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Risk factors and etiological subtype analysis of brainstem infarctions

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ABSTRACT

Objective: To evaluate the features of risk factors and etiological subtypes of brainstem infarctions (BSIs) patients in China.
Methods: One hundred and ninety-nine cerebral infarction patients with brainstem involvement were categorized into five groups according to Trial of Org 10172 in Acute Stroke Treatment classification: large artery disease (LAD), cardioembolism (CE), small vessel disease (SVD), stroke of other determined etiology (SOE) or stroke of undetermined etiology (SUE). The risk factors and percentage of the different etiological subtypes were assessed.
Result: A total of 199 patients were enrolled in this study. The number and percentage of patients in SVD, LAD, SUE, CE and SOE were 77 (38.7%), 74 (37.2%), 25 (12.6%), 23 (11.6%) and 0, respectively. There were significantly different incidences of hypertension, diabetes and coronary heart disease (CHD) without atrial fibrillation (AF) among different stroke subtypes ($P = 0.006$, $P = 0.002$, $P = 0.016$, respectively). Hypertension was more prevalent in LAD than in SVD and CE ($P = 0.001$ and $P = 0.039$, respectively) while the incidence of diabetes in LAD was higher than those in SVD and CE ($P < 0.001$ and $P = 0.015$, respectively). CHD without AF was more prevalent in CE than in SVD and LAD ($P = 0.044$ and $P = 0.012$, respectively). LAD was significantly associated with hypertension (OR = 3.18, $P = 0.009$) and diabetes (OR = 2.84, $P = 0.003$) in BSIs.
Conclusion: The pattern of etiological subtypes of BSIs in China has its own characteristics. It might result from the features of risk factors in Chinese patients.

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1. Introduction

Stroke is a main cause of neurologic morbidity and mortality worldwide. Ischemic brainstem strokes constitute 10% of all ischemic strokes [1]. Brainstem infarctions (BSIs), even if the extent is very small, may cause significant neurological deficits. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification was introduced in 1993 to improve the subclassification of ischemic stroke. Patients with ischemic stroke were divided into five subgroups according to the presumed etiological mechanisms: large artery disease (LAD), cardioembolism (CE), small vessel disease (SVD), stroke of other determined etiology (SOE) and stroke of undetermined etiology (SUE) [2,3].

It is critical to understand the pathogenic mechanisms involved in the development of stroke for management, prognosis and evaluating the risk of recurrence [4]. Many studies have investigated the associations between risk factors and various stroke etiologies but with divergent results [5–7]. Besides, few studies have focused on the etiological mechanisms underlying BSIs. The aim of our study is to evaluate the features of different etiological subtypes and risk factors of BSIs patients.

2. Methods

2.1. Ethics statement

This research was approved by the ethics committee of the Third Affiliated Hospital of Sun Yat-sen University. All participants involved in this study provided written informed consent.

2.2. Patients

Our database comprised 220 consecutive patients who were diagnosed as BSIs and admitted in the Department of Neurology of The Third Affiliated Hospital of Sun Yat-sen University from January 2007 to August 2013. Among them, 199 patients fulfilled the inclusion criteria: (a) onset age ≥18 years and (b) being diagnosed as having BSIs for the first time. Clinical and laboratory data were collected from these adult individuals.

2.3. Diagnosis of ischemic stroke

The diagnosis of stroke and the classifications were based on the history of symptoms and their acute presentation, clinical examination and cerebral MRI on diffusion weight imaging (DWI) and MRA examination according to the TOAST criteria. To be diagnosed of large artery

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disease (LAD), patients should have paraclinical brain imaging findings of either significant (>50%) stenosis or occlusion of vertebral or basilar arteries or their major branches presumably due to atherosclerosis. Diagnosis of cardioembolism (CE) requires paraclinical signs of a source of cardiac embolism. The category of small vessel disease (SVD) should have one of the traditional clinical lacunar syndromes and the MRI examination can be normal or have a relevant brainstem lesion with a demonstrated diameter of less than 1.5 cm. In this category, the potential of large-artery atherosclerosis and cardioembolism should be eliminated. Patients with either more than one potential cause or no probable etiology were classified as stroke of undetermined etiology [2,3].

All patients underwent brain MRI (including DWI and magnetic resonance angiography), electrocardiography (ECG), echocardiography, as well as ultrasonography of the carotid artery, subclavian artery and vertebral artery. Patients suspected of cardioembolic stroke and no source of embolism on ECG or echocardiography were monitored with 24-hour ECG.

2.4. Assessment

Known vascular risk factors such as hypertension (defined as receiving medication for hypertension or blood pressure > 140/90 mm Hg on repeated measurements), hyperlipidemia (defined as receiving cholesterol-reducing agents, total cholesterol > 5 mmol/L or LDL-cholesterol > 3 mmol/L), diabetes (defined as receiving medication for diabetes mellitus, fasting blood sugar ≥ 126 mg/dL or 2-hour postprandial blood sugar ≥ 200 mg/dL), atrial fibrillation, hyperhomocysteinemia (homocystein > 10 μmol/L), and coronary heart disease (present angina pectoris or previous myocardial infarction) were recorded [8,9]. The National Institutes of Health Stroke Scale (NIHSS) was assessed in the first day when patients were admitted to the hospital and at discharge by a stroke physician.

