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Not Just Another Stroke

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Keywords: Amyloid-beta-related angiitis; cerebral amyloid angiopathy; CNS biopsy; primary CNS vasculitis ; Stroke

Case presentation: Dr. Tayade

A 58-year-old right-handed male with well-controlled diabetes mellitus for 3 years presented with a history of recurrent transient neurological symptoms over a 3-year period. Initially, he had multiple episodes (lasting 15–20 minutes) of left facial deviation and speech arrest without impaired consciousness, suggestive of transient focal seizures. Approximately 7 months later, he developed persistent anomia. Two years into the illness, he experienced a sudden onset of agraphia and acalculia, which did not resolve. At 2.5 years, he had two generalized seizures.

Given the relatively young age, we specifically asked about a family history of early (<60 years) hemorrhagic stroke or early-onset dementia and about prior neurosurgical procedures (including cadaveric dura grafts or pituitary Growth Hormone exposure); none were identified.

On examination, the Mini-Mental State Examination (MMSE) score was 16/30. Neurological examination revealed apraxia (impaired skilled limb movements), prominent executive dysfunction (reduced verbal fluency and impaired set-shifting), and anomia with short-term memory impairment – findings localizing to frontal, parietal and dominant temporal involvement, respectively. The rest of the systemic examination was unremarkable.

The main differential diagnoses (Table 1) considered at presentation were primary Central Nervous System (CNS) vasculitis, infective meningoencephalitis, neurosarcoidosis, neoplastic meningitis, and cerebral amyloid angiopathy (CAA)-related inflammation (CAA-RI).

Routine laboratory investigations were normal. Cerebrospinal Fluid (CSF) was inflammatory (12 lymphocytes, protein 9 mg/dL and glucose 76.7 mg/dL). MRI brain revealed patchy T2/FLAIR hyperintensities in cortical and subcortical areas with sulcal enhancement (Figure 1, 2). Susceptibility-Weighted Imaging (SWI) showed punctate cortical microhemorrhages. Digital Substraction Angiography (DSA) of the cerebral vessels demonstrated irregularities suggestive of vasculitis (Figure 3). Electroencephalogram was normal. A brain biopsy was performed.

Radiology: Dr. Garg

Initial MRI brain showed multiple patchy T2 and FLAIR hyperintensities in the left posterior temporal lobe, thalamocapsular region, dentate nucleus, and left occipital and frontal lobes, with post-contrast enhancement. SWI revealed cortical microhemorrhages. Sulcal enhancement was evident on post-contrast T1-weighted images (Figures 1, 2). These findings were suggestive of an inflammatory process, possibly vasculitic.

DSA showed focal narrowing of distal cortical branches, consistent with small-vessel vasculitis (Figure 3).

Pathology: Dr. Nambirajan

Histopathological examination of the brain biopsy showed diffuse leptomeningeal expansion and vasculitis of leptomeningeal and cortical vessels. There was transmural inflammation with ill-defined granulomas composed of epithelioid histiocytes and lymphocytes. There was deposition of eosinophilic hyalinized material within the vessel walls.

Congo red staining revealed congophilic material with apple-green birefringence under polarized light. Immunohistochemistry was positive for beta-amyloid (Figure 4), confirming amyloid-beta-related angiitis (ABRA).

The same leptomeningeal and cortical vessels containing β-amyloid (Congo red and Aβ immunostain positive) also showed transmural granulomatous inflammation, lymphocytic infiltration, and vessel wall destruction. This co-localization strongly supports ABRA rather than an unrelated vasculitis with coincidental CAA – particularly given the patient's relatively young age, at which incidental CAA is uncommon.

Final discussion: Dr. Elavarasi

This case highlights the diagnostic complexity and clinical relevance of ABRA – a rare but distinct clinicopathologic entity that lies at the intersection of inflammatory vasculopathies and CAA.[1,2] The patient's subacute cognitive decline, focal neurological deficits, seizures and radiologic evidence of both inflammation and hemorrhagic lesions prompted a broad differential, ultimately resolved by histopathological confirmation.

