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CASE REPORT

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An unusual case of childhood onset spastic ataxia from South India—Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS)

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Abstract

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is an uncommon spastic-ataxic syndrome and a neurodegenerative disease that is characterized by the triad of cerebellar ataxia, spasticity, and peripheral neuropathy. Though initially reported from Quebec, Canada, this disorder has been reported from other regions of the world. There have been very few reports on this condition from India. We report a case from Southern India with typical clinical and imaging features.

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INTRODUCTION

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is an early onset neurodegenerative disease. It is a disorder of spastic ataxia that was first discovered in the population from the Charlevoix-Saguenay-Lac-Saint-Jean (CSLSJ) region in Québec, Canada back in the year 1978 [1]. The long name of this disorder stems from its high prevalence in the small regions of Quebec, where people with a particular point mutation settled after migrating from Europe in the mid-1800s. The high carrier frequency for this mutation arose from the descendants of these individuals propagating within a relatively small founder population of the French-Canadian [2,3]. Hence, this region of Québec, Canada, was previously regarded as a genetic isolate. However, in recent years, ARSACS has been reported in various countries across the globe [2–5].

The chromosomal locus for ARSACS was determined to be on chromosome 13q11. The genetic basis of this condition involves mutations in the *SACS* gene, which encodes sacsin, a protein crucial for the proper functioning of neurons [3]. ARSACS is clinically characterized by progressive motor dysfunction, including spasticity, truncal ataxia, peripheral neuropathy, and ocular manifestations.

CASE REPORT

A 23-year-old female, born of third-degree consanguineous marriage, presented to the out patient department with complaints of recurrent falls and gait instability since the age of 15 years, and she developed stiffness of bilateral lower limbs at the age of 19 which had progressively increased. She had no ocular symptoms or symptoms of peripheral neuropathy. No similar complaints were present in her parents or other family members. Her Developmental milestones were achieved on time and she showed good scholastic performance. On physical examination, deep tendon reflexes were increased and extensor plantar seen in all four limbs. Ataxic gait was present with a tendency to fall. Fundoscopy examination and nerve conduction studies were normal.

Magnetic Resonance Imaging (MRI) scan of the brain revealed atrophy of the superior vermis with mildly dilated fourth ventricle (Fig. 1), flattening, and atrophy of the visualized cervical spinal cord (Fig. 1). Pons appear bulky. Linear, striated T2, and FLAIR hypointensities were observed in pons on either side of the midline, creating a tigroid pattern (Figs. 2 and 3). No white matter signal abnormalities were seen.

We diagnosed ARSACS in this patient based on a combination of clinical and imaging findings.

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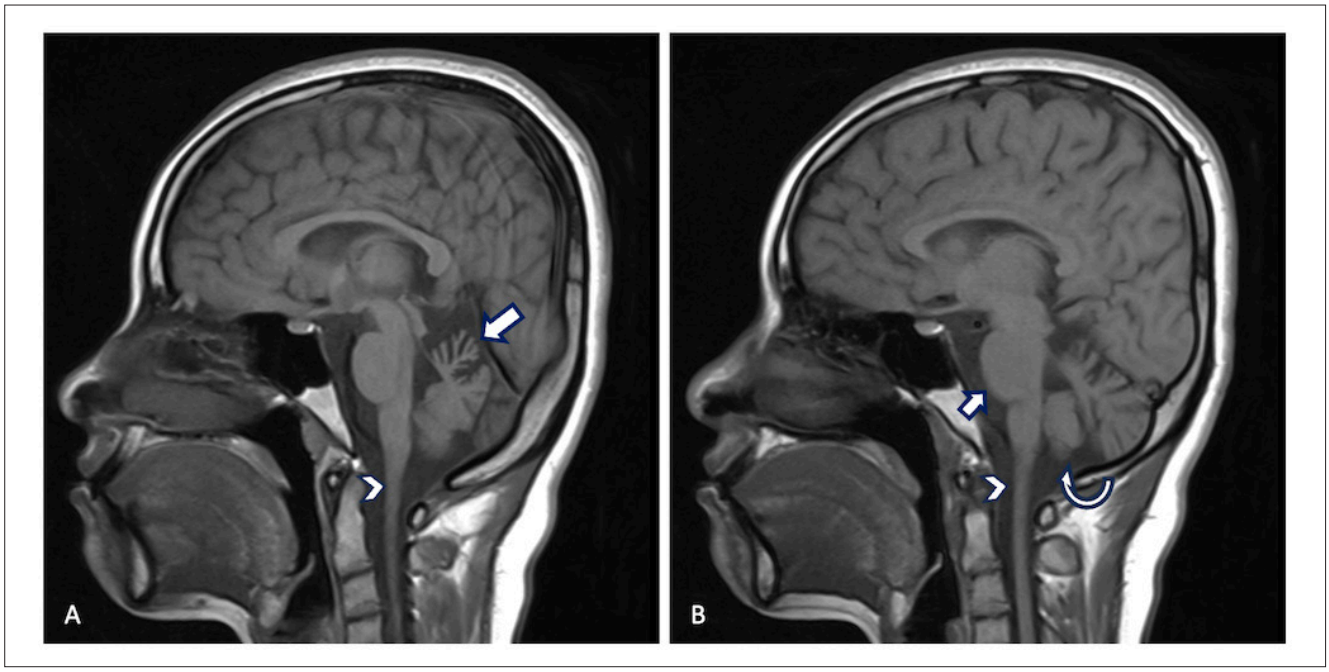


