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Title:

**Autonomic symptoms in hypertensive patients with post-acute minor
ischemic stroke**

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Abstract

Background

Most studies regarding autonomic dysfunction in ischemic stroke are limited to heart rate and blood pressure changes during the acute phase. However, there are few data on quantitative assessment of autonomic symptoms. We sought to assess autonomic symptoms in hypertensive ischemic stroke patients.

Methods

In 100 hypertensive patients (45 with symptomatic ischemic stroke (6 months after stroke onset) and 55 without stroke), we assessed autonomic symptoms using the Scale for Outcomes in Parkinson disease-Autonomic (SCOPA-AUT).

Results

The age (mean \pm standard deviation) for the stroke group was 66 ± 12 and 63 ± 15 for the without stroke group ($P = 0.8$). Orthostatic hypotension occurred in 3.6% of the stroke group and 4.4% in the group without stroke. The total SCOPA-AUT score was higher in the stroke group compared with the group without stroke ($P = 0.001$). Domain scores for gastrointestinal ($P = 0.001$), urinary ($P = 0.005$) and cardiovascular ($P = 0.001$) were higher in the stroke group. No differences were found when comparing the total SCOPA-AUT scores for stroke subtypes ($P = 0.168$) and for lateralization ($P = 0.6$). SCOPA AUT scores were correlated with depression scores ($P = 0.001$) but not with stroke severity ($P = 0.2$).

Conclusion

Autonomic symptoms, especially, gastrointestinal, urinary and cardiovascular function, were significantly increased in hypertensive patients with minor ischemic

stroke. Symptoms were associated with depression but not with the characteristic of the stroke.

Key words: autonomic, symptoms, minor, ischemic, stroke, hypertension

Introduction

Autonomic function is frequently altered in patients with ischemic stroke during acute and chronic stages. Cardiac arrhythmias and sudden death during acute stroke are related to autonomic function imbalance [1], [2] and [3]. Non-invasive tests have suggested sympathetic hyperactivity and cardiovagal dysfunction in acute stroke [1], [2], [4], [5], [6] and [7] with diverse results when considering the influence of lateralization, site and sub-type of ischemic stroke [1], [2], [3] and [8]. Autonomic cardiovascular dysfunction is associated with stroke severity [8].

Diminished heart rate variability (HRV) and baroreflex sensitivity (BRS) are related with worse prognosis [2] and [9]. Gastrointestinal, urinary, sudomotor and sexual dysfunction due to multiple factors, including autonomic dysfunction, also occur in stroke patients [10], [11], [12], [13], [14], [15], [16], [17] and [18]. Despite clear evidence of objective dysfunction in various autonomic domains there is less information about the assessment of autonomic symptoms in minor stroke patients. We sought to assess autonomic symptoms in hypertensive patients with minor ischemic stroke in comparison with hypertensive patients without symptomatic ischemic stroke.

Patients and Methods

Consecutive ischemic stroke patients (age ≥ 18 years old) and hypertensive patients without history of symptomatic stroke were recruited from an Outpatient clinic. Stroke patients fulfilled the following inclusion criteria; clinical evidence and neuroimaging study (computed tomography (CT) or magnetic resonance imaging (MRI)) showing a single ischemic lesion based upon AHA/ASA Expert Consensus [19]. Presumed etiology of stroke was based on criteria from the Acute Stroke Treatment (TOAST) study [20]. Stroke severity was evaluated by means of the National Institutes of Health Stroke Scale NIHSS (range 0–42 points) and for global disability the modified Rankin scale was used (range 0–6 points) [21]. Clinical classification of the sub-type of cerebral infarction was based on the Oxfordshire Community Stroke Project (OCSP) criteria; posterior circulation infarct (POCI), lacunar infarct (LACI), total anterior circulation infarct (TACI) and partial anterior circulation infarct (PACI) [22]. According to the TOAST classification, patients with strokes due to cardioembolism, strokes due to other causes (e.g., vasculitis, coagulation disorder), and strokes due to unknown or concurrent origin were not included. Patients were assessed between 3 and 12 months after their first symptomatic stroke. For patients without stroke, the following criteria were used; absence of clinical and neuroimaging evidence of ischemic lesion(s). Hypertension was defined as a diastolic blood pressure (supine or sitting) of at least 90 mmHg or a systolic blood pressure (supine or sitting) of at least 140 mmHg.

