Clinical Reasoning: A 55-Year-Old Woman With Recurrent Episodes of Aphasia and Vision Changes

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Neurology® 2022;98:330-335. doi:10.1212/WNL.0000000000013219

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Abstract

A 55-year-old woman presented with recurrent episodes of headache, vision changes, and language disturbances. Brain MRI showed multifocal white matter lesions, microhemorrhages, and enlarged perivascular spaces. After an extensive and unrevealing workup, she underwent a biopsy of brain and meninges that revealed thick and hyalinized leptomeningeal and cortical vessel walls that were strongly positive for β-amyloid by immunohistochemical staining, suggestive of cerebral amyloid angiopathy (CAA). CAA can present as a spectrum of inflammatory responses to the deposition of amyloid-β in the vessel walls. Her clinical presentation, radiologic, and histopathologic findings supported a diagnosis of probable CAA-related inflammation (CAA-ri). Although an uncommon entity, it is important to recognize it because most patients respond to immunosuppressive therapy.

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Section 1

A 55-year-old woman presented with acute onset of headache, inability to reach objects she could clearly see, vision changes (objects remaining in her vision after the stimulus was no longer present), and language disturbances. Her blood pressure ranged between 120/60 and 150/90. She was afebrile, with a normal heart rate. Neurologic examination was notable for difficulty naming and reading, with comprehension and repetition less affected, right homonymous hemianopsia. Her motor, sensory, and coordination functions were normal. Initial laboratory data were unremarkable, including HIV-negative status.

The visual phenomenon she described is known as palinopsia, a visual illusory phenomenon characterized by persistence of an image after the visual stimulus has been removed. It usually occurs with nondominant parieto-occipital lesions and associates with a visual field defect but can be seen with dominant or bilateral lesions, thought to be due to abnormal synthesis of visual information, occasionally related to focal seizures.[1] In addition, she described impairment of visually guided reaching, known as optic ataxia, typically associated with bilateral posterior parietal lesions.[2] Given the visual field defect and motor predominant aphasia, in the absence of hemiparesis, we suspected a multifocal process, likely involving the left occipital or parieto-occipital and frontal regions.

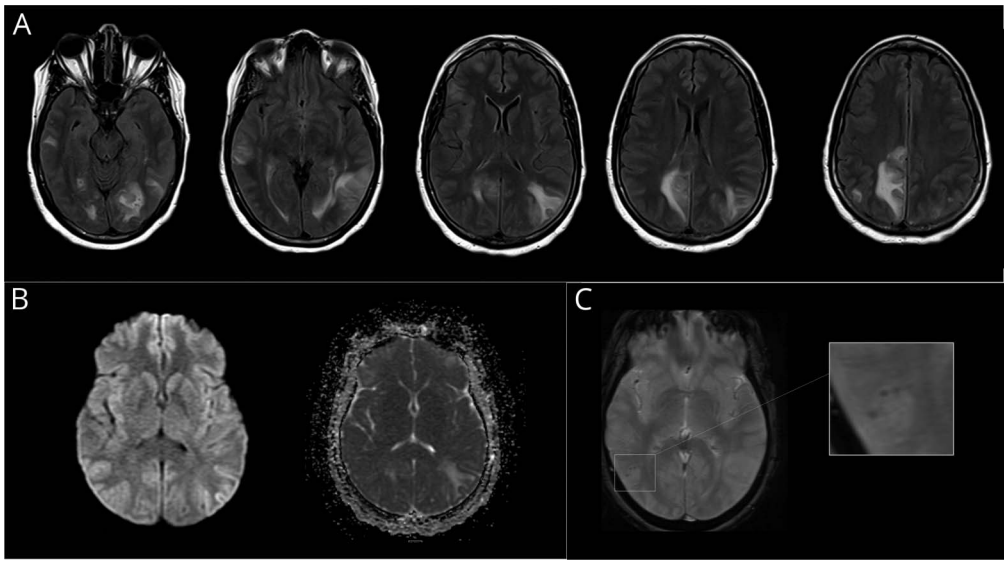
Given the acute presentation, multifocal ischemic or hemorrhagic strokes were on the differential diagnosis. Inflammatory conditions were a possibility given the multifocal nature of her presentation.

She underwent brain MRI that revealed bilateral asymmetric cortical and subcortical T2/fluid-attenuated inversion recovery (FLAIR) hyperintense signal abnormalities most prominent in the posterior regions (Figure 1, A), without enhancement, as well as cortical diffusion restriction of the left temporo-occipital region with features suggestive of vasogenic edema (Figure 1, B), and 2 punctate microhemorrhages within the right parietal lobe (Figure 1, C).

Questions for Consideration:

1. What is the localization?
2. What is the differential diagnosis?
3. What tests would you obtain?

Figure 1



(A) Fluid-attenuated inversion recovery (FLAIR) demonstrates multiple cortical and subcortical white matter FLAIR hyperintense signal changes that involve the subcortical U fibers, most prominently within the right frontoparietal, left temporo-occipital, and left greater than right occipital lobes. (B) Diffusion-weighted imaging (DWI, on the left) and apparent diffusion coefficient sequences (ADC, on the right) show cortical diffusion restriction and vasogenic edema, respectively, in the left temporo-occipital region. (C) Gradient echo sequence (GRE) reveals punctate microhemorrhages in the right parietal lobe.

