

Imaging findings in primary central nervous system vasculitis

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ABSTRACT

Primary central nervous system vasculitis (PCNSV) is a rare primary vasculitis limited to the brain and spinal cord. It can affect any age group, but has a predilection for subjects aged 40 to 60 years without clear gender predominance. Clinical manifestations are non-specific, including headache, non-focal neurological features and, less frequently, focal neurological signs. Brain biopsy is the diagnostic gold standard, but may be falsely negative when unaffected tissue is sampled. In addition, brain biopsy carries a small but significant risk of serious complications. Imaging procedures are a key part of the workup of PCNSV patients. They can be used to document the extent and type of lesions, to gauge response to treatment, and sometimes as surrogates for brain biopsy. Magnetic resonance is extremely sensitive but non-specific. The most common findings are multiple bilateral ischaemic lesions often involving white and grey matter. Conventional or magnetic resonance angiography (MRA) typically shows segmental narrowing and dilation in multiple cerebral arteries. However, atypical findings have also been described both with magnetic resonance and angiography. This review discusses the state-of-the-art of current imaging techniques in the workup of PCNSV patients and highlights future prospects.

Introduction

Primary central nervous system vasculitis (PCNSV) is a rare vasculitis that by definition does not extend beyond the confines of the brain and spinal cord. PCNSV is not recognised as a separate entity by most classification criteria, but it was classified as a large-vessel vasculitis by the Norwich group as far back as in 1994 (1). Now considered capable of affecting the full spectrum of vessels including those too small to be resolved by angiography, PCNSV cases with a

rapidly progressive clinical course and histopathology have been favoured to show large-vessel angiographic abnormalities (2, 3). Although the majority of cases present clinically as an insidious non-localising encephalopathy or a chronically progressive headache, focal neurological manifestations like transient ischaemic attack (TIA) occur in a sizeable number of patients, while aphasia, seizures and visual-field defects have also been described (4). This non-specificity of clinical features is accompanied by a lack of reliable serological markers. Autoimmune tests are usually negative, while inflammatory markers like erythrocyte sedimentation rate are normal in most patients, possibly a consequence of the disease confinement within the blood-brain barrier. Analysis of cerebrospinal fluid (CSF) shows non-specific alterations in the majority of adult patients, including mildly increased leukocyte count, increased total protein concentration, or both (5). However, CSF analysis is still useful to rule out central nervous system (CNS) infection. PCNSV can affect any age group with some predilection for subjects aged 40 to 60 years, while there is no clear gender preponderance in adults (6). The most widely used classification criteria are those proposed by Calabrese, which include a recent history or presence of an acquired neurological deficit unexplained by other causes; evidence of vasculitis in a CNS biopsy specimen, or a cerebral angiogram with changes characteristic of vasculitis (7).

Brain biopsy is the diagnostic gold standard, but its usefulness is hampered by the risk of procedural complications and the possibility of sampling unaffected parenchyma. The clinician should be prepared for a diversity of histopathological findings, including granulomatous, lymphocytic and fibrinoid necrotising patterns of vascular inflammation (8). A caveat in the inter-

