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Changes in visual acuity and intra-ocular pressure following bleb-related infection: the Japan Glaucoma Society Survey of Bleb-related Infection Report 2

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ABSTRACT.

Purpose: **To identify changes in visual acuity and intra-ocular pressure (IOP) 12 months after the development of bleb-related infection.**

Methods: **Data obtained from 146 eyes of 146 patients with bleb-related infection were analyzed as a part of the Japan Glaucoma Society Survey of Bleb-related Infection. Multiple logistic regression analysis was conducted to identify factors associated with poor prognosis in visual acuity and increased IOP and for being stage III.**

Results: **The logMAR increased by a mean of 0.140, 0.440, 1.099 and 1.122 at 12 months postinfection for stage I, II, IIIa and IIIb infections, respectively. The logMAR was significantly worse at 6 and 12 months postinfection in stage IIIb ($p = 0.002$ and $p = 0.003$, respectively; Wilcoxon signed-rank test) and at 6 months postinfection in stage IIIa ($p = 0.036$). The IOP was significantly elevated following infection in both stage IIIa and stage IIIb ($p = 0.028$ and $p = 0.008$ at 6 and 12 months, respectively, for stage IIIa; $p = 0.002$ and $p = 0.005$ for stage IIIb). The multiple logistic regression analysis revealed that being stage III and positive culture were significant risk factors for poor outcome for visual acuity (Odds ratio: 9.26 and 6.29, respectively) and that being stage III was a prognostic factor for increased IOP (Odds ratio: 8.33). Pseudophakia or aphakia was significantly associated with stage III and stage IIIb infections (Odds ratio: 2.85 and 6.30).**

Conclusions: **Stage III bleb-related infection causes significant visual loss and IOP elevation within 12 months after development. Therefore, preventative measures should be taken, especially in cases that are pseudophakic or aphakic.**

Key words: bleb-related infection – glaucoma – glaucoma surgery – intra-ocular pressure – trabeculectomy – visual acuity

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Introduction

Late-onset bleb-related ocular infection is a known, potentially blinding complication of glaucoma filtration surgery. (Katz et al. 1985; Mandelbaum et al. 1985; Greenfield et al. 1996; Kangas et al. 1997; Waheed et al. 1998; Song et al. 2002; Busbee et al. 2004; Leng et al. 2011; Rai et al. 2012). Although the reported incidence of bleb-related infection is highly variable (Mochizuki et al. 1997; Yamamoto et al. 2012), it is higher in cases of adjuvant antimetabolite use. Its incidence has been reported to be 1.5–13.8% in cases using intra-operative mitomycin C adjunctively, which were followed from 16 months to 8 years (Greenfield et al. 1996; Mochizuki et al. 1997; DeBry et al. 2002; Shigeeda et al. 2006; Sharan et al. 2009). Thus, this complication must be taken into consideration even before surgery is undertaken.

We have already reported on the clinical characteristics and microbial findings in bleb-related infection based on the Japan Glaucoma Society

Survey of Bleb-related Infection (JGSSBI), a 5-year-long, multicenter survey (Yamamoto et al. 2012). This survey compiled data on 170 bleb-related infections that developed in 156 patients involving 157 eyes. Among other findings, our analysis revealed that the period between the last glaucoma surgery and the development of infection was quite variable, lasting up to 41 years. Bleb leakage was noted significantly more frequently in eyes with repeated infection and Gram-positive bacteria were the major detected bacteria. In the present second report of the JGSSBI, we discuss the outcome of bleb-related infections in terms of visual acuity and intra-ocular pressure (IOP) 12 months after the development of a bleb-related infection.

Materials and Methods

The details of the JGSSBI are described elsewhere (Yamamoto et al. 2012). Briefly, this prospective study included a surveillance period of 5 years in which all patients with bleb-related infection were consecutively registered from 82 medical centres in Japan, and clinical and microbial data were collected. Institutional review board approval was obtained at each institution. In 36 clinics where there was no governing institutional review board, the Ethical Review Board of the Gifu University Hospital approved the study protocol for the clinics on the condition that the study would be conducted under the guidance of the University Hospital. All patients or their guardians gave written informed consent after thorough explanation of the study. The management of bleb-related infection was at the discretion of local investigators. Because cases from surgeries performed at ophthalmology clinics outside of the study centres were also included, pre-infection data collection might have been incomplete in some cases. Each infection was classified into one of three stages (Azuara-Branco & Katz 1998; Greenfield 1998): stage I denoted infections confined to the bleb site with a mild cell reaction in the anterior chamber; stage II denoted infections where the anterior chamber was the main locus and the vitreous was not involved; stage III denoted infections involving the vitreous. Stage III was subdivided into stages IIIa and IIIb (Yamamoto et al. 2011): stage IIIa denoted mild involvement to the vitreous and stage IIIb denoted more advanced involvement. The staging into category IIIa or IIIb was done mainly based on visibility of the fundus and vitreous opacity detected by B-mode echography.

A total of 170 infections developed in 157 eyes of 156 patients that were collected from 45 institutions. In the present study, only the cases where 6-month and/or 12-month follow-up results were available were analyzed. The following information was collected as postinfection data: use of glaucoma and other medication, postoperative complications, additional procedures or surgery, bleb appearance and results of ophthalmic examinations including visual acuity, refraction, IOP and visual field. Bleb appearance was determined according to a predetermined scoring system. The postinfection data were employed and analyzed if they were collected within 2 months of the designated period. In cases with multiple infections, we used data for the last infection.

Multiple logistic regression analysis was conducted to identify factors associated with poor prognosis in visual acuity and increased IOP. Poor visual prognosis was defined as an increase of logMAR of at least 0.5 units at 12 months following the development of bleb-related infection. Counting fingers was considered as 0.004, hand motion as 0.002, light sensation as 0.001 and no light sensation as 0.0004 for this calculation. Poor IOP prognosis was defined as IOP elevation of 5 mmHg or greater at 12 months. The following were considered to be potentially associated factors: age, gender, interval between surgery and development of infection, stage of the infection, detection of bacteria, detection of *Streptococcus* species, history of bleb leakage, type of conjunctival incision and pre-infection IOP. Stage factors were enrolled as nominal variables; for example, variable 'stage I' was able to take the value Yes which meant 'being stage I' or the value No meaning 'not being stage I' and so on. In addition, we conducted multiple logistic regression analysis to identify factors associated with being stage IIIa, stage IIIb or stage III, i.e. stage IIIa or stage IIIb. Candidates for associated factors were age, gender, interval between surgery and development of infection, lens status, detection of bacteria, detection of *Streptococcus* species, history of bleb leakage, type of conjunctival incision and pre-infection IOP.

Statistical analysis as well as logistic regression analysis was conducted via the SPSS 16.0 J software (SPSS Japan Inc., Tokyo, Japan) or the IBM SPSS Statistics software version 20.0 (IBM Japan Ltd., Tokyo, Japan). p-Values <0.05 were considered statistically significant.

Results

Six-month and 12-month follow-up data were available in 146 eyes of 146 patients. The 6-month data were available for 134 eyes and the 12-month data for 112 eyes. The backgrounds of the subjects were shown in Tables 1 and 2. All eyes were intensively treated with antibiotic therapy and surgery where indicated. In total, 45 eyes underwent vitreous surgery and four eyes required enucleation or evisceration of the eyeball. In addition, six eyes ended up with phthisis bulbi.

Visual acuity data were available for 113 eyes at 6 months postinfection and for 107 eyes at 12 months postinfection. Pairs of pre- and postinfection visual acuities were available for 96 eyes at 6 months postinfection and for 93 eyes at 12 months postinfection, respectively. A total of 10 eyes that were enucleated or eviscerated or had developed phthisis bulbi were included as having visual acuity described as no light sensation. Table 3 shows the pre and postinfection visual acuities and Figs 1–4 demonstrate the relationship between them in all cases where paired data were available. The postinfection logMAR was significantly deteriorated in all cases ($p = 0.000$ at both 6 and 12 months postinfection; Wilcoxon signed-rank test), in stage IIIb ($p = 0.002$ and $p = 0.003$ at 6 and 12 months postinfection, respectively) and in stage IIIa at 6 months postinfection ($p = 0.036$). It did not change in stages I and II, and at 12 months postinfection in stage IIIa. The logMAR increased by a mean of 0.140, 0.440, 1.099 and

Table 1. Patients' backgrounds.

Last glaucoma surgery	
Trabeculectomy	118 eyes
Trabeculectomy with PEA/IOL	19 eyes
Non-penetrating trabeculectomy	2 eyes
Trabeculectomy combined with IOL	1 eye
Scheie's thermal sclerostomy	3 eyes
Unknown	3 eyes
Sex	
Male	102 eyes
Female	44 eyes
Glaucoma subtype	
Primary open angle glaucoma	66 eyes
Normal tension glaucoma	8 eyes
Primary angle closure glaucoma	3 eyes
Developmental glaucoma	18 eyes
Secondary glaucoma	34 eyes
Use of antimetabolites	
Mitomycin C alone	116 eyes
Mitomycin C and 5-fluorouracil	2 eyes
5-Fluorouracil alone	1 eye
No antimetabolites	3 eyes
Unknown	24 eyes
Stage of bleb-related infection at diagnosis	
Stage I	73 eyes (50.0%)
Stage II	27 eyes (18.5%)
Stage IIIa	15 eyes (10.3%)
Stage IIIb	31 eyes (21.2%)
Bleb location	
Between the 10 to 2 o'clock positions	145 eyes
3 o'clock position	1 eye
Bleb leakage noticed before developing infection	
Yes	70 eyes (47.9%)
No	54 eyes (37.0%)
Unknown	22 eyes (15.1%)
IOP before infection (undetermined in four eyes)	
Mean ± standard deviation	10.0 ± 3.9 mmHg
Range	2–27 mmHg

PEA = phacoemulsification and aspiration, IOL = intra-ocular lens implantation, IOP = intra-ocular pressure.

Table 2. Result of bacterial cultures.

