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Prognostic factors for clinical outcomes in patients with Vogt–Koyanagi–Harada disease treated with high-dose corticosteroids

Ahmed M. Abu El-Asrar, Mamdouh Al Tamimi, Suhail Hemachandran, Hani S. Al-Mezaine, Abdulrahman Al-Muammar and Dustan Kangave

Department of Ophthalmology, College of Medicine, King Saud University, Riyadh, Saudi Arabia

ABSTRACT.

Purpose: **To determine prognostic factors in patients with Vogt–Koyanagi–Harada (VKH) disease who were treated with high-dose corticosteroids.**

Methods: **Retrospective analysis of 87 patients (174 eyes).**

Results: **At presentation, there were 53 patients with initial-onset acute VKH disease and 34 patients with chronic recurrent VKH disease. Chronic recurrent presentation was significantly associated with more severe anterior segment inflammation at presentation as indicated by presence of mutton-fat keratic precipitates, anterior chamber reaction ≥2+, iris nodules and posterior synechiae ($p < 0.001$ for all comparisons), less exudative retinal detachment at presentation ($p < 0.001$), more complications during the follow-up period ($p < 0.001$) and a worse visual outcome ($p < 0.001$). The use of immunomodulatory therapy (cyclosporine and mycophenolate mofetil) as first-line therapy significantly reduced the development of complications in the whole study group ($p = 0.006$) and in initial-onset acute group ($p = 0.024$) and improved visual outcome in the whole study group ($p = 0.004$) and in chronic recurrent group ($p = 0.024$). In the whole study group, final visual acuity of 20/20 was significantly associated with good initial visual acuity of >20/200 [odds ratio = 4.25; 95% Confidence interval (CI) = 1.53–11.89] and age older than 16 years was significantly associated with the development of complications (odds ratio = 3.15; 95% CI = 1.04–9.48).**

Conclusions: **Chronic recurrent VKH disease is significantly associated with more severe anterior segment inflammation and less exudative retinal detachment at presentation, more ocular complications and a worse visual outcome than initial-onset acute VKH disease. Use of immunomodulatory therapy significantly improved the clinical outcomes.**

Key words: complications – immunomodulatory therapy – outcome – Vogt–Koyanagi–Harada disease

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Introduction

Vogt–Koyanagi–Harada (VKH) disease is an autoimmune disease directed against one or more antigens found on or associated with uveal melanocytes, with subsequent chorioretinal atrophy giving rise to the characteristic 'sunset glow fundus' appearance (Yamaki et al. 2000a,b; Gocho et al. 2001). VKH is characterized by bilateral granulomatous panuveitis and exudative retinal detachment. During the acute phase, systemic manifestations include central nervous system and auditory signs. In the chronic or recurrent phase, poliosis, vitiligo and alopecia may develop. The prevalence of the disease varies among different populations of the world, and it commonly affects pigmented races and people of certain genetic predispositions (Moorthy et al. 1995; Fang & Yang 2008). VKH disease is one of the most common uveitis entities in Saudi Arabia (Al-Mezaine et al. 2010), and the visual prognosis is generally good with prompt diagnosis and appropriate immunosuppressive treatment (Al-Kharashi et al. 2007; Abu El-Asrar et al. 2008, 2012).

The natural history of VKH disease can be divided into acute, chronic and chronic recurrent stages (Moorthy et al. 1995; Fang & Yang 2008). The disease typically begins with choroiditis with exudative retinal detachment and optic disc hyperaemia and swelling, subsequently involving the anterior segment and finally developing into a recurrent granulomatous anterior uveitis if not properly treated with typical 'sunset glow fundus' and

chorioretinal atrophy (Yang et al. 2007; Fang & Yang 2008). Bacsal et al. (2008) demonstrated, with the use of indocyanine green angiography, the presence of concomitant subclinical choroidal inflammation in patients with clinically isolated anterior segment recurrence. 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. The occurrence of these complications is known to be associated with a worse visual outcome (Ohno et al. 1988; Moorthy et al. 1995; Read et al. 2001b; Al-Kharashi et al. 2007; Yang et al. 2007; Abu El-Asrar et al. 2008; Fang & Yang 2008).

