# CADASIL: Rare case presenting primarily to a psychiatrist

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**Abstract**

CADASIL (Cerebral Autosomal Dominant Arteriopathy with Sub Cortical Infarcts and Leukoenchephalopathy) is a rare autosomal dominant disease characterized by recurrent transient ischemic attacks, strokes, migraine, cognitive deficit and psychiatric symptoms which is associated with mutations in the NOTCH 3 gene on chromosome 19. Here we report a case that presented primarily to psychiatry with behavioral changes, migraine, aphasia, epilepsy and family history of stroke. The diagnosis was confirmed by the findings of brain Magnetic Resonance Imaging that revealed characteristic white matter lesions.

**Keywords:** CADASIL, Psychiatry, Behavioural change, Notch 3 gene, Migraine.

**Introduction :**

CADASIL is an autosomal dominant arteriopathy associated with mutations in the Notch 3 gene on chromosome 19. Clinical manifestations include recurrent cerebral ischemic episodes, progressive cognitive deficit, migraine with aura, dementia and psychiatric symptoms.[1-12] The neurological symptoms often develop between the 3rd and 6th decades. Head magnetic resonance image (MRI) often discloses diffuse white matter lesions, small subcortical lacunar infarcts, and cerebral microhemorrhages.[1-3] The diagnosis of CADASIL is established by the detection of mutations in the NOTCH 3 gene. This report aimed to discuss neurological and radiological characteristics of CADASIL through evaluation of a patient diagnosed with this rare disease.

**Case report :**

A 38-year-old male patient was admitted to the psychiatric ward of MGM hospital, Aurangabad with increased irritability, inability to walk without support, difficulty in communication, which had increased since the past 2 months. 7 years back patient initially had complaints of half sided headache associated with nausea and vomiting which used to aggravate on loud noises and decrease after lying down in dark places. He used to have these headaches on an average 1-2 times in a month and each

episode used to last for a period of 3 days. Subsequent to that relatives complained that patient started having suspiciousness towards his wife and started verbally abusing her of having an extra-marital affair. During that time patient used to consume around 180ml of country liquor about 2-3 times in a week. Due to these reasons his wife divorced him. 8 months following that patient developed high-grade fever with weakness in right upper and lower limbs for which treatment was sought. However the details of treatment were not available. Patient had decreased functioning on the right side even after treatment. Gradually his social interactions decreased and he stopped working.

In 2013, the patient started having episodes of tightening of hands and toes, during which time he used to throw things at people and did not respond to commands. These episodes happened once a week, lasting for an average duration of 20 minutes. Gradually these episodes increased in intensity and started occuring 2-3 times in a day. No History of incontinence or tongue bite during these episodes were reported.

Family history revealed that his father died at the age of 45 years from ischemic cerebrovascular disease.

On examination, patient was conscious; speech was incomprehensible, deep tendon reflexes were exaggerated andspasticity was felt on checking the tone of the muscles. There was past pointing on finger nose test however heel shin test could not be done. Mood was reported to be depressed and affect was labile and inappropriate. No delusions or hallucinations could be elicited. Digit span test, registration and recall were impaired.

Head MRI showed widespread lesions in bilateral periventricular and subcortical white matters, external capsules, and the white matter of both temporal lobes. Lesions close to the temporal poles were more marked. The lesions were iso-hypodense in the pons on T1-weighted sections and hyper-intense on T2-weighted and FLAIR sections. The lesions did not have edematous changes and contrast involvement.

The results of routine hematological, biochemical, coagulopathy and vascularity studies were normal.

No abnormality was detected in electroencephalogram (EEG)

Mini Mental State Examination scores were 21/30, which signified mild cognitive impairment.

The diagnosis of CADASIL was based on the presence of family history of stroke, clinical and head MRI findings. However due to non-affordability of the patient Genetic testing could not be done.

**Discussion:**

CADASIL is a hereditary vasculopathy affecting the small arteries and arterioles of the brain and other tissues.[1] It was first described in 1977 in a case with hereditary multi-infarct dementia syndrome.

The onset of the disease is usually between the ages of 30 and 60 years.[8] Eighty-five per cent of the patients

experience recurrent strokes and transient ischemic attacks.[8] The first stroke usually occurs in the ages of 35-45 years[6] however in our patient this happened relatively at an earlier age of 30 years.

Recurrent strokes may result in motor disability, pseudobulbar palsy, and urinary incontinence.[2,8]

Cognitive changes may develop after 35 years of age, which is similar to our patient.[3] However, in 70-80% of the patients, marked cognitive deficit develops parallel to the increased burden of lesions at about 60 years of age and is followed by dementia.

Migraine attacks generally present a few years before the first vascular event,[2, 3] which is similar to our patient as his first symptom was migraine, which occurred 1-2 times in a month.