Culture done	128/146 (87.7%)
Culture positive	69/128 (53.9%)
Conjunctival scraping	90
Anterior chamber tapping	28
Vitreous tapping	25
Strains isolated	73
Staphylococcus aureus (MRSA included)	14
CNS (MRSE included)	14
Streptococcus spp.	24
Corynebacterium spp.	7
Enterococcus spp.	4
Haemophilus influenzae	4
Others	6

MRSA = methicillin-resistant *Staphylococcus aureus*, CNS = coagulase-negative *Staphylococcus*, MRSE = methicillin-resistant *Staphylococcus epidermidis*, spp species.

1.122 at 12 months postinfection for stage I, II, IIIa and IIIb infections, respectively. Table 4 shows the visual acuity at the last available visit after infection for cases in which preinfection visual acuity was at least 20/40.

Data on IOP were available for 123 eyes at 6 months postinfection and for 102 eyes at 12 months postinfection. Pairs of pre and postinfection IOPs were available for 119 eyes at 6 months and for 98 eyes at 12 months, respectively, following development of infection. The eyes that were enucleated or eviscerated or had developed phthisis bulbi were excluded from the IOP analysis at postinfection. Table 5 shows the preinfection and postinfection IOPs and Figs 5–8 demonstrate the relationship between them. The IOP elevated significantly following infection in all cases ($p = 0.001$ and $p = 0.008$ at 6 and 12 months postinfection, respectively; Wilcoxon signed-rank test) and both stage IIIa and stage IIIb ($p = 0.028$ and $p = 0.008$ at 6 and 12 months postinfection, respectively, for stage IIIa; similarly, $p = 0.002$ and $p = 0.005$ for stage IIIb). The IOP did not change in stages I and II. The number of anti-glaucoma medications used was 0.34 ± 0.71 (0–3), 0.48 ± 0.95 (0–5) and 0.45 ± 0.99 (0–5) [mean ± standard deviation (range)] for preinfection and at 6 and 12 months postinfection, respectively.

As for the associated factor analysis with poor prognosis, the multiple logistic regression analysis revealed that being stage III and having a culture positive were statistically significantly associated with the deterioration of visual acuity 12 months following the development of bleb-related infection with an increase in logMAR of at least 0.5 units (Table 6). Similarly, the multiple logistic regression analysis demonstrated that only being stage III was statistically significantly associated with IOP elevation at 12 months following the development of bleb-related infection that was defined as an increase in IOP of 5 mmHg or greater (Table 7).

As for the risk factors for being stage III, the multiple logistic regression analysis revealed that only lens status was significantly associated with being stage III and stage IIIb, but no factors were found to be associated with being stage IIIa (Table 8).

Discussion

The present study reports the visual outcome of bleb-related infection and found that the visual acuity dropped by a mean of 0.504 logMAR units at 12 months postinfection, with marked variation among the stages. Being stage III and having a positive bacterial culture were identified as significant factors for poor visual prognosis. In previous reports, the visual outcome of bleb-related infection was poor in endophthalmitis cases. For example, Busbee et al. (2004) reported in a retrospective study of 68 eyes of 68 consecutive cases of bleb-associated endophthalmitis that the incidence of no light perception was 35% at 12 months after treatment and that the incidence of visual loss, defined as at least 5 Snellen lines was 64%. In addition, they found that a positive vitreous culture was associated with significantly worse visual acuity. Song et al. (2002) identified 49 eyes of 49

Table 3. Changes in logMAR.

	Preinfection		6-month postinfection			12-month postinfection		
	Mean ± SD	*N*	Mean ± SD	*N*	p-value	Mean ± SD	*N*	p-value
Stage I	0.524 ± 0.920	61	0.538 ± 0.893	60	0.688	0.664 ± 0.997	54	0.379
Stage II	0.906 ± 1.093	23	1.380 ± 1.151	18	0.116	1.346 ± 1.277	20	0.055
Stage IIIa	0.503 ± 1.010	14	1.071 ± 1.329	10	0.036	1.602 ± 1.456	9	0.068
Stage IIIb	0.726 ± 0.862	24	1.841 ± 1.285	25	0.002	1.838 ± 1.351	24	0.003
Total cases	0.634 ± 0.955	122	1.007 ± 1.189	113	0.000	1.138 ± 1.263	107	0.000

SD = standard deviation, *N* = number of eyes, p value: versus preinfection logMAR by Wilcoxon signed-rank test including only cases where paired data were available.

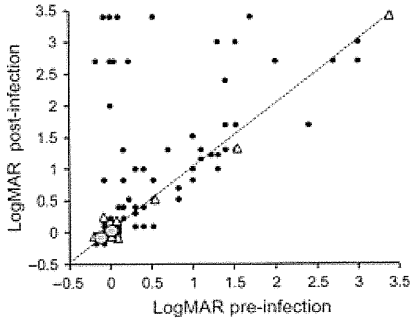

Fig. 1. Distribution of logMAR (preinfection versus 6 months postinfection). Small circles: one eye; triangles: 2–4 eyes; large circles: five eyes.

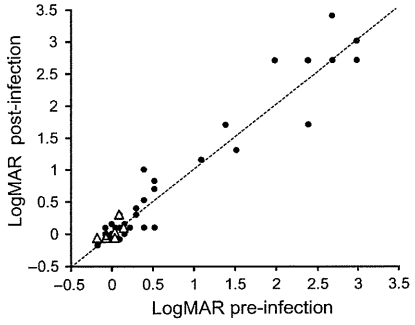

Fig. 2. Distribution of logMAR among stage I cases (preinfection versus 12 months postinfection). Circles: one eye; triangles: 2–4 eyes.

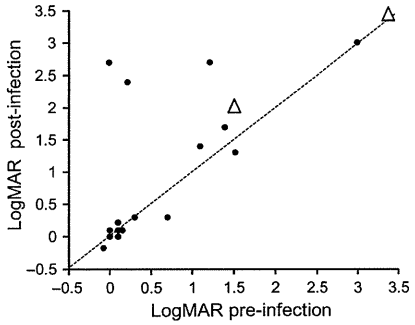

Fig. 3. Distribution of logMAR among stage II cases (preinfection versus 12 months postinfection). Circles: one eye; triangles: two eyes.

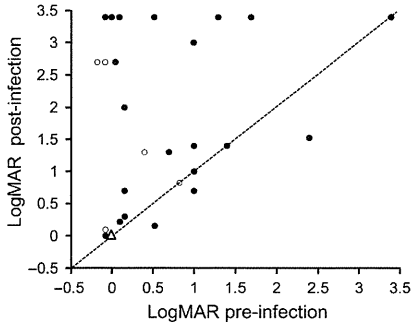

Fig. 4. Distribution of logMAR among stage III cases (preinfection versus 12 months postinfection). Open circles: 1 stage IIIa eye; closed circles: 1 stage IIIb eye; triangle: 2 stage IIIa eyes.

cases with delayed-onset bleb-associated endophthalmitis and reported that the final visual acuity was 20/40 or better in 10%, between 20/50 and 20/400 in 43% and < 5/200 in 45% of the eyes studied. The proportion of patients 20/400 or better was reported to be 47% by Kangas et al. (1997), 22% by Ciulla et al. (1997), 57% by Mandelbaum et al. (1985) and 55% by Leng et al. (2011) in bleb-associated endophthalmitis. In our series consisting of cases in which preinfection visual acuity was at least 20/40, the incidence of the ratio of visual acuity being 20/400 or better was 56% in stage III infections. Thus, the visual outcome data were similar to that reported previously for bleb-associated endophthalmitis cases. Greenfield et al. (1996) reported an average increase in logMAR of 1.42 units following bleb-related endophthalmitis and 62% showed 20/400 or better visual acuity after resolution. By contrast, Poulsen & Allingham (2000) reported much better visual outcome: 20/25 or better in each of three blebitis cases and 20/200 or better in 16 of 17 endophthalmitis cases. The mean increase in log MAR was 0.140, 0.440, 1.099 and 1.122 at 12 months postinfection for stage I, II, IIIa and IIIb infections, respectively, in the present study. Hence, our outcome data did not represent an improvement over those from previous reports on both blebitis and endophthalmitis. Even in this modern age of sophisticated technology including vitreoretinal surgery and anti-bacterial medications, bleb-related infection still posed a significant threat to visual acuity.

We also demonstrated that IOP did not change in stages I and II, and that it increased by a mean of 2.7 and 6.6 mmHg at 12 months postinfection for stage IIIa and IIIb, respectively, In addition, being stage III was again a significant risk factor for increased IOP. Thus, bleb-related infection did affect IOP control and this was especially the case in stage III infections. Previously, Song et al. (2002) focused on IOP outcomes in bleb-related infections and reported that the IOP

Table 4. Visual acuity at the final follow-up for cases in which preinfection visual acuity was at least 20/40.

Stage	20/40 or better	20/50 to 20/400	Worse than 20/400
I	36/38 (95%)	2/38 (5%)	0/38 (0%)
II	8/12 (67%)	1/12 (8%)	3/12 (25%)
III	7/18 (39%)	3/18 (17%)	8/18 (44%)
IIIa	5/8 (63%)	0/8 (0%)	3/8 (38%)
IIIb	2/10 (20%)	3/10 (30%)	5/10 (50%)
Total cases	51/68 (75%)	6/68 (9%)	11/68 (16%)

Table 5. Changes in intraocular pressure (mmHg).

	Preinfection		6-month postinfection			12-month postinfection		
	Mean ± SD (range)	*N*	Mean ± SD (range)	*N*	p-value	Mean ± SD (range)	*N*	p-value
Stage I	10.3 ± 3.9 (4–27)	70	11.0 ± 4.5 (4–26)	68	0.062	11.2 ± 3.9 (2–22)	57	0.207
Stage II	10.6 ± 4.4 (5–24)	27	10.1 ± 4.8 (0–24)	26	0.566	10.5 ± 5.5 (0–20)	22	0.944
Stage IIIa	10.2 ± 2.7 (7–15)	15	14.6 ± 5.7 (7–22)	10	0.028	12.9 ± 8.2 (0–24)	8	0.008
Stage IIIb	8.6 ± 3.8 (2–16)	30	13.3 ± 5.0 (3–21)	19	0.002	15.2 ± 6.5 (8–33)	15	0.005
Total cases	9.9 ± 3.8 (2–27)	142	11.5 ± 4.9 (0–26)	126	0.000	11.8 ± 5.2 (0–33)	102	0.008

SD = standard deviation, *N* = number of eyes. p-value: versus preinfection intra-ocular pressure by Wilcoxon signed-rank test including only cases where paired data were available.

