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Original Article

Leukoaraiosis rather than lacunes predict poor outcome and chest infection in acute ischemic stroke patients

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Abstract: In this study, we determine the effects of leukoaraiosis and lacunes on the clinical outcome and relative complications of acute ischemic stroke patients. From January 2007 to June 2008, 323 consecutive patients with acute brain infarction were prospectively studied. Leukoaraiosis was defined as moderate or severe white matter hyperintensities, and lacunes were counted as follows: none (0 lacune), few (1-2 lacunes), and many (≥3 lacunes). During a three-month period after the onset of stroke, patient outcomes and the incidence of complications were assessed. Backward stepwise logistic regression was used to identify the independent predictors of adverse outcome and complications after stroke. During the follow-up, 128 patients (39.63%) experienced adverse outcomes (i.e., death or disability), and 69 patients (21.36%) developed chest infections. Leukoaraiosis was an independent predictor of adverse outcome and chest infection (adverse outcome: odds ratio, 3.971, 95% confidence interval, 1.954-8.073; chest infection: odds ratio, 1.809, 95% confidence interval, 1.220-2.681), whereas no associations were observed between lacunes and adverse outcomes or complications after stroke. In conclusion, Leukoaraiosis but not lacunes was an independent predictor of adverse outcomes and chest infection in acute ischemic stroke patients. The difference between the effects of lacunes and leukoaraiosis may reflect the heterogeneity of these two primary features of small vessel diseases.

Keywords: Leukoaraiosis, lacunes, stroke, prognosis, complications

Introduction

Leukoaraiosis and lacunes are common imaging findings in older patients. Both conditions are considered to be features of small vessel diseases [1-4]; however, lacunes result from small artery occlusion, and leukoaraiosis primarily results from partial ischemia [5]. Previous evidence has shown that small vessel diseases are strong predictors of cognitive decline [6]. Leukoaraiosis has also been shown to be associated with patient mortality in population-based studies [7].

Stroke is a serious public health problem, with a high incidence, high mortality and high disability rates [8]. Acute stroke patients are at risk of developing a variety of complications that can have poor outcomes. Small vessel diseases increase the risk of stroke in the general population [9]. Stroke patients with lacunes and leukoaraiosis have higher mortality rates than other stroke patients [10]. However, few studies have investigated the effect of preexisting leukoaraiosis on stroke outcome, and the results have been inconsistent [10, 11]. Associations between small vessel diseases and acute ischemic stroke complications were also undetermined. This study evaluated the effect of leukoaraiosis and lacunes on the clinical outcomes and the relative complications of acute ischemic stroke patients.

Materials and methods

The procedure to obtain informed consent in this study was as follows: a subject's competence was evaluated using the Mini Mental State Examination (MMSE). If the subject's score was ≥20, he or she was deemed able to give informed consent and was then informed of the study characteristics. If the subject's

MMSE score was < 20 after adjusting for age and education, the subject was deemed unable to give informed consent and consent had to be obtained from a legally authorized representative.

Consecutive patients admitted to the Department of Neurology at the General Hospital of Beijing Military Command and diagnosed with acute brain infarction between January 2007 and June 2008 were prospectively selected. All patients were assessed by a neurologist to determine the diagnosis of brain infarction and were diagnosed according to the National Institute of Neurological Disorders and Stroke classification of cerebrovascular diseases III [12] and its subtypes, which are based on the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification [13]. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) [14]. The exclusion criteria included hospital admission 48 hours after of the onset of stroke and contraindications for magnetic resonance imaging (MRI). Patients who received thrombolytic therapy were also excluded. The study was approved by the General Hospital of Beijing Military Command Ethics Committee (2006-086).

