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Normal versus High Tension Glaucoma: A Comparison of Functional and Structural Defects

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Abstract

Purpose—To compare visual field defects obtained with both multifocal visual evoked potential (mfVEP) and Humphrey visual field (HVF) techniques to topographic optic disc measurements in patients with normal tension glaucoma (NTG) and high tension glaucoma (HTG).

Methods—We studied 32 patients with NTG and 32 with HTG. All patients had reliable 24-2 HVFs with a mean deviation (MD) of –10 dB or better, a glaucomatous optic disc and an abnormal HVF in at least one eye. Multifocal VEPs were obtained from each eye and probability plots created. The mfVEP and HVF probability plots were divided into a central 10-degree (radius) and an outer arcuate subfield in both superior and inferior hemifields. Cluster analyses and counts of abnormal points were performed in each subfield. Optic disc images were obtained with the Heidelberg Retina Tomograph III (HRT III). Eleven stereometric parameters were calculated. Moorfields regression analysis (MRA) and the glaucoma probability score (GPS) were performed.

Results—There were no significant differences in MD and PSD values between NTG and HTG eyes. However, NTG eyes had a higher percentage of abnormal test points and clusters of abnormal points in the central subfields on both mfVEP and HVF than HTG eyes. For HRT III, there were no significant differences in the 11 stereometric parameters or in the MRA and GPS analyses of the optic disc images.

Conclusions—The visual field data suggest more localized and central defects for NTG than HTG.

Keywords

normal tension glaucoma; multifocal visual evoked potential; visual fields; Heidelberg Retina Tomograph

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Introduction

It has been suggested that there may be structural and functional differences between normal tension glaucoma (NTG) and high tension glaucoma (HTG).¹ There is also controversy as to whether the pathogenesis of NTG and HTG differ. Although it has been established that intraocular pressure is part of the pathogenic process in NTG by the collaborative normal tension glaucoma study group, it has been suggested that pressure-independent vasogenic risk factors such as vascular dysregulation and ischemia are more important in the development and progression of NTG than in HTG.^{2–4} Evidence of structural and functional differences would provide support for different etiologies. With regard to evidence for structural differences, reports have claimed that the optic disc in eyes with NTG tends to have a greater degree of rim thinning, especially inferotemporally, more notching, a higher prevalence of acquired pits of the optic nerve, and larger cup areas and cup/disc ratios than in eyes with HTG.^{5–8} Retinal nerve fiber layer defects have been reported to be more localized.^{5,9} However, others have reported no differences in optic nerve topography between NTG and HTG eyes.^{10,11} There is also controversy regarding functional differences; some investigators having found that visual field defects in NTG are more likely to be deeper, steeper, more localized, unilateral and closer to fixation than in HTG.^{12–17} In contrast, others have found no significant differences in the pattern of visual field defects in NTG compared to HTG eyes.^{18,19}

There are a number of possible explanations for these disagreements. For example, findings of functional and structural differences could be attributed to the NTG and HTG eyes being at different stages of glaucomatous damage rather than to differences between them. On the other hand, failure to detect functional differences could be due to the techniques used to assess the pattern of visual field defects. Studies investigating functional differences between NTG and HTG have typically assessed visual field defects using standard automated perimetry (SAP) techniques. Although SAP is the current “gold standard” for detection of functional deficits, it is well known that significant retinal ganglion cell damage can occur before visual field changes are detected by SAP. We used both the mfVEP technique and 24-2 Humphrey visual fields (HVF) to investigate functional differences in NTG and HTG. The mfVEP is an objective method for detecting visual field deficits that can detect visual field defects in patients who do not show defects on conventional perimetry.^{20–23} Another advantage of the technique is that the sampling of the central/paracentral area of the visual field is greater than that of the 24-2 HVFs.

The purpose of this study was to determine whether we could find evidence of differences in functional and structural deficits in NTG and HTG eyes that were at a similar stage of glaucomatous damage. Functional differences were investigated with the HVF and mfVEP techniques and structural differences with the Heidelberg Retinal Tomograph (HRT) a confocal scanning laser ophthalmoscope.

