

Cerebral vasculitis—recognition, diagnosis and management

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Summary

Cerebral vasculitis is a serious but uncommon condition which presents considerable difficulties in recognition, diagnosis and treatment. We studied eight consecutive patients in whom this diagnosis was made. Despite the great diversity of symptoms and signs, we noted three clinical patterns: (i) acute or sub-acute encephalopathy, (ii) a picture with some similarities to multiple sclerosis ('MS-plus'), and (iii) features of a rapidly progressive space-occupying lesion. The identification of these patterns may help recognition of cerebral vasculitis. The diagnostic value of four investigative procedures not

previously studied in cerebral vasculitis was assessed: ophthalmological examination using low-dose fluorescein angiography with slit-lamp video microscopy of the anterior segment (abnormal in 4/5 patients); spinal fluid oligoclonal band analysis (abnormal in 3/6 patients); anti-neutrophil cytoplasmic antibody assay (abnormal in 3/8 patients); and indium-labelled white-cell cerebral imaging (positive in only one patient). Treatment was with steroid alone ($n=2$) or steroid with cyclophosphamide ($n=6$). Seven patients responded clinically.

Introduction

The vasculitides are a heterogeneous group of disorders which share certain pathological features, in particular intramural inflammation and leukocytoclastic changes within the walls of blood vessels. They may be classified according to additional histological characteristics, including the size of vessel involved and the presence of granulomata, or according to the clinical context. Primary vasculitic disorders include Wegener's granulomatosis, microscopic polyangiitis, and temporal arteritis; alternatively, vasculitis can be secondary to collagen vascular or rheumatological disorders, malignancy (particularly myeloproliferative disease), drugs, or infections such as hepatitis B.

Involvement of the central or peripheral nervous system can occur in any of the systemic vasculitides.^{1,2} Additionally, primary or isolated vasculitis of the CNS or of the PNS is recognized, where little or no inflammation is apparent outside the nervous system.^{3–5} In both isolated and secondary CNS vascu-

litis, the neurological features arising from inflammation and necrosis of the vasculature are similar, and represent principally the consequences of infarction. Cerebral vasculitis might therefore be considered a syndrome, of diverse aetiologies but a (largely) common cerebral pathological process. The manifestations may be devastating and permanent, but CNS vasculitis remains under-recognized and notoriously difficult to diagnose, further accentuating the clinical problem.

In recent years, there have been a number of significant advances in the diagnostic approach to multisystem vasculitis. Specifically, testing for anti-nuclear cytoplasmic antibodies, indium-labelled white-cell scanning, and ophthalmological examination of ocular vessels have all been shown to offer substantial diagnostic contributions.^{6–8} Novel immunological therapies have also been described, and there has been a significant improvement in the prognosis of systemic vasculitic disorders.^{7,9–12} It is

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therefore timely to re-examine vasculitic disease of the nervous system in the light of these recent advances, and to investigate whether they present new opportunities for improving the diagnosis, treatment and outlook of these difficult and challenging disorders.

As part of a structured clinical collaboration investigating vasculitis and the nervous system, we present an analysis of eight patients with the syndrome of cerebral vasculitis. We have included a spectrum of aetiologies, ranging from primary CNS vasculitis to intracranial vasculitis secondary to rheumatoid disease or lymphoma. This represents an attempt to address the practical diagnostic difficulties posed by the patient with suspected CNS vasculitis—where a history of rheumatoid arthritis (for example) might increase suspicion of cerebral vasculitis, but also (with an associated history of immune suppressant treatment) raise other diagnostic possibilities, increasing the importance of diagnostic accuracy. We have attempted to analyse clinical patterns of disease, to facilitate recognition of the disorder, and have assessed the diagnostic value of four clinical or investigational procedures not previously assessed in cerebral vasculitis: ophthalmological examination using low-dose fluorescein angiography with slit-lamp video microscopy of the anterior segment; spinal fluid oligoclonal band analysis; anti-neutrophil cytoplasmic antibody assay; and indium-labelled white-cell cerebral imaging. We have also assessed the therapeutic implications of the response of our patients to immune suppressive treatments.

Methods

Patients

Eight patients in whom a diagnosis of cerebral vasculitis had been made were studied. Six were studied prospectively from the time the diagnosis was first considered, and their previous courses retrospectively examined; the admission records of the remaining two were reviewed retrospectively.

Anti-neutrophil cytoplasmic antibody (ANCA) assay

All ANCA assays were performed in the same laboratory as previously described.¹³ Briefly, sera were tested by indirect immunofluorescence on alcohol-fixed normal human neutrophils, by acid-extract ELISA, and by proteinase 3 and myeloperoxidase ELISAs.

Radioisotope-labelled white-blood-cell scan

Autologous leucocytes were separated by differential centrifugation and labelled using 16 MBq ¹¹¹indium

tropolonate as previously described.^{8,14} Whole-body scans were performed at 3 h and 20–24 h after intravenous injection of labelled leucocytes, to obtain early and late images; local images of the brain were also obtained.

Cerebral perfusion scans by emission tomography (SPECT)

These were performed after injection of 500 mBq ^{99m}Tc-HMPAO in a quiet room with subdued lighting.

Medical ophthalmological assessment

Patients were examined using conventional slit-lamp microscopy and fundus fluorescein angiography to study both anterior and posterior ocular circulations, supplemented by video slit-lamp microscopy recording of erythrocyte flow¹⁵ and low-dose anterior segment fluorescein angiography, both as previously described.¹⁶

Results

Illustrative case histories

Patient 1, PT

This previously-well 28-year-old female became depressed one week after the uncomplicated delivery of her second child. She developed headaches, early morning vomiting, and became drowsy. A CT brain scan in her local hospital showed a non-enhancing left thalamic lesion with some space occupation (Figure 1a), felt most likely to be a glioma. She was transferred to the regional neurosurgery unit where no focal neurological signs were apparent on admission. A CT-guided stereotactic biopsy was performed. She recovered well from surgery, but two days later suffered a cardio-respiratory arrest; prompt resuscitation successfully re-established a normal cardiac output, but she did not recover consciousness and required continued mechanical ventilation. She remained deeply comatose, unresponsive to pain, with fixed gaze deviation to the right and bilateral decorticate rigidity.

