

# A Clinical Evaluation of Uveitis-associated Secondary Glaucoma

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Purpose: To investigate the clinical features of secondary glaucoma associated with uveitis.

**Methods:** The subjects of the study were 1,099 patients with uveitis (1,604 eyes) treated at the Miyata Eye Hospital, Miyakonojo, Miyazaki, between October 1974 and January 2000. The intraocular pressure (IOP) and clinical data were analyzed retrospectively. Secondary glaucoma was diagnosed in the patients when IOP was higher than 21 mm Hg at two consecutive visits and they needed treatment with medication to control the high IOP.

**Results:** Secondary glaucoma was found in 293 eyes (18.3%) of 217 patients (19.7%) among the uveitis patients. The clinical entity with the highest incidence of secondary glaucoma was Posner-Schlossman syndrome in 100%, followed by sarcoidosis in 34.1%, herpetic anterior uveitis in 30.4%, Behçet's disease in 20.8%, human leukocyte antigen-B27-related acute anterior uveitis in 20.0%, Vogt-Koyanagi-Harada's disease in 16.4%, and human T-lymphotropic virus type 1 uveitis in 16.2%. Among these 293 eyes with secondary glaucoma, the majority (72%) had active anterior uveitis at the time of high IOP. Only 7.5% of the secondary glaucoma eyes had peripheral anterior synechia wider than 180° of the trabecular meshwork. Steroid-induced glaucoma was found in only 8.9% of the secondary glaucoma eyes. Surgical therapy, mainly trabeculectomy with anti-metabolites, was performed in 38 eyes and the post-surgical IOP was controlled under 20 mm Hg in 34 eyes. Despite the medical and surgical therapy for secondary glaucoma, visual field defect was found in 39% of the secondary glaucoma eyes.

**Conclusions:** The incidence of secondary glaucoma in the 1,604 eyes with uveitis was 18.3%, but it differed depending upon the clinical entity of the uveitis. The evaluation and the management of IOP are very important in the treatment of patients with uveitis, in addition to the management of intraocular inflammation. Jpn J Ophthalmol 2002;46:556–562 © 2002 Japanese Ophthalmological Society

**Key Words:** Behçet's disease, human T-lymphotropic virus type 1 uveitis, sarcoidosis, secondary glaucoma associated with uveitis, uveitis.

## Introduction

Secondary glaucoma is one of the most important ocular complications in uveitis that can impair the vision of patients. <sup>1–14</sup> Therefore, early diagnosis of secondary glaucoma and its appropriate therapy are essential in the clinical management of uveitis patients, in addition to the control of intraocular inflammation. The incidence and the clinical features of secondary glaucoma appear to be different depending upon the etiology of the uveitis. The etiology of uveitis is known to vary among different ethnic groups and countries, and different regions even in the same country. Because the etiology of uveitis in southern Kyushu is known to be different from that in other areas of Japan, it would be of interest to analyze secondary glaucoma associated with uveitis in that area.

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The present study was, therefore, aimed at analyzing the clinical features of secondary glaucoma associated with uveitis in southern Kyushu.

## **Materials and Methods**

The subjects of this study were 1,099 patients (431 men and 668 women) with uveitis (1,604 eyes) who were followed for longer than 3 months at the Miyata Eye Hospital, Miyakonojo, Miyazaki, between October 1979 and January 2000. The followup period of the patients varied from 3 months to 21 years and 5 months, and the mean follow-up period was  $72.0 \pm 58.9$  months (mean  $\pm$  SD). In the present study, secondary glaucoma patients were defined as patients whose intraocular pressure (IOP) was higher than 21 mm Hg at two consecutive visits and who were treated with medication to control the high IOP. The clinical charts of all uveitis patients were retrospectively reviewed and patients with secondary glaucoma that met the above criteria were selected for evaluating the following: high IOP prior to the medical therapy to decrease IOP, intraocular inflammation at the time of high IOP, gonioscopic findings, relation between the high IOP and corticosteroid therapy, visual field, and therapy for high IOP. The IOP was measured with an applanation tonometer. The visual field was examined by Humphrey perimetry. A visual field of more than stage I, according to the grade described by Aulhorn et al <sup>15</sup> and modified by Greve and Geijssen, <sup>16</sup> was classified as an abnormal visual field related to secondary glaucoma. However, visual field abnormality related to optic nerve and chorioretinal lesions due to ocular inflammation was not considered as an abnormal visual field associated with glaucoma in uveitis patients.

