Neurological Complications of Acute Multifocal Placoid Pigment Epitheliopathy: A case series and review of the literature

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Abstract

Acute multifocal placoid pigment epitheliopathy (AMPPE) is an autoimmune chorioretinal disease that can be complicated by neurological involvement. There is limited information on this potentially treatable condition in the neurological literature. The objective of this patient series is to describe the neurological complications of AMPPE. We retrospectively identified patients with neurological complications of AMPPE seen at Auckland Hospital between 2008 and 2013 and summarised cases in the literature between 1976 and 2013. We identified five patients with neurological complications of AMPPE at Auckland Hospital and 47 reported patients. These patients demonstrated a spectrum of neurological involvement including isolated headache, stroke or transient ischaemic attack, seizures, venous sinus thrombosis, optic neuritis, sensorineural hearing loss and peripheral vestibular disorder. We propose criteria to define AMPPE with neurological complications. A cerebrospinal fluid (CSF) lymphocytosis in a patient with isolated headache may predict the development of cerebrovascular complications of AMPPE. Patients with cerebrovascular complications of AMPPE have a poor prognosis with high rates of death and neurological disability among survivors. Predictors of poor outcome in those who develop neurological complications of AMPPE are a relapsing course, generalised seizures and multifocal infarction on MRI. All patients with neurological complications of AMPPE, including headache alone, should be investigated with an MRI brain and CSF examination. Patients with focal neurological symptoms should receive intravenous (IV) methylprednisolone followed by a tapering course of oral steroids for at least 3 months. Patients with AMPPE and an isolated headache with a CSF pleocytosis should be treated with oral steroids

1. Introduction

Acute multifocal placoid pigment epitheliopathy (AMPPE) is an uncommon inflammatory chorioretinal disorder [1] and [2]. AMPPE presents in young adults with the acute onset of photopsias and painless visual loss that is frequently bilateral. Characteristic retinal changes are creamy lesions that evolve over several weeks leaving retinal pigmentary changes. On fluorescein angiography, acutely these areas demonstrate early hypofluorescence and late hyperfluorescence consistent with impaired choroidal blood flow thought to be due to an inflammatory choriocapillaritis [2]. It remains unclear whether the characteristic retinal lesions are exudative or ischaemic in nature. The course is usually self-limiting with recovery of vision, although there may be residual retinal scarring. The visual prognosis is related to the degree of foveal involvement. The cause of AMPPE is uncertain, but several lines of evidence suggest that it is immune-mediated: association with other ocular and systemic inflammatory diseases, post-infectious and post-vaccination cases and the association with certain HLA types [2].

Patients with AMPPE can develop neurological complications but usually present with retinal disease before headache or focal neurological deficits develop. Imaging studies suggest the cause is cerebral vasculitis and this has been confirmed in three pathological cases showing granulomatous inflammation in the large, medium and small vessels in the brain and meninges [3], [4], [5] and [6].

Articles on AMPPE are rarely published in the neurological literature. The objective of this patient series is to describe the neurological complications of AMPPE so as to facilitate early recognition of this disorder and to summarise the clinical and radiological characteristics of neurological complications of AMPPE from the literature.

2. Methods

We report five patients with AMPPE and neurological complications presenting to our institution and collected retrospectively between 2008 and 2013. Patients were included if they had AMPPE confirmed ophthalmologically and experienced neurological symptoms which included headache, focal neurological deficit, seizure or reduced level of consciousness. The findings of 47 published patients are combined with our five patients to examine the spectrum of neurological complications of AMPPE. To obtain the published cases of AMPPE, we performed an online medline search of the English literature. We used the search terms “AMPPE” and “APMPPE” as key words which identified 79 publications. We included all cases of AMPPE with neurological involvement including headache. Excluded were cases with isolated ocular disease. We analysed the clinical features of the combined series of patients to identify risk factors for poor outcome, defined as residual neurological deficit or death. Missing data points were omitted from the analysis. Follow-up data was collected from the most recently available clinic letter with a range of one to ten months following initial presentation, or as detailed in the published case reports.

