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Risk Factors for Silent Lacunar Infarction in Patients with Transient Ischemic Attack

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1,2 Ying Li
BDE 1,2 Nan Liu
BDEF 2 Yonghua Huang
DEF 2 Wei Wei
DEF 3 Fei Chen
ABCDEF 2 Weiwei Zhang

1 Postgraduate School, Third Military Medical University, Chongqing, P.R. China
2 Department of Neurology, Beijing Military General Hospital, Beijing, P.R. China
3 Department of Neurology, Beijing Military 254 Hospital, Tianjin, P.R. China

Corresponding Author: Weiwei Zhang, e-mail: neuroliy@sina.com
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Background: Lacunar infarctions represent 25% of ischemic strokes. Lacunar stroke and transient ischemic attack (TIA) share a number of symptoms. This study aimed to assess the potential risk factors for lacunar infarction in patients with TIA.

Material/Methods: This was a retrospective study performed at the Beijing Military General Hospital in patients with TIA admitted between March 2010 and December 2011. Patients were grouped according to lacunar *vs.* no lacunar infarction. All patients were diagnosed using diffusion-weighted imaging (DWI) on brain magnetic resonance imaging (MRI). Brain angiography (computed tomography and MRI) was used to measure intracranial stenosis. Carotid artery stenosis was measured by ultrasound.

Results: Patients with TIA and lacunar infarction (n=298) were older than those without lacunar infarction (n=157) (69.4±10.0 *vs.* 58.9±9.0 years, P<0.001) and showed a higher frequency of males (51.7% *vs.* 41.4%, P=0.037), hypertension (75.3% *vs.* 45.9%, P<0.001), diabetes (32.6% *vs.* 21.0%, P=0.010), hyperlipidemia (53.4% *vs.* 29.3%, P<0.001), carotid stenosis (73.2% *vs.* 40.1%, P<0.001), and intracranial stenosis (55.6% *vs.* 31.9%, P<0.001), but a lower frequency of alcohol drinking (8.1% *vs.* 14.0%, P=0.045). Lacunar infarction mostly involved the anterior circulation (62.8%). Multivariate analysis showed that age (odds ratio (OR)=1.085, 95% confidence interval (95%CI): 1.054–1.117, P<0.001), hypertension (OR=1.738, 95%CI: 1.041–2.903, P=0.035), hyperlipidemia (OR=2.169, 95%CI: 1.307–3.601, P=0.003), and carotid stenosis (OR=1.878, 95%CI: 1.099–3.206, P=0.021) were independently associated with lacunar infarction.

Conclusions: Age, hypertension, hyperlipidemia, and carotid stenosis were independently associated with silent lacunar infarction in patients with TIA.

MeSH Keywords: Atherosclerosis • Carotid Arteries • Stroke, Lacunar

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Background

Lacunar infarctions are responsible for about 25% of all cerebral ischemic strokes [1] and are defined as infarction lesions of 3–15 mm in diameter in the deep perforating arterial territory. Lacunar infarctions are usually found in elderly patients with hypertension and diabetes [2]. The prevalence of silent lacunar stroke at brain MRI was 5.6% in people >45 years old in a study carried out in the Netherlands [3]. Silent lacunar infarction may be a risk factor for subsequent stroke or dementia [4].

Traditionally, lacunar infarction has been considered as a small-artery disease (SAD) [5,6]. Recent studies have shown that intracranial artery stenosis might be associated with lacunar infarction [7–10], but this is still controversial [11,12]. Previous studies have suggested that the carotid intima-media thickness was more closely associated with non-lacunar stroke compared to lacunar infarction [13,14]. Lacunar infarction is usually considered as benign and appropriate secondary prevention is often neglected despite the higher risk of subsequent stroke and dementia [4,15,16]. A recent epidemiological study reported that the risk factors for silent brain infarction (including lacunar infarction) remain unclear [17] and no study is available for the Chinese population.

