ORIGINAL ARTICLE

Classification Criteria for Behçet Disease Uveitis

THE STANDARDIZATION OF UVEITIS NOMENCLATURE (SUN) WORKING GROUP[1,2,3,4,*]

• PURPOSE: **To determine classification criteria for Behçet disease uveitis.**

• DESIGN: **Machine learning of cases with Behçet disease and 5 other panuveitides.**

• METHODS: **Cases of panuveitides were collected in an informatics-designed preliminary database, and a final database was constructed of cases achieving supermajority agreement on the diagnosis, using formal consensus techniques. Cases were split into a training set and a validation set. Machine learning using multinomial logistic regression was used on the training set to determine a parsimonious set of criteria that minimized the misclassification rate among the intermediate uveitides. The resulting criteria were evaluated on the validation set.**

• RESULTS: **One thousand twelve cases of panuveitides, including 194 cases of Behçet disease with uveitis, were evaluated by machine learning. The overall accuracy for panuveitides was 96.3% in the training set and 94.0% in the validation set (95% confidence interval 89.0, 96.8). Key criteria for Behçet disease uveitis were a diagnosis of Behçet disease using the International Study Group for Behçet Disease criteria and a compatible uveitis, including (1) anterior uveitis; (2) anterior chamber and vitreous inflammation; (3) posterior uveitis with retinal vasculitis and/or focal infiltrates; or (4) panuveitis with retinal vasculitis and/or focal infiltrates. The misclassification rates for Behçet disease uveitis were 0.6% in the training set and 0% in the validation set, respectively.**

• CONCLUSIONS: **The criteria for Behçet disease uveitis had a low misclassification rate and seemed to perform sufficiently well for use in clinical and translational research. (Am J Ophthalmol 2021;228: 80–88. © 2021 Elsevier Inc. All rights reserved.)**

BEHÇET DISEASE IS AN IDIOPATHIC MULTISYSTEM disease named for the Turkish dermatologist who in 1937 described it as a triad of oral ulcers, genital ulcers, and uveitis.[1] Although named for him, similar cases were reported by Shigeta in 1924, Adamantiadis in 1931, and Whitwell in 1934.[2,3] In addition to the mucocutaneous and ocular lesions, Behçet disease may involve the joints, gastrointestinal tract, systemic vasculature, and central nervous system.[2,4,5] Although chronic in nature, Behçet disease tends to follow a remitting and relapsing course with acute "attacks" of uveitis and other manifestations. Oral ulcers, the most common manifestation, often considered the *sine qua non* for the diagnosis, typically are painful and come in crops and usually are distinguishable from common

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oral aphthae. The uveitis may be unilateral or bilateral, and it may be an isolated anterior uveitis, an anterior and intermediate uveitis, an isolated posterior uveitis, or a panuveitis. Although the anterior uveitis is classically described as hypopyon uveitis, the majority of cases do not have a hypopyon. The most serious ocular manifestation is an occlusive retinal vasculitis, which may infarct the macula, resulting in blindness. Recurrent focal retinal infiltrates ("white patches") also can be seen, and papillitis may result in visual loss.[6] Sustained intraocular inflammation between "acute" exacerbations may contribute to macular edema and visual impairment.[7]

Behçet disease is common in countries along the ancient Silk Road extending from Greece and Turkey in the West to China, Korea, and Japan in the East.[8,9] The estimated prevalence in Turkey ranges from 20 to 420 per 100,000 and elsewhere in Asia from 13.5 to 30 per 100,000.[4,5] The estimated prevalence is much lower in Western countries; in the United States it ranges from 0.12 to 0.33 per 100,000 and has been reported as 0.64 per 100,000 in the United Kingdom.[4,5] There is an association of Behçet disease with the HLA allele, HLA-B51, in particular with the subtype HLA-B*5101, and the HLA-B51 allele is more frequent among populations with a high prevalence of Behçet disease.[4,10] Men may be affected with Behçet disease uveitis more often than women, and the uveitis can be particularly severe in young men aged 15-25 years.[11]

