The diagnosis of primary central nervous system vasculitis

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ABSTRACT

The diagnosis of primary central nervous system (CNS) vasculitis is often difficult. There are neither specific clinical features nor a classical clinical course, and no blood or imaging investigations that can confirm the diagnosis. Contrast catheter cerebral angiography is neither specific nor sensitive, yet still underpins the diagnosis in many published studies. Here we describe an approach to its diagnosis, emphasising the importance of obtaining tissue, and present for discussion a new, binary set of diagnostic criteria, dividing cases into only 'definite' primary CNS vasculitis, where tissue proof is available, and 'possible,' where it is not. We hope that these criteria will be modified and improved by discussion among experts, and that these (improved) criteria may then be adopted and used as the basis for future prospective studies of the clinical features and diagnosis of this difficult and dangerous disorder, particularly for coordinated multicentre therapeutic trials.

INTRODUCTION

Cerebral vasculitis is a descriptive term rather than a specific disease, referring to inflammation within the wall of central nervous system (CNS) blood vessels associated with destructive changes, occlusion and infarction.[1 2] 'Secondary' CNS vasculitis is where the CNS becomes involved in a systemic vasculitic illness, including but not limited to the systemic vasculitides, such as microscopic polyarteritis, or granulomatosis with polyangiitis (formerly known eponymously as Wegener's granulomatosis; see table 1). Conversely, in 'primary' or 'isolated' vasculitis or angiitis of the CNS (here we will use the term primary CNS vasculitis), there is little or no overt generalised inflammation. All forms of cerebral vasculitis are relatively rare but all are serious and potentially life threatening.

Secondary CNS vasculitis can be a relatively straightforward diagnosis, often clearly suggested by clinically eloquent concurrent or recent disease in more accessible organs: lungs, kidneys, joints and skin. However, when CNS features occur in a patient with a long history of systemic vasculitic illness, the complex question can arise of distinguishing secondary CNS involvement of vasculitis from iatrogenic immunosuppressant-related opportunistic infection.

Diagnosing primary CNS vasculitis is, commonly, far more challenging, for several reasons. Its rarity means that few neurology units have extensive clinical experience of the disorder.[3] There is no diagnostically distinct clinical picture.[4–10] There are no fail-safe indirect diagnostic tests (including formal contrast/digital subtraction angiography; see further). The brain, and even more the spinal cord, is relatively inaccessible and potentially hazardous to biopsy.

But not least among these difficulties of diagnosis is that the criteria on which a clinical diagnosis of primary CNS vasculitis can be made have not been firmly established or uniformly accepted.[9 11] There is no real consensus on defining the disease; criteria for allowing a diagnosis based on angiography (either formal contrast or magnetic resonance (MR)/CT angiography) without histology are very commonly used in published studies and reports.[9 12–20] Other authors do recommend relying on histology.[10 11 20–23] Such variability of patient inclusion criteria naturally renders interpretation difficult and has restricted progress in optimising treatment. We suggest it would be valuable to divide patients into just two diagnostic groups according to the certainty of diagnosis. Here, in addition to refining our previously suggested investigational approach to suspected CNS vasculitis,[6] we propose simple draft diagnostic criteria delineating 'definite' and 'possible' primary CNS vasculitis. We hope that these criteria can be modified by consensus and improved in the future;

