Classification Criteria for Acute Posterior Multifocal Placoid Pigment Epitheliopathy

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

• 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 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 APMPPE, were evaluated by machine learning. Key criteria for APMPPE 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 APMPPE were 5% in the training set and 0% in the validation set.

• CONCLUSIONS: The criteria for APMPPE had a low misclassification rate and seemed to perform sufficiently well for use in clinical and translational research. (Am J Ophthalmol 2021;228: 174–180. © 2021 Elsevier Inc. All rights reserved.)

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In 1968 Gass described the disease he named acute posterior multifocal placoid pigment epitheliopathy (APMPPE).[1] 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.[2-5] Subsequently patients with recurrent disease and poorer visual outcomes have been reported.[6]

The disease typically affects young adults, both men and women, and has an estimated incidence of 0.15 per 100,000 population per year.[7] 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.[1-5] 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 APMPPE have been described in the context of systemic inflammatory diseases, particularly those with vascular involvement.[5,8,9] The most frequently reported associated systemic disease is cerebral vasculitis.[8,9] These associations raise the question of whether APMPPE is a specific disease or a phenotype of choroidal vascular and retinal pigment epithelial damage.

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A third possibility is that the eye-limited disease is a specific disease, whose appearance can be mimicked by systemic diseases that 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.[5,10-14]

As noted above, fluorescein angiography demonstrates early hypofluorescent lesions and uniform diffusely hyperfluorescent lesions in the late angiogram.[1-5] Fundus autofluorescence demonstrates hypoautofluorescent lesions acutely, with hyperautofluorescent lesions in later stages of the disease.[5,11] Indocyanine green angiography demonstrates hypofluorescent lesions, interpreted as choroidal hypoperfusion, corresponding to the lesions seen on fluorescein angiogram.[5,10] 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 hyperreflectivity 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.[12-14]

Untreated, APMPPE typically spontaneously remits and has a good visual prognosis.[15] A review of 15 case series[7] 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.[7] 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).[7]

The Standardization of Uveitis Nomenclature (SUN) Working Group is an international collaboration that has developed classification criteria for 25 of the most common uveitides using a formal approach to development and classification. Among the diseases studied was APMPPE.[16-21]

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.[18-21]

• **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.[18]

• **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.[20,21] 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.[20,21] Because the goal was to develop classification criteria,[20] only cases with a supermajority agreement (>75%) that the case was the disease in question were retained in the final database (ie, were "selected").[20,21]

• **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.[20] 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 APMPPE 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 posterior uveitis.

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 the individual institutional review boards.

RESULTS

One hundred forty-nine cases of APMPPE were collected and 82 (52%) achieved supermajority agreement on the