Figure 1. Sagittal T1 weighted MR images of the brain (A) shows atrophy of superior vermis (*arrow*) and prominent fourth ventricle. Atrophy of the proximal cervical spinal cord (*arrow head*). (B) Shows bulky appearing pons (*arrow*), intact inferior vermis (*curved arrow*), and atrophy of the proximal cervical spinal cord (*arrowhead*).

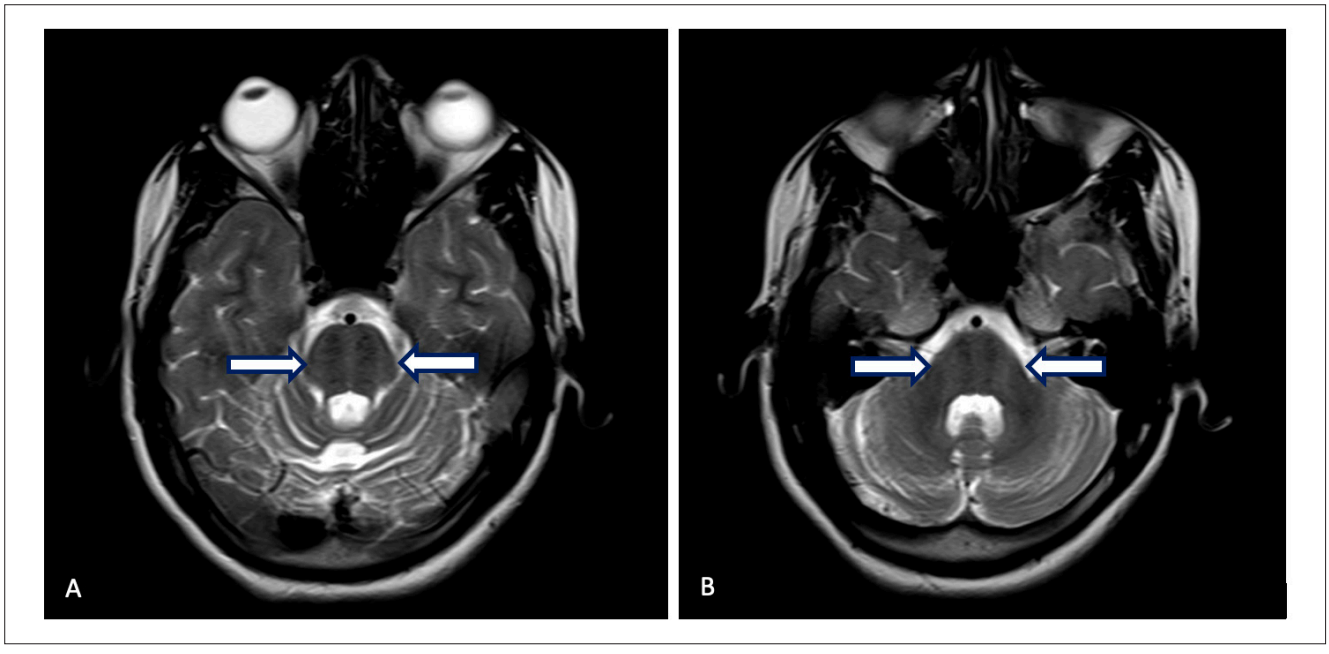


Figure 2. (A) Axial T2 weighted MR images at the level of superior cerebellar peduncle demonstrates linear T2 hypointense stripes in the pons on either side of midline (*arrows*). (B) Axial T2 weighted MR images at the level of middle cerebellar peduncle demonstrates linear T2 hypointense stripes in the pons on either side of midline representing the tigroid pattern (*arrows*).

