
CHAPTER 35

Cerebral vasculitis

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Introduction

Cerebral vasculitis is an uncommon disorder that offers unusual problems for the neurologist. It is notoriously difficult to recognize, producing a wide range of possible neurological symptoms and signs with no typical or characteristic features [1–3]. Potential clinical patterns that might facilitate recognition have been proposed [4] but have not been tested prospectively on large numbers of patients, and their value in consequence remains to be substantiated.

Suspicion of the disorder having been entertained, confirmation or exclusion of cerebral vasculitis presents a second serious set of problems. There are no serological or other blood or spinal fluid laboratory tests of any sensitivity or specificity; imaging by computed tomography (CT) or magnetic resonance imaging (MRI) is likewise lacking in sensitivity; angiography is of questionable use [4–10]. Finally, while intuitively this is a disorder most neurologists would regard as eminently treatable, there remains a complete absence of any therapeutic trials to provide an evidence base for this assumption.

This combination of difficulties in recognition and in diagnosis, in a disorder that is serious and indeed not uncommonly fatal, and yet (probably) highly treatable, emphasizes the importance of attempting to address the clinical problem of cerebral vasculitis [11]. It is, however, an uncommon disorder – there are no epidemiological data, but an estimate has been hazarded of an incidence of 1–2 million per year – creating additional difficulties;

even two or three neurological centres collaborating are unlikely to accumulate sufficient numbers of patients within a workable time frame for useful studies.

Methods

The European Federation of Neurological Societies (EFNS) Scientist Panel on Neuroimmunology considered that a European collaborative cohort might offer a powerful means of beginning to address the problems outlined above. A task force on cerebral vasculitis was established to improve the recognition, diagnosis, and management of cerebral vasculitis throughout Europe. This will be achieved by providing guidelines whose confirmation will ultimately depend on the establishment of a sound evidence base. A European-wide survey of current clinical practice was included.

A simple 10-point questionnaire covering various aspects of the diagnosis and management of cerebral vasculitis was sent to 51 expert neurologists in 26 European countries. Replies were received from 29 (57%) experts from 15 countries.

Statements about diagnosis and treatment were discussed among the task force members. Evidence was classified according to the EFNS guidelines [12]. As very few relevant controlled studies exist on the topic, the recommendations given should be regarded as Good Practice Points (GPP) [12], where advice is given on the basis of consensus in our group and available evidence.

Results of survey

The cumulative number of patients given the diagnosis of cerebral vasculitis by the 29 responding expert

neurologists is approximately 140 per year, a mean of 4.8 cases per neurologist per year.

Dependence on cerebral angiography varied widely, but 11 of 29 neurologists (38%) based this diagnosis on angiography in more than 75% of cases; a mean of 50% of patients throughout Europe had been diagnosed as having cerebral vasculitis based on angiography. Only three neurologists depended on cerebral biopsy in 80% or more of cases; conversely 12 of 25 neurologists (48%) based diagnosis on biopsy in more than 20% of cases. Most neurologists committed between 0 and five patients to biopsy per year, a mean of 2.3 biopsies per year. Thirteen of 29 neurologists (45%) only recommended biopsy if there was an identifiable lesion. Of the remainder, most used non-dominant frontal or temporal open biopsy, usually ensuring that parenchymal and meningeal tissue were included.

Eighty per cent of the patients with the diagnosis of cerebral vasculitis received steroids (orally or intravenously) alone as 'first-line treatment', and cyclophosphamide only if steroids failed. Most of the remaining neurologists used cyclophosphamide as first-line therapy. Fourteen used cyclophosphamide as second line treatment, others using azathioprine (three), intravenous immunoglobulin (two), methotrexate (one), and other 'potent immunosuppressive' agents (two). Only four respondents treated patients with potent immunosuppressive agents 'only if biopsy-proven', 84% administering such treatment without tissue confirmation of the diagnosis. All acknowledged the difficulties of assessing the therapeutic response – variably relying on clinical imaging, spinal fluid tests, and blood tests, particularly erythrocyte sedimentation rate (ESR) and C-reactive protein levels.

All 29 neurologists were interested in participating in further collaborative European research.

Conclusions and Discussion

Even European neurologists with particular interest in cerebral vasculitis see only a handful of cases per year. Nevertheless, the cumulative experience of some 140 cases per year emphasizes the potential power of the pooled response. A large prospective study would offer a number of valuable opportunities.

