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ORIGINAL COMMUNICATION

Autonomic dysfunction in non-paraneoplastic sensory neuronopathy: beyond sensory abnormalities

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Abstract Sensory neuronopathies (SN) represent a subgroup of peripheral nervous system disorders which are becoming increasingly recognized. Despite a few reports of autonomic dysfunction, this complication has not been fully appreciated. Autonomic function was quantified through tests of sympathetic and parasympathetic function (forming the Autonomic Tests Score, ATS), and through a 40-item questionnaire assessing autonomic symptoms (constituting the Autonomic Questionnaire Score, AQS). Twenty patients were enrolled. Forty-six age- and gender-matched controls were evaluated for the AQS and 15 for the ATS. All patients reported symptoms of autonomic dysfunction. Of the patients, 60% had one or more abnormal cardiovagal test, 60% orthostatic hypotension and 20% abnormal pupillary function. Their ATS was significantly different from the controls ($p < 0.0001$). Neither the ATS nor AQS were different between groups of SN associated disorders. Autonomic dysfunction is a frequent and important complication in SN, and it does not seem to be related to a specific etiology, as previously thought.

Keywords Autonomic dysfunction · Clinical neurophysiology · Heart rate variability · Sensory ganglionopathy · Sensory neuronopathy

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Introduction

Few neurological conditions can lead to the prominent sensory abnormalities seen in sensory neuronopathy (SN). This condition, first described in 1948 [1], constitutes a selective affection of dorsal root ganglion (DRG) neurons, resulting in a clinical phenotype of sensory ataxia, areflexia and patchy sensory symptoms [2–4]. Both afferent and efferent axonal projections of DRG T-shaped neurons undergo degeneration, leading to the distinct non-length dependent pattern of denervation [2–4]. This can be documented by both widespread sensory nerve abnormalities in electrophysiological studies and posterior columns hyperintensity in cervical spine MRI [5–7]. Besides the remarkable sensory dysfunction present in SN, there are studies which have also reported concomitant autonomic dysfunction [5, 8]. It may be due to postganglionic nerve fiber impairment [2]; however, concurrent involvement of DRG cells, sympathetic, and parasympathetic ganglia have also been described in some patients [9–11]. Tonic pupils, orthostatic hypotension, and gastrointestinal symptoms were eventually reported in some case series of SN and were thought to be more common in dysimmune or paraneoplastic disease, but its real prevalence is still unknown [2–4]. In this setting, we aimed to perform a systematic autonomic evaluation in patients with chronic acquired SN, in order to assess the frequency and extent of autonomic dysfunction in this condition.

Patients and methods

Study design

We retrospectively reviewed clinical and electrophysiological data of patients referred to our neuromuscular

disease outpatient clinic in the last 8 years for predominantly sensory disturbances, looking for patients with SN. Diagnosis was based on the following criteria: clinical-sensory ataxia, focal sensory signs, and normal muscle strength; and electrophysiological features—widespread decrease, involving both upper and lower limb nerves, of sensory nerve action potential (SNAP) amplitudes, normal sensory and motor conduction velocities, and normal needle electromyography. Mean sensory nerve amplitude (mSNAP) was defined as the arithmetic mean of radial, sural and median SNAPs amplitudes for each patient.

All patients fulfilling the SN criteria, after giving informed consent, underwent a novel complete neurological evaluation. Sensory ataxia was scored in accordance with the functional staging of Friedreich's Ataxia Rating Scale (FARS) [12, 13]. More detailed methodological aspects are described elsewhere [4]. This study was approved by the ethics committee of the faculty of medical sciences of State University of Campinas (Campinas, Brazil).

Autonomic function was quantified through tests of parasympathetic (cardiovagal) and sympathetic (cardiovascular and pupillomotor) function using a 40-item questionnaire. Sympathetic skin response (SSR) was also included as a test for sympathetic sudomotor function. For the autonomic tests, a 5-min period of supine rest preceded each of the procedures. Heart rate variability (HRV) examinations were performed between 9:00 and 11:30 a.m. to avoid diurnal variations and recorded on a continuous electrocardiogram machine [14, 15]. All HRV values were compared to age- and gender-based normative values [14, 16–18]. For comparison between patients and controls, each abnormal autonomic test was given a score of one; therefore, the maximum total score was six, which was the Autonomic Tests Score (ATS). Considering its methodological drawbacks, SSR was not included in the ATS. The tests were performed in the following order.

