A 46-year-old man was seen in the neurology clinic because of hemiparesis, aphasia, and abnormalities on neuroimaging studies.

The patient had been well, except for migraine headaches, until 4 years earlier, when right-sided weakness, clumsiness, and slurred speech developed during a period of 24 hours. A neurologist at another hospital found dysarthria and right central facial weakness; decreased muscle tone in the right arm, with strength 4+/5; and normal muscle tone in the right leg, with strength 4+/5. Strength on the left side was normal, with slightly increased tone in the left arm and normal tone in the left leg. Reflexes were brisker on the right side than on the left, with an extensor plantar response on the right and a flexor plantar response on the left. Computed tomography (CT) of the brain after the administration of contrast material showed numerous nonenhancing, hypodense lesions in the bilateral basal ganglia and deep white matter. The patient was admitted to that hospital. Magnetic resonance imaging (MRI) showed extensive nonenhancing hyperintense lesions in the basal ganglia and deep white matter on T₂-weighted images. The white-cell count was 13,600 cells per cubic millimeter (neutrophils, 11,800 cells per cubic millimeter), and the thyrotropin level was 0.11 μIU per milliliter (reference range, 0.49 to 4.67). Other test results, including hematocrit, platelet count, coagulation studies, erythrocyte sedimentation rate, tests of liver and renal function, and measurements of calcium, glucose, thyroxine, antinuclear antibody, anticardiolipin antibody, vitamin B₁₂, folate, angiotensin-converting enzyme, and very-long-chain fatty acids, were normal. Testing for Lyme disease was negative.

During the next 4 days, the patient's symptoms worsened, and dysphagia developed. Methylprednisolone was given intravenously, and he was transferred to a rehabilitation hospital on the fourth day. Testing of visual, somatosensory, and brainstem auditory evoked potentials was normal. MRI of the cervical spine after the administration of contrast material revealed no impingement on the spinal cord or intrinsic lesions. The dysphagia gradually improved; his right arm remained paretic and its tone increased.
Four months after discharge, interferon beta-1a (30 μg weekly by intramuscular injections) was begun. Four days after the first injection, the dysarthria suddenly worsened, and expressive aphasia developed. The patient returned to the emergency department of the other hospital. Repeat MRI of the brain after the administration of gadolinium revealed progression of the previously seen left-sided lesions and a new lesion near the posterior limb of the left internal capsule. He was discharged home later that day. Injections of interferon beta-1a were continued. Lumbar puncture was performed 2 months later. The cerebrospinal fluid contained 1 white cell per cubic millimeter; the protein level was 26 mg per deciliter and the glucose 67 mg per deciliter; there were no oligoclonal bands, and the IgG index and level of myelin basic protein were normal.

During the next 2 years, three additional exacerbations of the patient’s symptoms occurred, which improved after treatment with intravenous methylprednisolone; interferon beta-1a was discontinued; and glatiramer acetate was begun daily by subcutaneous injection. Severe fatigue developed, and modafinil was prescribed.

The patient came to the outpatient neurology clinic of this hospital for a fifth opinion on the diagnosis and management of his symptoms. He reported dysarthria, dysphasia, dysphagia, weakness and spasticity of the right arm and leg, and severe fatigue, but no bladder symptoms. Since his mid-20s, he had had migraine headaches without aura, which were hemicranial, on alternating sides, and associated with nausea, vomiting, photophobia, and phonophobia, without osmophobia; they occurred four to five times per year and lasted between 4 and 6 hours. He took ibuprofen or acetaminophen for the pain. There was no history of an elevated cholesterol level, hypertension, diabetes, blood clots, rashes, or joint pain. He had smoked and ingested alcohol in the past, but stopped both 15 years earlier; he did not use illicit drugs. He had no allergies to medications; his current medications included glatiramer acetate, baclofen, and modafinil. He was married, had no children, and had worked as a carpenter until becoming disabled by this illness. He was of German, Irish, and Scottish ancestry. His parents, three of his four brothers, his sister, and two nephews had migraine headaches. His 75-year-old mother had had a transient ischemic attack at mid-20s, he had had migraine headaches without aura, and the other (50 years of age) had arm spasms and difficulty speaking. Two other brothers (47 and 52 years of age) had psoriasis; a fifth brother had had mental retardation and died at 4 years of age from pneumonia. A paternal uncle had died of a stroke.

