CASE REPORT

Amyloid-Beta-Related Angiitis with Distinctive Neuro-Ophthalmologic Features

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ABSTRACT

Amyloid beta-related angiitis (ABRA) is a subtype of cerebral amyloid angiopathy-related inflammation, with distinctive pathology and prognosis compared with cerebral amyloid angiopathy (CAA). On a spectrum of increasing severity, ABRA is considered to be in-between the less aggressive inflammatory-CAA and the more severe primary central nervous system (CNS) angiitis. Whereas retinal pathological changes were described in subjects with primary or secondary CNS angiitis, and non-inflammatory CAA, bilateral posterior pole superficial and peripapillary retinal hemorrhages have not been reported as initial signs in patients with pathology-confirmed ABRA, accompanying neurological spells and characteristic neuroimaging findings.

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Introduction

Cerebral amyloid angiopathy (CAA) is a cerebral microangiopathy caused by vascular amyloid deposition and diagnosed clinically using Boston criteria.¹ CAA inflammatory subtypes forming the spectrum of CAA-related inflammation (CAA-RI) are under-recognized entities in clinical practice. Although accurate clinico-radiological criteria have been proposed for possible and probable CAA-RI, the definitive diagnosis is histopathological.

Retinal pathological changes are described in amyloid-related central nervous system diseases, such as Alzheimer's disease and classical CAA^{2,3}, but not in association with the inflammatory CAA subtypes. We report a case of amyloid-beta-related angiitis (ABRA) with distinctive neuro-ophthalmologic findings, reversible with systemic immunosuppressive therapy.

Case report

A 57-year-old right-handed gentleman, with past medical history significant for chronic insomnia and thoracic dermatomes shingles 5 years prior, presented with our neurology clinic for an evaluation of spells. The spells had different characteristics: some were

described as sudden disorientation associated with dizziness and imbalance, and others manifested with speech difficulties and behavioral arrest. The duration and frequency varied between 30 and 40 s, three to four times a day at onset, and gradually progressed to 3–20 min in duration, with multiple daily incidents in the following weeks. The spells were associated with dull holocephalic and continuous headaches, progressive cognitive decline, and gait instability. In addition, the patient developed blurry vision in both eyes associated with floaters and colorful and vivid binocular scotomas, which prompted him to pursue an ophthalmological consultation. The patient's family history was negative for autoimmune disease, inflammatory conditions, and dementia. His father had suffered from strokes in his seventies. The patient was a life-long non-smoker, with no history of illicit drug use and rare alcohol use. The constellation of ocular and neurologic symptoms and the spells of behavioral and speech arrest resulted in work and driving cessation.

On ophthalmological examination, his best corrected visual acuity was 20/30 in both eyes. The color vision tested using Ishihara plates was normal. Intraocular pressure and anterior ocular segment examination were unremarkable. Dilated

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fundusoscopic examination revealed moderate-to-severe bilateral optic disc edema, with peripapillary splinter retinal hemorrhages and posterior pole superficial retinal hemorrhages (Figure 1). There were cotton wool spots on the superior edge of the right optic disc indicative of axoplasmic stasis. The retinal periphery was unremarkable. With the exception of the aforementioned fundusoscopic features, the neurological examination was normal, with intact mental status examination, cranial nerves, sensory and motor exam, gait and coordination. Humphrey 30–2 Perimetry revealed scattered non-localizing visual field defects, with Pattern Standard Deviation (PSD) 5 and Mean Deviation (MD) -4.4 in the right eye and PSD 8.8 and MD -7.4 in the left eye (Figure 1). Retinal optical coherence tomography (OCT, Zeiss Cirrus Spectral Domain) showed right pigment epithelial detachment nasal to the fovea with some disruption of the outer nuclear layer (Supplemental Figure 3). The central retinal

thickness was $277\ \mu\text{m}$ in the right eye and $285\ \mu\text{m}$ in the left eye (of note, normal foveal thickness being $251 \pm 21\ \mu\text{m}$). Fluorescein angiography exhibited bilateral optic disk leakage, peripapillary and posterior pole superficial retinal hemorrhages, and pooling in the right macula. There was no evidence of a retinal vasculitis (Supplemental Figure 1).

