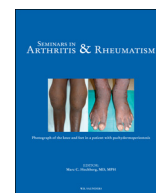




Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

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Amyloid Beta-Related Angiitis—A Case Report and Comprehensive Review of Literature of 94 Cases

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ARTICLE INFO

Keywords:

Amyloid Beta-Related Angiitis
Inflammatory cerebral amyloid angiopathy
Cerebral amyloid angiopathy
Vasculitis
Primary CNS vasculitis

ABSTRACT

Background: Amyloid Beta-Related Angiitis (ABRA) is a rare cause of central nervous system vasculitis complicating cerebral amyloid angiopathy. Data regarding its prevalence, clinical features, management, and outcomes are scant.

Objectives: To describe a patient with ABRA and discuss clinical features and management of ABRA.

Methods: A case report and review of literature were conducted of all reported cases of ABRA in the English literature.

Results: The exact etiology of ABRA is not clear, though it is thought to be secondary to an inflammatory response to beta amyloid ($A\beta$) in the walls of blood vessels. Role of ApoE e4/e4 genotype and its association with autoimmune diseases have been reported. ABRA shares many clinical features with primary CNS vasculitis. Patients with ABRA are relatively younger than those with non-inflammatory cerebral amyloid angiopathy (CAA), but older than patients with primary central nervous system vasculitis (PCNSV). Acute-onset cognitive behavioral abnormalities, focal neurological deficits, seizures, or unusual headaches are the most common presentations of ABRA. Majority have elevated CSF proteins. Up to 70% of patients have ApoE e4/e4 genotype. MRI is the most important diagnostic tool and is almost always abnormal. Characteristically, MRI shows hyperintensities on T2-weighted (T2W) or fluid-attenuation inversion recovery (FLAIR) images with minimal gadolinium enhancement. On susceptibility-weighted images (SWI), a majority of the patients have the presence of microbleeds at cortico-subcortical junction. It may be possible to diagnose typical patients based on clinical features and MRI findings alone, obviating the need for brain biopsy. Brain biopsy is the gold standard and shows transmural granulomatous vasculitis superimposed on CAA. ABRA responds well to steroids in majority. Patients usually need additional immunosuppressants, especially to prevent relapse. MRI abnormalities resolve with treatment and recur with the relapse.

Conclusions: ABRA is a rare but treatable cause of progressive dementia and should be considered in the differential diagnosis of rapid-onset CNS dysfunction in patients older than 60 years. It has characteristic MRI findings and responds well to steroids and other immunosuppressant therapy.

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Introduction

Amyloidosis is a disorder of protein folding in which normally soluble proteins are deposited in the extracellular space as insoluble fibrils that progressively disrupt the tissue structure and function [1]. Cerebral amyloid angiopathy (CAA) is localized amyloidosis affecting cerebral blood vessels, commonly resulting from imbalance between production and clearance of normally produced beta amyloid ($A\beta$) from the brain [2]. CAA is responsible for 12–15% of cases of lobar intracranial hemorrhages in elderly and can also cause cognitive decline [3], transient ischemic attacks,

and focal seizures [4]. Very rarely, patients with CAA develop secondary central nervous system (CNS) vasculitis triggered by immune response to $A\beta$, which is called “inflammatory CAA” or Amyloid Beta-Related Angiitis (ABRA).

We present our experience with this condition and the largest comprehensive case review about ABRA. We discuss several new insights into the etiopathogenesis, diagnosis as well as management of ABRA.

Case report

A 63-year-old right-handed Caucasian woman was admitted for evaluation of an episode of seizure. She was in her usual state of health until the day of admission when she had witnessed an

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episode of generalized tonic-clonic seizure preceded by aura consisting of seeing wavy dancing lines in front of her eyes. She was admitted to a local hospital where computed tomography (CT) scan of the brain was performed. The CT showed two subcortical hypodense lesions in the right and the left fronto-parietal lobes surrounded by edema. The lesions were suspected to be metastases given her history of breast cancer. She was referred to our hospital for neurosurgical evaluation. On arrival at our hospital, the patient was asymptomatic. There was no history of fever, night sweats, loss of appetite or weight, headaches, visual disturbances, loss of memory, abnormal behavior, and focal weakness. She did not have any symptoms suggestive of well-defined rheumatic disease including systemic vasculitides. Her medical history was significant for breast cancer diagnosed 1 year prior to the presentation, treated with lumpectomy followed by radiation therapy. The patient also had a history of pernicious anemia and Grave's disease treated with radioiodine therapy. Her home medications included anastrozole, levothyroxine, aspirin, calcium, monthly cyanocobalamin injections, ferrous sulfate, and subcutaneous injections of denosumab every 6 months for osteoporosis prophylaxis. Her sister and brother had rheumatoid arthritis. She lived with her husband and ran a candy business. She denied current or past smoking, alcohol, or illicit drug use.

