REVIEWS

Adv Clin Exp Med 2012, **21**, 5, 665–670
ISSN 1899–5276

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Heidelberg Edge Perimeter Employment in Glaucoma Diagnosis – Preliminary Report

Zastosowanie perymetru typu *Heidelberg Edge Perimeter* w diagnostyce jaskry – doniesienie wstępne

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

In recent years, the authors have seen huge progress in the diagnosis of eye diseases. One of the new diagnostic devices is HEP (Heidelberg Edge Perimeter) – for early diagnosis of glaucoma and its progression. It combines visual field test and HRT (Heidelberg Retina Tomograph), which allows authors to obtain the image of the mutual relation between the structure and the function of the sight organ. It could be also used to assess patients with impaired retina, optic nerve and neurological deficits. The SAP function is more suitable for the detection and monitoring of neurological deficits, moderately advanced and advanced glaucoma as well as other diseases associated with extensive or deep visual field deficits, such as ischemic optic neuropathy. FDF stimulus was designed specifically to detect early glaucoma-related changes in the visual field. For about a year, the Ophthalmology Clinic in Wrocław has owned a new, unique HEP perimeter. The authors present examples of patients diagnosed and treated at the Clinic, with respect to whom the perimeter results obtained using Octopus type perimeter and HEP contour perimeter have been compared. This method has its advantages: it is non-invasive, objective, provides the opportunity to repeat and compare results obtained from subsequent tests. The disadvantages are the difficulty in adapting to a new stimulus, which is not a circular light stimulus, but an outline that is hard to notice for some patients. Although according to the manufacturer the testing time should not exceed 4–5 minutes, it takes 14–15 minutes in many patients. The test is not suitable for patients showing lower manual skills and less attention and those who tire out easily. The HEP perimeter is an innovative method for diagnosing the earliest changes in ganglion cells, that is pre-perimetric glaucoma, or when changes in the visual field are undetectable in a standard test (**Adv Clin Exp Med 2012, 21, 5, 665–670**).

Key words: glaucoma, visual field, HEP (Heidelberg Edge Perimeter).

Streszczenie

W ostatnich latach obserwuje się duży postęp w diagnostyce chorób oczu. Jednym z nowych urządzeń diagnostycznych jest HEP (*Heidelberg Edge Perimeter*) – do wczesnej diagnostyki jaskry oraz jej progresji. Łączy ono badanie pola widzenia z HRT (*Heidelberg Retina Tomograph*), co pozwala na otrzymanie obrazu wzajemnej zależności struktury i funkcji narządu wzroku. Umożliwia to pełną ocenę perymetryczną pacjentów z zaburzeniami siatkówkowymi, nerwu wzrokowego, a także ubytkami neurologicznymi. Funkcja SAP jest bardziej odpowiednia do wykrywania i monitorowania ubytków neurologicznych, średniozaawansowanej i zaawansowanej jaskry oraz innych chorób związanych z rozległymi lub głębokimi ubytkami pola widzenia, takimi jak np. niedokrwienna neuropatia nerwu wzrokowego. Bodziec FDF został zaprojektowany specjalnie do wykrywania wczesnych zmian jaskrowych pola widzenia. Od około roku Klinika Oczna we Wrocławiu posiada nowy, unikatowy perymetr HEP. Autorzy przedstawiają przykłady pacjentów diagnozowanych i leczonych w Klinice, u których porównano wyniki perymetryczne, uzyskane za pomocą perymetru typu *Octopus* oraz perymetru konturowego HEP. Metoda ta ma swoje zalety: jest badaniem nieinwazyjnym, obiektywnym, dającym możliwość powtarzania i porównywania wyni-