2.5. Statical analyses

Differences of categorical variables in multiple groups were analyzed with χ^2 test or Fisher exact test. All tests in multiple groups with a P-value <0.05 were subjected to logistic regression analyses. Bivariate and multivariate logistic regression were used to determine risk factors in BSIs. The odds ratio (OR) and 95% confidence interval (CI) were obtained. Variables that were associated with the outcome with a P-value below 0.05 and OR above 1.0 in bivariate analysis were subjected to multivariate logistic regression. All statistical analyses were conducted by using the SPSS 13.0 package for Windows (SPSS Inc., Chicago, IL, USA). P-values <0.05 were considered statistically significant.

3. Results

3.1. Baseline demographics and clinical characteristics among patients with BSIs

Baseline demographics and clinical characteristics of patients with BSIs were summarized in Table 1. The patients enrolled included 117 males (58.8%) and 82 females (41.2%) with ages ranging from 29 to 95 years. The median NIHSS score was 4 (IQR, 2–6). Among the 199 patients, 152 (76.4%) had hypertension, 136 (68.3%) had HHCY, 131 (65.8%) had hyperlipidemia, 101 (50.8%) had DM, 46 (23.1%) were currently smoking, 21 (10.6%) had AF and 15 (7.5%) had CHD. Among them, 170 (85.4%) patients had pontine infarctions, 20 (10.1%) had medullary infarctions, 3 (1.5%) had midbrain infarctions and the remaining 6 (3.0%) had overlapping BSIs.

Table 1
Baseline characteristic of BSIs patients (n = 199).

	n (%) if not otherwise specified
Demographics	
Male	117 (58.8)
Female	82 (41.2)
Mean age, years (SD)	65.5 (11.8)
Risk factors	
Hypertension	152 (76.4)
Treated	64 (42.1)
Untreated	88 (57.9)
HHCY	136 (68.3)
Treated	5 (3.7)
Untreated	131 (96.3)
Hyperlipidemia	131 (65.8.)
Treated	10 (7.6)
Untreated	121 (92.4)
Diabetes mellitus	101 (50.8)
Treated	23 (22.8)
Untreated	78 (77.2)
Cigarette smoking	46 (23.1)
AF	21 (10.6)
CHD	15 (7.5)
CHD (with AF)	9 (60.0)
CHD (without AF)	6 (40.0)
TOAST classification	
SVD	77 (38.7)
LAD	74 (37.2)
SUE	25 (12.6)
CE	23 (11.6)
Topography	
Pons	170 (85.4)
Medulla oblongata	20 (10.1)
Midbrain	3 (1.5)
Overlapping	6 (3.0)
Assessments	
NIHSS day one, median (IQR)	4 (2–6)

Abbreviations and definitions: hyperlipidemia = receiving cholesterol-reducing agents, total cholesterol > 5 mmol/L or LDL-cholesterol > 3 mmol/L; LDL = low density lipoprotein; HHCY = homocysteine > 10 μmol/L; AF = atrial fibrillation; CHD = coronary heart disease; SVD = small vessel disease; LAD = large artery disease; SUE = stroke of undetermined etiology; CE = cardioembolism; NIHSS = National Institutes of Health Stroke Scale; SD = standard deviation; IQR = interquartile range.

3.2. Stroke etiological subtypes of BSIs (Table 1)

In terms of stroke etiological subtypes, 77 (38.7%) of the patients suffered from SVD, 74 (37.2%) from LAD, 25 (12.6%) from SUE, whereas 23 (11.6%) had a stroke of CE. No patients had SOE.

3.3. The prevalence of risk factors in the different TOAST subtypes

There were significantly different incidences of hypertension, diabetes and CHD among these four groups. Further analysis showed that hypertension was more prevalent in LAD than in SVD and CE (P = 0.001 and P = 0.039, respectively) while the incidence of diabetes in LAD was higher than those in SVD and CE (P < 0.001 and P = 0.015, respectively). The incidence of CHD without AF was more prevalent in CE than in SVD and LAD (P = 0.044 and P = 0.012, respectively) (Table 2).

The associations between risk factors and different stroke subtypes were analyzed. LAD was more associated with hypertension (OR = 3.18, P = 0.009) and diabetes (OR = 2.84, P = 0.003), compared to the other subtypes (Table 3).

4. Discussion

Risk factors and etiological subtypes of cerebral infarction have been widely researched. However, few studies have focused on the risk factors and etiological subtypes of BSIs. In this study, we found that SVD was the most prevalent etiology in BSIs followed by LAD and the incidence of CE was low. We found significantly different incidences of

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