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Autonomic dysfunction is frequent and disabling in non-paraneoplastic sensory neuronopathies

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ABSTRACT

Introduction: Sensory neuronopathies (SN) are characterized by asymmetric non-length dependent sensory deficits and sensory ataxia. Autonomic dysfunction in SN was not yet evaluated regarding its frequency, characteristics and relationship to sensory deficits. To address these issues, we performed a comprehensive clinical and neurophysiological evaluation of a large cohort of patients with non-paraneoplastic SN (np-SN).

Methods: We enrolled 50 consecutive patients with npSN and 32 age/sex-matched healthy controls. They were clinically evaluated (SCOPA-Aut scale) and underwent neurophysiological autonomic assessment (quantitative sudomotor axon reflex test, heart rate variability and sympathetic skin response).

Results: Mean age of patients was 50.9 ± 10.3 years and there were 18 men. npSN patients had higher SCOPA-Aut scores than controls (26.63 ± 12.72 *vs.* 12.66 ± 9.11, $p < .001$). QSART was abnormal in 92% of the patients - sweat volumes in all examined sites were smaller among patients ($p < .001$). Cardiovascular autonomic neuropathy was more frequent in these patients as well ($p < .001$).

Conclusion: Altogether our results suggest that autonomic dysfunction in distinct domains is frequent in npSN patients. These findings suggest that the clinical picture of npSN is related to a double neuronopathy: sensory and autonomic.

1. Introduction

In the 70th anniversary of the first sensory neuronopathy (SN) description made in 1948 [1,2], its full clinical and neurophysiological characterization is still pursued. The disease hallmark is sensory ataxia and multifocal non-length-dependent sensory deficits [3–5]. However, patients frequently present a wide symptom spectrum [6], and non-sensory symptoms have been receiving little attention.

In the very first SN description made by Professor Denny-Brown, he had already acknowledged autonomic manifestations in the patient from the "Case 1" who had transient urinary retention during the SN course [2]. Since then, basic questions on this topic remain unanswered. For instance, the frequency, clinical relevance, and pattern of autonomic signs in SN are still not precise. Moreover, how autonomic and sensory deficits correlate remains to be investigated. To address these issues, we performed a comprehensive clinical and neurophysiological evaluation of a large cohort of non-paraneoplastic sensory neuronopathy (npSN).

2. Methods

2.1. Patients

From 2015 to 2017, we prospectively invited all npSN patients followed at the University of Campinas (UNICAMP) hospital, Sao Paulo, Brazil, to undergo this study protocol. As inclusion criteria, all patients should be older than 18 years of age, fulfill the current SN diagnostic criteria proposed by Camdessanché and cols [3] and sign an informed consent form.

Our study protocol encompassed an interview and a chart review to gather data regarding the general demographics, age at disease onset and potential SN-associated diseases. All subjects underwent a detailed neurological examination. The scale for the assessment and rating of ataxia (SARA), Berg balance scale (BBS) and INCAT sensory sum score (INCATSS) were also employed to quantify disease severity.

In parallel, a group of age and sex-matched healthy individuals were invited to undergo the same study protocol. Most of them were

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husbands or spouses of the patients.

The Ethical Research Committee of the University of Campinas (UNICAMP) approved this study protocol, which was carried out under the 1964 Declaration of Helsinki and its later amendments. All patients agreed with it and signed an informed consent statement form before the enrollment process.

2.2. Autonomic evaluation

We performed a comprehensive autonomic evaluation that included: the Scale for Outcomes in Parkinson's disease for Autonomic Symptoms (SCOPA-Aut) [7,8], the assessment of the heart rate variability (HRV), quantitative sudomotor axon reflex test (QSART) and sympathetic skin response (SSR). All autonomic data were acquired in an interval shorter that one month and during the morning hours (8 am until 11 am) in order to equalize the subjects' circadian cycle variations. All patients were also required to avoid smoking and physical activities during the preceding hours of the tests, make light caffeine and chocolate-free breakfast and when possible, all drugs with potential autonomic action were withdrawn for at least two half-lives before the evaluation.

During the exam, the patients were positioned in dorsal decubitus after resting for at least 10 min before starting the tests. The room was quiet, lights dimmed and the temperature controlled (23 °C). The following sequence of tests was adopted: HRV, QSART, and SSR.

