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# Clinical Reasoning: An unusual diagnostic triad

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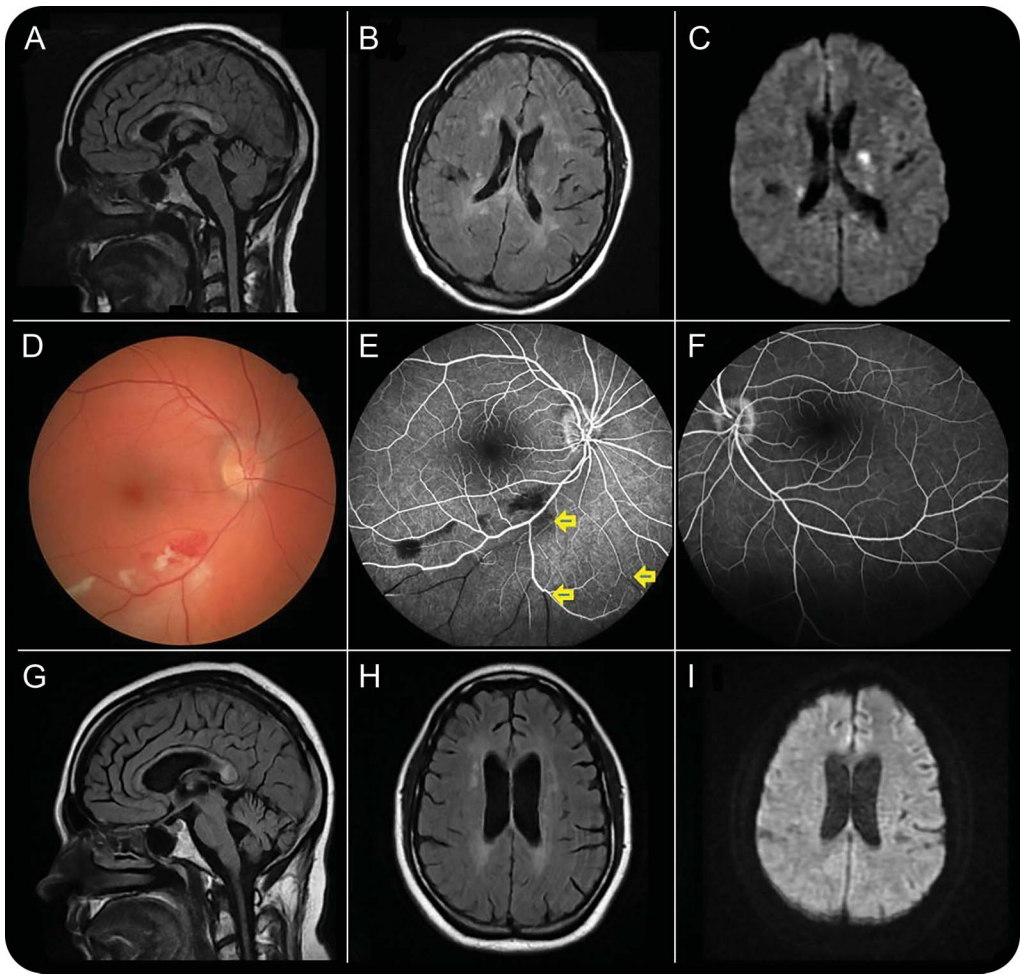
## SECTION 1

A 44-year-old woman with a history of hypothyroidism taking daily levothyroxine was admitted to an outside hospital with subacute cognitive decline. Her symptoms had started 3 weeks previously with headache, sore neck, and upper respiratory symptoms for which she sought care at a local emergency room. She did not complain of confusion or demonstrate signs of cognitive decline at that time and was discharged home with a prescription for antibiotics. A

