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Preliminary findings of the effects of autonomic dysfunction on functional outcome after acute ischemic stroke

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ABSTRACT

Background and purpose: Impaired autonomic function is common in the acute poststroke phase but little is known about its effects on functional outcome after acute ischemic stroke. This study sought to investigate the impact of autonomic dysfunction by Ewing's classification on functional outcome 2 months after acute ischemic stroke.
Methods: 34 consecutive acute ischemic stroke patients within 7 days after onset were enrolled. On admission, autonomic function was assessed by Ewing's battery tests. Stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS), autonomy in activities of daily living by the Barthel Index (BI), and global disability by the modified Rankin Scale (mRS). BI and mRS were also evaluated 2 months after ischemic stroke onset.
Results: On admission, eight patients were diagnosed as minor autonomic dysfunction and 26 patients as relatively severe autonomic dysfunction. The prevalence of relatively severe autonomic dysfunction in ischemic stroke patients was 76.5%. There were no significant differences in baseline characteristics between the minor and severe autonomic dysfunction groups. 2 months after stroke onset, the mean BI score of patients with minor autonomic dysfunction and severe autonomic dysfunction increased from 76.3 ± 15.3 on admission to 95.0 ± 7.1, 66.5 ± 15.2 on admission to 74.8 ± 15.9 respectively. The mean BI score after 2-month stroke onset and the change in BI from admission to 2-month outcome (delta BI) in patients with severe autonomic dysfunction were lower than those in patients with minor autonomic dysfunction (all $P < 0.05$).
Conclusions: Autonomic dysfunction occurs in acute stroke patients. Relatively severe autonomic dysfunction is related to an unfavorable functional outcome in patients with acute ischemic stroke.

1. Introduction

Initial severity of stroke and age are currently considered the most powerful predictors of functional recovery and eventual home discharge of ischemic stroke survivors [1,2]. However, studies have showed that ischemic stroke is associated with impairment of cardiac autonomic function [3,4]. Both a reduced heart rate variability (HRV) and an impaired cardiac baroreceptor sensitivity (BRS) have been identified to be associated with adverse clinical outcomes after the acute phase of ischemic stroke [5–7]. Recently, Sykora et al. [8] showed reduced BRS compromised autonomic adjustment of heart rate (HR) and vascular tone to sudden blood pressure (BP) changes in acute and subacute stroke patients. They concluded that sympathetic overactivity and blunted BRS predict poor prognosis after stroke [9,10]. Thus, early diagnosis of autonomic dysfunction has prognostic and therapeutic implications in acute stroke. Hilz et al. reported stroke severity assessed by National Institutes of Health Stroke Scale (NIHSS) scores correlates with autonomic dysfunction and can be used as premonitory signs of autonomic failure [11]. Till date, the relative impact of cardiac autonomic impairment on functional outcome after acute ischemic stroke has not been fully clarified. Accordingly, this prospective study was designed and undertaken to assess the impact of cardiac autonomic dysfunction by Ewing's autonomic function tests on functional outcome 2 months after acute ischemic stroke.

2. Methods

2.1. Subjects

Consecutive acute ischemic stroke patients within 7 days after onset were enrolled in Prince of Wales Hospital in Hong Kong between January 2007 and April 2009. Patients were included in the study only if they fulfilled all the following criteria: (1)

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age ≥45 years old; (2) Computed tomography (CT) or magnetic resonance imaging (MRI) showed cerebral ischemic stroke. None of the patients had insular involvement of their stroke lesions. Diagnosis of ischemic stroke was defined by the WHO definition. Exclusion criteria: (1) dementia; (2) any clinically relevant arrhythmia on admission, including atrial fibrillation; (3) any major concurrent illness, including chronic obstructive pulmonary disease, renal failure and malignancies; (4) fever, hypoxia, alterations in consciousness, or any relevant hemodynamic compromise on admission.

On admission, patients were submitted to clinical, neurological, and functional examinations. Stroke severity was assessed by the NIHSS [12], autonomy in activities of daily living (ADL) by the Barthel Index (BI) [13], and global disability by the modified Rankin Scale (mRS) [14]. Independence in ADL and global disability were also clinically re-evaluated 2 months after ischemic stroke onset. The change in BI from admission to 2 months after stroke onset (delta BI) was measured for each patient. Other studies have defined a poor outcome (dependence) as mRS > 2 [15]. Therefore, we specified the mRS ≤2 as favorable functional outcome in this study. The presumed etiology of stroke was classified according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria [16]. The diagnosis of carotid artery stenosis was made by gray-scale, color Doppler, and spectral Doppler ultrasonography.