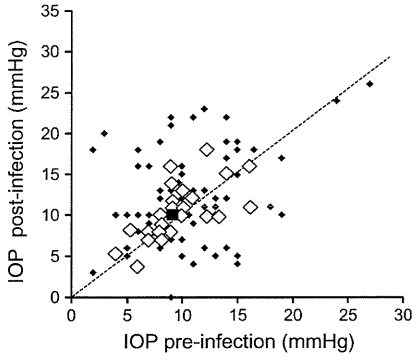

Fig. 5. Distribution of intra-ocular pressure (preinfection versus 6 months postinfection). Small diamonds: one eye; large diamonds: 2–4 eyes; large square: five eyes.

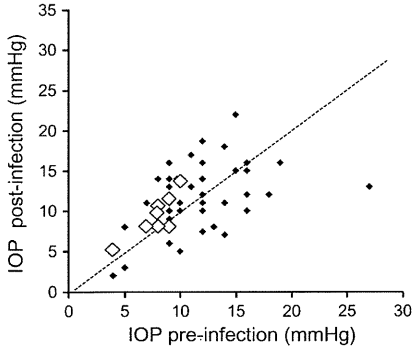

Fig. 6. Distribution of intra-ocular pressure among stage I cases (preinfection versus 12 months postinfection). Small diamonds: one eye; large diamonds: 2–4 eyes.

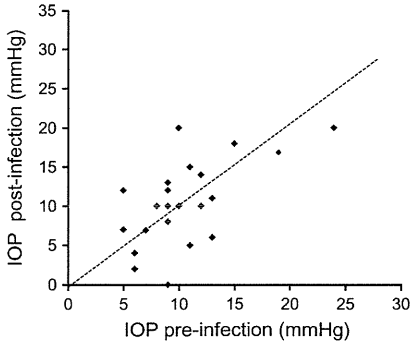

Fig. 7. Distribution of intra-ocular pressure among stage II cases (preinfection versus 12 months postinfection). Small diamonds: one eye.

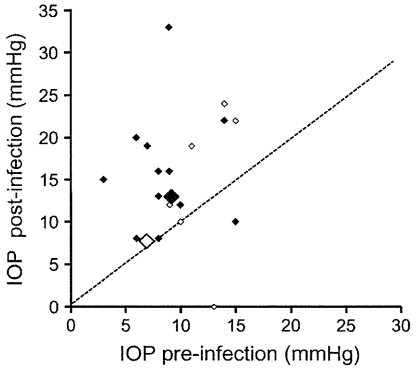

Fig. 8. Distribution of intra-ocular pressure among stage III cases (preinfection versus 12 months postinfection). Open diamonds: stage IIIa; closed diamonds: stage IIIb; small diamonds: one eye; large diamonds: two eyes.

was uncontrolled (>21 mmHg) in 11% of such cases. Chen et al. (1997) stated that 11 of 12 bleb infections were associated with good IOP control after the resolution of the infection in an outpatient sample. Greenfield et al. (1996) reported a mean IOP increase of 1.2 mmHg following endophthalmitis. Thus, the IOP outcome findings in the present study were consistent with those of previous reports.

The present study identified that being stage III infection was a significant prognostic factor for both poor visual acuity and increased IOP. Positive bacterial culture was also associated with poor visual acuity. Other factors such as age, gender, interval between surgery and development of infection, history of bleb leakage, type of conjunctival incision and preinfection IOP were not associated with a poor prognosis. The prognostic factors were apparently different from those related to the development of the infection. The latter included history of bleb leakage, use of antimetabolites, inferiorly located bleb, avascular bleb and history of diabetes mellitus (Soltau et al. 2000; Jampel et al. 2001; Matsuo et al. 2002; Hori et al. 2009).

We found that aphakia or pseudophakia was significantly associated with the development of a stage III or stage IIIb bleb-related infection, which was consistent with previous reports. Ciulla et al. (1997) identified 10 blebitis and 26 late endophthalmitis cases; six cases (60%) were phakic in the former, whereas 20 cases (77%) had prior cataract surgery in the latter series. In a series of cases reported by Poulsen & Allingham (2000), 12 cases (71%) of endophthalmitis after glaucoma filtering surgery were pseudophakic. A possible interpretation of our result in light of these previous reports (Ciulla et al. 1997; Poulsen & Allingham 2000) is that once the causative agents enter into the eyeball, they can swiftly invade into the vitreous in pseudophakic or aphakic eyes. Another important finding in the present study is that stage III bleb-related infection has significantly worse visual prognosis and poorer IOP control, which is consistent with previous reports (Ciulla et al. 1997; Song et al. 2002; Busbee et al. 2004). Some stage III infections develop quite rapidly and can even reach stage IIIb within 24 hr. Thus, patient education is essential, particularly in pseudophakic or aphakic cases, with special emphasis on attention to the early signs and symptoms of bleb-related infection. In addition, the use of antibiotics for emergencies should be emphasized to all patients with a functioning bleb,

Table 6. Results of the multiple logistic regression analysis for 0.5 unit change in logMAR.

Variable	Value	Odds ratio	95% Confidence interval	p-value
Stage III	Yes	9.26	2.03–26.53	0.002
	No	1		
Culture	Positive	6.29	1.50–26.40	0.012
	Negative	1		

Factors not significantly associated: age, gender, interval between surgery and development of infection, detection of *Streptococcus* species, history of bleb leakage, type of conjunctival incision, and preinfection intra-ocular pressure.

Table 7. Results of the multiple logistic regression analysis for intra-ocular pressure (IOP) elevation of 5 mmHg or greater.

Variable	Value	Odds ratio	95% Confidence interval	p-value
Stage III	Yes	8.33	2.51–27.71	0.001
	No	1		

Factors not significantly associated: age, gender, interval between surgery and development of infection, detection of bacteria, detection of *Streptococcus* species, history of bleb leakage, type of conjunctival incision, and preinfection IOP.

Table 8. Results of the multiple logistic regression analysis for associated factors with stage III.

Variable	Value	Odds ratio	95% Confidence interval	p-value
For stage III				
Lens status	Pseudophakic/Aphakic	2.85	1.22–6.66	0.015
	Phakic	1		
For stage IIIb				
Lens status	Pseudophakic/Aphakic	6.30	2.32–17.13	0.000
	Phakic	1		

Factors not significantly associated: age, gender, interval between surgery and development of infection, detection of bacteria, detection of *Streptococcus* species, history of bleb leakage, type of conjunctival incision, and preinfection intra-ocular pressure.

including in cases with pseudophakia or aphakia.

As previously reported (Yamamoto et al. 2012), the lack of a predetermined protocol for both treatment and bacterial culture is a major limitation to the present study. Certain missing data during the follow-up period have rendered some of our conclusions more tentative. In addition, this study was conducted in a particular region of the world and may not be generalizable to other populations. However, we believe that the results obtained are still relevant due to the large number of cases analyzed and are useful in determining the indication for trabeculectomy.

One of the most striking results of this collaborative study was that severe visual disturbance resulted in many cases following development of bleb-related infection. The proportion of 20/400 or less was 16% in eyes in which preinfection visual acuity was at least 20/40. Some of them were enucleated or ended up with phthisis bulbi. We should warn both patients and ophthalmologists against this sight-threatening complication. It is recommended to prescribe antibiotics in advance and ask the patients to administer it if they notice some symptoms of infection. Conjunctival hyperemia or conjunctivitis in eyes with a history of glaucoma filtration surgery should be treated as a medical emergency. Leaking blebs should be surgically treated before they become infected. Prevention, early detection and treatment are highly desirable to prevent severe visual loss caused by bleb-related infection from occurring.

The present study clearly indicates that the earlier the stage of the infection, the better the prognosis. Severe visual impairment is inevitable in some stage III infections and preventative measures are required to reduce the visual compromise caused by bleb-related infection, especially in pseudophakic or aphakic cases. Early consultation and treatment and thorough patient education are clearly essential to ensure the best prognosis in bleb-related infection. The JGSSBI has revealed important characteristics, outcomes and prognostic factors of bleb-related infections which have been reported here and in our previous report (Yamamoto et al. 2012). It is our hope that these findings will be of practical benefit to both practitioners and our patients.

Acknowledgments

The authors have no proprietary interest in the material described in this manuscript. The researcher list of the JGSSBI is available on the homepage of Acta Ophthalmologica related to a paper listed in the reference (Yamamoto et al. 2012).

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ORIGINAL RESEARCH

Morphological analysis of age-related iridocorneal angle changes in normal and glaucomatous cases using anterior segment optical coherence tomography

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Purpose: To analyze age-related morphological changes of the iridocorneal angle in normal subjects and glaucomatous cases, using anterior segment optical coherence tomography (AS-OCT).

Methods: This study involved 58 eyes of 58 open-angle glaucoma cases and 72 eyes of 72 age-matched normal-open-angle control subjects. Iridocorneal angle structures in nasal and temporal regions and anterior chamber depth (ACD) were measured using AS-OCT. Axial length and refractive error were measured by use of an ocular biometer and auto refractor keratometer. Angle opening distance (AOD), angle recess area (ARA), and trabecular-iris space area (TISA), measured at 500 μm (TISA500) and 750 μm (TISA750) distant from the scleral spur, were calculated, in the nasal and temporal regions. A new index, the peripheral angle frame index (PAFI), which represents the peripheral angle structure, was proposed, and was defined as (TISA750-TISA500)/TISA500.

