PERSPECTIVE

Acute posterior multifocal placoid pigment epitheliopathy

Nicholas P Jones

In 1968 Gass[1] described the clinical and angiographic findings in three young women, each presenting with painless visual disturbance in one or both eyes. On examination all exhibited multiple, discrete but occasionally contiguous, cream coloured lesions with ill defined margins, concentrated in the posterior pole, and apparently deep in the retina. These 'placoid' (plate-like) lesions cleared to reveal pigment mottling, and this change was accompanied by improved visual acuity. Discussion centred about the likely site of the lesions, and though considering the possibility of a primary choroiditis, Gass considered the retinal pigment epithelium (RPE) the primary site of inflammation. The condition was named *acute posterior multifocal placoid pigment epitheliopathy* (APMPPE).

Further reports soon followed[2–15] and a picture developed of an acute, self limiting inflammatory disorder with a typical clinical pattern sometimes with profound loss of vision, but usually with remarkable visual recovery despite substantial residual scarring of the RPE. Retrospective reports of earlier cases are sparse[6] and it is not clear whether APMPPE is a new disease or a newly recognised clinical pattern, previously considered within the wider realm of multifocal choroiditis. Demographic, clinical, and investigational evidence has accumulated and descriptions have emerged of a rather heterogeneous condition with variable outcome and frequent systemic complications, whose aetiology and pathogenesis remain the subject of debate.

Demography, clinical features, and course

Data from more than 200 patients with APMPPE demonstrate a disease which, although it has affected patients as young as 11 (possibly 8)[6] and as late as 66 years,[16] has a striking preponderance for young adults (Fig 1), with a mean age at onset of 26·5 years. Reported cases have a male to female ratio of 1·2:1. Suggestions that APMPPE has a marked affinity for white people[17] should be interpreted in the light of very incomplete data and a failure to compare with the demography of the source populations. It is said[18] that APMPPE may occur in clusters of patients.

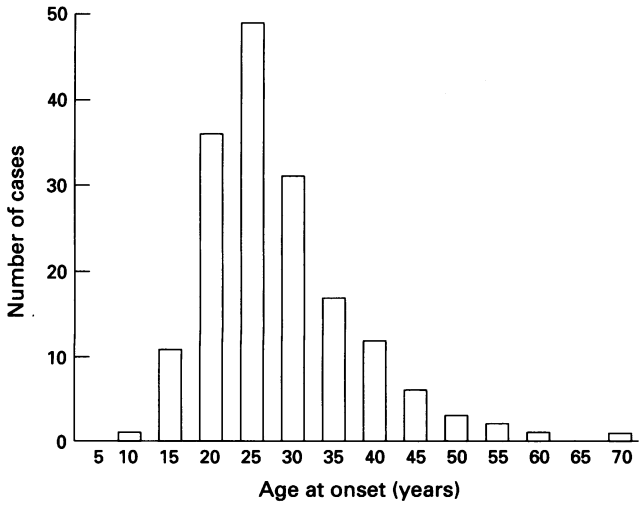

Figure 1 The age distribution of patients with acute posterior multifocal placoid pigment epitheliopathy at presentation. Data combined from published case reports and series.[1–7 8–19 21 22 25–29 32 33 36–38 40–49 51 64–66 68–72 74]

APMPPE presents with acute or subacute visual blurring, scotomas, or metamorphopsia. The condition is bilateral (simultaneously, or sequentially within a few days) in over 75% of patients. Longer term studies[16 19–22] show that in some patients recurrent disease or late sequential involvement of the second eye may occur, new episodes developing from a few weeks, up to 13 years after initial presentation.[16 19 23] However, most recurrences occur within 6 months of the initial episode.[23] Although the characteristic pattern for APMPPE is for a single self limiting episode, care should be taken when prognosticating for the patient, especially where the first episode has been unilateral. Indeed, it has been suggested[24] that the condition should be divided into two types; an 'acute diffuse placoid pigment epitheliopathy' which is self limiting and carries a good prognosis; and a recurrent disease with a less favourable outcome, though it seems more likely that disease severity and chronicity occupy a spectrum rather than distinct categories.

