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Original article

Subjective symptoms of glaucoma patients treated with topical medication

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Abstract

***Objective*:** The purpose of this study is to investigate the association between the frequency of ocular symptoms and laboratory values in glaucoma patients undergoing ophthalmic topical medication.

***Methods*:** A multivariate analysis was conducted to examine the association between major ocular symptoms (eye strain, blurred vision, photophobia, dryness, discomfort, and pain) and laboratory findings related to glaucoma and dry eye in 1,000 patients (mean age 67.5 years, 493 males) undergoing antiglaucoma eyedrops. The frequency of ocular symptoms during the same period and for the same age group was also obtained.

***Results*:** 37.3 % of the glaucoma group had any of the major ocular symptoms, and the percentages of patients with ocular symptoms were eye strain in 22.9 %, blurred vision in 23.0 %, photophobia in 13.1 %, dryness in 17.9 %, discomfort in 14.8 %, and pain in 6.3 %. These frequencies were less frequent than in all 1,804 patients aged 60-69 years (mean 64.9 years) seen in the same period. Test values were associated with symptoms: mean deviation (MD) values for visual field were associated with eye strain ($\beta = 0.073$, $p = 0.034$), photophobia ($\beta = -0.0720$, $p = 0.036$), and pain ($\beta = -0.074$, $p = 0.033$) and macular ganglion cell layer thickness was weakly associated with pain ($\beta = -0.0872$, $p = 0.0342$).

***Conclusion*:** The subjective symptoms of glaucoma patients are weakly and infrequently associated with test values, suggesting that topical medication is safely administered. Concurrently, adherence to periodic examinations and topical medication is a concern, so it is important to explain the condition and treatment carefully to increase adherence, even if subjective symptoms are poor.

***KEY WORDS*:** glaucoma, dry eye, topical medication, subjective symptoms

Introduction

In the Guidelines for Glaucoma Treatment (5th edition) published by the Japanese Glaucoma Society in 2022, glaucoma is defined as "a disease characterized by characteristic changes in the optic nerve and visual field and functional and structural abnormalities of the eye that can usually be corrected or suppressed by lowering the intraocular pressure sufficiently," and approximately 5% of patients over 40 years old are considered to have glaucoma [1,2]. The disease is asymptomatic in the early stages, and as optic neuropathy progresses, visual field constriction and visual impairment occur in the late stages, usually in a slow and irreversible manner. The form of glaucoma that causes glaucomatous optic neuropathy with an intraocular pressure (IOP) always below 20 mmHg is classified as normal tension glaucoma, which accounts for about 80 % of glaucoma cases in Japan, and is not easily detected by ordinary medical examinations [1,2]. Glaucoma is an important health problem because it is a typical aging disease with high frequency and is closely related to diabetes and glycative stress [3]. Diabetic patients are more susceptible to glaucoma than healthy individuals due to a tendency toward higher intraocular pressure and optic nerve fragility [4,5].

Neovascular glaucoma is the most common form of glaucoma associated with diabetes mellitus, and other forms include lens-capsular glaucoma caused by mature cataracts. Early detection and early treatment are important, and at the same time, adherence is crucial, as lifelong hospital visits and treatment are required. Studies have shown that glaucoma patients have difficulty perceiving visual field abnormalities because they are complemented by both eyes and adjusted in the brain [6-8]. Visual symptoms appear only in advanced cases, whereas preservatives, an additive in antiglaucoma eyedrops, cause ocular surface abnormalities [9,10] and develop as dry eye symptoms. Elderly patients are less likely to be aware of dry eye symptoms than younger patients [11].

Recent advances in diagnostic techniques and the development of topical medication have led to an increase

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in the number of cases that are detected early and treated with prostaglandin monotherapy, and it has been reported that many cases have few symptoms from glaucoma or dry eye [12]. Although glaucoma is a serious disease occasionally leading to blindness, the lack of symptoms and side effects may make it difficult to motivate patients to continue regular checkups and topical medication. In this study, we analyzed subjective symptoms in 1,000 glaucoma patients undergoing topical medication and reported new findings.

Methods

The subjects were 1,000 consecutive patients who visited ophthalmology outpatient clinics at four clinics in the Chubu and Kanto regions between January 2015 and December 2020, with corrected visual acuity of 0.8 or better in both eyes and at least six months after the start of antiglaucoma eyedrops, and were included in the glaucoma group. Subjective symptoms were defined as eye strain, blurred vision, photophobia, dryness, discomfort, and pain. These were the most common symptoms among patients who visited the ophthalmology outpatient clinic for the first time. All patients aged 60 to 69 years who visited the ophthalmology outpatient clinic at the same time were also asked about their symptoms.