When each patient was admitted, trained physicians obtained the following information: age, gender, history of cigarette smoking, alcohol intake, hypertension and diabetes mellitus. We categorized smokers and drinkers as current, past or never. Hypercholesterolemia was diagnosed when the total cholesterol level was > 5.2 mmol/L or if the patient was undergoing current treatment with lipid-lowering drugs. Atrial fibrillation was diagnosed with electrocardiograms by electrocardiograph technicians who were unaware of the clinical status of each study subject. Three months after stroke onset, the patients were interviewed in person or via telephone. Disability was assessed using a modified Rankin scale (mRS) score and defined as nondisabled (mRS score ≤2) or disabled (mRS score ≥3). Complications were recorded, including chest infection (i.e., fever, respiratory symptoms or other signs, such as cough, or inspiratory crackles with radiographic evidence), upper gastrointestinal bleeding (i.e., bloody vomit, nasogastric aspirate or feces with a positive occult blood test), symptomatic hemorrhage transformation (clinical worsening with newly appeared hyperdensity within the infarction area on computed tomography (CT)), diarrhea (i.e., frequent incidence of loose or watery feces), urinary tract infection (i.e., urinary symptoms with a positive urine leucocyte examination), and stroke progression (i.e., an increase > 2 points on the NIHSS score during the first 72 hours).

Brain MRI was performed with a 1.5 T MRI unit (GE Signa, GE, USA). The imaging protocol included T1 inversion recovery, T2, diffusion-weight imaging (DWI) and T2-weighted fluid-attenuated inverse recovery (FLAIR) scans. All MRI examinations were performed 72 hours after stroke onset. Cerebral CT examination without contrast was performed at admission to exclude intracranial hemorrhage. An additional CT examination was performed in cases of clinical worsening. For all patients, white matter hyperintensity on FLAIR scans were rated as none, mild, moderate or severe by two neurologists using a modified Fazekas' scale [12]. Leukoaraiosis was defined as moderate or severe white matter hyperintensity. Lacunes were defined as a lesion measuring < 10 mm, with cerebrospinal fluid-like signal on MRI surrounded by white matter or subcortical gray matter. The numbers of lacunes were counted as follows: none (0 lacune), few (1-2 lacunes), and many (3 or more lacunes). Cerebrospinal fluid-like foci that fulfilled three or more criteria were considered to be Virchow-Robin spaces and excluded from the count as follows: 1) ≤2 mm; 2) smooth round or oval or linear shape; 3) without surrounding hyperintensity on FLAIR images; 4) symmetric foci in bilateral hemispheres; and 5) located in the basal ganglia or vertex [13].

Statistical methods

The analysis was performed using the SPSS software package (version 12.0, SPSS Inc., USA). Quantitative values were expressed as the means ± standard deviation. First, univariate analysis was performed to identify the complications associated with leukoaraiosis or lacunes. The Kruskal-Wallis H test and chi-squared test or Fisher's exact test were used to analyze differences between groups for continuous variables and categorical variables, respectively. Then, Spearman's rank correlation coefficient test was performed to identify stroke outcomes and the risk factors of complications associated with leukoaraiosis or lacunes. Finally, to determine whether leukoaraiosis and lacunes were independent predictors

Table 1. Characteristics of the patients in the lacunes and leukoaraiosis subgroups

