

# Classification Criteria For Multiple Evanescent White Dot Syndrome



THE STANDARDIZATION OF UVEITIS NOMENCLATURE (SUN) WORKING GROUP<sup>1,2,3,4,\*</sup>

• **PURPOSE:** The purpose of this study was to determine classification criteria for multiple evanescent white dot syndrome (MEWDS).

• **DESIGN:** Machine learning of cases with MEWDS and 8 other posterior uveitides.

• **METHODS:** Cases of posterior uveitides were collected in an informatics-designed preliminary database, and a final database was constructed of cases achieving supermajority agreement on 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 infectious posterior, or panuveitides. The resulting criteria were evaluated in the validation set.

• **RESULTS:** A total of 1,068 cases of posterior uveitides, including 51 cases of MEWDS, were evaluated by machine learning. Key criteria for MEWDS included: 1) multifocal gray-white chorioretinal spots with foveal granularity; 2) characteristic imaging on fluorescein angiography (“wreath-like” hyperfluorescent lesions) and/or optical coherence tomography (hyper-reflective lesions extending from retinal pigment epithelium through ellipsoid zone into the retinal outer nuclear layer); and 3) absent to mild anterior chamber and vitreous inflammation. Overall accuracy for posterior uveitides was 93.9% in the training set and 98.0% (95% confidence interval: 94.3–99.3) in the validation set. Misclassification rates for MEWDS were 7% in the training set and 0% in the validation set.

• **CONCLUSIONS:** The criteria for MEWDS had a low misclassification rate and appeared to perform sufficiently well for use in clinical and translational research. (Am J Ophthalmol 2021;000: 1–7. © 2021 Elsevier Inc. All rights reserved.)

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IN 1984, JAMPOL AND ASSOCIATES<sup>1</sup> DESCRIBED A NEW posterior uveitis which they named multiple evanescent white dot syndrome (MEWDS). The disease occurred in young people (mean age: 28 years), predominantly in women (90%), and was characterized by unilateral, 100–200- $\mu$ m gray-white dots at the level of the retinal pigment epithelium or outer retina and a foveal granularity. Other common features included posterior vitreous cells, disc swelling with fluorescein staining, and less often vascular sheathing. The white spots had a characteristic wreath-like appearance on fluorescein angiography. The disease spontaneously remitted over ~2 months with recovery of normal or near normal acuity (20/30 or better) in all cases. No systemic disease was evident, and no treatment appeared warranted.

Subsequent case series have confirmed the clinical features of the disease.<sup>2–6</sup> The disease presents in young adults; approximately 80% of cases are in women; there is no evident racial or ethnic predilection. Rare cases of bilateral disease and recurrent disease have been reported,<sup>7</sup> but most cases are unilateral with a self-limited disease.<sup>4,6</sup>

MEWDS is a rare disease. The incidence has been estimated at 0.22 per 100,000 population per year, an incidence on the same order of magnitude as acute posterior multifocal

placoid pigment epitheliopathy (APMPPE).<sup>8</sup> The cause is unknown. A post-viral autoimmune or auto-inflammatory pathogenesis has been postulated, as case series suggest that ~50% of patients with MEWDS will have an antecedent influenza-like illness.<sup>1,4</sup> However, those case series show recall bias and lack of a control group, making inferences about pathogenesis speculative.

Multimodal imaging is helpful in evaluating the disease.<sup>5,6</sup> Fluorescein angiography demonstrates early hyperfluorescence of the multifocal white spots and a “wreath-like” pattern in ~80% of cases.<sup>4,6</sup> Indocyanine green (ICG) angiography demonstrates early to mid-phase hypofluorescence of the white dots and a peripapillary zonal hypofluorescence, the latter of which correlates with the enlarged blind spot often present in patients with MEWDS.<sup>4,6</sup> Optical coherence tomography (OCT) imaging demonstrates disruption of the ellipsoid zone and either dome-shaped hyperreflectivity over the retinal pigment epithelium or vertical linear hyper-reflectivity, or both, involving the ellipsoid zone and outer nuclear layer, the latter being seen in ~80% of cases evaluated with OCT.<sup>5,6,9</sup> Although there is debate about the exact pathogenesis and extent of the involvement of the choroid,<sup>10</sup> these outer retinal findings may help to distinguish MEWDS from other multifocal choroidopathies. Fundus autofluorescence, evaluated in a limited number of cases, demonstrates hyperautofluorescence of the lesions.<sup>11,12</sup>

Typically, no treatment is given as eyes spontaneously recover in ~10 weeks with 95% of eyes achieving 20/25 acuity or better.<sup>1,4,6</sup>

The Standardization of Uveitis Nomenclature (SUN) Working Group is an international collaboration, which is developing classification criteria for 25 of the most common uveitides by using a formal approach to development and classification. Among the diseases studied was MEWDS.<sup>13-18</sup>

