

Worsening neurologic deficits in a pilot

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A 58-year-old Caucasian man who worked as a pilot presented with symptoms of left-sided facial weakness, dysarthria, and incoordination of the left upper extremity. The patient reported a history of previous transient vision loss 9 years earlier, from which he recovered. He had no vascular risk factors based on his medical history, but his mother and many of his maternal relatives had suffered from strokelike symptoms. His mother and brother both died in their 50s. Laboratory studies during admission did not reveal a hypercoagulable state. Magnetic resonance (MR) imaging of the brain was performed (Figures 1–5).

What are the differential diagnostic considerations? What is the most likely diagnosis? What tests can confirm the diagnosis?

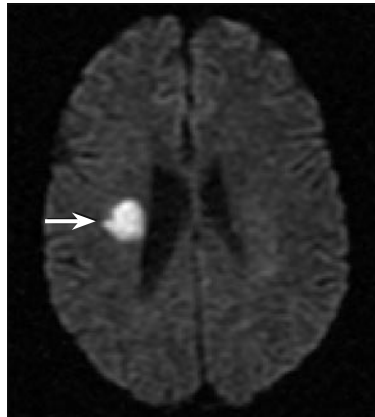


Figure 1. Axial diffusion-weighted MR image reveals hyperintense signal (arrow) within the right periventricular white matter compatible with restricted diffusion.

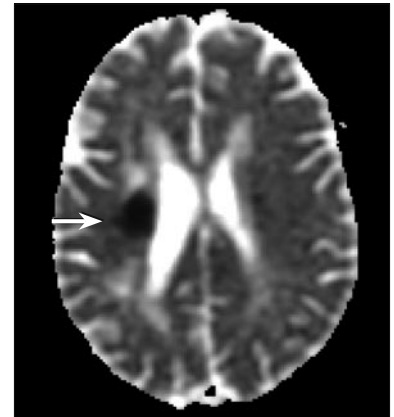


Figure 2. Axial apparent diffusion coefficient MR image shows right periventricular white matter hypointensity (arrow), which confirms that the diffusion-weighted hyperintensity is restricted diffusion and not T2 hyperintensity “shine through.”

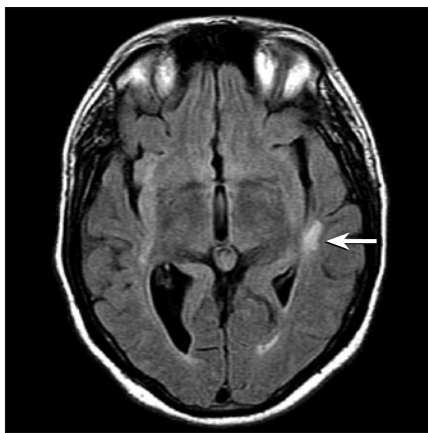


Figure 3. Axial FLAIR MR image shows focal hyperintensity of the left temporal lobe white matter (arrow).

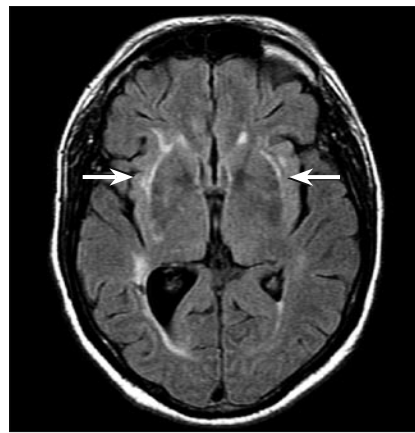


Figure 4. Axial FLAIR MR image reveals hyperintense signal of bilateral external capsules (arrows) and periventricular white matter.

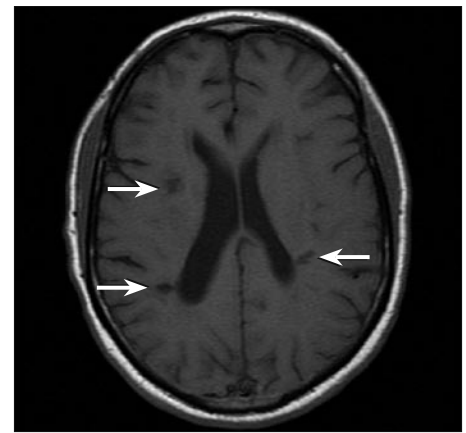


Figure 5. Axial T1-weighted MR image shows hypointense white matter foci (arrows) that did not demonstrate restricted diffusion on diffusion-weighted imaging (not shown) and are compatible with remote infarcts.

