

Acute Posterior Multifocal Placoid Pigment Epitheliopathy Associated with Stroke: A Case Report and Review of the Literature

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Background: Present a case report of acute posterior multifocal placoid pigment epitheliopathy (APMPPE) associated with stroke along with the serologic findings, diagnostic findings, and treatment in addition to presenting a review of other case reports to date in literature. With this information, we are attempting to identify key diagnostic features and appropriate treatment options for patients with this disease. *Methods:* Presentation of case report, background on APMPPE, review of the literature and previous case reports, and discussion of diagnostic workup and treatment options for these patients. *Results:* There are 28 well-described case reports in the literature to date, not including our case report; 23 had documented radiographic findings consistent with parenchymal injury, ischemic stroke, hemorrhagic stroke, or cerebral venous thrombosis. We report a 23-year-old right-handed man with left hemiparesis, ischemic strokes, and angiographic findings characteristic of cerebral vasculitis 4 months after he was diagnosed with APMPPE. *Conclusions:* Based on our present case and previously documented cases to date, corticosteroid therapy with potential escalation of care to immunomodulatory treatment appears to benefit clinical outcomes. **Key Words:** Vasculitis—stroke—chorioretinal disease—cerebral angiography—neuroradiology—inflammatory CNS disease. Published by Elsevier Inc. on behalf of National Stroke Association

Introduction

Acute posterior multifocal placoid pigment epitheliopathy (APMPPE) is an uncommon chorioretinal disease characterized by multiple cream-colored lesions located in the posterior pole.¹ It typically affects both eyes leading to visual blurring or scotomas.² APMPPE predominantly occurs in young adults and is typically self-limiting.^{3,4} A viral prodrome can be seen in one third of patients.⁵ Fundus lesions are observed within days of disease onset. They typically resolve and leave alterations in the pigmented epithelium weeks after symptom onset. The visual prognosis is typically good with spontaneous recovery. Although this is a disease of the eye, extraocular manifestations can occur.

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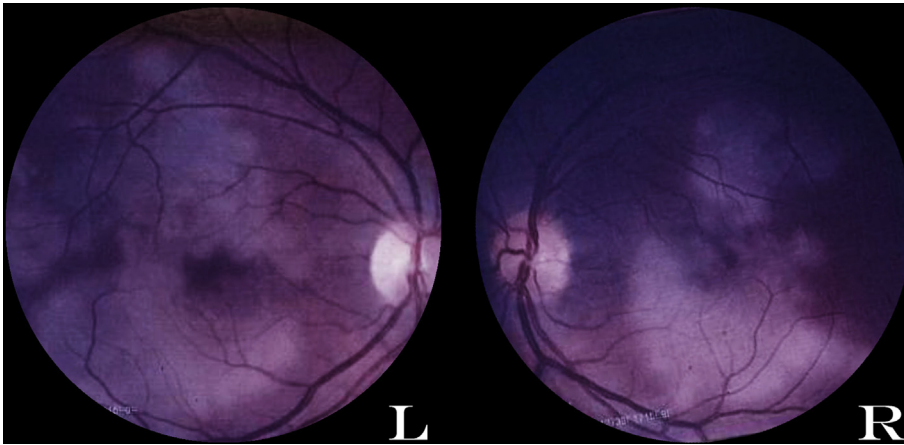


Figure 1. Fundus examination at diagnosis showing yellow white placoid regions and scarring in the retinal epithelium in both the left (labeled L) and right (labeled R) eyes.