The principles of therapy of VKH disease are to suppress the initial intraocular inflammation in the acute posterior uveitis stage with early and high-dose systemic corticosteroids followed by slow tapering (Rubsamen & Gass 1991; Moorthy et al. 1995). Despite proper treatment with corticosteroids, several studies reported the development of chronic recurrent granulomatous inflammation and 'sunset glow fundus' with peripapillary atrophy and depigmented small atrophic lesions at the level of retinal pigment epithelium (Al-Kharashi et al. 2007; Chee et al. 2007; Abu El-Asrar et al. 2008; Cuchacovich et al. 2010; Errera et al. 2011). Recently, several studies suggested that the use of nonsteroid immunomodulatory therapy with cyclosporine, azathioprine, methotrexate and mycophenolate mofetil as first-line therapy in addition to corticosteroids is associated with good clinical results (Paredes et al. 2006; Kim & Yu 2007; Cuchacovich et al. 2010; Abu El-Asrar et al. 2012).

Although the prognosis for VKH disease has greatly improved, further studies are needed to determine the optimal treatment regime for this disease. The purpose of this study was therefore to determine the prognostic factors that could assist us to optimize the management of this disease in a group of patients with VKH disease who were treated with high-dose corticosteroids. Several previous studies reported the predictive factors of final visual acuity and development of complications in patients with VKH disease Al-Kharashi et al. 2007; Abu El-Asrar et al. 2008; Ohno et al. 1988; Read et al. 2001a,b; Rubsamen & Gass 1991; Chee et al. 2009). Unlike most other studies, 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. Furthermore, initial-onset acute group was divided into two groups: those who received nonsteroid immunomodulatory therapy as first-line therapy combined with systemic corticosteroids and those who were treated with corticosteroid monotherapy. The outcome measures were final visual acuity and the occurrence of ocular complications.

Patients and methods

The records of all VKH patients seen in the Uveitis Clinic of King Abdulaziz University Hospital, Riyadh, Saudi Arabia, from January 2004 to April 2011 were retrospectively reviewed. Diagnosis of VKH disease was based on the Revised International Diagnostic Criteria (Read et al. 2001a).

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 visual acuity and the development of complications.

Statistical analysis

The Mann–Whitney test was used to compare means from two independent groups, and the Chi-square test or Fisher's exact test was used, as appropriate, to compare percentages relating to two categorical variables. A p-value less than 0.05 indicated statistical significance. Stepwise logistic regression analysis was conducted to identify the variables that influenced the attainment of visual acuity of 20 of 20 at last follow-up and the development of any complication of cataract or glaucoma or subretinal neovascular membranes during follow-up. Only variables that had complete data for the 174 eyes included in the study were used as the independent (predictor) variables during the conduction of the logistic regression analyses. Program LR (Logistic Regression) from the BMDP 2007 Statistical Software was used for conducting the logistic regression analyses, and SPSS Version 15 for Windows software was used for the rest of the analyses.

Results

A total of 87 patients (174 eyes) were identified. Patients were 50 (57%) females, and 37 (43%) were males. The age at presentation ranged from 4 to 52 years with a mean of 26.3 ± 10.7 years and a median of 26 years. There were 18 (20.7%) patients who were 16 years of age or younger.

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 17 ± 9 days and a median of 21 days. In chronic recurrent VKH disease, this interval ranged from 2 to 44 months, with a mean of 11.6 ± 13.7 months and a median of 6 months. Patients with initial-onset acute VKH disease typically showed exudative retinal detachment and optic disc hyperaemia 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). There were 53 patients with initial-onset acute VKH disease and 34 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. Afterwards, 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. The interval between starting treatment and tapering prednisone to 10 mg or less per day ranged from 4 to 10 months with a mean of 5.8 ± 2.3 months and a median of 5 months. The duration of systemic corticosteroid therapy ranged from 11 to 22 months with a mean of 17.3 ± 2.4 months and a median of 17.5 months. Immunomodulatory therapy as first-line therapy combined with systemic corticosteroids was prescribed for 36 patients. Immunomodulatory drugs were used in 25 patients with initial-onset acute VKH disease and in 11 patients with chronic recurrent VKH disease. The immunomodulatory drugs used in this group included mycophenolate mofetil in 22 patients and cyclosporine in 14 patients. The initial dosage of mycophenolate mofetil was 2 g daily and cyclosporine 5 mg/kg daily. The duration of immunomodulatory therapy ranged from 5 to 30 months with a mean of 16.8 ± 5.0 months and a median of 17.8 months. The follow-up period ranged from 9 to 87 months with a mean of 34.2 ± 15.9 months and a median of 32 months.

