

A rare case of cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy presenting as a progressive leukoencephalopathy and dysgraphia

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Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) is an autosomal recessive cerebral small vessel disease caused by mutations in the *HTRA1* gene on chromosome 10q26. This gene encodes a serine protease that represents transforming growth factor beta (TGF- β) signaling. Pathogenic variants lead to loss of function, resulting in increased TGF- β activity and concurrent arteriopathy.^[1] Clinical features include diffuse alopecia, spondylosis, mid to lower back pain, gait disturbance, cognitive impairment, and recurrent subcortical infarcts. On brain magnetic resonance imaging (MRI), T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences typically show confluent white matter hyperintensities and lacunar infarcts.^[2-4] The disease is often misdiagnosed as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), multiple sclerosis, or other leukodystrophies. Fewer than 50 genetically confirmed cases have been reported worldwide, with a majority from Japan. Herein, we presented a case of genetically confirmed CARASIL in a consanguineous Pakistani family.

A 22-year-old male, born to consanguineous parents (Figure 1), was seen in the neurology outpatient department with a one-year history of progressive frontal and bitemporal headaches,

dry eyes, blurred vision, and behavioral changes, including aggression, childlike behavior, and stubbornness. The patient also reported inability to write despite preserved drawing ability and poor sleep hygiene. Medical history included varicocele; however, there was no history of drug or food allergies. The family history was significant for fatal brain hemorrhage in the paternal uncle and grandfather, stroke in the maternal grandmother (related through paternal lineage), psychiatric issues in the maternal aunt, and death of an elder sister during pregnancy due to intracranial hemorrhage. Other siblings were asymptomatic. On examination, frontal balding was noted. The patient was alert and oriented. Fundoscopy was unremarkable. The patient was unable to write but could draw. Cranial nerve examination was normal. Motor examination revealed normal muscle tone, with muscle strength of 5/5 (Medical Research Council scale) in all extremities. Deep tendon reflexes were 2+ and symmetric, and plantar responses were flexor bilaterally. Contrast-enhanced brain MRI showed confluent bilateral frontoparietal, temporal, and occipital hyperintensities on T2-weighted and FLAIR sequences, consistent with diffuse leukoencephalopathy (Figure 2a, b, Figure 3). Electroencephalography was normal. Previous workup at a different center showed normal antinuclear antibody, extractable nuclear

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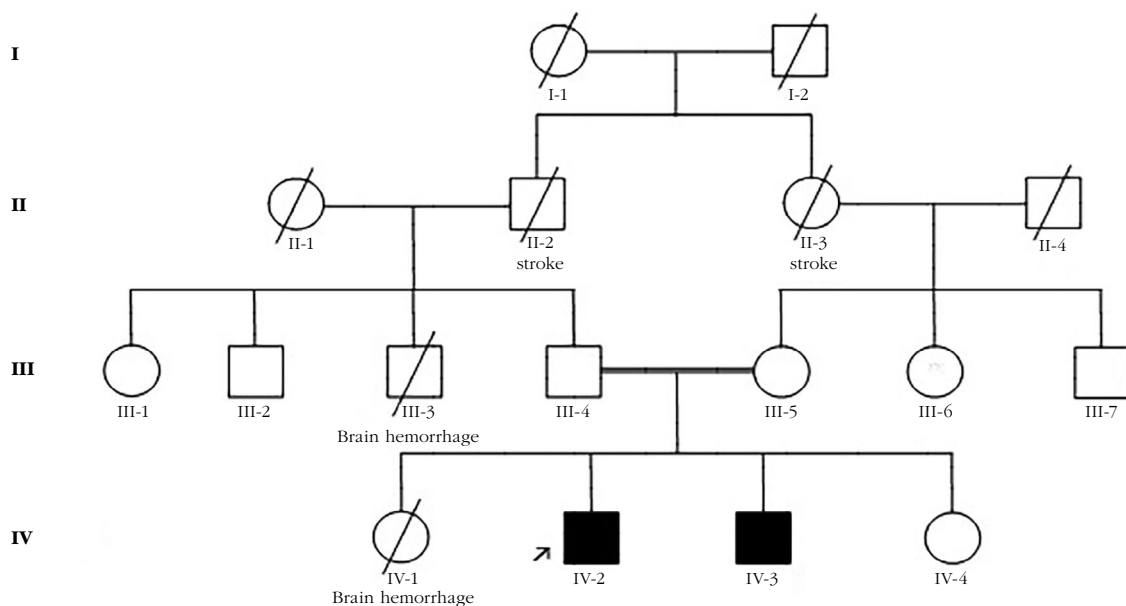


Figure 1. Pedigree of the family of the patient with CARASIL disease (IV-2). The elder sister (IV-1) died of brain hemorrhage at 24 years of age. One of the paternal uncles (III-3) died of brain hemorrhage. Paternal grand uncle and maternal grand aunt died of stroke. Squares represent males while circles represent females. Filled squares represent the affected males.

