Visual Field Progression Differences between Normal-Tension and Exfoliative High-Tension Glaucoma

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PURPOSE. To compare the pattern, location, and rate of visual field (VF) change in normal-tension (NTG) and exfoliative high-tension glaucoma (XHTG).

METHODS. Records of all patients with glaucoma in the New York Glaucoma Progression Study with five or more VF tests were reviewed. Patients were divided into NTG (all known IOP < 21 mm Hg) and XHTG (untreated IOP ≥ 21 mm Hg) groups. Automated pointwise linear regression analysis determined global and localized rates of change.

RESULTS. There were 139 NTG and 154 XHTG eyes. Patients with XHTG were significantly older than those with NTG (mean ± SD: 72.6 ± 9.4 years vs. 62.7 ± 12.8 years, P < 0.01), had higher mean IOPs (16.5 ± 3.2 mm Hg vs. 13.3 ± 2.0 mm Hg, P < 0.01) and greater central corneal thickness (CCT, 544.0 ± 35.7 μm vs. 533.9 ± 35.9 μm; P = 0.01). During a similar period, XHTG progressed globally almost twice as rapidly as did NTG (−0.64 ± 0.7 dB/y vs. −0.35 ± 0.3 dB/y, P < 0.01), which became nonsignificant after adjustment for differences in age, mean IOP, and CCT. In a multivariate model, variables significantly associated with progression were higher mean IOP (odds ratio [OR]: 1.09, P < 0.03) and decreased CCT (OR/40 μm thinner: 1.37, P = 0.03). Progression within the paracentral VF was more common in the NTG group (75% vs. 57.3%, P = 0.04). The most important factor associated with paracentral progression among eyes that reached a progression outcome was the diagnosis of NTG.

CONCLUSIONS. XHTG and NTG eyes progress at a similar global rate after adjustment for differences in IOP, CCT, and age. However, NTG eyes progress more often in the central VF, independent of other factors. Glaucoma surveillance in eyes with open-angle glaucoma and statistically normal IOP should include periodic assessment of the central field. (Invest Ophthalmol Vis Sci. 2010;51:1458–1465) DOI:10.1167/iovs.09-3806

Glaucosa is a progressive optic neuropathy characterized by pressure-dependent and -independent mechanisms that contribute to disease onset and progression. Although there are many genotypes and phenotypes, reduction of intraocular pressure (IOP) has been demonstrated to delay or prevent further injury across the glaucoma spectrum and IOP remains the only modifiable risk factor for which proven treat- ment is currently available.1–4

The relative importance of IOP-dependent and -independent risk factors varies among individuals and forms of glaucoma. For example, eyes with exfoliative glaucoma (XFG), a subtype of glaucoma characteristically associated with elevated IOP (high-tension glaucoma, HTG), may have a disease process in which IOP-dependent factors play a central role in disease onset and progression. Conversely, eyes with IOP within the normal statistical range (normal-tension glaucoma, NTG) may be less dependent on IOP for disease onset and progression. Although our current understanding of glaucoma pathophysiology is that this arbitrary division of patients into NTG and HTG is an oversimplification, it nonetheless continues to be widely used to classify them for purposes of research and, by some physicians, to determine treatment options. In addition, many of the distinctions between HTG and NTG, including severity, rates of progression, visual field (VF) loss, and other risk factors, have yet to be fully elucidated.

It remains unclear whether the same pattern of glaucoma-tous VF deterioration is present in both NTG and HTG.5–12 Likewise, little information is available regarding the relative rates of progressive VF loss in HTG compared with NTG. The purpose of this study was to determine differences in the pattern, location, and progression of functional injury between these two entities.

METHODS

The New York Glaucosa Progression Study (GAPS) consists of 43,660 consecutive subjects (132,512 VF tests) evaluated in the referral practice of the authors (JML, RR, CT) from January 1999 to December 2008. After an initial visit that consisted of a complete ophthalmic examination, perimetry (24-2 SITA-SAP, Humphrey Field Analyzer II; Carl Zeiss Meditec, Inc., Dublin, CA), and optic disc stereophotographs, patients were reexamined, usually at 3- to 6-month intervals, and the same tests were repeated within 6 to 12 months. The study was approved by the New York Eye and Ear Infirmary Institutional Review Board and adhered to the tenets of the Declaration of Helsinki.