In its typical form APMPPE presents a picture of discrete placoid lesions which in their active phase are creamy coloured with indistinct margins, blocking the ophthalmoscopic view of the underlying choroid (Fig 2). New lesions may arise within days and many patients will demonstrate fresh lesions concurrent with dwindling ones, the latter losing their 'substance' (Fig 3) and showing

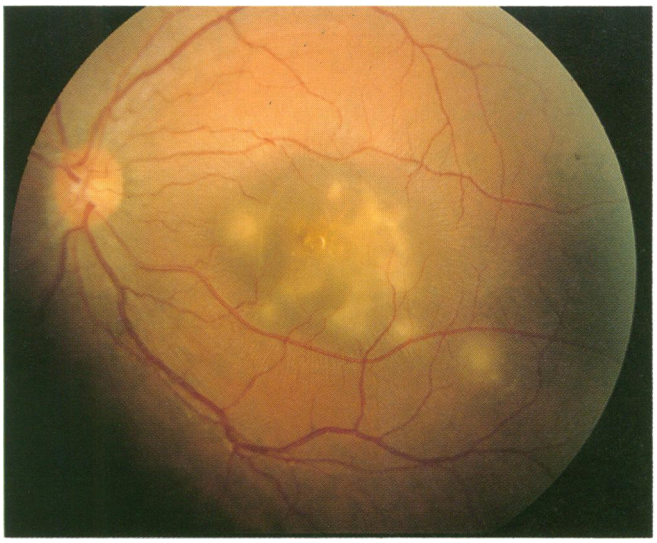

Figure 2 Unilateral acute posterior multifocal placoid pigment epitheliopathy in a 19-year-old male Asian: on presentation, visual acuity 6/36. Multiple cream coloured placoid lesions. Centrally some lesions are confluent.

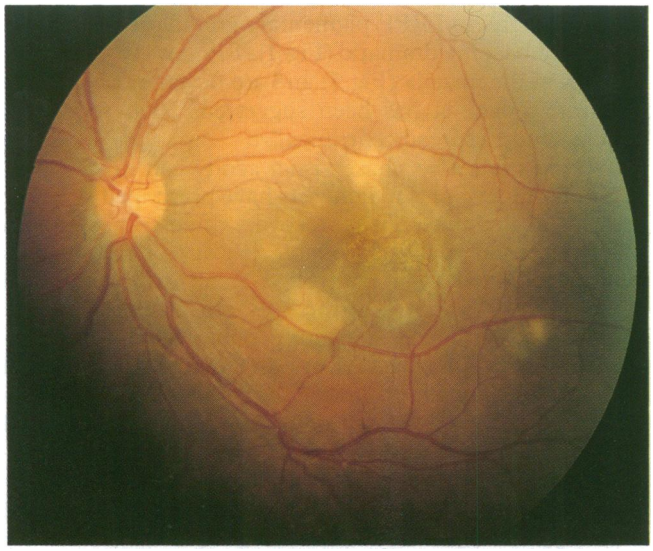

Figure 3 Left acute posterior multifocal placoid pigment epitheliopathy, same case as Figure 2: after 1 week the retina is flat and the placoid lesions are in varying stages of resolution. Visual acuity 6/60.

