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Original Article

The Impact of Peripheral Arterial Disease and Acute Ischemic Stroke

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Abstract Peripheral arterial disease (PAD) is associated with coronary artery disease (CAD) and stroke, but data on the relationship between PAD and acute ischemic stroke are lacking. Therefore, we investigated this relationship. A total of 101 patients were enrolled on admission to Harasanshin General Hospital (Fukuoka, Japan) with their first ischemic stroke. All 101 patients underwent cranial CT and/or brain magnetic resonance imaging, duplex ultrasonography of the extracranial carotid arteries, and transthoracic echocardiography.

The subjects were aged 41 to 92 years. PAD was present in 81/101 patients (80.2%), including 57/73 (78.1%) with small artery occlusion, 11/13 (84.6%) with large artery occlusion, and 13/15 (86.7%) with cardiogenic embolism. In 42 of these 81 patients (51.9%), PAD was asymptomatic. Serum apoprotein A1 levels were significantly higher and the intima-media thickness was significantly greater in the patients with PAD than in those without PAD. The modified Rankin scale score was significantly higher on admission in patients with PAD than in those without PAD. Stepwise logistic regression analysis revealed that the apoprotein A1 level and the modified Rankin scale score on admission were strongly associated with the occurrence of stroke in patients with PAD.

Our results suggest that PAD is frequently associated with acute ischemic stroke. It may be important to perform screening for PAD in patients who have suffered an ischemic stroke.

Key words : peripheral arterial disease, ischemic stroke, stroke subtypes, carotid atherosclerosis

INTRODUCTION

Atherosclerosis is a highly prevalent disease, and is currently the greatest cause of morbidity and mortality in developed societies. Many risk factors are involved in the occurrence of atherosclerosis, which manifests as coronary artery disease (CAD) and myocardial infarction (MI), including hyperlipidemia, hypertension, smoking, and diabetes mellitus[1]. It is also known that peripheral arterial disease (PAD) is associated with CAD and stoke, but data on the relationship between peripheral arterial disease and acute ischemic stroke are lacking. The pulse wave velocity can be used as an indicator of arterial stiffness[2)3)], and it is regarded as a marker of vascular damage[4)5)]. An instrument was recently developed that can measure the brachial-ankle

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pulse wave velocity (baPWV) by the volume-rendering method. Yamashina et al. have reported a high validity and reproducibility of baPWV measurements, suggesting that this parameter may be an acceptable indicator of vascular damage and may be suitable for screening large populations to detect vascular disease[6].

Recently, arteriosclerotic disease has been increasing in Japan as the population ages and the lifestyle becomes more westernized. The prevalence of arteriosclerosis is therefore anticipated to increase in Japan and the prevalence of PAD is also expected to increase. However, there have been few epidemiological studies on PAD in Japan and even fewer studies on the prevalence of PAD among stroke patients. This is partly because early PAD is asymptomatic and therefore difficult to diagnose and also because distinguishing PAD from other conditions, such as spinal cord disease, is difficult even after PAD symptoms like nocturnal leg pain become evident. PAD not only interferes with daily activities and reduces the quality of life in stroke patients, but also worsens their survival. PAD is associated with the occurrence of coronary artery disease and cerebrovascular disease[7] Therefore, PAD should be detected and treated as early as possible.

We performed the present prospective study to investigate whether PAD was an independent risk factor for acute ischemic stroke in Japanese patients.

METHODS

Subjects

All of the patients with acute ischemic stroke admitted to the Division of General Medicine at Harasanshin General Hospital (Fukuoka, Japan) during the period from August 1, 2003 to July 31, 2004 were eligible for the present study. As a result, a total of 101 patients who suffered their first ischemic stroke were registered for this study after meeting the following criteria: (a) first ischemic stroke, (b) admission to hospital for treatment, and (c) admission within 72 hours of the onset.