Methods

Thirty-two consecutive patients with NTG (maximum recorded IOP ≤ 21 mmHg) and 32 with HTG (maximum IOP ≥ 24 mmHg) who met the inclusion criteria described below were recruited from the practice of two of the authors (RR and JML). All the patients classified as NTG had a minimum of 5 consecutive untreated IOP measurements ≤ 21 mmHg. They ranged in age from 34 to 79 years (mean 64.4 ± 11.4 years) and the HTG patients from 33 to 81 years (mean 64.3 ± 13.3 years). Informed consent was obtained from all subjects prior to participation. Procedures adhered to the tenets of the Declaration of Helsinki and the protocol was approved by the Columbia University Institutional Review Board for Human Research.

The inclusion criteria were as follows: Each patient had at least one eye with glaucomatous damage, as defined by the presence of glaucomatous optic neuropathy (diffuse or focal rim thinning, cupping, notching, hemorrhages, retinal nerve fiber layer defect or asymmetry of vertical cup/disc ratio > 0.2), with a corresponding repeatable reliable visual field defect (pattern standard deviation (PSD) $< 5\%$ and glaucoma hemifield test results outside normal limits). Visual fields were obtained with the Humphrey Visual Field Analyzer ((HVF) Humphrey-Zeiss, San Francisco, California) using the 24-2 SITA standard program. Foveal thresholds were also obtained on all patients. The criteria for reliable HVF results were fewer than 20% fixation losses, 15% false positives, and false negatives. Patients were excluded if they had a mean deviation (MD) worse than -10 dB. Other inclusion criteria were visual acuity of 20/30 or better, refractive error not exceeding 6.00 diopters sphere and/or 2.00 diopters cylinder, clear ocular media with no clinically significant cataract, open angle and no previous ocular surgery aside from uncomplicated cataract extraction. Patients with secondary glaucoma (i.e. pigment dispersion, corticosteroid use, iridocyclitis and trauma) and other diseases that can affect visual fields (pituitary lesions, demyelinating diseases, autoimmune diseases, congenital optic neuropathy and retinal diseases) were excluded. If both eyes met the inclusion criteria, data from the more affected eye were analyzed.

The mfVEPs were recorded using VERIS 4.3 software (Electro-Diagnostic Imaging, Inc., Redwood City, CA). The stimulus was a dartboard pattern that consisted of 60 sectors, each with a checkerboard pattern of 16 checks, 8 white (luminance = 200 cd/m^2) and 8 black (luminance $< 3 \text{ cd/m}^2$). The sectors were cortically scaled with eccentricity. The dartboard stimulus had a radius of 22.3° and it was displayed on a black and white monitor driven at a frame rate of 75 Hz. The 16-element checkerboard of each sector had a probability of 0.5 of reversing on any pair of frame changes and the pattern of reversals for each sector followed a pseudo-random (m) sequence. On every frame change (every 13.3 ms) each sector could reverse contrast or stay at the same contrast. A refractor/camera was used to refract the subjects and monitor eye position and stability throughout the test. Subjects fixated on the center of a black cross in the middle of the display. Segments contaminated by eye movements, loss of fixation, unsteady fixation and/or external noise were discarded and re-recorded.

