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Clinical symptoms and results of autonomic function testing overlap in spontaneous intracranial hypotension and postural tachycardia syndrome: A retrospective study

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Abstract

Background and purpose: Orthostatic headache is a hallmark of patients with spontaneous intracranial hypotension (SIH) but may also occur in patients with postural tachycardia syndrome (POTS). Our aim was to compare the clinical symptoms and findings of autonomic function testing in patients with SIH and POTS.

Methods: This was a retrospective analysis of the clinical symptoms and findings of autonomic function testing, including sympathetic vasoconstrictor and parasympathetic cardiac function as well as head-up tilt in patients with SIH and POTS.

Results: Nine patients with confirmed SIH and 48 with POTS (neuropathic $N = 35$, hyperadrenergic $N = 5$, deconditioned $N = 8$) were included. SIH patients experienced on average a shorter disease duration than patients with POTS. Orthostatic headache was present in all patients with SIH and 27% of patients with POTS. There was a broad overlap of other clinical symptoms of orthostatic intolerance. Screening autonomic function testing revealed normal sympathetic and parasympathetic function in all patients. All patients with SIH showed an excessive clinically symptomatic heart rate increase during standing, fulfilling the diagnostic criteria for POTS.

Conclusion: Clinical symptoms and results of autonomic function testing overlap in SIH and POTS. Hence, patients with prominent orthostatic headache fulfilling the diagnostic criteria for POTS should also be evaluated for further testing of a spinal cerebrospinal fluid leak, in the absence of a history of lumbar puncture.

Keywords

autonomic function testing, autonomic nervous system, cerebrospinal fluid leak, diagnostic criteria, orthostatic headache, orthostatic intolerance

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Introduction

Postural tachycardia syndrome (POTS) is defined in adults as a clinically symptomatic heart rate (HR) increase of more than 30 beats per minute (bpm) or an increase in HR to $\geq$120 bpm within 10 min of standing or head-up tilt (HUT), in the absence of orthostatic hypotension.[1,2] Reported clinical symptoms strongly depend on the upright body posture and involve a broad spectrum: for example headache, light-headedness or dizziness, nausea, blurred

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vision, palpitations, presyncope, sense of weakness, tremulousness, shortness of breath and chest pain.[3] Moreover, patients can also experience non-orthostatic symptoms such as bladder disturbances, fatigue, sleep disturbances, myofascial pain and discomforts relating to the gastrointestinal tract, namely bloating, diarrhoea, constipation and abdominal pain.[4] Often symptoms are aggravated by heat exposure, after activities such as eating or physical training as well as menstruation.[3,4] The prevalence of POTS is estimated to be around 170/100'000, whereof only one-fifth is male.[3] POTS is considered a syndrome that may include a number of several disorders. There are three main subtypes described.[3] The neuropathic subtype (also called dysautonomic) is the most common subtype, as 50% of POTS patients have been estimated to suffer from this pathogenesis.[3] It is characterized by a neuropathic process affecting primarily the lower extremities, resulting in destruction of peripheral sympathetic nerve fibres with consecutive adrenergic impairment to the legs.[4] Hyperadrenergic POTS is characterized by an increased orthostatic norepinephrine release of at least 600 pg/ml. Patients show elevated sympathetic nerve activity at rest and because of exaggerated sympathetic vasoconstrictor response sometimes orthostatic hypertension.[3] The third subtype refers to patients who develop POTS due to prolonged immobility or deconditioning. An affirmation for this subtype is a decrease of at least some of the symptoms when physical exercising is performed.[5]

Symptoms of patients with POTS may overlap with the symptoms that patients experience who suffer from spontaneous intracranial hypotension (SIH).[6] SIH is caused by a spinal cerebrospinal fluid (CSF) loss.[7] The clinical diagnostic criteria of the International Headache Society (IHS) demand the presence of orthostatic headache and possibly neck stiffness and/or hearing symptoms for diagnosis. Furthermore, the IHS criteria point out that in patients with typical orthostatic headache and no apparent cause, POTS should be excluded before any treatment attempt with lumbar epidural blood patch is made.[8]

The aim of this study was to compare the clinical symptoms and findings of autonomic function testing in patients with SIH and POTS.