Categorization of Stroke

Stroke was defined according to World Health Organization criteria[8]. Cerebral infarction was diagnosed on the basis of the initial CT and MRI data. All patients underwent ultrasonography of the neck and intracranial arteries. The carotid arteries were assessed by color flow B-mode Doppler ultrasound (SONOS 5500, PHILIP) according to the standard method[9][10]. The vertebrobasilar system was evaluated by radionucleotide angiography to determine the presence/absence of atherosclerotic lesions. Patients without clinical or imaging evidence of atherosclerosis who had atrial fibrillation and/or echocardiographic findings suggestive of possible cardiogenic embolism were classified as having thromboembolic stroke. The other patients were diagnosed as having large artery stroke if there was $>50\%$ stenosis of the extracranial carotid artery or an intracranial artery, or as having small artery occlusion if they had a clinical lacunar syndrome associated with appropriate CT changes or a typical clinical syndrome despite normal CT scans. Patients were classified as having undefined stroke if they did not fit any of these categories[11]. Functional outcome was measured using the modified Rankin Scale[12]. During hospitalization, neurological evaluation was always done by a single neurologist who applied the study criteria for classification of the patients. All evaluations were performed at the

Department of Neuroradiology.

Laboratory Tests

All blood samples were stored at -80(C and were analyzed simultaneously by technicians who were unaware of the clinical data of the patients.

Brachial-Ankle Pulse Wave Velocity (baPWV)

The baPWV was measured using a volume plethymograph (PWV/ABI; Colin, Co., Ltd., Komaki, Japan), which simultaneously recorded the PWV, blood pressure, electrocardiogram, and heart sounds[6]. Each subject was examined in the supine position, with the electrocardiographic leads on both wrists, a microphone for detecting heart sounds taped at the left sternal edge, and cuffs on both arms and ankles. The cuffs were connected to a plethysmograph sensor that determined the pulse volume waveform and to an oscillometric pressure sensor that measured the blood pressure. Pulse volume waveforms were recorded using a semiconductor pressure sensor, with the acquisition frequency set at 1,200 Hz. Waveforms for the arm and ankle were stored in 10-sec batches with automatic gain analysis and quality adjustment. The baPWV data were obtained after the subjects had rested for at least 5 min. The reproducibility of baPWV values obtained in healthy subjects was reported to be reasonable, with an interobserver coefficient of variation of 2.4% (n=15) and an intraobserver coefficient of variation of 5.8% (n=17)[6].

Diagnosis of Peripheral Arterial Disease

PAD was diagnosed as follows: Criterion[1] was severe stenosis or occlusion of a lower extremity artery on MRA and/or no diastolic reverse flow (type II - VI) on lower extremity ultrasonography. Criterion 1 was positive when one of these two factors was detected. Criterion[2] was an ankle-brachial index <0.9, a pulseless artery, and/or symptoms of PAD. Criterion 2 was positive when two of these three factors were detected. PAD was defined as present when both criterion 1 and criterion 2 were positive.

Statistical Analysis

Data were recorded on standard forms and then entered into a database. Results are expressed as percentages or as the mean (standard deviation (SD). A nonparametric test (the Mann-Whitney U test) was used to compare variables between groups. Two-way analysis of variance (ANOVA) was used for comparison of the means of numerical variables between three groups. Multiple comparison with the Kruskal-Wallis test was also employed to compare three groups. The risk of ischemic stroke in patients with PAD was estimated by forward stepwise multiple logistic regression analysis with adjustment for the apoprotein A1 level, carotid intima-media thickness (IMT), and modified Rankin scale score (on admission).

Ethics

The design of this study was approved by the Ethics Committee and the Data Protection Committee of Harasanshin General Hospital (Fukuoka, Japan). Informed consent to participation was obtained from all patients (or their closest relatives).

RESULTS

One hundred and thirty-three patients with stroke were evaluated for enrollment in the study, but 32 patients were excluded because of an unclassified stroke subtype (n=13) or refusal to participate (n=19).