First, an analysis of the clinical features may provide means of improving the recognition of cerebral

Table 35.1 Cerebral vasculitis: suggested clinical patterns of presentation that might facilitate recognition [4].

- Acute or sub-acute encephalopathy, with headache with an acute confusional state, progressing to drowsiness and coma.
- Intracranial mass lesion -with headache, drowsiness, focal signs and (often) raised intracranial pressure.
- Superficially resembling atypical multiple sclerosis (MS-plus) in phenotype -with a relapsing-remitting course, and features such as optic neuropathy and brain stem episodes, but also accompanied by other features less common in multiple sclerosis: seizures, severe and persisting headaches, encephalopathic episodes, or stroke-like episodes.

vasculitis. Three clinical patterns have been previously suggested [4]. First, patients may present with acute, subacute, or recurrent encephalopathy; the second is presentation with features of a focal, space-occupying lesion (a presentation recently re-emphasized and separately analysed [13]). Third, patients may exhibit a clinical picture that in many ways resembles multiple sclerosis – a relapsing, remitting course, often including brainstem episodes and optic neuropathy, and often with multifocal white matter lesions on MRI scanning and oligoclonal bands on cerebrospinal fluid (CSF) analysis (table 35.1), but which usually includes atypical features. However, these patterns were suggested from an analysis of only 10–12 cases, and though reference to retrospective case series suggests the patterns might accommodate virtually all cases of cerebral vasculitis, their true value remains to be proven by large prospective studies. In the past, stroke-like presentation of CNS vasculitis has often been suggested, but a critical analysis suggests this may in fact be extremely uncommon [14]. Whether these or indeed better patterns might usefully aid recognition of cerebral vasculitis cannot be determined on the basis of small studies on pooled retrospective series with the case-selection biases they carry.

The value of a number of laboratory or imaging investigative procedures similarly requires a prospective study. Specifically, the negative predictive power of tests such as a normal ESR, or normal C-reactive protein [4], or normal spinal fluid analysis [4–6], together with the positive predictive power of these tests – or combinations of various test results with particular clinical and/or imaging features – all these also require prospective studies including relatively large numbers of patients.

There was particular variation in relation to the diagnostic weight given to cerebral angiography. In many instances, there was radiological uncertainty concerning the distinction between 'vasculopathy' and 'vasculitis'. Angiography is a test limited in both sensitivity and specificity in the diagnosis of cerebral vasculitis: retrospective series suggest a sensitivity of only 24–33% [5, 6, 8, 15, 16], with a specificity of a similar order – a number of inflammatory, metabolic, malignant, or other vasculopathies can accurately mimic angitis. Reversible cerebral vasoconstriction syndrome has in particular received recent attention [17].

There was a corresponding limited reliance on brain biopsy for diagnosis. Sometimes this was explained by local factors, such as difficulties in access to neurosurgical intervention. This test too is, of course, limited in sensitivity, and necessarily entails some iatrogenic risk [18, 19]. However, a retrospective study of some 61 patients biopsied for suspected cerebral vasculitis has usefully illuminated this topic [16]. No patient suffered any significant morbidity as a result of the procedure. Thirty-six per cent of the patients were confirmed as having cerebral vasculitis, but no less usefully and importantly, 39% biopsies showed an alternative, unsuspected diagnosis – lymphoma (six cases), multiple sclerosis (two cases), or infection (seven cases, including toxoplasmosis, herpes, and also two cases of cerebral abscess). Biopsy failed to yield a clear diagnosis in 25% of patients in this study, though even here, biopsy might arguably not be described as 'non-contributory', at least helping exclude some of the alternative diagnoses mentioned above.

This valuable retrospective study also provided some evidence first that biopsy of normal-appearing tissue was no less likely to yield diagnostic information than biopsy targeted upon discrete lesions [16]. The numbers (20 biopsies of normal appearing tissue, 40 of radiologically apparent lesions) were not very large and again a more substantial prospective study would be useful.

What lessons may be learnt, and does this preliminary and rather informal survey yield any provisional recommendations? First, the results confirm the relative uncommonness of the disorder, while emphasizing the potential strength of a collaborative effort, in which, additionally, there emerged considerable enthusiasm. According to current practice, 140 patients are given this diagnosis annually by the 29 responding neurologists, with perhaps 20–40 of these having biopsy confirmation. Expanding the collaborating neurologist pool – and

several regional specialists have, since this survey, expressed interest in joining – would yet further increase the power of any prospective study of both diagnostic approaches and of therapy.

