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Comparison of Clinical Features and Visual Outcome between Sympathetic Ophthalmia and Vogt–Koyanagi–Harada Disease in Chinese Patients

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Purpose: To characterize the clinical features of sympathetic ophthalmia (SO) and compare SO and Vogt–Koyanagi–Harada (VKH) disease in Chinese patients.

Design: Retrospective case series.

Participants: A total of 131 consecutive SO and 500 VKH disease patients randomly selected from among those referred to our uveitis center from April 2008 through June 2018.

Methods: History, extraocular and ocular findings, best-corrected visual acuity (BCVA), auxiliary examination findings, complications, and therapeutic effects were analyzed retrospectively in SO and VKH disease patients.

Main Outcome Measures: Visual outcome, extraocular and ocular findings, and therapeutic effects.

Results: Sympathetic ophthalmia manifested as posterior uveitis (68.8%) within 2 weeks and equal involvement of anterior and posterior segment (44.4%), respectively, was observed between 2 weeks and 2 months after disease onset. Two months after disease onset, SO patients showed sunset glow fundus (51.2%) and granulomatous anterior uveitis (27.3%). Vogt–Koyanagi–Harada disease patients mainly showed posterior uveitis (100%), anterior segment involvement (92.4%) associated with posterior uveitis (84.9%), and granulomatous anterior uveitis (97.4%) accompanying sunset glow fundus (91.5%) in the 3 periods mentioned above. The frequencies of extraocular manifestations were lower in SO patients (24.4%) as compared with VKH disease patients (84.8%; $P < 0.001$). Best-corrected visual acuity of SO patients improved from 0.68±0.86 logarithm of the minimum angle of resolution (logMAR) to 0.47±0.78 logMAR ($P = 0.01$), and BCVA of VKH disease patients improved from 0.67±0.79 logMAR to 0.24±0.53 logMAR ($P < 0.001$) at 12 months of follow-up. A worse BCVA was noted in SO patients compared with VKH disease patients after treatment ($P = 0.003$). Kaplan-Meier survival analysis showed that the risk of loss of useful vision in SO patients was significantly higher than that of VKH disease patients ($P < 0.001$).

Conclusions: Chinese SO and VKH disease patients have a different evolutionary process. The frequency of extraocular manifestations in SO patients is much lower as compared with VKH disease patients. Visual outcome is worse in SO as compared with VKH disease. *Ophthalmology 2019;■:1–9 © 2019 by the American Academy of Ophthalmology*

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Sympathetic ophthalmia (SO) is defined as a bilateral granulomatous uveitis occurring after penetrating ocular trauma or intraocular surgery in 1 eye. Sympathetic ophthalmia is a rare disease with an incidence ranging from 0.2% to 0.5% after injury and 0.01% after intraocular surgery.[1] It usually presents as bilateral anterior granulomatous uveitis in the anterior segment and choroiditis, retinal detachment, Dalen-Fuchs nodules, and sunset glow fundus in the posterior segment.[1,2] However, its clinical features in different stages have not been well addressed. It is known that SO and Vogt–Koyanagi–Harada (VKH) disease, a common uveitis entity affecting Asians, Native Americans, and Middle Easterners, share common clinical manifestations as well as pathologic and immunohistochemical features. However, the similarities and differences between SO and VKH disease have not been investigated in detail. In the present study, we compared the dynamic clinical features and visual outcomes in patients with these 2 uveitis entities.

Methods

This was a retrospective study that adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board of the First Affiliated Hospital of Chongqing Medical University (Chongqing, People's Republic of China). Patients with a clinical diagnosis of SO examined between April 2008 and June

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2018 at the Uveitis Center of the First Affiliated Hospital of Chongqing Medical University were included in this study. Five hundred gender- and age-matched VKH disease patients were selected randomly from among those referred during the same period for comparison. Consent was obtained from all SO and VKH disease patients. All patients were evaluated, diagnosed, and managed primarily by 1 senior uveitis specialist (P.Y.). Sympathetic ophthalmia was diagnosed when the patient reported a history of ocular trauma or intraocular surgery and showed evidence of bilateral inflammation after excluding other diseases. Vogt−Koyanagi−Harada disease was diagnosed based on the criteria reported recently.[3]

Data included age, gender, disease duration, ocular and systemic manifestations, ocular complications, best-corrected visual acuity (BCVA), and treatment at presentation and further follow-up visits.[4] History of ocular trauma or intraocular surgery and the interval between the insult and uveitis developing were also collected in SO patients. Active intraocular inflammation was defined as aqueous cells, flare, keratic precipitates, Koeppe and Busacca nodules, vitreous cells, and choroiditis.