Therefore, 101 patients were investigated.

Characteristics of the Subjects

Table 1 shows the characteristics of the 3 subgroups of stroke patients and their risk factors. The mean age of the small artery occlusion group was significantly higher than that of the patients with cardioembolic stroke. The mean serum triglyceride level of the small artery occlusion group was signifi-

Table 1-A Characteristics of the Stroke Patients

Risk Factors	Small artery occlusion (n=73)	Large artery atherosclerosis (n=13)	Cardioembolic stroke (n=15)	P value	Multiple comparison
Age [years, mean±SD]	68.9±12.1[a)]	75.6±9.1	79.3±10.2[b)]	0.0035	a) vs b)**
Male sex [%]	51(69.9%)	9(69.2%)	7(46.7%)	0.2172	
Blood pressure					
Systolic [mean±SD, mmHg]	159.2±26.4	172.5±45.9	167.5±27.9	0.4158	
Diastolic [mean±SD, mmHg]	85.3±14.4	87.5±21.4	87.6±13.8	0.7922	
BMI [kg/m²]	22.3±2.7	21.8±2.6	22.9±3.3	0.6084	
Smoking [%]	45(61.6%)	11(84.6%)	12(80.0%)	0.1399	
History:					
Hypertension [%]	67(91.8%)	11(84.6%)	14(93.3%)	0.6679	
Diabetes Mellitus [%]	29(39.7%)	4(330.8%)	2(13.3%)	0.1404	
Hyperlipidemia [%]	60(82.2%)	10(76.9%)	12(80.0%)	0.8972	
PAD [%]	57(78.1%)	11(84.6%)	13(86.7%)	0.5869	

ANOVA ; ** $p<0.01$

Table 1-B Characteristics of the Stroke Patients (contined)

Lipids	Small artery occlusion (n=73)	Large artery atherosclerosis (n=13)	Cardioembolic stroke (n=15)	P value	Multiple comparison
TC [mean±SD, mg/dl]	208.3±46.3	212.6±29.7	196.5±40.3	0.5664	
TG [mean±SD, mg/dl]	113.0±86.3[a)]	100.0±64.5	77.0±60.0[b)]	0.0307	a) vs b)*
HDL-C [mean±SD, mg/dl]	45.5±37.5	43.0±36.0	46.0±36.0	0.8837	
LDL-C [mean±SD, mg/dl]	127.1±106.0	137.0±117.8	138.0±92.2	0.6641	
Lipoprotein(a) [mean±SD, mg/dl]	17.1±10.0	23.3±8.83	12.1±7.7	0.4864	
Apoprotein A1 [mean±SD, md/dl]	124.0±112.0	125.5±103.0	119.0±96.0	0.1736	
Apoptotein B [mean±SD, md/dl]	100.0±84.0	103.5±89.0	103.0±79.0	0.5980	
Apoprotein E [mean±SD, md/dl]	4.364±1.097	4.813±1.092	4.100±0.700	0.3149	
RLP-C [mean±SD, md/dl]	3.3±2.7	4.15±3.3	3.6±2.2	0.2736	

TC; total cholesterol TG; Kruskal-Wallis test; * $p<0.05$
HDL-C; HDL cholesterol, LDL-C; LDL cholesterol
RLP-C; RLP cholesterol

