Introduction

Normal-tension glaucoma (NTG) is defined as “glaucomatous optic neuropathy in which the intraocular pressure (IOP) remains always in the statistically determined normal range during the course of onset and progression,” and it is regarded as a subtype of primary open-angle glaucoma (POAG) in the broad sense of the term. In addition to IOP, multiple factors such as papillary/peripapillary circulatory disorders and autoimmune abnormalities are thought to be involved in the onset of optic nerve disorders in NTG. It is widely accepted that IOP reduction is the only clinically reliable means of suppressing the progression of visual field loss.²⁻⁵

Since Maslenikow⁶ first reported in 1904 that “IOP shows diurnal variations,” based on tonometer results, numerous subsequent studies have documented this phenomenon. IOP is reported to be generally higher in the morning and lower in the evening, and this variation has been classified into several types. On the basis of past reports, Katavisto⁷ divided diurnal variation patterns into a regular type, which resembled a biorhythm, and an irregular type, with no such resemblance, and further subdivided the regular type into three subtypes: morning, day, and night types.

According to an epidemiological study carried out by the Japan Glaucoma Society in Tajimi in 2000–2001 (the Tajimi Study),³ the prevalence of POAG (in the narrow sense of the term) in Japanese people aged ≥40 years was reported as 0.3%, and the prevalence of NTG was 3.6%, indicating an extremely high ratio of NTG to POAG. It is thus helpful

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CLINICAL INVESTIGATION

Diurnal Variation of Intraocular Pressure in Suspected Normal-Tension Glaucoma

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Abstract

Purpose: To assess diurnal variations of intraocular pressure (IOP) in suspected normal-tension glaucoma (NTG) patients with subsequent long-term observation to detect changes that may lead to a new diagnosis.

Methods: Diurnal variation of IOP was measured in a sitting position at 2-h intervals for 24 h in a total of 569 subjects with suspected NTG.

Results: Thirty of the 569 subjects (5.3%) showed IOP values exceeding 20 mmHg during the 24-h monitoring and were diagnosed as having primary open-angle glaucoma (POAG). In subjects in whom NTG was definitely diagnosed based on the results of the 24-h monitoring, the average maximum, minimum, and mean IOP was 16.1, 11.7, and 13.9 mmHg, respectively, and the mean diurnal variation in IOP was 4.4 mmHg. The peak time was observed outside clinic hours (1800–0800) in 41.4% of patients, and the trough time was observed during clinic hours (1000–1600) in 15.9%. In 2.9% of NTG subjects, the diagnosis was eventually changed to POAG during follow-up.

Conclusion: Assessment of diurnal variations of IOP in suspected NTG patients is useful for the differential diagnosis of POAG from NTG and for establishment of a baseline, which may affect the management plan.

Key Words: diurnal variations, intraocular pressure, normal-tension glaucoma
to assess IOP in Japanese NTG patients, because diurnal variations of IOP are extremely useful for assessing disease status and for designing treatment plans. In this retrospective study, we determined the diurnal variations of IOP at a single medical institution in over 500 nonmedicated subjects with suspected NTG. We report the features of the diurnal variations of IOP in subjects diagnosed as having NTG and in those in which the diagnosis was changed to POAG during long-term follow-up.

