CARASIL; The Backache, Baldness, Brain Attack Syndrome: The Indian Scenario

Sir,

Cerebral autosomal-recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) is a rare single-gene disorder also known as Nemoto disease or Maeda syndrome.\[1\] It is transmitted through autosomal recessive mode and caused by a homozygous or compound heterozygous single-gene mutation in the \textit{HTRA1} (high-temperature requirement serine peptidase A1) gene on the long arm of chromosome 10 (10q26).\[2,3\] The exact prevalence of CARASIL is unknown especially in India and till date, approximately 50 patients have been reported, mostly from Japan. The cardinal clinical features of CARASIL are recurrent lacunar strokes or stepwise deterioration of motor ability, cognitive dysfunction, alopecia (premature baldness), and lumbago.\[3\] Herein, we report a genetically proven case of CARASIL in a young man with classical, clinical, and neuroimaging findings along with all other cases reported from India.

A 23-year-old male patient presented with a history of low backache and difficulty in walking for the past 5 years. He also had difficulty in speaking for the last 2 years. His cognitive abilities started deteriorating over the last 1 year and he needed assistance for daily life activities. He did not have hypertension or diabetes. He was the third child born out of non-consanguineous marriage. The other two siblings did not have any neurological complaints. His vital parameters were normal. General examination revealed alopecia [Figure 1]. Neurological examination revealed cognitive impairment in all domains including memory, language, and executive functions. He had spastic dysarthria, pseudobulbar affect, and quadriplegia. Deep tendon reflexes were pathologically brisk with bilateral extensor plantar responses. He also had release reflexes in the form of palmomental reflex and frontal grasp. Other systems examinations were normal. Magnetic resonance imaging (MRI) of the brain showed bilateral symmetrical periventricular white matter hyperintensities on fluid-attenuated inversion recovery (FLAIR) image with relative sparing of the subcortical U-fibers and gliosis in pons [Figure 2a and b]. MRI spine T2 FLAIR sagittal images showed multilevel disc herniation’s in the lumbosacral and cervical regions [Figure 2c]. Extensive workup for young stroke etiology yielded negative results. These included fasting blood sugar, lipid profile, serum homocysteine, ANA, APLA, immunoline, HIV, S.VDRL, EKG, Echo heart, and Holter monitoring. Genetic testing (next-generation sequencing, MEDGENOME) showed a pathogenic homozygous missense variation in exon 4 of the \textit{HTRA1} gene that resulted in the amino acid substitution of glutamine for arginine at codon 274, confirming the diagnosis of CARASIL.

A literature search showed 6 cases of CARASIL from India. In 2012, Diwan et al. from Pune, reported the first case of CARASIL in a 46-year-old man but it was not genetically proven.\[4\] Another case of CARASIL, in a 27-year-old man from rural Karnataka, south India, was reported by Devaraddi et al. but it was also not genetically proven.\[5\] Kumar et al. had described 3 CARASIL families carrying novel null \textit{HTRA1} mutations again from Karnataka and all their cases were genetically confirmed.\[6\] Nearly six out of seven cases of CARASIL reported were from Karnataka, south India. The majority\[6,7\] were males and their age ranged from

![Figure 1: Depiction of a pattern of baldness in CARASIL](attachment:image1)

![Figure 2: (a) Axial FLAIR sections at the supraventricular level showing diffuse deep white matter hyperintensities with sparing of subcortical “U” fibres. Multiple small lacunar infarcts seen dispersed in the white matter. (b) Coronal T2 weighted image showing periventricular white matter hyperintensities and lacunar infarcts in the pons. (c) Sagittal T2 WI showing C6–7 disc protrusion with cord compression and multilevel disc bulges along the lumbar spine](attachment:image2)
Letters to the Editor

23–46 years. All had classical clinical features of alopecia, lumbago, and neuropsychiatric manifestations, especially stroke. Consanguinity was absent in three cases. Five cases were genetically confirmed while two had been diagnosed on clinical grounds. One patient had postural tremor along with other classical features. Two patients had seizures and one died of status epilepticus. MRI brain also showed microbleeds along with characteristic changes in two cases. All the characteristics of the reported cases are summarized in Table 1.

CARASIL is the second known genetic form of the non-hypertensive, cerebral small-vessel disease, first being CADASIL, which is autosomal dominant. CARASAL, another autosomal dominant vasculopathy is characterized by ischemic or hemorrhagic strokes, therapy-resistant hypertension, and mid-frequency hearing loss. These inherited ischemic vasculopathies which can have similar clinical and imaging findings are summarized in Table 2.

The cardinal clinical features of CARASIL are leukoencephalopathy, lumbago, and alopecia.[7] Recurrent ischemic strokes or stepwise deterioration in neurological functions, premature baldness, and backache secondary to spondylosis deformans/disk herniation are needed to make a clinical diagnosis of CARASIL. Clinical manifestations usually develop in the third to a fourth decade while premature baldness develops in the second decade.[1] Although CARASIL was first described in 1976 by Maeda et al.[1] from Japan, the first case in India was recognized in 2012.[4] The first genetically confirmed case was reported in 2017 and was followed by more reports. This may be due to increased awareness of the disease manifestations, recognition of the characteristic neuroimaging features, and availability of the genetic tests especially next-generation sequencing (NGS) at affordable prices. Interestingly six out of seven case reports of CARASIL are from Karnataka, south India. Whether this regional clustering of cases in Karnataka is due to a reporting bias or due to a founder gene effect or is a mere chance occurrence is yet unknown. Identification and genetic confirmation of more and more cases in future will lead to a better understanding of the disease prevalence, regional clustering, and clinical manifestations.

