Early-Onset Spastic Ataxia Due to a Novel Mutation of the SACS Gene – A Case Report from North India with a Review of Indian Literature

Dear Sir,

21-year-old male (Bachelor of Arts student) born out of full-term normal delivery of non-consanguineous parentage, with normal developmental milestones in all four domains, presented to the neurology outpatient (OPD) for the evaluation of a gait abnormality that had been noticed by his relatives since the age of 6 years. It was insidious in onset and gradually progressive, starting simultaneously in both lower limbs. While walking, he used to cross over to either side, which was associated with stiffness, and he used to drag both feet while walking. After 4 years of these symptoms, he also developed swaying to either side while walking without any aggravating or relieving factors, but there were no falls while walking initially. After about 10 years, the patient also developed intermittent tripping in both feet while walking. It was not associated with any sensory symptoms. His difficulty was gradually progressive, such that since last 1 year, the patient has noticed that he is unable to run and has frequent falls while running, though he is still able to walk independently. There was no history of any change in the voice or cranial nerve involvement. He had no tremors when reaching out for objects and had no symptoms referring to bowel or bladder functions. There was no history suggestive of any cognitive decline or behavioral abnormalities. Family history was negative for neurologic disease, diabetes mellitus, or sudden cardiac death.

On general examination, he had pes cavus, hammer toes, a Swan neck deformity, and a Z deformity of the fingers [Figure 1]. There were no telangiectasias or tendon xanthomas. His higher mental functions were normal. The fundus examination was normal. He had normal visual acuity in both eyes. He had gaze-evoked nystagmus, saccadic pursuits, and hypermetric saccades. A power examination showed weakness of the shoulder abductors, elbow and wrist extensors, hip and knee flexors, and ankle dorsiflexors. There was spasticity in both upper and lower limbs. Sensory examination showed impaired joint position sense, vibration, and fine touch up to both ankle joints. Deep tendon reflexes were exaggerated with an absent ankle reflex, and the planters were bilaterally extensor. Cerebellar examination showed impaired finger-to-finger nose, and heel-shin tests. His tandem gait was impaired.

The differential diagnoses considered were Friedrich's ataxia, Autosomal Recessive Spastic Ataxia of Charlevoix Saguenay (ARSACS), complicated hereditary spastic paraplegia, cerebrotendinuous xanthomatosis, Refsum's disease, Spinocerebellar ataxias, and X-linked adrenomyeloneuropathy.

A detailed biochemical workup for ataxia and neuropathy was negative**.** In the nerve conduction study (NCS), demyelinating motor polyneuropathy was present while sensory nerves were not recordable.

Demyelinating neuropathy helped narrow down the differentials to ARSACS, CTX, and Refusum's disease. The very slow progression and distal limb deformities were favoring the possibility of ARSACS.

Magnetic resonance imaging (MRI) of the brain showed significant superior vermian atrophy, linear hypointensities in the pons on T2/FLAIR sequences (striped pons), called the tigroid pattern of the pons, along with thinning of the thoracic spinal cord, all pointing towards the diagnosis of ARSAC [Figure 2].

Clinical exome sequencing was performed, which showed a heterozygous frame shift variant c. 6114_6117dupAGAA in Exon 10 of the SACS gene that results in the amino acid substitution p.Ala2040fs*10. Another heterozygous frame shift variant, c. 2215_2216dupAA, that results in the amino acid substitution p.Asn739fs*13, was also detected in the same exon. Whole-family genetic studies are more helpful with negative family histories, but due to financial constraints, we could not perform the genetic testing of parents and siblings.

ARSACS is a rare early-onset neurodegenerative disease with a distinctive phenotype characterized by cerebellar ataxia, spasticity, polyneuropathy, nystagmus, and retinal changes.[1] ARSACS typically starts at the age of 1–2 years and results in a bed-bound stage at the age of 40 (range 17–58) years, with death usually around 50 (range 21–72) years.[2]

ARSACS is due to deletions or point mutations in a large, single-exon gene encoding sacsin (*SACS* gene). Sacsin contains a heat shock domain, which suggests that it serves a chaperone function. The *SACS* gene is located on chromosome 13q12.12 and encodes the large protein sacsin.[1,3]

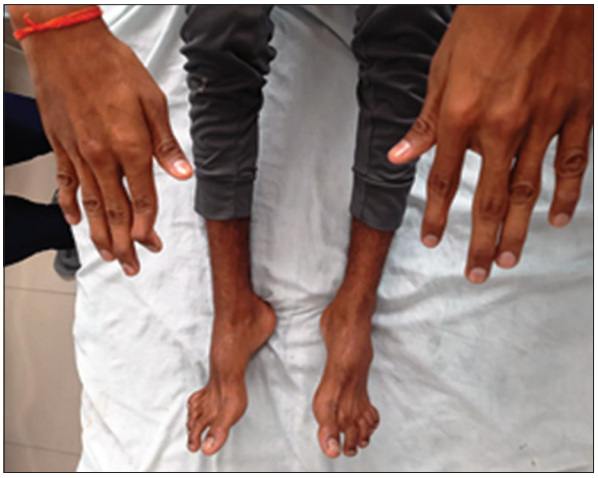

Figure 1: Pes cavus, hammer toes, swan neck deformity of fingers, and Z deformity of thumb

ARSACS was first described in the French-Canadian population in the regions of Charlevoix and Saguenay-Lac-St-Jean in Quebec, Canada.[1] Later, it was detected in several other countries, suggesting a worldwide distribution. However, only a few genetically proven cases of ARSACS have been reported from India.[4-7]

The worldwide incidence of ARSACS is unknown, though it is thought to be underdiagnosed. In this clinical case report, we describe the case of an ARSACS from North India, highlighting the clinical presentation, neurological imaging, and genetic analysis involved in the diagnosis.