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## 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.<sup>15-18</sup>

- **INFORMATICS:** As previously described, the consensus-based informatics phase permitted development of a standardized vocabulary and a standardized, menu-driven hierarchical case collection instrument.<sup>15</sup>

- **CASE COLLECTION AND CASE SELECTION:** Identified information was entered into the SUN preliminary database by the 76 contributing investigators for each disease, as previously described.<sup>17,18</sup> 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.<sup>17,18</sup> Because the goal was to develop classification criteria,<sup>19</sup> only cases with a supermajority agreement (>75%) that the case was the disease in question were retained in the final database (ie, were “selected”).<sup>17,18</sup>

- **MACHINE LEARNING:** The final database 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.<sup>18</sup> Machine learning was used in 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 MEWDS, the diseases against which it was evaluated included APMPPE; birdshot chorioretinitis (BSCR); multifocal choroiditis with panuveitis (MFCPU); punctate inner choroiditis (PIC); serpiginous choroiditis; sarcoidosis-associated posterior uveitis; syphilitic posterior uveitis; and tubercular uveitis.

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.

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## RESULTS

Ninety-five cases of MEWDS were collected, and 51 (54%) achieved supermajority agreement on the diagnosis during the “selection” phase and were used in the machine learning phase. These cases of MEWDS were compared to cases of posterior uveitides, including 82 cases of APMPPE; 207 cases of BSCR; 122 cases of serpiginous choroiditis; 138 cases of MFCPU; 144 cases of PIC; 12 cases of sarcoid posterior uveitis; 35 cases of syphilitic posterior uveitis; and 277 cases of tubercular posterior/panuveitis (including 96 cases of serpiginous-like tubercular choroiditis). Details of the machine learning results for those diseases are outlined in the accompanying article.<sup>19</sup> The characteristics of cases with MEWDS are listed in Table 1, and the classification criteria developed after machine learning are listed in Table 2. Key features of the criteria include multifocal white dots (Figure 1), the characteristic “wreath-like” hyperfluorescent lesions on fluorescein angiogram (Figure 2), and the hyper-reflective lesions extending from the retinal pigment epithelium inward on OCT (Figure 3). The overall

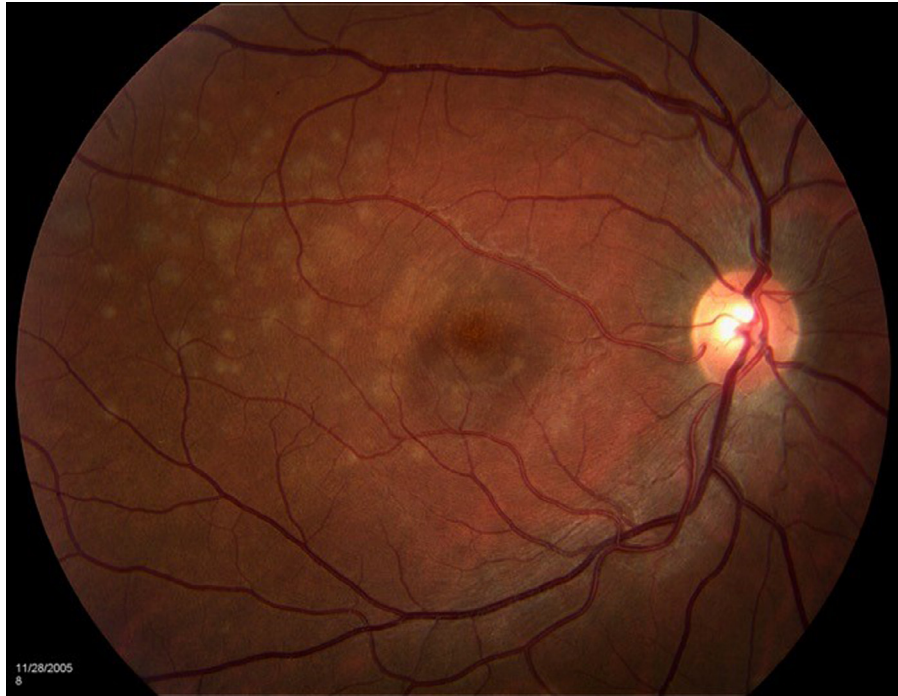


FIGURE 1. Fundus photograph from a case of multiple evanescent white dot syndrome, demonstrating the characteristic white chorioretinal lesions.

