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ORIGINAL ARTICLE

Chronic Recurrent Vogt–Koyanagi–Harada Disease and Development of 'Sunset Glow Fundus' Predict Worse Retinal Sensitivity

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ABSTRACT

Purpose: To investigate prognostic factors for retinal sensitivity assessed by microperimetry in patients with Vogt–Koyanagi–Harada (VKH) disease.

Methods: In total, 34 patients with initial-onset acute disease and 19 patients with chronic recurrent disease were retrospectively evaluated.

Results: The mean follow-up period was 40.4 ± 40.5 months. Sensitivity was significantly worse in eyes with more severe anterior segment inflammation at presentation, as indicated by the presence of mutton-fat keratic precipitates, anterior chamber reaction ≥2+, and posterior synechiae. Chronic recurrent presentation, development of complications, and 'sunset glow fundus' were significantly associated with worse sensitivity. Using logistic regression analysis, better sensitivity was significantly associated with initial-onset acute presentation (odds ratio, OR = 6.9; 95% confidence interval, CI = 1.53–9.66).

Conclusions: Chronic recurrent presentation and development of complications and 'sunset glow fundus' are associated with a worse sensitivity outcome.

Keywords: Immunomodulatory therapy, microperimetry, outcome, retinal sensitivity, Vogt–Koyanagi–Harada disease

Vogt–Koyanagi–Harada (VKH) disease is an autoimmune disease directed against one or more antigens found on or associated with uveal melanocytes.[1–3] The disease typically begins with granulomatous choroiditis with exudative retinal detachment and optic disc hyperemia and swelling subsequently involving the anterior segment and finally developing into a chronic recurrent granulomatous anterior uveitis if not properly treated with typical 'sunset glow fundus' and chorioretinal atrophy.[4,5] Vision-threatening complications have clearly been recognized to occur in the chronic recurrent phase of VKH disease, namely cataract, glaucoma, subretinal neovascular membranes, and subretinal fibrosis.[4–11] The prevalence of the disease varies among different populations of the world, and it commonly affects pigmented races and people of certain genetic predispositions.[4,7] VKH disease is one of the most common uveitis entities in Saudi Arabia,[12] and the visual prognosis is generally good with prompt diagnosis and appropriate immunosuppressive therapy.[6,9,11,13,14]

The principles of therapy of VKH disease are to suppress the initial intraocular inflammation in the acute posterior uveitis stage with early high-dose systemic corticosteroids followed by slow tapering.[7,13] However, despite appropriate treatment with corticosteroid monotherapy, many patients develop chronic

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recurrent granulomatous inflammation and progressive depigmentation of the fundus, resulting in 'sunset glow fundus' appearance even after the clinical disease appears to be under control.[6,9,15–19] Several studies suggested that the use of non-steroid immunomodulatory therapy with mycophenolate mofetil, cyclosporine, azathioprine, and methotrexate as first-line therapy in addition to corticosteroids early in the course of the disease, is associated with good clinical results.[11,14,16,20,21.]

Macular function of patients with VKH disease is usually tested by best-corrected visual acuity (BCVA) assessment as the primary endpoint to identify predictive factors for final outcome and to measure the effectiveness of therapies.[6,8–11,13,14,22] Although BCVA testing is an established modality to assess functional improvement, it may only represent foveal function and does not reflect structural changes of the neurosensory retina outside the foveal region. Macular involvement in patients with VKH disease extends to the larger macular area. Best-corrected visual acuity, therefore, poorly evaluates the functional impact of VKH disease involving the posterior pole. Thus, evaluation of the topographic sensitivity of the entire central retina is much more informative to better determine the effect of treatment and to identify prognostic factors for final outcome in these patients. The recently developed fundus microperimetry (MP-1; Nidek Technologies, Italy) is able to quantify macular sensitivity and to overlay a retinal sensitivity map on a color fundus photograph allowing better localization of the pathology. In addition, the tracking software ensures that repeated examinations test the same retinal points tested during baseline examinations.[23–25] Automated fundus microperimetry, therefore facilitates the accurate assessment and reassessment of a patient's central macular sensitivity and provides an objective and quantitative assessment of macular function over time. This may be a more comprehensive approach for quantifying macular function in VKH disease than BCVA measurement alone. The purpose of this study was to determine the predictive factors for final central retinal sensitivity and to study the correlation between final BCVA and mean retinal sensitivity in patients with VKH disease. For the purpose of analysis, we divided patients into two groups based on the clinical pattern of presentation: patients with initial-onset acute VKH disease and those with chronic recurrent VKH disease.

PATIENTS AND METHODS

The records of all VKH patients seen in the Uveitis Clinic of King Abdulaziz University Hospital, Riyadh, Saudi Arabia from January 2000 to April 2012, who had MP-1 microperimetric evaluation of retinal sensitivity at last follow-up, were retrospectively reviewed. The central retinal sensitivity of 14 of these patients at 12 months after treatment was previously reported.[26] Diagnosis of VKH disease was based on the Revised International Diagnostic Criteria.[27]

Charts were reviewed for: demographic data (age and gender); initial and final best-corrected Snellen visual acuities; results of slit-lamp examination of the anterior segment; results of dilated fundus examination; results of fluorescein angiograms; duration from onset of symptoms to presentation to our institute; details of therapy; ocular complications; and duration of follow-up. The main outcome measures were BCVA and the mean central sensitivity.

