

CADASIL as a Multiple Sclerosis Mimic

ANDREW J. BOULEY, MD; SHADI YAGHI, MD

KEYWORDS: CADASIL, stroke in young adults, multiple sclerosis, MRI

INTRODUCTION

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a well-described entity that causes progressive neurologic decline due to subcortical infarcts. We describe a patient diagnosed with CADASIL that has many atypical features suggestive of multiple sclerosis (MS) as an alternate diagnosis.

CASE REPORT

A 31-year-old man with no significant past medical or family history presented with a one-day history of left arm weakness and dysarthria. His blood pressure was 124/83 mm Hg, his heart rate was 63 and regular, and he was afebrile. The general physical examination and mental status were normal aside from dysarthria. He had mild, left upper motor neuron facial weakness, mild left hemiparesis of arm and leg, with mild left dysmetria and dysidiadochokinesia. Reflexes were 3+ on the left and 2+ on the right; Babinski sign was present on the left. Gait testing revealed left leg circumduction.

The head CT scan was unremarkable. The brain MRI revealed an area of restriction on diffusion weighted imaging (DWI) in the right corona radiata with extensive periventricular T2/FLAIR hyperintensities (Figure 1). Post-contrast brain MRI showed partial peripheral enhancement of the lesion that restricted on DWI (Figure 2). Magnetic resonance angiography (MRA) showed normal intracranial and extracranial vasculature. Transthoracic echocardiogram revealed normal left ventricular function without evidence of right-to-left shunting with agitated saline. ECG and inpatient cardiac telemetry showed normal sinus rhythm. Blood tests revealed a normal complete blood count and basic metabolic profile, low-density lipoprotein cholesterol of 165 mg/dl, urine toxicology screen positive for cannabinoids, and normal

Figure 1. Non-contrast MRI brain.

Axial FLAIR (A-C) and sagittal FLAIR (D) images showing extensive periventricular white matter disease with involvement of the external capsule and sparing of the temporal lobes and brainstem. Axial DWI and ADC (E and F) images showing restricted diffusion.

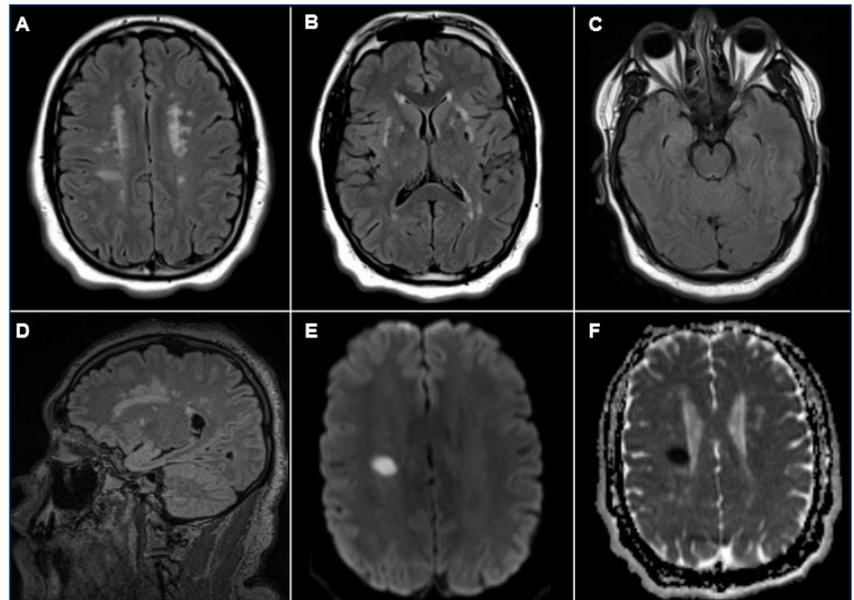
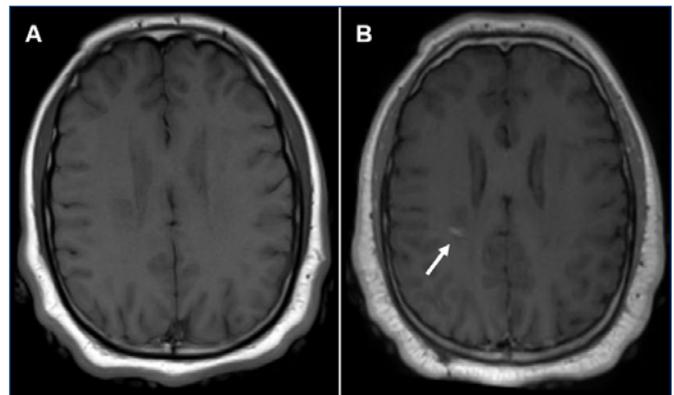


