Subclinical Peripheral Arterial Disease in Patients with Acute Ischemic Stroke: A Study with Ultrasonography

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Background: Peripheral arterial disease (PAD) is an advanced form of atherosclerosis defined by an abnormal ankle-brachial index (ABI). However, the ABI provides no information about the location of atherosclerosis. We investigated the clinical implication of PAD confirmed using lower-extremity ultrasonography (LEUS), with consideration of the atherosclerosis location. *Methods:* Patients with acute ischemic stroke who underwent LEUS were enrolled. Patients with PAD were further divided into those with PAD at the proximal (above-popliteal artery, PADP) and distal (below-tibialis artery, PADD) segments. The clinical outcome was compared between patients with and without PAD, and between PADP and PADD. The atherosclerosis location in the cerebral artery was also compared between groups. *Results:* Among 289 patients, PAD was observed in 108 (37.4%) patients (43 had PADP and 65 had PADD). Patients with PAD were slightly older ($P < .001$) and had more significant carotid artery stenosis (30.6% versus 12.7%, $P < .001$) than those without. Patients with PAD had poor 3-month functional outcome than those without (modified-Rankin Scale score: 3 [interquartile range, 1-4] versus 2 [1-3], respectively, $P = .003$). Diabetes, high-stroke severity, and the presence of PADP (odds ratio, 3.893; 95% confidence interval, 1.454-10.425; $P = .007$) were independently associated with poor functional outcome at 3 months. Patients with PADP showed higher prevalence of extracranial stenosis than those with PADD (41.9% versus 23.1%; $P = .038$). *Conclusions:* Our study suggests that subclinical PAD, especially PADP, is associated with poor functional outcome at 3 months after stroke onset. Interestingly, the location of cerebral atherosclerosis differed according to the location of PAD.

Key Words: Peripheral artery disease—acute stroke—atherosclerosis—ultrasonography

Introduction

Atherosclerosis is a systemic disease that involves various vascular beds, including the coronary, cerebral, and peripheral arteries.[1] Peripheral arterial disease (PAD) is considered an advanced stage of atherosclerotic disease. As ischemic stroke and PAD have common risk factors, the prevalence of PAD in patients with ischemic stroke is considerable. Previously, the prevalence of PAD was reported to be 10%-15% among patients with acute ischemic stroke.[2] Patients with ischemic stroke who have PAD showed higher mortality rate, higher recurrence rate, and poorer functional outcomes than those without PAD.[3]

These data were usually based on studies that defined PAD by abnormal ankle-brachial index (ABI). The ABI is a useful tool for screening PAD[4]; however, it does not detect earlier changes of peripheral artery and has low

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sensitivity when PAD involves upper extremities. ABI also does not provide information about the location of PAD.[5,6] The proximal large arteries are predominant in the elastic components, whereas the distal arteries are prevalent in the muscular components.[7] These histological and anatomical differences may cause differences in the nature of PAD and in its relationship with atherosclerosis occurring in other vascular beds.

In general, patients with PAD in a large proximal artery show poorer outcomes than those with PAD in a small distal artery.[8,9] However, data about the location of PAD among patients with ischemic stroke are scarce. In this study, we first investigated the association between the presence of subclinical PAD diagnosed by lower extremity ultrasonography (LEUS) and functional outcome of ischemic stroke. Second, the functional outcomes of ischemic stroke and the location of atherosclerosis in the cerebral artery were compared between proximal and distal PAD.

Materials and Methods

Participants

Patients who were admitted to Kyung Hee University stroke center because of acute ischemic stroke that occurred within 7 days from symptom onset were prospectively enrolled in our stroke database. Patients registered between January 2014 and December 2016 were retrospectively reviewed. Patients with ischemic stroke confirmed using (1) diffusion-weighted imaging, (2) cerebrovascular imaging (computed tomography angiography or magnetic resonance angiographyMRA), and (3) LEUS were enrolled. During the study period, all patients underwent LEUS for the diagnosis of PAD.

