CLINICAL INVESTIGATIONS

Spontaneous Intraocular Pressure Reduction in Normal-Tension Glaucoma and Associated Clinical Factors

Akihiro Oguri, Tetsuya Yamamoto and Yoshiaki Kitazawa

Department of Ophthalmology, Gifu University School of Medicine, Gifu-shi, Japan

Purpose: To investigate the intraocular pressure (IOP) reduction in certain normal-tension glaucoma (NTG) patients and clinical factors associated with this reduction.

Methods: Fifty-four NTG patients who met the following enrollment criteria were selected: IOP <21 mm Hg during a 24-hour pressure curve and throughout the subsequent 12 months; examined every 1 to 4 months for at least 3 years with no ocular hypotensive therapy. For each patient, the eye with the higher mean IOP during the 24-hour pressure curve was selected for this study.

Results: Six patients had an IOP reduction which was defined as a significant decrease ($P <$ .05) of IOP over time, determined by the Spearman rank correlation coefficient method. These 6 eyes were rated positive for subsequent IOP reduction. The IOP reduction was correlated to clinical factors by means of a logistic multiple regression analysis (LOGIST procedure using PC-SAS), which demonstrated that the larger difference between the maximum IOP and the minimum IOP during the initial 24-hour pressure curve and the absence of disc hemorrhage showed significant correlation with IOP reduction (P = .026 and P = .013, respectively). The odds ratios were 2.05 per 1 mm Hg increase of difference between the maximum IOP and the minimum IOP during the initial 24-hour pressure curve and 1.13 for the absence of disc hemorrhage.

Conclusions: The current study demonstrated that a significant reduction of IOP over time is not uncommon in NTG patients. One ninth of the NTG patients in this study showed a significant IOP reduction during a 3-year follow-up period. **Jpn J Ophthalmol 2000;44:263–267** © 2000 Japanese Ophthalmological Society

Key Words: Intraocular pressure, multiple regression analysis, normal-tension glaucoma.

Introduction

It is well-known that the intraocular pressure (IOP) in healthy individuals[1] fluctuates physiologically within a day, seasonally, and with aging. It is reported that IOP declines with age in the nonglaucomatous Japanese population.[2] Although little is known about IOP changes over time in patients with established normal-tension glaucoma (NTG), there is a report that IOP decreases to a normal level during follow-up in some untreated cases of primary open-angle glaucoma (POAG).[3] Some reports indicate that NTG and POAG belong to a spectrum of one disease because the cutoff level for IOP employed to differentiate the two categories is rather arbitrary and has no rationale.[4–6] Thus, it is highly probable that the IOP decreases during follow-up even in NTG patients, which makes the differentiation of the two categories difficult when a patient is examined for the first time after the IOP reduction occurs. This prompted us to conduct a study to determine whether IOP remains unchanged for a long period in NTG patients. We have already reported that the IOP of some NTG patients increases in the long run and that some clinical factors are associated with the IOP elevation.[4] We also found some cases

Received: September 9, 1998

Correspondence and reprint requests to: Akihiro OGURI, Department of Ophthalmology, Gifu University School of Medicine, 40 Tsukasa-machi, Gifu-shi, Gifu-ken, 500-8705, Japan

Published by Elsevier Science Inc.

0021-5155/00/$–see front matter
PII S0021-5155(99)00213-0

Jpn J Ophthalmol
Vol 44: 263–267, 2000

with spontaneous IOP reduction. In the current study, we investigated the rate of developing IOP reduction in NTG patients and the clinical factors associated with this reduction.

Materials and Methods

Fifty-four patients who met the following enrollment criteria were selected for retrospective studyfrom 327 consecutive NTG patients diagnosed at the Gifu University Hospital during the period from May 1985 to December 1994: IOP $\leq$ 21 mm Hg during the initial 24-hour pressure curve measurement and throughout the subsequent 12 months, excluding seasonal IOP change; normal open-angle; the presence of a typical glaucomatous visual field defect associated with glaucomatous disc changes and not attributable to other ocular or systemic pathology; no intracranial or otolaryngologic lesion; no history of massive hemorrhage or hemodynamic crisis; a follow-up examination every 1 to 4 months for at least 3 years; and no ocular hypotensive treatment. In some of the cases, ocular hypotensive treatment was started after the visual field deterioration was confirmed. Those patients who were followed with oral calcium-channel blockers were not excluded. For each patient, the eye with the higher mean IOP during the initial 24-hour pressure curve was selected for the study. Twenty-one patients were men and 33 were women. Their ages ranged from 34 to 73 years with a mean of 56.9 years.

