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Research Article

Glaucoma: May new technologies help in early diagnosis?

Abstract

Purpose: to identify new functional parameters that may help in the early primary open angle glaucoma (POAG) diagnosis.

Materials and Methods: 40 subjects were enrolled: 20 healthy subjects and 20 POAG patients, all aged between 30 and 65 years, for a total of 79 eyes, including 40 healthy and 39 POAG. All subjects underwent microperimetric test, Nidek MP-1 (NAVIS, software version 1.7.6; Nidek Technologies, Japan) using Humphrey 10-2 pattern with manual polygonize of upper and lower hemifields. Mean hemifield sensitivity was evaluated.

Results: Analysis reported significant differences of mean retinal sensitivity of the upper hemifields between POAG and healthy subjects ($p < 0.025$), thus highly significant. Equally significant ($p < 0.025$) was the comparison of ratio (upper / lower hemifield) between the two groups. There was not statistically significant difference of sensitivity of lower hemifields ($p > 0.05$).

Conclusion: significant difference was observed between healthy and POAG groups using Humphrey 10-2 vertical asymmetry index. Therefore, it appears to be an unprecedented microperimetric diagnostic tool.

Introduction

Glaucoma is a degenerative optic-nerve disease, characterized by progressive retinal ganglion cells loss that leads to visual field functional deficit and typical optic nerve head alterations. High intraocular pressure (IOP) represents the main risk factor.

Untreated glaucoma can lead to a severe loss of visual capacity, due to a total loss of peripheral visual field and, in 15% of cases, it degenerates in blindness [1]. Nowadays 90 million people in the world are suffering from glaucoma, of which 9 million in Europe [2].

High intraocular pressure (IOP) is the most important factor for onset and progression of optic nerve degeneration in glaucoma patients. Optic nerve head degeneration in glaucoma is characterized by progressive retinal ganglion cells and their axons loss, due to an apoptotic process, whose trigger, even today, remains matter of debate.

Current therapies are able to delay or, at best, to stop disease progression. However, once a ganglion non-reversible apoptotic damage occurred, it will be not possible to fully restore the functional deficit.

About that, it is highlighted the importance of identification of new functional parameters that can be used as markers of suffering ganglion cells, anticipating the occurring of non-reversible apoptotic damage.

Perimetry is the most commonly used functional test in glaucoma diagnosis and follow-up. This test examines the visual field, i.e. the region of space visible from a steady eye in the primary position. Visual field test provides parameters to define functional damage severity. Computerised perimetry is mainly applied in glaucoma diagnosis and follow-up. Microperimetry is a functional test that combines a standard computerised perimetry with retinography, providing a fundus perimetry. This technique allows us to study fixation and retinal sensitivity threshold, setting exactly retinal spots that are stimulated by a system implemented with eye movements tracking.

The main advantages of microperimetry are the possibility to obtain accurate fundus tracking during test execution, to study fixation stability and the possibility to overlay the sensitivity map with a retinography [3]. Moreover, thanks to eye tracking system, data are independent of eye movements and they are exactly related to the stimulated areas. This result

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cannot be obtained with standard computerised perimetry [4]. Typically, glaucoma damage, on the microperimeter, consists in decreased retinal sensitivity of macular area and, especially, of peripapillary area, in direct correlation with anatomical RNFL damage [5]. Sensitivity of MP-1 microperimeter in detecting subjects suffering from glaucoma, strongly correlates with standard Humphrey 10-2 perimetry [6]. In 2012, a study reported that MP-1 has a greater predictability than the standard Humphrey 10-2 perimetry [7].

In last years, research has been directed toward identifying the most effective test to screen at-risk subjects in order to detect those patients requiring an early treatment.

Thus, our study aims to identify new functional parameters that can help early POAG diagnosis.

According to the latest research trends, we carried out a microperimetric study dividing the whole field in two hemifields, upper and lower, with an approach that had never been reported in literature.

