CADASIL: A familial stroke syndrome which plagues the young

Danielle Carcia DO, Keona Cross MD, Cresandra Corbin MD

Capital Health Family Medicine Residency at Capital Health Medical Center- Hopewell

Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited vasculopathy which predisposes one to strokes and other neurological impairments.

CADASIL is the most common inherited cause of cerebral small vessel disease.

It is important to consider this rare disease because:

- It is often misdiagnosed as multiple sclerosis (MS).
- Genetic testing for NOTCH 3 is confirmatory
- An early clinical feature is migraine with or without aura
- It affects entire families

As family physicians, awareness of CADASIL and the privilege of caring for the entire family allows for earlier recognition and prevention of subsequent cerebrovascular events.

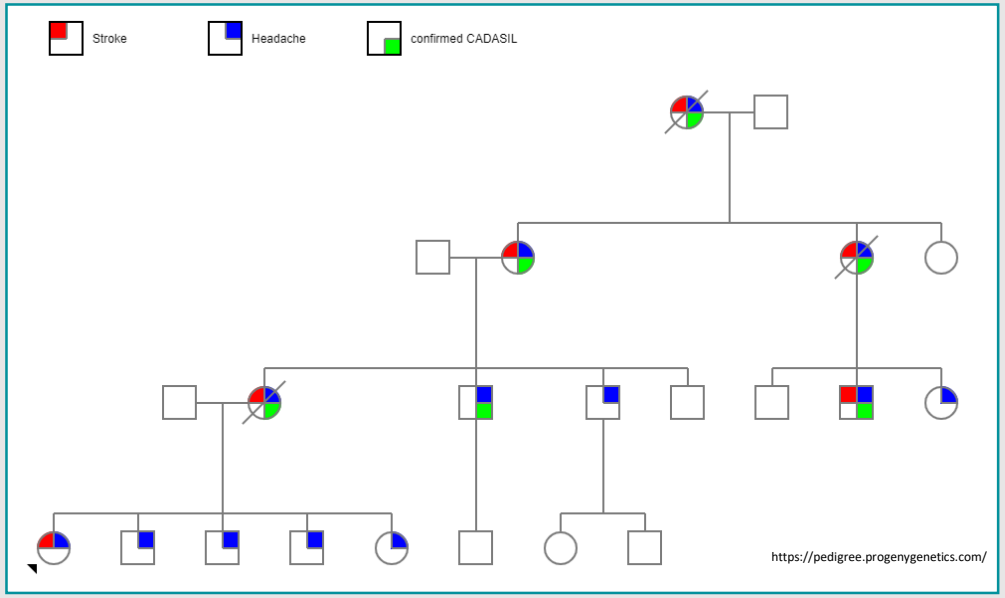
History of Present Illness

28-year-old female with a family history of MS presented to the family medicine office with concerns of worsening migraines and possible MS symptoms. Migraines were present for 5 years, however the frequency has increased to occurring 2 per week. She admits to an aura with vision changes and tinnitus prior to headache onset in addition to new onset paresthesia and infrequent nocturnal urinary incontinence.

Family History:

- MS in mother, maternal grandmother and maternal aunt.
- Cerebrovascular accident in mother, maternal grandmother and aunt
- Diabetes and hyperlipidemia in maternal grandmother.

Pedigree



Clinical Course

Initial labs including B12, ESR, CRP, TSH, CMP and CBC were ordered and normal

Subsequently, patient was admitted to an outside hospital for left hemiplegia of upper and lower extremity.

- **MRI Brain w/wo contrast showed 1. Multiple white matter lesions, the largest in the posterior right corona radiata measuring 16x13x15mm and demonstrating diffusion restriction. Multiple sclerosis with active plaque in the right corona radiata is favored, however clinical correlation is recommended.**

Upon discharge follow up, Neurologist suspected CADASIL and upon further questioning it became clear that CADASIL was previously diagnosed in multiple family members

NOTCH-3 gene sequencing is pending.

Discussion

CADASIL is due to a mutation in the NOTCH3 gene on chromosome 19 which causes the accumulation of extracellular material in vascular smooth muscle cells and impairs arterial contractility leading to artery stenosis and neurologic symptoms.

Natural history follows a predictable course including

Migraine +/- Aura → Cerebrovascular events → Dementia

Abnormalities on brain MRI are usually present by age 30 and mimic those seen in MS

- T2-white matter hyperintensities involving the external capsules and temporal lobe
- multiple lacunar infarcts.

While there is currently no disease-modifying treatment for CADASIL, preclinical trials are underway to develop a monoclonal antibody (MAB) which may provide future treatment options.

Early detection is crucial to help mitigate other risk factors such as diabetes, hyperlipidemia and hypertension in addition to genetic counselling for future family planning.

References

Ameer, M., Bhutta, B., Asghar, N., Haseeb, M. and Abbasi, R., 2021. Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy (CADASIL) Presenting as Migraine. *Cureus*,.

Bas Tersano A, Bedini G, Markus HS, et al. The role of clinical and neuroimaging features in the diagnosis of CADASIL. *J Neurol*. 2018;265(12):2934-2943. doi:10.1007/s00415-018-9072-8

Bersano, A., Kraemer, M., Burlina, A., Mancuso, M., Finsterer, J., Sacco, S., Salvarani, C., Caputi, L., Chabriat, H., Oberstein, S., Federico, A., Lasserve, E., Hunt, D., Dichgans, M., Arnold, M., Debette, S. and Markus, H., 2020. Heritable and non-heritable uncommon causes of stroke. *Journal of Neurology*, 268(8), pp.2780-2807.

Burkett, J. and Dougherty, C., 2017. Recognizing CADASIL: a Secondary Cause of Migraine with Aura. *Current Pain and Headache Reports*, 21(4).

Chabriat, H., Joutel, A., Tournier-Lasserve, E. and Bousser, M.G. (2020), CADASIL: yesterday, today, tomorrow. Eur J Neurol, 27: 1588-1595. https://doi.org/10.1111/ene.14293

Khan, A., Abedi, V., Li, J., Malik, M., Esch, M. and Zand, R., 2020. CADASIL vs. Multiple Sclerosis: Is It Misdiagnosis or Concomitant? A Case Series. *Frontiers in Neurology*, 11.

Lahkim, M., Laamrani, F., Andour, H., Gharbaoui, Y., Sanhaji, L., El-Fenni, J. and En-Nouali, H., 2021. Cadasil syndrome: A case report with a literature review. *Radiology Case Reports*, 16(11), pp.3540-3543.

Locatelli, M., Padovani, A. and Pezzini, A., 2020. Pathophysiological Mechanisms and Potential Therapeutic Targets in Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy (CADASIL). *Frontiers in Pharmacology*, 11.

Mizuno, T., Mizuta, I., Watanabe-Hosomi, A., Mukai, M. and Koizumi, T., 2020. Clinical and Genetic Aspects of CADASIL. *Frontiers in Aging Neuroscience*, 12.

Schoemaker, D. and Arboleda-Velasquez, J., 2021. Notch3 Signaling and Aggregation argets for the Treatment of CADASIL and Other NOTCH3-Associated Small-Vessel Diseases. *The American Journal of Pathology*, 191(11), pp.1856-1870.