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Risk factors and prognosis of acute ischemic stroke complicated with cerebral microbleeds

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Abstract

Objective: To observe the risk factors and prognosis of patients with acute ischemic stroke complicated with cerebral microbleeds (CMBs) to provide a theoretical basis for better prevention and treatment of acute ischemic stroke and reduction of bleeding risk. *Methods:* The clinical data of 200 patients with acute ischemic stroke who completed susceptibility weighted imaging (SWI) were retrospectively analyzed. They were divided into a CMB group and a non CMB group. Univariate analysis and multivariate logistic regression analysis were used to analyze the risk factors and prognosis of acute ischemic stroke. *Results:* Univariate analysis showed that systolic blood pressure, fasting plasma glucose, free triiodothyronine (FT3), infarct site in the cerebral lobe and total anterior circulation infarct (TACI) (using the Oxfordshire Community Stroke Project (OCSP) classification) were correlated with acute ischemic stroke complicated with CMBs ($P < 0.05$). Multivariate logistic regression analysis showed that systolic blood pressure (OR: 1.02, 95% CI: 1.009–1.032), fasting blood glucose (OR: 1.174, 95% CI: 1.082–1.274) and infarct site in the cerebral lobe (OR: 12.925, 95% CI: 7.412–22.540) were independent risk factors for acute ischemic stroke complicated with CMBs ($P < 0.05$). TACI (OR: 0.004, 95% CI: 0.002–0.007) may not be an independent risk factor ($P < 0.05$).
Conclusion: Systolic blood pressure, fasting blood glucose and infarct site in the cerebral lobe, but likely not TACI, were independent risk factors for acute ischemic stroke complicated with CMBs. The presence or absence of CMBs did not affect the prognosis of acute ischemic stroke.

Keywords: Acute ischemic stroke, risk factors, logistic regression analysis, analysis of prognosis, cerebral microbleeds

INTRODUCTION

Acute ischemic stroke is an acute disease caused by ischemia, hypoxia or cerebral blood circulation disorder.[1,2] Studies have shown that after patients had a first acute ischemic stroke, 91% of the recurrent strokes were acute ischemic stroke.[3] Ischemic stroke is characterized by a high incidence, disability rate, mortality and recurrence rate.[3-5] At present, there is no highly effective treatment for acute ischemic stroke, which places a heavy burden on patients and their families.[6] Cerebral microbleeds (CMBs) are one of the most common forms of small cerebral vascular disease. The pathological change is mainly due to microbleeding resulting in the deposition of hemosiderin in the brain substance. CMBs are a marker of the severity of basal vascular disease, and CMBs are associated not only with bleeding tendency but also with future ischemic events.[7] Therefore, the purpose of this study was to investigate the risk factors and prognosis of acute ischemic stroke complicated with CMBs to provide diagnosis and treatment ideas for the clinical treatment and prevention of acute ischemic stroke.

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METHODS

Clinical data

Susceptibility-weighted imaging (SWI) is a type of three-dimensional imaging developed from a simple two-dimensional T2*-weighted sequence. It improves the spatial resolution and the characteristics of the magnetic susceptibility contrast.[8] SWI can identify CMBs. In this paper, SWI was used to detect whether patients with acute ischemic stroke also had CMBs. Patients with acute ischemic stroke admitted to the Department of Neurology, Putuo Hospital, Shanghai University of Traditional Chinese Medicine from March 2021 to August 2022 who completed SWI imaging examination were selected.

Diagnostic criteria

The diagnostic criteria for acute ischemic stroke were based on the Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke 2018[9]: (1) acute onset; (2) focal neurological dysfunction or, in some cases, generalized neurological dysfunction; (3) imaging findings of responsible lesions or patient symptoms/signs lasting for more than 24 hours; (4) exclusion of nonvascular causes; and (5) exclusion of intracranial hemorrhage by magnetic resonance imaging (MRI).

Inclusion criteria: (1) Patients who met the diagnostic criteria for acute ischemic stroke and were able to undergo SWI imaging; (2) patients with an age ≥18 years; (3) patients without mental disorders.

Exclusion criteria: (1) Hemorrhagic stroke patients; (2) patients with severe heart disease, liver and kidney insufficiency, respiratory failure, malignant tumor; and (3) patients who abused alcohol or drugs.