Although case series derived from ophthalmology practices or clinics typically report uveitis in 100% of cases, those from multidisciplinary settings report ocular involvement in ~50%-75%.[4,12,13] Conversely, oral ulcers are consistently present in nearly all cases regardless of setting: 98%-100% of cases from multidisciplinary settings and 95% of cases from ophthalmology settings.[4,12] In case series from ophthalmology settings, skin lesions are present in ~70% and genital ulcers ~61%.[12] The uveitis may affect the anterior segment only or, more often, present with a panuveitis with retinal "vasculitis" and/or focal white infiltrates. In 1 large multicenter study from the United States, isolated anterior uveitis was present in only 11%.[13] In this series occlusive retinal vasculitis was seen on presentation in 22% but developed at the rate of 17% per person-year during follow-up.[13]

Untreated, the uveitis of Behçet disease has a poor prognosis, with high rates of blindness (>75%).[14] Systemic corticosteroids alone seemed to slow the rate of blindness, but were not sufficiently effective to alter the long-term prognosis.[14] Early immunosuppressive treatment approaches included antimetabolites, such as azathioprine and later mycophenolate; alkylating agents, such as chlorambucil; and calcineurin inhibitors, such as cyclosporine and later tacrolimus.[2,4-6] However, biologic agents, particularly monoclonal antibodies to TNF-α, such as infliximab and adalimumab, seem to be particularly successful in management of Behçet disease uveitis.[15-17] Uncontrolled case series have suggested that interferon-α-2a also may be useful in its management.[18] However, in 1 randomized clinical trial, interferon-α-2b demonstrated no benefit in attack number reduction or corticosteroid sparing, although an exploratory post hoc analysis suggested possible benefit among those receiving systemic corticosteroids at enrollment.[19] More recent case series suggest that ~23% of cases will have a presenting visual acuity of 20/200 or worse in at least 1 eye, with international variation in the prevalence from 9% to 39%.[12] Rates of visual impairment (20/50 or worse) and blindness (20/200 or worse) during follow-up on conventional immunosuppressive drugs have been estimated at 12% per eye-year and 9% per eye-year, respectively.[13] Long-term cohort studies have suggested superior visual outcomes with biologic therapies vs conventional ones.[17]

The Standardization of Uveitis Nomenclature (SUN) Working Group is an international collaboration that has developed classification criteria for 25 of the most common uveitic diseases using a formal approach to development and classification.[20-26] Among the diseases studied was Behçet disease uveitis.

METHODS

The SUN Developing Classification Criteria for the Uveitides project proceeded in 4 phases, as previously described: (1) informatics, (2) case collection, (3) case selection, and (4) machine learning.[22-25]

• **INFORMATICS:** As previously described, the consensus-based informatics phase permitted the development of a standardized vocabulary and the development of a standardized, menu-driven hierarchical case collection instrument.[22]

• **CASE COLLECTION AND CASE SELECTION:** De-identified information was entered into the SUN preliminary database by the 76 contributing investigators for each disease, as previously described.[23-25] Cases in the preliminary database were reviewed by committees of 9 investigators for selection into the final database, using formal consensus techniques, described in the accompanying article.[24,25] Because the goal was to develop classification criteria,[24-26] only cases with a supermajority agreement (>75%) that the case was the disease in question were retained in the final database.[25]

• **MACHINE LEARNING:** The final database then was randomly separated into a training set (~85% of cases) and a validation set (~15% of cases) for each disease, as described in the accompanying article.[25] Machine learning was used on the training set to determine criteria that minimized misclassification. The criteria then were tested on the validation set; for both the training set and the validation set, the misclassification rate was calculated for

each disease. The misclassification rate was the proportion of cases classified incorrectly by the machine learning algorithm when compared to the consensus diagnosis. For Behçet disease uveitis, the diseases against which it was evaluated were Vogt-Koyanagi Harada disease (both early- and late-stage), sympathetic ophthalmia, sarcoid panuveitis, syphilitic panuveitis, and tubercular panuveitis.

• **COMPARISON OF CASES BY REGION:** Cases were categorized by region as coming from the Middle East (and North Africa), Asia (primarily Japan, but also South Asia), and Other (primarily Europe and the United States). For categorical variables, comparison of cases was performed with the χ^2 test or the Fisher exact test if a cell was less than 5. For continuous variables, the Wilcoxon rank sum test was used. For semiquantitative variables, values above and below the median were analyzed. *P* values are nominal and 2-sided.