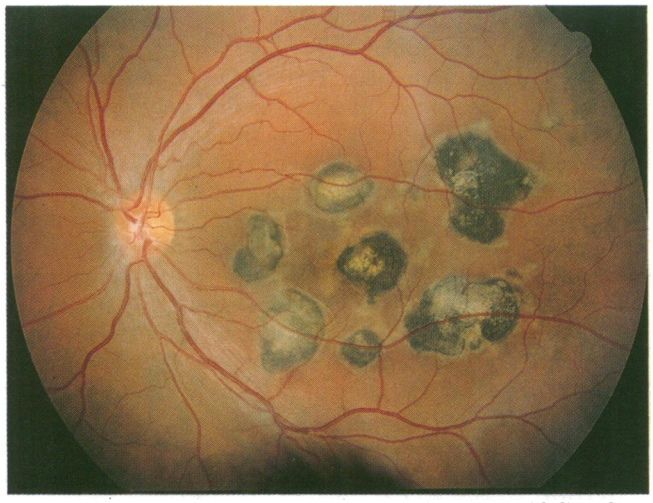

Figure 4 Left acute posterior multifocal placoid pigment epitheliopathy, same case as Figures 2 and 3: after 1 year, substantial pigmented retinal pigment epithelial scars have formed. Visual acuity 6/9, with awareness of relative paracentral scotomas.

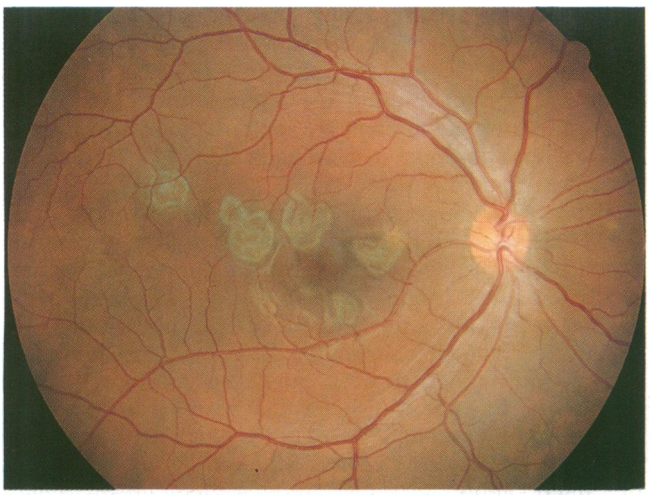

Figure 5 Right acute posterior multifocal placoid pigment epitheliopathy, same case as Figures 2–4: the patient attended again, 1 year after initial presentation, with new symptoms on the right side. Visual acuity 6/6. Lesions are already resolving.

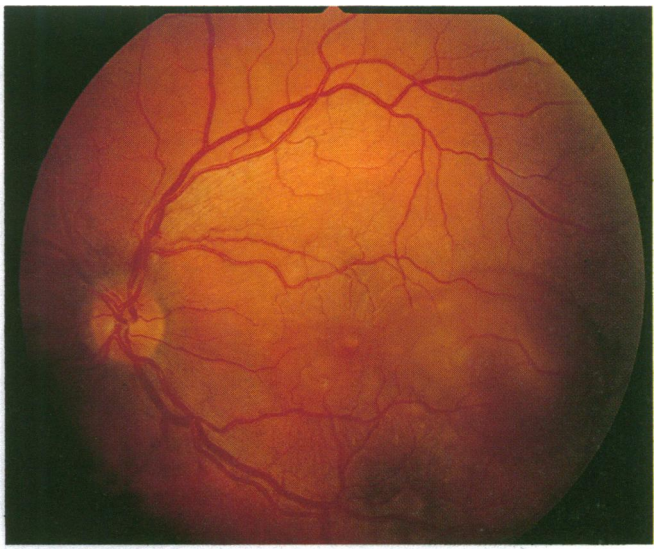

Figure 6 Acute posterior multifocal placoid pigment epitheliopathy with multifocal serous retinal detachment overlying placoid lesions.