On physical examination, pulse was 84 beats per min, blood pressure was 137/64 mmHg, and respiratory rate was 14 breaths per min. General examination included skin which was normal. Neurological examination was completely normal including higher cognitive functions, cranial nerves, motor, sensory as well as cerebellar examination results. Results of her routine laboratory tests were unremarkable and those of serological tests as well as CSF are shown in Table 1.

She underwent contrast-enhanced magnetic resonance imaging (MRI) of the brain (Fig. 1), which showed abnormal cortical and subcortical hyperintensities in both temporal and frontal lobes on T2W and FLAIR images with vague contrast enhancement of bi-temporal lesions and left frontal perisylvian lesion. Gradient-echo imaging (GEI) demonstrated innumerable punctate hypointense foci, probably due to micro-hemorrhages within or around each lesion. Cerebrospinal fluid studies were unremarkable except for elevated proteins.

As per the neurosurgery team, MRI features were atypical for metastases and biopsy was recommended to guide further management. Stereotactic right temporal lobe brain biopsy was done. It did not show any evidence of malignancy or infection.

Table 1

Lab test	Patient's result	Normal value
Cerebrospinal fluid	Clear colorless	
Proteins	57	15–45
Glucose	59	40–70
Cells		
WBC	4	0–5 per hpf
RBC	263	< 1 per hpf
Culture	Negative	
Flow cytometry	No malignant cells	
	Small lymphocytes	
	CD4:CD8 ratio 2.8:1.0	
ANA	Negative	
Rheumatoid factor	< 10	< 15
ANCA	Negative	
HBsAg	Negative	
HCV Ab	Negative	
Quantiferon	Negative	
SPEP	Normal	
Cryoglobulins	Negative	

