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CASE REPORTS

Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL): A rare cause of ischemic stroke in young

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Abstract

Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) is the second known genetic form of cerebral small vessel disease after cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). It is a very rare single gene disorder affecting cerebral small blood vessels. Diagnosis of CARASIL should strongly be suspected in a young non-hypertensive patient with lacunar stroke in the basal ganglia and brainstem and alopecia limited to scalp.

Keywords: CARASIL, Lacunar stroke, Scalp alopecia, lumbosacral spondylosis, *HTRA1* gene

INTRODUCTION

Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) is a very rare single-gene disorder affecting the cerebral small blood vessels. It is the second known genetic form of cerebral small vessel disease after cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).[1] Possibly the first case of genetically unproven of CARASIL was reported by Namato in 1960.[2] In 2009, Hara *et al*. applied linkage analysis and fine mapping in five consanguineous families with CARASIL and identified homozygous mutations in the *HTRA1* gene on chromosome 10q25.[3] The exact prevalence of the disease is unknown. Most of the reported cases of CARASIL were from Asian countries.[1,4,5] The age of onset of encephalopathy is earlier (mean age 32 years) than in CADASIL (mean age 45 years).[1] Recently Khandelwal *et al*.[5] reported a patient with CARASIL and reviewed the five patients published from India, of whom two did not have genetic studies. We report yet another case of CARASIL.

CASE REPORT

A male aged 31 years, born out of third-degree consanguineous marriage, presented with unsteadiness of gait and stiffness of lower limbs of three months duration. He had slurred speech for few days at the onset of the symptoms. There was no other relevant neurological history and also no family history of similar illness. He also complained of low backache. He was managed as a case of ischemic stroke at another facility based on the magnetic resonance imaging (MRI) findings. No further workup was done for possible mechanism of stroke. He made a significant improvement. Examination at our facility revealed normal pulse rate and blood pressure. He had alopecia over the scalp (Figure 1). He was conscious and the mini mental status examination (MMSE) score was 30/30. There were no language deficits and speech was normal. Ocular and cranial nerve examination was normal. There was mild spasticity in the lower limbs with motor weakness of pyramidal distribution. Deep tendon reflexes were bilaterally brisk in the lower limbs with bilateral extensor plantar response. Gait was spastic. There were no sensory and cerebellar

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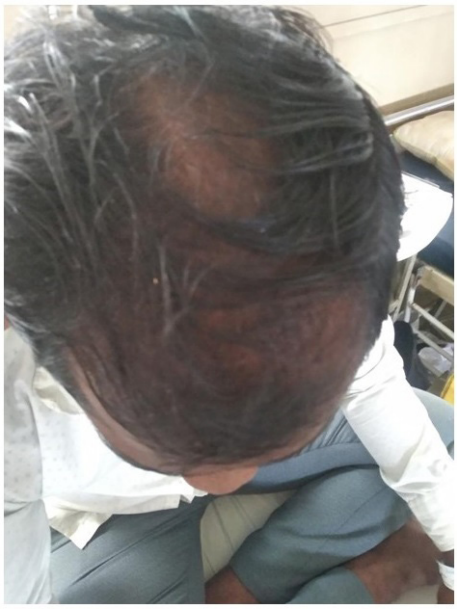

Figure 1. Scalp of the patient showing alopecia

deficits. Bladder and bowel functions were normal.

Magnetic resonance imaging of brain: T2 & FLAIR images showed multiple foci of hypointensity in the white matter of bilateral frontal and parietal lobes; characteristic anterior temporal white matter hyperintensity was also noted. Nearly symmetrical hyperintensity in bilateral basal ganglia was seen. Chronic lacunar infarct and poorly defined foci of hyperintensities were seen in the pons (Figure 2). Workup for possible etiology of young stroke was negative. X-Ray of the lumbosacral spine showed mild spondylosis changes. We considered the diagnostic possibility of CARASIL as the patient was young, non-hypertensive, had alopecia of scalp, and lumbosacral spondylosis. Genetic testing revealed that he had a homozygous pathogenic nonsense variant c.904C>T (p.Arg302Ter) in exon 4 of the *HTRA1* gene [ENST00000368984.8; chr10: 122506817C>T (GRCh38)] (Figure 3). The patient was counselled regarding the course of the disease and was advised appropriate physiotherapy. He was prescribed ecosprin 150 mg per day and vitamin supplements. At the last follow-up he had more difficulty in walking due to increased spasticity.