ków wykonywanych podczas kolejnych badań. Wadami są: trudność w adaptacji do nowego bodźca, którym nie jest okrągły bodziec świetlny, ale dla niektórych pacjentów trudno zauważalny kontur. Chociaż wg producenta czas badania nie powinien przekraczać 4–5 min, to u wielu współpracujących pacjentów wynosi 14–15 min. Do badania nie kwalifikują się pacjenci mniej sprawni manualnie i wykazujący mniejsze skupienie uwagi, łatwo męczący się. Zaprezentowany niedawno perymetr HEP jest innowacyjną metodą pozwalającą na zdiagnozowanie najwcześniejszych zmian w komórkach zwojowych, czyli jaskry przedperymetrycznej, gdy zmiany w polu widzenia są niewykrywalne w standardowym badaniu (**Adv Clin Exp Med 2012, 21, 5, 665–670**).

Słowa kluczowe: jaskra, pole widzenia, perymetr konturowy HEP.

In recent years the authors have seen huge progress in the diagnosis and treatment of eye diseases. One of the new diagnostic tools is HEP (Heidelberg Edge Perimeter). It is a device for early diagnosis of glaucoma and testing the progression of the disease. It combines visual field testing and HRT (Heidelberg Retina Tomograph), which allows us to obtain the image of the mutual relation between the structure and function of the sight organ.

The HEP perimeter was first presented at the World Glaucoma Congress in Singapore in 2007. It combines the functions of standard automated perimetry (SAP) and a new unique stimulus, specific to the visual functions, called FDF (Flicker Defined Form). This allows the full range of perimeter assessment in patients with impaired retina, optic nerve and neurological deficits. FDF stimulus was designed specifically to detect early glaucoma-related changes in the visual field. The SAP function is more suitable for the detection and monitoring of neurological deficits, moderately advanced and advanced glaucoma as well as other diseases associated with extensive or deep visual field deficits, such as ischemic optic neuropathy. HEP can be used separately as a perimeter or in combination with HRT (Heidelberg Retina Tomograph) for complete assessment of structure and function in glaucoma.

Research on the causes of glaucoma-related damage has been conducted for a long time. It is now known that information from the retina can be transmitted to the brain by means of two systems: parvocellular and magnocellular system [1]. 80% of nerve fibres form the parvocellular system (p-type ganglion cells). It transmits information from small retinal ganglion cells. It is responsible for colour information, spatial vision and contrast sensitivity. Nerve fibres creating the system are thin and the transmission of signal is slow. Response to a stimulus is linear, proportional to the degree of stimulation or inhibition. The magnocellular system (M-type ganglion cells) represents 10% of nerve fibres. It transmits information from large retinal ganglion cells. It is responsible for the transmission of information changing over time – on movement and contrast. The nerve fibres are thick and the transmission of information is fast.

It is now known that giant retinal ganglion cells are damaged first and are the earliest to undergo apoptosis. This means that the function of the M-type ganglion cells is damaged first. Perimeter methods used to assess of the magnocellular system make early diagnosis of glaucoma possible.

FDF (Flicker Defined Form) was first described in 1991 by Ramachandran et al [2]. It involves the use of a stimulus with high temporal frequency, which produces an illusory edge [3, 4]. The dominant impression from the magnocellular system is assessed. The combination of the two phases of image viewing provides the tested person with an impression of contour or edge of the appearing stimulus.

Frequency doubling technology (FDT) perimetry used to date seems to be an illusion, but it is not. The general flash test does not utilise the frequency doubling illusion. Patients detect only flashes or movement. They do not see the difference of frequency doubling – only flashes [5, 6].

In FDT, the patient can see the stimulus prior to the illusion. In HEP, if they are able to see the stimulus, they can see the illusion (EDGE). EDGE is more selective for the magnocellular system.

In HEP, contour is the genuine illusion, not a simple flash. The patient can recognise the illusion only when the dorsal magnocellular pathway is stimulated. Selective illusion of contour in the dorsal magnocellular pathway allows for earlier detection of functional changes.

For about a year, the Ophthalmic Clinic in Wrocław has owned a new, unique HEP perimeter. Below the authors present examples of three patients diagnosed and treated at the Clinic, with respect to whom the perimeter results obtained using Octopus type perimeter and HEP contour perimeter have been compared.

