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# Diagnostic Value of Neurophysiological Evaluation in Patients with ARSACS

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## Abstract

**Title:** Diagnostic value of neurophysiological evaluation in patients with ARSACS.

**Background:** Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is characterized by early-onset spastic ataxia with congenital deformity of the extremities and retinal striation. Although it has been known that ARSACS is frequently associated with peripheral neuropathy, it has not been described in detail using electrophysiology.

**Methods and finding:** We report the clinical, electrophysiological, and nerve ultrasonographic findings of three patients with ARSACS. Our patients exhibited electrophysiological signs of both myelinopathy and axonopathy, predominantly affecting the lower limbs, with slow MCV and prolonged F wave latency. These results suggested that the characteristics of neuropathy in ARSACS might arise from primary length-dependent peripheral myelinopathy associated with secondary axonal injury that worsened over a long period. Nerve ultrasonography revealed slight nerve enlargement, also suggestive of peripheral nerve demyelnation. These findings indicated that the peripheral neuropathy observed in patients with ARSACS might predominantly be demyelinating in origin with patchy demyelination.

**Conclusion:** These electrophysiological and ultrasonographical observations might be helpful for the accurate diagnosis of ARSACS because clinical features of ARSACS are diverse, including atypical cases with a spasticity-lacking phenotype or cases without a family history.

**Keywords:** ARSACS; Peripheral neuropathy; Myelinopathy; Nerve conduction study; Nerve ultrasonography; Sacsin gene

**List of abbreviations: ARSACS**: Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay; CIDP: Chronic Inflammatory Demyelinating Polyneuropathy; CMAPs: Compound Muscle Action Potentials; CSA: Cross-Sectional Area; DML: Distal Motor Latency; MCV: Motor Conduction Velocity; SCV: Sensory Conduction Velocity; SNAPs: Sensory Nerve Action Potentials

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## Introduction

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is a hereditary neurodegenerative disorder; Bouchard first reported this disorder in patients residing at Charlevoix-Saguenay in northern Quebec in 1978 [1]. In 2000, the gene responsible for ARSACS, *SACS,* was identified in Quebecois patients. *SACS* gene, mapping to chromosome 13q11, consists of a single large exon spanning 12,794 base pairs encoding the sacsin protein [2]. After mapping and identification of the gene in patients with ARSACS, non-Quebecois families with ARSACS have been reported from Italy [3], Tunisia [4], Turkey [5], Spain [6], and Belgium [7], thus showing a worldwide occurrence. Since Ogawa and colleagues first reported a Japanese family with ARSACS with a missense mutation in 2004 [8], additional such families have been reported in Japan [9,10].

ARSACS is characterized by early-onset spastic ataxia, dysarthria, nystagmus, distal muscle atrophy, finger or foot deformities, and retinal hypermyelination; it is always complicated with peripheral

neuropathy [1]. Although the clinical phenotype of the patients in Quebec is uniform, non-Quebecois cases including Japanese show phenotypic variability [1]. Especially in Japan, sacsin-related ataxia without spasticity and hyperreflexia has been reported [9,11,12]. These cases, lacking a core clinical feature of ARSACS, are sometimes difficult to diagnose. Severe peripheral nerve degeneration may mask any spasticity in these patients [9,11]. Therefore, it is important to evaluate the peripheral neuropathy of patients with ARSACS. To our knowledge, there have been only a few reports of the characteristics of peripheral neuropathy in ARSACS, especially those with detailed electrophysiological findings.

In this study, we describe the characteristics of neuropathy in ARSACS using nerve conduction studies and nerve ultrasonography.

# Subjects and Methods

## Nerve conduction studies

Motor nerve conduction studies were undertaken for the median, ulnar, peroneal, and tibial nerves by conventional procedures using a Viking Select EMG (Nicolet Biomedical Japan). The muscles measured in conjunction with these nerves were the abductor pollicis brevis, abductor digiti minimi, extensor digitorum brevis, and abductor hallucis, respectively. Measurements included distal motor latency (DML), motor conduction velocity (MCV), and the amplitude of compound muscle action potentials (CMAPs). CMAP amplitude was measured between the baseline and negative peak.