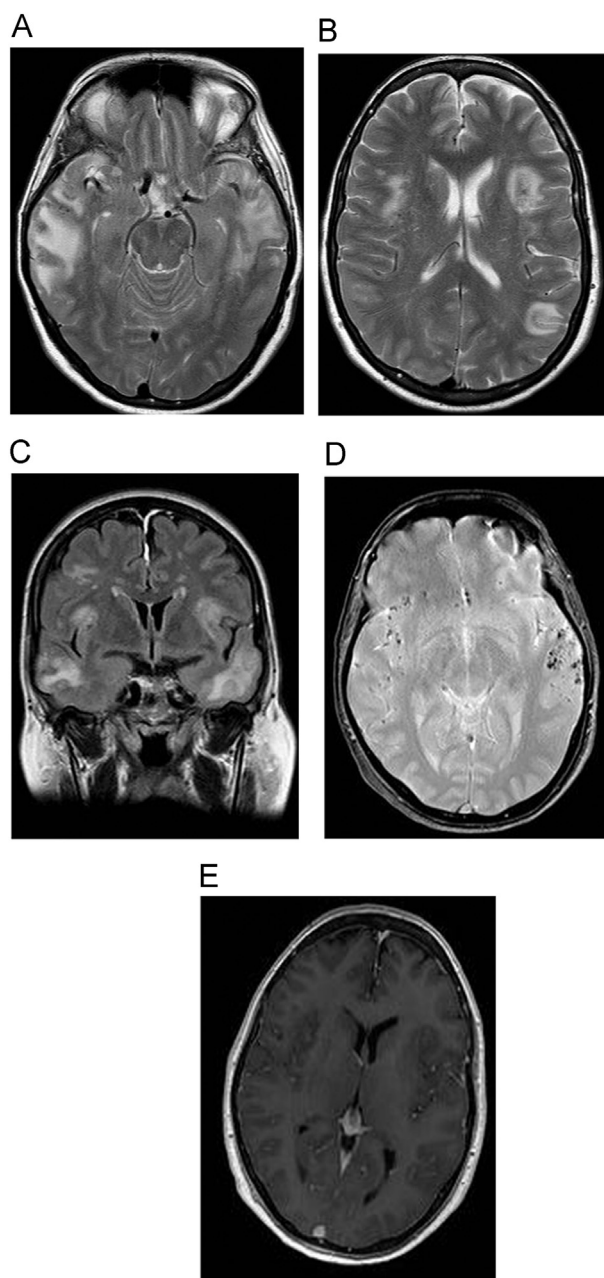


Fig. 1. (A–C) T2W sequences showing abnormal cortically and subcortically based hyperintensities throughout both temporal lobes, and in the frontal lobes. (D) Gradient-echo imaging study showing punctate hypointense foci due to microbleeds corresponding areas. (E) No significant enhancement with gadolinium contrast.

However, the brain biopsy showed typical findings of ABRA (Fig. 2), mainly transmural infiltration of vessel walls by lymphocytes and macrophages with the formation of granulomas and multinucleated giant cells in the background of cerebral amyloid angiopathy. Focal hemorrhage, fibrinoid necrosis, thrombosis, and recanalization were also present. No organism was identified on GMS, PAS, Gram, AFB, and Steiner stains. Immunohistochemical stains revealed A β in blood vessels walls and abundant CD68⁺ macrophages, some of which contained A β . CD3⁺ T cells with few CD20⁺ B cells were also seen.

The patient was treated with high-dose prednisone (1 mg/kg/day) and six monthly infusions of cyclophosphamide. She was also given Levetiracetam for seizure prophylaxis. Repeat MRI 3 months after the admission showed almost complete resolution