Neurologic complications of APMPE are rare and have been reported previously in the literature.⁶ Specifically, inflammatory and vasculitic-like changes have been described including cerebrospinal fluid (CSF) pleocytosis, headaches, transient hearing loss, optic neuritis,

meningoencephalitis, transient focal deficits, and strokes. After extensive review of the literature using PubMed and Google Scholar, 28 reported cases of APMPE-associated cerebrovascular complications have been well documented in the literature to date. We report a

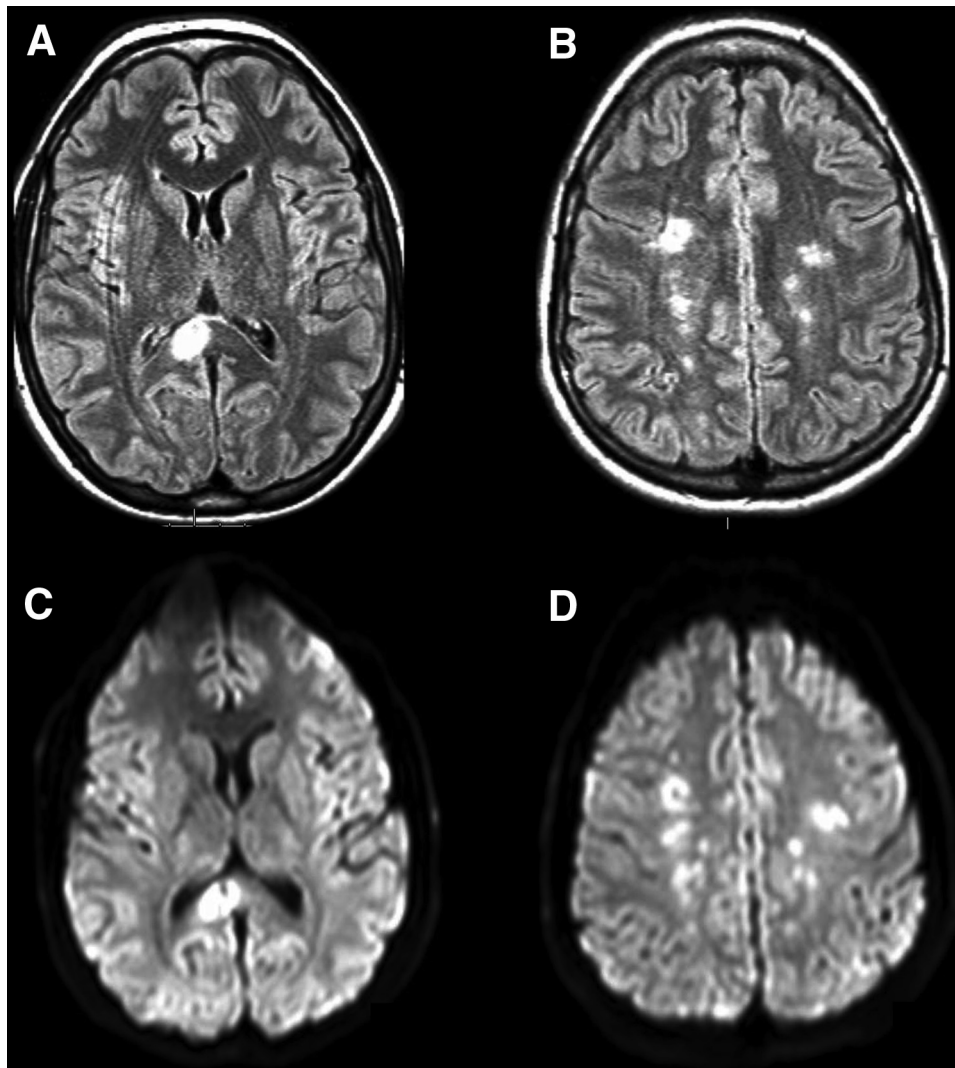


Figure 2. Magnetic resonance imaging brain sequence showing (A) T2 fluid-attenuated inversion recovery (FLAIR) sequence hyperintensity in the corpus callosum, (B) T2 FLAIR sequence hyperintensity in the white matter bilaterally, (C) corresponding restricted diffusion in the corpus callosum, and (D) corresponding restricted diffusion in the white matter bilaterally.

