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Comparison of Normal- and High-Tension Glaucoma: Nerve Fiber Layer and Optic Nerve Head Damage

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Key Words

Normal-tension glaucoma · High-tension glaucoma · Optic nerve head · Visual field · Heidelberg retinal tomography · Spectral-domain optical coherence tomography

Abstract

Purpose: The aim of this study was to investigate differences in the nerve fiber layer and glaucoma-induced structural optic nerve head (ONH) damage in patients with normal- (NTG) and high-tension (HTG) glaucoma. ***Methods:*** In this retrospective pair-matched comparative study, 22 NTG and 22 HTG eyes were matched according to the same glaucomatous damage based on rim volume, rim area and disk size, as measured by Heidelberg retinal tomography (HRT III). Visual fields (VF) were assessed by Humphrey perimetry, and nerve fiber layer thickness was determined both by scanning laser polarimetry (GDxVCC) and spectral-domain optical coherence tomography (SD-OCT). Comparisons of all measured parameters were made between NTG and HTG groups. ***Results:*** Based on HRT results, both NTG and HTG eyes displayed comparable structural damage to the ONH (NTG/HTG, mean: disk area, 2.30/2.31 mm^2, p = 0.942; rim area, 1.02/0.86 mm^2, p = 0.082; rim volume, 0.19/0.17 mm^3, p = 0.398). NTG eyes had significantly less VF damage than HTG eyes (NTG/HTG, mean deviation: –4.23/–12.12 dB, p = 0.002; pattern standard deviation: 5.39/8.23 dB, p = 0.022). The inferior nerve fiber layer of NTG patients was significantly thicker than that of HTG patients (NTG/HTG, mean: GDx inferior: 53.5/46.3 μm, p = 0.046). SD-OCT revealed a significantly thicker nerve fiber in NTG compared with HTG patients in all quadrants (NTG/HTG, total mean: 72.72/58.45 μm, p = 0.002). ***Conclusion:*** At comparable glaucomatous stages, nerve fiber loss was more advanced in HTG patients compared with NTG patients.

Introduction

Glaucoma, a group of disorders of heterogeneous etiologies, is characterized by progressive damage to retinal ganglion cells (including axons) and associated glial cells. Glaucoma causes characteristic morphological changes to the optic nerve head (ONH), resulting in associated defects of the visual field (VF).

Normal-tension glaucoma (NTG) is a special form of open-angle glaucoma. Despite advances in techniques for examining the optic nerve and VF, functional and

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morphological differences between NTG and open-angle high-tension glaucoma (HTG) remain controversial. Several studies have shown the morphology and function of the ONH in eyes with NTG to be identical to those with HTG, while other studies reveal contradictory results [1–6]. Compared with HTG, NTG causes more centrally located VF defects [7–9], deeper scotomas [10] and more extensive structural damage to the optic nerve [11–15]. Such controversial findings among the various studies may be due to a number of factors, including differences in study methodology (e.g. inclusion of patients at different stages of glaucoma) and selection bias. With regard to the latter, HTG is detected by high intraocular pressure (IOP) or VF defects, whereas NTG – especially in the early stages – is often not detected and diagnosed because of normal IOP values. These factors make a comparison of study results difficult. However, if differences between clinical and morphological findings truly exist, then different etiologies of glaucoma with and without elevated IOP may be hypothesized [16–18].

For the present study, a glaucoma database was used to assess VFs and nerve fiber layers in pairs of NTG and HTG patients. Patients were matched according to similar glaucomatous damage in order to circumvent problems in comparing patients with varying degrees of structural damage to the ONH.

Methods

The present study was a retrospective, comparative, case-matched analysis. The study protocol was approved by the ethics committee of the University of Dresden following the declaration of Helsinki. All subjects signed an informed consent before participating in this study.

Patients

Patient data were gleaned from the glaucoma database of the Department of Ophthalmology, University of Dresden, which includes data for all glaucoma and ocular hypertensive patients who presented to the Department from 2006 through 2009. Data include each patient's history, medication, IOP and 24-hour IOP (measurement by Goldmann applanation tonometry), refraction, and results of a complete eye examination, including evaluation of the optic disk.

For the present study a retrospective analysis of patients with NTG and HTG was performed. One eye of each patient was randomly assigned for further analysis. To provide a reliable case by case match of HTG and NTG eyes, an equal optic disk size as measured by HRT III and an equal estimated excavation of the optic disk were chosen. Both parameters were derived from the glaucoma data base. In case of multiple data records a further subanalysis using an equal age distribution in both groups was conducted. As HRT (except from optic disk size), GDx and VF parameters were not part of the data base, these data were collected manually from each patient's file after the above-mentioned subgroup analyses had been obtained. Overall, 22 NTG eyes were matched on a case by case basis to 22 HTG eyes according to the same morphological parameters, namely the same optic disk size and the same optic disk excavation.

