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【 ORIGINAL ARTICLE 】

Predictors of Stroke Events in Patients with Transient Ischemic Attack Attributable to Intracranial Stenotic Lesions

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Abstract:

Objective The purpose of this study was to identify the predictors of subsequent ischemic stroke events in patients with transient ischemic attack (TIA) attributable to intracranial arterial occlusive lesions.

Methods The study population included 82 patients (55 men; mean age, 69.3±12.1 years) with TIA caused by intracranial arterial occlusive lesions who were admitted to our stroke care unit within 48 h of the onset of a TIA between April 2008 and November 2015. TIA was diagnosed if focal neurological symptoms ascribable to a vascular etiology lasted less than 24 h, irrespective of the presence of ischemic insults on imaging. The primary endpoint was an ischemic stroke event within 90 days of the onset of a TIA.

Results The 90-day risk of ischemic stroke after the onset of a TIA was 14.6% [95% confidence interval (CI): 8.6-23.9%]. Cox proportional hazards multivariate analyses revealed that diffusion-weighted imaging (DWI) positivity [hazard ratio (HR), 8.73; 95%CI, 2.20-41.59; p=0.002], prior ischemic stroke (HR, 4.03; 95%CI, 1.07-15.99; p=0.040), and a high serum level of alkaline phosphatase (ALP) on admission (HR, 1.15; 95%CI, 1.05-1.26; p=0.002, for every +10 U/L) were significant independent predictors of ischemic stroke within 90 days after the onset of a TIA.

Conclusion Our results suggested that patients with a TIA attributable to intracranial artery disease who showed DWI lesions, prior ischemic stroke, or high serum levels of ALP on admission were at high risk of subsequent ischemic stroke events.

Key words: transient ischemic attack, intracranial artery, stenosis

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Introduction

Transient ischemic attack (TIA) is a medical emergency associated with a high risk of early ischemic stroke. Previous studies have demonstrated that occlusive lesions of the carotid or intracranial artery are related to subsequent stroke after a TIA (1-8). The TIAregistry.org project - an international, prospective, observational registry - recently showed that large-artery atherosclerosis was associated with the risk of recurrent stroke within 1 year after a TIA or minor stroke (9).

The distribution of atherosclerotic lesions in the cervicocephalic vascular systems is well known to vary among different ethnic groups. In Caucasians, atherosclerosis develops more frequently in the extracranial carotid arteries, whereas intracranial atherosclerosis is the most common cause of stroke in Asians (10-12). Several therapeutic strategies, including antiplatelet therapy, statin use, carotid endarterectomy, and carotid artery stenting, have been proven to reduce the risk of recurrent stroke in patients with symptomatic extracranial carotid stenosis (13). In contrast, patients with symptomatic intracranial artery stenosis are still at high risk of stroke recurrence, despite medical therapy

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(including antiplatelet therapy) and risk factor modification (14).

We have previously reported that among our patients with TIA due to large-artery disease, the incidence of intracranial artery occlusive lesions was higher and patients with intracranial artery occlusive lesions were at higher risk of early ischemic stroke in comparison to patients with occlusive lesions of the extracranial carotid artery (15). Although the identification of the high risk of subsequent ischemic stroke in TIA patients with intracranial artery disease is clinically important, the data on this issue are limited. The purpose of this study was to determine the predictors of subsequent ischemic stroke after a TIA attributable to intracranial arterial occlusive lesions.

Materials and Methods

Patient selection

The study population included 82 patients (55 men; mean age, 69.3±12.1 years) with TIA caused by intracranial arterial occlusive lesions who were admitted to our stroke care unit within 48 h of the onset of a TIA between April 2008 and November 2015. An attending physician experienced in stroke medical care made the ultimate diagnosis of TIA and was responsible for the management decisions. TIA was diagnosed if focal neurological symptoms ascribable to a vascular etiology lasted less than 24 h, irrespective of the presence of ischemic insults on imaging. Patients who received intravenous thrombolysis or acute catheter interventions were excluded from the study.

In this study, a significant occlusive lesion was defined by the presence of ≥50% stenosis or occlusion of the intracranial arteries, as detected by magnetic resonance angiography (MRA) and/or digital-subtraction angiography (DSA). The intracranial arteries included the internal carotid artery, middle cerebral artery, anterior cerebral artery, vertebral artery, basilar artery and posterior cerebral artery. Patients who were diagnosed with cervicocephalic artery disease, other than atherosclerosis (including dissection and cerebral angiitis), and patients with potential sources of cardioembolism, such as atrial fibrillation, were excluded from the present study. The ethics committee of the hospital approved the protocol of the present study.