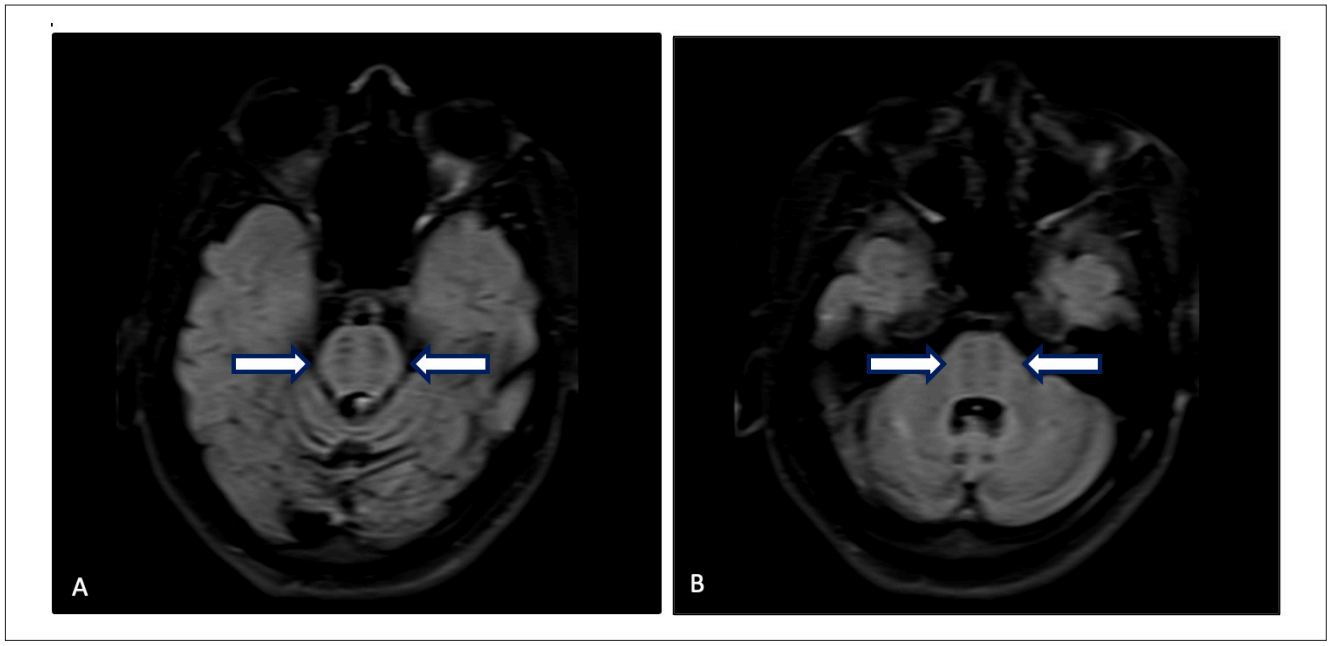


Figure 3. (A) Axial FLAIR MR images at the level of superior cerebellar peduncle demonstrates linear hypointense stripes in the pons on either side of midline (*arrows*). (B) Axial FLAIR MR images at the level of middle cerebellar peduncle demonstrates linear hypointense stripes in the pons on either side of midline (*arrows*) representing the tigroid pattern.

The clinical symptoms of cerebellar ataxia and spasticity, along with the characteristic imaging features of superior vermian atrophy, a bulky pons with a tigroid pattern, linear hypointensity on T2-weighted and FLAIR images, and cervical spinal cord atrophy, are strongly suggestive of ARSACS.

This diagnosis was confirmed through genetic analysis which detected homozygous pathogenic frameshift *c.6000_6004del (p.Arg2002CysfsTer25)* variant of *SACS* gene on exon10 of chromosome 13.

DISCUSSION

ARSACS is a rare autosomal recessive spastic ataxia which occurs due to mutations in *SACS* gene on chromosome 13q11. ARSACS consistently presents with a characteristic pattern of clinical symptoms, as well as specific electrophysiologic and imaging findings.

