

A 52-year-old woman with beading of intracranial arteries

A 52-year-old woman of Indian ethnicity with a history of well-controlled hypertension, hyperlipidaemia and recurrent transient ischaemic attacks presented with altered mentation and slurred speech. Physical examination revealed generalised weakness. Initial blood tests showed raised total white cell count, raised erythrocyte sedimentation rate at 35mm/h and fasting low-density lipoprotein of 1.7mmol/L. Magnetic resonance imaging (MRI) of the brain showed small acute infarcts scattered in bilateral deep white matter (Fig. 1A), with extensive periventricular, deep and subcortical white matter leukoariosis (Fig. 1B) indicative of advanced small vessel disease. Angiography showed stenosis along the right anterior cerebral artery and beading of the left posterior cerebral artery (Fig. 1C). Digital subtraction angiography (DSA) showed beading along the right posterior cerebral artery (Fig. 1D).

What is the most likely differential diagnosis?

- A. Atherosclerotic small vessel disease
- B. Central nervous system lymphoma
- C. Neurosyphilis
- D. Reversible cerebral vasoconstriction syndrome (RCVS)
- E. Vasculitis

In view of the imaging findings of advanced small vessel disease out of proportion to underlying cardiovascular risk factors, beading and stenosis of intracranial arteries, the clinical impression was that of vasculitis. Differentials were broad, including infective, inflammatory and neoplastic causes. Thorough systemic history revealed no recent fever, weight loss, chronic cough, haemoptysis, haematuria, change in bowel habits, rash, ulcers, alopecia, arthritis or sicca syndrome symptoms, and no previous history of venous thrombosis or miscarriages. Blood investigations demonstrated raised levels of anti-cardiolipin immunoglobulin M antibody and anti-nuclear antibody but anti-double-stranded DNA antibody, lupus anticoagulant and anti-beta-2-glycoprotein antibody were negative. Further physical examination revealed no clinical manifestations of systemic lupus erythematosus and anti-phospholipid syndrome. Other autoimmune, infective and malignancy tests, including anti-neutrophil cytoplasmic antibody, syphilis immunoglobulin G and rapid plasmin reagin were normal. A cerebrospinal fluid (CSF) evaluation revealed

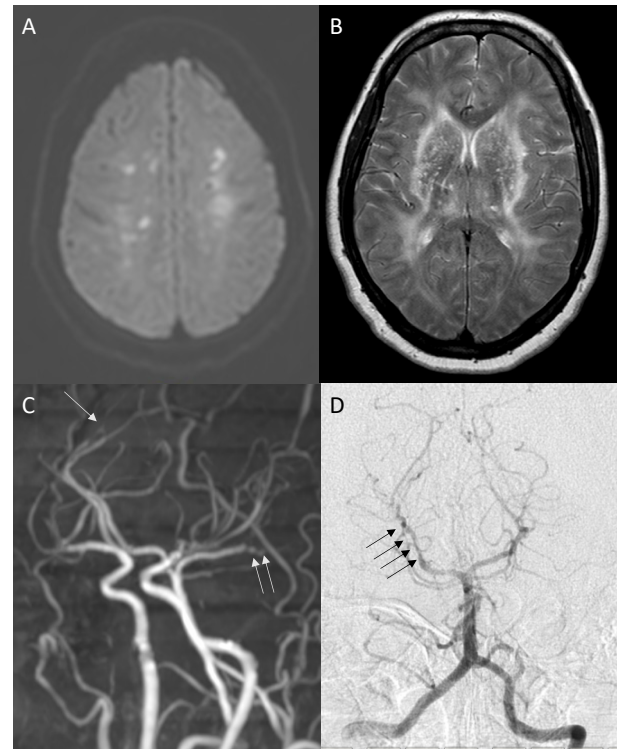


Fig. 1. (A) Magnetic resonance imaging revealed small acute infarcts scattered in bilateral deep white matter. (B) Evidence of advanced, chronic small vessel disease involving deep grey matter as well as periventricular, deep and subcortical white matter. (C) Magnetic resonance angiogram showed stenosis along the right anterior cerebral artery (single white arrow) and beading of the left posterior cerebral artery (double white arrows). (D) Digital subtraction angiography showed beading along the right posterior cerebral artery (black arrows).

raised nucleated cells at 75 cells/ μ L and protein 0.6g/L. The presence of advanced small vessel disease, elevated inflammatory markers and CSF nucleated cells and protein made RCVS less likely. In addition, atherosclerotic small vessel disease could not account for the non-lacunar infarct presentation in the presence of well-controlled cardiovascular risk factors of hypertension and hyperlipidaemia. A right parietal brain biopsy subsequently showed granulomatous vasculitis. Fungal stains (periodic acid-Schiff, periodic acid-Schiff with diastase, and Grocott methenamine silver), acid-fast bacillus stain and culture, and *Mycobacterium tuberculosis* polymerase chain reaction were negative.

