ORIGINAL ARTICLE

Amyloid β-related Angiitis of the Central Nervous System: Report of 3 Cases

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ABSTRACT: ***Objective:*** Amyloid-β (Aβ) related angiitis (ABRA) is a recently described clinicopathological entity characterized by cerebrovascular Aβ deposition and arteritis. Cerebral Aβ deposition is commonly present in cerebal amyloid angiopathy (CAA) and Alzheimer's disease (AD) but is rarely associated with inflammatory infiltration of vessel walls. Our objective is to help clarify the clinical spectrum, radiographic findings, response to treatment, and outcomes of ABRA. The neuropathological relationship between ABRA, cerebral amyloid angiopathy, and Alzheimer's disease is discussed. ***Methods:*** We present three cases of ABRA managed at a tertiary care centre. ***Results:*** All three patients presented with seizures and cognitive dysfunction; one had multifocal neurologic findings. Brain biopsies revealed inflammatory arteritis with Aβ deposits in the vessel walls. All were treated with steroids and cyclophosphamide. Two had favorable outcomes and one stabilized but with severe residual neurologic disability. ***Conclusions:*** ABRA is an unusual but likely under-recognized and potentially treatable disorder. As in other reported cases, our findings suggest that many patients respond favorably to immunosuppressive therapy. We believe that all biopsy specimens consistent with primary angiitis of the central nervous system (CNS) should be further examined for vascular Aβ deposition.

RÉSUMÉ: Trois observations d'angéite du système nerveux central reliée à la β-amyloïde. ***Objectif :*** L'angéite reliée à la β-amyloïde (ARβA) est une entité clinicopathologique qui a été décrite récemment. Elle se caractérise par la déposition cérébrovasculaire d'Aβ et par une artérite. La déposition cérébrale d'Aβ est fréquemment présente dans l'angiopathie amyloïde cérébrale (AAC) et la maladie d'Alzheimer (MA), mais elle est rarement associée à une infiltration inflammatoire de la paroi des vaisseaux. Notre objectif était d'aider à clarifier le spectre clinique, les constatations radiologiques, la réponse au traitement et l'évolution de la maladie. Nous discutons de la relation neuropathologique entre l'ARβA, l'angiopathie amyloïde cérébrale et la MA. ***Méthode :*** Nous présentons trois observations de patients atteints d'ARβA traités dans un centre de soins tertiaires. ***Résultats :*** Ces trois patients ont consulté pour des crises convulsives et une dysfonction cognitive et l'un d'entre eux présentait des signes neurologiques multifocaux. Les biopsies du cerveau ont montré la présence d'une artérite inflammatoire accompagnée de dépôts d'Aβ dans la paroi des vaisseaux. Ils ont tous reçu des stéroïdes et de la cyclophosphamide. Deux patients ont récupéré et l'état de l'autre s'est stabilisé, avec cependant une invalidité neurologique résiduelle importante. ***Conclusions :*** L'ARβA est une maladie rare, vraisemblablement sous-diagnostiquée, mais qui est potentiellement traitable. Comme dans les autres observations rapportées, nos constatations suggèrent que plusieurs patients répondent favorablement au traitement immunosuppresseur. Nous croyons qu'on devrait rechercher l'Aβ dans la paroi des vaisseaux de tous les spécimens obtenus par biopsie où l'on observe une angéite primaire du SNC.

