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Comparative study of the retinal nerve fibre layer thickness performed with optical coherence tomography and GDx scanning laser polarimetry in patients with primary open-angle glaucoma

Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
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Summary

Background:

We compared the parameters of retinal nerve fibre layer in patients with advanced glaucoma with the use of different OCT (Optical Coherence Tomograph) devices in relation to analogical measurements performed with GDx VCC (Nerve Fiber Analyzer with Variable Corneal Compensation) scanning laser polarimetry.

Material/Methods:

Study subjects had advanced primary open-angle glaucoma, previously treated conservatively, diagnosed and confirmed by additional examinations (visual field, ophthalmoscopy of optic nerve, gonioscopy). A total of 10 patients were enrolled (9 women and 1 man), aged 18–70 years of age. Nineteen eyes with advanced glaucomatous neuropathy were examined. 1) Performing a threshold perimetry Octopus, G2 strategy and ophthalmoscopy of optic nerve to confirm the presence of advanced primary open-angle glaucoma; 2) performing a GDx VCC scanning laser polarimetry of retinal nerve fibre layer; 3) measuring the retinal nerve fibre layer thickness with 3 different optical coherence tomographs.

Results:

The parameters of the retinal nerve fibre layer thickness are highly correlated between the GDx and OCT Stratus and 3D OCT-1000 devices in mean retinal nerve fibre layer thickness, retinal nerve fibre layer thickness in the upper sector, and correlation of NFI (GDx) with mean retinal nerve fibre layer thickness in OCT examinations. Absolute values of the retinal nerve fibre layer thickness (measured in μm) differ significantly between GDx and all OCT devices.

Conclusions:

Examination with OCT devices is a sensitive diagnostic method of glaucoma, with good correlation with the results of GDx scanning laser polarimetry of the patients.

key words:

scanning laser polarimetry • optical coherence tomography • primary open-angle glaucoma

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BACKGROUND

Apoptosis of retinal ganglion cells (RGC) underlies glaucomatous neuropathy, which results in pathologic changes of the nerve fibre layer [1]. A number of pathomechanisms triggering this type of 'programmed' cell death are recognized: hypoxia, increase of intraocular pressure, decrease of BDNF (Brain-Derived Neurotrophic Factor) concentration in cells, and local increase of glutamate concentration. The final effect of these processes is the loss of RGC population, with its initial number being 1.2–1.4 million cells. The degeneration of RGC is accompanied by the atrophy of their axons that create the nerve fibre layer in the retina. In its incipency, fibres become less parallel and form a less organized structure which, in imaging examination, results in polarization of the light passing through the layer. In subsequent stages the whole layer decreases in thickness, which is also visible in imaging examination as sectorial defects or spilled layers of retinal nerve fibres.

The basis of early diagnosis of glaucoma is the earliest detection of pathologic (morphologic) changes before other changes (ie, functional damage of visual field, initially as relative and later as absolute defects) appear in the cascade of glaucomatous neuropathy.

Recent reports of elements common between the pathomechanism of the damage of ganglion cells (which form the fibres of the optic nerve in glaucoma) and multiple sclerosis have appeared in the literature [2]. Due to this, it seems advisable to test the methods of measuring parameters of nerve fibre layer as a means of diagnosis and monitoring of multiple sclerosis, especially when it is accompanied by retrobulbar optic neuritis. Such tests are currently carried out by the research team of our clinic.

In recent years 2 types of devices were introduced to the early diagnosis of pathologic changes of nerve fibre layer: scanning laser polarimeter (GDx) and optical coherence tomographs (OCT) [3,4].

