

# A $\beta$ -related angiitis: primary angiitis of the central nervous system associated with cerebral amyloid angiopathy

Neil J. Scolding,<sup>1</sup> Fady Joseph,<sup>1</sup> Patricia A. Kirby,<sup>9</sup> Ingrid Mazanti,<sup>3</sup> Françoise Gray,<sup>10</sup> Jacqueline Mikol,<sup>10</sup> David Ellison,<sup>4</sup> David A. Hilton,<sup>6</sup> Timothy L. Williams,<sup>5</sup> James M. MacKenzie,<sup>7</sup> John H. Xuereb<sup>8</sup> and Seth Love<sup>2</sup>

*Departments of <sup>1</sup>Neurology and <sup>2</sup>Neuropathology, Institute of Clinical Neurosciences, University of Bristol, Frenchay Hospital, Bristol, <sup>3</sup>Department of Cellular Pathology, Division of Neuropathology, Southampton General Hospital, Southampton, <sup>4</sup>Department of Neuropathology, Newcastle General Hospital, <sup>5</sup>Department of Neurology, Royal Victoria Infirmary, Newcastle-upon-Tyne, <sup>6</sup>Department of Histopathology, Derriford Hospital, Plymouth, <sup>7</sup>Department of Pathology, Aberdeen Royal Infirmary, Aberdeen, <sup>8</sup>Division of Molecular Histopathology, Addenbrooke's NHS Trust, Cambridge, UK, <sup>9</sup>Department of Pathology, University of Iowa College of Medicine, Iowa City, IA, USA and <sup>10</sup>Service d'Anatomie et Cytologie Pathologiques, Hôpital Lariboisière, Paris, France*

*Correspondence:* Dr Seth Love, Department of Neuropathology, Institute of Clinical Neurosciences, Frenchay Hospital, Bristol BS16 1LE  
E-mail: [seth.love@bris.ac.uk](mailto:seth.love@bris.ac.uk)

## Summary

Idiopathic or primary angiitis of the CNS (PACNS) and cerebral amyloid angiopathy (CAA) are unusual vasculopathies generally regarded as unrelated disorders. A few case reports have, however, described granulomatous angiitis in patients with sporadic, amyloid  $\beta$  peptide (A $\beta$ )-related CAA. Here we describe the clinical, neuroradiological and neuropathological features of nine patients with A $\beta$ -related angiitis (ABRA). Combining these with the individual case reports drawn from the literature has allowed us to define ABRA as a clinical entity and to compare its features with those of PACNS. The mean age of presentation of ABRA (67 years) is higher than that of PACNS but lower than that of sporadic non-inflammatory A $\beta$ -related CAA. Alterations in mental status (59%), headaches (35%), seizures and focal neurological deficits (24%) are common. Hallucinations are a presenting manifestation in 12% of cases. Most patients have white matter hyperintensities on MRI but these are of similar appearance to

those in PACNS. Cerebrospinal fluid usually shows modest elevation of protein and pleocytosis. Neuropathology reveals angiolytic inflammation, often granulomatous, and meningeal lymphocytosis. A $\beta$  is consistently present in abundance in affected blood vessels but usually scanty within the parenchyma of the cerebral cortex. However, the cortex includes numerous activated microglia, occasionally in a plaque-like distribution and containing cytoplasmic A $\beta$ . The cerebral white matter shows patchy gliosis and rarefaction, in some cases marked. Our findings (i) help to dissect one separate clinicopathological entity from what is likely to be a spectrum of primary angiitides of the CNS; (ii) have important therapeutic implications for one category of patients with amyloid-related vasculopathy; and (iii) may provide valuable insights into the development of amyloid-associated inflammation, of relevance not only to ABRA but also to A $\beta$ -immunization-related encephalitis and to Alzheimer's disease.

**Keywords:** A $\beta$ -related angiitis; Alzheimer's disease; cerebral amyloid angiopathy; CNS vasculitis; primary angiitis of the CNS

**Abbreviations:** A $\beta$  = amyloid  $\beta$  peptide; ABRA = A $\beta$ -related angiitis; CAA = cerebral amyloid angiopathy; PACNS = primary angiitis of the CNS

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## Introduction

The term cerebral amyloid angiopathy (CAA) describes the localized deposition of amyloid in blood vessels within the cerebrum and overlying leptomeninges. The cerebellum may also occasionally be involved, and rarely the brainstem and spinal cord. CAA encompasses a heterogeneous group of hereditary and sporadic diseases, much the most common of which is sporadic CAA due to the vascular deposition of amyloid  $\beta$  peptide (A $\beta$ ). A $\beta$  vascular deposition affects about 30% of the otherwise normal elderly and over 90% of those with Alzheimer's disease, in whom CAA tends also to be more severe (Vinters and Gilbert, 1983; Esiri and Wilcock, 1986; Mandybur, 1986; Yamada *et al.*, 1987; Chalmers *et al.*, 2003; Love, 2004). The most frequent clinical manifestation is lobar cerebral haemorrhage, which may be multifocal and recurrent, but CAA can also cause cerebral infarction and ischaemic leucoencephalopathy (Greenberg *et al.*, 1993; Gray *et al.*, 1985; Imaoka *et al.*, 1999; Cadavid *et al.*, 2000; Olichney *et al.*, 2000).

Primary angiitis of the CNS (PACNS) is a rare disorder of unknown aetiology almost exclusively confined to the CNS; it usually involves the brain, less commonly the spinal cord (Scolding *et al.*, 1997; Schmidley, 2000). The angiitic process is focal and segmental in distribution, with a predilection for small arteries, particularly in the leptomeninges. Inflammation and associated mural damage are often multifocal, producing a series of 'skip lesions' along an affected blood vessel, with multiple associated foci of infarction or haemorrhage. At each point, the disease process may be circumferential or only segmental, and the inflammation may be granulomatous, necrotizing, lymphocytic or mixed in character. Most authorities now recognize the non-specificity of the angiographic changes and believe that a certain diagnosis depends on a positive biopsy. However, there are no widely accepted diagnostic criteria (Joseph and Scolding, 2002), which partly reflects the difficulty in obtaining ante-mortem pathological material. PACNS may affect patients of any age but is most frequently reported in middle life (mean age 45 years), with a slight male preponderance of 4:3 (Calabrese and Mallek, 1988; Lie, 1992). Clinical presentations can be highly variable, but often, multifocal symptoms and signs develop in a stepwise manner accompanied by headache or altered mental status.

PACNS and CAA are generally regarded as unrelated disorders. A few case reports have, however, described neuropathologically confirmed cerebral vasculitis in patients with sporadic, A $\beta$ -related CAA. The angiitis is centred on blood vessels carrying extensive A $\beta$  deposition, some of which can usually also be demonstrated in macrophages and multinucleated giant cells within the inflammatory infiltrate. The conjunction of these two types of cerebrovascular disease poses a number of questions. From a clinical perspective, it is important to determine whether vascular A $\beta$  has induced or is associated with inflammation, since vasculitis warrants immunosuppressive therapy, while CAA is otherwise resistant to such treatment.

No less important are the immunological and pathogenetic implications of a destructive inflammatory reaction to cerebral or cerebrovascular A $\beta$ . Clinical studies exploring the potential of A $\beta$  immunization in patients with Alzheimer's disease required premature discontinuation following the development of subacute meningo-encephalitis in a minority of patients (Check, 2002); post-mortem studies revealed patchy absence—probably representing clearance—of parenchymal A $\beta$ , but severe CAA as well as meningeal and perivascular inflammation (Nicoll *et al.*, 2003; Ferrer *et al.*, 2004).

Here we present the first description of the clinical and pathological findings in a substantial series of patients with A $\beta$ -related angiitis (ABRA) and explore further the hypothesis that this spontaneous association of CAA with vasculitic inflammation has important immunopathological parallels with A $\beta$  immunization-associated meningo-encephalitis. We propose that ABRA is a distinct clinicopathological entity, a specific form of primary CNS angiitis which we hypothesize is triggered by vascular deposition of A $\beta$  in susceptible patients and is part of a more widespread immune reaction to A $\beta$  within the CNS.

