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Extending The Genetic And Clinical Range Of Charlevoix Saguenay's Autosomal Recessive Spastic Ataxia- A Case Report

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ABSTRACT
A relatively rare neurological disease called Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS) is characterized by early-onset ataxia, neuropathy, and spasticity caused on by mutations in the SACS gene. This case report discusses a 23-year-old female presenting with progressive ataxia, sensory neuropathy, and bilateral sensorineural hearing loss. Genetic testing identified a single heterozygous variant in the SACS gene, potentially associated with ARSACS, though typically two variants are required for diagnosis. The absence of a second mutation poses a challenge, suggesting the need for further genetic analysis to detect possible intronic mutations or large deletions. This case expands the known clinical spectrum of ARSACS and highlights the importance of comprehensive molecular testing and genetic counseling to better understand the disease's genetic basis and presentation.

Keywords: ARSACS, SACS gene, Neurodegenerative disorders, Cerebellar ataxia, Sensorineural hearing loss, Genetic counseling

INTRODUCTION

Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS) is a rare hereditary neurodegenerative disorder characterized by early-onset cerebellar ataxia, peripheral neuropathy, and pyramidal tract signs.[1] First discovered in 1978 in the Quebec region of Canada, the condition has since been documented in diverse populations around the world.[2] It is caused by mutations in the SACS gene, which encodes sacsin, a molecular chaperone responsible for proper protein folding.[3] ARSACS is typically inherited in an autosomal recessive manner, requiring both parents to pass on the mutated gene for a child to develop the disease. However, phenotypic variability has been noted, which can complicate the diagnosis.[4]
The present case report describes a female patient with a clinical history of progressive ataxia, sensory neuropathy, and bilateral sensorineural hearing loss. Genetic testing revealed a heterozygous 'likely pathogenic' variant in the SACS gene, raising the possibility of ARSACS as a differential diagnosis despite the identification of only one variant. This case extends the clinical and genetic spectrum of ARSACS, underscoring the importance of comprehensive genetic and clinical evaluation in patients with neurodegenerative symptoms. Further molecular investigations are recommended to explore the potential presence of a second pathogenic variant and to provide a clearer understanding of the genotype-phenotype correlation in this patient.

CASE PRESENTATION

A 23-year-old female patient reported a gradual decline in neurological function, characterized by chronic ataxia and sensory peripheral neuropathy. Initial symptoms included decreased hearing in the right ear starting 4 years

prior, followed by bilateral hearing loss, difficulty walking, and tingling numbness. The patient also experienced swaying while walking, exaggerated knee and ankle reflexes, and increased muscle tone in the lower limbs, but retained normal upper limb function. Additional symptoms included hypothyroidism, facial pain after mastication, burning sensations behind the ears, and choking or coughing while eating and drinking.

Clinical Evaluation:

The patient was diagnosed with bilateral sensorineural hearing loss based on a BERA test.Nerve conduction velocity (NCV) tests indicated sensory axonal peripheral neuropathy affecting both lower limbs. Brain MRI, EEG, and abdominal ultrasound were unremarkable. The patient's father had a history of tonsil cancer and died at 38 years of age. Initial differential diagnoses included neuronal ceroid lipofuscinosis (NCL), spinocerebellar ataxia, mitochondrial disease, and inborn errors of metabolism.

Genetic Analysis:

The genetic test identified a heterozygous 'likely pathogenic' variant in exon 10 of the **SACS** gene, which is known to be associated with ARSACS. The identified variant (c.10298delC) is a deletion that causes a frameshift and a premature termination of the protein, likely resulting in loss of function. No clinically significant copy number variations (CNVs) or disease-causing variants in the mitochondrial genes were detected.

Additionally, the Exome Plus Test was conducted to analyze over 3,400 genes, including those associated with neurological, neurodegenerative, mitochondrial, and metabolic conditions. This test utilized next-generation sequencing (NGS) to achieve high coverage, with most regions sequenced to a depth greater than 100X. Despite the identification of only a single heterozygous variant, the possibility of a second pathogenic variant, either in the promoter/intronic regions or due to large deletions/duplications, cannot be ruled out.

The detection of this 'likely pathogenic' variant in the **SACS** gene suggests a possible association with ARSACS, a condition that typically requires two altered gene copies for disease manifestation. Despite the absence of a second variant, ARSACS remains a potential diagnosis given the patient's clinical presentation and genetic findings. Genetic counseling is recommended to discuss the test results, and further molecular diagnostic testing is advised to provide a more comprehensive genotype-phenotype correlation. Identifying any additional variants, possibly in non-coding regions, may help confirm the diagnosis.