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Amyloid beta-related angiitis (ABRA) of the central nervous system (CNS) was defined as a distinct clinicopathological condition in 2005 based on a case series and published case reports dating back to 1974.[1,2] It is a sporadic, granulomatous angiitis that combines features of both primary angiitis of the CNS (PACNS) and cerebral amyloid angiopathy (CAA). Amyloid beta-related angiitis fulfills the diagnostic criteria for PACNS which requires a history of an unexplained neurological deficit that is caused by vasculitis confined to the CNS.[3] The histopathologic hallmark of PACNS is a predominantly mononuclear infiltration of cells in and around leptomeningeal and cerebral vessels.[4] Amyloid beta-related angiitis possesses the additional feature of amyloid-beta (Aβ) peptide deposition in the cerebrovasculature, and is therefore distinct from PACNS.[1,5] Like ABRA, CAA also shares the distinct pathologic feature of Aβ deposition in the walls of arteries and arterioles. Both sporadic and familial forms of CAA may be associated with some perivascular inflammation,[6,7] but ABRA is distinguished by the presence of intramural multinucleated giant cell infiltration and vessel wall damage.[1]

It is uncertain whether Aβ deposition induces inflammation or, conversely, whether sporadic CNS vasculitis induces Aβ deposition. Scolding et al hypothesized that vascular deposition of Aβ in susceptible individuals triggers an immune reaction within the CNS.[1] This theory is supported by a transgenic mouse model in which a severe vasculitis has been observed in response to CAA.[8] Kinnecom et al found the APOE ε4/ ε4 genotype among 10 of 13 (76.9%) patients with CAA-related inflammation and suggested that this may play a pathogenic role in the immune response to vascular Aβ.[9]

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Amyloid beta-related angiitis shares many of the clinical, laboratory, and neuroradiologic features of PACNS and CAA but notable differences help distinguish these entities. The mean age at first neurologic presentation for ABRA is typically in the 7th decade (63-67 years)[1,5] which is younger than CAA which usually presents in the 8th decade[1,10] but older than the reported mean for PACNS (43-47 years).[1,5,11] Patients with PACNS are more likely to develop headaches, focal neurologic deficits, and seizures compared to those with ABRA.[1] However, hallucinations may be more common in ABRA.[1] The cerebrospinal fluid (CSF) may show modest protein elevation and CSF pleocytosis in both ABRA and PACNS. Radiographically, ABRA and PACNS cannot readily be distinguished.[1,5] Intracerebral hemorrhage is a common feature of both ABRA and CAA.[1]

The cerebral amyloidoses comprise a variety of distinct disease entities including Alzheimers' disease (AD). Alzheimers' disease is characterized by amyloid-associated inflammation but is distinguished from ABRA by its predilection for cerebral cortex rather than vessel walls. In the initial case series, none of the cases had cortical features of AD, suggesting that they are not associated.[1]

Knowledge of the clinical features of ABRA is derived from case series and individual case reports in the literature. We present three cases of ABRA managed at a single tertiary care centre. Our cases help clarify the clinical spectrum, radiographic findings, response to treatment, and outcome of ABRA.

Case Histories

Patient 1

A 66 year-old female presented to hospital with a generalized tonic clonic (GTC) seizure. This was preceded by a one day history of fatigue, dizziness, and gait imbalance. Neurologic examination revealed a left homonymous hemianopia, left motor and sensory neglect, impaired fine motor coordination on the left, left-sided hyperreflexia, and an extensor plantar response on the left. She had significant visuospatial dysfunction on initial cognitive testing.

Laboratory data were unremarkable. An electroencephalogram (EEG) revealed periodic lateralized epileptiform discharges in the right posterior occipital region. A magnetic resonance image (MRI) brain demonstrated bilateral T2W hyperintensities in the posterior hemispheres (Figure 1). Magnetic resonance angiography was normal.

She was treated with antihypertensive drugs for suspected posterior reversible encephalopathy syndrome (PRES). Her clinical status remained stable and she was discharged from hospital three months later with moderate functional impairment. She was readmitted to hospital two months after discharge with epilepsia partialis continua, worsening left sided sensori-motor neglect, and moderate global cognitive impairment. A repeat MRI revealed progression of the T2W hyperintensities and moderate cortical atrophy. Cerebrospinal fluid analysis was normal. A repeat EEG showed resolution of PLEDS but interictal epileptiform abnormalities in the right posterior region with bilateral slowing. A brain biopsy done seven months after her initial presentation confirmed the diagnosis of ABRA (Figure 2). She was treated with oral prednisone 50 mg daily for four weeks followed by a slow taper and one course of IV cyclophosphamide (500 mg/m^2 = 730mg IV).

