity (Snellen charts), colour test (Ishihara charts), RAPD by using swinging flashlight test, biomicroscopic examination of the anterior segment, applanation tonometry, direct and indirect ophthalmoscopy, Hertl's exophthalmometry, ocular motility and computerized visual field examination (30-2) white Humphrey threshold perimeter was performed.

Twenty two eyes from 11 healthy volunteers sex and age matched to the studied group served as a control.

All subjects gave informed consent to the investigations, and the study was confirmed by the Local Ethic Comity of Medical University in Bialystok.

The pattern electroretinogram

PERG was recorded with TE-1000 headset electrode using PRIMUS 2,5 (Tomey) (3). After local anesthesia (Alcaine), the transient PERG was recorded bilaterally using corneal DTL thread over the lower lid. Pupils were not dilated and the subject wore their full spectacle near correction without interfering with the electrodes. A fixation spot at the centre of the screen was provided.

The pattern was generated on a CRT (Cathode-Ray Tube) screen incorporated into the full-field dome with a total field diameter of 15 cm, at a viewing distance of 57 cm and the element dimension of 1°. The standard ISCEV check size for PERG is 0.8° ($\pm$0.16°). The low temporal frequencies transient PERG of 2 Hz was obtained.

PERG was performed and analysed according to the International Society Clinical Electrophysiology of Vision [ISCEV PERG standards – 2013 update (3)].

Statistical analysis

Student's t-test was used for the statistical analysis of mean and standard deviations by Statistica 8.0, Statsoft ®. Statistical significance was assumed at $p < 0.05$ for all analyses.

The receiver operating characteristic (ROC) curve was used to evaluate the goodness of fit for a binary classifier. It is a plot of the true positive rate (rate of events that are correctly predicted as events) against the false positive rate (rate of non-events predicted to be events) for the different possible cut-off points.

The trade-off between sensitivity and specificity of PERG parameters was assessed and displayed by ROC curves in Medcalc ®.

Results

In order to evaluate the performance of PERG recording for diagnosis of visual function impairment and to determine any cut-off value for the diagnosis of risk of optic neuritis we investigated the receiver operating characteristic (ROC).

When selecting a cut-off value $\leq$ 2.4 μV for P50 and $\leq$ 3.65 μV for N95-P50 amplitudes in terms of differential diagnosis for early DON between GO and controls high sensitivity of P50 amplitude and N95-P50 amplitude was obtained (78.9% and 81.8%, respectively). The specificity of P50 amplitude was fairly high (63.6%) for the values $\leq$ 2.4 μV (Fig. 1.). The specificity of N95-P50 amplitude for it's cut-off point was 47.4% (Fig. 1.).

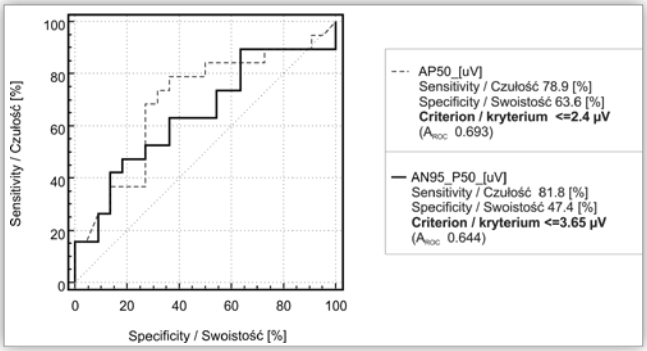

Fig. 1. Receiver operating characteristic (ROC) curves discriminating between eyes with GO and normal eyes (CTRL) for the method of PERG N95-P50 amplitude (bold line) and P50 amplitude (dot line). Areas under the ROC curves were $A_{ROC} = 0.644$ and $A_{ROC} = 0.693$, respectively. The closer ROC curve follows the left and the top border of the plot and the larger ROC field, the more accurate is the test.

Ryc. 1. Krzywa dyskryminacji ROC amplitudy fali N95-P50 (linia pogrubiona) oraz amplitudy fali P50 (linia przerywana) – różnice między oczami z orbitopatią Gravesa a oczami pacjentów z grupy kontrolnej. Pola pod krzywą ROC wynosiły kolejno $A_{ROC} = 0.644$ i $A_{ROC} = 0.693$. Im bliżej krzywa ROC skierowana jest do lewego i górnego brzegu wykresu oraz im większa powierzchnia pola ROC, tym test jest bardziej dokładny.