Total (n=323)		Lacunes				LA		
		Normal (n=94)	Few (n=109)	Many (n=120)	v	Normal (n=141)	LA (n=182)	*P*
Male	219 (67.80%)	67 (71.28%)	66 (60.55%)	86 (71.67%)	0.138	105 (74.47%)	114 (62.64%)	0.024
Age (years)	67.15 ± 12.58	62.57 ± 13.78	68.157 ± 11.94	69.83 ± 11.20	0.000	60.01 ± 11.73	72.69 ± 10.22	0.000
NIHSS on admission	6.73 ± 6.09	6.99 ± 6.10	6.91 ± 6.16	6.38 ± 6.06	0.601	6.57 ± 5.67	6.86 ± 6.41	0.926
Smoking status								
Never	202 (62.54%)	65 (69.15%)	60 (55.05%)	77 (64.17%)	0.143	77 (54.61%)	125 (68.68%)	0.003
Past	20 (6.19%)	2 (2.13%)	10 (9.17%)	8 (6.67%)		6 (4.26%)	14 (7.69%)	
Current	101 (31.27%)	27 (28.72%)	39 (35.78%)	35 (29.17%)		58 (41.13%)	43 (23.63%)	
Alcohol consumption								
Never	234 (72.45%)	67 (71.28%)	82 (75.23%)	85 (70.83%)	0.862	91 (64.54%)	143 (78.57%)	0.017
Past	45 (13.93%)	15 (15.96%)	12 (11.01%)	18 (15.00%)		24 (17.02%)	21 (11.54%)	
Current	44 (13.62%)	12 (12.77%)	15 (13.76%)	17 (14.17%)		26 (18.44%)	18 (9.89%)	
History of hypertension	253 (78.33%)	59 (62.77%)	87 (79.82%)	107 (89.17%)	0.000	95 (67.38%)	158 (86.81%)	0.000
History of diabetes	93 (28.79%)	22 (23.40%)	30 (27.52%)	41 (34.17%)	0.211	36 (25.53%)	57 (31.32%)	0.255
Atrial fibrillation	42 (13.00%)	15 (15.96%)	16 (14.68%)	11 (9.17%)	0.278	18 (12.77%)	24 (13.19%)	0.911
Hypercholesterolemia	108 (33.44%)	30 (31.91%)	45 (41.28%)	33 (27.50%)	0.082	60 (42.55%)	48 (26.37%)	0.002
Leukoaraiosis	182 (56.35%)	25 (26.60%)	54 (49.54%)	103 (85.83%)	0.000	-	-	-
Small-vessel occlusion	114 (35.29%)	35 (37.23%)	28 (25.69%)	51 (42.50%)	0.098	46 (32.62%)	68 (37.36%)	0.485
Large-artery	128 (39.63%)	33 (35.11%)	52 (47.71%)	43 (35.83%)		57 (40.43%)	71 (39.01%)	
Cardioembolism	22 (6.81%)	7 (7.45%)	10 (9.17%)	5 (4.17%)		9 (6.38%)	13 (7.14%)	
Other determined etiology	5 (1.55%)	2 (2.13%)	2 (1.83%)	1 (0.83%)		4 (2.84%)	1 (0.55%)	
Undetermined etiology	54 (16.72%)	21 (22.34%)	15 (13.76%)	18 (15.00%)		25 (17.73%)	29 (15.93%)	
Non-disabled	195 (60.37%)	62 (65.96%)	61 (55.96%)	72 (60.00%)	0.347	97 (68.79%)	98 (53.85%)	0.006
Dead or disabled	128 (39.63%)	32 (34.04%)	48 (44.04%)	48 (40.00%)		44 (31.21%)	84 (46.15%)	
Complications								
Stroke progression	40 (12.38%)	7 (7.45%)	16 (14.68%)	17 (14.17%)	0.224	11 (7.80%)	29 (15.93%)	0.028
Chest infection	69 (21.36%)	20 (21.28%)	18 (16.51%)	31 (25.83%)	0.228	18 (12.77%)	51 (28.02%)	0.001
Urinary tract infection	17 (5.26%)	3 (3.19%)	7 (6.42%)	7 (5.83%)	0.554	3 (2.13%)	14 (7.69%)	0.026
UGB	16 (4.95%)	2 (2.13%)	8 (7.34%)	6 (5.00%)	0.233	6 (4.26%)	10 (5.49%)	0.611
SHT	10 (3.10%)	1 (1.06%)	6 (5.50%)	3 (2.50%)	0.170	3 (2.13%)	7 (3.85%)	0.377
Diarrhea	17 (5.26%)	2 (2.13%)	6 (5.50%)	9 (7.50%)	0.215	5 (3.55%)	12 (6.59%)	0.224

LA: leukoaraiosis; UTI: urinary tract infection; UGB: upper gastrointestinal bleeding; SHT: symptomatic transformation.