Statistical analysis was performed using the Mann-Whitney U-test and the Fisher exact probability test.

# Results

## Frequency of Secondary Glaucoma in Uveitis

Secondary glaucoma was found in 293 eyes (18.3%) of 217 patients (19.7%) of the 1,604 eyes of 1,099 patients with uveitis (Table 1). Ninety-two patients were men (122 eyes) and 125 patients were women (171 eyes), and the mean age of the patients was  $48.5 \pm 17.7$ years. The proportion of patients with secondary glaucoma in each clinical entity of uveitis was 100% in Posner-Scholossman syndrome, 34.1% in sarcoidosis, 30.4% in herpetic anterior uveitis, 20.8% in Behçet's disease, 20.0% in human leukocyte antigen (HLA)-B27-related acute anterior uveitis, 16.4% in Vogt-Koyanagi-Harada's disease, 16.2% in human T-lymphotropic virus type 1 (HTLV-1) uveitis, 11.6% in ocular toxoplasmosis, 16.1% in other entities of defined etiology, and 15.1% in idiopathic uveitis (Table 1).

## *IOP Levels Before Glaucoma Therapy*

The highest IOP levels in each eye with secondary glaucoma before medical therapy for high IOP were compared among the clinical entities of uveitis. It was  $41.3 \pm 8.8$  mm Hg in Posner-Schlossman syndrome, followed by herpetic anterior uveitis (36.6  $\pm$ 7.1 mm Hg), Behçet's disease  $(34.8 \pm 7.1 \text{ mm Hg})$ , sarcoidosis (34.1  $\pm$  6.6 mm Hg), HTLV-1 uveitis (33.6  $\pm$ 8.1 mm Hg), HLA-B27-related acute anterior uveitis  $(33.4 \pm 4.6 \text{ mm Hg})$ , Vogt-Koyanagi-Harada's disease  $(31.7 \pm 6.8 \text{ mm Hg})$ , and ocular toxoplasmosis  $(32.1 \pm$ 7.2 mm Hg). The IOP in Posner-Schlossman syndrome was significantly higher than in all other uveitis entities (P < .05 by the Mann-Whitney U-test).

		Uveitis		
Clinical Entity*	Patients	%	Affected	

 Table 1.
 Secondary Glaucoma in Uveitis Patients

\*HTLV-1: human T-lymphotropic virus type 1, HLA: human leukocyte antigen.

	Uveitis			Secondary Glaucoma	
Clinical Entity*	Patients	%	Affected Eyes (A)	Eyes (B)	$B/A \times 100$ (%)
HTLV-1 uveitis	194	17.7	260	42	16.2
Vogt-Koyanagi-Harada's disease	107	9.7	214	35	16.4
Ocular toxoplasmosis	85	7.7	95	11	11.6
Sarcoidosis	71	6.5	129	44	34.1
Behçet's disease	55	5.0	96	20	20.8
Herpetic anterior uveitis	22	2.0	23	7	30.4
HLA-B27-related acute anterior uveitis	21	1.9	25	5	20.0
Posner-Schlossman syndrome	10	0.9	10	10	100
Others	92	8.4	116	23	16.1
Idiopathic uveitis	442	40.2	636	96	15.0
Total	1099	100	1604	293	18.3

The IOP level before the therapy was further compared among the anatomical diagnosis of uveitis. It was  $35.6 \pm 8.7$  mm Hg in anterior uveitis,  $31.5 \pm 7.2$ mm Hg in intermediate uveitis, and  $26.9 \pm 2.5$  mm Hg in posterior uveitis. There was a statistically significant difference among the three groups (P < .01by Mann-Whitney U-test).