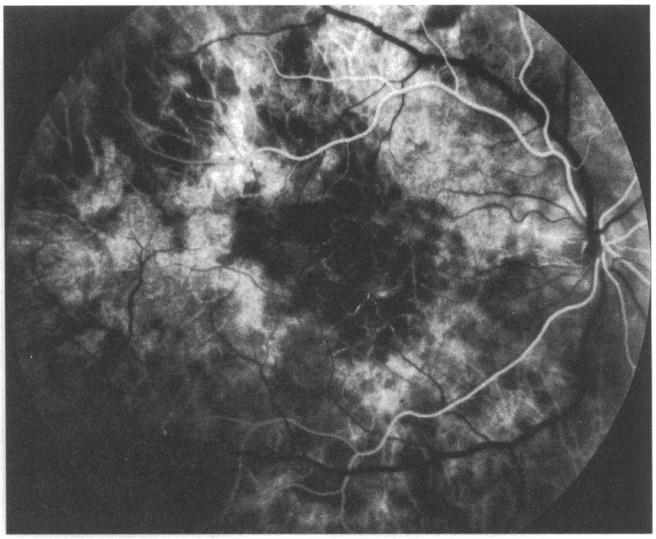

Figure 7 Arterial stage fluorescein angiogram of right eye with acute posterior multifocal placoid pigment epitheliopathy in the active stage. Dark areas are visible corresponding approximately to the overlying placoid lesions. Within the dark areas, fluorescence from larger choroidal vessels is visible.

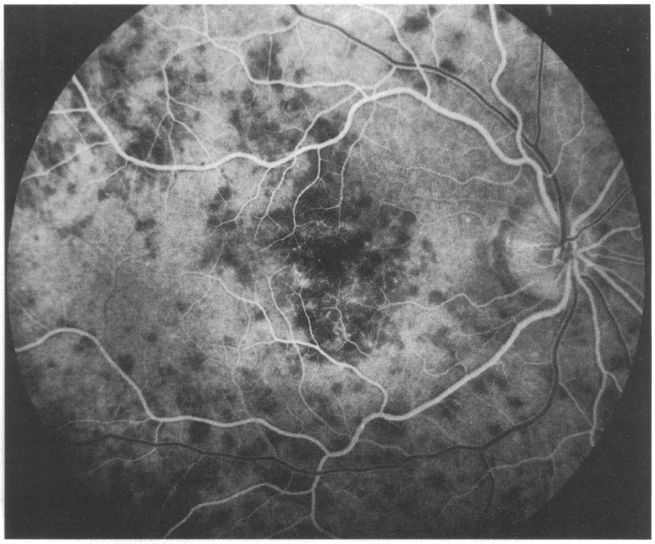

Figure 8 Early venous stage fluorescein angiogram, same case as Figure 7. Choroidal fluorescence remains incomplete.

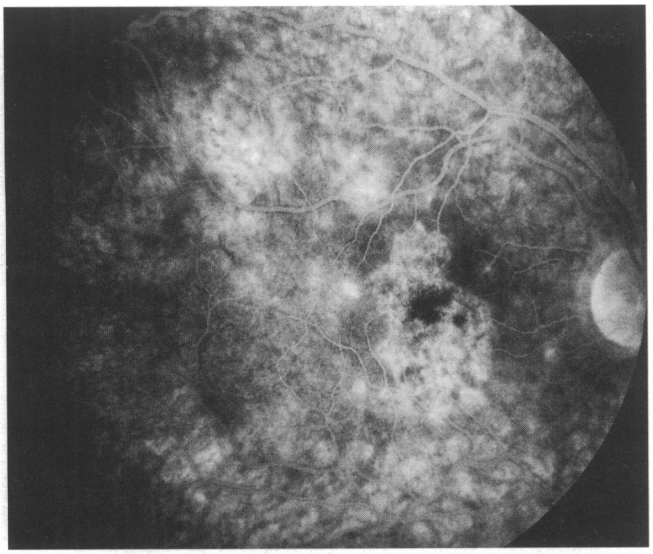

Figure 9 Late stage fluorescein angiogram, same case as Figures 7 and 8. Staining of the active lesions is now visible.