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Table 1. Amyloid-β–related angiitis (ABRA): differential diagnoses

Feature	ABRA	Primary CNS vasculitis (PACNS)	CAA-related inflammation (CAA-RI)	Infectious meningoencephalitis	Neurosarcoidosis	Neoplastic meningitis
Clinical presentation	Subacute cognitive decline, headache, stroke-like episodes; often seizures	Headache with progressive focal deficits (e.g., hemiparesis), cognitive impairment; seizures less common	Subacute dementia/ encephalopathy, headache, seizures, focal deficits	Acute onset fever, headache, encephalopathy, seizures; systemic infection signs often present	Cranial neuropathies (e.g., facial palsy, optic neuritis), meningitis-like symptoms, myelopathy; systemic sarcoid signs (e.g., lung involvement)	Known malignancy history; multifocal deficits (headache, cranial nerve palsies, encephalopathy)
Brain MRI findings	T2/FLAIR confluent white-matter hyperintensities and edema; **strictly lobar microbleeds** (cortical siderosis) on GRE; leptomeningeal or cortical enhancement	Multifocal infarcts/DWI lesions in cortex or white matter; nodular or gyral contrast enhancement; microbleeds **rare**	Extensive patchy white-matter hyperintensities and edema; **strictly lobar microbleeds** and cortical superficial siderosis; variable enhancement	Focal cortical lesions (e.g., bilateral temporal lobe hyperintensities in HSV encephalitis); may show meningeal enhancement (e.g., tubercular meningitis)	Leptomeningeal and dural enhancement (often at skull base); enhancing parenchymal nodules; multifocal nonenhancing white-matter lesions	Diffuse leptomeningeal enhancement along sulci/ cranial nerves; possible parenchymal nodules or metastases; hydrocephalus
CSF profile	Lymphocytic pleocytosis and elevated protein common, but can be normal	Lymphocytic pleocytosis (≈70–90%), high protein (median ~ 98 mg/dL); glucose normal	Lymphocytic pleocytosis and high protein (often similar to ABRA)	Pleocytosis (viral – lymphocytes; bacterial – neutrophils); high protein; low glucose in TB; **pathogen PCR/ culture positive**	Mild lymphocytic pleocytosis (≈30% have>5 cells/μL), elevated protein in ~ 46%; CSF ACE or oligoclonal bands sometimes	Elevated protein; pleocytosis common (≈79% of cases); **malignant cells on cytology** (definitive)
Histopathology	Granulomatous transmural angiitis with vascular amyloid-β deposits (Congo red+); often angio-destructive (fibrinoid necrosis)	Granulomatous or lymphocytic transmural vasculitis of small/ medium CNS vessels; **no amyloid** deposition	Vascular amyloid-β deposition with perivascular inflammatory infiltrate; if ABRA-type: granulomas and angio-destruction; ICAA-type: nondestructive perivascular inflammation	Pathogen-specific changes (e.g., viral inclusion bodies, acute inflammation; TB: caseating granulomas)	Noncaseating granulomas in leptomeninges and brain parenchyma (often perivascular)	Malignant tumor cells infiltrating leptomeninges/ vessels (corresponding to known primary cancer); no true vasculitis
Angiographic findings	Usually normal (involves small vessels)	"Beading"/segmental narrowing of medium-sized cerebral arteries	Usually normal (small-vessel involvement)	Generally normal; (tubercular vasculitis can rarely show stenoses)	Usually normal (rare large-vessel involvement)	Not applicable (no primary vasculitis of vessels)
Typical age group	Older adults (mean ~ 60–70s)	Middle-aged (mean ~ 40–50s)	Older adults (mean ~ 60–70s)	All ages (varies by etiology)	Young to middle-aged adults (≈20–50, mean ~ 42)	Middle-aged/older (often 50–70s, consistent with underlying malignancy)

ACE = Angiotensin Converting Enzyme; CNS = Central Nervous System; CSF = Cerebrospinal Fluid; DWI = Diffusion-Weighted Imaging; FLAIR = Fluid Attenuated Inversion Recovery; GRE = Gradient Recalled Echo; HSV = Herpes Simplex Virus; ICAA = Iatrogenic Cerebral Amyloid Angiopathy; MRI = Magnetic Resonance Imaging; TB = Tuberculosis.