Results: Refractive power in the glaucoma cases was less than in control cases ($P<0.0001$). Axial length ($P<0.0001$) and ACD ($P=0.0004$) were longer and deeper, respectively, in the glaucoma cases, compared with the control cases. In both control and glaucoma groups, ACD, AOD, ARA, and TISA decreased linearly in an age-dependent manner, while PAFI stayed at relatively constant values throughout the age distribution. AOD in the glaucoma group was longer than in the control group, in both the temporal and nasal regions; ARA and TISA were larger in the glaucoma than in the control group. However, no significant differences in nasal or temporal PAFI were found between the glaucoma and control groups.

Conclusion: The findings of this study show that AS-OCT is useful for the quantitative evaluation of age-related changes in peripheral angle structure in glaucoma and control cases.

Keywords: iridocorneal angle structures, anterior segment optical coherence tomography, AS-OCT, peripheral angle frame index, PAFI

Introduction

Previously used methods for evaluation of the anterior chamber angle of the eye, such as slit-lamp biomicroscopy, or gonioscopy, are known to be subjective. Ultrasound biomicroscopy (UBM) reportedly allows for a quantitative measurement of the anterior chamber angle.[1–4] However, due to the fact that UBM is a contact measurement, the utilization of this method is limited to patient screening, and for immediate postoperative use. Anterior segment optical coherence tomography (AS-OCT) is a new imaging technology that reportedly provides a non-contact quantitative evaluation of the anterior segment of the eye.[5–12] The recently released Visante® OCT version 2.0.1.88 system software

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(Carl Zeiss Meditec AG, Jena, Germany) includes several features that were previously not available. Of those, an enhanced anterior segment single mode provides an image averaged from four consecutive anterior segment scans, to improve contrast. Moreover, the new version includes a semiautomated program to assess the anterior chamber angle. One advantage of using AS-OCT for assessment of the anterior chamber angle is that image acquisition and subsequent measurement can be performed under light-controlled conditions, with patients in the sitting position, and without alternation of angle structure by irregular lighting and physical contact. However, some disadvantages have also been reported, such as poor agreement between gonioscopic and AS-OCT assessment.[7,13] In addition, reproducibility of the AS-OCT findings for evaluation of the anterior chamber angle has been questioned. In particular, the reproducibility of inferior quadrant findings is reported to be poor, due to variability of scleral spur placement; reproducibility of anterior chamber angle parameters in nasal and temporal angles was better than in the inferior quadrants.[7,14,15]

Recently, there have been many studies published that report the use of AS-OCT for assessment of the anterior segment.[15–19] Nongpiur et al used AS-OCT images to evaluate anterior chamber width, defined as the horizontal scleral spur-to-spur distance, and found that it was smaller in angle-closure patients than in open-angle patients.[20] Moghimi et al also found that the anterior segment was crowded in closed-angle eyes, compared with open-angle eyes.[21] Several cross-sectional studies have assessed the influence of age on anterior chamber depth (ACD).[22–24] However, there are few reports about age-related changes of the peripheral angle structure.[25] In this study, a new index, termed the peripheral angle frame index (PAFI), was developed and proposed for representing the peripheral angle structure. PAFI is defined as the difference between trabecular-iris space area (TISA) measured at a distance of 750 μm (TISA750) and TISA measured at a distance of 500 μm (TISA500), divided by TISA500. We used this index to investigate how peripheral angles changed with age. The TISA parameter was used instead of the angle recess area (ARA) because it has been proposed that ARA may be less sensitive for identifying narrow angles in eyes with deep angle recess.[26–28] The aim of this study was to analyze the cross-sectional, age-related morphological changes of the iridocorneal angle in normal subjects, and in open-angle glaucoma patients, using AS-OCT.

Materials and methods

This study involved 58 eyes of 58 open-angle glaucoma patients (35 females, 23 males) and 72 eyes of 72 age-matched, normal open-angle, volunteer control subjects (49 females, 23 males), diagnosed as non-glaucomatous by glaucoma specialists at the Glaucoma Clinic of Kyoto Prefectural University of Medicine, Kyoto, Japan, from 2007 to 2009. All 130 subjects included in the study were of Japanese race. The diagnostic criteria for normal-tension glaucoma (NTG) were 1) normal iridocorneal open angle, 2) no evidence of high intraocular pressure (IOP) (IOP ≤21 mmHg), 3) glaucomatous changes in the visual field, with optic nerve cupping, and 4) absence of other optic neuropathies. For the diagnosis of primary open-angle glaucoma (POAG), the criteria were the same as with (1), (3), and (4) above, but with a maximum IOP >21 mmHg. Both NTG and POAG were diagnosed according to the guidelines of the Japan Glaucoma Society[29] and the European Glaucoma Society.[30]

The normal open-angle control subjects comprised individuals with IOP ≤21 mmHg in both eyes, as measured by Goldmann applanation tonometry with normal optic discs, with open angles on gonioscopy, and with no suspicion of any form of glaucoma. When subjects exhibited a narrow angle equal to grade 2 or less, as determined using the Van Herick system, they were excluded from the study.[31]

Informed consent was obtained from all participants prior to their involvement in the study, in accordance with the tenets set forth in the Declaration of Helsinki.

In all eyes, Visante OCT was used in the enhanced high-resolution mode ("high-resolution corneal" protocol) to measure iridocorneal angle structures (Figure 1A–C), and in the enhanced anterior segment mode ("enhanced anterior segment single" protocol) to measure ACD (Figure 1D). AS-OCT images were obtained in darkroom lighting conditions.

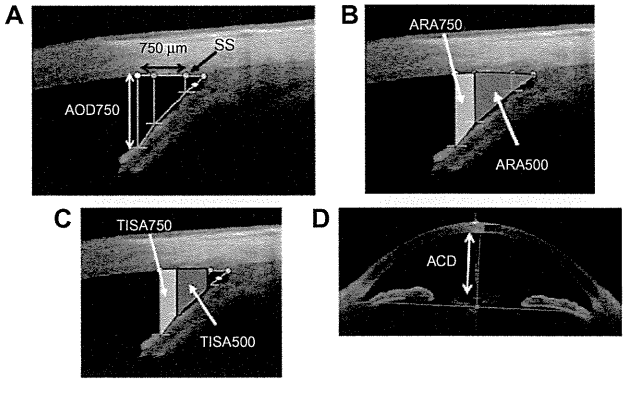

Figure 1 Anterior segment optical coherence tomography images.
Notes: Iridocorneal angle structures measured by use of the enhanced high resolution mode of anterior segment optical coherence tomography. The images show (**A**) AOD750, (**B**) ARA500/750, (**C**) TISA500/750, and (**D**) ACD.
Abbreviations: SS, scleral spur; AOD750, anterior opening distance at 750 μm; ARA500/750, angle recess area at 500/750 μm; TISA500/750, trabecular-iris space area at 500/750 μm; ACD, anterior chamber depth.

The enhanced anterior segment mode image was obtained first, and then nasal-side and temporal-side images were obtained using the enhanced high resolution mode. Images were captured at the nasal and temporal angle quadrants (3- and 9-o'clock meridians; nasal–temporal angles at 0°–180°). Internal fixation was used in all subjects. With each subject, the procedure was performed first on the right eye, and then on the left eye. Axial length and refractive error were measured using the IOL Master (Carl Zeiss Meditec AG), and the RKT-7700 autorefractor keratometer (Nidek, Gamagori, Japan), respectively. Angle-opening distance (AOD), at 500 μm and 750 μm distant from the scleral spur (AOD500 and AOD750, respectively) (Figure 1A), ARA at 500 μm and 750 μm distant (ARA500 and ARA750, respectively) (Figure 1B), and TISA at 500 μm and 750 μm distant (TISA500 and TISA750, respectively) (Figure 1C), were automatically calculated, in the nasal and temporal regions of the right eye of each subject, using Visante OCT device software. When the right eye could not be evaluated, due to extended measurement time required to capture the image, the left eye was used. Right eye data was used whenever possible. Subjects of whom the images produced were of inadequate quality, in whom there was difficulty in detecting the scleral spur, or in whom there had been previous surgical intervention that affected angle structure (such as cataract surgery or laser iridotomy), were excluded from the study.

Iridocorneal angle structures, axial length, and refractive error, in the nasal and temporal regions, were then compared between glaucoma patients against normal control subjects. The Student's *t*-test was used for statistical analysis. The slopes of the iridocorneal structural parameters were derived, to assess age-dependent differences, using a linear mixed effect model. Based on the absolute slopes of the various AS-OCT parameters, normalized slopes were calculated, as absolute slope divided by mean parameter value, in order to compare relative rates of change of all parameters.[25] A *P*-value lower than 0.05 was considered statistically significant.

Results

The mean ages of the 58 open-angle glaucoma patients (POAG: 20 cases, NTG: 38 cases) and 72 age-matched normal control subjects were 59.5±13.8 years and 62.1±12.8 years, respectively. Refractive power in the glaucoma group was lower than in control subjects ($P<0.0001$). Axial length ($P<0.0001$) and ACD ($P=0.0004$) were longer and deeper, respectively, in glaucoma cases, compared with control subjects (Table 1).

Table 1 Comparison of demographic and examination data between glaucoma patients and normal controls

	Glaucoma (n=58)	Control (n=72)	*P*-value
Age (years)	59.5±13.8	62.1±12.8	0.26
Male:female	23:35	23:49	0.46
Right:left	33:25	53:19	0.062
Refractive power (D)	−3.90±4.46	0.49±3.12	<0.0001[a]
Axial length (mm)	25.9±2.6	24.1±1.7	<0.0001[a]
ACD (mm)	2.96±0.40	2.74±0.30	0.0004[a]

Notes: [a]$P<0.05$ (independent samples *t*-test between glaucoma patients and normal controls). The values presented for age, refractive power, axial length and ACD are mean ± standard deviation.
Abbreviation: ACD, anterior chamber depth.

No differences in angle structure were observed between nasal or temporal regions in both glaucoma cases and control subjects. However, ACD ($P=0.0004$) (Table 1) and all peripheral angle parameter values (ACD, AOD, ARA, and TISA, but not PAFI) were higher in glaucoma cases than in control subjects (Table 2).

