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The Photopic Negative Response as a promising diagnostic tool in glaucoma. A review

Fotopowa Negatywna Odpowiedź – narzędzie wykorzystywane w diagnostyce jaskry. Przegląd piśmiennictwa

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Streszczenie: Cel: na podstawie dostępnej literatury autorzy opisali kliniczne zastosowanie Fotopowej Negatywnej Odpowiedzi (PhNR) błyskowego elektroretinogramu w diagnostyce jaskry.
Materiał i metody: dane opublikowane w bazie PubMed w latach 1999–2011. Przeanalizowano techniki uzyskiwania, badania i pomiaru PhNR. Opisano zależności między wynikami automatycznej perymetrii statycznej (SAP), Gdx, optycznej koherentnej tomografii (OCT), elektroretingramu wywołanego wzorcem (PERG) i PhNR pacjentów z jaskrą.
Wyniki: 1. Najczęściej stosowaną metodą do uzyskiwania PhNR był krótki (<6 ms), czerwony błysk na niebieskim tle, stosowano elektrody nitkowe typu DTL. 2. Opisywano redukcję amplitudy PhNR oraz współczynnika amplituda PhNR/amplituda fali b u pacjentów z różnym stopniem zaawansowania jaskrowych ubytków pola widzenia. 3. Udowodniono nieliniową oraz liniową zależność między czułością siatkówki (SAP) i grubością warstwy włókien nerwowych (RNFLT) a amplitudą PhNR i współczynnikiem amplituda PhNR/amplituda fali b. 4. Obserwowano silną zależność między amplitudą PhNR i amplitudą fali N95 PERG. 5. Ogniskowa PhNR może być bardziej czułą i swoistą metodą w porównaniu do PhNR.
Wnioski: PhNR jest obiecującym narzędziem w diagnostyce neuropatii jaskrowej. Do dzisiaj ewidentna wartość kliniczna tej metody nie została ostatecznie potwierdzona. Badania na większej grupie pacjentów są niezbędne dla potwierdzenia korzyści płynących z zastosowania PhNR w diagnostyce jaskry.

Słowa kluczowe: jaskra, fotopowa negatywna odpowiedź.

Summary: Purpose: Based on the available literature, the clinical usefulness of Photopic Negative Response (PhNR) of flash Electroretinogram (ERG) in detecting glaucoma has been described.
Materials and methods: Data published in the literature available at the Pub Med library between 1999–2011. Different techniques of eliciting, assessing and measuring PhNR have been analyzed. Relations between results of static automated perimetry (SAP), Gdx, optical coherence tomography (OCT), pattern electroretinogram (PERG) and PhNR in glaucomatous patients have been described.
Results: 1. The most frequent method of PhNR recording has been brief (<6 ms), red stimulus against the blue background with thread active DTL electrodes. 2. There has been a significant decrease of PhNR amplitude and PhNR/b-wave ratio in patients with different stages of glaucoma field defect. 3. Curvilinear and linear correlation between retinal sensitivity (SAP), retinal nerve fibre layer thickness (RNFLT), PhNR amplitude and PhNR/b-wave ratio has been found. 4. A significant correlation occurred between PhNR and PERG amplitudes. 5. Focal PhNR seems to be a more specific and sensitive tool in comparison to full field PhNR.
Conclusions: PhNR is a promising tool in glaucoma neuropathy assessment. Up to date the value of PhNR has not been definitely proved. More research is necessary to con rm the usefulness of PhNR in diagnosing glaucoma.

Key words: glaucoma, photopic negative response.

Introduction

Glaucoma is a progressive neuropathy with characteristic structural damage in the optic nerve head. This neuropathy is frequently accompanied by a specific type of vision field defect (1). Visual impairment caused by glaucoma progresses slowly and is irreversible.

A golden standard in detecting glaucoma is still SAP, usually performed on Humphrey Visual Field Analyzer (24–2 threshold test). It was shown (2) that repeatable defect in glaucomatous visual field occurred when at least 25 to 30% of retinal ganglion cells (RGC) had been lost. Additionally, SAP examination is a subjective way of detecting retinal sensitivity. Furthermore, it is not a proper test for RGCs loss assessment and in many cases it is found to be difficult to perform. That is why it is important to develop an objective method of assessing RGCs function loss before abnormalities in SAP can occur.