Table 1 Conditions associated with CNS vasculitis

Idiopathic/isolated/primary cerebral/CNS vasculitis
Amyloid-β-related angiitis (Eale's disease and Cogan's syndrome*)
Secondary CNS vasculitis
Systemic vasculitides
Granulomatosis with polyangiitis
Churg-Strauss syndrome
Behçet's disease
Microscopic polyarteritis nodosa
Classical polyarteritis nodosa
Small-vessel vasculitis (including Henoch-Schönlein purpura)
Kawasaki disease
Giant cell arteritis
Takayasu's arteritis
Connective tissue diseases
Systemic lupus erythematosus
Antiphospholipid antibody syndrome
Rheumatoid arthritis
Sjögren's syndrome
Dermatomyositis
Systemic sclerosis
Mixed connective tissue disease
Sarcoidosis
Drugs
Cocaine
Amphetamine
Epinephrine/mimics
Infections/immune complexes
Viral
Varicella zoster, HIV
Bacteria
Syphilis, tuberculosis, mycoplasma, rickettsia
Fungi
Aspergillosis, mucormycosis, histoplasma
Coccidioidomycosis, candidosis
Parasites
Cysticercosis, toxoplasma
Secondary cryoglobulins, immune complexes
Hepatitis C, hepatitis B, cytomegalovirus, Epstein-Barr virus, parvovirus B19
Lyme disease, malaria
Malignancy
Hodgkin's and non-Hodgkin lymphomas
Paraneoplasia
Lymphomatoid granulomatosis
Malignant angioendotheliomatosis

*Eales' and Cogan's syndromes are idiopathic disorders characterised histopathologically by vasculitis. Eales' disease mainly involves the retina and Cogan's syndrome involves mainly the eye and the inner ear; both can (uncommonly) involve brain parenchyma. Since the inner ear and the eye may both arguably be considered parts of the nervous system, they could be said to be primary CNS vasculitides, hence their guarded inclusion.
CNS, central nervous system.

they could then act as the foundation for more detailed prospective analyses and hopefully facilitate the design of future therapeutic trials.

CLINICAL FEATURES AND INVESTIGATION

Primary CNS vasculitis has no pathognomic clinical picture. Innumerable neurological features occur, depending on the site of the vasculature affected, with a clinical course that may be acute or subacute, more chronically progressive, or relapsing and remitting.[4 5 9 21 24 25] Headache is common, as are other non-specific or non-focal features, such as encephalopathy, cognitive change and generalised seizures; but focal neurological abnormalities are also common, including hemispheric, brainstem or spinal deficits, movement disorders and optic and other cranial neuropathies. Relatively non-specific systemic features of inflammatory disease, such as fever, night sweats, livedo reticularis and oligoarthropathy, may also be identified if specifically sought.

To aid the initial clinical suspicion and recognition of primary CNS vasculitis, three distinct presentations encompassing this wide diversity of clinical features were previously delineated[6 26]:

► An acute or subacute encephalopathy, commonly presenting as an acute confusional state, progressing to drowsiness and coma.

► A picture that superficially resembles multiple sclerosis (MS) but with atypical features ('MS-plus' or 'pseudo-MS'), a relapsing–remitting course including optic neuropathy and brainstem episodes, but also other features less common in multiple sclerosis, such as seizures, severe and persisting headaches, encephalopathic episodes, or hemispheric stroke-like episodes.

► Intracranial mass lesions with headache, drowsiness, focal signs and often raised intracranial pressure.

Of course, these are also non-specific and may occur in many neurological disorders, but unless there is an immediately obvious alternative explanation, their occurrence should at least mean that primary CNS vasculitis is included in the differential diagnosis.

As with the clinical features, so for investigations: there are no biochemical, immunological or serological or imaging investigations that are diagnostic of primary CNS vasculitis. Non-specific changes are common, for example, a normochromic anaemia and raised plasma viscosity. In a highly informative systematic review of published cases, MR scan of the brain was abnormal in 93% of patients (ie, it can be normal), and cerebrospinal fluid (CSF) was abnormal in 74%. In both cases, the abnormalities again were wholly non-specific.[27] Efforts to develop specific MRI-based approaches for demonstrating cerebral vasculitis continue, including vessel wall imaging,[28] but will require rigorous MR–neuropathological correlation before they can usefully be applied.