The study adhered to the principles of the Declaration of Helsinki. Institutional review boards at each participating center reviewed and approved the study; the study typically was considered either minimal risk or exempt by the individual institutional review boards.

RESULTS

Two hundred forty-eight cases of Behçet disease with uveitis were collected, and 194 (78%) achieved supermajority agreement on the diagnosis during the "selection" phase and were used in the machine learning phase. These cases of Behçet disease with uveitis were compared to 722 cases of other uveitides, including 110 cases of sympathetic ophthalmia, 156 cases of early-stage VKH, 103 cases of late-stage VKH, 102 cases of sarcoidosis-associated panuveitis, 70 cases of syphilitic panuveitis, and 277 cases of tubercular panuveitis. The details of the machine learning results for these diseases are outlined in the accompanying article.[23] The characteristics of cases with Behçet disease uveitis at the time of presentation to a SUN Working Group investigator are listed in Table 1. A comparison of cases from different regions is listed in Table 2. It appeared that Asian cases have more severe disease with higher grades of anterior chamber flare, vitreous haze, and a higher proportion of cases with focal retinal infiltrates. The criteria developed after machine learning for Behçet disease uveitis are listed in Table 3. Key features included a compatible uveitic syndrome—either anterior uveitis, anterior and intermediate uveitis, or posterior uveitis / panuveitis with evidence of retinal vascular involvement (Figures 1 and 2) or focal infiltrates (Figure 3)—and evidence of systemic Behçet disease. No case had choroiditis, either focal or multifocal, so posterior uveitis with isolated choroiditis and panuveitis with choroiditis (either focal or multifocal) should not be diagnosed as Behçet disease uveitis. The overall accuracy

TABLE 1. Characteristics of Cases of Behçet Disease Uveitis

Characteristic	Result
Number of cases	194
Demographics	
Age, median, years (25th, 75th percentile)	31 (24, 37)
Sex (%)	
Male	60
Female	40
Race/ethnicity (%)	
White, non-Hispanic	43
Black, non-Hispanic	4
Hispanic	0
Asian, Pacific Islander	29
Other (Middle East/North Africa)	15
Not specified	9
Uveitis history	
Uveitis course (%)	
Acute, monophasic	8
Acute, recurrent	12
Chronic	72
Indeterminate	9
Laterality (%)	
Unilateral	20
Unilateral, alternating	0
Bilateral	80
Ophthalmic examination	
Keratic precipitates (%)	
None	74
Fine	24
Round	2
Stellate	0
Mutton fat	0
Other	0
Anterior chamber cells, grade (%)	
0	28
½+	16
1+	17
2+	21
3+	11
4+	7
Hypopyon (%)	9
Anterior chamber flare, grade (%)	
0	55
1+	24
2+	14
3+	4
4+	3
Iris (%)	
Normal	92
Posterior synechiae	8
Sectoral iris atrophy	0
Patchy iris atrophy	0
Diffuse iris atrophy	0
Heterochromia	0

(*continued on next page*)

TABLE 1. (*continued*)

Characteristic	Result
IOP, involved eyes	
Median, mm Hg (25th, 75th percentile)	14 (12,16)
Proportion of patients with IOP > 24 mm Hg either eye (%)	3
Vitreous cells, grade (%)	
0	20
½+	10
1+	34
2+	27
3+	8
4+	1
Vitreous haze, grade (%)	
0	40
½+	14
1+	20
2+	17
3+	8
4+	1
Retinal vascular disease, either occlusive vasculitis or sheathing/leakage (%)	75
Focal retinal white infiltrates (%)	6
Anatomic uveitis class (%)	
Anterior only	6
Anterior and intermediate	10
Posterior only	4
Panuveitis	80

IOP = intraocular pressure.

for panuveitides was 96.3% in the training set and 94.0% in the validation set (95% confidence interval 89.0, 96.8).[25] The misclassification rates of Behçet disease uveitis were 0.6% in the training set and 0% in the validation set.