**Figure** Brain and retinal images




(A, B) Sagittal and axial fluid-attenuated inversion recovery (FLAIR) brain MRI sequences from the initial clinical presentation reveal small T2-hyperintense lesions in the periventricular periventricular white matter, corpus callosum, and basal ganglia. (C) Axial diffusion-weighted (DW) MRI sequence demonstrates restricted diffusion in some of the basal ganglia lesions. (D) Color fundus photograph of the right eye reveals retinal hemorrhage, edema, and axoplasmic blockage in a perivascular distribution consistent with a branch retinal artery occlusion. (E) Fluorescein angiography confirms several sites of obstruction with hypofluorescent areas distal to the well-perfused inferotemporal arcades (arrows). (F) The fluorescein angiogram of the left eye is normal and displayed for comparison. (G–I) Sagittal and axial FLAIR and axial DW brain MRI sequences 9 months after presentation demonstrate reduced lesion burden and no diffusion restriction.

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few days later, she was hospitalized after appearing disoriented, exhibiting signs of confusion, responding slowly, and running into things at work.

On examination, she was oriented only to self with poor verbal output and followed only rudimentary commands. She had grasp and left palmomental reflexes. Visual acuity measurement was precluded by her mental status. She blinked to threat and tracked a light with either eye. Upgaze was mildly restricted and she had gaze-evoked nystagmus. Cranial nerve examination was otherwise unrevealing. Muscle tone was normal. All extremities moved spontaneously against gravity. Reflexes were diffusely 3+ with Chaddock signs bilaterally. She responded to stimuli in all extremities. There was no ataxia noted during spontaneous movements. Further testing was limited by her inability to follow commands.

Testing performed at the outside hospital included toxicology screen, which was positive for cannabinoids and amphetamines. Blood count and metabolic panel including liver tests were within normal limits. MRI brain demonstrated multiple subcentimeter, nonenhancing T2 hyperintense lesions in supratentorial white matter. CSF analysis demonstrated elevated protein (196 mg/dL) and 5 oligoclonal bands, but normal cell count and glucose. Her mental status spontaneously improved, though not to baseline, and she was discharged with outpatient follow-up.

One week later, she was prescribed oral steroids for complaints of headache and hearing loss. Two weeks after her initial discharge, she was readmitted with recurrent and progressive cognitive decline. Repeat MRI demonstrated increased burden of T2 hyperintense lesions in the periventricular white matter and corpus callosum with a lower lesion burden in the subcortical white matter, basal ganglia, and infratentorial structures. None of the lesions demonstrated enhancement. Some of them demonstrated restricted diffusion (figure, A–C). She was transferred to our institution for further evaluation.

**Questions for consideration:**

1. What is the differential diagnosis?
2. What laboratory and imaging studies would you order next?

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## SECTION 2

The differential diagnosis for a middle-aged woman with subacute dementia is broad. In this case, the MRI appearance included multifocal small nonenhancing lesions, some with restricted diffusion, and corpus callosum involvement, which suggests either a microvascular or demyelinating process. The presence of oligoclonal bands suggests immunoreactivity in the CNS and makes a thromboembolic condition less likely. Her preceding viral symptoms suggest a postinfectious process, while the subacute nature of her presentation makes infectious etiologies less likely. Thus, major considerations are CNS vasculitis and acute disseminated encephalomyelitis. Since the latter is a diagnosis of exclusion, appropriate workup focuses on confirming vasculitis with angiographic imaging and possible brain biopsy in addition to testing for secondary causes of small vessel vasculitis such as systemic lupus erythematosus, Sjögren syndrome, granulomatosis with polyangiitis, and syphilis. Other rare diseases associated with CNS vasculitis have no serologic tests, but are defined by associated physical examination findings such as oral and genital ulcers in Behçet disease or branch retinal artery occlusions and auditory dysfunction in Susac syndrome.

**Clinical course.** Normal serologic studies included those for antinuclear antibody assay, antineutrophil cytoplasmic antibody, rapid plasma regain, fluorescent treponemal antibody, and anti-Ro/SSA and La/SSB antibodies. Repeat CSF analysis demonstrated 10 leukocytes/μL (100% lymphocytes), no erythrocytes, mildly elevated glucose (83 mg/dL), elevated protein (153 mg/dL), and negative venereal disease research laboratory. Magnetic resonance angiography of the head and neck and 4-vessel cerebral catheter angiography were unrevealing. EEG revealed diffuse slowing without epileptiform abnormalities.