#### Relationship Between IOP and Uveitis Activity

In order to determine the relationship between the high IOP and the activity of uveitis, the 293 eyes with secondary glaucoma were evaluated by slitlamp microscopy for active inflammation in the anterior segment when the eye had high IOP. It was found that 212 eyes (72.4%) had significant symptoms of active inflammation in the anterior segment of the eye, such as cells or fibrin in the anterior chamber, keratic precipitates, or nodules at the iris or the trabecular meshwork (Table 2). However, 81 eyes (27.6%) had no significant inflammation in the anterior segment of the eye. In Posner-Schlossman syndrome, herpetic uveitis and HLA-B27-related acute anterior uveitis, all eyes had active inflammation in the anterior segment of the eye. In all other clinical entities, but not in Behçet's disease, there was active inflammation in the majority of the eyes when IOP was high. In Behçet's disease, the majority (70%) of eyes had no active inflammation in the anterior segment of the eye when IOP increased (Table 2).

#### Gonioscopic Findings

The gonioscopic findings at the time of high IOP were evaluated in terms of the presence of peripheral anterior synechia (PAS) and its width. There were 22 eyes (7.5%) with PAS wider than 180° of the

trabecular meshwork. There were 109 eyes (37.2%) with PAS smaller than 180°; and the other 162 eyes (55.3%) had no PAS. PAS was most frequently seen in sarcoidosis (77.3%) but the majority of the PAS in sarcoidosis was smaller than 180° (Table 3).

#### Steroid-induced Glaucoma

The proportion of steroid-induced glaucoma was 26 of the 293 eyes (8.9%) with secondary glaucoma (Table 4). The diagnosis of steroid-induced glaucoma was made based on clinical observations: (1) an IOP increase in parallel with the use of topical or systemic corticosteroid therapy and (2) a decrease in the high IOP with discontinuation of the steroid therapy.

#### Surgical Treatment of Secondary Glaucoma

Surgical treatment was performed in 38 eyes. Regarding the preoperative condition, the mean IOP was  $40.7 \pm 10.2$  mm Hg, the mean number of instillations for the high IOP was 2.2  $\pm$  0.7, and systemic carbonic anhydrase inhibitor was given in 31 of the 38 eyes. The surgery performed was trabeculectomy with the use of mitomycin C in 33 eyes; triple surgery with trabeculectomy, phacoemulsification, and aspiration, and intraocular lens implantation in 4 eyes; and nonpenetrating trabeculectomy in 1 eye (Table 5). The postoperative follow-up period varied from 3 months to 222 months (71.6  $\pm$  47.1 months). The mean postoperative IOP and the mean number of topical instillations for the treatment of glaucoma were  $9.2 \pm 5.7$  mm Hg and  $0.2 \pm 0.8$  at 1 month (n = 38),  $11.4 \pm 5.7$  mm Hg and  $0.4 \pm 1.0$  at 6 months (n = 31),  $10.7 \pm 5.7$  mm Hg and  $0.2 \pm 0.6$  at 1 year (n = 31),  $11.9 \pm 7.5$  mm Hg and  $0.6 \pm 1.1$  at 3 years (n = 27),

Table 2. Inflammation in Anterior Segment at Time of High Intraocular Pressure

	Anterior Segment Inflammation		
Clinical Entity*	Yes (%)	No (%)	
Posner-Schlossman syndrome	10 (100)	0	
Herpetic anterior uveitis	7 (100)	0	
HLA-B27-related acute anterior uveitis	5 (100)	0	
Ocular toxoplasmosis	9 (82)	2 (18)	
HTLV-1 uveitis	33 (79)	9 (21)	
Sarcoidosis	29 (66)	15 (34)	
Vogt-Koyanagi-Harada's disease	19 (54)	16 (46)	
Behçet's disease	6 (30)	14 (70)	
Others	18 (78)	5 (22)	
Idiopathic uveitis	76 (79)	20 (21)	
Total	212 (72.4)	81 (27.6)	

\*HLA: human leukocyte antigen, HTLV-1: human T-lymphotropic virus type 1.

