Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)

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Abstract
Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is one of the most common heritable cerebral arteriopathy. Responsible for stroke and dementia in young adults and can be diagnosed by skin biopsy. We report a case of a 42 year old man with recurrent transient ischemic attacks (TIA). A detailed neurologic examination revealed poor score in MMSE (20/30) defect mainly seen in recall, repetitions. Executive dysfunction, memory and language impairment were also found. Motor system examination revealed grade 3 power in right upper and lower limb with more severe weakness of distal muscles in form of grip weakness and slippage of chappals. Neuroimaging and genetic analysis for Notch-3 confirmed the diagnosis. Imaging studies suggested greater involvement in the temporal and frontal lobes along with deep areas of the brain.

Introduction
Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is a hereditary early onset vascular disease causing recurrent ischemic subcortical infarcts featured by migraine with or without aura, cognitive impairment, psychiatric symptoms and progressively severe neurologic deficits.

The clinical manifestations include recurrent cerebral ischemic episodes, progressive cognitive deficit, and migraine mainly with aura, psychiatric symptoms and dementia.¹

Case Report
A 42-year-old, right-handed male presented with right sided hemiparesis and speech slurring. He had a similar episode 4 years back which recovered near-completely over a 10 month period. His wife noted that he had episodes of slurring of speech and sometimes transient weaknesses of right hand twice in the past 2 years. He also had sensitivity symptoms (paresthesia) and motor signs (faciobrachiofacial hemiparesis) to the left side two months prior to this stroke. The patient reported frequent episodes of migraine without any aura, frequency being more than four attacks per month. Clinical evolution progressed to cognitive impairment and worsening motor symptoms. Detailed physical and neurological examinations were done. The Mini-Mental State Examination (MMSE) revealed poor scores in recall, repetition, naming areas, total score being 20/30. However, an interview focusing on occupational aspects and activities of daily living (ADL), including the conducting and handling of personal finances, reported no significant functional problems, a finding corroborated by his wife. Electrocardiogram, laboratory investigations including glucose levels, lipid profile, and coagulation studies were normal. His serum vitamin B 12 was low (171pg/ml) and Homosysteine level was high (24.07umol/L). 2D echocardiography was normal.

The patient was submitted to MRI brain with MR angiography of neck vessels which revealed extensive areas of hypersignal in subcortical white matter, predominantly frontal, temporal and parietal, external and internal capsules, brain stem and presenting lacunar infarcts in the temporal and right parietal regions seen in T2 and FLAIR images (Figures 1, 2). Genetic analysis was carried out (DNA Laboratory INDIA located at Hyderabad) based on the direct DNA sequencing of exons 3 and 4 of the Notch 3 gene (chromosome 19), which revealed a heterozygous missense mutation c.397C > T (p.R 133C) at position 153 consistent with CADASIL diagnosis, confirming the etiology of the disease. We have called his siblings for clinicoradiological evaluation to look for any familial association.

Discussion
The term CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) refers to a hereditary systemic microangiopathy caused by mutations of the NOTCH3 gene located on chromosome 19.² It presents in young people with migraine attacks and recurrent ischemic strokes, leading to a progressive subcortical cognitive decline over several years.³

Though CADASIL is known for subcortical infarcts but intracortical involvement has been reported by Jouvent et al.⁴ Our patients presented with a clinical course and a radiological pattern similar to those described previously in the literature. The rarity of the case was the key factor to report it. There is delay in diagnosing because of low level of suspicion which is main cause for diagnostic errors. Multiple sclerosis was the most frequent misdiagnosis. Cognitive complaints in patients with advanced stages were common and the executive abilities were impaired in many cases as was in our case.

Several methods for diagnosing CADASIL have been proposed. The first Magnetic Resonance Imaging (MRI) characteristics of CADASIL were described in 1991.⁵ Notch 3 testing has been proposed as the primary

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diagnostic approach, allowing the detection of 90% of affected individuals. Despite concerted research efforts, the mechanisms underlying cognitive dysfunction in CADASIL remain unclear. However, evidence suggests disruption of corticosubcortical or corticocortical connections and lacunar infarcts. Gain of function for the mutant Notch3 protein is likely mechanism for the CADASIL mutations and could be related to Notch3 activation.

Our patient had decreased MMSE score indicating cognitive impairment. Several large studies have investigated the profile of cognitive decline in CADASIL. In the present case, changes were evident in global performance (MMSE) and in language, memory, apraxia and executive function domains.

In the language domain, both naming ability and semantic verbal fluency (animal’s category) were compromised. Deficit in verbal fluency is frequently observed in CADASIL showed by Buffon et al. Memory in patients with CADASIL compromise in register/learning (immediate memory) and free recall and preserved recognition. Ideomotor apraxia has been reported in 15% of individuals with lesions confined to the thalamic or lenticular region. Periventricular deep white matter may play a crucial role in the development of apraxias, particularly ideomotor. Buffon et al suggested executive dysfunction in almost 90% of individuals fewer than 50 years of age and the mechanisms may be related progressive damage to white matter augmented ventricular volume.

Conclusion

This case exhibited a characteristic neuroimaging pattern, of the disease and was further confirmed by Notch-3 gene analysis, the signature of CADASIL. The rarity of the case and its association with apraxias made it the focus of interest. The disease is probably underdiagnosed and should be considered in young patients with recurrent small subcortical infarcts leading to dementia, but also in the patients with migraine especially with aura, transient ischemic attacks, and mood disturbances, where MRI reveals typical abnormalities in the subcortical white matter and basal ganglia. Our patient had low vitamin B12 levels, whether this attributed to cognitive impairment is still under consideration. Early imaging of siblings can clinic the familial occurrence and may benefit other members of the family by cognitive rehabilitation.

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References


