



Section Editor
Mitchell S.V. Elkind,
MD, MS

Clinical Reasoning: A woman with subacute progressive confusion and gait instability

Jennifer M. Martinez-
Thompson, MD
Hugo Botha, MB, ChB
Brian S. Katz, MD

Correspondence to
Dr. Martinez-Thompson:
martinezthompson.jennifer@
mayo.edu

SECTION 1

A 20-year-old healthy woman developed sudden-onset, fluctuating gait unsteadiness. She became progressively confused over a 2-week time period and was sent home after she was found wandering the halls of her college dormitory. Her parents noted personality changes and slowed thinking. Several days later she developed a left facial droop and left-sided arm and leg weakness, prompting evaluation at her local emergency department.

Vital signs were within normal limits. Neurologic examination was notable for marked abulia and inattentiveness, right lateral end-gaze nystagmus, left hemiparesis, and left-sided dysmetria. She required 2-person assist for ambulation.

Questions for consideration:

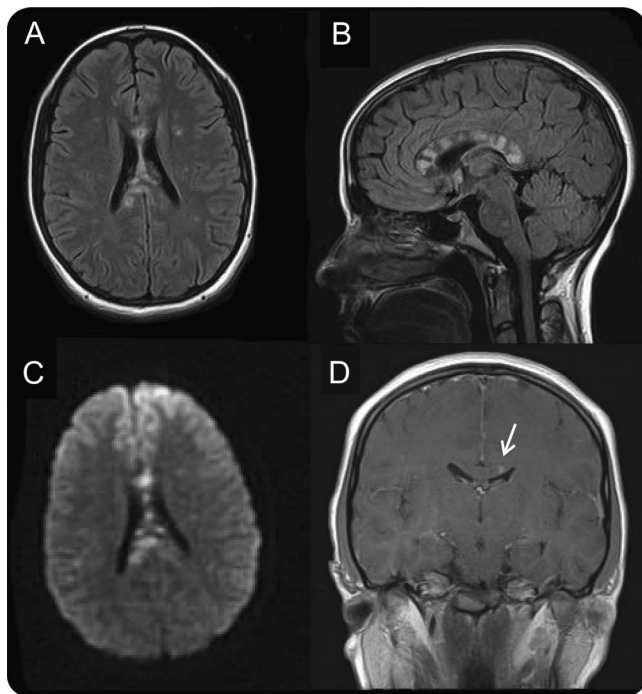
1. What level or levels of the nervous system are involved?
2. What is the most appropriate next diagnostic test?

[GO TO SECTION 2](#)

From the Department of Neurology, Mayo Clinic, Rochester, MN.

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

Figure 1 MRI brain



Axial fluid-attenuated inversion recovery (FLAIR) (A), sagittal FLAIR (B), diffusion-weighted (C), and coronal T1 postgadolinium (D) images. Multiple small foci of T2 hyperintensity are seen in the corpus callosum, subcortical white matter, and brainstem on FLAIR images. Many of these lesions are associated with restricted diffusion on corresponding diffusion-weighted imaging. Similar areas of T2 hyperintensity are present in the basal ganglia and thalamus (not pictured). A single enhancing callosal lesion is shown (D, white arrow).

SECTION 2

This patient's constellation of symptoms suggests a subacute progressive process with bihemispheric, brainstem, and cerebellar involvement. Given the focal findings on her examination, brain MRI without and with contrast was obtained as the first diagnostic step (figure 1).

Question for consideration:

1. Based on the imaging findings, what is your differential diagnosis?

[GO TO SECTION 3](#)

SECTION 3

The MRI showed multifocal abnormalities of both white and deep gray matter structures. The most striking feature was the multiple corpus callosum lesions. While not pathognomonic for a specific etiology, prominent corpus callosal involvement narrows the differential diagnosis (table).

Infarction isolated to the corpus callosum is relatively rare given its robust collateral blood supply.

When infarctions occur, the splenium is most often affected, followed by the body and genu.¹ Ischemic lesions are typically lateralized and confined to the anterior or posterior half of the corpus callosum given the dual contributions from the anterior and posterior circulations, respectively. Arteriopathies would be the exception to this pattern, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy and Susac syndrome (SS), both of which can diffusely involve white matter structures.²

With its predominance of myelinated fibers, the corpus callosum is also affected by demyelinating disease, including multiple sclerosis (MS) and acute disseminated encephalomyelitis (ADEM).¹ Callosal lesions in MS tend to be small and involve the inferior aspect. ADEM causes larger lesions that often cross the midline and may reach the upper and lower margins of the callosum. These are usually accompanied by other white and deep gray matter lesions.²