Metronomic deep-breathing

The subjects were instructed to take six deep breaths per minute (10 s per cycle). During the breathing cycle with the maximum HRV, the longest *R–R* interval during expiration (*E*) and the shortest *R–R* interval during inspiration (*I*) were determined to obtain the expiratory–inspiratory ratio (*E*/*I*) and the $E - I$ difference [19–21].

Active standing

The individuals were asked to stand up rapidly. Electrocardiographic analysis was started before standing up. The 30:15 ratio was calculated as the ratio of the longest *R–R* interval after approximately 30 heartbeats from beginning the challenge (between the 21st and 45th) divided by the shortest interval after approximately 15 heartbeats from standing-up (between the 5th and 25th) [19–21]. Blood pressure was recorded supine and following standing up at 1, 2, and 3 min. Orthostatic hypotension (OH) was defined as a reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg in any of these measures after standing up [22].

Valsalva maneuver

The subjects were trained to blow through a mouthpiece connected to a mercury manometer until a maintained expiratory pressure of 40 mmHg over 15 s was obtained. The Valsalva ratio was calculated as the ratio of the highest heart rate during expiration and the lowest heart rate during the first 20 s after the expiratory strain [19–21].

Sympathetic skin response

This was recorded from the palms of the hands with the reference electrode on the dorsum of the hand. SSR was evoked by electrical stimuli at randomized intervals and with increasing stimulus intensity. The response was considered normal if present and abnormal if persistently absent [19–21].

Reflex response to light

The reflex was tested in each eye individually. The light was shone into the eye obliquely with the patient fixing at distance. Brisk pupillary constriction followed by slight dilatation back to an intermediate state was considered a normal response [19, 23].

Questionnaire

We developed a 40-item instrument, based on the Autonomic Symptom Profile and the Autonomic Dysfunction Score [15, 24]. In short, these questionnaires were translated to Portuguese and a few recurring items were excluded. It assessed several domains of autonomic symptoms, including orthostatic, reflex syncope, vasomotor, secretomotor (including sudomotor symptoms), gastrointestinal, urinary, male sexual dysfunction, pupillomotor, and sleep function. Each domain included one to eight items, and each item was scored based on its presence, severity, and frequency, ranging from 0 to 3. The maximum total score was 113 for men and 106 for women and it constituted the Autonomic Questionnaire Score (AQS).

Control group

Healthy individuals were evaluated as a control group. Autonomic tests were performed in 20 patients and in 15 healthy subjects with similar age and gender distribution ($p = 0.42$ and 0.99, respectively). For the questionnaire, we included 31 more individuals (total = 46) also matching for age and gender distribution ($p = 0.83$ and 0.92, respectively).

Statistical analyses

Data were entered into STATISTICA software (Stat Soft, Inc., Tulsa, OC). Basic demographic, laboratorial, electrophysiological, and autonomic profiles of patients were represented by descriptive statistics. Comparison of means was performed with Mann–Whitney *U* tests (two independent groups) or Kruskal–Wallis analysis of variance (multigroup comparison). All correlations were made with linear regression (Spearman coefficient). The level of significance was established as $p < 0.05$.

Results

Clinical findings

Twenty patients were enrolled. Neurological and autonomic evaluations were performed 98 months (range 30–175) after disease onset (Table 1). None of the patients had other diseases that could potentially lead to autonomic dysfunction except for one, with recently diagnosed type 2 diabetes mellitus (<5 years). None of the patients were taking medications that could alter the results of autonomic tests. SN was associated with dysimmune conditions in six patients, three with Sjögren's syndrome, one with autoimmune active hepatitis, and one with monoclonal gammopathy of undetermined significance. One patient with positive antinuclear antibody (1:320) and elevated sedimentation rate (45 mm/h) without other findings, was considered unclassified dysimmune syndrome. Two of those with Sjögren's syndrome had autoimmune hypothyroidism controlled with hormone replacement. SN was related to active hepatitis C in one patient and to vitamin B12 deficiency in another. One patient had history of serious organophosphate intoxication preceding SN symptoms, without other findings at investigation and, therefore, was considered a toxic related SN. The remaining 11 patients were considered idiopathic SN. Investigation for malignancies was repeatedly normal. No patient had history of vitamin supplementation, heavy alcohol intake nor had undergone treatment with anti-neoplastic drugs. More detailed clinical findings are reported elsewhere [4].

