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ORIGINAL PAPER

A nationwide survey of factors influencing adherence to ocular hypotensive eyedrops in Japan

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Abstract

Introduction Few reports have investigated the status of adherence in Japan on a large scale. We aimed to investigate the status of adherence to topical glaucoma treatment and its associated factors.

Methods A nationwide survey was conducted as a prospective fashion. Participants in this survey were subjects with primary open-angle glaucoma, normal-tension glaucoma, or ocular hypertension or pseudoexfoliation glaucoma who had been prescribed anti-glaucoma ophthalmic eyedrops and whose ophthalmologist considered prescribing any fixed combination of ocular hypotensive eyedrops for the first time between 2011 and 2012. Subjects and their attending ophthalmologists independently completed a questionnaire by utilizing a fixed combination of ocular hypotensive eyedrops.

Results A total of 1358 ophthalmologists from 1071 medical institutions participated in this survey. We registered 4430 subjects (2049 males and 2381 females). In total, data from 3853 subjects (87.6%) were analyzed after inclusion of subjects based on inclusion and exclusion criteria. Good adherence was defined as not forgetting instillation during the past

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week. Rates of good adherence reported by subjects and ophthalmologists were 72.4 and 78.5%, respectively ($P < 0.0001$). The consistency of adherence evaluation between subjects and ophthalmologists was moderate [kappa score 0.5025 (95% confidence interval 0.4740–0.5309)]. Significant factors associated with adherence were size of clinic, age, gender, number of types of ocular hypotensive eyedrops, ease of instillation, preferred number of eyedrops, preferred frequency of instillation of eyedrops, and knowledge of glaucoma.

Conclusion Adherence to ocular hypotensive eyedrops among Japanese subjects was relatively good. Concordance of adherence between subjects' reports and ophthalmologists' responses was moderate. Size of clinic, number of types of ocular hypotensive eyedrops, ease of instillation, preferred number of eyedrops, preferred frequency of instillation of eyedrops, and knowledge of glaucoma were associated with adherence among Japanese glaucoma subjects.

Keywords Adherence · Eyedrops · Fixed combination · Glaucoma · Intraocular pressure · Japan

Introduction

Reduction in intraocular pressure (IOP) is the only treatment proven to retard progression of glaucoma [1]. IOP reduction may be achieved by medical treatment, laser treatment, and ophthalmic surgery. Currently, medical treatment is the first choice for glaucoma, especially among subjects whose eyes are diagnosed with open-angle glaucoma.

Prostaglandin-related ophthalmic solutions (PGs) are the first choice in many countries, including Japan [2]. Glaucoma is a lifelong disease, but a lack of glaucoma-related symptoms sometimes obstructs its proper care. Poor adherence to glaucoma treatment regimens negatively influences the progression of glaucomatous visual function loss [3–8].

Several factors affect adherence [9–11]. In Japan, glaucoma treatment dropout rates have been reported [7], but a large survey regarding the actual circumstances of adherence has not been performed. Many glaucoma subjects, especially those with advanced optic neuropathy, require further IOP reduction via multiple types of glaucoma eyedrops. Administration of many different types of ocular hypotensive eyedrops may help to enhance the magnitude of IOP reduction if adherence is good. However, adherence deteriorates when the number of required ocular hypotensive eyedrops increases [12–15]. The introduction of fixed combination eyedrops may help to enhance the efficacy of and adherence to glaucoma drugs by reducing the number of ocular hypotensive eyedrops [14–18]. A study group named the Glaucoma Research on Adherence to fixed Combination Eyedrops (GRACE) was established to investigate the effect of fixed combination glaucoma eyedrop use on adherence with a nationwide questionnaire survey across Japan, and all authors belonged to this study group. In the present report, we present this study and report the status of adherence and its associated factors based on the baseline data obtained.

Subjects and methods

The main aim of this study was to investigate adherence and its associated factors. As objectives, we investigated concordance in evaluations of adherence between the subjects' reports and ophthalmologists' assumptions. This study was performed according to the tenets of the Declaration of Helsinki. We invited 1719 hospitals and 6735 eye clinics that were members of the Japan Ophthalmologists Association to participate in this study because almost all trained ophthalmologists in Japan belong to this association. Approval for this study was obtained from the institutional review board (IRB) at each participating institute. Where the institute had no IRB, the IRB of Ishikawa Medical Association (Kanazawa, Japan) approved the study. Participating ophthalmologists and subjects submitted written informed consent to the council of the GRACE study group.

