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Diagnostic challenges and clinico-genetic features in ARSACS: A case series

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Early Onset Ataxia; Sacsin Protein; Human; Cerebellar Ataxia

Abstract

Background: Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is a rare neurodegenerative disorder characterized by early-onset cerebellar ataxia, spasticity, and distal amyotrophy. This descriptive retrospective case series focuses on patients with ARSACS from the Indian subcontinent, with disease durations exceeding 10 years.

Methods: This case series included patients with typical clinical features of ARSACS who were evaluated in a single neurology unit between 2016 and 2022. Data on age at onset, illness duration at the last follow-up, and clinical manifestations were recorded. Electrophysiology reports, neuroimaging findings, and genetic testing results were reviewed. Functional disability documented at the last available clinical evaluation was recorded.

Results: The study comprised eight Indian patients with ARSACS [male/female (M:F) = 5:3] from unrelated families. The age at onset was between 2-5 years of age, with walking difficulties being the initial symptom in all cases. The correct diagnosis was established after the first decade of life, with a mean age at diagnosis of 23 years (range: 17-30 years) and a mean time to diagnosis of 20 years (range: 14-27 years). Electrophysiological studies showed demyelinating sensorimotor neuropathy. Imaging revealed characteristic linear T2-hypointensities in the pons and cerebellar atrophy. Genetic testing identified novel homozygous sacsin molecular chaperone (SACS) gene variants.

Conclusion: This study provides valuable insights into the clinical and genetic features of ARSACS in the Indian subcontinent. The time taken to establish the diagnosis ranged from 14 to 27 years in this series. Recognizing characteristic clinical and imaging findings may facilitate earlier diagnosis. The identification of novel genetic variants further expands our understanding of ARSACS.

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Introduction

Early-onset autosomal recessive ataxia syndromes consist of numerous entities with distinctive phenotypes. In 1978, a peculiar spastic ataxic syndrome was reported in kinships hailing from the Charlevoix and Saguenay region in Quebec, Canada, and thus this disease was acronymized as ARSACS, autosomal recessive spastic ataxia of Charlevoix-Saguenay. They were uniformly characterized by an early onset of cerebellar ataxia, distal amyotrophy, and spasticity. In 2000, mutations in the sacsin molecular chaperone (SACS) gene were implicated to cause this syndrome.[1,2] SACS codes for sacsin which plays an important role in chaperone-mediated protein binding. Over the last two decades, similar phenotypes carrying known or novel homozygous mutations have been reported in probands unrelated to migrants from the Charlevoix-Saguenay area, from different parts of the world. We describe a case series of patients with ARSACS from the Indian subcontinent with more than 10 years of disease duration.

Materials and Methods

This case series retrospectively included patients from a single neurology unit between 2016-2022 at a large tertiary neurology teaching hospital in Southern India. Patients who presented clinical and radiological features that were typical of ARSACS and fulfilled the major clinical diagnostic criteria,[3] viz., early-onset gait disturbances, progressive ataxia with linear hypointensities in the pons, and superior vermis atrophy, were analyzed in this series. Patients whose magnetic resonance imaging (MRI) could not be reviewed were also excluded from the study. Clinical details regarding age at onset, duration of illness at last follow-up, clinical features, the initial diagnosis that was made, and time taken to establish the correct diagnosis were recorded. Clinical data that were detailed regarding development, history of consanguinity, and neurological examination findings were recorded. Available electrophysiology reports such as nerve conduction studies (NCSs) and evoked potentials were reviewed. Details of NCSs were analyzed, and neuropathy was classified into axonal or demyelinating based on distal latency, nerve conduction velocity (NCV), and compound muscle action potential (CMAP)/sensory nerve action potential (SNAP) amplitudes. Magnetic resonance (MR) images including diffusion tensor imaging (DTI) sequence findings were recorded. We specifically looked for other abnormalities associated with ARSACS, viz., anterolateral thalamic hyperintensities and parietal atrophy. Genetic testing results were also included if available. Details regarding the type of variant, zygosity, location, and functional significance were analyzed. Functional disability documented at the last follow-up was gathered after reviewing case records.

