Glaucoma

Progression to Legal Blindness in Patients With Normal Tension Glaucoma: Hospital-Based Study

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PURPOSE. To determine the probability of an eye with normal tension glaucoma (NTG) progressing to legal blindness under standard ophthalmic care.

METHODS. Patients diagnosed with NTG (n = 382) between 1985 and 2007 at Gifu University Hospital were followed for at least 5 years under standard ophthalmic care. The collected data included the best-corrected visual acuity (BCVA), intraocular pressure (IOP), and visual field status. Blindness was defined as a BCVA of <20/400 or a constriction of the central visual field to <10° according to the World Health Organization criteria. Kaplan-Meier life table analysis was used to estimate the probability of progressing to blindness in one or both eyes.

RESULTS. The mean follow-up period after diagnosis was 13.3 ± 5.4 years with a range of 5.0 to 29.1 years. At diagnosis, 18 patients (4.7%) had unilateral blindness due to glaucoma. At final examination, 34 patients had progressed to unilateral blindness and 5 to bilateral blindness. The Kaplan-Meier life table analysis estimate for unilateral blindness was 5.8 ± 1.3% at 10 years and 9.9 ± 1.9% at 20 years. Similarly, that for bilateral blindness was 0.3 ± 0.3% at 10 years and 1.4 ± 0.8% at 20 years. A Cox proportional hazard model analysis showed that a lower initial BCVA (P < 0.001), a worse initial AGIS (Advanced Glaucoma Intervention Study) score (P = 0.002), and the frequency of changing glaucoma medications during the follow-up periods (P < 0.001) were significantly correlated with the development of blindness in at least one eye.

CONCLUSIONS. The probability of blindness in eyes with NTG is much lower than previously reported in patients with high-tension glaucoma. Nevertheless, special care should be taken to follow NTG patients, and especially those with worse BCVA and more advanced visual field loss at diagnosis.

Keywords: normal tension glaucoma, blindness, visual field progression, visual acuity

Glaucoma is the leading cause of irreversible blindness and affects more than 60 million people worldwide. There are different types of glaucoma that can cause visual impairments, and the probability of progressing to blindness for the different types of glaucoma has been investigated in several studies. Estimates suggest that the incidence of blindness in one eye will be 14.6% to 54% and in both eyes will be 6.4% to 22%, depending on the type of glaucoma.

The prevalence of open-angle glaucoma (OAG) in Japanese individuals over 40 years of age is estimated to be 3.9%. Eyes with normal tension glaucoma (NTG), or OAG with low intraocular pressures (IOPs) of ≤21 mm Hg, make up a surprising 92.3% of all cases of OAG in Japan. Nevertheless, there is no information on the probability of eyes with NTG progressing to blindness.

The average rate of progression of the visual field defects in eyes with untreated NTG was reported to be −0.2 to −2 dB/year in the Collaborative Normal Tension Glaucoma Study and −0.36 dB/year in the Early Manifest Glaucoma Trial. By contrast, De Moraes et al. reported that the rate of progression of the visual field defects was −0.35 dB/year in eyes with treated NTG. Other studies have reported variations in the rate of visual field defect progression among patients, which varies with the subtype of glaucoma.

The primary objective of the present study was to determine the probability of developing unilateral or bilateral blindness in patients with NTG receiving standard ophthalmic care. A secondary objective was to identify factors predictive of the development of the blindness in these eyes.

MATERIALS AND METHODS

This was a retrospective hospital-based observational study. The study was approved by the Institutional Review Board of Gifu University Graduate School of Medicine, and the procedures conformed to the tenets of the Declaration of Helsinki.

The study included 1002 patients who were suspected of having NTG and had completed a 24-hour diurnal IOP measurement on admission at the Gifu University Hospital, Gifu, Japan, between 1985 and 2007. The initial ocular diagnostic examinations consisted of subjective refraction with an autorefractometer, best-corrected visual acuity (BCVA), slit-lamp examination, evaluation of the structure and width of the anterior chamber angle with a Goldmann two-mirror gonioscopic lens, IOP measurements with a Goldmann applanation tonometer (GAT; Haag-Streit AG, Köniz, Switzerland), and ophthalmoscopy. Perimetry with a Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA, USA) with the central 30-2 full-threshold program was also
performed. All subjects underwent computed tomography or magnetic resonance imaging that ruled out pathological disease in the brain. Other information assessed included the age at diagnosis, sex, ethnicity, and ocular history, including previous ocular surgeries. In subjects suspected of having NTG, the 24-hour diurnal IOP measurements were performed before the initiation of the ocular hypotensive therapy, or after a 4-week washout period for ocular hypotensive agents. In each subject, the 24-hour IOP was measured using a GAT in a sitting position at 2-hour intervals from 10 AM to 8 AM on the following morning.