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

Visual acuity at last follow-up	Visual acuity at presentation				Total eyes
	≤20/200	20/100–20/50	20/40–20/30	20/20	
20/20	23	27	18	42	110 (63.2%)
20/30–20/40	5	6	3	9	23 (13.2%)
20/50–20/100	8	12	0	0	20 (11.5%)
≤20/200	13	8	0	0	21 (12.1%)
Total eyes	49 (28.2%)	53 (30.5%)	21 (12.0%)	51 (29.3%)	174 (100%)

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 70 of 174 (40.2%) eyes that had no change in visual acuity. Improvement in vision occurred in a total of 87 of 174 (50%) eyes (frequencies above the diagonal line), and there was deterioration in vision in 17 of 174 (9.8%) eyes (frequencies below the diagonal line). The prevalence of worst vision of 20 of 200 or worse significantly reduced from 28.2% of the eyes at presentation to 12.1% of the eyes at last follow-up ($p = 0.001$; Student's *t*-test for comparing two percentages from the same sample). The prevalence of best vision of 20 of 20 significantly increased from 29.3% of the eyes at presentation to 63.2% of the eyes at last follow-up ($p < 0.001$).

Univariate analysis demonstrated a significant positive association between final visual acuity of 20 of 20 and clinical findings at presentation including initial visual acuity of better than 20 of 200 ($p = 0.009$), anterior chamber reaction $< 2+$ ($p = 0.043$), absence of mutton-fat keratic precipitates ($p < 0.001$), absence of posterior synechiae ($p = 0.003$), absence of iris nodules ($p = 0.049$), presence of exudative retinal detachment ($p < 0.001$) and initial-onset acute presentation ($p < 0.001$), use of immunomodulatory therapy ($p = 0.004$) 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 subretinal neovascular membranes ($p = 0.01$), absence of 'sunset glow fundus' ($p = 0.001$), absence of multiple areas of chorioretinal atrophy ($p = 0.011$), and absence of peripapillary atrophy ($p = 0.023$) (Table 2).

When logistic regression analysis was performed, final visual acuity of 20 of 20 was positively associated with age older than 16 years [odds ratio = 5.50; 95% Confidence interval (CI) = 1.63–18.5], initial visual acuity of better than 20 of 200 (odds ratio = 4.25; 95% CI = 1.53–11.8) and presence of exudative retinal detachment at presentation (odds ratio = 9.05; 95% CI = 1.67–49.1). During the follow-up period, the development of 'sunset glow fundus' (odds ratio = 0.092; 95% CI = 0.021–0.402) and cataract (odds ratio = 0.047; 95% CI = 0.015–0.142) was negatively associated with final visual acuity of 20 of 20 (Table 3).

Ocular complications

The ocular complications encountered during the follow-up period were cataract in 62 (35.6%) eyes, glaucoma that necessitated either medical or surgical intervention in 36 (20.5%) eyes and subretinal neovascular membranes in 12 (6.9%) eyes. Overall, 68 (39%) eyes developed at least one of these complications. Cataract extraction was performed on 18 eyes, and 14 eyes required surgical procedures for control of glaucoma.

Other complications encountered during the follow-up period were 'sunset glow fundus' in 84 (48.3%) eyes, multiple well-circumscribed areas of chorioretinal atrophy in midperiphery in 80 (46%) eyes and peripapillary atrophy in 30 (17.2%) eyes.

On univariate analysis, the development of any complication of cataract or glaucoma or subretinal neovascular membranes was significantly associated with findings at presentation including anterior chamber reaction $\geq 2+$ ($p < 0.001$), presence of mutton-fat keratic precipitates ($p < 0.001$), presence of posterior synechiae ($p = 0.001$), presence of iris nodules ($p = 0.005$), absence of exudative retinal detachment ($p < 0.001$) and chronic recurrent presentation ($p < 0.001$), nonuse of immunomodulatory therapy ($p = 0.006$), and findings during the follow-up period including development of 'sunset glow fundus' ($p < 0.001$), multiple areas of chorioretinal atrophy ($p < 0.001$), and peripapillary atrophy ($p < 0.001$) (Table 4).

