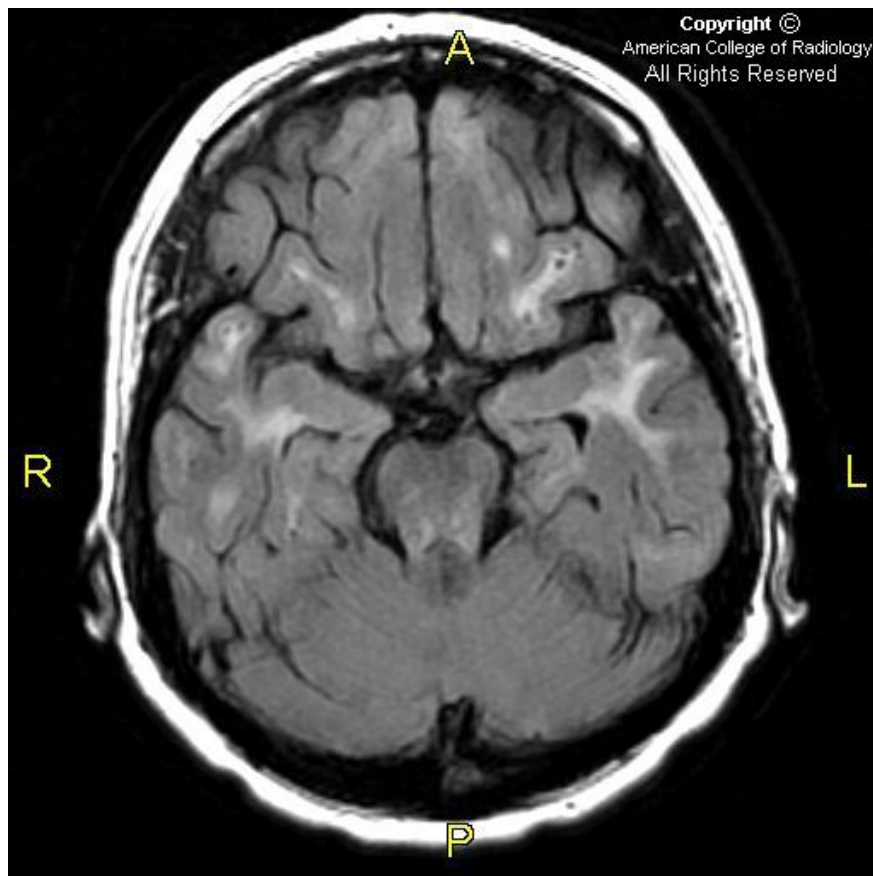
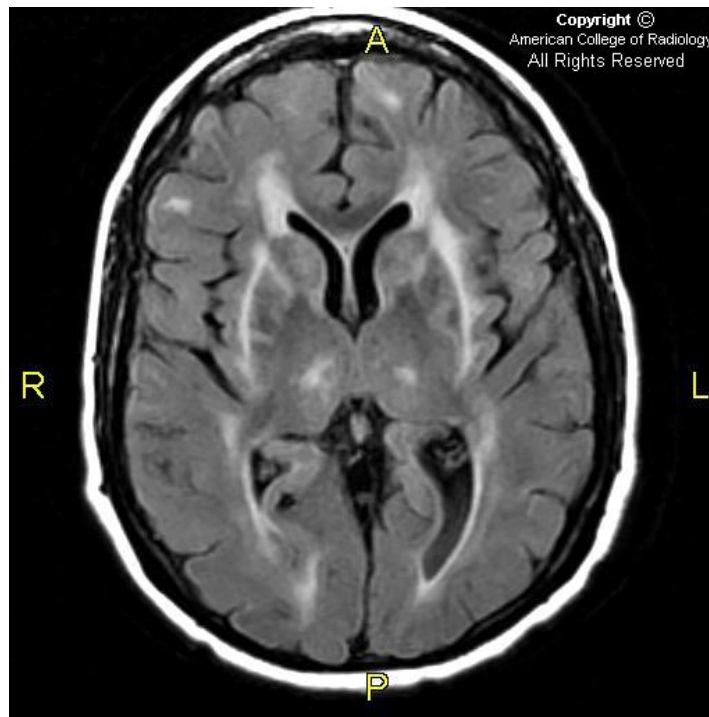
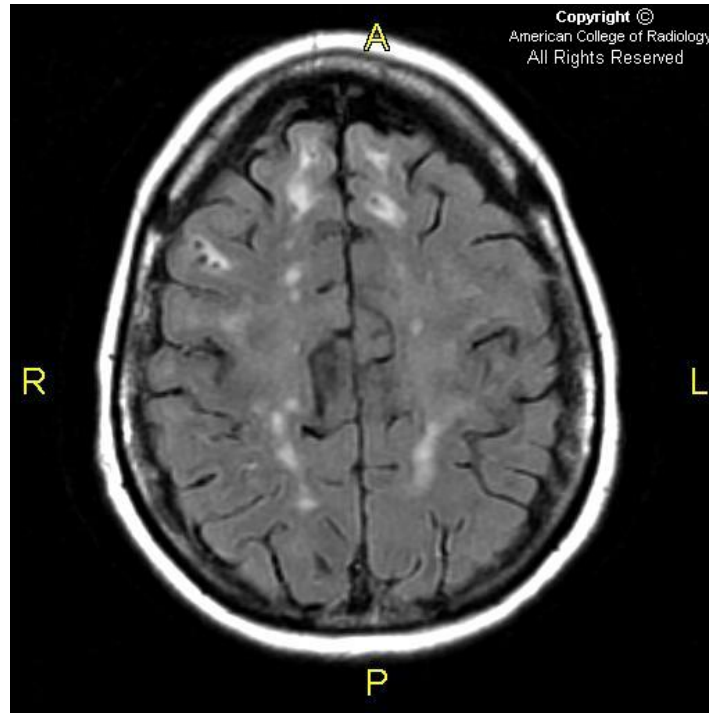