Materials and Methods

Between March 2015 and July 2015, at Division of Ophthalmology, "La Sapienza University of Rome" (" A. Fiorini" Hospital; Terracina, Italy), 40 subjects were enrolled (18 males and 22 females), of which 20 suffering from POAG (13 males and 7 females) and 20 healthy subjects (5 males and 15 females). Mean age of POAG group is 56.9 years. Mean age of control group was 53.7 years. The difference of ages between the two groups was not statistically significant (p = 0.15) (Table 1).

According to ICD-9 classification, mild or early stage glaucoma is defined as optic nerve abnormalities consistent with glaucoma but no visual field abnormalities on any white-on-white visual field test, or abnormalities present only on short-wavelength automated perimetry or frequency-doubling perimetry.

Inclusion criteria for early stage POAG patients were: IOP higher than 21mmHg in at least two separate measurements with Goldmann applanation tonometry corrected according to pachymetry; open iris - corneal angle at gonioscopy; no visual field abnormalities on any white-on-white visual field test, or abnormalities present only on short-wavelength automated perimetry or frequency-doubling perimetry; at least one RNFL quadrant out of limit values ; topical b-blockers or prostaglandins monotherapy in both eyes; refractive error not exceeding + 3,00D and -3,00D; corrected visual acuity at least 10/10 and smallest font in the near vision ; age between 30 and 65 years.

Table 1: Enrolled groups. M: male; F: female; SD: standard deviation.

	HEALTHY SUBJECTS	POAG
Number of subjects	20	20
Number of eyes	40	39
Gender M/F	5/15	13 / 7
Mean age ± SD	53.7 ± 7.7	56.9 ± 11.5

Exclusion criteria for POAG were: media opacities; primary narrow or closed angle glaucoma and secondary glaucoma; history of retina and/or posterior segment surgery; any other eye diseases; use of systemic diuretics/b-blockers and corticosteroid medications.

Inclusion criteria for healthy subjects were: age between 30 and 65 years; no eye diseases: media opacities, optic nerve diseases, retinopathy and uveitis; no retina and/or posterior segment surgery or a history about it; refractive error not exceeding + 3,00D and -3,00D; corrected visual acuity at least 10/10 and smallest font in the near vision; IOP less than or equal to 20 mmHg measured with Goldmann applanation tonometry, corrected according to pachymetry, with no current treatment.

Exclusion criteria for healthy subjects were: use of systemic diuretics/blockers and corticosteroid medications; family history for glaucoma.

In POAG group, one patient showed a unilateral retinopathy, so that one eye was excluded from our study. Therefore we studied a total of 79 eyes: 39 POAG eyes and 40 healthy eyes.

It was used a Nidek MP-1 (NAVIS, software version 1.7.6; Nidek Technologies, Japan) microperimeter , consisting of an infrared fundus camera, a second color fundus camera (CCD camera progressive scan color, resolution 780 x 580 pixels, equipped with xenon flash) and a PC with NAVIS operating system for data acquisition and processing.

IR fundus camera is equipped with a lens system for patient's refractive defects correction, in a range of -12.5 / +16 diopters, so that it is possible to obtain a more accurate functional assessment and a proper focus the retinal images. Through the color fundus camera, it is possible to take snapshots of fundus and to obtain a high quality digital picture. Functional sensitivity threshold tests can be executed directly, using the color retinography as landmark, overlaying with the sensitivity map obtained through IR fundus camera. Overlay is performed by a semiautomatic system, which places two landmarks on particular retinal areas; usually, it takes as reference the branches of superficial retinal vessels that offer a higher contrast on retinal structures. Test running is shown on a LCD display and directly controlled by the software.

For stimulation is used a 20 dB scale of attenuation, with maximum brightness of 400 asb. Target light is usually set at 100 asb. MP-1 also offers five sizes of targets that correspond to the I to V of Goldmann perimeter. We used a target size equivalent to Goldmann III.

To examine enrolled subjects, we used the Humphrey 10-2 pattern, projecting 68 stimuli in 20 central degrees and 200 ms projection time.