Statistical analyses were performed using SPSS software version 22 (SPSS, Inc, Chicago, IL) and GraphPad software version 6.01 (GraphPad Software, San Diego, CA). The BCVA (in logarithm of the minimum angle of resolution [logMAR] units) during the follow-up was assessed with the Friedman test in both diseases. A Kaplan-Meier survival analysis was used to assess the risks of loss of useful vision (10/200). Multiple linear regression analysis was performed to investigate the influence of various factors on logMAR BCVA in the sympathizing eye of SO patients at baseline and during follow-up. Stepwise variable selection was used to determine the factors to be included in the multivariate model. The independent variables were the specific ocular characteristics and complications at each visit. P values less than 0.05 were accepted as statistically significant.

Results

Patient Characteristics

A total of 131 SO patients, including 109 males (83.2%) and 22 females (16.8%), met the inclusion criteria. Mean age of the patients at the time of disease onset was 42.5 years (range, 4−73 years). Mean interval between the insult to the exciting eye and onset of SO in the sympathetic eye was 69.3±125.8 months (range, 5 days−50 years). The SO patients were followed up regularly and 69 of them had been followed up for more than 1 year. Four hundred males and 100 females were selected randomly from a group of 1175 VKH disease patients who had been followed up for more than 6 months. The mean age of these patients at the time of disease onset was 40.0 years (range, 12−77 years). The VKH disease patients were followed up regularly, and 421 of them had been followed up for more than 1 year.

Sympathetic ophthalmia developed in 101 patients (77.1%) after penetrating eye injury and 24 patients (18.3%) after intraocular surgery. Other causes of SO included corneal chemical burns with perforation in 4 patients (3.1%) and infectious corneal ulcer with perforation in 2 patients (1.5%). Eighty-four SO patients demonstrated visual acuity worse than 10/200 in the inciting eye at the first visit, and 30 patients underwent enucleation of the inciting eye before being referred to our uveitis center. Therefore, for the comparison of the visual outcomes between SO and VKH disease in this study, only the sympathizing eye was analyzed and compared with a VKH disease eye (the right eye was chosen in VKH disease patients for comparison).

In a previous study, we found a specific evolutionary process in VKH disease and divided it into a posterior uveitis stage (within 2 weeks after uveitis onset), anterior uveal involvement stage (from 2 weeks to 2 months after uveitis attack), and recurrent granulomatous anterior uveitis stage (more than 2 months after the uveitis attack).[5] In an attempt to gain insight into the clinical features of SO over time and compare the similarities and differences between SO and VKH disease, we also divided SO patients into these 3 time groups (Table 1). In SO patients referred within 2 weeks of disease onset, nongranulomatous anterior uveitis as evidenced by anterior chamber cells and dust keratic precipitates was observed in 43.8% of patients, and posterior segment involvement manifesting as choroiditis, retinal detachment, and papillary hyperemia were noted in 68.8% of patients. All the VKH disease patients referred within 2 weeks after disease onset showed posterior segment inflammation without anterior segment involvement. Sympathetic ophthalmia patients referred between 2 weeks and 2 months after disease onset showed nongranulomatous anterior uveitis and posterior segment inflammation in 44.4% of patients, respectively. However, most of the VKH disease patients at this stage showed nongranulomatous anterior uveitis, although more than 80% of the patients still showed posterior segment inflammation. In SO patients referred more than 2 months after disease onset, 27.3% of patients showed granulomatous anterior uveitis and 8.4% of patients showed active posterior segment inflammation as evidenced by choroiditis, retinal detachment, and papillitis. At this stage, VKH disease patients mainly showed granulomatous anterior uveitis. A small number of patients also showed posterior involvement, as evidenced by changes in the OCT, fundus fluorescein angiography, and indocyanine green angiography examination results. For example, 12.6% of patients showed choroiditis and 10.9% of patients showed retinal detachment (Table 1). Sunset glow fundus was found in 51.2% of SO patients after 2 months of disease onset, whereas it was noted in 91.5% of VKH disease patients in this stage.