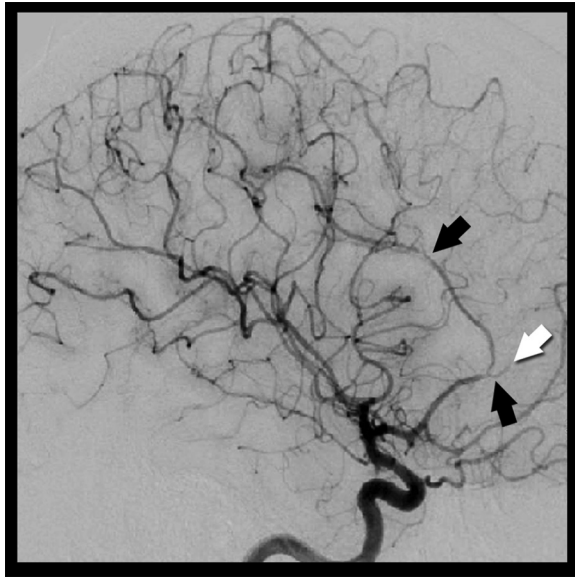


Figure 3. Cerebral angiogram demonstrating multiple areas of anterior cerebral artery narrowing (black arrows) and a branch artery occlusion (white arrow).

23-year-old right-handed man with left hemiparesis and imaging findings characteristic of cerebral vasculitis and ischemic stroke 4 months after he was diagnosed with APMPPE.

Case Presentation

A 23-year-old right-handed man presented with vision loss and multiple scotomas in his right eye followed a few weeks later by similar vision loss in his left eye. He had no medical history but described feeling malaise, headache, and flu-like symptoms 3 weeks before the onset of his visual complaints. He had returned from a trip to Southeast Asia a few months before this time but had received all required vaccinations before his travels. One month after his visual complaints began, he was found to have multiple cream-colored placoid subretinal lesions throughout the posterior poles of both eyes consistent with a diagnosis of APMPPE (Fig 1). Magnetic resonance imaging (MRI) brain was normal at the time, and he was given a 4-week course of high-dose corticosteroids and was subsequently tapered off after 2 additional weeks. His visual deficits did not improve.

Four months after being diagnosed with APMPPE (5 months after onset of ocular symptoms), he presented with headache and mild left-sided weakness, leg greater than arm. His weakness progressed to near-complete paresis of his left leg along with mild left arm weakness later the same day. Brain MRI showed multiple hyperintense, nonenhancing lesions. He was placed on methylprednisolone 1 g/d intravenously but over the course of 4 days had interval increase in lesion burden on MRI brain (Fig 2).

A lumbar puncture was performed, which revealed normal protein, normal white blood cell count, normal red blood cell count, and no oligoclonal bands. Serologic studies including hypercoagulability studies, rheumatologic panel, and infectious panel were all negative. A cerebral angiogram demonstrated occlusion of an anterior cerebral artery branch, focal narrowing of multiple right pericallosal artery branches, and a mild left pericallosal artery narrowing (Fig 3). After completing a 5-day course of intravenous corticosteroids, he was continued on oral prednisone 80 mg/d. His left leg weakness and mild left arm weakness stabilized. He was subsequently discharged to a rehabilitation facility where he remained on high-dose steroids.

By 6 weeks, he had significant improvement in his strength. His left arm weakness had resolved. His left leg was mildly weak, and he was able to ambulate without assistance. His visual deficits remained unchanged. He was continued on oral prednisone at a dose of 60 mg/d with scheduled clinic follow-up. No further diagnostic imaging or repeat cerebral angiography has been repeated to date.

Discussion

APMPPE is a rare multifocal, choroidal, occlusive vasculitis. Simultaneous or sequential onset in both eyes is typical. In 1968, Gass reported 3 cases with rapid loss of central visual acuity secondary to multifocal yellow-white placoid lesions at the level of the pigment epithelium and choroid of the retina.³ Further case reports revealed a clear preponderance for young adults. Ophthalmoscopic findings consist of cream-colored, flat, and discrete placoid lesions at the level of the retinal pigment epithelium, masking the fundus view of the underlying choroids.⁶ The lesions are mainly at the posterior pole and never anterior to the equator.⁵ The lesions begin to fade within days to weeks and are typically replaced by areas of depigmentation.