Antidromic sensory nerve conduction studies were performed in the median, ulnar, and sural nerves. Measurements included sensory conduction velocity (SCV) and sensory nerve action potentials (SNAPs). SNAP amplitude was measured between the baseline and negative peak.

## Nerve ultrasonography

Ultrasonography was performed with a 9-MHz electronic linear array transducer (LOGIQ7: GE Healthcare). The patients were placed in a supine position with the arms and neck relaxed. The cross-sectional area and the longitudinal nerve diameter of the median nerve were measured at the mid-forearm. The longitudinal nerve diameters of the cervical nerves were measured at C5, C6, and C7. Three measurements were obtained for each nerve to determine intra-rater reliability, and the mean value of the three measurements was used for analyses.

# Results

## Case report

**Case 1**: A 49-year-old woman complained of progressive gait disturbance and urinary incontinence. When she was around the age of 8 years, it was noticed that she could not run fast. Since the age of 31 years, she required a cane for walking and was confined to a wheel chair at age 39. Neurological examination at age 49 showed gaze-evoked nystagmus, spasticity, dysarthria, truncal and limb ataxia, and urinary incontinence. Bilateral distal muscle weakness and mild atrophy in the hands and feet were observed. She had deformity of the left toes with pes cavus. Tendon reflexes were absent in all limbs. Her younger sister had the same symptoms and they were born to consanguineous parents.

**Case-2**: This patient is the younger sister of the patient in Case 3. She is a 22-year-old woman with similar clinical presentation to proband. She also had spastic-ataxic gait, mild ataxic dysarthria, and saccadic eye movements with gaze evoked nystagmus. However, she also had hypoplasia in her left upper and lower extremities, without pes cavus.

**Case-3**: A 27-year-old man complained of slowly progressing gait disturbance. His mother noticed his unsteady gait while he was at elementary school. A neurological examination at age 27 showed a severe spastic-ataxic gait, mild ataxic dysarthria, and pes cavus. Ocular movements were full, but saccadic with nystagmus during lateral gaze. Cognitive function was normal. Bilateral distal muscle weakness was present, and his hands and feet were mildly amyotrophic. Pyramidal involvement was revealed by brisk upper and lower limb tendon reflexes, spasticity, and a positive bilateral Babinski sign.

Brain MRI showed moderate atrophy of the upper cerebellar vermis in all patients. Fundoscopy revealed hypermyelinated retinal fibers in Case 3. Genetic analysis of Case 1 revealed the homozygous mutation c. 10906C>T, whereas those of cases 2 and 3 revealed a novel compound heterozygous mutation c. 3769C>A / 11361-11362InsT, in the Sacsin gene.

## Nerve conduction studies

The results of the nerve conduction studies are summarized in **(Table 1)**. For the upper-limb nerves, the median and ulnar nerves showed slightly prolonged DMLs, and reduced MCVs with normal CMAPs. SNAPs were not evoked in the median or ulnar nerves except in Case 2 (which only had median nerve SNAPs detectable). Among the lower-limb nerves, CMAPs were not evoked in the peroneal nerve. Meanwhile, the tibial nerve showed reduced CMAPs (Case 3) and reduced MCVs (Case 2) with a prolonged DML (Case 2 and 3). SNAPs were not evoked in the sural nerve.

## Nerve ultrasonography

Nerve ultrasonography was performed in two cases (Cases 1 and 3) (**Table 2**). Both cases showed normal CSA in the median nerve and in the longitudinal nerve diameters at cervical nerve roots compared with the reference value [13]. However, some of the findings suggested a nerve enlargement: the CSA of the median nerve in Case 1, and the longitudinal nerve diameter at the C7 nerve root in Case 3.