Intraocular pressure was measured with a Goldmann applanation tonometer. During the initial 24-hour pressure curve measurement, IOP was monitored every 2 hours from 10 AM on the first day until 10 AM the next day. Perimetry was performed with a Humphrey Visual Field Analyzer (HFA; Model 630; Humphrey Instrument, San Leandro, CA, USA). The refractive error was determined using an autorefractometer (AR-3300; Nidek, Gamagori). We rated disc hemorrhage as positive when it was found in either eye of the patient during the follow-up period.

The first day of follow-up was defined as the day when the initial 24-hour pressure curve measurement was conducted. The follow-up period ranged from 3.0 to 7.8 years with a mean of 4.8 years. As for the IOP during the follow-up visits, IOP values measured between 9 AM and 12 AM were used in the study to exclude diurnal variation of IOP. It was measured every 1 to 4 months after the initial 24-hour pressure curve measurement. The number of IOP measurements ranged from 17 to 64 with a mean of 38.7. The Spearman rank correlation coefficient method was employed to evaluate the temporal course of the IOP change. We defined the eyes with significant IOP reduction as those with $P < .05$ by the same Spearman method.

To identify demographic and clinical factors for significant IOP reduction, we carried out a logistic multiple regression analysis by employing the following factors as possible explanatory variables for the IOP change: age, sex, IOP parameters during the initial 24-hour pressure curve (including maximum IOP, minimum IOP, average IOP, and the difference between the maximum IOP and the minimum IOP), visual acuity (logMAR), refractive error, development of disc hemorrhage during the follow-up period, presence of systemic hypertension, family history of glaucoma, and mean deviation (MD) of a reliable perimetric result (ie, < 20% fixation loss and < 33% false-positive or false-negative answers) examined with the Central 30-2 program of the HFA.

The LOGIST procedure of the PC-SAS[7] was used for the logistic multiple regression analysis and $P < .05$ was considered statistically significant. The values obtained on the day of the initial 24-hour pressure curve measurement were used for age, visual acuity, refractive error, presence of systemic hypertension, and MD. When the perimetric result on the day of the initial 24-hour pressure curve measurement was rated not reliable, a reliable result from one of the earlier follow-up visits within 4 months of the first day of follow-up was used. Each variable was compared between the two groups. A linear regression analysis was conducted for MD using the Statpac 2 program of the HFA, with $P < .05$ considered statistically significant for the progression of the visual field defects. An association of the subsequent IOP reduction with the progression of the visual field defects and development of disc hemorrhage was investigated. Fisher's exact probability test was used to compare nominal variables and the Mann–Whitney *U*-test was used for continuous variables. $P < .05$ was considered statistically significant.

Results

Six of the 54 eyes had a significant reduction in the IOP (Figure 1), 14 eyes had a significant IOP elevation and 34 eyes had no significant change.

Table 1 shows the demographic and clinical background of the IOP reduction group (6 cases) and the nonreduction group (48 cases). The difference be-

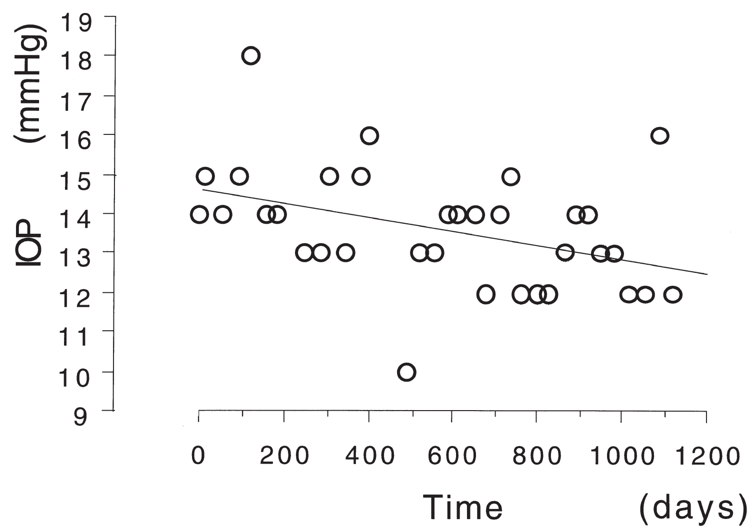

Figure 1. Time-dependent intraocular pressure (IOP) change of IOP reduction case is shown with linear regression slope drawn as a line (Y = −0.002X + 14.622, P = .013, R^2 = 0.158).