Figure 2. Pre- and post-contrast MRI brain.

Axial T1 pre-gadolinium (A) and post-gadolinium (B) images showing slight peripheral enhancement of the acute restricting lesion (arrow).



cerebrospinal fluid (CSF) profile with no oligoclonal bands and a normal IgG index. *NOTCH3* genetic testing revealed a heterozygous missense mutation, diagnostic of CADASIL.

DISCUSSION

The clinical presentation and neuroimaging suggested ischemic stroke with small vessel vasculopathy involving the external capsule. This led us to send *NOTCH3* genetic testing in pursuit of CADASIL. However, atypical features of the patient's presentation led us to pursue other diagnoses. Due to the patient's age and the predominance of periventricular white matter disease with Dawson finger-like projections on the sagittal FLAIR MRI, there was strong suspicion for MS. Prior to the return of the *NOTCH3* genetic testing, the patient was empirically treated with a three-day course of intravenous methylprednisolone 1,000 mg daily while simultaneously being treated with aspirin and atorvastatin for secondary stroke prevention. Acute demyelinating lesions in MS typically have increased signal on DWI with increased signal on ADC, presumably due to vasogenic edema and T2 shine-through caused by the breakdown in the blood-brain barrier.^{1,2} More rarely, acute demyelinating lesions can display a restricted diffusion pattern, leading to a diagnostic challenge for young adults presenting with stroke-like symptoms.³ The enhancement of the lesion was not helpful in differentiating stroke from demyelinating disease since both disease processes can demonstrate peripheral ring enhancement. In cases such as these, CSF analysis can be helpful as the presence of oligoclonal bands is highly sensitive for MS.⁴ Other disease entities, such as small vessel inflammatory and large vessel vasculitides, were lower on the differential given the lack of systemic symptoms, normal CSF profile, and normal MRA.

Stroke mechanisms in young adults include cardioembolism, dissection, moyamoya, vasculitis, drug abuse, hypercoagulable states, and neurogenetic disorders.⁵ Our patient's lack of traditional vascular risk factors suggested a possible genetic or metabolic etiology. MRI findings of lacunar infarcts and white matter changes are particularly prevalent in CADASIL and cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL).⁶

CADASIL is an autosomal dominant inherited small vessel disease of the central nervous system that leads to subcortical infarcts.⁷ Over 150 causative mutations of *NOTCH3* on chromosome 19 have been reported.⁷ While some groups have proposed incomplete penetrance for specific mutations,⁸ the overall penetrance for CADASIL mutations is thought to be complete or near complete.⁹ Although most reported cases are familial, de novo mutations can also occur; however, their frequency is not well defined.¹⁰ The various mutations result in a change in the number of cysteines, causing structural changes in the transmembrane receptor *NOTCH3*.¹¹ This protein is involved in arterial development, and mutation leads to damaged smooth-muscle cells of vessels, fibrosis, and the accumulation of *NOTCH3* and granular osmiophilic material (GOM).^{7,11} The vascular disease is an amyloid-negative arteriopathy that affects leptomeningeal and perforating arteries of the brain.⁷ *NOTCH3* genetic testing is the gold standard for diagnosing CADASIL and is nearly 100% sensitive and specific. Skin biopsies are also diagnostic, where immunostaining reveals *NOTCH3* in the vessel wall and electron microscopy reveals the presence of GOM in vascular smooth-muscle cells.⁷