Patients with CADASIL may also show behavioral anomalies and psychiatric disorders.[7-10] Psychiatric symptoms vary from mild personality disorders to severe depression and mania, psychotic events and rarely schizophrenia, which usually occur after 40 years of age, however in our patient those were the initial complaints. [2, 14]

The onset of migraine and psychiatric symptoms is usually in the early phases of the disease and in some families, they are the dominant clinical findings. [6, 9]

Ten per cent of CADASIL patients suffer epileptic attacks, and in some, subclinical polyneuropathy has been reported.[9, 11] Similarly our patient also had symptoms suggestive of epilepsy.

Hyperintense areas are observed in the subcortical white matter of CADASIL patients on T2-weighted sections of cranial magnetic resonance images. On MRI Brain, involvement of the white matter of the anterior temporal lobe and external capsule are characteristic. Hyperintensities in the white matter of the anterior lobe have been reported to provide high sensitivity (90%) and specificity (100%) rates for the diagnosis of the disease.[15] Similarly, in our patient, involvement of the periventricular and subcortical white matter as well as the temporal poles and bilateral external capsule was observed.

The disease develops due to the mutations in the NOTCH 3 gene on chromosome 19. This gene codes a large transmembrane receptor that is expressed in the arterial smooth muscle cells and has a role in the arterial development.[4, 5] The patient could not bear the cost of this investigation so these findings could not be confirmed and the diagnosis was based on clinical findings.

Lesions observed on the MRI of CADASIL patients mimic lesions in sporadic arteriopathies, including Binswanger disease. However, in such conditions, deep perforating arteries are affected, while the external capsule, corpus callosum, and anterior temporal lobes are intact.[11]

The treatment of CADASIL is symptomatic. Literature presents no specific studies on the use of acetylacidic acid in CADASIL patients. Nevertheless, it has been recommended for the treatment of

CADASIL because it is a general anti-aggregant agent used in cerebrovascular disease prophylaxis.[8]

In conclusion, particularly in young adult patients with no vascular risk factors, mild clinical findings, but a familial history of stroke and characteristic lesions on MRI, CADASIL should be suspected, and mutations in NOTCH 3 gene should be investigated.

***References***


1. 1. Scheid R, Preul C, Lincke T, et al. Correlation of cognitive status, MRI and SPECT imaging in CADASIL patients. Eur J Neurol 2006;13:363-370.
2. Buffon F, Porcher R, Hernandez K, et al. Cognitive profile in CADASIL. J Neurol Neurosurg Psychiatry 2006;77:175- 180.
3. Liem MK, van der Grond J, Haan J, et al. Lacunar infarcts are the main correlate with cognitive dysfunction in CADASIL. Stroke 2007;38:923-928.
4. Coto E, Menedez M, Navarro R, et al. A new de novo Notch3 mutation causing CADASIL. Eur J Neurol 2006;13:628-31.
5. Gurumukhani JK, Ursekar M, Singhal BS. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL): a case report with review of the literature. Neurol India. 2004;52:99-101.
6. Tuominen S, Juvonen V, Amberla K, et al. Phenotype of a homozygous CADASIL patient in comparison to 9 agematched heterozygous patients with the same R133C Notch 3 mutation. Stroke. 2001;32:1767-74.
7. Tang SC, Lee MJ, Jeng JS, et al. Arg332Cys mutation of NOTCH3 gene in the first known Taiwanese family with CADASIL. J Neurol Sci. 2005;228:125-8.
8. Opherk C, Peters N, Herzog J, et al. Long term prognosis and causes of death in CADASIL: a retrospective study in 411 patients. Brain. 2004;127:2533-9.
9. Hassan A, Markus HS. Genetics and ischemic stroke. Brain 2000;123:1784-812.
10. Dichgans M. Genetics of ischemic stroke. Lancet Neurol 2007;6:149-61.
11. Bowler JV. Vascular cognitive impairment. J Neurol Neurosurg. Psychiatry 2005;76:35-44.
12. Caeiro L, Ferro JM. Cognitive profile in CADASIL patients. J Neurol Neurosurg. Psychiatry 2006;77:144-5.

13. Charlton RA, Morris RG, Nitkunan A, et al. The cognitive profiles of CADASIL and sporadic small vessel disease. Neurology 2006;66:1523-6.

14. Andre C. CADASIL Pathogenesis, Clinical and Radiological findings and treatment. Arq Neuropsiquiatr. 2010;68(2):287-299.

15. O'Sullivan M, Jarosz J, Martin RJ, et al. MRI hyperintensities of the temporal lobe and external capsule in patients with CADASIL. Neurology 2001;56:628-34.

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