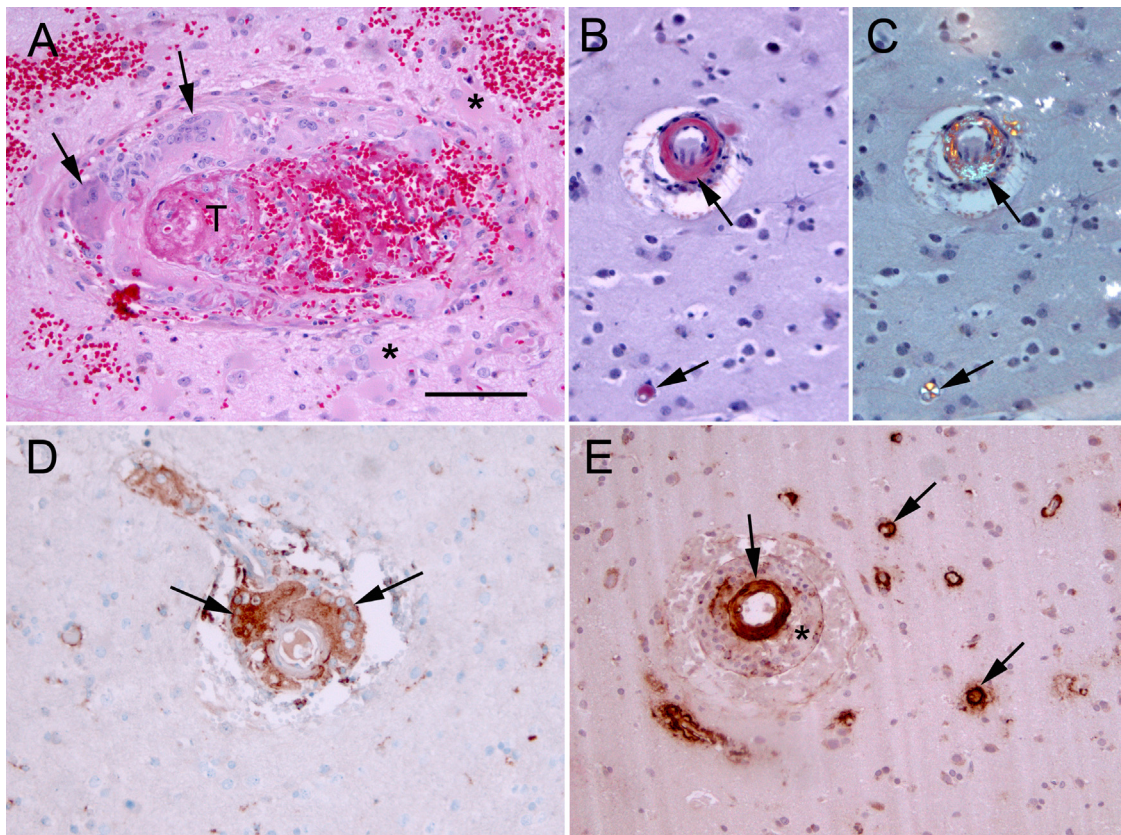


Fig. 2. (A) Hematoxylin and eosin stain demonstrates inflammation in the vessel wall, including multinucleated giant cells (arrows). There is thrombus (T) in the vascular lumen. The adjacent brain parenchyma has many reactive astrocytes (asterisks). (B) Congo red stain is positive in the wall of a small arteriole and a capillary (arrows). (C) The same Congo red-stained section viewed with polarized light shows green birefringence (arrows), confirming that the red staining is amyloid. (D) Multinucleated giant cells in a blood vessel wall are positive for CD68 (brown stain, arrows), as are scattered microglia in the brain parenchyma. (E) Immunohistochemical stain demonstrates A beta in the wall of a small arteriole and multiple capillaries (arrows on representative vessels). There is an inflammatory infiltrate in the wall of the arteriole (asterisk). Magnification bar in (A) = 100 μ m. All photographs are at the same magnification. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

of T2 and FLAIR hyperintense lesions in both the cerebral hemispheres with mild persistent hyperintensity in the right posterior temporal lobe. The patient had stable cortical and subcortical microbleeds on gradient-echo imaging in both the cerebral hemispheres suggestive of amyloid angiopathy. Prednisone was being tapered gradually and she was started on azathioprine. She developed acute liver injury in the form of elevated liver enzymes (up to 800 U/L) from azathioprine which resolved after discontinuation. Mycophenolate was then started as a steroid-sparing agent. At the follow-up visits after 3, 6, 8, and 11 months, she has been asymptomatic and has had no recurrent seizures. Repeat MRI again 11 months after admission shows almost complete resolution of T2W hyperintensities.

Methods

OVID MEDLINE was searched for relevant articles between 1946 and 2012 using the following key words: “cerebral amyloid angiopathy,” “vasculitis,” “inflammatory CAA,” and “A Beta-Related Angiitis.” All relevant articles were retrieved, and additional references quoted in these articles were checked. There have been case series and reviews in the literature, which include those by Schwab et al. [10], Scolding et al. [9], Kinnecom et al. [12], Salvarani et al. [5], and Chung et al. [7]. Information was extracted from these published reviews for 72 patients. We found 23 additional cases after 2009, excluding our case. Clinical data for two patients from Kinnecom et al. were not available, and two more patients' case reports were in a language other than English, hence

they were not included. Information about demographic data, clinical features, lab and imaging findings, treatment, and follow-up was extracted and is summarized in Table 2. We also discuss the possible etiology and differential diagnosis of ABRA.

Results

Clinical features

Of 94 patients, 50 were men (53%), and the mean age was 65.2 years (range 42–87). Patients had either acute (54%) or subacute (46%) presentation. The most common presenting symptom (71%) was cognitive or behavioral changes, which ranged from mild cognitive impairment to frank dementia, hallucinations, personality changes, confusion, and coma. The second commonest presentation was focal neurological deficits (FND) which affected 51% (47/92) of patients. FND included hemiparesis, hemisensory loss, aphasia, hemianopia, hemineglect, and cerebellar ataxia. Focal deficits caused by lesions in the posterior cerebral circulation predominated, probably because of preferential deposition of A β amyloid in occipital lobes. Moreover, 30% of patients presented with seizures and 35% with headaches. As opposed to previous studies where seizures occurred variably from 0% to 31% in patients, our review suggested the incidence of seizures to be 36%. Four patients had transient ischemic attack-like onset [5–8], and 77% had two or more of the four most commonly described clinical features.

