



AUTOSOMAL RECESSIVE SPASTIC ATAXIA OF CHARLEVOIX-SAGUENAY (ARSACS): CASE REPORT

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ABSTRACT

Background: Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is a rare neurodegenerative disorder characterized by early-onset cerebellar ataxia, spasticity, and sensorimotor polyneuropathy. It was initially described in Canada but is now being increasingly recognized worldwide. ARSACS is caused by pathogenic mutations in the *SACS* gene, with new mutations being continuously identified. **Case Presentation:** We report a 28-year-old male from India, born of a non-consanguineous marriage, who presented with progressive gait ataxia and recurrent falls from 3 years of age. Additional symptoms included dysarthria, lower limb stiffness, and distal muscle wasting. Examination revealed bilateral pes cavus, hammer toes, spasticity, brisk reflexes, extensor plantar response, and cerebellar signs. MRI brain showed superior cerebellar vermician atrophy and characteristic pontine linear T2 hypointensities. Nerve conduction studies indicated predominant demyelinating neuropathy. Genetic testing identified a novel pathogenic nonsense mutation (C,4232T > G) and another mutation of uncertain significance (C,8132C > T) in exon 10 of the *SACS* gene, confirming the diagnosis of ARSACS. **Discussion:** ARSACS is often misdiagnosed as cerebral palsy or other hereditary ataxias. The presence of early-onset ataxia with spasticity and peripheral neuropathy, combined with characteristic MRI findings, strongly suggests ARSACS. While previously reported mainly in Canada, this case highlights its occurrence in India and contributes to the expanding spectrum of SACS mutations. **Conclusion:** ARSACS should be considered in cases of early-onset ataxia with spasticity and neuropathy. MRI findings significantly aid in diagnosis, which is ultimately confirmed by genetic testing. This case not only adds to the global understanding of ARSACS but also reports a novel pathogenic mutation in the *SACS* gene, broadening the known genetic spectrum of the disease.

KEYWORDS : Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) , sensorimotor polyneuropathy, *SACS* gene, demyelinating neuropathy, early-onset neurodegenerative disorder.

INTRODUCTION:

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. in 1978 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 the rest of the world.[4]

Exome sequencing studies identified multiple causative mutations in the *sacs* 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 led to the discovery of a novel pathogenic *SACS* mutation.

CASE REPORT:

A 28-year-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, dysidiadochokinesia, nystagmus, and cerebellar gait. He had no Kayser-Fleischer ring, telangiectasias, or tendon xanthomas. Systemic examination was normal. Diagnosis of an autosomal recessive ataxia syndrome was made and the patient was evaluated along those lines.

MRI brain revealed superior cerebellar vermician 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 nonsense 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).

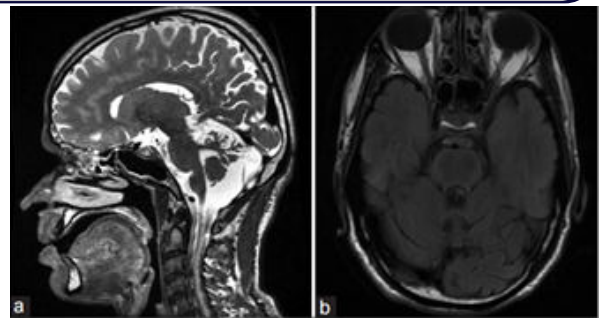


Figure 1: MRI brain T2 weighted image revealing superior cerebellar vermician atrophy (a) and linear "striped" hypointensities in pons (b)

DISCUSSION:

ARSACS is an early-onset cerebellar ataxia first described in 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 vermician atrophy and pontine linear T2/FLAIR hypointensities on T2/FLAIR). Confirmation of diagnosis is done by demonstration of pathogenic mutations in the *sacs* 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] 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.

Funduscopy may reveal hypermyelinated nerve fibers radiating from the optic disc in some patients,[8] and cognition tends to be preserved. Both funduscopy and cognition were normal in our patient. Imaging findings described on MRI brain include early and progressive

superior cerebellar vermis atrophy, with the inferior vermis remaining preserved throughout.[9] However, global cerebral atrophy may occur later in the disease course. Linear T2 and FLAIR hypointensities 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% of 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 fibers in our patient is probably explained by the same.

CONCLUSION:

ARSACS must be suspected in early-onset cerebellar ataxia combined with spasticity and peripheral neuropathy. Typical radiological features such as superior cerebellar vermis atrophy and linear pontine hypointensities 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

This study complied with all ethical standards and did not require approval from the Institutional Ethics Committee. Written informed patient consent was obtained. 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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