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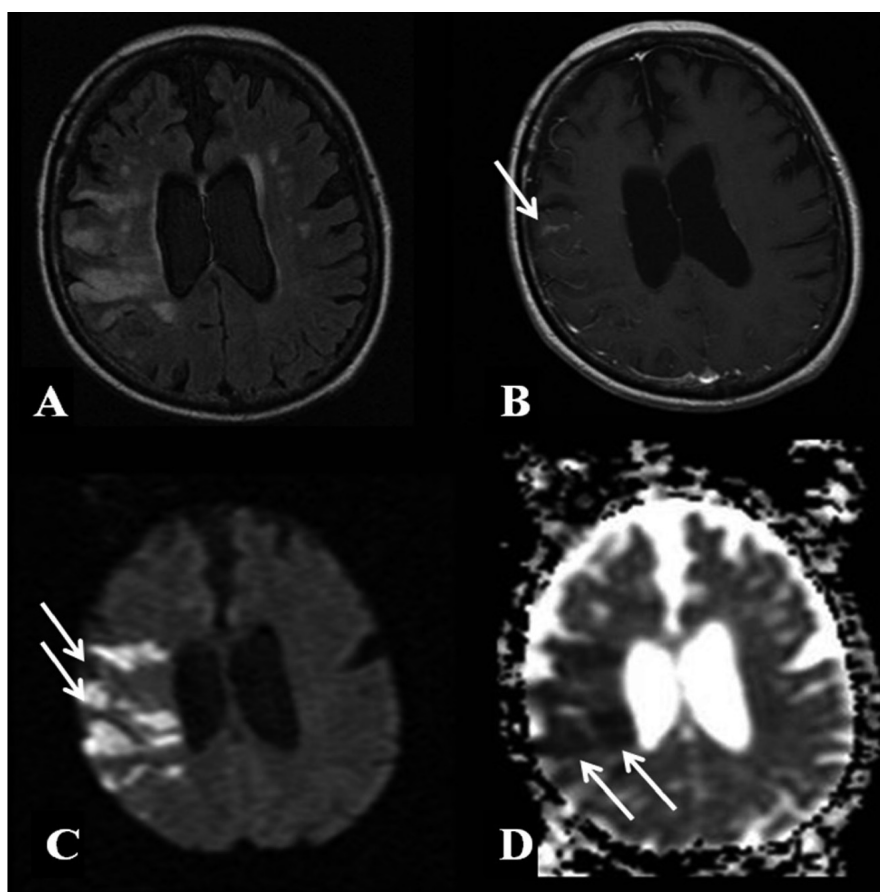


Fig. 1. Confluent foci of T2 prolongation indicating brain oedema are noted in the right frontal region on FLAIR images (A). Focal meningeal enhancement is seen on T1-weighted images (B, arrow). Restricted diffusion (C, arrows) and low ADC values (D, arrows) represent cytotoxic edema secondary to PCNSV-related hypoperfusion.

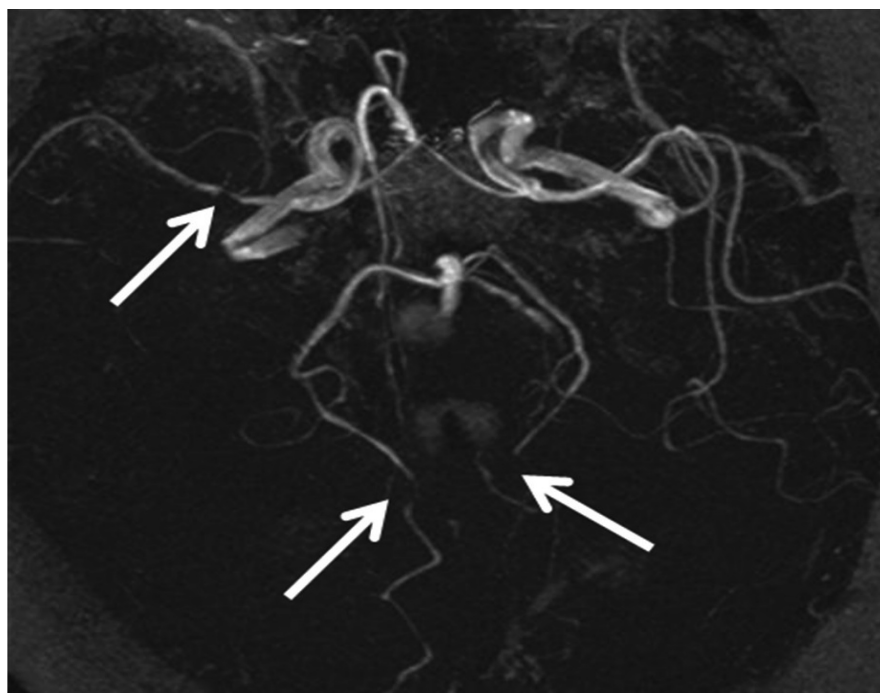


Fig. 2. MRA: Multiple areas of flow decreased calibre are noted in the anterior and posterior circulation, respectively (arrows).

pretation of histological findings is that they do not allow *per se* distinguishing isolated PCNSV from systemic vasculitis with CNS involvement. A variety of infectious agents can also provoke CNS vasculitis resembling PCNSV (9).