METHODS

The relevant information about patients with acute ischemic stroke was recorded by Excel, and included (1) general information, including name, age, gender; (2) previous history of ischemic stroke, hypertension, diabetes, coronary atherosclerotic heart disease, atrial fibrillation, smoking (currently smoking defined as 5 cigarettes a day for ≥2 years), alcoholism (long-term drinking defined as alcohol, consumption of >40 g/d for males and ≥20 g/d for females for > 2 years), as well as antiplatelet aggregation drugs, anticoagulant drugs, etc. taken before hospitalization; (3) investigatory findings of triglycerides, total cholesterol, low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), fasting blood glucose on admission, glycosylated hemoglobin, thyroid function (triiodothyronine (T3), thyroxine (T4), free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH)), creatinine, uric acid, glomerular filtration rate (GFR), fibrinogen, homocysteine (HCY), folic acid, vitamin B12 on admission; (4) indices for analysis included the National Institute of Health Stroke Scale (NIHSS) score on admission, systolic blood pressure on admission, diastolic blood pressure on admission, infarct site in the cerebral lobe, Oxfordshire Community Stroke Project (OSCP) classification, the Org 10172 Trial in the Treatment of Acute Stroke (TOAST) classification, hemorrhagic transformation during hospitalization, recurrence of ischemic stroke, modified Rankin Scale (mRS) at discharge, mRS at three months, number of deaths at three months.

Statistical analysis

SPSS 21.0 software was used for data analysis. $P<0.05$ was considered statistically significant. If data met the normal homogeneity test of variance, the two-sample t test was used. If data did not pass the normal homogeneity test of variance, the nonparametric rank sum test was used. The chi-square test was used for count data in univariate analysis. Logistic regression was used for multivariate analysis.

RESULTS

A total of 200 patients, 112 in the group with CMBs and 88 in the group without CMBs, were included in this study. Patients with CMBs accounted for 56% of the total included cases, and patients without CMBs accounted for 44% of the total included cases.

Table 1 shows the univariate analysis of risk factors for acute ischemic stroke complicated with cerebral microbleeds. Table 2 shows the multivariate logistic regression of risk factors for acute ischemic stroke complicated with cerebral microbleeds. Table 3 shows the prognosis of acute ischemic stroke complicated with cerebral microbleeds.

Table 1: Univariate analysis of risk factors for acute ischemic stroke complicated with cerebral microbleeds (CMBs)

Variable	CMBs group (112patients)	No CMBs group (88 patients)	P
Age (mean ± SD)	70.67 ± 8.58	65.30 ± 10.45	0.254
Sex, Males (n(%))	81 (72.3)	63 (71.6)	0.909
Ischemic stroke (n(%))	54 (48.2)	38 (43.2)	0.478
Hypertension (n(%))	83 (74.1)	60 (68.2)	0.357
Diabetes (n(%))	55 (49.1)	32 (36.4)	0.071
Coronary atherosclerotic heart disease (n(%))	11 (9.8)	7 (8.0)	0.647
Atrial fibrillation (n(%))	9 (8.0)	7 (8.0)	0.983
Smoking (n(%))	50 (44.6)	41 (46.6)	0.784
Alcoholism (n(%))	29 (25.9)	22 (25)	0.886
NIHSS score on admission (mean ± SD)	3.80 ± 3.21	3.36 ± 3.05	0.301
Systolic blood pressure (mean ± SD)	152.54 ± 20.92	144.68 ± 20.74	0.009★
Diastolic blood pressure (mean ± SD)	86.72 ± 10.92	86.06 ± 11.51	0.816
Total cholesterol (mean ± SD)	4.79 ± 1.37	4.58 ± 1.02	0.401
Triglycerides (mean ± SD)	1.55 ± 0.72	1.66 ± 0.87	0.547
HDL (mean ± SD)	1.07 ± 0.34	1.04 ± 0.24	0.546
LDL (mean ± SD)	3.16 ± 0.97	3.03 ± 0.79	0.131
Fasting plasma glucose (mean ± SD)	7.30 ± 3.10	5.96 ± 2.12	0.001★
Glycated hemoglobin (HbA1c) (mean ± SD)	7.08 ± 1.58	6.75 ± 1.81	0.095
T3 (mean ± SD)	1.44 ± 0.32	1.52 ± 0.29	0.333
T4 (mean ± SD)	104.41 ± 23.54	106.40 ± 23.65	0.518
FT3 (mean ± SD)	4.16 ± 0.65	15.92 ± 2.64	0.026★
FT4 (mean ± SD)	16.19 ± 8.42	1.67 ± 1.49	0.163
TSH (mean ± SD)	1.63 ± 1.11	16.00 ± 8.70	0.689
Creatinine (mean ± SD)	77.00 ± 23.67	73.48 ± 19.58	0.508
Uric acid (mean ± SD)	335.52 ± 95.90	337.01 ± 98.43	0.709
Glomerular filtration rate (GFR) (mean ± SD)	92.13 ± 25.84	96.93 ± 28.06	0.454
Fibrinogen (mean ± SD)	3.09 ± 0.91	2.94 ± 0.81	0.207
HCY (mean ± SD)	15.01 ± 7.76	16.00 ± 8.97	0.355
Folic acid (mean ± SD)	31.17 ± 102.62	18.93 ± 10.33	0.112
Vitamin B12 (mean ± SD)	245.68 ± 225.21	190.87 ± 118.57	0.079
Infarct site in cerebral lobe (n(%))	36 (32.1)	12 (13.3)	0.002★
Antiplatelet drugs			
Use aspirin (n(%))	53 (47.3)	38 (43.2)	0.56
Use clopidogrel (n(%))	3 (2.7)	6 (6.8)	0.29
Use dual-antiplatelet drug (n(%))	9 (8.0)	11 (12.5)	0.296
Anticoagulation	9 (8.0)	3 (3.4)	0.171
OCSP			
Total anterior circulation infarcts (TACI) (n(%))	11 (9.8)	2 (2.3)	0.032★
Partial anterior circulation ischemic stroke (PACI) (n(%))	53 (47.3)	32 (36.4)	0.12
Posterior circulation infarcts (POCI) (n(%))	21 (18.8)	23 (26.1)	0.211
Lacunar infarcts (LACI) (n(%))	27 (24.1)	31 (35.2)	0.085
TOAST			
Large artery atherosclerosis type (LA) (n(%))	19 (17)	13 (14.8)	0.675
Cardioembolic type (CE) (n(%))	9 (8.0)	7 (8.0)	0.983
Small-artery occlusion lacunar type (SA) (n(%))	84 (75)	68 (77.3)	0.709