On logistic regression analysis, the development of any complication of cataract or glaucoma or subretinal neovascular membranes was significantly associated with age older than 16 years

Table 2. Factors affecting final visual acuity of 20 of 20 in 174 eyes.

Variable	Final visual acuity of 20/20 (n = 110 eyes) Number (%)	p-value
Age (years)		
≤16 (n = 36)	18 (50.0)	0.098
>16 (n = 138)	92 (66.7)	
Initial visual acuity		
≤20/20 (n = 49)	23 (46.9)	0.009*
>20/200 (n = 125)	87 (69.9)	
Mutton-fat keratic precipitates		
Yes (n = 78)	34 (43.6)	<0.001*
No (n = 96)	76 (79.2)	
Anterior chamber reaction		
<2+ (n = 55)	41 (74.5)	0.043*
≥2+ (n = 119)	69 (58.0)	
Iris nodules		
Yes (n = 16)	6 (37.5)	0.049*
No (n = 158)	104 (65.8)	
Posterior synechiae		
Yes (n = 71)	35 (49.3)	0.003*
No (n = 103)	75 (72.8)	
Exudative retinal detachment		
Yes (n = 118)	91 (77.1)	<0.001*
No (n = 56)	19 (33.9)	
Type of presentation		
Initial-onset acute VKH (n = 106)	83 (78.3)	<0.001*
Chronic recurrent VKH (n = 68)	27 (39.7)	
Use of immunomodulatory therapy		
Yes (n = 72)	55 (76.4)	0.004*
No (n = 102)	55 (53.9)	
Cataract/glaucoma/subretinal neovascular membranes		
Yes (n = 68)	21 (30.9)	<0.001*
No (n = 106)	89 (84.0)	
Cataract		
Yes (n = 62)	16 (25.8)	<0.001*
No (n = 112)	94 (83.9)	
Glaucoma		
Yes (n = 36)	24 (66.7)	0.774
No (n = 138)	86 (62.3)	
Subretinal neovascular membranes		
Yes (n = 12)	3 (25.0)	0.001*
No (n = 162)	107 (66.7)	
'Sunset glow fundus'		
Yes (n = 84)	33 (39.3)	<0.001*
No (n = 90)	77 (85.6)	
Chorioretinal atrophy		
Yes (n = 80)	36 (45.0)	<0.001*
No (n = 94)	74 (78.7)	
Peripapillary atrophy		
Yes (n = 30)	13 (43.3)	0.023*
No (n = 144)	97 (67.4)	

* Statistically significant at 5% level of significance.

(odds ratio = 3.15; 95% CI = 1.04–9.48), presence of mutton-fat keratic precipitates at presentation (odds ratio = 4.60; 95% CI = 2.06–10.3) and chronic recurrent presentation (odds ratio = 11.70; 95% CI = 4.90–27.7). The development of any of these complications was negatively associated with the use of immunomodulatory therapy (odds ratio = 0.36; 95% CI = 0.155–0.832) (Table 3).

Comparisons of presenting clinical features and outcomes between initial-onset acute VKH disease and chronic recurrent VKH disease

At presentation, there were significantly more patients aged 16 years or younger in the chronic recurrent group (p = 0.037). Patients with chronic recurrent VKH disease had significantly more severe anterior segment inflammation than those with initial-onset acute VKH disease at presentation as indicated by the presence of anterior chamber reaction ≥2+ (p < 0.001), mutton-fat keratic precipitates (p < 0.001), posterior synechiae (p < 0.001) and iris nodules (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 5).

During the follow-up period, the rates of ocular complications including cataract (p < 0.001), glaucoma (p = 0.004), subretinal neovascular membranes (p < 0.001), '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 5).