A total of 32 SO patients (24.4%) and 424 VKH disease patients (84.8%) displayed a number of systemic manifestations ($P < 0.001$; Table 2). Meningismus, tinnitus, dysacusis, alopecia, poliosis, high sensitivity to touch of the hair, and vitiligo were observed in 24.4%, 25.1%, 19.8%, 12.9%, 10.7%, 3.8%, and 5.3% of SO patients, respectively. The frequencies of these manifestations in SO patients were all significantly lower than those observed in VKH disease patients (all $P < 0.001$). Because some of these nonocular findings may develop late in the disease course, we chose the 41 SO patients and 190 VKH disease patients with a disease duration of more than 1 year at presentation and compared the nonocular findings between the 2 diseases. The frequencies of these manifestations in SO patients were all significantly lower than those observed in VKH disease patients (all $P < 0.01$; Table S1, available at www.aaojournal.org).

Treatment and Control of Inflammation

Most SO and VKH disease patients had been treated transiently or intermittently with corticosteroids at other hospitals before being referred to our uveitis center. Systemic corticosteroids were administered in our center at an initial dose of 0.7 to 1.0 mg/kg daily or 0.5 to 0.8 mg/kg daily for SO patients referred within 2 months or more than 2 months after disease onset, respectively. Systemic corticosteroids were usually combined with cyclosporine (2−5 mg/kg daily at the beginning) or cyclophosphamide (normally 1−2 mg/kg daily at the beginning) and less commonly with chlorambucil or mycophenolate mofetil. Posterior sub-Tenon or intravitreal injection of triamcinolone was also used in case of refractory uveitis and cystoid macular edema.

Table 1. Disease Manifestations in Sympathetic Ophthalmia and Vogt–Koyanagi–Harada Disease Patients at Presentation

	≤2 Weeks			2 Weeks–2 Months			>2 Months		
	Sympathetic Ophthalmia (n = 16) %	*Vogt–Koyanagi–Harada Disease (n = 40) %*	P *Value*[†]	*Sympathetic Ophthalmia (n = 27) %*	*Vogt–Koyanagi–Harada Disease (n = 119) %*	P *Value*[†]	*Sympathetic Ophthalmia (n = 88)** %	*Vogt–Koyanagi–Harada Disease (n = 341) %*	P *Value*[†]
Anterior segment									
Anterior cells	43.8	0	0.00	44.4	92.4	0.00[‡]	27.3	97.4	<0.001[‡]
Keratic precipitates (dust-like/mutton fat)	12.5/0	0/0	0.02[‡]	11.1/0	57.9/5.8	0.00[‡]	15.9/11.4	10.9/83.9	<0.001[‡]
Iris nodule (Koeppe or Busacca)	0	0	—	0	12.6/0	0.051	3.4	25.5	<0.001[‡]
Iris synechiae	12.5	0	0.02[‡]	29.6	8.4	0.002[‡]	43.2	62.8	<0.001[‡]
Posterior segment									
Vitreous opacity	0	0	—	25.9	13.4	0.11	19.3	10.9	0.03[‡]
Choroiditis	68.8	100	<0.001[‡]	44.4	84.9	0.001[‡]	7.1	12.6	0.16
Retinal detachment	37.5	90.0	<0.001[‡]	29.6	67.2	0.001[‡]	4.7	10.9	0.09
Optic disc hyperemia	12.5	85.0	<0.001[‡]	44.4	58.0	0.2	8.4	8.5	0.97
Dalen–Fuchs nodules	0	0	—	7.4	4.2	0.48	83.3	77.4	0.24
Sunset glow fundus	0	0	—	3.7	2.5	0.73	51.2[§]	91.5[‖]	<0.001[‡]
Chorioretinal atrophy around optic disc	0	0	—	0	0	—	3.6	1.2	0.12

— = no statistical analysis was carried out. The Chi-square test was not performed because no SO or VKH patients presented with these ocular signs.
Data are percentages unless otherwise indicated.
*The fundus was observed in 84 eyes in patients who came to our clinic after 2 months of disease onset.
[†]Chi-square test.
[‡]$P < 0.05$.
[§]Sunset glow fundus was found at an average of 33.4 months (range, 2–240 months) after disease onset in sympathetic ophthalmia patients. However, because these patients did not come to our hospital immediately after disease onset, these data do not accurately reflect the development time of sunset glow fundus.
[‖]Sunset glow fundus was found at an average of 41.6 months (range, 2–444 months) after disease onset in Vogt–Koyanagi–Harada patients. However, because these patients did not come to our hospital immediately after disease onset, these data do not accurately reflect the development time of sunset glow fundus.