Inclusion Criteria

For NTG patients, inclusion criteria included glaucomatous optic disk appearance (based on neuroretinal rim thinning, notching or excavation), nerve fiber layer defects, asymmetry of the vertical cup-to-disk ratio of >0.2 between both eyes, history of IOP of <22 mm Hg without treatment, wide or open angles on gonioscopy, and no additional obvious causes for optic nerve damage.

For HTG patients, the above criteria applied, with the exception of IOP which had to be >21 mm Hg.

Exclusion Criteria

Exclusion criteria included best-corrected visual acuity <0.5 (decimal scale), apparent refractive media opacification, refractive error >5D, concomitant ocular disease, anomaly of the optic pit, micro- or macropapilla (<1.8 or >2.8 mm^2), poor SAP reliability scores (defined as false-negative rates >30%, false-positive rates >30%, or fixation losses >20%), surgical procedures within prior 12 months, and patients >65 years of age. This latter criterion was included to obviate the influence of possible cerebral lesions, e.g. silent infarcts in the VF or diminished VA due to lens opacification [19].

Procedures

Besides Goldmann applanation tonometry, additional diagnostic procedures included pachymetry (IOPac), Heidelberg retinal tomography (HRT III; Heidelberg Engineering, Heidelberg, Germany), ONH topography, scanning laser polarimetry (GDx-VCC; Carl Zeiss Meditec, Dublin, Calif., USA), standard automated perimetry 30-2 full threshold program (Carl Zeiss Meditec), and spectral-domain optical coherence tomography (SD-OCT; Heidelberg Engineering).

VF Analysis

VFs were analyzed using the Humphrey perimeter program 30-2 (Carl Zeiss Meditec). The mean deviation (MD), pattern standard deviation (PSD), and probability symbols of the PSD (VF PSD <5–0.5%) were used to describe our patient cohort.

Optic Disk Analysis

The optic disk of each eye was analyzed with HRT software version 3.1 (HRT III). This ONH analyzer records simultaneous stereoscopic images of the optic disk, yielding data on disk area, cup-to-disk ratio, neuroretinal rim area and neuroretinal volume. The optic disk margin was outlined using a computer mouse system and was verified by two observers (J.H. and N.T.). Details of the operational parameters of this instrument are published elsewhere [20–22].

Nerve Fiber Layer Analysis

The retinal nerve fiber layer (RNFL) of each eye was studied by laser polarimetry (GDxVCC; Carl Zeiss Meditec). The GDxVCC apparatus contains a confocal scanning laser ophthalmoscope with polarizing and polarization-analyzing units. Technical details of the GDxVCC system, as well as possible sources of error, are described elsewhere [23]. If polarized light travels faster in one direction than light polarized in a perpendicular direction, a phase shift occurs between the two light beams. This phenomenon is referred to as retardation. Assuming the density of birefringent structures to be homogenous, equal and constant, the phase shift is proportional to the thickness of the birefringent material. Since the optical axis of retinal birefringence is dependent on the orientation of the RNFL, the magnitude of retardation is thus correlated to its thickness [24]. The summed retardation patterns of the anterior segment and Henle fiber layer are used to eliminate the effects of anterior segment polarization [25]. For analysis, all retardation values were transformed into RNFL thickness values. GDx parameters used in the calculation included superior and inferior averages. Any RNFL thickness maps with atypical retardation patterns [26, 27] were not included in the study.

RNFL Thickness Analysis

All patients underwent peripapillary SD-OCT (Spectralis; Heidelberg Engineering) for measurement of RNFL thickness. The Spectralis OCT has a scan speed of 40,000 A-lines/s. Eye movement tracking was achieved using TruTrack image alignment software. With this system, multiple images can be obtained from the same exact location and then averaged to reduce speckle noise. Such real-time eye tracking also compensates for involuntary eye movements (often occurring during image acquisition) which result in motion artifacts. The scan circle diameter, therefore, depends on axial eye length. Typically, the diameter of the circle is about 3.5–3.6 mm. Spectralis OCT software (version 4.0) allows for automatic segmentation of the upper and lower borders of the RNFL, thereby calculating average RNFL thickness. Peripapillary RNFL was divided into four quadrants, and the superior and inferior quadrants further subdivided into nasal and temporal sectors [28].

