CASE REPORT

Cerebral vascular findings in PAPA syndrome: cerebral arterial vasculopathy or vasculitis and a posterior cerebral artery dissecting aneurysm

Kasra Khatibi,¹ Jeremy J Heit,² Nicholas A Telischak,² Jorina M Elbers,³ Huy M Do⁴

¹Department of Neurology, Stanford University, Stanford, California, USA

²Department of Radiology, Stanford University, Stanford, California, USA

³Department of Neurology, Stanford University, Stanford, California, USA

⁴Departments of Radiology and Neurosurgery, Stanford University, Stanford, California, USA

Correspondence to

Dr Kasra Khatibi, Department of Neurology, Stanford University, 300 Pasteur Drive h3142, Palo Alto, CA 94304, USA; kkhatabi@stanford.edu

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SUMMARY

A young patient with PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne) syndrome developed an unusual cerebral arterial vasculopathy/vasculitis (CAV) that resulted in subarachnoid hemorrhage from a ruptured dissecting posterior cerebral artery (PCA) aneurysm. This aneurysm was successfully treated by endovascular coil sacrifice of the affected segment of the PCA. The patient made an excellent recovery with no significant residual neurologic deficit.

BACKGROUND

PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne) syndrome is a rare autosomal-dominant autoinflammatory disorder primarily affecting joints and skin, manifesting as pyogenic arthritis, pyoderma gangrenosum and acne.¹ There are no reports of cerebral arterial vasculopathy/vasculitis (CAV) with PAPA syndrome. Here we describe the first report of CAV in PAPA syndrome resulting in a dissecting aneurysm. We demonstrate the feasibility and safety of endovascular coil treatment of dissecting aneurysms in patients with PAPA-related CAV.

CASE PRESENTATION

A patient with PAPA syndrome was hospitalized with disease exacerbation and methicillin-sensitive *Staphylococcus aureus* bacteremia. PAPA syndrome had been confirmed by a E3257K missense mutation of the *PSTPIP1* gene. The patient was being treated with anakinra and methotrexate, which predispose patients to bacterial infections. After admission, the patient was started on cefazolin and a methylprednisolone pulse for treatment of an autoimmune flare.

Shortly after methylprednisolone administration, the patient developed new periodic thunderclap headaches. A lumbar puncture demonstrated an opening pressure of 17 cm H₂O, no xanthochromia, white blood cell count 1/μL, and protein 53 mg/dL. Erythrocyte sedimentation rate and C-reactive protein were normal.

A non-contrast head CT was normal. A subsequent brain MRI demonstrated scattered subcortical T2 hyperintense foci, and MR angiography (MRA) demonstrated interval diffuse irregularity within the bilateral anterior and posterior circulation (figure 1), confirmed by CT angiography (CTA) (figure 2A). Diagnostic considerations for these findings included inflammatory mediated CAV, infectious vasculitis, or reversible cerebral

vasospasm syndrome (RCVS). In the absence of subarachnoid hemorrhage, negative cerebrospinal fluid (CSF) studies, and normal serum inflammatory markers, the patient was started on verapamil for presumed RCVS.

The headaches resolved over a month. The patient clinically improved and was discharged on verapamil. MRAs performed 2 and 3 months later demonstrated persistent irregularity of bilateral posterior cerebral artery (PCA) and anterior cerebral arteries. Follow-up CTA at 4 months demonstrated a new 7×4 mm fusiform aneurysm in the P2 segment of the right PCA (figure 2B). A mycotic aneurysm was considered in the context of intermittent bacteremia and the patient was treated with aggressive antibiotic regimen.

Two weeks later the patient was admitted with a new severe headache and photophobia. Head CT demonstrated subarachnoid hemorrhage within the basal cisterns (figure 2C).

INVESTIGATIONS

The patient was brought to the endovascular suite as an emergency and a diagnostic cerebral angiogram demonstrated a fusiform dissecting aneurysm within the P2 segment of the right PCA (figure 3).

DIFFERENTIAL DIAGNOSIS

Dissecting PCA aneurysm secondary to an underlying:

- ▶ Infectious vasculitis
- ▶ Inflammatory-mediated cerebral arterial vasculopathy
- ▶ Reversible cerebral vasospasm syndrome

TREATMENT

The aneurysm was treated by coil sacrifice of the right P2 segment. Under standard neurophysiologic monitoring using a 6 Fr triaxial system, a microcatheter was introduced into the basilar artery. Methohexital (Brevital) was injected into the P2 segment with no change in neurophysiologic monitoring parameters. Successful coil sacrifice of the P2 segment of the right PCA was then performed by serial placement of 10 coils through the microcatheter into the right P2 segment (figure 3). The P3 and more distal segments of the right PCA did not fill in an antegrade manner following injection of the left vertebral artery, consistent with coil sacrifice of this vessel (figure 3). On subsequent right internal carotid run, there was retrograde filling of the P4 segment through right middle cerebral

