# Classification Criteria for Multiple Sclerosis-Associated Intermediate Uveitis

THE STANDARDIZATION OF UVEITIS NOMENCLATURE (SUN) WORKING GROUP[1,2,3,4,5,*]

• PURPOSE: **The purpose of this study was to determine classification criteria for 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 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 in the training set to determine a parsimonious set of criteria that minimized the misclassification rate among the intermediate uveitides. The resulting criteria were evaluated in the validation set.**

• RESULTS: **A total of 589 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 training set and 99.3% in the validation set (95% confidence interval: 96.1-99.9). Key criteria for multiple sclerosis-associated intermediate uveitis included unilateral or bilateral intermediate uveitis and multiple sclerosis diagnosed by the McDonald criteria. Key exclusions included syphilis and sarcoidosis. The misclassification rates for multiple sclerosis-associated intermediate uveitis were 0 % in the training set and 0% in the validation set.**

• 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. (Am J Ophthalmol 2021;228: 72–79. © 2021 Elsevier Inc. All rights reserved.)**

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Multiple sclerosis is a neurologic disease characterized by demyelinating lesions in the brain or spinal column at 2 or more sites, occurring 2 or more times.[1,2] Typically, multiple sclerosis is a disease of young adults. Approximately 80% of cases present with a remitting and relapsing (remitting/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 the incidence and prevalence increase in populations farther away from the equator.[1,2] In Sub-Saharan Africa and East Asia, the prevalence of multiple sclerosis is estimated at 2.1-2.2/100,000 population, whereas in Canada it is estimated at 291/100,000 population. In the United States, the prevalence is estimated at 265-309/100,000 population.[2,3] Multiple sclerosis typically is diagnosed by using the



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McDonald criteria, which have been revised several times, most recently in 2017.[4-6]

The most common ocular lesion appearing in multiple sclerosis is optic neuritis. Approximately 25% of patients with multiple sclerosis will present with optic neuritis, and as many as 70% will experience at least 1 episode of 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%-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 69-114/100,000 population (approximately 0.1%).[8-10] The reported prevalence of multiple sclerosis in series of patients with uveitis has ranged from 0.9%-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 between multiple sclerosis and intermediate uveitis. The estimated prevalence of multiple sclerosis in intermediate uveitis has ranged from 2.3%-33% with an overall estimate of ~11%, ~10-fold higher than that in uveitis overall and ~30-100-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 to infections such as Lyme disease or syphilis; associated with systemic diseases, particularly sarcoidosis and multiple sclerosis; or may occur as an isolated, presumably immunity-mediated, ocular disorder of unknown cause.[12] Eye-limited intermediate uveitis diagnoses include pars planitis characterized by snowball or snowbank formation, or both, 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, or occlusion, or both. Given the absence of differences among 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 by 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 4 phases as previously described: 1) informatics, 2) case collection, 3) case selection, and 4) machine learning.[10,11,21,23]

• **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.[19]

• **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 inclusion into the final database, using formal consensus techniques described in the accompanying articles.[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 (ie, were "selected").[21,23]

• **MACHINE LEARNING:** The final database then was randomly separated into a training 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 for the training set to determine criteria that minimized misclassification. The criteria then were tested in 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 compared to the consensus diagnosis. 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[14] 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

A total of 183 cases of multiple sclerosis-associated intermediate uveitis were collected, and 112 cases (62%) achieved supermajority agreement for the diagnosis during the "selection" phase and were used in the machine learning phase. Those cases of multiple sclerosis-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 those diseases are outlined in the accompanying article.[23] The characteristics, at a presentation of 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 2017 McDonald criteria for the diagnosis of multiple sclerosis are outlined in Table 3. The overall accuracy for intermediate uveitides was 99.8% in the training set and 99.3% in the validation set (95% confidence interval [CI]: 96.1-99.9).[17] The misclassification rate for multiple sclerosis-associated intermediate uveitis in the training set was 0%[11] and 0% in the validation set.

## DISCUSSION

The classification criteria developed by the SUN Working Group for multiple sclerosis-associated intermediate uveitis had 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] criteria were evaluated for multiple sclerosis-associated intermediate uveitis. However, given the uncertainty of the relationships among other subsets of uveitic diagnoses and multiple sclerosis, whether criteria for other uveitis types might have been relevant was not evaluated. Population studies evaluating the relationship between other specific uveitic subsets and morphology and multiple sclerosis may 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, or occlusion, or both) 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 differences in frequency were not sufficient for diagnostic purposes, and only a diagnosis of multiple sclerosis distinguished the 2. 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 relationships between the 2 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 neuroimaging performed 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 it could not be verified that they all satisfied the 2017 revision of the McDonald criteria.[6] However, the McDonald criteria are widely used for the diagnosis of multiple sclerosis, so 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 was sufficiently uncommon that too few cases were collected for analysis. In regions where Lyme disease is not endemic, there appears to be little value to screening for Lyme disease, as nearly all tests with positive results will be false positives.[30] Even among patients from areas of Lyme endemicity 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 persons exposed to Lyme disease and those with symptoms suggesting Lyme disease.[31] Nevertheless, in prospective studies from Lyme disease-endemic regions (or in Lyme disease-exposed individuals), testing patients with intermediate uveitis for Lyme disease would appear to be appropriate. The presence of a positive Lyme serology (with appropriate confirmatory testing) excludes the diagnosis of multiple sclerosis-associated intermediate uveitis.