## Methods

We combined a systematic and ongoing survey of cases of CNS vasculitis in southwest England and south Wales, with a more specific direct request to collaborating departments for neuropathologically proven cases of ABRA. We studied the clinical records of nine cases of ABRA (Table 1) and six cases of PACNS without amyloid angiopathy (Table 2). Patient notes were studied for basic demography, presenting and other clinical features, investigations, therapeutic interventions and outcome. Further paraffin sections from the biopsies (five cases) or post-mortem brain tissue (four cases) were cut for immunohistochemistry.

We also obtained paraffin sections of brain tissue from 10 cases of CAA without associated angiitis, from the South West Dementia Brain Bank, Bristol (Table 3). All of these had been subjected to detailed neuropathological examination at the time of donation: five had a CERAD (Consortium to Establish a Registry for Alzheimer's Disease) diagnosis of 'definite Alzheimer's disease' and five had a CERAD classification of 'normal'.

In addition, we reviewed all cases of CAA-associated vasculitis previously reported in the literature and compared those with the nine histologically proven cases of ABRA in the present series.

## Immunohistochemistry

Immunohistochemistry was performed on paraffin sections of the biopsies or of available blocks of frontal lobe in the autopsy cases. The primary antibodies are listed in Table 4. These were directed at A $\beta$ , A $\beta$ <sub>1-40</sub>, A $\beta$ <sub>1-42</sub>, tau with phosphorylated Ser202,  $\alpha$ -synuclein, MHC class I and II antigens, CD3, CD20 and CD68. Sections 5  $\mu$ m in thickness were collected on slides coated with 3-aminopropyltriethoxysilane, dewaxed in xylene and rehydrated through graded alcohols to water. They were pretreated for antigen retrieval as indicated in Table 3, rinsed in cold water, and immersed for 30 min in methanol containing 3% H<sub>2</sub>O<sub>2</sub> to quench non-specific peroxidase activity. The sections were then incubated first in 20%

**Table 1** Summary of histology-positive cases of ABRA

Case no.	Age, sex	F/U (months)	Presentation	Later clinical features	Bloods	CSF	CT brain	MRI brain	EEG	Treatment	Outcome
1	70, F	18	Confusion, hallucinations, reduced conscious level	Similar deterioration, globally brisk reflexes	ESR 12, cholesterol 7.2	OP normal, Pr = 3.07, WC 0.9, OCB neg.	Temporal lobe swelling	Temporal lobe swelling with enhancement.	Widespread irregular theta, with delta burst (encephalopathy)	Cyclophosphamide and steroids; long-term improvement	
2	66, F	36	Amnesia, headache, visual disturbance, dysgraphia, impaired musical ability	TIAs and cognitive decline	NAD	OP normal, Pr = 1.23, WC 1, OCB neg.	Multiple diffuse WM lesions	Multiple occipital lobe diffuse WM lesions + haemorrhage in frontal lobe.	Bilateral slow wave activity	Prednisolone 60 mg/day, reduced to 10 mg on alternate days for 2 years; improved	Mild disability
3	66, M	2	Dysphasia, poor memory, paranoia	Worsening paranoia, confusion, parkinsonism, ataxia, GCS 5-8	Platelets 104, GGT 338	OP = 30, Pr = 3.7, WC 0, OCB neg.	Diffuse WM lesions, worse R frontal + mass effect, no enhancement	Not done	Non-specific generalized slow waves	IV dexamethasone 4 mg/day for 10 days, plus acyclovir and heparin	Death
4	54, M	14	Encephalopathy	Cortical blindness, visual hallucinations, labile mood, CPS, poor gait	Elevated CRP, PV 1.90, deranged LFTs	OP = 25, Pr and WC normal	Diffuse white matter lesions	Not available	High dose steroids	Severe disability	
5	74, F	3	Generalized seizure, Bell's palsy, anisocoria, dysmetria, up-going L toe	AI neg.	Low platelets, lymphocytes, eosinophils and basophils	Not done	Diffuse infiltrating 'tumour' extending from R parieto-occipital to temporal region	Not done	Not done	'Tumour' resection - brief improvement	Death

6	72, M	6	Bifrontal headaches, scotoma, slow speech, poor concentration with medication)	Cognitive decline (multifocal), depression (improvement with medication)	Raised WC, alkaline phosphatase, ALT, ESR 26	Not done	Hypodense area in right occiput	Non-enhancing hypodensity in right occiput	Not done	Cyclophosphamide Death 1.5 g in 3 cycles, prednisolone
7	72, M	2	Left-sided weakness, confusion, dysphasia, dyspraxia	Right hemiplegia and focal seizures	AI neg. ESR normal	Pr = 4.46, lymphocytes 21, glucose slightly low	L frontal lobe ischaemic changes	Left frontoparietal diffuse white matter abnormality + mass effect	Irregular slowing	'Tumour' resection, dexamethasone; brief initial improvement
8	72, F	6	Confusion, dementia, dyspraxia, dysphasia	None	ESR 35	Pr = 0.44, WC 0, OCB neg.	Symmetrical confluent low attenuation in white matter	Symmetrical diffuse white matter abnormality + mild swelling	Bifrontal complex slow activity	Death
					IgG 39	Dramatically improved			8 mg dexamethasone, single treatment	Mild disability
9	82, M	2.5	Bifrontal headaches, poor memory, behaviour disturbance	Confusion, dysarthria, coma	ESR normal	WC 18 (68% lymphocytes), Pr = 0.14	Normal	Not done	Frequent runs of bitemporal slowing	Steroids

AI = autoimmune screen; ALT = alanine aminotransferase; CRP = C-reactive protein; GGT =  $\gamma$ -glutamyl transferase; ESR = erythrocyte sedimentation rate; F/U = follow-up period; Neg = negative; OCB = oligoclonal bands; OP = opening pressure; Pr = protein; PV = plasma viscosity; TIA = transient ischaemic attack; WC = white cells.

**Table 2** Summary of histology-positive cases of PACNS

Age, sex	F/U (months)	Clinical features	Abnormal blood tests	CSF	Catheter angiography	MRI brain/MR angiography	CT	Treatment	Outcome
25, F	18	Encephalopathy and seizures (later: confusion, aphasia, apraxia, headache)	Weakly positive pANCA, ANF and antithyroid antibodies	Mildly raised protein	ND	L frontoparietal mass lesion. Angiography normal	Initially normal, later L frontoparietal mass lesion	Steroids	Severe disability
48, F	50	Hemiparesis, papilloedema, nausea, vomiting, vertigo, nystagmus, dysarthria	PV 1.78	OCB neg, Pr = 0.89, WCC 121L	Normal	R int. capsule infarct, L hemisphere WMLs, brainstem and cerebellar lesions. Angiography normal	R hemisphere infarct	Steroids, cyclophosphamide	Death
57, M	130	Ataxia, hemianopia, hemiparesis	Normal	Normal	Normal	R temporal and parietal haematoma and diffuse ischaemic changes	R temporal and parietal haematoma	IVIg (moderate improvement)	Minor disability
63, F	13	Memory impairment, papilloedema, myoclonus, fatigue	Normal	WC 17-22, OCB neg.	Reduced cerebral perfusion	Non-specific WMLs extending from frontal to occipital lobes and attenuation of peripheral vessels	Not available	Steroids, cyclophosphamide	Moderate disability
31 M	121	'Mass lesion' Headache, dysphasia, hemianopia, later encephalopathy and seizures 'MS-like'	Normal	Not done	Typical beading and attenuation of arteries.	WMLs in L occipital and anterior parietal region	Evidence of space occupying lesion in L occipital lobe	Steroids, cyclophosphamide, azathioprine (initially good response)	Moderate disability
32, M	18	Hemiparesis, ataxia, dysmetria, mental changes	Normal	Normal, OCB neg.	Not done	Multiple symmetrical enhancing lesions, especially cerebellum and internal capsule	Not available	Dexamethasone	Death

ANF = antinuclear factor; ESR = erythrocyte sedimentation rate; F/U = follow-up period; IVIg = intravenous immunoglobulin; neg. = negative; OCB = oligoclonal bands; Pr = protein; pANCA = perinuclear anti-neutrophil cytoplasmic antibody; PV = plasma viscosity; WC = white cells.

normal goat serum and subsequently for either 30 min or overnight (Table 4) at room temperature in primary antibody diluted in phosphate-buffered saline. Bound antibody was visualized by incubation with biotinylated Universal Antibody (Vectastain Universal Elite; Vector Laboratories, Burlingame, CA, USA) and avidin-biotin horseradish peroxidase, and reaction with 0.01% H<sub>2</sub>O<sub>2</sub>. The immunostained sections were counterstained with haematoxylin, dehydrated and mounted. Negative controls comprised sections

immunostained as above apart from the omission of primary antibody.