A diagnosis of NTG was made on the following criteria: untreated IOPs in diurnal measurements ≤ 21 mm Hg in both eyes; IOPs remaining ≤ 21 mm Hg in both eyes, irrespective of the presence or absence of treatment; presence of gonioscopically wide open angles of grade 3 or 4 based on the Shaffer classification; presence of characteristic visual field defects in at least one eye that corresponded to the location of the glaucomatous disc excavation; and absence of any pathological conditions that could account for the optic nerve damage. Glaucomatous optic neuropathy was considered to be present when an optic disc had a focal or diffuse defect of the rim exceeding 10% of the disc diameter. Any patients with possible secondary ocular hypertension in either eye were excluded. Patients with suspected NTG were diagnosed with primary open-angle glaucoma (POAG) if the IOP exceeded 21 mm Hg in either eye during the 24-hour assessment period.

Thereafter, all patients were followed for 1- to 3-month intervals at the Department of Ophthalmology, Gifu University Hospital. At each visit, examinations included measurement of BCVA, IOP (with a GAT), and direct ophthalmoscopy. Visual field examinations were conducted at intervals of 3 to 12 months.

Inclusion Criteria of Patients

We obtained the BCVA and visual field results from the hospital data bank for each patient. The inclusion criteria included follow-up periods of more than 5 years and visual field abnormalities in both eyes that met at least one of the following three criteria on the most recent three consecutive visual field measurements: an abnormal glaucoma hemifield test (borderline was not considered abnormal); three contiguous index points with a P value < 0.05 on the pattern deviation plot, with at least one point having a P value < 0.01; a full-threshold test showing a corrected pattern standard deviation (CPSD) P value < 0.05; and a Swedish Interactive Threshold Algorithm (SITA) standard test showing a pattern standard deviation (PSD) P value < 0.05. Prior to 2006 in our institution, most patients were followed with the Humphrey static automated perimeter with the full-threshold testing procedure, while since 2007, SITA static static automated perimetry has been used.

Patients who had an IOP exceeding 21 mm Hg in one eye without any other causative factors during their follow-up periods were diagnosed with POAG and excluded from the study. Patients were also excluded if one eye developed any other type of glaucoma, including exfoliative glaucoma and uveitic glaucoma, or if one eye developed other ocular pathologies capable of causing severe visual impairment such as retinal vein occlusion, trauma, neuroviscous disorders, active and chronic uveitis, and retinal detachment. The only exception was cataract or lens opacities. If an event developed during the follow-up period that precluded further information on blindness from glaucoma, the patient was dropped from the analysis at that time.

Definition of Blindness

The definition of blindness was based on criteria of the World Health Organization (WHO): a BCVA of <20/400 (decimal VA, 0.05) or a central visual field constriction of <10°. The degree of central visual field constriction was determined according to the recommendations of the U.S. Social Security Administration: A pseudoisopter was drawn by hand midway between points with threshold sensitivity values ≥ 10 decibels (dB) and those with values < 10 dB on the Humphrey Field Analyzer numerical dB printout. This pseudoisopter was used to measure the widest diameter of the remaining central visual field, which was used to determine if an eye was blind or had low vision.