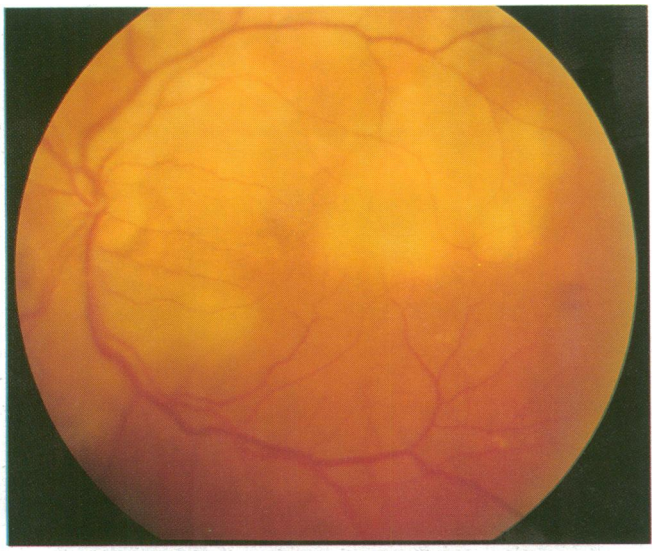

Figure 10 Probable recurrent geographic choroidopathy. Initially presenting multifocally and mimicking acute posterior multifocal placoid pigment epitheliopathy, the recurrent active lesions are seen at the edges of old scars, and contiguous with them.

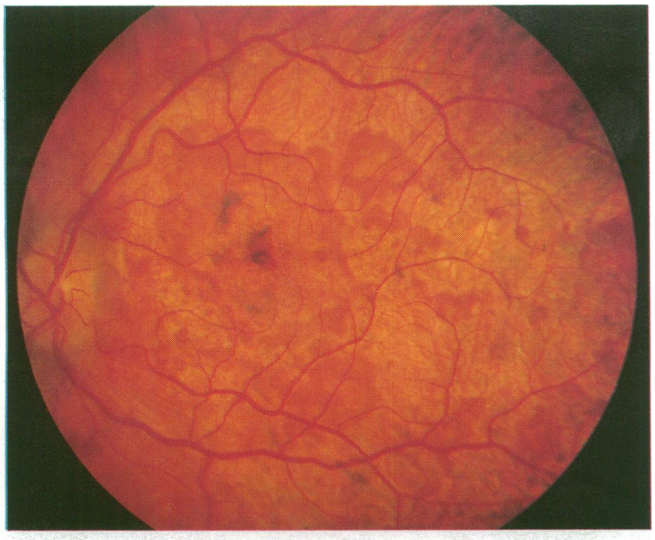

Figure 11 Extensive retinal pigment epithelial atrophy and scattered hyperpigmentation as a result of previous recurrent acute posterior multifocal placoid pigment epitheliopathy.

variable degrees of RPE pigmentary granularity which can with time become dramatic (Fig 4). Lesions are characteristically at the macula (Fig 5) and are never anterior to the equator, though it has been suggested[25] that sequential lesions tend to spread centrifugally.

During the active phase visual acuity can drop alarmingly and many ophthalmologists have prescribed systemic steroids at this time. Visual recovery often coincides with such treatment, but the possible efficacy of steroids has not been tested in a controlled trial. Relative central scotomas[6 21 26 27] are described, as are changes in cone pigment densitometry indicating photoreceptor involvement[28 29] which may last for up to 18 months after clinical resolution. Though prolonged dark adaptation and an abnormal Stiles-Crawford effect are reported,[27] normal or virtually normal electroretinography and electro-oculography are in accordance with the limited involvement of the retinal photoreceptor mass.[23] Though subtotal recovery of visual acuity is usual, most patients have long term visual symptoms and many have significant residual field defects.[21]

In a minority of patients one or more of the placoid lesions have an overlying localised serous retinal detachment[3 25 30–35] (Fig 6). Though in a small proportion these may become confluent, they are usually subtle and self limiting. The significance of these serous detachments is disputed. The resemblance of this form of APMPPE to Harada's disease has been commented upon by several authors; the association of sensorineural deafness in a few patients with APMPPE[25 36] stimulates this view, as do meningeal symptoms and signs in some others,[36–38] though anecdotal encephalomeningeal histology does not support a pathogenetic link.[39 40] It has been suggested[41] that APMPPE and Harada's disease may form a spectrum rather than being separate entities, and the similarity of early fluorescein angiography appearances in these two conditions has been cited as evidence of this. However, it has been stated[24] that serous retinal detachment or pigment epithelial detachment may occur in any pigment epitheliopathy; an aetiological connection is not necessarily indicated by these complications.