	Peripheral Anterior Synechia			
Clinical Entity*	None	<180°	180°≦	
Sarcoidosis	10	32	2	
HTLV-1 uveitis	28	11	3	
Vogt-Koyanagi-Harada's disease	24	9	2	
Behçet's disease	13	6	1	
Herpetic anterior uveitis	3	3	1	
Ocular toxoplasmosis	10	1	0	
HLA-B27-related acute anterior uveitis	4	1	0	
Posner-Schlossman syndrome	10	0	0	
Others	44	5	0	
Idiopathic uveitis	40	43	13	
Total	162/293 (55.3%)	109/293 (37.2%)	22/293 (7.5%)	

Table 3. Gonioscopic Findings at Time of High Intraocular Pressure

\*HTLV-1: human T-lymphotropic virus type 1, HLA: human leukocyte antigen.

 $10.4 \pm 4.2 \text{ mm}$  Hg and  $0.4 \pm 0.7 \text{ at 5 years}$  (n = 19). Re-operation was performed in 6 eyes. IOP in 34 of the 38 eyes (89.5%) was controlled under 20 mm Hg for a long period of time without medication, or with one or two anti-glaucoma instillations (Table 5). Complications of the glaucoma surgery were choroidal detachment in 6 eyes, advancement of cataract in 5 eyes, and low tension maculopathy in 3 eyes. Progression of visual field defect after the surgery was recorded in 15 eyes.

## Visual Field

Among the 293 eyes with secondary glaucoma, 179 eyes (61.1%) did not have any abnormality in the visual field, while 114 eyes (38.9%) had an abnormal visual field related to high IOP (Table 6). The proportion of eyes with abnormal visual field in each clinical entity was 50.0% in Behçet's disease, 41.7% in idiopathic uveitis, 38.6% in sarcoidosis, 38.1% in HTLV-1 uveitis, 34.6% in Vogt-Koyanagi-Harada's disease and others, whereas none of the eyes with Posner-Schlossman syndrome and HLA-B27-related acute anterior uveitis had an abnormal visual field (Table 6).

#### Discussion

The present survey to evaluate secondary glaucoma in uveitis was performed at the Miyata Eye Hospital located in southern Kyushu, where a unique feature of uveitis epidemiology had been reported, ie, a high prevalence of HTLV-1 uveitis and ocular toxoplasmosis as compared with other regions in Japan.<sup>1-4</sup> This unique feature was confirmed in the present study. Namely, HTLV-1 uveitis was the most prevalent clinical entity of the defined etiologies in our study, followed by Vogt-Koyanagi-Harada's disease,

Table 4. Incidence of Steroid-induced Glaucom	ıa
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Clinical Entity*	Secondary Glaucoma	Steroid-induced Glaucoma	%
Sarcoidosis	44	4	9.1
HTLV-1 uveitis	42	4	9.5
Vogt-Koyanagi-Harada's disease	35	4	11.4
Behçet's disease	20	2	10.0
Ocular toxoplasmosis	11	1	9.1
Posner-Schlossman syndrome	10	0	0
Herpetic anterior uveitis	7	0	0
HLA-B27-related acute anterior uveitis	5	0	0
Others	23	1	4.3
Idiopathic uveitis	96	10	10.4
Total	293	26	8.9

\*HTLV-1: human T-lymphotropic virus type 1, HLA: human leukocyte antigen.

