Aβ-related angiitis: primary angiitis of the central nervous system associated with cerebral amyloid angiopathy

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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 β peptide (Aβ)-related CAA. Here we describe the clinical, neuroradiological and neuropathological features of nine patients with Aβ-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 Aβ-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 hyper-intensities on MRI but these are of similar appearance to those in PACNS. Cerebrospinal fluid usually shows modest elevation of protein and pleocytosis. Neuropathology reveals angiodestructive inflammation, often granulomatous, and meningeal lymphocytosis. Aβ 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 Aβ. 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 Aβ-immunization-related encephalitis and to Alzheimer’s disease.

Keywords: Aβ-related angiitis; Alzheimer’s disease; cerebral amyloid angiopathy; CNS vasculitis; primary angiitis of the CNS

Abbreviations: Aβ = amyloid β peptide; ABRA = Aβ-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 of the most common of which is sporadic CAA due to the vascular deposition of amyloid β peptide (Aβ). Aβ 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 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).

PACNS and CAA are generally regarded as unrelated disorders. A few case reports have, however, described neuropathologically confirmed cerebral vasculitis in patients with sporadic, Aβ-related CAA. The angiitis is centred on blood vessels carrying extensive Aβ 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 Aβ 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 Aβ. Clinical studies exploring the potential of Aβ 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 Aβ, 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 Aβ-related angiitis (ABRA) and explore further the hypothesis that this spontaneous association of CAA with vasculitic inflammation has important immunopathological parallels with Aβ 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 Aβ in susceptible patients and is part of a more widespread immune reaction to Aβ 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 neuropathologically 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 Aβ, Aβ₁₋₄₀, Aβ₁₋₄₂, tau with phosphorylated Ser202, α-synuclein, MHC class I and II antigens, CD3, CD20 and CD68. Sections 5 μm 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% H₂O₂ to quench non-specific peroxidase activity. The sections were then incubated first in 20%
<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age, sex</th>
<th>F/U (months)</th>
<th>Presentation</th>
<th>Later clinical features</th>
<th>Bloods</th>
<th>CSF</th>
<th>CT brain</th>
<th>MRI brain</th>
<th>EEG</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70, F</td>
<td>18</td>
<td>Confusion, hallucinations, reduced conscious level</td>
<td>Similar deterioration, globally brisk reflexes</td>
<td>ESR 12, cholesterol 7.2</td>
<td>OP normal, Pr = 3.07, WC 0.9, OCB neg.</td>
<td>Temporal lobe swelling</td>
<td>Temporal lobe swelling with enhancement. Multifocal white matter lesions in R occipital lobe</td>
<td>Widespread irregular theta, with delta burst (encephalopathy)</td>
<td>Cyclophosphamide and steroids; long-term improvement</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>2</td>
<td>66, F</td>
<td>36</td>
<td>Amnesia, headache, visual disturbance, dysgraphia, impaired musical ability</td>
<td>TIAs and cognitive decline</td>
<td>NAD</td>
<td>OP normal, Pr = 1.23, WC 1, OCB neg.</td>
<td>Multiple diffuse WM lesions</td>
<td>Multiple diffuse WM lesions + haemorrhage in frontal lobe.</td>
<td>Bilateral slow wave activity</td>
<td>Prednisolone 60 mg/day, reduced to 10 mg on alternate days for 2 years; improved</td>
<td>Mild disability</td>
</tr>
<tr>
<td>3</td>
<td>66, M</td>
<td>2</td>
<td>Dysphasia, poor memory, paranoia</td>
<td>Worsening paranoia, confusion, parkinsonism, ataxia, GCS 5-8</td>
<td>Platelets 104, GGT 338</td>
<td>OP = 30, Pr = 3.7, WC 0, OCB neg.</td>
<td>Diffuse WM lesions, worse R frontal + mass effect, no enhancement</td>
<td>Not done</td>
<td>Non-specific generalized slow waves</td>
<td>IV dexamethasone 4 mg/day for 10 days, plus acyclovir and heparin</td>
<td>Death</td>
</tr>
<tr>
<td>4</td>
<td>54, M</td>
<td>14</td>
<td>Encephalopathy</td>
<td>Cortical blindness, visual hallucinations, labile mood, CPS, poor gait, Progressive weakness</td>
<td>Elevated CRP, PV 1.90, deranged LFTs</td>
<td>OP = 25, Pr and WC normal</td>
<td>Not available</td>
<td>Diffuse white matter lesions</td>
<td>Not available</td>
<td>High dose steroids</td>
<td>Severe disability</td>
</tr>
<tr>
<td>5</td>
<td>74, F</td>
<td>3</td>
<td>Generalized seizure, Bell's palsy, anisocoria, dysmetria, up-going L toe</td>
<td>AI neg.</td>
<td>Low platelets, lymphocytes, eosinophils and basophils</td>
<td>AI neg.</td>
<td>Not done</td>
<td>Diffuse infiltrating 'tumour' extending from R parieto-occipital to temporal region</td>
<td>Not done</td>
<td>Not done</td>
<td>‘Tumour’ resection - brief improvement</td>
</tr>
<tr>
<td>Case</td>
<td>Age</td>
<td>Gender</td>
<td>Symptoms and Findings</td>
<td>Investigations</td>
<td>Treatment</td>
<td>Outcome</td>
<td></td>
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<tr>
<td>6 72, M 6</td>
<td>Raised WC, cognitive decline (multifocal), depression (improvement with medication), scotoma, slow speech, poor concentration</td>
<td>Not done</td>
<td>Hypodense area in right occiput</td>
<td>Cyclophosphamide 1.5 g in 3 cycles, prednisolone</td>
<td>Death</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>7 72, M 2</td>
<td>Left-sided weakness, confusion, dysphasia, dyspraxia</td>
<td>AI neg, ESR normal</td>
<td>Pr = 4.46, lymphocytes 21, glucose slightly low</td>
<td>‘Tumour’ resection, dexamethasone; brief initial improvement</td>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 72, F 6</td>
<td>Confusion, dementia, dyspraxia, dysphasia</td>
<td>None</td>
<td>Pr = 0.44, WC 0, OCB neg.</td>
<td>Bifrontal complex slow activity</td>
<td>Mild disability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 82, M 2.5</td>
<td>Bifrontal headaches, poor memory, behaviour disturbance</td>
<td>ESR normal</td>
<td>WC 18 (68% lymphocytes), Pr = 0.14</td>
<td>Steroids</td>
<td>Death</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