At the final follow-up period, significantly more eyes in initial-onset acute VKH disease group achieved visual acuity of 20 of 20 compared with those in chronic recurrent VKH disease group (p < 0.001). On the other hand, significantly more eyes in the chronic recurrent VKH disease group had visual acuity of 20 of 50 or worse compared with those in the initial-onset acute VKH disease (p < 0.001) (Table 5).

Effect of immunomodulatory drugs as first-line therapy in patients with initial-onset acute VKH disease

There were no significant differences in baseline characteristics between the corticosteroid group and the corticosteroid + immunomodulatory therapy group. During the follow-up period, the use of immunomodulatory agents as first-line therapy significantly reduced the rates of development of any complication of cataract or glaucoma or subretinal neovascular membranes (p = 0.024), 'sunset glow fundus' (p = 0.038) and peripapillary atrophy (p = 0.028), (Table 6).

Effect of immunomodulatory drugs in patients with chronic recurrent VKH disease

There were no significant differences in baseline characteristics between the

Table 3. Results from stepwise logistic regression analysis showing the predictor variables for attainment of final VA of 20 of 20 and development of any complication of cataract or glaucoma or subretinal neovascular membranes in the whole study group of 174 eyes.

Outcome	Predictor variables	Regression coefficient	Coefficient / SE (Coefficient)	Odds ratio	95% Confidence interval
Final visual acuity of 20/20	Age (>16 years) (Yes)	1.704	2.77	5.50	1.63–18.5
	Exudative retinal detachment at presentation (Yes)	2.202	2.57	9.05	1.67–49.1
	Visual acuity >20/200 at presentation (Yes)	1.446	2.79	4.25	1.53–11.8
	'Sunset glow fundus' complication (Yes)	−2.378	−3.20	0.092	0.021–0.402
	Cataract complication (Yes)	−3.066	−5.44	0.047	0.015–0.142
Development of any complication of cataract/ glaucoma/subretinal neovascular membranes	Age (>16 years) (Yes)	1.147	2.05	3.15	1.04–9.48
	Mutton-fat keratic precipitates at presentation (Yes)	1.527	3.74	4.60	2.06–10.3
	Chronic recurrent presentation (Yes)	2.456	5.60	11.70	4.90–27.7
	Use of immunomodulatory therapy (Yes)	−1.023	−2.41	0.360	0.155–0.832

Table 4. Factors affecting development of any complication of cataract or glaucoma or subretinal neovascular membranes in 174 eyes.

Variable		p-value
Age (years)		
≤16 (n = 36)	12 (33.3)	0.547
>16 (n = 138)	56 (40.6)	
Initial visual acuity		
≤20/20 (n = 49)	24 (49.0)	0.133
>20/200 (n = 125)	44 (35.2)	
Mutton-fat keratic precipitates		
Yes (n = 78)	48 (61.5)	<0.001*
No (n = 96)	20 (20.8)	
Anterior chamber reaction		
<2+ (n = 55)	9 (16.4)	<0.001*
≥2+ (n = 119)	59 (49.6)	
Iris nodules		
Yes (n = 16)	12 (75.0)	0.005*
No (n = 158)	56 (35.4)	
Posterior synechiae		
Yes (n = 71)	39 (54.9)	0.001*
No (n = 103)	29 (28.2)	
Exudative retinal detachment		
Yes (n = 118)	28 (23.7)	<0.001*
No (n = 56)	40 (71.4)	
Type of presentation		
Initial-onset acute VKH (n = 106)	19 (17.9)	<0.001*
Chronic recurrent VKH (n = 68)	49 (72.1)	
Use of immunomodulatory therapy		
Yes (n = 72)	19 (26.4)	0.006*
No (n = 102)	49 (48.0)	
'Sunset glow fundus'		
Yes (n = 84)	55 (65.5)	<0.001*
No (n = 90)	13 (14.4)	
Chorioretinal atrophy		
Yes (n = 80)	51 (63.8)	<0.001*
No (n = 94)	17 (18.1)	
Peripapillary atrophy		
Yes (n = 30)	22 (73.3)	<0.001*
No (n = 144)	46 (31.9)	

* Statistically significant at 5% level of significance.

corticosteroid group and the corticosteroid + immunomodulatory therapy group. At the final follow-up period, significantly more eyes in the corticosteroid + immunomodulatory therapy group achieved visual acuity of 20 of 20 compared with those in the corticosteroid group (p = 0.024). On the other hand, significantly more eyes in the corticosteroid group had visual acuity of 20 of 50 or worse compared with those in the corticosteroid + immunomodulatory therapy group (p = 0.036) (Table 7).