Table 2

Study	Scolding et al. [9]	Kinnecom et al. [12]	Salvarani et al. [5]	Chung et al. [7]	Others ^e	Total
No of patients	34	14	8	16	22	94
Age	67.3 (43–82) ^a	63.2 (45–79) ^a	63 (42–84) ^a	69 (46–83) ^b	67.6 (52–87) ^a	65.2 (42–87) ^a
Sex (M/F)	17/17	9/5	6/2	7/9	11/11	50/44
Clinical features						
CB change	29/34	9/12	6/8	9/16	13/22	66/92 (71%)
Seizures	8/34	7/12	0/8	7/16	12/22	34/92 (36%)
Focal deficits	15/34	1/12	7/8	9/16	15/22	47/92 (51%)
Headache	12/34	6/12	4/8	7/16	4/22	33/92 (35%)
ApoE e4/e4	NA	10/13	NA	NA	2/4	12/17 (70%)
CSF						
Elevated proteins	11/18	4/5	7/8	8/11	12/17	42/59 (71%)
Pleocytosis	8/18	1/5	5/8	5/11	7/17	26/59 (44%)
Oligoclonal bands	12/21	NA	NA	1/1	3/3	16/16 (100%)
Repeat CSF						
MRI						
White matter changes ^c	13/20	12/12	6/8	14/14	21/21	66/75 (88%)
Micro-bleed on SWI/GEI	4	6/7 ^d	NA	4/4	11/13	21/24 (87%)
Enhancement	7/10		5/8	5/9	6/11	23/38 (60%)
Improvement with Rx	4/5	10/12	4/6	6/9	13/15	37/47 (79%)
Pathology						
Vasculitis or perivasculitis	34/34	14/14	8/8	16/16	19/20 ^f	91/92 (99%)
Response to therapy	12/20	10/12	6/8	10/12	19/20	57/72 (79%)
Relapse	NA	3/12	2/8	NA	3/14 ^g	8/34 (23%)

NA = not available; CB = cognitive behavioral.

^a Mean (range) age.

^b Median (range) age.

^c Hyperintensities on T2W or FLAIR images.

^d Little or no enhancement.

^e 22 Includes our case in Refs. [8,13–15,16,21,22,25,40–49].

^f 2 Patients were treated presumptively.

^g As per the reported information.

A total of 10 patients had a history of prior malignancy, including our patient [9]. The types of malignancies included were melanoma; cancers of pancreas ($n = 1$), prostate ($n = 2$), bowel ($n = 2$), breast ($n = 2$), and bladder ($n = 1$); multiple myeloma ($n = 1$); and basal cell carcinoma ($n = 1$). There were 11 patients with autoimmune diseases—hypothyroidism ($n = 4$), Grave's disease ($n = 2$), rheumatoid arthritis (RA) ($n = 2$), autoimmune hepatitis ($n = 1$), and pernicious anemia ($n = 2$) [6,10,11].

Investigations

Inflammatory markers including ESR and CRP were elevated in 14 of 47 (29.7%) patients where the information was available. ApoE was checked in 17 cases [12–16]. Genotype e4/e4 was present in 12, e2/e3 in four, and e2/e4 in one patient. CSF showed elevated protein ranging from 0.5 to 5.73 g/L in 42 of 59 patients (71%). Lymphocytic pleocytosis was present in 26 of 59 patients (44%). Oligoclonal bands were absent in all 16 patients where it was checked [9,13,15,17,18–21]. One patient had antibodies to A β 40 and A β 42 (A β amyloid can be 40 (A β 40) or 42 (A β 42) amino acid-long peptide chain) in the CSF [13]. There was a high CD4-to-CD8 ratio and an increased number of activated CD69⁺ T lymphocytes in CSF in one patient [15]. Repeat CSF was performed in two cases after the treatment and in both cases abnormalities resolved [13,15]. EEG was available for 28 patients: 22 had nonspecific findings, five had epileptogenic focus, and one had normal EEG.

MRI results were reported for 77 of 92 patients (83%). A total of 75 (97.4%) patients had abnormal MRI findings. The most common findings were asymmetrical bilateral white matter hyperintensity on T2W and FLAIR images, which was reported in 66 of 75 (88%) patients; 26% patients had mass like lesions, which were either non-enhancing or minimally enhancing. Where it was reported,

patchy enhancement was noticed in 23 of 38 patients (60%). SWI or GEI images were available for 24 patients, and 21 of them (87%) had evidence of micro-hemorrhages mainly in the cortical area near the sulci affecting parietal, occipital, and frontal lobes. Repeat MRI after the treatment showed improvement in white matter lesions in 38 of 47 (80%) patients.