On examination, the vital signs were normal. The patient was alert and oriented. His score on the Mini–Mental State Examination was 28 out of 30, with two errors recalling three objects at 5 minutes. He had a mild expressive aphasia, and his speech was dysarthric. Visual acuity and fields were normal; the pupils were symmetric and equally reactive to light, and there was no afferent pupillary defect. Disk margins were sharp, and there was nystagmus at extreme gaze. There was mild right central facial weakness. Muscle bulk was normal. Strength was 4/5 in the right deltoid, wrist extensors, and wrist flexors and 4+/5 in the biceps and triceps muscles. The right leg was spastic; strength was 4+/5 in the iliopectos and normal in the quadriceps, hamstring, and gastrocnemius muscles. The left arm and leg had normal power; tone was increased in the arm and normal in the leg. The reflexes were 3+/5 in both arms and legs. Plantar responses were extensor on the right side and flexor on the left side. The gait was hemiparetic. Coordination was normal in the left arm and both legs; the right arm could not be assessed because of paralysis. The sensory examination and the remainder of the physical examination were normal. Examination by a neuro-ophthalmologist disclosed no optic-nerve abnormalities.

A CT angiogram of the head and neck showed no evidence of atherosclerotic disease. Results of a repeat MRI scan of the brain were similar to those 3 years earlier, except for a slight increase in the extent of hyperintense lesions on T₂-weighted images. MRI scans from the patient’s two brothers who carried a diagnosis of multiple sclerosis were reviewed, and they showed findings similar to those of the patient. Testing of visual evoked potentials elicited normal results. The level of functional protein C was 153% (reference range, 70 to 140); the cholesterol level was 243 mg per deciliter (6 mmol per liter) (desirable, <200 mg per deciliter [<5 mmol per liter]); other test results, including a test for resistance to activated protein C, a complete blood count, tests of renal function, and measurements of lipoprotein A, electrolytes, glucose, calcium, lactic acid, thyrotropin, vitamin B₁₂, creatine kinase, angiotensin-convert-
ing enzyme, arylsulfatase A, phytanic acid, very-long-chain fatty acids, protein S (functional assay), antibodies to the human immunodeficiency virus (HIV) and Borrelia burgdorferi, antinuclear antibody, lupus anticoagulant and anticardiolipin antibodies, antithrombin III, and homocysteine, were normal. Cerebrospinal fluid analysis revealed 1 white cell, normal levels of protein (26 mg per deciliter) and glucose (67 mg per deciliter [3.7 mmol per liter]), and a normal IgG index (<0.85); no oligoclonal bands were noted. Sequencing of exons 1 through 33 of the NOTCH3 gene showed a mutation of unknown significance at codon 61, resulting in a substitution of arginine for tryptophan in the putative gene protein product; this mutation had not previously been associated with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). The patient reported that testing of one of his brothers for mutations in the NOTCH3 gene had been negative. Genetic testing for mitochondrial encephalomyelopathy, lactic acidosis, and strokelike episodes (MELAS) was negative.

A diagnostic test was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Steven D. Brass: This 46-year-old man with a history of migraine had recurrent acute neurologic events over a period of a few years. Examination revealed cognitive changes, aphasia, and hemiparesis, and neuroimaging revealed multifocal abnormalities in the basal ganglia and white matter. His family history was clinically significant for two brothers who carried a diagnosis of multiple sclerosis. He came to me for a second opinion, with a presumptive diagnosis of multiple sclerosis; I am aware of the final diagnosis in this case. Dr. Copen, may we review the neuroimaging studies?