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Figure 1 Cerebral vasculitis on brain MRI and MR angiogram (MRA). (A–C) Fluid-attenuated inversion recovery (FLAIR) images show multiple areas of abnormal hyperintense signal abnormality within the bilateral subcortical white matter (arrows), which is often seen in patients with vasculitis. (D–F) Multiple maximum intensity projection images from a brain MRA demonstrate irregularity within the P2 segment of the right posterior cerebral artery (D, arrow), the M1 segment of the left middle cerebral artery (E, arrow), and within the A2 segment of the right anterior cerebral artery (F, arrow).

artery collateral vessels, but no filling of the aneurysm. There were no changes to neurophysiologic monitoring throughout the case.

OUTCOME AND FOLLOW-UP

The following day the patient was noted to have mild proximal and distal weakness in the left face, arm and leg but no visual deficits. An MRI demonstrated restricted diffusion in the inferolateral right thalamus in the distribution of the right thalamogeniculate perforating arteries that arise from the P2 segment of the PCA (figure 4). Additional small areas of infarction were present in the right splenium and hippocampus (figure 4).

The patient was observed in the intensive care unit with routine transcranial Doppler examinations and treated with nimodipine to prevent vasospasm. The patient recovered to baseline function on discharge.

DISCUSSION

We report on the first case of CAV with an associated ruptured dissecting aneurysm in the setting of PAPA syndrome. The etiology of this patient's cerebral arterial narrowing remains uncertain in the absence of biopsy. The presentation with the sudden onset of a thunderclap headache, a benign CSF profile, and no evidence of intracranial hemorrhage most strongly suggests a diagnosis of RCVS.

However, RCVS typically resolves symptomatically and radiographically within 12 weeks, which argues for a different diagnosis.² A prolonged and dynamic cerebral arterial narrowing, complicated by the development of a dissecting aneurysm, is also atypical of RCVS. Because of intermittent bacteremia, a mycotic aneurysm was considered, although vascular imaging identified no other aneurysms and CSF was not suggestive of infection. Given the dynamic and extensive arterial

Figure 2 Development and subsequent rupture of a dissecting aneurysm within the right posterior cerebral artery (PCA). Axial maximum intensity projection images from CT angiography studies performed shortly after presentation (A) and 5 months after presentation (B) demonstrate subtle ectasia and irregularity within the P2 segment of the right PCA (A, dashed arrows) that progresses to a dissecting aneurysm within the P2 segment of the right PCA (B, arrows). The insets represent magnified views of the right PCA in (A) and (B). Axial images from non-contrast CT study performed 2 weeks after detection of the aneurysm (C) demonstrates subarachnoid hemorrhage within the basal cisterns.

Figure 3 Endovascular coil embolization for treatment of a dissecting aneurysm within the right posterior cerebral artery (PCA). (A and B) Digital subtraction angiography (DSA) images in the anteroposterior (A) and posterolateral (B) views demonstrate irregularity and expansion within the P2 segment of the right PCA (A and B, arrows) that are consistent with a dissecting aneurysm. Irregularity within the basilar artery is also present on these images. (C and D) DSA images acquired during coil embolization of the dissecting aneurysm demonstrate a coil mass within the P2 segment of the right PCA (C and D, arrow). A Navien distal access catheter is present in the V4 segment of the left vertebral artery (C and D, arrowheads), and a microcatheter (C and D, dashed arrows) is present in the basilar artery and P1 segment of the right PCA. (E and F) DSA images following successful coil embolization of the right PCA dissecting aneurysm demonstrate a coil mass in the P2 segment of the right PCA (E and F, arrows) and no residual filling of the aneurysm is present. There is normal filling of the left PCA (E and F, dashed arrows), but the right PCA is occluded distal to the coil mass.

Figure 4 Post-coil embolization cerebral infarction. A brain MRI was obtained following coil embolization of the right posterior cerebral artery (PCA) dissecting aneurysm. (A) Diffusion-weighted imaging demonstrates a small area of acute infarction within the inferolateral right thalamus (A, arrow), which is within the P2 segment, thalamogeniculate perforating, artery territory. A second small area of infarction is present within the right splenium of the corpus callosum (arrowhead), which is within the P2 segment splenial artery vascular territory. (B) Fluid-attenuated inversion recovery (FLAIR) imaging demonstrates hyperintense signal abnormality within the right inferolateral thalamus (arrow) that corresponds to the area of infarction seen in (A). Axial maximum intensity projection image from a brain MR angiogram demonstrates a normal left PCA (arrow), but no flow-related signal is present within the right PCA (arrowhead).

irregularities, it is very likely that our patient's CAV reflects an inflammatory vasculitis and the dissecting aneurysm resulted from the underlying arteriopathy.