3. Patient reports

3.1. Patient 1

A previously well 26-year-old man presented to an ophthalmologist with headache and photopsia. Visual acuity was 20/50 bilaterally. The optic discs were normal and mild swelling was identified at the macula. He was diagnosed with central serous chorioretinopathy. Two days later he awoke with worsening headache and visual disturbance, difficulty with language and right arm weakness. A neurological examination showed an expressive dysphasia, right homonymous hemianopia and mild right

hemiparesis. MRI, including diffusion-weighted imaging (DWI) of the brain was normal and a lumbar puncture showed a normal opening pressure at 190 mm H2O, a lymphocytic meningitis (white cell count 61 × 106/L [normal range ⩽5 × 106/L]: 75% lymphocytes [normal range 60–80%], protein 92 mg/dl [normal range 0.15–0.45 mg/dl] and glucose 61.2 mg/dl [normal range 2.8–4.4 mg/dl]). A further ophthalmology opinion was arranged. He was noted to have subretinal fluid over the maculae, ill-defined choroidal lesions in both eyes and early pigmentary changes. A fluorescein angiogram showed early hypofluorescence followed by later hyperfluorescence consistent with delayed choroidal filling (Fig. 1). He was treated with 1 g intravenous (IV) methylprednisolone for five days followed by a tapering dose of oral prednisone over two weeks. The patient's expressive dysphasia, hemianopia and hemiparesis began to improve prior to starting corticosteroids and resolved within 24 hours. At follow up four weeks later his visual acuity had improved to 6/6 bilaterally and he reported no further headaches.

3.2. Patient 2

A previously well 38-year-old man presented to an ophthalmologist with a two week history of headache, malaise and visual blurring. The visual acuity was 20/40 in the right eye and 6/6 in the left eye. There were patchy retinal changes around the macula in the right eye. These changes were seen in the area of the optic disc and more peripherally in the left eye (Fig. 2). There was no visual field defect and the rest of the neurological examination was normal. MRI showed a small acute infarct in the right parietal lobe. MR angiography was normal. The patient was diagnosed with AMPPE with neurological complications and he was started on prednisone 60 mg/day. Four weeks later, while receiving prednisone 30 mg/day his headache recurred, and he developed acute vertigo, nausea, unsteady gait and

worsening retro-orbital headaches. On examination he had left-beating nystagmus exacerbated by gaze to the left and a positive head thrust test to the right. He was unsteady walking but there were no focal signs in the limbs. Repeat MRI showed an old infarct in the right parietal lobe without any new lesion. CSF examination showed a normal opening pressure with a white cell count of 41 × 106/L: 82% lymphocytes, protein 55 mg/dl and normal glucose. He was diagnosed with a probable peripheral vestibular disorder although a small brainstem infarct could not be excluded. He was treated with one dose of 500 mg IV methylprednisolone, 3 days of 500 mg oral methylprednisolone and then a slowly reducing dose of methylprednisolone followed by oral prednisone. His symptoms slowly improved with persistent mild vertigo at 3 months, He remains on 20 mg/day of prednisone with a plan to continue a slow taper. The headache resolved promptly with IV methylprednisolone and has not recurred.

3.3. Patient 3

A 33-year-old woman presented with photophobia and visual loss in the right eye. Four days after the onset of symptoms she developed a frontal headache that slowly increased in intensity. Ophthalmological assessment showed visual acuity of counting fingers only with the right eye and 20/16 on the left. Fundoscopy showed multiple coalescing faint white subretinal opacities at the macula of the right eye. The left optic disc was normal. There was a mild relative afferent pupillary defect in the right eye. Fundoscopic examination of the left eye was normal. She was commenced on 80 mg of oral prednisone. She did not develop any further neurological symptoms and the remainder of the neurological examination was normal. MRI with angiography was normal and a CSF examination was normal including an opening pressure at 190 mm H2O. The dose of prednisone was

reduced over five weeks. Five months after symptom onset she was free of headaches. Visual acuity had improved to 20/100 in right eye and 20/16 in the left.

