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## Classification criteria for acute posterior multifocal placoid pigment epitheliopathy

The Standardization of Uveitis Nomenclature (SUN) Working Group<sup>\*,1,2,3</sup>

### Abstract

**Purpose:** To determine classification criteria for acute posterior multifocal placoid pigment epitheliopathy (APMPPE).

**Design:** Machine learning of cases with APMPPE 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 on the training set to

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<sup>\*</sup>**Corresponding author:** Douglas A. Jabs, MD, MBA, Department of Epidemiology, the Johns Hopkins University Bloomberg School of Public Health, 615 N Wolfe St, Baltimore, MD, 20215 USA. **Phone:** 410-955-1254. djabs@jhmi.edu.  
**CRedit roles:** **Douglas A. Jabs, MD, MBA:** Conceptualization, Methodology, Validation, Investigation, Data curation, Writing—Review and editing, Visualization, Supervision, Project administration, Funding acquisition. **Antoine P. Brezin, MD:** Investigation, Writing—Review and editing. **Andrew D. Dick, MBBS, MD, FRCP, FRCS, FRCOphth:** Investigation, Writing—Review and editing. **Ralph D. Levinson, MD:** Investigation, Writing—Review and editing. **Lyndell L. Lim, MD:** Investigation, Writing—Review and editing. **Peter McCluskey, MD:** Investigation, Data curation, Writing—Review and editing. **Neal Oden, PhD:** Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing—Review and editing. **Alan G. Palestine, MD:** Investigation, Writing—Original draft, Writing—Review and editing. **Jennifer E. Thorne, MD, PhD:** Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing—Review and editing. **Brett E. Trusko, PhD, MBA:** Methodology, Software, Resources, Data curation, Investigation, Writing—Review and editing. **Albert Vitale, MD:** Investigation, Writing—Review and editing. **Susan E. Wittenberg, MD:** Investigation, Writing—Review and editing.

<sup>1</sup>**Writing committee:** Douglas A. Jabs, MD, MBA<sup>2,3</sup>; Antoine P. Brezin, MD<sup>4</sup>; Andrew D. Dick, MBBS, MD, FRCP, FRCS, FRCOphth<sup>5–7</sup>; Ralph D. Levinson, MD<sup>8</sup>; Lyndell L. Lim, MD<sup>9</sup>; Peter McCluskey, MD<sup>10</sup>; Neal Oden, PhD<sup>11</sup>; Alan G. Palestine, MD<sup>12</sup>; Jennifer E. Thorne, MD, PhD<sup>2,3</sup>; Brett E. Trusko, PhD, MBA<sup>13</sup>; Albert Vitale, MD<sup>14</sup>; Susan E. Wittenberg, MD<sup>15</sup>

<sup>2</sup>**Affiliations:** <sup>1</sup>Members of the SUN Working Group are listed online at [ajo.com](http://ajo.com). From <sup>2</sup>the Department of Epidemiology, the Johns Hopkins University Bloomberg School of Public Health, and <sup>3</sup>the Wilmer Eye Institute, the Department of Ophthalmology, the Johns Hopkins University School of Medicine, Baltimore, MD, USA; <sup>4</sup>Department of Ophthalmology, University of Paris V – Hôpital Cochin, Paris, France; <sup>5</sup>the Academic Unit of Ophthalmology, Bristol Medical School, University of Bristol, Bristol, UK; <sup>6</sup>the National Institute for Health Research Biomedical research Centre at Moorfields Eye Hospital, London, UK; <sup>7</sup>University College London Institute of Ophthalmology, London UK; <sup>8</sup>the UCLA Stein Eye Institute and the Department of Ophthalmology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; <sup>9</sup>Center for Eye Research Australia, Royal Victorian Eye and Ear Hospital, Melbourne, Australia; <sup>10</sup>the Save Sight Institute, Department of Ophthalmology, University of Sydney School of Medicine, Sydney, NSW, Australia; <sup>11</sup>the Emmes Company, LLC, Rockville, MD, USA; <sup>12</sup>the Department of Ophthalmology, University of Colorado School of Medicine, Aurora, Co, USA; <sup>13</sup>the Department of Medicine, Texas A&M University, College Station, TX, USA; <sup>14</sup>the Department of Ophthalmology, the University of Utah School of Medicine, Salt Lake City, UT, USA; <sup>15</sup>Houston Eye Associates, Houston, TX, USA.