Transient ischemic attacks (TIA) share a number of symptoms with lacunar infarctions, and a lacunar infarction may be preceded by a number of short-duration TIA events [18–21], but the heterogeneous presentations make the clinical differentiation of the two entities difficult. A study has suggested that TIAs have a high positive predictive value for lacunar infarction [18], but the exact relationship between the 2 remains controversial. Another study has shown that a history of TIA was a risk factor for lacunar infarction [22]. Nevertheless, the presence of silent lacunar infarction in patients presenting with TIA is unknown. Since lacunar infarction can lead to severe long-term impairments, it is crucial to diagnose the silent forms of lacunar infarction in the presence of TIA. Since some patients with symptoms of TIA may also suffer from silent lacunar infarction, it is important to identify patients with lacunar infarction in order to provide appropriate early treatments.

Therefore, the aim of this study was to assess the risk factors for lacunar infarction in patients with transient ischemia attack (TIA), especially carotid and intracranial artery stenosis. We hope that our results will provide potential data for the prevention of lacunar infarction and subsequent stroke, as well as for better management of patients with silent lacunar infarction.

Material and Methods

Patients

This was a retrospective study performed in patients diagnosed with TIA at the Department of Neurology, Beijing Military General Hospital from March 2010 to December 2011. All included patients had to be diagnosed with TIA. Patients were then grouped according to silent lacunar infarction [23–25] or no lacunar infarction. All patients were diagnosed with lacunar stroke based on brain diffused-weighted imaging (DWI) magnetic resonance imaging (MRI). On MRI, lacunar infarctions are shown as 3–15 mm focal lesions, hypointense but with a hyperintense rim seen on T1 fluid-attenuated inversion recovery (FLAIR) sequences, located supratentorially according to the corresponding hyperintensity on T2-weighted and hypointensity on T1-weighted images [26–28]. Thirty-seven patients were diagnosed based on CT scan showing a subcortical low-density region of <15 mm [29,30]. All patients underwent MRI.

In addition, inclusion criteria were: 1) aged ≥45 years; and 2) scanned by MRI or CT scan based on TIA signs. Exclusion criteria were: 1) intracerebral hemorrhagic lesion; 2) intracranial tumor; 3) multiple sclerosis lesions; 4) unavailable blood tests; or 5) positive 3-month history of a vascular event.

Patients with TIA but without cerebral infarction were selected as controls (no lacunar infarction). This study was approved by the ethics committee of the Beijing Military General Hospital. All patients provided an written informed consent.

Data collection

The following information was collected for all included subjects: 1) demographic data (age and sex); 2) baseline clinical characteristics (medical history, blood pressure, blood glucose, blood lipids, smoking, and drinking habits); 3) brain imaging (brain MRI); and 4) angiography (including cerebral artery magnetic resonance angiogram [MRA] or intracranial artery computed tomography angiogram [CTA]).

Hypertension was defined as blood pressure ≥140/90 mmHg taken twice within 5 minutes, or if the patient was taking anti-hypertensive medication. Diabetes was defined as fasting blood glucose levels ≥7.0 mmol/L, HbA1c levels ≥6.5%, or if the patient was taking anti-diabetes medication. Dyslipidemia was defined as: 1) LDL cholesterol levels >3.6 mmol/L; 2) total cholesterol levels >5.7 mmol/L; 3) triglyceride levels >1.7 mmol/L; and/or if the patient was taking lipid-lowering drugs. Finally, smoking was defined based on past and current smoking habits.

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Table 1. Baseline characteristics of the patients.