Table 3 shows the effect of age on AS-OCT parameters. All parameters (except PAFI) decreased linearly in an age-dependent manner in control subjects and, in nearly the same manner, in glaucoma cases. Of these parameters, the steepest slope was shown by AOD750, of temporal sectors (slope constant: −0.00992 mm/year, for glaucoma patients; and −0.00867 mm/year, for control subjects). The representative scatter plot of AOD750 measurement at the temporal sector is shown in Figure 2.

In this study, a normalized slope was used to compare all parameters. Normalized PAFI slope values were less than −0.005 au/year in measurements of both nasal and temporal regions, in both glaucoma and normal control subjects. In comparison with other peripheral angle parameters, in both groups, PAFI values were found to stay relatively constant throughout the age distribution (Table 3). Moreover, among all iridocorneal parameters, only PAFI showed no differences between glaucoma cases and normal control subjects (Table 3). Van Herick measurement was used in the temporal side; thus, the temporal-side PAFI shown is representative. As shown also in Figure 3, PAFI values stayed relatively constant throughout the age distribution, in both glaucoma and control groups.

Discussion

It is well known that many glaucoma patients are myopic and have a longer axial length. In this study, we found significant myopia-related differences in refractive error, axial length, and ACD in glaucoma patients (Table 1). In glaucoma cases and control subjects, no significant differences were found

Table 2 Comparison of angle structure between glaucoma patients and normal controls

	Glaucoma (n=58)		*P*-value	Control (n=72)		*P*-value		
	Temporal (mean ± SD)	Nasal (mean ± SD)	T vs N	Temporal (mean ± SD)	Nasal (mean ± SD)	T vs N	G vs C-T[a]	G vs C-N[a]
Angular A (degrees)	47.3±11.7	44.8±11.5	0.25	39.2±11.3	37.5±12.3	0.40	<0.0001	0.0008
AOD500 (mm)	0.60±0.25	0.54±0.22	0.21	0.44±0.20	0.42±0.20	0.49	<0.0001	0.0008
AOD750 (mm)	0.82±0.31	0.75±0.26	0.18	0.61±0.25	0.58±0.24	0.43	<0.0001	0.0002
ARA500 (mm^2)	0.26±0.11	0.24±0.10	0.23	0.20±0.08	0.20±0.09	0.42	0.0006	0.0055
ARA750 (mm^2)	0.44±0.18	0.40±0.15	0.21	0.34±0.13	0.32±0.14	0.41	0.0002	0.0016
TISA500 (mm^2)	0.22±0.09	0.20±0.08	0.23	0.17±0.06	0.16±0.07	0.46	0.0003	0.0030
TISA750 (mm^2)	0.40±0.16	0.36±0.14	0.21	0.30±0.12	0.28±0.12	0.44	0.0001	0.0011
PAFI (au/year)	0.82±0.09	0.82±0.11	0.98	0.79±0.14	0.79±0.14	0.91	0.13	0.19

Note: [a]$P<0.05$ (independent samples *t*-test between glaucoma patients and normal controls), all except PAFI.

Abbreviations: T vs N, temporal versus nasal; G vs C-T, glaucoma patients versus normal controls in temporal regions; G vs C-N, glaucoma patients versus normal controls in nasal regions; AOD500/750, angle-opening distance at 500/750 μm; ARA500/750, angle recess area at 500/750 μm; TISA500/750, trabecular-iris space area at 500/750 μm; PAFI, peripheral angle frame index; SD, standard deviation; au, arbitrary unit.

in all peripheral parameters (AOD, ARA, and TISA), in temporal and nasal regions. However, when those parameters were compared between glaucoma and control subjects, all values, except PAFI, were found to be higher in glaucoma cases (Table 2), reflecting that glaucoma patients had more severe myopia.

ACD, AOD, ARA, and TISA were found to decrease linearly in an age-dependent manner in both glaucoma cases and control subjects, mirroring the findings of previous reports about age-related decreases in ACD, ARA, and TISA in Asian people.[18,25] However, to the best of our knowledge, ours is the first study to report upon age-related changes in ACD, ARA, and TISA in glaucomatous Asian patients.

In this study, a novel index, PAFI, was used in order to investigate how peripheral configuration changes with age. The findings of a previous study show that ACD decreases with age, due to age-related lens thickening.[21] Thus, the extent of cataract may affect peripheral configuration. Yet, we had no knowledge about how this affects peripheral angle structure. Moreover, we also wanted to know how changes in iris structure affect angle structure (because iris configuration changes with age due to muscle weakness and tension of the iris). Hence, we measured peripheral length parameters at 500 μm and 750 μm distant from the scleral spur. Being able to compare the values obtained at 500 μm and 750 μm distance from the scleral spur, with participants of various ages, we could elucidate age-related changes in these values. If AOD500 decreases more severely with age than AOD750, it indicates that the anterior chamber is shallower from the more peripheral area. However, if AOD500 and AOD750

Table 3 Absolute and normalized slopes of anterior segment parameters in glaucoma and control subjects

	Glaucoma (n=58)			Control (n=72)		
	A-slope	N-slope	*R*	A-slope	N-slope	*R*
ACD (mm/year)	−0.00599	−0.00202	−0.329	−0.00148	−0.00540	−0.429
Temporal AOD500 (mm/year)	−0.00599	−0.00998	−0.387	−0.00742	−0.0169	−0.480
Temporal AOD750 (mm/year)	−0.00992	−0.0121	−0.580	−0.00867	−0.0142	−0.504
Temporal ARA500 (mm^2/year)	−0.00270	−0.0104	−0.333	−0.00200	−0.0100	−0.334
Temporal ARA750 (mm^2/year)	−0.00415	−0.00943	−0.350	−0.00453	−0.0133	−0.414
Temporal TISA500 (mm^2/year)	−0.00214	−0.00972	−0.321	−0.00197	−0.0116	−0.388
Temporal TISA750 (mm^2/year)	−0.00413	−0.0103	−0.344	−0.00397	−0.0142	−0.447
Temporal PAFI (au/year)	−0.000381	−0.000465	−0.258	−0.00356	−0.00451	−0.316
Nasal AOD500 (mm/year)	−0.00630	−0.0117	−0.355	−0.00557	−0.0133	−0.411
Nasal AOD750 (mm/year)	−0.00809	−0.0108	−0.422	−0.00967	−0.0167	−0.519
Nasal ARA500 (mm^2/year)	−0.00199	−0.00829	−0.279	−0.00229	−0.0115	−0.340
Nasal ARA750 (mm^2/year)	−0.00369	−0.00922	−0.330	−0.00203	−0.00634	−0.398
Nasal TISA500 (mm^2/year)	−0.00178	−0.00890	−0.309	−0.00203	−0.0127	−0.366
Nasal TISA750 (mm^2/year)	−0.00347	−0.00964	−0.350	−0.00397	−0.0142	−0.418
Nasal PAFI (au/year)	−0.00119	−0.00145	−0.252	−0.00377	−0.00477	−0.343

Abbreviations: *R*, correlation coefficient; A-slope, absolute slope; N-slope, normalized slope; ACD, anterior chamber depth; AOD500/750, angle-opening distance at 500/750 μm; ARA500/750, angle recess area at 500/750 μm; TISA500/750, trabecular-iris space area at 500/750 μm; PAFI, peripheral angle frame index; au, arbitrary unit.

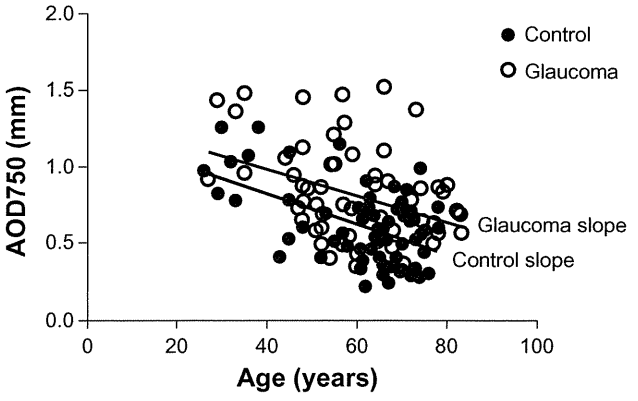

Figure 2 Relationship between temporal AOD750 and subject age in glaucoma and normal subjects.
Notes: Scatter plot showing distribution of temporal AOD750, determined by anterior segment optical coherence tomography. The lines show absolute slope in both glaucoma and control groups.
Abbreviation: AOD750, angle opening distance at 750 μm.

decrease in a similar manner, it indicates that the anterior chamber area may decrease at the same rate as the peripheral area, as in a more central part of the peripheral region. Thus, we posit that using this new index will help in understanding changes of the peripheral angle. A normalized slope was used to compare all parameters; PAFI was found to stay within relatively constant values throughout the age distribution, in both the glaucoma and control groups (Table 3). These findings suggest that the peripheral area will decrease at the same rate with age. In addition, PAFI was the only parameter with no difference found between the glaucoma and control groups (Table 3), as no age-related change of the peripheral angle structure was found in either group.

Ideally, the effect of age on ACD and other peripheral angle parameters is best studied by means of longitudinal

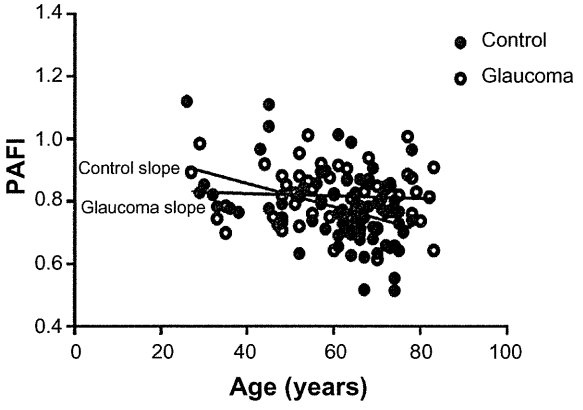

Figure 3 Relationship between PAFI and subject age in glaucoma and normal subjects.
Notes: The scatter plot showing distribution of temporal PAFI, determined by AS-OCT. The lines show absolute slope in both glaucoma and control groups. PAFI was found to stay within relatively constant values throughout the age distribution.
Abbreviation: PAFI, peripheral angle frame index; AS-OCT, anterior segment optical coherence tomography.

follow-up measurements, to determine whether aging people do indeed show gradual reduction in parameters based on quantitative measures, such as AS-OCT. Further study is needed to verify long-term changes of peripheral parameters.