Audiometry was precluded by her mental status, but auditory potentials demonstrated no significant abnormalities. Dilated ophthalmoscopic examination was notable for inferotemporal retinal whitening with edema and intraretinal hemorrhage in a perivascular distribution (figure, D), diagnostic of an inferotemporal branch retinal artery occlusion (BRAO). No arteriolar sheathing or Gass plaques were visualized. There was no associated uveitis.

Given the dramatic nature of her clinical presentation, a broad workup was performed for treatable subacute dementing illnesses in parallel with the focused evaluation described above. This included evaluation for vitamin deficiency, anti-NMDA encephalitis, Hashimoto encephalitis, Wilson disease, infectious encephalitis, neurosarcoidosis, and thromboembolic disease, which were all negative.

**Questions for consideration:**

1. What is the likely final diagnosis?
2. What is the appropriate management?

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## SECTION 3

The patient's subacute encephalopathy, hearing loss, and BRAOs, accompanied by white matter lesions with restricted diffusion seen on MRI, are consistent with the diagnosis of Susac syndrome, an immune-mediated vasculitis associated with infarcts in the cochlear apex, retina, and brain.[1,2] The clinical triad of subacute encephalopathy, BRAO, and sensorineural hearing loss is diagnostic for this syndrome.[3,4]

**Clinical course.** Based on expert guidelines, the patient was treated with IV methylprednisolone (1 g/daily for 3 consecutive days), IV immunoglobulin (IVIg), and IV cyclophosphamide followed by an oral prednisone taper and plans for monthly IVIg and cyclophosphamide infusions.[5] The patient initially improved, but 2 weeks later her mental status declined. MRI demonstrated a new corpus callosum lesion. Following repeat IVIg and cyclophosphamide infusion, her condition improved.

Outpatient audiology testing confirmed decreased hearing, especially in the low to mid frequencies. Follow-up ophthalmology examination revealed Snellen visual acuity of 20/20 in each eye. Dilated funduscopic examination demonstrated no new BRAOs or vasculitis. Fluorescein angiography confirmed the BRAOs seen on initial examination without any leakage (figure, E and F).

The patient received monthly cyclophosphamide and IVIg infusions for 6 months with further improvement. She had a child-like demeanor, was impulsive and disinhibited, and remained unable to work or live independently. She was maintained on lower dose cyclophosphamide for 3 additional months. A repeat MRI brain at 9 months was improved with no new lesions, no diffusion restriction, and no enhancement (figure, G–I). She was transitioned to mycophenolate mofetil for long-term immunosuppression.

## DISCUSSION

Susac syndrome, or retinocochleocerebral vasculopathy, is a microangiopathy with an unclear pathogenesis named for John O. Susac (1940–2012), a neuro-ophthalmologist, whose initial case series in 1979 described 2 young women with subacute encephalopathy, BRAOs, and sensorineural hearing loss.[6] Dr. Susac postulated that the brain lesions and retinal and cochlear findings shared a common vascular pathophysiology. He advocated careful ophthalmoscopic examination in any patient with otherwise unexplained subacute encephalopathy. He also advocated early, aggressive immunosuppression to treat the clinical manifestations of this disease.