### Assessment of parenchymal and vascular A $\beta$ load

This was made on the paraffin sections of biopsy or post-mortem frontal lobe that had been immunostained for pan-A $\beta$  with M0872 (raised against A $\beta$  residues 8–17). The measurements were made using an approach similar to that previously described (Chalmers *et al.*, 2003; Love *et al.*, 2003). With the help of Histometrix software (Kinetic Imaging, Nottingham, UK) driving a Leica DM microscope with a motorized stage, the percentage area of cortex and overlying leptomeninges occupied by A $\beta$  (i.e. the total amyloid load) was measured. The operator then traced around and excluded the A $\beta$ -laden blood vessels and measured the remaining percentage area occupied by A $\beta$  (i.e. the parenchymal amyloid load). The percentage area occupied by vessel-associated amyloid (i.e. the vascular amyloid load) was calculated as the total amyloid load minus the parenchymal amyloid load. Comparisons between cases of ABRA, non-inflammatory CAA without Alzheimer's disease, and non-inflammatory CAA with Alzheimer's disease were made using non-parametric analysis of variance (Kruskal-Wallis test) with Dunn's post-testing.

## Results

### Clinical features

We identified 34 cases of ABRA in all: 25 patients from 18 published case reports (Reid and Maloney, 1974; Murphy and Sima, 1985; Probst and Ulrich, 1985; Shintaku *et al.*, 1986; Briceno *et al.*, 1987; Ginsberg *et al.*, 1988; Powers *et al.*, 1990; Le *et al.*, 1991; Mandybur and Balko, 1992; Fountain and Eberhard, 1996; Anders *et al.*, 1997; Fountain and Lopes,

**Table 3** Cases of CAA without angiitis

Age, sex	Neuropathological diagnosis	Cause of death given on death certificate
63, M	Alzheimer's disease with CAA	1. Myocardial infarction due to coronary artery artherothrombosis 2. Dementia
76, F	Alzheimer's disease with CAA	1. Ischaemic heart disease due to coronary artery atheroma 2. Dementia
44, M	Alzheimer's disease with CAA	Bronchopneumonia due to Down's syndrome
60, F	Alzheimer's disease with CAA	Bronchopneumonia due to dementia
82, M	Alzheimer's disease with CAA	Bronchopneumonia due to dementia
73, F	CAA	Carcinoma
89, F	CAA	Bronchopneumonia
93, F	CAA	Congestive cardiac failure due to ischaemic heart disease
82, M	CAA	Acute left ventricular failure, due to ischaemic heart disease and burns
76, F	CAA	Renal failure and septicaemia, due to urinary tract infection

**Table 4** Antibodies, pretreatments and dilutions

Antigen	Source of antibody	Polyclonal/monoclonal	Pretreatment of sections	Dilution
A $\beta$ <sub>1-40</sub>	Biosource International (cat. 44-348)	Rabbit polyclonal	20-min incubation in 100% formic acid	1 : 1000 overnight
A $\beta$ <sub>1-42</sub>	Chemicon (cat. AB5078P)	Rabbit polyclonal	20-min incubation in 100% formic acid	1 : 1600 overnight
Pan-A $\beta$	Dako, Glostrup, Denmark (cat. M0872)	Mouse monoclonal	20-min incubation in 100% formic acid	1 : 100 for 30 min
Pan-A $\beta$	Zymed (cat. 71-5800)	Rabbit polyclonal	20-min incubation in 100% formic acid	1 : 200 for 30 min
Tau with phosphorylated Ser232	Autogen Bioclear (cat. BR-003, Innogenetics Clone AT8)	Mouse monoclonal	None	1 : 3000 overnight
$\alpha$ -synuclein	Novocastra (cat. NCL-ASYN)	Mouse monoclonal	Microwave in 1 mM EDTA buffer, pH 8.0, then immerse for 3 min in 100% formic acid	1 : 800 overnight
MHC class II antigen	Dako, Glostrup, Denmark (cat. 0775)	Mouse monoclonal	Microwave in 10 mM citrate buffer, pH 6.0	1 : 100 for 30 min
MHC class I antigen ( $\beta$ 2 microglobulin)	Dako, Glostrup, Denmark (cat. A072)	Mouse monoclonal	None	1 : 1500 for 30 min
CD3	Dako, Glostrup, Denmark (cat. M7254)	Mouse monoclonal	Microwave in 10 mM citrate buffer, pH 6.0	1 : 40 for 30 min
CD20	Dako, Glostrup, Denmark (cat. M755)	Mouse monoclonal	Microwave in 10 mM citrate buffer, pH 6.0	1 : 300 for 30 min
CD68	Dako, Glostrup, Denmark (cat. M0814)	Mouse monoclonal	Microwave in 10 mM citrate buffer, pH 6.0	1 : 4000 for 30 min

1999; Streichenberger *et al.*, 1999; Anon, 2000; Brotman *et al.*, 2000; Tamargo *et al.*, 2003; Schwab *et al.*, 2003; Jacobs *et al.*, 2004) plus our nine cases. Two cases we include here in our current description have been published previously in single case reports (Gray *et al.*, 1990; Harkness *et al.*, 2004). The total comprised 17 males and 17 females, followed up for a mean of 16.3 months (range 7 days to 13 years). Our six cases of PACNS included three females and three males who were followed up for a mean of 58 months (range 18–130 months). The mean age of first neurological presentation was 67.3 years (range 43–82 years) in the ABRA patients compared with 43 years (range 25–63 years) in the PACNS group.

The pattern of clinical presentation in the ABRA and PACNS groups was similar. The most common clinical features were mental status changes (confusional states, poor memory/concentration or impaired conscious level), often leading to frank dementia, headaches, hallucinations and seizures (Fig. 1). The earliest manifestations also included cerebellar features. Progression of the disease was associated with the onset of dementia, seizures and hallucinations.

None of the patients in either the ABRA or the PACNS group had features of systemic autoimmune disease, haematological malignancy or a family history of dementia. Seven (21%) had a history of malignancy. One patient with unequivocal pathological evidence of cerebral ABRA did have a prior history of excised malignant melanoma and was diagnosed as having pancreatic cancer 3 months after his neurological presentation with encephalopathy and headaches. There was a previous history of prostatic carcinoma in two patients, and of bladder (one case) or breast (one case) carcinoma and bowel tumours (two cases) in four others. Seven patients were known hypertensives and three of these also had diabetes.

## Investigations

### Blood tests

These appeared to be of little diagnostic value. An autoimmune screen (including antinuclear antibody and

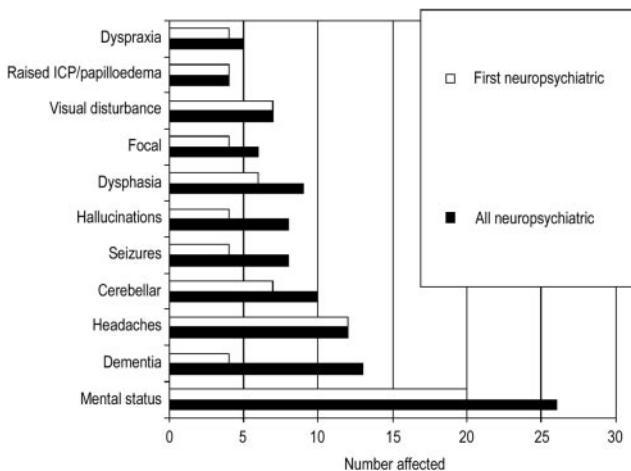


Fig. 1 Neuropsychiatric features of 34 cases of ABRA. Focal = focal weakness manifest as monoparesis or hemiparesis.

anti-neutrophil cytoplasmic antibody serology) was performed in 21 patients and all were negative. Erythrocyte sedimentation rate and/or plasma viscosity was elevated in nine of 22 (38%) in the range of 26–116 compared with 17% (1/6) of PACNS patients.