3.4. Patient 4

A 41-year-old man developed a headache with visual blurring and photopsia. A few days after the onset of symptoms he had three episodes of transient expressive dysphasia each lasting for several minutes over the course of a single day. Sumatriptan was prescribed for the headache, but made the headache worse. He then developed scotomas in his vision and visual distortion and presented to the ophthalmology service. Visual acuity was 6/6 in both eyes. There were creamy pigmented lesions classical for AMPPE at both posterior poles. He was started on prednisone 80 mg/day with improvement in the headaches. A neurological examination was normal. MRI was normal and a CSF showed white cell count 30 × 106/L: 93% lymphocytes with protein 39 mg/dl. An opening pressure was not recorded as the CSF was obtained in the seated position. The dose of prednisone was slowly reduced. Three months after symptom onset, while taking prednisone 40 mg/day, the patient had a recurrence of headaches and developed migratory left hemisensory paraesthesiae and numbness with mild left hand weakness. The focal symptoms resolved over 3 hours. A neurological examination and repeat MRI after symptom resolution were both normal. The patient was treated with a single dose of 500 mg IV methylprednisolone followed by 200 mg of oral methylprednisolone for 5 days and 100 mg for 3 days with a subsequent slow oral prednisone taper over 4 months. The patient’s headaches resolved and he experienced no further neurological symptoms.

3.5. Patient 5

A 27 year old presented to an ophthalmologist with a history of headache followed 3 days later by visual impairment with photopsia. His visual acuity was 20/20 bilaterally. Two placoid lesions were identified in the posterior pole of the left eye. He was diagnosed with AMPPE. Three days later he noted deterioration in his vision. Visual acuity at this time was 20/32 in the left eye and 20/16 in the right. He was started on 80 mg of prednisone. A neurological examination was normal as was MRI of the brain including MR angiography, MR venography was not performed. A CSF examination showed a normal opening pressure of 186 mm H2O, 68 × 106/L white cells: 81% lymphocytes, normal protein and glucose. The headache and visual symptoms slowly resolved. Two months after the onset of symptoms on a dose of 20 mg of prednisone his headaches recurred. The prednisone was increased to 40 mg with resolution of the headache and the prednisone was reduced by 5 mg per week until discontinued with no recurrence of the headache.

4. Review of the literature

A review of the published literature in the English language between 1976 and 2013 and including our five patients identified 52 patients in whom AMPPE was associated with neurological symptoms [4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29] and [30]. The mean age was 28.8 years (range 11–54 years) which is similar to that reported in a large series of patients with uncomplicated AMPPE [2] and [31]. Males accounted for more than two thirds of patients with neurological symptoms suggesting male gender may be a risk factor for neurological complications of AMPPE. No gender difference has been identified from case series of ocular AMPPE [28] and [32].

4.1. Neurological complications of AMPPE

The proportion of patients with ocular AMPPE that develop neurological complications has not been reported. One retrospective database review of all acute AMPPE patients presenting to one centre found 11/18 (61%) patients had neurological symptoms and one had a stroke [28]. Data missing from published case reports was not counted. In the majority of cases the visual symptoms preceded neurological complications.

Transient ischaemic attacks (TIA) or strokes occurred in 31/52 (60%) patients with neurological complications of AMPPE. Twenty two of 31 (71%) of patients with a TIA or stroke had evidence of an ischaemic lesion on CT scan or MRI. In the nine patients without a lesion, 5/9 had not had an MRI of the brain. The most common clinical presentation was that of a hemiparaesis, seen in 15/31 (48%), followed by a dysphasia or aphasia in 9/31 (29%). Other complications were a hemisensory disturbance in 6/31 (19%) or hemianopia in 5/31 (16%). Dysarthria in 4/31 (13%), ataxia in 3/31 (10%) and diplopia in 1/31 (3%) occurred less commonly.