DISCUSSION

The most common feature of CARASIL is recurrent lacunar strokes mainly in the basal ganglia or brainstem. Cognitive deficit is the second most frequent symptom. The non-neurological features are alopecia and attacks of severe low back pain.[1] MRI shows spondylosis deformans and/or disk degeneration in the cervical and/or thoracolumbar spine. Alopecia frequently

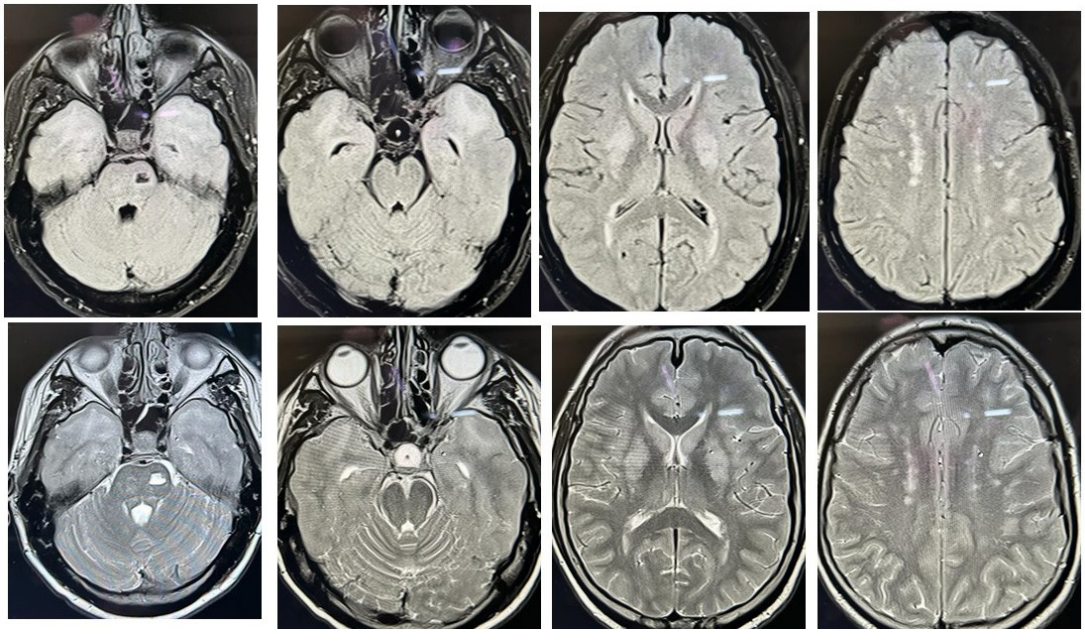

Figure 2. MRI: T2 & FLAIR images show multiple foci of hypointensity in the white matter of bilateral frontal and parietal lobes. Characteristic anterior temporal white matter hyperintensity is also noted. Nearly symmetrical hyperintensity in bilateral basal ganglia is seen. Chronic lacunar infarct and poorly defined foci of hyperintensities are seen in the pons.

Gene (transcript)	Location	Variant	Zygosity	Classification	Diagnosis
HTRA1 (ENST00000368984.8)	Exon 4	c.904C>T (p.Arg302Ter)	Homozygous	Pathogenic	CARASIL syndrome (OMIM#600142)

Figure 3. The results of the sequencing of the proband showing the homozygous 'pathogenic' variant c.904C>T (p.Arg302Ter) in the *HTRA1* gene.

occurs as early as adolescence and hair loss is confined to the head. In this patient alopecia was confined to head and he had mild low back pain.

In young non-hypertensive patients with alopecia limited to scalp and lacunar stroke and no other risk factors, the diagnostic possibility of CARASIL should strongly be suspected. Magnetic resonance imaging shows high-signal intensity lesions in the white matter and multiple lacunar infarctions in the basal ganglia and thalamus as seen in our patient.[1] These patients should have genetic testing.

Whole exome sequencing of the proband revealed a homozygous nonsense variant c.904C>T (p.Arg302Ter) in exon 4 of the *HTRA1* gene (ENST00000368984.8). This is a known, previously reported mutation [ClinVar Variation ID: 7488; Accession: VCV000007488.9; https://www.ncbi.nlm.nih.gov/clinvar/variation/7488/]. This loss-of-function variant is classified as a 'pathogenic' variant as per the variant classification guidelines of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP; criteria PVS1 + PP5 + PM2). Homozygous pathogenic variants in the *HTRA1* gene (OMIM * 602194) are known to cause CARASIL syndrome (OMIM #600142), a neurodegenerative disorder with an autosomal recessive pattern of inheritance. Hence, based on the mutation report, and the clinical and neuroimaging phenotype, the patient was diagnosed to have CARASIL syndrome. CARASIL is caused by dysregulation of transforming growth factor – beta (TGF-β) signalling, which results from loss-of-function mutations in the *HTRA1* gene. HTRA1 belongs to the HTRA (high temperature requirement) family of serine proteases. It contains several domains including a serine protease domain, a C-terminal PDZ domain, an insulin-like growth factor-binding protein domain, and an N-terminal Kazal-type serine protease inhibitor motif. HTRA1 acts as a chaperone as well as a serine protease.[8] One of its main roles is to repress TGF-β signalling and biallelic pathogenic variants in the *HTRA1* gene lead to loss of its protease activity and consequently to loss of repression of TGF-β signalling. This in turn leads to increased expression of TGF-β in the tunica media of small arteries, resulting in small vessel arteriopathy especially in the brain.[3] At present there is no effective treatment for this condition and is mostly symptomatic and physical therapy.

DISCLOSURE

Ethics: Informed consent obtained from the patient.

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Conflict of interest: None

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