2.2.1. Heart rate variability

The HRV was assessed using the Poly-Spectrum-8/E digital system® (Neurosoft Ltd., Ivanovo, Russia). R-R interval data were acquired with EKG electrodes placed in the four limbs and processed by the software Poly-Spectrum.NET® (Neurosoft Ltd., Ivanovo, Russia). We performed frequency and time domain analyses of the HRV with a standard protocol. The frequency domain analyses lasted 5 min. The fast-Fourier transformation algorithm converts time domain data into frequency domain data. This approach allows the identification of the different HRV frequency bands: high frequency (HF) (0.15–0.4 Hz), low frequency (LF) (0.04–0.15 Hz) and very low frequency (VLF) (0.0033–0.04 Hz). Their relative distribution in percentage and the LF/HF ratio were then computed. Detailed mathematical workflow of these analyses is described elsewhere [9–11]. The time domain analysis is composed by the cardiovagal tests: deep breathing, Valsalva maneuver and the heart rate and blood pressure (BP) responses to the orthostatic position. These cardiovagal tests were analyzed according to previously published data [12]. Moreover, we assessed the average heart rate, maximum and minimum RR intervals, mean RR normal-to-normal intervals (NN intervals (RRNN)), mean of the standard deviations of all the intervals without artifacts (SDNN) and the percentage of successive RR intervals that differ by > 50 ms (pNN50). One of the authors (ARMM) reviewed all series looking for gross errors and artifacts.

2.2.1.1. Deep breathing. Deep breathing index or the expiration/inspiration index (E:I) was defined as a mean of the six ratios of the higher and the lowest R-R intervals for each respiratory cycle during the test [12]. In addition, we assessed the expiratory sinus arrhythmia (RSA).

2.2.1.2. Valsalva maneuver. Subjects were told to exhale forcefully after a full inhalation process. The acquisition started after reaching and sustaining 40cmH_2O expiratory pressure for 15 s. The next 45 s were also recorded (recovery phase of the Valsalva maneuver). Two additional trials with a 3–5 min interval between them were obtained. The Valsalva ratio (VR) was computed using the longest and the shortest R-R interval [12].

2.2.1.3. Blood pressure and heart rate variability after orthostatic challenge. The BP measurements were performed with the patient in decubitus and one, three and 5 min after active orthostatic posture was adopted. Orthostatic hypotension (OH) was defined by a drop in the systolic BP or the diastolic BP of 20 and 10 mm Hg, respectively [13]. The 30:15 ratio, also obtained through this maneuver, was calculated after the division of the R-R interval around the 30th heartbeat by the R-R interval around the 15th heartbeat counted after the orthostatic position was reached [12].

2.2.2. Cardiovascular autonomic neuropathy

Cardiovascular autonomic neuropathy (CAN) was defined by the criteria proposed by Vinik and Ziegler [14]. These criteria include evaluation of the HF, LF and VLF bands, VR, 30:15 ratio, E:I index and systolic BP response to the orthostatic position. Two abnormal criteria suggest incipient CAN whereas 3 or more abnormal criteria indicate definite CAN [14].

2.2.3. Quantitative sudomotor axon reflex testing

The commercially available device QSWEAT® (WR Medical Electronics Co, Stillwater, MN, USA) evaluated the quantitative sudomotor axon reflex. The sweat volume readings were processed by a specific software system (WR TestWorks Application Software; WR Medical Electronics Co) that displayed the data graphically in a computer screen. We employed a slightly modified version of the classic protocol reported by Low and others [15–18]: SN patients underwent the Q-sweat examination in both body sides resulting in eight points examined per patient instead of the original four.

We qualitatively examined, considering sweat volumes, SSR and the ipsilateral (ulnar or sural nerves) sensory nerve action potential amplitude (SNAP), if these tests had concordant or discordant results (normal SNAP and abnormal sweat volume and *vice versa*). We later explored the eventual correlation between SNAPs and sweat volumes in the upper (ulnar plus radial SNAP amplitudes *vs.* sweat volume of the forearm) and the lower (sural SNAP amplitude *vs.* the lower limb sum of sweat volumes).

2.2.4. Sympathetic skin response

SSR was obtained simultaneously in the four limbs with a 4-channel Nihon Kohden Neuropack M1 Electromyographer (Nihon Kohden®, Tokyo, Japan) in accordance to previously reported protocol [19]. An electric stimulus was given in the forehead and the presence of SSR was visually evaluated. The onset latencies were than assessed when appropriate.