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determine a parsimonious set of criteria that minimized the misclassification rate among the posterior uveitides. The resulting criteria were evaluated on the validation set.

**Results:** One thousand sixty-eight cases of posterior uveitides, including 82 cases of APMPE, were evaluated by machine learning. Key criteria for APMPE included: 1) choroidal lesions with a plaque-like or placoid appearance and 2) characteristic imaging on fluorescein angiography (lesions “block early and stain late diffusely”). Overall accuracy for posterior uveitides was 92.7% in the training set and 98.0% (95% confidence interval 94.3, 99.3) in the validation set. The misclassification rates for APMPE were 5% in the training set and 0% in the validation set.

**Conclusions:** The criteria for APMPE had a low misclassification rate and appeared to perform sufficiently well 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 acute posterior multifocal placoid pigment epitheliopathy were developed. Key criteria included choroidal lesions with a plaque-like or placoid appearance and a characteristic fluorescein angiogram (lesions are hypofluorescent early and diffusely hyperfluorescent late). The resulting classification criteria had a low misclassification rate.

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In 1968 Gass described the disease he named Acute Posterior Multifocal Placoid Pigment Epitheliopathy (APMPE).<sup>1</sup> The characteristic lesions were thought to be at the level of the retinal pigment epithelium and choroid, were plaque-like in appearance, and had a characteristic fluorescein angiogram appearance described as early blockage and diffuse late staining. Early descriptions emphasized the self-limited nature of the disease with spontaneous remissions within 6 weeks and the good visual prognosis with most patients achieving 20/25 or better acuity, despite the poor presenting acuity.<sup>2-5</sup> Subsequently patients with recurrent disease and poorer visual outcomes have been reported.<sup>6</sup>

The disease typically affects young adults, both men and women, and has an estimated incidence of 0.15 per 100,000 population per year.<sup>7</sup> The etiology is unknown. Case series often emphasize a history of an antecedent viral flu-like illness in one-third of cases to suggest an autoimmune or autoinflammatory response to an infection.<sup>1-5</sup> However, these series all suffer from recall bias and the lack of a control group, making the interpretation speculative. Most cases are an isolated eye disease, but cases of APMPE have been described in the context of systemic inflammatory diseases, particularly those with vascular involvement.<sup>5,8,9</sup> The most frequently reported associated systemic disease is cerebral vasculitis.<sup>8,9</sup> These associations raise the question of whether APMPE is a specific disease or a phenotype of choroidal vascular and retinal pigment epithelial damage. A third possibility is that the eye-limited disease is a specific disease, whose appearance can be mimicked by systemic diseases which cause a “choriocapillaritis”. The pathogenesis has been debated with some suggesting a primary inflammation of the retinal pigment epithelium and others a primary inflammation of the choroid, perhaps the choriocapillaris, with secondary retinal pigment epithelial damage. Multimodal imaging, including indocyanine green angiography, fundus autofluorescence, optical coherence tomography (OCT), and OCT angiography, has suggested that the inflammation of the

choroid is primary as the choroidal lesions are more extensive than the retinal pigment epithelial damage noted on fluorescein angiography and fundus autofluorescence.<sup>5,10-14</sup>

As noted above, fluorescein angiography demonstrates early hypofluorescent lesions and uniform diffusely hyperfluorescent lesions in the late angiogram.<sup>1-5</sup> Fundus autofluorescence demonstrates hypo-autofluorescent lesions acutely with hyper-autofluorescent lesions in later stages of the disease.<sup>5,11</sup> Indocyanine green angiography demonstrates hypofluorescent lesions, interpreted as choroidal hypoperfusion, corresponding to the lesions seen on fluorescein angiogram.<sup>5,10</sup> However, indocyanine green angiographic lesions may be more extensive than those seen on fluorescein angiography. On OCT imaging there is disruption of photoreceptors acutely with outer retinal hyper-reflectivity and sometimes subretinal fluid. Nevertheless, macular edema is uncommon. On OCT angiography there are flow voids at the level of the choriocapillaris, again suggesting that the pathogenesis is ischemic damage, perhaps as a result of choroidal small vessel vasculitis or occlusion.<sup>12-14</sup>