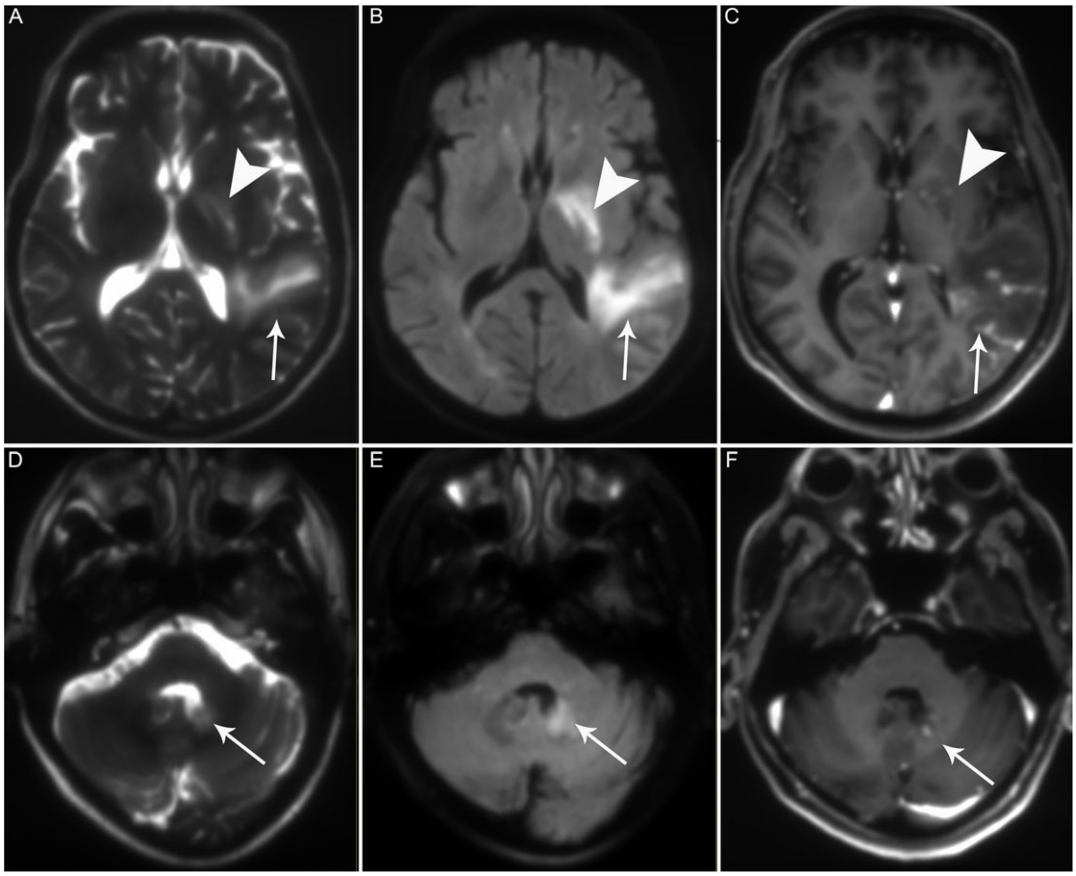


Figure 1. Axial T2-WI (A) and FLAIR images (B) at the level of basal ganglia show hyperintense lesions in the left posterior temporal lobe white matter (arrow) and left thalamocapsular region (arrowhead). Post-gadolinium T1-WI (C) shows patchy enhancement in these lesions. Axial T2-WI (D) and FLAIR images at the level of mid-pons show a hyperintense lesion in the left dentate nucleus region (arrow) with patchy enhancement in post-gad T1-WI (F).

