

Pearls & Oysters: CAA-related inflammation presents as subacute cognitive decline in a patient with Parkinson disease

Anjali Gera, MD, Natalie Witek, MD, and Meagan Bailey, MD, MS

Neurology® 2019;92:1116-1118. doi:10.1212/WNL.00000000000007610

Correspondence

Dr. Gera
anjali_gera@rush.edu

Pearls

- Progressive, subacute cognitive decline can be seen in patients with cerebral amyloid angiopathy-related inflammation (CAARI).
- Cognitive decline may be the first and only clinical presentation of CAARI.
- Brain MRI and lumbar puncture are warranted in patients with a subacute cognitive decline who have an unremarkable preliminary infectious and metabolic workup.

Oysters

- Cerebral amyloid angiopathy (CAA) and CAARI should be considered in elderly patients with subacute or rapid cognitive decline.
- Subacute cognitive decline in patients with Parkinson disease (PD) can often be misdiagnosed as progression of their parkinsonian symptoms.
- Subacute cognitive decline in patients with PD can mimic that which is seen with common infections and metabolic derangements.

A 66-year-old man with rest tremor, bradykinesia, and rigidity since July 2017 was diagnosed with idiopathic PD. His parkinsonian symptoms were mild, and he did not require medical therapy. In December 2017, his wife reported a subacute onset of odd behaviors. He left things on the stove, put soup in the oven, stopped reading books, which he usually enjoyed, and stopped responding to texts and emails. His behavioral changes were initially thought to be due to a recent increase to his antidepressant, vortioxetine, from 10 to 20 mg daily. However, his behavior progressed despite a reduction back to 10 mg daily.

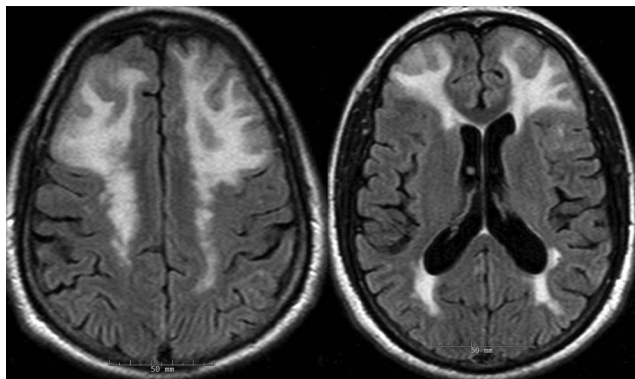
On initial visit, his Montreal Cognitive Assessment (MoCA) score was 26/30 and examination was revealing for rest tremor, bradykinesia, and rigidity. Seven months later, during his follow-up visit after his cognitive symptoms started, his MoCA was 19/30; however, his motor symptoms remained unchanged. Initial laboratory studies revealed a within normal range vitamin B₁₂, thyroid-stimulating hormone, complete blood count (CBC), comprehensive metabolic panel (CMP), and urinalysis. An MRI brain completed after his cognitive decline revealed substantial bilateral frontal white matter changes, as shown in figure 1. CSF was acellular and revealed normal protein and glucose levels. CSF varicella-zoster virus, herpes simplex virus, Epstein-Barr virus, and cytomegalovirus were all negative. CSF immunoglobulin G index was within normal range and there were no oligoclonal bands. Arylsulfatase A and very long chain fatty acids were also normal.

MRI brain was repeated with additional sequences per radiology's request 3 weeks after the initial scan. Repeat MRI revealed increase in edema in the right frontal lobe with mild increase in mass effect and minimal midline shift to the left, shown in figure 2A. There were also numerous bifrontal microhemorrhages, shown in figure 2B.

From the Movement Disorder Section, Rush University Medical Center, Chicago, IL.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Figure 1 Bifrontal white matter hyperintensities in March 2018



Substantial bilateral frontal white matter changes in March 2018.