Second, the wide variation in current clinical practice is of interest. The very limited sensitivity and specificity of cerebral angiography has arguably been under-emphasized in the past; some series of cerebral vasculitis patients have indeed rested wholly on this investigation for diagnosis. There has also perhaps been historically an over-emphasis on the value of steroids. While there have been no prospective placebo-controlled trials of immunosuppressive treatment in cerebral vasculitis, large retrospective series of patients with systemic Wegener's granulomatosis, or with microscopic polyangiitis, provide clear support for their use [20–23]. There is some merit in the argument that the absence of tissue confirmation properly directs neurologists away from prescribing cyclophosphamide and towards steroids, but responding neurologists in this survey indicated that it was not this factor that inhibited their use of potent immunosuppressives; only three of 29 neurologists used cyclophosphamide as part of their first-line therapeutic regimen.

Whether cyclophosphamide is best given by intravenous pulses or continuous oral therapy is not established [21, 24], and this question could of course usefully be incorporated into a large prospective study. Most regimes recommend an induction course of between 10 and 16 g cumulative dose; (retrospective) studies of patients with systemic vasculitis and other inflammatory disorders suggest that bladder carcinoma, perhaps the most notorious and serious toxic effect of cyclophosphamide, may be restricted very largely to patients who have received cumulative dose in excess of 100 g [25].

From a practical perspective, we now feel able to propose the diagnostic approach outlined in figure 35.1, and a pragmatic approach to therapy [26, 27] when a tissue diagnosis of cerebral vasculitis has been confirmed (table 35.2). These represent, in our view, reasonable syntheses emerging from the currently available evidence, but this evidence is not adequate for formal recommendations [11, 12]. We suggest therefore that a further prospective pan-European study of cerebral vasculitis is needed and could carry sufficient power to confirm or improve this management approach; it is also likely to yield valuable insights into the recognition, diagnosis, and treatment of this difficult, unusual, and often very serious neurological disorder.

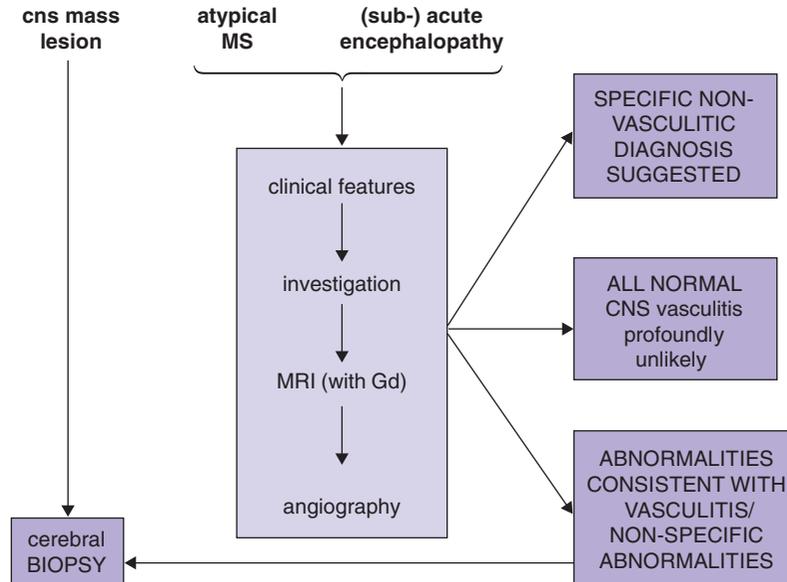


Figure 35.1 A diagnostic approach to suspected cerebral vasculitis

Table 35.2 Cerebral vasculitis: a common treatment regime.

Induction regime (3 months)	Maintenance regime (continued for a further 10 months)
High-dose steroids	Alternate-day steroids 10–20mg prednisolone
Intravenous methyl prednisolone, 1 g/day for 3 days	
Plus	Plus
Oral* cyclophosphamide 2.0 mg/kg [§] (max 200 mg/day)	Azathioprine [§] (2 mg/kg/day) instead of cyclophosphamide
Then	
Oral prednisolone 60 mg/day (after intravenous methyl prednisolone), decreasing at weekly intervals by 10 mg increments to 10 mg/day if possible	

[§]Methotrexate (10–25 mg once weekly) is an alternative to azathioprine.

Conflicts of interest

The authors have reported no conflicts of interest relevant to this manuscript.

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