# Temple PM&R Case of the Week

43-year-old male complains of multiple seizures, headaches, progressive forgetfulness, depression, right facial droop, and gait disturbance.

MRI of the brain was conducted on the patient.  
Multiple imaging sections are shown below.

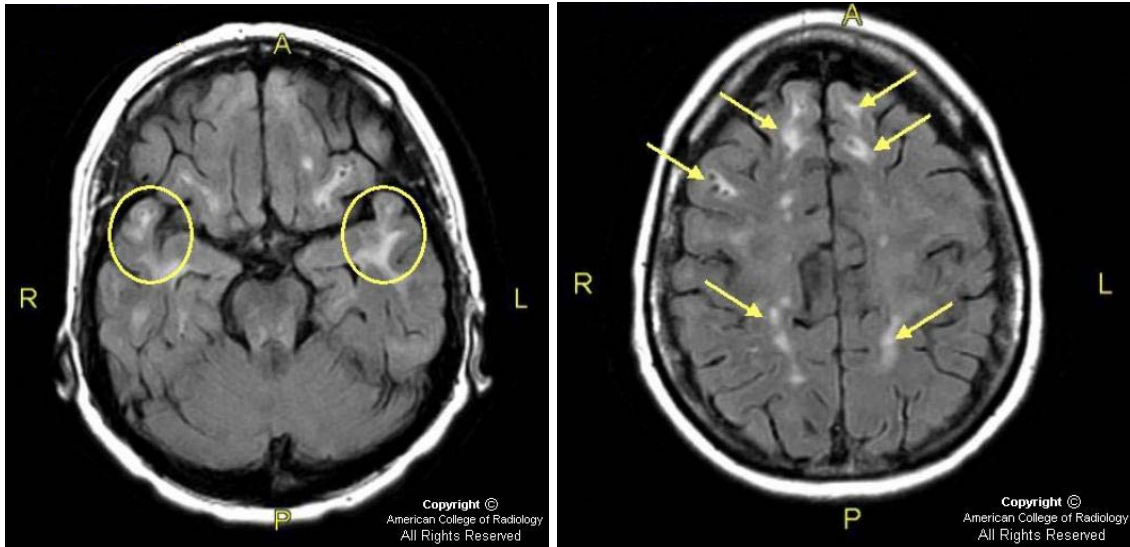




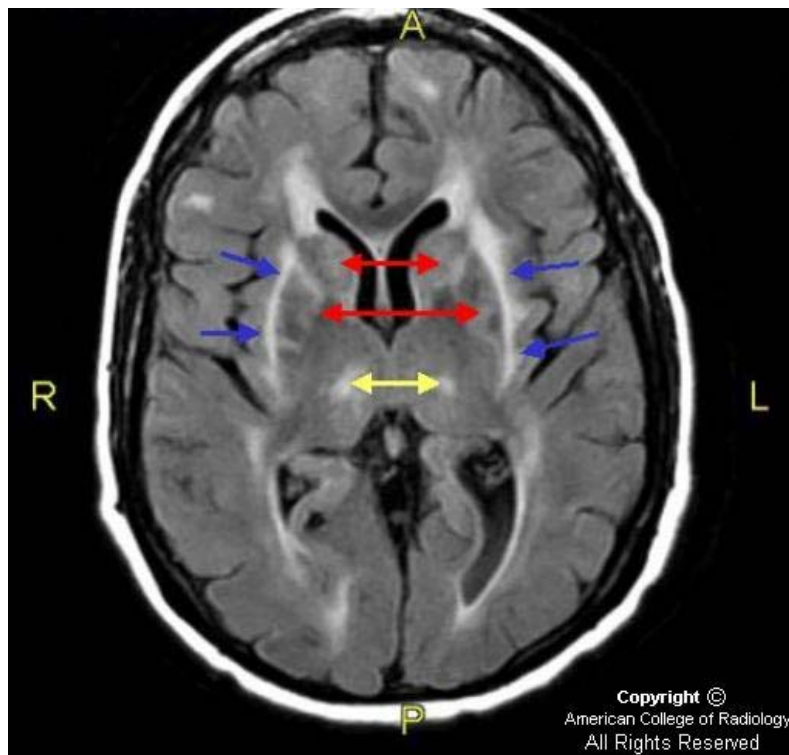
What is your differential diagnosis?