Statistical Analyses

Unpaired t-tests or χ² tests were used to compare the demographic data between blind and nonblind eyes. The data were also analyzed using the Kaplan-Meier life table method to calculate the probabilities of unilateral and bilateral blindness. When the BCVA or visual field constriction met the criteria at two consecutive examinations, the eye was classified as blind. The incidence of blindness was calculated based on the first day on which the eye was classified as blind. To identify risk factors for the development of blindness, we used a stepwise selection method for Cox proportional hazards regression. Exploratory variables at the time of diagnosis included age, sex, BCVA, refractive error (spherical equivalent), averaged diurnal IOP without medications, standard deviation of diurnal IOP without medications, and Advanced Glaucoma Intervention Study (AGIS) score. Similarly, the explanatory variables recorded during the follow-up periods included the averaged IOP, IOP fluctuations under therapy, the presence of disc hemorrhages (per eye and per patient), and the frequency of changing antiglaucoma medications. When examining the frequency of changing antiglaucoma medications, changes within the same category of drugs, for example, within prostaglandin analogues, were not considered to be a change. Also, the performance of filtering surgery counted as 3 points, and laser trabeculoplasty and revision of a filtering bleb counted for 1 point. The level of significance for each comparison was set at P < 0.05. All statistical analyses were performed using SPSS software version 16.0 (SPSS Japan, Tokyo, Japan).

RESULTS

A total of 764 eyes from 382 Japanese patients met the inclusion criteria. Patient demographic data are listed in Tables 1 and 2. The average age at diagnosis was 56.4 ± 11.7 years (mean ± SD; range, 16–81 years). There were 147 men and 255 women. The average diurnal IOP was 13.9 ± 1.9 mm Hg with a range of 8.8 to 18.7 mm Hg. The average of the maximum diurnal IOP was 16.2 ± 2.2 mm Hg with a range of 11 to 21 mm Hg, and the average minimum diurnal IOP was 11.6 ± 2.1 mm Hg with a range of 6 to 17 mm Hg. The difference in the maximum and minimum diurnal IOP was 4.6 ± 1.6 mm Hg with a range of 1 to 10 mm Hg. The average follow-up period was 13.3 years with a range of 5.0 to 29.1 years.

During the follow-up period, 157 eyes of 91 patients underwent cataract surgery and 138 eyes of 88 patients underwent glaucoma surgery. Fifty eyes of 36 patients underwent both cataract and glaucoma surgery. Two hundred fifty eyes of 500 patients had medical treatment without surgical interventions. The remaining 28 eyes of 18 patients
Table 1. Patients' Demographics

<table>
<thead>
<tr>
<th>Sex, men/women</th>
<th>147 cases/235 cases</th>
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<tr>
<td>Age at admission, y</td>
<td>56.4 ± 11.7 (16 to 81)</td>
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<tr>
<td>BCVA, logMAR</td>
<td>−0.01 ± 0.23 (−0.50 to HM)</td>
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<tr>
<td>Spherical equivalent refraction, diopters</td>
<td>−2.72 ± 3.97 (−17.50 to 5.00)</td>
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<tr>
<td>Diurnal IOP without medications, mm Hg</td>
<td></td>
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<tr>
<td>Average</td>
<td>13.9 ± 1.9 (8.8 to 18.7)</td>
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<tr>
<td>Maximum</td>
<td>16.2 ± 2.2 (11 to 21)</td>
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<tr>
<td>Minimum</td>
<td>11.6 ± 2.1 (6 to 17)</td>
</tr>
<tr>
<td>Range</td>
<td>4.6 ± 1.6 (1 to 10)</td>
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<tr>
<td>Humphrey program central 30-2</td>
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<tr>
<td>Mean deviation, dB</td>
<td>−7.90 ± 6.93 (−30.55 to 3.38)</td>
</tr>
<tr>
<td>AGIS score</td>
<td>6.9 ± 5.6 (0 to 20)</td>
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<tr>
<td>Follow-up periods, y</td>
<td>13.3 ± 5.4 (5.0 to 29.1)</td>
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Values are mean ± standard deviation (range). HM, hand movement.
* Data from both eyes.

received no medical treatment or surgical intervention throughout their follow-up periods.

At the time of diagnosis, 18 patients (4.7%) already had unilateral blindness attributed to glaucoma. The blindness determination was based on the BCVA in 6 eyes in 6 patients and on visual field constriction in 16 eyes in 16 patients. On their final visits, 52 patients (13.6%) were blind in only one eye and 12 patients (3.1%) were blind in both eyes. The blindness determination was based on the BCVA in 25 eyes in 25 patients and on visual field constriction in 57 eyes in 46 patients. Of the 18 patients who had unilateral blindness at diagnosis, 9 (50%) had progressed to bilateral blindness at their final visit. Of the 364 patients who were not blind in either eye at the time of diagnosis, 29 (8.0%) became blind in one eye, and 5 (1.4%) had developed bilateral blindness at the final visit.