2.3. Statistical analysis

Descriptive statistics was used to represent the demographic, autonomic and neurophysiologic data. Comparison of groups was accomplished with Mann-Whitney *U* test. We employed the Bonferoni correction to adjust for multiple comparisons. Groups correlations were performed with Pearson's or Spearman's Correlation Coefficient calculation when appropriate. *P* values < .05 were considered significant. We ran statistical analyses on Prism® (GraphPad Software, Inc., San Diego, CA) or the Matlab® (v. R2017b) softwares.

3. Results

3.1. Study population

We enrolled 56 npSN patients and 32 healthy controls. Six subjects were not able to undergo the autonomic testing protocol (Fig. 1). Hence, 50 patients underwent QSART and SSR testing whereas 44 patients had the HRV tested. The reasons for exclusions are depicted in Fig. 1. Patients and controls had similar age (50.9 ± 10.3 years *vs.* 47 ± 12.3 years, $p = .1$) and gender proportion (male: female ratio of 18:32 *vs.* 12:20, $p = 1$). Age at disease onset and disease duration were 41.3 ± 9.3 and 8.6 ± 7.2 years, respectively. Two-thirds of the

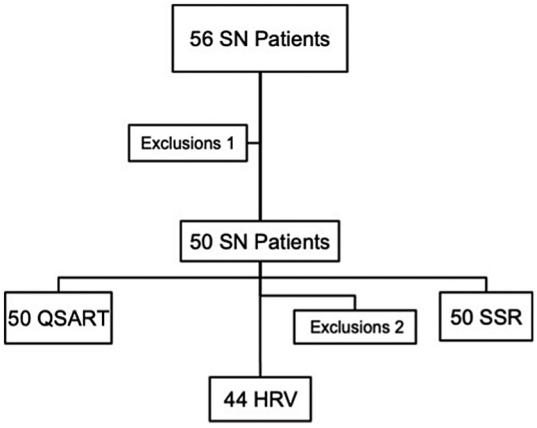

Fig. 1. Flowchart of the inclusion process and the performed evaluations. Exclusions 1: five lost to follow-up and one underwent an aortic surgery and was not able to participate. Exclusions 2: three could not withdraw autonomic-interfering medication, one had cardiac arrhythmia, one was lost to follow-up and one died. SN: Sensory neuronopathy; QSART: quantitative sudomotor axon reflex test; HRV: heart rate variability; SSR: sympathetic skin response.

patients had asymmetric sensory symptoms. Tonic pupils (Adie's pupil) were present in nine SN patients, but none of the control subjects ($p = .009$).

Twenty-eight patients had idiopathic SN, and 22 had SN in the context of other conditions (ten Sjögren syndrome (SS), five autoimmune hepatitis, two B12 vitamin deficiency, one systemic lupus erythematosus, one human T-cell lymphotropic virus type 1 infection, one hepatitis C virus, one toxic and one monoclonal gammopathy of undetermined significance). Five patients were taking medications that could interfere with the autonomic evaluations. These patients had their medications suspended a few days before the exams. Two patients had hypothyroidism under medication with physiologic hormonal levels during the past five years.

3.2. SCOPA-Aut

SN patients had significantly higher SCOPA-AUT scores when compared to controls. This result holds true not only for total scores (25.68 ± 12.89 *vs.* 12.16 ± 8.12, $p < .001$) but also for most of the subdomain scores (Table 1).

3.3. Heart rate variability

3.3.1. Frequency domain

We found no between-group difference regarding frequency domain parameters (Table 2).

3.3.2. Time domain

Patients had significantly worse performance in the cardiovagal tests and tended to have shorter means of maximum and minimum resting R-R intervals but the latter two differences did not reach statistical significance (Table 2).

3.4. Cardiovascular autonomic neuropathy

Thirty-one npSN patients had two or more abnormal tests suggesting CAN (21 patients with definite CAN and 10 with incipient CAN), whereas five controls fulfilled CAN criteria (2 definite and 3 incipient) ($p < .001$). There was not a specific characteristic associated to CAN, including gender, age at the autonomic evaluation, age at SN onset, SN duration and the presence of a dysimmune context (SS, autoimmune hepatitis and systemic lupus erythematosus) (p-values: 0.727, 0.141, 0.85, 0.541 and 1 respectively).

3.5. Orthostatic hypotension

Twenty-seven patients and four controls met the criteria for OH ($p < .001$). Despite that, only four of the SN patients and none of the controls had symptomatic hypotension with mild complaints of dizziness and blurred vision.

