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Frequency of Distinguishing Clinical Features in Vogt-Koyanagi-Harada disease

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Abstract

Purpose—To determine the frequency of occurrence of limited clinical features which distinguish patients with Vogt-Koyanagi-Harada (VKH) disease from those with non-VKH uveitis.

Design—Comparative case series.

Participants—1147 total patients.

Methods—All patients with bilateral ocular inflammatory disease presenting to any of ten uveitis centers in the three month period between 2006-January-01 and 2006-March-31 (inclusive) were asked to participate. The clinical and historical features of disease were obtained from the participants via direct interview and chart review. Patients were stratified based on whether they were diagnosed with VKH disease or non-VKH uveitis for statistical analysis.

Main Outcome Measures—Presence or absence of various clinical features in the two populations.

Results—Of 1147 patients, 180 were diagnosed with VKH disease and 967 with non-VKH uveitis. Hispanics and Asians were more likely to be diagnosed with VKH than non-VKH disease compared

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to other ethnicities. In acute disease, the finding of exudative retinal detachment was most likely to be found in VKH disease with a positive predictive value (PPV) of 100 and negative predictive value (NPV) of 88.4, while in chronic disease, sunset glow fundus was most likely to be found, with a PPV of 94.5 and NPV of 89.2.

Conclusions—Numerous clinical findings have been described in the past as important in the diagnosis of VKH. The current study reveals that of these, two are highly specific to this entity in an ethnically and geographically diverse group of patients with non-traumatic bilateral uveitis. These clinical findings are 1. exudative retinal detachment during acute disease and 2. sunset glow fundus during the chronic phase of the disease.

Vogt-Koyanagi-Harada disease (VKH) is a visually disabling bilateral intraocular inflammation usually associated with extraocular manifestations such as meningismus, vitiligo, poliosis, and dysacusis.^{1–3} The extraocular manifestations typically appear in different phases of the disease and may vary in different ethnic groups.^{1, 4–6} For example, cutaneous manifestations are typically absent during the acute phase and appear later in the disease course, while the neurologic and auditory manifestations generally precede ocular manifestations. The absence of concurrent extraocular manifestations may have significant implications for both clinical practice and the conduct of clinical studies, as follows. In the area of clinical practice, variation in manifestations and their timing may cause a delay in establishing the correct diagnosis and thus a delay in the initiation of appropriate treatment. This may result in the disease entering the chronic/recurrent phase and in the subsequent development of complications such as glaucoma, cataract, and subretinal neovascularization or fibrosis.^{1, 7–10} In the area of clinical research, in addition to the issue described for clinical practice, VKH is a relatively uncommon disease and future clinical studies will require international collaboration and pooling of patients of various ethnicities to achieve numbers of subjects sufficient for meaningful conclusions to be drawn. Variations in the presentation of VKH patients can make it difficult to ensure that all subjects enrolled in a clinical study truly have VKH disease. To this end, various diagnostic criteria have been created,^{4, 11, 12} but developing criteria that are broad enough to encompass the various ways in which VKH may present, while ensuring that non-VKH patients are excluded, is difficult. In addition, none of the published sets of criteria, to our knowledge, has been created based on a sound statistical analysis of the most common and distinguishing manifestations of the disease. As a basis for the development of a statistically and epidemiologically validated set of diagnostic findings, the current multinational study was undertaken to define the clinical features which distinguish VKH from other forms of uveitis.

Methods

Institutional Review Board (IRB)/Ethics Committee (or equivalent body) approval was obtained at each study site by each site's principal investigator and all research adhered to the tenets of the Declaration of Helsinki. For United States sites, all work was compliant with the Health Insurance Portability and Accountability Act (HIPAA). The study centers were Doheny Eye Institute; Postgraduate Institute of Medical Education and Research, Chandigarh; Singapore National Eye Center; Department of Ophthalmology, Kyorin University School of Medicine; Fattouma Bourguiba University Hospital, University of Paris 1V; University of Rome; Tokyo Medical and Dental University; Ramathibodi Hospital; and the University of Alabama at Birmingham. At each center, all patients with clinical features of bilateral intraocular inflammation, presenting as a new patient or in follow up during the 3-month period from 2006-January-01 to 2006-March-31 (inclusive) were prospectively identified. A standard data capture matrix was developed and distributed to all study sites. The matrix was based on the generally accepted clinical features of VKH and included the set of criteria proposed by the First International Workshop on VKH.¹¹ Sunset glow changes is defined as depigmented

fundus showing orange-red discoloration mimicking sunset.¹⁰ Standard images consisting of fundus photographs showing sunset glow changes, nummular chorioretinal scars, and retinal pigment epithelial alterations (Figure 1) were distributed to the participating uveitis centers for reference in documenting findings at the time of ophthalmic examination. These standards had been unanimously accepted by the participating international uveitis experts prior to initiation of the study. Data capture was completed at the time of examination by patient query and clinical examination. For patients presenting as a follow up during the study period, data that had been captured on previous visits was also extracted by chart review. Information collected included demographic data, symptoms and clinical findings, diagnostic investigations performed, and final diagnosis. The Standardization of Uveitis Nomenclature guidelines for reporting clinical data as regards duration of uveitis, anatomic classification, and course of the disease were utilized.¹³ Patients with a history of intraocular inflammation of duration of 3 months or less were classified as acute; those with a history of intraocular inflammation with duration of more than 3 months were classified as chronic. No patient was examined for the study more than once.

