Autosomal Recessive Spastic Ataxia of Charlevoix–Saguenay due to Novel Mutations in the SACS Gene

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Abstract
Autosomal recessive spastic ataxia of Charlevoix–Saguenay (ARSACS) is characterized by triad of progressive cerebellar ataxia, progressive spasticity, and axonal/demyelinating peripheral neuropathy. Other manifestations include dysarthria, weakness in lower extremities and distal muscle wasting, foot deformities, retinal striation, prolapse of the mitral valve and rarely intellectual disability, hearing loss, and myoclonic epilepsy. We describe a patient who developed peripheral sensorimotor neuropathy in the absence of spasticity on initial presentation. He had nerve root enhancement on magnetic resonance imaging (MRI) lumbar spine, and nerve conduction studies were suggestive of demyelinating polyneuropathy. Patient had mild cerebellar atrophy on MRI and some delay of motor milestones. Over the course of several months, he developed spasticity, and genetic analysis together with clinical presentation was consistent with ARSACS. He was noted to have a pathogenic mutation c.8108G>A (p. Arg2703His) inherited from mother and a variant of uncertain significance c.7216T>C (p. Ser2406Pro) inherited from his father in SACS gene. Atypical cases may present later in life or in absence of one of the classical features at the time of presentation, which may make diagnosis difficult. Our patient had such an atypical presentation of ARSACS. Young patients with neuropathy and concomitant cerebellar atrophy on MRI should raise suspicion for hereditary spastic ataxia syndrome. Follow-up examination can often reveal additional findings to aid the diagnosis.

Keywords
ARSACS, autosomal recessive spastic ataxia of Charlevoix–Saguenay, chronic inflammatory demyelinating polyradiculoneuropathy, CIDP, hereditary polyneuropathy

Case
The patient is a 14-year-old boy who presented with several year history of gait abnormality. He was born at term with no perinatal complications. He had delayed motor milestones. He was not able to pull himself up until the age of 1 year and started walking at the age of 2 years. He was noted to be clumsy and had frequent falls. His speech and language development were reportedly normal. He required physical therapy until middle school. At the age of 7 years, his neurologic examination was reportedly normal, and magnetic resonance imaging (MRI) brain showed mild cerebellar atrophy. His medical history and family history were otherwise noncontributory. Physical examination at the age of 14 years showed high arched palate and pes cavus.

Neurologic examination revealed low tone at ankles, mild atrophy of intrinsic hand and foot muscles, weakness of ankle dorsiflexors (4/5), and toe extensors (3/5) bilaterally. n=No ataxia was noted, Reflexes were absent at ankles, and Romberg’s was positive. Labs including blood counts, metabolic panel, vitamin B12, B1, B2, folate, Gliadin IgG/IgA, and tissue transglutaminase IgA/IgG were normal. The MRI brain revealed mild atrophy of cerebellar hemispheres and vermis. The MRI spine showed diffuse smooth thickening of bilateral brachial plexus, intracostal nerves, and lumbar and sacral plexus with diffuse thickening and enhancement of the cauda equina nerve roots (Figures 1 and 2).

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Cerebrospinal fluid (CSF) studies revealed normal glucose (51 mg/dL) and cell count (RBC 1, WBC 1) but elevated protein 106 mg/dL. Electomyography (EMG)/nerve conduction studies revealed markedly prolonged distal latencies with decreased velocities and reduced amplitude in motor nerves in bilateral upper and lower extremities. Sensory responses were unevocable (Table 1). Active and chronic neurogenic changes were noted in right tibialis anterior and gastrocnemius muscles. Patient was started on monthly intravenous immunoglobulin (IVIG) therapy for presumed chronic inflammatory demyelinating polyneuropathy. He underwent extensive evaluation for acquired causes of neuropathy which were unrevealing. He had normal acylcarnitine profile and lactate and pyruvate levels. Patient did not show any improvement in the next 6 months, and IVIG infusions were discontinued. At this time, genetic testing for inherited neuropathies and other neuromuscular conditions was sent. Testing showed a heterozygous variant of uncertain significance, c.80T>C (p. Val27Ala), in FIG4 gene which is associated with autosomal recessive Charcot Marie Tooth disease type 4J. This would not explain his clinical presentation.