Subject inclusion and exclusion criteria

Subjects were enrolled in this study from June 2011 to July 2012. Inclusion criteria were as follows: subjects with primary open-angle glaucoma (POAG), normal-tension glaucoma (NTG), exfoliation glaucoma (XFG), or ocular hypertension (OH); subjects aged 20 years or older who had been treated with ocular hypotensive eyedrops who had no history of prescription of any type of fixed combination of ocular

hypotensive eyedrops; and subjects whose attending ophthalmologist planned to prescribe fixed combination eyedrops due to clinical requirements. Subjects unable to answer the questionnaire, subjects with critical errors in their questionnaire, subjects whose IOP was difficult to measure using the Goldmann applanation tonometer, and subjects judged unsuitable for participation by their attending ophthalmologists were excluded from the study. The attending ophthalmologists explained the protocol and the aim of the study to their subjects and obtained written informed consent.

Study design and protocol

A council of the GRACE study group designed this study and prepared questionnaires for both subjects and ophthalmologists. The subjects and the attending ophthalmologists were required to complete the questionnaire prior to the prescription of fixed combination eyedrops. The questionnaires for both subjects and ophthalmologists are shown in Supplemental Fig. 1. In brief, questionnaires for participating subjects included their situation of glaucoma care, glaucoma-related visual function disability and symptoms, awareness of instillation-related difficulty, instillation interval between different kinds of eyedrops, frequency of forgetting instillations in a recent week, and the time most likely to forget instillations. We also gathered information regarding whether the subject had any assistance with instillation, use of instillation aid, preferred number of eyedrops, preferred frequency of instillation of eyedrops, and questions confirming knowledge of glaucoma, both in general and specifically (Supplemental Fig. 1a). Questions for ophthalmologists included the type of glaucoma, prescriptions of ocular hypotensive eyedrops before and after induction of fixed combination eyedrops, reasons for fixed combination eyedrops introduction, corrected visual acuity, recent IOP, mean deviation (MD) of Humphrey visual field analyzer program central 30-2 or 24-2, and presumed frequency of forgetting eyedrop instillation during the last week (Supplemental Fig. 1b). The participating subjects placed their questionnaire into the envelope so that the ophthalmologists would not see their answers. Questionnaires were sealed and mailed to the GRACE committee office. After council members of the GRACE study (RT, YS, TT, and KK) verified that the enrolled subjects satisfied the inclusion and exclusion criteria, only accepted data were subjected to the analysis.

Statistical analysis

The results of parameters were adjusted for logistic regression analysis. More than half of the subjects never missed an eyedrop instillation; therefore, we classified subjects into two groups: those who reported never forgetting an instillation (good adherence group) and those who missed eyedrop instillations one or more times (nonadherent group). The instillation interval between different types of eyedrops was compared between subjects who used an interval of five or more minutes between drops and those who used less than 4 min between drops because using a proper interval may improve the efficacy of eyedrops. Subjects who reported no difficulty of instillation were categorized as the "easy" group. Out of six questions regarding knowledge of glaucoma, one question regarding whether treatment induced visual function improvement showed a much lower rate of positive answers compared to the other questions (Supplemental Fig. 2). We eliminated this question from the analysis because employment of an extreme outlier may negatively influence statistical analysis, and subjects who correctly answered all questions were defined as having a good understanding. Visual acuity was converted into log MAR format for the analysis. The data were analyzed with JMP 11.0 software (SAS Institute Inc., Cary, NC, USA), and values are presented as the means ± standard deviations. Student's *t* test, the Wilcoxon signed rank test, the Mann–Whitney *U* test, the Chi-square test, a contingency table analysis, and multivariate logistic regression analysis were conducted. *P* values less than 0.05 were considered significant.

Results

Participating facilities and ophthalmologists

A total of 1071 facilities (12.7%) and 1358 ophthalmologists participated in this study. Participating facilities were evenly distributed throughout Japan (Supplemental Fig. 3).

