Prediction of Worse Outcome by Systemic Atherosclerosis Following Acute Ischemic Stroke

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Abstract-

Objective: To determine the relationship between atherosclerosis and the short-term outcome following an acute ischemic stroke.

Methods: Quantitative measurements of ankle brachial index (ABI), color-coded carotid duplex (CCD), electrocardiography (ECG), and other cardiovascular risk factors were performed for acute ischemic stroke patients. Prevalent cardiovascular disease (PCVD) was defined when there were evident abnormal findings of ABI, CCD, or ECG.

Results: Among the 68 patients, there were 19 with PCVD, 12 with abnormal ABI, 8 with abnormal CCD, and 4 with abnormal ECG. Patients with PCVD had worse Barthel index (BI) at discharge and BI difference between admission and discharge if compared to those with non-PCVD ($P < 0.05$).

Conclusions: Ankle brachial index, CCD and ECG may serve as convenient quantitative parameters of atherosclerosis. Patients with evident systemic atherosclerosis may have greater vascular burden, resulting in worse short-term functional outcome after acute ischemic stroke.

Key Words: Atherosclerosis, Ankle brachial index, Acute ischemic stroke, Outcome

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INTRODUCTION

Being a manifestation of systemic atherosclerosis, peripheral artery disease (PAD) may still be underdiagnosed in primary care practice[1]. Most studies on stroke have addressed incidence and risk factors[2-5]. Only few have focused on prognosis and outcome[6,7]. Ankle brachial index (ABI), a marker of PAD or systemic atherosclerosis, is valuable in the prediction of the incidence of cardiovascular events[8-12]. Recent studies have established a strong correlation between ischemic stroke and low ABI[8,9,13]. However, the relationship between ABI and the prognosis of ischemic stroke is still unknown. The measurements of ABI, color-coded carotid duplex (CCD) and electrocardiography (ECG) are non-invasive and thus are convenient tools for the

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detection of atherosclerosis[13]. A hospital-based investigation was conducted to analyze the relationship between atherosclerosis and the outcome following acute ischemic stroke.

MATERIALS AND METHODS

We prospectively recruited patients who were admitted within three days under the diagnosis of acute ischemic stroke to Chang Gung Memorial Hospital, Linkou, Taiwan, for a period of three months. The diagnosis of ischemic stroke was established by clinical features, and brain computed tomography or magnetic resonance imaging. Clinical and laboratory information, including ABI, CCD, and ECG were collected. Patients with age ≤ 40 years or ABI ≥ 1.5 were excluded. Sixty-eight consecutive eligible patients were enrolled in this study.

The clinical features and risk factors of stroke were determined by reviewing medical records in detail. Risk factors, including hypertension, diabetes mellitus, hyperlipidemia, heart diseases, previous strokes, smoking and alcoholism, were recorded[4]. Both at admission and at discharge, National Institutes of Health stroke scale (NIHSS)[14] and Barthel index (BI)[15] were measured to evaluate the neurological deficits and the functional status of these patients, respectively.

ECG findings such as depression in the S-T segment, T wave inversion or Q wave were interpreted by cardiologists. A trained member of the medical staff measured ABI. As a description of the severity and the spreading distribution of carotid atherosclerosis, plaque score ≥ 3 on the CCD was defined as significant carotid arterial stenosis[12,16]. Patients were classified as prevalent cardiovascular disease (PCVD) if they had one or more of the following conditions: (1) ABI ≤ 0.9, (2) ischemic heart disease or abnormal ECG, and (3) plaque score ≥ 3 on the CCD[12,17]. To analyze the characteristics of atherosclerosis in these patients, we subgrouped them in two different ways. The patients were classified by the presence or absence of PCVD in Table 1. The same 68 patients were also classified by the presence or absence of PAD in Table 2.