### Cerebrospinal fluid (CSF)

Some form of CSF abnormality was noted in 17/20 (85%) of the ABRA series. The CSF protein was elevated in 11/18 (61%) with a median of 1.0 g/l (range 0.5–4.46 g/l). CSF leucocytosis occurred in 8/18 (44%) with a mean cell count of 36 per ml (range 9–693 cells per ml). This was purely lymphocytic in four patients but four had a mixed pleocytosis (one had 40% eosinophils). One patient who presented with headaches had xanthochromic CSF but cerebral imaging was not available in this case. Oligoclonal bands in the CSF were sought in nine cases of ABRA but none was positive.

CSF analysis was carried out in five of the PACNS cases and was abnormal in three (60%): two had a high protein level (range 0.60–0.89 g/dl) and two had lymphocytosis. Three CSF samples were assessed for oligoclonal bands, and all were negative.

### CT and MRI

CT scans were available for 26 patients with ABRA and 24 (92%) of these were abnormal. Brain MRIs were available in 20, and 18 (90%) were abnormal. Both imaging modalities displayed variable and non-specific features: diffuse white matter lesions, mass lesions, focal oedema, haemorrhages, hypodensities consistent with infarcts, and atrophy. These are summarized in Table 5. There were no useful differences in CT or MRI between patients with ABRA and those with PACNS.

### Cerebral angiography

Contrast catheter angiography was performed in five of the ABRA group and only two showed abnormalities, with evidence of eccentric narrowing of a few medium-sized vessels in one case (which displayed multifocal areas of white matter high signal on MRI) and, in the other case, hypoplasia of the left anterior cerebral artery.

Two of the PACNS patients had contrast catheter angiography, which was normal in both.

Table 5 Cerebral imaging findings

	CT	MRI
White matter lesions	7 (27%)	13 (65%)
Mass lesions/oedema	8 (31%)	8 (40%)
Haemorrhages	3 (12%)	4 (20%)
Hypodensities/infarcts	3 (12%)	4 (20%)
Hydrocephalus	3 (12%)	1 (5%)
Atrophy	1 (4%)	1 (5%)

## EEG

All 15 EEG records obtained in the ABRA group were abnormal. One EEG from a patient with a clear history of generalized seizures demonstrated epileptiform discharges. Fourteen showed non-specific generalized slow-wave activity consistent with an encephalopathic process.

Similar non-specific EEG abnormalities were demonstrated in two patients with an encephalopathic type presentation in the PACNS group.

## Outcome and response to therapy

The outcomes in the ABRA patients varied considerably. Three patients were asymptomatic, six had mild disability, eight had moderate disability, two had severe disability and 15 died. Twenty patients were treated with steroids and eight of these received additional cyclophosphamide. One patient was given cyclophosphamide alone. Nine had surgical management and five of these received no additional immunosuppression. A favourable response to treatment with either steroids and/or cyclophosphamide was noted in 12 patients, although this was rather short-lived in two. CSF diversion procedures for hydrocephalus and resection of mass lesions were also associated with recovery in five patients. Two patients who had craniotomy and resection of mass lesions (assumed preoperatively to be tumours) made a significant improvement. Sustained or dramatic improvements were rarely observed, but four patients demonstrated reversal of MRI white matter lesions. The first was a 72-year-old female with rapidly progressive dementia and leucoencephalopathy who had a dramatic improvement in the MRI appearance after only one 8-mg dose of dexamethasone, and was left with only mild cognitive impairment. A second patient, a 66-year-old male with progressive dementia, hemianopia, dysphasia, dysarthria, ataxia and focal weakness, stabilized clinically after 1 month of treatment with steroids and cyclophosphamide. This was accompanied by the substantial reversal of MRI white matter changes and disappearance of CSF pleocytosis. A third patient, 71 years of age, was treated with cyclophosphamide without any steroids and demonstrated progressive improvement in MR brain imaging. He was noted to be asymptomatic 22 months after his initial presentation on a maintenance dose of cyclophosphamide.

Of the six histology-positive PACNS cases, two died, one suffered severe disability, two had moderate disability and one had minor disability. All had received steroids and/or further immunosuppression with no clear pattern of response to treatment.

## Neuropathology

Our nine cases of ABRA were all characterized by the presence of severe leptomeningeal and parenchymal amyloid angiopathy, and mild to moderate chronic inflammation within the leptomeninges and in and around the walls of many amyloid-laden blood vessels. The amyloid angiopathy showed

the full range of complications that have been described in non-inflammatory CAA: splitting of vessel walls, fibrinoid necrosis, acute thrombosis and evidence of previous thrombosis with recanalization (Fig. 2).

Adjacent to some of the blood vessels were clusters of haemosiderin-laden macrophages, indicating previous minor haemorrhage. A few amyloid-laden blood vessels were surrounded by foci of acute haemorrhage.

The perivascular and intramural inflammatory infiltrate consisted of lymphocytes, macrophages (many of which had an epithelioid appearance) and multinucleated giant cells. In every case, epithelioid macrophages and giant cells were present in and adjacent to the walls of at least some of the inflamed, amyloid-laden blood vessels. However, the infiltrate around many of the vessels consisted solely of lymphocytes and small macrophages.

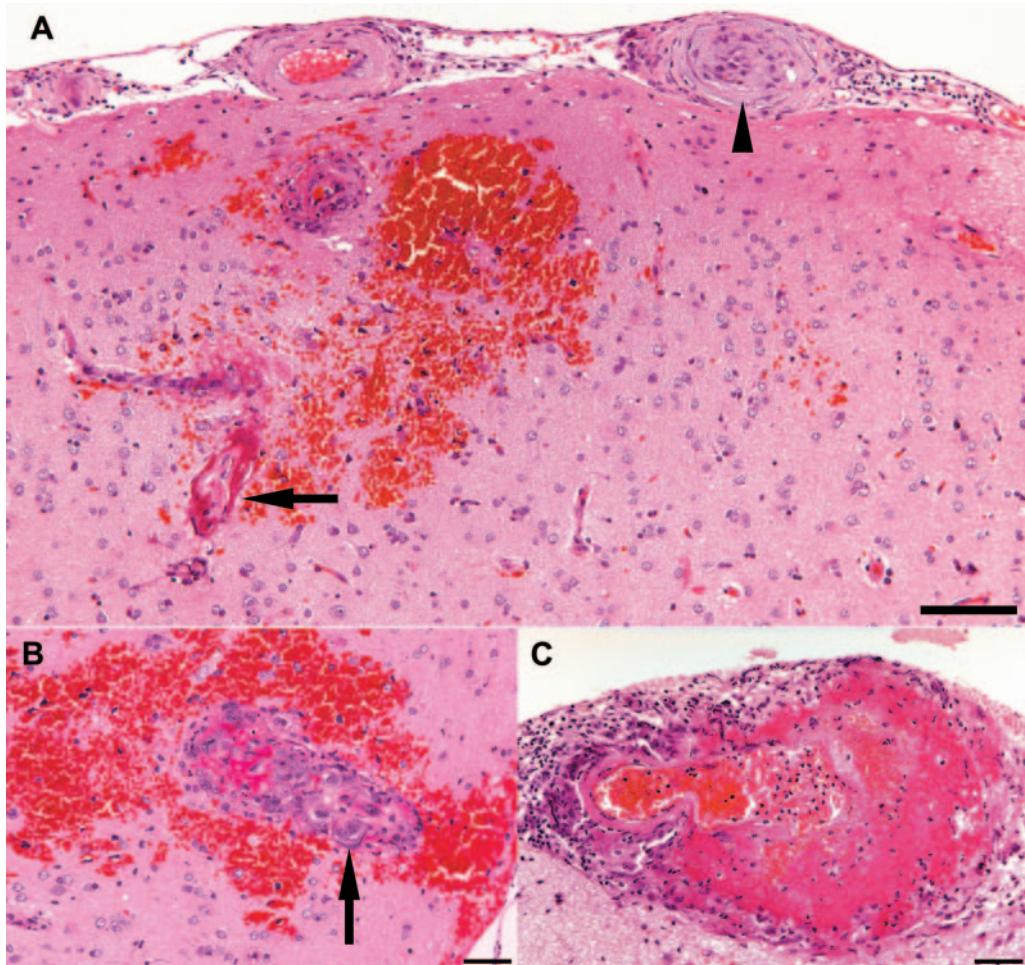
The biopsy specimens contained cerebral cortex and meninges, but little white matter. The cerebral white matter within the autopsy specimens showed patchy gliosis and rarefaction, in some cases marked (Fig. 3). Mild degenerative changes were noted in blood vessels within the white matter but there was no amyloid or perivascular inflammation.