Dr. William A. Copen: MRI of the brain performed at another institution 4 years before presentation at this hospital revealed extensive deep supratentorial white-matter lesions that are most prominent in T2-weighted fluid-attenuated inversion recovery (FLAIR) images (Fig. 1A). The lesions were hyperintense on T2-weighted images, with no associated mass effect or enhancement and no susceptibility effect to suggest hemorrhage. Images of the cervical spine showed mild degenerative changes but no spinal cord abnormalities. Magnetic resonance angiography of the head and neck was normal.

The patient's brain lesions could be consistent with multiple sclerosis, although several features are unusual for that diagnosis. In multiple sclerosis, the corpus callosum typically has disproportionately more lesions than do other white-matter structures; however, the corpus callosum is largely spared in this patient (Fig. 1B). Second, the patient has lesions in deep gray-matter structures, and MRI reveals deep gray-matter lesions in only a minority of patients with multiple sclerosis (Fig. 1C). Third, there are extensive regions of cavitation, with resulting signal suppression on FLAIR images; such widespread cavitation is unusual in multiple sclerosis. Finally, one lesion shows markedly restricted water diffusion (Fig. 1D). Although diffusion is often decreased in lesions of active multiple sclerosis, restriction of this degree is more typical of recent infarction. Therefore, in addition to multiple sclerosis, the differential diagnosis for these findings must include small-vessel vasculitides, as well as other pathologic processes that could result in deep infarcts, such as hypercoagulable states and inheritable or drug-induced small-vessel arteriopathies.

At a follow-up visit, the patient had with him the MRI scans from the two brothers who carried diagnoses of multiple sclerosis. These images showed findings remarkably similar to those in the patient, including widespread supratentorial hyperintense lesions on T2-weighted images, which predominantly, but not exclusively, affected white matter. In the brothers, involvement of the deep gray-matter structures was more pronounced than that in the patient, further suggesting an inheritable disease capable of causing small-vessel infarction (Fig. 2).

MULTIPLE SCLEROSIS

Dr. Brass: Multiple sclerosis is a challenging diagnosis to make and carries a misdiagnosis rate of 5 to 10%.1 The diagnosis relies on the presence of lesions in the central nervous system that are disseminated in space (i.e., various parts of the central nervous system) and time, with no better explanation for the disease process. MRI of the brain and spine, cerebrospinal fluid examination, and tests of visual evoked potentials may also help confirm the diagnosis. The diagnosis of multiple sclerosis necessitates the exclusion of alternative
For this reason, evaluation should include careful consideration of red flags, which are features in the history, examination, or diagnostic tests that are not typical or suggestive of multiple sclerosis (Table 1). If multiple red flags are present, further diagnostic tests may be indicated to look for one of the many mimics of multiple sclerosis. This patient had multiple red flags, including his acute stroke-like events, his history of two first-degree relatives who carried...
B R I E F R E V I E W
ried diagnoses of multiple sclerosis, his personal and family history of migraine, his aphasia as an early presenting symptom, the absence of optic-nerve involvement and sensory symptoms on examination, the predominant gray-matter involvement and the sparing of the corpus callosum on MRI, the normal results on testing of visual evoked potentials, and the absence of oligoclonal bands and the normal IgG index on cerebrospinal fluid examination. These features mandated consideration of other diagnoses.

OTHER POSSIBLE MULTIFOCAL WHITE-MATTER LESIONS
Of the many diseases that can present with multifocal white-matter lesions, infectious diseases such as Lyme disease, HIV encephalitis, progressive multifocal leukoencephalopathy, and neurosyphilis; metabolic conditions such as vitamin B\textsubscript{12} deficiency; toxic leukoencephalopathy; and inflammatory and immunologic diseases such as Behçet’s disease, vasculitis of the central nervous system, antiphospholipid-antibody syndrome, and neurosarcoidosis are unlikely in view of the patient’s clinical, laboratory, and imaging findings and his family history. I therefore focused on the three most probable diagnoses: leukodystrophies, mitochondrial diseases, and CADASIL.