Differential diagnosis and diagnostic dilemma (Table 1)

The initial working diagnosis included:

- CNS vasculitis, specifically primary angiitis of the central nervous system (PACNS).
- Recurrent embolic strokes from cardioembolic sources (e.g., atrial myxoma).
- Inflammatory demyelinating diseases or atypical neurodegenerative disorders.
- Structural causes of seizures, such as multifocal calcifications, neurocysticercosis or metastases.[3]

However, the patchy cortical–subcortical lesions, sulcal enhancement and microhemorrhages seen on MRI, along with angiographic evidence of small-vessel irregularities, pointed toward a vasculitic or inflammatory vascular pathology.[4,5,3] Notably, the absence of systemic inflammatory markers, negative autoimmune workup and non-inflammatory CSF findings made systemic vasculitis or infectious etiologies less likely.

ABRA vs PACNS

ABRA shares many features with PACNS, including clinical presentation, radiographic findings and responsiveness to immunosuppression.[4] However, the key distinguishing feature lies in the histopathology – specifically, the presence of amyloid-beta deposition in the vessel walls.[4,1]

In PACNS, inflammation affects small- to medium-sized CNS vessels but lacks amyloid deposition. In contrast, ABRA is essentially a vasculitic response mounted against beta-amyloid deposits, thus making it an overlap syndrome between CAA and PACNS.[6]

A crucial diagnostic step in this case was the Congo red staining and beta-amyloid immunohistochemistry, which revealed classic congophilic deposits with apple-green birefringence under polarized light.[6,7]

This differentiates ABRA from:

PACNS (no amyloid)

CAA without inflammation (no granulomatous response)

Infective granulomatous processes (e.g., tuberculosis and fungal infections)

Failure to perform amyloid staining can lead to misclassification, especially in Tuberculosis (TB)-endemic settings, where granulomatous inflammation is often presumed to be infective.

ABRA is best regarded as the angiodestructive end of the CAA-RI spectrum – the other end being nondestructive, perivascular (CAA-RI) inflammation. Histopathologic and clinicopathologic series first delineating inflammatory CAA described both transmural, granulomatous vasculitis (ABRA) and perivascular inflammatory forms, and later cohort studies and reviews have reaffirmed

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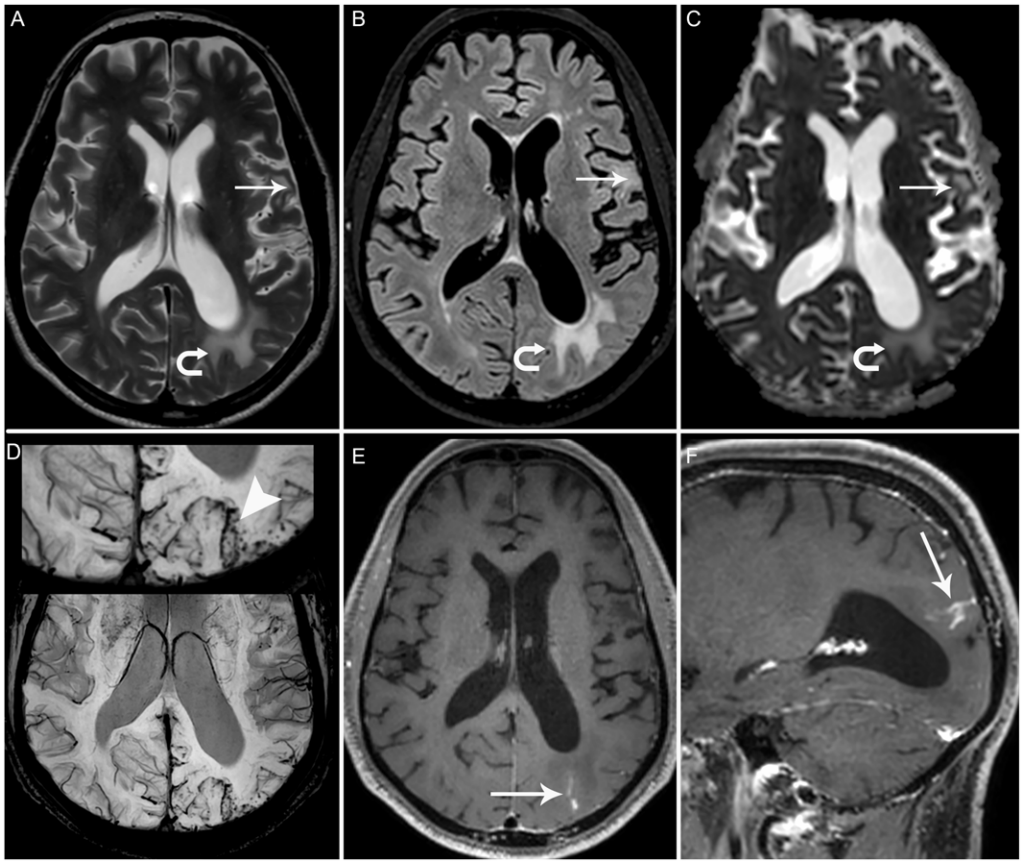