A total of 53 consecutive patients (106 eyes) who had MP-1 microperimetric evaluation of retinal sensitivity at last follow-up were included. Patients were 35 (66%) females, and 18 (34%) males. The age at presentation ranged from 10 to 58 years, with a mean (SD) of 33 ± 11.5 years. For the purpose of analysis, we classified these patients into two groups according to the pattern of clinical characteristics at presentation: patients with initial-onset acute VKH disease and those with chronic recurrent intraocular inflammation. In initial-onset acute VKH disease, the interval between the onset of symptoms and presentation ranged from 2 to 30 days, with a mean of 15 ± 9 days. In chronic recurrent VKH disease, this interval ranged from 2 to 72 months, with a mean of 9.0 ± 16.0 months. Patients with initial-onset acute VKH disease typically showed exudative retinal detachment and optic disc hyperemia and swelling with or without anterior uveitis. Patients with chronic recurrent VKH disease typically showed active granulomatous anterior uveitis manifesting as mutton-fat keratic precipitates, posterior synechiae, and iris nodules (Koeppe and Busacca) with 'sunset glow fundus' and chorioretinal atrophy[4,5,11] There were 34 (64.2%) patients with initial-onset acute VKH disease and 19 (35.8%) patients with chronic recurrent VKH disease in this series.

All patients were managed and followed-up by one of the authors (AMA). All patients were treated with systemic corticosteroids. Corticosteroid therapy began with intravenous methylprednisolone 1 g/day (15–30 mg/kg of body weight for children) for 3 days followed by oral prednisone (1 mg/kg of body weight/day) that was maintained for at least 3 weeks. The prednisone dose was gradually tapered following improvement of the intraocular inflammation to a maintenance dose of 5–10 mg/day. Prednisone was tapered at 10 mg every 2 weeks until a daily dose of 40 mg was reached. Thereafter, prednisone was tapered at 5 mg every 2 weeks until 5–10 mg/day was reached. The rate of taper was adjusted according to the patient's clinical evidence of disease activity. Anterior segment inflammation was treated with

topical corticosteroids and cycloplegic agents. Immunomodulatory therapy as first-line therapy combined with systemic corticosteroids was prescribed for 39 patients. Immunomodulatory drugs were used in 32 patients with initial-onset acute VKH disease and in seven patients with chronic recurrent VKH disease. The immunomodulatory drugs used in this group included mycophenolate mofetil in 32 patients and cyclosporine in seven patients. The initial dosage of mycophenolate mofetil was 2 g daily and cyclosporine 5 mg/kg daily. The follow-up period ranged from 9 to 156 months with a mean of 40.4 ± 40.5 months.

Microperimetry

Macular sensitivity was evaluated by MP-1 microperimetry with the software version 1.4.2 (Nidek Technologies). The MP-1 provides a 45-degree nonmydriatic view of the fundus with automated correction for eye movements. The patient was dark-adapted for 5 min before the test was initiated. Patients underwent brief training at the beginning of each repeat microperimetry during the follow-up.

In our study, the following testing parameters were used: a radial grid of 45 stimuli covering the central 12 degrees (centered onto the fovea); stimulus size equivalent to Goldmann III with a 200 ms projection time, white background set at 1.273 cd/m^2, and a bright red cross of 2–3 degrees used as the fixation target according to the patient's BCVA. A 4–2 double staircase strategy was used with an automatic eye tracker that compensates for eye movements. The intensity of the stimuli in the machine ranged from 0 to 20 decibels (dB).

Statistical Methods

Snellen visual acuities were converted to the logarithm of the minimum angle of resolution (logMAR) for statistical analysis. Data were collected and stored in Microsoft Excel 2010® where data management and coding were done. Data were then imported to SPSS® version 20.0 (*IBM* Inc., Chicago, IL) for conduct of the analysis. Descriptive analysis was done, where categorical variables were presented as frequencies and percentages while continuous variables as mean (± SD). The χ^2-test or Fisher's exact test were used as appropriate to compare percentages relating to two categorical variables. A comparison of proportion *t*-test was also used to compare pre- and post-treatment changes in visual acuities. The Mann–Whitney test was used to compare means from two independent groups. Pearson correlation coefficients were calculated to investigate the correlations between variables. Binary logistic regression was conducted to identify the variables that influence the attainment of visual acuity of 20/20 and mean retinal sensitivity cut-off 7.0 dB or better at last follow-up. Confidence interval level was set to 95%. A p value <0.05 indicated statistical significance.

RESULTS

Visual Outcome

Table 1 displays the baseline and final visual acuity of all eyes in the study. The frequencies along the left-to-right diagonal line represent a total of 27/106 (25.5%) eyes that had no change in visual acuity. Improvement in vision occurred in a total of 75/106 (70.8%) eyes (frequencies above the diagonal line), and there was deterioration in vision in 4/106 (3.8%) eyes (frequencies below the diagonal line). The prevalence of best vision of 20/20 significantly increased from 21.7% of the eyes at presentation to 66.0% of the eyes at last follow-up (p<0.001). The prevalence of worst vision of ≤20/200 significantly reduced from 29.2% of the eyes at presentation to 0.0% of the eyes at last follow-up (p<0.001).

Univariate analysis demonstrated a significant positive association between final visual acuity of 20/20 and clinical findings at presentation, including: initial visual acuity of better than 20/200 (p = 0.044); absence of mutton-fat keratic precipitates (p = 0.012); anterior chamber reaction <2+ (p = 0.003); absence of posterior synechiae (p<0.001); presence of exudative retinal detachment (p = 0.003); and initial-onset acute presentation (p = 0.002), use of immunomodulatory therapy (p<0.001); and findings during the follow-up period, including: absence of cataract (p = 0.018); absence of 'sunset glow fundus' (p = 0.026); absence of multiple areas of chorioretinal atrophy (p = 0.029); and absence of peripapillary atrophy (p = 0.002) (Table 2).