The collected data was coded for analysis. Statistical analyses were carried out comparing patients diagnosed with and without VKH. Demographic variables of age, gender and race were compared stratified by uveitis status. Means and standard deviations (sd) for age were compared between groups using independent sample t-tests, while the distributions for gender and race were compared between groups using Fisher's exact and Chi-square tests. Sensitivity, specificity, positive and negative predictive values and likelihood ratio (95% confidence interval) were calculated for symptoms and clinical findings for VKH and bilateral non-VKH subjects and stratified by acute and chronic uveitis status, as follows: sensitivity [True Positive/(** True Positive + False Negative)] (defined as the probability of correctly identifying subjects who have a disease); specificity [True Negative/(True Negative + False Positive)] (defined as the probability of correctly identifying subjects who do not have a disease); positive predictive value [True Positive/(True Positive + False Positive)] (the probability that if the test diagnoses a subject as having the disease, it is true); and negative predictive value [True Negative/(True Negative + False Negative)] (the probability that if the test is negative the subject does not have the disease). Multiple logistic regression models were constructed using stepwise selection to determine which variables were independently predictive of VKH status. For other models variables were combined using a stepwise analytical approach, first identifying which parameters by univariate assessment were statistically significant, then different combinations of these parameters were tested to see if the specificity or sensitivity improved. All statistical analyses were carried out using SAS 9.0 software (SAS Institute, Cary, North Carolina).

Results

A total of 1147 patients with bilateral ocular inflammatory disease presented to ten uveitis centers during the study period (Table 1). Of these, 180 patients (15.8%) were diagnosed with VKH. The demographic features of all patients are summarized in Table 2. As this table shows, of patients presenting in the acute phase of disease, Hispanics were more likely to be diagnosed with VKH than non-VKH uveitis. In patients examined during the chronic phase of uveitic disease, Hispanics and Asians were more likely to be diagnosed with VKH than non-VKH, while the reverse was true for Caucasians and African-Americans (Table 2).

Presenting symptoms and clinical findings in all patients are detailed in Table 3. Uveitis classifications for non-VKH patients are provided in Table 4. A comparison of clinical features in acute and chronic VKH with non-VKH patients with anterior, posterior or pan uveitis is provided in Table 5 and Table 6. The acute VKH cases were further compared with posterior or panuveitis non-VKH patients (Table 7). A stepwise logistic regression model for acute and chronic VKH identified exudative retinal detachment and sunset glow fundus as being

associated with acute and chronic VKH, (Table 8) with Odds Ratio of >999 (48.02, >999) and 141.66 (54.65, 367.2) respectively. The constellation of bilateral intraocular inflammation and subretinal focal collections of fluid or bullous retinal detachment had a PPV of 100 and a NPV for VKH disease of 88.4 (Table 5). Among patients with chronic uveitis, the findings of sunset glow fundus and vitiligo were more likely to occur in VKH patients as compared to non-VKH patients, with a likelihood ratio varying from 50.2 to 34.6 (Table 6; see Table 9, available at <http://aaojournal.org>)

Discussion

Uveitis is not a single disease but rather a multitude of entities with different pathophysiologies, prognoses, and treatment requirements. Thus establishing, as definitively as possible, a specific diagnosis in uveitic disease is important to allow appropriate counseling, treatment, and surveillance of patients. In the absence of definitive diagnostic testing, agreement on a set of features that are characteristic and typical for a given uveitic entity is necessary in order to allow the clinician to provide the above clinical services and in addition, to allow the clinical researcher to define homogeneous populations of patients for clinical study. As evidenced by the publication of multiple papers proposing or evaluating diagnostic criteria for VKH disease, 2, 3, 11, 12, 14 a definitive set of such criteria for this condition has not been universally agreed upon. In part, this stems from the multiphasic nature of VKH, with varying clinical features in different stages of the disease as well as the potential for ethnic variation in disease manifestations. One of the first steps in establishing diagnostic criteria is to determine, in as widely applicable a population as possible, the occurrence of clinical signs and symptoms felt by those clinicians with broad exposure in the condition to be prototypical. In the current study, the authors sought to determine the frequency of features considered typical for VKH in patients with acute or chronic uveitis, presenting to uveitis clinics in ten geographically and ethnically diverse centers. Initial analyses of the presence or absence of these findings in VKH and non-VKH anterior, posterior or panuveitis patients have revealed several distinguishing features.