The data on demographics and vascular risk factors were obtained from the stroke database. The stroke subtypes were categorized according to the TOAST (Trials of Org 10172 in Acute STroke) classification at discharge. The lipid profile was checked on the second day of admission after at least 8 hours of starvation. The severity of stroke was evaluated initially at admission according to the National Institutes of Health Stroke Scale (NIHSS) and at the outpatient clinic 3 months after stroke according to the modified Rankin Scale (mRS). Poor functional outcome was defined as an mRS score of 3-6. This study was approved by the local ethics committee, and the need for informed consent was waived owing to its retrospective design.

Neurovascular Imaging

The patients underwent magnetic resonance angiography or computed tomography angiography on the day of admission. The presence of atherosclerosis was investigated in intracranial (ICAS) and extracranial arteries (ECAS). A degree of stenosis greater than 50% was considered to indicate a significant stenosis. Tandem stenosis was defined as the presence of both ICAS and ECAS in a patient. Symptomatic ICAS or ECAS was defined as a significant stenosis in the corresponding artery proximal to the ischemic lesion. Patients with tandem stenosis, difficult to define the true culprit symptomatic stenosis were excluded from the analysis focusing on patients with symptomatic stenosis. Two experienced stroke neurologists (Y.Y.S. and S.H.H.) independently evaluated the presence of steno-occlusive lesions while blinded to all clinical data.

Lower-Extremity Ultrasonography

The patients underwent LEUS within 3 days from admission, and the procedure was conducted by an experienced radiologist blinded to the clinical data. Data were obtained from both legs and from the iliac to the dorsalis pedis artery. Based on previous studies, significant lower limb arterial stenosis was defined as luminal stenosis more than or equal to 50% and/or peak systolic velocity ratio of greater than or equal to 2.0 in at least 1 below-mentioned artery.[10] Proximal PAD was defined as significant atherosclerosis at the proximal arteries (iliac, femoral, and popliteal arteries). Distal PAD was defined as significant atherosclerosis in the distal arteries (tibialis and dorsalis pedis arteries). If atherosclerosis was observed from both proximal and distal arteries, the location of PAD was classified to the more severe segment. However, if the atherosclerosis was extending from the proximal to the distal segment continuously, it was considered proximal PAD.

Statistical Analysis

First, the demographics, risk factors, stroke subtypes, and outcomes were compared between patients with and those without PAD. Second, we performed a similar comparison between patients with proximal PAD and those with distal PAD. Student's t test, Fisher's exact test, chi-square test and the Mann-Whitney U test were used for the comparisons, as appropriate. Third, factors associated with poor functional outcomes at 3 months after stroke were investigated using univariable and multivariable analyses. Variables with a P value of less than .15 in the univariable analysis were entered into the multivariable analysis. Age, diabetes, smoking, initial NIHSS score, presence of ECAS, and presence of PAD were entered into the model. Finally, the association between the location of atherosclerosis in the cerebral and peripheral arteries was analyzed. A P value of less than .05 was considered to indicate statistical significance. All statistical analyses were performed with SPSS version 12.0 (SPSS Inc., Chicago, IL).

Results

During the study period, 331 patients were admitted to our center because of acute ischemic stroke and were registered in the database. Among them, 37 patients were

excluded (5 patients with poor neuroimaging quality and 32 patients with no LEUS data). Finally, 289 patients were enrolled, and significant PAD was observed in 108 (37.4%) patients. PAD was located in the proximal segment in 43 (39.8%) patients and in the distal segment in 65 (60.2%) patients. Two patients with proximal PAD had intermittent claudication and 1 of them demonstrated color change.