Variable	Lacunar infarction* N=298	No lacunar infarction N=157	*P*
Age (years), mean ±SD	69.39±10.01	58.87±9.02	<0.001
Male (%)	154 (51.7%)	65 (41.4%)	0.037
Hypertension	220 (75.3%)	72 (45.9%)	<0.001
Diabetes	97 (32.6%)	32 (21.0%)	0.010
Heart disease	92 (30.9%)	35 (22.3%)	0.112
Fasting glucose (mmol/L)	6.06±2.44	5.28±1.25	<0.001
Hyperlipidemia	159 (53.4%)	46 (29.3%)	<0.001
TC (mmol/L)	4.56±1.13	4.66±1.03	0.332
TG (mmol/L)	1.49±0.83	1.48±0.71	0.918
LDL (mmol/L)	3.06±0.98	3.14±0.88	0.402
HDL (mmol/L)	1.16±0.35	1.23±0.36	0.029
Smoking	34 (11.4%)	27 (17.2%)	0.085
Alcohol drinking	24 (8.1%)	22 (14.0%)	0.045
Carotid stenosis	218 (73.2%)	63 (40.1%)	<0.001
Intracranial stenosis	140 (55.6%)	46 (31.9%)	<0.001

Continuous variables are shown as means±standard deviation. Categorical variables are shown as n (%). * Patients with transient ischemic attack and silent lacunar infarction.

Imaging

MRI was performed using a 3.0 T system (Discovery MR750; GE Healthcare, Waukesha, WI, USA). All MRI protocols used a slice thickness of 5 mm and an inter-slice thickness of 1.5 mm. T1 FLAIR parameters were: TR of 1750 ms; TE of 23 ms; TI of 780 ms; and FOV of 24 cm. T2-weighted parameters were: TR of 7498 ms; TE of 105 ms; and FOV of 24 cm. CT (Lightspeed VCT 64 system, GE Healthcare, Waukesha, WI, USA) was performed using a slice thickness of 9 mm. All imaging results were recorded and independently examined by 2 radiologists. In cases of discrepancy, a consensus was achieved by discussion with a third radiologist.

Carotid and intracranial artery stenosis

Stenosis was defined as >50% stenosis of the carotid artery. Intracranial artery stenosis was defined as the presence of signs of stenosis of the internal carotid artery (ICA), MCA, anterior cerebral artery (ACA), posterior cerebral artery (PCA), basal artery, and/or intracranial segment of the vertebral artery (VA). All imaging examinations in all patients were performed with the same MRI and CT scanners. Carotid artery stenosis was evaluated by duplex ultrasound using a Philips L11-3 type ultrasound machine (Philips, Best, The Netherlands).

Statistical analysis

Continuous data are presented as means±standard deviation and were analyzed using the t-test. Categorical data are presented as proportions and were analyzed using the chi-square test. The potential risk factors for lacunar infarction were first evaluated using univariate analyses. Thereafter, a multivariate conditional logistic regression analysis (enter method) was performed to identify variables that were independently associated with lacunar infarction. Results are presented as odds ratio (OR) and 95% confidence interval (95%CI). Statistical analysis was performed using SPSS 16.0 (IBM, Armonk, NY, USA). Two-sided P-values <0.05 were considered significant.

Results

Baseline characteristics of the patients

The baseline characteristics of the patients are presented in Table 1. There were 298 patients with TIA and silent lacunar infarction and 157 patients with TIA but without lacunar infarction. Patients with silent lacunar infarction were older than patients without lacunar infarction (69.4±10.0 *vs.* 58.9±9.0 years,

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Table 2. Radiological characteristics of patients with transient ischemic attack and silent lacunar infarction.

Variable	Lacunar infarction (N=298)	
Site of lacunar infarction		
Anterior circulation	187	(62.8%)
Posterior circulation	4	(1.3%)
Both	108	(36.2%)
Number of lacunar infarctions		
One	80	(26.8%)
Multiple	218	(73.2%)
Leukoaraiosis		
No	230	(77.2%)
Yes	68	(22.8%)

P<0.001), and showed a higher frequency of males (51.7% *vs.* 41.4%, P=0.037), hypertension (75.3% *vs.* 45.9%, P<0.001), diabetes (32.6% *vs.* 21.0%, P=0.010), hyperlipidemia (53.4% *vs.* 29.3%, P<0.001), carotid stenosis (73.2% *vs.* 40.1%, P<0.001), and intracranial stenosis (55.6% *vs.* 31.9%, P<0.001), but a lower frequency of alcohol drinking (8.1% *vs.* 14.0%, P=0.045).