The imaging features are no less varied and non-specific, and are discussed in detail in this review (4). At the same time, any guidance that imaging can provide is extremely useful prior to going forward with an invasive diagnostic procedure like digital subtraction angiography or brain biopsy. Advances in magnetic resonance and molecular imaging could make early presumptive diagnosis, at least with enough certainty to begin treatment, a reality in the relatively near future.

Magnetic resonance imaging (MRI)

The negative predictive value of MRI has been reported to be higher than that of angiography. MRI is normal in less than 10% of patients with proven PCNSV (4, 5, 10). Imaging features are driven by the propensity of PCNSV pathophysiology to cause ischemia in a seemingly random distribution of vascular territories. Hence, multiple ischemic signal abnormalities involving grey or white matter can be a diagnostic clue, especially if these lesions are bilateral. Frank infarcts may be found in roughly half of all patients (4). Multifocal deep grey, cortical and subcortical lesions, particularly those that appear in multi-vessel tributaries, signify that PCNSV should be considered alongside the most common epidemiological atherosclerotic vascular diseases. Similarly, the radiologist should also have a heightened suspicion for small-vessel changes of ischaemic demyelination and microinfarcts on T2 and FLAIR sequences (Fig. 1A). Breakdown of small vessels can also lead to chronic petechial haemorrhages, best seen on T2* gradient-echo sequences, a valuable surrogate marker for supporting diagnosis of PCNSV (11).

Unfortunately PCNSV also manifests on MRI in ways seemingly unrelated to small-vessel inflammation and ischemia, which would normally raise suspicion for neoplasms or infection.

Presentation as an irregular mass lesion has been reported and postulated to herald a more aggressive subset of the disease (12, 13). Gadolinium-enhancement of the meninges has been reported in as many as 9% of patients with MRI findings (Fig. 1B) (5). Meningeal enhancement alone is an imaging sign attributed to infection, lymphoproliferative diseases, intracranial hypotension or other inflammatory conditions more often than it is to PCNSV. When seen in conjunction with other features confirming PCNSV diagnosis, it has been associated with concurrent cerebral amyloid angiopathy (14). Enhancement has been postulated to lead to a better overall prognosis (5). Additional non-specific MR findings include multifocal hypointensities on T1-weighted imaging and in acute cases, restricted diffusion on diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) sequences (Figs. 1A, 1B and 2). Recently, black-blood high-resolution *in vivo* MR imaging has been used to further characterise PCNSV lesions and holds promise for further development (15).

Magnetic resonance spectroscopy (MRS) is perhaps best utilised for excluding neoplasm in indeterminate cases of tumefactive lesions. A relatively elevated glutamate/glutamine and lipid peak, along with the absence of significant choline peak elevation, has been theorised to increase the likelihood of an inflammatory process over a neoplastic one (13). A decrease in N-acetylaspartate (NAA), a neuronal integrity marker, has been repeatedly demonstrated in vasculitis (16). An increase in the choline-to-creatine ratio is a feature of cellular breakdown commonly seen in brain SLE (17, 18). These general spectroscopic features of vasculitis can be extrapolated to PCNSV.