Table 2. Correlation analysis of the risk factors for stroke outcomes and complications

	Stroke outcome		Chest infection		Urinary infection		Stroke progression	
	Correlation coefficient	*P*	Correlation coefficient	*P*	Correlation coefficient	*P*	Correlation coefficient	*P*
Gender	0.146	0.009	0.125	0.024	0.164	0.003	0.023	0.686
Age	0.228	0.0001	0.318	0.0001	0.153	0.006	0.023	0.682
NIHSS upon admission	0.677	0.0001	0.357	0.0001	0.121	0.029	0.135	0.016
Smoking	-0.173	0.002	-0.130	0.019	-0.130	0.019	0.010	0.862
Alcohol consumption	-0.177	0.001	-0.113	0.043	-0.012	0.825	-0.057	0.309
History of hypertension	-0.050	0.370	-0.016	0.768	-0.044	0.428	-0.030	0.587
History of diabetes	0.030	0.591	-0.037	0.511	0.064	0.248	-0.031	0.573
Atrial fibrillation	0.214	0.0001	0.298	0.000	0.033	0.560	0.050	0.368
Hypercholesterolemia	-0.131	0.018	-0.174	0.002	0.068	0.223	-0.007	0.894
TOAST classification	0.352	0.0001	0.238	0.0001	0.053	0.341	0.080	0.153
Lacunes	0.042	0.451	0.056	0.318	0.044	0.435	0.077	0.169
Leukoaraiosis	0.152	0.006	0.190	0.0006	0.124	0.026	0.122	0.028

Table 3. Logistic regression analysis results

	OR	95% CI	*P*
Predictors for death and disability			
NIHSS at admission	1.646	1.465-1.849	0.0001
Leukoaraiosis	3.971	1.954-8.073	0.0001
Age	1.044	1.016-1.073	0.002
Predictors for chest infection			
Age	1.046	1.016-1.077	0.002
NIHSS upon admission	1.188	1.117-1.264	0.0001
Leukoaraiosis	1.809	1.220-2.681	0.003
Atrial fibrillation	2.747	0.923-8.179	0.069
Predictors for urinary tract infection			
Gender	3.737	1.329-10.505	0.012
Leukoaraiosis	3.295	0.916-11.853	0.068
Predictors for stroke progression			
NIHSS at admission	1.042	0.998-1.089	0.064
Leukoaraiosis	1.778	0.949-3.330	0.072

for adverse outcomes and complications, leukoaraiosis, lacunes and other risk factors were analyzed using binary logistic regression with a forward conditional method, for which the criterion for entry was a P value < 0.05 and that for removal was a P value > 0.10. Values of P < 0.05 were considered statistically significant.

Results

A total of 323 consecutive patients with brain infarct were (104 women, 219 men, age 67.15 ± 12.58 years). Patient characteristics are shown in **Table 1**. The univariate analysis demonstrated higher incidences of adverse outcomes, chest infection, urinary tract infection and stroke progression in the patients with leukoaraiosis compared with patients without leukoaraiosis, whereas no significant differences in upper gastrointestinal bleeding, symptomatic hemorrhage transformation and diarrhea were observed between the patients with and without leukoaraiosis. No differences in stroke outcomes and complications were observed between the patients with different numbers of lacunes. Age and hypertension were significantly associated with both lacunes and leukoaraiosis, whereas gender, smoking, alcohol consumption and hypercholesterolemia were significantly associated with only leukoaraiosis. Lacune incidence and leukoaraiosis were also strongly associated (**Table 1**).

Leukoaraiosis was correlated with stroke outcome, chest infection, urinary tract infection and stroke progression. In addition, gender, age, NIHSS score at admission, smoking, alcohol consumption, atrial fibrillation and stroke subtype were significantly correlated with both stroke outcome and chest infection. Gender, age, NIHSS score at admission and smoking were correlated with urinary tract infection. Only NIHSS score and leukoaraiosis were correlated with stroke progression (**Table 2**).

