

Clinical Reasoning: A case of subacute cognitive decline in a 76-year-old man

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SECTION 1

A 76-year-old, right-handed man presented to our emergency department with a 3-day history of cognitive decline following a motor vehicle collision. Medical history included hypertension, atrial fibrillation, and renal dysfunction. He was a high-functioning retired advertising executive who formerly smoked cigarettes, and used neither recreational drugs nor alcohol.

His family reported he was stuttering, having word-finding difficulties, taking longer to do simple tasks such as dressing, and had trouble using objects, such as cutlery. He described difficulty in reading, and simple math had become more challenging. Upon further questioning, these changes may have started 3 weeks before presentation, but were more pronounced following the accident. There were no other new focal neurologic or systemic symptoms.

At presentation, he was alert, although hypertensive at 190/106; other vital signs were normal. Montreal Cognitive Assessment total score was 12/30, scoring 0/5 in visuospatial/executive, 1/3 in naming, 3/6 in attention, 3/3 in language, 1/2 in abstraction, 0/5 in

delayed recall, and 4/6 in orientation. Speech was fluent with occasional word-finding difficulties, circumlocution, and phonemic paraphasias. Naming to low-frequency words was impaired, as was object recognition. He displayed evidence of finger agnosia. Comprehension of simple and complex commands was intact. Writing and reading were impaired, including words he had himself written, although he did not have letter agnosia. He had difficulty with simple arithmetic and difficulty distinguishing left from right. Tests of praxis revealed hand-as-tool errors. Cranial nerve examination was normal, including visual fields to confrontation and normal visual acuity. Motor and sensory examinations were normal. Cortical sensation was intact but processing was slow. Sensory inattention, extinction, and tactile neglect were absent. Coordination and gait were normal.

Questions for consideration:

1. In which area(s) could you localize a possible lesion?
2. Which initial tests would you order?

[GO TO SECTION 2](#)

SECTION 2

The majority of the history and physical findings were deficits in cognitive domains with primary involvement of the dominant hemisphere. Impaired naming and paraphasic errors were suggestive of left temporal dysfunction. The left parietal lobe was also affected given the ideomotor apraxia and the development of Gerstmann syndrome, a constellation of dysgraphia, dyscalculia, left/right confusion, and finger agnosia. The inability to read his own writing was suggestive of left occipital and corpus callosum dysfunction, and is known as pure alexia.

Given the multifocal cortical dysfunction, pertinent investigations would include neuroimaging with CT or MRI, as well as laboratory investigations to rule out treatable metabolic abnormalities. Basic

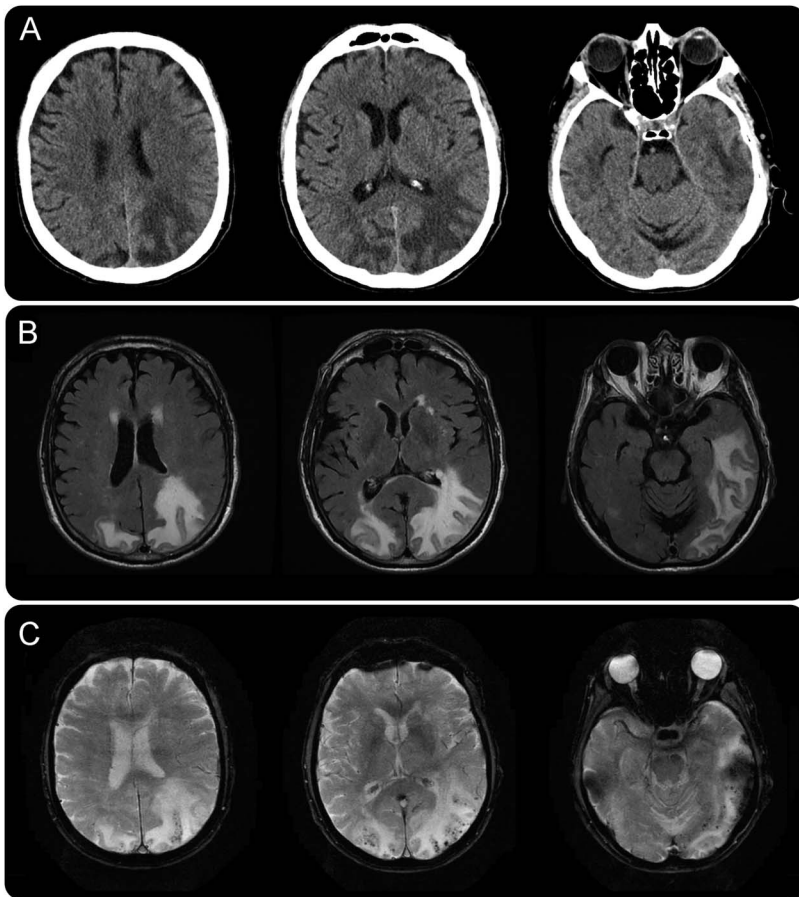
hematology, biochemistry, and metabolic profiles were normal aside from baseline renal dysfunction. Brain CT (figure 1A) showed hypodensity in the left and right parieto-occipital lobes with temporal involvement on the left. Brain MRI with gadolinium showed nonenhancing T2/fluid-attenuated inversion recovery (FLAIR) hyperintensity in these regions (figure 1B), while corresponding gradient-echo sequences showed cerebral microbleeds in the areas of FLAIR hyperintensity (figure 1C). There was no restricted diffusion on diffusion-weighted imaging.