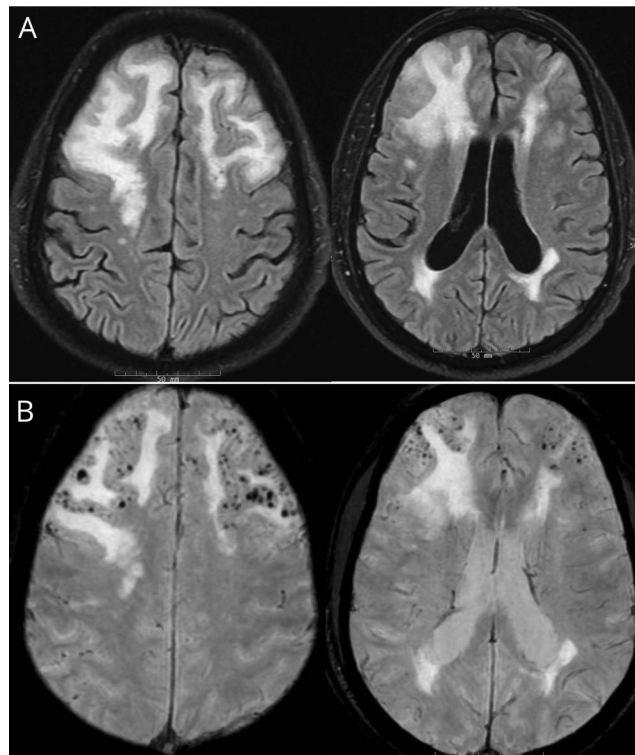
The patient was diagnosed with probable CAA-related inflammation. He was promptly admitted and initiated on IV methylprednisolone. He received 1 g/d of IV methylprednisolone for 5 days and was discharged home with a prednisone taper starting at 60 mg daily for 7 days, with plans to reduce to the lowest tolerated dose with a stable repeat MRI. Following initiation of immunotherapy, the patient had a gradual, significant improvement in his cognition. One month following treatment, repeat MoCA improved to 28/30 and repeat MRI showed interval significant improvement of ill-defined confluent vasogenic edema along the bifrontal lobes, shown in figure 3. His tremor and bradykinesia remained unchanged throughout his course.

Discussion

CAARI is a rare cause of subacute cognitive decline in a small group of patients with CAA. CAA is a condition in which β -amyloid protein deposits in the walls of cerebral vessels lead to intracerebral hemorrhages in the elderly. The amyloid deposition in rare cases can elicit a mainly cellular inflammatory response with or without edema.¹ While CAA can present as an acute intracerebral hemorrhage, CAARI presents with a more subacute syndrome of encephalopathy, which is the most common presenting feature,^{2,3} behavioral changes, headaches, seizures, focal neurologic deficits, and rarely, hallucinations. Most cases of CAA and CAARI are idiopathic; however, in rare familial cases, the inheritance is autosomal dominant.⁴ Men are affected as frequently as women, and the average age of patients with CAARI is 67 years, which is marginally younger than the average age of 76 for patients with CAA.⁵

Diagnostic workup for suspected CAARI should include MRI with gradient echo, erythrocyte sedimentation rate (ESR), C-reactive protein, CBC, CMP, CSF studies with cell count, differential, gram stain, cultures, glucose, total protein, cytology, flow cytometry, and infectious studies.⁶ Brain biopsy is often deferred although this creates room for diagnostic

Figure 2 Interval increase in edema with midline shift and microhemorrhages in April 2018

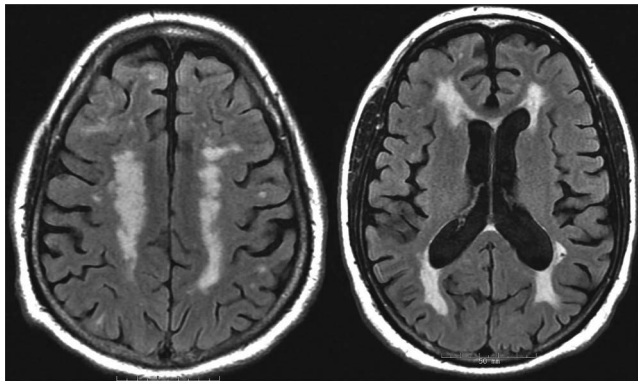


Mild increase in edema in bilateral frontal white matter with mild increase in mass effect and midline shift to the left noted on both T2 fluid-attenuated inversion recovery (A) and gradient recalled echo (B) and numerous bifrontal microhemorrhages (B) in April 2018.

uncertainty, and infection must be ruled out prior to initiation of immunosuppressive therapy and close follow-up should be maintained for many years in these patients. MRI demonstrates patchy or confluent areas of hyperintensities on T2 sequences and microhemorrhages on susceptibility-weighted imaging. ESR can be elevated and CSF may reveal a pleocytosis and elevated protein, although these laboratory studies can be normal, as they were in our patient. Angiography is usually negative.⁵ In many cases, the diagnosis can be made with MRI and clinical information alone with good sensitivity and specificity.⁷ Moreover, clinicoradiologic criteria have been proposed for probable CAARI with (1) acute/subacute onset, (2) age >40 years, (3) one of headache/cognitive changes/focal neurologic signs/seizures, (4) MRI with patchy or confluent T2/fluid-attenuated inversion recovery hyperintensity, (5) evidence of preexisting CAA on MRI, and (6) exclusion of infectious or malignant conditions.⁵

CAARI is treated with immunomodulatory therapy. Most patients are treated with corticosteroids and a steroid-sparing agent may be used if needed due to steroid-related side effects. There are case reports of successful treatment with methotrexate, cyclophosphamide, azathioprine, and IV immunoglobulin.^{5,8,9} Response to treatment is generally positive, with clinical response preceding improvement on neuroimaging. An

Figure 3 Improvement of edema and mass effect in May 2018 after treatment



Improvement of fluid-attenuated inversion recovery signal changes 1 month following IV dexamethasone in May 2018.

average of 72% of patients clinically improve, most of whom improve within a few weeks.^{3,5,10} However, the duration of treatment is anecdotal and should be based on the patient's clinical response. Relapses can also occur and may warrant repeat treatment with corticosteroids or additional immunosuppression. Patients should be followed closely and neuroimaging should be repeated for several years.