Table 2. Systemic Manifestations of Sympathetic Ophthalmia and Vogt–Koyanagi–Harada Disease Patients

Systemic Manifestations	Sympathetic Ophthalmia Patients (n = 131), %	Vogt–Koyanagi–Harada Disease Patients (n = 500), %	P Value*
Meningismus†	24.4	77.0	<0.001‡
Tinnitus	25.1	57.2	<0.001‡
Dysacusis	19.8	46.0	<0.001‡
Alopecia	12.9	48.6	<0.001‡
Poliosis	10.7	49.8	<0.001‡
High sensitivity to touch of the hair	3.8	26.2	<0.001‡
Vitiligo	5.3	19.8	<0.001‡

Data are percentages unless otherwise indicated.
*Chi-square test.
†Meningismus was defined as one of the following manifestations: headache, nausea, or stiffness of the neck and back.
‡$P < 0.05$.

Vogt–Koyanagi–Harada disease patients were treated according to the protocol described in a recent study[6]: an initial dose of 0.6 to 0.8 mg/kg daily or 0.4 to 0.6 mg/kg daily was used for VKH disease patients referred within 2 months or more than 2 months after disease onset, respectively. This was combined with cyclosporine (2–4 mg/kg daily at the beginning), cyclophosphamide (normally 1–2 mg/kg daily at the beginning), or other immunosuppressive agents. Gradual tapering of the corticosteroids and other immunosuppressive agents was planned for both SO and VKH disease patients as described previously.[6] The treatment usually lasted for at least 1 year. Corticosteroid eye drops and cycloplegic agents were used for the patients with anterior chamber cells. In case of recurrent episodes of uveitis during the treatment, a modified regimen was given, that is, reuse of the initial dose of corticosteroids and other immunosuppressive agents combined with corticosteroids and cycloplegic eye drops as described previously.[6] Two SO patients with recurrent uveitis also received a biological agent (infliximab).

For the 69 SO patients who had been followed up for at least 1 year, corticosteroids and immunosuppressive agents were withdrawn in 41 patients (59.4%) after treatment for a mean of 29.1 months (range, 12–80 months; median, 24 months). Six patients (14.6%) experienced a uveitis relapse. The other 35 patients were followed up for a mean of 35.7 months (range, 8–120 months) after medication withdrawal without relapse. For the 421 VKH disease patients who had been followed up for at least 1 year, corticosteroids and immunosuppressive agents were stopped in 358 patients (85.0%) after a mean of 16.2 months (range, 1–73 months; median, 12 months), and 29 of them (8.1%) experienced recurrent uveitis. The percentage of SO patients with a mean time of 35.7 months of drug-free remission (50.7% [n = 35]) was significantly lower as compared with VKH disease patients (78.1% [n = 329]; $P < 0.001$).

Visual Outcomes

The dynamic changes of the BCVA in both SO and VKH disease patients are summarized in Table 3 and Figure 1. Best-corrected visual acuity improved from 0.68±0.86 logMAR to 0.47±0.78 logMAR in all the SO patients ($P = 0.01$) and from 0.67±0.79 logMAR to 0.24±0.53 logMAR in all the VKH disease patients ($P < 0.001$) at 12 months of follow-up. A worse BCVA was noted in SO patients as compared with VKH disease patients at 12 months of follow-up ($P = 0.003$). Because there were only a few SO patients (8.7%) and VKH disease patients (9.0%) referred to our uveitis center within 2 weeks after disease onset, we considered the patients referred within 2 months after disease onset as a single group (group 1) and those referred more than 2 months after disease onset as group 2 for analysis and comparison. Best-corrected visual acuity of SO patients in group 1 improved significantly at 6 months ($P = 0.004$) and 12 months ($P = 0.006$) after treatment. However, in SO patients of group 2, there was no difference concerning BCVA between baseline and each follow-up visit. In VKH disease patients of group 1, BCVA showed a steady improvement at 3 and 6 months that was maintained until 12 months after treatment ($P < 0.001$–0.03). In VKH disease patients of group 2, BCVA improved significantly at 3 and 6 months (all $P < 0.001$), and further improvement was noted at 12 months as compared with the 6-month time point ($P = 0.02$). We also compared the visual outcomes between 33 SO and 115 VKH disease patients referred between 2 months and 1 year after disease onset and who had been followed up for more than 1 year. Best-corrected visual acuity improved from 0.63±0.82 logMAR to 0.24±0.53 logMAR in VKH disease patients at 12 months after treatment ($P < 0.0001$). However, there was no significant improvement in BCVA for SO patients. A better BCVA at 12 months was observed in VKH disease patients than in SO patients (0.51±0.83 logMAR; $P = 0.015$).