Neurologic complications are uncommon but can include CSF pleocytosis, headaches, transient hearing loss, optic neuritis, meningoencephalitis, transient focal deficits, and strokes.⁵ An underlying vasculitic process is thought to account for these findings. Lunea⁵ provides an excellent review of previously published APMPPE cases associated with cerebrovascular complications in the French and English literature. Given the rare nature of this disease, the debilitating cerebrovascular complications, and lack of equipoise regarding treatment options, we conducted a thorough review of the literature for well-described case reports in all languages to better characterize APMPPE-associated cerebrovascular disease diagnostic features and treatment experience. Using PubMed and Google Scholar, we searched for cases of APMPPE-associated stroke, APMPPE-associated vasculitis, and APMPPE-associated cerebrovascular disease.

Table 1. Documented case reports of APMPE associated with cerebrovascular complications to date

Study	Year reported	CNS symptoms	CNS symptom onset after ocular symptoms	CSF findings	Neurologic imaging	Treatment	Outcome
Holt et al ⁷	1976	Photophobia headache, aphasia, weakness	3 d	WBC 177, protein 156	Cerebral angiogram: small-vessel vasculopathy	Corticosteroids	Asymptomatic at 36 mo
Sigelman et al ⁸	1979	Headache, homonymous hemianopia	4 d	WBC 7, protein 52	Cerebral angiogram: small-vessel vasculopathy	No treatment	Persistent homonymous hemianopia
Smith et al ⁹	1983	Photophobia, headache, homonymous hemianopia	2 mo	“Lymphocytosis and elevated protein”	Cerebral angiogram: small-vessel vasculopathy	Corticosteroids	1 Exacerbation
Weinstein et al ¹⁰	1988	Bilateral vision loss, homonymous hemianopia, numbness, slurred speech	2-3 mo	WBC 9	MRI: occipital hemorrhage Cerebral angiogram: small-vessel vasculopathy	Corticosteroids	Persistent homonymous hemianopia
Wilson et al ¹¹	1988	Bilateral vision loss, headache, seizure	2 wk	WBC 0, protein 66	No imaging reported	Corticosteroids	Died after 2 d of treatment
Hammer et al ¹²	1989	Bilateral vision loss, hemiparesis	3 wk	None reported	CT head: anterior cerebral artery and MCA ischemic infarcts	Corticosteroids	Death from malignant cerebral edema from stroke
Stoll et al ¹³	1991	Bilateral vision loss, dysarthria, weakness, ataxia	4 mo	WBC 18, protein 67	MRI brain: multiple hemispheric white matter lesions Cerebral angiogram: small-vessel vasculopathy	Corticosteroids	Asymptomatic at 1 y
Bewermeyer et al ¹⁴	1993	Photophobia, hemiparesis, stupor, slurred speech, nystagmus	5 mo	WBC 55, protein 36	MRI brain: right pontine infarct	Corticosteroids and azathioprine	Asymptomatic at 2 y
Comu et al ²	1996	Bilateral vision loss, headache, hemiparesis,	3 wk	“Lymphocytosis”	MRI brain: bilateral parieto-occipital infarcts Cerebral angiogram: Normal	Corticosteroids and cyclophosphamide	Right parietal infarct when steroids tapered, no relapse at 24 mo with cyclophosphamide