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PERG	AP50 (μV)		LP50 (ms)		AN95-P50 (μV)		LN95 (ms)	
	Mean/ Średnia	SD/ Odch.st.	Mean/ Średnia	SD/ Odch.st.	Mean/ Średnia	SD/ Odch.st.	Mean/ Średnia	SD/ Odch.st.
GO	↓**2.04***	0.99	52.23	5.35	4.22	2.04	91.50	6.80
CTRL	2.69	0.88	54.24	2.84	5.01	1.63	92.42	3.39

* $p < 0.05$

Tab. I. Mean and standard deviation values of PERG parameters in patients with GO vs. control group.
Tab. I. Średnia oraz odchylenie standardowe (odch. st.) parametrów PERG u pacjentów z OG względem grupy kontrolnej.

However, there was no cut-off value for the P50 and N95 implicit times in the GO group with adequate sensitivity and specificity. In the ROC analysis for selected criterion ≥50.6 ms and ≥94.35 ms both parameters showed low sensitivity (36.8% with a high specificity 100 %, 81.8%, respectively).

The analysis of mean and SD values of PERG parameters revealed decreased mean of P50 amplitude in patients with GO in comparison to healthy controls (Tab. I).

Discussion

Pattern electroretinogram is related to retinal ganglion cell layer activity, therefore the PERG will be affected by any process that either distorts the input to the ganglion cells, directly damages the ganglion cell bodies or comprises the optic nerve.

Geovesi-Ebert et al. claimed that PERG may be a more sensitive indicator of optic nerve compression in DON than the pattern visual evoked potentials (PVEP) (4). In long-standing optic nerve compression the P50 component may show amplitude reduction and shortening of latency. N95 reduction may also occur in the ischaemic optic neuropathy (ION) or toxic neuropathies. However, unlike other optic neuropathies, in the ischaemic optic neuropathy (ION) the involvement of P50 amplitude to a greater degree than the N95 amplitude has been reported (8, 9).

Hence our results support the above thesis that the DON is a sort of ischaemic optic neuropathy.

The findings of the reduced amplitude of the main positive (P50) PERG's component may suggest dysfunction distal to the retinal ganglion cell layer and not those of optic nerve dysfunction (8). In contrast, Geovesi-Ebert et al. found P50 amplitude reduction the most sensitive parameter to demonstrate an early impairment of the optic nerve function in the course of Graves' disease. In addition, the author found a significant negative correlation between the optic nerve diameter and the P-ERG amplitude (4).

Among other electrophysiological procedures PERG has been shown to be a sensitive test for an early detection of not only optic neuropathies but also glaucoma (6, 10–12). Most of the studies show that in glaucoma P50 is reduced to a lesser extent than N95 (6, 12–14). In a prospective study the PERG ratio was shown to identify eyes at risk before manifest field damage; thus, PERG recordings under appropriate recording conditions may help to identify patients with elevated IOP in whom glaucoma damage is incipient before visual field changes occur (11).

Taking together that the prevalence of glaucoma in the population of patients with Graves' orbitopathy (0.8%) corresponds to the 1.1% prevalence of the POAG in the general population (15) researches tend to find some markers to monitor early visual dysfunction in Graves' orbitopathy sensitive for DON.

In our study we demonstrated that P50 and N95 amplitudes could be a sensitive test for diagnosis of functional impairment in GO. The sensitivity of both values is comparable 81.8% and 78.9% (P50 and N95-P50 amplitude, respectively). Nevertheless the amplitude of main positive P50 component is significantly diminished and more specific as a discriminator between GO and healthy control group. Similarly Bach et al. found PERG as an early indicator of dysfunction preceding glaucoma with the sensitivity of 80% and a specificity of 71% (11).

Conclusions

The reduction of the main positive P50 component amplitude could be a marker of early ischemic optic nerve dysfunction in patients with Graves' orbitopathy. The evaluation of PERG P50 and N95-P50 amplitude might be considered as a fairly sensitive test for visual impairment in patients with GO and could serve as a screening method for early DON.

Abbreviations:

CAS – Clinical Activity Score; DON – Dysthyroid optic neuropathy; EUGOGO – EUropean Group On Graves' Orbitopathy; GO – Graves' Orbitopathy; NOSPECS (Mnemonic: NO signs, Only sings, Soft tissue involvement, Proptosis, Extraocular muscle involvement, Corneal involvement, Sight loss); ROC – Receiver operating characteristic.

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