Table 1 Clinical and neurophysiological data of patients with SN

Characteristics	Mean (range)
Mean age (years)	50.95 (20–80)
Sex (male/female)	8/12
Age at disease onset (years)	43 (17–75)
FARS	3.45 (2–5)
Disease duration (months)	98 (30–175)
Presence of small-fiber sensory symptoms (% of patients)	
Positive	95%
Negative	90%
Etiology (number of patients)	
Dysimmune	6
Hepatitis C	1
B12 deficiency	1
Toxic	1
Idiopathic	11
Time of neurophysiological studies (months)	
After disease onset	72.8 (11–147)
Before autonomic evaluation	25.25 (0–92)
mSNAP (μV)	6.47 (0–21.67)

FARS Friedreich's Ataxia Rating Scale; *mSNAP* mean sensory nerve amplitude (including radial, median and sural nerves)

Autonomic tests

The ATS (which includes $E - I$, *E*:*I*, 30:15, Valsalva, OH, and pupils) was 2.0 (range 0–5) for the patients and 0.06 (range 0–1) for the controls ($p < 0.00001$) (Fig. 1). Of the patients, 60% had one or more abnormal cardiovagal test. There was no significant difference among groups of SN associated conditions and autonomic tests, neither individually nor in the ATS.

Parasympathetic function

Metronomic deep-breathing Mean *E*/*I* ratio was 1.21 for the patients and slightly higher for the controls (1.28, $p = 0.061$). Mean $E - I$ difference was 14.26 bpm for the patients and 17.4 bpm for the controls ($p = 0.19$) (Fig. 1). Comparing to age-based norms [14, 16–18], four patients but no controls had an abnormal E/I ratio ($p = 0.068$) (Fig. 2). Similarly, $E - I$ difference was abnormal in five patients and no control subject ($p = 0.037$). Both *E*/*I* and $E - I$ indexes were not related to disease duration or severity. Nevertheless, there was a significant positive correlation between $E - I$ and mSNAP ($r = 0.53$, $p = 0.023$).

Heart rate response to postural change The mean 30:15 ratio was 1.25 for the patients and 1.38 for the controls ($p = 0.043$) (Fig. 1). Five patients but no control had