LEUKODYSTROPHIES
Although most leukodystrophies present in childhood, some variants can present in adulthood, and they include adrenoleukodystrophy, metachromatic leukodystrophy, leukodystrophy with neuroaxonal spheroids, and galactocerebrosidase deficiencies such as Krabbe’s disease. However, leukodystrophies usually follow a slowly progressive course, rather than a relapsing–remitting one, and despite the family history of two brothers with white-matter disease, the patient’s clinical findings and neuroimaging studies did not conform to any of these entities. The normal values for very-long-chain fatty acids also argued strongly against adrenoleukodystrophy.

MITOCHONDRIAL DISEASES
Mitochondrial diseases can mimic multiple sclerosis by presenting with relapsing disease of the central nervous system. We considered MELAS in this case because of the family history, stroke-like episodes, headache, and cognitive problems. MRI in cases of MELAS often reveals infarcts in the cortical and subcortical white matter that do not follow vascular territories. Although the MRI scans in this case were not supportive of a diagnosis of MELAS, this patient’s constellation of clinical features compelled us to perform genetic testing for MELAS.\textsuperscript{11} The results did not reveal the most common mitochondrial DNA point mutation associated
lobe involvement was seen on the MRI scans.

In the fifth or early sixth decade of life typically presents with the onset of lacunar stroke would explain many features of this case, since it CADASIL is an autosomal dominant disease that possible diagnoses.

**CADASIL**

CADASIL is an autosomal dominant disease that would explain many features of this case, since it typically present with the onset of lacunar stroke in the fifth or early sixth decade of life and additional lacunar strokes and ischemic damage to the white matter ultimately lead to dementia after about 10 years. About a third of the patients have migraine, as this patient did; migraine, if present, typically begins in the middle of the fourth decade. Neuroimaging often reveals multifocal or symmetric white-matter lesions, classically involving the anterior temporal lobe and external capsule. In our patient, however, no temporal-lobe involvement was seen on the MRI scans.

Nonetheless, since two of the patient’s brothers had white-matter disease, we ordered genetic testing for CADASIL, which showed a missense mutation in the NOTCH3 gene at nucleotide position 259 that would predict a change from arginine to tryptophan. One of the brothers had been tested for a NOTCH3 mutation, and although the patient reported that the test was negative, we later learned that the brother had the same missense alteration at nucleotide position 259. Because of the long time course, absence of signs and symptoms such as deafness, neuropathy, headache, aphasia, or dementia Two or more first-degree relatives with “multiple sclerosis” Age at onset, >60 years

with MELAS and prompted us to explore other possible diagnoses.

**Table 1. Red Flags When Making a Diagnosis of Multiple Sclerosis.**

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Cerebrospinal Fluid Examination</th>
<th>Neuroimaging Studies</th>
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<tbody>
<tr>
<td>Systemic symptoms such as fever, weight loss, rash, night sweats, gastrointestinal symptoms</td>
<td>White-cell count, &gt;50 cells per microliter</td>
<td>Normal findings on repeated MRI scans of the brain and spine over time</td>
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<tr>
<td>Absence of any neurologic deficits over time, despite repeated examinations</td>
<td>Protein, &gt;100 mg per deciliter</td>
<td>Lesions predominantly in gray matter rather than white matter on MRI scans</td>
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<tr>
<td>Acute stroke-like events</td>
<td>Presence of neutrophils</td>
<td>Sparing of the corpus callosum</td>
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<tr>
<td>Prominent neurologic symptoms early in the disease, such as deafness, neuropathy, headache, aphasia, or dementia</td>
<td>Hypoglycorrhachia</td>
<td>A solitary closed-ring enhancing lesion</td>
</tr>
<tr>
<td>Two or more first-degree relatives with “multiple sclerosis”</td>
<td>Absence of oligoclonal bands (absent in 5 to 10% of cases of multiple sclerosis)</td>
<td>Meningeal enhancement</td>
</tr>
<tr>
<td>Age at onset, &gt;60 years</td>
<td></td>
<td>A solitary lesion with prominent mass effect increasing over time</td>
</tr>
</tbody>
</table>

Red flags are features that are not typical or suggestive of multiple sclerosis. Data are from Charil et al., Carmosino et al., Cohen and Rensel, Miller and Compton, Olek, Rolak and Fleming, Scolding, Scott, and Trojano and Paolicelli.