The details of the mfVEP recording and analysis have been published previously [see Hood and Greenstein for a review].²⁴ Briefly, three channels of recording were obtained simultaneously with gold cup electrodes. Recording electrodes were placed at the inion, 4 cm above the inion and at two lateral locations up 1 cm and over 4 cm to the left and right side of the inion. All three channels were filtered with a high and low frequency cutoff of 3 Hz and 100 Hz (Grass Instruments preamplifier P511J, Quincy, MA). An impedance of $< 5\text{K}$ was achieved for all subjects. The mfVEPs were low-pass filtered using a sharp cutoff at 35 Hz and a fast Fourier transform technique. This and all other analyses were performed with programs written in MATLAB (The MathWorks, Inc., Natick, MA). The mfVEP records were processed and an array of best channel responses derived as previously described.²⁴⁻²⁶ Root-mean-square (RMS) amplitudes were calculated for each mfVEP response over a 45 to 150 milliseconds time interval. The signal-to-noise ratio (SNR) was also measured for each response. The SNR was obtained by dividing the RMS amplitude of the response, i.e. the signal, by the RMS of the noise. Noise was defined as the mean of all 60 RMS amplitudes over a time interval of 325 to 430 milliseconds for a given eye.²⁴⁻²⁵ Analyses were performed on the “best” responses from the six channels. The arrays of “best” responses were derived as follows: For the interocular analysis at each of the 60 locations, the “best” response was the one with the largest SNR; it was selected from 12 possible responses (6 channels $\times$ 2 eyes). The response from the other eye at the same location and from the same channel contributed to the pair of responses. For the monocular analysis the “best” response was selected for each eye at each location; it was defined as the response with the largest SNR among the 6 channels. The 60 responses selected for each eye defined the “best” array for that eye.²⁴⁻²⁶

The amplitudes of each of the 60 local responses were compared to those of a normative group,²⁷ and interocular (comparison of 2 eyes) and monocular probability plots, analogous to the HVF probability plots, were derived.^{24,28} The normative group comprised 100 individuals with visual acuity $\geq 20/30$ in each eye, normal HVFs, and no evidence of any ocular or systemic disease. They ranged in age from 21 to 92 years; the mean age was 49 ± 13.6 years. There was no significant difference in age between the group of 100 normal controls and the patients.

Both mfVEPs and HVF probability plots were divided into 4 subfields: a central 10-degree (radius) and outer arcuate subfields in both superior and inferior hemifields (Fig. 1). A cluster analysis was performed for each subfield. For the mfVEPs, a cluster was defined as either 2 contiguous points at $p < 0.01$, or 3 contiguous points at $p < 0.05$ with at least one of these points at $p < 0.01$. The two points closest to fixation in each hemifield were excluded from the analysis.²⁹ For the HVFs, a cluster was defined as 3 contiguous points on the pattern deviation plot, with at least 1 point at $p < 0.005$. On the HVF plot, arcuate clusters could only include one point on the outer rim, and the most nasal point in each hemifield was excluded from the analysis. The total numbers of abnormal points and clusters in each subfield of mfVEPs (abnormal points at $p < 0.05$ and 0.01) and HVFs (abnormal points at $p < 0.01$ and 0.005) were counted.

Confocal scanning laser ophthalmoscopy was performed by a trained technician using the Heidelberg Retina Tomograph (HRT) (Heidelberg Engineering GmbH, Heidelberg, Germany). The margin of optic disc was outlined by the first author while viewing stereoscopic photographs of the optic disc. The 15° field of view centered on the optic disc was used to formulate a mean topographic image. Images with a standard deviation value > 50 (i.e. poor quality), and those obtained under conditions with significant eye movement were excluded. The data were analyzed with HRT III software. The conventional stereometric parameters relative to a reference plane $50 \mu\text{m}$ posterior to the mean retinal height were calculated. Moorfields regression analysis (MRA) and an automated analysis of the topographic image by glaucoma probability score (GPS) were also performed.

Statistical analyses of the data were performed using Fisher's exact test and Student's t-tests.

Results

Thirty-two patients with NTG and 32 with HTG were enrolled and data analyses were performed on one eye per patient. There were no significant differences in age, visual acuity, MD and PSD values between the two groups. The demographic characteristics of the participants are summarized in Table 1.