Table 1-C Others Factors

Lipids	Small artery occlusion (n=73)	Large artery atherosclerosis (n=13)	Cardioembolic stroke (n=15)	P value	Multiple comparison
CRP [mean±SD, mg/dl]	0.0±0.0[a)]	0.0±0.0[b)]	1.0±0.3[c)]	0.0004	a) vs c)** b) vs c)*
D-D [mean±SD, μg/dl]	0.6±0.3[d)]	1.2±0.4	3.1±0.98[e)]	0.0001	d) vs e)**
TAT [mean±SD, ng/dl]	2.50±1.75[f)]	2.60±1.65	8.65±3.58[g)]	0.0051	f) vs g)**
IMT [mean±SD, mm]	1.110±0.928	1.310±1.015	1.14±0.95	0.2481	
ABI [mean±SD]	1.14±1.02	1.04±0.8	1.15±1.08	0.1281	
baPWV [mean±SD, mmHg]	1934±1650	1847±131	2405±1896	0.1816	
modified Rankin Scale [mean±SD]					
on admission	3.0±2.0	4.0±2.0	5.0±5.0	0.0001	h) vs i)**
on discharge	1.0±0.0	2.0±1.0	4.0±2.0	0.0001	j) vs k)** j) vs l)**
Admission period [mean±SD, days]	23.0±18.0	23.5±20.0	2405±1896	0.0022	m) vs n)**

ANOVA; ** $p<0.01$ Kruskal-Wallis test; * $p<0.05$

CRP; C reactive protein D-D; D-dimer
TAT; thrombin-antithrombin III complex IMT; intima-media thickness
ABI; ankle brachial index baPWV; brachial-ankle pulse wave velocity,

cantly higher than that of the cardioembolic stroke group, although there were no significant differences among the D-dimer (D-D) three stroke subtypes with respect to the other serum lipids. Serum C reactive protein (CRP) and thrombin-antithrombin III complex (TAT) levels were significantly higher in the cardioembolic stroke patients than in those with small artery occlusion, while serum CRP was significantly higher in the cardioembolic stroke patients than in those with large artery atherosclerosis. The modified Rankin scale values on admission and discharge were significantly higher and the duration of admission was significantly longer in the cardioembolic stroke patients than in those with small artery occlusion.

Association Between PAD and Risk Factors

The associations between PAD and various risk factors are displayed in Table 2. PAD was present in 81 of the 101 stroke patients (80.2%), including 57 out of 73 patients with small artery occlusion, 11 out of 13 with large artery occlusion, and 13 out of 15 with cardiogenic embolism. In 42 of these 81 patients (51.9%), PAD was asymptomatic. When the associations between PAD and various risk factors were assessed, no significant differences of these risk factors were found between the stroke patients with and without PAD.

The serum apoprotein A1 level was significantly higher in the stroke patients with PAD than in those without PAD. However,

Table 2-A Association Between PAD and Risk Factors

Risk Factors	PAD		P value
	positive (n=81)	negative (n=20)	
Age [years, mean±SD]	72.0±11.9	68.6±12.6	0.2585
Male sex [%]	52(64.2%)	15(75.0%)	0.5148
Blood pressure			
Systolic [mean±SD, mmHg]	162.8±30.1	159.8±29.5	0.6925
Diastolic [mean±SD, mmHg]	86.7±15.6	82.7±13.3	0.2970
BMI [kg/m^2]	22.4±2.8	22.0±2.5	0.5521
Smoking [%]	55(67.9%)	13(65.0%)	1.0000
History:			
Hypertension [%]	75(92.6%)	17(85.0%)	0.5293
Diabetes Mellitus [%]	28(34.6%)	7(35.0%)	1.0000
Hyperlipidemia [%]	68(84.0%)	14(70.0%)	0.2669

Table 2-B Association Between PAD and Risk Factors (continued)

Lipids	PAD		P value
	positive (n=81)	negative (n=20)	
TC [mean±SD, mg/dl]	204.0±176.5	202.0±181.0	0.2585
TG [mean±SD, mg/dl]	107.0±76.3	102.5±79.0	0.6886
HDL-C [mean±SD, mg/dl]	45.0±37.0	55.0±38.0	0.0631
LDL-C [mean±SD, mg/dl]	134.9±106.5	118.8±108.7	0.2833
Lipoprotein(a) [mean±SD, mg/dl]	1.71±10.1	13.1±6.2	0.3644
Apoprotein A1 [mean±SD, md/dl]	121.0±110.0	143.0±116.0	0.0188*
Apoptotein B [mean±SD, md/dl]	100.0±85.5	95.0±81.0	0.4607
Apoprotein E [mean±SD, md/dl]	4.33±1.03	4.52±1.13	0.5266
RLP-C [mean±SD, md/dl]	3.6±2.6	3.7±3.1	0.3438