# Discussion

In this study, we characterized the neurophysiological features observed in patients with ARSACS. Upper-limb motor nerves presented with slowing conduction velocities and prolonged distal and F-wave latencies. In the lower-limb nerves, CMAPs were

**Table 1** Results of nerve conduction studies in three patients with ARSACS.

| Upper - limb nerves | | Case1 | Case2 | Case3 |
|---|---|---|---|---|
| Median nerve | DML (ms) | 4.4 | 5.7 | 5.5 |
| | MCV (m/s) | 44.3 | 42.9 | 42.5 |
| | Distal CMAP/ Proximal CMAP (mv) | 6.5/6.47 | 6.43/6.19 | 9.01/8.45 |
| | F-wave latency (ms) | 31.6 | 30.1 | 30.3 |
| | SCV(m/s)/SNAP (μV) | NR | 35.2/2.27 | NR |
| Ulnar nerve | DML (ms) | 3.5 | 3.5 | 3.6 |
| | MCV-1/MCV-2 (m/s) | 41.7/46.4 | 40/42.8 | 42.1/30.5 |
| | Distal CMAP/ Proximal CMAP (mv) | 6.15/6.32 | 9.82/9.6 | 5.64/5.65 |
| | F-wave latency (ms) | 30 | 24.2 | 30.2 |
| | SCV(m/s)/SNAP (μV) | NR | NR | NR |
| **Lower - limb nerves** | | | | |
| Peroneal nerve | DML (ms) | NR | NR | NR |
| | MCV (m/s) | NR | NR | NR |
| | Distal CMAP / Proximal CMAP (mv) | NR | NR | NR |
| Tibial nerve | DML (ms) | - | 8.7 | 10.2 |
| | MCV (m/s) | - | 29 | 48.5 |
| | Distal CMAP/ Proximal CMAP (mv) | - | 3.47/3.0 | 0.55/0.39 |
| | F-wave latency (ms) | - | 66.2 | 59.2 |
| Sural nerve | SCV(m/s)/SNAP (μV) | NR | NR | NR |

NR: No Response; DML: Distal Motor Latency; CMAP: Compound Muscle Action Potential; MCV: Motor Conduction Velocity; SNAP: Sensory Nerve Action Potential; SCV: Sensory Nerve Conduction Velocity.

either absent or severely reduced. SNAPs were absent in most of the upper- and lower-limb nerves, but were preserved in some upper-limb nerves. These findings suggest the possibility of both myelinopathy and axonopathy in peripheral nerves. In this study, we did not subject all patients to electromyography. Although our patients did not meet certain electrodiagnostic criteria proposed by Kelly, these findings suggested that neuropathy in ARSACS was predominantly demyelinating in origin [14]. The absence of a conduction block in the affected nerves is another characteristic feature of peripheral neuropathy in ARSACS. In Case 3, the grossly prolonged DMLs and F wave latency with normal MCV might be indicative of patchy demyelination of the tibial nerve—another characteristic of peripheral neuropathy in ARSACS.

The results of previous nerve conduction studies on ARSACS are summarized in **Table 3** [6,9,11,12,15-23].

Our findings along with those of previous studies, show that the electrophysiological features of peripheral neuropathy in ARSACS are the following: 1) a prolonged DML and reduced MCV with normal CMAPs in the upper-limb nerves, 2) absence or attenuation of lower-limb CMAPs in addition to prolonged DML and reduced MCV, 3) more severe injury in the lower-limb than in the upper-limb nerves, and 4) sensory nerve conduction waveform frequencies of around 50%. These results suggest that the characteristics of neuropathy in ARSACS are primary length-dependent peripheral myelinopathy and secondary axonal injury, which worsens over a long period.

In this study, we further performed nerve ultrasonography to measure the CSA of the median nerve and the longitudinal nerve

**Table 2** Results of nerve ultrasonographies in two patients with ARSACS.

| | | Case1 | Case3 | Reference value |
|---|---|---|---|---|
| C5 | Distance (mm) | 1.89 | 2.09 | 2.14 ±.0.3 |
| C6 | | 2.92 | 3.14 | 2.99 ± 0.45 |
| C7 | | 2.96 | **4.26** | 3.39 ± 0.48 |
| Median nerve (MedDist) | | 2.07 | 2.05 | - |
| | CSA (mm2) | **7.54** | 4.90 | 6.0 ± 1.3 |

MedDist, distal forearm along the median nerve.