tween the maximum IOP and the minimum IOP during the initial 24-hour pressure curve in the IOP reduction group was significantly greater than in the nonreduction group (P = .003). Table 2 shows the maximum and minimum IOP during the initial 24-hour pressure curve in the IOP reduction group. Disc hemorrhage was observed in 25 patients during the follow-up period (Table 3). The absence of disc hemorrhage were significantly correlated with IOP reduction (P = .028). There was no significant difference in progression of the visual field defect between the two groups (Table 3).

The logistic multiple regression model demonstrated that the greater difference between the maximum IOP and the minimum IOP during the initial 24-hour pressure curve and the absence of disc hemorrhage was significantly correlated with the subsequent IOP reduction (P = .026 and P = .013, respectively). The odds ratios were calculated to be 2.05 per 1 mm Hg increase of difference between the maximum IOP and the minimum IOP during the initial 24-hour pressure curve and 1.13 for the absence of disc hemorrhage.

Table 1. Clinical Factors Obtained on Day of Initial 24-Hour Pressure Curve Measurement in Subsequent Intraocular Pressure (IOP) Reduction Group and Nonreduction Group*

	IOP Reduction Group (6)†	Nonreduction Group (48)†	P‡
Age	50.3 ± 11.9	57.9 ± 9.3	NS§
Male/Female‡	2/4	19/29	NS‖
Maximum IOP	16.5 ± 1.8	15.9 ± 2.3	NS§
Minimum IOP	10.3 ± 1.9	11.6 ± 2.1	NS§
Mean IOP	14.3 ± 1.6	13.7 ± 2.1	NS§
IOP range	6.2 ± 0.4	4.2 ± 1.4	0.003§
Visual acuity	1.0 ± 0.6	1.1 ± 0.3	NS§
Refraction	−2.9 ± 3.7	−1.8 ± 4.1	NS§
Hypertension‡	1	14	NS‖
Family history of glaucoma‡	0	4	NS‖
Mean deviation	−8.1 ± 9.0	−8.0 ± 6.4	NS§

*Values are mean ± SD unless otherwise indicated.
†No. of patients.
‡NS: not significant.
§Mann–Whitney U-test.
‖Fisher's exact probability test.

Discussion

Little has been published about IOP changes over time in patients with established NTG except our

Table 2. Maximum and Minimum Intraocular Pressure (IOP) During Initial 24-Hour Pressure Curve Measurement in IOP Reduction Group

Patient	Maxiumum IOP (mm Hg) During 24-Hour Curve	Minimum IOP (mm Hg) During 24-Hour Curve
1	19	13
2	16	9
3	18	12
4	16	10
5	16	10
6	14	8

Jpn J Ophthalmol
Vol 44: 263–267, 2000

Table 3. Clinical Factors Obtained at End of Follow-Up in Intraocular Pressure (IOP) Reduction Group and Nonreduction Group*

	IOP Reduction Group (6)†	Nonreduction Group (48)†	*P*
IOP	13.0 ± 2.5	15.3 ± 2.7	NS‡
Visual acuity	1.0 ± 0.5	1.0 ± 0.3	NS‡
Mean deviation	−10.5 ± 9.0	−9.0 ± 6.2	NS‡
Disc hemorrhage†	0	25	0.028§
MD slope reduction†	0	7	NS§

*Values are mean ± SD unless otherwise indicated. MD: mean deviation, NS: not significant.
†No. of patients.
‡Mann–Whitney *U*-test.
§Fisher's exact probability test.

previous study,[4] where we reported some cases with spontaneous IOP elevation or reduction. The current study clearly demonstrated that one ninth of NTG patients diagnosed after a thorough check-up showed a significant IOP reduction during the subsequent follow-up period of at least 3 years.

