Optic Disc Findings in Normal Tension Glaucoma

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Abstract: One hundred thirty stereo photographs of optic discs in patients with normal tension glaucoma (NTG) were reviewed in order to identify characteristics of the three following types of NTG: focal ischemic, senile sclerotic, and generalized cup enlargement. Twenty patients in each group were selected. Focal ischemic patients were more frequently women, had a higher incidence of migraine, a relatively smaller disc size, and localized superior scotoma that often threatened fixation. Senile sclerotic patients were generally elderly, had a higher incidence of surgery under general anesthesia, had more ischemic heart disease or systemic hypertension, had a small rim area, and also had extensive peripapillary atrophy as well as combined diffuse and localized visual field defects. Generalized cup enlargement patients were younger, had a relatively larger disc size and a greater incidence of purely diffuse visual field loss. Results of our study suggest that the different characteristics of the groups are related to pathogenic mechanisms specific to each group. Jpn J Ophthalmol 1997:41:260-267 © 1997 Japanese Ophthalmological Society

Key Words: Normal tension glaucoma, optic disc, peripapillary chorioretinal atrophy, visual field defect.

Introduction

Normal tension glaucoma (NTG) refers to a type of glaucoma that is clinically similar to primary open angle glaucoma, except for a statistically high intraocular pressure (IOP). Many clinical factors, with or without elevated IOP, influence visual field defects in NTG. Vascular disorders involved include hypertension,2 migraine,3 and Raynaud's phenomenon.4 Spasms of peripheral vessels were more common in patients with NTG than in normal subjects.5 Disc hemorrhage, viewed as an ocular vasospastic sign, had a higher prevalence in patients with NTG than in those with primary open angle glaucoma.6 In color Doppler-image studies of ophthalmic arteries, we found that patients with NTG showed a statistically significant correlation between the vascular resistance of the ophthalmic artery and the mean depression of retinal sensitivity, but those with primary open angle glaucoma showed no correlation.7 However, when the mean IOP is asymmetric in NTG, the visual field defect appears to be greater on the side with the higher mean IOP.5,9 It seems that both IOP and clinical factors influence the development of glaucomatous damage in NTG.

Various patterns of disc damage in glaucoma have been described, suggesting that NTG results from different pathogenic mechanisms.4,10-12 Spaeth13 pointed out that some glaucoma patients develop a focal loss of disc tissue, usually at the inferior pole, and called it focal ischemic glaucoma because of the presence of a corresponding localized ischemic area found on fluorescein angiography. Geijssen and Greve4 described the senile sclerotic discs in glaucoma as pale and saucerized with peripapillary atrophy and choroidal sclerosis. Cup size, disc size and the presence of areas of peripapillary atrophy are indicators of an increased vulnerability of the optic nerve head in glaucomatous damage.10,11,14-16 We used stereophotography to identify disc characteristics in patients with
OPTIC DISCS IN GLAUCOMA

Subjects and Methods

Subjects

The diagnostic criteria for NTG are: (1) glaucomatous optic disc cupping with progressive visual field defects in one or both eyes; (2) IOP consistently lower than 21 mmHg, including diurnal variation, without medication to lower the IOP; (3) normal open angle; and (4) no other ocular pathology to account for the visual defects or the appearance of the optic nerve head.

To be included in the study, eyes had to have a visual acuity of 20/30 or better with no clinical evidence of media opacity. Patients with a history of intraocular surgery, except argon laser trabeculoplasty, were excluded from this study.

Optic disc stereo photographs of 130 NTG patients, taken with a stereo fundus camera (3-DX; Nidek, Tokyo) were classified according to the optic disk appearance in the photographs into the following four groups, by two investigators, independently. The investigators were unaware of the clinical status of the patients.

1. Focal ischemic NTG: Localized tissue loss in the superior or inferior poles but with a relatively intact neuroretinal rim in the other areas (Figure 1).
2. Senile sclerotic NTG: Saucerized and shallow cup, called a moth-eaten appearance, with peripapillary atrophy (PPA) and choroidal sclerosis also called fundus tessellation. The remaining neuroretinal rim is usually pale (Figure 2).
3. Generalized cup enlargement NTG: Diffusely enlarged round cup with no localized defect of the neuroretinal rim (Figure 3).
4. Non-classifiable NTG: Any discs not included above (all normal-looking, tilted, with myopic degeneration, poor photographs, advanced glaucomatous damage, mixtures of patterns) were excluded from further study.