The biopsy showed clear necrotizing leukocytoclastic vasculitis, with an infiltrate predominantly of neutrophils and no granuloma formation (Figure 2). Her ESR was 60 (5 days after surgery), C-reactive protein (CRP) 49; anti-nuclear factor, rheumatoid factor, hepatitis B, cryoglobulins, serum angiotensin-converting enzyme and ANCA assay were normal or negative. Her CSF contained no cells, protein 0.3 g/dl, normal glucose, and no evidence of oligoclonal immunoglobulin bands. MRI (Figure 1b–e) showed multiple T2-weighted high-signal-intensity lesions in the periventricular areas, with larger areas in the left

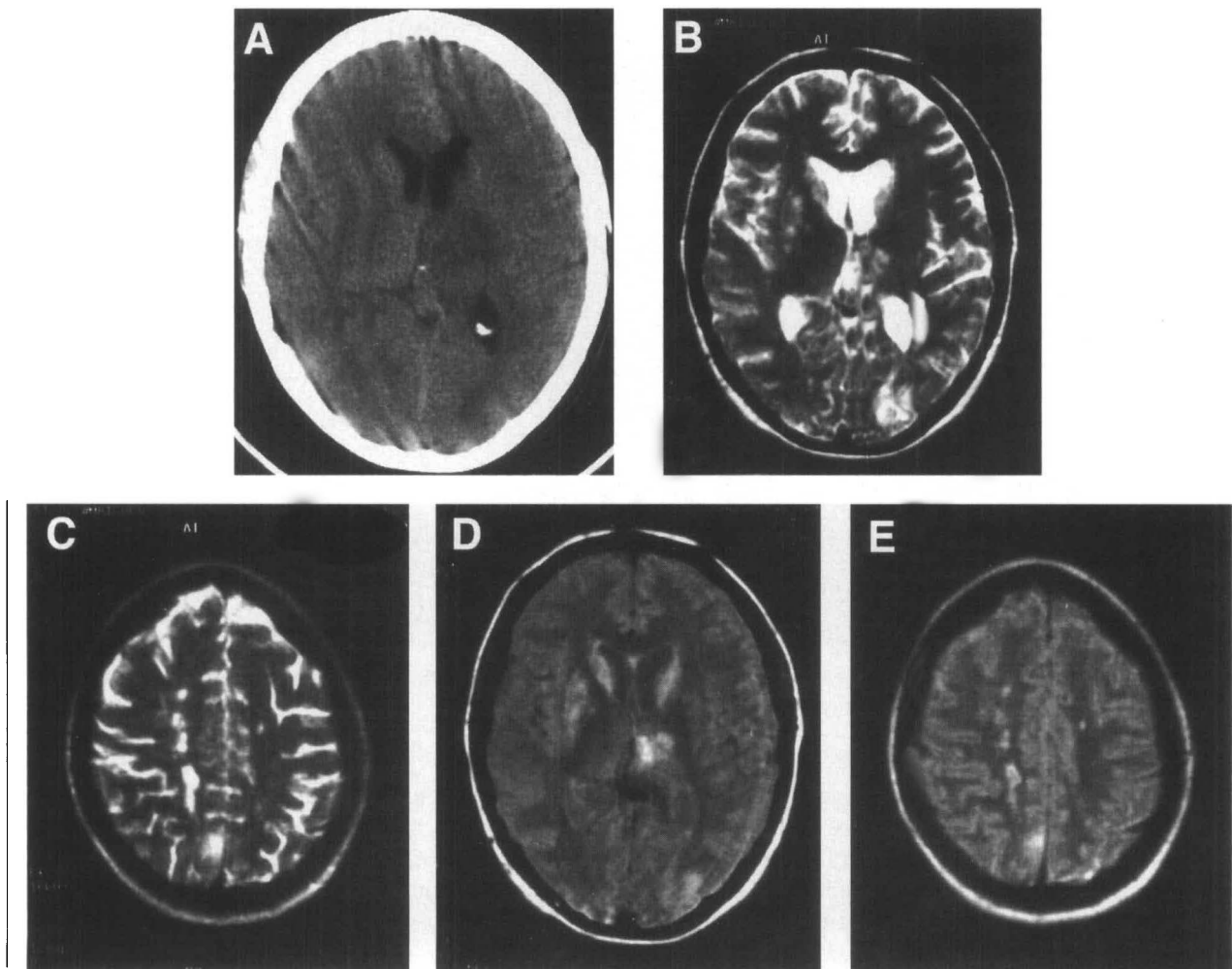


Figure 1. Cerebral imaging, patient 1. **a** CT brain scan. A non-enhancing lesion is shown in the left thalamus, exhibiting slight mass effect. MRI (**b–e**) showed multiple T2-weighted high-signal-intensity lesions in the periventricular areas, with larger areas in the left thalamus, the heads of both caudate nuclei, and the left occipital cortex. Some lesions showed high signal on T1-weighted images (**d,e**), suggesting a haemorrhagic element to focal ischaemic areas.