Therefore, rather than 'confirming' primary CNS vasculitis, the main role of blood tests, CT scans of the

chest, abdomen and pelvis, CSF examination, and MR scanning is to help exclude alternative inflammatory or autoimmune, infective, malignant or other disorders, not uncommonly identifying clinically occult systemic involvement and accessible targets for tissue biopsy. Ocular examination, including slit-lamp ophthalmoscopy,[29] together with whole-body CT–positron emission tomography scanning, can play a similarly important role.

It might be predicted that a disease of blood vessels is best diagnosed by imaging the affected area's vasculature, and cerebral catheter contrast angiography/ digital subtraction, and CT and/or MR angiography can indeed show abnormalities. There may be segmental (often multifocal) narrowing with areas of localised dilatation or beading; single stenotic areas in multiple vessels are probably more frequent in primary CNS vasculitis than multiple stenotic areas along a single vessel. Formal contrast/digital subtraction angiography continues to be associated with a small but significant risk of stroke and, with improvements in MR resolution, it is decreasingly likely that formal contrast/digital subtraction angiography will add diagnostic information above that provided by MR/CT angiography.

As mentioned previously, many published studies have depended on catheter angiography in their diagnostic confirmation (or exclusion) of primary CNS vasculitis. However, it has been clear since at least the early 1970s that similar, so-called 'vasculitic' changes may alternatively occur in atherosclerotic disease, as a reactive change following subarachnoid haemorrhage, in migraine, trauma, hypertension, infections, radiation vasculopathy and following illicit drug use.[22 30] Later, careful studies using histopathological evidence show catheter angiography to have both sensitivity and specificity of around 25%–35%.[9 25 27 31–34] CT-based or MR angiography, though not well studied with histopathological confirmation, appears even less sensitive.[35–38] A normal angiogram therefore cannot exclude primary CNS vasculitis (figure 1), while a large number of alternative inflammatory, metabolic, malignant or other vasculopathies mimic primary CNS vasculitis on angiography; 'vasculitic' changes, in fact, imply no more than a potential vasculopathy still requiring diagnosis. Reversible cerebral vasoconstriction syndrome can represent a particularly difficult diagnostic alternative, though an extremely careful and authoritative comparative study has valuably highlighted the key clinical and investigational differences.[39] MRI-based vessel wall imaging may also help.[40]

CEREBRAL BIOPSY
Given the lack of alternative methods of achieving a secure diagnosis, it would appear axiomatic that CNS tissue biopsy is required to diagnose primary CNS vasculitis (figure 2). There is, however, a natural reluctance to undertake such an invasive procedure, the
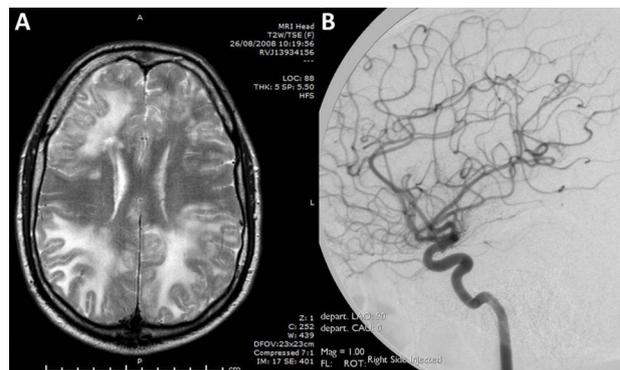

Figure 1 61-year-old man presenting with headache, cognitive decline and neuropsychiatric symptoms, together with episodic disequilibrium. T2 MRI of the brain showed a diffusely abnormal high signal, predominantly in the white matter of the anterior frontal, parietal and temporal lobes (A). Cerebral angiogram (B) was normal, but cerebral biopsy was diagnostic of cerebral vasculitis. T2W, T2 weighted; TSE, turbo spin echo.

more so should a particularly eloquent site be the only target, dominant temporoparietal lesions, for example, or those in the brainstem or spinal cord. In addition to the potential risks is the question of the imperfect sensitivity, those occasions when neuropathological examination shows only 'non-specific change' or 'end-stage tissue damage infarction/gliosis'.

