Just a Migraine? A Suspected Case of CADASIL

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♦ Learning Objectives

- Recognize the clinical features, diagnostic criteria, and management of CADASIL
  (**C**erebral **A**utosomal **D**ominant **A**rteriopathy with **S**ubcortical **I**nfarcts and **L**eukoencephalopathy)
- Explore biopsychosocial implications of diagnosis

♦ Case Description

HPI: A 37-year-old woman with history of prediabetes, tobacco use, anxiety and depression presented to urgent care with 3 weeks of worsening headaches.
• Headaches are left sided, throbbing, lasting from 20 minutes to 3 hours, and sometimes preceded by visual auras
• Also reported worsening memory
• Notably, six years earlier (2014), she had preeclampsia symptoms including severe headache during pregnancy.
• An MRI brain at that time demonstrated punctate areas of T2/FLAIR hyperintensity in the subcortical and periventricular white matter. Radiologic differential included demyelinating processes, infection such as Lyme disease, inflammatory processes such as vasculitis, or small vessel microangiopathic ischemic white matter disease.

FH:
Mother: Migraines
Father CADASIL (manifested as headaches and strokes in 40s, died at age 57)
Paternal grandmother: Strokes in her 50s

VS: Within normal limits
PE: Gen: well appearing, NAD, conversant.
HEENT: PERRL, no papilledema. No TMJ clicking or tenderness. Tympanic membrane normal. No sinus tenderness.
Neuro: AOx4, CN 2-12 exam intact, 5/5 motor strength of upper/lower extremity, sensory intact, negative Hoffman, negative palmar reflex, normal gait.

Plan: The patient was prescribed riboflavin 400 mg qd, NSAIDs PRN, recommended to keep a headache diary, and an MRI brain was ordered.

♦ Clinic Course

Result: Imaging revealed interval increase in number of FLAIR hyperintense foci in the periventricular and juxtacortical white matter, which radiology noted could be related to CADASIL.

March 2014 MRI Brain

July 2020 MRI Brain

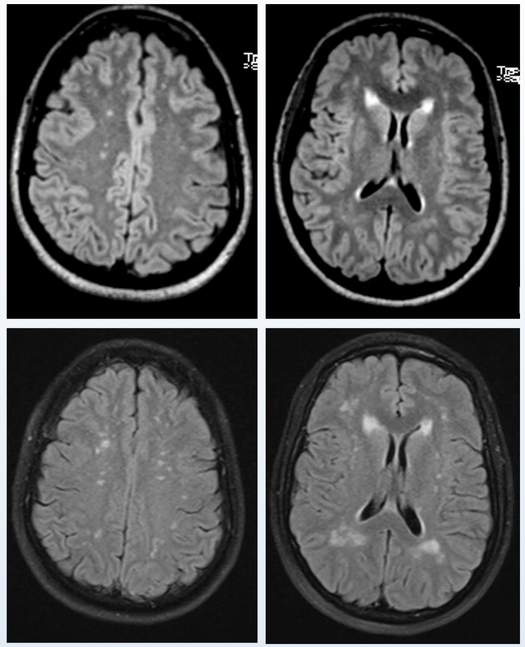

Image 1: Comparison of 2014 (top) and 2020 (bottom) brain MRIs, demonstrating progression of FLAIR hyperintense foci in subcortical and periventricular white matter

Plan continued:
- Referral to neurology with plans to obtain NOTCH3 genetic testing for CADASIL.
- Initiation of secondary stroke prevention including statin and aspirin medications, and counseling on smoking cessation (selected a quit date, downloaded smoking cessation app, prescribed NRT), reducing alcohol, increasing physical activity, and eating a healthy diet.
- Referral to psychotherapy, as well as close follow up with PMD

♦ Review of CADASIL

CADASIL is a rare autosomal dominant hereditary disease due to mutation of NOTCH3 gene leading to impairment of microvascular smooth muscle cells predominantly in the brain which causes recurrent migraines with auras, strokes, cognitive decline, and psychiatric disturbances.

Clinical features:
1 or more of the following:
• TIAs and strokes
• Migraine usually with aura
• Psychiatric disturbances/mood disorder
• Cognitive deficits
• Reversible acute encephalopathy

MRI brain findings:
• Radiologic features appear by age 35
• Subcortical lacunar lesions are typically in periventricular and subcortical white matter
• White matter T2 or FLAIR hyperintensities are usually seen in temporal lobe, external capsule or corpus callosum

Suspect CADASIL when see:
• Typical clinical signs (particularly migraines with auras or strokes)
PLUS
• Typical findings on brain MRI in the setting of family history of stroke or dementia

Diagnosis:
• Genetic testing positive for NOTCH3 gene mutation
OR
• Skin biopsy with characteristic granular osmiophilic material deposits within small blood vessels seen on electron microscopy
• No agreed upon clinical diagnostic criteria exist yet

Clinical Progression:
• Can be highly variable
• Often sequential starting with migraines with auras (age ~30s), TIAs and strokes (40-60 years), dementia (50-60 years), then abnormal gait (60s)

♦ Review of CADASIL continued

Management:
• No disease specific treatment yet available
• Secondary stroke prevention
  - Aspirin 81 mg
  - Reduction of vascular risk factors (optimizing management of HTN, DM, HLD, and smoking cessation)
• Symptomatic treatments of migraines and mood disorders
  - No evidence to avoid triptans due to vasoconstrictive effects (controversial)
• Neurology follow up
• Genetic counseling for patient and family members

♦ Case Review

- Presentation of headaches, family history of CADASIL, and MRI white matter hyperintensities and subcortical lacunar lesions increase suspicion of CADASIL in our patient.
- Genetic testing for NOTCH3 mutation or skin biopsies are necessary for definitive diagnosis. She has an upcoming genetic testing appointment in October 2020.
- The patient's headaches concerning for preeclampsia during pregnancy may have been the initial disease manifestation. There are case reports of pregnant women who presented with symptoms of stroke, migraine, or preeclampsia, and were later found to have CADASIL.
- This patient now has 3 young children. In the event she is diagnosed with CADASIL, her children should be advised to obtain genetic counseling with the option for testing when they become adults.

♦ Learning Points/Conclusions

- Include CADASIL on differential diagnosis in patients that present with migraines or strokes.
- CADASIL is a rare hereditary diagnosis without a definitive cure.
- Management involves early secondary stroke prevention, as well as management of symptoms (migraines, mood disorders, stroke).
- Given there is currently no disease specific treatment available and this is a challenging diagnosis to receive, it is imperative to consider the implications of the diagnosis of CADASIL and to incorporate the biopsychosocial model for comprehensive care.