Patients and methods

Patients referred for investigation with symptoms of orthostatic intolerance and/or orthostatic headache with a final diagnosis of POTS or SIH were identified from the database of the Autonomic Unit of the Department of Neurology, University Hospital Bern, Switzerland, from January 2003 to March 2016. The institutional review board of the University Hospital Bern and the local ethics committee (Kantonale Ethikkommission Bern, Switzerland) gave approval for the access and use of the data collective with the intention for retrospective clinical research. Written consent has been obtained from all included patients.

The final diagnosis of POTS and its subtype was based upon medical history, normal physical examination with the exception of possible cutaneous abnormalities because of reduced sweating, cardiovascular autonomic function testing (see below), quantitative sudomotor axon reflex testing and/or thermoregulatory sweat test, as well as measurement of plasma norepinephrine levels and cutaneous biopsy in selected cases.[1–4]

SIH was diagnosed according to the current IHS guidelines and only in patients with proven spinal CSF leak.[8] For localization of the site of spinal leak, a systematic diagnostic algorithm was applied,[9] consisting of cranial magnetic resonance imaging (MRI), measurement of the optic nerve sheath diameter in the supine and the upright body position,[10] fluid-sensitive thin-slice MRI of the spinal axis, measurement of lumbar opening pressure and lumbar infusion test, spinal T1-weighted MR sequences after intrathecal gadolinium application, dynamic myelography and postmyelography spine CT imaging including sometimes also repeated films (4 h later) if initially negative.

Cardiovascular autonomic function testing protocol

Patients had to stop vasoactive medication at least five half-lives before autonomic function testing and to fast overnight. Beat-to-beat blood pressure (BP) and HR were measured with the Finometer® PRO device (Finapres Medical Systems BV, Arnhem, the Netherlands) on the left arm. Additionally, brachial BP and HR were measured intermittently with a Dinamap Pro 100 sphygmomanometer (GE Medical Systems, Tampa, Florida, USA) on the right arm and a standard three-lead electrocardiogram was recorded throughout the autonomic testing. All patients underwent standard screening autonomic function tests according to the guidelines of our autonomic unit. The autonomic function screening composed of analysing sympathetic vasoconstrictor function by investigating the pressor response to a cutaneous cold stimulus at the right forearm/hand or to isometric exercise with the right hand, as well as examining parasympathetic cardiac function by observing the HR variability in response to deep breathing and the response to a pressure-controlled Valsalva manoeuvre in the supine position.[11] HUT was conducted with a tilt angle of 60° for 10 min after HR and BP remained stable in the supine position. In patients with a positive history of syncope, HUT was prolonged up to 30 min using a recently described protocol.[11]

Statistical analysis

Numerical data were compared using the Kruskal–Wallis test. Frequencies were compared using the χ^2 test with Yates's correction or two-tailed Fisher's exact test if the expected frequency was below 5. The null hypothesis was rejected at the 0.05 level of significance. Statistical analysis

Table 1. Clinical characteristics.

	POTS Neuropathic ($N = 35$)	Hyperadrenergic ($N = 5$)	Deconditioned ($N = 8$)	SIH ($N = 9$)	
Age (years)					
Mean (SD)	27 (11)	30 (9)	30 (13)	38 (11)	$p > 0.05$
Sex					
Women	23 (66%)	3 (60%)	7 (88%)	7 (78%)	
Men	12 (34%)	2 (40%)	1 (13%)	2 (22%)	
Disease duration (months)					
Mean (SD)	25.5 (49.9)	60 (89.1)	136.4 (140.1)	27.7 (57.6)	$p < 0.05$

SD: standard deviation; POTS: postural tachycardia syndrome; SIH: spontaneous intracranial hypotension.

Table 2. Patients fact sheet SIH.