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

DISCUSSION

CADASIL is an inherited disease, neither atherosclerotic nor amyloid in nature, that affects small cerebral arteries. Typically the long perforating and leptomeningeal arteries are involved. The affected vessels develop extensive granular osmiophilic deposits within the basal membrane (Figure 6), and the arteriopathy leads to widespread demyelination of the white matter and subcortical lacunar infarctions. In 1993, the disease locus was pinpointed to chromosome 19. Subsequent research demonstrated the *NOTCH3* gene, which encodes a large transmembrane receptor, as the defective gene (1–3).

The disease was originally described in 1977 as a syndrome of ischemic strokes and hereditary vascular dementia afflicting seven unrelated families. Symptoms tend to begin in the late 30s. The most common presenting symptoms are migraine and transient ischemic attack (TIA) or stroke. Migraine is typically more prevalent as the initial symptom in younger patients (average age, 28 years), whereas TIA or stroke typically presents as an initial symptom of older patients (average age, 41 years). Mood disorders, such as depression, are another common initial feature. As the disease progresses, the likelihood of stroke and a frontal lobe type of dementia increases. A mean age of death of 54.8 ± 10.6 years was reported in one database of 105 CADASIL patients. Currently there is no

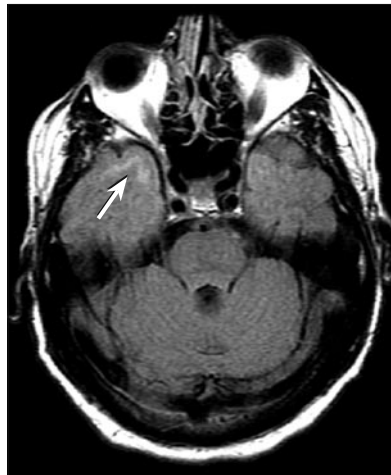


Figure 7. Axial FLAIR MR image demonstrates right temporopolar subcortical white matter hyperintensity (arrow), which is characteristic of CADASIL.

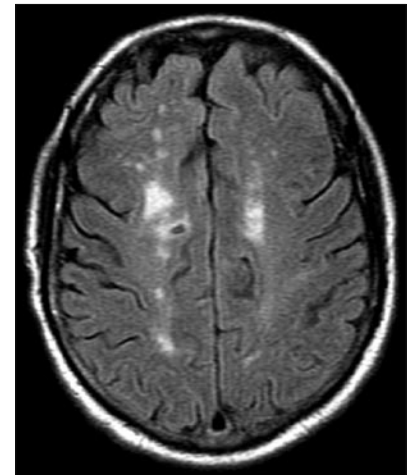


Figure 8. Axial FLAIR MR image reveals bilateral frontal lobe periventricular and subcortical white matter hyperintensity. A remote lacunar infarction is present in the right centrum semiovale.

specific effective treatment for CADASIL. Therapy is focused on treating the patient's symptoms. Antiplatelet therapy is usually advocated given its relatively low risk (4, 5).

Imaging findings

The MR imaging findings of CADASIL generally correlate with the histopathologic findings found on biopsy. CADASIL leads to leukoariosis (white matter pallor secondary to small vessel occlusive disease) represented by confluent areas of high T2 and fluid-attenuated inversion recovery (FLAIR) signal within the white matter. Leukoariosis in and of itself is quite nonspecific and is frequently observed in aging patients or in patients with risk factors for small vessel disease. It classically presents as symmetric periventricular white matter T2 and FLAIR hyperintensity. CADASIL white matter disease, unlike classic ischemic leukoariosis, has a predilection for the temporopolar and frontal lobe white matter (Figure 7). This feature is evident early in the disease process and is unlike ischemic leukoariosis and other white matter diseases, which typically spare the temporopolar white matter (6).