Statistical Analysis

SPSS (version 17.0) was used for statistical analyses. VA data were converted to a logarithmic scale (logMAR).The nonparametric Wilcoxon test for paired samples was used to compare morphological and functional variables between groups. To assess correlations between morphological and functional variables within each group, the Spearman rank correlation coefficient was used. Analysis of covariance was conducted to evaluate the effect of surgical procedures on the VF and nerve fiber layer. A p value <0.05 was considered statistically significant.

Table 1. Demographic data

	n	NTG	HTG	p
Age, years	22	56.9±7.00	58.5±6.00	0.57
Sex (M/F)	22	10/12	13/9	0.15
Visual acuity, logMAR	22	0.03±0.08	0.11±0.15	0.097
IOP max, mm Hg	22	18.1±2.39	29.8±7.52	*0.0001*
IOP, mm Hg	22	12.9±2.50	12.8±4.03	0.930
Pachymetry, μm	22	554±27	545±43	0.716

Values are presented as means ± SD. p values <0.05 are indicated in italics.

Table 2. History of surgical treatment

	n	NTG	HTG	p
Pseudophakia	22	0	3	0.083
ALT/SLT	22	5	4	1.000
CPC	22	2	4	0.236
Trabeculectomy	22	1	4	*0.046*

p values <0.05 are indicated in italics. ALT = Argon laser trabeculoplasty; SLT = selective laser trabeculoplasty, CPC = cyclophotocoagulation.

Table 3. Morphological parameters of NTG and HTG

Parameters	n	NTG	HTG	p
Cup/disk ratio (estimated)	22	0.87±0.08	0.85±0.08	0.109
Cup/disk ratio, HRT	22	0.74±0.07	0.78±0.08	0.085
Disk area, mm^2	22	2.30±0.25	2.31±0.22	0.942
Rim area, mm^2	22	1.02±0.25	0.86±0.31	0.082
Rim volume, mm^3	22	0.19±0.08	0.17±0.10	0.398

Values are presented as means ± SD.

Results

Included in the present analysis were 22 patients with NTG and 22 patients with HTG. Demographic data are shown in table 1.

There were no significant differences between age and gender between HTG and NTG patients (p = 0.57 and p = 0.15, respectively). The maximum untreated IOP was significantly lower in NTG compared with HTG patients (p = 0.0001). HTG patients had undergone significantly more trabeculectomies than NTG patients (p = 0.046; table 2).

Morphological parameters of the ONH, measured by HRT, did not differ significantly between groups (NTG/HTG: disk area: 2.30/2.31 mm^2, p = 0.942; rim area: 1.02/0.86 mm^2, p = 0.082; rim volume: 0.19/0.17 mm^3, p = 0.398; table 3).The thickness of the nerve fiber layer, as measured by confocal scanning laser polarimetry (GDx) revealed a significantly thicker inferior nerve fiber

Table 4. RNFL measurements by HRT and GDx and VF indices of NTG and HTG patients

	n	NTG	HTG	p
GDx superior, μm	22	51.2±9.0	48.01±13.8	0.242
GDx inferior, μm	22	53.5±10.5	46.32±14.15	*0.046*
HRT, mm	22	0.17±0.05	0.13±0.08	0.082
VF MD, dB	22	–4.23±5.11	–12.13±9.2	*0.002*
VF PSD, dB	22	5.39±4.79	8.23±4.68	*0.022*

Values are presented as means ± SD. p values <0.05 are indicated in italics.

Table 5. Nerve fiber layer measurements by SD-OCT of NTG and HTG patients

	NTG	HTG	p
Total, μm	72.72±14.64	58.45±16.17	*0.002*
Temporal, μm	57.00±12.92	46.77±15.25	*0.014*
Temporal superior, μm	93.72±26.17	74.95±31.38	*0.022*
Temporal inferior, μm	96.59±36.46	70.41±34.51	*0.014*
Nasal, μm	61.59±13.11	51.41±13.05	*0.022*
Nasal superior, μm	73.40±15.11	61.77±22.48	*0.026*
Nasal inferior, μm	80.36±21.23	62.77±18.21	*0.010*
Superior, μm	83.59±19.13	68.45±24.28	*0.009*
Inferior, μm	88.45±24.45	66.72±24.45	*0.003*

Values are presented as means ± SD. p values <0.05 are indicated in italics.

layer in NTG compared with HTG patients (NTG/HTG: GDx inferior: 53.5/46.3; p = 0.046; table 4).

VF defects differed significantly between NTG and HTG patients. Those with NTG had significantly fewer defects than those with HTG (NTG/HTG: VF MD: –4.23/–12.12 dB, p = 0.002; VF PSD: 5.39/8.23 dB, p = 0.022; table 4).Nerve fiber thickness measurements by SD-OCT showed that NTG patients had a thicker nerve fiber layer compared with HTG patients in all quadrants (NTG/HTG, total mean: 72.72/58.45 μm, p = 0.002; table 5).