Shiose and Kawase[2] reported that IOP declines with age in the nonglaucomatous Japanese population and that aging is one of the prognostic factors for IOP reduction. They also reported that there is a tendency for IOP to decline with age in men more than in women among normal Japanese. However, significant correlation between IOP reduction and age or sex was not observed in the current study. The course of IOP changes with age may be different between the nonglaucomatous Japanese and NTG patients.

There was no MD slope reduction case in the present IOP reduction group. The reason may be that IOP reduction to the normal range would have caused no MD slope reduction if the group had included POAG or cases with higher IOP level before the IOP measurement of this study.

NTG and POAG are differentiated clinically based on an arbitrary cutoff level of the IOP which is usually set around 20 to 24 mm Hg. Several reports[4–6] indicate that the arbitrary cutoff level of IOP, which is only one of the clinical risk factors for developing glaucomatous optic neuropathy, is not rational for the differentiation between NTG and POAG. Our findings of the significant IOP reduction in NTG cases are consistent with and support this theory. It was reported that IOP decreases to a normal level during follow-up in some untreated cases of POAG.[3] If NTG and POAG belong to one disease with a broad spectrum, it is probable that some cases show IOP reduction over time at any IOP level.

Our previous report[4] shows that a higher average IOP during the initial 24-hour pressure curve was a significant prognostic factor for the subsequent IOP elevation rather than a difference between the maximum IOP and the minimum IOP. In the current study, only the greater difference between the maximum IOP and the minimum IOP during the initial 24-hour pressure curve among the several IOP parameters seems to be a significant clinical factor for the subsequent IOP reduction, which does not contradict our previous report.

Disc hemorrhage is reportedly more prevalent in NTG patients than in POAG patients.[8] We reported a significant relationship between the subsequent IOP elevation and the development of disc hemorrhage.[4] This is compatible with our present result, which showed that the absence of disc hemorrhage was significantly correlated with the subsequent IOP reduction, although there seems to be no plausible explanation for the higher frequency of IOP reduction in eyes without disc hemorrhage than in eyes with disc hemorrhage. This suggests that patients with a larger diurnal variation of the initial 24-hour pressure curve at least had a compromised aqueous outflow pathway. This also makes us suspect that the IOP reduction cases could have been diagnosed as POAG if examined earlier, which supports the theory that an arbitrary cutoff level of IOP is not rational for the differentiation between NTG and POAG.

The current study demonstrates that significant reduction of IOP over time is not uncommon in NTG patients, and both the greater difference between the maximum IOP and the minimum IOP during the initial 24-hour pressure curve and the absence of disc hemorrhage are identified as significant factors for subsequent IOP reduction. These findings might help in the management of NTG patients because IOP reduction, which is the main target of present glaucoma therapy, spontaneously occurs in some untreated cases in the long run.

References

1. Shields MB. Textbook of glaucoma. 3rd ed. Baltimore: Williams & Wilkins, 1992:53–9.
2. Shiose Y, Kawase Y. A new approach to stratified normal intraocular pressure in a general population. Am J Ophthalmol 1986;101:714–21.
3. Levene RZ. Low tension glaucoma. A critical review and new materials. Surv Ophthalmol 1991;98:296–300.
4. Oguri A, Sogano S, Yamamoto T, Kitazawa Y. Incidence of el-

evation of intraocular pressure over time and associated factors in normal-tension glaucoma. J Glaucoma 1998;7:117–20.

5. Ido T, Tomita G, Kitazawa Y. Diurnal variation of intraocular pressure of normal-tension glaucoma. Ophthalmology 1991;98: 296–300.
6. Sogano S, Yamamoto T, Kitazawa Y. IOP change over time in normal-tension glaucoma. Nippon Ganka Gakkai Zasshi (Acta Soc Ophthalmol Jpn) 1993;97:65–70.
7. SAS/STAT User's Guide, Release 6.03 ed. Cary, NC: SAS Institute Inc, 1988.
8. Kitazawa Y, Shirato S, Yamamoto T. Optic disc hemorrhage in low-tension glaucoma. Ophthalmology 1986;93:853–7.