O'Halloran et al ⁴	2001	Scotoma in left eye, seizure, HA, numbness	1 y	WBC 28, protein 85	MRI brain: bilateral parietal hemorrhages Cerebral angiogram: superior sagittal sinus thrombosis	Corticosteroids	No relapse at 13 mo
O'Halloran et al ⁴	2001	Right eye vision loss, headache, hemiparesis	3 mo	WBC 28, protein 85	MRI brain: normal Cerebral angiogram: small-vessel vasculopathy	Corticosteroids, cyclophosphamide	No relapse at 13 mo
O'Halloran et al ⁴	2001	Headache, hemiparesis	3 wk	None reported	Cerebral angiogram: small-vessel vasculopathy	Corticosteroids	No relapse at 5 y
O'Halloran et al ⁴	2001	Bilateral vision loss, numbness	6 y	Protein 88	MRI brain: multiple T2 hyperintense thalamic and white matter lesions	Corticosteroids	Persistent numbness at 2 mo
O'Halloran et al ⁴	2001	Numbness	Simultaneous	Normal	MRI brain: right parasagittal contrast-enhancing lesion	Corticosteroids	Asymptomatic at 2 mo
O'Halloran et al ⁴	2001	Right eye vision loss	2 y	Normal	MRI brain: multiple periventricular T2 lesions	Corticosteroids	Normal vision at 3 mo
O'Halloran et al ⁴	2001	Homonymous hemianopia	Simultaneous	None reported	MRI brain: infarction in right temporal lobe	Corticosteroids	Persistent homonymous hemianopia, no relapse at 18 mo
de Vries et al ¹⁵	2006	Right eye vision loss, headache, hemiparesis, numbness, seizures	3 d	None reported	MRI/MRA brain: occlusion of left MCA and narrowing of the right posterior cerebral artery with infarction	No treatment	Death from infarction
Bugnone et al ¹⁶	2006	Vision loss, Right-sided weakness and paresthesia	1.5 mo	None reported	MRI brain: right caudate stroke and chronic right corpus callosum stroke	Corticosteroids	Neurologic symptoms arose after corticosteroids tapered off, spontaneous recovery 3 mo later
Kline et al ¹⁷	2007	Bilateral vision loss, headache, left third nerve palsy	Simultaneous	None reported	CT/CT angiography head: bilateral cavernous sinus thrombosis, sinusitis	Surgical drainage of sinuses, antibiotics, anticoagulation	Persistent partial left third nerve palsy

(Continued)

Table 1. (Continued)

Study	Year reported	CNS symptoms	CNS symptom onset after ocular symptoms	CSF findings	Neurologic imaging	Treatment	Outcome
Lunea et al ⁵	2009	Bilateral vision loss, headache, hemiparesis	2 wk	WBC 253, protein 57	MRI/MRA brain: infarction in the right MCA Cerebral angiogram: small-vessel vasculopathy	Corticosteroids, cyclophosphamide, azathioprine	New infarction 6 mo later while changing cyclophosphamide to azathioprine and still receiving steroids
Masse et al ¹⁸	2009	Bilateral vision loss, headache	1 wk	“Lymphocytosis”	Bilateral parieto-occipital infarcts	Corticosteroids and mitoxantrone	Improvement of headaches after starting mitoxantrone
Pagnoux et al ¹⁹	2011	Vision loss, left sided weakness	2 mo	WBC 14	MRI: multiple brain stem and left parietal infarcts	Corticosteroids and azathioprine	No residual neurologic deficits 6 mo after treatment with addition of azathioprine
Volbers et al ²⁰	2012	Bilateral vision loss, aphasia, right sided hemihypesthesia	1 mo	WBC 16	MRI/MRA brain: left MCA stenosis and stroke Cerebral angiogram: left MCA stenosis	Corticosteroids and azathioprine	Full recovery
El Sanhoury et al ²¹	2012	Headache, decreased responsiveness	2 wk	Not reported	CT head: bilateral cortical infarcts	Corticosteroids	Onset of neurologic symptoms and decline in examination during corticosteroid taper at 2 wk progressing to herniation and death
Matamala et al ²²	2013	Bilateral vision loss	1 y	WBC 16	MRI brain: bilateral ischemic lesions in lenticular nuclei and corona radiata Cerebral angiogram: Diffuse stenosis of mainly left posterior cerebral artery	Corticosteroids	No recurrence at 2 y
Oleszczuk and Saeed ²³	2013	Headache, left eye vision loss	6 mo	None reported	MRI brain: right basal ganglia infarct	Corticosteroids and azathioprine	Resolution of symptoms