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She was treated with intravenous cyclophosphamide, 2 mg/kg/day, commencing 6 days after biopsy, and intravenous methylprednisolone, 500 mg daily for 5 days, then 60 mg prednisolone orally per day. She remained comatose for 9 days, but thereafter steadily recovered, breathing independently 16 days after starting treatment, at which stage she had a right hemiparesis with bilateral extensor plantar responses. Her improvement continued and she was discharged home 4 weeks later. When examined at 6 months, she was asymptomatic, with no residual neurological signs on a tapering dose of cyclophosphamide and prednisolone.

Patient 2, JM

This 61-year-old retired, previously-well female presented with 2 weeks of increasing confusion and

forgetfulness, and suffered two generalized tonic-clonic convulsions. No abnormalities were apparent on general physical examination. She was disorientated, with poor and fluctuating registration, immediate recall, and episodic memory. She exhibited choreiform movements of the limbs, predominantly distal and symmetrical, together with facial grimacing, but no other focal neurological signs. Psychiatric assessment suggested periodical hallucinations without delusions, paranoid features, occasional Ganserian responses, and *crocydidmos*.

Investigations included normal blood count and film, ESR, CRP, liver function, urea and electrolytes and thyroid function, and negative rheumatoid factor, anti-nuclear factor and thyroid antibody. A CT head scan showed only minimal atrophic changes, while MR scanning was marred by gross movement artefact. CSF: normal protein and glucose, no organisms seen or cultured, 4 neutrophils and 2 lymphocytes were present (per μ l). ANCA serology was positive at 22% on RIA, with competitive inhibition

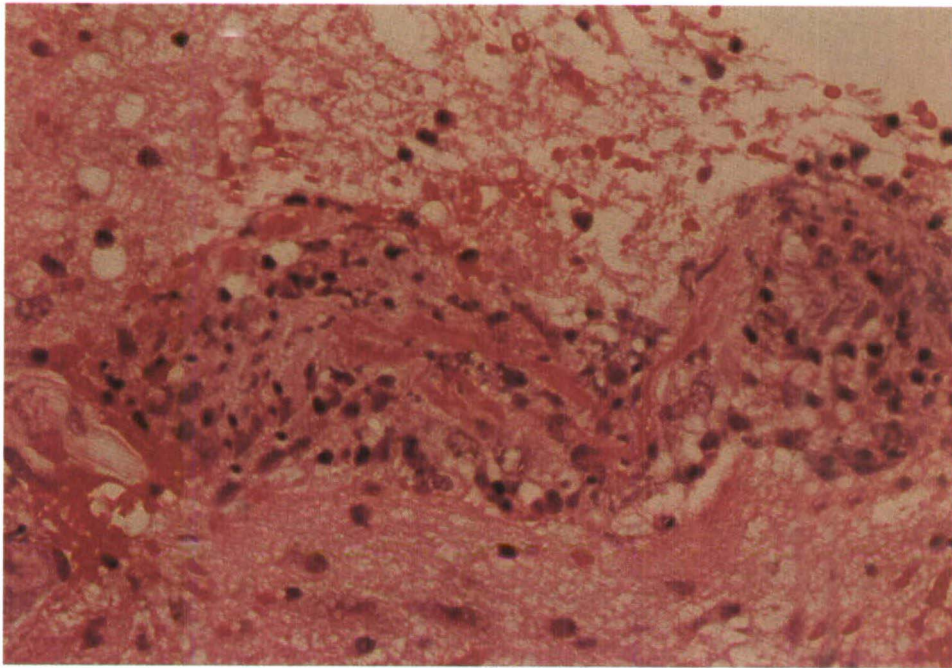


Figure 2. Cerebral biopsy, patient 1. Clear changes of necrotising leukocytoclastic vasculitis are present, with an intense cellular infiltrate composed predominantly of neutrophils.

revealing specific antibody. Indium-labelled white-cell scan showed patchy uptake in both cerebral hemispheres, more marked in the left (Figure 3), with additional more marked uptake in the lungs. Cerebral perfusion SPECT scanning showed an isolated area of reduced perfusion in the left parietal region. Bilateral carotid contrast arteriography showed variation in arterial calibre on both sides, particularly affecting the distal vessels.

A diagnosis of isolated cerebral vasculitis was made and she was treated with oral prednisolone (60 mg daily). She made a good if slow recovery, ANCA serology becoming negative within 6 weeks, but was re-admitted 2 months later (on 30 mg prednisolone daily) with recurring confusion, albeit less severe. She was treated with 150 mg daily of oral cyclophosphamide, and again recovered well. When seen 3 years later (6 months after changing cyclophosphamide to azathioprine) she was well, with no chorea, neurological signs or psychiatric abnormalities, although cognitive assessment revealed mild residual deficits of frontal and memory functions.

Patient 3, MF

This previously-well female had episodes of right-sided twitching starting in 1988 when aged 44. From 1990, she felt her memory steadily deteriorated. In early 1992 she developed nocturnal convulsions, and in March 1993, she had a short episode of status epilepticus. CT head scan (normal in 1988) showed a low-density area in the left temporal area. In July

1993, she developed acute visual loss in her left eye accompanied by headache. Visual acuity was reduced to 6/60, with an afferent pupillary defect and a pale optic disc. She had bilateral Babinski responses but no other neurological signs. ESR and temporal artery biopsy were normal. Other serological tests, CRP, coagulation screen, cardiolipin antibody, echocardiography, ACE, and ANCA tests were normal. Her headache, but not her vision, improved with 80 mg prednisolone daily.