3.6. Sudomotor function

Total sweat volume was significantly lower in the npSN group for all sites evaluated (Table 3 and Fig. 2). At least one abnormal site was present in 92% of the patients (46/50), and from the total of 400 assessed sites, 212 (53%) had a sweat volume under the 5th percentile adjusted for age and sex. This proportion was significantly higher than in controls, which had six points under the 5th percentile out of 128 assessed, $p < .001$. In 38 points from 17 different SN patients (range: 1–7 sites) the sudomotor reflex was absent (anhydrosis) and two sites, from two different patients, had sweat volumes in the forearm over the 95th percentile (hyperhidrosis).

Absolute number of abnormal sites, considering a maximum of 50, regarding the sweat volumes were: 18 in the right forearm, 20 in the left forearm, 29 in the right proximal leg, 20 in the left proximal leg, 32 in the right distal leg, 27 in the left distal leg, 31 in the right foot and 34 in the left foot. Asymmetric findings and non-length dependent sweat impairment were present in 66% and in 50%, respectively, of the SN patients. Fig. 3 summarizes the regions with abnormal sweat response in npSN patients.

A comparison made with the nerve conduction studies (NCS) revealed that the sweat volumes were normal whereas the SNAP amplitudes were abnormal in 32 patients in the right upper limb, five in the right lower limb, 29 in the left upper limb and nine in the left lower limb. Five patients (three in the left sural nerve, one in the right sural nerve e one in the left ulnar nerve) had normal SNAPs amplitudes and

Table 1
Comparison of SCOPA-Aut total scores and its subdomains for sensory neuronopathy patients and healthy controls.

	SN patients (n = 50)*	Controls (n = 32)*	p value†
Gastrointestinal dysfunction	6.2 ± 4.9	3.41 ± 2.89	**0.03**
Urinary dysfunction	8.14 ± 4.7	3.75 ± 3.3	< **0.001**
Cardiovascular dysfunction	3.14 ± 2.3	0.59 ± 0.95	< **0.001**
Thermoregulatory dysfunction	5.11 ± 3.04	3.03 ± 2.97	**0.018**
Pupillomotor dysfunction	1.23 ± 0.91	0.63 ± 0.83	**0.024**
Sexual dysfunction#	1.86 ± 2.36	0.75 ± 1.3	0.06
Sexual dysfunction men#	1.92 ± 2.07	0.25 ± 0.45	0.06
Sexual dysfunction women#	1.84 ± 2.49	1 ± 1.49	1
Total	25.68 ± 12.89	12.16 ± 8.12	< **0.001**

* Results expressed by mean ± standard deviation.
\# Analyses excluding those patients/controls who report no sexual activity.
† All p values are adjusted by Bonferoni Correction. SN: sensory neuronopathy.

Table 2
Heart rate variability parameters from frequency and time domains of sensory neuronopathy patients and controls.

	SN (n = 44)	Controls (n = 32)	*p* value†
Frequency domain			
High frequency (HF) (mean ± SD, ms^2)	730.6 ± 1566.6	609.3 ± 881.4	1
Low frequency (LF) (mean ± SD, ms^2)	540.5 ± 659.9	685.3 ± 550.4	1
Very low frequency (mean ± SD, ms^2)	887.6 ± 1239.5	840.8 ± 574.7	1
LF/HF (mean ± SD)	1.89 ± 1.89	1.95 ± 1.64	1
%HF/%LF/%VLF	27 ± 21/27 ± 12/45 ± 18	24 ± 15/31 ± 12/44 ± 14	1/1/1
Time domain			
Average HR (mean ± SD,bpm)	70.34 ± 11.83	67.31 ± 8.96	1
RR max (mean ± SD,ms)	1027.77 ± 197.8	1140.73 ± 277.53	0.24
RR min (mean ± SD,ms)	683.53 ± 16.42	759.18 ± 153.13	0.24
RRNN (mean ± SD,ms)	870.51 ± 147.1	918.76 ± 155.07	1
SDNN (mean ± SD,ms)	46.67 ± 30.55	49.43 ± 23.18	1
pNN50 (mean ± SD,%)	7.96 ± 12.6	9.29 ± 12.96	1
Valsalva ratio (mean ± SD)	1.3 ± 0.21	1.63 ± 0.45	< **0.001**
30:15 ratio (mean ± SD)	1.07 ± 0.08	1.24 ± 0.18	< **0.001**
RSA (mean ± SD,bpm)	12.86 ± 7.09	20.6 ± 8.84	< **0.001**
E:I (mean ± SD)	1.2 ± 0.12	1.39 ± 0.2	< **0.001**