Author	Year	Presenting symptoms	Duration	Lab findings	MRI brain findings	Treatment	Outcome
Del Saz-Saucedo et al ²⁴	2013	Headaches, right-sided weakness	Simultaneous	Normal	MRI brain: multiple vascular territory infarcts	Corticosteroids	Significantly improved
Tsang et al ²⁵	2014	Left-sided weakness, seizures	2 mo	WBC 17, protein 53	MRI brain: bilateral, anterior, and posterior circulation infarcts	Corticosteroids	Death from infarction at 14 d
Present case	2015	Left eye vision loss, headache, left-sided weakness	5 d	WBC <5, RBC <5, normal protein	MRI brain: multiple white matter and corpus callosum infarct Cerebral angiogram: anterior cerebral artery branch occlusion and narrowing	Corticosteroids	Improved left-sided weakness at 6 mo

Abbreviations: APMPPE, acute posterior multifocal placoid pigment epitheliopathy; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; MCA, middle cerebral artery; MRI, magnetic resonance imaging; WBC, white blood cell count; RBC, red blood cell count.

From our review, we found 28 well-documented cases of APMPPE-associated cerebrovascular complications (Table 1).

The majority of reported cases include parenchymal injury or ischemic changes (19 cases); however, hemorrhagic stroke (2 cases) and cerebral venous thrombosis (2 cases) have been reported. Of the 28 case reports to date, 12 included cerebral angiogram findings, of which only 1 was documented as normal. This supports the idea that the disease represents a “uveocerebral” vasculitic syndrome like Eales disease or Susac disease.⁶

Although APMPPE affects men and women equally, the majority of cases of cerebral vasculitis were in men.⁵ In addition, the majority of these patients were white.⁵ Ours was a young, white male patient. The mean latency from diagnosis of APMPPE to central nervous system involvement is typically 2 months, which is consistent with our reported case.⁴ Headache and CSF pleocytosis are common neurologic manifestations, and in our patient’s case, he did have headache but did not have abnormalities on his CSF profile. This could be explained by the delay in time of onset of symptoms to time of lumbar puncture. Previous case reports suggest an inflammatory mechanism based on lumbar puncture results; however, some of the previously documented cases reported normal lumbar puncture findings as well. In addition, multifocal segmental vessel narrowing seen on cerebral angiography is not specific for vasculitis. These findings could also suggest vasospasm or a vasculopathy. The diagnosis of cerebral “vasculitis” has been primarily made based on imaging findings in previous case reports. Only 2 previous case reports describe cerebral histopathologic descriptions.^{11,15}

The small number of reported cases does not allow for definitive recommendations regarding the management and treatment of patients with APMPPE-associated cerebrovascular complications. Patients with this disease have generally been treated with corticosteroids; however, 8 patients also received immunosuppressive therapy.^{2,4,5,14,17,19,20,23} It has been previously suggested to limit brain imaging to patients who have focal neurologic deficits and/or headache.⁵ Diagnostic testing should include a brain MRI with diffusion-weighted images along with consideration for cerebral angiogram and lumbar puncture. Treatment should be guided based on the severity of the clinical presentation. Previous case reports have described “escalation of care” to immunomodulatory medications including azathioprine, cyclophosphamide, or mitoxantrone when patients deteriorate clinically on corticosteroids alone. To date, there have been 5 case reports documenting death due to cerebrovascular complications.^{11,12,15,21,25} In the majority of these cases, death occurred when corticosteroids were rapidly tapered. From a previous review of 9 patients with APMPPE-associated strokes, patients were less likely to have another stroke or die if

they received high-dose corticosteroids with prolonged taper or initiation of immunomodulatory therapy.² In our patient's case, corticosteroid-based treatment was the agreed on choice after the onset of neurologic symptoms. The patient demonstrated clinical improvement on continued high-dose corticosteroids with eventual stabilization of his symptoms. Steroid sparing immunosuppressant regimens are a consideration particularly in severe cases, but the risks and benefits should be weighed and discussed with the patient before initiation.⁵

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