Untreated, APMPE typically spontaneously remits and has a good visual prognosis.<sup>15</sup> A review of 15 case series<sup>7</sup> totaling 295 involved eyes suggested that approximately one-third of eyes presented with visual acuity 20/40 or better, one-third between 20/40 and 20/200, and one-third 20/200 or worse. At last follow-up, approximately three-fourths of eyes had a visual acuity 20/40 or better, 20% between 20/40 and 20/200, and 5% 20/200 or worse. There was no evident difference in the visual outcome between eyes treated with medical therapy (~70% 20/40 or better) and those not treated (85% 20/40 or better), but these studies likely suffered from a treatment by indication bias.<sup>7</sup> Nevertheless, there was little evidence for the benefit of medical (anti-inflammatory) therapy. Foveal involvement was associated with worse visual outcomes (39% 20/25 or better vs 88% 20/25 or better without foveal involvement).<sup>7</sup>

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. Among the diseases studied was APMPE.<sup>16-21</sup>

## 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 learning.<sup>18-21</sup>

### 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.<sup>18</sup>

### 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.<sup>20,21</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>20,21</sup> Because the goal was to develop classification criteria,<sup>20</sup> 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”).<sup>20,21</sup>

### 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.<sup>20</sup> 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 APMPE the diseases against which it was evaluated were: birdshot chorioretinitis (BSCR), multifocal choroiditis with panuveitis (MFCPU), multiple evanescent white dot syndrome (MEWDS), punctate inner choroiditis (PIC), serpiginous choroiditis, sarcoidosis-associated posterior uveitis, syphilitic posterior uveitis, and tubercular (TB) posterior 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.

### Results

One hundred forty-nine cases of APMPE were collected and 82 (52%) achieved supermajority agreement on the diagnosis during the “selection” phase and were used in the machine learning phase. These cases of APMPE were compared to cases of posterior uveitides, including 122 cases of serpiginous choroiditis, 207 cases of BSCR, 51 cases of MEWDS, 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. The details of the machine learning results for these diseases are outlined in the accompanying article.<sup>21</sup> The characteristics of cases with APMPE are listed in Table 1, and the classification criteria developed after machine learning are listed in Table 2. Key features of the criteria included the plaque-like or placoid appearance of the lesions (Figure 1) and the characteristic fluorescein angiogram (Figure 2) with early hypofluorescence of the lesions and late uniformly diffuse hyperfluorescence of the lesions. The overall accuracies for posterior uveitides were 92.7% in the training set and 98.0% (95% confidence interval 94.3, 99.3) in the validation set. The misclassification rate for APMPE in the training set was 5%, and in the validation set 0%. The diseases with which APMPE was confused in the training set were MEWDS and tubercular uveitis.

## Discussion

The classification criteria developed by the SUN Working Group for APMPE have a low misclassification rate, indicating good discriminatory performance against other posterior uveitides. The appearance is dissimilar to BSCR, MFCPU, and PIC, and the angiogram different than that in serpiginous choroiditis and MEWDS. Key exclusions include placoid syphilitic uveitis and sarcoidosis.

Ampiginous choroiditis and relentless placoid choroiditis (which may be the same disease) are rare diseases that have lesions which are similar to APMPE in clinical appearance, but often have fluorescein angiograms more similar to serpiginous choroiditis (i.e.early hypofluorescence of the lesions and late hyperfluorescence of the lesion borders).<sup>23,24</sup> The course is more similar to serpiginous choroiditis than to APMPE, in that the disease is recurrent or chronic, and it appears to need immunosuppression as its treatment. Hence, despite the clinical appearance, ampiginous/relentless placoid choroiditis is distinct from APMPE and may be a variant of serpiginous choroiditis or a distinct disease related to serpiginous choroiditis. Our database had too few cases of relentless placoid choroiditis for formal analysis, but the reported descriptions appear distinct from APMPE.