Mann-Whitney U-test; * $p<0.05$

TC; total cholesterol TG;
HDL-C; HDL cholesterol, LDL-C; LDL cholesterol
RLP-C; RLP cholesterol

Table 2-C Association Between PAD and Risk Factors (continued)

Other Factors	PAD positive (n=81)	PAD negative (n=20)	P value
CRP [mean±SD, mg/dl]	0.2±0.0	0.0±0.0	0.2444
D-D [mean±SD, μg/dl]	0.8±0.4	0.9±0.2	0.4585
TAT [mean±SD, ng/dl]	2.7±1.9	2.4±1.8	0.1809
IMT [mean±SD, mm]	1.15±0.98	0.98±0.83	0.0126*
ABI [mean±SD]	1.13±1.01	1.12±1.08	0.5942
baPWV [mean±SD, mmHg]	1979±1712	1868±1371	0.0608
modified Rankin Scale [mean±SD]			
on admission	3.0±2.0	2.0±1.3	0.0376*
on discharge	1.0±1.0	1.0±0.0	0.1069
Admission period [mean±SD, days]	26.0±19.0	24.0±18.8	0.5650

CRP; C reactive protein D-D; D-dimer Mann-Whitney U-test; * $p<0.05$
TAT; thrombin-antithrombin III complex IMT; intima-media thickness
ABI; ankle brachial index baPWV; brachial-ankle pulse wave velocity,

there were no significant differences of the other lipid parameters between the patients with and without PAD.

The associations between PAD and several other factors are shown in Table 2 The carotid intima-media thickness and the modified Rankin scale score on admission were significantly larger in the stroke patients with PAD than in those without PAD, but there were no significant differences of the other factors between the patients with and without PAD.

Multiple Logistic Regression Analysis

Logistic regression analysis showed that the apoprotein A1 level and the modified Rankin scale score on admission were strongly related to the occurrence of stroke in patients with PAD (Table 3).

DISCUSSION

The present study showed that PAD is frequently associated with acute ischemic stroke due to either large or small artery occlusion, suggesting that it may be important to perform screening for PAD in patients with ischemic stroke. Our study also revealed that the prevalence of PAD is increased in stroke patients, suggesting that detection of PAD may help to improve the prognosis of patients with ischemic stroke. In general, an ABI of less than 0.9 is considered to indicate the presence of PAD Since blood pressure is higher in the lower limbs than in the upper limbs, the normal ABI ranges from 1.0 to 1.5[13]. Detection of PAD by measuring the ABI was previously found to have a 90% sensitivity and 95% specificity, so this method is generally accepted as the gold standard[14]. In many studies conducted in Europe and the USA, PAD was defined as being present when the ABI was less than 0.9[15)~20)]. Alternatively, an ABI greater than 0.90 at rest that decreases by 20% or more after exercise has been proposed to be diagnostic of PAD[21]. This suggests that patients with leg pain on exertion who have ABI values >0.90 should

Table 3 Forward Stepwise Multiple Logistic Regression Analysis Of PAD in Relation to Apoprotein A 1, IMT, and modified Rankin Scale (on admission)

	Coefficient	Odds ratio	95% CI		P value
Apoprotein A1	−0.02138	0.979	0.959	0.999	0.0312
modified Rankin Scale (on admission)	0.5041	1.660	1.01	2.71	0.0318

be considered for an exercise test. However, it is difficult to do such a test in high-risk patients like the acute ischemic stroke patients in this study, making it difficult to diagnose PAD from the ABI alone, particularly when vessels below the knee are involved. Therefore, we defined PAD as being present when either lower extremity MRA or ultrasonography showed severe stenosis or occlusion, or when at least two out of three clinical factors (ABI <0.9, a pulseless artery, and symptoms) were positive. The prevalence of PAD has varied in previous studies, depending on the age distribution of the subjects and the presence or absence of underlying disease.