It should be noted that this study has some limitations. First, this was a clinic-based study, not a population-based study. Second, there may have been some selection bias in regard to the samples, as glaucoma subjects were recruited from the glaucoma clinic of our university hospital.

It should also be noted that since all of the subjects involved in this study were Japanese, the results may not be applicable to other racial groups. Moreover, only open-angle participants were analyzed in this study; the results might differ from those obtained with other types of glaucoma or control subjects with shallow eyes. In addition, subjects who had undergone cataract surgery were excluded from the study, so that most parameters were measured with the participants own lens; the extent of cataract may have affected the results.

Finally, although AS-OCT was found to be useful, its use is associated with some limitations. For example, in many cases, data cannot be analyzed, due to inability to find the sclera spur.[14,32,33] In this study, only temporal-region and nasal-region data was used, as it is reportedly extremely difficult to obtain reproducible images in the superior and inferior regions.[15] It is hoped that in the future, AS-OCT devices will be able to provide improved, higher-quality images, and that peripheral angle parameters can be compared with other biometrics.[34]

In summary, the findings of this study show that AS-OCT is useful for the quantitative evaluation of age-related changes of the peripheral angle structure.

Disclosure

The authors report no conflicts of interest associated with this work.

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私の緑内障薬チョイス

企画・監修　山本哲也

8. 合剤（ごうざい）の功罪（こうざい）

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合剤は便利である．点眼回数が少なくて済み，点眼間隔も考えなくてよい．しかし必ずしも良いことずくめではない．アドヒアランス不良患者に有効だが，忘れてしまえばまったくのゼロ．副作用が出たら両方の薬が使えなくなるし，濃度を変える「さじ加減」ができなくなってしまう．やはり症例ごとに適否を熟慮すべきであろう．

□合剤花盛り

世は合剤が花盛り．緑内障のみならず高血圧[1]などの全身疾患薬でも合剤が頻用されている（表1）．最近はとくに緑内障分野において数多くの合剤が上市されており，製薬企業も盛んにプロモーションに注力している．ザラカム®（ラタノプロストとチモロールの合剤），デュオトラバ®（トラボプロストとチモロールの合剤），コソプト®（ドルゾラミドとチモロールの合剤），アゾルガ®（ブリンゾラミドとチモロールの合剤）の4剤が平成25年12月末現在，わが国で使用可能な緑内障関連の合剤であるが，世界的には表2に示すように，ほかにも数多くの種類の合剤が使用されており，今後さらに多くの合剤が日本でも使用可能になる可能性が高い．このように合剤がよく使われるようになってきた理由はなんであろうか．

表1　日本高血圧学会高血圧治療ガイドライン（表3-2）[1]

医療者と患者が共通の理解に到達し，パートナーとして治療を行う方法
- 患者と高血圧のリスク及び治療の効果について話し合う．
- 治療計画について書面及び口頭で明確に説明．
- 治療計画を患者の生活習慣に合わせる．
- 患者の配偶者及び家族に高血圧及び治療計画に関して情報を提供．
- 家庭血圧測定や飲み忘れ防止法などの行動論的方法を活用．
- 副作用によく注意し，必要に応じて用量変更，薬剤切替えを行う．
- 1日の服薬錠数，回数を減らし，合剤の使用を含め，処方を簡素化．
- 服薬忘れとその要因について話し合う．
- 服薬継続，受診継続，生活習慣修正の支援システムを提供．
- 生涯にわたる治療の費用と効果を説明．

高血圧治療ガイドラインにおいても合剤の使用を推奨している．

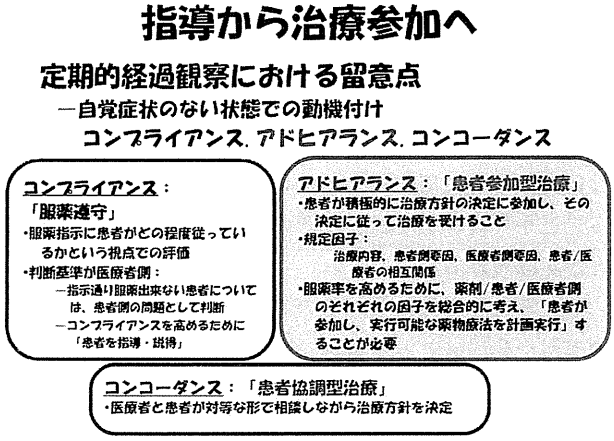

図1　服薬指導から治療参加へ
コンプライアンス，アドヒアランス，コンコーダンスの違いを説明した図．

□合剤のメリット

合剤使用の最大のメリットはアドヒアランスの改善である．従来はコンプライアンス（服薬遵守），最近ではアドヒアランス，コンコーダンス（図1）などの呼称で呼ばれることが多いが，緑内障のような自覚症状のない慢性進行性疾患においてはとくに重要とされる．実際，視野障害が進行していない群ではアドヒアランスが良好に保たれているのに対して，視野進行群ではアドヒアランス不良例が多いことが報告されている[2]．抗緑内障薬における合剤使用のメリットは，総服薬回数の減少，服薬間隔の考慮不要，薬剤管理の手間の減少，服薬ミス（片方忘れなど）の防止などの利便性があるとともに，

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表 2　抗緑内障薬の合剤一覧（海外も含む）

合　剤			PG 製剤	β 遮断薬	CAI*	その他
ザラカム®	(2001.8)	1/日	Lat	Tm		
デュオトラバ®	(2006.4)	1/日	Trav	Tm		
Ganfort®	(2006.5)	1/日	Bmt	Tm		
タプコム®	(2013)	1/日	Taf	Tm		
コソプト®	(1998.8)	2/日		Tm	Dor	
アゾルガ®	(2008.12)	2/日		Tm	Brnz	
Combigan®	(2007.1)	2/日		Tm		Brim
Simbrinza®	(2013.4)	2/日			Brnz	Brim

Lat：latanoprost, Trav：travoprost, Bmt：bimatoprost, Taf：tafluprost, Tm：timolol, Dor：dorzolamide, Brnz：brinzolamide, Brim：brimonidine

*炭酸脱水酵素阻害薬：carbonic anhydrase inhibitor

平成 25 年 12 月末現在，わが国において使用できる抗緑内障薬合剤はザラカム® とデュオトラバ®，コソプト® とアゾルガ® の 4 剤であり，いずれもチモロールとの合剤となっている．

単剤組み合わせよりも安価であることが多いために経済性に優れる点，塩化ベンザルコニウム曝露回数が減少することから角膜上皮障害などの副作用も軽減される点などがあげられる．

もちろん患者側にとってのメリットだけではなく，医療機関や薬局にとってもメリットがある．複数の薬剤を処方することに比べれば，処方の手間や間違いのリスクは軽減するし，保管スペースも節約される．さらに製薬企業にとっても，新規薬剤を開発することに比べれば，未知の副作用発現による開発中止のリスクが低いため，開発コストの節約になるだけでなく，他社に対するジェネリック対策ともなる．

本当に万人に対してすべて良いのか

このように合剤は患者，医療機関，製薬企業のすべてに対してメリットをもたらす，万人に対して好ましいものなのであろうか．本来ならば点眼回数の異なる点眼薬を合わせている場合（1 日 1 回点眼と 2 回点眼の合剤など）には，単剤組合せをしっかりと点眼した場合と比べてどうしても効果が弱くなる．また，合剤では各薬剤の配合割合が固定されているために投薬の自由度が喪失するし，プロスタグランジン（prostaglandin：PG）製剤と β 遮断薬の合剤については本来，夜に点眼する PG 製剤と朝に点眼する β 遮断薬を合わせているため，1 日 1 回とした場合には点眼時間の問題が生じる．さらに副作用が生じた場合に原因の特定が困難となり，いずれの成分によるものか，もしくは成分間の相互作用によるものか判断ができない．とくに今年米国において FDA に認可された Simbrinza® 以外は，すべての合剤にチモロールを含んでおり，全身副作用や禁忌，眼表面麻酔作用，long-term drift などチモロールの特徴は以前から知られているにもかかわらず，合剤となっているがためにこれらの存在を忘れてしまいがちとなる．チモロール以外の β 遮断薬が選択できないことは，薬剤選択の幅を狭めてしまうことにほかならない．アドヒアランスの改善に資するとはいえ，アドヒアランスに問題のある症例では，1 日 1 回の投与ですら忘れてしまうリスクが常に存在し，そうなると丸々 1 日は無治療の時間帯が生じてしまうことになる．すなわち，合剤は服薬忘れの影響が単剤組合せの場合よりも大きいといえる．

患者ごとに考えるべき

β 遮断薬の副作用を声高に喧伝していたメーカーが，掌を返したようにチモロールの含有されている合剤を宣伝するなど，メーカーの良識を疑うことがある．患者にとって治療法の選択肢が増えるのは喜ばしいが，複雑になりすぎて次のステップに進む時機を逸しない注意が必要である．メーカーの宣伝を鵜呑みにせず，合剤の誘惑に縛られることなく，それぞれの患者ごとに最良の治療薬の組合せを考えるようにしたい．

文　献

1) 日本高血圧学会高血圧治療ガイドライン作成委員会：高血圧治療ガイドライン 2009．日本高血圧学会，2009
2) Rossi GCM, Pasinetti GM, Scudeller L et al：Do adherence rates and glaucomatous visual field progression correlate? *Eur J Ophthalmol* **21**：410-414, 2011

白内障術後に生じた遅発型水晶体起因性続発緑内障の4例

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Four Cases of Lens-Induced Glaucoma That Developed Many Years after Lens Reconstruction Surgery

