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Association Between Watershed Zone and Visual Field Defect in Normal Tension Glaucoma

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Purpose: To evaluate the association between the watershed zone and glaucomatous optic nerve head (ONH) damage.

Methods: We performed indocyanine green fluorescence angiography with a scanning laser ophthalmoscope in 54 eyes of 27 patients with normal tension glaucoma (NTG).

Results: We identified 7 eyes of 8 patients (14.8%) with a watershed zone not including the ONH, 32 eyes of 20 patients (59.3%) with the watershed zone partially including the ONH, and 10 eyes of 14 NTG patients (25.9%) with the watershed zone including the ONH. Of the 27 NTG patients, 10 patients (37.0%) had different types in each eye.

Conclusions: In these patients, the mean deviation of visual field indices was greater in the eye with the watershed zone, which included a larger part of the ONH than in the contralateral eye. Conversely, the eye with the greater mean deviation had a watershed zone that included a larger part of the ONH. The location of the watershed zone appeared to influence the progression of the visual field defect. **Jpn J Ophthalmol 2000;44:39–45** © 2000 Japanese Ophthalmological Society.

Key Words: Indocyanine green fluorescence angiography, normal tension glaucoma, scanning laser ophthalmoscope, visual field defect, watershed zone.

Introduction

Based on fluorescence angiographic studies, Hayreh[1–3] suggested an association between glaucomatous optic nerve damage and the watershed zone, the border between the territories of any two end-arteries. He reported that the watershed zone was located in the peripapillary portions or it passed through the optic nerve head (ONH) in more than 80% of glaucoma patients, including those with normal tension glaucoma (NTG). He stressed that the watershed zone is an area of comparatively poor vascularity and thus vulnerable to ischemia in glaucoma, based on his anatomical studies,[1–6] in which he demonstrated that lamina and prelaminar lesions of the ONH were supplied by branches from a peripapillary choroidal artery that arises from short posterior ciliary arteries. However, Giuffre[7] later reported that the watershed zone included the ONH in more than 90% of normal subjects, thus raising an objection to Hayreh's assertions. There is presently no consensus about the relationship of the location of the watershed zone to glaucomatous optic nerve damage. Our knowledge of the watershed zone is lacking because of the difficulty in determining its location by fluorescein angiography: the watershed zone is visible for only a brief moment after dye is introduced to the fundus. Indocyanine green (ICG) fluorescein angiography with a scanning laser ophthalmoscope (SLO) has been reported to be a suitable method for analyzing choroidal hemodynamics.[8–10] In ICG fluorescein angiography, an infrared laser light is used, which penetrates through the retinal pigment epithelial layer. Little ICG leaks from fenestrated choroidal vessels because more than 98% of ICG molecules injected bind to serum proteins, forming a macromolecule. In addition, the quality of the fundus images visualized by the SLO is high due to the use of a single wavelength laser and a

Received: February 19, 1999
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Published by Elsevier Science Inc.

0021-5155/00/$–see front matter
PII S0021-5155(99)00148-3

Jpn J Ophthalmol
Vol 44: 39–45, 2000

Table 1. Background of Subjects

No. of Subjects	No. of Eyes	No. of Men/Women	Age* (y)	MD* (dB)	CPSD* (dB)	IOP* (mm Hg)†	Refractive Error (Diopter)
27	54	9/18	59.7 ± 14.8 (18–80)	−7.27 ± 6.40 (−23.32–1.38)	7.22 ± 4.66 (0.00–15.44)	14.5 ± 2.2 (9.7–18.7)	−2.04 ± 4.36 (−10.50–3.50)

IOP: intraocular pressure, MD: mean deviation, CPSD: corrected pattern standard deviation.
*Values are mean ± SD, range is in parentheses.
†Average of IOP measurements during three recent visits.

confocal aperture system. Furthermore, the SLO has the advantage of being able to analyze hemodynamics in a very early phase of angiography by evaluating frame by frame videotape images that are recorded every 1/30 second.

To evaluate the possible association between the location of the watershed zone and glaucomatous optic nerve damage, we performed ICG fluorescence angiography using an SLO system in both eyes of patients with NTG. We also assessed the differences in the location of the watershed zone between the left and right eyes of each patient relative to their differences in visual field indices.

