CLINICAL VIGNETTE

A Young Man with CADASIL Syndrome

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Case Report

The patient is a 53-year-old male with long history of migraine since his 20's. He developed acute right sided weakness and dysarthria during his routine morning run. Brain MRI confirmed acute left corona radiata stroke measuring 1.7x0.5cm in size. There was also mild generalized volume loss, moderate white matter T2 hyperintensities, bilateral frontal and temporal subcortical white matter changes. Echocardiogram was normal and he never smoked. There was no history of hypertension, hyperlipidemia, or diabetes.

He was started on aspirin, clopidogrel and atorvastatin. He was transferred to acute rehabilitation facility and a few days later, he got readmitted due to acute onset of SOB and chest pain. He was found to have right lower lobe pulmonary embolism which was felt to be provoked and was started on apixaban. Clopidogrel was discontinued.

The patient recalled seeing a neurologist for migraine about 25 years prior. After brain imaging he was told he likely has CADASIL (cerebral autosomal dominant arteriopathy with infarcts and leukoencephalopathy) syndrome. He has long standing migraine with aura but did not follow up with neurology. Three years ago, he had a severe migraine with right hemiparesis for 10 minutes. There were no changes in cognition, mood or seizures. Chronic meds are ibuprofen "migraine" and a homeopathic medication. He previously tried sumatriptan, which was not as effective as ibuprofen. There is no family history of CADASIL, stroke, migraine, or dementia. His brain MR a year prior to his stroke showed mild generalized volume loss and mild leukoaraiosis due to the combination of aging and chronic ischemic small vessel disease.

He underwent recent genetic testing which confirmed a pathogenic NOTCH3 c.268C>T heterogenous mutation.

Discussion

CADASIL is the most common hereditary stroke disorder that affects primarily small blood vessels in the white matter of the brain.[1] It is a rare autosomal dominant condition caused by mutation in the NOTCH3 gene located on chromosome 19.[2] The mutation was first recognized in 1993 through linkage analysis in two unrelated families.[3] Pathogenic variants in EGFR domains 1-6 appear to be fully penetrant and are associated with the classic CADASIL phenotype.[4] NOTCH3 is uniquely expressed in vascular smooth muscle cells and its mutation leads to angiopathy in small arteries especially in the brain.[5] Arterial involvement outside of brain is rare. Granular osmophilic material in the vascular basal lamina of involved arteries can be seen with electron microscopy.[6] Classic brain MR features include recent small subcortical infarcts, lacunes (of presumed vascular origin), and white matter hyperintensities.[7] Brain atrophy is another important feature which was seen in our patient prior to his stroke.

The estimated prevalence of individuals harboring NOTCH3 mutation is estimated around 0.8 to 5 per 100,000 individuals worldwide.[8] There is no sex predilection, though men tend to be slightly more severely affected than women. The clinical course can be variable and the age of symptom onset tends to be in the third or the fourth decade. Presenting symptoms include migraine with or without aura, recurrent TIA/stroke, seizure, cognitive decline, and possible psychiatric disorders. Migraine with aura occurs in nearly half of CADASIL patients and is often the initial manifestation.[9] The sequential development of migraine, followed by transient ischemic attacks, and ischemic strokes typically occur over decades. A large series of 411 patients reported mean age of death of 65 years in males and 71 years in females.[10] CADASIL patients have a higher rate of microhemorrhages and anticoagulation treatment should be considered with caution.[11] Our patient was started on apixaban for provoked pulmonary embolism with 6 months planned therapy.

CADASIL should be suspected if there is a positive family history for stroke or dementia. However, the diagnosis is not excluded by the apparent lack of family history. Recognition of this hereditary neurological entity is especially important when treating young patients without known risk factor present with subcortical ischemic stroke as with our patient. Identification of NOTCH3 mutation and subsequent genetic counseling of patients and family members are important. Our patient has 3 young children, and they will need mutation testing. Predictive genetic testing should follow published guidelines dealing with ethical, legal, and psychosocial issues. We do not recommend testing asymptomatic children. Adults at risk should be referred to a genetic counselor for pre- and post-test counseling. Certain pathogenic variants in NOTCH3 domains allow estimates of disease penetrance in siblings. The mutations involving 1 to 6 EGFR domains tend to cause a full penetrant disorder with classical CADASIL phenotype.

Unfortunately, there is no current effective treatment or preventive measures for this neurological disorder. Patients should take daily aspirin to lower risk of a heart attack or stroke. We also recommend risk reduction strategies for secondary stroke prevention including maximized management of hypertension, hyperlipidemia, and glycemic control, and smoking cessation. Migraine should be treated symptomatically. There are ongoing experimental approaches examining the role of antisense oligonucleotide (ASO) exon-skipping technology, immunotherapy with a monoclonal antibody targeting a domain of the NOTCH3 protein, vasoactive peptide therapy.[12,13] These treatments hope to transform the disease and offer new hope for CADASIL patients.

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