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RGCs activity can be objectively recorded by electrophysiological tests. From these tests multi-focal evoked potentials (mfVEPs) and pattern electroretinogram (PERG) aroused interest and usage in diagnosing and treating glaucoma (3-6).

MfVEP is a topographical, electrophysiological recording of numerous responses from inner retina, including RGC layer. Usually 40–50 degrees of visual field are covered by mfVEP (7). MfVEP results can overlap with the results from SAP. Numerous studies confirm that mfVEP can detect glaucomatous damage and that it is one of the promising tools in glaucoma diagnosis (3-5), but there are certain limitations because of which mfVEP is still not widely used in the clinic. First is the stimulus time. Each subject required approximately 30 minutes and the testing time is still not standardized (8). Second limitation is the contamination of records by the alpha wave, which is the low frequency wave generated from the occipital lobe in the relaxed state. Third limitation is still not satisfying signal to noise ratio (SNR) and large intersubject variability of the test. Several techniques have to be improved to reduce these differences and to increase of the mfVEP accuracy (7).

Nowadays, PERG is the most commonly used electrophysiological technique in the clinical practice for estimating activity of RGC population of the central retina (more than 40% of RGC is present in this region). Abnormal PERG result in glaucomatous patients is detected, when diffuse RGC loss appears (9). PERG stimulus covers approximately 15 central degrees of visual field, while early glaucomatous field defects arise typically in the more peripheral Bjerrum area (between 10 and 20 degrees from fixation) (10). PERG results are normal, when local RGC loss is present. That is why PERG sensitivity and specificity reaches only 50–80% and 71–87% respectively (11,12). Additional disadvantage of PERG is that this test is affected by opacities in the ocular media, and it does require refractive correction and good fixation (13).

Due to the fact that none of the above mentioned electrophysiological tests is perfect in glaucoma diagnosing, several researches are carried out to improve objective, more sensitive and specific testing in this disease. One of the most promising RGC damage indicators can be assessment of photopic negative response (PhNR) (6,13,14).

PhNR is a negative-going wave that follows the b-wave of the photopic ERG. Many studies' results suggest that PhNR amplitude of ERG reflects averaged function of RGCs population (6,13,15). Viswanathan et.al. (6) was the first, who showed the reduction of this negative wave in mammals with experimental glaucoma and after tetrodotoxin (TTX) injection. In this study (6) PhNRs recorded after TTX intravitreal injections and after argon laser induced glaucoma had been found absent. TTX works by blocking voltage-gated sodium channels of amacrine and RGCs. As a consequence of this action abnormal PhNR was seen one hour after injection and persisted for a few days before ERG recovery to normal.

The study results in monkeys attracted interest of PhNR as a diagnostic tool in humans. PhNR amplitude measuring seems to have a good diagnostic value in optic nerve disturbances with diffuse loss of RGCs (16). In previous studies the authors described PhNR reduction in patients with retinal ischemic disorders, such as diabetic retinopathy, central retinal vein occlusion, intraocular hypertension and glaucoma (13-19).

Methods

Preparation. Electrode types

Patients preparation for PhNR recording: pupil dilation to minimum of 7 millimeters in diameter and background adaptation for minimum of 5 minutes. Various types of corneal electrodes may be used, such as DTL electrodes (14,16,20), Burrian-Allen electrodes (19), Henkes contact lenses (21) and skin active electrodes (17). Application of Burrian-Allen and Henkes contact lenses electrodes requires local anesthesia. It is not necessary before placing DTL electrodes, although sometimes drops are given to very sensitive patients (19,21,22). The largest amplitudes of PhNR are recorded using Burrian-Allen electrodes. In comparison to those received by corneal electrodes the amplitudes obtained with DTL electrodes are significantly lower. Additionally, PhNR amplitudes obtained with skin electrodes are 50–60% smaller than those recorded when using DTL electrodes. Amplitudes obtained by skin electrodes have a higher coefficient of variation (CoV), but in some clinical situations the application of skin electrodes in place of corneal or conjunctival electrodes is necessary, e.g. by children. With an appropriate technique, a high stability and reproducibility of these electrodes can be obtained (it was found the intersession coefficient of variation was approximately 14.3% DTL; 23.2% skin) (23).