Results

Clinical features: Eight patients were diagnosed with ARSACS between 2016-2022 [male/female (M:F) = 5:3]. All patients were Indians and hailed from unrelated families except for one sib-pair. Consanguinity was present in 3 kindreds. The average age at onset was 3 years (range: 2-5 years). The initial symptom was difficulty in walking and delayed walking in all the subjects. Developmental delay was also uniformly observed in our patients which predominantly involved motor domains. Walking independently was attained between 3-4 years of age. Imbalance while walking was noticed from the onset in all cases. In addition, scholastic performance was universally below average and handwriting was poor in all subjects. Formal neuropsychological testing was done in 3 subjects. Social quotients ranged between 40-49 indicating moderate intellectual disability. Other relevant clinical features have been tabulated in table 1.

None of the patients were referred with the specific diagnosis of ARSACS. The initial diagnoses were ataxic cerebral palsy (CP) (n = 3), hereditary spastic paraplegia (HSP) (n = 1), spinocerebellar ataxia (SCA) (n = 2), hereditary motor and sensory neuropathy (HMSN) type 2 (n = 1), and non-specific gait abnormality (n = 1). The diagnosis was established in all our cases only after the first decade of life. Age at diagnosis ranged from 17 to 30 years. The mean time to diagnosis was 20 years (range: 14-27 years). At the time of diagnosis, only 3 individuals could walk unassisted, and 2 required wheelchairs for ambulation.

Ocular findings typical of ARSACS, viz., myelination of retinal nerve fibers, were demonstrated in 75%. Ophthalmological examination was otherwise normal. Visual evoked potentials (VEPs) were done in 4 subjects.

Electrophysiology: NCSs were done in all cases in the study in the ulnar, median, common peroneal, and sural nerves.

Table 1. Clinical characteristics of patients with autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS)

Patient	Age at onset (year)	Age at diagnosis (year)	Ataxia	Spasticity	Neuropathy	HMRF	MRI changes	Other features	Mobility at the time of diagnosis
1	4	18	+		+	+	P, AL	Scoliosis	Independent
2	3	30	+	+	+	-	P, AL	Pes cavus	Assisted walking with a walker
3*	4	22	+		+	+	P, AL	Pes cavus	Wheelchair
4*	5	23	+		+	+	P	SNHL, prolonged P100	Independent
5	2	27	+	+	+	+	P, AL	Pes cavus	Wheelchair
6	2	28	+		+	+	P, AL	Pes cavus	Independent
7#	3	17	+		+	-	P, AL	SNHL, prolonged P100	Assisted walking with a walker
8	3	21	+	+	+	+	P, AL	-	Independent

*Siblings; #Similar illness in maternal aunt
SNHL: Sensorineural hearing loss; MRI: Magnetic resonance imaging; P: Pontine hypointensities; AL: Anterolateral thalamus hyperintensities

Table 2. Sacsin molecular chaperone (SACS) variants harbored by probands

Patient	Variant	Exon	Domain	Zygosity	In silico analysis
P2	c.13469A>C	10	HEPN	Homozygous	Damaging
P7	c.831_837del	8	SIRPT1	Homozygous	Damaging
P8	c.9183_9185delCCT	10	SIRPT3	Homozygous	Damaging

HEPN: Higher eukaryotes and prokaryotes nucleotide-binding; SIRPT: Sacsin internal repeat

Demyelinating sensorimotor neuropathy was observed in 6 out of 8 cases, whereas only sensory neuropathy was documented in 2. Sensory amplitudes were diminished to absent in both upper and lower limbs in all our patients. Common peroneal CMAPs were affected more than median/ulnar CMAPs. Conduction blocks and temporal dispersion were not observed in any patient. Upper limb somatosensory evoked potentials (SSEPs), viz., N20, were prolonged in 2 probands and absent in the rest. Lower limb SSEPs could not be elicited in any. VEPs were done in 3 cases and P100 latencies were prolonged in all three subjects. However, visual acuity was affected. Sensorineural hearing loss (SNHL) was detected in 25% (n = 2).