Patients with PAD were older than those without. There was no significant difference in terms of risk factors or stroke mechanisms between the 2 groups. ECAS was more frequently observed in those with PAD (30.6% versus 12.7%, $P < .001$). Functional outcome measured at 3 months after stroke was poorer in patients with PAD than in those without PAD (median mRS = 3 [interquartile range, 1-4] versus 2 [1-3], respectively, $P = .003$; Table 1).

Proximal versus Distal PAD

Patients with proximal PAD showed a higher rate of current smoking than those with distal PAD (60.5% versus 38.5; $P = .025$, respectively; Table 2). Patients with proximal PAD also had a higher rate of previous stroke than those with distal PAD (27.9% versus 10.8%, $P = .022$). Hypertension and diabetes tended to be more prevalent in patients with distal PAD; however, the difference did not reach statistical significance. The prevalence of ECAS was higher in patients with proximal PAD than in those with distal PAD (41.9% versus 23.1%, $P = .038$). The functional outcome did not differ between patients with different locations of PAD.

Factors Associated with Functional Outcome

Of the enrolled patients, 196 (67.8%) obtained functional outcome at 3 months after stroke. The distributions of functional outcomes in patients with proximal and distal PAD and in those without PAD are presented in Figure 1. Old age, diabetes, high initial NIHSS score, and presence of proximal PAD were associated with poor functional outcome (Table 3). According to the results of multivariable analysis, the presence of diabetes (odds ratio [OR], 2.310; 95% confidence interval [CI], 1.160-4.604; $P = .017$), initial NIHSS score (OR, 1.196; 95% CI, 1.076-1.330; $P = .001$), and proximal PAD (OR, 3.893; 95% CI, 1.454-10.425; $P = .007$) were associated with poor functional outcome at 3 months.

Location of Cerebral Atherosclerosis and PAD

Of the enrolled patients, 174 (60.2%) did not have cerebral atherosclerosis, 59 (20.4%) had ICAS, 38 (13.1%) had ECAS, and 18 (6.2%) had both ICAS and ECAS. The location of atherosclerosis in the cerebral arteries differed according to the

Table 1. *Comparison between patients with and without PAD*

	PAD + (n = 108)	PAD - (n = 181)	*P* value
Age (years)	72.2 ± 9.7	65.7 ± 11.6	<.001
Male sex	65 (60.2)	110 (60.8)	.921
Hypertension	84 (77.8)	125 (69.1)	.109
Diabetes	34 (29.3)	53 (31.5)	.693
Hyperlipidemia	78 (72.2)	118 (65.2)	.216
Smoking	51 (47.2)	80 (44.2)	.617
Previous stroke	19 (17.6)	26 (14.4)	.464
Coronary disease	8 (7.4)	18 (9.9)	.466
Stroke mechanism			
Large-artery atherosclerosis	35 (32.4)	46 (25.4)	.519
Small-vessel occlusion	36 (33.3)	59 (32.6)	
Cardioembolism	13 (12.0)	24 (13.3)	
Other determined	0 (.0)	2 (1.1)	
Undetermined	24 (22.2)	50 (27.6)	
Presence of atherosclerosis			
Intracranial	28 (25.9)	49 (27.1)	.831
Extracranial	33 (30.6)	23 (12.7)	<.001
Lipid profile			
Total cholesterol	184.3 ± 50.0	177.8 ± 42.4	.259
Triglyceride	138.5 ± 132.9	132.6 ± 97.8	.664
HDL-cholesterol	46.3 ± 25.4	45.0 ± 12.6	.546
LDL-cholesterol	114.5 ± 41.4	110.5 ± 35.6	.387
Initial NIHSS score	4 [2-5]	4 [3-7]	.136
mRS score at 3 months	2 [1-3]	3 [1-4]	.003

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; PAD, peripheral arterial disease.

Values are expressed as number and percentage (column), mean ± standard deviation or median (interquartile range).