The older method, already common in the diagnosis of glaucoma, is the laser scanning polarimetry GDx. During the examination, light emitting from a laser diode and polarized in 2 perpendicular surfaces is introduced into the eye. Next, these 2 polarized beams pass through the retina. Because of the idiosyncratic, tubular structure of the nerve fibre layer, each of these beams passes through this layer at a slightly different velocity – the more 'accordant' the configuration of layers is with the direction of wave propagation, the faster this wave passes through. After the light is reflected off pigment epithelium, it returns to the detector, again passing through nerve fibre layer and the whole process repeats. Mutual delay of the 2 components of the polarized light registered by the device is converted to the thickness of nerve fibre layer in micrometers (called 'polarimetric micrometers' because this parameter also describes the level of arrangement of layers, before the change of thickness of the whole layer appears). The examination is performed in the ellipsoidal belt around the optic disc. In the state-of-the-art GDx devices several measurement issues have been overcome. These issues stem from the fact that other structures of the eye, possessing the feature of birefringence (cornea, sclera), can also generate changes

in the velocity at which laser beams pass through and which appear as artefacts in the examination.

Optical coherence tomography is a method of laser scanning imaging, initially introduced for displaying the longitudinal section of retina in different condition, and usually concerning macula. The currently used version of the tomograph, where measurements are based on Time-Domain (TD-OCT), is being gradually replaced by a newer one based on Spectral Domain (SD-OCT). In the analysis of the laser wave reflected off the retina to a detector, a system of rotating mirrors providing interference for the wave under examination and the reference wave (TD-OCT) was replaced by a static spectrometer (SD-OCT), which analyses the entire light spectrum reflected, absorbed and scattered by each layer of the retina in a different manner. Images of longitudinal sections of consecutive layers are in very high resolution, up to 4–5 micrometers.

In recent years many OCT devices were fitted with an additional glaucoma module, enabling a possibility of measuring the retinal nerve fibre layer. The device, after distinguishing the nerve fibre layer, measures its thickness in the entire measurement window and, similarly to GDx examination, in the ellipse around the optic nerve. The major problem with this type of examination of nerve fibre layer is artefacts, as this layer lies superficially, near the vitreoretinal junction, and different types of unevenness (vessels, adhesions, tractions, condensation of vitreous, epiretinal membranes) can generate errors. Such errors can be a result of an erroneous determination of the nerve fibre layer's external boundary, which may be a result of, for example, lowered clarity of optical media.

It is still disputed which of the above-mentioned devices reflects the actual image of the nerve fibre layer more faithfully and which will detect the earliest morphological changes specific for glaucoma [5–8], ocular hypertension, preperimetric glaucoma [9,10] or other diseases accompanied by the neuropathy of optic nerve such as multiple sclerosis [11,12].

The purpose of our study was to compare different types of optical coherence tomographs with scanning laser polarimeter in terms of measurements of the retinal nerve fibre layer thickness in patients with advanced primary open-angle glaucoma. The second aim was to study in this group the correlation of classifying parameter of the GDx VCC device (in accordance with internal normative databases) the NFI (Nerve Fibre Index), which allocates the results to groups 'normal', 'glaucomatously suspicious', or 'abnormal' with mean thickness of nerve fibre layer measured with different OCT devices.

MATERIAL AND METHODS

The study enrolled patients of the Clinic of Ophthalmology at the Medical Centre of Postgraduate Education with advanced primary open-angle glaucoma, diagnosed and confirmed by additional examinations (static computer perimetry, stereoscopic ophthalmoscopy of optic nerve, gonioscopy), previously treated conservatively.

A total of 10 patients were enrolled (9 women and 1 man), aged 18–70 years of age, in which 19 eyes with advanced

Table 1. Correlation of retinal nerve fibre layer thickness parameters between different optical coherence tomographs and a GDx scanning laser polarimeter. In the OCT Copernicus there are no separate measurements possible for upper and lower sectors.