Materials and Methods

In a consecutive series, 63 patients with NTG who met the enrollment criteria were selected and we performed ICG angiography. The enrollment criteria for all subjects in this study were no history of ocular surgery including laser photocoagulation, no adverse reaction to ICG skin test, and no ocular disease other than NTG.

The diagnostic criteria for NTG consisted of normal open angles in both eyes, glaucomatous optic disc cupping and nerve fiber layer defects in both eyes, normal intraocular pressure (IOP) on at least two or more occasions, including a diurnal curve measurement and glaucomatous visual field defects in at least one eye.

Of the 63 total subjects initially enrolled, 36 patients were excluded because of poor fixation during angiography or visual field examination, lenticular or corneal opacities, and no ICG angiography for the contralateral eye.

Fifty-four eyes of 27 patients with NTG (9 men and 18 women between 18–80 years, mean age ± SD = 59.7 ± 14.8 years) were enrolled in the study (Table 1).

The study protocol was approved by the Ethical Review Committee of Gifu University, and tenets of the Declaration of Helsinki were followed. Informed consent was obtained from all patients after the study was thoroughly explained to them.

After dilation of the pupil by 0.5% tropicamide eye drops, ICG fluorescence angiography was performed using an SLO (auto gain, infrared laser, and 40° acquisition field), and images were recorded on an 8-mm videotape recorder (Hi8 HG; Sony, Tokyo). The images were taken with the imaging field centered on the optic disc. One milliliter of saline so-

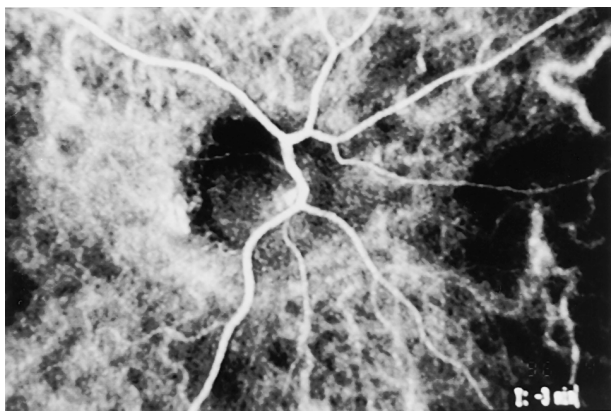

Figure 1. Example of type I indocyanine green angiogram, taken at 23.3 seconds. Watershed zone does not include optic nerve head.

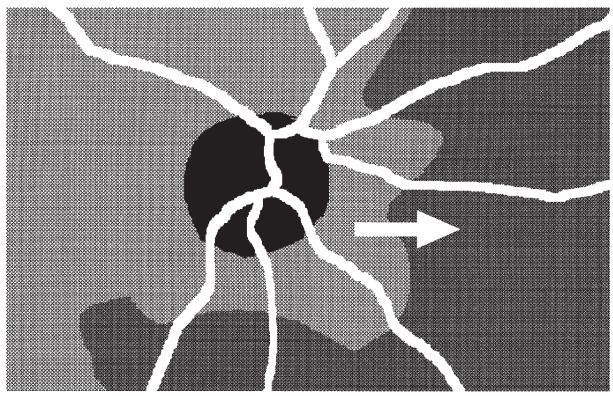

Figure 2. Schematic explanation of Figure 1. Arrow shows watershed zone.

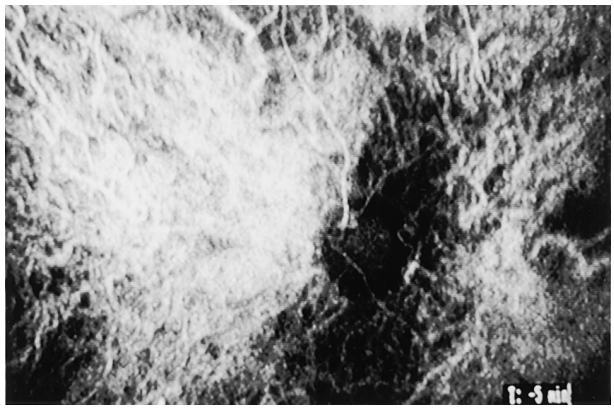

Figure 3. Example of type II indocyanine green angiogram, taken at 17.3 seconds. Watershed zone partially includes optic nerve head.

