ELECTROPHYSIOLOGICAL CHARACTERISTICS OF AUTOSOMAL-RECESSIVE SPASTIC ATAXIA OF CHARLEVOIX-SAGUENAY IN A TURKISH FAMILY*

CHARLEVOIX-SAGUENAY’IN OTOZOMAL RESESIF SPASTIK ATAKSİ SENDROMU: BİR TÜRK AİLESİNDE ELEKTROFİZYOLOJİK ÖZELLİKLER

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ABSTRACT
The autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS), presenting with spinocerebellar ataxia, dysarthria, nystagmus, and spastic paraparesis, is a gradually progressive hereditary disease. Sensorimotor polyneuropathy may also accompany the symptoms. Herein, we present the electrophysiologic findings of a Turkish family with ARSACS in combination with clinical and genetic features to better describe the characteristics of the polyneuropathy in ARSACS. Regarding the electrophysiologic findings, however, the demyelinating characteristics were prominent and there were findings compatible with secondary axonal degeneration. Rare hereditary diseases such as ARSACS must be suspected in the presence of polyneuropathies with demyelinating characteristics accompanying pyramidal findings and ataxia.

Keywords: Charlevoix-Saguenay, ARSACS, electrodiagnosis, demyelinating polyneuropathy

ÖZET
Charlevoix-Saguenay’ın otozomal resesif spastik ataksi sendromu (ARSACS), spinocerebellar ataksi, dizartri, nistagmus ve spastik paraparezi ile seyreden ilerleyici bir herediter hastalıdır. Sensörümotor polinöropati semptomlara eşlik edebilir. Bu vaka serisinde, ARSACS’la eşlik eden polinöropatinin niteliklerinin daha yani anlaşılaması amacıyla, ARSACS’li bir aileden klinik ve genetik özellikler ile birlikte elektrofizyolojik bulgular sunulmuştur. Elektrofizyolojik bulgular, demiyelinizan özellikte bir polinöropatı sendromu varlığı ile uyumlu olmadığı gibi, hastalarla ikinci aksonal dejenerasyonu işaret eden bulgularla mevcuttu. Demiyelinizan özellikli bir polinöropati yapan bulgular ve ataksi eşlik ettiği için ARSACS gibi nadir herediter hastalıktan şüphelenilmelidir.

Anahtar Kelimeler: Charlevoix-Saguenay, ARSACS, elektromiyografi, demiyelinizan polinöropati

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INTRODUCTION

The autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is a progressive hereditary disease characterized by ataxia and spastic paraparesis. Sensorimotor polyneuropathy may also accompany the symptoms (1).

The sacsin gene (SACS), responsible for ARSACS, is located on chromosome 13q12.12, encoding the protein of the same name, and has been described by Engert JC et al. in 2000 (2). More than 200 mutations have been reported worldwide since then (1, 3, 4).

Moderate-to-severe axonal neuropathy with demyelinating characteristics were demonstrated in patients with ARSACS by electrophysiologic studies, and these findings were confirmed in biopsies (5, 6).

We present clinical, genetic, and electrophysiologic findings of a Turkish family with ARSACS to describe the pattern of polyneuropathy.

CASE REPORTS

Patient 1. A 41-year-old man was considered the index case, and his symptoms developed when he was 15. He became wheelchair dependent at the age of 40. An electrophysiologic test revealed demyelinating features affecting motor and sensory fibers, and accompanying secondary axonal involvement. Whole exome sequencing (WES) was performed for the index patient. WES revealed a novel homozygous truncating variant in the SACS gene (ENST00000382292.3:c.7720dupA, p.Arg2574LysfsTer4) leading to a frameshift. VarSome indicated the variant c.7720dupA as “pathogenic.”

American College Of Medical Genetics And Genomics (ACMG) scores for the variant are PV51, PM2, and PP3, and the GERP score is 5.59. The variant was confirmed by Sanger sequencing in all available family members.

Patient 2. The elder brother of the index case was 55 years old, and he was bedbound due to similar symptoms that emerged when he was 15. Neurologic and electrophysiologic examinations could not be performed on this patient.

Patient 3. The 49-year-old sister of the index case developed sensorimotor polyneuropathy when she was four. She could hardly walk without support in the last ten years.