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白内障術後10年以上を経て発症し，複数の発症メカニズムの関与が示唆された水晶体起因性続発緑内障症例を4例経験したので報告する．症例1，2は抗炎症および抗緑内障薬点眼，内服加療にて軽快したが，経過中にステロイド緑内障を併発した．症例3は超音波生体顕微鏡にてプラトー虹彩形状を認めレーザー隅角形成術を施行した．症例4は急性緑内障発作，線維柱帯切除術/白内障手術の既往があり，眼内レンズ脱臼を認め，観血的加療により眼圧下降を得た．遅発型の水晶体起因性続発緑内障にはさまざまな発症メカニズムが関与するため，眼圧上昇機序をよく理解して適切な治療を行う必要がある．

Lens-induced secondary glaucoma sometimes occurs several years after cataract surgery, laser capsulotomy or penetrating corneal injury. Many mechanisms that result in increased intraocular pressure (IOP) are thought to be combined in this condition, such as blockage of fluid outflow through the trabecular meshwork by small residual lens particles, inflammation caused by lens anaphylactic reaction, angle closure mechanism due to residual swollen lens substances, and steroid therapy itself. Here we report 4 cases of lens-induced secondary glaucoma with combined mechanisms that developed several years after cataract surgery. Cases 1 and 2 responded well to treatment with steroid and anti-glaucoma eyedrops, but resulted in steroid-induced glaucoma during the time course. In Cases 3 and 4, residual lens particles or intraocular lens dislocation worsened the glaucoma, necessitating surgery to control IOP. Physicians should be aware of the existence of these several mechanisms, and choose the suitable therapy accordingly.

〔Atarashii Ganka (Journal of the Eye) **30**(4)：569～572，2013〕

Key words：水晶体起因性続発緑内障，白内障手術，残存皮質，ステロイド緑内障，アナフィラキシー反応．lens-induced glaucoma, cataract surgery, residual lens particles, steroid glaucoma, lens anaphylactic reaction.

はじめに

水晶体起因性続発緑内障は時に白内障術後や後嚢切開，穿孔外傷後数年を経て発症することがある．眼圧上昇機序はさまざまであり，残存水晶体蛋白による線維柱帯閉塞やアナフィラキシー反応，膨化水晶体による隅角閉塞，ステロイド薬による眼圧上昇など複数の発症メカニズムが関与することが知られている．

今回，白内障術後10年以上を経て発症し，複数の発症メカニズムの関与が示唆された水晶体起因性続発緑内障症例を4例経験したので，その特徴と治療経過について報告する．

Ⅰ　症　　例

〔**症例1**〕　30歳，男性．

既往歴：10年前に両眼白内障手術歴（右眼は後嚢破損）．

現病歴：6時間前からの右眼痛，霧視，嘔気を主訴に京都府立医科大学眼科（以下，当科）救急受診．初診時右眼の毛様充血と角膜浮腫，軽度前房炎症を認め，後房に残留水晶体皮質を認めた（図1a）．眼圧は右眼60mmHg，左眼14

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mmHg．隅角検査では下方180°にわたって周辺虹彩前癒着(peripheral anterior synechiae：PAS)および下方虹彩上に白色水晶体遺残物を認めた(図1b)．散瞳検査の結果，眼内レンズ(intraocular lens：IOL)は嚢外固定されており，残留水晶体上皮細胞の増殖/膨化とそれによるIOLの前方移動を認めた．PAS indexは50%であり上方は開放隅角であったため，眼圧上昇の主因は水晶体小片緑内障と考えられた．また，前房内に炎症所見を伴っており，水晶体アナフィラキシーによるぶどう膜炎の合併も考慮し，ラタノプロスト，0.5%マレイン酸チモロール，1%ドルゾラミドの点眼，アセタゾラミドの内服に加え0.1%ベタメタゾン点眼液右眼4回，プレドニゾロン15mg/日の内服による治療を開始した．治療開始5日目，毛様充血と角膜浮腫は消失し，眼圧も17mmHgまで下降した．隅角検査にてPASは残存するも下方虹彩上の白色水晶体遺残物は消失していた．アセタゾラミド内服を中止し0.1%ベタメタゾン点眼液，プレドニゾロン内服を減量し治療を継続したが，治療開始42日目，眼圧は21mmHgと再度上昇傾向を認め，ステロイド緑内障の合併が疑われたため，0.1%ベタメタゾン点眼液を0.1%フルオロメトロン点眼液に変更したところ眼圧は下降し，治療7カ月の時点で0.5%マレイン酸チモロールと0.1%フルオロメトロン点眼のみにて眼圧16mmHgに落ち着いている．

〔**症例2**〕 74歳，男性．

既往歴：20年前に両眼白内障手術歴あり，無水晶体眼．両眼ともに原発開放隅角緑内障の既往あり．右眼はすでに光覚なし，左眼は抗緑内障薬点眼3剤(ラタノプロスト，0.5%マレイン酸チモロール，1%ドルゾラミド)で眼圧15mmHg以下にコントロールされていた．視野は湖崎分類Ⅲb．

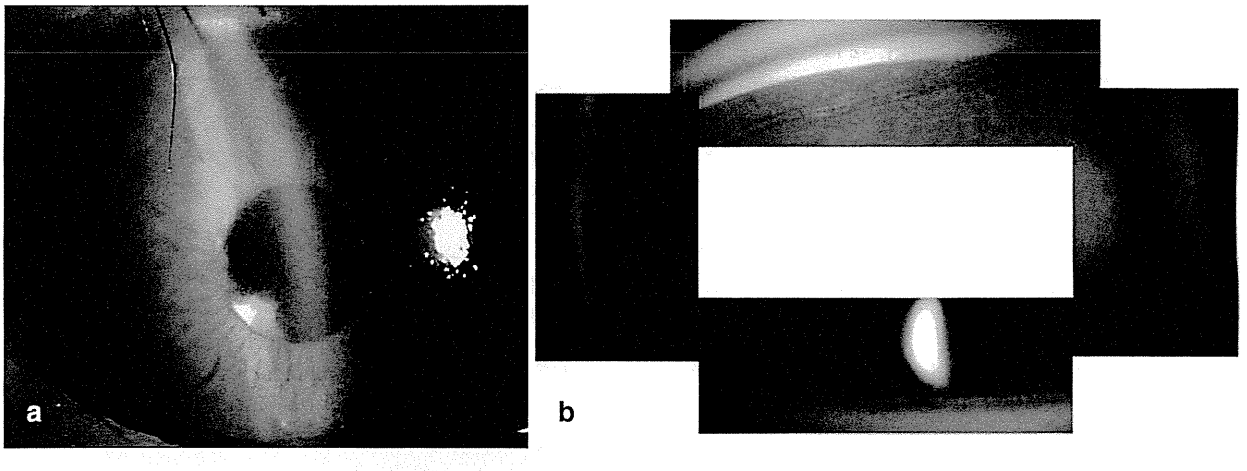

図1　症例1の前眼部および隅角写真
a：毛様充血，角膜浮腫をきたしている．前房は深く，白色の小物質が浮遊している．
b：症例1の隅角所見．下方180°にPASを認めた．