What is seen on the MRI?

The patient tells you that his uncle had similar episodes in his mid-40's, what is your diagnosis?



Multiple FLAIR images show marked abnormal T2 signal hyperintensity in the subcortical and deep white matter of the temporal and frontal lobes (circles and yellow arrows).



Signal hyperintensity involves the external capsules (blue arrows), basal ganglia (red arrows) and thalami (yellow arrow) bilaterally.

## Diagnosis

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)

### High Yield Facts

- the most common hereditary stroke disorder/cerebral angiopathy found in young and middle-aged adults.
- characterized by the **clinical tetrad of dementia**, psychiatric disturbances, migraine, and recurrent strokes.
- most frequent presentation is recurrent ischemic cerebrovascular episodes (transient ischemic attacks or cerebral infarctions)
- age at onset for stroke is 45-50 years
- a genetic disorder due to mutations in the *NOTCH3* gene
- characteristic bilateral subcortical lacunar infarcts are found most frequently in the frontal and temporal lobes, as well as the insula. Anterior temporal pole and external capsule lacunes have highest specificity and sensitivity.
- Aspirin is often used in an effort to prevent thrombotic occlusion of cerebral arteries

### Discussion

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a rare (1/100,000) hereditary, non-atheromatous vasculopathy found in young adults, but the most common form of hereditary cerebral angiopathy. As the name implies, it is dominantly inherited. Although CADASIL was first reported in European families, it has been observed in American, Middle Eastern, African, and Asiatic pedigrees

Patients suffer from a autosomal dominant mutation in the NOTCH3 gene, which codes for a large transmembrane receptor that is found in abnormally high concentrations on the surface of vascular smooth muscle cells. Pathologically this manifests as a non-arteriosclerotic amyloid-negative angiopathy primarily affecting perforating and meningeal arteries. Histologically, a characteristic granular osmiophilic material is found in the vascular basal membrane. This leads to two lesion types that have been described:

1. Degenerated and destroyed vascular smooth muscle cells leading to impaired vasodilation in response to hypercarbia
2. Fibrous thickening of the arteriolar wall leading to arteriolar narrowing and compromising basal cerebral blood flow

**Clinically**, CADASIL is characterized by the clinical tetrad of dementia, psychiatric disturbances, migraine, and recurrent strokes. Rarely, patients develop seizures and intracerebral hemorrhage. The classic profile is that of a young adult with recurrent TIAs and a history of migraine with aura. Ischemic strokes are the most frequent presentation of CADASIL with approximately 85% of symptomatic individuals developing transient ischemic attacks or stroke(s). The mean age of onset of ischemic episodes is approximately 46 years (range 30-70). A classic lacunar syndrome occurs in at least two-thirds of affected patients while hemispheric strokes are much less common. Notably, ischemic strokes typically occur in the absence of traditional cardiovascular risk factors. Recurrent silent strokes, with or without clinical strokes, often lead to cognitive decline and overt subcortical dementia. The disease progresses in a stepwise process. There is no gender predilection.

**Imaging findings** are most characteristic with MR. T2 and FLAIR images show diffuse white matter and lacunar subcortical hyperintensities. The frontal and temporal lobes as well as the insulae are most commonly involved. Anterior temporal poles and external capsule hyperintensities carry higher diagnostic accuracy for CADASIL. The presence of isolated T2 hyperintensities involving the temporal poles is a feature that can differentiate the condition from chronic microvascular ischemia due to hypertension. This finding is associated with a sensitivity and specificity of 95% and 80% respectively. The periventricular white matter and cortex are generally spared, but basal ganglia and brainstem can be involved. T1 images show both large coalescent white matter isointense lesions, as well as small well circumscribed subcortical hypointensities. Digital subtraction angiography is normal, and is done to exclude vasculitis and hypercoagulable states.

**Genetic testing** is commercially available to detect mutations in *NOTCH3*, with a small tube of blood.

**Treatment:** Aspirin and related medications are often used in an effort to prevent thrombotic occlusion of cerebral arteries. However, the benefit of antiplatelet agents for CADASIL has not been established. Moreover, because of the potential presence of microhemorrhages, using these drugs in patients with CADASIL may increase their risk of intracerebral hemorrhage.

The use of statins and Aricept has not proven any benefit in patients with CADASIL. Triptans are not routinely used in CADASIL-associated migraine due to a presumed potential to increase the risk of stroke. Medications for migraine prophylaxis are reasonable, although no study has clearly demonstrated their efficacy in CADASIL-related migraine.

**Rehab:** Physical and cognitive disability is progressive and may be quite severe. In patients with CADASIL, it is important to frequently assess their ability

in performing activities of daily living, ambulation, and self-care. A rehabilitation regimen should be prescribed when appropriate.

### **Case Compiled By:**

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