Since Dr. Susac's publication in 1979, fewer than 100 cases have been reported in the medical literature.[7] The average age at onset is 31.6 years (range 20–40 years) and it affects woman disproportionately.[3,7] In addition to encephalopathy, BRAOs, and hearing loss, common clinical manifestations include impaired cognition and memory, ataxia, dysarthria, vertigo, corticospinal tract dysfunction, and headache with migrainous features in approximately half of cases. There has been no evidence of hereditary transmission and the etiology is thought to be autoimmune.[7]

A high clinical suspicion must be maintained in order to diagnose Susac syndrome as it can mimic other disorders that produce encephalopathy, visual impairment, or hearing loss. Subacute encephalopathy is a presenting symptom in 75% of cases, but only 10% of cases present with hearing or visual symptoms.[7] This may be because the eye and ear involvement is subclinical or because the encephalopathy precludes expression of these symptoms. Ancillary testing that can help to secure a diagnosis includes fluorescein angiography of the retina to evaluate for BRAOs and pure tone audiometry testing to evaluate for low to mid-frequency sensorineural hearing loss.[1,4] Brain MRI can support the diagnosis by showing multiple small foci of high T2 signal intensity, diffuse restriction, and contrast enhancement throughout both gray and white matter in the cerebrum, particularly the corpus callosum.[7] The corpus callosum lesions favor central locations, as opposed to multiple sclerosis lesions, which favor the callosal-septal interface. Holes develop in the corpus callosum when the lesions resolve. CSF is often abnormal, with mild pleocytosis and elevated protein. The presence of oligoclonal bands in the CSF does not exclude a diagnosis of Susac syndrome.[3]

The natural course of Susac syndrome is unpredictable but can be classified into 3 groups: monophasic, polycyclic, and chronic continuous.[1] Most patients have a monophasic course, characterized by a single, self-limiting episode that lasts less than 2 years. Polycyclic recurrence up to 18 years after initial diagnosis and treatment has been reported.[8] There are no standardized treatment guidelines for Susac syndrome; however, multiple immunosuppressive treatment regimens have been proposed. Most regimens include acute high-dose corticosteroids and immunomodulating drugs with control of the active phase of the disease occurring in the majority of cases.[7,9] Reversal of vision loss has been reported with hyperbaric oxygen therapy.[10]

## AUTHOR CONTRIBUTIONS

Andrew W. Francis: design or conceptualization of the study, analysis or interpretation of the data, drafting or revising the manuscript. Claire L. Kiernan: drafting or revising the manuscript. Michael J. Huvard: drafting or revising the manuscript. Alejandro Vargas: drafting or revising the manuscript. Lawrence A. Zeidman: design or conceptualization of the study, analysis or interpretation of the data, drafting or revising the

manuscript. Heather E. Moss: design or conceptualization of the study, analysis or interpretation of the data, drafting or revising the manuscript.


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## DISCLOSURE

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## REFERENCES


1. Bitra RK, Eggenberger E. Review of Susac syndrome. Curr Opin Ophthalmol 2011;22:472–476.
2. Papo T, Biousse V, Lehoang P, et al. Susac syndrome. Medicine 1998;77:3–11.
3. Dörr J, Krautwald S, Wildemann B, et al. Characteristics of Susac syndrome: a review of all reported cases. Nat Rev Neurol 2013;9:307–316.
4. García-Carrasco M, Mendoza-Pinto C, Cervera R. Diagnosis and classification of Susac syndrome. Autoimmun Rev 2014;13:347–350.
5. Rennebohm R. Susac syndrome. Available at: https://my.clevelandclinic.org/health/diseases_conditions/susac-syndrome. Accessed October 26, 2014.
6. Susac JO, Hardman JM, Selhorst JB. Microangiopathy of the brain and retina. Neurology 1979;29:313–316.
7. Do TH, Fisch C, Evoy F. Susac syndrome: report of four cases and review of the literature. AJNR Am J Neuroradiol 2004;25:382–388.
8. Petty GW, Matteson EL, Younge BR, McDonald TJ, Wood CP. Recurrence of Susac syndrome (retinocochleocerebral vasculopathy) after remission of 18 years. Mayo Clin Proc 2001;76:958–960.
9. Zeidman LA, Melen O, Gottardi-Littell N, et al. Susac syndrome with transient inverted vision. Neurology 2004;63:591.
10. Li HK, Dejean BJ, Tang RA. Reversal of visual loss with hyperbaric oxygen treatment in a patient with Susac syndrome. Ophthalmology 1996;103:2091–2098.