Angiography

Magnetic resonance angiography (MRA) is an imaging modality with great potential for simplifying the diagnosis of PCNSV. It is imagined that patients with suspicious neurological symptoms may already be triaged for imaging with magnetic resonance, and the addition of MRA sequences repre-

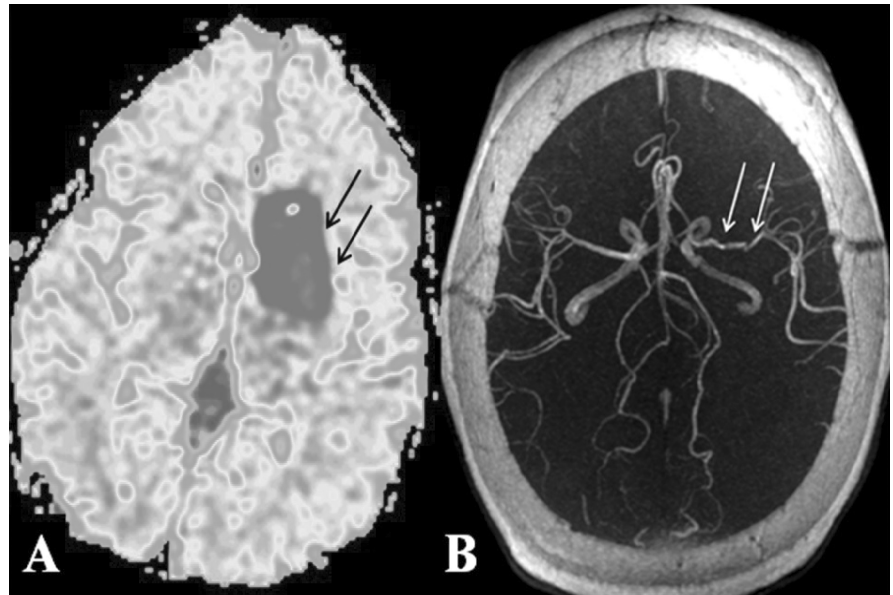


Fig. 3. EADC colour map demonstrates cytotoxic oedema in the basal ganglia (A, arrows). MRA shows focal stenosis in the left middle cerebral artery (B, arrows).

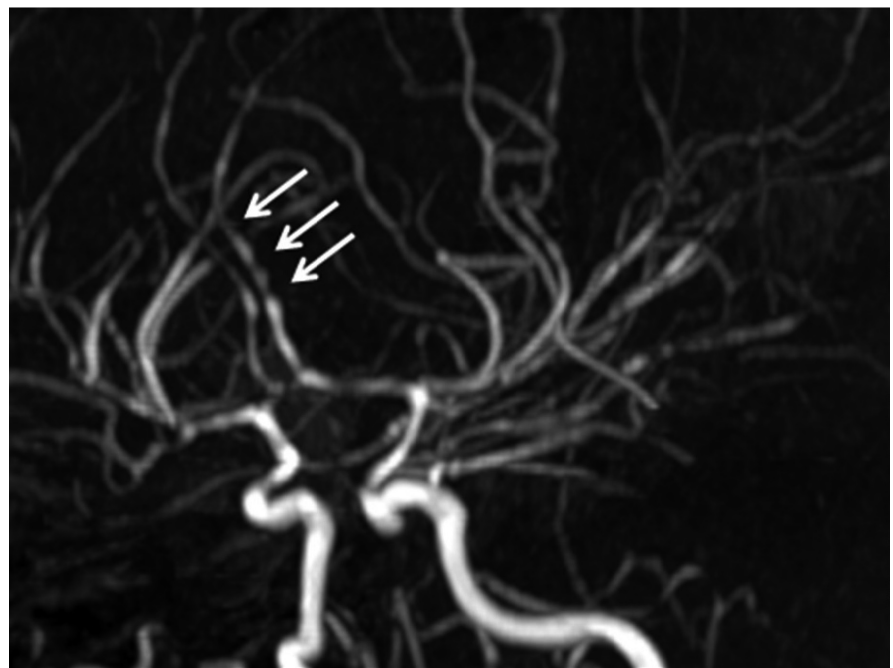


Fig. 4. MRA discloses string-of-beads appearance particularly seen in the anterior circulation (arrows).