A better BCVA at 12 months was observed in group 1 of both the SO and VKH disease patients as compared with group 2 for both uveitis entities (all $P < 0.001$). There was no difference concerning BCVA during the follow-up between SO and VKH disease patients in group 1. However, a better BCVA at 12 months was observed in VKH disease patients of group 2 as compared with SO patients of group 2 ($P = 0.001$). An increased percentage of patients with a BCVA of 20/40 or better (0.30 logMAR) was noted in VKH disease patients of both groups (all $P < 0.001$) at 12 months after treatment. However, similar results were found only in SO patients of group 1 ($P < 0.001$; Fig 1A).

In the 69 SO patients being followed up for at least 1 year, 13 inciting eyes had been removed surgically before visiting our uveitis center. For the remaining inciting eyes, the BCVA was counting fingers or worse in 80.4% of them (45 eyes). At the end of the first year, visual improvement was noted in only 10 inciting eyes.

Kaplan-Meier survival analysis was used to estimate the risk of loss of useful vision (10/200; 1.30 logMAR) after treatment in both SO and VKH disease. The results showed that the risk of loss of useful vision in SO patients was significantly higher than that of VKH disease patients ($P < 0.001$). When 2 groups of SO and VKH disease patients were analyzed separately, it was found that the risk of loss of useful vision in SO patients of group 1 was significantly lower than that of group 2 ($P = 0.03$). Vogt–Koyanagi–Harada

Table 3. The Dynamic Changes of Best-Corrected Visual Acuity during the First Year of Follow-up

Time	Baseline			3 Months			6 Months			12 Months		
	*Sympathetic Ophthalmia**	*Vogt–Koyanagi–Harada Disease*†	P *Value*‡	*Sympathetic Ophthalmia**	*Vogt–Koyanagi–Harada Disease*†	P *Value*‡	*Sympathetic Ophthalmia**	*Vogt–Koyanagi–Harada Disease*†	P *Value*‡	*Sympathetic Ophthalmia**	*Vogt–Koyanagi–Harada Disease*†	P *Value*‡
All patients: SO (n = 69) and VKH (n = 421)	0.68±0.86	0.67±0.79	0.66	0.42±0.68	0.34±0.55	0.34	0.37±0.62	0.28±0.51	0.11	0.47±0.78	0.24±0.53	0.003§
≤2 mos: SO (n = 25) and VKH (n = 147)	0.84±1.07	0.67±0.75	0.74	0.29±0.54	0.23±0.41	0.44	0.23±0.59	0.14±0.26	0.47	0.34±0.83	0.09±0.22	0.43
>2 mos: SO (n = 44) and VKH (n = 274)	0.60±0.72	0.67±0.82	0.78	0.49±0.75	0.40±0.60	0.45	0.45±0.63	0.36±0.59	0.12	0.54±0.74	0.32 ± 0.63	0.001§

SO = sympathetic ophthalmia; VKH = Vogt–Koyanagi–Harada.
Data are logarithms of the minimum angle of resolution units.
*Sympathizing eye.
†Right eye.
‡Student *t* test.
§$P < 0.05$.

disease patients showed a similar risk in both groups 1 and 2. The risk of loss of useful vision in SO patients was significantly higher than that in VKH disease patients in both groups ($P < 0.001-0.001$).

We also performed a multiple linear regression analysis with a stepwise method to identify factors associated with visual outcome in SO patients (Table 4). The factors included disease duration, BCVA at baseline, inflammation activity, cataract, papillary abnormality (papillitis, papillary atrophy), macular abnormality, and vitreous floaters. At baseline, cataract, vitreous floaters, and macular abnormality were associated negatively with visual acuity ($R^2 = 0.26$). At 12 months, BCVA was associated negatively with macular abnormality, papillary abnormality, and vitreous floaters ($R^2 = 0.46$).

