Classification Criteria for Intermediate Uveitis, Non–Pars Planitis Type

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

• PURPOSE: To determine classification criteria for intermediate uveitis, non–pars planitis type (IU-NPP, also known as undifferentiated intermediate uveitis).
• DESIGN: Machine learning of cases with IU-NPP and 4 other intermediate uveitides.
• METHODS: Cases of intermediate uveitides 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: Five hundred eighty-nine of cases of intermediate uveitides, including 114 cases of IU-NPP, were evaluated by machine learning. The overall accuracy for intermediate uveitides was 99.8% in the training set and 99.3% in the validation set (95% confidence interval 96.1, 99.9). Key criteria for IU-NPP included unilateral or bilateral intermediate uveitis with neither snowballs in the vitreous humor nor snowbanks on the pars plana. Other key exclusions included multiple sclerosis, sarcoidosis, and syphilis. The misclassification rates for IU-NPP were 0% in the training set and 0% in the validation set.
• CONCLUSIONS: The criteria for IU-NPP had a low misclassification rate and seemed to perform well enough for use in clinical and translational research. (Am J Ophthalmol 2021;228: 159–164. © 2021 Elsevier Inc. All rights reserved.)

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THE INTERMEDIATE UVEITIDES ENCOMPASS SEVERAL diseases characterized by the vitreous humor being the primary site of clinically evident inflammation and an absence of choroiditis or retinitis.[1-3] Intermediate uveitides may be due to infections, such as Lyme disease or syphilis, or associated with systemic diseases, such as sarcoidosis or multiple sclerosis.[3] In the absence of a demonstrable infection or related systemic disease, they are presumed to be eye-limited and immune-mediated.[3] One specific intermediate uveitic disease, pars planitis, was described in 1960 and was characterized by vitritis and pars plana snowbank formation (a collection of fibrinoinflammatory debris).[3-10] However, not all cases of noninfectious intermediate uveitis without a systemic disease have snowbanks; and these cases sometimes have been lumped with pars planitis and sometimes not, leading to confusion as to what represents pars planitis.[6-10] At the First International Workshop of the Standardization of Uveitis (SUN) Working Group, it was decided by a supermajority of participants to classify noninfectious intermediate uveitides unassociated with a systemic disease as pars planitis if there were snowballs or snowbanks, and as intermediate uveitis,

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non–pars planitis type, if there were not.[2] An alternative term for intermediate uveitis, non–pars planitis type would be undifferentiated intermediate uveitis. Intermediate uveitides, including pars planitis, account for up to 15% of uveitis cases in series from tertiary eye care referral centers.[11]

The 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.[12-16] Among the diseases studied was intermediate uveitis, non–pars planitis type.

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.[12-15]

• **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.[12]

• **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.[14,15] 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.[14,15] Because the goal was to develop classification criteria,[10] only cases with a supermajority agreement (>75%) that the case was the disease in question were retained in the final database (ie, were "selected").[14,15]

• **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.[15] 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 intermediate uveitis, non–pars planitis type, the diseases against which it was evaluated were multiple sclerosis–associated intermediate uveitis, pars planitis, sarcoid intermediate uveitis, and syphilitic intermediate uveitis. Too few cases of Lyme disease uveitis (14) were collected in the database for analysis by machine learning.

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 individual institutional review boards.

RESULTS

Two hundred nine cases of intermediate uveitis, non–pars planitis type were collected, and 114 (55%) achieved supermajority agreement on the diagnosis during the "selection" phase and were used in the machine learning phase. These cases of intermediate uveitis, non–pars planitis type were compared to cases of other intermediate uveitides, including 112 cases of multiple sclerosis–associated intermediate uveitis, 226 cases of pars planitis type, 52 cases of sarcoidosis-associated intermediate uveitis, and 85 cases of syphilitic intermediate uveitis. The details of the machine learning results for these diseases are outlined in the accompanying article.[16] The characteristics at presentation to a SUN Working Group investigator of cases with intermediate uveitis, non–pars planitis type are listed in Table 1. The criteria developed after machine learning are listed in Table 2. Key features are the presence of inflammation primarily in the vitreous humor, absence of snowballs and snowbanks, and the exclusion of syphilis, multiple sclerosis, and sarcoidosis. The overall accuracy for intermediate uveitides was 99.8% in the training set and 99.3% in the validation set (95% confidence interval 96.1, 99.2).[16] The misclassification rate for intermediate uveitis, non–pars planitis type was 0% in the training set and 0% in the validation set.[16]

DISCUSSION

The classification criteria developed by the SUN Working Group for intermediate uveitis, non–pars planitis type have a low misclassification rate, indicating good discriminatory performance against other intermediate uveitides.