Marchiafava-Bignami disease is a rare hemorrhagic demyelinating disease primarily involving the corpus callosum and classically associated with chronic alcohol consumption. The corpus callosum degenerates and splits into 3 layers, with marked necrosis and eventual cavitation of the central layer.¹

High-grade gliomas can involve the corpus callosum through extension from the surrounding brain parenchyma, but circumscribed lesions are possible. Central necrosis and heterogeneous enhancement are common. Fibrillary astrocytomas are a notable exception as they usually lack enhancement and can spread along callosal white matter tracts.¹ CNS lymphoma also commonly involves the corpus callosum, periventricular white matter, and deep gray matter. The radiographic presentation of lymphoma is highly variable, with some lesions showing homogenous enhancement due to dense cellularity and lack of central necrosis.²

Although rare, infectious etiologies can cause T2 hyperintense lesions in the corpus callosum. Virally associated lesions are typically focal and may resolve with time.³ In younger patients, leukodystrophies and mitochondrial disorders should be considered, as several may involve the corpus callosum among other white matter regions. Chronic hydrocephalus can cause signal abnormalities under the falx cerebri due to pressure by the falx on the corpus callosum.^{1,2} In our patient, some of the callosal lesions on MRI were associated with diffusion restriction. A single callosal lesion showed enhancement (figure 1D), but the clarity of the contrast sequences was limited by motion artifact. Given the morphology of the lesions, demyelinating and vascular disease were the most likely etiologies.

Table Differential diagnosis of corpus callosum lesions¹⁻³

Vascular	Infectious
Infarction	Progressive multifocal leukoencephalopathy
CNS vasculitis	Subacute sclerosing panencephalitis (measles)
Primary: ABRA	Viral encephalitis
Systemic: Granulomatosis with polyangiitis, Sjögren syndrome, systemic lupus erythematosus	Nipah virus, enterovirus, influenza A, EBV, VZV, herpesvirus 6, adenovirus, rotavirus
Arteriopathies	Bacterial
CADASIL	Lyme disease, tuberculosis, <i>Escherichia coli</i> O157:H7, <i>Legionella</i> , <i>Salmonella enteritidis</i>
Susac syndrome	Toxoplasmosis
Vascular malformations	Toxic
Posterior reversible encephalopathy syndrome	Disseminated leukoencephalopathy secondary to systemic chemotherapy
Periventricular leukomalacia	Methotrexate, 5-fluorouracil, melphalan, carmustine, fludarabine, cytarabine, cisplatin
Inflammatory	Transient lesions associated with AED changes
Demyelinating	Whole-brain radiation therapy
Multiple sclerosis	Metabolic/developmental
ADEM	Agensis/hypoplasia
Marchiafava-Bignami disease	Phakomatoses
Neurosarcoidosis	Leukodystrophies
Neuro-Behçet disease	Metachromatic leukodystrophy
Neoplasm	X-linked adrenoleukodystrophy
Glioblastoma multiforme/high-grade glioma	Alexander disease
Primary CNS lymphoma	Mucopolysaccharidoses
Gliomatosis cerebri	Mitochondrial disorders
Lipoma	MELAS, Kearns-Sayers syndrome
Juvenile pilocytic astrocytoma	Artifact
Traumatic	Dilated Virchow-Robin spaces
Diffuse axonal injury	
Chronic hydrocephalus	

Abbreviations: ABRA = amyloid β -related angiitis; ADEM = acute disseminated encephalomyelitis, AED = antiepileptic drug; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; EBV = Epstein-Barr virus; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; VZV = varicella-zoster virus.

Laboratory testing for systemic inflammatory or hypercoagulability disorders was notable only for positive anti-Smith antibodies, which on repeat testing were absent. The patient underwent lumbar puncture, with the following CSF results: 8 nucleated cells/ μ L (93% lymphocytes), glucose 58 mg/dL, protein 119 mg/dL, normal immunoglobulin G index, 0 oligoclonal bands, and negative infectious evaluation. MRI of the

cervical and thoracic spine and magnetic resonance angiography of the head vessels were unremarkable.

Questions for consideration:

1. What is the most likely diagnosis based on imaging and the initial evaluation?
2. What additional testing would you perform to confirm the diagnosis?

GO TO SECTION 4

SECTION 4

There was high suspicion for SS based on the initial imaging. Mild CSF pleocytosis with elevated protein but no signs of active inflammation is consistent with SS. Audiometry showed bilateral mild middle-to-lower frequency sensorineural hearing loss. Dilated fundoscopic examination and retinal fluorescein angiography showed bilateral branch retinal artery occlusions, confirming the diagnosis of SS (figure 2). The patient was treated with a 5-day course of IV methylprednisolone, followed by daily oral prednisone and 7 treatments of plasmapheresis. Mycophenolate mofetil was started prior to discharge with the plan of a slow steroid taper over several months.