PhNR amplitude, flash stimuli and background conditions

Stimulus conditions differ considerably in previous studies and PhNR-ERG standards have not yet been generally established. Some of the studies have been based on ERG recordings made with brief red flashes against a blue background (6,13,14,16,20,24) – originally described by Viswanathan et al. (6). Others have used white flashes against white background (19,21,22,24) or different stimuli colors. Rangaswamy et al. (24) in the study on macaques with experimental glaucoma and healthy humans showed that the best stimulus for maximizing PhNR amplitude was red flash against the blue background, because red stimuli primarily stimulated one cone type (longwave) and blue background suppressed adaptive effect on rods. However, white stimuli are also a good option to obtain the PhNR if strong enough stimulus has been used (24). Recently, Sustar et al. (25) published the results on the glaucomatous PhNR responses. In this paper they reported greater reduction of PhNR in response to red against the broadband stimulus (68% to 38%, respectively). PhNR to red stimuli appeared to be more sensitive parameter, with receiver operating characteristic (ROC) 0.97 comparing to 0.76 of the broadband stimulus. Additionally, the PhNR amplitude to red stimulus showed a more significant correlation with the PERG amplitude and the visual field defects ($p<0.05$) than the PhNR elicited with the broadband stimulus. The impact of stimuli duration on PhNR also attracted the interest of researches. The clinically most frequently employed ERG uses short flashes (<6 ms) according to the recommendation of the International Society for Clinical Electrophysiology of Vision (ISCEV) (26). These conditions are commonly used in the studies on PhNR and glaucoma (6,8,12-14,16, 20,21,24). However, long duration flash stimulation (>200 ms) allows a separate analysis of the on and off response of RGC,

as presented in many studies (6,13,15,22,24). Horn et al. (22) showed that inclusion of the PhNR off response can provide additional information for diagnosing and monitoring glaucoma. Further studies are needed to confirm this hypothesis.

PhNR amplitude and implicit time measurements techniques

Up to date there is a consensus what is the best way to measure PhNR parameters. The PhNR amplitude was measured from the baseline to the trough of negative peak following the b-wave (fig. 1a) (22) or from the peak of the b-wave to the PhNR trough (fig. 1b) (23). To reduce the variations of the PhNR amplitude among individuals PhNR/b-wave amplitude ratio in a few studies was measured (fig. 1c) (16,20). Determining the location of PhNR maximal value is difficult because PhNR trough is broad. To objectify and standardize the implicit time of PhNR amplitude the authors averaged PhNR amplitudes in 5 ms steps from 55 to 85 ms and picked out the largest ones. In Rangaswamy et al. study this fixed time point was at 70 ms (15). Results of Mortlock et al. (23) study suggest that PhNR should be measured from the peak of the b-wave to either the trough of the PhNR or some pre-determined (15) fixed time point, rather than from the baseline. Clinically time point measurements confer one great benefit: they allow the objective measurement of traces where the trough of the PhNR is not clearly defined. It should be mentioned that PhNR implicit time increases with age (13).

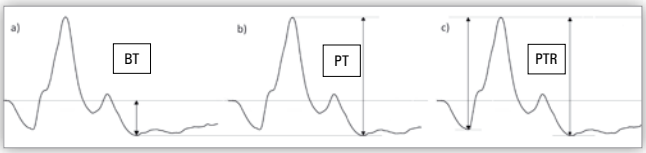

Fig. 1a-c. PhNR measurements techniques: PhNR amplitude measured from baseline to negative through following the b-wave (baseline-through BT) – a., PhNR amplitude measured from peak of the b-wave to the negative through of the following negative wave (peak to through PT) – b., ratio of the PT amplitude/ b-wave amplitude (peak to through ratio PTR) – c.

Ryc. 1a-c. Metody pomiarów PhNR: amplituda PhNR mierzona od linii izoelektrycznej do najniższego punktu negatywnej fali pojawiającej się za falą b (BT) – a., amplituda PhNR mierzona od szczytu fali b do najniższego punktu fali pojawiającej się za falą b (PT) – b., współczynnik PTR: amplituda PT/ amplituda fali b – c.

Variability of PhNR

PhNR recording requires great accuracy and practice. Results of examination depend on many different external factors, such as: electrodes type and placement, tissues impedance, drugs, eye movements, eye adaptation, anesthesia, etc. PhNR amplitude variability by healthy subjects was reported to be at 14.3% (23), which is similar to test-retest variability that were reported for the PERG (27). Machida et al. (16) found out that the CoV of PhNR amplitude in advance glaucoma increased significantly in comparison to that in normal eyes, indicating that reproducibility declines in eyes with low PhNR amplitudes. On the other hand, variability for PhNR of flash ERG is still smaller than PhNR amplitude of focal ERG (28) and can be decreased with PhNR/b-wave ratio application.