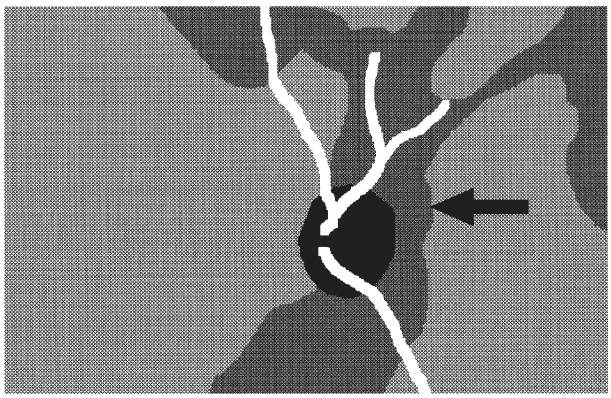

Figure 4. Schematic explanation of Figure 3. Arrow shows watershed zone.

lution containing 5 mg ICG was injected rapidly via an antecubital vein catheterized with a 21-gauge butterfly needle. Three days or more after 1 eye was examined, its contralateral eye was examined.

In a masked manner, one observed (YS) evaluated the video images frame by frame and classified the watershed zone as one of three types based on the location of the watershed zone relative to the ONH: in type I, the watershed zone does not include the ONH (Figures 1 and 2); in type II, the watershed zone partially includes the ONH (Figures 3 and 4); and in type III, the watershed zone completely includes the ONH (Figures 5 and 6) (Table 2).

This classification was made based on images recorded within 5 seconds after the introduction of ICG to the fundus. Cases in which the watershed zone could not be observed were classified as type I.

The mean deviation (MD) and corrected pattern standard deviation (CPSD) of the visual field indices were obtained from the Humphrey Visual Field Central 30-2 program with a Humphrey Visual Field Analyzer (Zeiss-Humphrey Systems, Dublin, CA, USA).

The relationship between the watershed zone types and visual field indices for both eyes of each patient was evaluated.

The mean of age, IOP, and refractive error in spherical equivalents measured by an autokeratometer (Model KP-7100P; Topcon, Tokyo) were compared among the types of watershed zone. An average of IOP readings at three consecutive visits nearest to the date of ICG angiography was used.

To evaluate differences between the two eyes of each patient, the Wilcoxon signed-rank test was used. To examine differences among the three watershed zone types, the Kruskal–Wallis analysis of

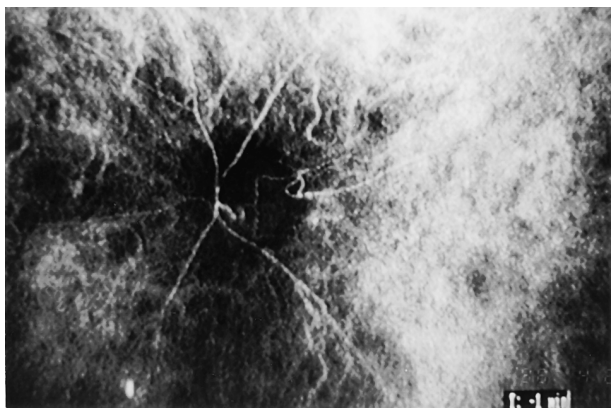

Figure 5. Example of type III indocyanine green angiogram, taken at 23.1 seconds. Watershed zone includes whole optic nerve head.

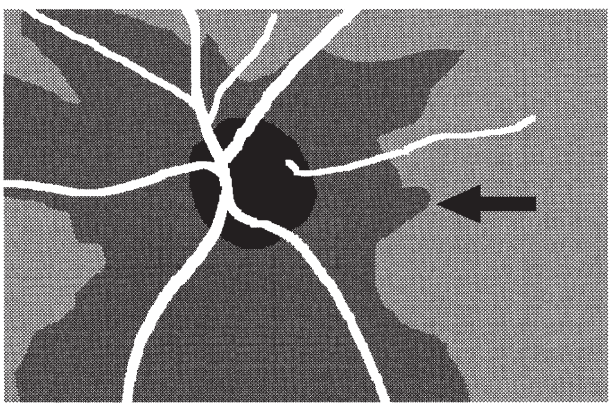

Figure 6. Schematic explanation of Figure 5. Arrow shows watershed zone.