The timing of vascular events in relation to the onset of the ocular symptoms was reported in 26/31 (84%) patients. In 17 of these 26 (65%) patients, the events occurred less than 4 weeks after the onset of visual symptoms. There are no reported cases in which ischaemic events occurred prior to visual symptoms and only 1/52 (2%) patients in which headache preceded the visual symptoms. Late presentations occurred in three patients at 6 and 12 months and 5 years after the onset of ocular symptoms. The mean time to onset of neurological symptoms from eye symptoms was 19 weeks. The anterior circulation was involved in 12/31 (39%), the posterior circulation in 9/31 (29%) and in 10/31 (32%) patients cerebral infarcts occurred in multiple vascular territories. MRI was consistent with ischaemic

strokes in the majority of patients but in one case series, one patient had an intracerebral haemorrhage complicating superior sagittal sinus thrombosis [17]. Seventy percent of patients with cerebrovascular complications were male. The majority of patients 23/31 (74%) who developed cerebrovascular complications reported a headache. All patients who developed stroke or TIA, in whom a CSF result was reported had increased CSF lymphocytes, although one such patient had an initially normal result [28].

Cerebrovascular complications in patients with AMPPE are thought to be secondary to cerebral vasculitis as this has been demonstrated pathologically in three published cases, included in this case series, with autopsy findings. A granulomatous vasculitis affecting the left middle cerebral artery was seen in one patient and in the meningeal arteries in two [4], [5] and [6]. Perivascular cuffing was also evident in the small intracerebral arteries [4]. Of the patients presenting with cerebrovascular complications 11/31 (35%) had evidence of a possible vasculitis on MR angiography or catheter angiography. Formal catheter angiography has shown evidence of small vessel disease with findings of diffuse narrowing, segmental narrowing and in some cases a typical beading appearance [3], [10], [12], [14], [19], [23] and [29].

Isolated headache, defined as headache without other neurological symptoms, with normal brain imaging and CSF examination, occurred in 11/52 (21%) patients. The features of headache complicating AMPPE are poorly characterised in published case histories but where described the headaches were severe [5], [6], [17], [22] and [23], persistent [17], [26] and [27], localised [5] or diffuse [6]. Meningitic symptoms were described in the minority with only 4/52 (8%) patients experiencing either neck stiffness [9] and [10], fever [18] or photophobia [22].

Seizures occurred in four patients, one of unspecified type. One patient had focal seizures associated with a new DWI lesion on MRI imaging [26]. Two other patients had generalised seizures; both patients died. At autopsy ischaemic change was found in large areas of the cerebral cortex in both patients [4] and [5].

4.2. Prognosis

The prognosis of patients with AMPPE with neurological involvement is variable. At least short term follow up information is available for 40/52 (77%) patients. 25/40 (62%) made a full recovery, 10/40 (25%) had residual neurological disability, 5/40 died (13%). If the analysis is limited to patients who presented with a TIA or stroke then the prognosis is relatively poor with half of patients having a residual neurological disability or dying. The two patients who experienced generalised seizures died [4] and [5]. There was no statistically significant difference in outcome based on the age of the patient at presentation or severity of the ocular disease as measured by visual acuity.

In this review, 23/31 (74%) of patients with cerebrovascular complications had the results of MRI reported. Multifocal infarction on MRI was seen in 10/31 (32%) patients. Of these, 4/10 (40%) patients died. Multifocal infarction on imaging was a risk factor for poor outcome. ($p < 0.004$). There was no statistically significant difference in outcome based on whether the initial MRI result was normal although the numbers are low. Normal MRI was seen in 5 of 23 (22%) patients with cerebrovascular complications of AMPPE, four of whom had no residual deficit. Caution is needed when using normal imaging at presentation to prognosticate as one patient with initial normal imaging went on to have a fulminant course and died with multifocal brain involvement.

Patients with a relapsing course had a worse outcome compared with those with a monophasic course ($p = 0.005$). 11/39 (26%) patients had a relapsing course, of whom 6/11 (55%) had a residual neurological deficit. 29/35 (85%) patients with a monophasic neurological presentation made a full recovery, none died. Five patients presented with a rapidly progressive course defined as dying within 4 weeks of neurological presentation [4], [5], [6], [13] and [27].

The number of CSF white cells did not predict whether patients made a full recovery or had residual deficit or died ($p = 0.2$). However, only 2/5 (40%) of the patients who died had the results of CSF analysis recorded.

