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ORIGINAL PAPER

Pattern of Peripheral Nerve Involvement in Spinocerebellar Ataxia Type 2: a Neurophysiological Assessment

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Abstract Peripheral neuropathy is frequent in spinocerebellar ataxia type 2 (SCA2), but the pattern and characteristics of nerve involvement are still an unsettled issue. This study aimed to evaluate the prevalence, extent, and distribution of nerve involvement in SCA2 patients through neurophysiological studies. Thirty-one SCA2 patients and 20 control subjects were enrolled in this study. All subjects were prospectively evaluated through electromyography, including nerve conduction, needle electromyography in proximal and distal muscles of the upper and lower limbs, and sural radial amplitude ratio (SRAR). We aimed to differentiate distal axonopathy from diffuse nerve commitment, characterizing neuronopathy. Nerve involvement was observed in 83.6 % (26 individuals) of SCA2 patients. Among these, 19 had diffuse sensory abnormalities on nerve conduction predominantly on the upper limbs, with diffuse chronic denervation on needle electromyography and elevated SRAR values. Four individuals had only diffuse sensory involvement, and 2 had only motor involvement on needle evaluation and normal nerve conduction. These were interpreted as neuronopathy due to the diffuse distribution of the involvement. One individual had distal sensory axonopathy, with lower limb predominance. In this study, we found neuronopathy as the main pattern of nerve involvement in SCA2 patients and that motor involvement is a frequent feature. This information brings new insights into the understanding of the pathophysiology of nerve involvement in SCA2 and sets some key points about the phenotype, which is relevant to guide the genetic/molecular diagnosis.

Keywords Spinocerebellar ataxias · Spinocerebellar ataxia type 2 · SCA2 · Peripheral neuropathy · Neuronopathy

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Introduction

Spinocerebellar ataxia type 2 (SCA2), SCA3 (also known as Machado Joseph disease), and SCA6 are the most frequent autosomal dominant spinocerebellar ataxias worldwide [1, 2]. The genetic cause of SCA2 lies in a heterozygous expansion of CAG triplet repeats (CAGexp) located in the 5-prime end of the exon 1 of the ATXN2 gene, which leads to a toxic form of ataxin-2 protein with long polyglutamine tract, causing gradual neuronal degeneration in specific locations [1, 3]. Clinical features include progressive cerebellar ataxia, markedly slow saccadic eye movements [4], and other manifestations, such as cognitive dysfunction, parkinsonism, and sleep disturbances [2, 3].

Peripheral neuropathy is a commonly described feature in SCA2 and SCA3 and is also reported, although less frequently, in SCA1, SCA6, and SCA7 [5–7]. However, the pattern of peripheral nerve involvement in SCA2 is still a matter of debate and prior studies have demonstrated conflicting results. Several studies showed the predominance of a distal axonal sensory neuropathy in SCA2 patients [8–11], with unusual and late involvement of motor fibers [8–10, 12, 13]. In contrast to a sensory-predominant distal axonopathy, Crum et al. found a high prevalence of motor involvement in a small sample of 6 SCA2 patients [14] and other authors have proposed that the initial dysfunction may be actually in the neuronal body of the dorsal root ganglion and anterior horn, based on abnormalities found in the peripheral and central nervous system [3, 12].

Few reports of motor neuron disease in ataxic patients with SCA2 also support the motor neuronopathy pattern of peripheral involvement [2, 15, 16]. Indeed, ataxin-2 protein has been implicated as a potent modifier of TAR DNA-binding protein 43 (TDP-43) toxicity in animal and cellular models, and intermediate-length polyglutamine tracts in ataxin-2 confer an increased risk for developing motor neuron disease [2, 15, 16].

This study aims to evaluate the pattern of peripheral nerve involvement in a large sample of SCA2 patients from Brazil, through an extensive neurophysiological examination. We also correlated and compared these findings with phenotypic and genotypic features.