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

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% H₂O₂. 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 Aβ load

This was made on the paraffin sections of biopsy or post-mortem frontal lobe that had been immunostained for pan-Aβ with M0872 (raised against Aβ 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 Aβ (i.e. the total amyloid load) was measured. The operator then traced around and excluded the Aβ-laden blood vessels and measured the remaining percentage area occupied by Aβ (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 Balke, 1992; Fountain and Eberhard, 1996; Anders et al., 1997; Fountain and Lopes,
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 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 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**

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>White matter lesions</td>
<td>7 (27%)</td>
<td>13 (65%)</td>
</tr>
<tr>
<td>Mass lesions/oedema</td>
<td>8 (31%)</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>Haemorrhages</td>
<td>3 (12%)</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>Hypodensities/infarcts</td>
<td>3 (12%)</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>3 (12%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Atrophy</td>
<td>1 (4%)</td>
<td>1 (5%)</td>
</tr>
</tbody>
</table>

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

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

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**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 μm. (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 μm. (C) Inflammation (to the left) and extensive fibrinoid necrosis of a meningeal artery. Bar = 50 μm.

**Fig. 3** White matter changes in ABRA. (A) Low-magnification view of cerebral cortex and rarefied superficial white matter. Bar = 400 μm. (B) Higher magnification reveals gliotic white matter with a reduced density of nerve fibres. Bar = 50 μm.
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. 4** PACNS. (A) Focal, segmental inflammatory destruction of the wall of a small cerebral artery by non-caseating granulomatous inflammation. Bar = 100 μm. (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 μm.