DISCUSSION

The classification criteria developed by the SUN Working Group for Behçet disease uveitis have a low misclassification rate, indicating good discriminatory performance against other panuveitides.

Behçet disease is a clinical diagnosis. There are no laboratory tests that establish the diagnosis. As such, over the last 50 years there have been multiple sets of diagnostic criteria proposed, including those by Mason and Barnes, the Japanese Criteria, the Hamza criteria, the O'Duffy criteria, the Chen and Zhang criteria, the Dilsen criteria, and the International Study Group (ISG) for Behçet Disease criteria.[27-34] A comparative evaluation suggested that the Hamza criteria and the ISG criteria had the highest specificity,[35] and the ISG criteria (Table 4) seem to be straightforward, easy to use, and the most widely used. Therefore, the SUN Working Group adopted the ISG criteria for the diagnosis of Behçet disease. Although the diagnosis of systemic Behçet disease in the SUN database was a clinical one, and we could not always confirm adherence to the ISG criteria, going forward a standard set of criteria are needed, and the ISG criteria were chosen for classification criteria.

One study using photographs suggested that many of the clinical features of the uveitis of Behçet disease are rela-

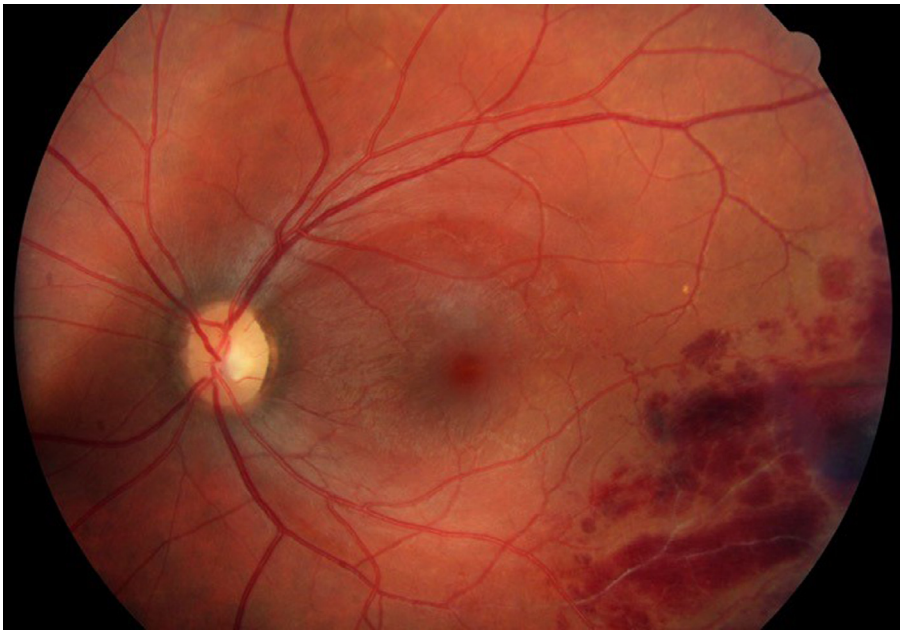

FIGURE 1. Fundus photograph of occlusive retinal vasculitis in a patient with Behçet disease.

