Commentary

CADASIL is an acronym for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. It is caused by mutations in the NOTCH 3 gene on chromosome 19q12.[1] Although this is an autosomal dominant condition, occasionally this is caused by *de novo* mutations. The mutations occur in the epidermal growth factor (EGF) - like repeats encoded by exons in the NOTCH 3 gene. There is an accumulation of granular osmiophilic material in the basement membranes of small arteries and arterioles (100–400 μm) in the brain and other organs causing severe fibrotic thickening and stenosis. This leads to ischemia and demyelination of the affected brain and brainstem tissue.

CADASIL usually presents at a mean age of 45–50 years. The cardinal symptoms of CADASIL are usually recurrent ischemic strokes (70–85%), migraine (20–35%), psychiatric disturbances (20%), and progressive cognitive decline (50%).[2] Patients with CADASIL can develop strokes in the absence of vascular risk factors. Subcortical ischemia leads to cognitive deficits and dementia in the long-term. Dementia is frequently of the frontal lobe variety and can occur in the absence of previous strokes. Depression is more common with deep white matter changes. In a small percentage of patients, there is an acute encephalopathy with confusion, coma, and seizures.[3,4] Occasionally, the clinical course is mild, or atypical with intracerebral hemorrhage, seizures, or visual disturbances on presentation or patients may have only subtle cognitive deficits initially.[5] Some patients with CADASIL can present without a family history. Magnetic resonance imaging (MRI) is an invaluable tool in the diagnosis of CADASIL. Ischemia in the periventricular white matter (especially frontal and occipital caps), external capsule, basal ganglia and brainstem are seen on T2-weighted imaging (T2-WI) and fluid-attenuated and inversion recovery (FLAIR) images as diffuse hyperintensities in those areas.[6] There is also the preferential involvement of the anterior temporal lobes and external capsule by hyperintensities on FLAIR images and T2-WI, and this has a high specificity and sensitivity for CADASIL. Involvement of the anterior temporal poles by confluent hyperintensities has a higher specificity for CADASIL, and this point is emphasized well by Eswaradass *et al*. in their paper.[7] The superior frontal region white matter may also be involved by CADASIL preferentially in addition to the anterior temporal lobes and external capsule. While there can be a disparity between apparent disease progression and the MRI

picture, generally all patients with dementia and functional disability due to CADASIL tend to have severe disease on MRI.[6] As individuals with CADASIL age, the subcortical ischemic vascular lesions tend to become confluent. Lesion load tends to be low in the corpus callosum, caudate nucleus, midbrain and medulla.[8] Diffusion tensor imaging has been shown to be highly sensitive in demonstrating the progression of tissue damage.

Other disorders can mimic CADASIL and are the differential diagnosis. These are Binswanger's disease, which is characterized by multiple lacunar infarcts in patients with small vessel disease and vascular risk factors. Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes can occasionally present with subcortical white matter lesions. Central nervous system vasculitis can also present with cortical and subcortical infarcts. Cerebral autosomal recessive arteriopathy with subcortical infarcts and leucoencephalopathy (CARASIL) can mimic CADASIL. However, this is more commonly seen in the Japanese population. Occasionally, multiple sclerosis can have an imaging appearance similar to CADASIL with demyelination of the anterior temporal lobes and subcortical white matter. Metachromatic leukodystrophy can present with symmetrical confluent subcortical hyperintensities on T2-WI and FLAIR images and mimic CADASIL.

CADASIL should be considered in patients with migraine with or without aura, strokes, psychiatric disturbances or cognitive impairment with subcortical hyperintensities on T2-WI and FLAIR images especially if the anterior temporal lobes are involved. The above changes may occur in the absence of vascular risk factors. In the absence of a typical clinical presentation, involvement of the anterior temporal lobes with or without involvement of the external capsule by hyperintensities should raise the possibility of CADASIL and such patients can be tested further. A definitive diagnosis of CADSIL would require a positive skin biopsy and/or genetic testing. On the other hand, it should be borne in mind that involvement of the anterior temporal lobes with or without the involvement of the external capsule though highly characteristic of CADASIL can be absent occasionally.[8]

There is a need for large, prospective studies to further study clinical and MRI features and clinically correlate with mutations in the EGF-like repeats in the NOTCH 3 gene. This will improve clinical diagnosis of this multi-faceted disorder.

Monica S. Badve[1,2]

[1]Department of Neurology, Gold Coast University Hospital,
[2]School of Medicine, Griffith University, Southport, Queensland 4215, Australia

Address for correspondence:
Dr. Monica S Badve,
Gold Coast University Hospital, Level 5, A-Block, 1 Hospital Boulevard, Southport, Queensland 4215, Australia.
E-mail: monicabadve@gmail.com

References

1. Liu X, Zuo Y, Sun W, Zhang W, Lv H, Huang Y, *et al*. The genetic spectrum and the evaluation of CADASIL screening scale in Chinese patients with NOTCH3 mutations. J Neurol Sci 2015;354:63-9.
2. Chabriat H, Joutel A, Dichgans M, Tournier-Lasserve E, Bousser MG. Cadasil. Lancet Neurol 2009;8:643-53.
3. Fan Y, McGowan S, Rubeiz H, Wollmann R, Javed A, Mastrianni J. Acute encephalopathy as the initial manifestation of CADASIL. Neurol Clin Pract 2012;2:359-61.
4. Schon F, Martin RJ, Prevett M, Clough C, Enevoldson TP, Markus HS. CADASIL coma: An underdiagnosed acute encephalopathy. J Neurol Neurosurg Psychiatry 2003;74:249-52.
5. Pantoni L, Pescini F, Nannucci S, Sarti C, Bianchi S, Dotti MT, *et al*. Comparison of clinical, familial, and MRI features of CADASIL and NOTCH3-negative patients. Neurology 2010;74:57-63.
6. Chabriat H, Levy C, Taillia H, Iba-Zizen MT, Vahedi K, Joutel A, *et al*. Patterns of MRI lesions in CADASIL. Neurology 1998;51:452-7.
7. Eswaradass VP, Ramasamy B, Kalidoss R, Gnanashanmugham G. Anterior temporal lobe involvement: Useful MRI sign to diagnose CADASIL. J Neurosci Rural Pract 2015;6:622-23.
8. Singhal S, Rich P, Markus HS. The spatial distribution of MR imaging abnormalities in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy and their relationship to age and clinical features. AJNR Am J Neuroradiol 2005;26:2481-7.

Access this article online	
Quick Response Code:	Website: www.ruralneuropractice.com