The degree of ocular inflammation that accompanies APMPPE varies widely, though in most patients it is subtle. More than half of patients will exhibit cells in the vitreous or aqueous humour[7 10 23 25 33 35 42] though frank iridocyclitis is rare[10] and mutton fat keratic precipitates have been noted on only one occasion.[16] Involvement of the optic disc has been frequently reported[5 11 23 33 41 43–45] and episcleritis has accompanied APMPPE in one case.[7] Evidence of accompanying vasculitis, both in the retina[1 5 16 34 46–49] and in the choroid[49] has occurred in a few patients. Central retinal vein occlusion has been reported.[45] An uncommon late complication of APMPPE, as with all post-inflammatory[49] or post-traumatic scars at this level, is subretinal neovascularisation[34 47 49] which has caused permanent visual loss.

Fluorescein angiographic studies on patients with APMPPE characteristically show complete or partial absence of early background choroidal fluorescence underneath the active lesions (Figs 7 and 8), and later in the sequence, bright staining (Fig 9). After resolution of active lesions, permanent changes to RPE pigment dispersion causes transmission defects, but late staining or leakage disappears. In some cases choroidal vessels can be seen in the centre of dark areas[41 50] (Fig 7). Arguments about the pathogenesis of APMPPE have centred on interpretations of angiographic pictures. Indocyanine green angiography[51 52] is superior to fluorescein angiography in visualising the choroidal vascular structure and has been used to study patients with APMPPE.[53] The implications of these

findings on the possible pathogenesis of APMPPE are discussed below.

Differential diagnosis

The clinician, in facing a patient with acute or subacute visual loss and multifocal pale areas of subtle inflammation in the posterior segment, must consider several possibilities. Multifocal choroiditis in its typical form, with significant vitreous involvement and distinct 'substance' to the involved areas, resolves leading to heavily pigmented punched out scars. While active such lesions often cause overlying serous detachment; indeed, Gass[23] feels that some described patients with APMPPE and overlying serous detachment have features more suggestive of underlying multifocal choroiditis. The ability of sarcoidosis to cause multifocal RPE involvement not dissimilar to APMPPE, has been described[54] but this is usually most prominent inferiorly in the fundus, rather than at the posterior pole.

In birdshot retinochoroidopathy[55] the lesions are typically smaller, more widely scattered throughout the fundus, often associated with significant vitritis, macular or disc oedema, and retinal vasculitis, the latter being vividly shown on fluorescein angiography. The condition occurs characteristically in a young woman who carries the HLA-A29 antigen. The multiple evanescent white dot syndrome,[56] though also commoner in young women and usually following a flu-like illness, is typically unilateral, causing acute visual loss associated with reasonably discrete white lesions apparently at the level of the RPE. The lesions are typically smaller than in APMPPE and although concentrated posteriorly, as in birdshot retinochoroidopathy may involve the midperiphery. In contrast with APMPPE, the lesions hyperfluoresce early during angiography, though in common with APMPPE, visual recovery is the rule.

Acute retinal pigment epitheliitis[57] occurs in young patients who present, as in APMPPE, with acute visual loss or metamorphopsia. The disease may be unilateral or bilateral, and the characteristic lesions are often small and clustered at the posterior pole, being centrally pigmented and surrounded by a pale, depigmented halo. The lesions are much smaller than those typically observed in APMPPE. Sympathetic uveitis in its typical form is not a diagnostic problem, yet it has presented in a form which masqueraded as APMPPE.[58] Recently, patients have been described[59–61] with a diffuse posterior pigment epitheliopathy associated either with multifocal RPE detachments or inferior serous retinal detachment. The association between this condition and APMPPE, if any, is unclear.