Leukoaraiosis, lacunes and the variables significantly correlated with stroke outcome or complications were further investigated in a multivariate analysis. Leukoaraiosis was an independent predictor of adverse outcomes and chest infection (adverse outcomes: odds ratio, 3.971; 95% confidence interval, 1.954-8.073; chest infection: odds ratio, 1.809; 95% confidence interval, 1.220-2.681). Higher NIHSS at admission and older age were also independent predictors of adverse outcomes and chest infection. Female gender was an independent predictor of urinary tract infection (**Table 3**).

Discussion

The present study found that leukoaraiosis was an independent predictor of adverse stroke outcome and chest infection after acute brain infarct. No significant associations were observed between lacunes and clinical outcome or complications. In addition, high NIHSS at admission and advanced age were independent predictors of adverse outcome and chest infection.

The predictive ability for stroke outcomes by leukoaraiosis was independent of age, neurologic deficit, concomitant diseases, and stroke subtype, which is consistent with an earlier study reporting that leukoaraiosis was associated with morbidity and pneumonia in hospitalized veterans [15]. Both leukoaraiosis and stroke had high prevalence in elderly subjects, and abundant evidence has indicated a close association between leukoaraiosis and stroke. Several studies have shown that the presence of leukoaraiosis was a predictor of stroke, particularly lacunar infarction [16, 17]. Although leukoaraiosis has a high incidence in stroke patients [18], the effect of preexisting leukoaraiosis and lacunes on stroke outcome and complications remains undetermined. Several studies have shown that leukoaraiosis is an adverse

predictor of outcome for stroke patients [10], whereas contrasting results have been reported in other studies [11]. The presented study confirmed the association between leukoaraiosis and adverse stroke outcome, providing further evidence for the prognostic significance of leukoaraiosis.

Complications are frequently observed in patients with acute ischemic stroke and threaten patient survival and successful rehabilitation. Chest infection was one of the most prevalent complications after stroke and was associated with poor outcomes [19]. Greater stroke severity, older age, male gender, history of diabetes and stroke subtype were risk factors for chest infection [19]. However, the significance of leukoaraiosis and lacunes for chest infection after acute ischemic stroke has been rarely studied. In the present study, leukoaraiosis was a predictor of chest infection in acute stroke patients. The relationship between leukoaraiosis and chest infection of acute stroke patients may be mediated by multiple factors, such as inflammatory response [20] and dysphagia [21]. Susceptibility to chest infections may cause the poor outcomes observed in stroke patients with leukoaraiosis. In addition, the cognitive impairment and poor functional ability of leukoaraiosis patients may impede their rehabilitation, and the tendency for infarct growth may contribute to illness deterioration [22].

Because of the risk of adverse outcomes and chest infections, patients with both leukoaraiosis and acute ischemic stroke may require extra care. However, there is still no definitive effective treatment for leukoaraiosis to date. In a multi-center, double-blind trial, antihypertensive therapy delayed the progression of leukoaraiosis in patients with cerebrovascular disease [23]. Currently, the active management of risk factors may be important for patients with leukoaraiosis to improve clinical outcome.

In accordance with previous reports [24], a strong association between leukoaraiosis and lacunes was found in the present study. This finding is unsurprising because leukoaraiosis and lacunes share similar pathologic bases of small vessel diseases. Extensive evidence has demonstrated that both leukoaraiosis and lacunes are closely associated with age, hypertension and cognitive deficit [6]. Furthermore, both conditions were also strongly associated with stroke recurrence. Therefore, the fact that lacunes were not significantly associated with stroke outcome or complications was somewhat unexpected. The different effects on stroke outcome and complications incidence may reflect the heterogeneity of lacunes and leukoaraiosis. Different effects of lacunes and leukoaraiosis on depressive symptoms have also been observed in previous studies [25]. However, it is difficult to discuss the mechanisms of such a difference with the current findings, and further research on the heterogeneity of leukoaraiosis and lacunes is needed.

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Disclosure of conflict of interest

None.

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