Figure 2 and Figure 3 show examples of HVF and mfVEP probability plots obtained from two patients with NTG (Fig. 2) and HTG (Fig. 3). Both the percentage of points that were abnormal and the number of clusters were analyzed. The cluster of abnormal points for the left eye on the interocular mfVEP probability plot in Figure 2A corresponds to the abnormality in the pattern deviation probability plot for the left eye. Similarly, the cluster of abnormal points for the right eye of another patient with NTG on the mfVEP plot in Figure 2B corresponds to the abnormality on the pattern deviation plot. In contrast Figure 3 shows examples of clusters of abnormal points obtained from two patients with HTG. The abnormal points are in the arcuate subfields on the HVF and mfVEP probability plots.

The percentage of abnormal points within each of the four subfields for HVFs and mfVEPs was compared. The percentage of abnormal points was calculated based on the total number of points in each subfield for 32 NTG eyes and 32 HTG eyes. The second column of Table 2 shows the total number of data points per subfield. In each case, the number of test locations was multiplied by 32, the number of eyes. The NTG and HTG columns contain the percentage (number) of these points that were abnormal at the 5% or better level. NTG eyes had a higher

percentage of abnormal points in the central subfields of both mfVEP and HVF probability plots. In particular, NTG eyes had a higher percentage of abnormal points in the central superior subfield for both the mfVEP [28.1% (NTG) vs. 22.7% (HTG)] and HVF [30.7% (NTG) vs. 27.1% (HTG)]. This difference was significant for the mfVEP ($p = 0.045$, Fisher's exact test). NTG eyes also had a higher percentage of abnormal points in the central inferior subfield for both mfVEP [17.2% (NTG) vs. 15.4% (HTG)] and HVF [15.6% (NTG) vs. 8.3% (HTG)]. This difference was significant for the HVF ($p = 0.04$, Fisher's exact test).

The percentage of clusters of abnormal points within each of the four subfields for HVFs and mfVEPs was compared. This was calculated based on the maximum number of possible clusters in each subfield. As seen in Table 3, the analysis of the percentage of subfields with clusters of abnormal points showed that NTG eyes had a higher percentage of subfields with clusters in the central superior subfield for both the mfVEP as compared to HTG eyes [19.9% (NTG) vs. 11.7% (HTG)], and the HVF [18.8% (NTG) vs. 14.1% (HTG)]. This difference was significant for the mfVEP ($p = 0.015$, Fisher's exact test). There was also a significant difference for NTG eyes for the central inferior subfield for the HVF [18.8% (NTG) vs. 4.7% (HTG), $p = 0.025$, Fisher's exact test).

Eleven HRT stereometric parameters were calculated with HRT III software and compared between both groups. The image quality had standard deviation values less than 30 (i.e. defined as good quality) for 81.2% of NTG eyes and 72.4% of HTG eyes. There were no significant differences between NTG and HTG eyes in any of the following parameters: disc area, cup area, rim area, cup/disc area ratio, cup volume, rim volume, height variation contour, cup shape measure, mean retinal nerve fiber layer thickness, retinal nerve fiber layer cross section area and vertical cup/disc ratio. The optic nerve head was also analyzed by GPS. There were no significant differences in GPS parameters between NTG and HTG eyes in cup size, cup depth, vertical retinal nerve fiber layer (RNFL) curvature, horizontal RNFL curvature, rim steepness and GPS numeric score. In addition we found no significant differences between the two groups for rim area or disc area for any of the following segments: temporal, superotemporal, inferotemporal, nasal, superonasal, or inferonasal. MRA of the optic nerve head however showed that the nasal segment was classified as abnormal in more HTG than NTG eyes the difference approached significance [43.75% (HTG) vs 18.75% (NTG), $p=0.058$, Fisher's exact test]. The GPS final classification showed no significant differences for the segments.