The majority of patients with PAD are asymptomatic; in fact, only 22% of them have symptoms like leg pain or intermittent claudication[22]. In the present study, no attempt was made to identify PAD on the basis of symptoms such as intermittent claudication for the following two reasons: 1) it is difficult to distinguish PAD from other diseases based on symptoms alone and 2) PAD is usually asymptomatic (most of our patients had early disease).

Our findings were consistent with the results of some previous studies that have addressed the relationship between PAD and ischemic stroke. Risk factors for an abnormal ABI have been investigated by several authors. In the ARIC study, a high total cholesterol level was found to be a major risk factor for PAD[14]. In another study, the non-HDL cholesterol level was more strongly correlated with ApoproteinB than LDL cholesterol as a predictor of coronary atherosclerosis[23]. We found that both non-HDL and LDL levels were higher in men without PAD, while logistic regression analysis showed that the apoprotein A1 level was strongly correlated with the occurrence of stroke in patients who had PAD. However, this was a small sample size and cross-sectional study, so a causal relationship cannot be deduced from our results. Therefore, a large-scale investigation will be necessary to determine the relationship between PAD and ischemic strok.

PAD not only interferes with daily activities and affects QOL, but also worsens the prognosis of patients with ischemic stroke. The present study revealed that that PAD is frequently associated with ischemic stroke, suggesting that it is important to screen stroke patients for PAD.

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(和文抄録)

末梢動脈閉塞と虚血性脳卒中との関連

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【目的】脳血管障害における末梢動脈閉塞(PAD)の関与を明らかにするために, 虚血性脳卒中を対象に末梢動脈閉塞合併率および動脈硬化の危険因子を検討した.

【方法】対象は平成14年7月から平成15年12月まで原三信病院救急外来に救急搬送された虚血性脳卒中と診断された70例(平均年齢71歳)である. NINDS(1990年)の分類に従ってラクナ脳梗塞(LAC), アテローム血栓性脳梗塞(ATI), 心原性脳梗塞(CE)に分けた. 採血, 心電図, 頭部CT, MRI・MRA, 超音波(頸動脈, 心, 下肢動脈), 下肢造影MRA, フォルム(ABI/baPWV), ホルター心電図等の検査を施行. 下肢造影MRA, 下肢動脈エコーで閉塞あるいは有意狭窄を認め, かつABI<0.9, 動脈触知不良, 自覚症状のうち2つ以上を満たすものをPADと診断した.

【結果】PADの合併は, 70例(83.3%)と高率にみられ, 病型別では, LACで51例(72.8%), ATIで7例(10.0%), CEで12例(17.2%)であった. Fontaine分類では, I度が38例(58.5%), II度が29例(41.0%)でIII度が3例(0.5%)と, 半数以上がI度の無症候性のPADであった. ABIはPAD群で1.09±0.13と非PAD群(1.15±0.08)比較し, 低値傾向を示すも有意差は認めなかったが, baPWV, IMTはPAD群が非PAD群と比較し有意に高値を示した. 血清CRP, D-D, 及びTATでは有意差は認めなかったが, PAD群で高値を示し, HDL-CはPAD群が非PAD群と比較し有意に低値を示した. modified Rankin Scaleは入院時(3.21 vs 2.64)及び退院時(1.96 vs 1.78)のいずれもPAD群が高値傾向を示した.

【考察】虚血性脳卒中にPADを合併した場合, 機能予後や生命予後に悪影響を及ぼす可能性があり, PADを早期診断をすることが重要であると考えられた.