When logistic regression analysis was performed, final visual acuity of 20/20 was negatively associated with the presence of posterior synechiae at

TABLE 1. Relationship between initial visual acuity and final visual acuity.

	Visual acuity at presentation									
	≤20/200		20/100–20/50		20/40–20/30		20/20		Total eyes	
Visual acuity at last follow-up	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
20/20	17		19		15		19		70	66.0
20/30–20/40	8		10		4		4		26	24.5
20/50–20/100	6		4		0		0		10	9.4
≤20/200	0		0		0		0		0	0.0
Total eyes	31	29.2	33	31.1	19	17.9	23	21.7	106	100

TABLE 2. Factors associated with final visual acuity of 20/20 (106 eyes).

	Final visual acuity of 20/20 (n = 70 eyes)		
Variable	n	(%)	p value
Age (years)			0.370
≤16 (n = 16)	9	56.3	
>16 (n = 90)	61	67.8	
Initial visual acuity			0.044
≤20/200 (n = 31)	16	51.6	
>20/200 (n = 75)	54	72	
Mutton-fat keratic precipitates			0.012*
Yes (n = 44)	23	52.3	
No (n = 62)	47	75.8	
Anterior chamber reaction			0.003*
<2+ (n = 65)	50	76.9	
≥2+ (n = 41)	20	48.8	
Posterior synechiae			<0.001*
Yes (n = 38)	14	36.8	
No (n = 68)	56	82.4	
Exudative retinal detachment			0.003*
Yes (n = 80)	59	73.8	
No (n = 26)	11	42.3	
Type of presentation			0.002*
Initial-onset acute VKH (n = 68)	52	76.5	
Chronic recurrent VKH (n = 38)	18	47.4	
Use of immunomodulatory therapy			<0.001*
Yes (n = 78)	60	76.9	
No (n = 28)	10	35.7	
Cataract/glaucoma/subretinal neovascular membranes			0.073
Yes (n = 49)	28	57.1	
No (n = 57)	42	73.7	
Cataract			0.018*
Yes (n = 29)	14	48.3	
No (n = 77)	56	72.7	
Glaucoma			0.104
Yes (n = 28)	15	53.6	
No (n = 78)	55	70.5	
'Sunset glow fundus'			0.026*
Yes (n = 46)	25	54.3	
No (n = 60)	45	75.0	
Chorioretinal atrophy			0.029*
Yes (n = 38)	20	52.6	
No (n = 68)	50	73.5	
Peripapillary atrophy			0.002*
Yes (n = 43)	21	48.8	
No (n = 63)	49	77.8	

*Statistically significant at 5% level of significance.

presentation (OR = 0.18; 95% CI = 0.07–0.48) and the use of corticosteroid monotherapy (OR = 0.14; 95% CI = 0.05–0.41).

Ocular Complications

The ocular complications encountered during the follow-up period were cataract in 29 (27.4%) eyes, glaucoma that necessitated either medical or surgical intervention in 28 (26.4%) eyes, and subretinal neovascular membranes in six (5.7%) eyes. Overall, 49 (46.2%) eyes developed at least one of these complications.

Comparisons of Presenting Clinical Features and Outcomes between Initial-onset Acute VKH Disease and Chronic Recurrent VKH Disease

At presentation, patients with chronic recurrent VKH disease had significantly more severe anterior segment inflammation than those with initial-onset acute VKH disease, as indicated by the presence of mutton-fat keratic precipitates (p<0.001), anterior chamber reaction ≥2+ (p<0.001), and posterior synechiae (p = 0.001). On the other hand, patients with initial-onset acute VKH disease had significantly more exudative retinal detachment compared with those with chronic recurrent VKH disease at presentation (p<0.001) (Table 3).

During the follow-up period, the rates of development of any complication of cataract or glaucoma or subretinal neovascular membranes (p = 0.001), cataract (p = 0.001), glaucoma (p = 0.003), 'sunset glow fundus' (p<0.001), multiple areas of chorioretinal atrophy (p<0.001) and peripapillary atrophy (p<0.001) were significantly more in patients with chronic recurrent VKH disease compared with those with initial-onset acute VKH disease (Table 3).

TABLE 3. Comparisons of baseline characteristics and clinical outcomes between initial-onset acute and chronic recurrent Vogt–Koyanagi–Harada (VKH) disease eyes.

	Initial-onset acute VKH disease (n = 68 eyes)		Chronic recurrent VKH disease (n = 38 eyes)		
Variable	n	(%)	n	(%)	p value
At presentation					
Age (years) ≤16	10	14.7	6	15.8	0.896
Mutton-fat keratic precipitates	16	23.5	28	73.7	<0.001*
Anterior chamber reaction ≥2+	5	7.4	36	94.7	<0.001*
Posterior synechiae	16	23.5	22	57.9	0.001*
Exudative retinal detachment	68	100.0	12	31.6	<0.001*
During follow-up					
Cataract/glaucoma/subretinal neovascular membranes	22	32.4	27	71.1	0.001*
Cataract	10	14.7	19	50.0	0.001*
Glaucoma	11	16.2	17	44.7	0.003*
'Sunset glow fundus'	12	17.6	34	89.5	<0.001*
Chorioretinal atrophy	10	14.7	28	73.7	<0.001*
Peripapillary atrophy	9	13.2	34	89.5	<0.001*
At final follow-up					
Visual acuity 20/20	52	76.5	18	47.4	0.005*

*Statistically significant at 5% level of significance.