Comparison of the demographics of nonblind patients to those designated as blind in at least one eye during the follow-up periods (based on the eyes with the worse mean deviation at the time of diagnosis) showed that the blind patients had significantly worse BCVAs at diagnosis (P < 0.001) and had higher maximum diurnal IOPs without medications (P = 0.054), worse mean deviations (P < 0.001), and worse AGIS scores at diagnosis (P < 0.001). In addition, those blind in at least one eye had significantly worse BCVAs at the final visit (P < 0.001), greater IOP variations during the follow-up period (P < 0.001), higher frequency of changing glaucoma medications during the follow-up periods (P < 0.001), worse mean deviations (P < 0.001), and worse AGIS scores at the final visit (P < 0.001) and longer follow-up periods (P = 0.008). The Cox proportional hazard model analysis showed that a worse initial BCVA (P < 0.001), worse AGIS score at diagnosis (P < 0.001), and greater IOP variations during the follow-up periods (P < 0.001) were significantly associated with the development of blindness in one eye.

**DISCUSSION**

Our results showed that the probability of patients with NTG progressing to unilateral blindness was 9.9% at 20 years and to bilateral blindness was 1.4% at 20 years.

It is difficult to compare our findings on the probability of blindness to those of other studies due to variations in the types of glaucoma studied, definitions of blindness used, inclusion criteria, follow-up period, and research methodology. Hattenhauer and associates previously reviewed 270 patients diagnosed with POAG and estimated that blindness developed in at least one eye in 26% of patients, and in both eyes in 9% of patients at 20 years. They also concluded that the prognosis of exfoliative glaucoma and pigmentary glaucoma tended to be worse than that of POAG. Chen investigated the prevalence of blindness in 186 patients with OAG including POAG, exfoliative glaucoma, pigmentary glaucoma, and NTG. The author estimated the probability of blindness to be 14.6% in

<table>
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<th>Table 2. Demographic Data for Better and Worse Eyes</th>
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<tr>
<td><strong>Better Eyes</strong></td>
</tr>
<tr>
<td>BCVA, logMAR</td>
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<td>Spherical equivalent refraction, diopters</td>
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<td>Diurnal IOP without medications, mm Hg</td>
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Better and worse eyes were determined based on mean deviation at diagnosis. Values are mean ± standard deviation (range).
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one eye and 6.4% in both eyes at 15 years. Chang et al. reported a 28.6% probability of unilateral blindness at 16 years in eyes with POAG and chronic angle closure glaucoma. Kwon and colleagues evaluated 40 eyes in 40 patients with POAG with a minimum follow-up of 8 years, and reported that legal blindness was present in 21% of patients at 15 years in eyes with POAG. Peters et al. investigated the lifetime risk for OAG, including POAG and exfoliation glaucoma, and ocular hypertension, and reported that legal blindness was present in 19% of the eyes at 22 years. Forsman and colleagues examined 106 consecutive patients with POAG, and reported a 28.6% probability of unilateral blindness at 16 years. Chang et al. examined 106 consecutive patients with POAG, exfoliation glaucoma, and ocular hypertension, and reported that legal blindness was present in 21% of patients at 15 years in eyes with POAG. Peters et al. investigated the lifetime risk for OAG, including POAG and exfoliation glaucoma, and reported that the percentage of blindness was 75.2% in at least one eye and 42.7% in both eyes at 20 years using Kaplan-Meier life table analysis. In addition, Sauders et al. retrospectively examined the visual disabilities occurring within the expected life span of 3790 patients with glaucoma or suspected glaucoma in patients over 35 years of age. They estimated that only 5.2% of these patients progressed to blindness based on a mean deviation worse than −22 dB. Most previous studies examined types of glaucoma and ethnic populations different from those in the present study, which was confined to Japanese patients with NTG. Importantly, within the population of the present study, the probability of unilateral and bilateral blindness from glaucoma was much lower in eyes with NTG than has been previously reported.