While considered a systemic condition, VKH can present with disease findings limited to intraocular inflammation. In patients with acute VKH, 54% had only ocular manifestations, while in chronic disease, 40.9% had findings limited to the eyes.¹⁵ As previously published diagnostic criteria include, as a variable requirement, the presence of extraocular manifestations, this raises the question of what ocular features were considered by the uveitis experts to be specific to VKH.

It is generally agreed that diffuse choroidal thickening is a hallmark of acute VKH disease.^{1, 11} While the number of acute cases with choroidal thickening documented by ultrasonography was limited in the current study, all such patients also had retinal findings (Table 4, Table 5 and Table 7). This indicates that in acute uveitis, the presence of bilateral intraocular inflammation with the retinal findings considered typical for VKH (as detailed in Table 4) may be sufficient evidence that choroidal involvement and thickening exist. However, in patients with uveitis without clinically apparent exudative retinal detachments, ultrasonography and fluorescein angiography can detect choroidal and retinal findings.^{16–20} In the current report, robust positive and negative predictive values and likelihood ratios of the various documented clinical findings indicate that in acute uveitis, the presence of bilateral exudative retinal detachments (Figure 2) in a patient with bilateral intraocular inflammation strongly suggests acute VKH.

In those patients with chronic disease diagnosed as VKH, the findings of sunset glow fundus and Sugiura sign were distinguishing. Sugiura sign appears to be observed mostly in patients from Japan,^{1, 2, 21} suggesting that either non-Japanese VKH patients do not develop perilimbal depigmentation or that the sign is under-recognized outside Japan.

Extraocular signs such as vitiligo, alopecia, poliosis and hearing loss develop during the course of VKH disease and are seen mainly in patients with chronic disease.¹ However, the combination of these extraocular findings with sunset glow fundus changes did not improve the likelihood ratio or the positive and negative predictive values (Table 6), indicating that the sunset glow fundus is a uniquely distinctive feature of chronic VKH disease, and clearly suggests that sunset glow fundus alone is sufficient to diagnose chronic VKH.

Ancillary testing is frequently utilized in support of the diagnosis of VKH. In the current study, 127 VKH patients underwent fluorescein angiography and had results available; 487 non-VKH patients underwent fluorescein angiography. Of the 127 VKH patients, 106 (83%) showed one or more angiographic findings (Table 3). In contrast, of the 487 patients with non-VKH disease, 80 (16%) showed one or more angiographic findings. Pleocytosis of the cerebrospinal fluid (CSF) is a common finding in patients with acute VKH and in fact is listed in the diagnostic criteria currently published.^{2, 3, 15, 16} In the current study, of 44 patients who underwent CSF analysis and whose results were available, 34 (77%) were found to have pleocytosis. In 34 non-VKH patients undergoing CSF analysis with available results, 10 (29%) were found to have pleocytosis (Table 3). Thus while such data shows that CSF analysis may be a useful procedure for supporting the diagnosis of VKH, it is probably no superior to fluorescein angiography.

It is interesting to note that VKH disease can present in patients with clinical features limited to the eye in the acute phase in the form of bilateral uveitis associated with exudative retinal detachment, while in the chronic phase VKH patients may present with sunset glow fundus without extraocular finding. Recognition of this isolated ocular variant of acute and chronic VKH is important for prompt diagnosis. More over the current study clearly shows in patients with bilateral uveitis, the importance of exudative retinal detachment and sunset glow fundus changes as the main diagnostic findings in acute and chronic VKH respectively. Sunset glow fundus is a descriptive and somewhat subjective clinical term; but the definition has not been a matter of disagreement among uveitis specialists in the setting of the diagnosis of chronic VKH. However, the definition of the term has not been standardized/validated, and the condition might be confounded with the albinotic fundi of some Caucasian individuals. In chronic VKH, the sunset glow changes result from depigmentation of the choroid, which leads to a discoloration of the fundus; the change may be from brunette to blonde, or it may present as an exaggerated reddish glow, resembling an albinotic fundus, but there is usually migration and clumping of pigment and discrete atrophic spots.^{22, 23, 24} In the current study the possible similarities between the sunset glow fundus and the fundus of normal Caucasian individuals may have played a role in the under recognition and/or difficulty in differentiating normal fundus from the depigmented fundus in Caucasians. Of note, only 15% of those individuals diagnosed with chronic VKH (when the presence of sunset glow fundus is a prominent feature, observed in 65%) are Caucasian; in comparison, Caucasians represented 35% of those individuals diagnosed with acute VKH (Table 2 and Table 6). However, a further standardized approach in VKH individuals, in particular in Caucasians, may address the need for a more precise recognition of this important clinical finding, allowing its differentiation from a normally hypopigmented fundus.