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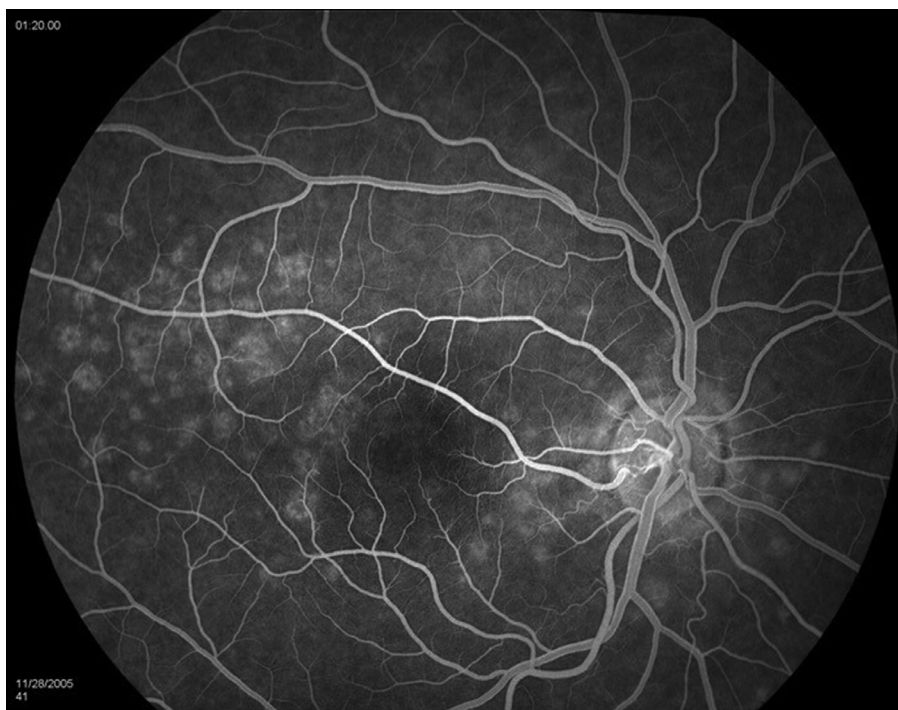


FIGURE 2. Fluorescein angiogram of a case of multiple evanescent white dot syndrome, demonstrating the “wreath-like” nature of the chorioretinal lesions.

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**TABLE 1.** Characteristics of Cases with Multiple Evanescent White Dot Syndrome

Characteristic	Result
Number cases	51
<i>Demographics</i>	
Age, median, years (25 <sup>th</sup> 75 <sup>th</sup> percentile)	27 (22, 34)
Gender (%)	
Men	24
Women	76
Race/ethnicity (%)	
White, non-Hispanic	61
Black, non-Hispanic	0
Hispanic	4
Asian, Pacific Islander	6
Other	10
Missing	19
<i>Uveitis History</i>	
Uveitis course (%)	
Acute, monophasic	87
Acute, recurrent	6
Chronic	2
Indeterminate	5
Laterality (%)	
Unilateral	96
Unilateral, alternating	2
Bilateral	2
<i>Ophthalmic examination</i>	
Keratic precipitates (%)	
None	100
Anterior chamber cells (%)	
Grade 0	90
½+	6
1+	4
2+	0
3+	0
4+	0
Anterior chamber flare (%)	
Grade 0	100
Iris (%)	
Normal	100
Intraocular pressure (IOP), involved eyes	
Median, mm Hg (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	14 (12, 16)
Proportion patients with IOP>24 mm Hg either eye (%)	0
Vitreous cells (%)	
Grade 0	59
½+	22
1+	14
2+	6
3+	0
4+	0
Vitreous haze (%)	
Grade 0	96
½+	4
1+	0
2+	0

(continued on next column)

**TABLE 1.** (continued)

Characteristic	Result
3+	0
4+	0
<i>Chorioretinal lesion characteristics</i>	
Lesion number (%)	
Unifocal (1 lesion)	0
Paucifocal (2-4)	16
Multifocal (≥5)	75
Missing	9
Lesion shape & character (%)	
Ameboid or serpentine	0
Oval or round	85
Placoid	0
Punched-out atrophic	0
Punctate	14
Missing	1
Lesion location (%)	
Posterior pole involved	47
Mid-periphery and periphery only	53
Typical lesion size (%)	
<125 μm	14
125-250 μm	55
250-500 μm	29
>500 μm	2
Other features (%)	
Retinal vascular sheathing	8
Retinal vascular leakage	14
Choroidal neovascularization	0
Imaging results	
"Wreath-like" staining of spots on fluorescein angiogram*	65
Hyperreflective lesions extending from retinal pigment epithelium into or through ellipsoid zone on optical coherence tomography†	88

\*Based on 40 cases with fluorescein angiography. †Based on 26 cases with optical coherence tomography results.

accuracies for posterior uveitides were 93.9% in the training set and 98.0% (95% confidence interval: 94.3-99.3) in the validation set. The misclassification rate for MEWDS in the training set was 7% and 0% in the validation set.

