Clinical Reasoning: An 81-year-old woman with decreased consciousness and fluctuating right facial droop

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Section 1

An 81-year-old woman presented to the hospital after a week of intermittent episodes of decreased level of consciousness, right facial droop, and slurred speech, lasting approximately 30 minutes. Her medical history included chronic obstructive pulmonary disease, dyslipidemia, orthostatic hypotension, and 2 previous TIAs. She had fallen once in the preceding week, presumably as a result of her drowsiness. On examination, she was afebrile with a heart rate of 81 bpm and a blood pressure of 108/65 mm Hg. She was alert and cooperative, but disoriented to the year and location. Language examination was normal. Cranial nerves, motor, coordination, and sensory examinations were all normal without any focal deficits. However, when assessed during one of her episodes, she was less responsive, had decreased verbal output, and was noted to have a right facial droop. Basic serologic tests (complete blood count, electrolytes, renal function tests) were unremarkable. A head CT showed bilateral subarachnoid hemorrhage over the cerebral hemispheres without further abnormality.

Questions for consideration:

1. What is your differential diagnosis?
2. Which investigations would you perform at this point?

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Section 2

The differential diagnosis for a patient with this presentation is broad. Categories that should be considered include meningitis, viral encephalitis, other infectious etiologies, toxic or metabolic encephalopathies, seizure disorders, cerebrovascular

events, conditions causing increased intracranial pressure, and neuroinflammatory/autoimmune disorders, amongst others.

An MRI scan demonstrated extensive white matter T2 fluid-attenuated inversion recovery signal abnormality asymmetrically affecting the left occipital and bilateral frontal lobes (figure).

Figure Radiologic and pathologic findings

Fluid-attenuated inversion recovery (FLAIR) (A), diffusion-weighted imaging (DWI) (B), and multiplanar gradient recalled (MPGR) (C) axial images demonstrate widespread asymmetric T2 FLAIR hyperintensities with right frontal and left occipital predilection. Signal abnormality extends predominantly to the subcortical white matter with questionable regions of cortical involvement suspected within the right frontal and left occipital lobes. Several foci of diffusion restriction are evident within the bilateral frontal, left parietal, and right occipital lobes consistent with microinfarcts within multiple vascular territories. Gradient imaging demonstrates multiple regions of cortical superficial siderosis and microhemorrhages. Hematoxylin and eosin (H&E)/Luxol fast blue stain of the left frontal cortex (D) shows microinfarcts in both the cortex and underlying white matter, with patchy infiltration of macrophages into these regions demonstrated on a CD163 immunostain (E). High-power H&E view of intraparenchymal (F) and leptomeningeal (G) vessels shows deposition of amorphous, eosinophilic material throughout the vessel wall layers. The vessels are round, with thickened and abnormal wall architecture, and fibrinoid necrosis. Prominent reactive surrounding gliosis is also appreciated. (H) Immunostaining of a frontal cortical section with amyloid- β antibody confirms vascular amyloid deposition and vessel wall disruption.

Multiple punctate foci of diffusion restriction consistent with acute infarction were evident on diffusion-weighted imaging within subcortical white matter and widespread within the supratentorial cortex and peripheral cerebellar hemispheres (figure). Susceptibility-weighted imaging using multiplanar gradient recalled acquisition sequences demonstrated multiple regions of microhemorrhages and cortical superficial siderosis (figure). A lumbar puncture was performed, which showed an elevated protein level (623 mg/L), mild leukocytosis (47 cells/ μ L), and negative cytology, cultures, and serology for cryptococcus; testing for antibodies against N-methyl-D-aspartate receptor, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

receptor, and voltage-gated potassium channel in the CSF was negative. On serologic studies, C-reactive protein was slightly elevated (58 mg/mL); erythrocyte sedimentation rate (ESR) was normal (50 mg/mL); antinuclear antibody (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), and extractable nuclear antigen were negative; and serology for West Nile virus and syphilis were negative. EEG testing showed a “focal polymorphism possibly indicative of recent seizure activity.”

