

Tomography findings in optic nerve head and retina in differential diagnosis between normal-tension glaucoma and ischemic optic neuropathies

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Aim – to determine tomography findings in optic nerve head (ONH) and retinal nerve fiber layer (RNFL) that may be valuable for differential diagnosis between normal-tension glaucoma (NTG) and ischemic optic neuropathy (ION) outcome. **Material and methods.** Group 1 consisted of 17 patients (32 eyes) with NTG, group 2 — 17 patients (24 eyes) with ION outcome. The control group included 22 patients (22 eyes) with no signs of optic neuropathy. Optic nerve head and retina assessment included scanning laser ophthalmoscopy (HRT III) and optical coherence tomography (Stratus OCT 3000). Statistical analyses were performed using Statistica 10 software suite. **Results.** Statistically significant changes in HRT parameters, namely, the mean RNFL thickness, retinal height variation along the contour line, and RB discriminant function, were observed in both study groups as compared to the controls. NTG patients also showed lower rim indices, larger cups, smaller values of the FSM discriminant function, and lower GPS (glaucoma probability score) than both ION patients and the controls. OCT findings included a statistically significant decrease in RNFL thickness in both study groups as compared to the controls. As for the difference between the groups, it was unreliable. Quadrant comparisons of RNFL thicknesses revealed that lower quadrant RNFL thinning was more significant in NTG patients, while temporal quadrant RNFL thinning — in ION patients. **Conclusion.** Both conditions are associated with a similar degree of RNFL thinning, as confirmed by OCT, however, HRT changes are much more pronounced in NTG than in ION patients.

Keywords: optical coherence tomography, scanning laser ophthalmoscopy, ischemic optic neuropathy, normal-tension glaucoma, differential diagnosis of ischemic optic neuropathies.

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Modern methods of retinal tomography are used for diagnosis as well as differential diagnosis of a number of posterior eye segment diseases, including optic neuropathy of different origin [1]. Scientists are now focused on exploring advantages and disadvantages of this or that method [2-5]. Identifying distinctive changes in morphometric parameters of the optic nerve head (ONH) and retinal nerve fiber layer (RNFL) would aid the differentiation between optic neuropathies, especially in cases of suspected so-called ‘normal-tension glaucoma’ (NTG). Morphological and functional changes in glaucomatous and non-glaucomatous optic neuropathies can be very similar. According to some authors, patients who have had an ischemic optic neuropathy (ION) often develop a glaucoma-like cup and field loss [6]. Moreover, optic nerve cupping is believed to be even more severe after an arteritic ION than that after a non-arteritic ION [7]. Disc size, however, does not seem to differ significantly from either the control (healthy) group, or the unaffected paired eye [8]. According to other authors, ION more often occurs in patients with ophthalmoscopically small optic nerve head and no cup — not even a physiological depression [9-12].

It is known that the results of scanning laser ophthalmoscopy performed with the Heidelberg Retina Tomograph (HRT) depend on the size of optic nerve head, whereas values obtained using optical coherence tomog-

raphy (OCT) or laser polarimetry (GDx VCC device) do not [5]. Evidence exists that the diagnostic value of HRT indices, such as ONH stereoparameters, Moorfield’s Regression Analysis (MRA), and Glaucoma Probability Score (GPS), is reduced in ‘non-standard’ disc sizes [13-16], which means that if, indeed, small discs are more likely to develop ION, scanning laser ophthalmoscopy may be less appropriate in them.

Because of high informative value of OCT, it has now become the most widely used method for optic neuropathy diagnosis. Multiple studies were performed to determine particular changes typical of this or that entity. It has been found, for example, that in Alzheimer’s disease RNFL thinning occurs in the upper and lower quadrants, while in Parkinson’s disease — in the upper and temporal quadrants. It is also known that temporal quadrant RNFL thinning is most likely to manifest in non-glaucomatous optic neuropathy. At the same time, upper and lower quadrant loss in peripapillary RNFL thickness that usually develops after an ION or drusen-associated optic neuropathy may resemble glaucomatous damage [1, 17]. It is also believed that RNFL loss following ION occurs in the temporal, nasal, and upper quadrants, which agrees with classical patterns of visual field defects [8,

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18]. As for those retinal quadrants that correspond to the intact half of the visual field, RNFL there is much thinner in glaucoma as compared to ION cases [19]. Moreover, in glaucoma, the global and most of sectoral neuroretinal rim areas provided by HRT software correlate with OCT measurements of RNFL thickness, while in an ION outcome they do not [20]. In ION also, RNFL thicknesses determined by optical coherence tomography correlate with the visual field mean deviation (Humphrey Field Analyzer), while those obtained with scanning laser ophthalmoscopy do not [2].