Figure 2. Axial T2-WI (A) and FLAIR images (B) at the level of upper basal ganglia show hyperintense lesions in the left occipital lobe (curved arrow), frontal lobe (arrow in a, b) without any evidence of diffusion restriction in ADC maps (arrow and curved arrow) (C). Axial SWI image shows sulcal and cortical punctate foci (arrowhead in inset) of susceptibility signal suggesting microhemorrhages. Axial (F) and sagittal (G) T1-WI show sulcal enhancement in the left parieto-occipital sulcus.

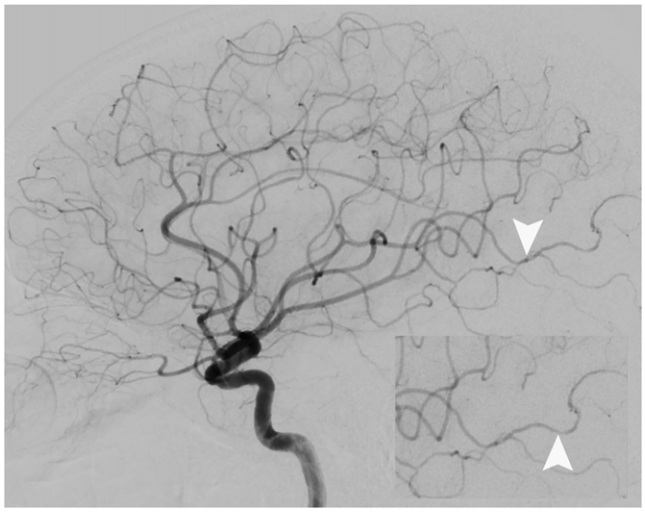


Figure 3. Digital subtraction angiography of the left internal carotid artery shows irregularity of posterior parietal branch (arrowhead).

that ABRA and CAA-RI represent related manifestations of an immune response to vascular Aβ deposits.[8,9,1]

CSF findings

Although cerebrospinal fluid in ABRA is often normal or shows only mild nonspecific abnormalities, a modest lymphocytic pleocytosis (typically<50 cells/μL) has been documented in several series.[1,11] In our patient, the presence of 12 lymphocytes/μL supports an underlying inflammatory process and is consistent with prior reports of ABRA, in which such mild lymphocytic responses are attributed to perivascular and leptomeningeal inflammation.

Radiological clues

While nonspecific, imaging plays a critical role in raising suspicion for ABRA.[12]

- Patchy T2/FLAIR hyperintensities in cortex and subcortical white matter.
- Sulcal or leptomeningeal enhancement.
- Cortical microbleeds on SWI.
- Absence of deep white matter or basal ganglia involvement, distinguishing ABRA from other vasculitides

In our case, cerebellar dentate involvement is atypical for CAA, which preferentially affects leptomeningeal and cortical vessels and – when cerebellar – usually the superficial cerebellar cortex. Deep-nuclear microbleeds (dentate) are therefore generally considered inconsistent with classic CAA distribution. However, histopathologic proof of transmural granulomatous vasculitis with vascular Aβ in our patient confirms ABRA despite the unusual location. This finding likely represents a rare extension of inflammatory CAA into deep cerebellar structures (or, less likely, a concurrent small-vessel process), and pathology takes precedence over imaging.