Question for consideration:

1. How would you refine your differential diagnosis based on these results?

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Section 3

The MRI finding of leptomeningeal enhancement in combination with multiple foci of hemorrhage and superficial siderosis provide significant direction as to the etiology of this patient's symptoms. Differential diagnoses for diffuse leptomeningeal enhancement include infection (fungal, mycobacterial), neoplasm (melanocytosis, carcinomatosis, lymphomatosis), and inflammation (sarcoidosis, inflammatory amyloid angiopathy).

The elevated CSF protein without increased red blood cells, in the context of known hemorrhage and siderosis on imaging, points to a subacute or chronic pattern of bleeding. Negative

CSF cytology and culture reduce the likelihood of a neoplastic or infectious etiology. In this case, the pattern of asymmetric white matter hyperintensity and hemorrhage with superficial siderosis in a patient with elevated CSF protein and altered level of consciousness suggested a possible diagnosis of inflammatory amyloid angiopathy such as cerebral amyloid angiopathy (CAA)-related inflammation or β -amyloid (A β)-related angiitis (ABRA).

Questions for consideration:

1. What would be your management for this patient?
2. What are the histopathologic features of CAA and ABRA?

GO TO SECTION 4

Section 4

The history and radiologic findings are highly suggestive of a diagnosis of inflammatory amyloid angiopathy. At admission, this patient was treated with phenytoin and then levetiracetam for suspected seizure activity. Her mental status continued to fluctuate, and she developed recurrent episodes of aspiration pneumonia. Pulsed steroids were initiated for a suspected diagnosis of inflammatory amyloid angiopathy. Her clinical condition did not improve and a repeat MRI showed worsening T2 hyperintense parenchymal edema with scattered acute infarcts. She eventually sustained a final aspiration event, went into hemodynamic shock, developed multiorgan failure, and died in the intensive care unit.

Definitive diagnosis of ABRA requires neuropathologic examination, either by brain biopsy or autopsy. Consent for postmortem examination was obtained. At macroscopic postmortem examination, the brain was swollen, showed significant leptomeningeal opacification, and several cerebral infarcts were seen. Microscopically, numerous subacute and remote microinfarcts were identified throughout the cortex and underlying white matter (figure) with variable infiltration of CD163 immunopositive macrophages (figure). There was extensive granulomatous inflammation and fibrinoid necrosis within vessels of the superficial brain parenchyma (figure) and leptomeninges (figure) with numerous multinucleated giant cells and associated gliosis. A β immunohistochemistry confirmed amyloid deposition in the affected vessels (figure), with the additional finding of amyloid within activated microglia in adjacent parenchyma. Collectively, these findings permitted a definitive diagnosis of ABRA.

Discussion

CAA with perivascular inflammation or granulomatous (giant cell) angiitis has been described in the literature spanning the last 4 decades. These cases have different clinical and pathologic presentations than primary angiitis of the CNS or CAA alone, which lack findings of amyloid deposition and inflammation, respectively. Concurrent findings of CAA and perivascular inflammation have been designated as CAA-related inflammation (CAA-RI); when frank vessel wall inflammation with fibrinoid necrosis is present (as in our case), the term ABRA is used.^{1,2}

The average age at CAA-RI and ABRA onset is >50 years, which is older than in primary angiitis of the CNS but younger than in CAA.^{3,4} The clinical presentation varies significantly between patients, but generally includes some combination of subacute cognitive or functional decline over a period of several months, new onset of seizure-like episodes, recurring or persistent headaches, perceptual disturbances such as hallucinations, or neurologic deficits such as visual disturbance or hemiparesis.^{1,3,5} Similar to patients with noninflammatory CAA, lobar hemorrhages caused by

vessel wall rupture can result in a more acute clinical presentation.⁶ Imaging and biochemical testing of patients suspected to have ABRA is critical for timely and accurate diagnosis of this entity. In general, serum testing for ANA and ANCA is negative, and the ESR is normal in most patients (though elevated in some). CSF analysis frequently shows protein elevations >70 mg/dL, and a lymphocyte-predominant leukocytosis well above 10 cells/mm³.^{3,5-7} Of note, the APOE ϵ 4/ ϵ 4 genotype is enriched in patients with inflammatory angiopathy relative to noninflammatory CAA, suggesting a role for genetic (and downstream immunologic) contributions in the initiation or maintenance of the disease.⁶