This case broadens the clinical spectrum of ARSACS, underscoring the importance of thorough clinical and genetic evaluation in patients presenting with progressive neurological symptoms and sensorineural hearing loss.

DISCUSSION

The diagnosis of ARSACS in this patient is supported by the clinical presentation and the identification of a heterozygous 'likely pathogenic' variant in the SACS gene. ARSACS typically presents with early-onset cerebellar ataxia, peripheral neuropathy, and spasticity, along with other symptoms such as dysarthria, distal muscle wasting, and sensorineural hearing loss. The patient's symptoms, including progressive ataxia, sensory neuropathy, and bilateral sensorineural hearing loss, align with the phenotypic characteristics associated with ARSACS. However, the identification of only a single heterozygous variant poses a diagnostic challenge, as ARSACS is classically inherited in an autosomal recessive manner, which usually requires two pathogenic variants for full disease expression.[4] Similar symptoms were seen in the case report described by **Synofzik, M. et al.[5]**

In this case, the variant found in the SACS gene is a frameshift mutation that results in an early stop codon., likely resulting in a truncated, non-functional protein.[6] Previous reports in the literature have established that loss-of-function mutations in SACS are associated with ARSACS.[7] However, the absence of a second detectable variant raises the question of whether this patient's condition could result from a different genetic mechanism, such as a second variant located in non-coding regions, large deletions not covered by standard sequencing techniques, or a potential digenic inheritance involving another gene.

The phenotypic variability observed in ARSACS could be due to several factors, including incomplete penetrance, modifier genes, or environmental influences.[8] Some cases have been reported where individuals with a single heterozygous pathogenic variant exhibit clinical features of ARSACS, suggesting that haploinsufficiency or a dominant-negative effect might play a role.[4] Alternatively, a second, unidentified variant might be present in the intronic or promoter regions, or there could be a large heterozygous deletion not detectable by the current testing methods. These possibilities underscore the need for comprehensive genetic counseling and further molecular analysis, including whole-genome sequencing or multiplex ligation-dependent probe amplification (MLPA), to search for other potential mutations or large deletions.

The patient's family history of tonsil cancer in her father raises the question of a broader genetic predisposition, though more detailed information is required to establish a connection with the patient's neurological symptoms.Similar cases have been reported where family members, particularly from the Charlevoix-Saguenay region, present with early-onset neurological symptoms. For example, **Martin et al.[8]** described several cases where young patients exhibited early signs of ataxia and increased deep tendon reflexes, with some having a

positive family history, while others did not show any clear familial link to neurodegenerative diseases. A 9-year-old girl exhibited mild ataxia and heightened deep tendon reflexes, with a family background showing her mother's pregnancy and delivery were uneventful. In a different case, the patient exhibited difficulties with walking and frequent falls. Similarly, a girl presented with early signs of an ataxic gait, though her family history was largely unremarkable, except for her father, who displayed a slow walking pace and delayed speech development.[9] These observations suggest that while ARSACS can occur sporadically, there may be cases with familial aggregation or a broader genetic predisposition that requires further investigation.

The difficulty of detecting ARSACS and the significance of taking a wide differential diagnosis into account in patients exhibiting increasing neurological symptoms are both highlighted by this case. The presence of a single heterozygous variant in the SACS gene, while suggestive of ARSACS, requires careful interpretation and further investigation. Genetic counseling is crucial to discuss the implications of these findings, guide additional testing, and provide appropriate support to the patient and her family. Continued re-evaluation of the genetic data, including periodic reanalysis as new knowledge emerges, will be important for reaching a definitive diagnosis and understanding the full genetic and phenotypic spectrum of ARSACS.

CONCLUSION

This case report extends the understanding of ARSACS by presenting a patient with a clinical phenotype consistent with ARSACS and a heterozygous 'likely pathogenic' variant in the SACS gene. While ARSACS typically requires two pathogenic variants for manifestation, this case underscores the potential for phenotypic expression with a single detected variant, raising the need for further exploration into other genetic mechanisms, such as intronic mutations, large deletions, or modifier genes. Comprehensive genetic counseling and additional molecular testing are recommended to achieve a more definitive diagnosis and to enhance our understanding of the genotype-phenotype relationship in ARSACS. This case emphasizes the complexity of diagnosing rare neurodegenerative disorders and highlights the importance of ongoing genetic evaluation in patients with such presentations.

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