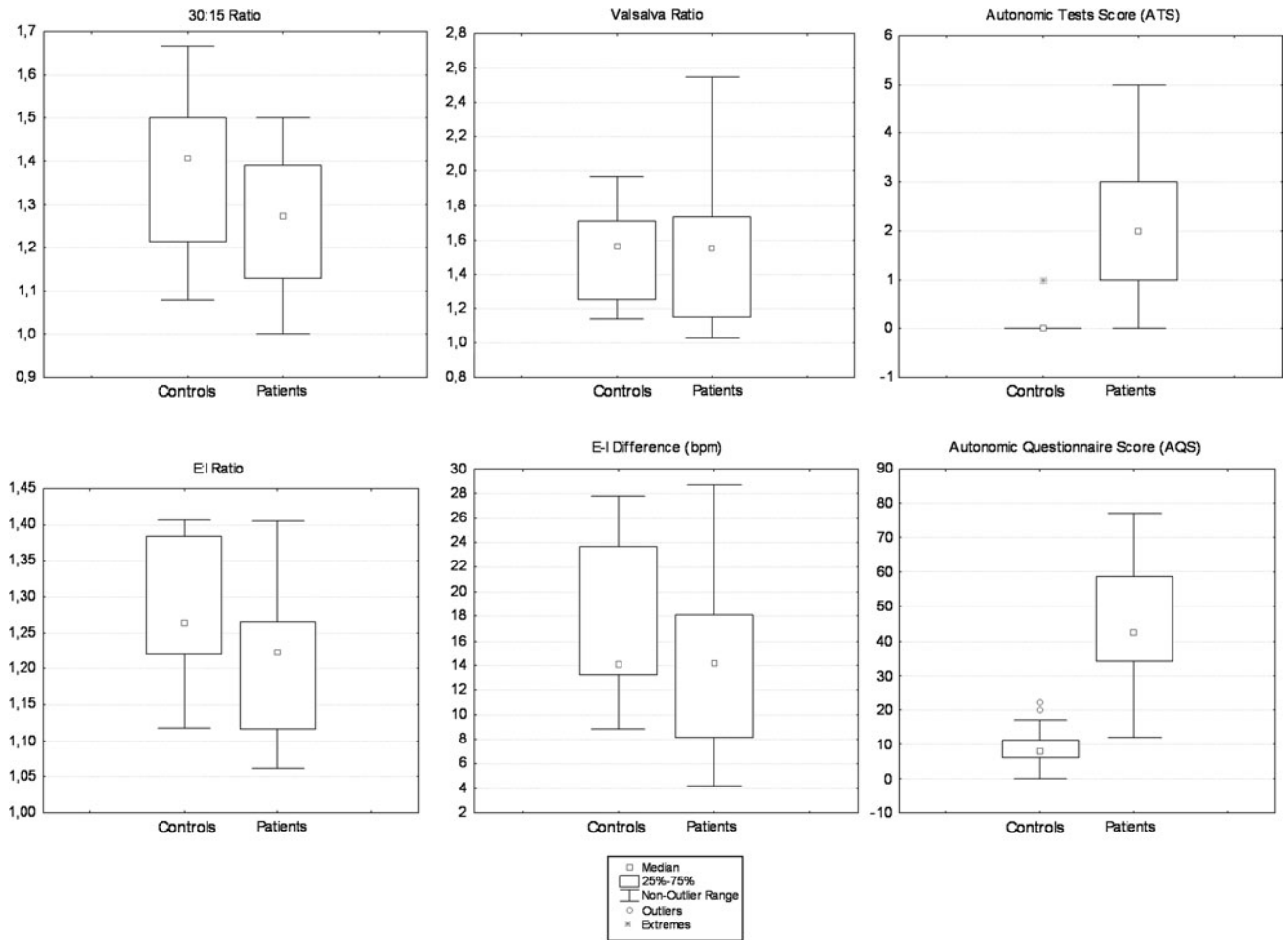

Fig. 1 *Box–whisker plots* for mean autonomic tests scores (*E:I*, 30:15 and Valsalva ratio and $E - I$ difference), ATS and AQS. Statistically significant differences between patients and controls were found for the 30:15 ratio ($p < 0.05$), and especially for ATS and AQS ($p < 0.0001$)

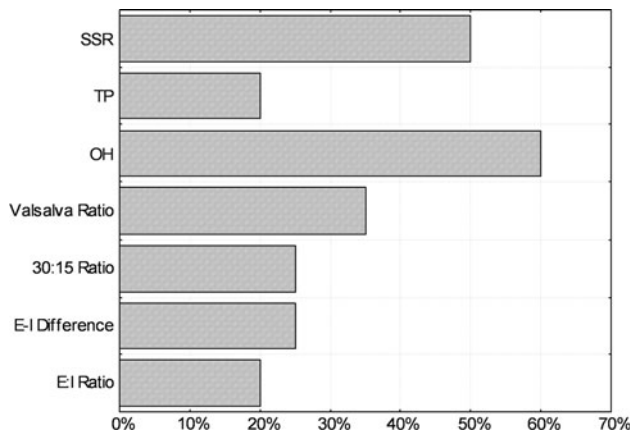

Fig. 2 Percentage of patients with abnormal autonomic tests. *TP* tonic pupils, *SSR* sympathetic skin response, *OH* orthostatic hypotension

abnormal values ($p = 0.037$) when compared to age-based normative data (Fig. 2) [14, 16–18]. The 30:15 ratio was inversely associated with longer disease duration ($r = -0.54$, $p = 0.014$) and had a weak association with disease severity as rated by the functional staging of FARS ($r = -0.42$, $p = 0.065$). Nevertheless, mSNAP was not related to 30:15 ratio.