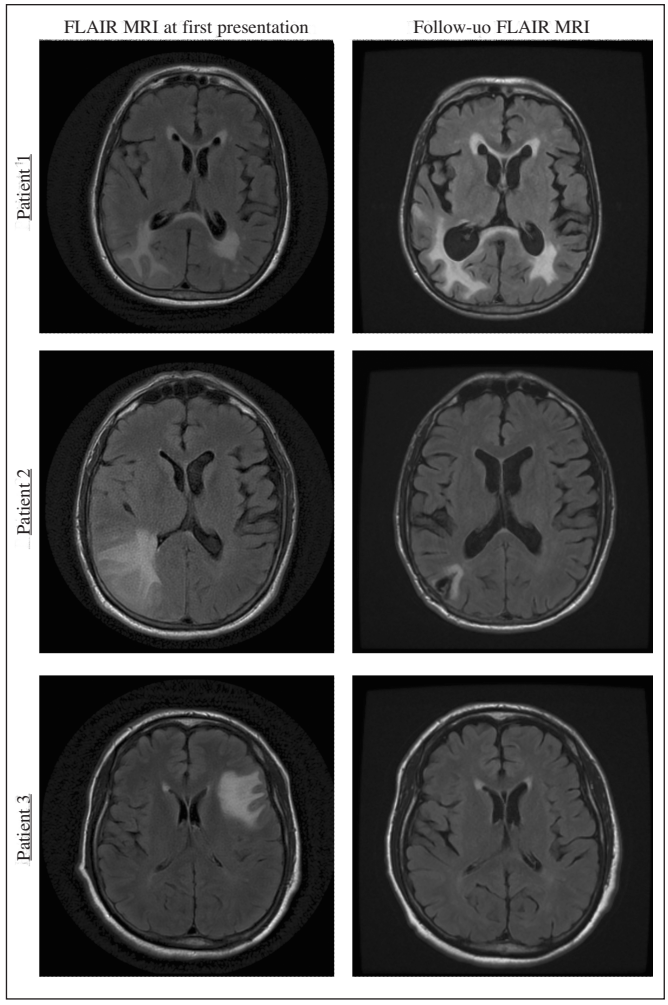

Figure 1: *Magnetic resonance imaging (MRI) appearance in patients with ABRA. In Patient 1, the MRI revealed bilateral subcortical T2 hyperintensities and cortical atrophy. Radiographic progression occurred prior to diagnosis (two month interval). In Patients 2 and 3, the focal T2 hyperintense areas noted at presentation largely or completely resolved following treatment.*

In the four weeks following initiation of treatment she demonstrated progressive neurologic deterioration and a decision was made to stop immunomodulating therapy and initiate supportive measures only. However, over subsequent weeks she recovered some neurologic function. She was maintained on prednisone 5 mg daily.

At last follow-up ten months after initial presentation she was neurologically stable with a residual left homonymous hemianopia, left-sided sensorimotor neglect, left-sided pyramidal tract signs and moderate cognitive dysfunction. She continued to have severe functional disability. A brain MRI was unchanged from the pre-treatment MRI.

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Patient 2

A 57 year-old male with mild cognitive dysfunction at baseline presented to hospital with a GTC seizure. Examination revealed global cognitive impairment but no focal neurologic signs.

Laboratory data were unremarkable. A brain MRI revealed a large area of T2W hyperintensity in the right parietal and temporal lobes with mass effect (Figure 1). A second small (2 cm) hyperintense lesion was present in the right frontal lobe. An EEG showed polymorphic delta and right hemispheric epileptiform discharges. A lumbar puncture was not performed. A brain biopsy done one week following symptom onset confirmed the diagnosis.

