RESEARCH ARTICLE

Autonomic symptoms, cardiovascular and sudomotor evaluation in de novo type 1 narcolepsy

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Abstract

Purpose To evaluate cardiovascular and sudomotor function during wakefulness and to assess autonomic symptoms in de novo patients with type 1 narcolepsy compared to healthy controls.

Methods De novo patients with type 1 narcolepsy (NT1) and healthy controls underwent cardiovascular function tests including head-up tilt test, Valsalva maneuver, deep breathing, hand grip, and cold face, and sudomotor function was assessed through Sudoscan. Autonomic symptoms were investigated using the Scales for Outcomes in Parkinson's Disease–Autonomic Dysfunction (SCOPA-AUT) questionnaire.

Results Twelve de novo patients with NT1 and 14 healthy controls were included. In supine rest condition and at 3 min and 10 min head-up tilt test, the systolic blood pressure values were significantly higher in the NT1 group than in controls ($p < 0.05$). A lower Valsalva ratio ($p < 0.01$), significantly smaller inspiratory–expiratory difference in deep breathing ($p < 0.05$), and lower delta heart rate in the cold face test ($p < 0.01$) were also observed in the NT1 group. The mean hand electrochemical skin conductance values were significantly lower ($p < 0.05$) and the mean SCOPA-AUT total scores were significantly higher in patients with NT1 than in healthy subjects ($p < 0.001$), with greater involvement of cardiovascular and thermoregulatory items.

Conclusion De novo patients with NT1 exhibit blunted parasympathetic activity during wakefulness, mild sudomotor dysfunction, and a large variety of autonomic symptoms.

Keywords Narcolepsy type 1 (NT1) · Autonomic nervous system (ANS) · Cardiovascular reflexes · Sudomotor function · Scales for Outcomes in Parkinson's Disease–Autonomic Dysfunction questionnaire (SCOPA-AUT)

Introduction

The link between narcolepsy and the autonomic nervous system (ANS) has been observed since the early descriptions of the disease and includes cardiovascular, pupillomotor, sexual, gastrointestinal, respiratory dysfunction, and metabolic and body temperature abnormalities during sleep and wakefulness [1–4].

First studies on the matter reported attenuation of autonomic reactivity to cardiovascular reflexes, which were partially modified by amphetamines [5], and a central origin of the sympatho-vagal imbalance was hypothesized [6]. Confirmation of such a hypothesis stems from the discovery of orexins, whose projections modulate both vagal and sympathetic outflows [4]. Lack of orexin in type 1 narcolepsy (NT1) may influence a wide variety of autonomic functions, but mechanisms and pathways are not yet completely known. As to cardiovascular autonomic impairment, previous authors have reported conflicting results, possibly deriving from different methodological approaches and conditions concerning the sleep–wake cycle [3]. Regarding core body and skin temperature regulation, a few authors have described abnormalities in narcoleptic patients [1, 7], although, to date, sudomotor function has not been investigated. On the basis of these assumptions, we studied

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untreated de novo patients with NT1 using clinical autonomic evaluation by means of the Scales for Outcomes in Parkinson's Disease-Autonomic Dysfunction questionnaire (SCOPA-AUT), for the first time together with comprehensive autonomic testing under rigorous controlled conditions, hypothesizing a link between subjective and objective findings.

The objectives of this study were:

(i) To evaluate autonomic responses by means of cardiovascular reflexes during wakefulness
(ii) To study sudomotor function using Sudoscan
(iii) To evaluate possible autonomic impairments assessed through SCOPA-AUT.

All the above in de novo patients with NT1 were compared to healthy controls.

Methods

Subjects

Consecutive de novo untreated patients with NT1 according to the International Classification of Sleep Disorders -Third Edition (ICSD-3) criteria [8] were recruited at the Sleep Medicine Center of Policlinico Tor Vergata. The diagnosis of NT1 was based on the presence of excessive daytime sleepiness, a mean sleep latency below 8 min on the Multiple Sleep Latency Test, with at least two sleep-onset REM periods, typical cataplexy, and/or low orexin-A cerebrospinal fluid levels (< 110 pg/mL). Patients with Apnea-Hypopnea Index values greater than 5 per hour were excluded by means of polysomnographic monitoring. Patients were matched with healthy subjects comparable for age and sex, screened by a neurologist with expertise in sleep medicine in order to exclude sleep disorders. Exclusion criteria for NT1 and control subjects were diabetes mellitus, hypertension, heart, endocrine, metabolic and renal diseases, smoking habit, mental illness, and use of drugs affecting the ANS.