Enrolled subjects

A total of 4430 subjects were enrolled. Among these subjects, 577 were excluded for the following reasons: 200 had a history of previously prescribed fixed combination eyedrops, six subjects were under 20 years of age, and 371 subjects had critical errors in their questionnaires. In total, 3853 subjects (87.6%) were evaluated. Demographics of the enrolled subjects are depicted in Table 1. The mean subject age was 68.5 ± 12.2 years. Women occupied 53.4% of all, and there were more patients with POAG. Their visual function was relatively good. The mean IOP was 16.1 ± 3.8 mmHg. The many subjects had been treated over a 5-year period upon study entry, and the mean number of ocular hypotensive eyedrops used per subject was 1.93 ± 0.78.

Frequency of forgetting instillations

Figure 1 shows the distribution of the number of subjects who forgot an instillation during the past week according to the subjects' reports and ophthalmologists' assumptions. Although about three-quarters of respondents reported never forgetting to instill eyedrops in both questionnaires, the prevalence reported by ophthalmologists was higher than that reported by subjects. Rates of good adherence reported by subjects and ophthalmologists were 72.4 and 78.5%, respectively ($P < 0.0001$, contingency table analysis). Both subject and ophthalmologist questionnaires showed that adherence was significantly better among female subjects than males ($P < 0.0001$, a contingency table analysis).

Instillation of eyedrops was most commonly missed at noon (48.2%), before sleeping (20.5%), in the evening (15.8%), and in the morning (14.0%). The forgetting rate at noon was significantly higher than at other times ($P < 0.0001$, a contingency table analysis).

Table 1 Demographics of enrolled patients at the entry

	Mean ± SD
Age (years)	68.5 ± 12.2
Gender (male/female)	1794/2059
Glaucoma type	
POAG	89.70%
XFG	4.10%
OH	6.20%
MD value (dB)	− 4.1 ± 5.7
Visual acuity	0.008 ± 0.31
Intraocular pressure (mmHg)	16.1 ± 3.8
Period of past treatment	
Within a year	10.60%
1–3 years	21.70%
4–5 years	13.70%
More than 5 years	54.00%
Numbers of eyedrops use	1.93 ± 0.78
One type	17.80%
Three types	40.30%
Three types	28.40%
Four or more types	13.50%

Concordance between ophthalmologists and subjects

The correlation between the subjects' reported and ophthalmologists' reported adherence regarding forgetting eyedrop instillations was significant. Kappa coefficient values were 0.5025 (95% confidential interval (CI) 0.4740–0.5309) among all subjects, and those among males and females were 0.4606 (95% CI 0.4196–5016) and 0.5423 (95% CI 0.5030–0.5816), respectively.

Adherence-associated factors

Age and the number of eyedrops used at each instillation significantly and negatively affected adherence according to both the subjects' reports and the ophthalmologists' assumptions (Figs. 2 and 3). The effect of age was linear (Fig. 2a, b), while subjects using three kinds of eyedrops had the worst adherence (Fig. 3a, b). In contrast, effect of the treatment duration on adherence was different between ophthalmologists and subjects (Fig. 3c, d). Both questionnaires showed that an increase in the duration of treatment tended to decrease adherence, and subject questionnaires showed that a treatment duration of 4–5 years significantly deteriorated adherence compared to other treatment durations.

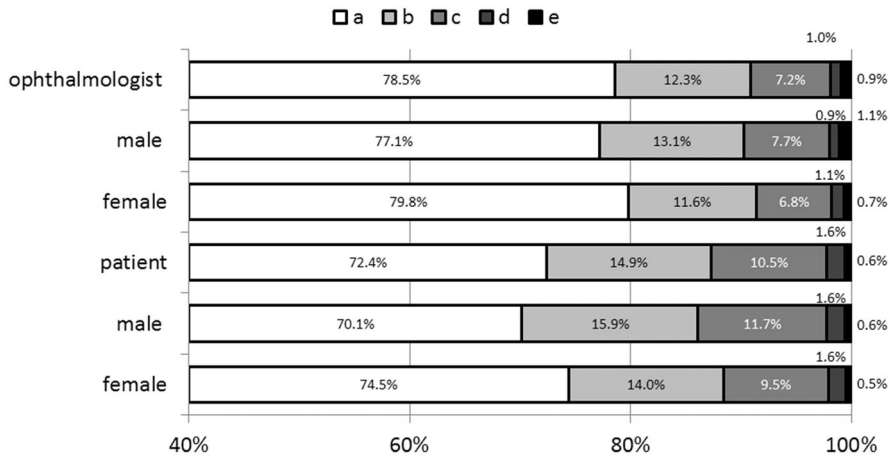

Fig. 1 Frequency of forgetting instillation. *a*: Never. *b*: One a week. *c*: Two–three times a week. *d*: Four or more times a week. *e*: At least half the time