sents a relatively low barrier for immediately obtaining further information. While valuable in patients with large- and medium-vessel disease, MRA has only recently become capable of uncovering the finer vascular abnormalities that are more sensitive findings of PCNSV. Classic angiographic findings reflect the intramural vascular inflammation underway in the vessel wall

and lumen. There is diffuse segmental arterial wall narrowing, followed by post-stenotic dilation, an appearance referred to as 'beading' or "string-of-beads" (Fig. 4) (5, 19). As with MRI, multi-vessel and bilateral involvement increases the suspicion for PCNSV. 'Beading' may be smooth or irregular, and although classically involving the small vessels may extend to the larger

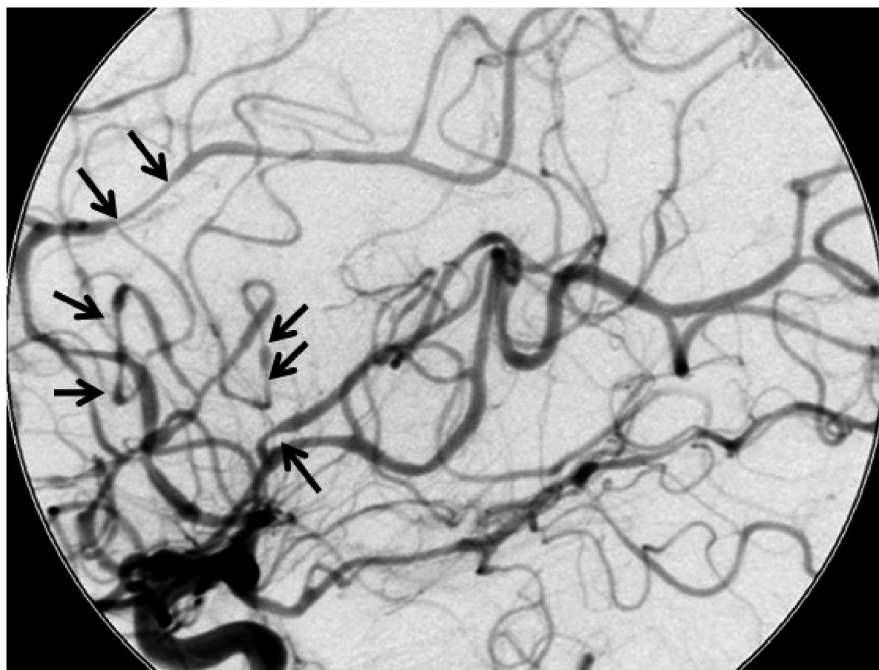


Fig. 5. DSA shows marked vessel irregularity consistent with arterial "beading" typical of PCNSV (arrows).



Fig. 6. DSA shows multiple arterial "beading" in the posterior circulation (arrows).

ones usually affected by atherosclerosis. Angiographic abnormalities do not cluster around sites of vessel bifurcation in PCNSV as they do in the systemic vasculitides (4). The absence of abnormalities in hemodynamically turbulent

areas typically associated with atherosclerotic plaques, such as the carotid siphon and intracranial vessels, can be a clue to the diagnosis of PCNSV. Long segment stenoses, microaneurysms and complete occlusions are relatively

uncommon in PCNSV (20). When the sites of infarct on MRI (Figs. 1 and 2) do correlate with angiographic abnormalities, as shown in Figure 2, this can be further confirmation of PCNSV.