Careful radiopathologic correlation studies by several groups in recent years have delineated clinical and imaging features proposed to serve as a surrogate to invasive brain biopsy.⁸ Recently, clinikoradiologic criteria for a diagnosis of probable CAA-RI have been published, though the extent to which these apply to ABRA requires further validation.⁸ These criteria include (1) age over 40 years; (2) presence of one of headache, decreased consciousness, behavioral change, focal neurologic signs, or seizures; (3) unifocal or multifocal white matter hyperintensity (WMH) that is asymmetric and extends to the immediately subcortical white matter; (4) presence of one or more of cortical or subcortical hemorrhage, cerebral macrobleed or microbleed, or superficial siderosis; and (5) exclusion of other causes. In a validation cohort of 17 patients with pathologically confirmed CAA-RI, these criteria had a sensitivity and specificity of 82% and 97%, respectively.⁸ Similar criteria for a diagnosis of possible CAA-RI, which broadened the permissible range of WMH, did not improve sensitivity, and reduced specificity significantly (82% and 68%, respectively).⁸

The radiologic and clinical features of ABRA have been shown to be more responsive to immunosuppressive therapy than those of CAA, though a subset of patients have been shown to relapse and consequently show a poor prognosis.^{5,9} The primary treatment modality described in the literature is corticosteroid therapy, usually consisting of a course of oral prednisone or IV methylprednisolone pulse therapy. The use of other agents such as cyclophosphamide, methotrexate, azathioprine, mycophenolate mofetil, and IV immunoglobulin has also been described.^{4,7} Many patients show complete or near complete resolution of symptoms within a few weeks or months, though in a subset of patients (~18% in one published study) symptoms will relapse after discontinuation of therapy.¹ In some cases, these patients will respond well to a second iteration of immunosuppressive therapy.^{5,7} Treatment is generally well-tolerated, though patients should be monitored for the side effects of short-term, high-dose corticosteroid therapy (such as hyperglycemia or psychosis). The lack of standardized therapeutic regimens and paucity of specific clinical, biochemical, or radiologic biomarkers predictive of prognosis mean that tailored approaches for agent or dose selection are not yet available.

Neuropathologically, the findings in our case mirror those of other ABRA cases described in the literature, namely leptomeningeal and parenchymal inflammation around and within amyloid-laden blood vessels, comprising lymphocytes, macrophages, and giant cells (vasculitis). Both A β ₄₀ and A β ₄₂ isoforms are present, though the former is predominant. Vessels can show splitting, fibrinoid necrosis, and thrombosis, sometimes with recanalization. Finally, associated hemorrhage and parenchymal infarcts of varying ages are frequent findings.¹⁰ Together, these findings strongly suggest that the radiopathologic findings of ABRA are caused by immunologic response to A β deposits in brain vasculature. This hypothesis is supported by in vivo experimental findings of severe vasculitis and vessel obliteration in an amyloid precursor protein transgenic mouse model, and by postmortem pathologic findings of severe meningoencephalitis in patients undergoing A β vaccination for experimental treatment of Alzheimer disease.⁵

Consent

The patient's family consented to postmortem examination for diagnostic and research purposes.

Data availability

All available data are provided within this article.

Study funding

No targeted funding reported.

Disclosure

R. Van Ommeren, A. Izenberg, S. Shadowitz, R. Aviv, and J. Keith report no relevant disclosures. Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures.

Appendix Authors

Name	Location	Contribution
Randy Van Ommeren, MD	University of Toronto, Canada	Drafted manuscript body and generated figure
Aaron Izenberg, MD	University of Toronto, Canada	Assisted with drafting and review of clinical aspects of manuscript
Steven Shadowitz, MD	University of Toronto, Canada	Assisted with drafting and review of clinical aspects of manuscript
Richard Aviv, MD	University of Toronto, Canada	Assisted with drafting and review of radiology aspects of manuscript
Julia Keith, MD	University of Toronto, Canada	Supervised writing process, reviewed all aspects of publication, including pathologic descriptions

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