At the final follow-up, significantly more eyes in initial-onset VKH disease group achieved visual acuity of 20/20 compared with those in chronic recurrent VKH disease group ($p = 0.005$) (Table 3).

Factors Predicting Mean Retinal Sensitivity at Last Follow-Up

At last follow-up, microperimetry mean retinal sensitivity ranged from 0.0 dB to 18.4 dB (7.5 ± 4.1 dB). Mean retinal sensitivity was significantly lower in eyes with more severe anterior segment inflammation at presentation, as indicated by the presence of mutton-fat keratic precipitates ($p = 0.004$), anterior chamber reaction of ≥2+ ($p<0.001$) and posterior synechiae ($p = 0.015$). Mean retinal sensitivity was significantly better in eyes with exudative retinal detachment at presentation ($p<0.001$) and initial-onset acute presentation ($p<0.001$) (Figures 1 and 2). Use of immunomodulatory therapy was significantly associated with better mean retinal sensitivity ($p<0.001$). The development of any complication of cataract or glaucoma or subretinal neovascular membranes ($p = 0.002$), cataract ($p = 0.001$), glaucoma ($p = 0.014$), 'sunset glow fundus' ($p<0.001$), multiple areas of chorioretinal atrophy ($p = 0.001$), and peripapillary atrophy ($p<0.001$) were significantly associated with lower mean retinal sensitivity (Figures 3 and 4 and Table 4).

Factors Predicting Mean Retinal Sensitivity Cut-off 7.0 dB or Better at Last Follow-up

Univariate analysis demonstrated a significant positive association between final mean retinal sensitivity cut-off 7.0 dB or better and clinical findings at presentation, including: absence of mutton-fat keratic precipitates ($p = 0.001$); anterior chamber reaction <2+ ($p<0.001$); absence of posterior synechiae ($p = 0.014$); presence of exudative retinal detachment ($p<0.001$); and initial-onset acute presentation ($p<0.001$) (Figures 1 and 2); use of immunomodulatory therapy ($p<0.001$); and findings during the follow-up period, including: absence of any complication of cataract or glaucoma or subretinal neovascular membranes ($p<0.001$); absence of cataract ($p = 0.001$); absence of glaucoma ($p = 0.002$); absence of 'sunset glow fundus' ($p<0.001$); absence of multiple areas of chorioretinal atrophy ($p<0.001$); and absence of peripapillary atrophy ($p<0.001$) (Table 5).

When logistic regression analysis was performed, the final mean retinal sensitivity of 7.0 dB or better was positively associated with initial-onset acute presentation (OR = 6.9; 95% CI = 1.53–9.66).

Correlations

There was a significant correlation between logMAR BCVA and mean retinal sensitivity in the central 12 degrees at the final follow-up ($r = –0.42$; $p<0.001$) (Figure 5). Mean retinal sensitivity in eyes with visual acuity of 20/20 at the final follow-up period (8.9 ± 3.1 dB) was significantly better than that in eyes with a worse visual acuity (5.8 ± 4.6 dB) ($p<0.0001$). Moreover, 50/70 (71.4%) eyes with final visual acuity of 20/20 achieved mean retinal sensitivity cut-off 7.0 dB or better compared with 14/36 (38.9%) eyes with final visual acuity of <20/20 ($p = 0.024$).

There was a significant negative correlation between the mean retinal sensitivity and the interval between onset of symptoms and presentation ($r = –0.31$; $p = 0.01$).

DISCUSSION

VKH disease typically begins with granulomatous choroiditis associated with exudative retinal detachment and optic disc hyperemia and swelling. The disease will proceed to chronic recurrent granulomatous anterior uveitis if not properly treated with typical 'sunset glow fundus' and chorioretinal atrophy.[4,5] Studies using a laser flare-cell meter demonstrated that both aqueous flare values and cell counts were significantly higher in patients with chronic recurrent VKH disease than those with initial-onset acute VKH disease. Furthermore, chronic recurrent granulomatous inflammation in the anterior segment is more refractory to treatment.[28] Consequently, complications are more common in patients with chronic recurrent VKH disease who present with recurrent granulomatous anterior uveitis with 'sunset glow fundus'.[5,11] Keino et al.[19] showed a significant association between the incidence of chronic ocular inflammation and the appearance of 'sunset glow fundus'. In addition, indocyanine green angiographic studies of patients during episodes of apparent isolated granulomatous anterior segment recurrence showed concomitant subclinical choroidal inflammation, despite the absence of clinical signs of posterior segment involvement and this could contribute to the development of 'sunset glow fundus' appearance of chorioretinal atrophy.[29] In agreement with previous studies, we demonstrated that patients with chronic recurrent VKH disease had significantly more severe anterior segment inflammation than those with initial-onset acute VKH disease at presentation. Conversely, patients with initial-onset acute VKH disease had significantly more exudative retinal detachment compared with those with chronic recurrent VKH disease at presentation. During the follow-up period, the rates of ocular complications including cataract, glaucoma, subretinal neovascular membranes,