Glaucoma-related examinations included visual acuity, IOP, fundus, visual field (Humphrey® perimetry, Carl Zeiss Meditec, Inc, Dublin, CA, USA), and optical coherence tomography (RS-3000, Nidek Co., Ltd, Gamagori, Aichi, Japan). Corneal tear tests included corneal staining with fluorescein (classified as score 0 to 2 according to severity), and tear break-up time (Tear Break-up time, BUT; cases shorter than 5 seconds were considered as shortened cases).

Topical medication used was as follows. For antiglaucoma eyedrops, prostanoid receptor agonists were 0.005% latanoprost, 0.004% travoprost, 0.0015% tafluprost, 0.03% bimatoprost, 0.12% isopropyl unoprostone, beta blockers were 0.5% timolol, 2% carteolol, and combination products were latanoprost/timolol, travoprost/timolol, tafluprost/timolol, timolol/dorzolamide, timolol/brinzolamide, carteolol/dorzolamide. For dry eye eyedrops, hyaluronan preparation was 0.1% hyaluronic acid, mucin secretagoque were 0.3% dicuafosol and 2% levapamide, and steroid was 0.1% fluorometholone.

Ethical standards

This study was approved by the Kanagawa Medical Association (approved November 12, 2018, approval number krec2059006), Shinseikai Toyama Hospital (approved May 3, 2015, approval number 150503-1), Komoro Kosei General Hospital (approved July 4, 2016, approval number 2802), Tsukuba Central Hospital (approved June 1, 2018, approval number 180602), and the Ethics Review Committee of Tsukuba Central Hospital (approved June 1, 2018, approval number 180602). This study was conducted in accordance with the "Declaration of Helsinki" and the "Ethical Guidelines for Medical Research Involving Human Subjects".

Statistical analysis

Data from the right eye were used for statistical analysis, and the MD value of the visual field was the sum of the two eyes. Standardized partial regression coefficients were calculated using ophthalmologic examination values and contents of the topical medication as dependent variables and ocular symptoms as independent variables, adjusted for age and sex, and correlations were examined. Symptoms were divided into visual symptoms (eye strain, blurred vision, photophobia) and non-visual symptoms (dryness, discomfort, pain). Statistical software StatFlex (Artec, Osaka, Japan) was used.

Results

The mean age of the 1,000 glaucoma patients was 67.5 ± 13.3 years, 493 were male, and antiglaucoma eyedrops consisted of prostanoid receptor agonists in 85.1% (latanoprost 54.1%, tafluprost 14.0%, travoprost 11.0%, bimatoprost 6.0%), beta-blockers in 18.1% (timolol 11.9%, carteolol 6.2%), and combination drugs in 9.7%. Dry eye topical medication consisted of hyaluronic acid, 28.6%, dicuafosol 18.8%, levapamide 1.0%, and steroids 1.1%.

The mean equivalent spherical power was −2.44 ± 3.43 D, IOP was 13.37 ± 3.42 mmHg, MD of visual field was −7.38 ± 6.47 dB, macular nerve fiber layer thickness was 76.34 ± 14.76 μm, peripapillary nerve fiber layer thickness was 88.78 ± 19.50 μm, the number of glaucoma medication averaged 1.4 ± 0.6 vial, and the frequency of glaucoma medication per day was 1.8 ± 1.2. BUT was 3.86 ± 2.07 seconds (58.5% of shortened cases), corneal staining score was 0.43 ± 0.68.

In the glaucoma group, 37.3% had any of the major symptoms, and the percentages of patients with ocular symptoms were eye strain in 22.9%, blurring in 23.0%, photophobia in 13.1%, dryness in 17.9%, discomfort in 14.8%, and pain in 6.3%. All 1,804 patients aged 60 to 69 years (mean 64.9 ± 2.7 years, 777 males) in the same period had subjective symptoms of eye strain in 28.1%, blurring in 24.6%, photophobia in 18.6%, dryness in 21.7%, discomfort in 19.7%, and pain in 7.1%; BUT was 4.01 ± 2.08 seconds (55.9% of shortened cases); corneal staining score was 0.26 ± 0.55.

Multivariate analysis showed that test values correlated with symptoms as follows: visual field MD and eye strain ($\beta = 0.073$, $p = 0.034$), photophobia ($\beta = -0.072$, $p = 0.036$), pain ($\beta = -0.074$, $p = 0.033$), macular ganglion cell layer thickness and pain ($\beta = -0.087$, $p = 0.034$), and prostaglandin analogues and pain ($\beta = -0.0851$, $p = 0.0123$, ***Table1***). Visual symptoms were associated with peripapillary optic ganglion cell layer thickness ($\beta = 0.099$, $p = 0.011$) and number of glaucoma topical medication ($\beta = 0.073$, $p = 0.028$); none were associated with non-visual symptoms. There were 28.7% of dry eye topical medication users, which correlated with dryness ($\beta = 0.141$, $p = 0.003$, ***Table 2***).