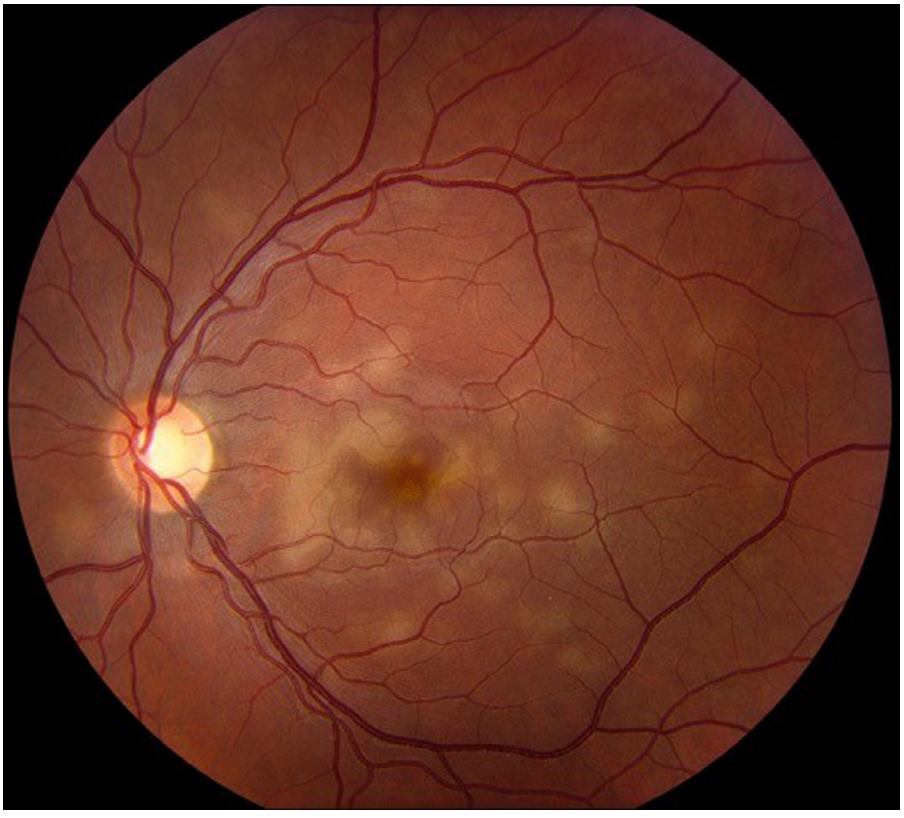

FIGURE 1. Fundus photograph of a case of acute posterior multifocal placoid pigment epitheliopathy, demonstrating the placoid chorioretinal lesions.

diagnosis during the "selection" phase and were used in the machine learning phase. These cases of APMPPE 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 uveitis / panuveitis. The details of the machine learning results for these diseases are outlined in the accompanying article.[21] The characteristics of cases with APMPPE 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 APMPPE in the training set was 5%, and in the validation set 0%. The diseases with which APMPPE was confused in the training set were MEWDS and tubercular uveitis.

DISCUSSION

The classification criteria developed by the SUN Working Group for APMPPE 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 from 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 that are similar to APMPPE in clinical appearance, but often have fluorescein angiograms more similar to serpiginous choroiditis (ie, early hypofluorescence of the lesions and late hyperfluorescence of the lesion borders).[22,23] The course is more similar to serpiginous choroiditis than to APMPPE, in that the disease is recurrent or chronic, and it seems to need immunosuppression as its treatment. Hence, despite the clinical appearance, ampiginous/relentless placoid choroiditis is distinct from APMPPE 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 seem distinct from APMPPE.

TABLE 1. Characteristics of Cases of Acute Posterior Multifocal Placoid Pigment Epitheliopathy

Characteristic	Result
Number of cases	82
Demographics	
Age, median, years (25th, 75th percentile)	25 (21, 30)
Sex (%)	
Male	61
Female	39
Race/ethnicity (%)	
White, non-Hispanic	77
Black, non-Hispanic	4
Hispanic	1
Asian, Pacific Islander	2
Other	9
Missing	7
Uveitis history	
Uveitis course (%)	
Acute, monophasic	83
Acute, recurrent	6
Chronic	5
Indeterminate	6
Laterality (%)	
Unilateral	9
Unilateral, alternating	0
Bilateral	91
Ophthalmic examination	
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
4+	0
Anterior chamber flare, grade (%)	
0	94
1+	3
2+	2
3+	1
4+	0
Iris (%)	
Normal	100
IOP, involved eyes	
Median, mm Hg (25th, 75th percentile)	14 (12,16)
Proportion patients with IOP > 24 mm Hg either eye (%)	0

(*continued on next page*)

TABLE 1. (*continued*)

Characteristic	Result
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
Chorioretinitis characteristics	
Number of lesions (%)	
Unifocal (1 lesion)	7
Paucifocal (2-4 lesions)	26
Multifocal (≥5 lesions)	67
Lesion shape and character (%)	
Ameboid or serpentine	0
Oval or round	1
Placoid	97
Punched-out atrophic	0
Punctate	0
Missing	1
Lesion location (%)	
Posterior pole involved	96
Midperiphery and periphery only	4
Typical lesion size (%)	
<125 μm	0
125-250 μm	4
250-500 μm	37
>500 μm	55
Missing	4
Classic fluorescein angiogram[a]	96
Other features (%)	
Retinal vascular sheathing	1
Retinal vascular leakage	6
Choroidal neovascularization	0

IOP = intraocular pressure.