The diagnosis of primary angiitis of the central nervous system (PACNS) was made and the woman received intravenous methylprednisolone followed by

Table 1. Key findings of 5 patients with primary angitis of the central nervous system in our institution

Case	Age	Sex	Medical history	Presenting symptoms	Inflammatory markers ^a	Immune markers	CSF	MRI	MRA	Biopsy
1	76	Female	Hypertension, hyperlipidaemia	Ataxia	Normal	Normal	Normal	Predominantly white matter lesions in the middle cerebellar peduncles, brainstem and right anterior temporal lobe; no diffusion restriction	Normal	Lymphocytic vasculitis
2	59	Male	Hyperlipidaemia, presumptive TIA	Altered cognition, headache	Raised WCC	Normal	Normal	Right temporo-occipital parietal gyral swelling and enhancement	Normal	Lymphocytic vasculitis
3	82	Male	None	Altered cognition, unilateral weakness	Raised WCC, CRP, ESR	Normal	Raised nucleated cells 22 cells/ μ L and protein 2.32g/L	Bilateral deep white matter lesions with patchy and ring enhancement	Normal	Granulomatous vasculitis
4	87	Female	Hypertension, hyperlipidaemia	Unilateral weakness, slurred speech	Normal	Normal	Normal	Small infarcts scattered in the right parietal cortices, sulcal subarachnoid haemorrhage and diffuse, thick leptomeningeal and patchy parenchymal enhancement	Normal	Vasculitis, unspecified
5 ^b	52	Female	Hypertension, hyperlipidaemia, recurrent ischaemic strokes	Altered cognition, unilateral weakness, slurred speech	Raised WCC, ESR	Positive ANA and anti-cardiolipin antibody titres	Raised nucleated cells 75 cells/ μ L and protein 0.7g/L	Small acute infarcts scattered in bilateral deep white matter with extensive periventricular, deep and subcortical white matter leukoariosis	Multifocal stenosis and beading	Granulomatous vasculitis

ANA: anti-nuclear antibody; CRP: C-reactive peptide; CSF: cerebrospinal fluid; ESR: erythrocyte sedimentation rate; MRA: magnetic resonance angiography; MRI: magnetic resonance imaging; TIA: transient ischaemic attack; WCC: white cell count

^a C-reactive peptide, erythrocytes sedimentation rate and white cell count

^b Patient 5 was presented with full details in our case illustration

tapering doses of oral prednisolone and methotrexate. At a review after 6 months, the patient was neurologically stable with residual memory impairment and frontal lobe dysfunction.

PACNS is a rare form of vasculitis that is limited to the brain and spinal cord. The underlying cause and pathogenesis are unknown, but possible triggers include viral infections such as varicella-zoster virus infection. The association between cerebral amyloid angiopathy and PACNS also suggests that amyloid deposition could trigger vascular inflammation.

PACNS has neither pathognomonic features nor a typical clinical course.¹ Common presenting symptoms are stroke-like events, headache and altered cognition.² Typical MRI findings of PACNS include infarcts in small to medium-sized vessel territories, haemorrhage and microhaemorrhage, and multifocal stenosis and beading on magnetic resonance angiography (MRA). However, there is heterogeneity in the clinical presentation, neuroimaging, blood and CSF workup. Of note, 7% of PACNS cases have normal MRI.³ Additionally, CSF analysis can be normal in up to 26% of cases.³ Hence, a low threshold of suspicion is required for diagnosis and the value of investigations lies in excluding a secondary cause of vasculitis and other PACNS mimics including infection and malignancy. Table 1 demonstrates the experience of our institution and reflects the heterogeneity in clinical manifestations of PACNS.

The gold standard for diagnosis of PACNS is the demonstration of transmural vessel wall inflammation on cerebral and/or leptomeningeal biopsy.¹ Although there is a relatively high rate of false negative due to the inherent patchy nature of the disease,³ biopsy is useful to rule out other conditions such as central nervous system intravascular lymphoma and reversible cerebral vasoconstriction syndrome.⁴ One study showed that brain biopsy confirmed vasculitis and alternative diagnoses in 75% of patients.⁵ It is noteworthy that brain biopsy has been shown to be relatively safe with mortality and morbidity rates of less than 1% and 3.5%, respectively.⁶ Early brain biopsy should be considered in patients due to the importance of histological diagnosis.

Digital subtraction angiography, which is inherently less invasive than a craniotomy, has been considered a potential replacement for brain biopsy. However, the utility of DSA remains controversial due to the lack of concordance between DSA and histology.^{1,3,5,7} While superior to MRA, DSA has a limited resolution in detecting abnormalities at the level of small arteries and arterioles. In addition, similar to computed tomography and MRA, DSA provides luminal but not vessel wall

information, hence vessel wall disease that has not resulted in luminal abnormality may not be detected. In studies with pathological correlation, both sensitivity and specificity of DSA was shown to be only 25–35%.^{3,5} High-resolution MRI of the vessel wall, or “black blood imaging” is an emerging and promising imaging choice that may help to differentiate PACNS from other vasculopathies such as RCVS,² and it can direct a brain biopsy target to allow for more diagnostic histology.⁸ However, black blood imaging remains non-routine as resolution at the level of small arteries/arterioles remains a challenge,⁹ with additional studies needed to demonstrate direct histological correlation.

There is no standardised treatment regime for PACNS. It is generally accepted that initial treatment consists of high-dose corticosteroids, followed by steroid-sparing agents such as azathioprine or mycophenolate mofetil.¹⁰ In more severe cases, cyclophosphamide is added. Treatment is further escalated to tumour necrosis factor- α (TNF- α) inhibitors or rituximab for patients who do not respond.² Nonetheless, treatment-related complications, including life-threatening infections due to chronic immunosuppression, may arise. At our institution, of 5 patients histologically diagnosed with PACNS who achieved clinical stability with immunosuppressive therapy (Table 1), 3 patients succumbed to life-threatening pneumonia within 1 year of treatment, highlighting the risks associated with immunosuppressive agents. Consistent with recent efforts to advocate pathological diagnosis,⁷ we recommend early biopsy for histological confirmation prior to aggressive immunosuppressive therapy.

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