Clinical features of CADASIL include migraines with aura, recurrent strokes, cognitive decline progressing to dementia, and psychiatric disturbances, typically with migraines being the presenting clinical feature. Intracranial hemorrhage and seizures are also common.^{7,11} Commonly, the first clinical ischemic event occurs after 40 years of age, but it can occur by age 20.⁷ MRI imaging shows diffuse white matter T2 hyperintensities, often periventricular, and involving the centrum semiovale, multiple circumscribed lacunar infarcts, and early brain atrophy. A propensity for involvement of the external capsule and the anterior poles of the temporal lobes is particularly suggestive of CADASIL.⁷ Treatment is limited to symptomatic treatment of migraines and neuropsychiatric features, as well as secondary prevention of additional strokes via antiplatelet therapy, statins, and management of hypertension and diabetes when clinically indicated. Genetic counseling is mandatory.⁷

References

- Schaefer P, Grant P, Gonzalez R. Diffusion-weighted MR imaging of the brain. *Radiology*. 2000;217(2):331-345.
- Cotton F, Weiner H, Jolesz F, Guttmann C. MRI contrast uptake in new lesions in relapsing-remitting MS followed at weekly intervals. *Neurology*. 2003;60(4):640-646.
- Balashov K, Lindzen E. Acute demyelinating lesions with restricted diffusion in multiple sclerosis. *Mult Scler*. 2012;18(12):1745-1753.
- Przybek J, Gniatkowska I, Mirowska-Guzel D, Czlonkowska A. Evolution of diagnostic criteria for multiple sclerosis. *Neurol Neurochir Pol*. 2015;49(5):313-321.
- Ji R, Schwamm L, Pervez M, Singhal A. Ischemic stroke and transient ischemic attack in young adults: risk factors, diagnostic yield, neuroimaging, and thrombolysis. *JAMA Neurol*. 2013;70(1):51-57.
- Craggs L, Yamamoto Y, Deramecourt V, Kalaria R. Microvascular pathology and morphometrics of sporadic and hereditary small vessel diseases of the brain. *Brain Pathol*. 2014;24(5):495-509.
- Chabriat H, Joutel A, Dichgans M, Tournier-Lasserre E, Bousser M. Cadasil. *Lancet Neurol*. 2009;8(7):643-653.
- Vyshka G, Kruja J. Clinical variability of the cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy phenotype in two siblings of a large family showing the same mutation. *Int Med Case Rep J*. 2013;6:59-63.
- Chabriat H, Vahedi K, Iba-Zizen M, et al. Clinical spectrum of CADASIL: a study of 7 families. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Lancet*. 1995;346(8980):934-939.
- Joutel A, Dodick D, Parisi J, Cecillon M, Tournier-Lasserre E, Bousser M. De novo mutation in the Notch3 gene causing CADASIL. *Ann Neurol*. 2000;47(3):388-391.
- Meng H, Zhang X, Yu G, Lee S, Chen Y, Prudovsky I, Wang M. Biochemical characterization and cellular effects of CADASIL mutants of NOTCH3. *PLoS One*. 2012;7(9):e44964.

Authors

Andrew J. Bouley, MD, Department of Neurology, The Warren Alpert Medical School of Brown University, Providence, RI.
Shadi Yaghi, MD, Department of Neurology, The Warren Alpert Medical School of Brown University, Providence, RI.

Correspondence

Andrew J. Bouley, MD
Rhode Island Hospital, 593 Eddy Street, APC 5th Floor
Providence, RI 02903
617-688-4988, Fax 401-444-6858
andrew.j.bouley@gmail.com