Methods

Patients and Molecular Tests

Symptomatic individuals with a molecular diagnosis of SCA2 were consecutively evaluated at the Ataxia Unit of the Universidade Federal de São Paulo and a rural area of Acre state at the north side of Brazil. Subjects with concomitant medical conditions known to predispose to polyneuropathy or those taking any medications toxic to peripheral nerves were excluded. After consent, an interview underwent and data such as age, age of onset (AO) of the first symptom, disease duration (DD), and gender were obtained. Ataxia severity was evaluated through a Brazilian version of the Scale for the Assessment and Rating of Ataxia (SARA) [17].

Data on clinical signs that could give us information about the peripheral nervous system was collected retrospectively from the medical records. The collected data was deep tendon reflexes, vibratory sensitivity, superficial plantar reflex, and muscle strength. Additional sensory modalities were not available.

Molecular tests were performed as described previously [18]. Briefly, genomic DNA was extracted from peripheral blood and used in multiplex PCR using fluorescence-labeled primers flanking the respective CAG repeats of the ATXN1, ATXN2, ATXN3, ATXN6, and ATXN7 genes. Amplified PCR products were genotyped on an ABI3130xl Genetic Analyzer for quantification of the CAG repeat length. All patients in this study had negative tests for SCA1, SCA3, SCA6, and SCA7. SCA2 was considered positive if one allele had more than 34 CAG triplet repeats.

Healthy, unrelated volunteers were enrolled as the control group for neurophysiological studies. They were selected randomly and personally interviewed. Those with any symptoms or previous neurological conditions were excluded. Our institutional research ethics board approved this study, and a written informed consent was obtained from all patients and control subjects.

Neurophysiological Evaluation

SCA2 patients and the control group underwent four-limb electromyography (EMG). All studies were performed in a Neurosoft Neuro-MEP-Micro, with needle EMG and surface recording and stimulation. Temperature was kept above 32 °C in the evaluated limb. Sensory nerve conduction was performed in the median, ulnar, and radial nerves on the right side of the body and the sural nerve bilaterally, using antidromic technique. Motor nerve study was carried out in the median, ulnar, and peroneal nerves on the right side of the body, using orthodromic technique.

Needle EMG was performed bilaterally in the biceps brachii, first dorsal interossei, tibialis anterior, and vastus medialis muscles. Additional muscles were evaluated as needed. We analyzed insertional and rest activity, as well as the motor unit action potential morphology and interference pattern during slight and maximal muscle activation.

The cutoff amplitude values for sensory nerve action potential (SNAP) of the nerves under study were as follows: sural ≥ 6 μV; ulnar ≥ 10 μV; median ≥ 10 μV; and radial nerve ≥ 15 μV. Normal values for the compound motor action potential (CMAP) for the nerves under study were as follows: fibular ≥ 4 mV; median ≥ 5 mV; and ulnar nerve ≥ 4 mV. Reference values were based on data from the control group and also from our laboratory [19].

Peripheral neuropathy was determined by the presence of at least one of the following criteria: (1) two or more nerves affected; (2) diffuse or distally distributed denervation on needle EMG [20]. Whenever neuropathy was present, we further observed the distribution and nature of the damage, whether axonal or demyelinating.

The sural/radial amplitude ratio (SRAR) was used aiming to differentiate axonopathy from neuronopathy in those patients with peripheral neuropathy. It is calculated by dividing the sural SNAP by the radial SNAP. In patients already classified with peripheral neuropathy (by the criteria

aforementioned), values ≤ 0.3 indicate distal peripheral axonopathy [21, 22], on the other hand, values > 0.3 suggest that nerves are affected diffusely, rather than in a length-dependent pattern, indicating neuronopathy. This approach was used in previous works [7, 12, 23].

Statistical Analysis

All results were expressed as mean ± SD. Comparisons between groups were performed using chi-square test for categorical data and using two-sample *t* test or Mann–Whitney test for continuous variables. The Spearman's rank correlation was used to analyze the correlations between CAGexp, AO, DD, age, SARA, and neurophysiological data. Statistical significance was considered at $p < 0.05$.