GO TO SECTION 2

Section 2

Imaging was suggestive of posterior reversible encephalopathy syndrome (PRES), which is associated with bilateral asymmetric T2/FLAIR hyperintensities in the subcortical white matter (WM) in the parieto-occipital lobes, occasionally associated with blood products.[3] Although subcortical restricted diffusion can be seen in some cases, it is typically heterogeneous, with punctate lesions surrounded by vasogenic edema.[3] The cortical pattern of restricted diffusion raised the concern for seizures,[4] which prompted continuous EEG (cEEG) demonstrating abundant left posterior temporal lateralized periodic discharges. She was started on levetiracetam, with improvement of her aphasia.

The lack of enhancement made inflammatory and neoplastic conditions less likely. Although extensive WM hyperintensities (WMHs) without postcontrast enhancement raised the possibility of progressive multifocal leukoencephalopathy, this was considered unlikely given her immunecompetent status and the absence of hypointense core with a hyperintense rim on the DWI sequence.[5] PRES was highest in our differential diagnosis, and the lack of clear trigger led to extensive workup. Urine drug screen was negative. CSF analysis revealed 1 WBC, 6 RBCs, protein 48 mg/dL (normal 15–45), and normal glucose. CSF cytology was negative for malignancy, and cultures were sterile. Extensive infectious workup was negative in the serum and CSF. No oligoclonal bands were detected. Her erythrocyte sedimentation rate (51 mm/hr, normal <30) and C-reactive protein (12.0 mg/L, normal <10) were mildly elevated. She had a positive antinuclear antibody in a nucleolar pattern (titer 1:160) but no clinical evidence of lupus, scleroderma, or other connective tissue disease. Extractable nuclear antigen, double-stranded DNA, and antineutrophil cytoplasmic antibodies were negative, and complement levels were normal.

Although there were no clear triggers, except for mild hypertension, she was discharged with a presumed diagnosis of PRES. At 2-month follow-up, she had normal neurologic examination, including language, attention, and memory. Shortly after, she was readmitted with a similar episode of headache and visual and language difficulties. Repeat MRI (eFigure 1, links.lww.com/WNL/B709) showed new subcortical foci of FLAIR signal abnormalities with interval improvement of some of the previous lesions, asymmetric pachymeningeal and leptomeningeal enhancement, and new punctate microhemorrhage.

Questions for Consideration:

1. What is your differential diagnosis?
2. What further steps would you take?

GO TO SECTION 3

Section 3

PRES can recur in 5%–10% of cases; however, it usually occurs with poorly controlled hypertension.[3] Our patient was normotensive. Given recurrent headaches and focal neurologic symptoms, we considered CNS vasculitis, although the presence of confluent areas of T2 hyperintensity without evidence of infarction would be unusual.[6] Reversible cerebral vasoconstriction syndrome (RCVS) was considered as well. Similarities between PRES and RCVS have been described,[7] and PRES-like reversible cerebral edema has been reported in 17%–38% of patients with RCVS.[8] She had a normal MRI angiogram on her initial presentation, as well as normal head CT angiogram and contrast angiogram this visit, making vasculopathy such as RCVS unlikely.

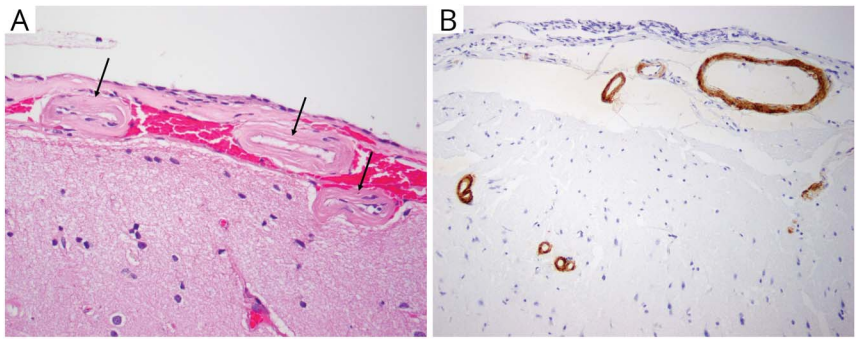
Autoimmune and inflammatory disorders such as recurrent ADEM or autoimmune encephalopathies were considered. Repeat CSF analysis showed no pleocytosis, normal glucose and protein. Antibody screening including serum and CSF autoimmune encephalopathy panels, serum anti-aquaporin-4 IgG, and myelin oligodendrocyte glycoprotein antibodies were negative. Malignancy and infection were considered unlikely given improvement of some of the previously seen lesions without treatment.

Clinically, she improved after a few days and was discharged home. Subsequently, she had 2 additional hospitalizations with similar presentations. Given the recurrent episodes without a clear diagnosis, she underwent biopsy of brain and meninges near a left frontal lesion, which revealed thick and hyalinized leptomeningeal and cortical vessel walls strongly positive for β-amyloid by immunohistochemical staining (Figure 2). In addition, subcortical vessels showed widened perivascular spaces and sparse perivascular inflammatory cells. Based on her clinical presentation and imaging and biopsy results, she was diagnosed with cerebral amyloid angiopathy-related inflammation (CAA-ri).