CARASIL, cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy.

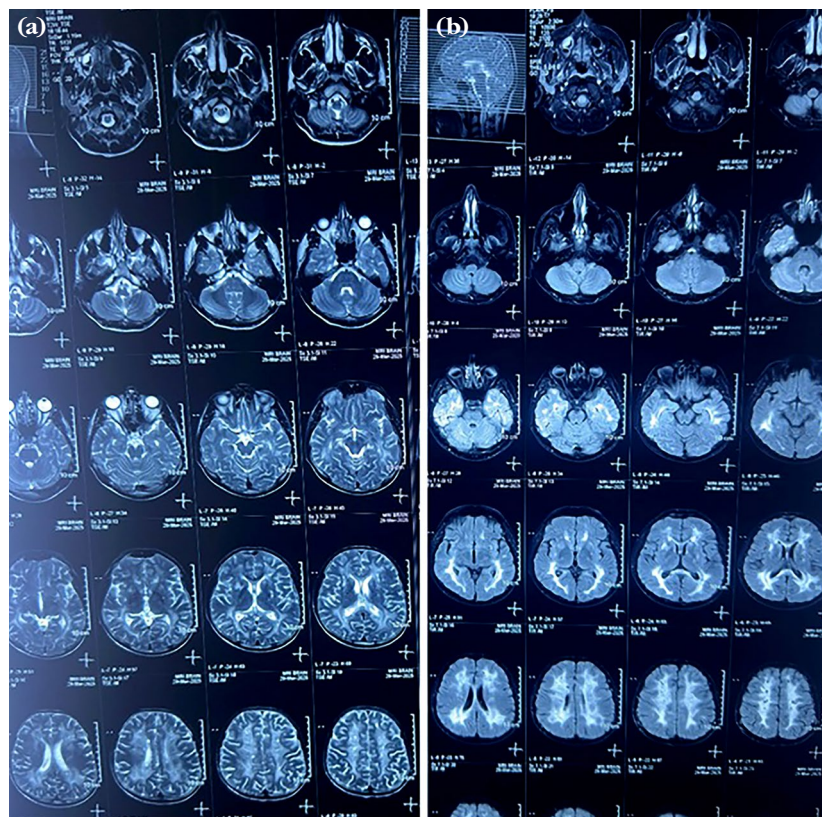


Figure 2. (a) Axial T2-weighted sequences demonstrating diffuse white matter hyperintensities involving the periventricular and deep white matter. (b) Axial FLAIR sequences demonstrating extensive white matter hyperintensities with preserved U-fibers.

FLAIR, fluid attenuated inversion recovery.