In our view, a number of considerations, combined with a growing body of observational research evidence, very strongly tilt the balance in favour of biopsy.

First, several studies attest to the relative safety of brain biopsy. The qualifier 'relative' is crucial, given the life-threatening nature of the disease in question, of some of the alternative diagnostic possibilities, and indeed of treatments that may be required if CNS vasculitis is present. In one retrospective study of 61 patients biopsied for suspected CNS vasculitis, there were no mortalities and not a single patient suffered any permanent ill effects from the procedure.[31] In our study of 56 brain biopsies in cryptogenic neurological disease, there were no deaths or permanent deficits.[41] A much larger, more general brain biopsy series assessed the safety of stereotactic biopsy in over 7000 procedures: the mortality rate was less than 1% and the morbidity rate was 3.5%, though only few of
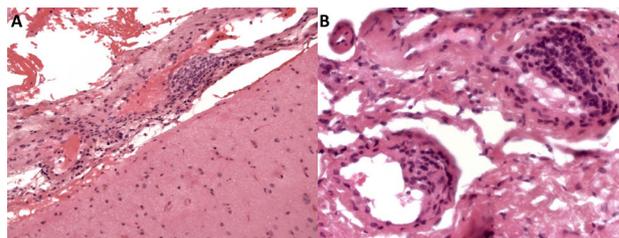

Figure 2 Inflammatory infiltrate in central nervous system vasculitis with extension into the vessel wall (A) and the perivascular lymphocytic cuffing (B).

these had permanent disability.[42] In fact, there is some evidence that the mortality and morbidity in biopsying suspected malignancy are higher than with cryptogenic neurological disease: in a biopsy meta-analysis restricted to 831 cases of cryptogenic neurological disease, procedure-related mortality was zero.[43] It is also becoming clear that even brainstem and spinal cord biopsies are less hazardous than previously thought.[44] Various authorities have presented data indicating that the risks of immunosuppressive treatments are greater than those of biopsy.[13 45]

Second, we now know more of the diagnostic yield and clinical utility of biopsy. The sensitivity is probably in the range of 50%–70%.[9 25 31 41] Perhaps more importantly, some 75% of patients receive a clear diagnosis—of vasculitis or some other specific pathology—following biopsy.[31 41 45] Not uncommonly, the alternative, unsuspected diagnosis to emerge from biopsy is infective—10 out of 61 biopsies in one series[31]—emphasising the importance of not 'assuming' vasculitis and treating with immunosuppressants. A very recent meta-analysis suggested no significant difference between frame-based and frameless biopsy in terms of diagnostic yield, morbidity and mortality.[46]

Finally, as mentioned in the first sentence, cerebral vasculitis is a descriptive term, not a disease, and it has always been anticipated that the term 'primary CNS vasculitis' would comprise a spectrum of specific disorders. These are now slowly being dissected and described.[47–49] Aβ-related angiitis (ABRA) is one such disorder, likely a subtype of cerebral amyloid angiopathy (CAA), wherein intramural amyloid deposits have triggered an antiamyloid inflammatory reaction and so vasculitic change. Clearly, only biopsy can distinguish ABRA from other forms of primary CNS vasculitis (and from CAA-related inflammation, in which perivascular inflammation is apparent in the context of CAA—again perhaps triggered by amyloid deposition—but without vasculitis); similarly, only biopsy can identify the other recognised forms of the condition.[47–49] In addition, though plainly not an argument that should sway the decision in any specific individual case, it is only by looking at tissue that further specific entities will come to be described.

