The diagnosis of primary central nervous system vasculitis

Claire M Rice, Neil J Scolding

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 euponymously 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;
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 pathognomonic 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. Headache is common, as are other non-specific 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:

- 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 neuritis 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. Efforts to develop specific MRI-based approaches for demonstrating cerebral vasculitis continue, including vessel wall imaging, 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

### Table 1 Conditions associated with CNS vasculitis

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

**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.

**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 crypto-
genetic 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 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 series31—emphasising the importance of not
‘assuming’ vasculitis and treating with immunosup-
pressants. A very recent meta-analysis suggested no
significant difference between frame-based and frame-
less 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 angiop-
athy (CAA), wherein intramural amyloid deposits have
triggered an amyloid inflammatory reaction and
so vasculitic change. Clearly, only biopsy can distin-
guish ABRA from other forms of primary CNS vascu-
litis (and from CAA-related inflammation, in which
perivascular inflammation is apparent in the context
of CAA—again perhaps triggered by amyloid depo-
sition—but without vasculitis); similarly, only biopsy
can identify the other recognised forms of the condi-
tion.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. Cyclo-
phosphamide and corticosteroids remain the core of
treatment,6 10 22 30 the former yielding to less toxic
immunosuppressants such as azathioprine or metho-
trexate 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 sero-
logically 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 signifi-
cantly 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 consid-
ered 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 signifi-
cantly improved by others who have experience of the
disorder, and indeed we hope they will. But more
than this, we hope that the principle of histopatholog-
ical 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
angiographical changes and emphasised the recommendation of therapy with high-dose corticosteroids and cytotoxic drugs, specifically cyclophosphamide. 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. Ongoing series continue to use these criteria, or variations of them, allowing diagnosis to rest on angiography without biopsy. 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%. 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. 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. Powers, 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, 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

**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.

**Table 2** Conditions that may show ‘vasculitic’ changes on contrast angiography

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diagnosis Proof</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial atherosclerosis</td>
<td>Subarachnoid haemorrhage</td>
</tr>
<tr>
<td>CADASIL</td>
<td>Intracerebral haematomata</td>
</tr>
<tr>
<td>Reversible cerebral vasoconstriction syndrome</td>
<td>Migraine</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td>Sickle cell disease</td>
</tr>
<tr>
<td>Fibromuscular dysplasia</td>
<td>Alzheimer disease</td>
</tr>
<tr>
<td>Intravascular lymphoma</td>
<td>Multiple cerebral emboli (eg, SBE)</td>
</tr>
<tr>
<td>Herpes zoster arteritis syndromes</td>
<td>Marfan’s syndrome, Ehlers-Danlos syndromes</td>
</tr>
<tr>
<td>Vasospasm (eg, drug-related)</td>
<td>Severe hypertension</td>
</tr>
<tr>
<td>Moyamoya disease and syndrome</td>
<td>Acute trauma</td>
</tr>
<tr>
<td>Radiation vasculopathy</td>
<td>CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; SBE, sub-acute bacterial endocarditis</td>
</tr>
</tbody>
</table>

**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.

Correction notice This article has been corrected since it was published Online First. Table 1 has been updated from a two-column format to one column.

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