Geographic choroidopathy[62] may present a difficult challenge to diagnosis. Its paradigm is a bilateral (though often sequential) disorder commencing in the peripapillary area and progressing either inexorably or through multiple contiguous recurrences, leading to deeper scarring than is seen after APMPPE, with loss of both choriocapillaris and larger choroidal vessels. Where the fovea is involved irreversible visual loss ensues. However, APMPPE can occupy the peripapillary area and geographic choroidopathy may not. The fluorescein angiogram in the active stages of both diseases can be similar. Both conditions may be recurrent. A useful distinguishing feature in the latter situation is that geographic recurrences or extensions tend to be contiguous (Fig 10), whereas those in APMPPE are often multifocal. The contrasting features of the two conditions have been tabulated by Gass.[23]

For completeness, it should be stated that in its burnt out stage, APMPPE may lead to striking RPE scarring with scattered hyperpigmentation, occupying a large proportion of the posterior fundus (Fig 11); in such cases a tapetoretinal degeneration may be a differential diagnosis. The absence of optic atrophy, normal retinal vasculature, and near normal electrophysiological tests in APMPPE allow the distinction to be made.

Systemic associations

About one third of patients with APMPPE have concurrent or recent systemic symptoms or signs. Many will complain of a 'viral' prodrome with fever, malaise, headache, dizziness, and myalgia or arthralgia,[6 10 16 21 22 25 36 37 40 42 43–46 48 50 63–67] and occasionally a fleeting rash,[16] bowel upset,[6 10 25] upper respiratory tract infection,[2 6 7 19 21 23 25 42 44 68] or lymphadenopathy.[6 10 19 25 64] Less frequently symptoms of hearing loss, tinnitus, or vertigo[25 36 44] are described. Some patients will recently have received systemic antibiotics[3 7 10 19 25] or have been immunised.[46] Only one patient has been satisfactorily demonstrated to have a concurrent viral infection,[68] with adenovirus 5.

In a small but significant minority of patients, evidence of a systemic vasculitis exists. Erythema nodosum, histologically a necrotic subcutaneous thrombophlebitis, has been described in several patients.[2 4 9 19 34] Concurrent nephritis has arisen[66] and the presence of urine casts, possibly indicating a microvascular nephropathy, has been identified.[42] Perhaps the most convincing evidence of vasculitis elsewhere comes from case reports of patients with concurrent cerebral vasculitis (supported by cerebral angiographic evidence) or meningoencephalitis,[25 38 40 63 69–71] leading to two deaths, with histological confirmation in one case of multifocal granulomatous arteritis of medium sized arteries with fibrinoid necrosis,[40] not dissimilar to the microscopic findings in temporal arteritis. This association between APMPPE and proved cerebral vasculitis has led to speculation that some symptoms, such as headache, dizziness, and stiff neck may be attributable to a low grade cerebral vasculitis or meningoencephalitis. Circumstantial support for this hypothesis comes from the finding of an abnormal lymphocyte pleocytosis in some, though not all, patients with APMPPE in whom lumbar puncture has been performed.[5 6 8 10 11 25 37 71 72] General symptoms of headache, malaise, and myalgia are of course common in systemic vasculitis syndromes.[73]

Aetiology and pathogenesis

Gass,[1] in his initial description of APMPPE, concluded, because of the manifest widespread involvement of RPE, the apparent flat (placoid) nature of the acute lesions in comparison with focal choroiditis, the absence of overlying serous retinal detachment (later disputed), and the absence of apparent choroidal damage following resolution of the lesions, that the RPE itself was the primary focus of inflammation in APMPPE. Such an interpretation has been widely debated. Argument has centred around angiographic studies, which characteristically demonstrate early dark areas (Figs 7 and 8) corresponding approximately, but not always precisely, to the placoid lesions themselves. Gass[1] and others attributed this to blockage of choroidal fluorescence by cloudy swelling within the RPE layer. However, the observation of larger choroidal vessels within these dark areas[4 74] (Fig 7) lent support to the suggestion that these dark areas represented malperfusion of the choriocapillaris rather than blockage of fluorescence. The clear association of intraocular (retinal or choroidal), extraocular (episcleritis), or systemic (renal, cutaneous, and cerebral) vasculitis is strong circumstantial evidence

for a choroidal vasculitis process. Indeed, choroidal vasculitis has been observed ophthalmoscopically.[48]