Intermediate uveitis, non–pars planitis type is to some extent a diagnosis of exclusion. It must have the features of an intermediate uveitis, but not be pars planitis, multiple sclerosis–associated intermediate uveitis, sarcoidosis, syphilis, or Lyme disease. The type of uveitis most often seen with Lyme disease is an atypical intermediate uveitis or an anterior and intermediate uveitis, but disease indistinguishable from intermediate uveitis, non–pars planitis type has been described.[17,18] Lyme uveitis is sufficiently uncommon that we were able to collect too few cases for analysis. In Lyme disease–nonendemic regions, there seems to be little value to screening for Lyme disease, as nearly all positive tests will be false-positives.[19] Even among patients

TABLE 1. Characteristics of Cases of Intermediate Uveitis, Non–Pars Planitis Type

Characteristic	Result
Number of cases	114
Demographics	
Age, median, years (25th, 75th percentile)	37 (23, 52)
Sex (%)	
Male	37
Female	63
Race/ethnicity (%)	
White, non-Hispanic	68
Black, non-Hispanic	5
Hispanic	4
Asian, Pacific Islander	3
Other	8
Missing	12
Uveitis history	
Uveitis course (%)	
Acute, monophasic	4
Acute, recurrent	4
Chronic	86
Indeterminate	6
Laterality (%)	
Unilateral	29
Unilateral, alternating	0
Bilateral	71
Ophthalmic examination	
Keratic precipitates (%)	
None	82
Fine	13
Round	3
Stellate	0
Mutton fat	1
Other	1
Anterior chamber cells, grade (%)	
0	59
½+	17
1+	16
2+	7
3+	2
4+	0
Hypopyon (%)	0
Anterior chamber flare, grade (%)	
0	82
1+	16
2+	3
3+	0
4+	0
Iris (%)	
Normal	91
Posterior synechiae	9
Sectoral iris atrophy	0
Patchy iris atrophy	0
Diffuse iris atrophy	0
Heterochromia	0
IOP, involved eyes	
Median, mm Hg (25th, 75th percentile)	14 (12, 17)
Proportion of patients with IOP > 24 mm Hg either eye (%)	4

(*continued on next page*)

TABLE 1. (*continued*)

Characteristic	Result
Vitreous cells, grade (%)[a]	
0	3
½+	14
1+	39
2+	35
3+	9
4+	1
Vitreous haze, grade (%)[a]	
0	31
½+	14
1+	34
2+	17
3+	3
4+	2
Vitreous snowballs[b]	0
Pars plana snowbanks[b]	0
Peripheral retinal vascular sheathing or leakage	19
Macular edema	47

IOP = intraocular pressure.

[a]All cases had either vitreous cells or haze; only 2 cases had haze without evident cells.

[b]No cases had snowballs or snowbanks, as the diagnosis then would be pars planitis.

TABLE 2. Classification Criteria for Intermediate Uveitis, Non–Pars Planitis Type

Criteria

1. Evidence of intermediate uveitis
   a. vitreous cells AND/OR vitreous haze
   b. if anterior chamber cells are present, anterior chamber inflammation less than vitreous humor
   c. no evidence of retinitis

AND

2. No evidence of pars planitis
   a. neither vitreous snowballs NOR
   b. pars plana snowbanks

Exclusions

1. Multiple sclerosis, defined by the McDonald criteria[28]
2. Positive serology for syphilis using a treponemal test
3. Evidence of sarcoidosis (either bilateral hilar adenopathy on chest imaging or tissue biopsy demonstrating noncaseating granulomata)
4. Positive serology for Lyme disease, either IgG or IgM (eg, positive ELISA AND Western blot with requisite number of bands for assay used)
5. Evidence of intraocular lymphoma on diagnostic vitrectomy

from Lyme-endemic areas undergoing routine testing, the frequency of Lyme disease uveitis has been estimated as no more than 0.35% of uveitis cases, and it has been proposed by some uveitis experts that Lyme disease testing should be reserved for Lyme disease–exposed persons and those with symptoms suggesting Lyme disease.[20] Nevertheless, in prospective studies from Lyme disease–endemic regions (or in Lyme disease–exposed individuals) testing patients with intermediate uveitis for Lyme disease would seem to be appropriate. The presence of a positive Lyme serology (with appropriate confirmatory testing) excludes the diagnosis of intermediate uveitis, non–pars planitis type.