Patient characteristics

The following demographic and clinical characteristics of the patients were obtained from a review of our stroke database and medical records: sex, age, prior ischemic stroke, prior ischemic heart disease, hypertension (blood pressure ≥140/90 mmHg or the use of antihypertensive medications), diabetes mellitus (fasting blood glucose ≥126 mg/dL, a positive 75-g oral glucose tolerance test result, or the use of insulin or oral hypoglycemic agents), and dyslipidemia [serum low-density lipoprotein cholesterol (LDL-Chol) ≥140 mg/dL, high-density lipoprotein cholesterol (HDL-Chol) <40 mg/dL, triglycerides (TG) ≥150 mg/dL, or the use of antidyslipidemic medications], and current smoking and drinking habits. Multiple TIA was defined as the occurrence of at least two TIAs (the qualifying TIA and another TIA) in the 90 days preceding the qualifying TIA. We also calculated the $ABCD^2$ score of each patient (16).

Blood tests

Peripheral venous blood samples were obtained on admission. The tests included the measurements of the white blood cell count, hemoglobin, hematocrit, platelets, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, alkaline phosphatase (ALP), creatinine, total cholesterol (T-Chol), LDL-Chol, HDL-Chol, TG, glucose, high-sensitivity C-reactive protein, and fibrinogen.

Imaging

We used the results of diffusion-weighted imaging (DWI) to evaluate whether acute ischemic lesions were present on admission. The intracranial arteries were estimated by MRA and/or DSA. The degree of occlusive lesions was classified into three grades: moderate (50-69% stenosis), severe (70-99% stenosis), and occlusion. DSA data were used whenever available. The degree of intracranial artery stenosis was estimated according to the Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial (17, 18). The grade of intracranial artery stenosis on MRA was identified according to a previously published method (10, 12, 19).

Clinical outcomes

All 82 patients underwent a follow-up examination at 90 days via a direct clinical visit or telephone interview. The outcome measure was the occurrence of ischemic stroke within 90 days of the onset of the TIA. Ischemic stroke was defined by a focal neurological deficit lasting for more than 24 h. Treatments with oral agents (including aspirin, dual antiplatelet therapy, anticoagulant agents, and statins) after the qualifying TIA event were recorded.

Statistical analysis

All of the analyses were performed using the JMP® 10 software program (SAS Institute, Cary, USA). Continuous variables are expressed as the mean (standard deviation (age, blood pressure on admission, and blood test findings), and as the median and interquartile range ($ABCD^2$ score). Categorical data are expressed as percentages. Differences between groups were analyzed using Student's t test and the Mann-Whitney U test for continuous values and Pearson's chi-squared test and Fisher's exact test for categorical variables, as appropriate. The risk of ischemic stroke after the onset of a TIA was estimated from Kaplan-Meier event-free survival curves. Cox proportional hazards multivariate analyses were performed to identify the predictors of ischemic stroke within 90 days after the onset of a TIA. Sex, age, and variables that showed a p value of <0.10 in a univariate analysis were included in the multivariate analyses. p values

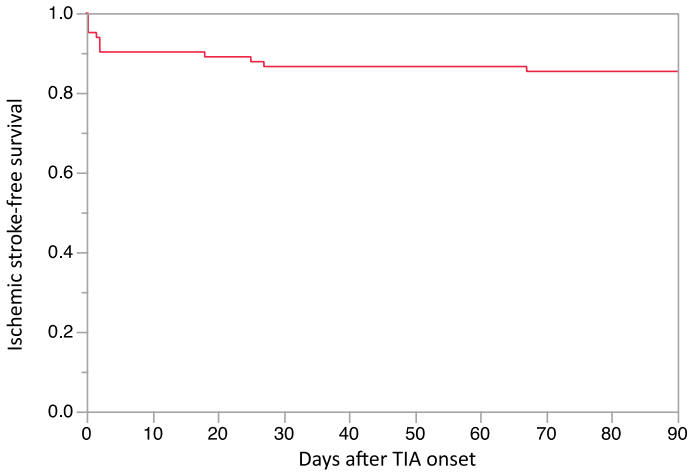

Figure 1. **Kaplan-Meier curves for ischemic stroke-free survival after a TIA. TIA: transient ischemic attack**

of <0.05 were considered to indicate statistical significance. In the case of blood test findings that showed statistical significance, thresholds were calculated by constructing receiver operating characteristic (ROC) curves.