Discussion

In the current series, there were 18 (20.7%) patients who were 16 years of age or younger. Our multivariate analysis identified a significant association between age older than 16 years at presentation and the development of any complication of cataract or glaucoma or subretinal neovascular membranes. Similarly, previous studies found that an older age at the onset of the disease was significantly associated with the development of cataract (Read et al. 2001a,b; Al-Kharashi et al. 2007; Chee et al. 2009). On the other hand, our analysis showed a significant association between age older than 16 years at presentation and final visual acuity of 20 of 20. In the current study, the initial presenting visual acuity was found to correlate well with final visual acuity. Eyes that had good visual acuity at presentation were more likely to have good final visual acuity. This association retained statistical significance in the multivariate analysis. Initial visual acuity was also shown to be significantly associated with final visual acuity in previous studies (Ohno et al. 1988; Read et al. 2001a,b; Al-Kharashi et al. 2007). In addition, Chee et al. (2009) found that good visual acuity at one month after starting treatment was an important good prognostic factor.

The current study has identified a significant association between severity of anterior segment inflammation

Table 5. Comparisons of baseline characteristics and clinical outcomes between initial-onset acute and chronic recurrent Vogt–Koyanagi–Harada (VKH) disease eyes.

Variable	Initial-onset acute VKH disease (n = 106 eyes) (%)	Chronic recurrent VKH disease (n = 68 eyes) (%)	p-value
At presentation			
Age (years) ≤ 16	16 (15.1)	20 (29.4)	0.037*
Visual acuity ≤ 20/200	26 (24.5)	23 (33.8)	0.247
Mutton-fat keratic precipitates	34 (32.1)	44 (64.7)	< 0.001*
Anterior chamber reaction ≥2+	54 (50.9)	65 (95.6)	< 0.001*
Iris nodules	0 (0.0)	16 (23.5)	< 0.001*
Posterior synechiae	21 (19.8)	50 (73.5)	< 0.001*
Exudative retinal detachment	106 (100.0)	12 (17.6)	< 0.001*
During follow-up			
Cataract/glaucoma/subretinal neovascular membranes	19 (17.9)	49 (72.1)	< 0.001*
Cataract	17 (16.0)	45 (66.2)	< 0.001*
Glaucoma	14 (13.2)	22 (32.4)	0.004*
Subretinal neovascular membranes	0 (0.0)	12 (17.6)	< 0.001*
'Sunset glow fundus'	16 (15.1)	68 (100.0)	< 0.001*
Chorioretinal atrophy	12 (11.3)	68 (100.0)	< 0.001*
Peripapillary atrophy	6 (5.7)	24 (35.3)	< 0.001*
At final follow-up			
Visual acuity 20/20	83 (78.3)	27 (39.7)	< 0.001*
Visual acuity ≤ 20/50	9 (8.5)	31 (45.6)	< 0.001*

* Statistically significant at 5% level of significance.

Table 6. Comparisons of baseline characteristics and clinical outcomes in initial-onset acute Vogt–Koyanagi–Harada (VKH) disease patients (n = 106 eyes) treated with or without immunomodulatory therapy.

Variable	Immunomodulatory therapy		p-value
	Yes (n = 50 eyes) (%)	No (n = 56 eyes) (%)	
At presentation			
Age (years) ≤ 16	8 (16.0)	8 (14.3)	0.999
Visual acuity ≤ 20/200	15 (30.0)	11 (19.6)	0.312
Anterior chamber reaction ≥2+	29 (58.0)	25 (44.6)	0.239
Posterior synechiae	9 (18.0)	12 (21.4)	0.843
During follow-up			
Cataract/glaucoma/subretinal neovascular membranes	4 (8.0)	15 (26.8)	0.024*
Cataract	4 (8.0)	13 (23.2)	0.033*
Glaucoma	4 (8.0)	10 (17.9)	0.227
'Sunset glow fundus'	4 (8.0)	12 (21.4)	0.038*
Chorioretinal atrophy	4 (8.0)	8 (14.3)	0.476
Peripapillary atrophy	0 (0.0)	6 (10.7)	0.028*
At final follow-up			
Visual acuity 20/20	42 (84.0)	41 (73.2)	0.267
Visual acuity ≤ 20/50	2 (4.0)	7 (12.5)	0.167