A great deal of research has sought to identify the risk factors that affect the progression of glaucoma. The results of earlier studies suggest that higher IOP at diagnosis, more advanced visual field defects at the time of diagnosis, older age at diagnosis, and at death, female sex, and low compliance to medications are the major risk factors for progression to blindness, according to multivariable regression analysis. By contrast, univariate analysis has shown that the development of blindness is significantly associated with ethnicity, male sex, older age at diagnosis, and at death, female sex, and low compliance to medications. Additionally, the Collaborative Normal-Tension Glaucoma Study Group’s large-scale...
multicenter prospective trial reported that even in NTG, a reduction of the IOP had a favorable effect on glaucomatous visual field defect progression. This is consistent with our previous findings. However, greater IOP variation under therapy has failed to qualify as a prognostic factor of legal blindness in many other reports. In a clinical setting, more intense therapies, including surgical intervention, are usually required for more advanced stages of glaucomatous optic neuropathy. This comprises an inevitable bias due to the retrospective nature of such studies, and may account for the tendency to identify such risk factors for blindness as a history of surgical interventions and lower IOP at the final visit. In the present study, the IOP variation during the follow-up periods was identified as a significant risk factor for blindness by univariate analysis, but not by multivariate analysis. However, when the frequency of changing between ocular hypotensive agents was excluded from the explanatory variables, the IOP variation during the follow-up periods was significantly related to progression to blindness (odds ratio, 1.43; confidence interval 1.00–2.04; P = 0.048). The frequency of changing glaucoma medications may indicate either the need for more intense therapy or the presence of more side effects. Thus, greater IOP fluctuations could be the result of medical and surgical treatment, especially in eyes with rapidly progressing glaucoma, as Bengtsson and colleagues pointed out.

An older age at initial diagnosis is highly correlated with the development of blindness in glaucoma. In the present study, patients blind at the initial diagnosis were significantly older than nonblind patients, and this may reflect the fact that diagnosis was made at an older age.

Previous studies have reported an association between the presence of disc hemorrhages and the progression of NTG, but the present study did not find disc hemorrhages to be a risk factor for blindness. One possible explanation for this discrepancy might be that a considerable proportion of eyes that had filtering surgery had already progressed to unilateral blindness. This is because trabeculectomy signifi-
cantly reduces the incidence of disc hemorrhages in glaucomatous eyes.30

It is a strength of the present study that all subjects had a 24-hour diurnal IOP assessment before the initiation of ocular hypotensive therapy. In addition, all subjects had undergone computed tomography or magnetic resonance imaging that ruled out any pathological disease in the brain. However, the retrospective nature of the present study gave rise to at least four limitations. First, our patients did not receive a rigid therapeutic protocol with set and targeted IOP, which may have affected the identification of prognostic factors of future blindness. Second, there was a selection bias in the population since, during the 5-year follow-up periods, a considerable proportion of initially diagnosed NTG cases may have been lost. Third, we analyzed perimetric data derived from results combining the SITA standard and the full-threshold program. The threshold values obtained with SITA are reported to be slightly higher than those using the full-threshold strategy, which has been attributed to the presence of less fatigue in patients undergoing the relatively brief SITA.31 Although the American Academy of Ophthalmology recommends the SITA over the full-threshold strategy in most patients, they and others recommend establishing new baseline fields when changing strategies.31,32 Fourth, the length of the follow-up periods was set at minimum of 5 years, and only approximately 50 patients had follow-up periods over 20 years. Anderson et al.12 reported that, even in untreated NTG patients, only approximately half of cases demonstrate a confirmed localized visual field defect aggravation by 7 years. They concluded that the glaucoma progression is often insufficient to measurably affect the mean deviation index.

In summary, the present findings suggest that the number of patients under standard ophthalmic care who went blind from NTG, either unilaterally or bilaterally, was much lower in eyes with NTG than that reported for other types of glaucoma. In general, the rates of blindness are low, but if a patient presented without blindness in either eye, the probability that he or she would progress to bilateral blindness during the study was extremely low. The number of blind patients identified here was defined by the WHO criteria for blindness. Future prospective studies will be needed to determine the validity of the present findings as well as to more accurately define the limits and potential for preventing blindness going forward.

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