Both patients and controls were assessed for autonomic function using SCOPA-AUT [9]. The SCOPA-AUT questionnaire explores the following domains: gastrointestinal, urinary, cardiovascular, thermoregulatory, pupillomotor, and sexual. The SCOPA-AUT total score ranges from 0 to 69, with higher scores reflecting worse autonomic functioning.

Subjective daytime somnolence was evaluated by means of the Epworth Sleepiness Scale (ESS) [10, 11].

All subjects were tested in the morning between 8 a.m. and 10 a.m. for cardiovascular and sudomotor function.

All subjects gave their informed consent to undergo the procedures, and the study was approved by the Ethics Committee of Policlinico Tor Vergata.

Cardiovascular reflexes

Autonomic function was evaluated in an autonomic laboratory (23 ± 1 °C). Beat-to-beat systolic blood pressure (SBP) and diastolic blood pressure (DBP) (Finometer PRO, Finapres Medical Systems, Amsterdam, Netherlands), heart rate (HR), and oronasal breathing (Grass model 15-LT) were continuously recorded according to standard procedures [12]. The tests were performed allowing a period of rest to restore basal blood pressure (BP) and heart rate (HR) values between investigations. The results were automatically obtained using Light-SNV software (SparkBio Srl, Bologna, Italy), which is able to visualize, store, and analyze the data, providing a final report with the results [13].

The following tests were executed: head-up tilt test (HUTT), Valsalva maneuver, deep breathing, hand grip test, and cold face testing. The subject was tilted up at 65° for 10 min after 20 min of supine rest, and the changes in SBP, DBP, and HR were calculated at each minute of HUTT with respect to basal values. Pre-HUTT supine values (baseline) for SBP, DBP, and HR were set at 0, and changes were expressed as Δ(raw data) from baseline. The Valsalva maneuver was performed by blowing through a mouthpiece attached to a manometer and maintaining pressure of 40 mmHg for 15 s. The maneuver has four phases. As indices of autonomic activity, we considered the ratio between HR in phases II and IV (VR) and the BP variations in phase IV. In the deep breathing test, the sinus arrhythmia calculated in beats per minute was evaluated. The difference between the maximum HR during inspiration and minimum HR during expiration (I–E difference) in an individual respiratory cycle was calculated and expressed as the mean of the differences over 10 respiratory cycles. In the hand grip test, subjects were asked to exert 30% of maximal voluntary contraction of the dominant hand on a dynamometer for 5 min. BP and HR were measured in the non-exercising arm at rest, and ΔSBP and ΔDBP were calculated at the fifth minute of the test. In the cold face test, synthetic ice (0–1 °C) was applied to the forehead for 60 s, and changes in HR and DBP were compared to baseline values.

Sudomotor function test

Sudomotor function was assessed by Sudoscan (Impeto Medical; Paris, France), which measures peripheral small fiber and autonomic nerve activity by detecting abnormal sweat gland function through electrochemical skin conductance (ESC). The test was performed in patients with NT1 and controls. Individual right and left hands

and feet were evaluated, and a final mean score for both hands (hands ESC) and both feet (feet ESC) was given automatically and considered for analysis [14]. Sudomotor dysfunction was considered absent, moderate, or severe if the ESC measured on the feet was > 70 µS, between 70 and 50 µS, or < 50 µS, respectively, and if the ESC measured on the hands was > 60 µS, between 60 and 40 µS, or < 40 µS, respectively [14].

Statistical analysis

Data were reported as mean and standard deviation. The normally distributed data, as assessed by the Kolmogorov–Smirnov test, were compared using Student's unpaired two-tailed t test.

Non-normally distributed autonomic function test data were analyzed using the Mann–Whitney rank-sum test for between-group analysis. Spearman correlation analysis was used to evaluate the relationships between autonomic tests and demographic and clinical data. Statistical analysis was performed with Statistica 10.0 software (StatSoft Inc, Tulsa, OK, USA). Statistical significance was set at $p < 0.05$.

Results

Demographic and clinical data

Twelve patients with NT1 (7 women, 5 men, mean age 34.3 ± 12.4 years) and 14 healthy controls (8 women, 6 men, mean age 37.4 ± 8.2 years) were included in the study. Six of the 12 patients with NT1 underwent orexin cerebrospinal fluid (CSF) measurement (mean value 37.1 ± 20.84 pg/mL, range: 10–65). The remaining six patients refused lumbar puncture. No significant difference in age or body mass index (BMI) was observed between patients with NT1 and controls. Subjective daytime somnolence, evaluated by the ESS, was significantly higher in de novo patients with NT1 compared to controls.