Photopic negative response evaluation in ocular hypertension and different stages of glaucoma

Ocular hypertension patients

Only one report on PhNR in OHT patients has been published (14). The results of this study suggest that the loss of RGC function by OHT patients was the result of an increase in intraocular pressure (IOP). Normalization of IOP may have effect RGC activity restoration. North et al. (14) reported 23% ($p = 0.018$) mean PhNR amplitude reduction in patients with untreated OHT compared to the controlled group. PhNR values of patients with OHT treated with anti-glaucomatous drops were normal. In the same study similar changes were seen in N95 amplitude of PERG. Based on the above described results, it seems that RGC function loss in OHT patients is present and can be detected in PhNR and PERG tests, even in patients with morphological changes in the optic nerve head. N95 amplitude of PERG was reduced by 22% in OHT patients and that change was similar to PhNR amplitude.

Glaucoma

Researches on human trials proved the relationship between the occurrence of glaucoma and the PhNR amplitude reduction (13,14,16,17,19, 22). PhNR sensitivity and specificity for detecting glaucoma, published by Viswanathan and Machida et al. (13,16) were 77–83% and 90% (70% and 87% for PhNR/b-wave ratio), respectively, indicating that this criterion can quite effectively distinguish glaucomatous from normal eyes (13,14,16,17,19). PhNR implicit time was reported to be prolonged in patients with POAG (19).

PhNR amplitude of POAG patients is reduced and the decrease in amplitude correlates with the degree of optic nerve damage represented by optic disc cupping and visual field loss. PhNR amplitude is reduced even when retinal sensitivity losses are small (13,14) or even not seen. Reduction of the PhNR amplitude and PhNR/b-wave amplitude ratio correlate significantly with the decrease in the MD of SAP patient with POAG (16). The PhNR and PhNR/b-wave ratio correlate linearly with decrease in the rim area and an increase of cup-to-disc ratio. Machida et al. (16), in studies on large number of patients (99 eyes of 53 patients with open-angle glaucoma) with wider range of disease stages, found the curvilinear regression comparing PhNR amplitude and PhNR/b-wave ratio against the MD. The curvilinear association of the PhNR with MD (dB) indicates that large changes of the PhNR amplitude correspond with a small loss of the MD, and the MDs could still be in the normal range, even when RGC loss is significant (14,16).

There is a linear correlation between RNFLT and PhNR or PhNR/b-wave ratio (16), which indicates that the function of RGCs declines proportionally to the neural loss in glaucoma.

Early glaucoma (MD > -6 dB)

Only three studies concerning PhNR have been based on patients with early glaucomatous visual field disturbances. The early changes appear locally and PhNR amplitude could be slightly reduced for a long time. PhNR amplitude and PhNR/b--wave ratio decrease in glaucomatous eyes even with mild visual field defect ($p < 0.05$) (16). When North et al. (14) excluded

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patients with advanced glaucoma with visual field mean deviation greater than -6 dB, he obtained 22% PhNR amplitude reduction in glaucoma patients. Sensitivity of PhNR amplitude in determining early glaucomatous changes is between 29–57% and 53% for PhNR/b-wave ratio (16,20).

Moderate glaucoma (-6 dB ≥ MD ≥ -12 dB)

In comparison to early glaucomatous damage, sensitivity of PhNR amplitude and PhNR/b-wave ratio in determining eye with and without glaucoma were 88% and 65% (16). There is no significant difference between PhNR and a special method, which obtains focal PhNR amplitudes in determining eyes with moderate glaucomatous impairment.

Advanced glaucoma (MD < -12 dB)

It should be emphasized that most scientific reports on the photopic negative response in the diagnosis of glaucoma compares the results of healthy individuals with those of glaucoma patients, without dividing patients according to the stage of desease, and are usually based on patients with advanced glaucoma (13,14,16,19,21,22,29). Kim et al. (19) analyzing PhNR amplitudes of patient with severe glaucoma found 48% of PhNR mean reduction. Means PhNR amplitudes of glaucoma and control group were: 15.83 ± 8.1 μV and 30.67 ± 10.02 μV, respectively (19). Sensitivity of PhNR amplitude and PhNR/b-wave ratio is the highest when severe glaucomatous changes occur and are on the level on 89% and 93% (16).