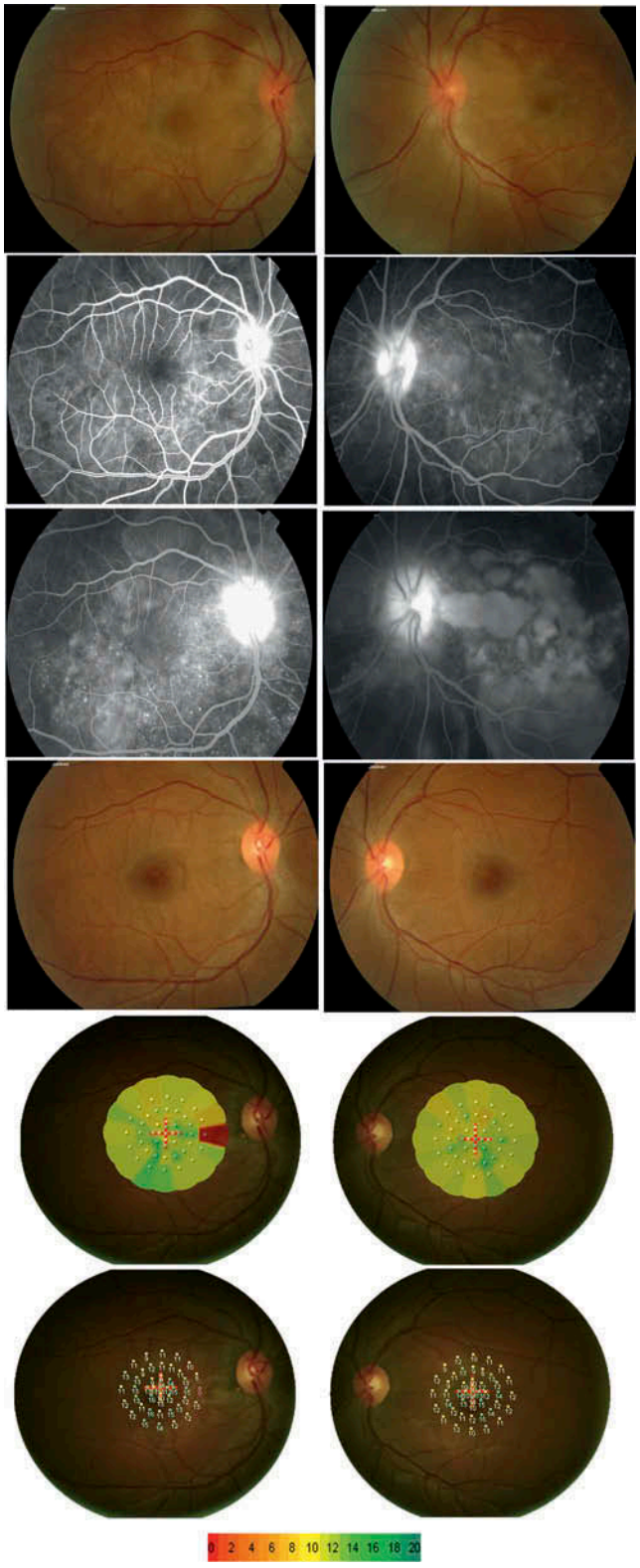

FIGURE 1. A 26-year-old female with initial-onset acute Vogt–Koyanagi–Harada disease at presentation. Note the exudative retinal detachments with the hyperemic optic discs (top). Fluorescein angiography shows multiple pinpoint hyperfluorescence at the level of the retinal pigment epithelium and late pooling of dye in the areas of exudative retinal detachment (second and third rows). The patient received systemic corticosteroids combined with mycophenolate mofetil. At 72 months after treatment, best-corrected visual acuity (BCVA) was 20/20 in both eyes. Note the absence of 'sunset glow fundus' and chorioretinal atrophy (fourth row). The mean central retinal sensitivity was 11.9 dB in the right eye and 11.7 dB in the left eye (fifth and sixth rows). (Color-coded, numeric scale shows the threshold in 2 dB steps from 0 to 20 dB. Normal sensitivity is indicated in green and decreased sensitivity is indicated in red).