The six cases of PACNS all had pathologically confirmed changes of CNS vasculitis as classically described, with focal segmental inflammatory destruction of the walls of small leptomeningeal and parenchymal blood vessels by discrete, non-caseating granulomas (Fig. 4). Some of the blood vessels showed fibrinoid necrosis.

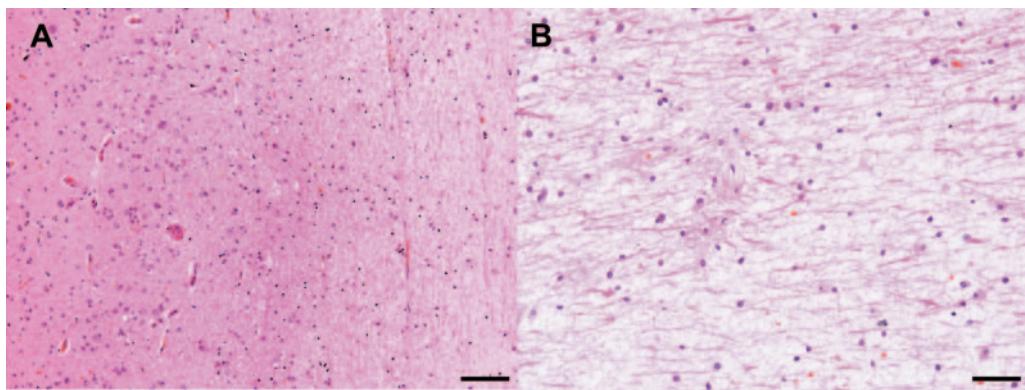
In the cases of CAA without vasculitis, the extent of vascular deposition of amyloid varied from segmental involvement of many leptomeningeal and parenchymal vessels and circumferential involvement of a few, to widespread severe vascular amyloid with associated dyshoric change (i.e. extension of tufts of amyloid from the vessel wall into the adjacent brain parenchyma). The specimens with the most severe CAA were all from patients with Alzheimer's disease and also showed the characteristic changes of that disease, in the form of diffuse and neuritic plaques, many neurofibrillary tangles and neuropil threads, moderate to marked astrocytosis, and a moderate increase in the number of microglia. Neither the Alzheimer nor the non-Alzheimer cases with CAA had lymphocytic inflammation in the meninges or brain parenchyma. Occasional amyloid-laden blood vessels showed splitting of the wall, fibrinoid necrosis or thrombosis, but these changes were not accompanied by lymphocytic infiltration, epithelioid macrophages or multinucleated giant cells. The white matter was slightly gliotic but in none of these cases was there the marked rarefaction or hypocellularity seen in several of the autopsy cases of ABRA.

## Immunohistochemistry

Positive reaction with antibodies to tau was largely confined to the cases of Alzheimer's disease with CAA, in which the neurofibrillary tangles and neuropil threads were strongly immunopositive. No more than a very occasional, solitary



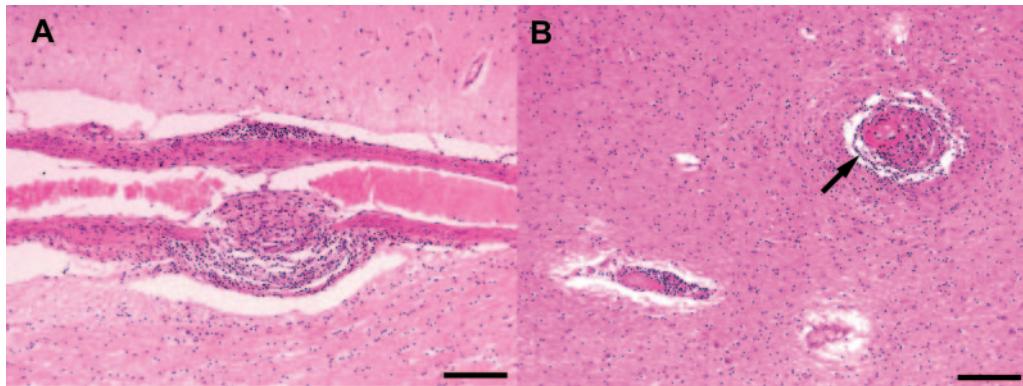
**Fig. 2** Amyloid angiopathy in ABRA. (A) One cortical blood vessel has undergone fibrinoid necrosis (arrow) and others are surrounded by petechial haemorrhages. One of the meningeal arteries shows evidence of previous thrombosis and organization (arrowhead). Note the lymphocytic infiltrate in the adjacent subarachnoid space. Bar = 100  $\mu$ m. (B) This blood vessel is largely replaced by a granulomatous inflammatory infiltrate and is surrounded by haemorrhage. The arrow indicates a multinucleated macrophage. Bar = 50  $\mu$ m. (C) Inflammation (to the left) and extensive fibrinoid necrosis of a meningeal artery. Bar = 50  $\mu$ m.



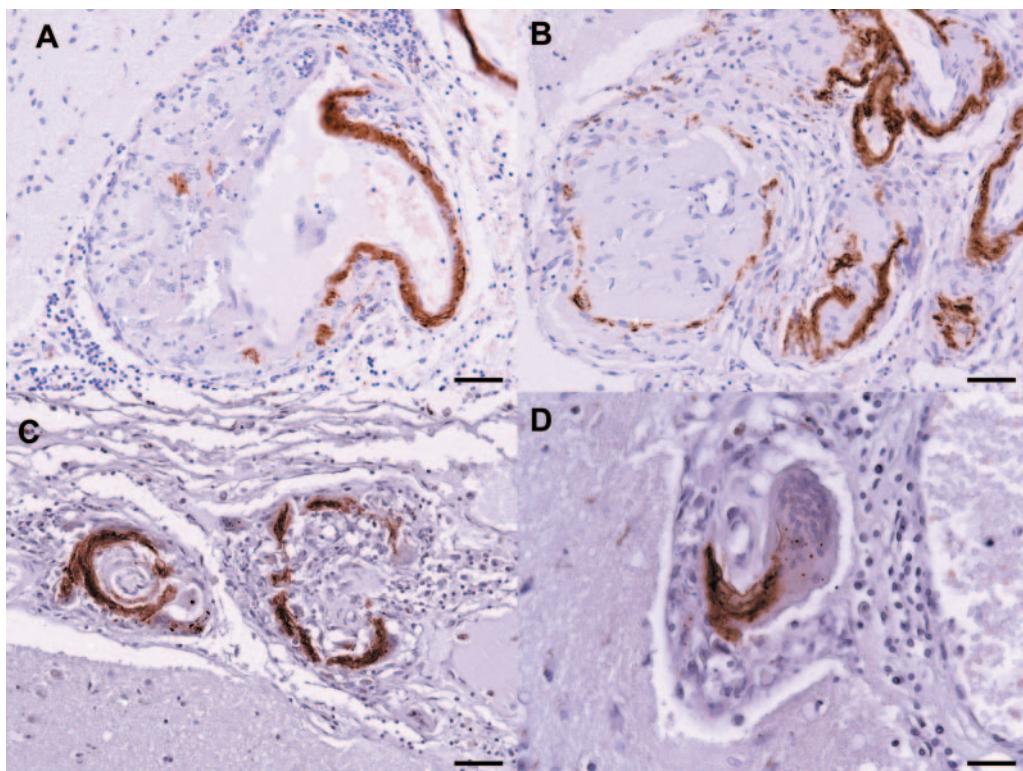
**Fig. 3** White matter changes in ABRA. (A) Low-magnification view of cerebral cortex and rarefied superficial white matter. Bar = 400  $\mu$ m. (B) Higher magnification reveals gliotic white matter with a reduced density of nerve fibres. Bar = 50  $\mu$ m.

immunopositive thread-like structure was seen in the cortex in the cases of ABRA, and none included neurofibrillary tangles. None of the cases in any of the groups examined showed abnormal labelling for  $\alpha$ -synuclein.