GDx VCC	OCT Stratus			3D OCT 1000			OCT Copernicus
	Mean	In upper sector	In lower sector	Mean	In upper sector	In lower sector	Mean
Mean	0.556** (0.674**)			0.413* (0.617**)			-0.118 (-0.133)
In upper sector		0.527** (0.681**)			0.553** (0.477*)		
In lower sector			0.165 (0.257)			0.041 (0.103)	
NFI	-0.527** (-0.763**)			-0.275 (-0.610**)			-0.104 (-0.064)

* $p < 0.05$ (Pearson's Correlations); ** $p < 0.01$ Correlations for small groups Kendall's Tau b.

glaucomatous neuropathy were examined. As an indicator of the advancement of glaucoma, we considered specific morphological changes of the optic disc, with the cup measured by the C/D ≥ 0.7 ratio and the existence of absolute, specific for glaucoma visual field defects of nasal step type, and quadrant defect connected or not with the blind spot, with mean deviation of perimetry MD > 6 dB.

The condition for enrolling patients in the study was obtaining permission to perform examination and the existence of clear media, allowing an accurate OCT examination and GDx VCC polarimetry resulting in high-quality scans, and a lack of surgical operations and laser surgeries related to the organs of sight in patients' medical histories.

In all patients enrolled for the study, full ophthalmological examination was performed, consisting of visual acuity examination, measurement of intraocular pressure, biomicroscopic examination of the anterior segment and funduscopy by Volk lens. In all patients Octopus 101 perimetry was also performed, threshold strategy G2 in the area of 30 degrees, to confirm defects specific for advanced primary open-angle glaucoma.

In the next stage, GDx scanning laser polarimetry of the retinal nerve fibre layer was performed with a VCC (Variable Corneal Compensation) version of the device, allowing an individual compensation of birefringence of the cornea, which (without applying such optical compensation) can generate artefacts affecting the quality of the examination's results. Within a month, measurement of the retinal nerve fibre layer thickness was performed in all patients, with 3 different optical coherence tomographs with the use of the glaucoma diagnostic module.

The optical coherence tomographs used in the study were: OCT Stratus (Zeiss) – a time-domain tomograph (TD-OCT), OCT Copernicus (Optopol), and 3D OCT 1000 Topcon, both spectral domain tomographs (SOCT).

Statistical analysis included the results of measurements of retinal nerve fibre layer thickness in the upper and lower sectors (defects in these regions are most characteristic for glaucoma); total, mean thickness of nerve fibre layer in the

entire examined area; and the NFI (Nerve Fibre Index), which describes the probability of glaucoma on the basis of collective analysis of all parameters of examination. The NFI can range from 0 to 100. In the classification determining the probability of glaucoma, the following division is applied: 0–25 = normal results, 26–50 = suspicious results, and 51–100 = abnormal results.

RESULTS

The parameters of the retinal nerve fibre layer thickness are highly correlated between the GDx and OCT Stratus and 3D OCT-1000, especially in terms of nerve fibre layer mean thickness, nerve fibre layer thickness in the upper sector, and correlation of NFI (GDx) with mean nerve fibre layer thickness in OCT examinations (Table 1).

A good correlation occurs in statistical classification that allocates the examined sectors of the nerve fibre layer to 'normal', 'suspicious', and 'abnormal' groups between the GDx device and the results of measurements of retinal nerve fibre layer thickness in OCT Stratus and 3D OCT-1000.

Absolute measured values of the retinal nerve fibre layer thickness (in μm) differ significantly (almost 2-fold) between GDx and all OCT devices (Table 2).

DISCUSSION

Parameters of the retinal nerve fibre layer thickness, both mean and for each individual sector, which were performed with OCT Stratus and 3D OCT 1000, correlated highly with analogical measurements performed with GDx. These 2 tomographs were the best in distinguishing both the inner (vitreo-retinal) as well as the outer boundary of the retinal nerve fibre layer. In the case of OCT Copernicus, more artefacts appeared and this could have been the reason for a lower correlation of these parameters.

As for the NFI index, considered as the most important one in the case of GDx examination, it correlated well (which means negatively) with the thickness of nerve fibre layer measured with OCT devices, which also allocated patients to the 'suspicious' or 'abnormal' group. This is why patients who

Table 2. Absolute retinal nerve fibre layer thickness (in μm) measured with different devices. In the OCT Copernicus there are no separate measurements possible for upper and lower sectors.