A repeat EMG nerve conduction studies done a year later showed stable findings consistent with a chronic, length-dependent, demyelinating, sensory motor polyneuropathy. There were markedly prolonged distal latencies with reduced amplitude and slowing of the conduction velocity in the demyelinating range of the right tibial and peroneal motor responses. Right medial and ulnar motor responses showed prolonged distal latencies and slowing of the conduction velocity. Right median and ulnar F-wave latencies were prolonged as well. Right radial sensory response showed prolonged peak latency, reduced amplitude, and slowing of the conduction velocity in the demyelinating range (Table 1).

Patient was later found to have mild spasticity in his bilateral lower extremities and appendicular ataxia on the follow-up visit. Whole exome sequencing was sent which revealed...
2 heterozygous variants in SACS gene: a pathogenic variant c.8108G>A (p.Arg2703His) inherited from mother and a variant of uncertain significance c.7216T>C (p.Ser2406Pro) inherited from his father. The c.8108G>A sequence change replaces arginine, which is basic and polar, with histidine, which is basic and polar, at codon 2703 of the SACS protein. This missense change had not been reported in patients with autosomal recessive spastic ataxia of Charlevoix–Saguenay (ARSACS). This variant is listed in ClinVar with conflicting interpretations, the most recent being pathogenic. Advanced modeling of protein sequence and biophysical properties performed at the lab that conducted this testing indicated that this missense variant was expected to disrupt SACS protein function. This variant was determined to be pathogenic. The c.7216T>C variant inherited from his father replaces serine with proline at codon 2406 of the SACS protein. This variant is not present in population databases.

Based on his clinical presentation of ataxia, spasticity, neuropathy, and cerebellar atrophy, and genotypic findings, he was diagnosed with ARSACS. His ophthalmologic examination and echocardiogram were unremarkable. He remained stable at his most recent follow-up at the age of 18 years.

**Discussion**

Charlevoix–Saguenay spastic ataxia is a autosomal recessive hereditary ataxia syndrome that was first diagnosed in regions of Charlevoix and Saguenay–Lac-St-Jean in Quebec, Canada. It is caused by mutations in SACS gene on chromosome 13 which encodes the protein Sacsin. There are several specific mutations that are linked to familial clusters, and several distinct mutations have been reported for sporadic cases. Both intra- and interfamilial phenotypic variability has been observed in ARSACS.