The mean SCOPA-AUT total score and all the domains (cardiovascular, gastrointestinal, urinary, pupillomotor, thermoregulatory, and sexual) were significantly higher in the NT1 group relative to controls. All data are reported in Table 1.

Cardiovascular reflexes

No patients were positive for orthostatic hypotension. In supine rest condition and at 3 min and 10 min of HUTT, the SBP values were significantly higher in patients with NT1 compared to controls ($p < 0.05$), whereas DBP and HR were comparable. ΔHR at 3 min was higher in the control group

Table 1 Demographic characteristics and subjective scales in de novo patients with type 1 narcolepsy (NT1) and healthy controls

	NT1 $n = 12$	Controls $n = 14$	p value*
Age	34.3 ± 12.4	37.4 ± 8.2	0.5
Sex F:M	7:5	8:6	0.9
BMI	28.4 ± 7.6	24 ± 3.8	0.1
ESS	13.8 ± 6.7	2.4 ± 2.2	**< 0.001**
SCOPA-AUT total score	20.6 ± 8.4	6.2 ± 3.8	**< 0.001**
Gastrointestinal	4.7 ± 3.2	1.7 ± 1.8	**0.01**
Urinary	4.3 ± 2.4	2.1 ± 2.4	**0.03**
Cardiovascular	3.2 ± 2.4	0.1 ± 0.3	**0.001**
Oversensitivity to bright light	1.4 ± 1	0.4 ± 0.6	**0.01**
Thermoregulatory	5.7 ± 2.7	1.6 ± 1.7	**< 0.001**
Sexual	1.3 ± 1.6	0.1 ± 0.5	**0.04**

Bold values denote statistical significance at the $p < 0.05$ level

Data are mean ± SD

BMI body mass index, *ESS* Epworth Sleepiness Scale, *SCOPA-AUT* Scales for Outcomes in Parkinson's Disease–Autonomic questionnaire

*p value: comparison between NT1 group and controls

than the NT1 group, but this was not evident at 10 min. Data are shown in Table 2.

In the Valsalva maneuver, patients with NT1 had lower VR than healthy subjects ($p < 0.01$). In addition, in the deep breathing test, patients with NT1 showed a significantly reduced I–E difference compared to controls ($p < 0.05$). In cold face tests, patients with NT1 demonstrated lower delta HR ($p < 0.01$), while no differences were detected in isometric hand grip. See Table 3.

Sudomotor function test

The mean ESC values for hands were significantly lower in the NT1 group ($p < 0.05$), and three out of 12 patients showed pathological hand ESC values (moderate in two and severe in one patient). The mean ESC values for feet were comparable between groups. Nevertheless, two out of 12 patients with NT1 had pathological ESC values for feet, showing moderate and severe sudomotor dysfunction, respectively. Data are reported in Table 4.

Correlation between autonomic tests and demographic and clinical data

A positive correlation between BMI and SBP at 10 min of HUTT ($R = 0.713$, $p < 0.01$) and a weak correlation between BMI and SBP at rest ($R = 0.671$, $p < 0.05$), SBP at 3-min HUTT ($R = 0.594$, $p < 0.05$), and overshoot (OV) ($R = 0.629$, $p < 0.05$) were detected. No further correlation between autonomic tests and demographic and clinical data was found.

Table 2 Cardiovascular responses at supine rest and the 3rd and 10th minute of head-up tilt test in de novo patients with type 1 narcolepsy (NT1) and healthy controls