A brain MRI with and without contrast revealed multifocal patchy and confluent vasogenic edema in the cerebral hemispheres with prominent subcortical and cortical involvement, associated with multiple foci of magnetic susceptibility in the cortex and subcortical white matter related to hemosiderin deposition from microhemorrhages (Figure 2). An MR angiogram and CT angiogram of the head and neck were unremarkable. Serologic work-up comprised normal erythrocyte sedimentation rate, C-reactive protein, C3, C4, immunoglobulin G 100 and negative Sjogrens-Syndrome A, Sjogrens-Syndrome B, myeloperoxidase and proteinase-3 antibodies. Lumbar puncture

Figure 1. Retinal fundus photographs and Humphrey visual field images of the right eye (A) and left eye (B) at the time of diagnosis (upper rows) and two weeks after therapy initiation (bottom rows).

Figure 2. Brain MR images at the time of diagnosis (A) and six weeks post-therapy initiation (B) showing cerebral microbleeds (on susceptibility-weighted images, upper row) and multifocal patchy hyperintense lesions on T2-FLAIR images (bottom row).

showed elevated opening pressure of 22 mmHg. Cerebrospinal fluid (CSF) analysis revealed colorless CSF with elevated protein at 127 (normal less than 45 mg/dl), normal glucose (65 mg/dl), 5 nucleated cells, 12 red blood cells, and normal IgG Quant 18.5, IgG index 0.8, albumin 82, myelin basic protein 4.8. The Lyme PCR, West Nile IgM and IgG and oligoclonal bands were negative. Routine electroencephalogram in the awake and asleep state was unremarkable.

Based on the constellation of clinical symptoms, CSF analysis, and brain imaging findings, a presumptive diagnosis of probable amyloid beta-related angitis of the central nervous system was made. High-dose intravenous methylprednisolone (1 g daily for 5 days), followed by oral prednisone 60 mg daily, was administered. Topiramate 50 mg twice daily was titrated for symptomatic management of spells and resulted in their resolution in approximately 1 week. Acetazolamide 500 mg twice daily was started given moderate-to-severe optic disc edema and visual field abnormalities.

In order to guide long-term immunosuppressive therapy, a right frontal brain biopsy was conducted prior to the completion of intravenous corticosteroids. The grey and superficial white matter histopathological analysis revealed cortical and leptomeningeal vessels with thick vascular wall with deposition of amorphous eosinophilic material consistent with amyloid (positive Congo Red stain and beta-amyloid immunostain). Blood vessels revealed perivascular chronic inflammatory infiltrate (Supplemental Figure 2).

Repeat retina fundus photography 2 weeks after intravenous corticosteroid therapy showed improved bilateral optic disc edema and resolving retinal hemorrhages. Humphrey 30–2 Visual Field examination exhibited improvement: MD -3.1 and PSD 3.0 in the right eye and MD -2.8 and PSD 3.5 in the left eye (Figure 1). Visual fields remained stable at repeat checkup a week later and were accompanied by substantial reduction in optic nerve head elevation on OCT.

Given the diagnosis of definite ABRA, the patient was initiated on intravenous cyclophosphamide 600 mg/m², and oral Prednisone 60 mg daily was continued. Repeat brain MR 6 weeks later showed significant improvement on FLAIR imaging with less associated edema surrounding subcortical and periventricular whitematter areas of prior involvement, and stable appearance of the bilateral hemispheric foci of susceptibility related to microhemorrhages (Figure 2). At 6 week follow-up, patient is spell and headache-free. He denies any visual symptomatology, remains neurologically intact and plans to return to work.

Discussion

CAA is caused by amyloid- β fibril deposition in the walls of small and medium-sized vessels, causing lumen obliteration and secondary ischemic leukoencephalopathy and cerebral infarction. Vascular rupture also causes lobar micro- or macrohemorrhages and high-convexity subarachnoid hemorrhages.