In all cases of ABRA and of non-inflammatory CAA, the vessel-associated amyloid labelled strongly with antibodies to A $\beta$  (Fig. 5). A $\beta$  was also demonstrable within some of the epithelioid macrophages and giant cells in the vasculitic



**Fig. 4** PACNS. (A) Focal, segmental inflammatory destruction of the wall of a small cerebral artery by non-caseating granulomatous inflammation. Bar = 100  $\mu$ m. (B) In this case, there are discrete foci of granulomatous inflammation associated with two parenchymal blood vessels, one of which (arrow) shows fibrinoid necrosis. Bar = 100  $\mu$ m.

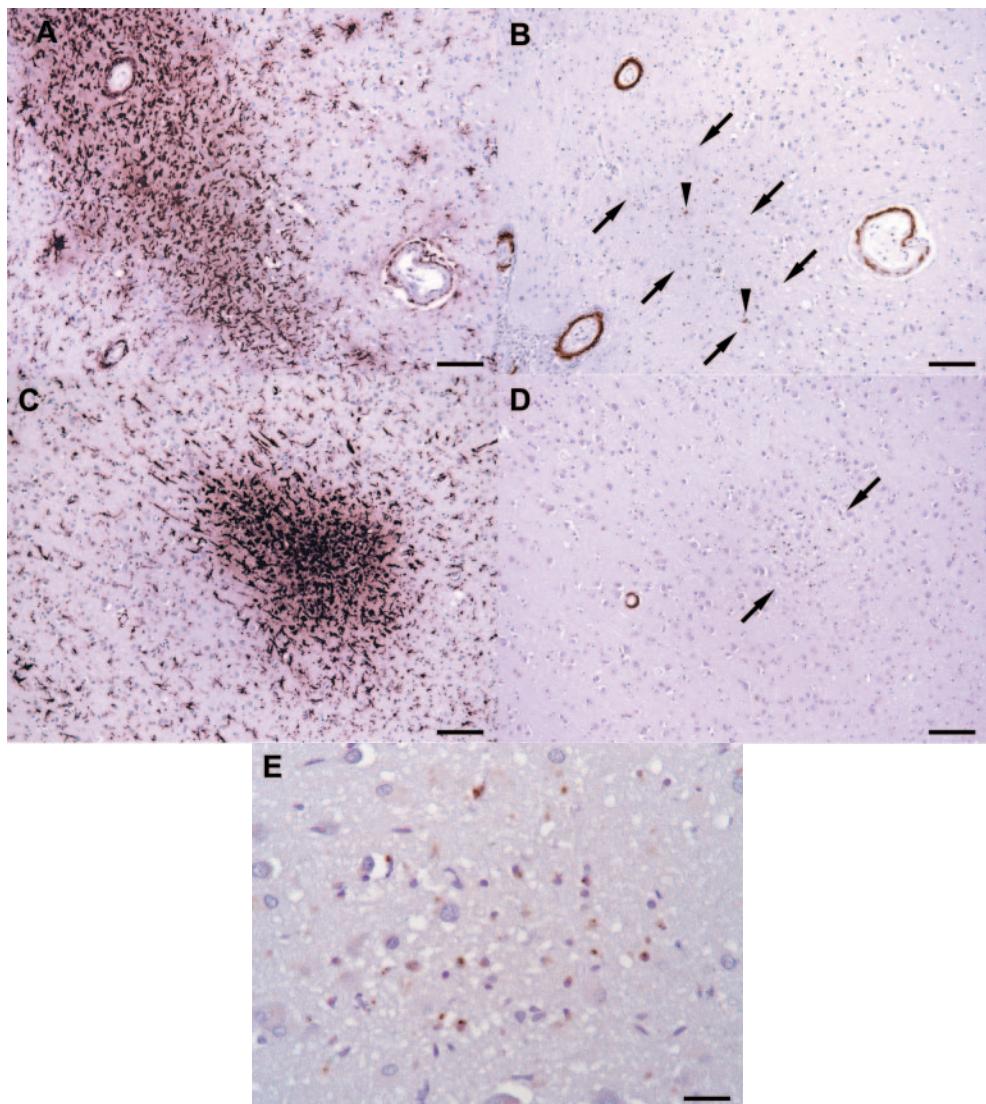


**Fig. 5** Immunolabelling of A $\beta$  in ABRA. (A, B) Granulomatous destruction of A $\beta$ -laden leptomeningeal arteries. The artery towards the left in B has undergone thrombosis and recanalization. (C, D) Fragments of A $\beta$  are present within epithelioid macrophages and multinucleated giant cells (e.g. arrows in C). Bars = 50  $\mu$ m.

infiltrate. Comparison of labelling for A $\beta_{1-40}$  with that for A $\beta_{1-42}$  showed A $\beta_{1-40}$  to be more abundant but there was considerable overlap in the distribution of the two forms of A $\beta$  within affected blood vessels. None of the ABRA cases included neuritic plaques, and diffuse plaques were sparse. These were predominantly composed of A $\beta_{1-42}$  but some also contained A $\beta_{1-40}$ . Occasional diffuse plaques were related to amyloid-laden blood vessels but most appeared to be quite separate. In ABRA, vasculitic changes and perivascular aggregates of inflammatory cells were restricted to blood

vessels with A $\beta$  in their walls. No parenchymal or vascular A $\beta$  was present in the cases of PACNS.

Immunohistochemistry for MHC class II antigen revealed scattered clusters of activated microglia within the cortex (Fig. 6). Most were in the region of the diffuse plaques but some dense clusters were in areas that lacked plaques. Close examination of the plaque-negative clusters showed several of the microglia to contain small amounts of A $\beta$ . This finding in ABRA, of plaque-negative clusters of microglia, some containing small amounts of A $\beta$ , was not a feature of



**Fig. 6** Relationship of activated microglia to A $\beta$  in ABRA. Adjacent pairs of sections (A, B and C, D) have been immunostained for MHC class II antigen (A, C) or A $\beta$  (B, D). The cortex includes dense clusters of activated microglia that express MHC class II antigen. No plaques are seen in adjacent sections stained for A $\beta$ , although an increase in cellularity and a slight coarsening of the neuropil are evident in the areas that contain the microglial clusters (arrows). Some of the microglia show cytoplasmic immunopositivity for A $\beta$  (e.g. arrowheads in B). Note that A $\beta$  is also present in some of the cortical blood vessels. Bars = 100  $\mu$ m. (E) Higher magnification view of the arrowed area in D, showing more clearly the presence of A $\beta$  within microglia. Bar = 25  $\mu$ m.

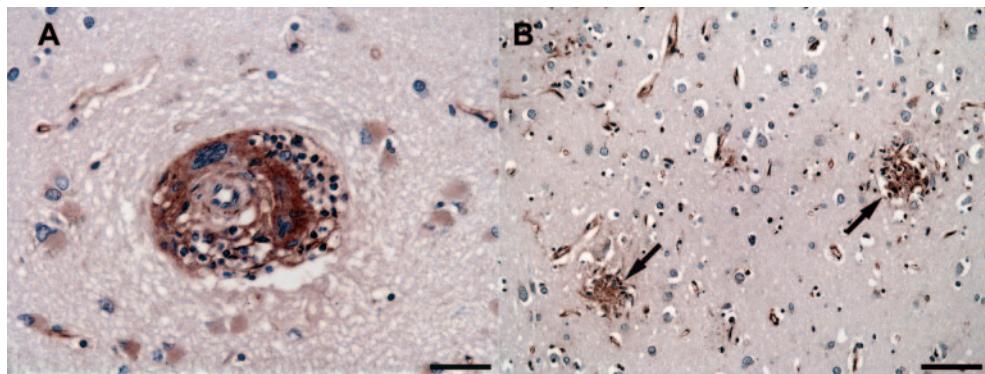
non-inflammatory CAA, either with or without Alzheimer's disease. In Alzheimer's disease with CAA, microglia were associated with A $\beta$  plaques and with some amyloid-laden blood vessels but were otherwise quite sparsely distributed within the cortical parenchyma; in the absence of Alzheimer's disease, very few activated microglia could be demonstrated.