Table 1. Correlation between ocular symptoms and glaucoma test values.

	MD [A]	Macular nerve fiber layer thickness	Peripapillary nerve fiber layer thickness	Number of glaucoma medication	Frequency of glaucoma medication	Use of prostaglandin analogue
Age	-0.1868 <0.0001*	-0.1106 0.0059	-0.1767 <0.0001*	0.0093 0.7780	0.0221 0.5048	-0.0050 (0.8801)
Sex	-0.0180 0.6001	-0.0101 0.8035	-0.0843 0.0360*	0.0060 0.8571	-0.0256 0.4457	0.0324 (0.3346)
Eye strain	0.0737 0.0346*	0.0471 0.2562	0.0651 0.1077	0.0177 0.6038	0.0271 0.4287	-0.0330 (0.3342)
Blurred vision	-0.0519 0.1297	-0.0361 0.3770	0.0458 0.2563	0.0112 0.7382	0.0042 0.8998	0.0165 (0.6238)
Photophobia	-0.0720 0.0359*	0.0056 0.8923	0.0097 0.8091	0.1094 0.0012*	0.0835 0.0134*	-0.0167 (0.6200)
Dryness	0.0559 0.1395	-0.0249 0.5901	0.0064 0.8854	-0.0129 0.7297	-0.0090 0.8107	-0.0277 (0.4602)
Discomfort	0.0113 0.7599	-0.0245 0.5867	-0.0326 0.4538	0.0132 0.7200	-0.0004 0.9905	0.0305 (0.4066)
Pain	-0.0739 0.0333*	-0.0872 0.0342*	-0.0686 0.0851	-0.0228 0.5008	-0.0151 0.6561	-0.0851 (0.0123*)
Visual symptoms	-0.0172 0.6122	0.0133 0.7404	0.0985 0.0113*	0.0728 0.0282*	0.0630 0.0574	-0.0279 (0.3989)
Nonvisual symptoms	0.0183 0.5907	-0.0766 0.0560	-0.0465 0.2320	-0.0069 0.8355	-0.0105 0.7514	-0.0433 (0.1918)

Upper numbers indicate standardized partial regression coefficients, lower numbers indicate p values; *p < 0.05, adjusted for age and sex. A = sum of MD values for both eyes in the Humphrey visual field meter 24-2 program. MD, mean deviation.

Table 2. Correlations between ocular symptoms and lacrimal corneal test items.

	Corneal staining score	Tear break-up time	Use of dry eye medication	History of intra- ocular lens surgery
Age	0.0352 0.2779	-0.0072 0.8217	0.0263 0.5456	0.2465 <0.0001*
Sex	-0.1773 <0.0001*	0.2423 <0.0001*	-0.1750 0.0001*	-0.0488 0.1342
Eye strain	0.0560 0.6579	0.0483 0.1447	0.0515 0.2597	-0.0252 0.4472
Blurred vision	0.0117 0.9214	-0.0105 0.7464	0.0337 0.4465	0.0094 0.7740
Photophobia	-0.0651 0.5964	-0.0612 0.0618	0.0352 0.4222	-0.0490 0.1341
Dryness	0.0332 0.3674	-0.0499 0.1722	0.1410 0.0030*	0.0194 0.5950
Discomfort	0.1014 0.5047	-0.0905 0.0115*	0.0921 0.0516	0.0057 0.8723
Pain	-0.0686 0.5796	-0.0884 0.0074*	0.0404 0.3796	-0.0123 0.7087
Visual symptoms	0.0250 0.4462	-0.0100 0.7599	0.0456 0.1477	-0.0427 0.1837
Nonvisual symptoms	0.1610 <0.0001*	-0.1617 <0.0001*	0.1945 <0.0001*	0.0065 0.8403

Upper numbers indicate standardized partial regression coefficients, lower numbers indicate p values; *p < 0.05, adjusted for age and sex.

Discussion

Subjective symptoms of glaucoma patients under topical medication were not strongly correlated with glaucoma-related items and were more strongly related to dry eye-related tests. Also, compared to 60～69 year olds in the same age group, BUT and corneal staining scores were slightly poorer, but subjective symptoms were somewhat less frequent. In comparison, hyaluronic acid products were used in 28.1%, mucin products (Dicuafosol and Levapamide) in 35.3%, and steroids in 9.4% of the general outpatients in the previous report [9] on dry eye treatment, and there was a trend toward more hyaluronic acid products and less mucin products and steroids. This may be due to the large number of patients with mild disease and the objective of counteracting the side effects of antiglaucoma eyedrops, which may have led to less aggressive treatment. These results suggest that there is little increase in subjective symptoms or abnormalities in lacrimal corneal findings during glaucoma topical medication. This is consistent with a previous report that examined lacrimal corneal findings, sleep disturbance, and mood disturbance in patients treated with glaucoma topical medication alone and found little effect of topical medication [12].