	NT1 $n=12$	Controls $n=14$	p value*
Supine rest			
SBP (mmHg)	131.8 ± 21.4	112 ± 15.1	**0.01**
DBP (mmHg)	68.2 ± 14.9	60.3 ± 5.6	0.1
HR (bpm)	72.3 ± 8.4	71.1 ± 8.7	0.71
Differences after 3-min HUTT			
Δ SBP (mmHg)	44.7 ± 13.7	33.8 ± 10.1	0.07
Δ DBP (mmHg)	40.4 ± 7.7	35.8 ± 9	0.3
Δ HR (bpm)	8.8 ± 6.2	14.4 ± 4.5	**0.04**
3-min tilt			
SBP (mmHg)	176.5 ± 29.9	150.6 ± 21.4	**0.04**
DBP (mmHg)	108.7 ± 20.4	97.6 ± 11.3	0.14
HR (bpm)	81.1 ± 11.8	85.3 ± 10.1	0.43
Differences after 10-min HUTT			
Δ SBP (mmHg)	43.7 ± 16.6	35.2 ± 10.2	0.1
Δ DBP (mmHg)	43.2 ± 6.4	37.9 ± 10.7	0.15
Δ HR (bpm)	10.9 ± 9.9	13.5 ± 6.9	0.46
10-min tilt			
SBP (mmHg)	175.1 ± 28.9	148.7 ± 17	**0.01**
DBP (mmHg)	111.2 ± 18	99.1 ± 12.5	0.07
HR (bpm)	83.2 ± 11.3	84.2 ± 113.8	0.84

Bold values denote statistical significance at the $p < 0.05$ level

Data are mean $\pm$ SD

SBP systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, Δ change with respect to the basal value. *Supine rest*: values of supine rest assessed averaging all blood pressure and HR values from the last 5 min before HUTT. *Differences after 3-min tilt*: changes in SBP and DBP and in HR obtained by calculating the mean value at the 3rd min of HUTT. *Differences after 10-min tilt*: changes in SBP and DBP and in HR obtained by calculating the mean value at the 10th min of HUTT

*p value: comparison between NT1 group and healthy controls

Discussion

It is well known that there is wide-ranging impairment of the ANS in narcolepsy, and among all ANS functions, cardiovascular activity has been the most extensively studied by means of heart rate variability, cardiovascular reflexes, and blood pressure monitoring [1, 3].

In our study, we observed a significant increase in the SBP values, both in supine rest condition and at 3 min and 10 min of HUTT, in de novo untreated patients with NT1 compared to controls. In supine rest, SBP values were not indicative of hypertension. However, at 3 and 10 min of HUTT, mean SBP reached high values suggestive of sympathetic hyperactivity. The changes in systolic and diastolic blood pressure between supine rest and HUTT in our sample are higher than those reported by other authors, who studied cardiovascular reflexes in 10 patients with narcolepsy [15]. In our sample, a significant and positive correlation was found between BMI and SBP at rest and at 3 and 10 min of HUTT; thus we may hypothesize that body weight plays a role in blood pressure in patients with NT1. On the other hand, daytime somnolence does not seem to influence cardiovascular responses, since we found no significant correlations with the ESS.

The impairment of BP control in narcolepsy is still controversial, as previous studies have reported that narcoleptic patients exhibit normal BP circadian rhythm in 24-h Holter monitoring [16], whereas other authors have demonstrated a nighttime non-dipping BP pattern, with daytime BP comparable to healthy controls [17–20]. It was suggested that such a discrepancy in BP findings could be due to the difference in the ability to modulate BP in narcoleptic patients compared to controls, but these changes may be explained by the relatively wide between-subject differences in the 24-h average BP values [4]. Despite the different results reported, most authors agree that patients with NT1 exhibit increased sympathetic tone [15, 21, 22].

Table 3 Cardiovascular responses to Valsalva maneuver, deep breathing, cold face, and hand grip tests in de novo patients with type 1 narcolepsy (NT1) and healthy controls

	Valsalva		Deep breathing	Cold face			Isometric hand grip		
	VR	OV mmHg	I–E	Δ SBP mmHg	Δ DBP mmHg	Δ HR bpm	Δ DBP mmHg	Δ SBP mmHg	ΔHR
NT1, $n=12$	1.4 ± 0.2	28.6 ± 14.7	15 ± 3.3	12.8 ± 7.6	22.4 ± 12.7	-8 ± 3.7	16.2 ± 8.5	28.73 ± 10.92	9.6 ± 9.9
Controls, $n=14$	1.6 ± 0.2	38.6 ± 16.3	20.6 ± 7	19.4 ± 9.2	21.9 ± 15	$-12. \pm 5.0$	18.6 ± 5.6	28.75 ± 14.4	8 6.4
p values	**0.005**	0.12	**0.01**	0.09	0.88	**0.03**	0.43	0.99	0.7

Bold values denote statistical significance at the $p < 0.05$ level

Data are mean $\pm$ SD

VR Valsalva ratio, *OV* overshoot, *I–E* inspiration–expiration difference, Δ change with respect to the basal value, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate

*p value: comparison between NT1 group and healthy controls

Table 4 Values of electrochemical skin conductance (ESC) tests of feet and hands in de novo patients with NT1 and healthy controls

	Feet ESC (μS)	Hands ESC (μS)
NT1 n = 12	75.2 ± 18.7	63.9 ± 14.7
Controls n = 14	80.7 ± 6	75 ± 6.3
p value*	0.35	**0.03**

Bold values denote statistical significance at the p < 0.05 level

Data are mean ± SD

ESC electrochemical skin conductance (μS)

*p value: comparison between NT1 group and healthy controls

Patients with NT1 showed a significantly reduced VR in the Valsalva maneuver, which is mostly dependent on cardiovagal integrity and thus on parasympathetic activity. Such possible lower parasympathetic system activity in narcolepsy is supported by the significant reduction in I–E difference during deep breathing and significantly lower delta HR in the cold face test observed in our sample, together with smaller respiratory sinus arrhythmia and reduced VR as reported by previous papers [5, 6]. Furthermore, we detected a reduced delta HR during the cold face test, which evaluates the parasympathetic function through trigeminal afferents, differently from the Valsalva maneuver and deep breathing test [23]. Thus, our results suggest that, during wakefulness and under rigorously controlled conditions, de novo patients with NT1 exhibit reduced parasympathetic activity compared to controls. Animal studies have reported the vagotonic effect of orexin on the nucleus ambiguus, which is the main site of preganglionic parasympathetic neurons [24]. The lack of vagotonic effect, induced by orexin deficiency in narcolepsy, can lead to reduced cardiac vagal modulation, as observed by several studies [4, 17, 25–29]. Our findings, confirmed by different tests, support the hypothesis of blunted parasympathetic activity in NT1.

Among autonomic dysfunctions, core body and skin temperature abnormalities have been described in narcoleptic patients [1, 7, 30], but to date sudomotor function has not been investigated. We found significantly lower hand sudomotor activity in NT1, whereas mean ESC values for feet were comparable between groups. Both normal core body temperature circadian rhythm [30] and decreased core body temperature have been reported in NT1 [7, 31]. Fronczek et al. demonstrated elevated distal skin temperature in untreated patients with narcolepsy and ascribed the skin temperature alterations to decreased sympathetic distal vasoconstrictor tone. We measured sudomotor function, which is mediated by the cholinergic sympathetic nervous system, and detected a significant reduction in hand sweat gland function associated with NT1, which led us to infer an impairment in sympathetic activity. However, this result was evident only in hands, as the mean ESC values for feet were comparable between the groups; nevertheless, two out of 12 patients with NT1 had pathological ESC values for feet, showing moderate and severe sudomotor dysfunction, respectively. These data conflict with the hypothesis of sympathetic hyperactivity that we observed in orthostatic stress testing. However, autonomic control of sweating involves different areas of the central autonomic network, predominantly the cholinergic sympathetic neurons, whereas cardiovascular function is mediated by noradrenergic neurons, and such differences may explain our findings. The reduction in sudomotor function in the upper but not lower extremities is unusual; however, similar results have been observed by other authors using the same technique in patients with Parkinson's disease [32], although the primary mechanism is unclear. Moreover, Sudoscan as a measure of sympathetic function is still debated, since the relationship between ESC and other neurophysiological techniques such as sympathetic skin response and quantitative sudomotor axon tests needs to be clarified [33, 34].

No correlation was found between daytime somnolence and ESC values in our sample; however, further studies involving larger cohorts of patients with NT1 are needed to evaluate sudomotor function.

In support of sudomotor impairment, patients with NT1 reported subjective thermoregulatory disturbance on the SCOPA-AUT scale, showing statistically higher scores than controls. The total SCOPA-AUT score was also significantly higher than in healthy subjects, in line with a recent paper [35]. Barateau et al. reported mean values lower than our findings, perhaps because of their larger sample size [35]. Regarding single domains, it is of note that our patients mainly reported cardiovascular and thermoregulatory symptoms.

The main limitation of this study is the small sample size, but we applied rigorous inclusion criteria. Another limitation is the lack of a statistical power analysis a priori. In addition, only six of 12 patients with NT1 underwent orexin CSF measurement; thus a possible correlation between orexin deficiency and autonomic findings was not assessed.

In conclusion, our findings show that, under controlled conditions, de novo patients with NT1 exhibit reduced parasympathetic activity during wakefulness and mild sudomotor dysfunction, together with a large variety of autonomic symptoms.

Compliance with ethical standards

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