Pt. No.	Sex	Age (years)	Cause of CSF leakage	Spinal level of CSF leakage
1	F	26	Diskogenic microspur	Th5–7
2	F	31	Spontaneous CSF leak	C6–Th2
3	F	30	Tarlov cyst	Th10/11
4	F	30	Herniated disk	Th6/7
5	F	45	Herniated disk	L3
6	F	43	Tarlov cyst	Th9/10
7	M	57	Diskogenic microspur	Th7/8
8	M	50	Diskogenic microspur	Th5/6
9	F	29	Diskogenic microspur + Tarlov cyst	Th12/L1

SIH: spontaneous intracranial hypotension; CSF: cerebrospinal fluid.

was performed with SPSS Statistics 21.0 (IBM, Armonk, New York, USA). For Fisher's exact test, GraphPad InStat 3.05 (GraphPad, San Diego, California, USA) was used. Data are given as mean $\pm$ standard deviation (SD).

Results

From the data collective, 57 patients were identified who met the inclusion criteria and for whom the complete clinical data and test results were available. Forty-eight patients were finally diagnosed with POTS and 9 with SIH. The most frequent POTS subtype was neuropathic ($N = 35$). Five patients suffered from hyperadrenergic and eight from deconditioned POTS. Demographics are shown in Table 1. In all nine patients with SIH, the spinal dural CSF leak could be identified and localized using our dedicated diagnostic algorithm (Table 2). Overall, patients with SIH tended to be older than patients with POTS (38 $\pm$ 11 (mean $\pm$ SD) years vs. 28 $\pm$ 11 years, $p = 0.052$). There was a female predominance both in POTS subgroups and SIH. Average disease duration until diagnosis was for POTS 48.3 $\pm$ 85.4 months and for SIH 27.7 $\pm$ 57.6 months. Deconditioned POTS had the longest diagnostic delay (136.4 $\pm$ 140 months, $p = 0.035$), followed by hyperadrenergic POTS (60 $\pm$ 89.1 months).

Clinical symptoms

Frequencies of distinct clinical symptoms are shown in Table 3. Orthostatic headache was reported by 27% of patients with POTS and all patients with SIH ($p = 0.001$). The following symptoms were reported only by POTS patients: sense of weakness, breathlessness, exacerbation due to heat, meal intake or menstruation, gastrointestinal complaints, motion sickness and sleep disturbances. In contrast, neck stiffness and tremulousness were only reported by patients with SIH, but by none of the POTS patients. Neck stiffness was present in three of nine patients with SIH. The symptoms reported most frequently by all patient groups were dizziness and nausea. Patients of all groups reported syncope. The occurrence was highest in deconditioned and neuropathic POTS ($p = 0.033$).

Screening autonomic function testing

Results of autonomic function tests are shown in Table 4. All patients showed normal supine sympathetic and parasympathetic function tests. Numerical values for Valsalva ratio, HR variability in response to deep breathing and haemodynamic response to a pressor stimulus did not differ between the groups. All patients including all patients with SIH showed an excessive increase in HR in the upright position paralleled by symptoms of orthostatic intolerance, fulfilling the diagnostic criteria for POTS. None of the patients fulfilled the diagnostic criteria for orthostatic hypotension.[1,2] Whereas HR increase and changes of diastolic BP did not differ between groups ($p = 0.62$ and $p = 0.33$, respectively), there was a significant difference in the change of systolic BP ($p = 0.017$), with a most prominent fall in patients with SIH.

Discussion

It is known that the clinical symptoms of patients with POTS and SIH overlap.[6] Whereas the diagnostic criteria of the IHS mention POTS as a potential differential diagnosis of SIH, which has to be considered in patients with no apparent cause,[8] this issue is not addressed in the consensus statement on the definition of POTS issued together by the

Table 3. Clinical symptoms.

