Title: Classification criteria for multiple sclerosis-associated intermediate uveitis

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ABSTRACT

Purpose: To determine classification criteria multiple sclerosis-associated intermediate uveitis

Design: Machine learning of cases with multiple sclerosis-associated intermediate uveitis and 4 other intermediate uveitides.

Methods: Cases of intermediate uveitides were collected in an informatics-designed preliminary data base, and a final data base was constructed of cases achieving supermajority agreement on the diagnosis, using formal consensus techniques. Cases were split into a learning set and a validation set. Machine learning using multinomial logistic regression was used on the learning 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 112 cases of multiple sclerosis-associated intermediate uveitis, were evaluated by machine learning. The overall accuracy for intermediate uveitides was 99.8% in the learning set (95% confidence interval [CI] 98.7, 100) and 99.3% in the validation set (95% CI 96.1, 99.9). Key criteria for pars planitis included unilateral or bilateral intermediate uveitis and a diagnosis of multiple sclerosis by the McDonald Criteria. Key exclusions included syphilis and sarcoidosis. The misclassification rates for multiple sclerosis-associated intermediate uveitis were 0 % in the learning set and 0% in the validation set, respectively.

Conclusions: The criteria for multiple sclerosis-associated intermediate uveitis had a low misclassification rate and appeared to perform sufficiently well enough for use in clinical and translational research.

PRECIS

Using a formalized approach to developing classification criteria, including informatics-based case collection, consensus-technique-based case selection, and machine learning, classification criteria for multiple sclerosis-associated intermediate uveitis were developed. Key criteria included intermediate uveitis a diagnosis of multiple sclerosis by the McDonald Criteria. Exclusions included sarcoidosis and syphilis. The resulting criteria had a low misclassification rate.

Multiple sclerosis is a neurologic disease characterized by demyelinating lesions in the brain or spinal column at two or more sites occurring two or more times.[1,2] Typically it is a disease of young adults. Approximately 80% of cases present with a remitting and relapsing course, and ~20% with a primary progressive course. Patients presenting with remitting/relapsing multiple sclerosis typically have full recovery initially, but may progress to relapse with persistent deficit, and ultimately secondary progression. There is a strong environmental effect as incidence and prevalence increase in populations further away from the equator.[1,2] In Sub-Saharan Africa and East Asia the prevalence of multiple sclerosis is estimated at 2.1 to 2.2/100,000, whereas in Canada it is estimated at 291/100,000. In the United States, the prevalence is estimated at 265 to 309/100,000.[2,3] The diagnosis of multiple sclerosis typically is made using the McDonald Criteria, which have been revised several times, most recently in 2017.[4-6]

The most common ocular lesion in multiple sclerosis is optic neuritis. Approximately 25% of patients with multiple sclerosis will present with optic neuritis and as many as 70% will have at least one episode of experience optic neuritis during their lifetime.[2]

Patients with multiple sclerosis are reported to have an increased prevalence of uveitis. The reported prevalence of uveitis in patients with multiple sclerosis has ranged from 0.7% to 28.6%, with the higher estimates from small case series, and with an overall estimate of ~1%. [2,7] These estimates are greater than the estimated prevalence of uveitis in the United States, which has been estimated at 69 to 114/100,000 (about 0.1%).[8-10] The reported prevalence of multiple sclerosis in series of patients with uveitis has ranged from 0.9% to 3.1%, with an overall estimate of ~1%, again higher than the estimated prevalence of multiple sclerosis in the general population. [2] However, interpretation of these data often has been hampered by “lumping” together all cases of uveitis or by anatomic “lumping”, making associations with specific types of uveitis difficult. Hence for many types of uveitis, it is uncertain whether the reported association is merely chance alone or a real statistical increase. Nevertheless, there appears to be a clear-

cut association of multiple sclerosis with intermediate uveitis. The estimated prevalence of multiple sclerosis in intermediate uveitis has ranged from 2.3% to 33% with an overall estimate of ~11%, ~10-fold higher than that in uveitis overall, and ~30 to 100-fold higher than that in the general population.[2]