Cerebral angiography was performed in 21 patients, and only two had mild abnormalities reported. One patient had subtle bilateral vascular narrowing affecting small branch vessels of the middle and anterior cerebral arteries, and the other patient had alternating areas of vasoconstriction and normal caliber involving large and medium-sized cerebral arteries. When performed, MRA was normal in all 11 patients.

Biopsy was performed in all 94 but two patients. These two patients were diagnosed to have probable ABRA based on typical clinical features and MRI and were treated empirically with steroids [16,22].

Of 92 patients, 74 had brain biopsy and 18 underwent autopsy. Biopsy showed vasculitis in 80 (78%) patients and perivasculitis in 20% of patients. One patient had an inconclusive biopsy. Among the patients with vasculitis, transmural inflammation with CD68⁺ macrophages and CD3⁺ T cells was the main findings. Frequently multinucleated giant cells were described and a few macrophages had A β engulfed in the cytoplasm, these macrophages were present in close vicinity to CD4 cells. There were fewer CD20⁺ cells as compared to CD4 cells. Vasculitis was present only in the vessels affected by the amyloid deposition but not in deeper white matter vessels. There was striking colocalization of vasculitis in amyloid-laden blood vessels, and vessels which do not have CAA were spared. Immunohistochemical stains show predominantly beta amyloid deposition with increased ratio of A β 40 to A β 42.

Treatment

Treatment details were reported for 90 patients; 73 patients received corticosteroids. Cyclophosphamide (CYC) was administered in 31 patients, azathioprine in six, methotrexate in two, and mycophenolate mofetil in two patients [20,23]. One patient received only CYC without corticosteroids [24]. Of 73 patients treated with steroids, 57 (78%) patients showed clinical improvement which was either complete or partial. Patients who were started on immunosuppressive therapy early had better prognosis. Of 57 patients, who showed improvement, 15 had a relapse (26%), either after reduction or cessation of immunosuppression, but responded well after reinstatement of therapy. One patient had relapse of disease twice and both times he responded to the azathioprine monotherapy [25]. Follow-up was reported in 84 patients, which ranged from 3 to 13 years. In review of 22 patients reported after 2009, only one patient died acutely from massive intracranial hemorrhage, but overall majority of the patients responded well to immunosuppressive therapy.

Discussion

Cerebral amyloid angiopathy (CAA) is a form of localized amyloidosis affecting mainly the cortical and leptomeningeal vessels of cerebral lobes, preferentially occipital lobes and cerebellum [26]. As per the autopsy studies, the prevalence of CAA could be as high as 21% in people aged 61–70 years and increases further with age [27]. Sporadic CAA with A β deposition is the most common of various forms of CAA. It results from chronic imbalance between production and clearance from the brain of the normally present but inherently amyloidogenic protein called A β amyloid [2]. Neurons and other parenchymal cells of the brain are the

major source of A β which is usually cleared by enzymatic degradation, absorption by transcytosis, or perivascular drainage [28,29,30] (Fig. 3). Deposition of amyloid in the blood vessels leads to vasculopathy, which is responsible for clinical features of CAA, like intracranial bleed, cognitive decline, and dementia.

Very rarely CAA is associated with the development of CNS vasculitis, which shares many clinical features with primary CNS vasculitis. It has been reported in the literature by various names—Amyloid β -Related angiitis (ABRA), primary angiitis of the CNS associated with CAA; amyloid angiopathy and granulomatous angiitis of the CNS; cerebral amyloid inflammatory vasculopathy; and cerebral amyloid angiitis and cerebral amyloid angiopathy associated with giant cell arteritis [9,17,18,31–34]. It was first reported by Reid and Maloney in 1974.

Why only a few patients with CAA develop secondary CNS vasculitis is unclear. Clinically ABRA behaves more like PCNSV than typical CAA, which may raise suspicion that ABRA is a chance association between CAA and PCNSV. Several observations have ruled out this possibility. Firstly, it has distinct radiological features, which are not commonly seen in case of PCNSV. Secondly, there is striking co-localization of areas of vasculitis and vessels affected by CAA. Thirdly, A β is found to be engulfed by macrophages expressing MHC class II antigens which are in close vicinity of CD4 helper cells, implying causative role of amyloid in inducing the inflammation [15]. Vasculitis appears to be an auto-immune response to A β [35]. It was observed that immunization with A β reduced plaque burden in patients with AD and hence a trial of A β 42 immunization of patients with moderate AD was initiated in 2001 [36]. Later the trial was halted because of development of subacute meningoencephalitis in 18 of 372 (6%) patients who had clinical features, imaging findings, and pathological features very similar to ABRA [37]. Similarly, vasogenic edema and microbleeds were reported in a subgroup of subjects in phase 1 and phase 2a studies of a humanized anti-amyloid antibody [38].