In conclusion, to our knowledge this is the first prospective international study on the features of VKH in an ethnically and geographically diverse study group. This data provides information regarding clinical features of VKH as compared to non-VKH disease and reveals several of these features as distinctive for VKH. It is true that an argument of circular reasoning could be made against the methodology utilized, in that cases of uveitis were diagnosed based on the opinion of various uveitis experts, which certainly have established ideas of what constitutes VKH disease. It thus is not surprising that the features these experts considered key to a diagnosis of VKH are more common in those patients diagnosed with VKH. However, in diseases such as VKH, which lack definitive, objective diagnostic testing, establishing criteria

for diagnosis typically begins with a consensus agreement on what clinical features typify that disease. We thus believe that the current study provides a foundation toward development of widely accepted diagnostic criteria, by establishing those features that uveitis specialists consider diagnostic for VKH. The next step in establishing diagnostic criteria is to compile a selection of cases possessing and lacking these features, followed by review by uveitis specialists with determination of the features considered essential in establishing the diagnosis of VKH disease. However, the current study shows that limited clinical features are adequate in arriving at the diagnosis of VKH that can be agreeable to international experts on this disease entity.

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Figure 1.

Chronic Vogt-Koyanagi-Harada disease. Sunset glow fundus (A) and nummular chorioretinal scars (B) in a 54-year-old Asian male with chronic Vogt-Koyanagi-Harada disease (VKH). Note, there is also peripapillary atrophy. Retinal pigment epithelial changes (C) are present in the fundus of a 36-year-old Hispanic woman with chronic VKH.

Figure 2.

Acute Vogt-Koyanagi-Harada disease. Fundus shows bilateral exudative retinal detachments involving the macula (A and B). The fluorescein angiogram reveals pinpoint leaks at the level of retinal pigment epithelium during the arterio-venous phase (C) and collection of the dye in the subretinal space during the late phase (D).

Vogt-Koyanagi-Harada disease and Non-Vogt-Koyanagi-Harada disease uveitis patients from ten uveitis centers: the number of patients by center

Table 1

Center #	VKH	Non-VKH	Total
1. U.S. (Doheny)	35 (21.6%)	127 (78.4%)	162
2. France	15 (9.1%)	150 (90.9%)	165
3. India	22 (12.8%)	150 (87.2%)	172
4. Italy	6 (9.7%)	56 (90.3%)	62
5. Japan (K)	29 (19.3%)	121 (80.7%)	150
6. Japan (M)	8 (14.5%)	47 (85.5%)	55
7. U.S. (RWR)	2 (1.8%)	109 (98.2%)	111
8. Singapore	32 (22.2%)	112 (77.8%)	144
9. Thailand	15 (34.9%)	28 (65.1%)	43
10. Tunisia	16 (19.3%)	67 (80.7%)	83
Total	180 (15.7%)	967 (84.3%)	1147

U.S.=United States; M=Kyorin University School of Medicine; M=Tokyo Medical and Dental University; RWR= University of Alabama at Birmingham

Table 2

Demographic features of all patients with Vogt-Koyanagi-Harada disease compared to non-Vogt-Koyanagi-Harada disease

	VKH	Non VKH	P-value
Patients	180	967	
Mean age, years			
Acute uveitis	40.8 (13.4)	35.7 (18.3)	0.23
Chronic uveitis	44.6 (15.1)	44.7 (17.6)	0.98
Gender			
Acute uveitis			
Female	75%	59.1%	0.17
Male	25%	40.9%	
Chronic uveitis			
Female	68.1%	60.6%	
Male	31.9%	39.4%	
Race			
Acute uveitis			
Asian	35%	19%	0.14
African-American	0%	3.7%	1
Caucasian	35%	51.8%	0.23
Hispanic	25%	4.4%	0.006
Asian Indian	5%	21.2%	0.13
Chronic uveitis			
Asian	47.2%	34.1%	0.003
African-American	2.5%	9.2%	0.002
Caucasian	15.1%	36.0%	<0.001
Hispanic	19.5%	4%	<0.001
Asian Indian	15.7%	16.7%	0.82

VKH= Vogt-Koyanagi-Harada disease; the figures in parenthesis represent standard deviation.

Table 3

Symptoms, Clinical Findings, and Diagnostic study results in All Patients with Vogt-Koyanagi-Harada disease Compared to Non-Vogt-Koyanagi-Harada disease *