Table 1. *Risk factors in patients with and without prevalent cardiovascular diseases (PCVD) following acute ischemic stroke*

N (%)	PCVD, N=19	Non-PCVD, N=49	Odds raito (95% CI)
Male	8 (42)	23 (47)	0.82 (0.28 - 2.40)
Age ≥65 years	17 (89)	24 (49)	8.85 (1.84 - 42.50)#
Hypertension	18 (95)	32 (65)	9.66 (1.10 - 84.58)*
Diabetes mellitus	10 (53)	18 (37)	1.91 (0.66 - 5.59)
Old stroke	10 (53)	16 (33)	2.29 (0.78 - 6.75)
Heart disease	8 (42)	10 (20)	2.83 (0.90 - 8.92)
Smoking	4 (21)	14 (29)	0.67 (0.19 - 2.36)
Alcoholism**	2 (11)	5 (10)	1.04 (0.18 - 5.86)
Hyperlipidemia	11 (58)	19 (39)	2.17 (0.74 - 6.37)

# $P<0.05$ after adjustment for sex; * $P<0.05$ after adjustment for age and sex; ** Inference from Fisher's exact test.
CI: confidence interval; N: case number.

Table 2. *Risk factors in patients with and without peripheral artery diseases (PAD) following acute ischemic stroke*

N (%)	PAD, N=12	Non-PAD, N=56	Odds Raito (95% CI)
Male	4 (33)	27 (48)	0.53 (0.14 - 1.99)
Age ≥ 65**	11 (92)	30 (54)	9.53 (1.15 - 78.90)*
Hypertension**	11 (92)	39 (70)	4.79 (0.57 - 40.14)
Diabetes mellitus**	8 (67)	20 (36)	3.60 (0.96 - 13.46)
Old stroke**	7 (58)	19 (34)	2.73 (0.76 - 9.75)
Heart Disease**	4 (33)	14 (25)	1.50 (0.39 - 5.75)
Smoking**	3 (25)	15 (27)	0.91 (0.22 - 3.82)
Alcoholism**	1 (8)	6 (11)	0.75 (0.09 - 6.94)
Hyperlipidemia**	7 (58)	23 (41)	2.00 (0.57 - 7.12)

* $P <0.05$ after adjustment for sex; ** Inference from Fisher's exact test.
CI: confidence interval; N: case number.

Ankle brachial index

A 5 MHz Doppler device (Elite-100R, Nicolet Vascular Inc, Golden, Colo) was used to measure ABI. Systolic blood pressure was recorded at the brachial, the dorsal pedal, and the posterior tibial arteries on both sides in supine position in each subject. The ABI of each leg was calculated by the ratio between the higher of the two ankle systolic pressures in that leg by the brachial systolic pressure. The subject was considered to have

PAD if the ABI of either leg was ≤ 0.90[8]. The sensitivity of ABI is 95%, and the specificity is almost 100% for an angiographically defined stenosis of at least 50% in a major leg artery[18].

Carotid ultrasound

Color flow imaging with ATL (Bothell, Wash) HDI 3000 was used to evaluate the extent and severity of carotid atherosclerosis in each patient. The plaque scoring system is modified from that of Sutton et al[18]. The examination sites included the proximal (≥ 20 mm proximal to bulb bifurcation) and distal (< 20 mm proximal to bulb bifurcation) common carotid arteries, carotid bulb bifurcations, internal carotid arteries, and external carotid arteries bilaterally. Each chosen segment was graded as the following: grade 0, normal; grade 1, a diameter stenosis < 30%; grade 2, 30% to 49% stenosis; grade 3, 50% to 99% stenosis; grade 4, 100% occlusion. The plaque score was the sum of plaque grades in each segment of the carotid arteries. Duplex sonographic criteria for the examination of the carotid artery were detailed in another report[19]. The overall accuracy of the diagnosis of occlusive carotid artery disease exceeded 90% at our neurosonology laboratory. All of the duplex scans were conducted by an experienced ultrasonographer and the results were interpreted by the same neurologist, who didn't know the patients' underlying conditions.

Statistical methods

SAS version 9.0 programs (SAS Institute Inc., New York, USA) were used for statistical analyses. The effects of risk factors on the presence or absence of PCVD and PAD were analyzed using the chi-square test or Fisher's exact test if the sample was small. Multiple logistic regression was adopted to adjust for age and sex. The outcome of acute ischemic stroke was measured by NIHSS and BI. The comparisons of length of hospital stay, NIHSS, and BI between patients with or without PCVD and PAD were analyzed with Wilcoxon rank sum test. Multiple linear regression was performed to examine whether the association between atherosclerosis (measured by PCVD and PAD) and stroke outcome (measured by NIHSS and BI) was independent of other risk factors, including age, sex, hypertension, diabetes mellitus, previous strokes, ischemic heart diseases, and hyperlipidemia. In addition, the initial disability and the length of hospital stay were also taken into consideration when referring to the effects of PCVD and PAD on the neurological and functional status at discharge and improvement capacity. P values < 0.05 were regarded as significant.