Results

Fig. 1 shows the Kaplan-Meier ischemic stroke-free survival curves. Twelve patients showed subsequent ischemic stroke within 90 days after the onset of a TIA, and ischemic stroke occurred within 2 days after the onset of the TIA in 8 of these 12 patients. The 90-day risk of ischemic stroke after the onset of a TIA was 14.6% [95% confidence interval (CI): 8.6-23.9%]. All 12 infarcts were found in the territory of arteries with occlusive lesions responsible for the neurological symptoms of the qualifying TIA. Cerebral infarctions were detected in the carotid system of 9 patients and in the vertebrobasilar system of 3 patients.

The characteristics of patients with and without ischemic stroke within 90 days after the onset of a TIA are shown in Table 1. Patients with ischemic stroke within 90 days more frequently showed DWI lesions (p=0.0388) and the frequency of prior ischemic stroke among these patients tended to be higher (p=0.0876) in comparison to patients without ischemic stroke. The serum ALP levels on admission of patients with ischemic stroke were significantly higher than those of patients without ischemic stroke (p=0.0020). Fig. 2 shows a comparison of the serum ALP levels on admission of the patients with and without ischemic stroke events after a TIA. The threshold ALP level, calculated by constructing ROC curves, was 292 U/L (area under the curve, 0.76; sensitivity, 58%; specificity, 87%). Table 2 shows the results of the Cox proportional hazards multivariate analyses to identify the predictors of ischemic stroke within 90 days after the onset of a TIA. We used two models: Model 1 included ALP levels for every 10 U/L and Model 2 included ALP levels of ≥292 U/L as variables. Prior ischemic stroke [hazard ratio (HR), 4.37; 95%CI, 1.15-17.31; p=0.030], serum ALP ≥292 U/L on admission (HR, 6.77; 95%CI, 2.10-23.53; p=0.002), and DWI positivity (HR, 7.04; 95%CI, 1.79-31.72; p=0.005) were found to be significant independent predictors of ischemic stroke events.

Discussion

The present study demonstrated that the 90-day risk of subsequent ischemic stroke after a TIA attributable to intracranial artery disease was 14.6%. In the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial of high-risk patients with acute TIA or minor stroke, the 90-day stroke risk was 12.5% in patients with intracranial arterial stenosis, while that in patients without intracranial arterial stenosis was 5.4% (14). The results of both our study and the CHANCE trial showed that the risk of recurrent stroke was quite high in patients with TIA or minor stroke who showed symptomatic intracranial artery disease.

This is the first study to find an association between increased serum ALP levels and subsequent ischemic stroke in TIA patients with symptomatic intracranial artery disease. Recent epidemiological studies have demonstrated that ALP elevation was associated with the presence of atherosclerosis in the coronary and peripheral arteries, increased cardiovascular events, and mortality (20, 21). In relation to stroke, a high serum ALP level was associated with the functional outcome and mortality after acute stroke (22, 23). Such findings suggest that increased serum ALP levels may play a pathophysiological role in the development of atherosclerotic vascular disease of the heart and brain (24). ALP might enhance medial calcification and vessel stiffening, and might thus promote atherosclerosis. ALP is also considered to represent a surrogate marker of systemic inflammation, malnutrition, and metabolic syndrome, which may lead to worse clinical outcomes in patients with stroke (22). It is noteworthy that ALP has been shown to be strongly induced by oxidative stress in vascular tissue and bone (25). An autopsy

Table 1. The Characteristics of the Patients with and without Ischemic Stroke within 90 Days after the Onset of a TIA.