	VKH	Non-VKH
Symptoms		
Headaches	85/173 (49%)	180/940 (19%)
Photophobia	84/175 (48%)	441/939 (47%)
Tinnitus	61/171 (36%)	63/938 (7%)
Neck stiffness	57/173 (33%)	122/943 (13%)
Difficulty hearing	45/139 (32%)	40/835 (5%)
Weakness	36/173 (21%)	101/928 (11%)
Flu like symptoms	29/170 (17%)	77/930 (8%)
Nausea	22/174 (13%)	35/947 (4%)
Clinical Findings		
Sunset glow fundus	103/178 (58%)	9/951 (1%)
Nummular chorioretinal. scars	82/178 (46%)	83/952 (9%)
RPE clumping/migration	79/176 (45%)	103/948 (11%)
Vitreous cells	66/175 (38%)	351/954 (37%)
Cataract	66/180 (37%)	323/964 (34%)
Anterior chamber cells	64/180 (36%)	377/965 (39%)
Poliosis	50/179 (28%)	113/959 (12%)
Anterior chamber flare	43/179 (24%)	243/947 (26%)
Keratic precipitates	39/180 (22%)	188/963 (20%)
Vitiligo	36/178 (20%)	8/959 (1%)
Choroidal thickening	23/113 (20%)	7/505 (1%)
Hearing loss	32/179 (18%)	24/957 (3%)
Alopecia	32/179 (18%)	46/957 (5%)
Disc hyperemia/swelling	22/176 (13%)	84/951 (9%)
Ocular hypertension	20/180 (11%)	84/964 (9%)
Glaucoma	18/179 (10%)	76/958 (8%)
Subretinal fibrosis	15/178 (8%)	19/951 (2%)
Bullous detachment	11/178 (6%)	9/954 (1%)
Sugiura sign	9/175 (5%)	1/953 (0%)
Subretinal fluid	8/178 (4%)	15/958 (2%)
Subretinal neovascularization	4/177 (2%)	11/952 (1%)
Diagnostic Testing Results		
FA: D or M or L or P or Choroidal thickening	111/124 (90%)	86/282 (30%)
FA: D or M or L or P	106/127 (83%)	80/487 (16%)
CSF pleocytosis	34/44 (77%)	10/34 (29%)
FA: Optic disc staining	90/128 (70%)	176/506 (35%)

	VKH	Non-VKH
FA: Multifocal leaks (M)	89/127 (70%)	43/503 (9%)
FA: Subretinal pooling of dye (P)	71/127 (56%)	10/502 (2%)
FA: Large placoid areas of hyperfluorescence (L)	54/126 (43%)	44/504 (9%)
FA: Choroidal perfusion delay (D)	50/122 (41%)	15/485 (3%)
FA: D or M or L or P <i>and</i> Choroidal thickening	18/83 (22%)	1/248 (0%)
Choroidal thickening on ultrasound	23/113 (20%)	7/505 (1%)

VKH, Vogt-Koyanagi-Harada disease; RPE= retinal pigment epithelium; FA, fluorescein angiography; D, Choroidal perfusion delay; M, Multifocal leaks on FA; L, Large placoid areas of hyperfluorescence; P, subretinal pooling of dye

* In this group there were 8 patients who could not be further classified as acute or chronic ocular inflammations and one of these patients had sunset glow fundus.

Table 4
Classification of ocular inflammation entities in 967 patients with non-Vogt-Koyanagi-Harada disease

Uveitis Entity	Anterior uveitis	Intermediate uveitis	Posterior uveitis	Panuveitis	Without anatomic classification	TOTAL
Total	274*	107*	120*	110	309	920*
HLA B27 Associated	72					72
Fuchs uveitis syndrome	6					6
Juvenile arthritis associated	20					20
Herpetic associated anterior	5					5
Viral retinitis			1			1
Tuberculosis	3	10	11	4	21	49
Toxoplasmosis			1		3	4
Cytomegalovirus retinitis	1		4			5
Lyme				2		2
Syphilis	4	1			1	6
Pars Planitis		84				84
Sarcoidosis	8	7		3	95	113
Sympathetic ophthalmia				16		16
Birdshot chorioretinopathy			32	1		33
Serpiginous			13			13
Multifocal choroiditis				19		19
Systemic lupus erythematosus associated	2		4	1		7
Multiple sclerosis associated		3				3
Behcets	1			2	108	111
Masquerade Syndrome					11	11
Others	152	2	54	62	70	340

* Total number of cases based on anatomic classification; 42 patients had scleritis/episcleritis and 5 had optic neuritis

Table 5

Acute Disease: Clinical Findings in Patients with Vogt-Koyanagi-Harada disease Compared to Non-Vogt-Koyanagi-Harada disease (non-Vogt-Koyanagi-Harada subjects included only for anterior, posterior or panuveitis)