Clinical Entity*	Trabeculectomy (Eyes)	Triple <sup>†</sup> (Eyes)	NPT <sup>‡</sup> (Eyes)	Control Rate
Behçet's disease	3	2	0	5/5
HTLV-1 uveitis	2	1	0	3/3
Vogt-Koyanagi-Harada's disease	2	1	0	3/3
Sarcoidosis	2	0	0	2/2
Others	8	0	1	9/9
Idiopathic uveitis	16	0	0	12/16
Total	33	4	1	34/38

Table 5. Glaucoma Surgery in Secondary Glaucoma Associated with Uveitis

\*HTLV-1: human T-lymphotropic virus type 1, HLA: human leukocyte antigen.

<sup>†</sup>Triple: phacoemulsification and aspiration, intraocular lens implantation, and trabeculectomy.

<sup>‡</sup>NPT: non-penetrating trabeculectomy.

ocular toxoplasmosis, sarcoidosis, Behçet's disease, and others. Based on this unique group of patients, the present study disclosed that secondary glaucoma was found in 293 of 1,604 eyes (18.3%) or 217 of 1,099 patients (19.7%) with uveitis. This incidence of secondary glaucoma (18.3%) was in accord with data reported in previous studies from other regions in Japan (17–23% of uveitis patients). <sup>5,6,8</sup> Despite the fact that our patients with uveitis and those in the previous studies were epidemiologically very different, the present survey showed an incidence of secondary glaucoma in southern Kyushu similar to that in other regions of Japan. It was considered that the discrepancy can be attributed to HTLV-1 uveitis, which has been the most prevalent uveitis in this region. The incidence of secondary glaucoma in the disease was 42 of 260 eyes (16.2%) and was similar to the average of overall incidence of secondary glaucoma in uveitis. HTLV-1 uveitis is characterized by intermediate uveitis with moderate or intense vitreous opacities, and its ocular symptoms have been

reported to be very similar to those in sarcoidosis. <sup>2,13,14</sup> Thus, in the present study for the first time we analyzed secondary glaucoma in HTLV-1 uveitis patients and found a significantly lower incidence of secondary glaucoma in HTLV-1 uveitis patients than in sarcoidosis patients (16.2% vs. 34.1%, P = .0001 by the Fisher exact probability test).

The IOP level before medical treatment for secondary glaucoma was significantly higher in Posner-Schlossman syndrome patients (41.3  $\pm$  8.8 mm Hg) than in the patients with all other entities of uveitis (P < .05 by Mann-Whitney U-test). The high level of IOP and high incidence of glaucoma in Posner-Schlossman syndrome patients are understandable, because the diagnostic criteria of the syndrome is mild iridocyclitis with a transient but very high IOP. The precise mechanism in the increase of the IOP in this disease is not fully understood, but soluble factors in the aqueous humor such as prostaglandins have been suggested as playing a role.<sup>17</sup> The present study showed that the IOP level in HTLV-1 uveitis

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	Yes	No	A/(A+B)
Clinical Entity*	(A)	(B)	× 100 (%)
Behçet's disease	10	10	50.0
Sarcoidosis	17	27	38.6
HTLV-1 uveitis	16	26	38.1
Ocular toxoplasmosis	4	7	36.4
Vogt-Koyanagi-Harada's disease	12	23	34.3
Herpetic anterior uveitis	2	5	28.6
Posner-Schlossman syndrome	0	10	0.0
HLA-B27-related acute anterior uveitis	0	5	0.0
Others	13	10	56.5
Idiopathic uveitis	40	56	41.7
Total	114	179	38.9

**Table 6.** Visual Field in Secondary Glaucoma Associated with Uveitis

\*HTLV-1: human T-lymphotropic virus type 1, HLA: human leukocyte antigen.

patients was similar to that in sarcoidosis patients  $(33.6 \pm 8.1 \text{ mm Hg vs. } 34.1 \pm 6.6 \text{ mm Hg}).$ 