Question for consideration:

1. What would you consider in the differential diagnosis, given the imaging findings?

GO TO SECTION 3

Figure 1 Neuroimaging at the time of presentation



Axial slices of a noncontrast brain CT (A) showing hypodensity in the left parietal, occipital, and temporal lobes, also with involvement of the right occipital lobe. Axial MRI fluid-attenuated inversion recovery sequence (B) showing asymmetric, confluent areas of subcortical hyperintensity, with evidence on the gradient-echo sequence (C) of lobar microbleeds. There was no enhancement or restricted diffusion.

SECTION 3

The neuroimaging findings, in concert with clinical presentation, were concerning for a number of etiologies. The degree of edema and multifocal nature of the process on CT, combined with the history of smoking, raised suspicion for metastatic cancer, but no discrete lesions were seen on MRI. Primary malignancies such as glioblastoma or primary CNS lymphoma were in the differential, as both entities may cross the midline, but the lack of enhancement made them less likely. Acute demyelinating encephalomyelitis was considered given the predominant white matter involvement, but lack of enhancement would be atypical. Infectious causes, namely progressive multifocal leukoencephalopathy were considered

given the appearance on CT, but historically there were no risk factors or infectious prodrome, and with atypical MRI findings, a JC virus titer was not sent. A number of vascular causes were considered in the differential, including posterior reversible encephalopathy syndrome given the patient's hypertension on presentation, although often this is accompanied by visual disturbance and/or seizure. Vasculitis may also clinically present in this manner, but the lack of acute infarction, and confluent white matter changes on MRI, argued against this.

Questions for consideration:

1. What further investigations would you order?
2. What treatment might you initiate?

[GO TO SECTION 4](#)

SECTION 4

A complete autoimmune and vasculitic profile was ordered, including antinuclear antibodies, antineutrophil cytoplasmic antibodies, antiphospholipid antibodies, erythrocyte sedimentation rate, and C-reactive proteins; all results were negative. A lumbar puncture was performed, which showed normal leukocyte and erythrocyte counts, glucose of 6.2 mmol/L (reference range 2.2–4.4 mmol/L), with an elevated protein of 1.03 g/L (reference range 0.15–0.45 g/L). Complete microbiologic analysis was negative. *APOE* genotyping revealed homozygosity for the *APOE* $\epsilon 3$ allele.

In discussion with our neuroradiologists, the imaging features in combination with clinical presentation were most consistent with cerebral amyloid angiopathy (CAA)-related inflammation. Although brain biopsy was considered, the morbidity associated with the procedure and the suggestive clinicoradiologic features led us to treat empirically with a 5-day course of IV methylprednisolone (1,000 mg/d). After the initial corticosteroid pulse, the patient's reading and writing improved to near baseline, although mild left/right confusion and finger agnosia persisted. He was discharged on a tapering regimen of oral corticosteroids. Repeat brain MRI at 3 months (figure 2) showed complete resolution of the leukoencephalopathy with no increase in the amount of cerebral microbleeds, while Montreal Cognitive Assessment score at follow-up in 6 months was 24/30.