The patient's hemiparesis improved with the steroid and plasmapheresis therapy, and she transitioned to a cane for ambulation. While not cognitively at her baseline at discharge, she was interacting appropriately with staff.

DISCUSSION SS is characterized by the triad of encephalopathy, branch retinal artery occlusions (BRAO), and sensorineural hearing loss. Since its first description in 1979, approximately 200 cases have been reported. Individuals aged 7–72 years have been diagnosed with SS, but most are 20–40 years old at presentation.⁴ It preferentially affects women, with a ratio of 3:1 women to men, and no racial or ethnic predilection.⁵

While the pathogenesis of SS is not fully understood, findings on histopathology and electron microscopic examination of brain tissue have shown microinfarction and lymphocytic infiltration of small vessels, suggesting

that it is an immune-mediated process affecting small vessels of the retina, inner ear, and deep brain structures.⁵ The autoimmune hypothesis is supported by the presence of anti-endothelial cell antibodies in cases of SS, which have also been reported in dermatomyositis.⁶ It is unclear whether these antibodies are the cause or a by-product of the underlying disease process.

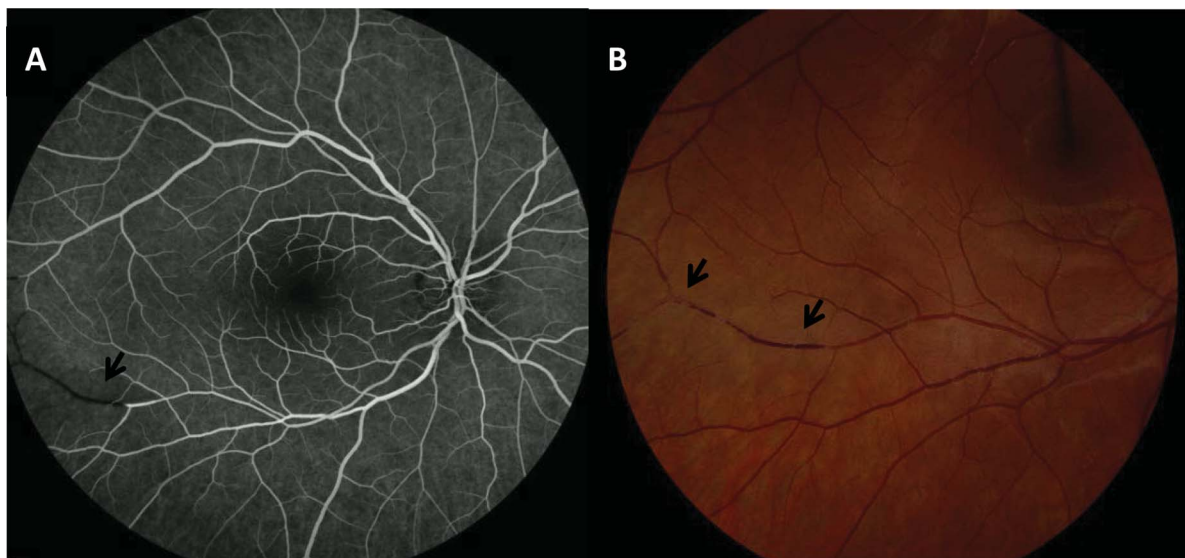
SS has a highly variable clinical course that can sometimes be predicted by the affected individual's initial symptoms. The monophasic form of the disease is characterized by subacute headaches, neuropsychiatric symptoms, long tract signs, and (less commonly) seizures with prominent encephalopathy within the first 2 years.^{4,7,8}

Patients with a polyphasic course experience bilateral BRAO and hearing loss at symptom onset with very mild or no encephalopathy. These individuals tend to have recurrent episodes of BRAO with progressive tunnel vision because peripheral arterioles are preferentially affected.⁵ The hearing loss is abrupt at onset and accompanied by tinnitus and vertigo. It can be unilateral on presentation but will quickly progress to bilateral involvement. This tends to affect low to middle frequencies and is irreversible.⁴

A diagnosis of SS is made with the aid of brain MRI and retinal fluorescein angiography to confirm BRAO, as these are not always visible on dilated funduscopy. The occlusions involve the middle segments of arterioles, which differentiate them from embolic phenomena that are typically seen at arteriolar bifurcations.⁵

MRI classically shows multiple small (3–7 mm) white matter lesions involving periventricular and