Imaging: Imaging studies (MRI) were available for review in all patients. Varying degrees of cerebellar atrophy were present in all cases. Linear T2-hypointensities in pons which are characteristic of this condition were present in every patient. In addition, a rim of T2 hyperintensity in the anterolateral aspect of the thalamus was documented in 75%. DTI sequences were available in only 3 patients and showed small corticospinal tracts interrupted by thick transverse pontine fibers (Figure 1, a-d).

Genetics: Genetic testing reports were available for scrutiny in 3 probands. All the tested probands harbored homozygous variants in the SACS gene. All 3 variants were novel and illustrated in figure 2 and table 2. Variants were identified in exon 8 and 9 of the gene and two were considered to be damaging in silico (MutationTaster2, PolyPhen). A novel in-frame deletion c.9183_9185 was detected in one proband which had typical ARSACS features.

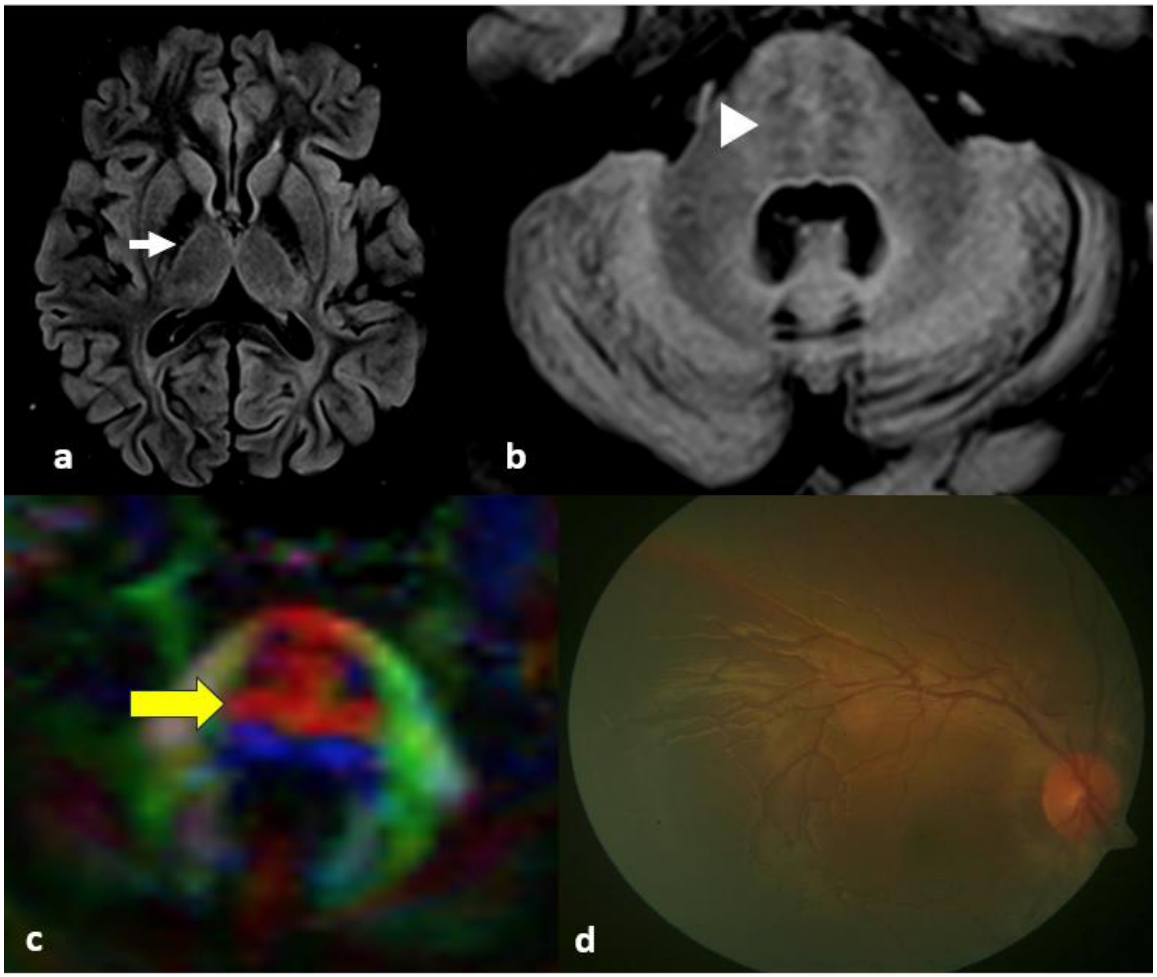

Figure 1. a) T2-fluid attenuated inversion recovery (T2-FLAIR) axial image highlighting anterolateral thalamus hyperintensities (white arrow); b) Linear T2 hypointensities in the pons characteristic of autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) (white arrowhead); c) diffusion tensor imaging (DTI) sequence demonstrating thickened transverse pontine fibers (yellow arrow); d) Hypermyelinated retinal nerve fibers seen as whitish streaks over the retina extending from the disc

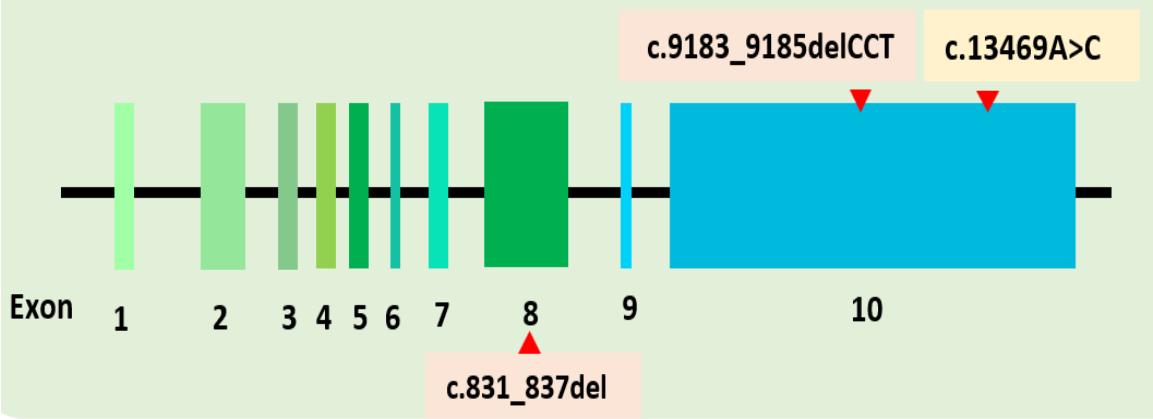

Figure 2. Simplified exon structure of the autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) gene (identified variants have been marked on the figure.)

Discussion

ARSACS is a neurodegenerative disorder characterized by early-onset cerebellar ataxia, distal amyotrophy, and spasticity.[4] Currently, it is believed to be the third most common cause of early-onset inherited ataxia after Friedreich's ataxia and ataxia telangiectasia.[5-7] The identification of mutations in the SACS gene as the underlying cause of ARSACS has provided insights into the pathogenesis of this condition. Sacsin, the protein encoded by the SACS gene, plays a crucial role in chaperone-mediated protein binding.[8] Mutations in SACS lead to impaired protein quality control mechanisms, resulting in the accumulation of misfolded proteins and subsequent neurodegeneration.

