Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited, nonatherosclerotic, arteriopathy caused by NOTCH3 gene mutations on chromosome 19p. The arteriopathy is associated with arterial wall thickening, granular osmophilic material (GOM) deposition, and smooth muscle cell (SMC) degeneration. The patients present clinically with episodes of migraine with aura, recurrent ischemic strokes, and cognitive and behavioral symptoms in the 3rd and 4th decade of life. Neuroimaging characteristically reveals bilateral, subcortical white matter involvement (especially involving the external capsule and temporal lobes) suggestive of extensive small vessel disease. Large vessel involvement in CADASIL is rarely evaluated and reveals predominant vessel stenosis and hypoplasia. We present the first case of CADASIL associated with fusiform aneurysms in both anterior and posterior intracranial circulation.

A 38-year-old gentleman presented with two episodes of sudden onset right hemiparesis in the past 3 years (the second episode on single antiplatelet) with good recovery along with progressively increasing cognitive impairment since the past 2 years. He had become forgetful for his things and recent events. However, remote memory was preserved. A few months later, he developed difficulty in speech. His speech became nonfluent, and he was unable to enunciate the word that he wanted to and would instead use similar sounding words repeatedly. He also forgot how he used to sign or write the alphabet. Occasionally, he would have difficulty buttoning his shirt and has switched to T-shirts for the same reason. For the last 6 months, he had become increasingly withdrawn and tried to communicate only when spoken to and stopped doing all previously pleasurable activities. He also would forget the way outside his house and had become slow in all activities of daily living. He was diagnosed to have hypertension 2 years back (well controlled) and was a reformed smoker (used to smoke 10–15 bidis/day for the past 10 years, till 1 year back). There was no history of headache, trauma, constitutional symptoms, or any addictions. Family history was negative for similar complaints.

On examination, all peripheral pulses were palpable, vitals were normal, and pseudobulbar affect was present. He had spasticity (right > left), power: 4+/5 on the Medical Research Council (MRC) scale, and bilateral extensor plantars with exaggerated reflexes in all limbs. Cognitive functions were impaired with the most pronounced impairment of frontal and temporal lobes on detailed assessment.

The patient was evaluated as a case of stroke in young. His routine investigations were normal. Thyroid profile, serum
homocysteine levels, erythrocyte sedimentation rate, and C-reactive protein were normal, and viral markers were negative. Magnetic resonance imaging (MRI) brain revealed multiple small vessel strokes (Figure 1A-D) and computed tomographic (CT) angiography showed multiple fusiform aneurysms in the bilateral distal cervical internal carotid artery and right V1 vertebral artery (Figure 2a, b, and c respectively). Luminal narrowing and irregularity were also seen in large vessels. Considering a systemic large vessel etiology, angiography of upper limbs, iliac, and renal vessels was done and found to be normal. Work up for hyperaldosteronism revealed normal renin and aldosterone levels. Extractable nuclear antigen (ENA) profile was negative, and ultrasound abdomen and pelvis (with renal doppler) was also within normal limits. Cardiac evaluation with 2D-echocardiography and Holter monitoring was normal. The cerebrospinal fluid examination was also within normal limits. In the absence of a clear cause for the findings, consideration of noninflammatory vascular etiology and genetic vasculopathy was made, and clinical exome sequencing was sent. This revealed a heterogenous c.4745T>C (p.Val1582Ala) mutation on the exon 26 of NOTCH3 gene confirming a diagnosis of CADASIL.

Our case demonstrates that despite CADASIL being a predominantly small vessel arteriopathy, patients might have large vessel abnormalities as well. Large vessel involvement in CADASIL was studied in 37 consecutive CADASIL patients by Zhang et al.\(^5\) in a cross-sectional study and documented in 28 cases (75.7%). Most had congenital abnormalities like fenestration, hypoplasia, or agenesis, and acquired abnormalities like stenosis or tortuosity were documented in 17 patients (45.9%). None of them had aneurysms as reported by us. They also found a correlation between small vessel disease (SVD) imaging markers like white matter hyperintensity patterns (especially when asymmetric) and ipsilateral large vessel involvement, thereby necessitating the latter’s evaluation.

Vertebral artery aneurysm along with cerebellar malformation in a CADASIL patient has been previously reported by Pescini et al.\(^6\). However, this case was asymptomatic and had aneurysms only in the vertebral artery, unlike our patient who had multiple strokes with cognitive impairment and aneurysmal involvement of both the anterior and posterior cerebral circulation. NOTCH3 gene encodes for a transmembrane receptor on the vascular smooth muscle cells (SMCs), and its mutations could be responsible for these vascular abnormalities.\(^7\) These mutations could induce a conformational change of the receptor, thereby blocking effective signal transduction and preventing apoptosis of vessel SMCs.\(^8\) The notch3 receptor is also involved in the Notch signaling pathway, which is involved in vascular development.\(^9\) Alagille syndrome is another (apart from CADASIL) autosomal dominant genetic disorder with multisystemic vascular abnormalities (including intracranial aneurysms) caused by dysregulation of the aforementioned Notch pathway.\(^10\) We could therefore infer that the vascular anomalies in our patient were causational rather than a chance association of the pathology.

Large artery evaluation should always be carried out in CADASIL patients despite its small vessel disease predominant phenotype not only because studies have shown an association between large artery involvement and SVD-related imaging parameters but also to diagnose these commonly missed findings (like aneurysms) to better understand the disease and its pathophysiology (since ours was a single case and more cases need to be evaluated).

**Learning points**

1. CADASIL is an autosomal dominantly inherited, nonatherosclerotic, arteriopathy caused by NOTCH3 gene mutations on chromosome 19p
2. In view of our case and previous reports of the presence of large artery abnormalities in CADASIL, vascular evaluation of large extra and intracranial arteries should be carried out in CADASIL patients that may yield useful information.

**Declaration of patient consent**
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**
There are no conflicts of interest.

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**Letters to the Editor**

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**Figure 2:** CT angiogram showing fusiform aneurysms in bilateral ICA (a and b) and right V1 vertebral artery (c)
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Address for correspondence: Prof. Achal K. Srivastava, Room No 60, Cardioneurosciences Centre, All India Institute of Medical Sciences, New Delhi, India.
E-mail: achalsrivastava@hotmail.com

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