Figure 2 Fluorescein angiography and fundus photography



Fluorescein angiography (A) and fundus photography (B) of the right retina. A right branch retinal artery occlusion is seen inferotemporally on both retinal fluorescein angiography and fundus photography (black arrows). There is no evidence of Gass plaques.

subcortical regions as well as linear defects involving the central fibers of the corpus callosum best seen on sagittal T1 or fluid-attenuated inversion recovery. Estimates of callosal involvement range from 79% to 100%.^{9,10} White matter of the brainstem, middle cerebellar peduncles, and cerebellum is variably affected (30%–50% of patients). MS and ADEM are frequently in the differential because of the white matter involvement, but SS also involves deep gray matter within the basal ganglia and thalamus in about 70% of cases. Leptomeningeal enhancement is seen in about one-third of cases, which is an uncommon finding in MS or ADEM.⁹

CSF evaluation is generally nonspecific, with variable elevation in protein ranging from normal to 200 mg/dL, mild pleocytosis, and rarely oligoclonal bands.^{4,10}

The approach to treatment has largely been based on anecdotal reports and has included use of IV and oral steroids, IV immunoglobulin (IVIg), azathioprine, cyclophosphamide, mycophenolate mofetil, and plasmapheresis. Treatment response is variable and should be tailored based on the severity of a patient's initial presentation.^{4,10}

A conventional treatment approach has been proposed,⁴ with initial treatment consisting of pulsed IV methylprednisolone followed by oral prednisone and IVIg early on in acute treatment, with consideration for additional steroid-sparing immunosuppressive therapy in the first few weeks of treatment. While there is no evidence on the efficacy of plasmapheresis in treating SS, it has been suggested as an adjunctive therapy for patients who do not improve with initial steroid and IVIg treatment.¹⁰ Also important to note is the recommendation that patients with SS should be started on antiplatelet therapy, with aspirin as the first-line agent.⁴

Lifelong monitoring is required for these patients and relapses after decades have been reported.⁸ Most individuals have residual symptoms after initial therapy, but their prognosis improves if they are treated early in the disease course.⁴

AUTHOR CONTRIBUTIONS

Dr. Martinez-Thompson: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. H. Botha: drafting/revising the manuscript, study concept or design, accepts responsibility for conduct of research and final approval. Dr. Katz: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, acquisition of data, study supervision.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

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

REFERENCES

1. Uchino A, Takase Y, Nomiya K, Egashira R, Kudo S. Acquired lesions of the corpus callosum: MR imaging. *Eur Radiol* 2006;16:905–914.
2. Fries SA, Bitzer M, Freudenstein D, Voigt K, Kuker W. Classification of acquired lesions of the corpus callosum with MRI. *Neuroradiology* 2000;42:795–802.
3. Krupa K, Bekiesinska-Figatowska M. Congenital and acquired abnormalities of the corpus callosum: a pictorial essay. *Biomed Res Int Epub* 2013 Aug 6.
4. Kleffner I, Duning T, Lohmann H, et al. A brief review of Susac syndrome. *J Neurol Sci* 2012;322:35–40.
5. Rennebohm RM, Egan RA, Susac JO. Treatment of Susac's syndrome. *Curr Treat Options Neurol* 2008;10:67–74.
6. Magro CM, Poe JC, Lubow M, Susac JO. Susac syndrome: Cn organ-specific autoimmune endotheliopathy syndrome associated with anti-endothelial cell antibodies. *Am J Clin Pathol* 2011;136:903–912.
7. Susac JO. Susac's syndrome: the triad of microangiopathy of the brain and retina with hearing loss in young women. *Neurology* 1994;44:591–593.
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. Susac JO, Murtagh FR, Egan RA, et al. MRI findings in Susac's syndrome. *Neurology* 2003;61:1783–1787.
10. Mateen FJ, Zubkov AY, Muralidharan R, et al. Susac syndrome: clinical characteristics and treatment in 29 patients. *Eur J Neurol* 2012;19:800–811.

Neurology®

Clinical Reasoning: A woman with subacute progressive confusion and gait instability

Jennifer M. Martinez-Thompson, Hugo Botha and Brian S. Katz

Neurology 2014;83:e62-e67

DOI 10.1212/WNL.0000000000000648

This information is current as of July 28, 2014

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/83/5/e62.full
References	This article cites 9 articles, 2 of which you can access for free at: http://n.neurology.org/content/83/5/e62.full#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Other cerebrovascular disease/ Stroke http://n.neurology.org/cgi/collection/other_cerebrovascular_disease__stroke Stroke in young adults http://n.neurology.org/cgi/collection/stroke_in_young_adults
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 © 2014 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