Thus, given insufficient knowledge in this field and conflicting data in the literature, it is essential to specify objective criteria for evaluating ONH and RNFL parameters and differentiating between ION and NTG. And there is no doubt that ONH sizing should be done in patients who have had an ION to clarify the informative value of scanning laser ophthalmoscopy.

The aim of this study was to determine morphometric features of the optic nerve head and retinal nerve fiber layer valuable for differential diagnosis between normal-tension glaucoma and an outcome of ischemic optic neuropathy.

Material and methods

Group 1 consisted of 17 patients (32 eyes) with advanced and far-advanced NTG diagnosed from the following signs: glaucomatous ONH cup, thin RNFL, visual field defects typical of glaucoma, and intraocular pressure (IOP) far beyond the upper limit of the individual normal range, or ‘personalized ocular pressure upper limit’ (POPUL), which is calculated according to an original method developed in the Research Institute of Eye Diseases [21, 22]. In all patients the IOP at baseline (i.e. before initiating any hypotensive therapy) was less than 21 mmHg. Several methods were used for IOP measurement, namely, pneumatic tonometry, flowmetry (Blood Flow Analyzer, Paradigm), and bidirectional applanation tonometry (Ocular Response Analyzer, or ORA, Reichert). If corneal-compensated IOP exceeded 21 mmHg, the patient would be excluded from the NTG group. Additional examination (morphofunctional and laboratory tests, MRI/CT of the brain and orbits with optic nerve visualization, Doppler ultrasound of the major arteries of the head, and color Doppler mapping of eye vessels) was performed by necessity in order to rule out non-glaucomatous origin of neuropathy. Medically induced compensation of IOP (by ‘compensation’ we

imply IOP being within the patient’s individual normal range) was achieved in all cases leading to stabilization of glaucomatous optic neuropathy. The follow-up period of NTG patients lasted from 3 to 5 years.

Group 2 consisted of 17 patients (24 eyes) after an acute non-arteritic anterior ION. A so called ‘ION outcome’ was diagnosed if the patient had initially presented to the Research Institute of Eye Diseases with an acute ION and then underwent a supervised course of conservative therapy, or, otherwise, had a past history of acute ION proved by medical records from some other institution. Retinal tomography data obtained at least 6 months after the acute ION were analyzed.

The control group consisted of 22 patients (22 eyes) with no evidence of optic neuropathy. We also excluded retinal comorbidity that could affect the results of retinal tomography.

Ophthalmoscopic appearance of ONH in both NTG and ION outcome groups varied greatly (glaucoma-like cupping, however, was not uncommon in patients who have had an ION). Visual field defects mostly involved central and paracentral zones. Peripheral scotomas were also present.

The Heidelberg Retina Tomograph III was used to assess stereoparameters of the optic nerve head and Stratus OCT 3000 — to determine the mean and quadrant peripapillary RNFL thickness. Ocular axial lengths were measured with the IOL Master biometer. The data were analyzed with nonparametric statistical methods using Statistica 10 software.

Results and discussion

The NTG group consisted of 71% women and 29% men, the ION group — 65% women and 35% men. Of the controls 68% were women and 32% men. Age distribution in the groups was abnormal, hence, nonparametric statistical methods were applied. Patients with NTG appeared significantly ($p < 0.005$) older than those with an ION outcome and the controls (median [quartiles] — 68 [64, 73] years, 58 [46, 66] years, and 62 [47, 70] years, respectively).

The current dominant view is that ischemic optic neuropathy develops more frequently in patients whose optic discs appear smaller than average at ophthalmoscopy. Therefore, we analyzed the frequency of occurrence of different optic nerve head areas in the three study groups: ION outcome, NTG, and ‘norm’ (i.e. eyes with no signs of optic neuropathy) (**Table 1**). Contrary to popular belief, only 14% of ION outcome cases had a smaller than average disc

Table 1. Percentage occurrence of different optic nerve head areas in study groups

ONH area, mm ²	Group		
	norm	NTG	ION
<1.63	9	28	14
1.63-2.43	82	47	81
>2.43	9	25	5

Table 2. Morphometric parameters of the optic nerve head obtained by HRT in different study groups