Results

Demographics

Thirty-one SCA2 patients and 20 healthy volunteers (control group) were included in this study. SCA2 patients and control volunteers had similar age at enrollment (40.13 ± 13.90 versus 41.05 ± 14.09; $p = 0.818$) and gender distribution (51 % versus 40 % male, $p = 0.781$). The mean age at onset (AO) of symptoms of SCA2 was 31 ± 12.1 (ranging from 15 to 50 years), and mean disease duration was 9 ± 5.3 (ranging from 2 to 21 years). Mean length of CAGexp of SCA2 patients was 42 ± 3.6 (ranging from 36 to 50 repeats), and mean SARA values were 17 ± 10.9. There was a negative correlation between CAGexp and AO ($r = -0.84$; $p < 0.001$), but CAGexp did not correlate with SARA scores ($r = 0.260$; $p = 0.219$).

Electrophysiological Studies and Clinical Data

Twenty-six SCA2 patients (83.8 %) had peripheral neuropathy, determined by the presence of two more nerves affected *and/or* diffuse or distally distributed denervation on needle EMG. Affected nerves showed reduced potential amplitudes, suggesting axonal neuropathy. Almost all sensory and motor nerve potentials had mean amplitude values significantly lower in SCA2 patients than in the controls (Table 1). The sensory nerve amplitudes were more attenuated in the upper limbs (Fig. 1).

The SCA2 patients with peripheral neuropathy had significantly longer DD (9.85 ± 5.22 years) compared to those without neuropathy (4.6 ± 3.57 years; $p = 0.041$). SCA2 patients with or without neuropathy had similar CAGexp (42.52 ± 3.86 versus 44 ± 2.12; $p = 0.412$), AO of symptoms (31.23 ± 12.5 versus 30.6 ± 11.1; $p = 0.917$), and SARA values (18.89 ± 11.35 versus 12.8 ± 16.25; $p = 0.881$).

Table 1 Nerve conduction studies in SCA2 individuals and controls

	SCA2 ($n = 31$)	Controls ($n = 20$)	p
Motor nerves	CMAP amplitude (mV)		
Ulnar CMAP	9.2 (±1.4)	10.6 (±1.7)	0.003
Median CMAP	10 (±2.8)	11.2 (±2.5)	0.202
Fibular CMAP	5.4 (±2.2)	7.7 (±1.9)	<0.001
Sensory nerves	SNAP amplitude (μV)		
Sural right SNAP	8.6 (±5.1)	17.8 (±5.8)	<0.001
Sural left SNAP	7.1 (±3.8)	18.2 (±6.7)	<0.001
Median SNAP	8.5 (±6.7)	42.8 (±17.5)	<0.001
Ulnar SNAP	8.4 (±6.2)	38.6 (±16.6)	<0.001
Radial SNAP	8.5 (±5.2)	44.3 (±16.9)	<0.001
SRAR	1.19 (±0.65)	0.42 (±0.15)	<0.001

n number of patients, when $n > 1$, the results are expressed as mean ± SD, *CMAP* compound motor action potential, *mV* millivolt, *μV* microvolt

The comparison of nerve conduction velocities between patients and controls showed a significant difference in the median motor nerve fibers and in the median, ulnar, and radial sensory nerve fibers (Table 2). Of note, motor and sensory conduction velocity slowness did not reach the criteria for demyelinating neuropathy. Sural conduction velocities were similar between the two groups (Table 2). Incidental median neuropathy at the wrist was seen in 3 patients, based on increased distal latency difference between the antidromic median and ulnar sensory potential in the fourth digit (data not shown).

Among the 26 SCA2 patients with peripheral neuropathy, 25 (96 %) were classified as neuronopathy and one (4 %) as distal axonopathy (Table 3). Nineteen (61.3 %) patients had upper limb nerves predominantly affected, presenting with sensory and motor on nerve conduction studies, diffuse chronic denervation on needle EMG and mean SRAR value was 1.3 (±0.74). These features are not to be expected in a distal axonopathy (Table 3). Therefore, these 19 individuals were considered as sensory and motor neuronopathy. Additionally, among these 19 subjects, nine had nerves with reduced sensory amplitudes on the upper limbs and normal on lower limbs (Fig. 1). Given the severity of denervation sings present in all evaluated muscles, needle EMG was additionally performed in the genioglossus muscle in 5 of them. All showed sings of chronic denervation. Only one of these patients showed spontaneous activity in all muscles studied (fibrillations and positive sharp waves).