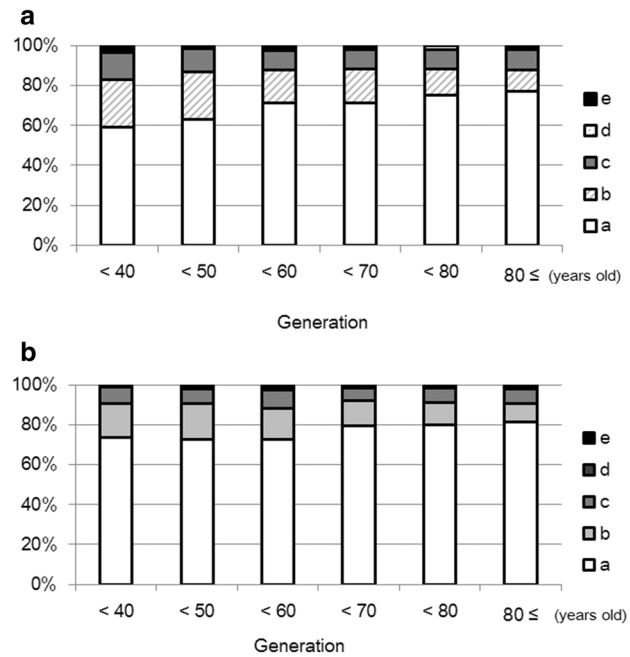

Fig. 2 Age and forgetting instillation. **a** Subjects' report, $P < 0.0001$, **b** ophthalmologists' assumption, $P = 0.03$ (a contingency table analysis). *a*: Never. *b*: One a week. *c*: Two–three times a week. *d*: Four or more times a week. *e*: At least half the time (a contingency table analysis)

Multivariate logistic regression analysis

Table 2 summarizes the results from a multivariate logistic regression analysis of the questionnaire parameters. Significant factors for adherence from the subject questionnaire were gender, size of institution, number of eyedrops, MD value in the better eye, treatment duration, difficulty of eyedrop use, knowledge of glaucoma, number of acceptable kinds of eyedrops, and acceptable frequency of instillation. In contrast, significant factors affecting adherence according to the ophthalmologists were limited to the number of eyedrops used each time, the kinds of acceptable eyedrops, and the acceptable frequency of instillation. Other factors, including type of glaucoma, did not affect adherence.

Discussion

The present study conducted a nationwide questionnaire survey for Japanese glaucoma subjects regarding adherence to ocular hypotensive eyedrops and associated factors. More than 3800 subjects and 1300