Since we wanted to investigate VF characteristics and progression in this population, only patients with five or more VF tests (SITA Standard 24-2 VF tests; SITA-SAP; Carl Zeiss Meditec, Inc.) in either eye were included. We enrolled eyes with established glaucoma, as defined by the presence of glaucomatous optic neuropathy associated with typical, reproducible VF defects on SITA-SAP. Glaucomatous optic neuropathy was defined as a vertical cup-to-disc ratio ≥0.6, asymmetry of cup-to-disc ratio ≥0.2 between eyes, and the presence of localized retinal nerve fiber layer (RNFL) or neuroretinal rim defects or a splinter

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hemorrhage in the absence of any other abnormalities that could explain such findings. The minimum criteria for a VF abnormality were a glaucoma hemifield test (GHT) result outside normal limits on at least two consecutive reliable examinations or the presence of at least three contiguous test points on the pattern standard deviation (PSD) plot with \( P < 1 \% \), with at least one of \( P < 0.5 \% \), not including points on the edge of the field or those directly above and below the blind spot. All baseline VF tests had reliability indices of \(< 25\%\) fixation losses, false-positive responses, and false-negative responses. All eyes had visual acuities \( \geq 20/40 \) and refractive errors \(< 6.00 \) D sphere and \( 2.00 \) D cylinder.

From that database, we further selected only patients with treated NTG and HTG. NTG was defined by the presence of glucomatous VF loss, and all recorded IOP measurements \( < 21 \) mm Hg with Goldmann applanation tonometry. To avoid diagnostic confusion, minimize overlap with the NTG eyes, and emphasize the IOP-dependent disease process, we limited our HTG group to those eyes with XFG, a glaucoma that typifies a highly IOP-dependent disease process (exfoliative [XHITG]). We defined XFG by the presence of glucomatous damage as previously described, untreated IOP \( > 21 \) mm Hg, and the presence of exfoliation material on the anterior lens capsule and/or pupillary margin. Eyes with angle closure or conditions other than glaucoma that were recorded based on patient self-report obtained from a questionnaire filled out at the initial visit, as well as from each office visit, if the patient reported any new medical condition. Baseline central VF loss was defined by the presence of at least one point with \( P < 0.01 \) within the four centralmost points of the pattern deviation plot in the two consecutive baseline tests. The mean deviation (MD) of the first baseline test was recorded to determine the amount of global field damage. The number and location of the significantly progressing points shown on the final printout was compared with the division of VF sectors described by Garway-Heath et al. This information was further used to establish the most common location of progressing points in each group. Since we were particularly interested in damage and progression at the four centralmost points, we also evaluated the location of progressing points with respect to the central field. If any of the four central points or their adjacent 12 centralmost points of the VF progressed, we defined it as paracentral progression.

### Statistical Analysis

Student's \( t \)-test was used to compare the two groups based on two-tailed probabilities, assuming that parametric tests perform well in large samples. Categorical variables were compared by \( \chi^2 \) test. A general linear model was used to compare global rates of change between groups after adjustment for potential differences in the assessed variables. Logistic regression was used to evaluate the association between baseline and intercurrent factors and a binary outcome. First, we used our predefined progression endpoint as an outcome (yes or no) and then assessed whether progression occurred within the central field. Variables with \( P < 0.20 \) in the univariate model were entered in the multivariate model. Multivariate analysis was performed by using a backward approach: All variables were entered into the model first and then the nonsignificant variables were removed sequentially. Statistical significance was set at \( P < 0.05 \) (MedCalc software; MedCalc, Inc., Mariakerke, Belgium; and; SPSS, ver. 17.0; SPSS, Chicago, IL).