	Ischemic stroke within 90 days		
	With (n=12)	Without(n=70)	p
Background characteristics			
Male, n (%)	10 (83.3)	45 (64.3)	0.1945
Age, years, mean (SD)	70.7 (10.5)	69.1 (12.4)	0.6521
History of			
Ischemic stroke, n (%)	6 (50.0)	18 (25.7)	0.0876
Ischemic heart disease, n (%)	0 (0.0)	8 (11.4)	0.2177
Hypertension, n (%)	8 (66.7)	58 (82.9)	0.1910
Diabetes mellitus, n (%)	4 (33.3)	19 (27.1)	0.6592
Dyslipidemia, n (%)	5 (41.7)	41 (58.6)	0.2756
Multiple TIA, n (%)	3 (25.0)	26 (37.1)	0.4163
Current smoking, n (%)	7 (58.3)	30 (42.9)	0.2438
Current drinking, n (%)	7 (58.3)	30 (42.9)	0.3195
Premorbid antiplatelet agents, n (%)	4 (33.3)	27 (38.6)	0.7295
$ABCD^2$ score			
SBP on admission, mmHg, mean (SD)	157.5 (34.0)	162.0 (23.6)	0.6777
DBP on admission, mmHg, mean (SD)	93.1 (18.8)	88.8 (22.9)	0.5095
Clinical features			0.2292
Unilateral weakness, n (%)	10 (83.3)	48 (68.6)	
Speech disturbance without weakness, n (%)	2 (16.7)	8 (11.4)	
Duration of symptoms			0.6420
≥60 min, n (%)	3 (25.0)	19 (27.1)	
10-59 min, n (%)	8 (66.7)	36 (51.4)	
$ABCD^2$ score, median [IQR]	5 [4, 5.25]	5 [4, 5]	0.3206
Blood test findings, mean (SD)			
White blood cell, $\times 10^3/\mu L$	8.2 (3.0)	7.1 (2.5)	0.2568
Hemoglobin, g/dL	14.4 (2.0)	13.4 (1.8)	0.1206
Hematocrit, %	43.0 (6.5)	39.8 (4.9)	0.1235
Platelets, $\times 10^3/\mu L$	232.8 (129.5)	223.2 (62.3)	0.8056
Albumin, g/dL	4.3 (0.4)	4.2 (0.5)	0.4878
Aspartate aminotransferase, U/L	25.5 (6.9)	23.8 (9.3)	0.4553
Alanine aminotransferase, U/L	22.1 (10.9)	18.5 (10.3)	0.3004
γ-glutamyl transpeptidase, U/L	33.4 (15.8)	42.2 (74.5)	0.3813
Lactate dehydrogenase, U/L	246.2 (86.5)	223.9 (76.1)	0.4161
Alkaline phosphatase (ALP), U/L	283.7 (67.8)	223.1 (59.2)	0.0020
Creatinine, mg/dL	0.96 (0.43)	0.91 (0.41)	0.7124
Total cholesterol, mg/dL	202.1 (53.7)	194.9 (39.4)	0.6656
LDL-cholesterol, mg/dL	126.3 (40.7)	116.5 (37.5)	0.4517
HDL-cholesterol, mg/dL	45.9 (10.9)	51.4 (15.7)	0.1527
Triglyceride, mg/dL	169.1 (136.1)	157.6 (141.0)	0.7822
Glucose, mg/dL	144.9 (58.2)	127.3 (36.2)	0.3305
Hemoglobin A1c, %	6.6 (2.0)	6.1 (0.8)	0.4085
hsCRP, mg/dL median [IQR]	0.04 [0.0225, 0.14]	0.07 [0.03, 0.19]	0.2776
Fibrinogen, mg/dL	305.5 (61.0)	327.4 (74.9)	0.3018
D-dimer, ng/mL median [IQR]	0.9 [0.525, 1.4]	0.8 [0.5, 1.5]	0.9155
Imaging findings			
Grade of occlusive lesions			0.7290
Moderate, n (%)	3 (25.0)	25 (35.7)	
Severe, n (%)	7 (58.3)	37 (52.9)	
Occluded, n (%)	2 (16.7)	8 (11.4)	
DWI lesions, n (%)	7 (58.3)	18 (25.7)	0.0388
Acute treatment with oral agents			
Aspirin, n (%)	11 (91.7)	63 (90.0)	0.8573
Dual antiplatelet therapy, n (%)	3 (25.0)	37 (52.9)	0.1172
Anticoagulant, n (%)	0 (0.0)	0 (0.0)	
Statin, n (%)	6 (50.0)	45 (64.3)	0.3457

TIA: transient ischemic attack, SD: standard deviation, SBP: systolic blood pressure, DBP: diastolic blood pressure, IQR: interquartile range, LDL: low-density lipoprotein, HDL: high-density lipoprotein, hsCRP: high-sensitivity C-reactive protein, DWI: diffusion-weighted imaging