## DISCUSSION

The classification criteria developed by the SUN Working Group for MEWDS have an acceptable misclassification rate, indicating good discriminatory performance relative to other non-infectious posterior and panuveitides. Because the goal of the SUN criteria was classification at presentation and because MEWDS spontaneously resolves, these criteria were most appropriate for the early, active stage of the disease.<sup>20</sup>



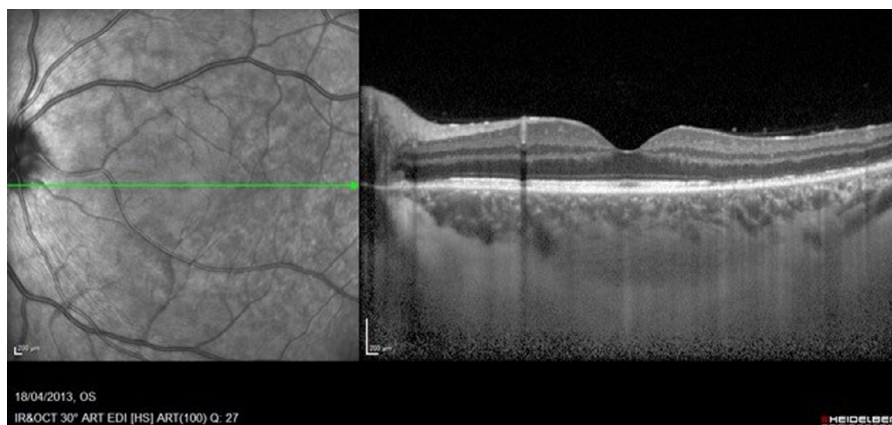


FIGURE 3. Optical coherence tomogram of a case of multiple evanescent white dot syndrome, demonstrating the characteristic lesions in the ellipsoid zone and outer nuclear layer.

**TABLE 2.** Classification Criteria for Multiple Evanescent White Dot Syndrome

**Criteria**

1. Multifocal chorioretinal gray-white spots with foveal granularity  
AND
2. Characteristic fluorescein angiogram or optical coherence tomogram (OCT)
  - a. "Wreath-like" hyperfluorescent lesions on fluorescein angiogram OR
  - b. Hyperreflective lesions on OCT extending from the retinal pigment epithelium, into and/or through the ellipsoid zone into the outer nuclear layer of the retina

**AND**

3. Absent to mild anterior chamber and vitreous inflammation

**Exclusions**

1. Positive serologic test 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. Bilateral simultaneous disease onset

Unlike other diseases in this class, the primary lesion appears to be at the level of the retinal pigment epithelium or outer retina or both. The OCT appearance, therefore, is helpful in distinguishing MEWDS from other posterior uveitides. Placoid syphilitic posterior uveitis has a "ratty" appearance to the retinal pigment epithelium<sup>21</sup> but typically is a unifocal or paucifocal disease. Nevertheless, its exclusion appears warranted. Similarly, the fluorescein angiographic appearance, when present, distinguishes MEWDS from the other diseases in this class and is useful in the diagnosis. Features which do not discriminate between diseases, such as hypofluorescent spots on ICG angiography and choroidal thickening, would not be selected.<sup>22,23</sup> Although peripapillary zonal hypofluorescence on ICG an-

giography is highly suggestive of MEWDS, it was not reported often enough to be selected as a criterion. Further study evaluating this finding in a series of cases diagnosed using standardized criteria could lead to a revision of the criteria.

The presence of any of the exclusions in Table 2 suggests an alternate diagnosis, and the diagnosis of MEWDS 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 clinical care, not all of those tests may have been performed. In those studies, the presence of an exclusionary criterion excludes MEWDS, but the absence of such testing does not always exclude the diagnosis of MEWDS if the criteria for the diagnosis are met. Cases mimicking the clinical and imaging features of MEWDS have been reported, including cases of syphilis and sarcoidosis; most of the diseases mimicking MEWDS were bilateral at presentation (bilateral simultaneous onset).<sup>24</sup> Nearly all cases of MEWDS are unilateral at onset. Going forward, it would seem appropriate to evaluate patients for more common masquerading diseases, using appropriate serology for syphilis and chest imaging for sarcoidosis.<sup>25,26</sup>

Classification criteria are used to diagnose individual diseases for research purposes.<sup>19</sup> 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,<sup>19</sup> 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 in this study did not explicitly use sensitivity and specificity; instead, it minimized the misclassification rate. Because the study purpose was to develop classification criteria and because the typical

agreement between 2 uveitis experts on diagnosis was moderate at best,<sup>17</sup> 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 MEWDS may not be so classified by classification criteria.

In conclusion, the criteria for MEWDS outlined in Table 2 appear to perform sufficiently well for use as classification criteria in clinical research.<sup>18</sup>

## CREDIT ROLES

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ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and none were reported.

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