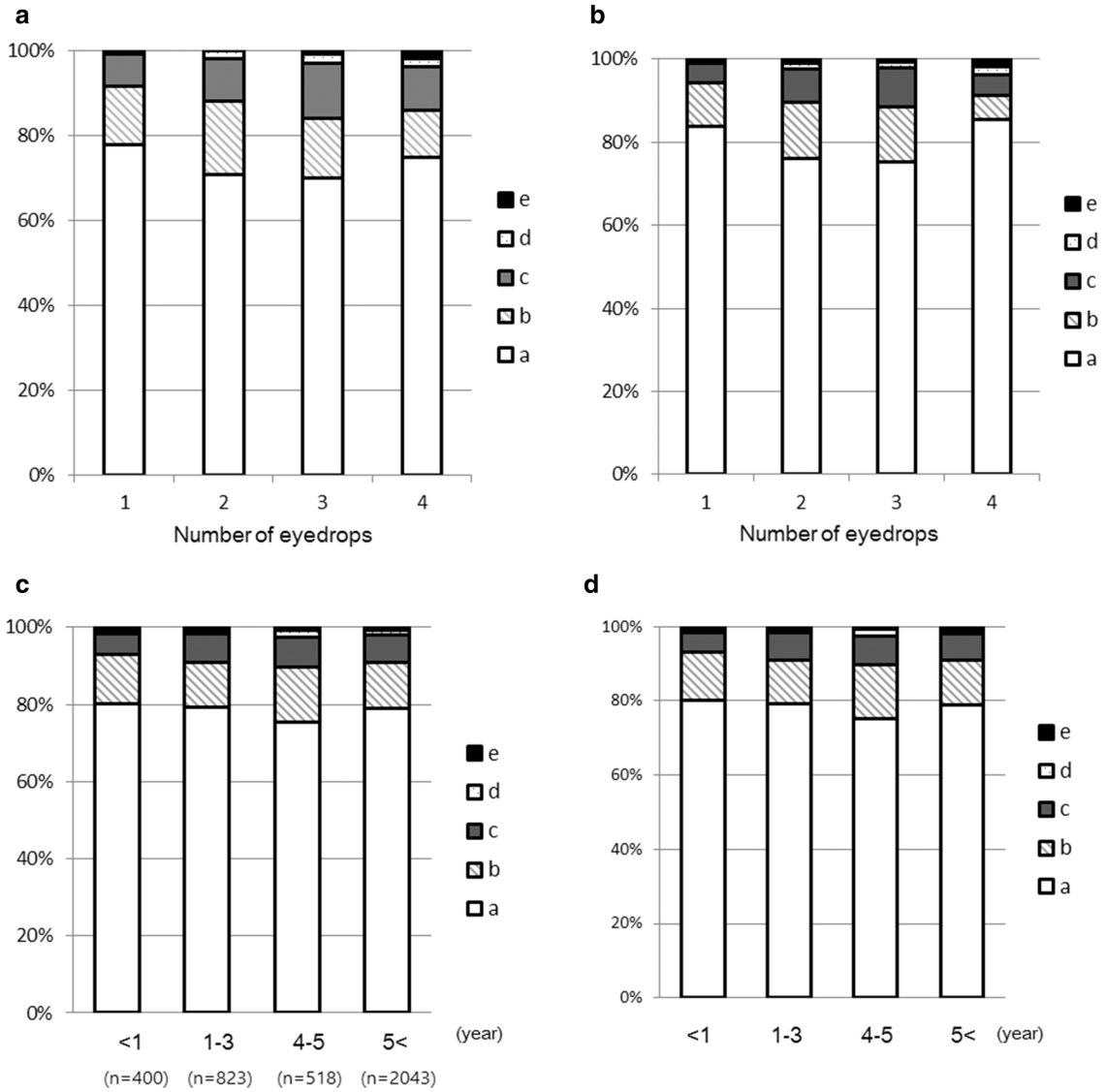

Fig. 3 Other factors associated with forgetting instillations. **a** Subjects' report regarding forgetting instillations and number of eyedrops used, $P < 0.0001$ (a contingency table analysis). **b** Ophthalmologists' assumptions regarding forgetting instillations and number of eyedrops used, $P < 0.0001$ (a contingency table analysis). **c** Subjects' report regarding forgetting instillations and treatment duration, $P = 0.4741$ (a contingency table analysis). **d** Ophthalmologists' assumptions regarding forgetting instillations and treatment duration, $P = 0.022$ (a contingency table analysis). *a*: Never. *b*: One a week. *c*: Two–three times a week. *d*: Four or more times a week. *e*: At least half the time (a contingency table analysis)

ophthalmologists participated in this study across Japan, which may contribute low bias and high reliability of our results. Concordance of adherence between subject reports and ophthalmologist assumptions matched moderately, and we identified several factors affecting adherence that had never been reported before.

Adherence is important for all medical treatments, especially among subjects with chronic diseases, such as glaucoma. A 2003 WHO report listed glaucoma as one disease in which adherence is very important to treatment [19]. Adherence directly results in a therapeutic effect [13]. Some previous studies reported that poor adherence destabilized IOP control in glaucoma

Table 2 Multivariate logistic regression analysis

	P value	Odd ratio	Lower 95%	Upper 95%
Patient report				
Clinic versus hospital	0.0132	0.71	0.54	0.93
Number of eyedrops	< 0.0001	1.31 (bottle)	1.16	1.49
MD in better eye (− dB)	0.0045	1.02 (unit)	1.01	1.04
Gender (M/F)	0.02	1.25	1.04	1.5
Period of treatment(long/short)	0.0345	1.31 (range)	1.02	1.68
Burden of eyedrops	< 0.0001	1.51	1.25	1.83
Acceptable kinds of eyedrops	< 0.0001	1.67 (bottle)	1.44	1.93
Acceptable frequency of instillation	< 0.0001	1.43	1.24	1.64
Number of correct answers	0.0079	0.41 (range)	0.22	0.76
IOP (higher eye)	0.1058	0.98 (mmHg)	0.95	1.02
Assumption of ophthalmologist				
Number of eyedrops	< 0.0001	1.38 (bottle)	1.24	1.54
Acceptable kinds of eyedrops	< 0.0001	1.51 (bottle)	1.33	1.72
Acceptable frequency of instillation	0.0005	1.24	1.1	1.4

treatment [9, 20], and adherence improvement is essential for better glaucoma treatment [12, 21].