Table 2. *Comparison between patients with proximal and distal PAD*

	Proximal PAD (n = 43)	Distal PAD (n = 65)	*P* value
Age (years)	71.4 ± 9.3	72.6 ± 10.0	.510
Male sex	28 (65.1)	37 (56.9)	.395
Hypertension	30 (69.8)	54 (83.1)	.103
Diabetes	10 (23.3)	24 (36.9)	.134
Hyperlipidemia	34 (79.1)	44 (67.7)	.196
Smoking	26 (60.5)	25 (38.5)	.025
Previous stroke	12 (27.9)	7 (10.8)	.022
Coronary disease	4 (9.3)	4 (6.2)	.541
Stroke mechanism			
Large-artery atherosclerosis	16 (37.2)	19 (29.2)	.755
Small-vessel occlusion	13 (30.2)	23 (35.4)	
Cardioembolism	4 (9.3)	9 (13.8)	
Other determined	0 (0)	0 (0)	
Undetermined	10 (23.3)	14 (21.5)	
Presence of atherosclerosis			
Intracranial	10 (23.3)	18 (27.7)	.607
Extracranial	18 (41.9)	15 (23.1)	.038
Lipid profile			
Total cholesterol	179.2 ± 56.1	186.0 ± 45.4	.493
Triglyceride	128.3 ± 118.5	143.3 ± 118.5	.567
HDL-cholesterol	49.0 ± 36.9	44.7 ± 11.6	.407
LDL-cholesterol	111.5 ± 46.3	114.9 ± 37.9	.678
Initial NIHSS score	4 [3-7]	4 [3-6]	.721
mRS score at 3 months	3 [1-5]	2 [1-4]	.259

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; PAD, peripheral arterial disease.

Values are expressed as number and percentage (column), mean ± standard deviation or median (interquartile range).

location of atherosclerosis in the peripheral arteries (Table 4; $P = .001$). The prevalence of ECAS was higher in patients with proximal PAD, whereas ICAS was slightly more frequent in those with distal PAD (Table 2).

Among 81 patients with large artery atherosclerosis, after excluding 13 patients with tandem lesion, 68 patients had symptomatic ICAS or ECAS. In cases of symptomatic cerebral artery stenosis, patients with proximal PAD more frequently had symptomatic ECAS than ICAS (73.3% versus 26.7%, respectively), whereas patients with distal PAD more frequently had symptomatic ICAS than ECAS (72.2% versus 27.8%, respectively). The location of symptomatic stenosis at the cerebral vessel was different between those with proximal and distal PAD ($P = .009$; Fig 2).

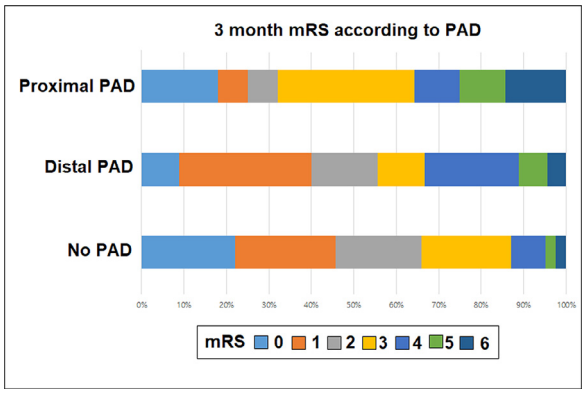

Figure 1. *Functional outcome according to the presence and location of peripheral artery disease.*

Table 3. *Factors associated with poor functional outcome at 3 months (modified Rankin Scale score 3-6)*

	OR (95% CI)	*P* value
Age (years)	1.042 (1.014-1.072)	.003
Female sex	.726 (.401-1.314)	.291
Hypertension	1.531 (.793-2.955)	.204
Diabetes	1.917 (1.027-3.578)	.041
Hyperlipidemia	1.345 (.726-2.492)	.346
Smoking	.567 (.319-1.014)	.056
Previous stroke	1.030 (.473-2.243)	.940
Coronary disease	.775 (.250-2.404)	.659
Initial NIHSS score	1.203 (1.091-2.326)	<.001
Presence of atherosclerosis		
Intracranial	1.516 (.791-2.906)	.210
Extracranial	1.776 (.812-3.882)	.150
Previous antiplatelet use	1.399 (.769-2.548)	.272
PAD		
None	1	
Distal PAD	1.543 (.769-3.095)	.222
Proximal PAD	4.071 (1.695-9.780)	.002

Abbreviations: CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PAD, peripheral arterial disease.