**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 μm.
non-inflammatory CAA, either with or without Alzheimer’s disease. In Alzheimer’s disease with CAA, microglia were associated with Aβ 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 multinucleated 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 Aβ load**

The parenchymal Aβ load in the frontal cortex (i.e. the percentage area of cortex immunopositive for Aβ after

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**Fig. 6 Relationship of activated microglia to Aβ in ABRA.** Adjacent pairs of sections (A, B and C, D) have been immunostained for MHC class II antigen (A, C) or Aβ (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 Aβ, 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 Aβ (e.g. arrowheads in B). Note that Aβ is also present in some of the cortical blood vessels. Bars = 100 μm. (E) Higher magnification view of the arrowed area in D, showing more clearly the presence of Aβ within microglia. Bar = 25 μm.
excluding vessel-associated Aβ) 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 Aβ 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 Aβ load was significantly lower than in Alzheimer’s disease (\( P < 0.01 \)) but the percentage area occupied by vessel-associated Aβ was significantly greater than in CAA without Alzheimer’s disease (\( P < 0.05 \)).

**Discussion**

We have described the clinical, neuroradiological and neuropathological 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).
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 Aβ-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 more severe.

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 lymphocytes—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 Aβ-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.

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

<table>
<thead>
<tr>
<th></th>
<th>ABRA (present study of 34 cases)</th>
<th>PACNS(^a) (63 cases)</th>
<th>CAA(^b) (140 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental status changes</td>
<td>59%</td>
<td>44%</td>
<td>64%</td>
</tr>
<tr>
<td>Dementia</td>
<td>12%</td>
<td>NR</td>
<td>33%</td>
</tr>
<tr>
<td>Headaches</td>
<td>35%</td>
<td>63%</td>
<td>36%</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>12%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Focal deficits/seizures</td>
<td>24%</td>
<td>81%</td>
<td>61%</td>
</tr>
</tbody>
</table>

\(^{a}\)Based on combination of data from Calabrese and Mallek (1988) and Lie (1992). \(^{b}\)Based on combination of data from Gilles et al. (1979), Mandybur (1986) and Okazaki et al. (1979). NR = not recorded.

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 of 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 Aβ 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 Aβ 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-Aβ antibodies, no clear conclusion could be reached.

It is conceivable that vasculitis, by chronically increasing vascular permeability, may allow leakage of soluble Aβ, 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 Aβ. However, this would not explain the plaque-negative clusters of Aβ-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. Aβ 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 Aβ stimulate local microglial activation (Uchihara et al., 1997). McGeer and others have long argued that inflammatory processes, perhaps triggered by deposition of Aβ, contribute significantly to the pathogenesis of Alzheimer’s disease (Ahuwalia and Vellas, 2003; McGeer and McGeer, 2003; Ringheim and Conant, 2004).

In 1999, a beneficial effect of active immunization against the human Aβ 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 Aβ 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 Aβ (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 Aβ plaques. However, small amounts of Aβ 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 Aβ. 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 Aβ 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 Aβ (Ferrer et al., 2004). It is noteworthy that similar structures were found in two of the cases in the present series.

The findings in Aβ-immunization-related meningo-encephalitis, taken together with those recently reported in sporadic, non-vasculitic, Aβ-related inflammation (Eng et al., 2004) and our own observations in ABRA, suggest that Aβ 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 Aβ-containing microglia and paucity of parenchymal Aβ 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 Aβ-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, Aβ immunization-induced meningo-encephalitis, sporadic Aβ-associated parenchymal inflammation and ABRA may share a common disease mechanism: an immune response directed against Aβ and causing leptomeningeal and parenchymal inflammation, clearance of parenchymal Aβ, and increased deposition of Aβ 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 Aβ. 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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