Whether the inflammation is triggered by A β or its associated components like ApoE, Serum amyloid P component, or cystatin C is not clear. Genotypes e4/e4 and e2/e4 of ApoE have been found to be associated with development of ABRA. As we know, e4 genotype is associated with increased burden of amyloid in the vessels. Also the mean age of patients with ABRA is lesser than that of those with CAA without inflammation [5,7,9,12]. Why these patients develop CAA at an earlier age is not clear. Many of these patients were reported to have autoimmune diseases like hypothyroidism, Grave's disease, pernicious anemia, rheumatoid arthritis, and autoimmune hepatitis. It is possible that autoimmunity plays a role in the causation of this vasculitis. Also upon review of literature, we found 10 patients who had various malignancies reported which were treated prior to the development of vasculitis. Two of these patients had received radiation therapy. In an autopsy study of 123 brains from patient who died of malignant neoplasms, radiation therapy to brain was more likely to be associated with the development of CAA [39].

Patients with ABRA are younger (mean age 67 years) than those with non-inflammatory CAA (77 years) but older than patients with primary CNS vasculitis (45 years) [5]. They usually do not have features of systemic vasculitis.

There are no specific diagnostic lab tests or serologies. Inflammatory markers do not help in diagnosis or monitoring of treatment. CSF examination helps to exclude infections or malignancies. About 71% of patients have variably elevated CSF protein levels, and 40% have CSF pleocytosis with predominant lymphocytes. ApoE genotyping may help in diagnosis and may have a role in causation of CAA and possibly ABRA.

MRI is probably the most important diagnostic test next to the cerebral biopsy. MRI findings are quite characteristic and may

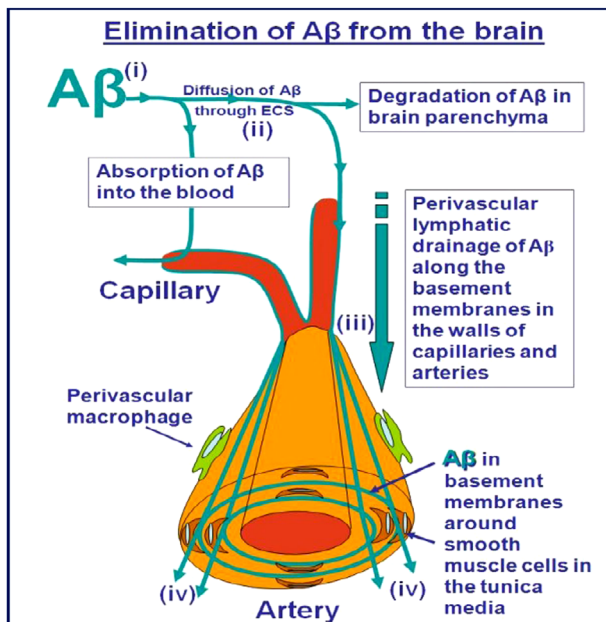


Fig. 3. Elimination of A β from the brain. A β is (i) produced by neurons and other cells in the brain and then (ii) diffuses with interstitial fluid and other solutes through the narrow extracellular spaces (ECS) of the brain to (iii) the bulk flow lymphatic drainage pathways in the basement membranes of capillaries and in the tunica media of artery walls, and (iv) out of the brain to cervical lymph nodes. Smooth muscle cells and perivascular macrophages take up A β and are part of the elimination pathway. Degradation of A β occurs in the brain parenchyma, by neprilysin and other enzymes, and A β is absorbed into the blood by LRP-1 (lipoprotein receptor-related protein-1)-mediated mechanisms in capillary endothelia. These mechanisms for the elimination of A β from the brain tend to fail with age and in Alzheimer disease.