Subject was seated in a dark room and was instructed to place the head on the chin rest and to press the button every time a light stimulus of varying intensity is seen. One eye at a time is examined, covering the other one. No mydriatic drugs

are used. The eye is automatically detected by MP-1 and the working distance is about 50 mm. Once data has been analysed and processed, we performed a manual polygonize on the overlay image, consisting of retinography and sensitivity map, dividing the full field in two symmetrical hemifields: upper and lower. Vertical ratio, asymmetry index, was calculated as upper hemifield/lower hemifield.

Statistical analysis

For the descriptive statistics we used quantitative and qualitative variables analysed using a general linear model. Qualitative variables concerning the study population were analysed using the $\chi2$ test. Quantitative data were reported as mean ± standard deviation. The quantitative data analysis was performed using the Shapiro-Wilk test to verify the normality of distribution. Normality was rejected for values of p > 0.05. For the normal distributions has been used an unpaired Student's t test to compare the two populations. The Pvalue (probability value) obtained was considered statistically significant for values ($p \leq 0.05$).

Results

Analysis of the 40 enrolled subjects reported significant differences of mean retinal sensitivity of the upper hemifields between POAG and healthy subjects ($p < 0.025$), thus highly significant (Table 2).

Equally significant ($p < 0.025$) was the comparison of ratio (upper / lower hemifield) between the two groups (Table 2).

Instead, there was not statistically significant difference of sensitivity of lower hemifields ($p > 0.05$) (Table 2).

Discussion

Data obtained with Nidek MP-1 using Humphrey 10-2 pattern and polygonize, showed that retinal sensitivity is higher in healthy group compared to POAGs, confirming that glaucoma leads to retinal sensitivity decrease [4].

In upper hemifields, difference was statistically significant ($p < 0.025$).

In lower hemifields, difference between the control group and POAGs was not significant ($p = 0.071$). However, the mean of healthy subjects is higher than POAGs. Also lowest peak values indicate a greater performance of healthy subjects compared to POAGs: regarding upper hemifield, lowest sensitivity recorded in POAGs is 8.4 dB, compared to 14.8 dB recorded in the worst healthy subject; about lower hemifield, the lowest sensitivity recorded in POAGs was 9.9 dB, compared to 14.8 dB recorded in the control group. Highest sensitivity, however, were found to be 20 dB in both hemifields both in the control group and in POAGs.

Particularly interesting is ratio between the upper/lower hemifields. Comparison between control group ratio and POAG group's one, revealed significantly higher asymmetry ($p < 0.025$) in the POAGs.

These data confirms diagnostic power of hemifield-test in identifying glaucoma retinal damage. Our results are in agreement with findings of other studies on asymmetry, confirming that patients suffering from POAG have higher vertical asymmetry than healthy subjects [8]. A recent study showed that different asymmetry indices, have different sensitivity in detecting the POAG damage [9]. In contrast to our results we have found a 2013 study, with a similar number of patients, showing no advantages in using microperimetry in predicting a preperimetric defect in early POAG patients. In this study, Klamann et al, demonstrate that only reduction of RNFL thickness seem to occur earlier than visual field defects in early POAG [10].

However, to date, it has not ever been reported any study adopting our protocol.

Our vertical asymmetry index, obtained through hemifields polygonize on Humphrey 10-2, had never been described before. Therefore, it appears to be an unprecedented microperimetric diagnostic tool.

Conclusion

Microperimetry is confirmed as useful test in detecting glaucoma functional damages, especially using hemifield-tests.

Moreover, it provided an innovative vertical asymmetry index, potentially useful in early POAG diagnosis.

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Table 2: Results. dB: decibel; SD: standard deviation.

	HEALTHY SUBJECTS	POAG	p value
UPPER Hemifield	19.1 dB ± 1.38 (SD)	18.1 dB ± 2.33 (SD)	0,022
LOWER Hemifield	19.16 dB ± 1.38 (SD)	19.0 dB ± 1.94 (SD)	0,071
RATIO (Upper/Lower)	1.0 dB ± 0.03 (SD)	0.9 dB ± 0.05 (SD)	0,024

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