	GDx VCC	Stratus	3D OCT 1000	Copernicus
Mean thickness	45.184 (35.7–56.0 SD=5.3406)	76.2811 (51.26–101.50 SD=13.4210)	78.3737 (19.25–108.75 SD=17.8585)	77.470 (32–112 SD=23.063)
Mean thickness in upper sector	54.105 (35.5–65.4 SD=8.5655)	89.260 (50–124 SD=23.340)	91.050 (16–129 SD=24.605)	–
Mean thickness in lower sector	50.926 (39.0–62.7 SD=7.1924)	93.890 (55–133 SD=22.178)	89.890 (4–122 SD=25.370)	–

were enrolled in this study had a perimetrically confirmed advanced glaucoma, to avoid uncertainty as to whether a person actually has neuropathy.

The most interesting aspect of the obtained results is the discovery of a significant difference in the mean thickness of the nerve fibre layer, expressed in μm , between GDx and OCT devices, ranging up to twice the value obtained from GDx. Our results remain in accordance with the few similar reports of other authors [13,14]; however, there were no similar comparisons performed in a group with such advanced primary open-angle glaucoma. Our results can be indirectly compared to studies examining the nerve fibre layer thickness in a group of healthy persons with the devices used by us. Liu et al. [15] report that the GDx VCC *in vivo* examination of the nerve fibre layer thickness in healthy people revealed the following results of the nerve fibre layer thickness: mean – 56.87 μm ; upper sector – 70.30 μm ; lower sector – 67.35 μm . On the other hand, studies by Knight et al. [16] with SOCT and TD-OCT devices show that the nerve fibre layer thicknesses were, respectively, mean – 92.0 μm for SOCT and 99.4 μm for TD-OCT. Thus, in a group of healthy people, the 2-fold difference in mean thickness of nerve fibre layer in OCT and GDx is also demonstrated.

What seems interesting is how the above-mentioned studies, as well as our results, relate to the study by Cohen et al. [17], which examined the actual nerve fibre layer thickness with a microscopic method in a retina isolated post-mortem from persons previously healthy. Results of the nerve fibre layer thickness obtained by this team – mean 60.3 μm ; upper sector 75.3 μm , lower sector 69.4 μm ; nasal sector 48.1, temple sector 49.2 – are very similar to GDx VCC examination in healthy persons. This suggests that polarimetric examination can more precisely reflect the actual nerve fibre layer thickness in the peripapillary region.

CONCLUSIONS

Both analyzed methods of examining retinal nerve fibre layer show significant disparity in establishing its absolute thickness (in micrometers); however, mean values of measurements remain in good correlation between the devices.

When the internal classification of these devices, consistent with the normative database assigned to the software, is taken into consideration, then both OCT and GDx VCC devices are efficient tools in the diagnosis of glaucoma. This is because each one of them matches the acquired data of

nerve fibre layer thickness with a comparative database specifically made for that particular device.

Glaucoma neuropathy at the microstructural level is not only a change in nerve fibre layer thickness, but also a disorder of the organized tubular structure of its nerve fibres, resulting in earlier stages of the disease in a disorder of the polarization phenomenon itself. This is where the advantage of the laser polarimeter, GDx, can be noticed. Firstly, the measurement method is based on determining the changes of the polarization of perpendicularly set laser beams. Secondly, as shown by comparative results from literature, values of nerve fibre layer thickness obtained in polarimetry correspond with actual anatomical values measured morphometrically during histological examination, which favor measurements performed with a polarimeter.

Further research is needed to establish which of these devices provides measurements closer to the actual thickness of the retinal nerve fibres. It is possible that the optimal approach would be to combine both devices into one. However, a Polarimetric Sensitive OCT is not yet commercially unavailable, but is currently undergoing clinical trials.

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