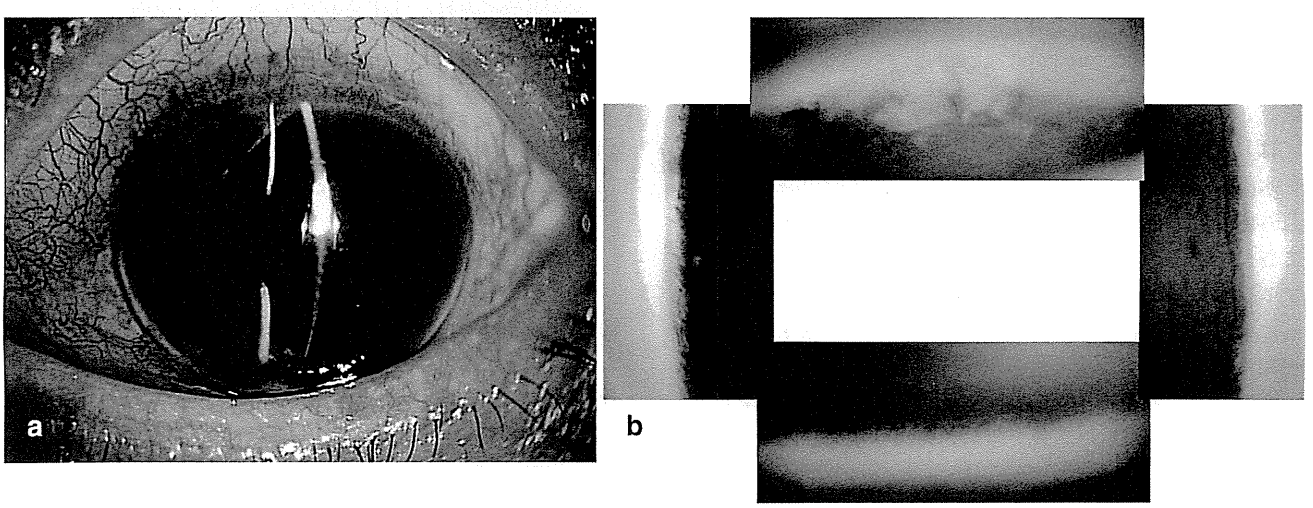

図2　症例2の前眼部および隅角写真
a：症例1同様に毛様充血，角膜浮腫をきたしている．
b：症例2の隅角所見．PASは認めず，虹彩上に白色物質を認める．

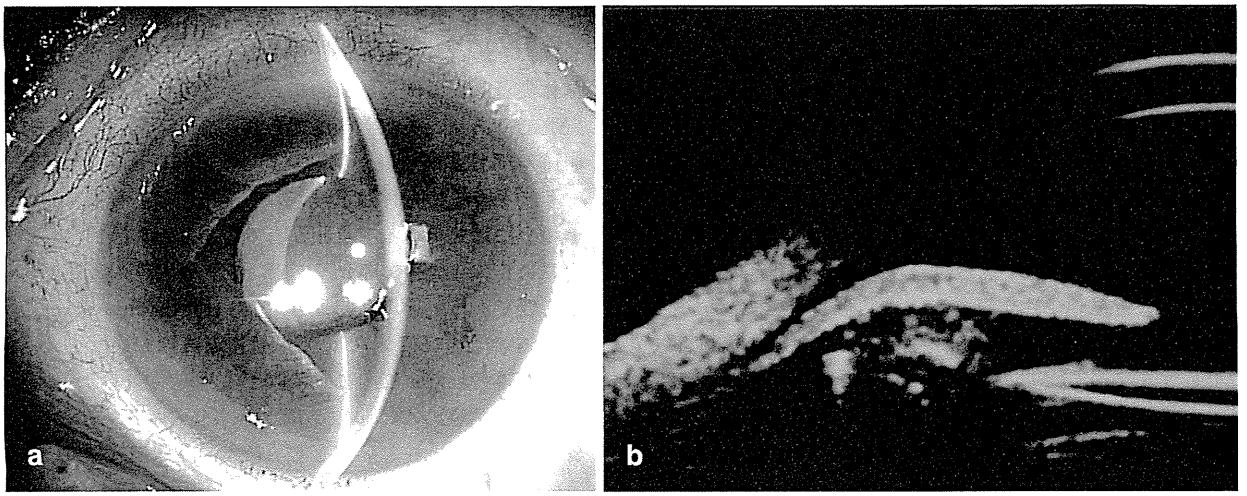

図3　症例3の前眼部写真およびUBM
a：前房深度は中央においては正常であるが，周辺部においてはきわめて狭くプラトー虹彩である．
b：症例3のUBM．残存水晶体小片により周辺部虹彩が前方に押されている．

現病歴：前日からの左眼視力低下を主訴に当科受診．初診時左眼毛様充血と角膜浮腫を認め（図2a），眼圧は右眼15 mmHg，左眼55 mmHg．隅角検査にてPASを認めず，虹彩上に白色塊状の水晶体遺残物を認めた（図2b）．消炎，眼圧下降を目的に0.1%ベタメタゾン点眼，アセタゾラミド内服を追加したところ，眼圧はいったん下降傾向を示したが，治療開始21日目に眼圧39 mmHgと再上昇した．ステロイド緑内障を疑い0.1%ベタメタゾン点眼を中止したところ，中止後1カ月で眼圧は24 mmHgまで下降し，8カ月後には14 mmHgと安定した．

〔**症例3**〕　74歳，男性．

既往歴：11年前に左眼網膜剝離に対し硝子体手術および水晶体再建術を施行．その後も網膜剝離を2回発症し計3回硝子体手術の既往あり．

現病歴：近医にて散瞳検査後より左眼眼圧が上昇し当科救急紹介受診．初診時左眼毛様充血と角膜浮腫を認め（図3a），眼圧は右眼10 mmHg，左眼60 mmHg．IOLは嚢内固定されており隅角検査にて左眼は全周性に隅角底が確認できなかった．超音波生体顕微鏡（ultrasound biomicroscope：UBM）にて全周性にプラトー虹彩形状を認め（図3b），一部では残留水晶体皮質の膨化により虹彩が前方へ圧排されていることが確認された．レーザー隅角形成術（laser gonioplasty：LGP）を施行したところ，耳側ならびに鼻側隅角は閉塞が開放され，眼圧は25 mmHgまで下降．0.1%ベタメタゾン，0.5%マレイン酸チモロール，1%ドルゾラミド点眼，アセタゾラミド内服により，治療開始3日目には眼圧は10 mmHg．その後，保存的経過観察にて8カ月後には8 mmHgと安定．

〔**症例4**〕　72歳，女性．

既往歴：右眼は12年前に急性緑内障発作に対しレーザー虹彩切開術（laser iridotomy：LI），線維柱帯切除術（trabeculectomy：TLE）および水晶体超音波乳化吸引術（PEA）＋IOL挿入術を施行されるも，眼圧コントロール不良にて前部硝子体切除術（A-vit）＋隅角癒着解離術（goniosynechialysis：GSL）の既往あり．6年前から右眼眼圧が再上昇し，1年前からは30 mmHg程度．左眼はLI既往があり2年前に白内障手術を受けた後は眼圧が安定した．

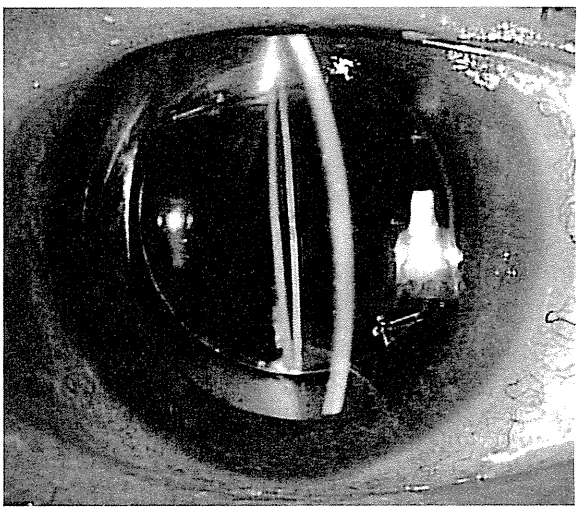

図4　症例4の前眼部写真
毛様充血と角膜浮腫を認め，IOLは前上方に脱臼している．

現病歴：右眼圧コントロール不良および角膜内皮細胞障害（932/mm^2）にて当科紹介受診．初診時右眼毛様充血と角膜浮腫を認め，眼圧は右眼33 mmHg，左眼12 mmHg．IOLは前上方に脱臼しており（図4），隅角検査にて全周性にPASを認めた．TLE＋IOL摘出/縫着術を施行，術中に水晶体遺残物を水晶体嚢とともに摘出した．眼圧は術翌日11

mmHgまで下降，4カ月後には18mmHgと安定している．

II 考　　察

一般的に水晶体起因性緑内障はその発症機序により，1）水晶体融解緑内障，2）水晶体小片緑内障，3）水晶体アナフィラキシーによる緑内障の3種類に分類される[1]．水晶体小片緑内障は水晶体嚢外摘出術または超音波水晶体乳化吸引術，Nd-YAGレーザーによる後嚢切開術，穿孔性水晶体外傷後に正常な水晶体小片が浮遊し線維柱帯間隙を閉塞することによって生じる緑内障であり，手術あるいは外傷後数日以内に発症することが多いとされる[1]．稀に数年を経てから生じることもあり[3,4]，過去には術後65年を経て発症した水晶体小片緑内障の報告もある[2]が，先天白内障術後に発症する症例が多い．通常，幼児や小児の水晶体にはheavy molecular weight protein（HMWP）がほとんど存在せず，75歳以上になると著しく増加することが報告されている[5]．HMWPはその高分子量のために線維柱帯を閉塞して眼圧上昇をひき起こす[1]．先天白内障術後の残存水晶体皮質が変性しHMWP濃度が増加してから，これらが小片化して水晶体融解緑内障および水晶体小片緑内障をひき起こすまでには長期の経過を要すると考えられている[2]．したがって，今回のように成人例の白内障手術長期経過後の発症の報告は少ない．

今回，筆者らが経験した4症例は，眼圧上昇においてそれぞれ異なるメカニズムの関与が示唆された．症例1では，眼圧上昇機序として水晶体小片緑内障（開放隅角緑内障）と閉塞隅角緑内障の両者が関与していたと考えられる．つまり，残存皮質から産生された水晶体小片や水晶体蛋白が線維柱帯間隙を閉塞，さらに残存皮質が膨化して形成されたSoemmering's ringがIOL越しに虹彩を前方移動させてPASを形成し，眼圧上昇に至ったと考えられる．Soemmering's ringは後発白内障の一種とされ，白内障術後に前後嚢が癒着してできた閉鎖腔内で水晶体上皮細胞が水晶体線維細胞に分化・再生して形成されるリング状の白色組織である[6]．近年では超音波水晶体乳化吸引術の普及により発生頻度は少なくなっているが，ECCE（嚢外摘出）後にはより高頻度にみられていた．Soemmering's ringが単独で閉塞隅角緑内障を発症したという報告は少なく，また眼圧上昇程度は，通常房水中に浮遊する水晶体小片の量と相関するとされている[1,7]．したがって，白内障術後に皮質残存が疑われる症例では長期経過後に眼圧が上昇する可能性があることを認識しておくことは非常に重要であり，そのような既往のある症例の診断，眼圧上昇機序を考えるうえで隅角検査やUBM検査は非常に有用であるといえる．症例2～4のように既往歴に緑内障を有している例でも白内障術後に眼圧上昇がよく認められること[8]から，元来の房水流出能が水晶体小片緑内障発症に関わっているとされる[1]．

これらの水晶体起因性緑内障に対する治療に関して，水晶体小片緑内障に対する過去の報告では，保存的治療のみで眼圧下降を得られたとの報告は少なく，最終的に残留水晶体皮質除去を施行している場合が多い．確かに治療として残留水晶体皮質除去は確実な原因除去となるが観血的な治療として侵襲的であり，炎症が軽度であればまずは保存的治療による眼圧下降および消炎が第一選択となる[1]．一方，水晶体アナフィラキシーの合併が示唆される症例では，軽度の眼圧上昇の場合にはステロイド点眼が有効であるが，長期にわたる場合には症例1，2のようにステロイド緑内障の合併にも注意が必要である．症例3ではplateau iris configurationを認めLGPを施行することで残留水晶体皮質除去をせずとも眼圧下降が得られた．このように眼圧上昇機序を正しく理解すれば保存的治療のみで眼圧下降が得られる症例も少なくない．保存的治療抵抗性の症例もしくは水晶体起因性緑内障を繰り返す症例，全周性PASを伴う症例や症例4のようにIOL脱臼を伴う症例では，保存的治療のみでの眼圧コントロールは困難であり観血的治療が必要と考える．

以上から，水晶体起因性続発緑内障はさまざまな機序が複合して発症することがあり，経過観察時にはこれらの眼圧上昇機転をよく理解して適切な治療を行っていく必要がある．

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