CASE REPORT / OLGU SUNUMU
DOI: 10.26650/IUITFD.984032
İst Tıp Fak Derg 2022 / J Ist Faculty Med 2022

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

CHARLEVOİX-SAGUENAY'IN OTOZOMAL RESESİF SPASTİK ATAKSİ SENDROMU: BİR TÜRK AİLESİNDE ELEKTROFİZYOLOJİK ÖZELLİKLER

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Cite this article as: Mehdikhanova L, Sirin NG, Bilgic B, Hanagasi H, Basak AN, Baslo MB, et al. Electrophysiological characteristics of autosomal-recessive spastic ataxia of charlevoix-saguenay in a Turkish family. J Ist Faculty Med 2022;85(2):275-8. doi: 10.26650/IUITFD.984032

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 (ARSCAS), spinoserebellar ataksi, dizartri, nistagmus ve spastik paraparezi ile seyreden ilerleyici bir herediter hastalıktır. Sensörimotor polinöropati semptomlara eşlik edebilir. Bu vaka serisinde, ARSACS'a eşlik eden polinöropatinin niteliklerinin daha iyi anlaşılması amacıyla, ARSACS'lı bir ailede klinik ve genetik özellikler ile birlikte elektrofizyolojik bulgular sunulmuştur. Elektrofizyolojik bulgular, demiyelinizan özellikte bir polinöropati sendromu varlığı ile uyumlu olsa da, hastalarda ikincil aksonal dejenerasyonu işaret eden bulgularda mevcuttu. Demiyelinizan özellikli bir polinöropatiye piramidal bulgular ve ataksi eşlik ettiğinde ARSACS gibi nadir herediter hastalıktan şüphelenilmelidir.

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

*The study was previously published in abstract form: "32. Ulusal Klinik Nörofizyoloji EEG-EMG Kongresi, Bodrum, 2016," Poster presentation number 30, page 63.

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Submitted/Başvuru: 03.10.2021 • **Revision Requested/Revizyon Talebi:** 15.11.2021 •
Last Revision Received/Son Revizyon: 07.02.2022 • **Accepted/Kabul:** 07.02.2022 • **Published Online/Online Yayın:** 14.03.2022

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 PVS1, 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 poliomyelitis 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 Turkiye 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).

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- L.M., M.B.B., E.K.O.; Data Acquisition- L.M., M.B.B., E.K.O., B.B., H.H., A.N.B., N.G.S.; Data Analysis/Interpretation- L.M., M.B.B., E.K.O., B.B., H.H., A.N.B., N.G.S.; Drafting Manuscript- L.M., M.B.B., E.K.O., B.B., H.H., A.N.B., N.G.S.; Critical Revision of Manuscript- L.M., M.B.B., E.K.O., B.B., H.H., A.N.B., N.G.S.; Approval and Accountability- L.M., M.B.B., E.K.O., B.B., H.H., A.N.B., N.G.S.

Conflict of Interest: Authors declared no conflict of interest

Financial Disclosure: This study was partially funded by Scientific Research Projects Coordination Unit of Istanbul University. Project number: 37697.

Acknowledgements: The molecular analysis of the family was performed at Boğaziçi University. We gratefully acknowledge the generous support of Suna and Inan Kıraç Foundation and the assistance of Fulya Akçimen, Aslı Gündoğdu, and Irmak Şahbaz from NDAL.

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