Valsalva maneuver The Valsalva ratio was 1.54 in the patient group and 1.52 in the control group ($p = 0.76$) (Fig. 1). When compared to age- and gender-based normative data [14, 16–18], seven patients but no control had an abnormal ratio (Fig. 2) ($p < 0.01$). The mSNAP was not correlated to Valsalva ratio. However, those with an abnormal index had a slightly longer disease duration (122.5 vs. 78.0 months, $p = 0.062$) and higher ataxia score (3.9 vs. 3.1, $p = 0.073$).

Sympathetic function

Blood pressure response to active standing Mean orthostatic variation in blood pressure within 3 min of active standing was −6.85 mmHg for the systolic and −4.81 mmHg for the diastolic in the patients group, and +2.02 and +7.11, respectively, for the controls ($p = 0.092$ and $p < 0.001$, respectively). OH was found in 12 patients and one control ($p < 0.01$). Its presence was not related to disease duration, severity, or mSNAP.

Pupillary reflex response to light *Adie's* tonic pupils were found in four patients (three of them bilaterally), but in no healthy subject ($p = 0.069$) (Fig. 2). The presence of tonic pupils was not related to disease duration, severity or mSNAP.

Sympathetic skin response The SSR was absent in ten patients and one control ($p = 0.035$) (Fig. 2). The absence of the response was not related to disease duration, severity or mSNAP.

Questionnaire

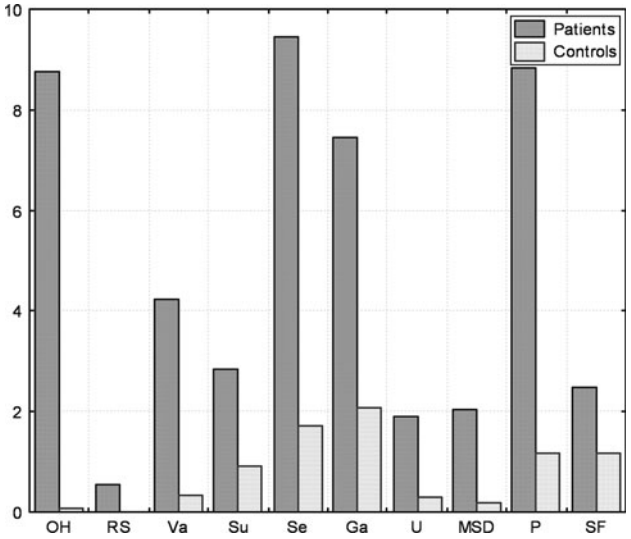

Fig. 3 Mean scores on each questionnaire individual domain. Patients scored significantly higher than controls on all individual domains of the questionnaire, and particularly on orthostatic, vasomotor, secretomotor, gastrointestinal and pupillomotor ($p < 0.001$) *OH* orthostatic, *RS* reflex syncope, *Va* vasomotor, *Su* sudomotor, *Se* secretomotor, *Ga* gastrointestinal, *U* urinary, *MSD* male sexual dysfunction, *P* pupillomotor, *SF* sleep function

All patients reported symptoms in at least one domain of autonomic function, most frequently on orthostatic (85% of the patients), secretomotor (95%), gastrointestinal (95%), pupillomotor (80%), and sleep function (85%). Indeed, patients scored significantly higher than controls on all individual domains of the questionnaire (Fig. 3). The patients' total AQS was also higher than controls ($p < 0.001$) (Fig. 1).

We did not find significant differences among groups of SN associated conditions and scores of the questionnaire, neither by comparing each domain separately nor by the total score (AQS). Likewise, the total score was not related to disease duration ($p = 0.235$). Nonetheless, AQS was significantly correlated to the ATS ($r = 0.66$, $p < 0.0001$), and to mSNAP ($r = -0.512$, $p = 0.029$). There was also a weak relation between total score and disease severity ($r = 0.409$, $p = 0.073$). In addition, presence of OH was related to higher scores in the orthostatic domain ($p < 0.001$), and Valsalva ratio was inversely associated with scores in the reflex syncope domain ($r = -0.41$, $p = 0.016$).