TREATMENT

The treatment of primary CNS vasculitis has no direct clinical trial evidence base, and recommendations have changed little, if at all, in several decades. Cyclophosphamide and corticosteroids remain the core of treatment,[6 10 22 50] the former yielding to less toxic immunosuppressants such as azathioprine or methotrexate after an induction period generally of 10–12 weeks,[51] this approach based principally on evidence from renal and/or rheumatological trials where the diagnosis can be robustly determined either serologically or following tissue biopsy. Mycophenolate mofetil—at least in systemic vasculitis—appears less effective in maintaining remission than azathioprine or methotrexate.[52] There are reports of the potential efficacy of rituximab,[53] but again these are often based on cases lacking histopathological verification and so are open to question.

PROPOSED DIAGNOSTIC CRITERIA FOR PRIMARY CNS VASCULITIS

Neither our understanding of the causes of primary CNS vasculitis, nor approaches to diagnosis, nor treatment recommendations have advanced significantly over the past two or three decades or more, perhaps with the exception of the recognition of distinct pathological subtypes. We continue to have no randomised treatment trials to provide evidence-based treatment—some of the earliest studies of the disease over 30 years ago recommended cyclophosphamide for definite disease—and this remains the treatment of choice, based almost entirely on evidence from studies of vasculitis in other tissues. Primary CNS vasculitis is an uncommon disorder, but progress in relation to many other diseases of comparable rarity has been far greater.

A major contributing factor to this stasis has been the enormous variation in diagnostic approach: perhaps 75% of published cases lack histopathological proof.[54] Given (a) the consistent range of disorders revealed by published biopsy-based studies of cases considered likely cerebral vasculitis, and with this, (b) the commensurate low yield of vasculitis (in one study of brain biopsies performed at one (major) US academic hospital for consideration of CNS vasculitis within an 8-year window, none of the 14 patients with clinical and angiographical features thought to be diagnostic for primary CNS vasculitis had vasculitis on biopsy)[55] combined with (c) the extensive range of non-vasculitic disorders now known to show the angiographical changes of 'vasculitis', it is hard to defend the current accepted practice that cases lacking biopsy proof can still be labelled as definite diagnoses of primary CNS vasculitis in published series and studies.

We therefore propose simple, readily applied binary diagnostic criteria (box 1): 'possible' or 'definite' primary CNS vasculitis. We have no doubt that the details of these criteria can be modified and significantly improved by others who have experience of the disorder, and indeed we hope they will be. But more than this, we hope that the principle of histopathological proof may ultimately be accepted generally.

Vasculitis confined to the CNS was first fully described 60 years ago by Cravioto and Feigin, who delineated the classical histopathological features of the disorder, definitively describing it as a 'diffuse disorder of the central nervous system with some focal accentuation'.[2] However, it was Calabrese and Mallek's landmark study three decades later that provided a lasting account of the clinical features, summarised the

Box 1 Proposed criteria for the diagnosis of central nervous system (CNS) vasculitis

Definite

► *Clinical presentation suggesting CNS vasculitis with exclusion of alternative possible diagnoses and of primary systemic vasculitic syndrome.*
► Plus the presence of positive CNS histology, that is, biopsy or autopsy showing CNS angiitis (granulomatous, lymphocytic or necrotising), including evidence of vessel wall damage.

Possible

► *Clinical presentation compatible with CNS vasculitis with exclusion of alternative possible diagnoses and of primary systemic vasculitic syndrome.*
► Plus laboratory and imaging support for CNS inflammation (elevated levels of cerebrospinal fluid protein and/or cells, and/or the presence of oligoclonal bands and/or MR scan evidence compatible with CNS vasculitis), with angiographic* exclusion of other specific entities.
► But without histological proof of vasculitis.