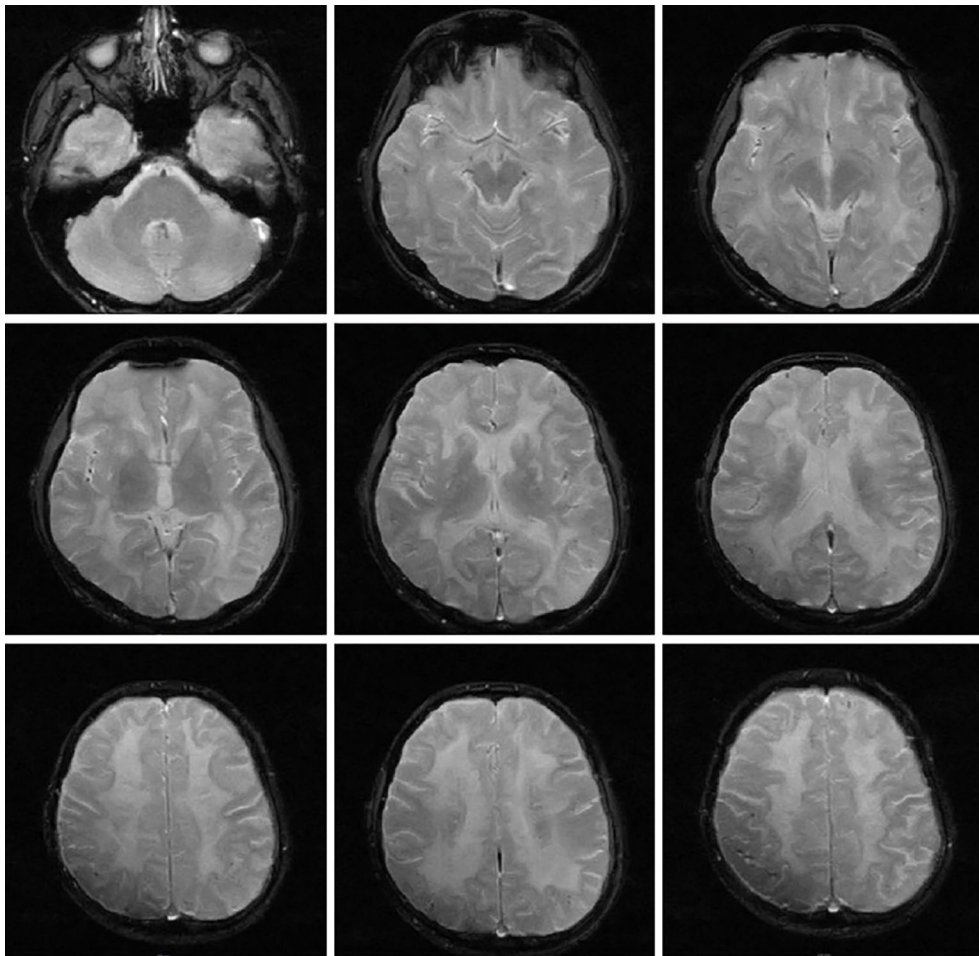


Figure 3. Susceptibility-weighted imaging demonstrates no microbleeds.

antigen, anti-Sjögren, anti-Scl, anti-Mi, and anti-Jo antibodies. Screening for hepatitis B and C were negative. A written informed consent was obtained from the patient. Approval was sought and provided by our Institutional Review Board and Ethical Committee for publication of this case report (IRB # 473-25).

Whole exome sequencing performed by BGI Genomics, China, identified a novel homozygous pathogenic deletion of C nucleotide in *HTRA1* gene at cDNA position 660 (NC_000010.11:g.124249025del, NM_002775.5:c.660del, p.His220Glnfs*3). Minor allele frequency in South Asians has not been reported for this variant in online genome databases. This deletion likely resulted in a frameshift and a downstream premature stop after incorporation of three false amino acids in the peptide (His220Glnfs*3). This variant was considered pathogenic as per American College of Medical Genetics criteria

(PVS1+PM2_supporting+PM3_supporting). Pathogenic variations in this gene are a known cause of CARASIL.^[3,5] The patient was treated with oral acetylsalicylic acid 75 mg daily, atorvastatin 10 mg daily, folic acid 5 mg daily, memantine 10 mg daily.

Family segregation analysis of this variant in the brother (Figure 1, IV-3), who was initially considered asymptomatic as frontal baldness was the only symptom, and sister (Figure 1, IV-4) revealed that the sister was a heterozygous carrier of this variant. However, the brother was found to carry homozygous pathogenic variant (Figure 4). Therefore, the brother was reevaluated with brain MRI. The report concluded bilateral hyperintense white matter signal abnormalities on T2/FLAIR sequences involving the centrum semiovale and the parietal periventricular white matter, with several lacunar infarcts. Given the clinical history and imaging features, findings were considered

Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy typically presents before age 30 with gait disturbance and alopecia, followed by cognitive decline and stroke.^[8] Our patient's presentation with behavioral and cognitive symptoms was consistent, although spondylosis was absent. Brain MRI findings were similar to CADASIL, but brainstem involvement (e.g., the arc sign) may help differentiate.^[9] Genetic testing is essential for confirmation. Further family screening of the identified variant is essential to identify presymptomatic individuals. Management is supportive, focusing on symptom relief and risk factor modification. Genetic counseling is critical, particularly in consanguineous families.^[10] This case adds to the limited reports of CARASIL in South Asia and underscores the need for increased awareness and genetic testing in regions with high consanguinity. To our knowledge, this is the first genetically confirmed case reported from Pakistan, carrying a novel pathogenic variant in *HTRA1*.

The first genetically confirmed case in India was reported in 2017, and more have since been identified, with a significant number originating from the state of Karnataka. The Indian cases resembled the Japanese phenotype, but there were variations in severity and onset, possibly due to genetic heterogeneity.^[11] A case report described Iran's first documented case of CARASIL in 2024, initially misdiagnosed as multiple sclerosis, highlighting the importance of distinguishing hereditary small vessel disease from demyelinating disorders.^[12] One case report of patient with CARASIL, an Arabic woman from Bahrain in 2023, emphasized the need to consider hereditary small vessel diseases in young patients with recurrent strokes and systemic features such as alopecia and back pain.^[13] In Turkish patients, Rüstemoğlu et al.^[14] reported two different *HTRA1* variants, including one nonsense and one missense variant. In another study, clinical and genetic features of a rare case of typical CARASIL from Türkiye were documented, and genetic testing established the diagnosis after years of follow-up with uncertain diagnoses.^[15]

In conclusion, early genetic testing in CARASIL and related phenotypes may help in diagnosis and management of patients. Genetic counselling, prenatal testing, and carrier screening of the identified variant may help reduce the incidence of such cases in future.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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