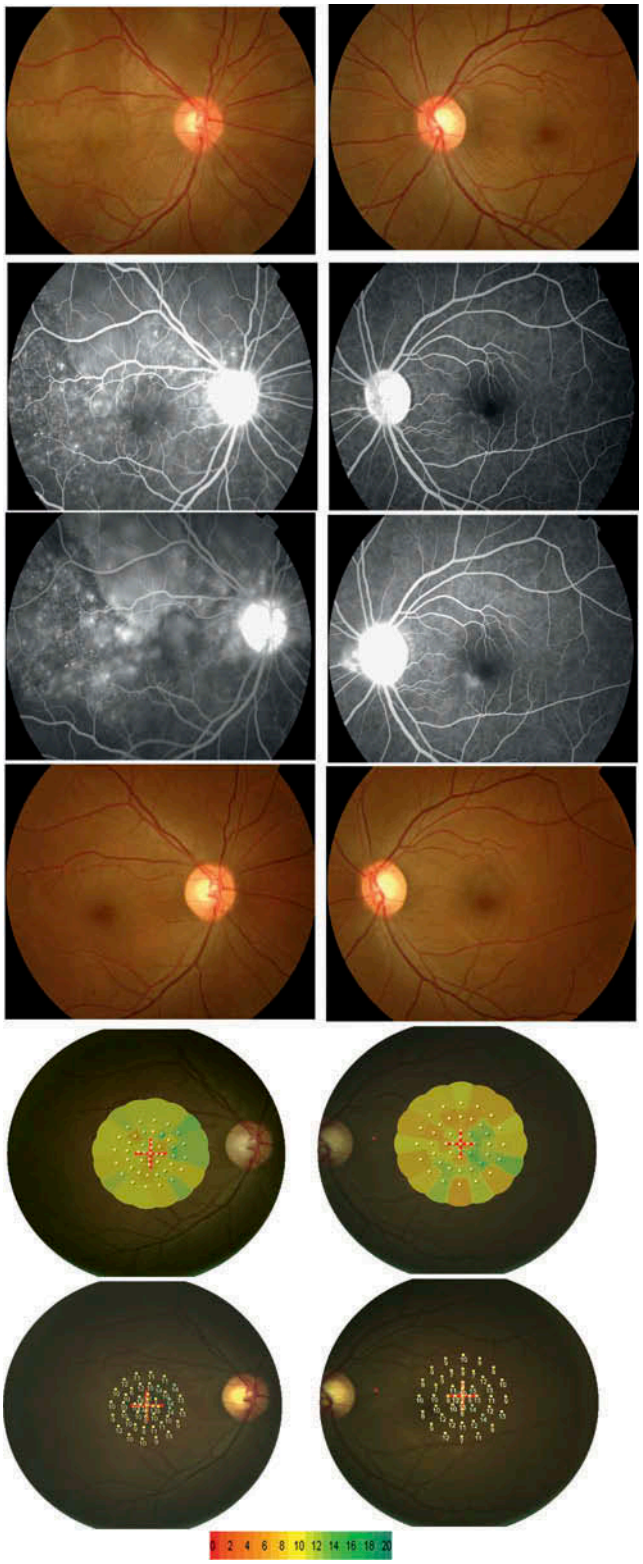

FIGURE 2. A 32-year-old female with initial-onset acute Vogt–Koyanagi–Harada disease at presentation. Note the exudative retinal detachments with the hyperemic optic discs (top). Fluorescein angiography shows multiple pinpoint hyperfluorescence at the level of the retinal pigment epithelium and late pooling of dye in the areas of exudative retinal detachment (second and third rows). The patient received systemic corticosteroids combined with mycophenolate mofetil. At 36 months after treatment, best-corrected visual acuity (BCVA) was 20/20 in both eyes. Note the absence of 'sunset glow fundus' and chorioretinal atrophy (fourth row). The mean central retinal sensitivity was 10.1 dB in the right eye and 10.0 dB in the left eye (fifth and sixth rows)

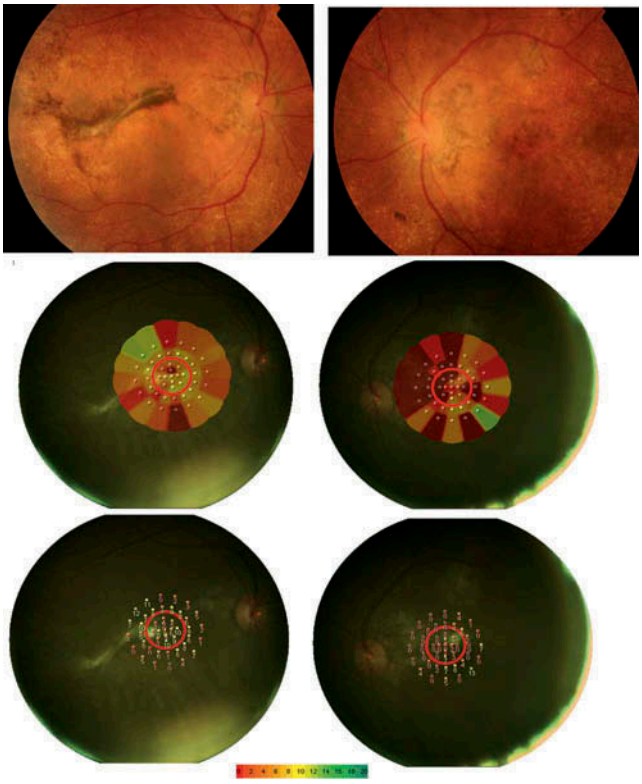

FIGURE 3. A 32-year-old female with chronic recurrent Vogt–Koyanagi–Harada disease at presentation. The patient received systemic corticosteroids combined with mycophenolate mofetil. At 96 months after presentation, best-corrected visual acuity (BCVA) was 20/30 in both eyes. Note the presence of 'sunset glow fundus', chorioretinal atrophy, and pigmented subretinal fibrous bands (top). The mean central retinal sensitivity was 5.3 dB in the right eye and 1.9 dB in the left eye (second and third rows)

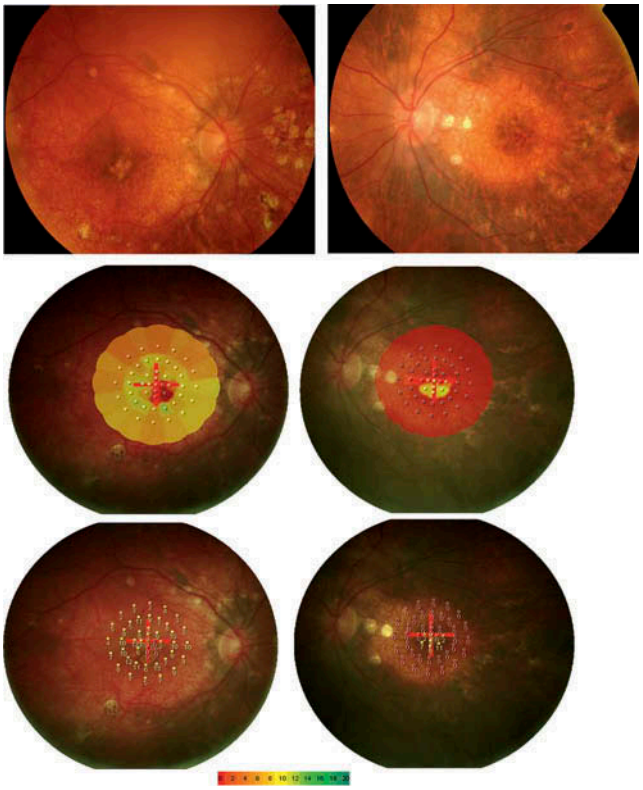

FIGURE 4. A 25-year-old female with chronic recurrent Vogt–Koyanagi–Harada disease at presentation. The patient received systemic corticosteroids combined with mycophenolate mofetil. At 87 months after presentation, best-corrected visual acuity (BCVA) was 20/30 in the right eye and 20/20 in the left eye. Note the presence of 'sunset glow fundus' and chorioretinal atrophy (top). The mean central retinal sensitivity was 6.4 dB in the right eye and 1.0 dB in the left eye (second and third rows)