Table 4. *Location of atherosclerosis in cerebral arteries and peripheral arteries*

	No PAD (n = 181)	Distal PAD (n = 65)	Proximal PAD (n = 43)	*P* value
No cerebral atherosclerosis	118 (65.2)	37 (56.9)	19 (44.2)	<.001
Intracranial atherosclerosis	40 (22.1)	13 (20.0)	6 (14.0)	
Extracranial atherosclerosis	14 (7.7)	10 (15.4)	14 (32.6)	
Tandem lesion	9 (5.0)	5 (7.7)	4 (9.3)	

Abbreviations: PAD, peripheral artery disease.
Values are expressed as number and percentage (column).

Discussion

In this study, more than one-third of the patients with acute ischemic stroke had subclinical PAD that was diagnosed using LEUS. Patients with PAD had more ECAS and poorer functional outcome at 3 months after stroke. PAD more frequently developed in the distal segment than in the proximal segment. Proximal PAD was more associated with smoking, previous stroke, and extracranial atherosclerosis. Diabetes, initial NIHSS score, and proximal PAD were independently associated with poor functional outcome at 3 months after stroke.

Previous studies reported that the incidence of PAD defined by an abnormal ABI was 17%-18% in Asian patients with acute ischemic stroke.[11,12] The functional outcome of stroke was more poor in those with PAD than those without.[13] The poor functional outcome was explained by the higher rate of platelet activation, procoagulative conditions, impaired endothelial functions, and increased systemic inflammation in those with PAD, which are all associated with atherosclerosis progression.[14,15] In those with low ABI, there may be a higher chance of progressing to a more severe systemic atherosclerosis affecting the long-term vascular outcomes. As even high normal ABI (.91 ≤ ABI ≤ .99) also were associated with higher mortality, subclinical PAD diagnosed by LEUS, which can find those with earlier stage of atherosclerosis may have shown a significant association with poor functional outcome.[16]

However, still the chance of increased systemic progression of atherosclerosis in PAD patients has a limitation in explaining the difference between proximal and distal PAD in predicting the functional outcome. According to