The presence of any of the exclusions in Table 2 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 those tests will be performed routinely and the alternative diagnoses excluded. However, in retrospective studies based on clin-

**TABLE 1.** Characteristics of Cases With Multiple Sclerosis-Associated Intermediate Uveitis

| Characteristic | Result |
|---|---|
| Number of cases | 112 |
| Demographics | |
| Median IQR (25th 75th percentile), y | 37 (30, 48) |
| 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 |

(*continued on next page*)

**TABLE 1.** (*continued*)

| Characteristic | Result |
|---|---|
| IOP-involved eyes | |
| Median IQR (25th, 75th), mm Hg | 14 (12, 16) |
| Proportion of patients with IOP >24 mm Hg in either eye (%) | 1 |
| Vitreous cells, %[a] | |
| Grade 0 | 6 |
| ½+ | 24 |
| 1+ | 42 |
| 2+ | 25 |
| 3+ | 3 |
| 4+ | 0 |
| Vitreous haze, %[a] | |
| 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 |

IOP = intraocular pressure; IQR = interquartile range.
[a]All cases had either vitreous cells or haze; 1 case had haze without evident cells.

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

| Criteria |
|---|
| 1. Evidence of intermediate uveitis |
| a. Vitreous cells or vitreous haze or both; |
| b. If anterior chamber cells are present, anterior chamber inflammation is less than that of vitreous; |
| c. No evidence of retinitis or choroiditis; |
| And |
| 2. Evidence of multiple sclerosis using the revised McDonald diagnostic criteria[6a] |
| Exclusions |
| 1. Serology positive for syphilis, using a treponemal test; |
| 2. Evidence of sarcoidosis (either bilateral hilar adenopathy on chest imaging or tissue biopsy demonstrating noncaseating granulomata); |
| 3. Serology positive for Lyme disease; either IgG or IgM (eg, positive ELISA and Western blot results, with the requisite number of bands for assay used. |

ELISA = enzyme-linked immunosorbent assay; IgG/M = immunoglobulin G/M.
[a]See Table 3.

ical care, not all of those 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.[32]

Classification criteria are used 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 tradeoff 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 used did not explicitly use

**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 diagnose multiple sclerosis |
|---|---|
| In a person who has experienced a typical attack or a clinically isolated syndrome at onset: | |
| • ≥2 or more attacks and clinical evidence of ≥2 lesions; or<br>• ≥2 attacks and clinical evidence of 1 lesion with clear historical evidence of a prior attack involving a 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 the following criteria:<br>• Additional clinical attack implicating different CNS site<br>• ≥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 the following criteria:<br>• Additional clinical attack<br>• Simultaneous presence of both enhancing and non-enhancing MS-typical CMR lesions or new T2 or enhancing CMR lesion compared to baseline scan (without regard to timing of baseline scan)<br>• CSF oligoclonal bands |
| • 1attack and clinical evidence of 1 lesion | Dissemination shown by 1 of the following criteria:<br>• Additional clinical attack, implicating a different CNS site<br>• ≥1 MS-typical T2 lesion in ≥2 areas of CNS: periventricular, cortical, juxtacortical, infratentorial, or spinal<br>And<br>Dissemination in time shown by 1 of the following criteria:<br>• Additional clinical attack<br>• Simultaneous presence of both enhancing and non-enhancing MS-typical CMR lesions, or new T2 or enhancing CMR lesion compared to baseline scan (without regard to timing of baseline scan)<br>• 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 the following criteria:<br>• ≥1 MS-typical T2 lesion (periventricular, cortical, juxtacortical, or infratentorial)<br>• ≥2 T2 spinal cord lesions<br>• CSF oligoclonal bands |

MRI = magnetic resonance imaging; CNS = central nervous system; CSF = cerebrospinal fluid; MS = multiple sclerosis.
Table 3 was adapted from Thompson and associates.[6]

sensitivity and specificity; instead, learning minimized the misclassification rate. Because the study was developing classification criteria and because the typical agreement between 2 uveitis experts for diagnosis was moderate at best,[21] the selection of cases for the final database ("case selection") included only cases which achieved supermajority agreement for the diagnosis. As such, some cases that clinicians would diagnose with multiple sclerosis-associated uveitis will not be so classified by classification criteria. The selection of cases which achieved supermajority agreement on the diagnosis for inclusion in the final data base was used, because the study sought to develop classification criteria and 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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