Discs that were not assigned to the same group by both investigators were also excluded. When both discs of a patient were eligible for the study, the more typical disc was chosen, or one was randomly selected if both were similar.

Methods

After the subjects were selected from their disc photographs, information was collected from their clinical charts: demographic data, including sex, age, refraction, axial length, mean IOP without medication, and systemic blood pressure (BP); presence of systemic risk factors such as vascular hypertension, diabetes, ischemic heart disease, migraine, hyperlipidemia, and any history of undergoing pulmonary, gastrointestinal, or gynecological surgery while under general anesthesia. The diagnosis of migraine was defined according to the Ad Hoc Committee classification of headache.37

We examined visual fields using program 30-2 of the Humphrey field analyzer (Allergan-Humphrey, San Leandro, CA, USA) and calculated the mean deviation and corrected pattern standard deviation as indices for visual field defects, using statistical analysis software (Statpac, Allergan-Humphrey). Visual defects were classified as localized, diffuse, or a combination. Localized defect was defined as the presence of a cluster of two points whose pattern deviation probability level was less than 0.01, located above or below the horizontal meridian. Diffuse defect was defined as having at least 80% of the points plotted in a cumulative defect curve (Bebie curve)18 located below percentile 95 and parallel to the normal curve. Localized and diffuse defect was defined as a localized cluster associated with a diffuse defect of the remaining points, as defined above. Also noted was any visual field defect that threatened fixation, based on a depression of at least 10 dB in one or more of the four most central points.

Optic disc characteristics were evaluated in a masked fashion, using the 15-degree color stereoscopic optic disc photographs. For morphological analysis, the optic disc transparencies were projected onto white paper and the outlines of zones α and β were plotted while simultaneously viewing the corresponding stereoscopic pair. The optic disc edge coincided with the inner side of the peripapillary scleral ring. The disc cup margin was defined as being either "sloped" or "steep" and not defined by pallor. The disc rim area was defined as the area between the cup rim margin and the disc edge. Zone α was defined as irregular hypo- and hyper-pigmentation, suggesting thinning of the chorioretinal tissue layer. Zone β was defined as visible sclera and visible large choroidal vessels close to the optic border, as described by Jonas.11 We digitized the plotted data, using an image scanner (GT-6000, Epson, Tokyo) and stored this in a microcomputer (PC-9801, NEC, Tokyo). Disc area, rim area, peripapillary atrophy area, which is the sum of zones α and β, and the zone β area were computed as parameters of the optic disc topography, using a digital image processor (Micro Sparc, Fujitsu,
**Figure 1.** Stereophotograph of an optic disc with focal ischemic normal tension glaucoma. Localized tissue loss at the inferior poles with relatively intact neuroretinal rim in the superior areas.

**Figure 2.** Stereophotograph of an optic disc with senile sclerotic normal tension glaucoma. Saucerized and shallow with a "moth-eaten" appearance, showing peripapillary chorioretinal atrophy and choroidal sclerosis. The remaining neuroretinal rim was pale.

**Figure 3.** Stereophotograph of an optic disc with generalized enlargement cup normal tension glaucoma. Diffusely enlarged, round cups without a localized defect of the neuroretinal rim.
Table 1. Clinical Data of Patients With Different Disc Appearances

<table>
<thead>
<tr>
<th>Data</th>
<th>FINGT (n = 20)</th>
<th>SSNTG (n = 20)</th>
<th>GENTG (n = 20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>4/16</td>
<td>12/8</td>
<td>8/12</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Age (y)</td>
<td>63.1 ± 9.2</td>
<td>68.9 ± 6.8</td>
<td>59.6 ± 9.3</td>
<td>&lt;0.01 b</td>
</tr>
<tr>
<td>Refraction (D)</td>
<td>-0.64 ± 2.1</td>
<td>2.35 ± 3.33</td>
<td>-1.11 ± 1.41</td>
<td>n.s.</td>
</tr>
<tr>
<td>Axial length (mm)</td>
<td>23.6 ± 1.1</td>
<td>24.2 ± 1.53</td>
<td>24.0 ± 0.87</td>
<td>n.s.</td>
</tr>
<tr>
<td>Mean IOP (mmHg)</td>
<td>14.0 ± 2.0</td>
<td>14.2 ± 2.0</td>
<td>14.4 ± 2.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>131 ± 14</td>
<td>130 ± 13</td>
<td>126 ± 9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>78 ± 9</td>
<td>76 ± 8</td>
<td>73 ± 6</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

FINTG: Focal ischemic NTG. SSNTG: Senile sclerotic NTG. GENTG: Generalized cup enlargement NTG.

aChi-square test.
bKruskal-Wallis test.