Four months later she was re-admitted in coma. Her consciousness level fluctuated over the next 3 days but then improved and stabilized; at this stage, she was amnesic, with reduced registration. She had a pout reflex, an exaggerated jaw jerk, a right spastic paretic arm (MRC grade 4) with hyper-reflexia, bilateral flexor plantar responses and a non-specifically unsteady gait. Re-investigation revealed an ESR of 29 (repeated at 30), with a CRP of 68. CSF was acellular, but contained oligoclonal immunoglobulin bands: identical serum bands were present. CT head scan now showed non-enhancing low attenuation areas in the left frontal and both occipital lobes, and perfusion HMPAO SPECT scanning showed multiple focal ischaemic defects, affecting the left posterior parietal region, the left fronto-parietal, and the right temporal areas (Figure 4). Bilateral carotid angiography was normal. An open cerebral biopsy of the left frontal lobe (abnormal on CT), which included meninges, white matter and cortex, showed multiple small ischaemic areas, with nerve cell loss, myelin pallor, some

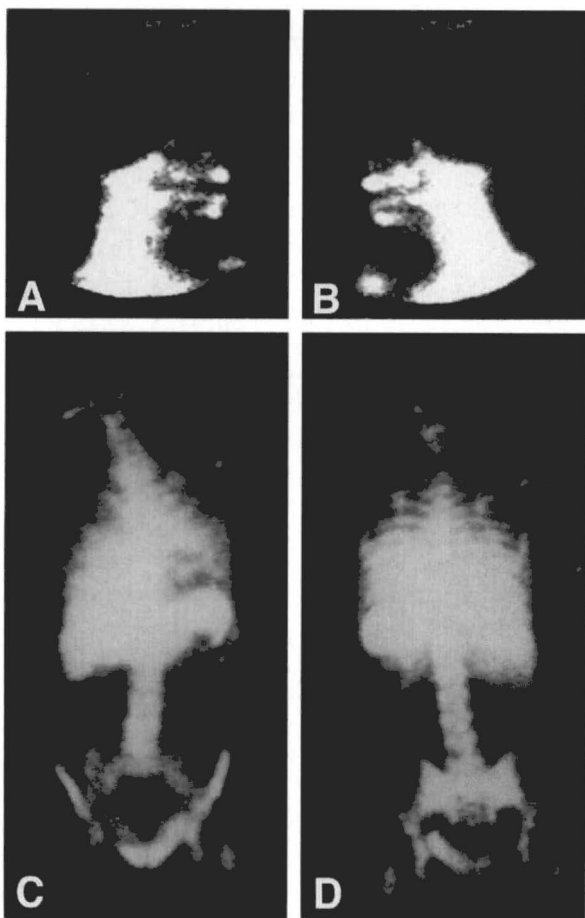


Figure 3. Indium-labelled white-cell scan, patient 2. Patchy uptake is apparent in both cerebral hemispheres, more marked in the left. Additional pulmonary uptake was also apparent and was found also in patient 7, who had normal brain images.

macrophages but no vasculitic changes. Fluorescein angiography, however, showed clear changes of retinal vasculitis.

She was treated with intravenous cyclophosphamide (four 750 mg doses over 6 weeks), followed by oral steroids. While symptomatically well thereafter, she had a bilateral inferior altitudinal hemianopia when examined 4 months later.

Clinical features

Details of all patients are summarized in Table 1. As expected, a wide variety of clinical features were encountered. Three patients (3, 5 and 7) had relapsing and spontaneously remitting disease characterized by optic neuropathy (3 episodes), brain stem events (2), acute or sub-acute encephalopathic episodes (3), generalized or partial seizures (2 patients), and hemispheric stroke-like episodes (one patient, three events). Two such patients had additional progressive cognitive or neuropsychological disturbance.

The remaining five patients presented with acute or subacute neurological encephalopathic illnesses; two had raised intracranial pressure. Three experienced seizures, two had accompanying focal neurological signs, and one had chorea.

Three patients had an associated systemic disease: two had previously-established rheumatoid disease (without active arthritis at the time of neurological presentation), and one had cerebral and systemic vasculitis in the context of lymphoma. The remaining five patients had isolated CNS vasculitis (though one had livedo reticulares).

Investigation and diagnosis

An elevated ESR or CRP accompanied neurological symptoms in 5/8 patients; during two episodes (in one patient), dissociation was found, with a raised CRP in the presence of a normal ESR. Conventional autoimmune serology was abnormal in three, while ANCA serology was positive in two (patients 2 and 8), with an additional false-positive result in one patient with rheumatoid arthritis. Routine spinal-fluid examination was abnormal in only 2/8, in one of whom (patient 2) the abnormality was very marginal (6 white cells). CSF oligoclonal bands were present in 3/6 patients, in one (patient 7) showing a shifting pattern during the protracted course.

Ophthalmological examination made an important contribution to the diagnosis of cerebral vasculitis (Table 2). Vasculitic changes were found in 4/5 patients studied (patient 8 illustrated, Figure 5). Abnormalities revealed by dynamic video recording variably included marked slowing of flow, multifocal attenuation of arterioles, and erythrocyte aggregates. Fluorescein studies confirmed the variation in vessel calibre, slowing of flow and red-cell aggregation, and also demonstrated areas of small-vessel infarction, together with multifocal segments of intense leakage from post-capillary and collecting venules.

CT scanning was abnormal in 7/8 patients, MRI in all four patients imaged. Cerebral perfusion SPECT was abnormal in 2/3 patients, while labelled white-cell scanning indicated cerebral inflammation in 1/2 patients—although in the patient with normal brain appearances, increased uptake in other sites was found and contributed usefully to diagnosis.

Cerebral biopsy was carried out in three patients; all were abnormal though only two showed unequivocal vasculitis, the third (patient 3), showed multiple small infarcts but no active vasculitis.