He was started on prednisone 50 mg daily for six months followed by a gradual taper and monthly cyclophosphamide ($750mg/m^2$ = 1370mg IV) for six months.

He remained neurologically stable and a repeat MRI at four months following presentation showed marked improvement (Figure 1). At last follow-up five months after presentation he had returned to his baseline level of function without any residual neurologic deficits.

Patient 3

A 58 year-old male presented with a GTC seizure. Neurologic examination was normal. An MRI revealed prominent left frontotemporal subcortical signal change with the appearance of vasogenic edema suggestive of a primary glioma (Figure 1). An EEG revealed a non-specific right temporal dysrhythmia. Cerebrospinal fluid analysis was normal.

Four weeks later, plans were made for a brain biopsy and a pre-operative MRI was done. This demonstrated marked reduction in the size of the lesion and biopsy was deferred.

The patient had a second GTC seizure three months following his initial presentation and a repeat MRI showed that the lesion had increased in size. He subsequently developed an expressive language deficit and recurrent seizures refractory to medical therapy. He had mild cognitive deficits and personality change. A brain biopsy done 16 weeks after symptom onset confirmed the diagnosis of ABRA.

He was treated with oral prednisone (60 mg daily for one month tapered to a maintenance dose of 20 mg) and cyclophosphamide (150mg PO daily, followed by monthly injections). He remained on prednisone and cyclophosphamide for nine months after which he was switched to azathioprine alone.

Neuropsychology testing was performed four months after initiating treatment and revealed mild to moderately severe dysexecutive syndrome, social disinhibition and perseveration. Similar abnormalities were found when re-tested 15 months later. He remained neurologically stable at last follow up, two years after initial presentation. A repeat MRI at that time demonstrated complete resolution of the lesion (Figure 1).

Biopsy Results

Vasculitis was seen in all three patients. Sections of cortex showed an inflammatory arteritis with infiltration of the walls of arterioles by CD68 positive macrophages, CD3 positive T lymphocytes and, in some cases, multinucleated giant cells. These vessels, and others around them, also contained deposits of β-amyloid, positive on PAS and by immunohistochemistry (see Figure 2). In Patients 1 and 2, rare leptomeningeal vessels were involved, not seen in Patient 3. Involvement was largely confined to cortical vessels. The percentage of cortical vessels larger than capillaries involved by vasculitis was 20.2% (33/163) in Patient 1, 36.4% (71/195) in Patient 2 and 37.9% (44/116) in Patient 3, with an average of about a third or 31.5%. Vasculitis was accompanied by mild lymphocytic inflammation in the leptomeninges (meningitis). This was associated with diffuse astrocytosis in both cortex and white matter, pallor of the white matter (reflecting myelin depletion) and small infarcts. Blood vessel damage consisted of fibrinoid deposits, fibrosis and thickening, luminal occlusion and hypertrophy of endothelial cells. In Patient 1, there was also some deposition of tau positive neuritic plaques in the cortex, but not enough to make a firm diagnosis of Alzheimer's disease by current criteria (see Figure 2).[12] In Patients 2 and 3, tau stains were negative. Immunohistochemistry was performed using the following primary monoclonal antibodies: mouse anti human β-amyloid (clone 6F/3D, code#M0872, Dako), rabbit-anti human CD3 (clone 2GV6, cat#790-4341, Ventana) and mouse anti-human CD68 (clone KP1, code# M0814, Dako). A polyclonal rabbit anti-human tau antibody (code# A0024, Dako) was also used.

Discussion

To date, most of our knowledge of ABRA comes from published case reports or small case series. Our three patients provide further insight into the clinical characteristics of this unusual but likely under-recognized and potentially treatable disorder.