Characteristics of the lacunar infarction

Many patients with lacunar infarction had multiple lesions (n=218, 73.2%). The lesions involved the anterior circulation (n=187, 62.8%), posterior circulation (n=4, 1.3%), or both (n=108, 36.2%). Sixty-eight patients (22.8%) also showed leukoaraiosis (Table 2).

Univariate and multivariate analyses

Univariate analyses showed that age (P<0.001), gender (P=0.037), hypertension (P<0.001), diabetes (P=0.01), hyperlipidemia (P<0.001), alcohol drinking (P=0.045), carotid stenosis (P<0.001), and intracranial stenosis (P<0.001) were significantly different between the 2 groups. Multivariate analysis showed that age (OR=1.085, 95%CI: 1.054–1.117, P<0.001), hypertension (OR=1.738, 95%CI: 1.041–2.903, P=0.035), hyperlipidemia (OR=2.169, 95%CI: 1.307–3.601, P=0.003), and carotid stenosis (OR=1.878, 95%CI: 1.099–3.206, P=0.021) were independently associated with lacunar infarction (Table 3).

A sensitivity analysis demonstrated that similar results were obtained when excluding patients with intracranial stenosis. Furthermore, partial correlation analysis adjusted for age, hypertension, and hyperlipidemia showed a significant correlation between lacunar infarction and carotid stenosis (P=0.002).

Subgroup analysis

In patients aged ≥60 years, multivariate analysis showed that age (OR=1.145, 95%CI: 1.080–1.213, P<0.001), hyperlipidemia (OR=2.011, 95%CI: 1.023–3.956, P=0.043), and carotid stenosis (OR=2.411, 95%CI: 1.188–4.894, P=0.015) were independently associated with lacunar infarction (Table 4). In patients aged 45–60 years, multivariate analysis showed that only hyperlipidemia (OR=2.606, 95%CI: 1.133–5.993, P=0.024) was associated with lacunar infarction (Table 4).

Table 3. Univariate and multivariate analyses of the risk factors for the presence of silent lacunar infarction in patients with transient ischemic attack.

Risk factors	Univariate OR (95% CI)		P	Multivariate OR (95% CI)		P
Age	1.113	(1.087, 1.139)	<0.001	1.085	(1.054, 1.117)	<0.001
Gender	0.661	(0.447, 0.976)	0.037	0.767	(0.441, 1.332)	0.345
Hypertension	3.330	(2.218, 5.000)	<0.001	1.738	(1.041, 2.903)	0.035
Diabetes	1.813	(1.152, 2.855)	0.010	1.260	(0.722, 2.198)	0.417
Hyperlipidemia	2.760	(1.828, 4.168)	<0.001	2.169	(1.307, 3.601)	0.003
Smoking	0.620	(0.359, 1.072)	0.087	1.186	(0.513, 2.742)	0.690
Alcohol drinking	0.537	(0.291, 0.993)	0.048	1.007	(0.396, 2.562)	0.988
Heart diseases	1.564	(0.998, 2.451)	0.051	0.666	(0.369–1.202)	0.177
Carotid stenosis	4.194	(2.729, 6.447)	<0.001	1.878	(1.099, 3.206)	0.021
Intracranial stenosis	2.663	(1.733, 4.092)	<0.001	1.465	(0.873, 2.460)	0.148

OR – odds ratio; 95%CI – 95% confidence interval.

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Table 4. Univariate and multivariate analyses of the risk factors for the presence of silent lacunar infarction in patients with transient ischemic attack according to age.