The results of our study also showed that the IOP levels before glaucoma therapy varied, depending upon where the major site of inflammation was located. The IOP was highest in eyes with anterior uveitis, followed by intermediate uveitis and posterior uveitis (35.6  $\pm$  8.7 mm Hg vs. 31.5  $\pm$  7.2 mm Hg vs.  $26.9 \pm 2.5$  mm Hg), respectively, and a statistically significant difference was found among the three groups (P < .01 by Mann-Whitney U-test). These data suggest that inflammation in the anterior segment of the eye plays a significant role in high IOP. This theory was further supported by the present data that the majority (212/293 eyes, 72.4%) had significant inflammation in the anterior segment at the time of high IOP and only a small proportion (81 eyes, 27.6%) exhibited high IOP without inflammation. However, in Behçet's disease, the majority (14/20 eyes, 70%)showed high IOP with minimal or no inflammation in the anterior segment. High IOP without inflammation in the anterior segment is considered to be associated with either angle closure secondary glaucoma or steroid-induced glaucoma. Therefore, gonioscopic findings and response to corticosteroids were further evaluated in each eye. As for gonioscopic findings, PAS larger than one half circumference of trabecular meshwork was found in only 22 eyes (7.5%), suggesting that the majority of secondary glaucoma cases in uveitis was not caused by an angle closure mechanism. Sarcoidosis and Behçet's disease are well known to cause some pathological changes in the angle. However, in our patients with Behçet's disease, eyes with PAS larger than one half circumference were found in only 1 of 20 eyes. Similarly, in sarcoidosis, all 44 eyes did not have large PAS; and 32 of the 44 eyes had small tent-shaped PAS. In 66% of eyes with sarcoidosis, high IOP was accompanied by active inflammation in the anterior segment with nodules in the trabecular meshwork. It was considered that the major cause of high IOP in sarcoidosis is inflammation in the outflow pathway of the aqueous humor.

In the present study steroid-induced glaucoma was found in 26 of the 293 secondary glaucoma eyes (8.9%), which was much lower than the incidence of steroid-induced glaucoma reported in the literature (18–30%).<sup>18</sup> The present survey was a retrospective study and the diagnosis of steroid-induced glaucoma was based on the clinical course of each patient as described in his clinical chart.

A test to evaluate the response to steroid by giving instillations of corticosteroids to the fellow eye was not performed in this study. Therefore, it is assumed that the actual incidence of steroid-induced glaucoma is higher than the present results. In Behçet's disease, steroid-induced glaucoma was found in only 2 of 20 eyes. The data recorded here indicate that the majority of secondary glaucoma cases in Behçet's disease were in eyes with open angle and minimal inflammation in the anterior segment, and they were not steroid-induced glaucoma eyes. The mechanism by which high IOP occurred in Behçet's disease is not clear, but it is assumed to be attributed to several mechanisms, such as disruption of the blood-ocular barrier due to longlasting inflammation in the eye, or release of cytokines and other mediators in the aqueous humor.

This study also showed that a certain proportion (38/293 eyes, 13.0%) in secondary glaucoma underwent filtration surgery due to poor control of high IOP even with full medical therapy. The majority received trabeculectomy with anti-metabolites (mitomycin C). Despite the high mean preoperative IOP ( $40.7 \pm 10.2 \text{ mm}$ Hg), the mean postoperative IOP was  $10.4 \pm 4.2 \text{ mm}$ Hg even after 5 years with minimum anti-glaucoma instillation, indicating that IOP control by filtration surgery was relatively good. However, the visual field defect progressed in 15 of the 38 operated eyes.

In conclusion, secondary glaucoma associated with uveitis is one of the most important ocular complications in uveitis. The incidence, clinical features and the mechanism of high IOP vary depending upon the clinical entity of the uveitis. Because it can lead to significant impairment in visual function, careful attention to the IOP and visual field as well as to ocular inflammation is essential in the clinical management of uveitis patients.

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