Complications

A variety of ocular complications was observed at presentation and each follow-up examination in both diseases. The most common complications were cataract, macular abnormality, secondary ocular hypertension, and band-shaped keratopathy. We compared the differences concerning these complications between SO and VKH disease patients (Table 5). A significantly higher percentage of macular abnormality was observed in VKH disease patients of group 1 as compared with SO patients of group 1 at baseline. However, a reversed percentage of cases with a macular abnormality was noted at 12 months between these 2 diseases in both group 1 and 2 patients. We further analyzed the percentages of macular edema in both groups and found that the percentage of macular edema at 12 months in SO patients of groups 1 and 2 after treatment was significantly higher than that of VKH disease patients in both groups ($P < 0.001-0.03$).

Complicated cataract, usually presenting as posterior subcapsular opacities, was observed in 48 eyes (36.6%) from SO patients and 173 eyes (34.6%) from VKH disease patients. Phacoemulsification with intraocular lens implantation was carried out in 16 SO patients (33.3%) with cataract and 42 VKH disease patients (24.3%) with cataract after the inflammation was controlled completely. A significant increase of the BCVA was achieved after surgery in both diseases ($P = 0.002$ and $P < 0.001$, respectively). Secondary elevated intraocular pressure was observed in 34 eyes (26.0%) from SO patients and 103 eyes (20.6%) from VKH disease patients. A well-controlled intraocular pressure was achieved in most eyes after intraocular inflammation was controlled or anti–ocular hypertension agents were used. Seven SO patients and 7 VKH disease patients underwent surgical interventions, including iridectomy or trabeculectomy, and all of them achieved good control of intraocular pressure after surgery.

Discussion

This study characterized the clinical features of 131 SO patients from all over China. The sympathizing eye of SO patients typically demonstrates nongranulomatous uveitis clinically at the beginning and then progresses to granulomatous uveitis. The common manifestations included choroiditis, papillitis, serous retinal detachment, Dalen-Fuchs nodules, and anterior inflammation with dust or mutton-fat keratic precipitates. We also compared the similarities and differences between SO and VKH disease. Sympathetic ophthalmia does not show a typical evolutionary process, unlike VKH disease. The visual prognosis of SO was worse and the treatment duration was longer as compared with VKH disease. Various complications were observed in both

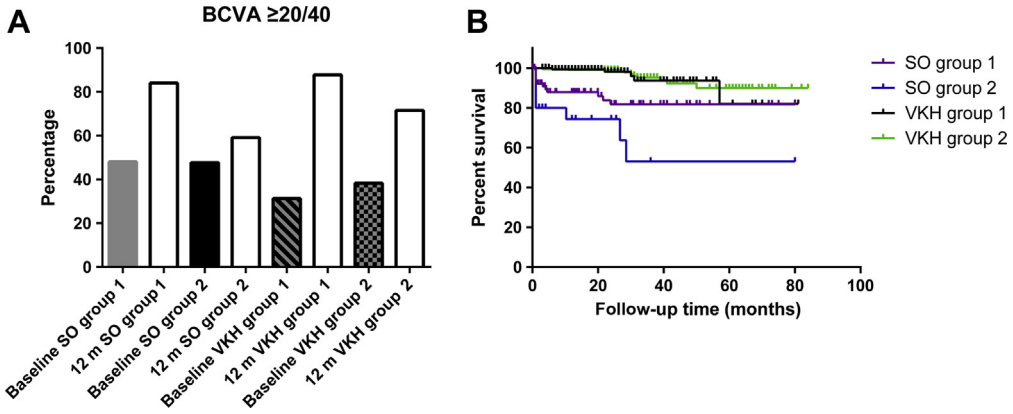

Figure 1. **A**, Bar graph showing the percentage of patients with best-corrected visual acuity (BCVA) of 20/40 or better (0.30 logarithm of the minimum angle of resolution [logMAR]) in sympathetic ophthalmia (SO) and Vogt–Koyanagi–Harada (VKH) disease at baseline and 12 months after treatment. **B**, Kaplan-Meier survival curves showing cumulative survival of SO and VKH patients with a BCVA of better than 10/200 (1.30 logMAR).

diseases. However, macular abnormalities occur more frequently in SO than VKH disease after treatment.