*Certain disorders, perhaps most particularly moyamoya disease, may require formal contrast angiography for definitive diagnosis.[57,58]

Table 2 Conditions that may show 'vasculitic' changes on contrast angiography

Intracranial atherosclerosis	Subarachnoid haemorrhage
CADASIL	Intracerebral haematoma
Reversible cerebral vasoconstriction syndrome	Migraine
Antiphospholipid syndrome	Sickle cell disease
Fibromuscular dysplasia	Alzheimer's disease
Intravascular lymphoma	Multiple cerebral emboli (eg, SBE)
Herpes zoster arteritis syndromes	Marfans' syndrome, Ehlers-Danlos syndromes
Vasospasm (eg, drug-related)	Severe hypertension
Moyamoya disease and syndrome	Acute trauma
Radiation vasculopathy	

CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; SBE, sub-acute bacterial endocarditis.

angiographical changes and emphasised the recommendation of therapy with high-dose corticosteroids and cytotoxic drugs, specifically cyclophosphamide.[9] They defined the disorder as 'an acquired clinical disease characterised by CNS dysfunction that remains unexplained following thorough clinical, laboratory, and neurological investigations; appears to be unassociated with systemic illness, and yields evidence by cerebral angiography or biopsy of CNS tissue of vasculitis confined to the CNS.' Working from this definition, they also proposed the first diagnostic criteria for primary angiitis of the CNS: (1) a history or clinical finding of an acquired neurological deficit, which remained unexplained after a thorough initial basic evaluation; (2) *either* classic angiographical *or* histopathological features of angiitis within the CNS [our italics]; and (3) no evidence of systemic vasculitis or of any other condition to which the angiographical or pathological features could be secondary.[9] Ongoing series continue to use these criteria, or variations of them, allowing diagnosis to rest on angiography without biopsy.[12 13]

Subsequent studies over the next two decades, however, confirmed that contrast cerebral angiographical changes considered typical and diagnostic of vasculitis were not at all specific to the disorder (table 2). Furthermore, many cases of confirmed primary CNS vasculitis had normal cerebral angiograms. Calabrese himself subsequently confirmed in a direct study that both the diagnostic specificity and

the positive predictive value of cerebral angiography in this context were less than 30%.[34] Therefore, so low is the specificity that patients with 'typical' vasculitic changes can be said not just possibly to have a disorder other than primary CNS vasculitis but also statistically more likely to have an alternative disorder.[11 27 45 55] Consequently, many authors have stressed the importance of tissue biopsy to confirm the diagnosis, and there have been sporadic proposals of diagnostic criteria that require biopsy proof for a definite diagnosis.[4 6 11 20 56] Powers,[11] for example, asserted that 'patients without histological confirmation should not be included in case reports, case series, or reviews'.

Such proposals have, however, been far from universally accepted. In a highly informative 2017 systematic study of diagnostic test results in primary CNS vasculitis,[27] the authors identified 701 published cases. The diagnosis had been confirmed by biopsy in just 248 of these patients (35.4%). In 99 people with vasculitis on biopsy, cerebral angiography was normal. Looking at trends over time, the authors also reported an increasing diagnostic reliance on angiography and decreasing histopathological testing over the past two decades. They too recommended a definite category for diagnosis restricted to those cases where tissue proof confirmation was available. Despite these recommendations, current ongoing studies and even

Key points

► In primary central nervous system (CNS) vasculitis, cerebral angiography without histology is *not* diagnostic.
► CNS biopsy is diagnostically important and relatively safe.
► We propose binary diagnostic criteria, categorising cases as either 'definite' or 'possible', and abandoning any 'probable' category.

nationwide prospective surveys continue to include patients without histological confirmation.[13]

The draft criteria we propose also require tissue proof for a definite categorisation. They are more rigorous than perhaps any used in any published study of the disease, but we believe this is absolutely justified by the range of disorders that mimic primary CNS vasculitis (particularly angiographically). We propose that there is no 'probable' category, given the low specificity of contrast angiography. Rather, we suggest that all suspected cases lacking histological proof should be described as possible and the role of angiography therefore implicitly restricted to excluding other specific disorders (eg, moyamoya disease and fibromuscular dysplasia). These new criteria could be used as the basis for retrospective literature-based studies of the disease and, we hope in particular, for future prospective studies of the clinical features, diagnosis and treatment of this difficult and dangerous disorder.

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