Clinical Assessment	VKH	Non VKH	PPV	NPV	Sensitivity	Specificity	Likelihood Ratio	(95% CI)
Sunset glow fundus	0/20	0%	1/76	1%	0.0	98.7	0.0	.
Bullous detachment	10/20	50%	0/76	0%	50.0	100.0	.	.
Choroidal thickening	5/10	50%	1/32	3%	50.0	96.9	16.0	(2.2,113.8)
Subretinal fluid	6/20	30%	1/76	1%	30.0	98.7	22.8	(3.2,163.6)
Hearing loss	4/20	20%	2/77	3%	20.0	97.4	7.7	(1.8, 33.8)
Vitiligo	1/20	5%	1/77	1%	5.0	98.7	3.8	(0.4, 42.0)
Alopecia	2/20	10%	0/77	0%	10.0	100.0	0.0	.
Nummular chor. scars	0/20	0%	4/76	5%	0.0	94.7	0.0	.
RPE clumping/migration	2/19	11%	5/76	7%	10.5	93.4	1.6	(0.4, 6.8)
Disc hyperemia/swelling	9/19	47%	12/76	16%	47.4	84.2	3.0	(1.5, 6.1)
Poliosis	1/20	5%	7/77	9%	12.5	78.7	5.0	(0.1, 3.9)
Vitreous cells	12/19	63%	27/76	36%	63.2	64.5	1.8	(1.0, 3.1)
Anterior chamber cells	12/20	60%	52/76	68%	60.0	31.6	0.9	(0.5, 1.5)
Anterior chamber flare	5/20	25%	30/76	39%	14.3	75.4	0.6	(0.3, 1.5)
Keratic precipitates	2/20	10%	22/77	29%	8.3	75.3	0.4	(0.1, 1.4)
Sugiura sign	0/19	0%	0/75	0%	0.0	100.0	.	.
(Subretinal Fluid or Bullous retinal detachment)	11/20	55%	1/76	1%	91.7	89.3	41.8	(5.9,295.1)
(Subretinal Fluid or Bullous retinal detachment)	5/10	50%	0/32	0%	50.0	100.0	.	.
(Subretinal Fluid or Bullous retinal detachment and choroidal thickening)	0/20	0%	0/76	0%	0.0	100.0	.	.
(Subretinal Fluid or Bullous retinal detachment and alopecia)	3/20	15%	0/76	0%	15.0	100.0	.	.
(Subretinal Fluid or Bullous retinal detachment and hearing loss)								

Clinical Assessment	VKH	Non VKH	PPV	NPV	Sensitivity	Specificity	Likelihood Ratio	(95% CI)
(Subretinal Fluid or Bullous retinal detachment and (headache or neck stiffness)	6/20 30%	0/74 0%	100.0	84.1	30.0	100.0	.	.

PPV= Positive predictive value; NPV= Negative predictive value; CI= confidence interval

Table 6

Chronic Disease: Clinical Findings in Patients with Vogt-Koyanagi-Harada disease Compared to Non-Vogt-Koyanagi-Harada disease (Non-Vogt-Koyanagi-Harada subjects included only for anterior, posterior or panuveitis)

Clinical Assessment	VKH	No VKH	PPV	NPV	Sensitivity	Specificity	Likelihood Ratio	(95% CI)
Sunset glow fundus	103/158 65%	6/462 1%	94.5	89.2	65.2	98.7	50.2	(22.6, 111.3) .000
Sugiura sign	9/156 6%	1/467 0%	90.0	76.0	5.8	99.8	26.9	(3.8, 193.0) .002
Vitiligo	35/158 22%	3/469 1%	92.1	79.1	22.2	99.4	34.6	(11.2, 107.4) .000
Choroidal thickening	18/103 17%	3/225 1%	85.7	72.3	17.5	98.7	13.1	(4.2, 40.9) .000
Nummular chor. scars	82/158 52%	45/463 10%	64.6	84.6	51.9	90.3	5.3	(3.9, 7.3) .000
RPE clumping/migration	77/157 49%	67/461 15%	53.5	83.1	49.0	85.5	3.4	(2.6, 4.4) .000
Hearing loss	28/159 18%	13/469 3%	68.3	77.7	17.6	97.2	6.4	(3.6, 11.3) .000
Alopecia	30/159 19%	33/469 7%	47.6	77.2	18.9	93.0	2.7	(1.8, 4.1) .000
Poliosis	49/159 31%	63/470 13%	43.8	78.7	30.8	86.6	2.3	(1.7, 3.1) .000
Vitreous cells	54/156 35%	114/466 24%	32.1	77.5	34.6	75.5	1.4	(1.1, 1.9) .014
Disc hyperemia/swelling	13/157 8%	28/464 6%	31.7	75.2	8.3	94.0	1.4	(0.8, 2.4) .329
Keratic precipitates	37/160 23%	84/470 18%	30.6	75.8	23.1	82.1	1.3	(0.9, 1.8) .146
Anterior chamber flare	38/159 24%	111/464 24%	25.5	74.5	23.9	76.1	1.0	(0.7, 1.4) .995
Anterior chamber cells	52/160 33%	167/472 35%	23.7	73.8	32.5	64.6	0.9	(0.7, 1.2) .508
Bullous detachment	1/158 1%	3/463 1%	25.0	74.6	0.6	99.4	1.0	(0.1, 7.5) .984
Subretinal fluid	2/158 1%	7/466 2%	22.2	74.6	1.3	98.5	0.8	(0.2, 3.5) .830
Sunset glow fundus or Nummular chor. scars	117/159 74%	48/463 10%	70.9	90.8	73.6	89.6	7.1	(5.3, 9.4) .000
Sunset glow fundus or Nummular chor. scars or Sugiura sign	118/158 75%	49/459 11%	70.7	91.1	74.7	89.3	7.0	(5.3, 9.3) .000
(Sunset glow fundus or Nummular chor. scars) and (vitiligo or alopecia or poliosis or hearing loss)	63/158 40%	8/461 2%	88.7	82.7	39.9	98.3	23.0	(11.5, 45.9) .000
(Sunset glow fundus or Nummular chor. scars or Sugiura sign) and (vitiligo or alopecia or poliosis or hearing loss)	64/157 41%	8/458 2%	88.9	82.9	40.8	98.3	23.3	(11.7, 46.6) .000
Sunset glow fundus and	58/157 37%	0/802 0%	100.0	89.0	36.9	100.0	.	.