The results of our initial study describing PhNR responses in patients with advanced glaucoma are in agreement with those published by Kim et al. (19). Using similar conditions of stimulation: red against blue, brief stimulus, we performed PhNR recording in 8 glaucomatous eyes and in 8 healthy, age matched eyes. Reduction of mean PhNR amplitude in glaucomatous eyes in comparison to mean of PhNR amplitude of control group were 62% (glaucoma group: 12.21 ± 7.95 μV; control group: 32.21 ± 14.57 μV). Figure 2 presents example of PhNR amplitude in patient with advanced glaucomatous field loss, compared to PhNR amplitude in normal subject.

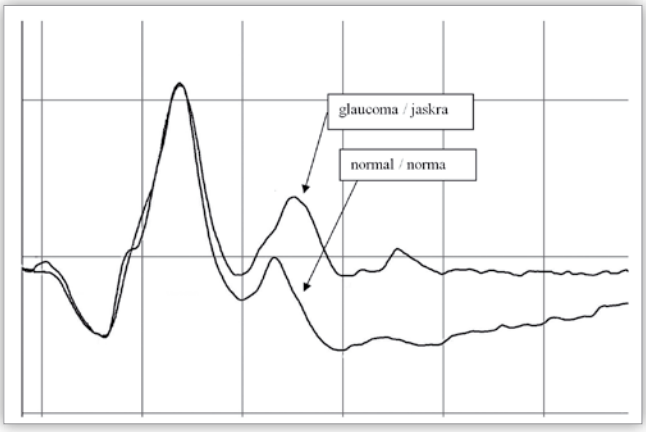

Fig. 2. Example of the patient with advanced glaucomatous field loss and PhNR amplitude reduction, compared to normal subject.
Ryc. 2. Przykładowe badanie pacjenta z zaawansowanym jaskrowym ubytkiem pola widzenia oraz redukcją amplitudy PhNR – dla porównania prawidłowy zapis.

Correlation between PERG and PhNR results

PERG amplitude is highly correlated with PhNR amplitude (9). It suggests a common origin of these potentials, which is in general agreement with previous studies (18,30). Also, a strong correlation between imaging parameters, such as retinal nerve fiber layer (RFNL) thickness (OCT), PERG and PhNR amplitudes is present. There is a reproducible relationship between optic nerve head topography and retinal function measured in the mentioned electrophysiological tests (14,29). Despite many convincing and reliable studies, the definite clinical value of PhNR amplitude in glaucoma is still not proved. In the publication of Cursiefen (21), only non-significant tendencies of an amplitude reduction in advanced glaucoma was found and there was no association between heavier or less severely damaged eyes with corresponding electrical responses. The explanation of these results could be the difference in stimuli condition to those usually used.

Focal PhNR in glaucomatous eyes

The focal ERG, first described by Colloto et al. (17), is now commercially available in Japan. The results from Machida's studies (16,20,28) demonstrated that specificities and sensitivities of tests were higher for the focal PhNR than for the full-filed PhNR, especially at the early stage of glaucoma. Sensitivity, when the combined criteria were used, reached 90.6% and 96.9% for the focal PhNR amplitude in the early stage of glaucoma (38.1% and 23.8% for full-field PhNR in the previous study, respectively) (20,28). There is a curvilinear relationship between MD (dB) of static perimetry and focal PhNR amplitude. For instance, 3 dB loss in the retinal sensitivity is approximately associated with 50% decrease in the focal PhNR amplitude at the early stage of glaucoma (20). Nakamura et al. (31) found that ganglion cell complex thickness gradually decreased through all the stages of glaucoma, PhNR response amplitude was reduced severely in early glaucoma and progress little as visual field defects increased.

The focal PhNR is impossible to record in patients with dense opacities of the ocular media, such as cataracts and vitreous opacities. In these cases full-field PhNR would be more reliable than focal PhNR. Additionally, full-field PhNR is more reliable and has lower CV than focal PhNR. Furthermore, it required approximately 5 min to accomplish all of the recording sessions of focal PhNR for each subject and 1 min of fixation, without eye movements during the recording, on each retinal area (28). Therefore cooperation of the patient is necessary for stable and reliable recordings.

Conclusion

PhNR is a promising tool in glaucoma neuropathy assessment. Up to date, definite value of PhNR has not been proved. Further studies are necessary to confirm the usefulness of PhNR in diagnosing glaucoma.

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