4.3. Treatment

There is information on medical management in 40/52 (77%) of the cases. The majority, 36/40 (90%), were treated with steroids or other immunosuppressive agents. 8/40 (20%) with IV steroids, 5/40 (13%) with azathioprine, 4/40 (10%) with cyclophosphamide and one patient received IV methylprednisolone without oral steroid in combination with mitoxantrone. There was a large variation in the duration of therapy with patients receiving weeks to years of immunosuppressant therapy. Immunosuppressant agents were added to steroids for a clinical deterioration with the development of neurological complications in 6/10 patients (60%). In 4/10 (40%) patients additional immunosuppression was used for steroid sparing.

5. Discussion

AMPPE is an inflammatory chorioretinal disorder complicated by neurological involvement. Patients with AMPPE may present to neurologists with headache or focal neurological symptoms and a history of reduced visual acuity or photopsia. In an appropriate clinical setting a careful slit-lamp examination looking for presence of intraocular inflammation and for the characteristic retinal lesions is the most important part of reaching the ocular diagnosis. Investigations such as fluorescein angiography and ocular coherence topography will further support this diagnosis.

Patients with cerebrovascular complications of AMPEE have a relatively poor prognosis with high rates of death and neurological disability among survivors. Imaging studies suggest the cause is a cerebral vasculitis and this has been confirmed in three pathological cases showing granulomatous inflammation of vessels. Given the proposed immune mechanisms of AMPPE and the possibility of an unfavourable outcome, early consideration should be given to the use of immunosuppression.

This case series and review of the literature has summarised the neurological complications of AMPPE. These range from isolated headache without evidence of meningeal inflammation, to headache with evidence of meningeal inflammation, to stroke or TIA. In the majority, the onset of neurological symptoms is preceded by symptoms of retinal disease. Based on the published cases we propose the criteria in Table 1 for the diagnosis of AMPPE with neurological complications.

5.1. Predictors of developing cerebrovascular complications of AMPPE

The ability to identify patients at risk of progressing from isolated eye disease to central nervous system involvement would be helpful to guide treatment. There is uncertainty about how aggressively patients should be treated with immunosuppression and for what duration.

The majority of patients with cerebrovascular complications of AMPPE had a CSF pleocytosis. In those patients with AMPPE presenting with an isolated headache, the presence of a CSF pleocytosis may indicate impending cerebrovascular ischaemia.

5.2. Predictors of poor outcome in neurological AMPPE

Several factors identified in this review appeared to be associated with a poor outcome. These are a relapsing or rapidly progressive clinical course, generalised seizures and multifocal neuroimaging findings.

There are no randomised controlled trials to guide the treatment of neurological complications of AMPPE. Given the proposed immune mechanisms of AMPPE and the possibility of residual neurological deficits or death, early consideration should be given to starting immunosuppression. We suggest that all patients with AMPPE with neurological symptoms, including isolated headache, have an MRI and CSF examination. Those patients with focal neurological symptoms should be treated with a short course of 500 mg IV methylprednisolone followed by a tapering course of oral steroids for a period of at least 3 months. Patients with AMPPE and an isolated headache, with either an abnormal MRI or CSF, should be treated with 1 mg/kg of oral prednisone tapering down over a period of 3 months.

Patients presenting with a relapsing course, generalised seizures or multifocal abnormalities on brain imaging may require more protracted treatment. Patients who are already receiving corticosteroids when cerebrovascular complications develop may require more intensive immunosuppression with azathioprine, cyclophosphamide or mitoxantrone [16], [17], [23] and [24].

The published literature likely reflects a bias to more severe patient presentations and therefore the above results may not be generalisable to individual patients with neurological complications of AMPPE. The five patients from our site had relatively mild complications. The predictors we identified were from a collation of data from several sources and therefore statistical analysis to determine their significance may not be robust. There is a need for a prospective study of patients with AMPPE to document the incidence and spectrum of neurological complications and statistically confirm the predictive factors identified in this literature review.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this.

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Table 1. Proposed criteria for the diagnosis of AMPPE with neurological complications

Ophthalmological evidence of AMPPE
Multiple yellow-white subretinal lesions, typically bilateral Predilection for posterior pole Pigmentary change over lesions within days to months Variable degree of anterior chamber and vitreous activity (may be absent) Supported by characteristic findings on fluorescein and indocyanine green angiography
And one or more of the following
Headache Stroke or transient ischaemic attack CSF pleocytosis