MHC class I antigen was expressed by vascular endothelium, by epithelioid and multinucleated macrophages, and weakly by astrocytes but not by most microglia (Fig. 7). In addition, sections from two of the cases, 66- and 72-year-old males (cases 3 and 6 in Table 1), contained occasional dense clusters of admixed microglia and granular material that labelled with antibody to MHC class I antigen.

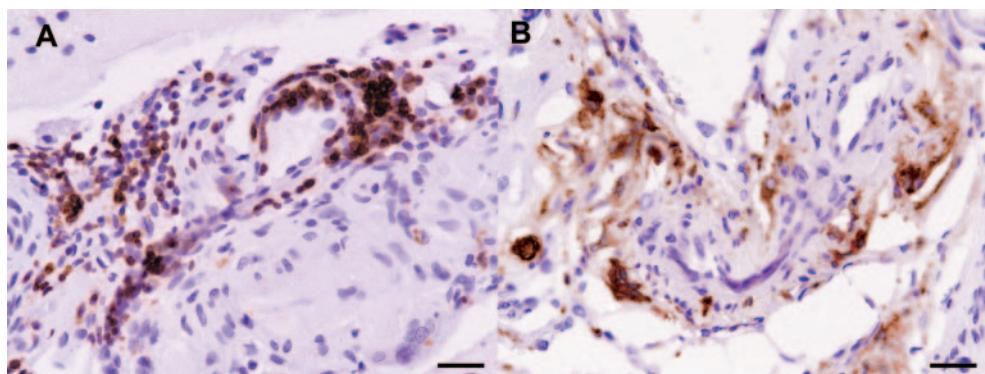
The inflammatory cells in the meninges in ABRA were mostly CD3-positive T cells (Fig. 8). CD3-positive cells were also present in the perivascular and intramural infiltrates, admixed with moderate to large numbers of CD68-positive macrophages (many with abundant cytoplasm) and multi-nucleated giant cells. In addition, antibody to CD68 labelled some of the cortical microglia. Very few lymphocytes were immunohistochemically demonstrable in parts of the cortex away from amyloid-laden blood vessels, or in the white matter.

#### Quantitation of A $\beta$ load

The parenchymal A $\beta$  load in the frontal cortex (i.e. the percentage area of cortex immunopositive for A $\beta$  after



**Fig. 7** MHC class I antigen in ABRA. (A) Abundant MHC class I antigen in multinucleated macrophages surrounding an amyloid-laden cortical arteriole. Surrounding reactive astrocytes are weakly immunopositive. MHC class I antigen is also present in capillary endothelium. Bar = 25  $\mu$ m. (B) Clusters of microglia admixed with granular material (arrows) that is strongly immunopositive for MHC class I antigen. Bar = 50  $\mu$ m.



**Fig. 8** Inflammatory infiltrate in ABRA. (A) Most of the perivascular and leptomeningeal lymphocytes are CD3-immunopositive T cells. (B) The epithelioid and multinucleated giant cells (arrows) express the macrophage marker, CD68. Bar = 25  $\mu$ m.

excluding vessel-associated  $\text{A}\beta$ ) was greatest in CAA with Alzheimer's disease (mean = 1.73%, median = 1.87%, interquartile range = 1.07–2.31), intermediate in ABRA (mean = 0.31%, median = 0.10%, interquartile range = 0.06–0.54) and least in CAA without Alzheimer's disease (mean = 0.02%, median = 0.01%, interquartile range = 0–0.05) (Kruskal–Wallis test,  $P$  = 0.002). In contrast, the mean percentage area occupied by vessel-associated  $\text{A}\beta$  was greatest in ABRA (mean = 0.81%, median = 0.53%, interquartile range = 0.13–1.05), intermediate in CAA with Alzheimer's disease (mean = 0.31%, median = 0.25%, interquartile range = 0.16–0.84) and least in CAA without Alzheimer's disease (mean < 0.001%, median < 0.001%, interquartile range < 0.001 to 0.003) (Kruskal–Wallis test,  $P$  = 0.02). Dunn's post-testing showed that in ABRA the parenchymal  $\text{A}\beta$  load was significantly lower than in Alzheimer's disease ( $P$  < 0.01) but the percentage area occupied by vessel-associated  $\text{A}\beta$  was significantly greater than in CAA without Alzheimer's disease ( $P$  < 0.05).

## Discussion

We have described the clinical, neuroradiological and neuro-pathological features of nine patients with ABRA. Adding a

further 25 cases drawn from the literature has allowed us to define ABRA as a clinical entity and to compare its features with those of idiopathic or primary cerebral angiitis of the CNS (PACNS).

From a clinical perspective, ABRA may be regarded as a close relation of PACNS. The clinical features, laboratory and neuroradiological abnormalities and the response to treatment are not readily distinguishable, although on close comparison of these groups of patients certain differences are apparent. A useful comparison of features may be made by drawing together collections of large series of PACNS and CAA alone, as previously performed by Fountain and Eberhard (1996) (Table 6).

Thus, dementia appears to be more frequent in CAA than in ABRA, while headaches, focal neurological deficits and seizures are more common in PACNS than in ABRA—though the differences are not sufficient to allow clinical diagnostic distinction. Hallucinations are more frequently observed in ABRA. Our study shows an equal male : female ratio, but the mean age of first presentation in ABRA (66.5 years) is considerably greater than that of PACNS [44.8 years from Calabrese and Mallek (1988) and 43 years from our six biopsy cases], but is less than for CAA (76.3 years).

**Table 6** Summary of common first neuropsychiatric presentations of ABRA, PACNS and CAA (modified from Fountain and Eberhard, 1996)

	ABRA (present study of 34 cases)	PACNS <sup>a</sup> (63 cases)	CAA <sup>b</sup> (140 cases)
Mean age	Mean age	Mean age	
67.3 years	44.8 years	76.3 years	
Mental status changes	59%	44%	64%
Dementia	12%	NR	33%
Headaches	35%	63%	36%
Hallucinations	12%	0%	0%
Focal deficits/seizures	24%	81%	61%

<sup>a</sup>Based on combination of data from Calabrese and Mallek (1988) and Lie (1992). <sup>b</sup>Based on combination of data from Gilles *et al.* (1984), Mandybur (1986) and Okazaki *et al.* (1979).

NR = not recorded.

T2-weighted MR brain imaging in ABRA showed multifocal patchy or confluent white matter hyperintensities in 65% of cases. Similar appearances were seen in the PACNS group in this study and other published series. Eng and colleagues reported similar changes in all of their patients with non-vasculitic A $\beta$ -associated cerebral inflammation and noted clear improvement following immunosuppression (Eng *et al.*, 2004). In our ABRA cases, insufficient follow-up MRI was available for detailed comparison, although three did show improvement with time. Cerebral haemorrhage was found in approximately one-fifth of this series, suggesting that ABRA behaves less like CAA, in which haemorrhage is a well-recognized but proportionately less frequent complication, and more like PACNS.

CSF analysis similarly appeared a sensitive but wholly non-specific investigation in ABRA. Modest protein elevation and CSF pleocytosis were observed, as in PACNS [pooled case reviews suggesting raised cell counts—mainly lymphocytosis—and protein, in the range of 50–80%, broadly comparable to this ABRA series (Calabrese and Mallek, 1988; Hankey, 1991; Joseph and Scolding, 2002)] and in non-vasculitic A $\beta$ -associated inflammation (Eng *et al.*, 2004). Of those tested, neither amyloid group had evidence of intrathecal synthesis of immunoglobulins, although these have been found in CSF in up to 40–50% of patients with PACNS in previous series (Scolding *et al.*, 1997).