Patient FI, aged 43, with wide angle glaucoma in both eyes diagnosed in March 2003, started her treatment at the Ophthalmic Clinic in September 2009, used Lumigan q.d. both eyes (BE) and Trusopt b.i.d. left eye (LE). Visual acuity was bilaterally 1.0, intraocular pressure in the right eye (RE) was 13 mmHg, and in LE was 12 mm Hg. Front sections bilaterally normal, central corneal thickness (CCT) 600 micrometers (–3) bilaterally, wide angle glaucoma bilaterally. Fundus in RE: disc no. 2 0.5–0.6, slight narrowing of the neuroretinal rim

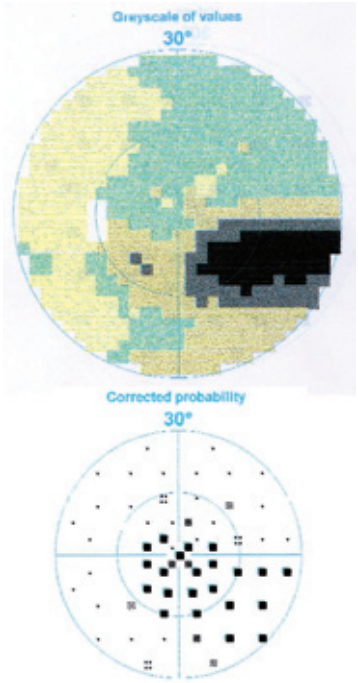

Fig. 1a. OCTOPUS LE

Ryc. 1a. OCTOPUS oko lewe

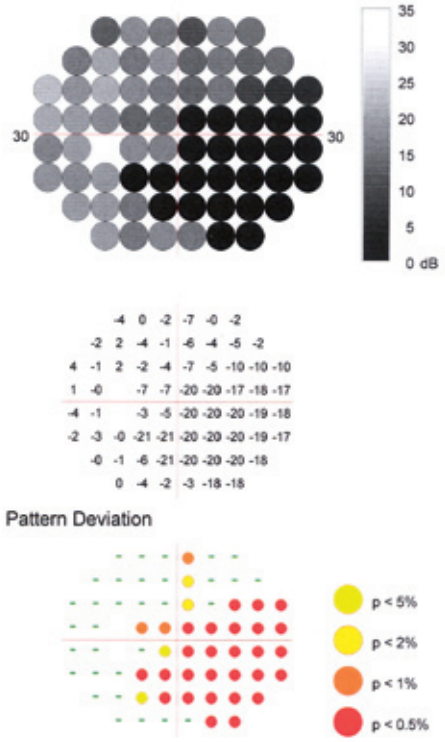

Fig. 1b. FDF LE

Ryc. 1b. FDF oko lewe

area from the top. Fundus in LE: disc no. 2 clearly damaged due to glaucoma, c/d = 0.8 vertical, a distinct narrowing of the neuroretinal rim area from the top and bottom, visible holes in the cribriform plate. Visual field in RE – correct, LE – curved, deep scotoma in the lower-nasal quadrant, reaching the centre.

In follow-up tests performed until August 2010, the visual field in RE was correct, in LE – stable deficits in the centre and bottom of the visual field. In optical coherence tomography (OCT) nerve fibre layer thickness: RE – within normal limits from the bottom, LE – glaucoma-related damage: top-temple, reaching from the top. During follow-up, intraocular pressure in BE remained in the range of 9–14 mm Hg.

In August 2010, a follow-up perimeter test was performed on the Octopus perimeter, and FDF test on HEP perimeter (ASTA Standard 30-2). In the visual field (Octopus perimeter), single relative central and paracentral deficits were found in RE (MD 0.0, LV 6.7, RF 0.0). In the visual field in LE, merging scotoma was found in the lower-nasal quadrant covering the central visual field (MD 8.4, LV 85, FF 0.0). In the FDF test, deficits in the lower-nasal visual field in LE were found, covering the central field, and in addition scotoma in the upper-nasal quadrant, that is more lesions were found than in standard perimetry (Fig. 1a, Fig. 1b).