### Results

One hundred thirty-nine NTG (mean MD, \(-6.5 \pm 5.4 \) dB) and 154 XHTG (mean MD, \(-6.7 \pm 7.0 \) dB, \( P = 0.78 \)) eyes were included. The mean follow-up period was similar for NTG and XHTG eyes (5.2 \pm 2.0 years vs. 5.6 \pm 1.8 years; \( P = 0.57 \)), as was the mean number of VF tests (8.2 \pm 3.5 vs. 8.1 \pm 2.9; \( P = 0.78 \)). Patients with XHTG were significantly older than those with NTG (72.6 \pm 9.4 years vs. 62.7 \pm 12.8 years; \( P < 0.01 \)), had greater CCT (544.0 \pm 35.7 \( \mu \)m vs. 533.9 \pm 35.9 \( \mu \)m; \( P < 0.01 \)), and had higher mean IOP during follow-up (16.5 \pm 3.2 mm Hg vs. 13.3 \pm 2.0 mm Hg; \( P < 0.01 \)). Baseline central VF loss (within the central four points on the 24-2 VF) occurred more frequently in NTG (58.9\%) than in XHTG (31.8\%) eyes (\( P < 0.01 \); Table 1).

The mean global rate of change for XHTG was almost twice as fast as that for NTG (\(-0.64 \pm 0.7 \) dB/y vs. \(-0.35 \pm 0.3 \) dB/y; \( P < 0.01 \)). After adjustment for differences in age, CCT, and

### Table 1. Baseline Characteristics of the Studied Population

<table>
<thead>
<tr>
<th></th>
<th>NTG (n = 139)</th>
<th>XHTG (n = 154)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.7 \pm 12.8</td>
<td>72.6 \pm 9.4</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Sex, female (%)</td>
<td>92 (66.1)</td>
<td>88 (57.1)</td>
<td>0.14</td>
</tr>
<tr>
<td>Ethnicity, European ancestry, n (%)</td>
<td>106 (76.2)</td>
<td>144 (93.5)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Migraine/Raynaud's/hypotension, n (%)</td>
<td>53 (38)</td>
<td>6 (4)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Cardiovascular diseases, n (%)*</td>
<td>59 (42)</td>
<td>86 (56)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean number of VF</td>
<td>8.2 \pm 3.5</td>
<td>8.1 \pm 2.9</td>
<td>0.78</td>
</tr>
<tr>
<td>Mean follow-up time, y</td>
<td>5.2 \pm 2.0</td>
<td>5.6 \pm 1.8</td>
<td>0.07</td>
</tr>
<tr>
<td>Baseline mean deviation, dB</td>
<td>-6.5 \pm 5.4</td>
<td>-6.7 \pm 7.0</td>
<td>0.78</td>
</tr>
<tr>
<td>Central defect at baseline VF, n (%)</td>
<td>82 (58.9)</td>
<td>49 (31.8)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>CCT, ( \mu )m</td>
<td>553.9 \pm 35.9</td>
<td>544.0 \pm 35.7</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean follow-up IOP, mm Hg</td>
<td>13.3 \pm 2.0</td>
<td>16.5 \pm 3.2</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

* Includes: hypertension, coronary ischemia, and stroke. Italic denotes a significant difference.
mean IOP, there was no longer a statistically significant difference between groups regarding global rates of change (−0.58 ± 0.7 dB/y vs. −0.46 ± 0.6 dB/y; P = 0.20; Table 2).

There was no difference between groups with respect to the number of eyes with at least one point showing our definition of progression (NTG, 46%; XHTG, 48%; P = 0.75). The mean number of points in the field that reached a progression endpoint among progressing eyes was similar between groups after adjustment for differences in age, mean IOP, and CCT (XHTG, 5.5 ± 8.1; NTG, 5.7 ± 8.3; P = 0.35). After adjustment for the same variables, the mean rate of change for the significantly progressing points was similar in XHTG and NTG eyes (−2.8 ± 2.1 dB/y vs. −2.0 ± 2.2 dB/y; P = 0.08). The NTG eyes had more significantly progressing VF points at or adjacent to the four central points of the field than did the XHTG eyes (75% vs. 57%; P = 0.04).