For both patient groups a patient with mild global disability (Rankin <3) and any neurological disease affecting the autonomic nervous system, like Parkinson's disease, multiple system atrophy, pure autonomic failure, autoimmune neuropathies, were excluded. 45 stroke patients (17 women, 28 men) and 55 hypertensive patients without stroke (36 women, 19 men) fulfilled the inclusion criteria. 45 age-matched (mean age 64.6 ± 9.8 years, 25 women, 20 men) healthy individuals were recruited as a control group for a comparison of SCOPA scores. They were screened to have not clinical history of hypertension, stroke or other neurological disease, diabetes mellitus, systemic disease affecting autonomic nervous system. They were not using medication known to affect autonomic function.

All patients and healthy gave their written informed consent, approved by the Ethical Committee of the Hospital and the University of Valparaiso.

Autonomic nervous system evaluation

Orthostatic stress testing

Orthostatic blood pressure (BP) testing was performed in the morning between 10 and 12 h. Patients were requested to eat a light breakfast no later than 2 h prior to the test and abstain from caffeine and alcohol during the previous 12 h. Patients laid in the supine position in a quiet room, for 10 min. Patients then assumed the upright posture and stood for 10 min. BP and heart rate were measured intermittently (DINAMAP monitor, Critikon, Tampa, FL), while the subject was lying down and again at 1, 5 and 10 min after standing up. The maximum difference in

systolic BP from supine to standing was taken as the orthostatic BP change [13]. A systolic BP fall ≥ 20 mmHg was considered as indicative of orthostatic hypotension [23].

Autonomic symptoms evaluation

AUT-symptoms were examined using the Scale for Outcomes in Parkinson's disease for Autonomic Symptoms (SCOPA-AUT), a questionnaire divided into six domains, gastrointestinal (7 items), urinary (6 items), cardiovascular (3 items), sudomotor (4 items), pupillomotor (1 item) and sexual in men (2 items). The four response options for each item ranged from 0 (never) to 3 (often) with higher total scores reflecting worse autonomic functioning [24]. We evaluated symptoms related to five domains: gastrointestinal (Gastro), urinary (Uri), cardiovascular (Cardio), sudomotor (Sudo) and sexual (in men) (Sex) dysfunction. All questions referred to symptoms within the past month. In patients with aphasia the answers were obtained from caregivers. We did not explore the Pupillomotor domain. This scale has been demonstrated to be reliable and valid [24]. Patients were screened for depressive symptoms with the Hamilton depression rating scale (HAM-D); a validated method for measuring depression [25].

Statistics

Comparisons were made between groups using Student's independent t tests, Fisher's exact tests or Wilcoxon tests, as appropriate. Analysis of variance (ANOVA) and post hoc Tukey–Kramer HSD tests were used to compare SCOPA scores between groups. Kruskal Wallis tests were used to compare sex scores

between males. Correlations between SCOPA AUT scores and stroke parameters were assessed with Spearman's rank correlations. Significance was set at 0.05. All data were analyzed (STATA).

Results

Baseline characteristics

There were no differences in age, body mass index, hyperlipidemia and current drug use, between patients with and without stroke (all $P > 0.05$). Stroke patients had a mean NIHSS score of 1.5 ± 2.5 and a mean Rankin score of 0 in 2 and 1–2 in 43 patients. Half of the stroke patients had a lacunar stroke, according to the OCSP classification: LACI = 51.1%, PACI = 31.1%, POCI = 17.8%, TACI 0%. Stroke patients showed male predominance, more smokers and diabetics. The MMES and HAM-D scores showed worse outcomes in stroke patients (Table 1).

Autonomic evaluation

The number of stroke patients that reported autonomic symptoms was significantly higher than those patients without stroke. Nocturia (37.8%), orthostatic intolerance (31.1%), subjective dysphagia (28.9%), increased urinary day time frequency (24.4%) and urinary incontinence (24.4%) were among the principal symptoms in stroke patients (Table 2). There was no difference in supine BP between groups. Orthostatic hypotension occurred in 2 patients with stroke and in 2 patients without stroke (Table 2).