Tokyo). Bengtsson’s method was used for calculation of optic disc topography.19
To determine the reliability of the data obtained by the optic disc measurements, color stereoscopic optic disc photographs of 10 normal subjects had been re-evaluated 10 times by each of two investigators. Intraobserver variation coefficients for disc area were 1.1% and 1.6%, 4.2% and 5.3% for rim area, and 4.1% and 4.7% for rim area/disc area ratio. Interobserver variation coefficient for disc area was 9.8%, for rim area, 9.9%, and 7.3% for rim area/disk area ratio.
Chi-square analysis of the categorical data was done; analysis of variance and non-parametric techniques (Kruskal–Wallis test) were used to analyze quantitative data. P equal to or less than 0.05 was considered significant.

Results
Of the 130 patients whose optic disc appearance had been classified, 60 met the criteria and were selected for this study: 20 patients in each of the three types of NTG, focal ischemic, senile sclerotic, and generalized cup enlargement. The agreement ratio in identifying patients by optic disc appearance was 93.8%. Clinical data shown in Table 1. There was a statistically significant difference (P < 0.05) between groups in sex distribution: focal ischemic NTG was found more frequently in women and senile sclerotic NTG was found more frequently in men. There also was a statistically significant difference (P < 0.01) in age distribution: the senile sclerotic NTG group was older than both the focal ischemic NTG (P < 0.05) and generalized cup enlargement NTG (P < 0.01) groups. There was no statistically significant difference between groups in refraction, axial length, systemic BP, and mean IOP without medication.

Systemic risk factor occurrence is shown in Table 2. There was a statistically significant difference in the prevalence of ischemic heart disease between the groups, being more frequent in focal ischemic NTG and senile sclerotic NTG groups. In the senile sclerotic NTG group, there was a statistically significant difference (P < 0.01) in history of surgery under general anesthesia. Migraine was significantly more

Table 2. Systemic Risk Factors in Patients With Different Disc Appearances

<table>
<thead>
<tr>
<th>Factor</th>
<th>FINGT (n = 20)</th>
<th>SSNTG (n = 20)</th>
<th>GENTG (n = 20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (10.0)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>0 (0.0)</td>
<td>11 (55.0)</td>
<td>7 (35.0)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>5 (25.0)</td>
<td>7 (35.0)</td>
<td>0 (0)</td>
<td>n.s.</td>
</tr>
<tr>
<td>General anesthesia</td>
<td>4 (20.0)</td>
<td>10 (50.0)</td>
<td>1 (5.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Migraine</td>
<td>4 (20.0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>4 (20.0)</td>
<td>0 (0)</td>
<td>1 (5.0)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

FINTG: Focal ischemic NTG. SSNTG: Senile sclerotic NTG. GENTG: Generalized cup enlargement NTG.
a| n = 20.  
b| n = 20.  
c| n = 20.  
dChi-square test.
Table 3. Visual Field Defects in Patients With Different Disc Appearances