Systemic comorbidities were present in a substantial number of patients from both groups. The NTG group characteristically had a higher prevalence of migraine, Raynaud’s phenomenon, and hypotension (38% vs. 4%, P = 0.01), whereas the XHTG patients were more likely to have cardiovascular diseases (coronary ischemia, stroke, and hypertension; 56% vs. 42%, P = 0.02; Table 1).

Table 3 shows the results of the logistic regression evaluating factors associated with a progression endpoint in the entire population. In the multivariate analysis, mean IOP (odds ratio [OR]: 1.09, P = 0.05) and CCT (OR per 40 μm thinner: 1.37, P = 0.03) remained statistically significant. Table 4 shows the results of the logistic regression looking at factors associated with progression in the central field. In the multivariate analysis, only the diagnosis of NTG (OR: 2.69, P = 0.02) was significantly associated with progression in the central field. The presence of preexisting damage within the four centralmost points was not associated with either general progression or progression within the paracentral field.

The distribution of significantly progressing points of the two groups based on Garway-Heath VF mapping is shown in Figure 1. In NTG eyes, progression was more concentrated within the central and superotemporal fields. On the other hand, XHTG eyes showed a more random distribution of progressing points mostly concentrated in the superotemporal and inferotemporal sectors, with no clear tendency to affect the central field.

**Discussion**

NTG and HTG can be thought to be opposite ends of a spectrum of pressure-independent and pressure-dependent glaucomatous optic nerve damage. Elucidation of additional biomarkers predisposing to IOP-dependent and -independent glaucomatous damage would allow more precision in managing these disorders, including initiation of IOP-lowering treatment, frequency of monitoring for VF loss, where to search for progression, and how aggressively to treat individual patients.

In this study, we optimized the evaluation of the velocity and pattern of VF progression associated with IOP by comparing a group of patients in whom factors other than IOP are believed to play a more significant role and one in which IOP is believed to play a predominant role. These findings are particularly relevant, as we found that NTG and XHTG eyes reached the predefined progression outcome with the same frequency, and the difference between groups regarding the global rate of change became nonsignificant when adjusted for age, mean IOP, and CCT. However, patients with XFG may be more likely to present higher IOP variability and peaks during follow-up,17 which could have accounted for a higher mean IOP in this group, regardless of treatment.10

In the present study we did not find a significant association between baseline central damage and functional progression. In consonance with our results, Membrey et al.19 investigated a population with NTG and found that the presence of VF loss threatening fixation did not constitute an increased risk of overall VF progression using PLR. They also found that 32% of NTG eyes progressed within the central VF. Our map (Fig. 1) shows that in eyes with significantly elevated IOP, the superior
XFG is an age-related disease, whereas clinicians may now be diagnosing NTG in younger patients with greater frequency based on the appearance of the optic disc and VFs, rather than on IOP only.

In contrast to most of the large clinical trials in glaucoma, we used trend analysis by PLR to evaluate progression. Despite that difference, there are similarities between our results and those in other studies. For instance, the CNTGS data suggested highly variable rates of change in patients with NTG. Their patients had a mean of 2042 days to progression, defined as the deterioration of two or more points by at least 10 dB from the average of baseline values. Using PLR, we found that progressing patients had an average time to progression of 2102 days, similar to those in the CNTGS. Moreover, we can estimate the rate of change of progressing points in the CNTGS by dividing 10 dB over a mean period of 5.6 years, resulting in a mean rate of −1.8 dB/y. Our automated calculation of progression showed a mean localized loss of threshold sensitivity of −2.0 dB/y. The CNTGS investigators also calculated their population’s global rate of change by regressing the VF MD values over time and found a mean slope of −0.37 dB/y. These results are very similar to ours (−0.35 dB/y), showing congruence between the results of a prospective controlled clinical trial and those from a diversely treated, heterogeneous population. With regard to our defining progression by using PLR, we did not use any of the previously described confirmatory methods, as we sought to increase the sensitivity and likelihood of detecting significantly progressing points. This method allows us to map the most frequent locations of VF progression in the two groups, regardless of the expected decrease in specificity that this method may have caused.