Clinically, ARSACS comprises the classic triad of cerebellar ataxia, spasticity, and peripheral neuropathy [4,5]. Patients exhibit early onset signs of spasticity in the lower limbs, typically observed when they begin walking (around 12–18 months of age). Pyramidal tract and cerebellar signs like gait ataxia appear early in life, and manifestations of polyneuropathy typically occur later, in the third decade of life. Muscle tone and deep tendon reflexes progressively increase. Saccadic interruptions in smooth eye movements occur and prominent myelinated fibers radiating from the optic disc are seen on fundoscopic examination, reflecting abnormal myelination [4].

From the genetic and molecular perspective, the majority of patients from Quebec, where ARSACS was first discovered, had a single mutation—a nucleotide deletion in the largest exon of the *SACS* gene-exon 10, that results in a truncated sacsin protein [2,3]. Ever since, over 200 different pathogenic mutations have been identified in the *SACS* gene globally [3], which were either homozygous or compound heterozygous mutations. Mutations are either missense mutations, or frameshift variants. This explains the diverse phenotypes of the disease which are currently recognized and also accounts for the absence of abnormal myelinated retinal fibers in our patient. In addition to the classic symptoms of ataxia and spasticity, other atypical symptoms such as intellectual disability and memory issues may also be present [3]. In most cases nerve conduction studies (NCS) demonstrate signs of both early dysmyelination and progressive axonal neuropathy.

Why is ``sacsin'' protein important? Sacsin is present in various tissues, with its expression being more pronounced in the central nervous system and skin, and less so in the pancreas and skeletal muscle [6]. In the brain, Sacsin expression is highest in the motor system, particularly in the cerebellum, the granular system, and Purkinje cells [3,6].

The Imaging features of ARSACS—atrophy of the superior cerebellar vermis is consistently observed on CT or MRI, even in younger patients, and it progresses over time. The inferior vermis remains intact throughout the disease. Although, there is a gradual atrophy of the cerebellar cortex.

There is marked atrophy of the cervical spinal cord. Additionally, cerebral atrophy occurs in late stages of the disease. Bulky pons with linear striated hypointensities on T2 and FLAIR images can be seen on either side of the midline which resembles a tigroid pattern [7]. The anatomical basis for the tigroid pattern is the involvement of the corticospinal tracts which are located within the central pons and the transverse pontocerebellar fibers and/or pontine nuclei. The abnormal hypointensities are seen on both sides of the midline, centrally and in the lateral pons and the crossing of pontocerebellar fibers at the midline, corroborates this finding. This also supports the clinical picture of motor system involvement in ARSACS.

Recent studies have identified several MRI measurements of infratentorial structures in ARSACS, with the pons-to-superior vermis area ratio being the most reliable [9]. A cut-off value of 1.67 for the pons-to-superior vermis area ratio has shown high diagnostic accuracy in identifying patients with ARSACS and distinguishing it from other types of spastic ataxias. Diffusion MRI is a quantitative technique that was explored to evaluate the degree of white matter involvement and microstructural integrity [10]. It revealed severe involvement of commissural fibers (particularly the corpus callosum and the fornix) and the infratentorial structures (pons, middle cerebellar peduncles). Diffusion tensor Imaging (DTI) showed reduced fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD) values [10]. These parameters reflect a widespread loss of axonal and dendritic integrity, secondary demyelination, and a reduction in white matter volume in ARSACS.

From a practical standpoint, the combination of clinical symptoms, imaging features, early NCS findings, and ocular signs collectively provide a diagnosis of ARSACS and help differentiate it from cerebral palsy and Friedrich's ataxia, which are close clinical differentials. The other differential diagnosis for childhood onset cerebellar ataxia and cerebellar atrophy include *Spinocerebellar ataxias*, mitochondrial disorders, neuronal ceroid lipofuscinoses, ataxia telangiectasia, infantile neuroaxonal dystrophy [11].

In our case, the patient had clinical features of cerebellar ataxia and spasticity, this combined with the classic imaging features of superior vermian atrophy and tigroid pattern of T2/FLAIR hypointensities in the pons helped us clinch the diagnosis of ARSACS.

CONCLUSION

Considering that ARSACS is being reported with increasing frequency from various parts of the world, it should be considered in cases of early-onset cerebellar ataxia accompanied by spasticity and peripheral neuropathy. Diagnostic accuracy is significantly improved with characteristic radiological features, such as atrophy of the superior cerebellar vermis and linear pontine hypointensities. Ultimately, the specific diagnosis of ARSACS is confirmed through genetic testing.

ABBREVIATIONS

FLAIR - Fluid attenuated inversion recovery
CT - Computed Tomography.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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