<table>
<thead>
<tr>
<th>Defect</th>
<th>FINTG a</th>
<th>SSNTG b</th>
<th>GENTG c</th>
<th>P Value d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of visual field defect</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized</td>
<td>10(50.0)</td>
<td>1(5.0)</td>
<td>3(15.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diffuse</td>
<td>0(0)</td>
<td>3(15.0)</td>
<td>10(50.0)</td>
<td></td>
</tr>
<tr>
<td>Localized and diffuse</td>
<td>10(50.0)</td>
<td>16(80.0)</td>
<td>7(35.0)</td>
<td></td>
</tr>
<tr>
<td>Hemifield affected</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior hemifield</td>
<td>10(50.0)</td>
<td>2(10.0)</td>
<td>2(10.0)</td>
<td></td>
</tr>
<tr>
<td>Inferior hemifield</td>
<td>4(20.0)</td>
<td>1(5.0)</td>
<td>2(10.0)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Both hemifields</td>
<td>6(30.0)</td>
<td>14(70.0)</td>
<td>6(30.0)</td>
<td></td>
</tr>
<tr>
<td>Threat to fixation</td>
<td>18(90.0)</td>
<td>11(55.0)</td>
<td>7(35.0)</td>
<td></td>
</tr>
<tr>
<td>Visual field indices</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD mean ± SD (dB)</td>
<td>-11.3 ± 5.7</td>
<td>-13.5 ± 5.5</td>
<td>-9.1 ± 5.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>CPSD mean ± SD (dB)</td>
<td>10.2 ± 2.9</td>
<td>8.6 ± 3.6</td>
<td>7.6 ± 4.6</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

FINTG: Focal ischemic NTG. SSNTG: Senile sclerotic NTG. GENTG: Generalized cup enlargement NTG.

| n = 20. |
| n = 20. |
| n = 20. |

Discussion

Our study confirmed previously published findings and also indicated that new associations with distinct appearances of the optic disc might contribute to increased understanding of the underlying pathogenic mechanisms of NTG. There are suggestions in the literature that different disc findings in open angle glaucoma represent different clinical entities with specific pathogenic mechanisms. Geijssen reported that patients with NTG showed some differences in local and systemic risk factors, in fluorescein angiography, and in rate of progression of the disease among groups classified by the appearance of the optic disc. Spatah also suggests that NTG patients with different disc appearances probably represent varying clinical entities. To investigate the pathogenesis of the optic nerve damage in NTG, we used statistical analysis of the relationships of optic disc appearance to a number of systemic and focal risk factors.

Pure focal ischemic NTG was significantly more prevalent in women (four-fifths of the patients), as in previous reports. Our study found that migraine was significantly more prevalent in patients with focal ischemic NTG; Phelps and Corbett first reported the association between NTG and migraine. Vasospastic disorders, particularly migraine and Raynaud’s phenomenon, occur much more often in women than in men. Some studies showed that cold-induced vasospasm is more prevalent in NTG patients than in normal subjects or in primary open angle glaucoma patients. Having demonstrated in the present study that focal ischemic NTG is more frequent in women, as are migraine and vasospastic disorders, it appears that vasospasm may be an important factor in the pathogenesis of focal ischemic NTG. The signifi-
Table 4. Optic Disc Measurements in Patients With Different Disc Appearances

<table>
<thead>
<tr>
<th>Area</th>
<th>FINTG (n = 20)</th>
<th>SSNTG (n = 20)</th>
<th>GENTG (n = 20)</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disc area (mm²)</td>
<td>2.27 ± 0.42</td>
<td>2.47 ± 0.52</td>
<td>2.83 ± 0.46</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Rim area (mm²)</td>
<td>1.12 ± 0.27</td>
<td>0.92 ± 0.25</td>
<td>1.18 ± 0.24</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PPA area (mm²)</td>
<td>0.30 ± 0.55</td>
<td>0.82 ± 0.66</td>
<td>0.16 ± 0.22</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Zone β area (mm²)</td>
<td>0.18 ± 0.40</td>
<td>0.60 ± 0.71</td>
<td>0.13 ± 0.23</td>
<td>n.s.</td>
</tr>
<tr>
<td>Rim area/Disc area</td>
<td>0.49 ± 0.08</td>
<td>0.37 ± 0.07</td>
<td>0.42 ± 0.08</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

FINTG: Focal ischemic NTG. SSNTG: Senile sclerotic NTG. GENTG: Generalized cup enlargement NTG.
a Kruskal–Wallis test.

cance of a higher prevalence of focal tissue loss in women requires further study.

The senile sclerotic NTG patients had a significantly higher prevalence of a positive history of surgery under general anesthesia, and were significantly older, with a relatively high prevalence of systemic hypertension and ischemic heart disease. According to Drance et al.,24 the term hemodynamic crisis includes gastrointestinal and uterine hemorrhage, cardiac arrest, and severe hypotension during general anesthesia. They described the incidence of hemodynamic crisis in NTG patients as varying significantly from that in ocular hypertensives, and concluded that hemodynamic crisis could be related to the optic nerve damage in NTG.24,25 Although the present study did not reveal whether the history of surgery with general anesthesia involved a hemodynamic crisis, our results suggest that the hemodynamic effects of a systemic condition or of general anesthesia may influence the pathogenesis of senile sclerotic NTG.