Intermediate uveitis refers to a class of uveitic diseases characterized by inflammation predominantly in the vitreous and an absence of retinitis and choroiditis.[11,12] Intermediate uveitides may be due infections, such as Lyme disease or syphilis, associated with systemic diseases, particularly sarcoidosis and multiple sclerosis, or may occur as an isolated, presumably immune-mediated, ocular disorder of unknown etiology.[12] Eye-limited intermediate uveitis diagnoses include pars planitis, characterized by snowball and/or snowbank formation, and intermediate uveitis, non-pars planitis type, also known as undifferentiated intermediate uveitis. [11-17]

Peripheral retinal vascular involvement is a characteristic feature of pars planitis and of multiple sclerosis-associated intermediate uveitis, but is reported to be more common in multiple sclerosis-associated intermediate uveitis.[15-17] It is typically asymptomatic and best appreciated on wide field digital imaging, particularly fluorescein angiography. Angiographically there may be venous leakage, staining, and /or occlusion. Given the absence of differences in the multiple sclerosis disease features between multiple sclerosis patients with and without intermediate uveitis or peripheral retinal vascular changes,[18] the pathogenetic significance of the association between peripheral retinal vascular changes and multiple sclerosis remains uncertain.

The Standardization of Uveitis Nomenclature (SUN) Working Group is an international collaboration, which has developed classification criteria for 25 of the most common uveitides using a formal approach to development and classification.[11,19-23] Among the intermediate uveitides studied was multiple sclerosis-associated intermediate uveitis.

Methods

The SUN Developing Classification Criteria for the Uveitides project proceeded in four phases as previously described: 1) informatics, 2) case collection, 3) case selection, and 4) machine learning10[11,21,23]

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.[11,21,23] Cases in the preliminary database were reviewed by committees of 9 investigators for selection into the final database.[21,23] Because the goal was to develop classification criteria,[22] only cases with a supermajority agreement (>75%) that the case was the disease in question were retained in the final database (i.e. were "selected").[21,23]

Machine learning. The final database then was randomly separated into a learning set (~85% of the cases) and a validation set (~15% of the cases) for each disease as described in the accompanying article.[23] Machine learning was used on the learning set to determine criteria that minimized misclassification. The criteria then were tested on the validation set; for both the learning set and the validation set, the misclassification rate was calculated for each disease. For multiple sclerosis -associated intermediate uveitis, the diseases against which it was evaluated were: pars planitis, intermediate uveitis, non-pars planitis type, sarcoid intermediate uveitis, and syphilitic intermediate uveitis. Too few cases of Lyme disease-associated uveitis were collected in the data base for analysis by machine learning.

The study adhered to the principles of the Declaration of Helsinki. Institutional Review Boards (IRBs) at each participating center reviewed and approved the study; the study typically was considered either minimal risk or exempt by the individual IRBs.

Results

One hundred eighty-three cases of MS-associated intermediate uveitis were collected, and 112 (62%) achieved supermajority agreement on the diagnosis during the "selection" phase and were used in the machine learning phase. These cases of MS-associated intermediate uveitis were compared to 477 cases of other intermediate uveitides, including 226 cases of pars

planitis, 114 cases of intermediate uveitis, non-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.[17] The details of the machine learning results for these diseases are outlined in the accompanying article.[23] The characteristics at presentation to a SUN Working Group Investigator of cases with multiple sclerosis-associated intermediate uveitis type are listed in Table 1. The criteria developed after machine learning are listed in Table 2. Key criteria were the presence of an intermediate uveitis and a diagnosis of multiple sclerosis. The overall accuracy for intermediate uveitides was 99.8% in the learning set (95% confidence interval [CI] 98.7, 100) and 99.3% in the validation set (95% CI 96.1, 99.2).[17] The misclassification rate for multiple sclerosis-associated intermediate uveitis in the learning set was 0%[11] and in the validation set 0%.

Discussion

The classification criteria developed by the SUN Working Group for multiple sclerosis-associated intermediate uveitis have a low misclassification rate, indicating good discriminatory performance against other intermediate uveitides. Because of the well documented relationship between intermediate uveitis and multiple sclerosis,[2] we evaluated criteria for multiple sclerosis-associated intermediate uveitis. However, given the uncertainty of the relationship of other subsets of uveitic diagnoses to multiple sclerosis, we did not evaluate whether criteria for other uveitis types might be relevant. Population studies evaluating the relationship of other specific uveitic subsets and morphology to multiple sclerosis might lead to a need for further classification criteria for multiple sclerosis associated uveitides.