As all patients reported in this study underwent brain biopsy or came to autopsy, the series may be biased towards more severe cases of ABRA or PACNS. There was, however, no clear relationship between outcome and treatment: 50% of those receiving steroids and/or cyclophosphamide improved but only two patients regained their baseline level of functioning. Improvement with immunosuppression is consistent with an underlying cerebral inflammatory disorder similar to PACNS, and contrasts with the common non-inflammatory form of CAA, which is regarded as an untreatable disorder.

Both PACNS and ABRA are rare—PACNS has a crudely estimated incidence of 1–2 per million per year—though the incidence may have been inaccurately estimated because the difficulty in obtaining biopsy samples, and the high rate of false-negative biopsies (approximately 35%) due to the patchy nature of the inflammatory response in PACNS (Alrawi *et al.*, 1999). Significant numbers of patients are presumptively diagnosed as having PACNS not on the basis of neuropathology but on clinical or angiographic evidence. Furthermore, even when histological examination is performed, vascular A $\beta$  may go unnoticed unless specifically sought by immunohistochemistry with appropriate antibodies. In the light of the common clinical and investigational features of the two disorders, it seems likely that a significant proportion of patients given a diagnosis of PACNS, particularly if not histopathologically confirmed, may in fact have ABRA.

CAA is frequent in the elderly, and so the coincidental occurrence of vasculitis and CAA cannot be entirely excluded. However, several findings argue against this possibility. The first is the striking colocalization of inflammatory changes and amyloid in the same regions of the same intracranial blood vessels. The second is the tendency of epithelioid macrophages and multinucleated giant cells to abut and phagocytose the deposits of A $\beta$  within the walls of the affected vessels. Finally, it is noteworthy that the ages of patients with ABRA, although usually greater than those with PACNS, still tend to be considerably less than those of patients with spontaneous CAA (Esiri and Wilcock, 1986; Yamada *et al.*, 1987; Love *et al.*, 2003)—in our series 19/34 patients (56%) were in their 50s or 60s.

There are at least two ways in which the core pathological features of amyloid deposition and vasculitis may be linked: vasculitis could precipitate amyloid deposition, or *vice versa*. Schmidley (2000) discussed this question but felt that at that time, with only 10 cases reported, three of which antedated the availability of anti-A $\beta$  antibodies, no clear conclusion could be reached.

It is conceivable that vasculitis, by chronically increasing vascular permeability, may allow leakage of soluble A $\beta$ , either from the circulation or from perivascular interstitial fluid, leading to its accumulation and eventual deposition in insoluble form in and around the damaged vessels. If this were the case, the age of presentation of ABRA might be expected to be closer to that of PACNS. Also, it would be surprising that amyloid deposition were not more prominent in other forms of primary and secondary CNS vasculitis. Perhaps ABRA develops only in those vasculitis patients in whom a combination of age-related and genetic predisposing factors favour perivascular accumulation of A $\beta$ . However, this would not explain the plaque-negative clusters of A $\beta$ -containing microglia in ABRA.

An arguably more likely possibility is that amyloid deposition in some individuals with CAA acts as a direct trigger of vasculitis. This, precipitating earlier presentation, would be consistent with the younger age of ABRA patients compared with CAA. A $\beta$  has been shown to induce an inflammatory

cascade in endothelial cells *in vitro* (Suo *et al.*, 1998). Increased numbers of macrophages and microglia are present in a perivascular distribution in brains with (non-vasculitic) CAA compared with normal controls (Yamada *et al.*, 1996), while in Alzheimer's disease it is reported that perivascular deposits of A $\beta$  stimulate local microglial activation (Uchihara *et al.*, 1997). McGeer and others have long argued that inflammatory processes, perhaps triggered by deposition of A $\beta$ , contribute significantly to the pathogenesis of Alzheimer's disease (Ahluwalia and Vellas, 2003; McGeer and McGeer, 2003; Ringheim and Conant, 2004).

In 1999, a beneficial effect of active immunization against the human A $\beta$  in a transgenic mouse model of Alzheimer's disease was reported (Schenk *et al.*, 1999). Subsequent studies in a variety of transgenic mouse models confirmed that immunization produces clearance of parenchymal A $\beta$  and reverses other Alzheimer's disease-like pathological and clinical features (Bard *et al.*, 2000; Janus *et al.*, 2000; Morgan *et al.*, 2000; Sigurdsson *et al.*, 2001; Schenk, 2002; Lombardo *et al.*, 2003; Das *et al.*, 2003). These animal studies led to early clinical trials in patients with Alzheimer's disease. Initially, the results were encouraging in terms of slowing the development of dementia and promoting the clearance of parenchymal A $\beta$  (Check, 2002; Schenk, 2002). However, of 298 patients treated, 18 (6%) developed a meningo-encephalitic illness, as a result of which the trial was halted (Check, 2002; Schenk, 2002; Orgogozo *et al.*, 2003).

Recently, reports on the first two autopsies of patients with this syndrome were published (Nicoll *et al.*, 2003; Ferrer *et al.*, 2004). The patients had developed rapidly progressive cognitive decline, associated with prominent white matter abnormalities on MRI. At autopsy, they were found to have severe CAA, with inflammatory cells (primarily macrophages and T lymphocytes) in the leptomeninges and surrounding amyloid-laden blood vessels in the meninges and cerebral cortex. Several regions of cerebral cortex were largely devoid of A $\beta$  plaques. However, small amounts of A $\beta$  were still present in the cytoplasm of microglia that had clustered within the plaque-free zones. These appearances were interpreted as suggesting immune-mediated clearance of parenchymal A $\beta$ . The parts of the cortex that lacked plaques also lacked the clusters of tau-immunopositive dystrophic neurites that are usually associated with plaques, raising the possibility that at least some of the neurofibrillary tangle-related pathology of Alzheimer's disease may be reversible if A $\beta$  is removed. In the case reported by Ferrer and colleagues, the cortex also contained dense clusters of granular material that labelled with antibody to MHC class I antigen; these were described as 'collapsed' plaques and were thought to be a manifestation of the immune response to plaque-related A $\beta$  (Ferrer *et al.*, 2004). It is noteworthy that similar structures were found in two of the cases in the present series.

The findings in A $\beta$ -immunization-related meningo-encephalitis, taken together with those recently reported in sporadic, non-vasculitic, A $\beta$ -related inflammation (Eng *et al.*, 2004) and our own observations in ABRA, suggest that A $\beta$

may be associated with a spectrum of inflammatory reactions localized to the CNS. Several of the clinical and neuroradiological expressions of this inflammation are broadly uniform across this spectrum. Furthermore, although the classical vasculitic changes in ABRA are histopathologically distinct, severe CAA is a feature of all of these disorders, and the plaque-negative clusters of A $\beta$ -containing microglia and paucity of parenchymal A $\beta$  in at least parts of the cerebral cortex are common to immunization-related meningo-encephalitis and ABRA. Severe sporadic CAA, such as that in both ABRA and A $\beta$ -immunization related meningo-encephalitis, most often occurs in the context of Alzheimer's disease (Chalmers *et al.*, 2003); in the absence of Alzheimer's disease, sporadic CAA in the elderly is usually mild (Love *et al.*, 2003).

Thus, A $\beta$  immunization-induced meningo-encephalitis, sporadic A $\beta$ -associated parenchymal inflammation and ABRA may share a common disease mechanism: an immune response directed against A $\beta$  and causing leptomeningeal and parenchymal inflammation, clearance of parenchymal A $\beta$ , and increased deposition of A $\beta$  in cortical and leptomeningeal blood vessels. Further and more detailed neuropathological and immunological studies are under way to determine whether ABRA is indeed a spontaneous form of autoimmune disease directed at A $\beta$ . A better understanding of the pathogenesis of ABRA may help not only in its treatment and prevention but also in the development of safer and more effective immunotherapy for Alzheimer's disease.

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