Note: If homogeneity of variance is satisfied, a t test was used. ★The results showed that systolic blood pressure, fasting plasma glucose, FT3, infarct site in the cerebral lobe and TACI all had p values < 0.05, which were statistically significant and therefore indicated that they were related risk factors.

Table 2: Multivariate logistic regression analysis of risk factors for acute ischemic stroke complicated with cerebral microbleeds

Variable	β	SE	P	OR (95% CI)
Systolic blood pressure	0.02	0.006	0.001★	1.02 (1.009–1.032)
Fasting plasma glucose	0.161	0.042	0.001★	1.174 (1.082–1.274)
Infarct site in cerebral lobe	2.559	0.284	0.001★	12.925 (7.41–22.540)
TACI	-5.612	0.302	0.001★	0.004 (0.002–0.007)

Note: ★The results showed that the P values of systolic blood pressure, fasting plasma glucose and infarct site in the cerebral lobe were all < 0.05, which were statistically significant and therefore indicated that these factors are independent risk factors. TACI (P< 0.05, OR<1) may not be an independent risk factor.

DISCUSSION

Acute ischemic stroke is characterized by high recurrence, disability and fatality rates and is a serious threat to human health.[3] Cerebral microangiopathies include atherosclerosis, fibrous hyaluronic disease and cerebral amyloid vessels. CMBs are currently considered to be the result of microangiopathy.[10] In this study, the detection rate of microbleeds in acute ischemic stroke was as high as 56%, indicating that CMBs were closely related to ischemic stroke.[11,12]

This study shows that systolic blood pressure, fasting blood glucose and infarct site in the cerebral lobe are independent risk factors for acute ischemic stroke complicated with CMBs; however, TACI may not be an independent risk factor for acute ischemic stroke complicated with CMBs.

The infarct site in the cerebral lobe is an independent risk factor for acute ischemic stroke complicated with CMBs. The pathological mechanisms of CMBs are mainly related to amyloid cerebrovascular disease and hypertensive artery disease.[13] Amyloid cerebrovascular disease is closely related to the occurrence of microbleeding in the cerebral lobe. The causes of amyloid cerebrovascular disease are as follows: (1) pathological vascular damage caused by the deposition of β-amyloid protein in the pia meningeal, cortex and other parts of the small blood vessels, tiny blood vessels, and capillary walls; and (2) the loss or distortion of the normal anatomic components of the vascular wall that can trigger the formation of localized structural lesions of CMBs, which is the main cause of cerebral lobe CMBs.[14,15]

Fasting blood glucose is an independent risk factor for patients with acute ischemic stroke complicated with CMBs. Studies have shown that patients with high blood glucose are more likely to develop atherosclerosis than those with low blood glucose. Hyperglycemia is the main cause of microvascular disease. Atherosclerosis with hyperglycemia is more invasive than nonhyperglycemia. Hyperglycemia has a negative impact on the growth reserve and healing of the vascular wall. This is mainly due to the self-perpetuating process caused by the accumulation of macrophages, which leads to plaque formation and accelerates atherosclerosis, making blood vessels more likely to leak and rupture.[12,16,17] Leakage and rupture of blood vessels can lead to the formation of brain microbleeds.