Patient WJ, aged 59, observed due to periodic increases in intraocular pressure, subject to follow-up in the Ophthalmic Clinic from August 2010. The previously performed diurnal curve test showed pressure in the following ranges: RE 16–21, LE 19–24. Pressure on the day of the first test in the clinic (after CCT) was 20 (RE) and 22 (LE). Corrected visual acuity bilaterally 0.9/1.0, corrected visual acuity for near vision bilaterally D-0.5. HRT in RE and LE – normal (c/d RE = 0.37, c/d LE = 0.27), nerve fibre layer thickness in OCT – normal. Optic disc test showed no indication of glaucoma-related damage bilaterally: optic discs are pink, c/d = 0.3.

In a standard perimetric test single paracentral relative deficits were found in BE: LE (MD -1.22, LV 4.03, RF 0.92), LE (MD –2.1, LV 2.81, RF 0.91) (Fig. 2a, Fig. 2b). The patient was twice subject to the ASTA Standard 30-2 test using HEP edge perimeter. In the first test, several relative, absolute defects were found in RE in the lower-nasal quadrant, while in the second test conducted 2 months later the quantity of defects in the same quadrant was smaller. In LE in the first test, few relative, absolute defects in the lower and upper nasal quadrant were detected, and single defects in the temporal-bottom quadrant. The follow-up test did not confirm the existence of these defects, since only single scotomas in the lower-nasal quadrant were found (Fig. 2c, Fig. 2d).

Patient BM, aged 38, reported to the glaucoma clinic at the Ophthalmic Clinic after 8 years of treatment in the local clinic because of glaucoma.