All three patients in our study presented in the 6th or 7th decade (ages 66, 57, and 58). In a review of 34 patients by Scolding et al (25 of whom were derived from published case reports), the mean age at presentation was 67.3 years.[1] Salvarani et al reported a median age at diagnosis of 63 years in their series of eight patients.[5]

The clinical features of ABRA are highly variable. In the review by Scolding et al, the most common clinical features were altered mental status (59%) often leading to dementia, headaches (35%), seizures and focal neurologic deficits (24%).[1] In the patients described by Salvarani et al, focal manifestations and cognitive dysfunction were the most common symptoms at presentation. In that series, the presentation was often acute with the time from onset of symptoms to diagnosis of less than one month in four of those eight patients.[5]

All three of our patients presented with seizure as the leading clinical feature. Two were otherwise asymptomatic and one had focal neurologic deficits. Cognitive dysfunction, though not reported by any of our patients at presentation, was present in all three on formal testing. Two of our patients had a stuttering course at onset with a several month period of stability followed by rapid progression of neurologic dysfunction prior to diagnosis and treatment. The third had an acute course with a diagnosis made within a month of symptom onset. The stage of rapid progression in our patients is in keeping with the pattern of acute decline noted by Salvarani et al.[5]

Brain MRI scans are typically abnormal in ABRA. Diffuse white matter lesions, mass lesions, focal edema, hemorrhages,

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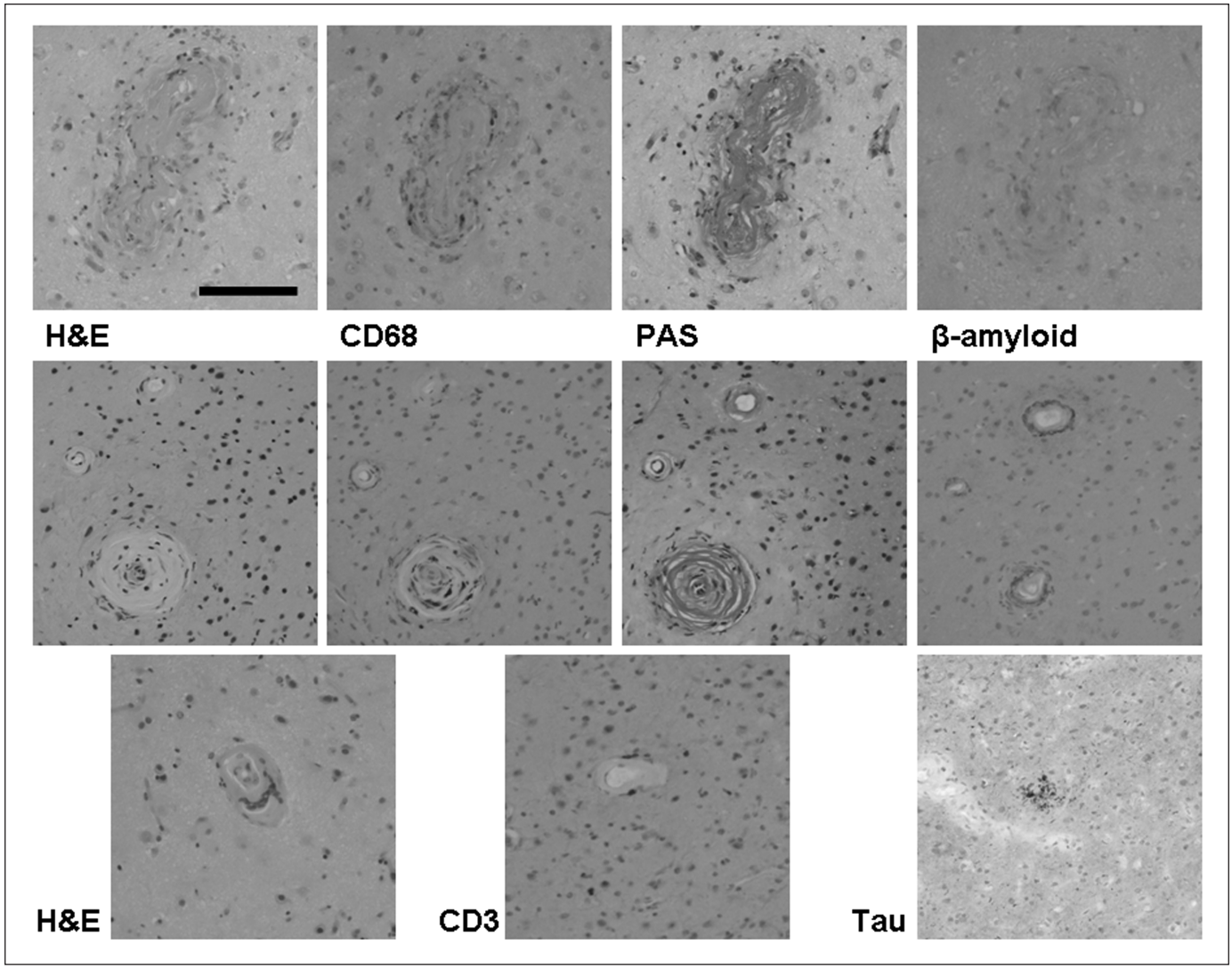