This study describes a series of patients diagnosed with ARSACS from the Indian subcontinent with a disease duration of more than 10 years. The clinical features observed in these patients are consistent with previous reports of ARSACS. The mean age at onset was 3 years, which is in line with the early-onset characteristic of the disease.[1] The initial symptom reported by all patients was difficulty in walking and delayed walking, further highlighting the cerebellar ataxia component of ARSACS. Developmental delay, predominantly affecting motor domains, was uniformly observed in this series, emphasizing the neurodevelopmental aspect of the disease. Walking independently was achieved between 3-4 years of age, suggesting a progressive deterioration of motor function over time. Scholastic performance was also consistently below average or poor, indicating the impact of ARSACS on cognitive abilities. These findings are characteristic of this autosomal recessive ataxia syndrome.[9] Ocular findings, specifically myelination of retinal nerve fibers, were demonstrated in 75% of the patients, supporting the previously reported ocular manifestations of ARSACS. This has also been found in heterozygote carriers; however, it was not examined in the family members.[10]

One significant observation in this study was that none of the patients were initially referred with a specific diagnosis of ARSACS, and the initial diagnoses ranged from ataxic CP to various other neurodegenerative conditions. The mean age at diagnosis was 23 years, with a mean time to diagnosis of 20 years. The time taken to precisely establish the diagnosis can be attributed to the rarity of ARSACS and the lack of awareness among healthcare professionals about this condition. Improved awareness and recognition of the characteristic clinical features and neuroimaging findings associated with ARSACS may aid in clinical suspicion of ARSACS.

Electrophysiological studies conducted revealed characteristic abnormalities. NCSs showed demyelinating sensorimotor neuropathy in the majority of cases, with more pronounced involvement of the common peroneal nerve. Absent or prolonged upper limb SSEPs and prolonged VEPs further supported the neurophysiological abnormalities associated with ARSACS; findings that are consistent with available literature.[6] Sacsin malfunctions result in secondary mitochondrial abnormalities which could explain the multi-axial nature of this syndrome.

Neuroimaging findings, particularly MRI, have been valuable in diagnosing ARSACS. Linear T2-hypointensities in the pons, a characteristic feature of ARSACS, were observed in all patients.

Additionally, a rim of T2 hyperintensity in the anterolateral aspect of the thalamus was documented in 75% of the cases. These imaging findings provide supportive evidence for the diagnosis of ARSACS. DTI sequences, available in a subset of patients, revealed interruption of the small corticospinal tracts by thick transverse pontine fibers. This finding is consistent with the known involvement of the corticospinal tracts in ARSACS.[4]

Numerous genetic variants have been reported in the SACS that are implicated in ARSACS. Interestingly, most of these variants have been identified in exon 10 which is also the largest exon in vertebrates.[11] Genetic testing confirmed the diagnosis of ARSACS in three probands, and all of them harbored novel homozygous variants in the SACS gene; two of these variants were located in exon 10 and the other was situated in exon 8. In silico analysis predicted these variants to be damaging, further supporting their pathogenicity. SACS encodes a 4579 amino acid long protein called sacsin.

Many functional domains have been recognized within this protein such as the ubiquitin-like (UBL) domain in its N-terminal region, three sacsin internal repeat (SIRPT or SRR) domains, the helical xeroderma pigmentosum complementation (XPC)-binding domain, J-domain, and the higher eukaryotes and prokaryotes nucleotide-binding (HEPN) domain in its C-terminal region.[12] Sacsin is highly expressed in the cerebellum, granular system, and Purkinje cells. In our cases, mutations were identified in the SIRPT and HEPN domains which are required for interactions between sacsin and heat shock protein 70 (Hsp70) and nucleotides, respectively. The identification of novel variants expands the mutational spectrum associated with ARSACS and highlights the genetic heterogeneity of this condition. Genetically confirmed cases of ARSACS have been reported from India but have been limited to single case reports.[13,14] Another significant aspect of this series was that follow-up was available even after 10-15 years of disease duration.

Conclusion

This study provides valuable insights into the clinical features, diagnostic challenges, and genetic characteristics of ARSACS in patients from the Indian subcontinent. The findings highlight the importance of early recognition and diagnosis of ARSACS, as the disease presents with specific clinical features such as early-onset cerebellar ataxia, spasticity, and distal amyotrophy. The delay in establishing the correct diagnosis observed in this study underscores the need for increased awareness among healthcare professionals to expedite earlier diagnosis.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

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