Discussion

We have described eight patients with vasculitis of the central nervous system—in five confined to the

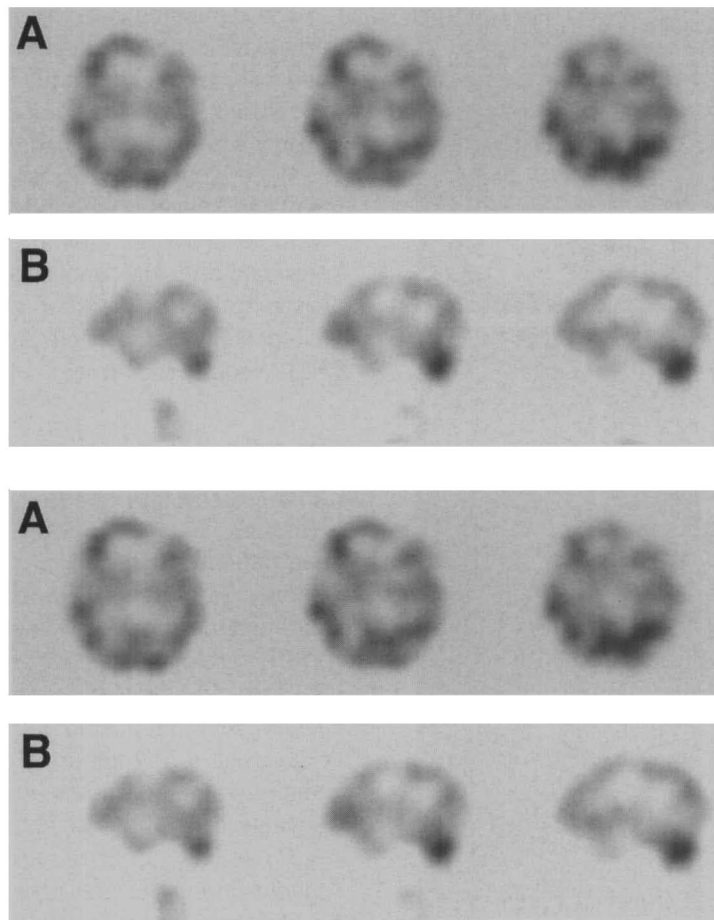


Figure 4. Perfusion HMPAO SPECT scanning, patient 3. Multiple focal ischaemic defects are visible; these involved the left posterior parietal region, the left fronto-parietal, and the right temporal areas.

brain, the remainder proving to have CNS vasculitis with laboratory evidence or past history of systemic disease. Of the latter three, two (patients 5 and 8) had established seropositive rheumatoid disease, of which cerebral vasculitis is a rare but well-reported complication.^{2,17} The third (patient 7) exhibited a raised lymphocyte count at the onset of his illness which eventually proved a consequence of a low-grade B-cell lymphoma; his illness clinically resembled lymphomatoid granulomatosis which not uncommonly transforms to lymphoma¹⁸, a recognized cause of systemic and cerebral vasculitis.

We elected to describe all eight patients together for three reasons. Firstly, in all patients inflammatory disease of the brain was overwhelmingly the principal cause of morbidity at the time of presentation, regardless of the underlying cause. Secondly, it seems likely that all share similar cerebral processes. Thirdly, the investigation and management of all patients was largely independent of any systemic process—which was either clinically quiescent at the time of neurological presentation, or diagnosed only in the course of investigation for suspected cerebral vasculitis. As mentioned above, the clinical diagnostic problems presented by all eight patients

were similar, regardless of their underlying medical background.

Cerebral vasculitis is unusual—in our unit accounting for a maximum of 0.5% admissions, no more than 3–4 patients per year (with a neurological catchment area of approximately 2.4 million). It is difficult to recognize, to diagnose, and to treat, but reports of successful therapies for other inflammatory neurological diseases (β -interferon and monoclonal antibodies for multiple sclerosis, plasmapheresis and intravenous immunoglobulin for inflammatory neuropathies and myopathies^{19–21} and for multi-system vasculitis^{9,12}) provide new hope for the treatment of cerebral vasculitis, placing new emphasis on recognition and treatment.

Our patients reflect the previously emphasized wide variation in manifestations, course and severity, and the absence of a pathognomonic or even typical clinical picture.^{1,2,5,22} Focal and generalized seizures, stroke-like episodes, acute and sub-acute encephalopathies, brain-stem events, progressive cognitive changes, chorea, optic and other cranial neuropathies all were seen. Despite this variability, it is possible (and may be useful) to divide our patients into three broad clinical groups.

Table 1 Summary of the clinical features and investigation results in all eight patients

Patient	Clinical features	Ocular findings	Inflammatory indices		ANCA testing	Spinal fluid	Imaging	Histopathology	Diagnosis based on
			ESR	CRP					
Patient 1, PT (F) dob 7.4.66	Subacute post-partum headache, vomiting, drowsiness; cardiorespiratory arrest and persistent coma after biopsy; no systemic features.	ND	60	49	N	N, ogc -ve	CT—thalamic lesion MRI—multiple lesions caudate, thalami, periventricular area	Thalamic bx: necrotizing leukocytoclastic vasculitis	Thalamic biopsy
Subacute isolated CNS disease									
Patient 2, JM (F) dob 27.4.40	Sub-acute confusion with choreiform movements and generalized fits	ND	N	N	N	4n,2l ogc -ve	CT—N (slight prominence of ventricles) wcs—patchy cerebral uptake SPECT—single ischaemic area angiography—variation of vessel calibre	ND	ANCA, white-cell scan and carotid angiography
Subacute isolated CNS disease									
Patient 3, MF (F) dob 4.12.44	5 year evolution, starting with unilateral twitching nocturnal fits. Cognitive symptoms. Optic neuropathy. Acute encephalopathy.	FFA: retinal vasculitis	30	68	N	No cells ogc + ve serum + ve	CT—low density temporal lobe SPECT—multiple perfusion defects angiography—normal	temporal artery bx.—N cerebral bx (meninges cortex & white matter): multiple small infarcts; no visible vasculitis	ESR/CRP; CSF electrophoresis; SPECT; cerebral biopsy and FFA
Chronic isolated relapsing CNS disease									
Patient 4, VS (F) dob 25.4.35	Acute psychosis, followed by confusional state + cognitive failure. Extensor l. plantar. P/H rheumatoid disease	N	78	90	RhF +ve 1230lu/ml ACA +ve (IgM-68)	N, ogc-ve	CT—periventricular low densities SPECT—normal	None	Past history, current rheumatoid & cardioliopin serology, ESR & CRP, CT scan
Acute CNS disease in the context of rheumatoid arthritis									

