

## The recognition, diagnosis and management of cerebral vasculitis: a European survey

N. J. Scolding<sup>a</sup>, H. Wilson<sup>b</sup>, R. Hohlfeld<sup>c</sup>, C. Polman<sup>d</sup>, I. Leite<sup>e</sup> and N. Gilhus<sup>f</sup>  
(The EFNS Cerebral Vasculitis Task Force)

<sup>a</sup>Department of Neurology, Institute of Clinical Neurosciences, Frenchay Hospital, University of Bristol, Bristol, UK; <sup>b</sup>National Hospital for Neurology and Neurosurgery, Queen Square, London, UK; <sup>c</sup>Klinikum Grosshadern, Marchionistrasse, Munich, Germany; <sup>d</sup>Free University Hospital, Amsterdam, The Netherlands; <sup>e</sup>Department of Neurology, Hospital Geral Santo Antonio, Porto, Portugal; and <sup>f</sup>Department of Neurology, Haukeland University Hospital, Bergen, Norway

Received 29 January 2002  
Accepted 29 January 2002

We have completed a survey of European neurological practice concerning cerebral vasculitis. Twenty-nine respondents from 15 countries provided information concerning the diagnosis and management. The results confirmed the anticipated low frequency of the disease, but also illustrated the power of any putative collaborative effort. Interestingly, there was a wide variation in clinical practice, in particular concerning the perceived importance of cerebral angiography as a diagnostic test and the very common use of steroids as first-line treatment, rather than more potent immunosuppressive agents. This variation is probably to be explained at least, in part, by the absence of any firm evidence base to inform clinical practice. A European collaborative effort – in which there has emerged considerable interest – offers a realistic opportunity to generate sound clinical evidence and thence scientifically robust practical guidelines.

### Introduction

#### The nature of the problem

Cerebral vasculitis is an uncommon disorder that offers unusual if not unique problems for the neurologist. It is notoriously difficult to recognize, producing a very wide range of possible neurological symptoms and signs and no typical or characteristic features (Moore and Fauci, 1981; Moore, 1998; Scolding, 1999). Potential clinical patterns that might facilitate recognition have been proposed (Table 1; Scolding *et al.*, 1997), but are yet to be 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 – and in some cases, quite insurmountable – set of problems. There are no serological or other blood or spinal fluid laboratory tests of any sensitivity or specificity; imaging by computed tomography or magnetic resonance imaging (MRI) is likewise wholly lacking in sensitivity; angiography is of questionable use (Calabrese and Mallek, 1988; Hankey,

1991; Greenan *et al.*, 1992; Vollmer *et al.*, 1993; Alhalabi and Moore, 1994; Stone *et al.*, 1994; Scolding *et al.*, 1997). Finally, whilst intuitively this is a disorder most neurologists would regard as eminently treatable, there are no therapeutic trials to provide an evidence base for this assumption.

This perhaps unique combination of difficulties in recognition and in diagnosis, in a disorder which 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. 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.

#### Aim of the EFNS Cerebral Vasculitis Task Force

The 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. The long-term aim of this Task Force is to improve the recognition, diagnosis and management of cerebral vasculitis throughout Europe. This will be achieved by providing guidelines which in

Correspondence: N. J. Scolding, Department of Neurology, University of Bristol, Institute of Clinical Neurosciences, Frenchay Hospital, Bristol BS16 1LE, UK (e-mail: N.J.Scolding@bristol.ac.uk).

**Table 1** Cerebral vasculitis: suggested clinical patterns of presentation which might facilitate recognition (adapted from Scolding *et al.*, 1997)

Acute or subacute encephalopathy with headache and 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 hemispheric stroke-like episodes

turn will depend on the establishment of a sound evidence base.

The first phase of this project has now been completed – a European-wide survey of current clinical practice.

### Cerebral vasculitis and European neurologists

A simple 10-point questionnaire was sent to each national representative covering various aspects of the diagnosis and management of cerebral vasculitis. Additionally, each representative was asked to name one (or more) neurologists within his or her own country who were particularly interested in, and had subspeciality expertise in cerebral vasculitis. The same 10-point questionnaire was then sent to these individuals.