Discussion

Primary affection of DRG neurons is a condition that has become better recognized in the last few decades. Features of small- and particularly large-sized neuron degeneration have been well described and include typical sensory ataxia, areflexia and patchy sensory symptoms [2–4]. Conversely, despite a few reports of autonomic dysfunction in patients with SN, these features have been mostly related to a paraneoplastic etiology, and this complication has not been fully appreciated [4]. Indeed, even in neurological diseases with higher prevalence, such as diabetes related neuropathy, the autonomic nervous system affection can still be overlooked [19, 25]. This becomes particularly clear when comprehensive evaluation for dysautonomia is performed in patients with such neuropathies [19, 25]. Assessment of autonomic dysfunction is best accomplished by using standardized tests which evaluate both the sympathetic and parasympathetic nervous system. HRV tests as well as orthostatic challenge are particularly reliable for this purpose [14, 17, 21]. We found significant differences between controls and patients with SN in all the tests; mostly impaired were blood pressure response to orthostatic challenge and Valsalva ratio. Both the parasympathetic and sympathetic nervous system were affected. Although not included in the ATS, SSR was also frequently absent. However, significant sensory loss, such as expected in this condition, can diminish the afferent loop of the reflex and produce false positive results. Despite being easy to perform, results in SSR should be interpreted carefully, and better understanding of sudomotor function in SN requires other procedures such as the quantitative sudomotor axon reflex test.

The dysfunction observed in some tests was related to longer disease duration (30:15) and lower SNAPs

amplitudes ($E - I$), and it was also slightly related to disease severity rated by the functional staging of FARS. These findings suggest that despite a relative stability of somatic symptoms reported by most of the patients with a chronic SN [4], there can be an ongoing process of autonomic nervous system impairment. Nonetheless, follow-up studies are warranted to answer this question.

Also noteworthy was the remarkable impairment disclosed by the questionnaire. Although not yet validated, this 40-item questionnaire was derived from two previously validated and published instruments and their design was mostly translated to Portuguese [15, 24]. It was also obtained from 46 controls, showing statistically significant differences on all individual domain scores when comparing to the patients group. Moreover, presence of OH was related to higher scores in the orthostatic domain and a strong correlation between AQS and ATS was found, similar to what has been reported for other questionnaires [15]. Symptoms in any domain of autonomic function were reported by all patients, irrespective of the SN related condition, and, once again, orthostatic related symptoms were among the most frequent, together with secretomotor, gastrointestinal, and pupillomotor function. The total score tended to be higher in those with lower SNAPs amplitudes and worse disease severity, as observed with the autonomic tests.

Still unclear is the underlying mechanism leading to autonomic dysfunction in SN. Some consider it the result of postganglionic nerve fiber impairment [2], but several cases of concurrent autonomic ganglia involvement have also been documented [9–11]. Moreover, like acquired SN, autonomic ganglionopathy may be an autoimmune, antibody-mediated, neurological disorder, and, in fact, many patients have antibodies that specifically recognize the alpha-3 subunit of the ganglionic acetylcholine receptor [26]. DRG neurons also convey afferent visceral impulses that arise in both sympathetic and parasympathetic fibers, either small myelinated or unmyelinated, and, hence, are involved in autonomic reflexes [23]. Therefore, damage to the DRG neurons may also lead to autonomic nervous system dysfunction. However, further studies are necessary to better establish its pathophysiology.

Although an extensive autonomic evaluation is indeed demanding, it does provide valuable information concerning the spectrum of neurological manifestations in SN, as well as insights into the pathological mechanism of the disease. We conclude that autonomic dysfunction, both sympathetic and parasympathetic, is a common finding among patients with non-paraneoplastic SN, and it does not seem to be related to a specific etiology, as previously thought. An immune mediated or idiopathic process can affect both sensory and autonomic ganglia; however, damage to the DRG alone may also lead to autonomic abnormalities. We propose that autonomic dysfunction should be routinely assessed in such patients.

Conflict of interest The authors report no conflicts of interest.

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