Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS): Case Report of a Novel Nonsense Mutation in the *SACS* Gene

Sir,

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is an autosomal recessive neurodegenerative disorder characterized by a triad of early onset cerebellar ataxia, spasticity, and sensorimotor polyneuropathy (distal muscle wasting with finger and foot deformities).[1] Dysarthria, nystagmus, and retinal hypermyelination may sometimes be observed.[1] It was first described by Bouchard *et al*. in1978 as an uncommon cause of autosomal recessive cerebellar ataxia.[2,3] Although initially thought to be prevalent only in Canada, it has now been increasingly reported from rest of the world.[4] Exome sequencing studies identified multiple causative mutations in the sacsin molecular chaperone gene (*SACS*) on chromosome 13q.[5] However, new pathogenic mutations continue to be identified. We report a patient with typical clinical and imaging features of ARSACS, where targeted *SACS* gene testing lead to the discovery of a novel pathogenic *SACS* mutation.

A 28-years-old male, born of non-consanguineous marriage, presented with progressive gait ataxia and recurrent falls from 3 years of age. He also developed dysarthria and lower limb stiffness at 10 years of age, followed by thinning of feet. Family history was negative. On examination, he had bilateral pes cavus with hammer toes. Neurological examination revealed lower limb spasticity, brisk reflexes, and extensor plantar response. Sensory and fundus examination were normal. He also exhibited dysmetria, dysdiachokinesia, nystagmus, and cerebellar gait. He had no Kayser-Fleischer ring, telengiectasias, or tendon xanthomas. Systemic examination was normal. Diagnosis of an autosomal recessive ataxia syndrome was made and patient evaluated along those lines.

MRI brain revealed superior cerebellar vermian atrophy and T2 linear "striped" hypointensities in pons [Figure 1a and b]. Nerve conduction studies (NCS) demonstrated prolonged distal latencies with decreased velocities in motor nerves of all limbs while sensory NCS was not recordable. ARSACS and Refsum's disease are the ataxia syndromes associated with predominant demyelinating neuropathy. Genetic testing for Friedreich's ataxia and Spinocerebellar ataxia was negative. 2D-Echocardiography, serum albumin, lipid profile, and alpha fetoprotein were normal. Clinical exome (targeted *SACS* gene) sequencing revealed a heterozygous pathogenic non-sense mutation on exon 10 of *SACS* gene (C,4232T > G) resulting in a stop codon and premature truncation of the protein. Another mutation of uncertain significance was found on the same exon (C,8132C > T).

ARSACS is an early onset, cerebellar ataxia first described from Quebec, Canada in 1978. Canadian patients formed a majority of these cases initially, but an increasing number have been described from other countries as well, possibly pointing toward an earlier underdiagnosis.[6] Many of these cases were initially diagnosed as spastic diplegia type of cerebral palsy.[2] Approximately 30 mutations in the *SACS* gene have been reported and newer ones are being continuously discovered.[7]

It usually presents in early childhood (12 months to 5.5 years of age)[3] and diagnosis is based on typical clinical manifestations (cerebellar ataxia with spasticity and peripheral neuropathy) and radiological findings (superior vermian atrophy and pontine linear T2/FLAIR hypo-intensities on T2/FLAIR). Confirmation of diagnosis is done by demonstration of pathogenic mutations in the sacsin gene located on chromosome 13q.[5]

The cardinal clinical features of ARSACS are gait instability with frequent falls, both of which were present in our patient. The disease progression is slow with patients becoming wheelchair bound around the third to fourth decade of life.[3]

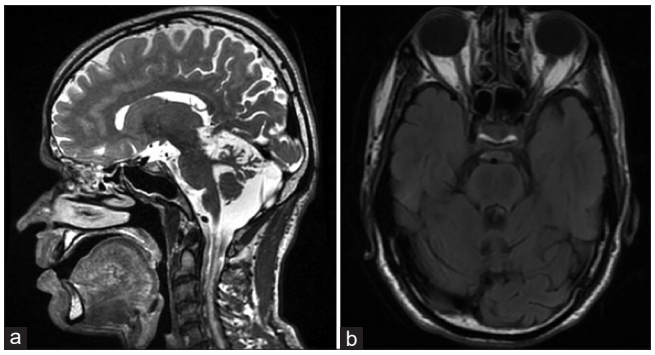

Figure 1: MRI brain T2 weighted image revealing superior cerebellar vermian atrophy (a) and linear "striped" hypointensities in pons (b)

The initial features are a combination of early onset cerebellar signs like ataxia, dysarthria, and nystagmus, with pyramidal signs in the lower limbs like spasticity, hyperreflexia and extensor plantar response. Lower limb sensorimotor peripheral neuropathy tends to develop later in the disease course causing distal atrophy, pes cavus, and hammer toes.[8] These findings were present in our patient.

Fundoscopy may reveal hypermyelinated nerve fibres radiating from the optic disc in some patients[8] and cognition tends to be preserved. Both fundoscopy and cognition was normal in our patient.

Imaging findings described on MRI brain include early and progressive superior cerebellar vermian atrophy with the inferior vermis remaining preserved throughout.[9] However, global cerebral atrophy may occur later in the disease course. Linear T2 and FLAIR hypo-intensities have also been described.[1] Cerebral white matter remains preserved throughout. All these findings were present in our patient.

The causal mutations in the *SACS* gene vary between individuals. The founder mutations discovered from Quebec were a single-base deletion at position 6594 (6594delT) and a nonsense mutation 5254C > T.[10] Approximately 95% Canadian patients harbor these mutations.[5] Several novel mutations have been described with some variations in the disease phenotype. The absence of abnormal myelinated retinal fibres in our patient is probably explained by the same.

ARSACS must be suspected in early onset cerebellar ataxia combined with spasticity and peripheral neuropathy. Typical radiological features such as superior cerebellar vermian atrophy and linear pontine hypo-intensities greatly enhance the diagnosis. Ultimately, the diagnosis is confirmed by genetic studies. We describe such a case from India, and also demonstrate the occurrence of a novel pathogenic nonsense mutation in the *SACS* gene.

Ethical compliance statement

The study complied with all Ethical standards and did not require the consent of the Institutional Ethics Committee.

Written informed patient consent was taken.

All authors have read and complied with the journal's ethical publication guidelines.

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Conflicts of interest

There are no conflicts of interest.

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Appendix 1:

Name	Location	Contribution	Role
Ayush Agarwal	Department of Neurology, Dr RML Institute of Medical Sciences, Lucknow	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content	Author
Divyani Garg	Department of Neurology, Lady Hardinge Medical College, New Delhi	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content	Author
Akash Kharat	Department of Neurology, Dr RML Institute of Medical Sciences, Lucknow	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content	Author
Abdul Qavi	Department of Neurology, Dr RML Institute of Medical Sciences, Lucknow	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content	Author