Although conventional angiography is not performed in every case of ABRA, several series have documented multifocal narrowing of small- and medium-sized leptomeningeal and cortical vessels.[1]

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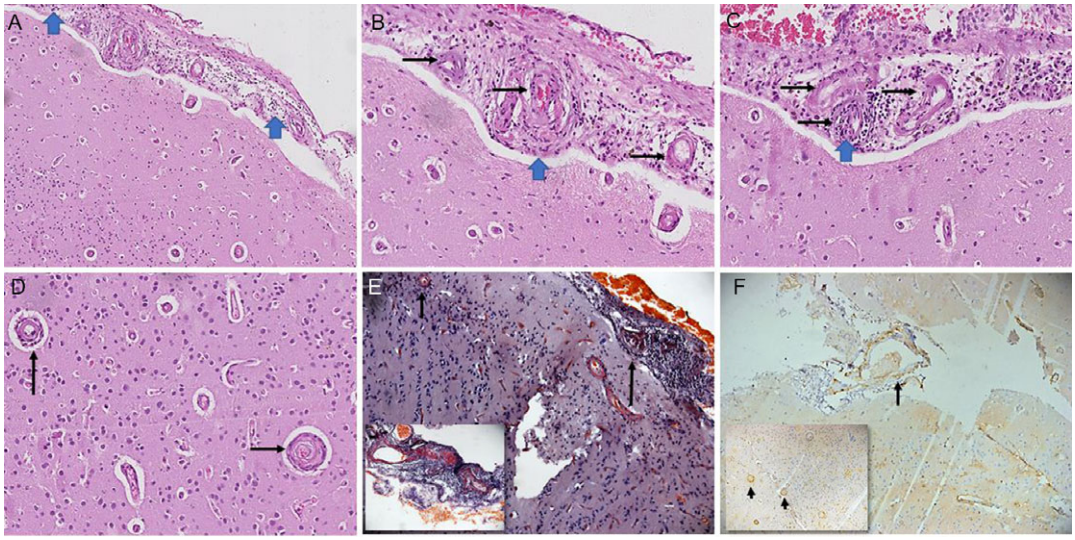


Figure 4. Hematoxylin and eosin-stained sections from brain biopsy show diffuse expansion of the leptomeninges (blue solid arrows) (A, 200x). The leptomeningeal vessels (black arrows) show thickening of the media by pale eosinophilic material with leucocytoclasis, fibrin deposition, and ill-defined epithelioid cell granulomas (blue solid arrows) (B–C, 400x). Perivascular hemosiderin deposition and lymphocytic infiltration are also seen. Thickening of the media with deposition of similar material is also seen in the cortical vessels (D, black arrows, 400x). The deposited material in both leptomeningeal (long arrows) and cortical vessels (short arrows) is congophilic (E, 100x, Congo Red Stain; inset 400x), which showed apple-green birefringence on polarizing microscopy and is immunopositive for beta-amyloid protein (F, 100x; inset 400x). Cortical and leptomeningeal vessels showing co-localization of β-amyloid deposition (Aβ immunohistochemistry) and transmural inflammatory infiltrates (H&E), confirming that the vessels involved by vasculitis are the same as those affected by CAA. Incidental CAA would be unusual in a 58-year-old, further supporting ABRA.

In relation to ABRA, the MRI findings of multiple strictly lobar microbleeds and leptomeningeal/parenchymal contrast enhancement are among the characteristic imaging features listed by Auriel et al for CAA-RI.[13] However, Auriel's criteria require asymmetric, confluent subcortical white-matter hyperintensities reaching the immediate subcortical white matter to call a case probable CAA-RI; if those asymmetric White Matter Hyperintensitys are absent in our patient, the imaging classification is limited to possible CAA-RI. Crucially, ABRA represents the angiodestructive (granulomatous vasculitic) pole of the CAA-RI spectrum, so histopathologic confirmation (biopsy showing transmural granulomatous inflammation with vascular Aβ) is needed to distinguish ABRA from nondestructive perivascular CAA-RI even when imaging criteria are met.