SN: sensory neuronopathy; HR: heart rate; max: maximum,; min: minimum; RRNN: mean RR normal-to-normal intervals; SDNN: Mean of the standard deviations of all the intervals without artifacts (NN intervals); pNN50: percentage of successive RR intervals that differ by > 50 ms; RSA: respiratory sinus arrhythmia; bpm: heartbeats per minute; E:I: expiration/inspiration ratio.
† All *p* values are corrected by Bonferoni's Correction.

abnormal sweat volumes in the ipsilateral limb. Only two patients (one for the left ulnar nerve and one for the right sural nerve) had normal SNAPs and sweat volumes in the examined limb. No correlation between SNAPs amplitudes and sweat volumes was obtained in the upper (right: R = −0.01 p = .9; left: R = −0.145 p = .31) or in the lower (right: R = 0.04 p = .77; left: R = −0.01 p = .94) limbs. The same was true for the analysis of the total sweat volume and the disease duration, SARA, BBS and INCATSS and SCOPA-Aut (R = −0.21 p = .14; R = −0.04 p = .76; R = −0.02 p = .88; R = 0.07 p = .62; R = 0.009 p = .95, respectively). The rates of normal and abnormal sweat evaluations were similar between the groups considering the presence or absence of a dysimmune condition (p = 1).

3.7. Sympathetic skin response

SSR was absent in at least one point in 30 (60%) npSN patients while it was present in all points of the controls (left hand: p < .001; right hand: p < .001; left foot: p < .001 and right foot: p < .001). For ten patients, SSR was absent in all limbs, and eight had a non-length dependent pattern (SSR present in at least one foot and absent in an upper limb). In the upper limbs SSR latencies were similar for both groups (left: 1440.67 ± 382 ms *vs.* 1317.14 ± 259 ms p = .2; right: 1369.55 ± 453.62 *vs.* 1299.76 ± 290.37 p = .53) whereas in the lower limbs latencies were significantly longer in the SN group (left: 2143.18 ± 478.44 ms *vs.* 1765.71 ± 353.93 ms p = .005; right: 2193.63 ± 571.44 ms *vs.* 1856.19 ± 270.03 ms p = .01). Considering the underlying conditions related to SN, the presence of a dysimmune-related SN was not associated to higher prevalence of absent SSR when compared to those SN patients without a dysimmune background (p = .8).

We compared responses of NCS and SSR in the four limbs. Twenty-three patients had normal SSR with absent SNAPs in that limb. Meanwhile, for 15 patients there was an absent SSR with present SNAPs (either with normal or reduced amplitudes).

3.8. Results summary

Table 4 highlights the proportion of abnormal responses for each test in the patient and control groups.

4. Discussion

Non-paraneoplastic sensory neuronopathies are considered rare diseases and many aspects of the phenotype still deserve investigation, such as autonomic nervous system involvement. In this study, we recruited a large cohort of patients with npSN and performed a comprehensive clinical and neurophysiological evaluation of the autonomic function. As a group, patients had frequent and severe clinical manifestations of autonomic failure, such as postural hypotension. The more detailed neurophysiological assessment revealed combined dysfunction

Table 3
Sweat volume and latencies in each anatomical site (forearm, proximal leg, distal leg and foot) for patients with sensory neuronopathy and healthy controls.

	SN patients (n = 50)	Controls (n = 32)	*p* value*
Right forearm (μL)	0.80 ± 0.76	1.22 ± 0.65	**0.011**
Left forearm (μL)	0.71 ± 0.93		**0.008**
Latency right/left (s)	107.6 ± 58.57/107.02 ± 47.44	95.03 ± 33.53	0.27/0.21
Right proximal leg (μL)	0.53 ± 0.54	1.04 ± 0.42	< **0.001**
Left proximal leg (μL)	0.61 ± 0.52		< **0.001**
Latency right/left (s)	94.24 ± 50.79/106.06 ± 81.29	78.06 ± 35.86	0.12/0.07
Right distal leg (μL)	0.41 ± 0.53	1.08 ± 0.54	< **0.001**
Left distal leg (μL)	0.50 ± 0.57		< **0.001**
Latency right/left (s)	104.02 ± 54.98/105.04 ± 50	85.91 ± 33.48	0.1/0.06
Right foot (μL)	0.3 ± 0.43	0.75 ± 0.42	< **0.001**
Left foot (μL)	0.22 ± 0.29		< **0.001**
Latency right/left (s)	144.56 ± 56.09/152.73 ± 75.06	133.28 ± 55.66	0.38/0.22

SN: sensory neuronopathies; μL: microliters; s: seconds; *significant differences are in bold.