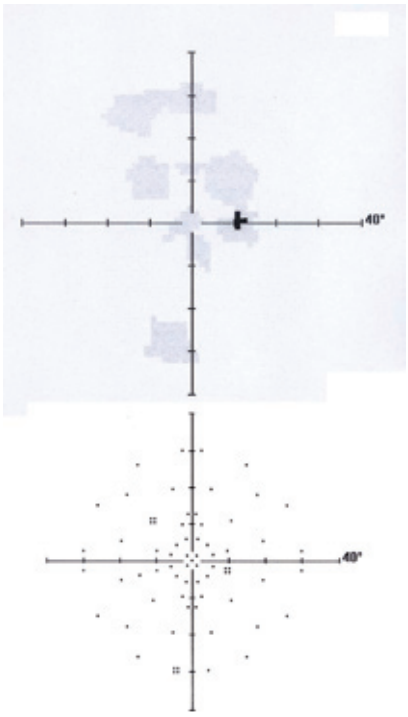

Fig. 2a OCULUS RE

Ryc. 2a OCULUS oko prawe

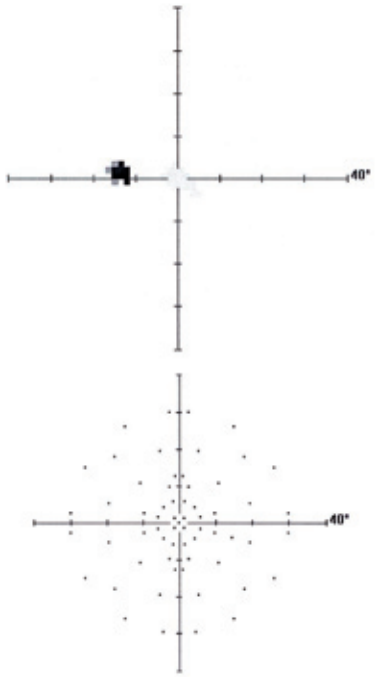

Fig. 2b. OCULUS LE

Ryc. 2b. OCULUS oko lewe

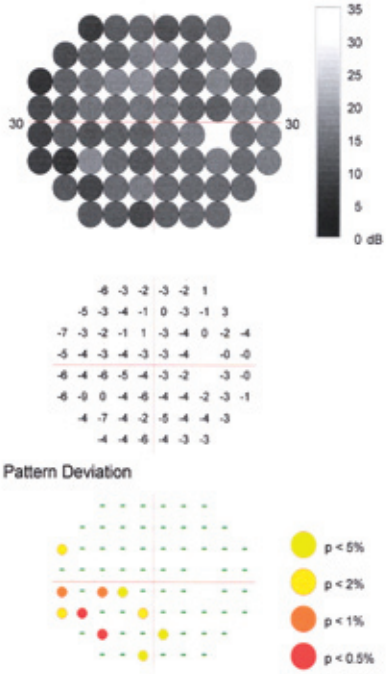

Fig. 2c. FDF RE

Ryc. 2c. FDF oko prawe

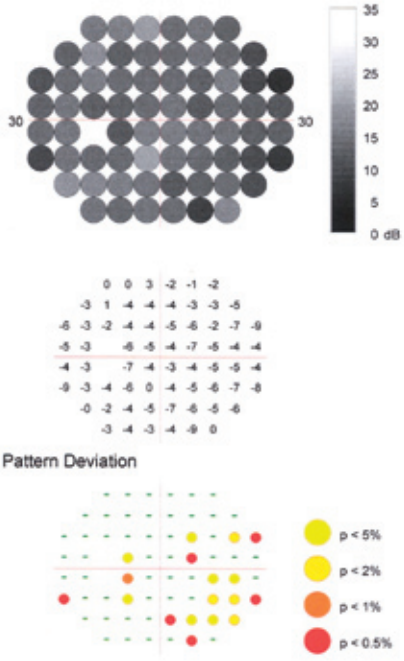

Fig. 2d. FDF LE

Ryc. 2d. FDF oko lewe

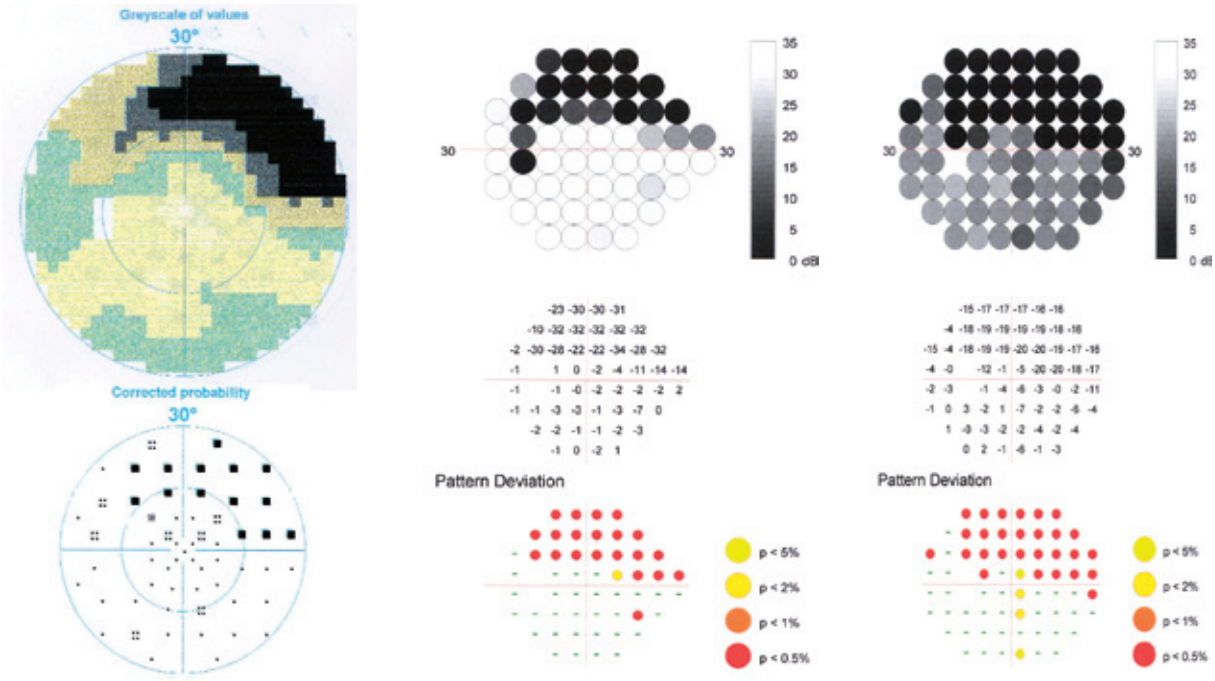

Fig. 3. a) OCTOPUS LE, b) SAP LE, c) FDF LE

Ryc. 3. a) OCTOPUS oko lewe, b) SAP oko lewe, c) FDF oko lewe

She applied Travatan q.d. LE. Intraocular pressure in RE = 12, in LE = 11. Visual acuity in BE was 1.0. Filtration angles were open bilaterally. The front section was normal bilaterally. Fundus in RE normal, disc correct, c/d = 0.3. Fundus in LE: optic nerve disc no. 2 with a sloping temporal wall, c/d = 0.7, neuroretinal rim area narrowed from top to bottom. Standard visual field test using Octopus apparatus: RE – normal (MD 0.2, CV 4.3), LE – visible defect in the nasal-upper field reaching the centre (MD 7.6, CV 78.0) (Fig. 3a). In HEP visual field defects visible in the SAP test were similar to those seen on Octopus, while the FDF test demonstrated deeper defects in the nasal-upper field proving the progression of glaucoma-related damage and the subsequent changes in the field of view, still invisible in standard perimetry (Fig. 3b, Fig. 3c).

Discussion

For many years, researchers have been looking for the optimal perimeter test method allowing us to detect early deficits. The blue on yellow method (short-wave automatic perimetry, SWAP) seemed to be a good method to detect early changes. It differs from classical perimetry by appropriately selected wavelength of blue light used for stimulus presentation, the size of the point as well as the colour and brightness of the background on which the point is presented. Yellow colour of the background light (light with a wavelength of