Diseases that affect small cerebral arteries and need to be considered in this case include arteriosclerosis, cerebral amyloid angiopathy, vasculitis, and hereditary vasculopathies. Arteriosclerosis, often associated with aging and hypertension, is overall the most common small-vessel disease, but it is unlikely in this patient because of his age and the lack of typical risk factors, except for a remote history of smoking and the presence of hyperlipidemia. Sporadic cerebral amyloid angiopathy is unlikely because of the patient’s young age and the lack of characteristic lobar intracerebral hemorrhages. Cerebral vasculitides are improbable because of the long time course, absence of signs of systemic vasculitis, and absence of pleocytosis or elevated protein levels in the cerebrospinal fluid. The most likely cause of the patient’s disease is therefore an adult-onset hereditary vasculopathy.
The neurologic symptoms, family history, and strikingly similar MRI lesions in the patient and two of his brothers are consistent with an autosomal dominant inherited disease. The lack of neurologic symptoms in the parents may indicate partial or incomplete penetrance. Hereditary cerebral amyloid angiopathies are caused by mutations in various genes, including amyloid precursor protein, cystatin C, gelsolin, and transthyretin.\(^\text{14}\) Lobar intracerebral hemorrhages, including microhemorrhages detected with the use of MRI, are characteristic, as they are in sporadic cerebral amyloid angiopathy. Mutations in the COL4A1 gene encoding the α1 chain of type IV collagen cause basement-membrane abnormalities and are associated with intracerebral hemorrhage, porencephaly, intracranial aneurysms, and cystic kidney disease.\(^\text{19}\) Both hereditary cerebral amyloid angiopathy and COL4A1-associated disease are unlikely in this case because of the absence of intracerebral hemorrhages and the prominent cavitating lacunar lesions.

Fabry’s disease is an X-linked recessive disease caused by mutations in the GLA gene encoding α-galactosidase A, leading to accumulation of globotriaosylceramide in the vascular media and other tissues. Although Fabry’s disease is an underrecognized cause of ischemic stroke in younger persons,\(^\text{20}\) the absence of angiokeratoma, small-fiber neuropathy, and cardiac abnormalities makes that diagnosis unlikely.

Homocystinuria is an autosomal recessive disease caused by mutations in one of four genes that are involved in methionine metabolism; the classic form is caused by mutations in the CBS gene encoding cystathionine β-synthase. Accelerated atherosclerosis, large-vessel and small-vessel ischemic infarcts, and extensive white-matter lesions may be seen.\(^\text{21}\) In this case, homocystinuria is ruled out by the normal serum homocysteine level.

The signs and symptoms in this case most closely resemble the phenotype of CADASIL. The extensive lacunar lesions and white-matter lesions seen on MRI in this case are consistent with CADASIL. However, the mutation in NOTCH3 identified in this case is not typical of those that cause CADASIL.\(^\text{14}\) This raised the question of whether the observed mutation causes disease or is merely a coincidental polymorphism. Other findings in this case that cast some doubt on the diagnosis of CADASIL are the lack of symptomatic disease in either parent, despite the reported high penetrance of CADASIL, and the relative lack of characteristic anterior temporal white-matter lesions.\(^\text{15}\) The possibility of a new small-vessel disease with a CADASIL-like phenotype, as has recently been described,\(^\text{22}\) must be considered as an alternative diagnosis.