Various amounts of perivascular inflammation may be observed.⁴ It is not completely understood whether the deposition of amyloid in vessel walls triggers the inflammatory response or if the inflammation leads to amyloid deposition.⁵

A spectrum of entities is described, comprising CAA, CAA-RI (inflammatory CAA (I-CAA) and ABRA), and primary angiitis of the central nervous system (PACNS). Patients with ABRA are typically younger (mean age 67 years) than those with non-I-CAA (77 years) and older than patients with PACNS (45 years).⁶ Identifying the inflammatory subtypes of CAA is of paramount importance, in view of a different management plan and overall prognosis. Cyclophosphamide, methotrexate, azathioprine, and mycophenolate have been successfully used in ABRA⁷, with approximately 26% relapse rate on reduction or cessation of immunosuppressive therapy. The advantages of prolonged immunosuppressant treatment, which is recommended in ABRA and PACNS, remain unproven in I-CAA.⁸

Non-invasive clinico-radiological criteria for CAA-RI are reported by Auriel et al.⁹ The role of brain and leptomeningeal biopsy is to confirm the pathological diagnosis of CAA-RI subtypes and differentiate from PACNS. The vasculitic destruction of the vessel wall (transmural and granulomatous) described in ABRA¹⁰ and PACNS is absent in the I-CAA, which displays mainly perivascular inflammation.^{8,11} Amyloid- β deposits co-localize with inflammatory changes in ABRA; whereas, they are absent or do not co-localize with the inflammatory changes in PACNS.⁸

Retinal and cerebral vasculature share similarities in morphology and pathophysiology. Hence, the dysfunction of the blood–retina barrier and the blood–brain barrier may be concomitant and analogous, contributing to the development of retinal and cerebral microangiopathy, respectively.¹² Various forms of amyloid retinal deposits are described in the literature. Dominantly inherited oculoleptomeningeal amyloidosis with characteristic leptomeningeal and retinal vessel deposits caused by circulating transthyretin deposition and good response to plasmapheresis was reported.¹³ Dot and blot retinal hemorrhages and microaneurysms identified on retinal fundus pictures and fluorescein angiography were shown in seven patients with sporadic noninflammatory CAA.³ Retinal deposits of beta-amyloid and p-tau in

Alzheimer's Disease (AD) are well recognized.^{14,15} In addition to perivascular amyloid- β deposition, the retinal vascular pattern changes in AD include the reduction of venous blood flow, arteriolar and venular fractal dimensions, branching complexity, changes to arteriolar and venular tortuosity.¹⁵ Frank retinal hemorrhages in AD are not reported. In addition, there is no clear differentiation between AD-specific retinal amyloid- β and amyloid- β found in different amyloid-related diseases.²

Conversely, inflammatory retinal vascular changes and optic disc edema have been described in CNS vasculitis secondary to systemic lupus erythematosus, granulomatosis with polyangiitis, and antiphospholipid antibody syndrome.^{4,16} Optic neuritis and neuroretinitis were reported in association with PACNS^{17,18}, but not with CAA-RI. Bilateral disc edema and anterior uveitis responsive to topical ophthalmic steroids were described in one patient with ABRA.¹⁹

Our case report illustrates that the bilateral superficial retinal and the peripapillary hemorrhages can be observed in association with ABRA. The retinal changes also improve with systemic immunosuppressive therapy, paralleling the clinical and neuroradiological improvement. These findings underscore the potential usefulness of retinal imaging for the diagnosis and monitoring of patients with different CAA subtypes. This becomes critically important in patients with CAA-RI in need of early diagnosis and prompt initiation of immunosuppressive therapy.

Modern applications of advanced retinal amyloid imaging in entities such as AD to screen for pre-symptomatic disease^{14,15} may perhaps be extended to the CAA spectrum. Although novel amyloid-modifying therapies for AD and CAA are under investigation^{20–22}, amyloid-related imaging abnormalities (ARIA) reported in subjects with AD treated with passive amyloid- β immunotherapy share various imaging characteristics with CAA-RI.²² Non-invasive retinal imaging might be a useful tool to study the association between retinal and brain amyloid burden and inflammation.

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