All subjects gave their written informed consent for this study, which was approved by New Territories East Cluster clinical research ethics committee.

2.2. Clinical autonomic function tests

On admission, clinical autonomic function tests were carried out in these patients within 7 days after acute stroke onset according to Ewing's battery [17]. The ECG was recorded during supine rest, and finger BP was monitored using a Task Force Monitor 3040i (CNSystems Medizintechnik AG Graz, Austria) which enables non-invasive beat to beat BP measurement. All participants were asked to refrain from caffeine ingestion on the day of the investigations and to take only a light breakfast. All investigations were performed between 9:00 AM and 11:00 AM in a warm, quiet room. There was a 10-min supine rest phase before investigations commenced and a 2-min rest phase after individual rests.

2.3. Parasympathetic tests

2.3.1. Valsalva maneuver

The Valsalva maneuver was performed by having the participant exhale for 15 s, while maintaining an expiratory pressure of 40 mmHg. Expiratory pressure can be measured by having the patient blow into a mouthpiece connected to a pressure transducer. The maneuver was performed at least three times in order to maximize participant compliance and ensure reproducibility. The Valsalva ratio was an index of HR changes that occur during a Valsalva maneuver. The Valsalva ratio was taken as the maximum R–R interval (RRI) in the 15 s following expiration divided by the minimum RRI during the maneuver.

2.3.2. Deep breathing

Respiratory sinus arrhythmia was assessed by performance of 6 deep breaths at a frequency of 0.1 Hz. Participants were given adequate rehearsal to achieve the required frequency and counted through the 6 breaths with slow inhalation and exhalation (5 s each). The timed breathing was performed with the aid of verbal coaching. The response was taken as the mean of the differences between the maximum and minimum instantaneous HR for each cycle. A minimum of 3 breaths was required for inclusion.

2.3.3. The 30:15 ratio

This was performed by rising from the supine to a standing position. The 30:15 ratio was the RRI at the 30th beat divides by the RRI at the 15th beat immediately after standing.

2.4. Sympathetic tests

2.4.1. Orthostasis

Change in systolic BP was calculated as the difference between the nadir systolic BP immediately after standing and the mean systolic BP for the 20 beats immediately prior to standing.

2.4.2. Sustained handgrip

First of all, this was performed by having the participant holding the handgrip with maximal grip, then having the participant holding 30% of the maximal grip for 5 min. Change in diastolic BP was calculated as the difference between the maximal diastolic BP before releasing the handgrip and the mean diastolic BP for the 20 beats immediately prior to handgrip.

2.5. Ewing classification of autonomic failure

Results for each autonomic test were classified as normal, borderline and abnormal. Ewing's classification of autonomic failure [17] was determined as shown below for each participant who had complied with sufficient tests for the classification scheme to be applied.

(1) Normal: all tests normal or one borderline.
(2) Early: one of the three heart rate tests abnormal or two borderlines.
(3) Definite: two or more of the heart rate tests abnormal.
(4) Severe: two or more of the heart rate tests abnormal plus one or both of the blood pressure tests abnormal or both borderlines.
(5) Atypical: any other combination.

2.6. Statistical analysis

Mean values (±standard deviation) were calculated for continuous variables, while frequencies were measured for categorical variables. Distributions of continuous variables were determined by the Kolmogorov–Smirnov test. In case of normal distribution, group differences for continuous data were examined by independent-samples *t* test. Group differences for categorical variables were examined by Chi-square or Fisher's exact test, as appropriate. In particular, Fisher's exact test was applied in case of an expected count <5. The differences of 2-month outcome versus on admission in each group were examined by paired-samples *t* test or two-related-samples nonparametric test, as appropriate.

All statistical analysis was performed with SPSS version 17.0. Differences with $P < 0.05$ were considered significant.

3. Results

3.1. Baseline characteristics of acute stroke patients according to Ewing classification

A total of 34 acute ischemic stroke patients (23 males; mean age 71.7; mean NIHSS score on admission 4.4) were recruited. According to Ewing classification, the total cohort was categorized into two groups: group 1 was diagnosed as normal or early (minor) autonomic dysfunction and group 2 was diagnosed as definite, atypical or severe (relatively severe) autonomic dysfunction. On admission, eight patients were diagnosed as minor autonomic dysfunction and 26 patients as relatively severe autonomic