The issue of systemic disease findings (e.g. cerebral vasculitis) in some cases of APMPE raises the question of whether these findings are a complication of APMPE or these are diseases in which ocular involvement mimics APMPE. Our data on systemic diseases were not adequate to address the issue at this time. Hence, we recommend that all cases of APMPE be sub-classified as “eye-limited” with only ocular involvement or with systemic features (e.g. cerebral vasculitis). Antecedent viral or other flu-like illnesses should not be included in the group with systemic features.

The presence of any of the exclusions in Table 2 suggests an alternate diagnosis, and the diagnosis of APMPE 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. In these studies the presence of an exclusionary criterion excludes APMPE, but the absence of such testing does not always exclude the diagnosis of APMPE if the criteria for the diagnosis are met.

Classification criteria are used to diagnose individual diseases for research purposes.<sup>22</sup> 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.<sup>22</sup> 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,<sup>20</sup> the selection of cases for the final database (“case selection”) included only cases which achieved supermajority agreement on the diagnosis. As such there may be cases which clinicians would diagnose as APMPE, which would not meet the criteria outlined in Table 2.

In conclusion, the criteria for APMPE outlined in Table 2 appear to perform sufficiently well for use as classification criteria in clinical research.<sup>21</sup>

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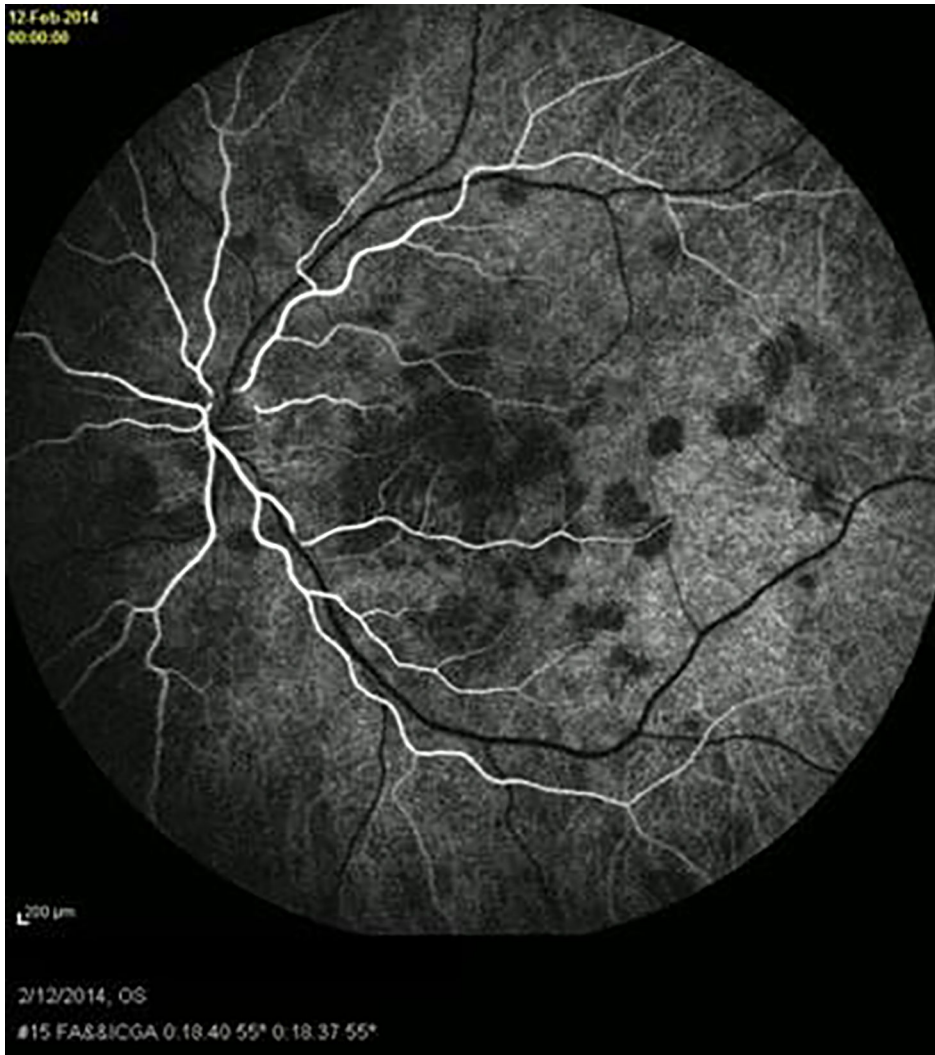
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**Figure 1.** Fundus photograph of a case of acute posterior multifocal placoid pigment epitheliopathy, demonstrating the placoid chorioretinal lesions.