Figure 2: *Histology of arterial vessels involved by ABRA. Upper panel: cortical vessel from Patient 3; middle and lower panels: images from Patient 1. Stains are hematoxylin and eosin (H&E), periodic acid-Schiff (PAS) and immunohistochemistry for CD68, β-amyloid, CD3 and tau. Upper and middle panels show vessel damage with macrophage (CD68) infiltration and β-amyloid deposits (PAS, β-amyloid positive). Lower panel shows an intramural multinucleated giant cell, scattered intramural T cells (CD3) and tau positive neuritic plaque (only seen in Patient 1, see text). Scale bar=100μm.*

hypodensities consistent with infarcts, and atrophy have all been observed.[1,5,9] Cortical microbleeds have also been described.[13] In our series, one patient had diffuse posterior hemispheric white matter hyperintensities mimicking PRES and two had focal lesions with a tumor-like appearance.

Many patients with ABRA have been reported to respond favorably to immunosuppressive therapy. In the review by Scolding et al,[1] patients were treated with steroids +/- cyclophosphamide. A favorable response was seen in 12 (57%) with 4 (19%) showing a dramatic improvement with reversal of MRI white matter lesions.[1] All eight patients reported by Salvarani et al were treated with steroids +/- cyclophosphamide and six demonstrated improvement. Response to treatment was rapid with clinical improvement generally apparent within two to three weeks of initiating therapy.[5]

All three of our patients were treated with steroids and cyclophosphamide and all achieved clinical stability with some residual deficits. Two had a rapid response to treatment whereas the other had initial deterioration before stabilization.

In our series, one patient had deposition of tau positive neuritic plaques in the cerebral cortex but did not meet criteria for a firm diagnosis of AD. Alzheimers' disease has rarely been described in the setting of PACNS[14] and to our knowledge has not specifically been reported in a patient with ABRA including the initial case series.[1] However, Alzheimer's-type histological changes are frequently found in patients with CAA.[15] Our case raises the possibility of an etiologic correlation between ABRA and AD although there is insufficient evidence at this point to draw any further conclusions.

The incidence of PACNS is estimated to be one to two per million per year[4] but the proportion of those that represent ABRA is unknown. Salvarani et al reported 31 patients with biopsy proven PACNS, of whom eight (25.8%) showed Aβ deposition consistent with a diagnosis of ABRA.[5] The neuropathologic diagnosis of ABRA requires specific immunohistochemical testing to detect vascular Aβ. It is likely that many cases of PACNS could be reclassified as ABRA if that diagnosis is specifically sought.

The optimal treatment and prognosis of ABRA is not well established but evidence suggests that many patients respond favorably to immunosuppressive therapy. We believe that all biopsy specimens consistent with PACNS should be further examined for vascular Aβ deposition. There is a need for increased surveillance and larger case studies in order to determine the true incidence of ABRA and to obtain a better understanding of its clinical features.

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