A second classic feature of CADASIL is subcortical lacunar infarctions (Figure 8). The lacunar infarctions are typically small, ranging from 1 to 2 mm. Microscopically they lie within the subcortical white matter and are perpendicular to the junction of the gray and white matter. They are T2 and FLAIR hyperintense and usually isointense to cerebrospinal fluid signal intensity because of distention of the small vessel perivascular spaces (7–9).

Imaging findings also vary according to the stage of disease progression, which is related to patient age. At 20 to 30 years of age, patients typically present with supratentorial white matter lesions. At 30 to 50 years of age, patients develop white matter lesions that involve infratentorial structures, the thalamus, and basal ganglia. Beginning around 40 years of age, patients also begin to have cerebral microbleeds, demonstrated as punctate subcentimeter areas of low signal intensity on gradient echo MR images involving the supratentorium, brainstem, and thalamus. By their 50s, all CADASIL patients demonstrate hyperintense



Figure 6. Electron micrograph of a skin biopsy from a different CADASIL patient that shows the granular osmiophilic deposits (arrows) that are diagnostic of CADASIL.

T2 and FLAIR lesions involving the cerebral and cerebellar hemispheres (10).

Laboratory findings

Peripheral blood leukocytes drawn from a peripheral vein can be sent for polymerase chain reaction (PCR) followed by single-strand conformational polymorphism to detect the *NOTCH3* gene mutation. There are 33 potentially affected exons; however, mutations in exons 3, 4, 5, and 6 typically account for 90% of CADASIL cases. Exons 3 through 6 can be screened for as an initial step, and if no mutation is detected, the remaining exons can then be screened. The overall mutation carrier frequency has been shown to be very low, and screening of the general population would not be economically practical. Nevertheless, patients with lacunar infarctions at a young age may benefit from screening. It should be noted that a small percentage of CADASIL patients' mutations may not be detected via PCR analysis. This may relate to deletional mutations or mutations within the noncoding sequence of the gene that can be missed by PCR (2, 11).

Skin biopsy is another diagnostic tool that is not as sensitive as PCR analysis but is highly specific. CADASIL is diagnosed based upon granular osmiophilic deposits within the basal membrane of vascular smooth muscle cells of skin arterioles. Biopsy may be helpful in the diagnosis of PCR-negative cases when the clinical and radiographic suspicion remains elevated (12).

Differential diagnosis

A wide variety of neurologic and nonneurologic diseases may need to be considered, especially in younger patients. In such patients, migraine headaches and sources of embolic infarction should be considered. Diffusion-weighted MR scans are advantageous in the detection and confirmation of even small sites of acute ischemic injury. Young patients with strokelike migraine symptoms can simulate many of the signs and symptoms of CADASIL. Small foci of increased T2 and FLAIR signal can be found in the subcortical white matter of the frontal lobes in chronic migraine sufferers; however, these patients should not typically manifest the MR signal abnormalities in the temporopolar white matter. Abnormalities in that region are more characteristic of CADASIL or perhaps demyelinating disease.

Demyelinating diseases such as multiple sclerosis (MS) or acute disseminated encephalomyelitis are also diagnostic possibilities. MS may be difficult to differentiate from CADASIL clinically and radiographically. Classic signs of MS by MR imaging—such as calloseseptal ovoid T2 and FLAIR hyperintense lesions, periventricular Dawson's fingers, optic neuritis, and transverse myelitis—can be helpful in facilitating this differentiation.

Other diagnostic possibilities include Lyme disease and central nervous system vasculitis. By MR imaging, vasculitis

can be highly variable, with areas of T2 and FLAIR hyperintensity, abnormal enhancement, infarction, and hemorrhage. The diagnosis can be considered based on MR and computed tomographic angiography findings, although cerebral angiography is considered the gold standard for suggesting the diagnosis. Lyme disease, unlike CADASIL, can result in meningeal or cranial nerve enhancement in addition to white matter T2- and FLAIR-hyperintense lesions.

Involvement of the temporopolar white matter in CADASIL can help in differentiating it from other white matter diseases. In combination with clinical and laboratory findings, the diagnosis of CADASIL can typically be offered with confidence.

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