Table 1 (continued)

Patient	Clinical features	Ocular findings	Inflammatory indices		ANCA testing	Spinal fluid	Imaging	Histopathology	Diagnosis based on
			ESR	CRP					
Patient 5, KR (M) dob 3.12.46	Acute jaw, tooth & scalp pain, then <i>l.</i> visual loss, followed by <i>r.</i> : then transient <i>l.</i> hemispheric episodes. Livedo reticulares. Cognitive changes with impaired frontal function.	Suggests vasculitis	14	<6	ACA +ve, (IgM-69)	N	CT—periventricular low densities, probable infarcts, generalised atrophy	TA—normal Liver—mild cirrhotic change	ACA serology, CT scan and ocular findings
Subacute relapsing CNS disease, livedo reticulares.									
Patient 6, SP (M) dob 29.8.58	Subacute headache, vomiting, papilloedema, ataxia	ND	1	<6	N	38L, 1N protein 0.3 pressure—80 cm water	CT—cerebellar mass lesion with hydrocephalus MRI—focal high signal <i>r.</i> cerebellar hemisphere + upper pons, mid-brain, external capsule and <i>r.</i> putamen, periventricular areas and centrum semiovale	Stereotactic bx:- granulomatous vasculitis with epithelioid and giant cells, lymphocytic cuffing, reactive changes, swollen astrocytes Kveim -ve	CT, MRI and biopsy High dose steroids and cyclosporin A. Relapsing course, died with hydrocephalus and localized haemorrhagic changes (on CT)
Subacute isolated CNS disease									

<p>Patient 7, JW (M) dob 11.10.34</p>	<p>1986: wt loss, cough, headache; pulmonary infiltrate, raised lymphocyte count 1992: diarrhoea, night sweats, wt loss; followed by acute febrile encephalopathy 1993: fever, night sweats, abdo. pain headaches, brain stem episode 1994: recurrent brain stem episode with l. VI palsy</p>	<p>61 6 4</p>	<p>ND 27 39</p>	<p>N N N</p>	<p>ND ogc +ve, 1 band serum ogc +ve, serum +ve (diff bands) ogc +ve, serum -ve</p>	<p>CT—small infarct, r. corona irradiata CT—N MRI—multiple high signal lesions WCS—increased uptake lungs and iliac fossa, normal brain angiography— normal MRI—high signal periventricular area, internal capsule, sub- cortical area, pons, l. globus pallidus</p>	<p>lung bx.— inflammatory cells rectal bx.— arteritis with fibrinoid necrosis Kveim—normal bone marrow— low grade B-cell lymphoma</p>	<p>Rectal biopsy, MRI, ocular findings</p>
<p>Patient 8, LH (M) dob 4.9.29</p>	<p>Subacute fluctuating encephalopathy, headache, painful numb extremities, fever, night sweats; dysarthria, peripheral sensory loss, transient punctate macular rash lower legs. Past treatment for RA included Campath-1H, gold, azathioprine, cyclosporine</p>	<p>94 70</p>	<p>191 239</p>	<p>True +ve, ag not defined</p>	<p>N ogc +ve serum +ve</p>	<p>CT—extensive low attenuation cerebral white matter MRI—diffuse high signal intensity centrum semi- ovale, posterior frontal lobe, external capsules, periventricular areas</p>	<p>Renal Bx—N (transient impaired renal function)</p>	<p>Systemic symptoms, active rheumatoid serology, ESR, CRP, ANCA, ocular findings. Good response to cyclophosphamide</p>

dob, date of birth; ND, not done; N, normal; ogc, oligoclonal band analysis; l, left; r, right; wcs, white-cell scan; bx, biopsy; FFA, fundus fluorescein angiography; n, neutrophil; l, lymphocyte; RhF, rheumatoid factor; ACA, anticardiolipin antibody.

Table 2 Details of ocular findings in the five cases fully examined

Patient	Visual activity	Examination	Results	Ocular diagnosis
3	<i>r</i> 1/60 <i>l</i> 1/60	Anterior segment	IOP 31/30	Steroid-induced ocular hypertension
		Posterior segment	Pale discs; arterial attenuation, venous beading, old venous sheathing <i>r</i>	Large vessel ischaemia in ophthalmic artery territories
4	<i>r</i> 6/9 <i>l</i> 6/18	FFA	No active vasculitis	Previous clear retinal vasculitis
		Conjunctival vessels	No rbc aggregation	No vasculitis
		Posterior segments	<i>l</i> -focal arteriolar narrowing & dry macular degeneration	
5	<i>r</i> 6/5 <i>l</i> 6/5	Fields	<i>r</i> -homonymous inferior quadrantanopia	<i>l</i> -posterior parietal infarct
		Conjunctival vessels	Multifocal venular dilation and stasis	Consistent with vasculitis
		Anterior and posterior segments	Normal	
7	<i>r</i> 6/6 <i>l</i> 6/6	Conjunctival vessels	Normal	Compatible with systemic vasculitis
		Anterior segment	Normal	
		Fundus	<i>r</i> -cotton wool spot (nerve fibre layer infarct)	
8	Not reliable	FFA	No other vascular abnormality	Characteristic of systemic vasculitis
		Ocular examination	Normal	
		Conjunctival fluorescein videoangiogram	Multifocal microvascular non-perfusion and leakage	