'sunset glow fundus', chorioretinal atrophy, and peripapillary atrophy were significantly more in patients with chronic recurrent VKH disease compared with those with initial-onset acute VKH disease. The current study identified significant associations between severe anterior uveitis and chronic recurrent VKH disease at presentation and a worse final visual acuity and mean retinal sensitivity. In addition, we demonstrated the presence of a significant negative correlation between the interval between the onset of symptoms and presentation to our institute and the mean retinal sensitivity at last follow-up. Binary logistic regression analysis revealed that the presence of posterior synechiae at presentation is an independent significant predictor for a worse final visual acuity and that initial-onset acute VKH disease at presentation is significantly associated with a better final mean retinal sensitivity.

The current study has identified a significant association between the development of 'sunset glow fundus' and a worse final visual acuity and mean retinal sensitivity. The development of 'sunset glow fundus' and chorioretinal atrophy despite apparent control of ocular inflammation suggests ongoing subclinical choroidal inflammation.[29–31] In a histopathologic analysis of eyes with 'sunset glow fundus' in patients with VKH disease, scattered inflammatory infiltrate of predominantly T-lymphocytes in the thickened choroid with notable disappearance of choroidal melanocytes was observed supporting the presence of ongoing subclinical inflammation in the convalescent stage of VKH disease.[32] There is accumulating evidence to suggest that despite proper treatment with corticosteroid monotherapy, many patients develop chronic, recurrent granulomatous inflammation and progressive depigmentation of the fundus, resulting in 'sunset glow fundus' appearance even after the clinical disease appears to be under control.[6,9,15–19] Recently, Sakata et al.[18] demonstrated that in spite of early high-dose corticosteroid therapy, 79% of patients with VKH disease progressed to chronic recurrent disease. In previous studies, we demonstrated that addition of immunomodulatory therapy with mycophenolate mofetil and cyclosporine as first-line therapy combined with systemic corticosteroids in patients with initial-onset acute VKH disease leads to significant reduction in recurrences of uveitis and development of complications and 'sunset glow fundus' suggesting that immunomodulatory therapy was effective in controlling progressive subclinical choroidal inflammation.[11,14.]

TABLE 4. Factors predicting mean retinal sensitivity at last follow-up (106 eyes).

Variables	Sensitivity (mean ± SD)	*p* value
Age (years)		0.296
≤16 (*n* = 16)	7.9 ± 4.5	
>16 (*n* = 90)	7.4 ± 4.0	
Initial visual acuity		0.247
≤20/200 (*n* = 31)	6.8 ± 4.7	
>20/200 (*n* = 75)	7.7 ± 3.9	
Mutton-fat keratic precipitates		0.004*
Yes (*n* = 44)	6.2 ± 4.0	
No (*n* = 62)	8.4 ± 3.9	
Anterior chamber reaction		<0.001*
<2+ (*n* = 65)	9.1 ± 3.3	
≥2+ (*n* = 41)	4.9 ± 4.0	
Posterior synechiae		0.015*
Yes (*n* = 38)	6.5 ± 4.6	
No (*n* = 68)	8.0 ± 3.7	
Exudative retinal detachment		<0.001*
Yes (*n* = 80)	8.5 ± 3.8	
No (*n* = 26)	4.3 ± 3.5	
Type of presentation		<0.001*
Initial-onset acute VKH (*n* = 68)	9.1 ± 3.0	
Chronic recurrent VKH (*n* = 38)	4.5 ± 4.1	
Use of immunomodulatory therapy		<0.001*
Yes (*n* = 78)	8.5 ± 4.6	
No (*n* = 28)	4.6 ± 4.1	
Cataract/glaucoma/subretinal neovascular membranes		0.002*
Yes (*n* = 49)	6.3 ± 4.3	
No (*n* = 57)	8.5 ± 3.7	
Cataract		0.001*
Yes (*n* = 29)	5.7 ± 4.2	
No (*n* = 77)	8.1 ± 3.9	
Glaucoma		0.014*
Yes (*n* = 28)	5.9 ± 4.3	
No (*n* = 78)	8.0 ± 3.9	
'Sunset glow fundus'		<0.001*
Yes (*n* = 46)	5.0 ± 4.0	
No (*n* = 60)	9.4 ± 3.0	
Chorioretinal atrophy		0.001*
Yes (*n* = 38)	5.8 ± 4.6	
No (*n* = 68)	8.4 ± 3.5	
Peripapillary atrophy		<0.001*
Yes (*n* = 43)	5.2 ± 4.2	
No (*n* = 63)	9.0 ± 3.2	

*Statistically significant at 5% level of significance.

TABLE 5. Factors predicting final mean retinal sensitivity cut-off 7.0 decibels (dB) or better (106 eyes).