Clinical Assessment	VKH	No VKH	PPV	NPV	Sensi- tivity	Speci- ficity	Likelihood	
							Ratio	(95% CI)

(vitiligo or alopecia or poliosis or hearing loss)

chor=chorioretinal; RD= retinal detachment; CI=Confidence interval; PPV=Positive predictive value; NPV=Negative predictive value; RPE=Retinal pigment epithelium; VKH= Vogt-Koyanagi-Harada disease

Table 7

Acute Disease: Clinical Findings in Patients with Vogt-Koyanagi-Harada disease Compared to Non-Vogt-Koyanagi-Harada disease (non-Vogt-Koyanagi-Harada subjects included only for posterior or panuveitis)

Clinical Assessment	VKH	Non VKH	PPV	NPV	Sensitivity	Specificity	Likelihood Ratio	(95% CI)
Sunset glow fundus	0/20	0%	1/30	3%	0.0	96.7	0.0	. .
Bullous detachment	10/20	50%	0/30	0%	100.0	75.0	50.0	100.0 . .
Choroidal thickening	5/10	50%	0/14	0%	100.0	73.7	50.0	100.0 . .
Subretinal fluid	6/20	30%	1/30	3%	85.7	67.4	30.0	96.7 9.0 (1.3, 63.3)
Hearing loss	4/20	20%	1/30	3%	80.0	64.4	20.0	96.7 6.0 (0.8, 43.3)
Vitiligo	1/20	5%	0/30	0%	100.0	61.2	5.0	100.0 . .
Alopecia	2/20	10%	0/30	0%	100.0	62.5	10.0	100.0 . .
Nummular chor. scars	0/20	0%	4/30	13%	0.0	56.5	0.0	86.7 0.0 . .
RPE clumping/migration	2/19	11%	5/30	17%	28.6	59.5	10.5	83.3 0.6 (0.2, 2.6)
Disc hyperemia/swelling	9/19	47%	6/30	20%	60.0	70.6	47.4	80.0 2.4 (1.0, 5.4)
Poliosis	1/20	5%	4/30	13%	20.0	57.8	5.0	86.7 0.4 (0.1, 2.7)
Vitreous cells	12/19	63%	17/29	59%	41.4	63.2	63.2	41.4 1.1 (0.6, 1.8)
Anterior chamber cells	12/20	60%	18/29	62%	40.0	57.9	60.0	37.9 1.0 (0.6, 1.6)
Anterior chamber flare	5/20	25%	6/30	20%	45.5	61.5	25.0	80.0 1.3 (0.5, 3.3)
Keratic precipitates	2/20	10%	9/30	30%	18.2	53.8	10.0	70.0 0.3 (0.1, 1.3)
Sugiura sign	0/19	0%	0/28	0%	. .	59.6	0.0	100.0 . .
(Subretinal Fluid or Bullous retinal detachment)	11/20	55%	1/30	3%	91.7	76.3	55.0	96.7 16.5 (2.4,114.2)
(Subretinal Fluid or Bullous retinal detachment)	5/10	50%	0/14	0%	100.0	73.7	50.0	100.0 . .
(Subretinal Fluid or Bullous retinal detachment and choroidal thickening)	0/20	0%	0/30	0%	. .	60.0	0.0	100.0 . .
(Subretinal Fluid or Bullous retinal detachment and alopecia)	3/20	15%	0/30	0%	100.0	63.8	15.0	100.0 . .
(Subretinal Fluid or Bullous retinal detachment and hearing loss)								

Clinical Assessment	VKH	Non VKH	PPV	NPV	Sensitivity	Specificity	Likelihood Ratio	(95% CI)
(Subretinal Fluid or Bullous retinal detachment and (headache or neck stiffness))	6/20 30%	0/28 0%	100.0	66.7	30.0	100.0	.	.