* Statistically significant at 5% level of significance.

at presentation and the final visual acuity and the development of complications. There was a significant association between severe anterior uveitis at presentation as indicated by the presence of mutton-fat keratic precipitates, anterior chamber reaction of 2+ or more, iris nodules and posterior synechiae and a worse final visual acuity and the development of complications. Using logistic regression analysis, the presence of mutton-fat keratic precipitates at presentation was an independent significant predictor for the development of any complication of cataract or glaucoma or subretinal neovascular membranes. In this study, the presence of exudative retinal detachment, a manifestation of initial-onset acute VKH disease, at presentation was significantly associated with final visual acuity of 20 of 20 and a lower risk of developing any complication of cataract or glaucoma or subretinal neovascular membranes. The association between exudative retinal detachment at presentation and final visual acuity at 20 of 20 retained statistical significance in the multivariate analysis. The development of ocular complications was significantly associated with a worse final visual acuity. Our observations are consistent with previous reports showing a significant association between poor final visual acuity and greater numbers of complications (Ohno et al. 1988; Read et al. 2001a,b).

Patients with VKH disease show different clinical manifestations depending on the duration of the disease before presentation. The disease typically begins with choroiditis associated with exudative retinal detachment and optic disc hyperaemia and swelling. The disease will proceed to chronic recurrent granulomatous anterior uveitis if not properly treated with typical 'sunset glow fundus' and chorioretinal atrophy (Yang et al. 2007; Fang & Yang 2008). In the current study, 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. These results are consistent with those of Fang et al. (2008) who demonstrated, using laser flare-cell meter, that both aqueous flare value and cell counts were significantly higher in patients with chronic recurrent VKH disease than in those with initial-onset acute VKH disease. In addition, recurrent inflammation in the anterior segment was more refractory in patients with recurrent VKH disease. During the follow-up period, the rates of ocular complications including cataract, glaucoma, subretinal neovascular membranes, '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. In multivariate analysis, chronic

Table 7. Comparisons of baseline characteristics and clinical outcomes in Chronic recurrent Vogt–Koyanagi–Harada (VKH) disease patients (n = 68 eyes) treated with or without immunomodulatory therapy.

Variable	Immunomodulatory therapy		p-value
	Yes (n = 22 eyes) (%)	No (n = 46 eyes) (%)	
At presentation			
Age (years) ≤ 16	8 (36.4)	12 (26.1)	0.384
Visual acuity ≤ 20/200	7 (31.8)	16 (34.8)	0.809
Mutton-fat Keratic precipitates	14 (63.6)	30 (65.2)	0.898
Anterior chamber reaction ≥2+	22 (100.0)	43 (93.5)	0.231
Iris nodules	6 (27.3)	10 (21.7)	0.615
Posterior synechiae	18 (81.8)	32 (69.5)	0.284
Exudative retinal detachment	5 (22.7)	7 (15.2)	0.447
During follow-up			
Cataract/glaucoma/subretinal neovascular membranes	15(68.2)	34 (73.9)	0.622
Cataract	12 (54.5)	33 (71.7)	0.161
Glaucoma	5 (22.7)	17 (37.0)	0.241
Peripapillary atrophy	8 (36.4)	16 (34.8)	0.898
At final follow-up			
Visual acuity 20/20	13 (59.1)	14 (30.4)	0.024*
Visual acuity ≤ 20/50	6 (27.3)	25 (54.3)	0.036*

* Statistically significant at 5% level of significance.