RESULTS

Among the 68 consecutive ischemic stroke inpatients, 19 (28%) were regarded to have PCVD for the presence of at least one positive atherosclerotic result in the ABI, CCD and ECG examinations. Out of the 19 patients, abnormal ABI was observed in 12 patients, abnormal CCD in 8, and abnormal ECG in 4. The mean age was 66.3±12.1 years. The incidence of age ≥ 65 years ($P < 0.01$, odds ratio = 8.85) and hypertension ($P = 0.04$, odds ratio = 9.66) were statistically significant higher in patients with PCVD after adjustments for age or sex (Table 1). Patients with abnormal ABI tended to be older ($P = 0.04$, odds ratio = 9.53) (Table 2).

In Table 3, the length of hospital stay, the values of NIHSS and BI at admission as well as at discharge, and the difference between these two values (the admission-discharge difference) were compared between patients with or without PCVD and PAD by Wilcoxon rank sum test. No statistical significance was observed in the length of hospital stay and NIHSS scores. The patients with PCVD had lower BI scores both at admission and at discharge, and a smaller admission-discharge BI score difference than the patients with non-PCVD. Similar results were also noted in the comparison between PAD and non-PAD patients. With multiple linear regression after adjustment for the initial functional status at admission, the length of hospital stay, age, sex, and other major stroke risk factors, the BI at discharge and the BI difference were significantly lower in PCVD patients than in non-PCVD patients (Table 3).

In this study, there were 3 patients with coronary artery disease, 1 with angina pectoris, and 3 with con-

Table 3. *Comparison of the length of hospital stay, National Institute of Health stroke scale (NIHSS) and Barthel index (BI) in patients with and without evidence of atherosclerosis following acute ischemic stroke*

	Systemic Atherosclerosis			Peripheral Atherosclerosis		
	PCVD	Non-PCVD	P-value[#]	PAD	Non-PAD	P-value[#]
Length of hospital stay (N)	19	49		12	56	
days	16 (10-27)	7 (11-20)	0.06	16 (10.5-33)	12.5 (6.5-20.5)	0.08
NIHSS scores (N)	19	49		12	56	
at admission	6 (4-20)	6 (3-8)	0.42	5.5 (2-14)	6 (3-10)	0.99
at discharge	5 (3-15)	4 (2-6)	0.19	4.5 (1.5-11.5)	4 (2.5-7)	0.81
difference	0 (0-2)	1 (0-3)	0.29	1 (0-2)	1 (0-2.5)	0.96
BI scores (N)	18	49		11	56	
at admission	42.5 (20-95)	55 (35-95)	0.28	45 (20-100)	55 (30-90)	0.83
at discharge	52.5 (10-100)	90 (55-100)	0.05*	55 (10-100)	82.5 (50-100)	0.42
difference	0 (0-10)	10 (0-25)	0.03*	0 (0-5)	7.5 (0-25)	0.04

[#] P-value was inferred from Wilcoxon rank sum test. * P-value < 0.05 was inferred from multiple linear regression after adjustment for the BI at admission, length of hospital stay, age, sex, hypertension, diabetes, old stroke, ischemic heart disease, and hyperlipidemia.
The numbers in the cells represent median with the first and third quantiles.
N: Case number; PCVD: prevalent cardiovascular disease; PAD: peripheral artery disease; NIHSS difference: subtraction of NIHSS at discharge from NIHSS at admission; BI difference: subtraction of BI at admission from BI at discharge.

gestive heart failure of New York Heart Association function class II. However, these three cardiac factors didn't show significant association with BI at admission, BI at discharge, and BI difference.