above 530 nm) blocks the ability to receive light pulses through the rods, which are responsible for the reception of red and green, while exerting little effect on the cells responsible for the reception of blue. Stimulation of retina with blue light (with a wavelength of about 440 nm) allows for the selective diagnosis of the blue rods. The basic premise of this test is a theory of selective damage to cells responsible for the reception of blue (earlier than the cells responsible for the reception of green and red) in the early stages of glaucoma. It is also believed that this test verifies one of the pathways of the vision system that cannot be replaced by other mechanisms of reception [7].

The detection of p- and M-type ganglion cells and the definition of their functions have been revolutionary. Early studies described ganglion cell death in glaucoma as being morphologically similar to a process apoptosis [8]. Glial cells, including both astrocytes and Müller cells in the retina, and astrocytes and microglia in the optic nerve head, show dramatic changes in their behaviour and patterns of gene expression in glaucoma. The results of Vickers et al. research demonstrated that experimental glaucoma can lead to changes in neurochemical features of both the M- and p-pathways in the lateral geniculate nucleus [9]. The data is consistent with the notion that while glaucoma may preferentially cause damage to M cells in the retina, p cells are also affected. Many scientists are looking for rapid and objective assessment methods of magnocellular deficits associated with glaucoma, such as, for example, electrophysiological

techniques [10]. Zemon et al. have shown that the magnocellular pathway can be assessed through the application of the icVEP (Visual Evoked Potential) technique.

The discovery that M cells are damaged first has become the basis for further research.