(i) *Atypical multiple sclerosis (more accurately 'MS-plus')*. Three patients (patients 3, 5 and 7) exhibited a spontaneously relapsing and remitting course, with neurological features which included optic neuropathy and brain stem episodes. Two had CSF oligoclonal bands, one (of two scanned) had multifocal white-matter lesions on MRI; multiple sclerosis had been considered a possible diagnosis in all at some time. Each, however, had additional features less common in multiple sclerosis: seizures (1/3), severe headaches (2/3), encephalopathic episodes (2/3), or hemispheric stroke-like events (1/3). Systemic features were found in 2/3, including livedo reticulares, fever, or oligoarthropathy.

(ii) *Intracranial mass lesion*. This was found in two patients on 'first pass' investigation (CT).

(iii) *Acute or sub-acute encephalopathy* the presentation in the remaining three patients.

The great majority of cases detailed in the literature also conform to these patterns, which we do not suggest carry pathological or therapeutic implications. Their occurrence might, however, lead to a suspicion of cerebral vasculitis, so they may improve recognition of this condition.

ANCA assays are now routinely used in the serological diagnosis of systemic vasculitis; these antibodies may also have a pathogenic role.²³ A number of case reports indicate the expected positive ANCA testing in patients with Wegener's granulomatosis complicated by direct cerebral spread,^{24,25} but

we have been unable to identify any previous investigation of the role of ANCA serology in the diagnosis of cerebral vasculitis. We tested all eight patients. Two had true-positive ANCA testing; in one (patient 2), the result was particularly useful since she had isolated CNS disease and (otherwise) normal blood tests. We also performed ANCA-testing on one CSF sample (patient 8, with a positive serum test). No antibody was detectable, concurring with our experience of CSF ANCA testing in cerebral disease from ANCA-positive Wegener's granulomatosis (unpublished observations).

Spinal fluid was examined in all eight patients. Only one had a substantially elevated cell count (patient 6; 38 lymphocytes); Patient 2 had a very marginally abnormal count (6 white cells). None had a raised total protein level. Previous published series report abnormal results in 50–80% of cases,^{2,3,26–28} but comparisons are difficult, since the definition of an abnormal result varies considerably (from >1, to >4 cells per high-power field³).

There have been no published systematic studies of CSF oligoclonal immunoglobulin band analysis in cerebral vasculitis, although 2/4 cases of herpes-zoster-related cerebral vasculitis were positive,²⁹ as were '25–66%' of cases with various manifestations of cerebral lupus.³⁰ 3/6 of our patients showed abnormalities. Patient 3 had different immunoglobulin bands in CSF and in serum, patient 8 had identical bands. In patient 7, a fluctuating pattern

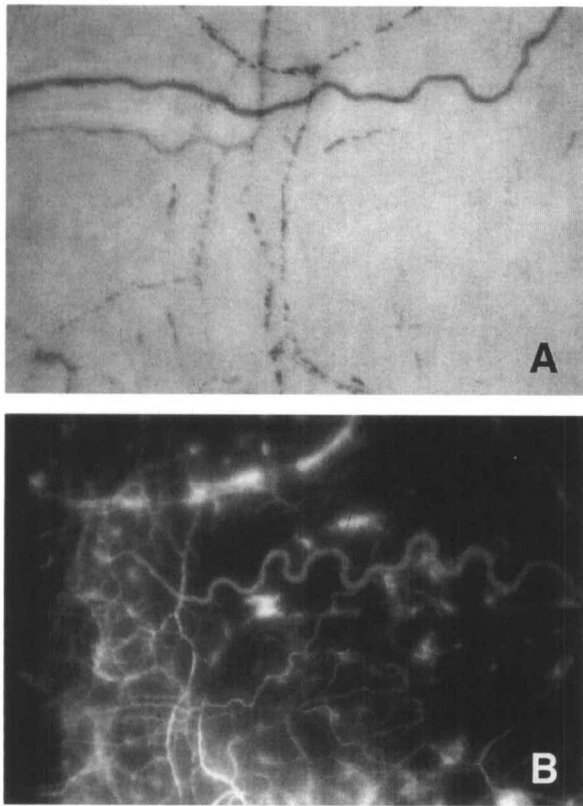


Figure 5. Anterior ocular vascular study, patient 8. Still frames from slit-lamp video recording are shown. Abnormalities included multifocal attenuation of arterioles, and erythrocyte aggregates (a) Low-dose fluorescein studies (b) confirmed the variation in vessel calibre, and also demonstrated areas of small-vessel infarction, together with multifocal segments of intense leakage from post-capillary and collecting venules.

was found on serial testing over a 2-year period (see Table 1). We suggest that oligoclonal band analysis is therefore worthwhile in suspected cerebral vasculitis, an abnormal result (and perhaps particularly of variable pattern, or indicating intrathecal and systemic immunoglobulin synthesis) providing some diagnostic support, albeit without specificity.