In accordance with other studies, we found a significant role for IOP-dependent mechanisms in VF progression. In a model that included all patients, mean IOP and CCT remained the only significant factors associated with progression, even in a treated population with substantially low IOP during follow-up. The fact that the percentage of progressing eyes was similar between groups may suggest that there are two different patterns of progressive VF loss (localized and global) that should be differentiated.

We did not evaluate the role of eccentricity on the variability of the tested points, which could be a caveat regarding the interpretation of the results on global rates of change. The two groups showed similar MD at baseline assessment. Since the MD is a weighted average of the points in the total deviation plot (with greater weight of central points), it is possible that the proximity of MDs between groups was largely due to more abnormal points in the central field of NTG eyes, as shown in our results. As glaucoma progression is less likely to occur in areas of deep scotomata, but rather at adjacent areas of the field with borderline sensitivities, progression in NTG eyes followed an outward pattern, whereas in XHTG eyes it tended to occur more diffusely. Even though we found no association between baseline central VF loss and the location of future progression, this point should be taken into consideration when interpreting our results.

We chose XFG as our HTG group, to avoid the overlap that normally exists when NTG and POAG are artificially divided into two groups. Exfoliative glaucoma, one type of HTG, is a complex systemic disease involving the deposition of a characteristic abnormal fibrillar matrix product. Development of XFG is primarily due to elevated IOP. In XFG, friction between the iris pigment epithelium and exfoliation material on the anterior lens capsule leads to liberation of both exfoliation material and iris pigment from ruptured epithelial cells at the pupillary ruff and sphincter. A combination of exfoliation material and pigment accumulates in the intertrabecular spaces, in the juxtacanalicular meshwork, and adjacent to the

and inferior arcuate areas progress faster, whereas the central field may be more influenced by IOP-independent factors that require further clarification. This observation is supported by the fact that neither the presence of baseline damage in the central field nor other ocular or systemic factors were independently associated with paracentral progression. Rather, only the diagnosis of NTG remained a significant predictor of worsening in the paracentral field. Our proposed map could be clinically useful, as it allows the practitioner to easily search for locations more likely to progress in each group of patients and to use this information to monitor VF progression more closely.

Distinctions between the locations of VF progression in each disease remain controversial. Multiple studies have compared VF loss in NTG and primary open-angle glaucoma. Hitchings and Anderton found with manual perimetry that patients with NTG had a tendency toward steeper VF defects, as well as defects closer to fixation. Likewise, another report identified VF defects that were steeper, deeper, and closer to fixation in NTG than in HTG (IOP > 30 mm Hg) (Octopus perimetry; Haag-Streit, Kóniz). Chauhan et al. found that VF defects in NTG were more likely to be localized, as opposed to the diffuse defects in HTG. Arai et al. (using STATPAC to compare 30-2 VFs; Humphrey Field Analyzer, Carl Zeiss Meditec), found that NTG VF defects occurred more often just above the horizontal meridian, whereas HTG defects tended to be more diffuse. A review of this topic likewise found that NTG defects were more likely to be localized and close to fixation. Most recently, Thonglummetra et al. showed that NTG eyes had more localized and central defects on both HVF and mVFP than did HTG eyes with similar MD and PSD. However, other studies have failed to confirm these findings. Motolkol et al. did not identify any quantitative or qualitative VF differences between eyes with NTG and those with POAG with the same degree of optic nerve damage. Unlike our findings, King et al. did not identify differences in slope or depth of scotomas in NTG and HTG perimetry (Octopus; Haag Streit), but found that scotomata in HTG were on average closer to fixation than NTG. Last, no patterns of VF loss specific to XFG have yet been identified. Konstas et al. found that mean VF loss was worse on presentation in XFG than in POAG, but did not differentiate specific VF patterns.