In our patient, these findings were evident and aligned with known ABRA patterns.

Pathophysiology and immunopathogenesis

The underlying pathogenesis of ABRA is presumed to be an autoimmune reaction to vascular beta-amyloid deposits. Histologically, ABRA is characterized by:

- Granulomatous transmural and perivascular inflammation.
- Infiltrates of CD4+ T cells, epithelioid histiocytes and multinucleated giant cells.
- Leukocytoclasia, fibrin deposition and vessel wall necrosis.[6]
- The inflammatory cells appear to phagocytose amyloid, and their close spatial association with amyloid-laden vessels supports a causative relationship.[6,10] Some authors consider ABRA as a subset of CAA-RI, where an aberrant immune response is mounted to accumulated Aβ peptides.[4,5]

In our case, the biopsy shows florid, angiodestructive CAA consistent with Vonsattel grade 3 (severe) – media largely replaced by Aβ with focal wall fragmentation and fibrinoid change. These findings indicate widespread, destructive vessel wall involvement in the sampled tissue (supporting ABRA), although cortical biopsy may not capture whole-brain burden.

Treatment and outcome

High-dose corticosteroids are the mainstay of therapy.[12,14] Our patient showed marked improvement in cognition and seizure control with steroids alone, supporting literature that reports a favorable prognosis in most ABRA cases when diagnosed and treated early.

In relapsing or severe cases, steroid-sparing agents such as cyclophosphamide, azathioprine or mycophenolate mofetil may be used. However, there are no randomized controlled trials to guide therapy.[7] Clinical improvement typically precedes radiological resolution.

Diagnostic criteria and importance of biopsy

The patient fulfilled Chung et al.'s criteria for definite ABRA:[15]

- Subacute neurologic symptoms
- MRI and angiographic findings suggestive of vasculitis
- Histopathologic evidence of granulomatous angiitis with beta-amyloid deposition

Brain biopsy remains the gold standard for diagnosis but is often avoided due to invasiveness and potential sampling errors.[6,10] In this case, targeted biopsy yielded a definitive diagnosis

Treatment and outcome: Dr. Vibha

The patient was treated with high-dose corticosteroids. Seizures and neurologic deficits did not recur post-treatment. Cognitive improvement was evident on follow-up. Repeat MRI showed resolution of some white matter changes.

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No additional immunosuppressive agents were required. The diagnosis and early steroid therapy potentially prevented further deterioration.

A key limitation of this report is the lack of long-term clinical and radiological follow-up, which precludes assessment of sustained remission, relapse risk, and potential delayed complications of ABRA or its treatment.

Conclusion

ABRA is a rare but treatable cause of subacute cognitive decline and seizures. Brain biopsy with amyloid staining is crucial for accurate diagnosis. Early recognition and immunosuppression can result in clinical stabilization or improvement. In TB-endemic countries, distinguishing ABRA from infective granulomatous diseases is vital.

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Author contributions. Kamalesh Tayade, Arunmozhimaran Elavarasi, Deepti Vibha, and Rajesh Kumar Singh contributed to the conception and design of the study, data acquisition, analysis, interpretation, preparation of first draft and revision of final draft. Aruna Nambirajan provided pathological expertise and contributed to histopathological data analysis. Ajay Garg was responsible for neuroimaging acquisition and interpretation. Manjari Tripathi contributed to clinical evaluation and critical revision of the manuscript. Bhargavi Ramanujam assisted in data collection and manuscript drafting. Hitesh Gurjar performed neurosurgical procedures and contributed to surgical data interpretation. All authors reviewed and approved the final version of the manuscript.

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Ethical standards. Informed patient consent was obtained. Institutional review board or ethics committee approval not required. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

AI use. None done.

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