obviate the need for brain biopsy in typical cases. In 2007, Kinnecom et al. [12] and in 2010, Greenberg et al. [35] suggested that typical clinical and MRI features may be sufficient for the treatment of ABRA without requiring biopsy. As per literature, three patients have been treated successfully for ABRA [16,22,35] based on clinical and imaging findings without biopsy. MRI may be dramatically abnormal with paucity of clinical findings. One-fourth of patients can present with variably enhancing mass like T2W and FLAIR lesions on T2W and FLAIR which can be misdiagnosed as primary or metastatic brain malignancy especially if they have a history of solid tumor in the past. GEI or SWI shows micro-hemorrhages which are typically located at cortico-subcortical junction predominantly in temporal and occipital lobes. MRI shows resolution of white matter abnormalities after treatment and recurrence with relapse, thus making it an important test for monitoring disease. MRA is usually normal and does not help in diagnosis or monitoring. Gadolinium leptomeningeal enhancement is far less frequent in patients with CAA as compared to those in ABRA, whereas lobar hemorrhage and microbleeds without enhancing lesions are more frequent.

It is important to stress that cerebral angiography, a common investigation in CNS vasculitis, is usually normal probably because of the small caliber of affected vessels, which are not captured with angiography. Cerebral biopsy is the gold standard for diagnosis of ABRA. It should preferably be obtained from a radiologically abnormal area.

Age of presentation, MRI findings, and biopsy features help to differentiate ABRA from PCNSV. Other diseases which present with white matter changes and micro-hemorrhages like PRES should be differentiated from ABRA. Other differentials include primary and secondary CNS malignancies, infections like tuberculosis and fungal diseases, rare diseases like Hashimoto's encephalitis, neuro-sarcoidosis, and acute disseminated encephalomyelitis.

Diagnostic criteria

In 2011 Chung et al. [7] proposed diagnostic criteria for definite and probable ABRA, based on review of clinical, imaging, and biopsy findings of 72 patients reported in the literature (Table 3).

In the past, treatment of ABRA consisted of surgery, short-course steroids, and even no treatment in a few cases. This led to apparent poor prognosis as described in previous case series.

Table 3
Proposed diagnostic criteria by Chung et al.

<p><i>Probable CAA-I</i> All of the following:</p> <ol style="list-style-type: none"> 1. Acute or subacute onset of symptoms 2. 40 years of age or older 3. At least one of the following clinical features: headache, mental status or behavioral change, focal neurological signs, and seizures 4. MRI shows patchy or confluent T2 or fluid-attenuation inversion recovery hyperintensity which is: <ol style="list-style-type: none"> a. usually asymmetric b. with or without mass effect c. with or without leptomeningeal or parenchymal enhancement 5. Evidence of pre-existing CAA on susceptibility-weighted MRI sequences: <ol style="list-style-type: none"> a. multiple cortical and subcortical hemorrhages or microhemorrhages and/or b. recent or past lobar hemorrhage 6. Absence of neoplastic, infectious, or other cause <p><i>Definite CAA-I</i> All of the above plus histopathological confirmation with</p> <ol style="list-style-type: none"> 1. Perivascular, transmural, and/or intramural inflammation 2. Amyloid deposition within vessels of affected area in the cortex and leptomeninges

Lately earlier diagnosis of ABRA with MRI and biopsy has changed the natural history of ABRA. As per review by Chung et al. [7] 10 of 12 patients responded to steroids, and in our review (2009–2012), 19 of 20 patients have responded to the corticosteroids. Thus, the majority responds well to immunosuppressive therapy with complete remission even up to 5 years. But few patients could have relentless disease progression despite aggressive treatment leading to disability and even death.

Treatment needs to be individualized based on patient characteristics and comorbidities, but it may be reasonable to start with high-dose corticosteroids. The initial response is usually seen within the first few weeks [7]. There have been reports of relapse of ABRA in about 26% of patients on reduction or cessation of immunosuppressive therapy. Hence, further immunosuppression is advisable. CYC, methotrexate, azathioprine, and mycophenolate have been successfully used in various cases. Almost all the relapsed patients respond to reinstitution of the treatment.

Conclusion

ABRA is a rare but treatable cause of progressive dementia and neurological dysfunction in patients older than 60 year years and should be considered in the appropriate clinical settings.

Acknowledgment

We would like to thank Ms. Lisa Perry (PharmD) for her assistance in proofreading.

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