CADASIL: An Often Misdiagnosed Cause of Stroke, Dementia & Psychiatric Disturbance

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Introduction

CADASIL, or cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, is a small vessel disease that is often misdiagnosed or overlooked. It is characterized by recurrent subcortical ischemic events, cognitive impairment that is progressive, mood disturbances, and acute encephalopathy. In a patient that presents with weakness, cerebral small vessel diseases are important to include in the differential, and CADASIL is one of the most common monogenic causes.

Case Description

A 57 year-old female with past medical history of cerebrovascular accidents, anxiety, depression, and alcohol dependence presented with worsening lower extremity weakness. The patient reported inability to ambulate without assistance and a fall at home. Physical exam was notable for multiple areas of healing bruises on the forehead, forearms, and bilateral lower extremities. Patient appeared withdrawn, anxious, and often confused regarding her history. Muscle strength in her lower extremities was 3/5 bilaterally with metatarsus adductus of the left ankle. The patient had limited insight into her deficits and displayed pseudobulbar affect.

To diagnose this condition, genetic testing was conducted to assess for pathogenic variation in the NOTCH3 gene on chromosome 19 associated with CADASIL. This gene encodes for a cell surface receptor that is essential for arterial development. Variation in this gene can cause thickening of arterial walls and degeneration of vascular smooth muscle cells resulting in recurrent strokes, cognitive decline, dementia, and mood disturbances.

Case Continued: Imaging Findings Associated With CADASIL

- MRI of the brain with and without contrast demonstrated extensive confluent T2/FLAIR hyperintensity in the cerebral periventricular and subcortical white matter with symmetric involvement of the frontal, parietal and anterior temporal lobes. There was noted chronic lacunar infarction in bilateral thalami and pons and few scattered chronic micro-hemorrhages.
- CT scan of the head without contrast showed extensive chronic ischemic changes out of proportion to the patient's age. This constellation of physical exam manifestations and imaging findings favored to reflect CADASIL.

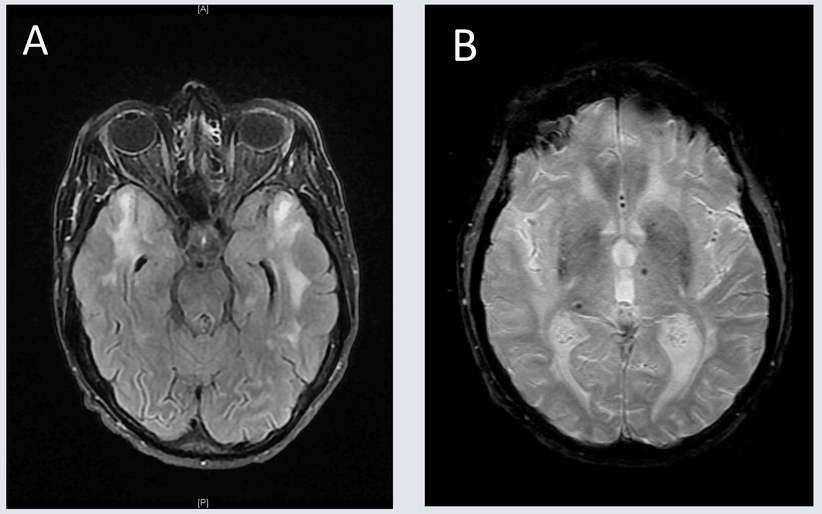

Fig 1. A. *Confluent T2/FLAIR hyperintense signal involving the periventricular and subcortical white matter, including bilateral anterior temporal lobes. There are chronic bilateral basal ganglia, thalamic and pontine lacunar infarcts.* ***B.*** *AX SWU- Severe chronic microvascular ischemic changes and mild generalized volume loss. Scattered, supratentorial micro-hemorrhages.*

Discussion

After waiting three months, genetic testing returned and the patient was found to have a heterozygous missense variation in the gene. Upon communication with the family, a half-sister was identified to have similar symptoms consistent with the autosomal dominant nature of inheritance for CADASIL. During the beginning of workup, there was consideration for multiple sclerosis or other demyelinating conditions. Steroids were initiated at one point until MRI prompted further evaluation for CADASIL. Considering this diagnosis early on for recurrent strokes, lower extremity weakness and muscle spasticity can aid in acceleration of needed genetic testing and limit exposure to unnecessary diagnostics, such as lumbar puncture.

Discussion Cont'd

Mainstay of therapy is symptomatic management as there is no definitive cure. Our patient benefited from antipsychotic medication and muscle relaxants for her mood and muscle spasms. She was also started on daily aspirin to lower the risk of heart attack or stroke and was safely transitioned to inpatient rehabilitation for further conditioning and support.

References

1. Di Donato, I., Bianchi, S., De Stefano, N. *et al.* Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) as a model of small vessel disease: update on clinical, diagnostic, and management aspects. *BMC Med* 15, 41 (2017).