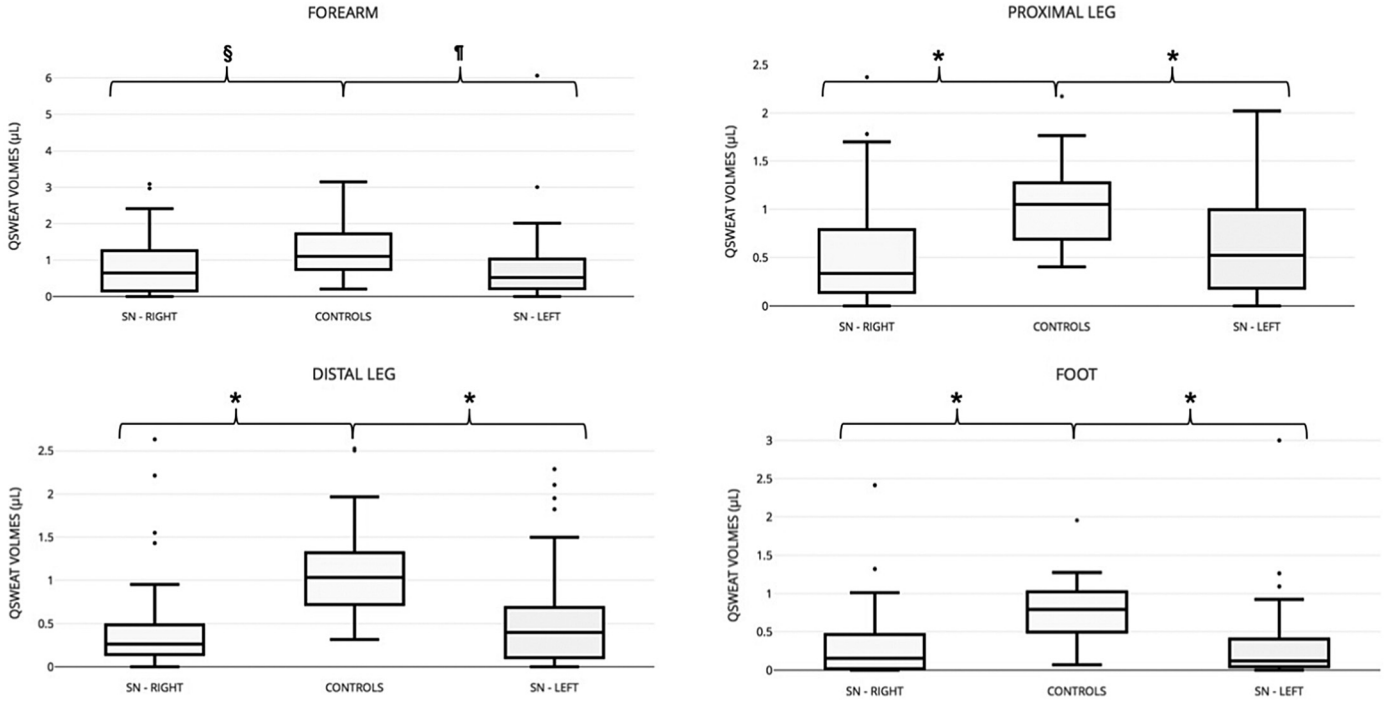

Fig. 2. Box-plot of sweat volumes for each assessed point in patients with sensory neuronopathy and healthy controls. §: $p = .011$; ¶: $p = .008$; *$p < .001$. SN: sensory neuronopathy; µL: microliters.

of both sympathetic and parasympathetic divisions in a remarkable proportion of patients.