Morphologically, multiple sclerosis and pars planitis could not be distinguished based on ocular features alone.[23,24] Although peripheral vascular changes (leakage, sheathing, and/or occlusion) have been reported as risk factors for multiple sclerosis, and although they were present more often in cases with multiple sclerosis-associated intermediate uveitis than in cases of pars planitis, the difference in frequency was not sufficient for diagnostic purposes and only a

diagnosis of multiple sclerosis distinguished the two. Pars planitis and multiple sclerosis share genetic risk factors, namely HLA-DR2 and its split antigen HLA-DR15, emphasizing their relationship,[17,25] but rendering HLA typing unhelpful in the differential diagnosis.[26] Complicating the relationship between the two are intermediate-term data that suggest that patients with pars planitis without multiple sclerosis will develop multiple sclerosis at the estimated rate of ~2% to 4%/year,[16,17,25] so that neuro-imaging to exclude multiple sclerosis is likely to have a low yield and is not routinely recommended.[27] As such some cases initially diagnosed as pars planitis will have their diagnosis changed with longer-term follow-up if they subsequently develop multiple sclerosis.

All of the cases in this series had clinically diagnosed multiple sclerosis, but we could not verify that they all satisfied the 2017 Revision of the MacDonald Criteria.[6] However, the MacDonald criteria are widely used for the diagnosis of multiple sclerosis, so that it is likely that cases were diagnosed using it or an earlier version of the criteria.[4-6] Nevertheless, going forward, it is seems appropriate to use the current version of the MacDonald Criteria (Table 3),[6] and to adapt as they are revised.

The type of uveitis most often seen with Lyme disease is an atypical intermediate or anterior and intermediate uveitis, but the disease may be indistinguishable from pars planitis and the intermediate uveitis associate with multiple sclerosis.[28,29] Complicating the distinction is the presence of neurological lesions in Lyme disease. Lyme uveitis is sufficiently uncommon that we were unable to collect a sufficient number of cases for analysis. It would be prudent to exclude Lyme disease in cases of intermediate uveitis from Lyme disease endemic regions and in Lyme disease exposed persons. However, in Lyme disease non-endemic regions, there is little value to screening for Lyme disease,[30] so that its exclusion is needed only for case series from Lyme endemic areas.

The presence of any of the exclusions in Table 3 suggests an alternate diagnosis, and the diagnosis of multiple sclerosis-associated intermediate 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 multiple sclerosis-associated intermediate uveitis, but the absence of such testing does not always exclude its diagnosis 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 at a minimum chest imaging, for all cases of multiple sclerosis-associated intermediate uveitis.[31]

Classification criteria are employed to diagnose individual diseases for research purposes.[22] 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,[22] 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 two uveitis experts on diagnosis is moderate at best,[21] the selection of cases for the final database ("case selection") included only cases which achieved supermajority agreement on the diagnosis. As such, some cases which clinicians would diagnose with multiple sclerosis-associated uveitis will not be so classified by classification criteria. The selection of cases during case selection of cases which achieved supermajority agreement on the diagnosis for inclusion in the final data base was used because we were developing classification criteria and sought to define an appropriately homogeneous group.

In conclusion, the criteria for multiple sclerosis-associated intermediate uveitis outlined in Table 2 appear to perform sufficiently well for use as classification criteria in clinical research.[23]

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297 **Table 1. Characteristics of Casess with Multiple Sclerosis-associated Intermediate**

298 **Uveitis**

Characteristic	Result
Number cases	112
Demographics	
Age, median, years (25th 75th percentile)	37 (30, 48)
Gender (%)	
Men	15
Women	85
Race/ethnicity (%)	
White, non-Hispanic	76
Black, non-Hispanic	4
Hispanic	2
Asian, Pacific Islander	1
Other	16
Missing	1
Uveitis History	
Uveitis course (%)	
Acute, monophasic	3
Acute, recurrent	2
Chronic	85
Indeterminate	10
Laterality (%)	
Unilateral	20
Unilateral, alternating	0
Bilateral	80
Ophthalmic examination	
Keratic precipitates (%)	
None	74
Fine	10
Round	3
Stellate	2
Mutton Fat	5
Other	0
Anterior chamber cells (%)	
Grade 0	52
½+	21
1+	19
2+	9
3+	0
4+	0
Hypopyon (%)	0
Anterior chamber flare (%)	
Grade 0	75
1+	21
2+	4
3+	0