An association between cerebral or systemic vasculopathy/vasculitis and PAPA syndrome has not been reported previously. Familial Mediterranean fever (FMF) is an autoinflammatory disorder that is closely related to PAPA. PAPA and FMF affect a common pathway that leads to a proinflammatory state with heightened response to environmental triggers. PAPA syndrome is caused by missense mutation in the lymphocytic CD2 binding protein-1 (CD2BP).³ The CD2BP protein interacts with pyrin, and the gene encoding pyrin is mutated in patients with FMF. Impaired function of either CD2BP or pyrin results in interleukin 1 β upregulation and an autoinflammatory state.⁴

In contrast to PAPA syndrome, both systemic small vessel (Henoch–Schonlein purpura, HSP) and medium vessel (polyarteritis nodosum, PAN) vasculitis has been reported with FMF.⁵ HSP and PAN may involve the cerebral arteries.^{6–7} Behcet's disease is another autoinflammatory syndrome associated with intracranial large and small vessel vasculitis and cerebral aneurysm formation.^{8–9} Furthermore, coil embolization of aneurysms caused by Behcet's vasculitis has been described.¹⁰

Here we propose the association of PAPA syndrome and CAV complicated by the formation of a dissecting PCA aneurysm.

Learning points

- PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne) syndrome is an uncommon autoinflammatory syndrome that may result in cerebral vasculopathy or vasculitis.
- Dissecting aneurysms in the setting of PAPA syndrome can be safely treated with endovascular coil embolization.
- In the setting of autoinflammatory vasculopathy and the use of immune-modulating agents, it is important to consider underlying infectious or reactive etiology.

The similarities between PAPA and FMF, the latter of which has been previously associated with vasculitis, suggest a common genetic influence on the development of a vasculopathy. Furthermore, given that both PAPA and FMF result in a hyperactive immune system, an inflammatory vasculitis in our patient with PAPA is likely. We also demonstrate that dissecting aneurysms in the setting of PAPA syndrome may be safely treated by coil embolization.

Contributors The patient was evaluated and managed by JME, KK, HMD, JJH and NAT. KK prepared the initial draft of the manuscript. JJH edited and provided the images. All other authors contributed to refinement of the case report and approved the final manuscript.

Competing interests None declared.

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REFERENCES

- 1 Lindor NM, Arsenault TM, Solomon H, *et al.* A new autosomal dominant disorder of pyogenic sterile arthritis, pyoderma gangrenosum, and acne: PAPA syndrome. *Mayo Clin Proc* 1997;72:611–15.
- 2 Calabrese LH, Dodick DW, Schwedt TJ, *et al.* Narrative review: reversible cerebral vasoconstriction syndromes. *Ann Intern Med* 2007;146:34–44.
- 3 Smith EJ, Allantaz F, Bennett L, *et al.* Clinical, molecular, and genetic characteristics of PAPA syndrome: a review. *Curr Genomics* 2010;11:519–27.
- 4 Shoham NG, Centola M, Mansfield E, *et al.* Pyrin binds the PSTPIP1/CD2BP1 protein, defining familial Mediterranean fever and PAPA syndrome as disorders in the same pathway. *Proc Natl Acad Sci USA* 2003;100:13501–6.
- 5 Ozdogan H, Arisoy N, Kasapcapur O, *et al.* Vasculitis in familial Mediterranean fever. *J Rheumatol* 1997;24:323–7.
- 6 Ozkaya O, Bek K, Alaca N, *et al.* Cerebral vasculitis in a child with Henoch-Schonlein purpura and familial Mediterranean fever. *Clin Rheumatol* 2007;26:1729–32.
- 7 Moore PM, Cupps TR. Neurological complications of vasculitis. *Ann Neurol* 1983;14:155–67.
- 8 Nakasu S, Kaneko M, Matsuda M. Cerebral aneurysms associated with Behcet's disease: a case report. *J Neurol Neurosurg Psychiatry* 2001;70:682–4.
- 9 Houman MH, Bellakhal S, Ben Salem T, *et al.* Characteristics of neurological manifestations of Behcet's disease: a retrospective monocentric study in Tunisia. *Clin Neurol Neurosurg* 2013;115:2015–18.
- 10 Kizilkilic O, Albayram S, Adaletli I, *et al.* Endovascular treatment of Behcet's disease-associated intracranial aneurysms: report of two cases and review of the literature. *Neuroradiology* 2003;45:328–34.

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