Table 8

Acute and Chronic Vogt-Koyanagi-Harada disease clinical features: Stepwise logistic regression models

Dependent variable = VKH	Odds Ratio Estimate (95% CI)	p-value
<u>Model 1: Acute disease</u>		
Exudative RD	>999 (48.02,>999)	<0.0001
Alopecia	81.23 (2.47, >999)	0.01
Disc hyperemia	5.28 (1.02, 27.42)	0.05
Asian	24.48 (2.38,251.9)	0.007
Hispanic	59.76 (3.77, 948.2)	0.004
<u>Model 2: Chronic disease</u>		
Sunset glow fundus	141.66 (54.65, 367.2)	<0.0001
Vitiligo	11.73 (3.59, 38.33)	<0.0001
Alopecia	3.20 (1.40, 7.31)	0.0005
Nummular chorioretinal scars	2.83 (1.34,5.98)	0.01
Vitreous cells	0.39 (0.18,0.83)	0.02
Asian	3.48 (1.60, 7.60)	0.002
Hispanic	13.25 (4.63, 37.88)	0.0003

VKH= Vogt-Koyanagi-Harada disease; CI=Confidence interval; RD=Retinal detachment

Table 9

Chronic Disease: Clinical Findings in Patients with Vogt-Koyanagi-Harada disease Compared to Non-Vogt-Koyanagi-Harada disease (Non-Vogt-Koyanagi-Harada subjects included only for posterior or panuveitis)

Clinical Assessment	VKH	No VKH	PPV	NPV	Sensitivity	Specificity	Likelihood Ratio	(95% CI)
Sunset glow fundus	103/158 65%	5/195 3%	95.4	77.6	65.2	97.4	25.4	(10.7, 60.5)
Sugiura sign	9/156 6%	0/196 0%	100.0	57.1	5.8	100.0	.	.
Vitiligo	35/158 22%	1/198 1%	97.2	61.6	22.2	99.5	43.9	(6.2,310.1)
Choroidal thickening	18/103 17%	2/96 2%	90.0	52.5	17.5	97.9	8.4	(2.1, 33.3)
Nummular chor. scars	82/158 52%	40/196 20%	67.2	67.2	51.9	79.6	2.5	(1.9, 3.4)
RPE clumping/migration	77/157 49%	59/194 30%	56.6	62.8	49.0	69.6	1.6	(1.2, 2.1)
Hearing loss	28/159 18%	6/198 3%	82.4	59.4	17.6	97.0	5.8	(2.6, 13.0)
Alopecia	30/159 19%	16/198 8%	65.2	58.5	18.9	91.9	2.3	(1.4, 3.9)
Poliosis	49/159 31%	28/198 14%	63.6	60.7	30.8	85.9	2.2	(1.5, 3.2)
Vitreous cells	54/156 35%	68/195 35%	44.3	55.5	34.6	65.1	1.0	(0.8, 1.3)
Disc hyperemia/swelling	13/157 8%	15/195 8%	46.4	55.6	8.3	92.3	1.1	(0.6, 2.0)
Keratic precipitates	37/160 23%	29/198 15%	56.1	57.9	23.1	85.4	1.6	(1.1, 2.4)
Anterior chamber flare	38/159 24%	40/195 21%	48.7	56.2	23.9	79.5	1.2	(0.8, 1.7)
Anterior chamber cells	52/160 33%	52/199 26%	50.0	57.6	32.5	73.9	1.2	(0.9, 1.7)
Bullous RD	1/158 1%	1/195 1%	50.0	55.3	0.6	99.5	1.2	(0.1, 13.6)
Subretinal fluid	2/158 1%	4/196 2%	33.3	55.2	1.3	98.0	0.6	(0.1, 2.8)
Sunset glow fundus or Nummular chor. scars	117/159 74%	42/196 21%	73.6	78.6	73.6	78.6	3.4	(2.6, 4.6)
Sunset glow fundus or Nummular chor. scars or Sugiura sign	118/158 75%	42/194 22%	73.8	79.2	74.7	78.4	3.4	(2.6, 4.6)
(Sunset glow fundus or Nummular chor. scars) and (vitiligo or alopecia or poliosis or hearing loss)	63/158 40%	8/195 4%	88.7	66.3	39.9	95.9	9.7	(4.9, 19.3)
(Sunset glow fundus or Nummular chor. scars or Sugiura sign) and (vitiligo or alopecia or poliosis or hearing loss)	64/157 41%	8/194 4%	88.9	66.7	40.8	95.9	9.9	(5.0, 19.6)
Sunset glow fundus and	58/157 37%	0/802 0%	100.0	89.0	36.9	100.0	.	.

Clinical Assessment	VKH	No VKH	PPV	NPV	Sensi- tivity	Spec- ficity	Likelihood Ratio	(95% CI)
(vitiligo or alopecia or poliosis or hearing loss)								

chor= choroidoretinal; RD= retinal detachment; CI=Confidence interval; PPV=Positive predictive value; NPV=Negative predictive value; RPE=Retinal pigment epithelium