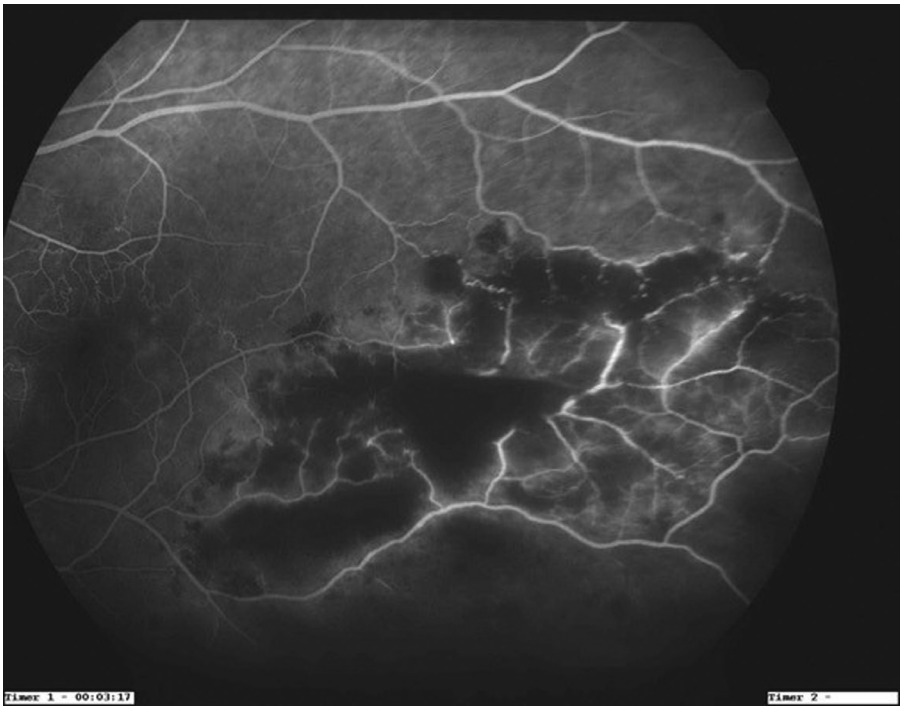

FIGURE 2. Fundus fluorescein angiogram in a patient with Behçet disease, demonstrating retinal nonperfusion and vascular staining due to retinal vasculitis.

FIGURE 3. Fundus photograph of focal infiltrates ("white patches") in a patient with Behçet disease.

TABLE 2. Characteristics of Cases of Behçet Disease Uveitis by Region

Characteristic	Region[a]			*P* Value
	Middle East	Asia	Other	
Number of cases	30	56	108	
Demographics				
Age, median, years	27	32	31	.64
(25th, 75th percentile)	(20, 30)	(28, 35)	(24, 40)	
Sex (%)				<.001
Male	73	78	47	
Female	27	22	53	
Uveitis history				
Laterality (%)				.49
Unilateral	17	25	19	
Bilateral	83	75	81	
Ophthalmic examination				
Keratic precipitates (%)				.003
None	83	57	80	
Present	17	43	20	
Anterior chamber cells, grade (%)				.08
≤1+	73	50	64	
≥2+	27	50	36	
Anterior chamber flare, grade (%)				<.001
0	60	27	68	
≥1+	40	73	32	
Hypopyon (%)	7	11	9	.89
Iris (%)				.63
Normal	93	95	90	
Posterior synechiae	7	5	10	
IOP (mm Hg), median (25th, 75th percentile)	15 (12, 18)	12 (11, 16)	14 (12, 16)	.88
Vitreous cells, grade (%)				.08
≤1+	86	71	88	
≥2+	14	29	12	
Vitreous haze, grade (%)				.03
≤½+	63	32	63	
≥1+	37	68	37	
Retinal vasculitis (%)	83	84	69	.06
Focal retinal white infiltrates (%)	13	30	9	.003
Anatomic uveitis class (%)				.04
Anterior only	0	2	9	
Anterior and intermediate	3	8	14	
Posterior only	10	4	2	
Panuveitis	87	86	75	

IOP = intraocular pressure.

[a]Middle East also includes cases from North Africa. Asia includes cases from Japan and India. Other includes cases from Europe and North America.

tively distinct and can be identified by uveitis experts with moderate-to-substantial agreement, including hypopyon uveitis, occlusive retinal vasculitis, and focal infiltrates.[36] A minority of the cases in the SUN database of cases with Behcet disease (9%) had a hypopyon. Hypopyon classically is associated with endophthalmitis and Behçet disease, but also is seen in eyes with HLA-B27-associated anterior uveitis.[37,38] In 1 large series, risk factors for hypopyon uveitis included Behçet disease (adjusted relative risk [RR] 5.30), spondyloarthritis (RR 2.86), and HLA-B27 (RR 2.04).[37] In the United States hypopyon uveitis is seen most often among patients with spondyloarthritis/HLA-B27-associated anterior uveitis, whereas in regions where Behçet disease is more prevalent than in the United States, it will be seen more often with Behçet disease.[37,38] Because of its occurrence in other diseases, hypopyon uveitis was not included in the criteria.