Risk factors	Univariate OR (95% CI)		P	Multivariate OR (95% CI)		P
>60 years old (n=305)						
Age	1.151	(1.098, 1.205)	<0.001	1.145	(1.080, 1.213)	<0.001
Gender	0.737	(0.429, 1.268)	0.271	0.928	(0.451, 1.910)	0.840
Hypertension	2.247	(1.274, 3.964)	0.005	1.455	(0.720, 2.941)	0.296
Diabetes	1.194	(0.669, 2.131)	0.547	1.056	(0.528, 2.114)	0.877
Hyperlipidemia	2.111	(1.209, 3.687)	0.009	2.011	(1.023, 3.956)	0.043
Smoking	0.550	(0.235, 1.287)	0.168	1.602	(0.468, 5.484)	0.453
Alcohol drinking	0.373	(0.144, 0.967)	0.043	0.597	(0.156, 2.288)	0.451
Heart diseases	1.032	(0.585, 1.823)	0.913	0.414	(0.194, 0.883)	0.022
Carotid stenosis	3.440	(1.867, 6.337)	<0.001	2.411	(1.188, 4.894)	0.015
Intracranial stenosis	1.792	(1.022, 3.144)	0.042	1.396	(0.703, 2.771)	0.341
45–60 years old (n=150)						
Age	1.119	(1.030, 1.217)	0.008	1.041	(0.939, 1.154)	0.446
Gender	0.468	(0.241, 0.907)	0.024	0.544	(0.211, 1.404)	0.209
Hypertension	3.118	(1.586, 6.129)	0.001	2.115	(0.937, 4.775)	0.071
Diabetes	2.203	(0.957, 5.068)	0.063	2.560	(0.937, 6.996)	0.067
Hyperlipidemia	3.643	(1.818, 7.299)	<0.001	2.606	(1.133, 5.993)	0.024
Smoking	1.353	(0.627, 2.920)	0.442	0.930	(0.272, 3.183)	0.908
Alcohol drinking	1.402	(0.607, 3.238)	0.428	1.475	(0.389, 5.590)	0.568
Heart diseases	1.520	(0.633, 3.650)	0.349	1.176	(0.410, 3.372)	0.763
Carotid stenosis	2.374	(1.191, 4.732)	0.014	1.371	(0.581, 3.233)	0.471
Intracranial stenosis	2.583	(1.196, 5.580)	0.016	2.267	(0.910, 5.646)	0.079

Discussion

The objective of this study was to assess potential risk factors for the presence of lacunar infarction in patients with TIA. Results showed that age, hypertension, hyperlipidemia, and carotid stenosis were independent risk factors for the presence of lacunar infarction in patients with TIA.

The association between intracranial stenosis and lacunar infarction is controversial. Previous studies have suggested that SAD was mainly associated with lacunar infarction [5,6]. However, other studies have shown that intracranial artery stenosis might be associated with lacunar infarction [7,8], which support the results of this study. Indeed, a study by Lu et al. [9] has shown that intracranial stenosis was associated with lacunar infarction, but a study by Wardlaw et al. [11] suggested that it was unlikely that MCA stenosis was associated with lacunar infarction, and the study by Rajapakse et al. [12] has suggested that lacunar stroke does not arise from large-artery stenosis or thrombosis. This results of the present study are consistent with these previous reports. Baumgartner et al. [22] showed that patients with non-SAD lacunar stroke had worse clinical outcome than patients with SAD lacunar stroke, indicating that lacunar infarction may be due to both small and large arteries. Van Dijk et al. [31] suggested that patients with lacunar infarction had a higher calcification volume in the aortic arch. These discrepancies might be explained by a number of factors, including the study populations, the imaging modalities, and the evaluation criteria.

Previous studies have shown that carotid stenosis is a risk factor for stroke in patients with a history of TIA [32–34]. On the

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other hand, a review has shown that the association between carotid stenosis and lacunar stroke was highly variable between studies [12]. A large study reported a negative association between carotid stenosis and lacunar infarction [35]. Mead et al. suggested that carotid stenosis in patients with lacunar infarction might be an incidental finding [36]. Nevertheless, these previous studies did not specifically study patients with TIA. In the present study, carotid stenosis was independently associated with lacunar infarction in patients with TIA. Additional studies are necessary to further assess this relationship.