Previous studies have shown that there are similar features between SO and VKH disease,[1,5,7] but they have never been compared in detail. In this study, SO and VKH disease patients were shown to have a different evolutionary disease process. Vogt–Koyanagi–Harada disease patients mainly show 3 successive stages: posterior uveitis, anterior segment involvement associated with posterior uveitis, and finally anterior granulomatous uveitis. Anterior uveitis and posterior uveitis both are present in SO patients seen within 2 weeks of disease onset. After 2 weeks of disease onset, the percentage of VKH disease patients with anterior uveitis is more prominent than in SO patients. Recently, subclinical posterior inflammation in the anterior granulomatous uveitis stage was reported in some studies.[8–10] The results in this study were consistent with those of these previous reports, because posterior inflammation also was found in the chronic VKH disease patients in the present study (Table 1). Posterior inflammation is always more common in VKH disease as compared with SO during the disease course. A lower percentage of SO patients shows sunset glow fundus as compared with VKH disease patients seen after 2 months of disease onset. Studies have also stated that systemic findings in SO are uncommon, but the frequencies of these manifestations have never been reported in detail.[1,11] We calculated the frequencies of extraocular manifestations in SO patients in this study and observed that all had a lower frequency when compared with that seen in VKH disease. These findings show that SO and VKH disease are different disease entities. Interestingly, although a number of differences were found between these 2 diseases in the current study, there is little difference concerning the ocular pathologic findings between the 2 diseases.[1,12] Vogt–Koyanagi–Harada disease has been presumed to be mediated by an autoimmune reaction against melanocyte-associated antigens.[13] Although S-antigen, rhodopsin, interphotoreceptor retinoid-binding protein, recoverin, and melanin antigen are putative autoantigens,[1] the particular antigen for SO has not yet been identified. Therefore, the mechanism underlying the different clinical course needs to be investigated further.

Concerning the treatment of SO, previous studies have shown some success leading to long-term remission.[14,15] One study showed that 3 of 19 patients maintained in remission without any systemic medications for more than 5 years. These 3 patients were initially treated with corticosteroids and later with mycophenolate mofetil, Cyclosporine A, or chlorambucil.[14] Other studies report that 75% of SO patients demonstrate a drug-free remission with high-dose short-term chlorambucil.[15] A slightly higher dose of corticosteroids was used for the patients being referred to our uveitis center within 2 months of disease onset because they usually showed more severe intraocular inflammation as compared with those being referred after 2 months of disease onset. We usually use systemic corticosteroids combined with Cyclosporine A for initial treatment, and more than half of SO patients achieve

Table 4. Multiple Linear Regression for Predicting Visual Acuity

	Baseline			12 Months		
	B (95% Confidence Interval)	*β*	*P Value*	*B (95% Confidence Interval)*	*β*	*P Value*
Cataract	0.94 (0.61–1.26)	0.43	0.000			
Papillary abnormality				0.61 (0.18–1.05)	0.28	0.006
Macular abnormality	0.38 (0.07–0.68)	0.19	0.017	0.65 (0.31–0.99)	0.40	<0.001
Vitreous floaters	0.63 (0.34–0.93)	0.32	<0.001	0.57 (0.26–0.88)	0.39	0.001
Adjusted R^2	0.26			0.46		

B = unstandardized coefficients.

Table 5. Number of Sympathetic Ophthalmia and Vogt–Koyanagi–Harada Disease Patients with Various Ocular Complications

	≤2 Months (Group 1)						>2 Months (Group 2)					
	Baseline			*12 Months*			*Baseline*			*12 Months*		
Complications	*Sympathetic Ophthalmia (n = 25) %*	*Vogt–Koyanagi–Harada Disease (n = 147) %*	*P Value**	*Sympathetic Ophthalmia (n = 25) %*	*Vogt–Koyanagi–Harada Disease (n = 147) %*	*P Value**	*Sympathetic Ophthalmia (n = 44) %*	*Vogt–Koyanagi–Harada Disease (n = 274) %*	*P Value**	*Sympathetic Ophthalmia (n = 44) %*	*Vogt–Koyanagi–Harada Disease (n = 274) %*	*P Value**
Cataract[†]	8.0	3.4	0.28	16.0	8.2	0.21	34.1	45.3	0.17	47.7	51.8	0.61
Macular abnormality[‡]	48.0	80.3	<0.001[§]	24.0	1.4	<0.001[§]	29.5	24.8	0.50	18.2	4.4	<0.001[§]
Macular edema	4.0	2.0	0.55	12.0	0	<0.001[§]	9.1	4.7	0.23	9.1	2.6	0.03[§]
Ocular hypertension	20.0	8.2	0.07	8.0	4.1	0.39	20.5	21.9	0.82	4.5	1.1	0.09
Band-shaped keratopathy	0	0	—	0	0	—	4.5	1.5	0.16	4.5	1.8	0.25