SCOPA-AUT scores

ANOVA analysis indicated significant differences in total SCOPA-AUT, gastrointestinal, urinary and cardiovascular scores between groups (with stroke and without stroke hypertensive patient groups and healthy subjects). Post hoc

analysis identified significant differences between hypertensive patients with and without stroke in SCOPA total, gastrointestinal, urinary and cardiovascular ($P < 0.01$) domains. Also between patients with stroke and healthy subjects in SCOPA total, gastrointestinal, urinary, cardiovascular and sudomotor ($P < 0.01$). Significant differences for SCOPA total, urinary, cardiovascular and sudomotor scores ($P < 0.01$) were evident between hypertensive patients without stroke and healthy subjects. Kruskal Wallis tests did not show a difference in sexual scores between the 3 groups (males) (Table 2).

In the stroke patients group the SCOPA AUT scores correlated significantly with HAM-D depression scores ($R = 0.6$, $P = 0.001$). There were no significant correlations between SCOPA AUT scores and age ($R = 0.047$), MMSE scores ($R = -0.1$), NIHSS scores ($R = 0.186$) and Rankin scores ($R = 0.131$).

In stroke patients, the total score was not different between patients with and without diabetes ($P = 0.3$). The total SCOPA-AUT score was not different between left side and right side hemispheric lateralization ($P = 0.6$). Total SCOPA-AUT scores were not different between OCPS ischemic stroke subtypes: median (IQR) for PACI = 11 (10–45), for LACI = 14 (5–18), for POCI = 7 (3.5–10.5) ($P = 0.168$). The following domains did not show significant differences between stroke subtypes: urinary scores for PACI = 4 (2–6), for LACI = 4 (1–6), for POCI = 1 (0–2) ($P = 0.122$), cardiovascular scores for PACI = 3 (1–5), for LACI = 4 (2–5), for POCI = 2.5 (1.5–3.5) ($P = 0.476$), thermoregulatory scores for PACI = 2.5 (0–3), for LACI = 1 (0–3), for POCI = 2 (0–1) ($P = 0.914$) and sexual function scores for PACI = 0 (0–

4), for LACI = 0 (0–1), for POCl = 0 (0–1) (P = 0.571). Only the gastrointestinal score was higher in patients with PACI (P = 0.025).

Discussion

The main findings are that in poststroke patients the total autonomic symptoms score and domain scores for gastrointestinal, urinary and cardiovascular function were significantly higher than in patients without stroke and that these symptoms were associated with depression. Characteristics of stroke, including, severity, lateralization and global disability, were not associated with autonomic symptoms. Urinary symptoms during post-acute stroke are mainly related with age, severity of neurological signs and depression [15], [26] and [27]. A study showed more incontinent patients in total anterior circulatory infarction and fewer incontinent patients in a lacunar stroke group [15]. We found that nocturia and urge incontinence were common in the post stroke period and that the urinary symptoms score was associated with depression scores. Regarding cardiovascular autonomic symptoms, there is less information about orthostatic intolerance symptoms. OH in poststroke patients could be due neurogenic and non-neurogenic factors. A study showed that OH was common in elderly stroke patients with severe disability [28]. In addition, OH in stroke patients was associated with falls [29]. Xiong et al. [6] found that OH was significant in large but not in small vessel infarctions. OH was not prevalent in our patients with minor stroke and little disability; however, we found that symptoms of orthostatic intolerance that were associated with depression scores but not with age and characteristics of stroke.

Gastrointestinal dysfunction in the post stroke period could include dysphagia that is detected by clinical and instrumental assessments [12]. Constipation is related

with clinical severity of stroke and is associated with poor outcome and increased hospital length of stay [12]; we did not find significant constipation in minor stroke, factors like bedridden and reduced consciousness that may cause constipation, were not present in our patients.

Autonomic symptoms in stroke patients are related to neurological and non-neurological factors. Ischemic lesions involving specific areas of the central autonomic network, associated diseases, like diabetes mellitus, and medications with autonomic effects could be responsible for autonomic dysfunction. In addition, end organ pathology, prolonged immobilization and psychological factors may also influence autonomic symptoms. Factors like age, BMI, medication and hyperlipidemia did not differ between stroke and non-stroke patients. Our patients presented with mild disability and half of them had a lacunar stroke, so immobilization did not contribute to autonomic symptoms. Hypertensive patients without symptomatic stroke showed significantly higher scores than healthy subjects for urinary, cardiovascular and sudomotor domains. Factors like medication and presence of silent stroke may contribute to those symptoms; hypertension is strongly associated with silent brain infarction that may produce subtle deficits in cognitive and physical function [30].