Patient 4. The niece of the index case was 18 years old; her symptoms developed at the age of 10. Her clinical process was moderate, compared with other family members. She managed to perform her daily activities independently.

Regarding the electrophysiologic characteristics, the median, sural, and peroneal superficial sensory nerve action potentials (SNAPs) of patients 1 and 3 could not be obtained. In patient 4, the amplitudes of median, sural, and peroneal superficial SNAPs were reduced and conduction velocities (CVs) of these nerves were slow. However, ulnar SNAP could not be obtained in patient 3. The amplitudes of ulnar SNAPs and CVs were reduced in patients 1 and 4. Tibial and peroneal compound muscle action potentials (CMAPs) could not be obtained in patient 1. The amplitudes of tibial and peroneal CMAPs were reduced, distal latencies were prolonged, and CVs were slow compatible with demyelination in patients 3 and 4. The amplitudes of ulnar CMAPs of all patients were normal, with reduced CVs.

The distal latencies of median CMAPs were prolonged and CVs were slow in all patients. The amplitude of median motor CMAP was reduced in patient 1, and the amplitudes of median CMAPs were normal in patients 3 and 4. In needle electromyography (EMG), denervation was not detected in muscles that were evaluated, and moderate neurogenic changes were detected on distally located muscles. The needle EMG of patient 3 revealed chronic neurogenic changes with significant asymmetric characteristics in lower extremities, which were interpreted as the sequela of poliomyelitis.

DISCUSSION

Charlevoix-Saguenay disease was first reported in 1978 in the Charlevoix-Saguenay-Lac-Saint-Jean region in Quebec, Canada among Canadians of French origin (7). The earliest finding is spasticity in the lower extremities, becoming apparent in early childhood, followed by ataxia (1, 8). Absent deep tendon reflex generally develops around the age of 25 due to progressive distal neuropathy (5).

Most of the mutations found in SACS gene were in exon 10, consisting of missense mutations, nonsense mutations, or frameshift variants (3). Besides the French-Canadian variants which were mainly truncating, several mutations were identified across Europe as well as in Turkiye (9-13). The clinical findings in these cases presented from Turkiye were consistent with the common clinical presentation of ARSACS, similar to our family. We reported a novel homozygous variant in the SACS gene leading a frameshift.

In our patients, the electrophysiologic pattern of polyneuropathy reveals a demyelinating type with secondary axonal degeneration. The type of peripheral nerve involvement is controversial in ARSACS. It was previously suggested that it was similar to axonopathy, myelinopathy, and intermediate forms of Charcot–Marie–Tooth disease (CMT) neuropathy (1, 5, 14). In patients 1 and 3, indiscernible motor and sensory responses were related to a more advanced stage of the disease.
when compared to those in patient 4. Demyelinating features were present predominantly in motor nerve fibers. Secondary axonal degeneration was compatible with a length dependent pattern. None of the patients demonstrated equally homogenous deceleration of motor and sensory nerves CVs, which are characteristics for hereditary demyelination neuropathies. In addition, CMAPs showed an increased temporal dispersion as a sign of demyelination, particularly in lower extremity distal muscles.

As compared to our family, it was reported that neuropathy had both axonal and demyelinating characteristics in a Spanish family with ARSACS. Researchers suggested that this involvement, similar to intermediate forms of CMT neuropathy, was associated with both axon and myelin dysfunction in peripheral nerves (14). In another study consisting of five patients, the authors suggested that a myelin sheath defect had multifocal distribution; the process was associated with defect in myelin development, and the degeneration of peripheral axons accompanied the process (15). Previous cases reported from Turkey also revealed both axonal, demyelinating or mixed types of polyneuropathy (9-13). These findings indicate that within autosomal recessive ataxias accompanied with axonal, demyelinating or mixed polyneuropathy, ARSACS disease should be considered in the diagnosis.

In conclusion, hereditary ataxias must be kept in mind when polyneuropathy accompanies in patients who present with symptoms of imbalance and family history. Although the involvement pattern of polyneuropathy is heterogeneous in electrophysiologic evaluation, rare hereditary diseases such as ARSACS should be suspected in the presence of polyneuropathy with demyelinating characteristics, accompanying pyramidal findings, and ataxia. This hereditary ataxia should be considered in the differential diagnosis of demyelinating neuropathies, some of which are immune mediated and responsive to immunosuppressant treatment.

