CADASIL

CADASIL (Cerebral Autosomal Dominant Arteriopathy with Sub-cortical Infarcts and Leukoencephalopathy) is an inherited form of ischemic cerebrovascular disease that occurs when the thickening of blood vessel walls blocks the flow of blood to the brain.

see Vasculopathy.

Key concepts

- clinical: migraines, dementia, TIAs, neuropsychiatric disorders
- MRI: white matter abnormalities
- autosomal dominant inheritance
- anticoagulants controversial, generally discouraged

An acronym for Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy [1)].

A familial disease with onset in early adulthood (mean age at onset: 45 ± 11 yrs), mapped to chromosome 19. Clinical and neuroradiologic features are similar to those seen with multiple subcortical infarcts from HTN, except there is no evidence of HTN. The vasculopathy is distinct from that seen in lipohyalinosis, arteriosclerosis, and amyloid angiopathy, and causes thickening of the media (by eosinophilic, granular material) of leptomeningeal and perforating arteries measuring 100–400 mcm in diameter.

Clinical involvement

Recurrent subcortical infarcts (84%), progressive or stepwise dementia (31%), migraine with aura (22%), and depression (20%). All symptomatic and 18% of asymptomatic patients had prominent subcortical white matter and basal ganglia hyperintensities on T2WI MRI.

Treatment

Warfarin (Coumadin®) is used by some.

Retrospective cohort studies

NOTCH3 variants are the leading cause of hereditary cerebral small vessel disease (SVD). While monoallelic cysteine-involving missense variants in NOTCH3 are well-studied in cerebral autosomal

dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), patients with biallelic variants in NOTCH3 are sporadic and not well characterized.

Iruzubieta et al. present clinical and genetic data from 25 patients with biallelic NOTCH3 variants and conduct a literature review of another 25 cases (50 patients in total). Brain magnetic resonance imaging (MRI) was analyzed by expert neuroradiologists to better understand the phenotype associated with biallelic NOTCH3 variants.

The systematic analyses verified distinct genotype-phenotype correlations for the two types of biallelic variants in NOTCH3. Biallelic loss-of-function variants (26 patients) lead to a neurodevelopmental disorder characterized by spasticity, childhood-onset stroke, and periatrial white matter volume loss resembling periventricular leukomalacia. Conversely, patients with biallelic cysteine-involving missense variants (24 patients) fall within the CADASIL spectrum phenotype with early adulthood onset stroke, dementia, and deep white matter lesions without significant volume loss. White matter lesion volume is comparable between patients with biallelic cysteine-involving missense variants and individuals with CADASIL. Notably, monoallelic carriers of loss-of-function variants are predominantly asymptomatic, with only a few cases reporting nonspecific headaches.

They propose a NOTCH3-SVD classification depending on dosage and variant type. This study not only expands our knowledge of biallelic NOTCH3 variants but also provides valuable insight into the underlying mechanisms of the disease, contributing to a more comprehensive understanding of NOTCH3-related SVD [2].

[1]
Chabriat H, Vahedi K, Iba-Zizen MT, et al. Clinical Spectrum of CADASIL: A Study of Seven Families. Lancet. 1995; 346:934–939

[2]
Iruzubieta P, Alves CAPF, Al Shamsi AM, ElGhazali G, Zaki MS, Pinelli L, Lopergolo D, Cho BPH, Jolly AA, Al Futaisi A, Al-Amrani F, Galli J, Fazzi E, Vulin K, Barajas-Olmos F, Hengel H, Aljamal BM, Nasr V, Assarzadegan F, Ragno M, Trojano L, Ojeda NM, Çakar A, Bianchi S, Pescini F, Poggesi A, Al Tenalji A, Aziz M, Mohammad R, Chedrawi A, De Stefano N, Zifarelli G, Schöls L, Haack TB, Rebelo A, Zuchner S, Koc F, Griffiths LR, Orozco L, Helmes KG, Babaei M, Bauer P, Chan Jeong W, Karimiani EG, Schmidts M, Gleeson JG, Chung WK, Alkuraya FS, Shalbafan B, Markus HS, Houlden H, Maroofian R. Clinical and neuroradiological spectrum of biallelic variants in NOTCH3. EBioMedicine. 2024 Aug 26;107:105297. doi: 10.1016/j.ebiom.2024.105297. Epub ahead of print. PMID: 39191170.