Before putting the HEP perimeter into use, the best diagnostic method was frequency doubling perimetry (FDT, Matrix apparatus), using light stimuli in the form of varying stripes to test the visual field. The human eye can see twice as many "flickering" bars than is actually presented. These stimuli selectively stimulate M cells, which allows for early detection of glaucoma. It has high sensitivity in distinguishing healthy subjects from those suffering from glaucoma. The printout of the graphic test is similar to the result obtained using the Humphrey apparatus.

The recently presented HEP perimeter is a innovative method for diagnosing the earliest changes in ganglion cells, that is pre-perimetric glaucoma, or when changes in the visual field are undetectable in a standard test.

This method has its advantages: it is non-invasive, objective, provides the opportunity to repeat and compare results obtained from subsequent tests.

Authors' short experience allows them to describe the disadvantages of the device. It is the difficulty in adapting to a new stimulus, which is not a circular light stimulus, but an outline that is hard to notice for some patients. Although according to the manufacturer the testing time should not exceed 4–5 minutes, it takes 14–15 minutes in many patients. The test is not suitable for patients showing lower manual skills and less attention and those who tire out easily.

As in any perimetric test, it should be taken into account that only the scotoma reappearing in follow-up tests should be assessed. Therefore, the effect of learning must be taken into account. It is very well visible in the second patient described by us, in whom the number of deficits in the visual field was reduced in the second test, and also the testing time was shortened by approximately 2 minutes. It should be also noted that the observed visual field deficits are not always related to glaucoma, so the interpretation of results should be thoughtful. Undoubtedly, however, despite these above-mentioned defects, the HEP test represents a breakthrough in perimetry and, with the improvement of the method, will allow for early detection of early deficits.

References

[1] Basic and Clinical Science Course: Jaskra. Urban&Partner, Wrocław 2006, 1st ed., 5–128.

[2] **Ramachandran VS, Rogers-Ramachandran D:** Phantom Contours: A New Class of Visual Patterns that Selectively Activates the Magnocellular Pathway in Man. Bull Psychonom Soc 1991, 29, 391.

[3] **Rogers-Ramachandran D, Ramachandran VS:** Psychophysical Evidence for Boundary and Surface Systems in Human Vision. Vision Res 1998, 38, 71–77.

[4] **Flanagan JG, Williams-Lyn D, Trope GE, Hatch W, Harrison E:** The Phantom Contour Illusion Letter Test: A New Psychophysical Test for Glaucoma? Perimetry Update 1994/1995.

[5] **Quaid PT, Flanagan JG:** Defining the limits of flicker defined form: effect of stimulus size, eccentricity and number of random dots. Vision Res 2005, 45(8), 1075–1084.

[6] **Quaid PT, Simpson TL, Flanagan JG:** Frequency doubling illusion: detection vs. form resolution. Optom Vis Sci 2005, 82(1), 36–42.

[7] **Teesalu P, Airaksinen PJ, Tuulonen A:** Blue-on-yellow visual field and retinal nerve fiber layer in ocular hypertension and glaucoma. Ophthalmology 1998, 105(11), 2077–2081.

[8] **Nickells RW:** Ganglion cell death in glaucoma: from mice to men. Vet Ophthalmol 2007, 10 Suppl 1, 88–94.

[9] **Vickers JC, Hof PR, Schumer RA, Wang RF, Podos SM, Morrison JH:** Magnocellular and parvocellular visual pathways are both affected in a macaque monkey model of glaucoma. Aust N Z J Ophthalmol 1997, 25(3), 239–243.

[10] **Zemon V, Tsai JC, Forbes M, Al-Aswad LA, Chen CM, Gordon J, Greenstein VC, Hu G, Strugstad EC, Dhrami-Gavazi E, Jindra LF:** Novel electrophysiological instrument for rapid and objective assessment of magnocellular deficits associated with glaucoma. Doc Ophthalmol 2008, 117(3), 233–243.

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Conflict of interest: None declared

Received: 19.12.2011
Revised: 11.07.2012
Accepted: 8.10.2012