Discussion

NTG is a condition consisting of typical glaucomatous disc and visual field changes, an open angle, and IOP within the statistically normal range.¹ Patients with NTG are reported to have a higher incidence of disc hemorrhage than patients with HTG.^{29–31} Although intraocular pressure is part of the pathogenic process in NTG and treatment for lowering IOP is beneficial in patients who are at risk of progression, factors other than IOP may contribute to optic nerve damage or may make the nerve more susceptible to damage at lower IOP levels.² It has been suggested that there may be differences in the pathogenesis of NTG compared to HTG. For example, it has been proposed that the average blood flow is decreased and that vascular dysregulation may be a risk factor particularly for patients with NTG.^{3,4} Autoimmune factors may also play a role in the pathogenesis of NTG.^{32–35}

In this study, we compared the results of functional and structural measures to determine whether there were differences between these two types of glaucoma. We found no significant difference in HVF PSD. Perhaps this is not surprising as this global index is not an ideal measure of the extent of localized visual field defects. The PSD gives the same weighting to central locations as it does to peripheral locations even though a cluster in a central location covers a far higher number of retinal ganglion cells than the same size cluster (in terms of number of

field locations) in a more peripheral location. However we demonstrated that NTG eyes had a higher prevalence of abnormal points and clusters of abnormal points in the central subfields than did the HTG eyes on both the mfVEP and HVF tests. The results are in agreement with previous studies that found that visual field defects in NTG are more likely to be closer to fixation, more localized and deeper,^{12–17} but in disagreement with others, although these used different tests and methods of analyses. Motolko et al¹⁹ have reported no difference in visual field deficits in central 5-degree of fixation for 160 eyes of NTG and 154 eyes of HTG patients using Tübingen perimetry and Goldmann perimetry. Furthermore, King et al¹⁸ showed the scotomas were close to fixation in 23 eyes of HTG than 23 eyes of NTG patients using Octopus 201 perimetry program 32. We suggested in the introduction that one of the possible explanations for these disagreements was that the NTG and HTG eyes were at different stages of glaucomatous damage. Another possible explanation relates to selection bias. If patients with NTG are in the early stages of the disease process, with a normal IOP and no symptoms, they are unlikely to be motivated to have a full glaucoma examination. However, if they have developed a visual field deficit near fixation, they may be more aware of it than if they had deficits in the arcuate nerve fiber bundle area. Thus, selection bias could also be a possible explanation for the functional differences between NTG and HTG patients that we and others have found.

Previous studies have also reported differences in optic disc and nerve fiber layer parameters. For example, Kiriyama et al⁵ and Eid et al⁸ studied HRT topographic parameters and reported that NTG eyes tend to have larger cups, smaller rims and thinner retinal nerve fiber layers as compared to POAG eyes. Although we found no significant differences in the total rim area or in any of the other stereometric parameters as measured by HRT in agreement with Lester et al³⁶ and Nakatsue et al³⁷ we did find more abnormal nasal segments using MRA in HTG than NTG eyes. This suggested greater peripheral damage in HTG and that it occurred in visual field areas outside those measured by the 24-2 HVF. It is possible, however, that the nasal border of the optic disc may be masked by the crowding of blood vessels.³⁸ Because of our concern we re-analyzed the data using the contour line independent GPS classification and found no significant differences between optic disc tomography of NTG and HTG eyes. In general, MRA and GPS have similar diagnostic capabilities^{39,40} and both classification algorithms show poor sensitivity to damage in eyes with small optic discs and poor specificity in large optic discs.³⁹ However, specificity tends to lower for GPS compared to MRA and it is more influenced by optic disc size.^{40–42}

In summary, we have evaluated NTG and HTG patients using functional and structural tests and have found functional differences between these two groups. The results have clinical implications for the evaluation of visual field defects in NTG and HTG eyes. Because of the finding of a higher prevalence of visual field defects in the central region, we recommended that intensive testing of the central 10-degrees of the visual field (10-2 strategy) should be performed on patients with NTG.

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Figure 1.

HVF and mfVEP probability plots divided into 4 subfields: a central 10-degree (radius) and outer arcuate subfields in both superior and inferior hemifields. (A) HVF probability plot, the 2 most nasal points (rectangle) were excluded from the analysis. (B) mfVEP, the two points that were closest to fixation in each hemifield were excluded from the analysis.