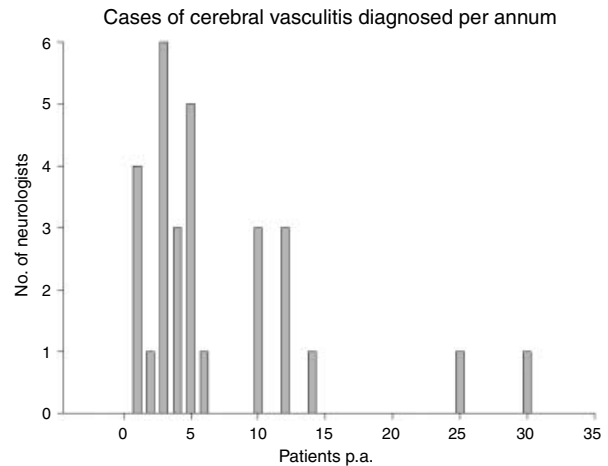
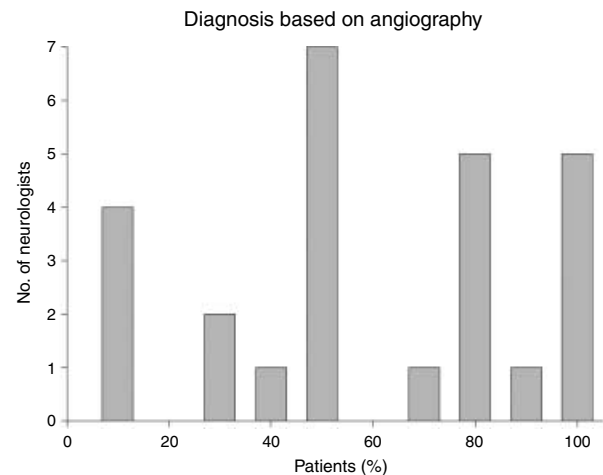
### Results

Ultimately, 51 questionnaires were despatched to neurologists in 26 countries. Replies were received from 29 (57%) from 15 countries and these formed the basis of the current survey.

Figure 1 shows the number of patients diagnosed as having cerebral vasculitis by the 29 responding neurologists (Q1). Some gave a range (e.g. 3–5); taking even the lowest in the range, the cumulative number of patients given this diagnosis amongst these neurologists is approximately 140 per year, a mean of 4.8 cases per neurologist per year.

Questions 2–6 concerned the approach to diagnosis. Figure 2 shows the proportion of patients in whom the diagnosis of cerebral vasculitis was 'based on' cerebral angiography (Q2). Dependence on this investigation varied widely, but 11/29 neurologists (~38%) based this diagnosis on angiography in over 75% cases; a mean of 50% patients throughout Europe had been diagnosed as having cerebral vasculitis based on angiography.

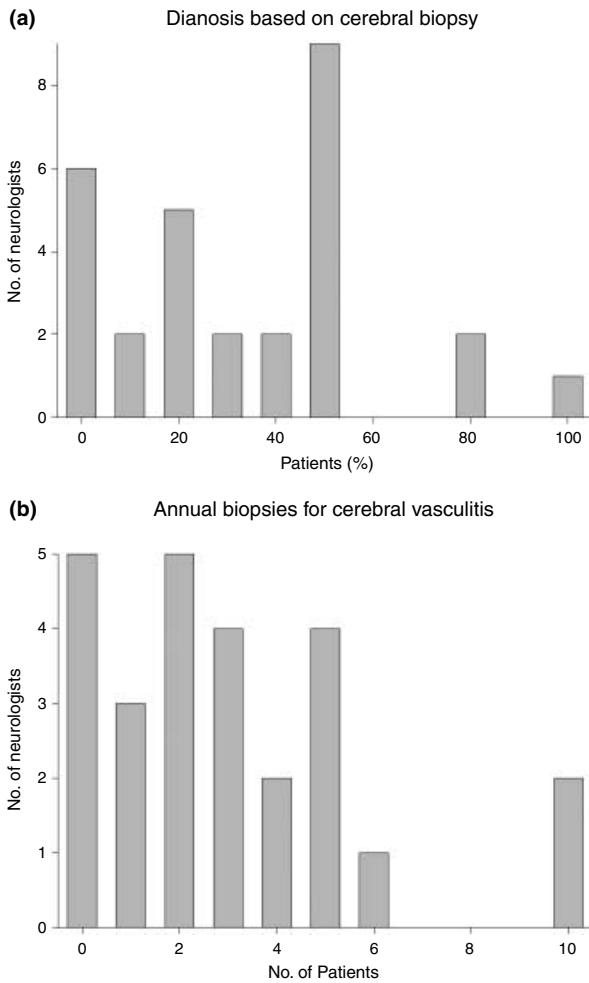
There was less variance in the use of cerebral biopsy as a basis for diagnosis (Q3). As shown in Fig. 3(a),

**Figure 1** Number of patients diagnosed per annum as having cerebral vasculitis.**Figure 2** Proportion of patients with a diagnosis based on cerebral angiography.

only three neurologists depended on biopsy in 80% or more of cases; conversely 12/25 neurologists (48%) based diagnosis on biopsy in no more than 20% of cases. Most neurologists committed between zero and five patients to biopsy per annum [Fig. 3(b); Q4], a mean of 2.3 biopsies per year (and a total of 68 per year amongst all the responding neurologists).