Four out of the 26 SCA2 individuals with neuropathy had sensory involvement, predominantly in upper limbs, with no signs of motor involvement (Table 3), being classified as sensory neuronopathy. Furthermore, 2 SCA2 patients had diffuse chronic denervation on needle EMG and no conduction abnormalities, being considered as motor neuronopathy. Only one individual had sensory nerve involvement predominantly

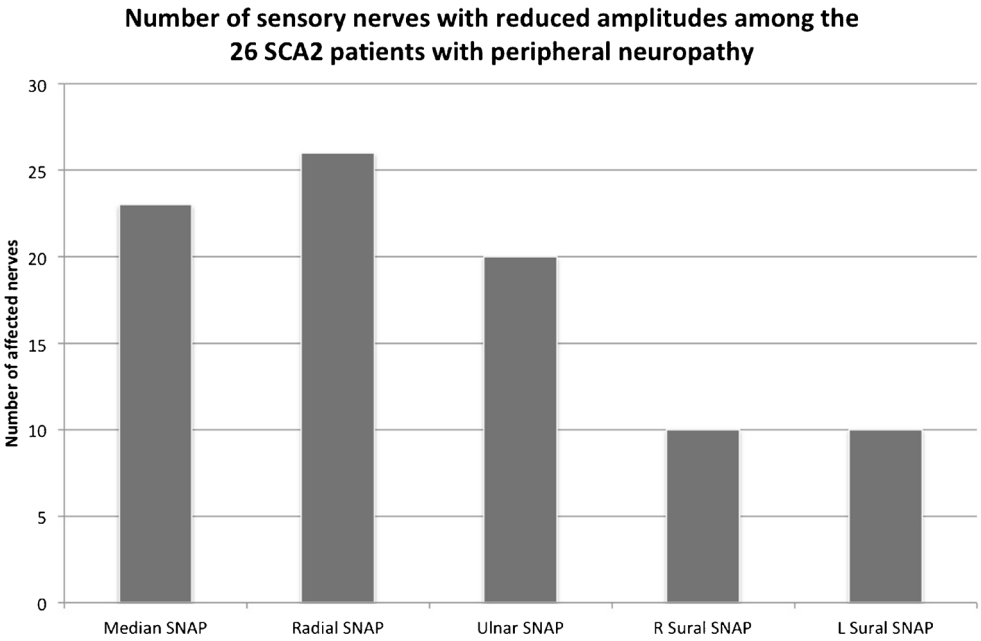

Fig. 1 Number of nerves with reduced amplitudes among the 26 SCA2 patients with polyneuropathy. *SNAP* sensory nerve action potential. *Vertical axis* number of affected nerves (i.e., nerves with reduced amplitudes). The graph shows a predominance of upper limb involvement, instead of a distal distribution

in lower limbs, with no motor involvement and SRAR value of 0.3 and therefore was classified as a distal sensory axonopathy.

Five SCA2 patients did not have peripheral nerve involvement, although SRAR (mean 0.97) was significantly larger than in healthy subjects (mean 0.43; $p < 0.00$).

Among all SCA2 patients with peripheral neuropathy, 77.7 % had reduced deep tendon reflexes, 45.5 % had reduced vibratory sensitivity, and no patients had reduced muscle strength. In the group of SCA2 individuals with no neuropathy detected by neurophysiologic evaluation, only one of them had exalted deep tendon reflexes and the remaining features were normal (additional details in Table 3). In four patients from the SCA2 group with peripheral neuropathy, the data for the physical signs of peripheral neuropathy was not available from medical records. These individuals were all classified as sensory and motor neuronopathy.

Discussion

This study demonstrated that peripheral neuropathy is frequent in SCA2, affecting 83.6 % of subjects. Almost all SCA2 patients with peripheral nerve involvement, with one exception, had a neuronopathy pattern. These patients had diffuse sensory and motor involvement instead of a length-dependent axonopathy. We also observed that disease duration was longer in those SCA2 with peripheral neuropathy, while CAG repeat length was not significantly different in patients with neuropathy or without it.