Parameter	Group				
	Norm	NTG	significance level, <i>p</i> (as compared to the norm)	ION	significance level, <i>p</i> (as compared to the norm)
	median [quartiles]	median [quartiles]		median [quartiles]	
Disc area, mm ²	2 [1.9; 2.3]	2.14 [1.62; 2.46]	0.95	2.06 [1.83; 2.26]	0.8
Cup area, mm ³	0.6 [0.36; 0.88]	1.22** [0.71; 1.65]	0.001	0.47 [0.08; 0.84]	0.5
Rim area, mm ³	1.43 [1.24; 1.68]	0.92** [0.67; 1.08]	<0.00001	1.47 [1.27; 1.8]	0.6
Cup volume, mm ³	0.12 [0.04; 0.29]	0.22** [0.12; 0.54]	0.04	0.06 [0.01; 0.18]	0.14
Rim volume, mm ³	0.37 [0.33; 0.57]	0.16** [0.1; 0.32]	<0.00001	0.29 [0.25; 0.5]	0.05
C/D area ratio	0.3 [0.15; 0.42]	0.57** [0.41; 0.71]	<0.00001	0.2 [0.05; 0.41]	0.5
C/D linear ratio	0.55 [0.38; 0.65]	0.76** [0.64; 0.85]	<0.00001	0.45 [0.22; 0.64]	0.4
Mean cup depth, mm	0.26 [0.19; 0.36]	0.31** [0.21; 0.37]	0.7	0.18 [0.08; 0.21]	0.004
Maximum cup depth, mm	0.67 [0.51; 0.87]	0.63* [0.49; 0.76]	0.2	0.4 [0.19; 0.55]	0.001
Cup shape	-0.14 [-0.22; -0.11]	-0.05** [-0.1; 0.01]	<0.00001	-0.14 [-0.16; -0.12]	0.8
HCV, mm	0.44 [0.35; 0.55]	0.37 [0.29; 0.44]	0.04	0.37 [0.26; 0.41]	0.03
RNFL, mm	0.27 [0.23; 0.34]	0.14 [0.09; 0.23]	<0.00001	0.17 [0.13; 0.22]	0.00004
FSM	0.93 [0.21; 2.79]	-1.93** [-3.11; -1.19]	<0.00001	0.87 [-0.78; 2.15]	0.4
RB	1.49 [1.12; 1.88]	-0.34 [-0.74; 0.64]	<0.00001	0.38 [-0.5; 0.92]	0.00006
GPS	0.4 [0.11; 0.78]	0.87* [0.66; 0.91]	0.00007	0.52 [0.29; 0.83]	0.09

Note. * – a significant difference between morphometric parameters of the optic nerve head in NTG and ION outcome patients at $p < 0.05$, ** – at $p < 0.005$

Table 3. Distribution of MRA results in study groups

Optic nerve head sectors	MRA proportions in the groups, %								
	NTG			ION			Norm		
	Within normal limits	Borderline	Outside normal limits	Within normal limits	Borderline	Outside normal limits	Within normal limits	Borderline	Outside normal limits
Temporal	41	9	50	81	5	14	77	18	5
Superior temporal	22	16	62	68	9	23	77	23	0
Inferior temporal	3	22	75	91	0	9	90	5	5
Nasal	16	22	62	73	9	18	82	18	0
Superior nasal	18	16	66	68	18	14	77	14	9
Inferior nasal	22	3	75	82	9	9	91	9	0

area. The vast majority of optic nerve heads in ION patients (81%) were of perfectly average size as compared to the HRT normal database. The strongest scatter has been observed for optic nerve head areas in the NTG group.

Analysis of HRT stereoparameters of the optic nerve head has revealed a direct correlation between disc area and cup parameters (area, volume, cup/disc ratios) in all three study groups ($p < 0.03$). In the NTG group an additional correlation has been established between disc area and cup depth (both mean and maximum). One can reasonably suppose that a deeper cup is formed in those NTG patients who have large optic nerve heads from the very beginning. No dependence of disc area on rim parameters (area and volume) has been found in either of the groups.

Given that there were no significant differences in disc areas (HRT data) between the groups, we performed

inter-group comparisons of ONH parameters (**Table 2**). NTG patients were notable of a significant decrease in rim parameters (area and volume), FSM discriminant value, and GPS as well as an increase in cup parameters (area, volume, and cup/disc ratios) as compared to the controls and ION outcome group. In patients with NTG, cups did not differ significantly in depth from those in the control group. The ION outcome group presented with much more shallow cups than the controls. Such parameters, as the average RNFL thickness, height variation of the retinal surface along the contour line (HCV), and RB discriminant function, differed significantly in the control group from both NTG and ION patients.