MRI abnormalities were present in 4/5 of our patients. In the fifth, the images were not interpretable due to movement. MRI has been suggested as a sensitive but not specific screening test in cerebral vasculitis: Harris *et al.*³¹ reported significant abnormalities in 9/9 cases of proven disease, and no false-negative scans. However, in an interesting correlative study, Greenan *et al.*³² found on careful regional analysis that 12/33 vascular territories with angiographic vasculitis exhibited no lesions on MR. Up to 25% of cases may in fact have normal MRI scans,^{28,33} some additionally with normal angiography.³⁴

The value of angiography is difficult to assess, many published series relying on this investigation for diagnostic confirmation.^{26,28} Studies depending on pathological examination indicate a false-negative

rate for angiography of 30–45%,^{3,27} although other series suggest angiography is diagnostically useful in only 20–27% of cases.^{35,36} A 10% risk of transient neurological deficit is reported,³⁷ with permanent deficit in 1%. Only 1/4 of our patients had abnormal angiography, and although the value of this investigation may have been over-emphasized in the past, it clearly remains important to exclude atheromatous and other disease, and when positive, affords more specificity than MRI.

We have found no reference to labelled-white-cell nuclear scanning in cerebral vasculitis, notwithstanding its increasingly recognized value in systemic vasculitides.⁸ We found abnormal cerebral accumulation of indium-labelled leucocytes in 1/2 patients tested, although the (clinically silent) increased pulmonary uptake in both was also diagnostically useful. Vasculitis in other organs is demonstrated indirectly by leucocyte uptake in necrotic tissue, or ischaemic areas supplied by vasculitic vessels,¹⁴ whereas leucocyte infiltration of intracerebral vessels is unlikely to be visualized directly. Nevertheless, further studies may be worthwhile. Functional cerebral imaging, including SPECT, was abnormal in 8/12 patients in a recent series,³⁶ and in 1/2 patients we examined. Cerebral perfusion SPECT may well therefore be a useful if non-specific test in cerebral vasculitis, demonstrating focal ischaemia secondary to the vasculitic process.

Most helpfully, we found ophthalmological examination with video microscopy and low-dose fluorescein angiography of the anterior chamber to be extremely valuable in the assessment of our patients. Four of five patients examined had abnormal findings suggestive of vasculitis. Studies of the ocular vasculature have been shown to contribute to the diagnosis of multi-system vasculitis,⁶ and retinal vasculitis has been much studied in multiple sclerosis (where vasculitis generally refers to vascular leakage and occlusion without implying a histopathology of leukocytoclastic vascular damage). We have, however, been unable to find any reference in the literature to the diagnostic contribution of these ophthalmological techniques to cerebral vasculitis. Previous studies have confirmed the clinicopathological correlation between fluorescein angiographic changes and (localized ocular) vasculitis,^{38,39} and our findings suggest that ophthalmological assessment is a useful and important addition to the investigation of patients with suspected cerebral vasculitis.

Our study might be criticized for lacking pathological data. This issue is, however, far from straightforward. In two of the largest series surveying previously published cases,^{3,27} biopsies had been performed in only 29% (14/48) and 52% (37/71) of cases, and were diagnostic only in 10 and 26 patients, respect-

ively. Three of our eight patients underwent cerebral biopsy: two in the course of urgent assessment for acute space-occupying lesions, biopsy revealing unsuspected vasculitis, the third undergoing 'blind' biopsy of cortex, white matter and meninges for suspected vasculitis; in this patient, the findings were non-specific and not diagnostic. Our results are therefore numerically typical and representative of published reports and series.

Cerebral biopsy is not a trivial procedure, carrying a significant risk of serious morbidity estimated at 0.5–2%⁴⁰, and in the majority of our patients we found it impossible to justify. Patient 8 is illustrative: findings included strongly positive rheumatoid serology, positive ANCA serology, marked elevations of both ESR and CRP, and unequivocal evidence of small-vessel vasculitis in the anterior ocular circulation, with no other explanation for his subacute encephalopathy after extensive investigation. We felt unable to build a compelling case for biopsy, particularly since, with our own experience of one non-diagnostic biopsy and published data consistently showing the diagnostic yield of biopsy to be relatively low at 70%,^{3,27} the decision to treat with cyclophosphamide would not have been influenced by a non-diagnostic biopsy. A pronounced response to treatment in this patient provided further retrospective support for the diagnosis.

The low incidence of vasculitic cerebral disease renders formal prospective therapeutic trials extremely difficult: none has so far been reported. An informed approach to treatment therefore depends on the cumulative experience described in published retrospective and pooled series, and our patients may offer some useful lessons. Patients 1 and 6 had very similar features: biopsy-proven isolated cerebral vasculitis presenting with single cerebral mass lesions on CT but MRI evidence of multifocal disease, both with negative routine and ANCA serology. One was treated with cyclophosphamide and steroids and made a complete recovery with no further symptoms some 6 months later; the other received high-dose steroids with cyclosporin and suffered a chronic relapsing and ultimately fatal illness. Four other patients received cyclophosphamide. One had a single further episode of optic neuropathy (whilst on oral steroid maintenance treatment alone, 3 months after four pulses of intravenous cyclophosphamide) and remained well thereafter, and three others experienced a striking resolution of their illness. The fourth patient, who had B-cell lymphoma, also died (of pseudomonas pneumonia).

Two patients received steroids alone: one (patient 4) with past rheumatoid disease, and one (patient 5) whose initial presentation had suggested giant cell arteritis. Both responded well. Interestingly, Calabrese *et al.* have defined a group of patients

with cerebral vasculitis who have more benign disease which may, in fact, not require any treatment,⁴¹ a suggestion supported by others.²⁶ In many cases of cerebral vasculitis, however, relapses may occur when steroids alone are used³⁵ and we would advocate early recourse to cyclophosphamide in patients not responding rapidly to high dose intravenous steroids—as previously recommended in both cerebral and systemic vasculitis.^{5,22,43} We have not as yet treated patients with cerebral vasculitis with any of the more experimental approaches, although the promise of Campath-1H humanized monoclonal antibody treatment in inflammatory demyelination²⁰ and in systemic vasculitis¹² may indicate significant potential, cerebral vasculitis unresponsive to cyclophosphamide being well-described.²⁶

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