**Subjects and Methods**

The subjects were 569 Japanese patients (1138 eyes) who attended the glaucoma clinic of the Gifu University Hospital, Gifu, Japan, between January 1989 and December 2003 and who had completed the following diurnal IOP measurement series because of suspected NTG. The diurnal variation of IOP was measured before the start of treatment with antiglaucoma medication, or at least 4 weeks after the antiglaucoma medication was washed out. The study group comprised 237 men and 332 women, aged 57.8 ± 12.9 years (mean ± standard deviation; range, 15–86 years). The criteria for suspected NTG were (1) an IOP chronically ≤20mmHg in both eyes, irrespective of the presence or absence of treatment; (2) a normal open angle (grade 3 or 4 according to Shaffer’s classification); (3) the presence of a glaucomatous optic nerve change (a cup/disc ratio of ≥0.7, thinning of the disc rim, retinal nerve fiber layer defect, or a difference of ≥0.2 in the cup/disc ratio between the left and right eyes); (4) the presence of a corresponding glaucomatous visual field change in the full-threshold central 30–2 program using a Humphrey Field Analyzer (HFA, model 740; Carl Zeiss Meditec, Dublin, CA, USA); and (5) the absence of an intraocular or intracranial lesion affecting the optic nerve or visual field, which were examined with computed tomography and magnetic resonance imaging. All subjects had fulfilled the NTG criteria shown above. Subjects with a history of surgery (including laser surgery) such as for cataract or glaucoma were excluded from this study. The IOP was determined at 2-h intervals from 1000 to 0800 the next morning, for a total of 12 measurements taken by a Goldmann applanation tonometer. IOP was measured at each time point with the same tonometer, with the patient in a sitting position. When asleep at night, the subject was awakened by gently touching the shoulder, and the position change and assessment of IOP were completed within 5 min. Each subject was assessed with the same tonometer. The IOP measurement was taken three times at each time point by experienced physicians; however, the same subject might have been assessed, in a masked fashion, by different physicians depending upon the time of the assessment. The procedure for measuring diurnal variation of IOP was explained in advance to all subjects. In subjects with suspected NTG, we diagnosed primary open-angle glaucoma (POAG) if an IOP value exceeding 20mmHg in at least one eye was found during the 24-h assessment period. Subjects whose IOP values were chronically ≤20mmHg in both eyes throughout the 24-h assessment period were diagnosed as having NTG.

In subjects diagnosed as having NTG, the diurnal variation pattern of IOP was analyzed. Subjects with NTG and with pseudoxfoliative materials (PE materials) were excluded from subsequent analysis. The time point of maximum IOP during the day was defined as the “peak time,” and the time point of minimum IOP was defined as the “trough time.” When a peak was observed at least twice, the sum of the values observed before and after the time point were compared and the time point at which the sum was highest was defined as the peak time. When a trough was observed at least twice, the sum of the values observed before and after the time point were compared and the time point at which the sum was lowest was defined as the trough time. Subjects in whom it was difficult to identify a peak time or trough time as a single time point were excluded from the analysis. In subjects for whom the peak time and trough time could be identified in both eyes, we determined whether the peak time or trough time was coincident in the two eyes.

When an IOP value of >20mmHg was noted twice during follow-up under no treatment, or during treatment with medication in subjects in whom NTG was diagnosed after completing the assessment of the diurnal variation of IOP, a change of diagnosis to POAG was made, and the period from completing the assessment of the diurnal variation of IOP to the change of diagnosis to POAG was determined. The follow-up period continued until the end of December 2004, and the subjects were then divided into three groups, depending on the time period from completing the assessment of the diurnal variation of IOP to the change of diagnosis to POAG, as follows: ≤1 year, from 1 to 5 years, and >5 years.

**Results**

Of the 569 subjects in whom the 24-h measurements were completed, 30 (5.3%) showed an IOP value exceeding 20 mmHg in at least one eye, and were thus diagnosed as having POAG. Thirteen of the 30 POAG subjects (43.3%) showed an IOP value that exceeded 20mmHg between 1800 and 0800, which was outside the clinic hours ( clinic hours, 1000 to 1600). The remaining 539 subjects were diagnosed as having NTG. Of the 539 subjects in whom NTG was diagnosed, PE materials were recognized in 15 subjects (2.6%), and these subjects were excluded from further evaluation in this study. The remaining 524 subjects (1048 eyes), who were definitely diagnosed as having NTG without PE material, comprised 218 men and 306 women aged 57.5 ± 12.8 years (mean ± SD, range 15–85 years), with 94.6% being ≥40 years old. The mean refraction value (equivalent spherical value) was −2.5 ± 4.0 D (−20.0 to +5.5 D); 317 eyes (30.2%) were emmetropic or hypermetropic with a refraction value of ≥0D; 521 eyes (49.8%) were mildly or moderately myopic with a refraction value of ≥6D and ≤0D; and 210 eyes...