Table 1: Details of Indian cases of CARASIL from literature

| Study | Age/Sex/Consanguinity | General | Neurological | MRI | Genetics |
|-------|-----------------------|---------|--------------|-----|----------|
| Diwan et al., 2012 (Pune) | 46/Male/Consanguineous | Alopecia | Recurrent strokes, cognitive decline | Classical features present | Not done |
| Preethish Kumar et al. 2017 (Karnataka) | 26/Male/Consanguineous | Alopecia | Progressive altered gait for 14 months, memory impairment, emotional lability, slurred speech, and bladder and bowel incontinence for 6 months. Spastic dysthria with the ataxic component, spasticity of lower limbs (LL), Babinski sign, and broad-based rigido-spatistic gait. | Classical features present | HTRA1—homozygous mutation c. 739delG (p.E247Rfs) |
| | 24/M/Non-consanguineous | Alopecia | Personality and behavioral changes, inappropriate laughter mutism, appendicular rigidity and postural tremors. | Classical features present | HTRA1—homozygous mutation c. 830_831delAG (p.E277Vfs) |
| | 24/M/Non-consanguineous | Alopecia | Personality and behavioral changes of 3 years duration. Spasticity of lower limbs for 2 years, memory impairment, executive function deficits, and mutism for 6 months. | Classical features present | HTRA1—homozygous mutation c. 830_831delAG (p.E277Vfs) |
| | 33/F/Consanguineous parentage | Alopecia | Migraine like headaches, multiple episodes of TIA/Stroke, dysarthria cognitive decline | Diffuse leukoaraiosis with distinct sparing of the U fibers, extensive microbleeds in supratentorial and infratentorial regions | HTRA1—homozygous mutation c. 502A.T (p.K168ter) |
| Devarradi et al. 2018 (Karnataka) | 27 years/M/Consanguineous | Alopecia | Stroke | Classical features present | Not done |
| Present study 2019 (Karnataka) | 23 years/M/Non consanguineous | Alopecia | Spastic Dysarthria | Classical features present | HTRA1(+) - homozygous mutation c. 821G>A (p-Arg274Gln) |
Table 2: Inherited vascular leukoencephalopathies

| Inheritance | Arteriopathy | Clinical Manifestations | Gene and Chromosome |
|-------------|--------------|-------------------------|---------------------|
| CADASIL     | Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy | Leukoencephalopathy, migraine headaches with aura (30-40% of individuals), mid-adult (the 30s-60s) onset of cerebrovascular disease, mood disturbance, apathy, cognitive disturbance progressing to dementia | Mutations of the Notch 3 gene on chromosome 19 |
| CARASIL     | Cerebral Autosomal Recessive Arteriopathy with Subcortical infarcts and Leukoencephalopathy | Leukoencephalopathy, Alopecia, Lumbago | Mutations in the HTRA1 gene, the long arm of chromosome 10 (10q26) |
| CARASAL     | Cathepsin A-related Arteriopathy with Strokes and Leukoencephalopathy (Autosomal dominant) | Ischemic and Hemorrhagic strokes, Therapy resistant hypertension, Brainstem symptoms, mid-frequency hearing loss | CTSA gene mutations, chromosome 20q13.12 |

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.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

Sagar Badachi, Saji K. John, Mithun Sekhar, Thomas Mathew
Department of Neurology, St. John’s Medical College Hospital, Sarjapura Road, Bengaluru, Karnataka, India

Address for correspondence: Dr. Thomas Mathew, Department of Neurology, St. John’s Medical College Hospital, Sarjapura Road, Bengaluru - 560 034, Karnataka, India. E-mail: chakkuthom@hotmail.com

References
1. Maeda S, Nakayama H, Isaka K, Aihara Y, Nemoto S. Familial unusual encephalopathy ofBinswanger’s type without hypertension. Folia Psychi atr Neurol Jpn 1976;30:165-77.
2. Nozaki H, Nishizawa M, Onodera O. Features of cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy. Stroke 2014;45:3447-53.
3. Hara K, Shiga A, Fukutake T, Nozaki H, Miyashita A, Yokoseki A, et al. Association of HTRA1 mutations and familial ischemic cerebral small-vessel disease. N Engl J Med 2009;360:1729-39.
4. Diwan AG, Bhosle DG, Vikram A, Biniwale A, Chaudhary S, Patodiya B. CARASIL. JAPI 2012;60:59-60.
5. Devaraddi N, Jayalakshmi G, Mutalik NR. CARASIL, a rare genetic cause of stroke in the young. Neurology 2017;89:2392-4.
6. Prereethish-Kumar V, Nozaki H, Tiwari S, Vengalil S, Bhat M, Prasad C, et al. CARASIL families from India with 3 novel null mutations in the HTRA1 gene. Neurology 2017;89:2392-4.
7. Fukutake T. Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL): From discovery to gene identification. J Stroke Cerebrovasc Dis 2011;20:85-93.

Submitted: 17-Jan-2020 Revised: 27-Jan-2020 Accepted: 30-Jan-2020 Published: 29-Jun-2020

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

DOI: 10.4103/aian.AIAN_31_20