	POTS Neuropathic ($N = 35$)	Hyperadrenergic ($N = 5$)	Deconditioned ($N = 8$)	SIH ($N = 9$)	
Orthostatic headache	10 (29%)	2 (40%)	1 (13%)	9 (100%)	$p = 0.001$
Dizziness	22 (63%)	4 (80%)	4 (50%)	6 (67%)	$p = 0.74$
Nausea	18 (54%)	2 (40%)	5 (63%)	7 (78%)	$p = 0.50$
Syncope	18 (51%)	1 (20%)	6 (75%)	1 (11%)	$p = 0.033$
Effort intolerance	20 (57%)	1 (20%)	3 (38%)	1 (11%)	$p = 0.052$
Sense of weakness	10 (29%)	2 (40%)	2 (25%)	0 (0%)	$p = 0.28$
Palpitations	13 (37%)	2 (40%)	1 (13%)	1 (11%)	$p = 0.28$
Lightheadedness	5 (14%)	1 (20%)	2 (25%)	2 (22%)	$p = 0.87$
Breathlessness	4 (11%)	2 (40%)	1 (13%)	0 (0%)	$p = 0.18$
Chest pain	1 (3%)	0 (0%)	0 (0%)	1 (11%)	$p = 0.56$
Tremulousness	0 (0%)	0 (0%)	0 (0%)	1 (11%)	$p = 0.14$
Exacerbation due to physical activity	10 (29%)	3 (60%)	3 (38%)	1 (11%)	$p = 0.27$
Exacerbation due to heat	6 (17%)	2 (40%)	2 (25%)	0 (0%)	$p = 0.27$
Exacerbation due to meal	5 (14%)	0 (0%)	1 (13%)	0 (0%)	$p = 0.53$
Exacerbation due to menstruation	0 (0%)	1 (33%)	3 (43%)	0 (0%)	$p = 0.004$
Gastrointestinal symptoms	8 (23%)	1 (20%)	1 (13%)	0 (0%)	$p = 0.59$
Tiredness	9 (26%)	1 (20%)	4 (50%)	1 (11%)	$p = 0.32$
Sleep disturbance	6 (17%)	0 (0%)	0 (0%)	0 (0%)	$p = 0.24$
Migraine	4 (11%)	2 (40%)	2 (25%)	1 (11%)	$p = 0.34$
Tension headache	4 (11%)	2 (40%)	1 (13%)	1 (11%)	$p = 0.38$
Myofacial pain	1 (3%)	2 (40%)	0 (0%)	1 (11%)	$p = 0.018$
Motion sickness	4 (11%)	2 (40%)	0 (0%)	0 (0%)	$p = 0.084$
Hearing symptoms	5 (14%)	1 (20%)	1 (13%)	2 (22%)	$p = 0.59$
Neck stiffness	0 (0%)	0 (0%)	0 (0%)	3 (33%)	$p = 0.008$

POTS: postural tachycardia syndrome; SIH: spontaneous intracranial hypotension.

Table 4. Screening autonomic function testing.

	POTS Neuropathic ($N = 35$)	Hyperadrenergic ($N = 5$)	Deconditioned ($N = 8$)	SIH ($N = 9$)	
Head-up tilt					
Δ systolic BP (mmHg)	−3.5 (16.7)	3.4 (20.2)	1.5 (16.0)	−13.1 (9.5)	$p = 0.017$
Δ diastolic SBP (mmHg)	8.7 (13.1)	11.2 (13.8)	6.6 (6.3)	6.3 (6.9)	$p = 0.33$
Δ HR (bpm)	38.0 (16.6)	33.6 (10.0)	37.0 (4.9)	38.6 (7.9)	$p = 0.62$
Pressor response					
Δ systolic BP (mmHg)	20.5 (9.7)	25.8 (9.7)	18.4 (4.0)	25.7 (10.7)	$p = 0.20$
Δ diastolic SBP (mmHg)	14.0 (7.9)	14.6 (6.5)	7.9 (5.1)	12.1 (6.9)	$p = 0.11$
Δ HR (bpm)	3.3 (7.8)	4.6 (7.2)	2.8 (10.1)	6.8 (5.3)	$p = 0.33$
Valsalva ratio	2.1 (0.6)	2.2 (0.4)	1.9 (0.3)	2.2 (0.5)	$p = 0.28$
HR variability deep breathing (bpm)	22.0 (7.3)	21.6 (6.0)	24.0 (9.9)	16.0 (4.0)	$p = 0.070$

Data are given as mean (SD). SD: standard deviation; POTS: postural tachycardia syndrome; SIH: spontaneous intracranial hypotension; BP: blood pressure; bpm: beats per minute; HR: heart rate.