We were therefore faced with the question of determining the pathogenic relevance of a previously undescribed genetic mutation. This situation may become more frequent in cases of CADASIL and other diseases as molecular diagnostic testing becomes more commonplace. To determine definitively whether the CADASIL phenotype was present, we recommended obtaining a skin-biopsy specimen for pathological examination of the small dermal arteries. Dermal arteries show pathological findings that are pathognomonic for CADASIL, even though skin lesions do not occur. The sensitivity and specificity of a skin-biopsy specimen for the diagnosis of CADASIL are both greater than 90%, provided that dermal arteries can be adequately visualized in the specimen.\(^\text{23}\)

Before the patient could undergo a skin biopsy, however, his brother who had the same NOTCH3 alteration died of a stroke. An autopsy was performed.

**Clinical Diagnosis**

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

**Pathological Discussion**

Dr. Matthew P. Frusch: An autopsy limited to examination of the central nervous system was performed on the patient’s brother at another institution, and the brain was delivered to this hospital. The brain weighed 1390 g and showed evidence of a recent, large infarct in the left hemisphere involving the striatum and extending to the external capsule (Fig. 3A). The gross appearance and the microscopical findings of early accumulation of macrophages at the edges of the infarct suggested that the lesion was approximately 7 to 10 days old. The overall macroscopic appearance and consistency of the white matter were normal, but microscopical examination revealed a series of small infarcts in the brain stem and in the contralateral basal ganglia. These ranged in age from remote to recent. In addition, many medium-sized vessels showed marked thickening of their walls,
associated with granular deposits and increased space between the vessel and the surrounding parenchyma (Fig. 3B). These granular deposits in the vessel walls were strongly stained with the periodic acid–Schiff (PAS) method (Fig. 3C). Ultrastructural examination of the vessels of the white matter showed the presence of granular osmiophilic material along the abluminal aspect of the vascular basement membrane (Fig. 3D). The combination of the light-microscopical findings of the changes in blood-vessel walls, including the PAS-positive granular deposits, and the presence of granular osmiophilic material as detected on electron microscopy is diagnostic of CADASIL.

Dr. Joseph F. Arboleda-Velasquez: The NOTCH3 C259T mutation that was found in the patient and his brother is predicted to result in a nonconservative amino acid change of arginine to tryptophan at position 61 (R61W) of the Notch3 protein, a member of a family of transmembrane receptors that coordinate cell-fate decisions during development.24-26 The R61W change, like all other CADASIL mutations reported to date, is positioned in 1 of the 34 EGF-like repeats located in the extracellular domain of Notch3.14,27 How-
ever, in contrast to typical CADASIL mutations, this change does not result in an EGF-like repeat that contains an odd number of cysteine residues.\textsuperscript{16,28,29} The presence of presumably free sulf-hydryl moieties in Notch3 proteins carrying typical changes of CADASIL has triggered proposals about the effect of the mutations on signaling, folding, trafficking, and increased reactivity of the receptor, but efforts to address these issues experimentally have not produced conclusive results.\textsuperscript{30-35} Several Notch3 alterations that do not affect cysteine residues have been reported in families with CADASIL,\textsuperscript{36-40} although the effects of these changes on Notch3 activity and their ability to induce the vascular pathology of CADASIL are also unclear (Table 2). Thus, whether the R61W change in Notch3 in this family resulted in molecular aberrations leading or contributing to the small-vessel disease requires further investigation.

Dr. David N. Louis (Pathology): Dr. Viswanathan, what is the patient’s current condition?

Dr. Anand Viswanathan (Neurology): The patient has remained neurologically stable without clinical or imaging evidence of new stroke. He continues on aspirin therapy with aggressive efforts to control blood pressure to reduce disease-related disability and cognitive impairment.

\textbf{ANATOMICAL DIAGNOSIS}

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

Dr. Brass reports receiving consulting fees from or serving on paid advisory boards for Teva Neuroscience, EMD Serono, Bögen, and Bayer. No other potential conflict of interest relevant to this article was reported.

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