**Table 3** Analysis of NCS data of previous reports in ARSACS patients.

| MCS | | Mean ± SD (n) | Frequency of waveform, n (%) |
|---|---|---|---|
| **Median nerve** | | | 27/27 (100%) |
| | DML (ms) | 6.0 ± 1.1 (8) | |
| | MCV (m/s) | 36.5 ± 5.7 (27) | |
| | Distal CMAP (mV) | 4.6 ± 2.3 (22) | |
| | Proximal CMAP (mV) | 4.5 ± 0.5 (2) | |
| **Ulnar nerve** | | | 12/12 (100%) |
| | DML (ms) | 4.3 ± 1.3 (7) | |
| | MCV (m/s) | 35.4 ± 5.9 (12) | |
| | Distal CMAP (mV) | 4.3 ± 2.2 (11) | |
| **Peroneal nerve** | | | 5/12 (41.7%) |
| | DML (ms) | 9.0 ± 3.1 (3) | |
| | MCV (m/s) | 25.4 ± 3.4 (5) | |
| | Distal CMAP (mV) | 0.6 ± 0.5 (3) | |
| **Tibial nerve** | | | 10/14 (71.4%) |
| | DML (ms) | 7.9 ± 1.5 (3) | |
| | MCV (m/s) | 29.2 ± 4.7 (9) | |
| | Distal CMAP (mV) | 0.6 ± 0.4 (8) | |
| **SCS** | | | |
| **Median nerve** | | | 15/27 (55.6%) |
| | SCV (m/s) | 32.3 ± 4.8 (15) | |
| | SNAP (μV) | 1.6 ± 1.2 (13) | |
| **Ulnar nerve** | | | 5/9 (55.6%) |
| | SCV (m/s) | 33.8 ± 5.4 (5) | |
| | SNAP (μV) | 1.6 ± 0.4 (4) | |
| **Sural nerve** | | | 6/27 (22.2%) |
| | SCV (m/s) | 26.4 ± 6.2 (6) | |
| | SNAP (μV) | 3.3 ± 2.0 (6) | |

MCS: Motor Nerve Conduction Study; SCS: Sensory Nerve Conduction Study.

diameter of cervical nerves. To our knowledge, this is the first case series evaluating nerve ultrasonography in patients with ARSACS.

Recently, high-resolution ultrasonography has emerged as a technology for the evaluation of the peripheral nervous system [24]. Ultrasonographic median nerve CSA enlargement has been found in various demyelinating neuropathies, including multifocal motor neuropathy, Charcot-Marie-Tooth disease, and chronic inflammatory demyelinating polyneuropathy [25-27]. Measurement of the median and cervical nerves using ultrasonography is a supportive tool to evaluate the pathology of peripheral nerves. Although our cases showed normal CSA values in the median nerve and longitudinal nerve diameters at the cervical nerve roots [13], some findings suggested nerve enlargement. We identified focal nerve enlargement in case 1 and 3 by using nerve ultrasonography. This was suggestive of predominant demyelinating neuropathy with a patchy demyelinating lesion as shown in the nerve conduction studies.

One of the limitations of this study is that we examined the peripheral nerve at predetermined sites; however, measurements at sites other than these should be considered for evaluating the peripheral nerve in detail.

In previous ARSACS studies in which a nerve biopsy was performed, the pathology of the peripheral nerves was shown to be consistent with axonal neuropathy associated with mild demyelinating features [28,29]. Electrophysiological and ultrasonographic findings also suggest these peripheral nerve conditions.

The observations described above might be helpful for the accurate diagnosis of ARSACS, because its clinical features could be diverse, and include atypical cases with a spasticity-lacking phenotype, or cases without a family history of autosomal recessive genes.

## Conclusions

The results of this study indicate that the characteristics of peripheral neuropathy in ARSACS are consistent with those of axonopathy associated with mild myelinopathy described previously. Nerve conduction and ultrasonography studies are useful tools to evaluate these findings, and they might be helpful for the diagnosis of ARSACS. When examining patients having spastic-ataxia without a family history, physicians should ensure peripheral nerve examination with both, nerve conduction and nerve ultrasonography methods.

## Competing Interests

The authors declare that they have no competing interests.

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