**Informed Consent:** Written consent was obtained from the participants.

**Ethics Committee Approval:** This study was approved by the Ethical Committee of the Istanbul University, Istanbul Faculty of Medicine (Date: 05.02.2021, No: 04).

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**REFERENCES**

1. Bouhlal Y, Amouri R, El Euch-Fayeche G, Bentati F. Autosomal recessive spastic ataxia of Charlevoix-Saguenay: an overview. Parkinsonism Relat Disord 2011;17(6): 418-22. [CrossRef]
2. Engert J, Berube P, Mercier J, Dore C, Lepage P, Ge B, et al. ARSACS, a spastic ataxia common in northeastern Quebec, is caused by mutations in a new gene encoding an 11.5-kb ORF. Nat Genet 2000;24(2):120-5. [CrossRef]
3. Bagaria J, Bagyinsky E, An SSA. Genetics of autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) and role of saccin in neurodegeneration. Int J Mol Sci 2022;23(1):552. [CrossRef]
4. Longo F, De Ritis D, Miluzio A, Fraticelli D, Baets J, Scarlato M, et al. Assessment of saccin turnover in patients with ARSACS: Implications for molecular diagnosis and pathogenesis. Neurology 2021;97(23): e2315-27. [CrossRef]
5. El Euch-Fayache G, Lalani I, Amouri R, Turki I, Ouahchi K, Hung WY, et al. Phenotypic features and genetic findings in saccin-related autosomal recessive ataxia in Tunisia. Arch Neurol 2003;60(7):982-8. [CrossRef]
6. Peyronnard JM, Charron L, Barbeau A. The neuropathy of Charlevoix-Saguenay ataxia: an electrophysiological and pathological study. Can J Neuro Sci 1979;6(2):199-203. [CrossRef]
7. Bouchard JP, Barbeau A, Bouchard R, Bouchard RW. Autosomal recessive spastic ataxia of Charlevoix-Saguenay. Can J Neurol Sci 1978;5(1): 61-9. [CrossRef]
8. Bouchard JP, Richter A, Mathieu J, Brunet D, Hudson TJ, Morgan K, et al. Autosomal recessive spastic ataxia of Charlevoix-Saguenay. Neuromuscul Disord 1998;8(7):474-9. [CrossRef]
9. Gucuyener K, Ozquil K, Paternotte C, Erdem H, Prud’homme JF, Ozguc M, et al. Autosomal recessive spastic ataxia of Charlevoix-Saguenay in two unrelated Turkish families. Neuropediatrics 2001;32(3):142-6. [CrossRef]
10. Richter AM, Ozguc RK, Poisson VC, Topaloglu H. Private SACS mutations in autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) families from Turkey. Neurogenetics 2004;5(3):165-70. [CrossRef]
11. Kurt S, Kartal E, Aksoy D, Cevik B, Eken AG, Sahbaz I, et al. Coexistence of autosomal recessive spastic ataxia of Charlevoix-Saguenay and spondyloepiphyseal dysplasia in a Turkish patient. J Neurol Sci 2015;357(1-2):290-1. [CrossRef]
12. Samanci B, Gokalp EE, Bilgic B, Gurvit H, Artan S, Hanagasi HA. A novel SACS p.Pro4154GlnfsTer20 mutation in a family with autosomal recessive spastic ataxia of Charlevoix-Saguenay. Neurol Sci 2021;42(7):2969-73. [CrossRef]
13. Oguz KK, Haliloglu G, Temucin C, Gocmen R, Has AC, Doerschner K, et al. Assessment of whole-brain white matter by DTI in autosomal recessive spastic ataxia of Charlevoix-Saguenay. AJNR Am J Neuroradiol 2013;34(10):1952-7. [CrossRef]

14. Garcia A, Criscuolo C, de Michele G, Berciano J. Neurophysiological study in a Spanish family with recessive spastic ataxia of Charlevoix-Saguenay. Muscle Nerve 2008;37(1):107-10. [CrossRef]

15. Albers JW, Kelly JJ, Jr. Acquired inflammatory demyelinating polyneuropathies: clinical and electrodiagnostic features. Muscle Nerve 1989;12(6):435-51. [CrossRef]