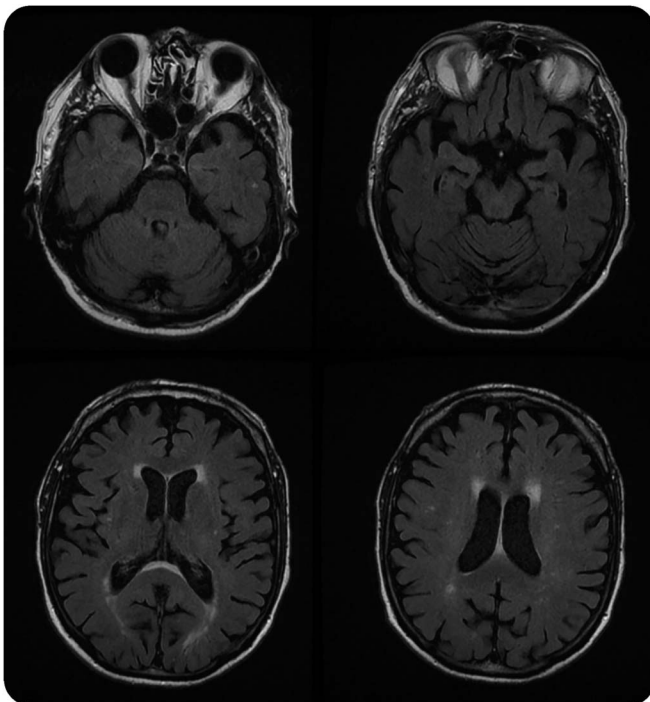
DISCUSSION CAA is characterized by the deposition of β -amyloid in small- to medium-sized vessels of the brain and leptomeninges.¹ Vascular disruption by amyloid, and subsequent vessel leakage and rupture, leads to conditions more commonly associated with CAA such as lobar microbleeds, lobar hemorrhages, and superficial siderosis. Less frequently, an intraparenchymal perivascular inflammatory reaction toward vascular β -amyloid can develop and is termed CAA-related inflammation, as demonstrated in our case. A similar condition is β -amyloid-related angiitis, which is an inflammatory vasculitis caused by an intravascular autoimmune response to β -amyloid leading to vessel obliteration and infarction.^{2,3} β -Amyloid-related angiitis is distinguished from CAA-RI by its true vasculitic nature causing infarcts, and is not as strongly associated with cerebral microbleeds.

The pathophysiology of CAA-RI is unclear. There appears to be an autoimmune response directed against β -amyloid but the exact inciting factor is unknown. Case studies have shown that titers of β -amyloid autoantibodies are elevated in the CSF of patients with CAA-RI, with return to near baseline levels following immunosuppressive treatment.⁴ Further evidence is inferred from β -amyloid immunization studies performed in patients with Alzheimer dementia in which patients developed a subacute meningoencephalitis following immunization with β -amyloid antibodies, very similar to the leukoencephalopathy described in CAA-RI.⁵

The gold standard for diagnosis is neuropathologic examination. However, clinicoradiologic criteria have been proposed for probable CAA-RI, consisting of the following: (1) acute/subacute onset, (2) age 40 years or older, (3) one of headache/cognitive changes/focal neurologic signs/seizures, (4) MRI with patchy or confluent T2/FLAIR hyperintensity, (5) evidence of preexisting CAA on MRI, and (6) exclusion of other causes.⁶ With some revision, when applied to pathology-confirmed cases of CAA-RI vs noninflammatory-CAA, these criteria have been reported to show up to 82% sensitivity and 97% specificity.⁷ As in our case, the differential diagnosis often includes other vasculopathies such as hypertensive vasculopathy, posterior reversible encephalopathy syndrome, or vasculitis; inflammatory parenchymal disease and structural/infectious lesions should also be considered if suggested clinically.