Other than the presence of snowballs and snowbanks with pars planitis, and a diagnosis of multiple sclerosis with multiple sclerosis–associated intermediate uveitis, there are no other differences on ocular examination that reliably distinguish among the 3 diseases.[16,21,22] HLA-DR2 and its split antigen HLA-DR15 are risk factors for both pars planitis and multiple sclerosis,[9,10,23] so it is unhelpful in distinguishing between them.[24] There are patients, albeit few, with pars planitis with bilateral vitritis and

unilateral snowbanks.[6,7] There has been a suggestion that snowbanks might herald more severe disease,[7] but the SUN cross-sectional data did not confirm that.[21] In our opinion, these patients should be classified as having pars planitis and not 2 diseases. Patients with pars planitis with snowballs without snowbanks tend to be older and seem to have an age distribution similar to that of intermediate uveitis, non–pars planitis type. Long-term follow-up studies, perhaps with immunogenetic typing and neuroimaging, might clarify whether these should be considered 3 distinct diseases or whether pars planitis without snowbanks should be lumped with intermediate uveitis, non–pars planitis type. However, at this time, it is recommended that patients be classified as (1) pars planitis with snowbanks; (2) pars planitis without snowbanks; or (3) intermediate uveitis, non–pars planitis type.

None of the cases included in this series had clinical evidence of multiple sclerosis. However, the data did not include whether every case underwent neuroimaging for multiple sclerosis. Among patients with intermediate uveitis without multiple sclerosis at presentation, the rate of developing multiple sclerosis can be estimated at ~2% to 4% per year,[9,10] so neuroimaging to exclude multiple sclerosis is likely to have a low yield and is not routinely recommended.[25] Instead, exclusion should be based on clinical grounds (the absence of relevant neurological lesions or a history of relevant neurological lesions). Nevertheless, some patients with follow-up will develop multiple sclerosis and have their diagnosis updated over time.

About 10% of the patients in the SUN database for intermediate uveitis, non–pars planitis type were over 50 years of age and thus at greater risk for intraocular lymphoma.[26] Intraocular lymphoma accounts for ~1.5% of cases of "uveitis" in the elderly presenting to tertiary eye care referral centers and ~10% of cases that undergo diagnostic vitrectomy.[27] Hence it would be unreasonable to require vitrectomy confirmation of the absence of intraocular lymphoma as part of the criteria. Nevertheless, suspicion of lymphoma based on ocular characteristics should lead to appropriate diagnostic studies (eg, diagnostic vitrectomy) in clinical care.

The presence of any of the exclusions in Table 2 suggests an alternate diagnosis, and the diagnosis of intermediate uveitis, non–pars planitis type 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 intermediate uveitis, non–pars planitis type, but the absence of such testing does not always exclude the diagnosis of intermediate uveitis, non–pars planitis if the criteria for the diagnosis are met. Nevertheless, because of the overlapping features of sarcoidosis-associated intermediate uveitis, including snowballs, a reasonable effort should be made to exclude sarcoidosis—including, as a minimum, chest imaging—for all cases of intermediate uveitis, non–pars planitis type.[28]

Classification criteria are employed to diagnose individual diseases for research purposes.[14] 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,[15] 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,[14] the selection of cases for the final database ("case selection") included only cases that achieved supermajority agreement on the diagnosis. As such, some cases that clinicians would diagnose with intermediate uveitis, non–pars planitis type may not be so classified by these classification criteria.

In conclusion, the criteria for intermediate uveitis, non–pars planitis outlined in Table 2 seem to perform sufficiently well for use as classification criteria in clinical research.[15,16]

CREDIT ROLES

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