Few reports have investigated the status of adherence in Japan on a large scale. Kashiwagi et al. reported the persistence to glaucoma medication regimens among newly prescribed subjects in Japan. In their study, approximately 40% of subjects stopped using ocular hypotensive eyedrops within 1 year, which is better than other reports from outside of Japan [3, 5, 7]. Recently, poor adherence and dropout from glaucoma medication have received much attention in glaucoma care. We cannot directly compare adherence with previous studies, but the condition of glaucoma care may be better in Japan than other countries. We hypothesize reasons for this observation as follows. All Japanese are covered by public medical insurance, and private expenses for medical care are relatively low in Japan. Education levels are high, and knowledge of medicine also presumably high, including knowledge of glaucoma. The relatively older cohort in this study may have affected the result.

According to the current study, better knowledge of glaucoma, being female, being elderly, and having fewer eyedrops to administer were significantly associated with adherence, which is consistent with previous reports [22, 23]. The current study revealed a negative association between the treatment duration and adherence. It is not clear why longer treatment period deteriorated adherence, but some possible explanations are available. Patient could get no positive effects such as comfortableness and recovery of their symptom by instilling ocular hypotensive eyedrops. Longer treatment period will lose patient's motivation keeping their medication.

Treatment persistence is another important factor for glaucoma treatment, and some previous reports, including those by Kashiwagi et al. [5, 7], indicate that the prevalence of dropout from glaucoma treatment was greater during the early period of glaucoma medication, which indicates that factors affecting adherence and persistence are not the same. Knowledge of glaucoma may contribute to adherence. We previously reported that providing subjects with glaucoma care information reduced the number of eyedrops prescribed and reduced IOP with the same regimen [24]. Thus, discussion between subjects and ophthalmologists regarding glaucoma care and deepening subject understanding may contribute to adherence. As a new finding in the current study, a prescription considering the acceptable kinds of eyedrops and frequency of instillation also contributed to adherence. Ophthalmologists need to pay attention to these findings when considering glaucoma care.

It is not easy to evaluate adherence correctly. Okeke et al. [3] reported very low agreement between adherence evaluations among subjects and ophthalmologists. Agreement of adherence evaluations

between subjects and ophthalmologists was moderate in this study. Difference in subjects, race, study design, and methods may have affected the results.

This study had some limitations. It enrolled subjects who planned to be prescribed fixed combination eyedrops, which may have resulted in selection bias. We previously reported that the average number of ocular hypotensive eyedrops among Japanese subjects was approximately two and that this number has continuously increased in Japan [2]. Taken together, the present results could be representative of the status of adherence among Japanese glaucoma subjects. Some previous studies employed electronic monitoring devices [3, 15, 25]. Because the number of enrolled subjects was very large, it was not feasible to employ an electronic monitoring in this study. We were not able to evaluate whether the subjects instilled eyedrops in the cul-de-sac of the eye. Furthermore, even if we had used an electronic monitoring device, it would have been necessary to develop methods evaluating adherence more accurately and objectively. Evaluation of glaucomatous optic neuropathy was not mandatory in this study, and only visual field defects were used as indicators of glaucomatous damage, which may have affected the results. Although ophthalmologists across Japan participated in the study, selection bias may not have been completely eliminated.

In this nationwide study, we identified some factors affecting adherence and its concordance between subjects and ophthalmologists. These results may help improve adherence from both the subjects' and ophthalmologists' perspectives. We plan to further investigate whether the induction of fixed combination eyedrops or providing an informational leaflet to subjects can improve adherence.

The concordance of adherence between subjects' reports and ophthalmologists' assumptions was modest. The status of adherence was moderate, and several factors were significantly associated with adherence, including size of clinic, age, gender, number of ocular hypotensive eyedrops used each time, difficulty of instillation, acceptable kinds of ophthalmic solutions, acceptable times of instillation, and knowledge of glaucoma. Considering the status of adherence and its associating factors may improve glaucoma care.

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