Complaints related to the autonomic dysfunction were assessed through the SCOPA-Aut questionnaire since it is a comprehensive autonomic symptom survey. Even though it was designed to address autonomic symptoms in Parkinson's disease (PD), it is the only Brazilian Portuguese validated instrument to address the autonomic system clinically [8]. Lately, this instrument has been used successfully in

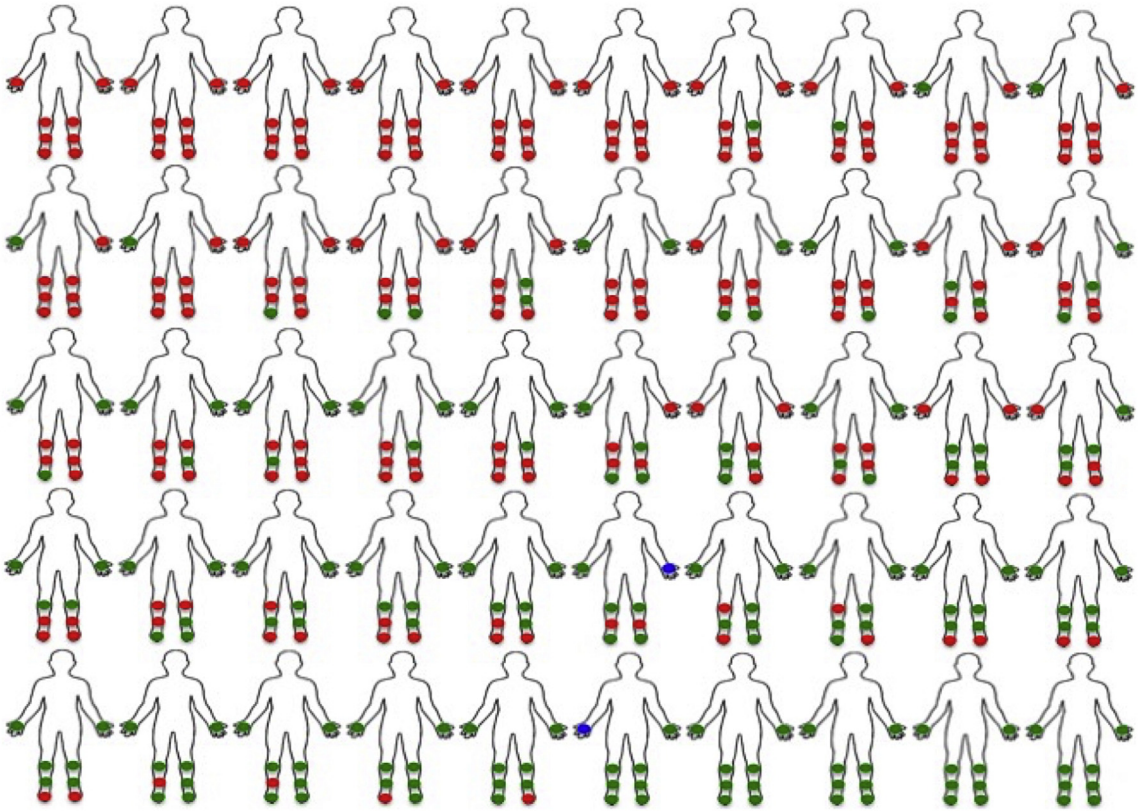

Fig. 3. The localization of abnormal sweat volumes. Red circles: sweat volume < 5th percentile; Blue circles: sweat volumes > 95th percentile; Green circles: > 5th percentile and < 95th percentile.

Table 4
Proportion of abnormal responses for each test in the patient and control groups.

	SN patients Abnormal[†]/normal	Controls Abnormal[†]/normal	*p*-Value
HRV – frequency domain	11/33	4/28	0.28
HRV – time domain	38/6	19/13	**0.01**
CAN	31/13	5/27	< **0.001**
OH	27/17	4/28	< **0.001**
QSART	46/4	5/27	< **0.001**
SSR	30/20	0/32	< **0.001**

[†] At least one abnormal test in site/point when appropriate. SN: sensory neuronopathy; HRV: heart rate variability; CAN: cardiovascular autonomic neuropathy; OH: orthostatic hypotension; QSART: quantitative sudomotor axon reflex test; SSR: sympathetic skin response.

different conditions other than PD [20–22]. It was able to demonstrate that npSN patients' complaints extended to all autonomic subdomains in a pattern similar to other peripheral neuropathies [23–25]. Autonomic signs were also conspicuous in this cohort, such as OH. Such postural drop in BP, when combined with sensory ataxia, may result in an increased risk of falls adding significant hazard for these individuals. Tonic pupils were also a routine finding - present in one out of five npSN patients. This latter finding may reflect damage to the ciliary ganglion, which is in accordance with previous descriptions in SN and case reports of other autoimmune conditions, such as SS [26,27].