Peripheral nerve involvement in SCA2 is still an unsettled issue. It has been described as a subclinical feature, with few symptoms [8], but there have been some discordance among authors about the pattern of nerve damage disclosed by the EMG. There are some reports highlighting neurophysiological features and peripheral

Table 2 Nerve conduction velocity in SCA2 individuals and controls

	SCA2 ($n = 31$)	Controls ($n = 20$)	p
Motor nerves	CMAP velocity (m/s)	CMAP velocity (m/s)	
Ulnar CMAP	61.1 (±6.4)	62.2 (±5.3)	0.501
Median CMAP	55.2 (±4.6)	58.5 (±3.5)	0.008
Fibular CMAP	48.0 (±6.1)	50.9 (±7.4)	0.127
Sensory nerves			
Sural right SNAP	51.1 (±10.3)	53.3 (±7.8)	0.424
Sural left SNAP	51.2 (±8.7)	53.2 (±5.1)	0.341
Median SNAP	53.4 (±8.3)	58.1 (±3.5)	0.019
Ulnar SNAP	54.6 (±7.1)	59.5 (±4.6)	0.009
Radial SNAP	59.4 (±8.6)	65.4 (±5.9)	0.009

n number of patients, when $n > 1$, the results are expressed as mean ± SD, *CMAP* compound motor action potential, *m/s* meters per second

Table 3 Patterns of peripheral neuropathy in SCA2 patients and clinical data

Patterns of peripheral neuropathy	Sensory and motor neuronopathy	Sensory neuronopathy	Motor neuronopathy	Distal axonopathy	No peripheral neuropathy
Patients ($n = 32$)	19 (61.3 %)	4 (12.9 %)	2 (6.4 %)	1 (3.2 %)	5 (16.2 %)
Electrophysiological findings					
NCS	Abnormal UL	Abnormal UL	Normal	Abnormal LL	Normal
Needle EMG	Diffuse chronic denervation	Normal	Diffuse chronic denervation	Normal	Normal
SRAR	1.3 (±0.74)	0.67 (±0.32)	0.75 (±0.07)	0.3	0.97 (±0.35)
Clinical findings ($n = 28$)	$n = 15$	$n = 4$	$n = 2$	$n = 1$	$n = 5$
Reduced deep tendon reflexes	13 (86.6 %)	2 (50 %)	1 (50 %)	0	0
Reduced vibratory sensitivity	7 (46 %)	1 (25 %)	1 (50 %)	1 (100 %)	0
Exalted deep tendon reflexes	0	1 (25 %)	0	0	1 (20 %)
Extensor plantar reflex	3 (20 %)	1 (25 %)	0	0	0

Abnormal UL more than two nerves involved, with most nerves in upper limbs, *Abnormal LL* more than two nerves involved with most nerves in lower limbs, *UL* upper limbs, *LL* lower limbs, *SRAR* sural/radial index, *EMG* electromyography, *n* number of patients, when $n > 1$, the results are expressed as mean ± SD, % percent

nerve involvement in SCA2, but few studies have a large number of individuals and a thorough evaluation [8, 10–13, 24]. Polyneuropathy has been described as highly prevalent in these patients and primarily as an axonal neuropathy, with few reports of minor demyelination [8, 10, 13]. Abnormalities were detected mostly in sensory fibers with some degree of motor involvement only on later stages [3, 8–10, 12, 24]. Crum et al., on the other hand, through a retrospective analysis, observed a high frequency of motor involvement in their sample of six individuals [14]. The distribution of nerve involvement has been said to be indicative of distal axonopathy by most authors [3, 8–10], although Velazquez-Perez et al. in a study using evoked potentials studies described the disease as a neuronopathy [24]. Furthermore, van de Warrenburg et al. in the neurophysiological description of three SCA2 patients detected diffuse sensory involvement, rather than a distal axonopathy, with mild motor degeneration [12].