recurrent presentation was significantly associated with the development of any complication of cataract or glaucoma or subretinal neovascular membranes. Our observations are consistent with previous reports showing that complications were more common in patients with chronic recurrent VKH disease who presented with recurrent granulomatous anterior uveitis with 'sunset glow fundus' (Yang et al. 2007). In addition, Keino et al. (2002) demonstrated a significant association between the incidence of chronic ocular inflammation and the appearance of 'sunset glow fundus'. Furthermore, indocyanine green angiographic studies of patients during episodes of apparent isolated anterior segment recurrence showed choroidal changes suggestive of ongoing inflammation despite the absence of clinical signs of posterior segment involvement, and this could contribute to the development of 'sunset glow fundus' appearance and chorioretinal atrophy (Bacsal et al. 2008). Consequently, the final visual outcome was worse in patients with chronic recurrent VKH disease compared with those with initial-onset acute VKH disease. Similarly, previous reports demonstrated a significant association between chronic recurrent anterior segment inflammation and poor final visual acuity and the development of long-term complications (Rubsamen & Gass 1991; Read et al. 2001a,b; Keino et al. 2002; Al-Kharashi et al. 2007).

In the present study, we administered high-dose systemic corticosteroids with gradual tapering in all cases. Nonsteroid immunomodulatory therapy with cyclosporine and mycophenolate mofetil as first-line therapy combined with systemic corticosteroids was used in 36 patients. On univariate analysis, the use of immunomodulatory therapy significantly improved visual outcome and reduced the development of late complications in the whole study group. Using logistic regression analysis, the use of immunomodulatory therapy was significantly associated with a lower risk of developing any complication of cataract or glaucoma or subretinal neovascular membranes. Our observations are consistent with previous reports showing that the use of immunomodulatory therapy as first-line therapy in addition with systemic corticosteroids is associated with good clinical results (Paredes et al. 2006; Kim & Yu 2007; Cuchacovich et al. 2010; Abu El-Asrar et al. 2012).

In patients with initial-onset acute VKH disease, the use of immunomodulatory therapy as first-line therapy combined with systemic corticosteroids significantly reduced the development of any complication of cataract or glaucoma or subretinal neovascular membranes, peripapillary atrophy and 'sunset glow fundus'. There is accumulating evidence to suggest that despite proper treatment with corticosteroids, many patients develop progressive depigmentation of the fundus resulting in 'sunset glow fundus' appearance and chorioretinal atrophy, even after the clinical disease appears to be under control (Keino et al. 2002; Al-Kharashi et al. 2007; Lai et al. 2009). The current study has indentified a significant association between the development of 'sunset glow fundus' and a worse final visual acuity and the development of any complication of cataract or glaucoma or subretinal neovascular membranes. The negative association between 'sunset glow fundus' and final visual acuity of 20 of 20 retained statistical significance in the multivariate analysis. The development of 'sunset glow fundus' and chorioretinal atrophy despite apparent control of ocular inflammation suggests ongoing subclinical choroidal inflammation (Bacsal et al. 2008; Lai et al. 2009; Kawaguchi et al. 2010). 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. These findings support the presence of ongoing subclinical inflammation in the convalescent stage of VKH disease (Inomata & Sakamoto 1990). In the present study, the use of immunomodulatory therapy as first-line therapy in patients with initial-onset acute VKH disease significantly reduced the development of 'sunset glow fundus' suggesting that immunomodulatory therapy was effective in controlling progressive subclinical choroidal inflammation. Therefore, uveal depigmentation and chorioretinal atrophy should not be regarded as convalescent signs. Rather, we suggest that they be considered signs of ongoing subclinical inflammation due to inadequate immunosuppressive therapy. Clearly, randomized clinical trials with larger sample sizes are necessary to confirm our results.

In conclusion, poor visual acuity and severe anterior segment inflammation at presentation are significantly

associated with a worse outcome. Chronic recurrent VKH disease is significantly associated with more severe anterior segment inflammation and less exudative retinal detachment at presentation, more ocular complications and a worse visual outcome compared with initial-onset acute VKH disease. The use of immunomodulatory therapy as first-line therapy combined with systemic corticosteroids significantly improved the clinical outcomes.

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Correspondence:
Ahmed M. Abu El-Asrar, MD, PhD
Department of Ophthalmology
King Abdulaziz University Hospital
Old Airport Road
P.O. Box 245
Riyadh 11411
Saudi Arabia
Tel: 966-1-4775723
Fax: 966-1-4775724
Email: abuasrar@ksu.edu.sa;
abuelasrar@yahoo.com