Discussion

In the present study, structural and functional parameters (i.e. VF loss and nerve fiber layer thickness) were compared between NTG and HTG patients based on the same glaucomatous ONH damage (as measured by HRT). Significant differences in VF loss and RNFL thickness were observed between NTG and HTG patients. Differences in the nerve fiber layer between both groups (as measured by GDx) were confirmed by SD-OCT analysis. Patients with NTG had thicker and more well-preserved RNFLs compared with those of HTG patients with equivalent levels of structural ONH damage. For a reliable comparison of ONH appearance or VF loss between NTG and HTG, one or other of these parameters must be similar [14]. For the present study, we chose a pair-wise assignment of NTG and HTG patients at equivalent levels of ONH damage.

Our findings are consistent with the results of some studies, but in conflict with those of others. Chauhan et al. [7] demonstrated that NTG causes more localized damage than HTG, which causes a more diffuse damage. Caprioli and Spaeth [9] showed that NTG patients had a significantly thinner optic disk rim than HTG patients. Yamagami et al. [15] indicated that the rim area of patients with glaucomatous VF defects was significantly smaller in NTG compared with HTG. Kiriyama et al. [16] conducted a study of HTG, NTG and ocular hypertensive patients and showed that NTG patients had a significantly reduced rim area and higher cup-to-disk ratio and rim volume than patients with similar VF damage.

In contrast, other studies did not reveal any significant differences in VF or HRT parameters between NTG and HTG [1, 4, 6, 8, 16]. Iester and Mikelberg [1] investigated 182 glaucoma patients and reported no statistically significant differences in HRT or VF parameters between NTG and HTG, even after allocating patients to the parameter of optic disk size. Similarly, Nakatsue et al. [6] detected no significant differences between HRT parameters (disk area, cup area, cup-to-disk area ratio, rim area, cup volume, rim volume, cup shape measure, and height variation contour) and VF indices (MD, corrected PSD and total deviation) in 60 NTG and 60 HTG Japanese patients.

In the present study, RNFL was analyzed not only indirectly (HRT, GDx) but also directly (SD-OCT), revealing a remarkably thicker nerve fiber layer in NTG compared with HTG patients with equivalent levels of glaucomatous ONH damage.

To the best of our knowledge, ours is the first study to investigate the RNFL directly by SD-OCT in a pair-matched study design. In previous studies, RNFL was analyzed indirectly (primarily by HRT). In this latter context, Iester and Mikelberg [1] could reveal no significant differences in RNFL between 132 HTG and 50 NTG patients with equivalent amounts of VF loss. Thonginnetra

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et al. [8] were also unable to detect any significant differences in HRT parameters between 32 NTG and 32 HTG patients with comparable VF defects. However, in that study, HRT parameters were not specifically mentioned and, in VF testing, respective best arithmetic means for NTG patients (without statistical significance) were included.

Differences in results among the various studies might be related not only to selection bias but also to differences in methodology. Unfortunately, the aforementioned studies cannot be used for a direct comparison of RNFL between NTG and HTG, as they highlighted differing structural ONH damages at equivalent functional levels. Therefore, it is likely that RNFL thickness differed between the two groups.

The ONH consists of nerve fibers, glial cells and vascular tissue. Nerve fibers comprise about 90% of the volume at the level of the anterior ONH and around 50% at the level of the posterior lamina [29]. In glaucoma, thinning of the rim area can be ascribed either to damaged nerve fibers or damaged glial cells. Gramer et al. [14] indicated a higher excavation of the optic disk in glaucomatous eyes with no elevated IOP compared to that in glaucomatous eyes with elevated IOP. These authors concluded that the ONH in NTG eyes either has less connective tissue or that nerve fiber loss in NTG is preceded by impairment of the connective tissue. Taken together, these results suggest that the number of nerve fibers does not differ between NTG and HTG. Furthermore, differences in the rim area are present at very early stages of the disease and are attributable primarily to a reduction in numbers of glial cells or the amount of connective tissue. Further studies are needed to investigate this issue in more detail.

Although the present study was limited by its retrospective design, a comparison of equivalent structural and functional damage of the ONH would not otherwise be possible on a case by case basis between HTG and NTG patients.

In conclusion, the present study shows that the RNFL of NTG patients, as measured in vivo by SD-OCT, is more well preserved than in that of HTG patients at an equivalent level of structural glaucomatous damage to the ONH. Consistent with results of previous studies, our results confirm the notion that the loss of glial cells and connective tissue is more advanced in NTG compared with HTG.

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