Systolic blood pressure is an independent

Table 3: Prognosis analysis of acute ischemic stroke complicated with cerebral microbleeds (CMBs)

Variable	CMBs group (112 patients)	No CMBs group (88 patients)	P
Hemorrhagic transformation during hospitalization (n)	5	0	0.121
Recurrent ischemic stroke at 3 months (n)	0	1	0.919
mRS at discharge (mean±SD)	1.62±1.442	1.59±1.274	0.879
mRS at 3months (mean±SD)	1.22±1.32	1.10±1.083	0.815
Deaths at 3 months (n)	1	0	1

Note: The results showed that the P values of hemorrhagic transformation during hospitalization, recurrent ischemic stroke at 3 months, mRS at discharge, mRS at 3 months and deaths at 3 months were all > 0.05, and therefore indicated that these factors did not affect the prognosis of acute ischemic stroke complicated with microbleeds (n stands for number of cases).

risk factor for acute ischemic stroke complicated by CMBs. Klarenbeek *et al*.[18] have shown that systolic blood pressure is associated with ischemic stroke complicated with CMBs. In humans, any increase in blood pressure leads to an increase in blood pressure load, which can cause changes in cerebral microvascular structure and ultimately result in blood extravasation and cerebral microbleeding.[19] Studies have shown that strict control of blood pressure can prevent the progression of small blood vessel damage and the formation of new microbleeds.[20]

In this study, history of neither hypertension nor diabetes was an independent risk factor for acute ischemic stroke complicated with CMBs, while systolic blood pressure and fasting blood glucose were independent risk factors for acute ischemic stroke complicated with CMBs. However, previous studies have shown that histories of hypertension and diabetes are closely related to acute ischemic stroke complicated with CMBs.[17,19] There are two possible reasons for this difference in findings. First, the sample size included in this study was small, which may have affected the results. Second, most patients with hypertension and/or diabetes were taking medicines to control their blood pressure and blood glucose, thus delaying the progression of the disease. As a result, there were no statistically significant differences in histories of hypertension and diabetes between the two groups.

TACI may not be an independent risk factor for acute ischemic stroke with CMBs. According to a literature review, there are few studies on the correlation between TACI and acute ischemic stroke complicated with CMBs. We plan to perform a correlation study in the future.

In this study, there were no significant differences between the two groups in hemorrhagic transformation during hospitalization, recurrent ischemic stroke at 3 months, mRS at discharge, mRS at 3 months or number of deaths at 3 months. This result was supported by other studies. Takahashi *et al*.[21] showed that there was no significant difference in hemorrhagic transformation risk for patients with acute ischemic stroke complicated with or without CMBs after 2 days of antiplatelet aggregation therapy. Nagaraja *et al*.[22] showed that there was no significant difference in hemorrhagic transformation between patients with acute ischemic stroke with or without CMBs during hospitalization. Sakuta *et al*.[23] found that there were no significant differences in the recurrence rate and mRS at 3 months for patients with acute ischemic stroke complicated with or without CMBs.

In conclusion, systolic blood pressure, fasting blood glucose and infarct site in the cerebral lobe, but likely not TACI, are independent risk factors for acute ischemic stroke complicated by CMBs. The presence or absence of complicated CMBs does not affect the prognosis of acute ischemic stroke. This study has certain limitations. First, this study divided patients with CMBs into only two groups, patients with and without CMBs, and was not a stratified study that considered the number and location of CMBs to further reveal the influence of these factors on acute ischemic stroke. We propose to perform a stratified study in the future. Second, this study is a retrospective study with certain limitations, so prospective studies can be carried out in the future to further confirm the conclusions of this study.

DISCLOSURE

Ethics: This study protocol was reviewed and approved by Putuo Hospital, Shanghai University of Traditional Chinese Medicine (PTEC-R-2021-3-1).

Data availability: Data available on request from the corresponding authors.

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Conflict of interest: None

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