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Table 2. Classification of Watershed Zone

Type I: Watershed zone does not include optic nerve head (ONH)
Type II: Watershed zone partially includes ONH
Type III: Watershed zone completely includes ONH

variance test was used. We considered $P < .05$ to be statistically significant.

Results

Visual field indices, IOP, and refractive errors are shown in Table 1. In all but 2 eyes, the watershed zone was present at the posterior pole of the fundus.

In 7 eyes of 8 patients (14.8%), the watershed zone did not include the ONH (type I), in 32 eyes of 20 patients (59.3%) the watershed zone partially included the ONH (type II), and in 14 eyes of 10 patients (25.9%) the watershed zone completely included the ONH (type III).

There were no significant differences between patients in the watershed zone types with regard to age, visual field indices, IOP, and refractive error (Table 3). Of the 27 NTG patients, 17 (53.0%) had the same type of watershed zone in both eyes (Table 4).

In the 10 patients who had a different type of watershed zone in each eye, the MD of the visual field indices was greater in the eye with the watershed zone that included a larger part of the ONH than in the contralateral eye ($P < .05$) (Figure 7), but we found no statistically significant difference in the CPSD (Figure 8).

After scoring each of the watershed zone types (ie, type I = 1, type II = 2, type III = 3), we selected 11 patients who had a difference in the MD values of their eyes exceeding 4.29 dB that represented the mean value of the difference in MD value between the 2 eyes of the patient. In this subgroup, we found that the eye with the greater MD had a higher score of watershed zone type ($P < .05$) (Figure 9). In other words, the eye with more advanced visual field defects had a watershed zone that included a larger part of the optic disc than the contralateral eye.

Table 4. Watershed Zone Type in Subjects

	No. of Subjects (%)
Same type in both eyes	17 (63.0)
Type I	1 (3.7)
Type II	12 (44.4)
Type III	4 (14.8)
Different types	10 (47.0)
Types I and II	4 (14.8)
Types I and III	2 (7.4)
Types II and III	4 (14.8)

Similarly, we selected 11 patients who had a difference in the CPSD values of their eyes exceeding 3.98 dB. In this subgroup, we found no statistically significant difference in the score of the watershed zone type between the eye with the greater CPSD and the eye with the smaller CPSD (Figure 10).

Discussion

In this study, we performed ICG angiography on patients with NTG using SLO. We identified the location of the watershed zone in the fundus and evaluated the relationship between the interocular difference in the location of the watershed zone and the difference in visual field defects. About 60% of patients had the same type of watershed zone in both eyes. In the patients who had different types of watershed zone in their eyes, the visual field defects were more advanced in the eye with the watershed zone that included a larger part of the ONH than in the contralateral eye. On the other hand, the patients who had a difference in the MD values of their eyes exceeding the mean value of 4.29 dB had a higher score in the watershed zone type. In other words, the eye with the more advanced visual field defects had a watershed zone that included a larger part of the optic disc than the contralateral eye.

Table 3. Results by Watershed Zone Classification

Type	No. of Subjects	No. of Eyes	No. of Men/Women	Age*† (y)	MD*† (dB)	CPSD*† (dB)	IOP*† (mm Hg)	Refractive Error*† (Diopter)
I	7	8 (14.3)	0/7	62.8 ±10.0	−5.56 ± 4.49	8.16 ± 5.35	15.1 ± 2.9	−1.06 ± 4.65
II	20	32 (59.3)	7/13	56.4 ± 15.9	−7.31 ± 6.10	8.40 ± 4.12	14.5 ± 2.1	−1.77 ± 3.99
III	10	14 (25.9)	4/6	58.1 ± 18.3	−10.14 ± 7.97	7.97 ± 4.58	13.6 ± 2.1	−3.89 ± 5.00

There were no significant differences among the watershed zone types with regard to age, mean deviation (MD), corrected pattern standard deviation (CPSD), intraocular pressure (IOP), and refractive error.

*Values are mean ± SD.

†NS (Kruskal–Wallis analysis of variance test).