The comparison of cases from different regions suggested more severe disease in Asians and a higher proportion of women in cases not from the Middle East or Asia. Some

TABLE 3. Classification Criteria for Behçet Disease Uveitis

Criteria
1. Compatible uveitic syndrome
a. Anterior uveitis
b. Anterior and intermediate uveitis
c. Posterior uveitis with retinal vasculitis and/or focal retinal infiltrates[a]
d. Panuveitis with retinal vasculitis and/or focal retinal infiltrates[a]
AND
2. A diagnosis of Behçet disease using International Study Group for Behçet Disease criteria[b]
Exclusions
1. Positive serology for syphilis using a treponemal test
2. Evidence for sarcoidosis (either bilateral hilar adenopathy on chest imaging or tissue biopsy demonstrating noncaseating granulomata)

[a]Posterior uveitis or panuveitis with a choroiditis is not a Behçet disease–compatible uveitis.
[b]See Table 4.

TABLE 4. International Study Group Criteria for the Diagnosis of Behçet Disease

Oral ulcers
PLUS any 2 of the following features:
• Genital ulcers
• Uveitis (typical defined eye lesions)
• Typical defined skin lesions
• Positive pathergy test

Adapted from International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. *Lancet* 1990;335:1078-1080.

case series have suggested that more severe disease may occur in men.[11] Nevertheless, the difference in severity seemed to be quantitative in nature (eg, higher grades of inflammation) and not qualitative (ie, different features), suggesting that the criteria should be generalizable.

The presence of any of the exclusions in Table 3 suggests an alternate diagnosis, and the diagnosis of Behçet disease uveitis should not be made in their presence. In prospective studies many of these tests will be performed routinely, and the alternative diagnoses excluded. However, in retrospective studies based on clinical care, not all of these tests may have been performed. Hence the presence of an exclusionary criterion excludes Behçet disease uveitis, but the absence of such testing does not always exclude the diagnosis of sympathetic ophthalmia if the criteria for the diagnosis are met.

Classification criteria are employed to diagnose individual diseases for research purposes.[26] Classification criteria differ from clinical diagnostic criteria in that although both seek to minimize misclassification, when a trade-off is needed, diagnostic criteria typically emphasize sensitivity, whereas classification criteria emphasize specificity,[26] in order to define a homogeneous group of patients for inclusion in research studies and limit the inclusion of patients without the disease in question that might confound the data. The machine learning process employed did not explicitly use sensitivity and specificity; instead, it minimized the misclassification rate. Because we were developing classification criteria and because the typical agreement between 2 uveitis experts on diagnosis is moderate at best,[24] the selection of cases for the final database ("case selection") included only cases that achieved supermajority agreement on the diagnosis.

There will be cases with a uveitis that resembles that seen in Behçet disease, particularly those with a similar occlusive retinal vasculitis, but without any systemic features. Whether these cases represent a *forme fruste* of Behçet disease or simply an unrelated undifferentiated retinal vasculitis is unknown, and at this time they are not included in the classification of Behçet disease uveitis. Future studies, perhaps including immunogenetics and demonstrating similar risk factors, clinical course, and treatment responses, may lead to a revision, but at this time they should not be diagnosed as Behçet disease. Although there is already an immunogenetic risk factor for Behçet disease, HLA-B51,[10] its relatively high prevalence in the general population (particularly in those regions where Behçet disease is common) and poor positive predictive value preclude its use in diagnosis.[39]

In conclusion, the criteria for Behçet disease outlined in Table 2 seem to perform sufficiently well for use as classification criteria in clinical research.[25,26]

CREDIT ROLES

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TOC

Using a formalized approach to developing classification criteria, including informatics-based case collection, consensus technique–based case selection, and machine learning, classification criteria for Behçet disease uveitis were developed. Key criteria included a diagnosis of Behçet disease using the International Study Group for Behçet Disease criteria and a characteristic type of uveitis, including anterior uveitis, anterior and intermediate uveitis, and posterior uveitis or panuveitis with retinal vasculitis and/or focal retinal infiltrates. The resulting criteria had a low misclassification rate.

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