**Table 1. Nerve Conduction Study Findings in Our Patient at Initial Presentation and at 1-Year Follow-up.**

| Nerve          | Stimulus | Recording site | Latency (ms) | Amplitude (motor = mV, sensory = µV) | Conduction velocity (m/s) |
|----------------|----------|----------------|--------------|--------------------------------------|--------------------------|
| Motor nerve conduction studies |           |                | Initial presentation |                  |                          |
| Right median   | Wrist    | APB            | 7            | 8.1                                  |                          |
|                | Elbow    | APB            | 13.3         | 8.1                                  | 35                       |
| Right ulnar    | Wrist    | ADM            | 5.7          | 8.0                                  |                          |
|                | Below elbow | ADM          | 10.3         | 7.9                                  | 35                       |
|                | Above elbow | ADM          | 12.8         | 7.9                                  | 40                       |
| Right tibial   | Ankle    | AH             | 26.8         | 0.3                                  |                          |
| Popliteal fossa | AH        |                | 45.0         | 0.3                                  | 15                       |
| Right peroneal | Ankle    | EDB            | 21.0         | 0.1                                  |                          |
| Fibula head    | EDB      |                | 45.1         | 0.1                                  | 10                       |
| Popliteal fossa | EDB       | No response    | No response  | No response                          |                          |
| Sensory nerve conduction studies |           |                | At 1-year follow-up |                  |                          |
| Right sural, median, and ulnar sensory responses were unequivocal | | | | |
| Motor nerve conduction studies |           |                |                   |                          |                          |
| Right median   | Wrist    | APB            | 7              | 9.0                                  |                          |
|                | Elbow    | APB            | 12.8          | 8.6                                  | 36                       |
| Right ulnar    | Wrist    | ADM            | 5.7           | 9.3                                  |                          |
|                | Below elbow | ADM          | 10.9          | 9.3                                  | 40                       |
|                | Above elbow | ADM          | 13.4          | 8.9                                  | 40                       |
| Right tibial   | Ankle    | AH             | 27.4          | 0.3                                  |                          |
| Popliteal fossa | AH        |                | 47.4          | 0.2                                  | 16                       |
| Right peroneal | Ankle    | EDB            | 20.2          | 0.2                                  |                          |
| Fibula head    | EDB      |                | 44.8          | 0.1                                  | 11                       |
| Popliteal fossa | EDB       | No response    | No response  | No response                          |                          |
| Right peroneal | Fibula head | TA            | 2.1           | 1.1                                  |                          |
| Popliteal fossa | TA        | No response    | No response  | No response                          |                          |
| Sensory nerve conduction studies |           |                |                   |                          |                          |
| Right radial   | Forearm  | Forearm-snuff box | 7.5       | 8                                     | 13                       |
| Right sural, median, and ulnar sensory responses were unequivocal | | | | |

Abbreviations: ms, milliseconds; mV, millivolts; µV, microvolts; m/s, meter/second; APB, abductor pollicis brevis; ADM, abductor digitorum minimi; AH, abductor hallucis; EDB, extensor digitorum minimi; TA, tibialis anterior.
The ARSACS is characterized by a triad of progressive cerebellar ataxia, progressive spasticity, and axonal/demyelinating peripheral neuropathy, and may manifest with myriad features such as dysarthria, weakness in lower extremities and distal muscle wasting, foot deformities, retinal striaion, prolapse of the mitral valve and rarely intellectual disability, hearing loss, and myoclonic epilepsy.\(^{1,3,6-9}\) It typically manifests with gait ataxia in the first decade of life with progressive decline over the next few decades, with patient becoming wheelchair-bound by the fifth decade of life.\(^{10}\) Some patients can manifest with atypical cases that may present later in life or in absence of one of the classical features at the time of presentation.\(^{11-13}\) Postmortem studies have revealed cerebellar atrophy with absence of Purkinje cells and spino-cerebellar demyelination.\(^{14}\) Nerve conduction studies usually reveal neuropathy with demyelinating features\(^{15}\) but may present with axonal polyneuropathy as well.\(^{10}\)

Our patient initially presented with marked demyelinating neuropathy without any involvement of other organ systems. It was not until the patient developed spasticity and ataxia that was perceived on the follow-up visit that the suspicion for spastic ataxia was raised. His genetic studies revealed one pathogenic mutation and one variant of uncertain significance in \(SACS\) gene inherited from his asymptomatic mother and father, respectively. Both parents were completely asymptomatic and were carriers of these changes. It is possible that the confluence of these 2 variants caused a milder version of spastic paraparesis where the neuropathy presented prior to the spasticity. Nerve root enhancement on MRI is often seen with inflammatory neuropathies but can also be seen in patients with hereditary neuropathies\(^{16}\) as this case, which can confound the clinical picture.

**Conclusion**

Autosomal recessive spastic ataxia or Charlevoix–Saguenay spastic ataxia can manifest as demyelinating polyneuropathy at first presentation, and index of suspicion should be higher in young patients with cerebellar atrophy in the brain imaging. The novel variants in \(SACS\) gene noted in our patient should be added to the repertoire of pathogenic variants causing ARSACS.

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**Ethical Approval**

Our institution does not require ethical approval for reporting individual cases or case series.

**Informed Consent**

Verbal informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

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