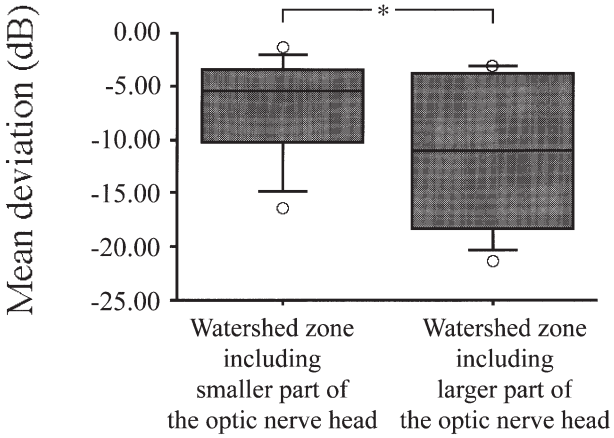

Figure 7. Box plot of mean deviation (MD) of patients who had different types of watershed zone in their eyes. Mean deviation of visual field indices were greater in eye with watershed zone that included larger part of optic nerve head than in contralateral eye. Bottom bar represents 10th percentile and top bar represents 90th percentile. Boxes represent plots of 25th, 50th, and 75th percentiles. Open circles represent plots below 10th percentile and higher than 90th percentile. *$P < .05$, n = 10, Wilcoxon signed-rank test.

With regard to the participation of choroidal hemodynamics in glaucoma, Lambrou et al[11] and Duijm et al[12,13] reported that the refreshment time (flow/volume) of choroid, determined by analyzing the brightness of the dye used in fluorescein angiography during SLO, is longer in the NTG group than in the control subjects and patients with ocular hypertension and primary open angle glaucoma.

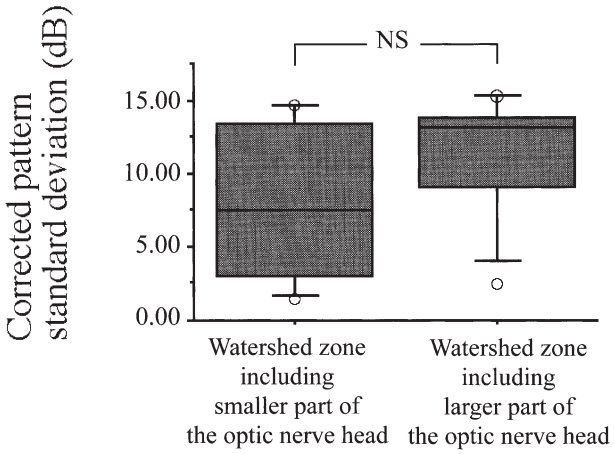

Figure 8. Comparison of corrected pattern standard deviations between the left and right eyes of patients who have different types of watershed zones. NS: $P > .05$. n = 10 pairs.

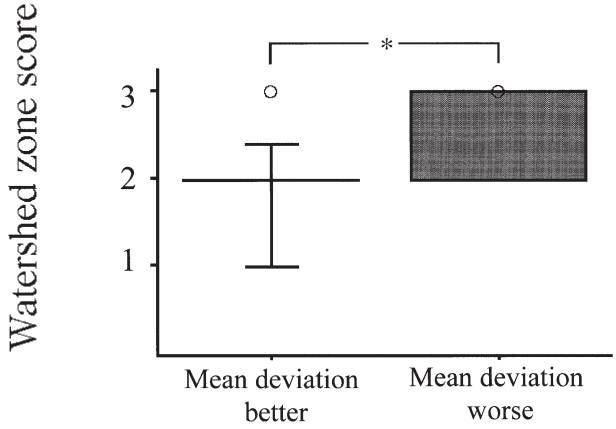

Figure 9. Watershed zone types were scored as type I = 1, type II = 2, and type III = 3. In patients who had differences in mean deviation values of their eyes exceeding 4.29 dB, eye with greater mean deviation had watershed zone that included larger part of optic disc than contralateral eye. *$P < .05$. n = 11 pairs.