In the present study, lacunar infarction lesions were most frequently located in the anterior circulation, which is mainly supplied by perforating arteries or terminal arteries. These results suggest that lacunar infarction might be more often associated with SAD, which is supported by a previous study [37]. However, we also showed that large-artery stenosis might be involved in lacunar infarction, but we did not extensively and comprehensively explore the mechanisms leading to lacunar infarction in patients with TIA. Future studies should aim at determining the exact factors involved (e.g., embolism, hemodynamic failure, and coexistence with SAD). Nevertheless, previous studies from the Lausanne Stroke Registry have shown that most cases (96%) of symptomatic atypical lacunar infarction were caused by SAD [38]. In addition, in patients with lacunar infarction, hypertension was more frequent in patients without cardioembolic causes of stroke, while hypertension was more frequent in patients with non-lacunar stroke with a cardioembolic cause of stroke [39]. In another study, from the Lausanne Stroke Registry, lacunar stroke was mainly caused by SAD in patients who developed progressive motor deficit, while lacunar stroke was mainly caused by embolisms in patients without progressive motor deficit [19]. Another study has shown that hypertension could predict severe recurrent events after TIA [40].

Previous studies have shown that older age is a risk factor for silent lacunar infarction in patients with TIA, especially in those older than 60 years, and that the prevalence and lesion size increase with age [41]. A previous study has suggested that silent lacunar infarction might affect as much as 25% of patients older than 70 years [42]. In this study, patients with TIA and lacunar stroke were older than patients with TIA only. Fisher et al. [25] reported that small lacunar lesions were usually caused by hypertensive SAD. Previous studies reported that traditional risk factors such as hypertension, diabetes, and smoking were major risk factors for the incidence of ischemic strokes, regardless of subtypes [43]. In this study, results from the multivariate analysis showed that age, hyperlipidemia, and carotid stenosis were independently associated with lacunar infarction in patients with TIA. Therefore, these results suggest that hyperlipidemia, a modifiable risk factor, should be the target of interventions to decrease the risk of lacunar infarction in patients with TIA. Statins are essential in the treatment of hyperlipidemia. A previous study has shown that statins improved the outcomes in patients with cerebral ischemia [44]. Statins also help to reduce carotid atherosclerosis and stenosis [45]. Unfortunately, data about statins were not collected in the present study.

A previous study has shown that 36% of patients presenting with clinical and radiographic evidence of lacunar infarction had a potential non-SAD etiology [22]. A study on carotid and intracranial large arteries between people with ipsilateral stenosis and infarction and people with contralateral stenosis and infarction has shown that there was no difference between these 2 groups of patients, suggesting that major cerebral vessel disease frequently coexists with silent lacunar infarction [46].

Age was an important confounding factor in this study. The subgroup analysis showed that age, hypertension, hyperlipidemia, and carotid stenosis were associated with silent lacunar stroke in patients with TIA. However, in the subgroup of younger patients, hyperlipidemia was the only risk factor.

This study has from a number of limitations. The number of patients was relatively small and all patients were from a single institution. No matching was performed with controls. In addition, an age criterion was used in an attempt to improve the similarity of the 2 groups, but that might have led to a selection bias. Finally, some known risk factors for stroke (e.g., hypertension, diabetes, and hyperlipidemia) were more frequent in patients with lacunar infarction. A multivariate analysis was used and showed that the effect of intracranial stenosis on the risk of lacunar infarction was independent of hypertension, but additional studies should be performed in patients matched for those risk factors. Larger multicenter trials are necessary to correctly assess the risk factors and the pathogenesis of lacunar infarction.

Conclusions

In this study, age, hypertension, hyperlipidemia, and carotid stenosis were independently associated with the presence of silent lacunar infarction in patients with TIA, but further study is necessary to draw definite conclusions about the pathogenesis of silent lacunar infarction.

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Conflict of interests

All authors declare that they have no conflict of interests.

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