DISCUSSION

An ABI cut-off point of 0.9 or less has been used in clinical practice and epidemiologic studies as an indicator of PAD[20-22]. It has been associated with clinical coronary heart disease, stroke and preclinical carotid plaques[10,12,23]. Atherosclerosis is a systemic disorder and may be implicated by low ABI, coronary heart disease and carotid stenosis on the CCD[10,13]. The relationship between low ABI and cerebral infarction has been confirmed in earlier investigations[8-13]. In outcome studies of cerebral infarction, stroke etiology, initial severity of stroke, age, and onset-admission interval were found to be prognostic factors relevant to functional outcome[7,24-26]. However, knowledge of the relationship between systemic atherosclerosis and prognosis of stroke is limited.

Both NIHSS and BI are widely applied in the assessment of stroke outcome. NIHSS emphasizes the deficits in neurological performance, while BI is designed to evaluate the limitations in the activities of daily living[14,15]. In this work, the functional outcome and improvement following acute ischemic stroke measured by BI are worse in patients with the composites of PCVD. In the stepwise linear regression model used to analyze the effects on the functional outcome, the explanatory variables include the PCVD, the BI at admission, the length of hospital stay, age, sex, hypertension, diabetes mellitus, previous strokes, ischemic heart diseases and hyperlipidemia. Both the PCVD and the BI at admission showed significant adverse effect on the BI at discharge and the BI difference. The neurological deficits and improvement (NIHSS) also tend to be worse in PCVD and PAD groups, although statistical significance was not reached (Table 3). These findings suggest a worse compensatory capacity in patients with evidences of systemic atherosclerosis that may be a vascular burden on the functional outcome and improvement in addition to the initial disability.

Despite the systemic atherosclerotic vascular burdens, the subtypes of cerebral infarctions are also an important predictor of stroke outcome. For example, cardioembolic infarct is associated with the worst short-term prognosis, which may be related to cardiac comorbidities and neurological deficits[27]. In this study, about 10% of cerebral infarction was attributed to cardioembolism, the patients of which had worse BI at admission and at discharge. However, the functional improvement capacity was similar to the other subtypes of stroke (data not shown). The interaction between systemic atherosclerosis or cardioembolism and stroke prognosis should be investigated in further studies.

A similar discordance has been noted in relation to the risk factor of age[28]. Age has been established in prior studies to be an important factor in the determination of stroke outcome[6,7,18,28]. Older patients had a ten times lower response rate to rehabilitation than younger patients[6]. Age also influenced the level of activity of daily living at discharge[28,29]. In this study, the prognostic effect of atherosclerosis on functional improvement is evident following adjustment for age, sex and other cardiovascular risk factors. The reason why the functional improvement is significantly better than the neurological improvement under the influence of atherosclerosis remains unknown. The implication from our study is that the decrease of the atherosclerotic load may be helpful for the functional outcome after acute stroke, and the hypothesis remains to be confirmed by further studies.

Ankle brachial index is related to age and sex, as well as to a history of hypertension, diabetes mellitus and smoking[23]. In this study, age and hypertension were significantly associated with atherosclerosis (Tables 1 and 2). Other risk factors, including diabetes mellitus, coronary heart diseases, previous strokes and hyperlipidemia, also had relatively high odds ratios for atherosclerosis, although statistical significance is not reached. Increase of the sample size might strengthen the statistic significance.

This study had some limitations. It was conducted in a tertiary medical care center. The selection of patients was therefore biased toward more severe neurological impairment, diminishing the possible effect of atherosclerosis on stroke recovery. The mean observational time of the patients was around one month, when the improvement on neurological deficits in acute stroke patients may have not been well established. Although we have considered the major atherosclerotic risk factors, there may still be other factors that may affect the stroke prognosis in clinical practice. In addition, the study must be considered to be a pilot study given that the number of enrolled patients was relatively small, and this may result in false-positive or false-negative predictor variables. Further large-scale studies thus are necessary to elucidate the effects of systemic atherosclerosis on short-term and long-term outcomes following acute ischemic stroke.

CONCLUSIONS

Ankle brachial index, CCD and ECG are low-cost, simple and non-invasive examinations, and may be used to evaluate atherosclerosis quantitatively[13]. Patients with systemic atherosclerosis, especially PAD, have worse short-term outcome after acute ischemic stroke. The relationship between atherosclerosis and long-term outcome following stroke should be further investigated.

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