Questions 5 and 6 concerned mode of biopsy. Forty-five per cent (13/29) of neurologists only recommended biopsy if there was an identifiable lesion (Q5). Of the remainder, most used non-dominant frontal or temporal lobe open biopsy, usually ensuring that parenchymal and meningeal tissue were included (Q6).

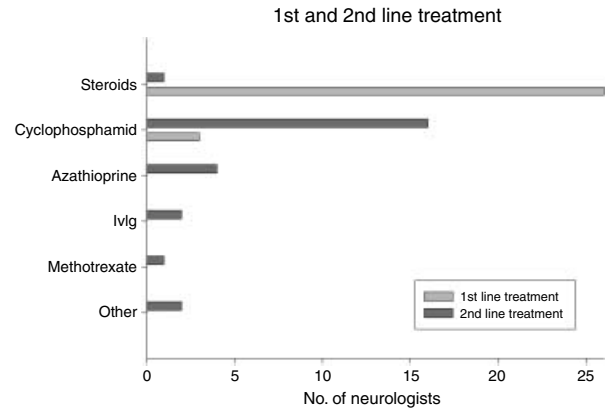
Questions 7–9 concerned treatment. As Fig. 4 shows, 80% patients received steroids (orally or intravenously)



**Figure 3** (a) Proportion of patients with a diagnosis based on cerebral biopsy. (b) Number of biopsies per year undertaken in patients with suspected cerebral vasculitis.

alone as 'first-line treatment', cyclophosphamide only if steroids failed. Most (2/25) of the remaining neurologists used cyclophosphamide as first-line therapy (Q7). 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' (Q8), 84% administering such treatment without tissue confirmation of the diagnosis.

All acknowledged the difficulties of assessing the therapeutic response (Q9) – variably relying on clinical imaging, spinal fluid and/or blood tests, particularly ESR and C-reactive protein levels. Finally (Q10), all 29 were interested (24 definitely, five probably) in participating in further collaborative European research.



**Figure 4** Therapeutic choices used in treating patients with cerebral vasculitis.

## Conclusions and discussion

We have completed a survey looking into clinical practice in relation to cerebral vasculitis in 26 European countries. A number of findings of interest emerged.

European neurologists – and those responding were self, or peer-selected as having a particular interest in the disorder – 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 vasculitis. Three clinical patterns have been previously suggested (Table 1; Scolding *et al.*, 1997). First, patients may present with acute, subacute or recurrent encephalopathy; the second is presentation with features of a focal, space-occupying lesion. Thirdly, patients may exhibit a clinical picture which in many ways resembles multiple sclerosis – a relapsing, remitting course, often including brain stem episodes and/or optic neuropathy, and often with multifocal white matter lesions on MRI scanning and oligoclonal bands on CSF analysis. 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. 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 prospective study. Specifically, the negative predictive power of

tests such as a normal ESR, or normal C-reactive protein (Scolding *et al.*, 1997), or normal spinal fluid analysis (Calabrese and Mallek, 1988; Hankey, 1991; Scolding *et al.*, 1997), together with the positive predictive power of these tests – or, more possibly, of combinations of various test results with particular clinical and/or imaging features – also require prospective study 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 suggests a sensitivity of only 24–33% (Calabrese and Mallek, 1988; Koo and Massey, 1988; Hankey, 1991; Vollmer *et al.*, 1993; Alrawi *et al.*, 1999), with a specificity of a similar order – an enormous number of inflammatory, metabolic, malignant or other vasculopathies can accurately mimic angiitis.

There was a corresponding limited reliance on biopsy for diagnosis. In a few instances 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 (Barza and Pauker, 1980; Chu *et al.*, 1998). However, a recent retrospective study of some 61 patients biopsied for suspected cerebral vasculitis has usefully illuminated this topic (Alrawi *et al.*, 1999). No patients suffered any significant morbidity as a result of the procedure. Thirty-six per cent of 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 decreasing the likelihood of the alternative diagnoses mentioned above.

This valuable retrospective study also provided some evidence first that biopsy of normal-appearing tissue was no less probably to yield diagnostic information than biopsy targeted upon discrete lesions (Alrawi *et al.*, 1999). 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, but emphasize 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.

Second, the wide variation in current clinical practice is perhaps a matter for concern. 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 upon this investigation for diagnosis. There has also perhaps been historically an over-emphasis on the value of steroids. Whilst there have been no prospective placebo-controlled trials of immunosuppressive treatment in cerebral vasculitis (or indeed in the systemic vasculitides), large retrospective series of patients with systemic Wegener’s granulomatosis, or with microscopic polyangiitis provide clear support for their use (Hoffman *et al.*, 1990, 1992; Adu *et al.*, 1997; Scolding, 2000). 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 which inhibited their use of potent immunosuppressives; only 3/29 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 (Cupps, 1990; Adu *et al.*, 1997) 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 (Talar *et al.*, 1996).