Questions for Consideration:

1. Does this change your differential diagnosis?
2. What further testing would you obtain?

Figure 2



Biopsy of the leptomeninges, cortex, and subcortical white matter showed (A) small arteries with thickened and hyalinized walls on hematoxylin and eosin stain, ×400 (see arrows), containing eosinophilic material that is positive for β-amyloid by immunohistochemical staining (B), ×200.

GO TO SECTION 4

Section 4

She received IV Solu-Medrol 1 g daily for 5 days followed by prednisone 60 mg daily, tapered to discontinuation over 12 weeks. She was started on mycophenolate 1,000 mg twice daily and continued on levetiracetam 2000 mg and lacosamide 200 mg, both twice daily.

She returned to baseline, except for subjective word-finding difficulties, and remained seizure-free. A brain MRI 3 months after starting treatment showed marked improvement (eFigure2, links.lww.com/WNL/B709).

Questions for Consideration:

1. What treatment would you consider?

Discussion

CAA is a disorder seen in the elderly, characterized by deposition of amyloid-β in small- and medium-sized cortical and leptomeningeal arteries. Patients present with spontaneous symptomatic lobar hemorrhage, cognitive impairment, and transient focal neurologic episodes.[9,10] The imaging features include lobar microbleeds, cortical superficial siderosis (cSS), WMH, cortical microinfarcts, cortical atrophy, and centrum semiovale MRI-visible perivascular spaces.[9]

Less commonly, CAA can present as a spectrum of inflammatory responses to the deposition of amyloid-β in the vessel wall. The inflammatory forms include CAA-ri, with perivascular inflammation, and amyloid-β–related angiitis, with transmural inflammation of the vessel wall.[11-14] The pathophysiology of CAA is thought to be related to protein elimination failure in the perivascular drainage pathways, with amyloid-β deposits along the basement membrane[10] triggering an immune response.[12,13]

CAA-ri occurs in younger individuals than those with conventional CAA, with a mean age at onset of 67 years.[13] Women and men are affected equally. CAA-ri manifests with acute or subacute cognitive and behavioral changes, headache, focal neurologic deficits, or seizures.[12,13] MRI reveals WMH, predominantly posterior and typically asymmetric and extending to the immediately subcortical WM, along with associated edema.[10,13] Microhemorrhages are frequently present, often of maximal concentration in areas of abnormal WM and in lobar locations, in contrast to the deep location seen in patients with hypertensive arteriopathy.[15] At times, leptomeningeal or parenchymal enhancement is seen.[13] Another radiologic feature is enlarged perivascular spaces, due to impairment of perivascular drainage by amyloid-β deposition,[16] seen in the centrum semiovale, as opposed to the basal ganglia in patients with hypertensive arteriopathy.[15] Patients can have increased inflammatory markers in serum and mild to moderate pleocytosis and elevated protein in the CSF.[13]

A definite diagnosis requires histopathologic confirmation; however, a diagnosis of possible or probable CAA-ri is made using diagnostic criteria[14] (eTable) based on clinical (≥40-year-old, presence of ≥1 clinical features: headache, impaired consciousness, behavioral changes, focal neurologic signs, or seizures) and radiologic findings (asymmetric WMH involving U fibers and ≥1 cerebral macro- or micro-bleeds or cSS), and the exclusion of other causes. These criteria have sensitivity and specificity of 82% and 97%, respectively, for probable CAA-ri, and 82% and 68%, respectively, for possible CAA-ri.[14] Stereotactic brain biopsy is generally safe; however, it is important to balance the risks of brain biopsy vs empirical immunosuppression. Considering biopsy only after the lack of clinico-radiologic improvement after 3 weeks of immunosuppressants has been proposed.[13] A retrospective study[17] found that immunosuppression, with varied regimens including corticosteroids, cyclophosphamide, and mycophenolate, improves the clinical, radiographic, and recurrence rates in patients with CAA-ri.

Our patient's clinical features, including headache, focal neurologic deficits and seizures, and radiologic findings of multifocal WMH, microhemorrhages, and enlarged perivascular spaces, supported a diagnosis of probable CAA-ri. Although histologic perivascular inflammatory changes were not prominent, this could be attributed to sampling because of the focal and segmental nature of the inflammatory changes.[11] The significant clinical and radiographical improvement after initiation of immunosuppression further supports the diagnosis. Albeit uncommon, CAA-ri is an important diagnosis to consider in the proper clinical setting because most patients respond to immunosuppressive therapy.

Study Funding

No targeted funding reported.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Appendix Authors

Name	Location	Contribution
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Olivia Groove, MDr	Emory University, Atlanta	Literature and manuscript review
Carlos S. Kase, MD	Emory University, Atlanta	Literature and manuscript review

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Neurology 2022;98;330-335 Published Online before print December 14, 2021
DOI 10.1212/WNL.0000000000013219