Figure 2.

HVF gray scale, pattern standard deviation and mfVEP probability plots. Examples of clusters of abnormal points in the subfields on the HVF and mfVEP probability plots obtained from the left eye (A) and right eye (B) of two patients with NTG. Each mfVEP plot shows a cluster of points in the central superior subfield that correspond to the cluster in the HVF probability plot.

Figure 3.

HVF gray scale, pattern standard deviation and mfVEP probability plots. Examples of clusters of abnormal points in subfields on the HVF and mfVEP probability plots obtained from the left eye (A) and right eye (B) of two patients with HTG. Each mfVEP plot shows a cluster of points in the superior arcuate subfield that correspond to the cluster in the HVF probability plot

Table 1

Demographics data of patients

	NTG (n=32)	HTG (n=32)	<i>P</i>
Age (yrs), mean $\pm$ SD	64.4 $\pm$ 11.4	64.3 $\pm$ 13.3	0.323 [†]
Gender (male/female)	7/25	15/17	0.041 [*]
Eye (right/left)	21/11	15/17	0.142 [*]
CCT (μ m), mean $\pm$ SD	535.4 $\pm$ 36.5	554.7 $\pm$ 33.1	0.035 [†]
Visual acuity (log MAR)	0.028 $\pm$ 0.06	0.034 $\pm$ 0.06	0.729 [†]
MD (dB), mean $\pm$ SD	-3.61 $\pm$ 2.08	-4.47 $\pm$ 2.60	0.155 [†]
PSD (dB), mean $\pm$ SD	2.82 $\pm$ 3.54	4.98 $\pm$ 2.46	0.116 [†]
SD of HRT scans (μ m)	19.91 $\pm$ 11.27	22.68 $\pm$ 10.05	0.307 [†]

[†] Student's t-test^{*} Fisher's exact test

Table 2

Percentage (number) of abnormal points in each subfield for mfVEP and HVF

	Total no. of points in subfields	Percent (no.) of abnormal points NTG	Percent (no.) of abnormal points HTG	<i>P</i> *
HVF				
Superior, central	192 (6×32)	30.70% (59)	27.10% (52)	0.500
Superior, arcuate	608 (19×32)	15.13% (92)	16.45% (100)	0.531
Inferior, central	192 (6×32)	15.63% (30)	8.33% (16)	0.040**
Inferior, arcuate	608 (19×32)	9.21% (56)	11.35%(69)	0.222
mfVEP				
Superior, central	512 (16×32)	28.13% (144)	22.66% (116)	0.045**
Superior, arcuate	384 (12×32)	13.28% (51)	14.32% (55)	0.754
Inferior, central	512 (16×32)	17.19% (88)	15.63% (80)	0.555
Inferior, arcuate	384 (12×32)	14.84% (57)	14.06% (54)	0.837

* Fisher's exact test

** Statistically significant

Table 3

Percentage (number) of abnormal clusters in each subfield for mfVEP and HVF

	Total no. clusters in subfield	Percent (no.) of abnormal clusters NTG	Percent (no.) of abnormal clusters HTG	<i>P</i> *
HVF				
Superior, central	64 (2×32)	18.80% (12)	14.06% (9)	0.634
Superior, arcuate	160 (5×32)	13.75% (22)	14.38% (23)	1.000
Inferior, central	64 (2×32)	18.75% (12)	4.69% (3)	0.015**
Inferior, arcuate	160 (5×32)	10.00% (16)	10.00% (16)	1.000
mfVEP				
Superior, central	256 (8×32)	19.92% (51)	11.72% (30)	0.015**
Superior, arcuate	192 (6×32)	5.21% (10)	2.60% (5)	0.292
Inferior, central	256 (8×32)	9.38% (24)	7.42% (19)	0.524
Inferior, arcuate	192 (6×32)	6.25% (12)	3.13% (6)	0.158

* Fisher's exact test

** Statistically significant