[a]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

Criteria
Paucifocal or multifocal choroidal lesions on clinical examination with
1. Plaque-like or placoid appearance to the lesions
AND
2. Characteristic fluorescein angiogram in the acute phase of the disease (lesions are hypofluorescent early and diffusely hyperfluorescent late)
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 noncaseating granulomata)

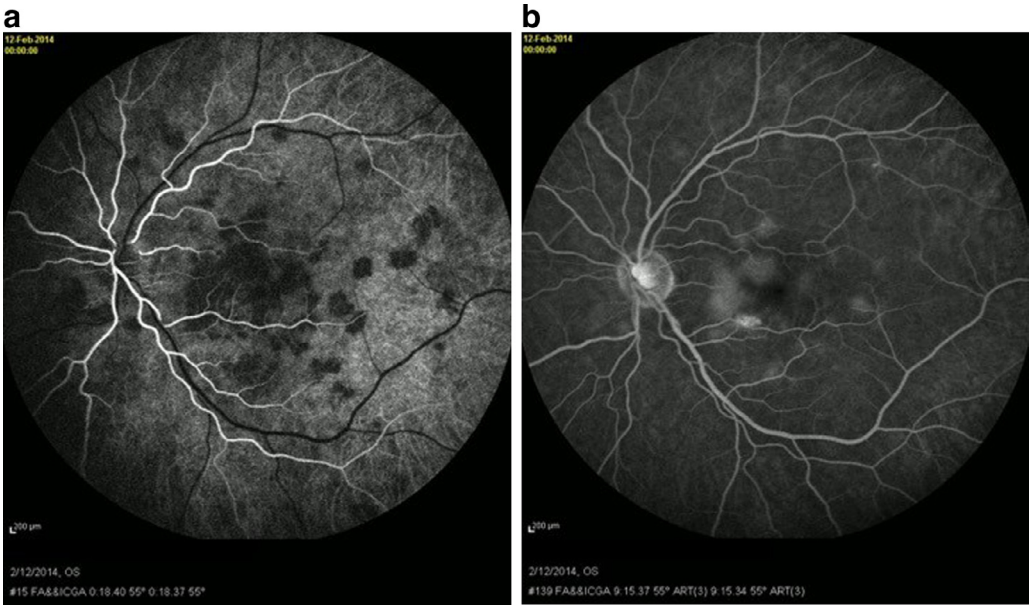

FIGURE 2. Fluorescein angiogram of a case of acute posterior multifocal placoid pigment epitheliopathy, demonstrating the features of early fluorescein blockage (A) and diffuse late staining of the lesion (B).

The issue of systemic disease findings (eg, cerebral vasculitis) in some cases of APMPPE raises the question of whether these findings are a complication of APMPPE or these are diseases in which ocular involvement mimics APMPPE. Our data on systemic diseases were not adequate to address the issue at this time. Hence, we recommend that all cases of APMPPE be subclassified as "eye-limited" with only ocular involvement or with systemic features (eg, 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 APMPPE 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 APMPPE, but the absence of such testing does not always exclude the diagnosis of APMPPE if the criteria for the diagnosis are met.

Classification criteria are used to diagnose individual diseases for research purposes.[24] 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.[24] 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,[20] the selection of cases for the final database ("case selection") included only cases that achieved supermajority agreement on the diagnosis. As such, there may be cases that clinicians would diagnose as APMPPE that would not meet the criteria outlined in Table 2.

In conclusion, the criteria for APMPPE outlined in Table 2 seem to perform sufficiently well for use as classification criteria in clinical research.[21]

CREDIT ROLES

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