NERVE CONDUCTION STUDIES IN SPASTIC PARAPLEGIA, OPTIC ATROPHY, AND NEUROPATHY (SPOAN) SYNDROME

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ABSTRACT: *Introduction:* SPOAN (spastic paraplegia, optic atrophy, and neuropathy) syndrome is an autosomal recessive neurodegenerative disorder identified in a large consanguineous Brazilian family. *Methods:* Twenty-seven patients with SPOAN syndrome (20 women), aged 4–58 years, underwent nerve conduction studies (NCS) of the median, ulnar, tibial, and fibular nerves, and sensory NCS of the median, ulnar, radial, sural, and superficial fibular nerves. *Results:* Sensory nerve action potentials were absent in the lower limbs and absent in >80% of upper limbs. Motor NCS had reduced amplitudes and borderline velocities in the upper limbs and absent compound muscle action potentials (CMAPs) in the lower limbs. *Conclusion:* The neuropathy in SPOAN syndrome is a severe, early-onset sensory–motor axonal polyneuropathy. Normal NCS seem to rule-out this condition.

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Spastic paraplegia, optic atrophy, and neuropathy (SPOAN) syndrome is an autosomal recessive neurodegenerative disorder found in northeastern Brazil.[1] Clinical features include non-progressive congenital optic atrophy, progressive spastic paraplegia, axonal neuropathy, auditory startle, dysarthria, spinal and foot deformity, and extrapyramidal signs. Linkage studies map the responsible locus to a 2-Mb region on chromosome 11q13.[1,2] The responsible gene for SPOAN syndrome remains elusive.[2]

Nerve conduction studies (NCS) were reported previously in 2 patients with SPOAN syndrome.[1] Here we describe NCS in a large series, which provides better characterization of the neuropathy.

METHODS

This cross-sectional study was conducted from 2009 to 2011. We evaluated 27 patients (20 women), aged 4–58 years. All patients shared the same phenotype (spastic paraplegia, optic atrophy, and peripheral neuropathy) and had the same homozygous 11q13 haplotype. Patients with a history of diabetes mellitus or alcoholism were excluded.

All subjects or their guardians gave written informed consent; the study was approved by the institutional review board. Patients were evaluated only once, by the same investigator (S.A.).

The study was based on 27 patients from 19 nuclear families, including 16 consanguineous pairings.

Neurological evaluation included modified neuropathy symptom (NSS) and neuropathy disability (NDS) scores.[3,4] Strength was assessed using the Medical Research Council (MRC) scale.[5] Sensation testing included small-fiber (pain and temperature) and large-fiber modalities (128-Hz tuning fork, 10-g monofilament, and joint position sense). Spine deformities and atrophy in the lower limbs were recorded. We also evaluated tendon and plantar reflexes.

NCS were performed with a portable apparatus (Nicolet Viking Quest; Viasys, USA). Skin temperature was maintained at >32°C. Motor conduction studies were recorded using Kendall surface electrodes and included right axillary, median, ulnar, femoral, tibial, and fibular nerves. Sensory NCS of right median, ulnar, sural, and superficial fibular nerves were recorded using a 3-cm bar electrode at standard fixed distances. Tibial H-reflexes were evaluated with a standard technique. Minimal F-wave latencies were obtained after 10 stimuli from ulnar and tibial nerves. A few tests could not be done in every patient due to severe deformities.

Abbreviations: CMAP, compound motor action potential; CMT, Charcot–Marie–Tooth; CV, conduction velocity; DOA, dominant optic atrophy; HSMN, hereditary sensory motor neuropathy; HSP, hereditary spastic paraplegia; *MFN*, mitofusin; MUNE, motor unit number estimation; NCS, nerve conduction studies; NDS, neuropathy disability score; NSS, neuropathy symptoms score; OPA, optic atrophy; SNAP, sensory nerve action potential; SPG, spastic gait; SPOAN, spastic paraplegia, optic atrophy, and neuropathy; TFG, Trk-fused gene

Key words: axonal neuropathy; nerve conduction; recessive genes; spastic paraplegia; SPOAN

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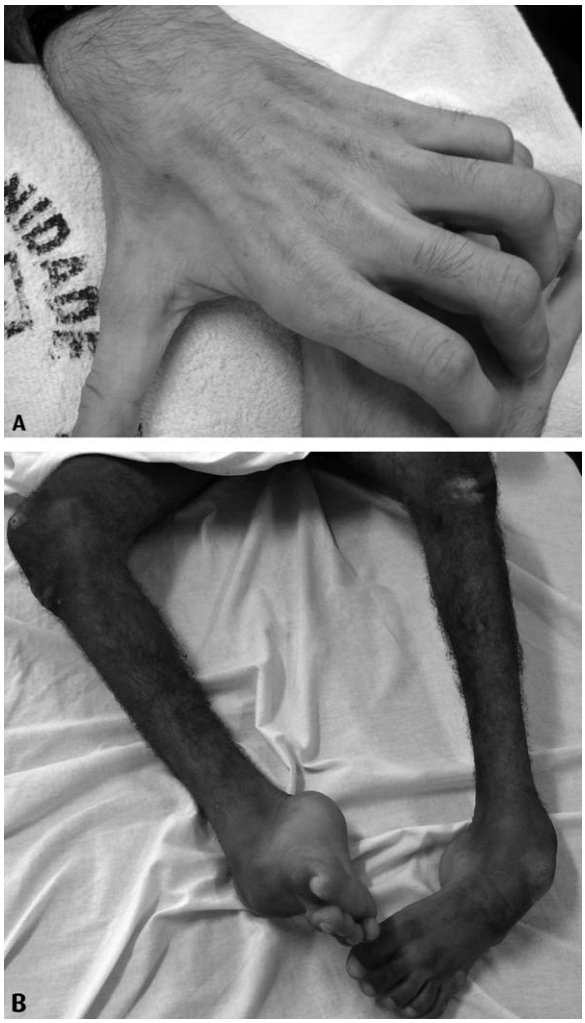