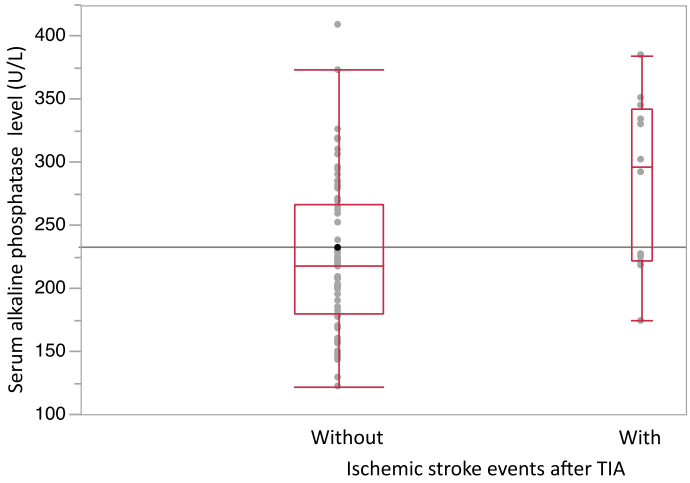

Figure 2. **The serum alkaline phosphatase levels on admission in patients with and without ischemic stroke events within 90 days after the onset of a TIA. Boxes represent the interquartile range. Lines in boxes indicate the median values. Whiskers represent the 10th and 90th percentile values. TIA: transient ischemic attack**

Table 2. **The Results of the Cox Proportional Hazard Multivariate Analyses of Variables Associated with Ischemic Stroke within 90 Days after the Onset of a TIA.**

	Model 1			Model 2		
	HR	95%CI	p	HR	95%CI	p
Male	1.47	0.34-10.20	0.634	1.37	0.32-9.37	0.690
Age (for every 10 years)	1.15	0.64-2.82	0.473	1.25	0.62-2.65	0.535
Prior ischemic stroke	4.03	1.07-15.99	0.040	4.37	1.15-17.31	0.030
ALP (for every +10 U/L)	1.15	1.05-1.26	0.002			
ALP ≥292 U/L				6.77	2.10-23.53	0.002
DWI positivity	8.73	2.20-41.59	0.002	7.04	1.79-31.72	0.005

TIA: transient ischemic attack, HR: hazard ratio, CI: confidence interval, ALP: alkaline phosphatase, DWI: diffusion-weighted imaging

study revealed that intracranial arteries were susceptible to oxidative stress and predisposed to respond with accelerated atherogenesis when antioxidant protection was decreased (26). The results of our study may indicate that an increased serum ALP level is a surrogate marker for vulnerability to symptomatic intracranial artery disease in patients with TIA. In contrast to our findings, however, two previous studies found that an increased serum level of ALP was not associated with the presence or severity of intracranial arterial stenosis (22, 24). Larger studies are needed to confirm our findings.

DWI positivity is a well-known predictor of ischemic stroke after TIA. In the WASID trial, which enrolled patients who had experienced a TIA or nondisabling stroke within the preceding 3 months and who showed 50-99% stenosis of a corresponding major intracranial artery on angiography, the presence of cerebral infarction on baseline neuroimaging was the only statistically significant predictor of a higher risk of early stroke (18). The results of our study confirmed DWI positivity as a predictor of subsequent stroke in TIA patients with symptomatic intracranial artery disease.

We found that prior ischemic stroke was a significant independent predictor of ischemic stroke after TIA. Kernan et al. reported that prior stroke was a predictor of recurrent stroke after a TIA or stroke (27). In the PROMAPA study-a multicenter prospective TIA registry operating from 30 Spanish centers-prior stroke and coronary heart disease were independent predictors of late (from 7 days to 1 year after the onset of a TIA) recurrent stroke after a TIA (28).

Our study is associated with several limitations. First, the sample size was too small to avoid type 1 and 2 errors. Second, we only analyzed inpatients with TIA using a retrospective design, which might have led to a selection bias. However, most TIA patients were hospitalized for urgent work-up and treatment in our unit if they presented to the hospital within 48 h after the onset of a TIA. Thus, our study patients were essentially consecutive cases. Finally, this study was conducted in a single center. These findings should be confirmed in a large multicenter setting to determine if they can be generalized.

In conclusion, our results suggested that patients with TIA attributable to intracranial artery disease who had DWI lesions, prior ischemic stroke, and a high serum level of ALP on admission were at high risk of subsequent ischemic

stroke events.

The authors state that they have no Conflict of Interest (COI).

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