Despite advances in MRA, the spatial resolution (0.2mm) and temporal resolution (0.25s) of digital subtraction angiography (DSA) are currently the best of all imaging techniques in use (21). However, conventional angiography involves invasive cannulation *via* femoral access, and carries with it risks of complication including permanent stroke (0.25%) (22). Imaging findings are congruent to those described for MRA, with additional haemodynamic information and the increased resolution of smaller vessels (16). Figures 5 and 6 show angiograms that are characteristic for PCNSV, with diffuse 'beading' in multiple medium- and small-vessel tributaries. From their study of 92 patients selected for angiography, Harris *et al.*, concluded that the relative utility of negative angiography is minimal after negative MR imaging, as MR excludes the disease more definitively (23). Others have stated that the two modalities convey complementary information and that both are needed for a complete assessment of the disease (24). Case series have been published where angiographic evidence of cerebral vasculitis was found despite no lesions being identified on prior MR images (25). Regardless, as the ability of MRA to detect lesions in smaller vessels improves, and the correlation of these lesions with MRI parenchymal changes is formalised, magnetic resonance is certain to eclipse conventional DSA angiography as the imaging modality of choice.

Less commonly used modalities

MR and conventional angiography are by far the most often used in clinical practice for the imaging diagnosis of suspected PCNSV, but the appearance of the disease in other modalities deserves mention. Ultrasonography has the advantage of having high spatial resolution up to 0.1mm and hemodynamic information conveyed through Colour Doppler, but the adult cranium significantly limits its penetration

through bone (16). It is perhaps most useful in the evaluation of children, particularly if large vessels are involved, as the normalisation of flow velocities can be used to evaluate response to therapy (20). Nuclear medicine studies using fludeoxyglucose (FDG) could theoretically demonstrate hypometabolism from inflammatory changes, as they do in SLE, but such studies are of limited usefulness for PCNSV due to high adjacent uptake in brain parenchyma and the need for involvement of larger vessels greater than 4mm (16, 26). Patchy hypoperfusion seen in SPECT imaging of SLE could similarly be extrapolated to PCNSV, but is not commonly used in practice due to the same reasons (16). CT is notoriously insensitive in picking up the subtle secondary signs of vasculitis-related infarct and ischaemia. Its utility is higher in cases of petechial haemorrhage, which are a small minority of presenting cases. As with MRI, the presence of lesions in a bilateral distribution, involving multiple vascular territories, can be a clue to diagnosis.

A promising new nuclear medicine molecular imaging agent known as (11C)-PK11195 preferentially binds to the peripheral benzodiazepine binding site of activated macrophages. These cells are predominant along the vessel wall in areas of vascular inflammation, and could help illuminate cases in which MRI findings are ambiguous. The agent has been demonstrated to show PET/CT angiography focal uptake allowing for visual analysis of a large-vessel vasculitis (27). Such results could be extended to PCNSV in the near future. The agent has been demonstrated to show abnormal uptake within abnormal brain parenchyma affected by Alzheimer's disease (28).

Conclusions

As detailed above, the role of imaging in the diagnosis of PCNSV is to exclude other items on the differential in order to allow for prompt treatment, even prior to confirming diagnosis with brain biopsy. A secondary goal is to help guide biopsy and to aid sampling of actual lesions. With improvements in MRI/MRA resolution, an eventual aim could be to replace biopsy altogether,

as has already been achieved in vasculitis of basal brain arteries by demonstration of mural thickening (29).

The differential diagnosis for PCNSV is vast, encompassing non-inflammatory vasculopathies, infections, demyelinating syndromes, secondary CNS vasculitis (as part of a primary systemic vasculitis) and malignancy (4). The non-specificity of the clinical, angiographic, radiographic and even histopathological spectrum makes diagnosis a special challenge. As Hellmann *et al.* have suggested, appreciating a constellation of signs and symptoms can help sharpen diagnostic contrast (4). Even with this approach, PCNSV ends up sharing many of the characteristics of reversible vasoconstriction syndrome (RVCS) which is mediated by vasospasm and not vascular inflammation. Exclusion of RVCS must occur prior to starting cytotoxic therapy like cyclophosphamide. Molecular imaging agents, like the one mentioned above, could help differentiate PCNSV not only from RVCS, but also from other entities such as an infection that could significantly worsen under the wrong treatment.

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