*Chi-square test.
[†]Some patients underwent cataract surgery during the follow-up. They were still included in the table to accurately reflect the development of cataract with time.
[‡]Macular abnormality included macular edema, epiretinal membrane, macular hole, choroidal neovascularization, subretinal fibrosis, and retinal detachment that involved the macular area.
[§]$P < 0.05$.

long-term remission after withdrawal of all medications. Cyclophosphamide was used in certain SO patients with severe or refractory uveitis in our center, and many of them also achieved long-term drug free remission. These results suggest that both alkylator-based and non–alkylator-based immunosuppressive agents may be useful for the long-term sustained remission of SO. The exact role of these agents is not yet clear because there are no formal control studies comparing treatment with the natural history of the disease. Our study also confirms a beneficial effect in SO patients with refractory uveitis. When compared with VKH disease, the treatment in SO has a longer duration and the percentage of patients with long-term drug-free remission is lower in SO, suggesting that SO is more challenging concerning its treatment. Sympathetic ophthalmia patients thus generally receive a higher dose of medication and prolonged treatment when compared with VKH disease patients.

To the best of our knowledge, there are no studies to address the comparison of the BCVA between SO and VKH disease. In this study, the BCVA of SO patients of group 1 (within 2 months of disease onset) increased after treatment and showed no difference as compared with VKH disease patients of group 1. However, BCVA of SO patients of group 2 (after 2 months of disease onset) did not improve even after treatment. These results indicate that the visual outcome is worse in SO than that in VKH disease. Previous studies showed that 50% to 60% of them achieved a BCVA of 20/40 or better after treatment.[7,14,16] One study reported a BCVA of 20/40 or better in 13 of 16 patients (81.3%).[15] The authors suggested that relatively good vision at presentation may be one of the factors affecting the visual outcomes in their study. We found that more than 80% of SO patients of group 1 and approximately 60% of SO patients of group 2 achieved a BCVA of 20/40 or better after 12 months of treatment. Moreover, 20% and 6.8% of patients demonstrated a BCVA worse than 10/200 at baseline in groups 1 and 2, respectively, which suggests that the treatment we used was effective.

A number of ocular complications have been described in patients with SO and VKH disease.[5,11,17] Our study generally showed similar findings. The frequency of cataracts and secondary ocular hypertension showed no difference between SO and VKH disease. In patients referred within 2 months after disease onset, the percentage of VKH disease patients with a macular abnormality was much higher than that observed in SO patients. This may result from the fact that choroiditis and retinal detachment are more prominent in VKH disease during this stage. After appropriate treatment, most patients showed a normal contour of the fovea. However, more SO patients demonstrated recurrent cystoid macular edema or choroidal or retinal scars than VKH disease patients, which may lead to irreversibly decreased vision. This is in agreement with the observation that a higher percentage of patients with a macular abnormality was observed among SO patients as compared with VKH disease patients at 12 months after disease onset.

There are some limitations in the present study. Because the incidence of SO is low, we had to use a retrospective approach to obtain a sufficient sample size. If a prospective study can be carried out in the future, it may possibly reveal a

more exact disease progression of SO. In addition, although we found that SO and VKH disease have a different clinical evolutionary process, the pathologic mechanism causing these differences is not clear. Earlier reports describe a large number of genes to be associated with VKH disease.[13] Our recent study showed that only 1 of these single nucleotide polymorphisms was also associated with SO.[18] This shows that the genetic predisposition to both diseases is different, supporting the idea that one is dealing with 2 separate entities. However, because the number of SO patients (n = 114) included in this latter genetic study was limited, further research with larger numbers of patients may be needed to confirm the hypothesis.

In conclusion, our study addressed the similarities and differences between SO and VKH disease concerning the clinical features and visual outcomes. Although both entities share similar ocular manifestations, they have a different clinical disease progression. Complicated cataract, secondary ocular hypertension, and macular abnormalities are the most common complications in both diseases. Corticosteroids combined with immunosuppressive agents should be used for a relatively long time in SO patients. Although the prognosis is not as good as in VKH disease patients, SO patients can achieve stable visual acuity if appropriate and prompt treatment is administered.

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Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
BCVA = best-corrected visual acuity; **FFA** = fundus fluorescein angiography; **ICGA** = indocyanine green angiography; **logMAR** = logarithm of the minimum angle of resolution; **SO** = sympathetic ophthalmia; **VKH** = Vogt–Koyanagi–Harada.

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