ARSACS is mainly characterized by progressive cerebellar ataxia, spasticity, and peripheral neuropathy. Other symptoms and signs include dysarthria, nystagmus, and hypermyelination of the retinal fibers.[1] Ataxia is progressive, and additional cerebellar features like dysarthria and nystagmus typically appear in late childhood. Clinical signs of neuropathy tend to appear later. In many patients, the neuropathy only becomes clinically obvious in the late teenage years.[8] Additional atypical cases include patients with epilepsy, a CMT-like phenotype, or hearing loss.[9] In our patient, all these findings except for the retinal changes and dysarthria were present. The onset of the illness and slow progression were also indicators toward ARSACS.

Axonal neuropathy with demyelinating features on NCS with or without myelinated retinal fibers is highly suggestive of ARSACS.[7,8] This feature helps in narrowing down the differential diagnosis, as seen in the NCS of our patient as well.

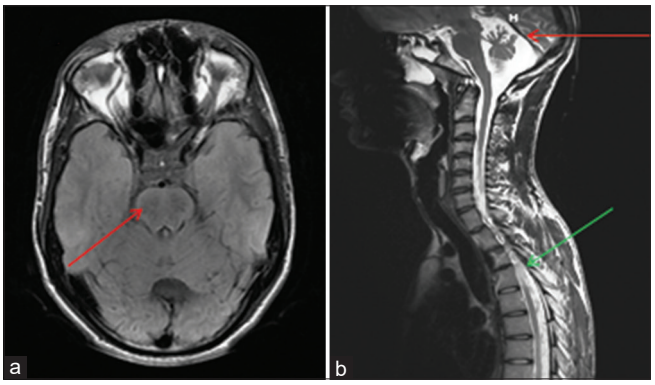

Figure 2: (a) MRI Brain T2 FLAIR image showing the striped appearance of the pons (Tigroid pons); (b) MRI Brain T2W image showing superior vermian atrophy (red arrow) and thoracic spinal cord atrophy (green arrow)

Table 1: Comparison of genetic variants in the SACS gene in studies previously reported from India

Previous reports	Gene	Exon	Zygosity	Variation	Variant
Present case	SACS	10	Heterozygous	Frame shift variant	c.6114_6117dupAGAA
				Frame shift variant	c.2215_2216dupAA
Agarwal, *et al*.[4]	SACS	10	Homozygous	Single-base-pair deletion	c.8793delA;p.Lys2931AsnfsTer22
Kuchay, *et al*.[5]	SACS	10	Homozygous	Single-base-pair deletion	c8793 del A;p.Lys2931AsnfsTer22
Sheetal, *et al*.[7]	SACS	10	Homozygous	Four-base-pair duplication	c.11690_11693dupGTGA: p.Asp3898GlufsTer2
Sheetal, *et al*.[11]	SACS	10	Homozygous	Single-base-pair deletion	c.8605delT:p.Cys2869 ValfsTer15
Agarwal, *et al*.[12]	SACS	10	Heterozygous	Non-sense variant Missense variant	c.4232T>G;p.Leu1411Ter c.8132C>T;p.Ser2711Leu
Menon, *et al*.[13]	SACS	9	Homozygous	Deletion	c.8844delT;p.Ile22949PhefsTer4 variant

Brain MRI features include early and progressive superior vermis atrophy and linear hypointensities on T2-weighted images in the pons near the pyramidal tracts. Recent studies also found T2-hyperintensities of the lateral pons when merging into the middle cerebellar peduncles that appear thickened, probably related to abnormally large transverse ponto-cerebellar fibers, along with a frequent association with posterior fossa arachnoid cysts. Furthermore, bilateral parietal atrophy, short-stretchedness and thinning of the posterior mid-body of the corpus callousum were also demonstrated in ARSACS patients. Other useful imaging features include the T2 hyperintense rim around the thalami (known as bithalamic stripes) and thinning of the cervical spinal cord.[10]

Our patient also had linear pontine hyperintensities and superior vermian atrophy. However, the thinning of the thoracic spinal cord in our case was in contrast to the thinning of the cervical spinal cord reported in the literature.

The founder mutations in the *SACS* gene discovered in Quebec were a single-base deletion at position 6594 (6594delT) and a nonsense mutation 5254C > T[17]. The causal mutations vary between individuals. The presence of the novel mutation can explain minor changes in the phenotype in our case. Table 1 shows other novel gene mutations detected in other parts of the country.

Conclusion

The early diagnosis of hereditary ataxias is difficult because of evolving phenotypes and overlapping features. However, a good clinical evaluation and carefully selected ancillary tests can narrow down the differential diagnosis. ARSACS must be suspected in patients with early-onset spastic cerebellar ataxia and peripheral neuropathy with the typical imaging findings. The diagnosis can be confirmed by genetic analysis. Physical therapy and oral medications such as baclofen to control spasticity in the early phase of the disease may prevent tendon shortening and joint contractures, and hence, may help to postpone major functional disabilities. Carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk can be done, if both pathogenic variants have been identified in an affected family member.

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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