Moorfield's Regression Analysis was affected to a much greater degree in NTG patients as compared to those with an ION outcome (**Table 3**). It is noteworthy that the frequency of MRA being abnormal in the NTG

Table 4. RNFL thicknesses in different study groups (OCT data)

RNFL thickness	Group				
	Norm		NTG	ION	
	median [quartiles]	median [quartiles]	significance level, <i>p</i> (as compared to the norm)	median [quartiles]	significance level, <i>p</i> (as compared to the norm)
Mean for all quadrants	98.3 [91.4;105]	66 [54;78.6]	0.00001	60.75 [48.4;74]	0.00001
Lower quadrant	127.5 [114;137]	62.5** [48;88]	0.00001	82.5 [65.5;122.5]	0.0005
Upper quadrant	122 [112;133.5]	71 [56.5;88]	0.00001	65.5 [57;88]	0.00001
Nasal quadrant	73.5 [64;85]	51 [40;61.5]	0.00001	56.6 [50.5;64]	0.00005
Temporal quadrant	69.5 [60;76.5]	49.5* [42.5;61]	0.0001	41 [38;48]	0.00001

Note. * — a significant difference between RNFL thicknesses in NTG and ION outcome patients at $p < 0.05$, ** — at $p = 0.01$

group was the highest in inferior sectors (inferior/temporal and inferior/nasal), while in the ION outcome group in these particular sectors it was the lowest.

Thus, common findings in ION outcome patients included medium-sized optic discs and abnormal HRT parameters, such as the average RNFL thickness, HCV, and RB discriminant function (all changes being statistically significant). In NTG, not only the above-mentioned parameters of ONH, but also those of the cup and rim deviated from the norm. The size of the disc was judged as medium in only half of NTG patients.

As suggested by the results of scanning laser ophthalmoscopy, ischemic optic neuropathy outcome should be considered the most likely diagnosis in normal-tension glaucoma suspects with significant RNFL thinning accompanied by HCV and RB reduction, but only if their cup and rim parameters remain mostly unchanged (slight changes are acceptable).

Since peripapillary RNFL thickness measurements done with OCT may be affected by the axial length of the eye [23], we compared the latter between the NTG and ION outcome groups and found no significant differences ($p > 0.05$). Therefore, possible measurement errors could be neglected when analyzing retinal tomography data obtained from these patients. A statistically significant peripapillary RNFL thinning (the mean and quadrant values) has been revealed in both NTG and ION outcome groups as compared to the norm (Table 4). The difference between the two groups was, however, insignificant. It has also been found that lower quadrant RNFL loss tends to be more severe in NTG patients, while temporal quadrant changes are more typical of ION outcomes.

As shown, RNFL damage being the same (by OCT), stereoparameters of the optic nerve head (by HRT) change to a much greater extent in patients with NTG than in those who have had an ION. Similar data was obtained by Danesh-Meyer HV et al. (2010), who reported optic disc parameters being affected to a greater extent in glaucomatous optic neuropathy patients than in post-ischemic optic neuropathy patients with comparable retinal ganglion cell and vision field loss [24].

Thus, comprehensive assessment of optic disc parameters and retinal nerve fiber layer thickness by means of scanning laser ophthalmoscopy and optical coherence tomography can be of significant value in the differential diagnosis between normal-tension glaucoma and an ischemic optic neuropathy outcome.

Conclusions

Morphometric features of the optic nerve head and retinal nerve fiber layer have been comparatively studied by means of scanning laser ophthalmoscopy (HRT) and optical coherence tomography in patients with non-progressive and compensated (judging from the POPUL) advanced or far-advanced normal-tension glaucoma and those who have had an acute non-arteritic anterior ischemic optic neuropathy.

In ION patients, the vast majority of optic nerve heads (81%) were found to be medium-sized, while in NTG patients, only 47% of disc areas fell into the average range.

In NTG as well as ION, the following HRT parameters differed from the control group, the difference being statistically significant: the average RNFL thickness, HCV, and RB discriminant function.

Patients with NTG also showed a significant decrease in rim parameters (area and volume), FSM discriminant value, and GPS as well as an increase in cup parameters (area, volume, and cup/disk ratios) as compared to the controls and the ION outcome group.

The frequency of MRA being abnormal in the NTG group was the highest in inferior sectors. In the ION outcome group, in these particular sectors it was the lowest.

A statistically significant peripapillary RNFL thinning has been revealed by OCT in both NTG and ION outcome groups (both mean and quadrant values were decreased as compared to the controls). At the same time, the difference between the NTG and ION outcome groups was insignificant.

It has also been found that RNFL damage being the same (as determined by OCT), HRT stereoparameters of

the optic nerve head change to a much greater extent in patients with NTG than in those who have had an ION.

Comparative analysis of RNFL thicknesses by quadrants (OCT data) between NTG and ION patients has revealed that RNFL thinning in patients with NTG predominantly occurs in the lower quadrant and in those with an ION outcome — in the temporal.

Author contributions:

Study conception and design — V.M., N.G., N.Sh.

Acquisition and handling of data — N.G., N.Sh., E.K., O.Sh-D., A.R.

Statistical analysis of data — N.G.

Drafting of manuscript — N.G.

Critical revision — V.M., N.Sh.

The authors declare no conflict of interest.

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