The limitations of our study included: (1) a small sample size which reduced the power to establish an association between autonomic symptoms and

characteristics of stroke, (2) assessment of autonomic symptoms scores with the SCOPA-AUT questionnaire, which was initially developed for Parkinson's disease patients [24]. This is a valid instrument which explores the full spectrum of autonomic symptoms. Currently, there is not an instrument for the assessment of autonomic symptoms in stroke patients.

In conclusion, hypertensive patients with minor stroke had more autonomic symptoms than hypertensive patients without stroke. The severity, lateralization and subtype of the stroke were not associated with autonomic symptoms scores. An association between autonomic and depression symptoms was also found. Our study supports the need to perform a quantitative assessment of different autonomic symptoms domains, in stroke patients.

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Table 1

Demographic data and clinical characteristic of hypertensive patients without and with symptomatic ischemic stroke

	Without stroke (n= 55)	With stroke (n=45)	P
Age (mean \pm SD)	65.2 \pm 15.1	65.8 \pm 11.7	0.811 ^a
Sex, male (%)	19 (34.5)	28 (62.2)	0.009 ^b
BMI (mean \pm SD)	27.2 (3.1)	26.7 (3.2)	0.44 ^a
Hyperlipidemia (%)	13 (23.6)	9 (20)	0.809 ^b
Diabetes Mellitus (%)	8 (14.6)	14 (31.1)	0.055 ^b
Depression n (%)	7 (12.7)	16 (35.6)	0.009 ^b
Smoker n (%)	14 (25.5)	23 (51.1)	0.012 ^b
MMSE (mean \pm SD)	27.9 \pm 2.6	25.8 \pm 4.2	0.0025 ^a
NIHSS (mean \pm SD)	0	1.54 \pm 2.5	
HAM-D median (IQR)	4 (2-6)	6 (3-9)	0.0004 ^c
B blockers n (%)	7 (12.7)	6 (13.3)	0.579 ^b
ACE inhibitor n (%)	17 (30.9)	16 (35.5)	0.389 ^b
CCB n (%)	7(12.7)	6 (13.3)	0.5 ^b
Diuretic n (%)	6 (10.9)	7 (15.6)	0.347 ^b
Antidepressant n(%)	3(6.7)	5(9.1)	0.8 ^b

^a Student T test

^b Fisher exact test

^c Wilcoxon

ACE angiotensin-converting enzyme inhibitor

CCB calcium channel blocker

Table 2 Table Hypertensive patients without and with ischemic stroke referring frequent autonomic symptoms n(%)

	Without stroke (n 55)	With stroke (n 45)	P ^a
Symptoms			
Gastrointestinal domain			
Dysphagia	1(1.8)	13(28.9)	0.0001
Constipation	5(9.1)	4(8.9)	0.645
Fecal incontinence	0	2(4.4)	0.0000
Urinary domain			
Nocturia	8(14.5)	17(37.8)	0.0073
Incontinence	5(9.1)	11(24.4)	0.0351
Increased day time frequency	4(7.3)	11(24.4)	0.0171
Difficulty to voiding	3(5.5)	6(13.3)	0.0784
Cardiovascular domain			
Dizzy or "goofy" on standing	3(5.5)	14(31.1)	0.0007
Syncope	0	0	
Sweating domain			
Nocturnal hyperhidrosis	2(3.6)	2(4.4)	0.574
Asymmetric sweating	0	0	
Sexual domain (men) †			
Erection dysfunction	3(10.7)	9(47.3)	0.0065

^a Fisher exact test

† without stroke n = 28, with stroke n = 19

Table 3 Orthostatic hypotension and autonomic symptoms scores in hypertensive patients without and with symptomatic ischemic stroke

	Without stroke	With stroke	P
Supine SBP mmHg ^a	140 (130-150)	138 (124-148)	0.878 ^a
Orthostatic hypotension n (%)	2 (3.6%)	2 (4.4%)	1 ^c
Autonomic symptoms ^a			
Total score	6 (2-9)	11 (6-16)	0.001 ^b
Gastrointestinal	0 (0-1)	2 (0-2)	0.001 ^b
Urinary	1 (0-3)	3 (1-6)	0.005 ^b
Cardiovascular	1 (0-3)	3 (2-5)	0.001 ^b
Thermoregulatory	1 (0-2)	2(0-3)	0.182 ^b
Sexual (men)	0(0-0)	0 (0-1)	0.038 ^b

^a median (IQR)

^b Wilcoxon

^c Fisher exact test