Our baseline patient demographics correlate well with previous studies of NTG and XHTG. Patients in each group had similar levels of baseline VF damage (MD), although the mean age was older in the XHTG group than in the NTG group. The mean age of patients with NTG in our study was 62.7 years, similar to 63.6 years in the Collaborative Normal Tension Glaucoma Study (CNTGS). The mean age of our patients with XFG (72 years) is also in agreement with the literature. The observed age difference could be explained by the fact that

FIGURE 1. Mapping of the location of significant visual progression in glaucomatous eyes that reached a progression endpoint (modified from Garway-Heath et al.16). A significant progression was defined by any test point with a slope showing loss of >1.0 dB/y with P < 0.01 (or >2.0 dB/y for edge points). (A) NTG; (B) HTG; (C): <50% of eyes progressing; (D): <30% of eyes progressing.

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endothelium of Schlemm’s canal. This deposition causes decreased aqueous outflow, and the resulting imbalance between production and outflow in turn raises IOP.27,28 The elevated IOP often seen in these patients is most likely the proximate cause of the onset and progression of glaucomatous optic neuropathy and the pattern of VF loss documented in the present study.

Like most glaucomas, not all the damage in XFG can be attributed to elevated IOP, and IOP-independent factors may contribute to glaucomatous damage as well. Reported IOP-independent factors include impaired ocular and retrobulbar perfusion29 and elastotic changes in the lamina cribrosa.30 Puska et al.31 found that normotensive patients with clinically unilateral XFS and equal IOP throughout follow-up showed disc changes only in the exfoliation eye, possibly implicating the exfoliation process in optic nerve damage independent of its role in raising IOP. Despite these potential issues, the role of IOP-independent factors in XFG progression is likely to be less than in a corresponding group of subjects with primary open-angle glaucoma.

In contrast, IOP-independent mechanisms may play a relatively larger role in the onset and progression of glaucomatous optic neuropathy in individuals with NTG. Age is one of the main IOP-independent risk factors and has been associated with glaucoma onset and progression in some of the major clinical trials.3,4 Our univariate analysis showed a significant association between older age and reaching a progression outcome when both groups were combined. However, it became nonsignificant when other factors (mean IOP and CCT) were entered in the model, despite a trend toward the predicted direction (OR: 1.01, P = 0.09). Optic disc splinter hemorrhages have been reported to occur more frequently in NTG eyes and may be evidence of a vascular process.32 Also, NTG has been associated with primary systemic vascular dysfunction, with a higher incidence of NTG in patients with vasospastic syndromes such as migraine and Raynaud’s phenomenon.33,34 Disturbances of vascular autoregulation may predispose susceptible patients to unstable ocular perfusion with changes in blood pressure or IOP.35,36 Our study was consistent with these reports, as patients with NTG more often reported conditions such as migraine, Raynaud’s phenomenon, and hypotension.21 These factors, nevertheless, were not significantly associated with a progression outcome, but rather with an increased risk of progression in the central field in the univariate analysis. This suggests that functional changes in the central field may be influenced by disturbances in vascular autoregulation. Of interest, patients with XHTG showed a different pattern of systemic comorbidities (i.e., cardiovascular diseases) which is consistent with the literature.25–29 However, these conditions did not show significant association with progression or its location in the VF.

IOP-independent and -dependent factors may interact in ways that are as yet unknown. Decreased perfusion pressure, measured as the difference between systolic blood pressure and IOP, may make the onset and progression of glaucoma more likely.36–38 Also, glaucomatous eyes may have lower macular perfusion, which could be associated with the pattern of VF damage.39 Evidence that other IOP-independent mechanisms play a role in NTG was provided by the Low-Pressure Glaucoma Study,40 which found no correlation between baseline IOP asymmetry and VF damage in NTG. These mechanisms may still be important over time, as 20% of NTG eyes may progress despite successful IOP reduction.21

The core clinical implications of this study are that progression in NTG eyes should not be underestimated and that greater surveillance of the central field in NTG is warranted. Such oversight could lead to more widespread use of alternative methods of observing these patients, such as visual field strategies assessing the central 10°, multifocal visual evoked potential techniques and microperimetry.

In conclusion, in a population with treated and established glaucoma, NTG and XHTG eyes tended to progress at similar rates of change and frequency when adjusted for differences in IOP, CCT, and age. However, NTG eyes were at increased risk of field loss close to fixation, which may require more careful monitoring and aggressive treatment.

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