We suggest that a pan-European prospective study of cerebral vasculitis is likely to have sufficient power to yield valuable insights into the recognition, diagnosis and treatment of this difficult, unusual and often very serious neurological disorder.

## Conclusions and recommendations

- Twenty-nine responding European neurologists collectively make a diagnosis of cerebral vasculitis in 140 patients per annum.

- In between 20 and 40 of these patients, the diagnosis has been based on biopsy.
- There is a great variation in clinical practice, particularly relating to the role of angiography, the role of biopsy and drug treatment.
- A pan-European prospective study would offer powerful means of establishing an evidence base to inform clinical practice.

## References

- Adu D, Pall A, Luqmani RA *et al.* (1997). Controlled trial of pulse versus continuous prednisolone and cyclophosphamide in the treatment of systemic vasculitis. *QJM* **90**:401–409.
- Alhalabi M, Moore PM (1994). Serial angiography in isolated angiitis of the central nervous system. *Neurology* **44**:1221–1226.
- Alrawi A, Trobe J, Blaivas M, Musch DC (1999). Brain biopsy in primary angiitis of the central nervous system. *Neurology* **53**:858–860.
- Barza M, Pauker SG (1980). The decision to biopsy, treat, or wait in suspected herpes encephalitis. *Ann Intern Med* **92**:641–649.
- Calabrese LH, Mallek JA (1988). Primary angiitis of the central nervous system. Report of 8 new cases, review of the literature, and proposal for diagnostic criteria. *Medicine* **67**:20–39.
- Chu CT, Gray L, Goldstein LB, Hulette CM (1998). Diagnosis of intracranial vasculitis: a multi-disciplinary approach. *J Neuropathol Exp Neurol* **57**:30–38.
- Cupps TR (1990). Cyclophosphamide: to pulse or not to pulse? *Am J Med* **89**:399–402.
- Greenan TJ, Grossman RI, Goldberg HI (1992). Cerebral vasculitis: MR imaging and angiographic correlation. *Radiology* **182**:65–72.
- Hankey G (1991). Isolated angiitis/angiopathy of the CNS. Prospective diagnostic and therapeutic experience. *Cerebrovasc Dis* **1**:2–15.
- Hoffman GS, Kerr GS, Leavitt RY *et al.* (1992). Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* **116**:488–498.
- Hoffman GS, Leavitt RY, Fleisher TA, Minor JR, Fauci AS (1990). Treatment of Wegener's granulomatosis with intermittent high-dose intravenous cyclophosphamide. *Am J Med* **89**:403–410.
- Koo EH, Massey EW (1988). Granulomatous angiitis of the central nervous system: Protean manifestations and response to treatment. *J Neurol Neurosurg Psychiatry* **51**:1126–1133.
- Moore PM (1998). Central nervous system vasculitis. *Curr Opin Neurol* **11**:241–246.
- Moore PM, Fauci AS (1981). Neurologic manifestations of systemic vasculitis. A retrospective and prospective study of the clinicopathologic features and responses to therapy in 25 patients. *Am J Med* **71**:517–524.
- Scolding NJ (1999). Cerebral vasculitis. In: Scolding NJ, ed. *Immunological and Inflammatory Diseases of the Central Nervous System*. Butterworth-Heinemann, Oxford, pp. 210–258.
- Scolding NJ (2000). Systemic inflammatory diseases and the nervous system. In: Scolding NJ, ed. *New Treatments in Neurology*. Butterworth-Heinemann, Oxford, pp. 187–215.
- Scolding NJ, Jayne DR, Zajicek JP, Meyer PAR, Wraight EP, Lockwood CM (1997). The syndrome of cerebral vasculitis: recognition, diagnosis and management. *QJM* **90**:61–73.
- Stone JH, Pomper MG, Roubenoff R, Miller TJ, Hellmann DB (1994). Sensitivities of noninvasive tests for central nervous system vasculitis: a comparison of lumbar puncture, computed tomography, and magnetic resonance imaging. *J Rheumatol* **21**:1277–1282.
- Talar WC, Hijazi YM, Walther MM *et al.* (1996). Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. *Ann Intern Med* **124**:477–484.
- Vollmer TL, Guarnaccia J, Harrington W, Pacia SV, Petroff OAC (1993). Idiopathic granulomatous angiitis of the central nervous system: diagnostic challenges. *Arch Neurol* **50**:925–930.