There is no strong correlation between glaucoma test values and subjective symptoms, and there are three possible reasons: patients are older [10], glaucoma is a mild disease, and antiglaucoma eyedrops have fewer side effects. The mean IOP was well controlled at 13.37 mmHg with an average of 1.4 topical medication and an average of 1.8 drops per day, indicating that the treatment was effective enough with minimal medication and few side effects. This may be due to the fact that prostanoid receptor agonists, which require only once-daily topical medication, were used in most cases (85.1%), and their strong IOP-lowering effect and minimal number of topical medication may have contributed to the good results. The results of this study were based on a large number of cases, and it seems safe to assume that recent antiglaucoma eyedrops are generally being implemented without problems. Concurrently, adherence to periodic checkups and topical medication is a concern, and it is important to explain the condition and treatment carefully to increase adherence, even if subjective symptoms are not apparent.

The main problem with antiglaucoma eyedrops is side effects related to the ocular surface, such as discomfort in the eye area due to dry eye symptoms, hyperemia, and eye pain [13]. These are believed to be largely due to the additive benzalkonium chloride [10, 13, 14]. Benzalkonium chloride is used as a preservative in most ophthalmic eyedrops at concentrations ranging from 0.001% to 0.02%. Because of the interaction with the main drug, numerous cytotoxicity studies with topical medication have been conducted, and eye drops with lower concentrations of benzalkonium chloride or with preservatives other than benzalkonium chloride have lower cytotoxicity [15]. However, when patients actually experience subjective symptoms, factors on the drug side include the nature of the main drug, the number of drops, the number of drops, and factors on the patient side include the cornea, conjunctiva, eyelid, blinking eye, tear fluid, and adherence. In particular, the recently frequently used brimonidine has a strong effect on the ocular surface and eyelids, which may impair the continuation of topical medication [16]. In addition, many glaucoma patients are elderly, and it is necessary to be aware of the development of meibomian gland dysfunction caused by topical medication [17]. In the present case, only prostanoid receptor agonists, β-blockers, and carbonic anhydrase inhibitors, which have been used in many cases without problems, were used, so there may have been few complaints of subjective symptoms.

Diabetes mellitus is a representative disease with high glycative stress and various ocular complications such as retinopathy, cataract, keratopathy, glaucoma and neuropathy. With the onset of age-related macular degeneration and dry eye, which are ocular diseases that increase with age, the number of cases of multiple ocular complications is expected to increase with age. Dry eye caused by topical medication is also expected to be more likely to occur in the elderly and diabetic patients [18]. On the other hand, there is a reality in which subjective symptoms are scarce in the elderly despite the presence of multiple diseases. As a result, we should be aware of the potential progression of glaucoma.

Two types of glaucoma closely related to diabetes mellitus are neovascular glaucoma and lens cystic glaucoma. The latter type of glaucoma originates in the lens and involves glycosylation of lens proteins (crystallins), while the former is caused by proliferative membranes and pathological angiogenesis due to proliferative diabetic retinopathy and the production of vascular endothelial growth factor (VEGF). When diabetes causes impaired blood flow or ischemia in the retina, retinal cells such as vascular endothelial cells, amacrine cells, retinal ganglion cells, and müller glia cells in the non-perfused region produce VEGF [19-22]. From the viewpoint of glycative stress, it is possible that excessive AGEs production may induce increased secretion of VEGF and various inflammatory cytokines via stimulation of RAGE on retinal cells. The mechanism of the effects of glycative stress on glaucoma should be elucidated.

Research issues

The problem of this study is that future measurements of quality of life and neuropsychiatric function would allow for a more detailed assessment of the life and psychological impact of glaucoma. Furthermore, comparisons with before treatment can be made to clarify the effects of glaucoma notification and treatment on patients. Although there are some problems, a sufficient number of cases have been studied and compared with a control group, so it is thought that certain findings have been obtained.

Conclusion

In patients undergoing antiglaucoma eyedrops, both visual symptoms due to glaucoma and non-visual symptoms due to dry eye were generally unremarkable. In the treatment of glaucoma patients undergoing ophthalmic treatment, it is important to recognize that patients' subjective symptoms are often mild, and to explain test data, periodic examinations, and the purpose and significance of treatment in detail, in

order to improve and maintain adherence. We did not analyze from the viewpoint of glycative stress in this study, but would like to do so in the future.

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Conflict of interest declaration

There are no conflicts of interest regarding this study.

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