American Autonomic Society, the European Federation of Autonomic Societies, the Autonomic Research Group of the World Federation of Neurology and the Autonomic Disorders section of the American Academy of Neurology.[1,2] In our retrospective study, we analysed the clinical symptoms and findings of screening autonomic function testing in patients with diagnosed POTS and proven SIH, both of which were referred to our autonomic unit because of the prominent symptoms of orthostatic intolerance. Orthostatic headache, the major symptom of SIH, was reported by all SIH patients and also by 27% of patients with POTS. In the IHS criteria, the other reported clinical symptoms of SIH are neck stiffness and hearing symptoms. In our cohort, neck stiffness was limited to patients with SIH but occurred only in one-third of them. Hearing symptoms were present in 13–20% of POTS patients depending on the subtype and 22% of SIH patients. Hence, neck stiffness can be considered a specific symptom of SIH but with a rather low

prevalence, whereas hearing symptoms are rather unspecific signs. In addition, all patients with SIH also reported other symptoms of orthostatic intolerance. Most frequent symptoms were nausea (78%), dizziness (67%) and lightheadedness (22%). The latter are considered to be typical symptoms of POTS.[3] There were some clinical symptoms, which were only associated with POTS (sense of weakness (40%), breathlessness (20%), exacerbation due to heat (29%), meal intake (17%) or menstruation (20%), gastrointestinal complaints (23%), motion sickness (17%) and sleep disturbances (17%)). Although most of them had a rather low frequency, the presence of one or more of these may facilitate differential diagnosis.

Screening autonomic function testing showed normal supine sympathetic and parasympathetic function and an excessive clinically symptomatic increase in HR in the upright body position in all patients with SIH, which fulfilled the diagnostic criteria for POTS. Hence, autonomic function tests cannot discriminate between SIH and POTS. The more prominent fall of systolic BP during HUT in SIH patients is, in our opinion in daily practice, of no diagnostic help.

Although the mechanism of orthostatic headache in POTS is not entirely clear, there are suggestions that a relative CSF hypotension, in terms of reduction in spinal venous pressure and in CSF volume, might be the underlying cause.[12] In SIH, three related mechanisms have been proposed to evoke orthostatic headache as a leading symptom: (i) orthostatic brain sagging causes painful tearing at the cranial meninges, (ii) reduced CSF volume and (iii) increase compliance at the caudal part of the dural tube.[13]

Both patient groups showed similar findings during HUT. The cause of the excessive clinically symptomatic HR increase in SIH is unknown. Since first line treatment of patients with SIH consists in bed rest with or without additional caffeine medication,[8,14] we hypothesis that these patients may develop as a result of therapy POTS because of deconditioning. The fact that mean disease duration was significantly shorter in SIH than in deconditioned POTS is maybe due to a stricter bed rest of these patients or a longer diagnostic delay in patients with deconditioned POTS.

The major limitation of our study is its retrospective design and that it is based on a single centre. All our patients with SIH were refractory to standard therapy (bed rest, caffeine supplementation, repeated lumbar epidural blood patch) and none of them developed SIH as a consequence of lumbar puncture. Furthermore, all patients with SIH suffered from rare causes of spinal leak, which caused a diagnostic delay. Hence, a very selected group of SIH patients was investigated and the findings may not be valid for patients with a shorter disease duration.

In conclusion, our results show that in SIH and POTS, the clinical symptoms and results of autonomic function testing can overlap. Hence, patients with prominent orthostatic headache fulfilling the diagnostic criteria for POTS should also be evaluated for further testing of a spinal CSF leak, in the absence of a history of lumbar puncture. This is essential, as SIH requires a different therapy.

Clinical implications

- Clinical symptoms of SIH and POTS overlap.
- Autonomic function tests cannot discriminate between SIH and POTS.
- Patients with prominent orthostatic headache fulfilling the diagnostic criteria for POTS should be evaluated for further testing of a spinal CSF leak.

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