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**Figure 2.** Fluorescein angiogram of a case of acute posterior multifocal placoid pigment epitheliopathy, demonstrating the features of early fluorescein blockage (a.) and diffuse late staining of the lesion (b.).

**Table 1.**

Characteristics of Cases with Acute Posterior Multifocal Placoid Pigment Epitheliopathy

Characteristic	Result
Number cases	82
<i>Demographics</i>	
Age, median, years (25 <sup>th</sup> 75 <sup>th</sup> percentile)	25 (21, 30)
Gender (%)	
Men	61
Women	39
Race/ethnicity (%)	
White, non-Hispanic	77
Black, non-Hispanic	4
Hispanic	1
Asian, Pacific Islander	2
Other	9
Missing	7
<i>Uveitis History</i>	
Uveitis course (%)	
Acute, monophasic	83
Acute, recurrent	6
Chronic	5
Indeterminate	6
Laterality (%)	
Unilateral	9
Unilateral, alternating	0
Bilateral	91
<i>Ophthalmic examination</i>	
Keratic precipitates (%)	
None	94
Fine	5
Round	1
Stellate	0
Mutton Fat	0
Other	0
Anterior chamber cells (%)	
Grade 0	78
½+	6
1+	9
2+	5
3+	2

Characteristic	Result
4+	0
Anterior chamber flare (%)	
Grade 0	94
1+	3
2+	2
3+	1
4+	0
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	72
½+	22
1+	5
2+	1
3+	0
4+	0
Vitreous haze (%)	
Grade 0	99
½+	1
1+	0
2+	0
3+	0
4+	0
<i>Chorioretinitis characteristics</i>	
Lesion number (%)	
Unifocal (1 lesion)	7
Paucifocal (2–4)	26
Multifocal (≥ 5)	67
Lesion shape & character (%)	
Ameboid or serpentine	0
Oval or round	1
Placoid	97
Punched-out atrophic	0
Punctate	0
Missing	1
Lesion location (%)	

Characteristic	Result
Posterior pole involved	96
Mid-periphery and periphery only	4
Typical lesion size (%)	
<125 $\mu\text{m}$	0
125–250 $\mu\text{m}$	4
250–500 $\mu\text{m}$	37
>500 $\mu\text{m}$	55
Missing	4
Classic fluorescein angiogram *	96
Other features (%)	
Retinal vascular sheathing	1
Retinal vascular leakage	6
Choroidal neovascularization	0

\* Fluorescein angiogram demonstrating early lesion hypofluorescence and diffuse late hyperfluorescence of the lesions. Based on reading center review of 49 angiograms.

**Table 2.**

## Classification Criteria for Acute Posterior Multifocal Placoid Pigment Epitheliopathy

<p><b>Criteria</b></p> <p>Paucifocal or multifocal choroidal lesions on clinical examination with</p> <ol style="list-style-type: none"><li>1. Plaque-like or placoid appearance to the lesions</li></ol> <p>AND</p> <ol style="list-style-type: none"><li>2. Characteristic fluorescein angiogram in the acute phase of the disease (lesions are hypofluorescent early and diffusely hyperfluorescent late)</li></ol> <p><b>Exclusions</b></p> <ol style="list-style-type: none"><li>1. Positive serologic test for syphilis using a treponemal test</li><li>2. Evidence of sarcoidosis (either bilateral hilar adenopathy on chest imaging or tissue biopsy demonstrating non-caseating granulomata)</li></ol>
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