As aforementioned, we found peripheral neuropathy in 83.6 % of SCA2 patients with diffuse sensory and motor nerve involvement in all of them, with one exception. The clinical signs of nerve involvement were indeed more prevalent in this group of patients with neuropathy compared with SCA2 patients without neuropathy (Table 3). Our findings did not suggest a classical length-dependent axonopathy. Actually, these SCA2 individuals with diffuse nerve involvement had most of the affected nerves from the upper limbs and denervation on needle EMG was present in a diffuse distribution: in distal, proximal, and tongue muscles (Table 3). Additionally, the SRAR was above 0.4 in all of them, what is not to be expected in a distal axonopathy [12, 21]. Only one of our patients had polyneuropathy resembling a distal process with low SRAR and lower limb predominance. These data suggests that the process of nerve involvement in these individuals is not in the axon but in the sensory and motor neuronal body, that is, a neuronopathy.

The protein responsible for the SCA2 is ataxin-2. Ataxin-2 becomes dysfunctional when there are more than 32 CAG repetitions at *ATXN2* with an increased penetrance at 37 repeats (3). This polyglutamine (polyQ) inclusion in the protein ultimately threatens the normal function of the cell through aggregates of inclusion bodies that accumulates in the nucleus and cytoplasm leading to neurodegeneration [3, 5, 12, 25]. The protein is ubiquitously expressed; recent reports showed that ataxin-2 was strongly labeled in Purkinje cells and in the medulla [25]. Correspondingly, besides the cell loss in the cerebellar tissue, necropsy studies showed neurodegeneration of motoneurons and Clark's column in the medulla [26, 27]. These studies did not define whether this degeneration is caused by a "dying back" effect or by a primary neuronopathy. Our findings suggest that the process starts at the neuronal body and not distally in the axon, in line with van the Warrenburg et al. [12].

There are some data reporting that ATXN2 alleles with 27 CAG repeats or more are associated with an enhanced toxicity from protein TDP-43, possibly leading to the amyotrophic lateral sclerosis (ALS) phenotype [28, 29]. Indeed, we noticed that 2 of the 31 SCA2 individuals evaluated had EMG compatible with motor neuron disease, with diffuse chronic denervation on needle evaluation and normal nerve conduction. We also observed that additionally to these two individuals, 19 also had chronic denervation, along with other neurophysiological abnormalities (Table 3), and it was diffuse

in all segments, including the bulbar region in 5 individuals in whom it was tested. Patients with molecular proven SCA2 presenting with a motor neuron disease phenotype have already been described [15, 16, 30]. This highlights the importance of adding SCA2 as a possibility when a motor neuron phenotype comes associated with ataxia and suggests that the process starts at the neuron body.

SCA2 individuals with neuropathy had longer DD than those without neuropathy, a finding already described by previous researchers [3]. Our data brings additional evidence indicating that the main factor causing damage to cells of the dorsal ganglia and motoneurons is the time over which the CAGexp at *ATXN2* exerts its effects.

This study has some shortcomings. The clinical data collected was retrospective, and for this reason, with some limitations. The clinical signs of peripheral nerve involvement obtained were restrained by what was present in medical records. In addition, we did not evaluate bulbar segments in all patients and further motor neuron involvement may be missed.

In conclusion, neurophysiological studies in SCA2 patients showed a clear neuronopathy pattern with sensory nerve conduction revealing a diffuse affection, as shown by a preferential involvement of upper limbs and by the SRAR values. Motor involvement was also spread out; chronic denervation was frequent and present in all evaluated segments, including the bulbar region. Our data suggests that the neuronal body is the primary site of disease, in opposite to the axon, and that the motor involvement is significant. We recommend that needle evaluation and nerve conduction, including the upper limbs, should be performed in SCA2 patients in order to disclose the full range of peripheral involvement in these individuals. One of the most important points of this paper is the technical effort in differentiating subtypes of neuropathies involved in SCA2 and, in short, to distinguish distal axonal neuropathy from neuronopathy whose subclinical manifestations have rarely been evaluated. This information brings new insights into the understanding of the pathophysiology of nerve involvement of SCA2 and sets some key points about the phenotype, which is relevant to guide the genetic/molecular diagnosis.

Compliance with Ethical Standards

Conflict of Interests We have no conflict of interest.

Financial Disclosure We have nothing to disclose.

Ethical Statement Full consent was obtained from the patients to be enrolled in this study. Our Institutional Research Ethics Board approved this study.

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