The differential diagnosis of subacute cognitive decline or behavioral changes includes vascular etiologies, toxic, metabolic, and infectious etiologies, autoimmune encephalitis, neurologic malignancy including primary CNS malignancy, CNS metastases, or paraneoplastic syndrome, primary angiitis of the CNS, posterior reversible leukoencephalopathy syndrome, and acute disseminated encephalitis.⁵ Although

patients with PD presenting with subacute cognitive decline have a negative initial infectious and metabolic workup, it is crucial for these patients to be evaluated aggressively for etiologies other than cognitive changes related to PD.

Author contributions

A. Gera drafted and revised the article. N. Witek and M. Bailey revised the article. All authors approved the final version to be submitted.

Study funding

No targeted funding reported.

Disclosure

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

References

1. Yamada M, Itoh Y, Shintaku M, et al. Immune reactions associated with cerebral amyloid angiopathy. *Stroke* 1996;27:1155–1162.
2. Eng JA, Frosch MP, Choi K, Rebeck GW, Greenberg SM. Clinical manifestations of cerebral amyloid angiopathy-related inflammation. *Ann Neurol* 2004;55:250–256.
3. Kinnecom C, Lev MH, Wendell L, et al. Course of cerebral amyloid angiopathy-related inflammation. *Neurology* 2007;68:1411–1416.
4. Zhang-Nunes S, Maat-Schieman M, Van Duinen S, et al. The cerebral beta-amyloid angiopathies: hereditary and sporadic. *Brain Pathol* 2006;16:30–39.
5. Chung K, Anderson N, Hutchinson D, Synek B, Barber P. Cerebral amyloid angiopathy related inflammation: three case reports and a review. *J Neurol Neurosurg Psychiatry* 2011;82:20–26.
6. Yamada M. Cerebral amyloid angiopathy: emerging concepts. *J Stroke* 2015;17:17–30.
7. Auriel E, Charidimou A, Gurol M, et al. Validation of clinicoradiological criteria for the diagnosis of cerebral amyloid angiopathy-related inflammation. *JAMA Neurology* 2016;73:197–202.
8. Brotman D, Eberhart C, Burger P, McArthur J, Hellmann D. Primary angiitis of the central nervous system and Alzheimer's disease: clinically and pathologically evident in a single patient. *J Rheumatol* 2000;27:2935–2937.
9. Greenberg SM, Parisi JE, Keegan BM. A 63-year-old man with headaches and behavioral deterioration. *Neurology* 2007;68:782–787.
10. Salvarani C, Hunder G, Morris J, Brown R, Christianson T, Giannini C. Abeta-related angiitis: comparison with CAA without inflammation and primary CNS vasculitis. *Neurology* 2013;81:1596–1603.

Disputes & Debates: Rapid online correspondence

The editors encourage comments on recent articles through Disputes & Debates:

Access an article at Neurology.org/N and click on “COMMENT” beneath the article header. Responses will be posted within 3 business days.

Before submitting a comment to Disputes & Debates, remember the following:

- Disputes & Debates is restricted to comments about studies published in *Neurology* within the last eight weeks
- Read previously posted comments; redundant comments will not be posted
- Your submission must be 200 words or less and have a maximum of five references; reference one must be the article on which you are commenting
- You can include a maximum of five authors (including yourself)

Neurology[®]

Pearls & Oy-sters: CAA-related inflammation presents as subacute cognitive decline in a patient with Parkinson disease

Anjali Gera, Natalie Witek and Meagan Bailey

Neurology 2019;92;1116-1118

DOI 10.1212/WNL.00000000000007610

This information is current as of June 3, 2019

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/92/23/1116.full
References	This article cites 10 articles, 5 of which you can access for free at: http://n.neurology.org/content/92/23/1116.full#ref-list-1
Citations	This article has been cited by 1 HighWire-hosted articles: http://n.neurology.org/content/92/23/1116.full##otherarticles
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Clinical Neurology http://n.neurology.org/cgi/collection/all_clinical_neurology All Immunology http://n.neurology.org/cgi/collection/all_immunology Memory http://n.neurology.org/cgi/collection/memory MRI http://n.neurology.org/cgi/collection/mri Parkinson's disease/Parkinsonism http://n.neurology.org/cgi/collection/parkinsons_disease_parkinsonism
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2019 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