FIGURE 1. Clinical picture of SPOAN neuropathy. **(A)** Distal muscle atrophy. **(B)** Lower limb deformities.

We calculated Pearson correlation coefficients between age and nerve conduction parameters, including velocities, latencies, and amplitudes. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical Data. Neuropathic symptoms such as pain and paresthesias were rare. One patient had mild symptoms (NSS = 3), 7 (26%) had moderate symptoms (NSS = 5–6), and 19 (70%) denied neuropathic symptoms. However, all patients had signs of severe neuropathy (NDS = 10).

All subjects had distal weakness and atrophy. Foot deformities were present in all patients, and spine deformities were seen in 14 of 27 (58%) (Fig. 1A and B). Upper limb tendon reflexes were brisk in 25 of 27 (92%) and in the patellar reflex in 17 of 27 (63%). Ankle reflexes were absent in all patients. Sensation was affected predominantly in the lower limbs.

Electrodiagnostic Data. ***Sensory Nerve Conduction.*** Median sensory nerve action potentials (SNAPs) were absent in all patients. Ulnar SNAPs were absent in 23 of 24 (96%), whereas radial SNAPs were absent in 20 of 25 (80%) patients. Superficial fibular and sural SNAPs were absent in all patients.

Motor Nerve Conduction. Distal motor latencies of axillary and femoral nerves were normal in all patients. CMAP amplitudes were reduced in 4 of 26 median nerves (15%) and in 14 of 27 (52%) ulnar nerves. Conduction velocities (CVs) were reduced in 13 of 26 (50%) median nerves and in 11 of 27 (41%) ulnar nerves. CV was >80% of the lower normal limit for all nerves, except for a single ulnar nerve with severe CMAP amplitude reduction. Ulnar F-waves were prolonged in all patients, but <120% of the upper normal limit in 22 of 23 (96%) patients.

CMAPs were absent in 25 of 27 (93%) fibular nerves and in 23 of 27 (84%) tibial nerves. A single fibular nerve had >20% CV reduction, but also had severely reduced CMAP amplitude. H-reflexes were absent in 21 of 24 (88%) patients. There was no correlation between age and NCS parameters.

All results of clinical and neurological evaluation are shown in Table S1A–C, and the nerve conduction studies are listed in Table S2A–C (refer to Supplementary Material available online).

DISCUSSION

The NCS in this group fulfilled the criteria for primary axonal neuropathy.[6] No patient had conduction block or temporal dispersion. Abnormalities in CV and F-waves are probably related to loss of fast-conducting nerve fibers.[7] We could not demonstrate a correlation between age and nerve conduction. In a previous study, we found a correlation between hand-grip strength and age, suggesting that the neuropathy was clinically progressive.[8] CMAP amplitudes are not good parameters to measure disease progression. Motor unit estimation (MUNE) could possibly provide a better measure of disease progression, but this was not available.

Recessive forms of Charcot–Marie–Tooth (CMT) disease are rare and clinically heterogeneous.[9] In the past, hereditary axonal neuropathy, when associated with spastic paraplegia, was called hereditary sensory–motor neuropathy type 5 (HSMN5), or HSMN6 when it was accompanied by optic atrophy.[10,11] Severe axonal neuropathy and optic atrophy can be found in patients with dominantly inherited CMT type 2A caused by a mutation in the *MFN2* gene.[12]

Among the recessive hereditary spastic paraplegias, mutation of the *SPG7* gene may cause spastic paraplegia, optic atrophy, and neuropathy, but also deafness, ataxia, and cortical atrophy, which were not found in our study.[13]

Optic atrophy, spastic paraplegia, and neuropathy have also been described in dominant optic atrophy

(DOA) related to mutations of the *OPA1* gene.[14] Recently, a SPOAN-like phenotype was reported in a Japanese family with homozygous mutation of *C12orf*65 (chromosome 12, locus SPG55),[15] and also in an Indian family with a homozygous mutation in the Trk-fused gene (*TFG*, chromosome 3).[16] Axonal neuropathy is described in SPG55 and DOA, but usually with a later onset than in SPOAN syndrome.[14,15] Peripheral neuropathy is also described in the *TFG* gene mutation, but with only mild sensory involvement.[16]

In conclusion, SPOAN syndrome is a severe form of complicated spastic paraplegia, with early-onset axonal neuropathy. The phenotype is very stereotyped, but unique electrodiagnostic findings have not been observed. Finally, in this cross-sectional study we were unable to demonstrate a clinical correlation between severity of NCS abnormalities and disease progression.

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