4+	0
Iris (%)	
Normal	82
Posterior synechiae	18
Sectoral iris atrophy	0
Patchy iris atrophy	0
Diffuse iris atrophy	0
Heterochromia	0
Intraocular pressure (IOP), involved eyes	
Median, mm Hg (25^{th}, 75^{th} percentile)	14 (12, 16)
Proportion patients with IOP>24 mm Hg either eye (%)	1
Vitreous cells (%)*	
Grade 0	6
½+	24
1+	42
2+	25
3+	3
4+	0
Vitreous haze (%)*	
Grade 0	36
½+	28
1+	24
2+	11
3+	2
4+	0
Vitreous snowballs	54
Pars plana snowbanks	13
Peripheral retinal vascular sheathing or leakage	48
Macular edema	31

*All cases had either vitreous cells or haze; 1 case had haze without evident cells.

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300 **Table 2. Classification Criteria for Multiple Sclerosis-associated Intermediate Uveitis**

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 c. no evidence of retinitis or choroiditis AND 2. Evidence of multiple sclerosis using the Revised McDonald Diagnostic Criteria*
Exclusions
1. Positive serology for syphilis using a treponemal test 2. Evidence of sarcoidosis (either bilateral hilar adenopathy on chest imaging or tissue biopsy demonstrating non-caseating granulomata) 3. Positive serology for Lyme disease, either IgG or IgM (e.g. positive ELISA AND Western blot with requisite number of bands for assay used)

*Reference 6; see Table 3.

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Table 3. 2017 McDonald Criteria for the Diagnosis of Multiple Sclerosis

Requires demonstration of dissemination of lesions in the central nervous system in space and time.	
Clinical Presentation	**Additional Criteria to make Multiple Sclerosis Diagnosis**
In a person who has experience a typical attack/clinically isolated syndrome at onset:	
• ≥2 or more attacks and clinical evidence of ≥2 lesions; OR • ≥2 attacks and clinical evidence of 1 lesion with clear historical evidence of a prior attack involving lesion in a different location	None. Dissemination in space and dissemination in time have been met.
• ≥2 or more attacks and clinical evidence of 1 lesion	Dissemination in space shown by 1 of these criteria: ▪ Additional clinical attack implicating different CNS* site ▪ ≥1 MS†-typical T2 lesions in ≥2 areas of CNS: periventricular, cortical, juxtacortical, infratentorial, or spinal
• 1 attack and clinical evidence of ≥2 lesions	Dissemination in time shown by 1 of these criteria: ▪ Additional clinical attack ▪ Simultaneous presence of both enhancing and non-enhancing MS-typical MRI‡ lesions, or new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) ▪ CSF§ oligoclonal bands
• 1 attack and clinical evidence of 1 lesion	Dissemination shown by 1 of these criteria: ▪ Additional clinical attack implicating different CNS site ▪ ≥1 MS-typical T2 lesions in ≥2 areas of CNS: periventricular, cortical, juxtacortical, infratentorial, or spinal AND Dissemination in time shown by 1 of these criteria: ▪ Additional clinical attack ▪ Simultaneous presence of both enhancing and non-enhancing MS-typical MRI lesions, or new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) ▪ CSF oligoclonal bands
In a person who has steady progression of disease since onset	
1 year of disease progression	Dissemination in space shown by ≥2 of these criteria: ▪ ≥1 MS-typical T2 lesions (periventricular, cortical, juxtacortical, or infratentorial) ▪ ≥2 T2 spinal cord lesions ▪ CSF oligoclonal bands
*CNS = central nervous system. †MS = multiple sclerosis. ‡MRI = magnetic resonance imaging. §CSF = cerebrospinal fluid.	

Adapted from Thompson AJ, Banwell BL, Barkhof, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17:162-73.

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