Analysis of time-domain parameters of HRV revealed parasympathetic dysfunction in a great proportion of patients with npSN. Orthostatic hypotension, present in nearly half of npSN patients, highlighted a concurrent sympathetic failure as well. Despite previous mentions of parasympathetic dysfunction in SN [28], the originality of this study relies on the comprehensive clinical and neurophysiological evaluation of a larger npSN cohort. This approach enabled, for example, the accurate assessment of npSN-related CAN. Our results indeed demonstrated that definitive or at least an incipient CAN is present in almost three-quarters of npSN patients.

Interestingly, individual analysis of specific subjects brings exciting insights into how this impairment takes place. Three patients, for instance, had OH and abnormal sweat volumes but no cardiovagal abnormalities. These findings are in striking contrast to those found in diabetic CAN, where vagal dysfunction appears long before signs of sympathetic failure [25,29]. Much like somatic diabetic neuropathy, the diabetic CAN is a length-dependent phenomenon, which explains why the vagus nerve is preferentially affected. These considerations taken together, suggest that at least for some patients npSN-related CAN is a non-length dependent process.

A significant finding in this study is the description of the pattern of sudomotor abnormalities in npSN. QSART analyses revealed that sudomotor dysfunction was a seemingly universal feature of the disease. Moreover, most patients had an asymmetric and non-length dependent pattern of sweat loss. Interestingly, the distribution of areas of sudomotor and sensory deficits over the body surface was mostly non-overlapping. Many subjects indeed had dramatically reduced sweat responses in limbs and/or absent SSR where clinical findings were normal and SNAPs were present (either normal or with reduced amplitudes). These results suggest that sudomotor dysfunction in npSN cannot be attributed to damaged sensory fibers *per se*. There must be direct involvement of sympathetic cholinergic post-ganglionic fibers. Besides, the multifocal rather than "polyneuropathic" pattern of sweat loss raises the hypothesis that autonomic ganglia, not distal autonomic axons are the actual target of the lesion. In such a scenario, many patients would indeed have a double neuronopathy – sensory and autonomic. This mechanism agrees with the experimental study of Collins and Weiner [30] who could not elicit a sweat response in a cat's pad after stimulating its dorsal roots proximal to the DRG. A possible explanation for this double neuronopathy hypothesis lay in the functional and structural characteristics shared by both sensory and autonomic neurons. Evidence may be found in animal models [31–33] and confirmed by the existence of a group of hereditary neuropathies, such as the hereditary sensory and autonomic neuropathies (HSANs), which target selectively autonomic and sensory neurons.

Another argument towards the simultaneous sensory and autonomic neuronopathy emerges from the lack of association between sweat volumes and severity of ataxia/sensory deficits. Despite a tendency towards an inverse correlation between the total sweat volume and the disease duration, this was not statistically significant ($p = 0{,}14$). This lack of correlation was also true for the CAN. Patients with and without criteria for CAN had similar ages, disease duration, gender, and associated etiologies. These data suggest that the random DRG destruction that takes place in the disease, also happens in the autonomic structures.

Overall, this study suggests that individuals with npSN have sympathetic and parasympathetic dysfunction as part of the clinical disease phenotype. Dysautonomia was rather frequent and sometimes severe. It included both sudomotor and cardiac abnormalities. This study has some limitations. Our cohort size of 50 patients is reasonably large for such a rare disease but precludes analysis of etiology-defined subgroups of npSN since patients with paraneoplastic, genetic and toxic-related SN were not evaluated here. Indeed, patients with paraneoplastic SN were already evaluated before [34] with estimates that 30% of them have associated autonomic neuropathy.One certainly needs to move towards multicentric studies in order to fully appreciate how frequent and severe autonomic dysfunction is in distinct subtypes of npSN, such as SS-related. The natural history of these abnormalities should also be pursued in prospective surveys. Neurologists should be aware of autonomic dysfunction not only in paraneoplastic but also in npSN since this is frequent, often disabling but a potentially treatable manifestation.

Acknowledgments/funding

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Conflicts of interest

Dr. Martinez received a PhD scholarship from Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (Grant #2013/26410-0). On behalf of all other authors, the corresponding author states that there is no conflict of interest.

Data availability

The authors are not authorized to make these data publicly available. Data may be obtained upon reasonable request directly through the corresponding author who owns the dataset used and analyzed in the present study.

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