By fluorescein angiographic studies, Hayreh et al[1–3] determined the incidence of the various locations of the watershed zone: in 60% of subjects, the watershed zone was located in the temporal part of the optic disc; in 16%, it extended over the entire optic disc; and in 10%, it was in the nasal part of the optic disc. Hayreh stressed the importance of the watershed zone in glaucoma, suggesting that in the event of decreased perfusion pressure in the vascular bed of one or more end-arteries, the watershed zone—being an area of comparatively poor vascularity—is

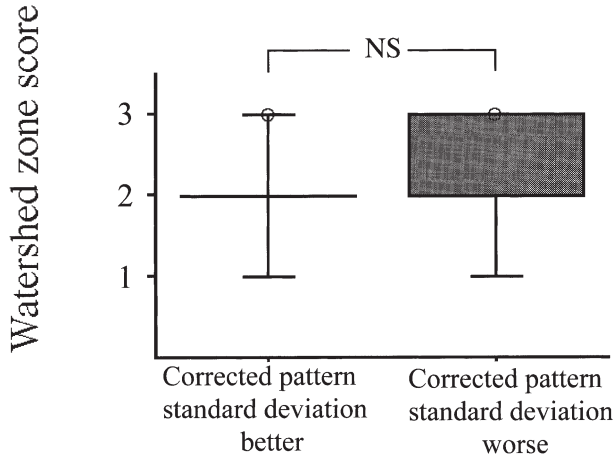

Figure 10. Comparison of watershed zone scores between the left and right eyes of patients who had differences in corrected pattern standard deviation values of their eyes exceeding 3.98 dB. NS: $P > .05$. n = 11 pairs.

most vulnerable to ischemia, which could be a possible cause of glaucomatous optic neuropathy.[1–6] As a basis for his hypothesis, he has demonstrated that the prelaminar region is supplied by the peripapillary choroid and that branches arising from the large peripapillary choroidal arteries supply adjacent sectors. The lamina cribrosa and prelaminar regions are usually supplied by afferent branches arising directly from the short posterior ciliary arteries (SPCAs) with some supply from the recurrent pial branches from the peripapillary choroid. The arterial branches supplying the lamina and the prelaminar region originate from SPCAs, which are end-arteries, each feeding its own territory of choroid. Thus, the choroidal watershed zone is the border for distribution of any two end-arteries (SPCAs), making it an area of comparatively poor vascularity. These findings support the theory that the location of the watershed zone relative to the ONH may play an important role in the development of ischemia of the ONH. However, it has also been reported that the watershed zone included the ONH in more than 90% of the eyes of normal subjects.[7] Also, our previous study[14] and the present study have revealed no significant difference between the glaucomatous and normal eyes in the proportion of subjects with watershed zones that included the ONH.

The vascular anatomy of the anterior optic nerve has been studied using casting techniques and scanning electron microscopy.[15–17] Using postmortem human eyes, Fryczkowski[16] observed that SPCAs feed the laminar region directly or through Zinn-Haller's vascular circle, and that the branches of SPCAs that irrigate the peripapillary choroid feed the prelaminar region. Recently, Onda et al[17] reported that branches of SPCAs feed the prelaminar and laminar regions directly or through Zinn-Haller's vascular circle in human eyebank eyes. However, no direct connection was observed between the peripapillary choriocapillaries and the anterior optic nerve. They concluded that the watershed zone reflects the location of SPCAs in the choroid and choroidal hemodynamics, but does not necessarily reflect the hemodynamics of the ONH.[18] While reports have suggested an association between choroidal hemodynamics and glaucoma, there is no consensus on the relation between the location of the watershed zone in the fundus and glaucomatous optic nerve damage.

Evaluating the differences in glaucomatous optic nerve damage among groups with different watershed zone locations would require that those groups have the same duration of the disease. However, matching disease duration among patients is practically impossible. Instead, we chose to evaluate interocular differences. In patients with different types of watershed zones in their eyes, there were differences in visual field indices. There were no significant differences in IOP and refractive errors. These findings suggest that the location of the watershed zone has an influence on the progression of visual field defects in at least some patients with NTG. However, the difference in optic nerve damage in a patient's eyes may not be fully explained by the location of the watershed zone alone. The pathogenesis of glaucoma seems to include other factors in a complex manner. It is expected that the association between choroidal circulation and the progression of visual field defects may be clarified by the long-term observation of visual field defects from an early stage in those patients with different types of watershed zones in their eyes.

This article was published in the Nippon Ganka Gakkai Zasshi (J Jpn Ophthalmol Soc) 1998;102:502–8. It appears here in a modified form after peer review and editing for The Japanese Journal of Ophthalmology.

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