	Mean sensitivity ≥7 dB (64 eyes)		
Variables	*n*	(%)	*p* value
Age (years)			0.194
≤16 (*n* = 16)	12	75.0	
>16 (*n* = 90)	52	57.8	
Initial visual acuity			0.820
≤20/200 (*n* = 31)	17	58.6	
>20/200 (*n* = 75)	47	61.0	
Mutton-fat keratic precipitates			0.001*
Yes (*n* = 44)	17	38.6	
No (*n* = 62)	47	75.8	
Anterior chamber reaction			<0.001*
<2+ (*n* = 65)	54	83.1	
≥2+ (*n* = 41)	10	24.4	
Posterior synechiae			<0.014*
Yes (*n* = 38)	17	44.7	
No (*n* = 68)	47	69.1	
Exudative retinal detachment			<0.001*
Yes (*n* = 80)	59	73.8	
No (*n* = 26)	5	19.3	
Type of presentation			<0.001*
Initial-onset acute VKH (*n* = 68)	57	83.8	
Chronic recurrent VKH (*n* = 38)	7	18.4	
Use of immunomodulatory therapy			<0.001*
Yes (*n* = 78)	58	74.4	
No (*n* = 28)	6	21.4	
Cataract/glaucoma subretinal neovascular membranes			<0.001*
Yes (*n* = 49)	19	42.2	
No (*n* = 57)	45	73.8	
Cataract			0.001*
Yes (*n* = 29)	10	34.5	
No (*n* = 77)	54	70.1	
Glaucoma			0.002*
Yes (*n* = 28)	10	35.7	
No (*n* = 78)	54	69.2	
'Sunset glow fundus'			<0.001*
Yes (*n* = 46)	11	23.9	
No (*n* = 60)	53	88.3	
Chorioretinal atrophy			<0.001*
Yes (*n* = 38)	11	28.9	
No (*n* = 68)	53	77.9	
Peripapillary atrophy			<0.001*
Yes (*n* = 43)	11	25.6	
No (*n* = 63)	53	84.1	

*Statistically significant at 5% level of significance.

In this study, we investigated the correlation between BCVA and central retinal sensitivity in patients with VKH disease at last follow-up. We identified a significant correlation between logMAR BCVA and mean retinal sensitivity. In addition, mean retinal sensitivity was significantly better in eyes with full recovery of visual acuity compared with eyes with visual acuity of <20/20 at last follow-up. Midena et al.[33] examined healthy subjects with a BCVA of 20/20 or better with the MP-1 microperimeter. In the same age range as in our study, the authors showed that the mean macular sensitivity was 19.6 ± 0.5 dB. In our study, the mean central retinal sensitivity in eyes with final visual acuity of 20/20 was only 8.9 ± 3.1 dB. These findings suggest that retinal sensitivity, assessed by the MP-1 microperimeter, even in eyes with full recovery of visual acuity, was reduced in patients with VKH disease. In a previous study, we longitudinally evaluated the central retinal sensitivity in patients with VKH disease in the acute uveitis phase following immunosuppressive therapy. We demonstrated that mean retinal sensitivity significantly increased from baseline after treatment, however, retinal sensitivity was significantly reduced at the final follow-up.[26] Similarly, Yang et al.[34] demonstrated that immunosuppressive therapy in patients with

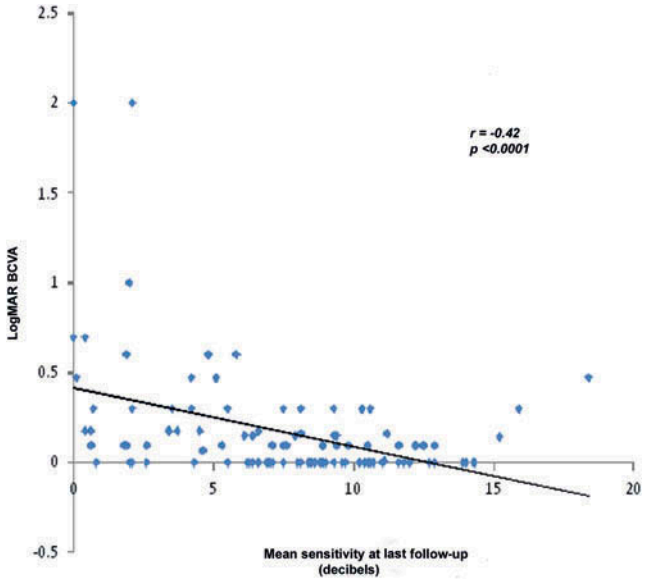

FIGURE 5. Significant correlation between logarithm of the minimum angle of resolution (logMAR) best-corrected visual acuity (BCVA) and mean retinal sensitivity (decibels) in the central 12 degrees at last follow-up.

active uveitis associated with VKH disease leads to earlier and faster recovery of BCVA and a delayed but limited recovery of multifocal electroretinography. Our results are similar to a previous report that demonstrated that not all eyes with birdshot chorioretinopathy may recover their full retinal sensitivities.[35] The reduced retinal sensitivity in patients with VKH disease at last follow-up may reflect photoreceptor dysfunction attributable to subretinal fluid or photoreceptor loss itself. Another possibility is that this photoreceptor dysfunction may be secondary to diffuse pathologic changes in the choroid and/or retinal pigment epithelium in patients with VKH disease. Persistent reduced retinal sensitivity suggests that prolonged photoreceptor dysfunction is a feature of uveitis associated with VKH disease.

In conclusion, chronic recurrent VKH disease is significantly associated with a worse visual acuity and mean retinal sensitivity at last follow-up, compared with initial-onset acute VKH disease. Our data also reveal that distant BCVA alone significantly underestimates the impairment of photoreceptor function and that subclinical macular dysfunction is a permanent damage in VKH disease. In this study, the data were collected retrospectively, nevertheless, these findings stress the importance of a full assessment of macular function by integrating microperimetry and BCVA in patients with VKH disease.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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