Angiographic studies of choroid vascular structure[75] in Rhesus monkeys have demonstrated a strict lobular configuration. Human fluorescein studies show a similar effect,[76] and anatomical studies[74] confirm that a lobule is supplied by a single precapillary end arteriole, the lobular perimeter being separated from its neighbours by a zone of postcapillary venules. Fluorescein angiography is inadequate for the full evaluation of choroidal vasculature, especially at the posterior pole – firstly, because macular xanthophyll is an effective partial barrier to fluorescence and, secondly, because fluorescein, only partially (40–60%) protein bound, leaks early and profusely from the fenestrated choriocapillaris staining interstitial tissue and obscuring later vascular patterns within the choroid. Indocyanine green[51 52] has peak excitation and fluorescence wavelengths in the near infrared, at 805 nm and 835 nm respectively, to which the intervening pigments of melanin and xanthophyll are relatively transparent. Indocyanine green, being almost fully (98%) protein bound, remains intravascular even within the choriocapillaris, allowing more accurate and prolonged assessment of choroidal vascular structure. Dhaliwal and others[53] have demonstrated widespread choroidal flow abnormalities in APMPPE using indocyanine green angiography, affecting possibly both lobular precapillary arterioles and larger supply arterioles emanating from the posterior ciliary circulation, these abnormalities improving with functional visual recovery. Their study provides strong evidence for severely decreased choroidal blood flow under affected RPE areas. However, Gass[23] disputes the anatomical correlation of dark areas with lobular choroidal anatomy. There is as yet no histology available on an eye with active APMPPE; although cerebral tissue was obtained, the eyes were not available for examination following two deaths from concurrent cerebral vasculitis.

Wolf *et al*[77] have demonstrated, in a group of 30 patients with APMPPE, an increased incidence of both a class I (HLA-B7, relative risk 3·38) and a class II HLA antigen (HLA-DR2, relative risk 3·32). These two antigens are in linkage disequilibrium and higher incidences of both have been found in patients with the presumed ocular histoplasmosis syndrome,[78] a high incidence of HLA-B7 also appearing in those with geographic choroidopathy.[79] The authors allude to the possibility that the possession of these antigens may predispose to choroidal vasculitis. The association of the same HLA antigens with optic neuritis in some patients[80] is interesting in the light of a report linking ocular inflammatory episodes in three members of a family, all of whom carried HLA-B7 and HLA-DR2. Within a 4 month period, two family members developed optic neuritis, and one APMPPE. Such linked episodes strongly suggest an infective aetiology in the predisposed.[81] It does not, however, explain the diverse forms of ocular inflammation that can occur in those possessing these HLA antigens. Sensitisation to retinal S-antigen has been found in patients with geographic choroiditis, but not in those with APMPPE,[82] possibly reflecting more severe photoreceptor damage in the former condition.

Prolonged but varied attempts to identify an infective agent for patients with APMPPE have met with little success. The lack of standardisation of investigations in these patients does not allow firm statements on probabilities. Several patients, in their prodromal period of illness, have been treated for bacterial infections with a variety of antibiotics, and a few have been found to have significant tuberculin tests. In one patient an adenovirus serotype 5 infection was proved.[68] A suggestion that APMPPE may be linked to infection with *Borrelia burgdorferi*[83] has not been supported by negative serology for Lyme disease in a group of 18 patients with APMPPE.[18] Though the association of infective or presumed infective systemic disease in a substantial minority of patients with APMPPE is suggestive, it is by no means conclusive.

Though the ophthalmoscopic findings in APMPPE may reflect involvement of the RPE, evidence has accumulated that the primary lesion lies posterior to this and that choroidal perfusion is abnormal. The alternative terms 'acute multifocal choriocapillaritis'[4] or 'precapillary choroidal arteriolitis'[84] have been suggested, yet new evidence[53] of more widespread choroidal vascular closure suggests that these names may be too limiting. Perhaps the simpler term 'placoid chorioretinopathy' would allow the future use of a descriptive term which was not tied to an as yet unproved pathogenesis.

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