As a rare diagnosis, the clinical presentation and disease course of CAA-RI is not well described. Chung et al.⁶ have summarized the findings of 69 patients described in the literature; 76% presented with acute/subacute cognitive decline, 46% with focal neurologic signs, 41% with headaches, and 36% with seizures. The mean patient age was 63 years, with slight male predominance. CSF profile showed elevated protein in 71% of patients. Regarding disease course, Kinnecom

Figure 2 Neuroimaging in follow-up



Axial MRI fluid-attenuated inversion recovery sequence at 3 months posttreatment demonstrating resolution of previous asymmetric, confluent white matter hyperintensity. There was no change in the burden of cerebral microbleeds.

et al.⁸ described 12 patients with biopsy-proven disease; 7 cases were monophasic, and the remaining cases were either relapsing or stable/progressive courses. They further assessed for *APOE* genotype, with the most common association being the *APOE* $\epsilon 4/\epsilon 4$ genotype, seen in nearly 80% of patients as opposed to 5% of patients with noninflammatory CAA. Of note, our patient is a rare case that was homozygous for the *APOE* $\epsilon 3$ allele, not often described in cases of CAA-RI but representing the most common genotype in the general population.⁹ While there is no consensus-derived first-line treatment at this time,¹⁰ Chung et al.⁶ reported that 52 of 53 treated patients received corticosteroids acutely; 73% showed clinical response, occurring within 1 to 3 weeks. Our patient responded to immunosuppressive treatment over a similar time course to that reported in the literature with an excellent outcome.

CAA-RI is a rare cause of subacute cognitive decline and should be considered in the differential diagnosis of diffuse leukoencephalopathy. It has been associated with the *APOE* $\epsilon 4/\epsilon 4$ genotype, is often monophasic when treated with immunosuppression, and clinicoradiologic diagnostic criteria are proposed to facilitate early treatment while avoiding potential morbidity of biopsy when clinically appropriate. Longitudinal follow-up is necessary to describe the long-term outcome of patients with CAA-RI and to determine whether these patients are at increased risk of other amyloid-related pathologies.

AUTHOR CONTRIBUTIONS

Dr. Adam MacLellan contributed to drafting/revising the manuscript, analysis/interpretation of data, and figure preparation. Dr. Ari Breiner contributed to drafting/revising the manuscript and analysis/interpretation of data. Dr. David Tang-Wai contributed to drafting/revising the manuscript and analysis/interpretation of data. Dr. Leanne Casaubon contributed to drafting/revising the manuscript and analysis/interpretation of data.

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DISCLOSURE

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

REFERENCES

1. Yamada M. Cerebral amyloid angiopathy: emerging concepts. *J Stroke* 2015;17:17–30.
2. Moussaddy A, Levy A, Strbian D, Sundararajan S, Berthelet F, Lanthier S. Inflammatory cerebral amyloid angiopathy, amyloid- β -related angiitis, primary angiitis of the central nervous system: similarities and differences. *Stroke* 2015;46:e210–e213.
3. Salvarani C, Hunder GG, Morris JM, Brown RD Jr, Christianson T, Giannini C. A β -related angiitis: comparison with CAA without inflammation and primary CNS vasculitis. *Neurology* 2013;18:1596–1603.
4. DiFrancesco JC, Briosci M, Brighina L, et al. Anti-A β autoantibodies in the CSF of a patient with CAA-related inflammation: a case report. *Neurology* 2011;76:842–844.
5. Orgogozo JM, Gilman S, Dartigues JF, et al. Subacute meningoencephalitis in a subset of patients with AD after A β 42 immunization. *Neurology* 2003;61:46–54.
6. Chung KK, Anderson NE, Hutchinson D, Synek B, Barber PA. Cerebral amyloid angiopathy related inflammation: three case reports and a review. *J Neurol Neurosurg Psychiatry* 2011;82:20–26.
7. Auriel E, Charidimou A, Gurol ME, et al. Validation of clinicoradiological criteria for the diagnosis of cerebral amyloid angiopathy-related inflammation. *JAMA Neurol* 2016;73:197–202.
8. Kinnecom C, Lev H, Wendell L, et al. Course of cerebral amyloid angiopathy-related inflammation. *Neurology* 2007; 68:1411–1416.
9. Mahley RW, Rall SC Jr. Apolipoprotein E: far more than a lipid transport protein. *Annu Rev Genomics Hum Genet* 2000;1:507–537.
10. Kirshner HS, Bradshaw M. The inflammatory form of cerebral amyloid angiopathy, or “cerebral amyloid angiopathy-related inflammation” CAARI. *Curr Neurol Neurosci Rep* 2015;15:54.

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