There have been several reports that there were statistically significant correlations between the disc rim area reflecting the amount of retinal ganglion cell axons and the visual field indices expressing the reduction of retinal sensitivity.17,26–28 In the present study, the senile sclerotic NTG group showed significantly smaller rim area and smaller rim area/disc area ratio compared with the other groups; nevertheless, there was no significant difference in the visual field indices among the three groups. This result suggests that, in senile sclerotic NTG, there might be a relative loss of rim area preceding the progression of visual field defect. The senile sclerotic NTG group showed a significantly larger peripapillary atrophy area compared with the other groups. Peripapillary atrophy showed decreased vascularity in fluorescein angiography.29 Kubota et al.30 noted that the retinal pigment epithelium in peripapillary atrophy was structurally altered, but the retinal photoreceptors were still present, suggesting that parapapillary cho-

riocapillaris may be responsible for peripapillary atrophy. Earlier, we reported there was a tendency for zone β to be associated with serum triglyceride, high density lipoprotein cholesterol, and HbA1C.31 Geijser and Greve suggested that senile sclerotic NTG may be age-related as a systemic vascular abnormality that could lead to a chronic ischemia of the optic disc. This chronic ischemia could also explain the marked peripapillary atrophy found in the senile sclerotic NTG patients as secondary to the ocular ischemia.29,32 Our findings of more vascular abnormalities in senile sclerotic NTG group implies that this pathogenesis may be involved in the circulatory insufficiency of the optic disk.

Recent reports observe that optic disc size is greater in eyes with NTG than in those with primary open angle glaucoma.14,16 Several described a relationship between the vulnerability of the optic nerve head to glaucomatous damage and the absolute optic disc size with statistically normal IOP.11,15,16,19 These descriptions assumed that the lamina and prelamina region of the larger disc may be damaged more easily by localized hypoperfusion due to a longer diffusion distance, and that an increase in lamina cribrosa diameter may be vulnerable to low IOP due to qualitative properties of the extracellular matrix. The present study demonstrated that the generalized cup enlargement NTG group had a significantly larger optic disc area than the others, implying that the pathogenesis of optic disc damage may arise from the structural vulnerability of the larger optic disc.

Some researchers have indicated that a difference in the visual field defect pattern is involved in the pathogenesis of optic nerve damage in glaucoma.17,33–35 There is some evidence that diffuse mechanical damage to the axon, such as that caused by pressure, results in diffuse retinal nerve fiber layer (RNFL) damage and a diffuse depression of the visual field. Localized damage, possibly from circulatory insufficiency and vascular risk factors, may result in local-
ized RNFL damage and a localized depression of the visual field. RNFL changes were found to be consistent with optic disc findings. In most glaucomatous eyes, localized disc changes were associated with localized RNFL changes, and generalized cup enlargement with diffuse RNFL damage.

The present study identified the pattern of visual field defects and disc characteristics. None of the focal ischemic NTG patients had a pure diffuse visual field defect; they typically had localized scotomas, with about half the group also having an associated diffuse visual field defect. The marked predominance of superior scotomas in this group corresponded to the high frequency of focal loss at the inferior pole. Of the senile sclerotic NTG patients, 80% had a combined diffuse and localized defect involving both hemifields. Diffuse visual field defect was the only finding in 50% of the generalized cup enlargement NTG group; of those with localized defects, about one-third were associated with scotoma. There was no significant difference in the mean deviation or corrected pattern standard deviation of visual field damage in the three groups, although our data suggest that there may be a relationship to the pathogenesis of optic nerve damage.

Identification of NTG patient subgroups based on clinical characteristics may result in recognition of the role of risk factors in glaucomatous optic nerve damage. The optimum classification system, using optic disc findings as we have in the present study, or by other factors, remains to be defined. Further research is also required to clarify the relationship of optic disc appearance and risk factors that may be associated with optic nerve damage. The optimum classification system, using optic disc findings as we have in the present study, or by other factors, remains to be defined. Further research is also required to clarify the relationship of optic disc appearance and risk factors that may be associated with optic nerve damage.

References