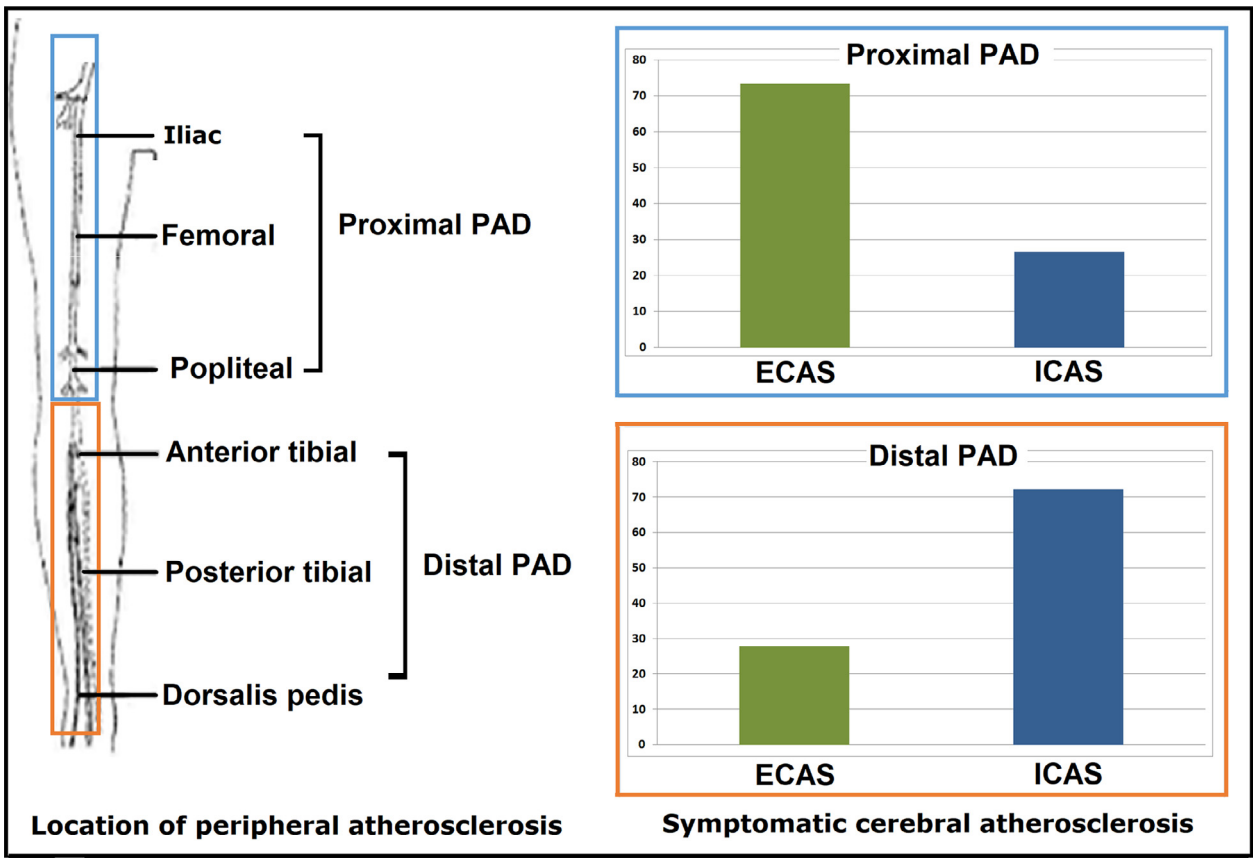

Figure 2. *Location of symptomatic cerebral atherosclerosis (intracranial versus extracranial) according to the location of peripheral artery disease.*

our result, proximal PAD was associated with poor functional outcome. One of the explanations is that decreased blood flow to the lower extremities may limit the functional recovery, as muscle atrophy in the legs may occur more easily in patients with PAD.[17] Considering that proximal leg strength is highly associated with independent gait, proximal PAD may be a critical factor affecting the functional recovery after stroke.[18,19] Therefore, evaluation with LEUS may be helpful in detecting PAD at an earlier stage, which may lead to earlier treatment and, consequently, improved outcomes.

The risk factors associated with proximal and distal PAD differ among studies.[20] Smoking and hyperlipidemia are more closely associated with proximal PAD, whereas diabetes is more known to be associated with distal PAD.[5,21] Our results well correspond with those of previous studies. Some studies also described the association between carotid disease and the presence of PAD.[22,23] Our results also seem to be in accordance with those reports. In this study, we have additionally looked at the association between the location of PAD and cerebral atherosclerosis. Interestingly, proximal PAD was more associated with ECAS, whereas ICAS was more frequently observed in patients with distal PAD.[24] It is well known that ICAS is more associated with metabolic syndrome, including diabetes, whereas ECAS is more associated with hyperlipidemia.[20] The difference in the relative importance of atherosclerotic risk factors between ECAS and ICAS may at least partially explain the difference between proximal and distal PAD. Atherosclerosis at more proximal arteries with large diameter may be more associated with hyperlipidemia, whereas diabetes may be more associated with distal arteries with smaller diameters.

There are several noteworthy limitations in our study. First, the study was performed in a single center and included a small number of patients. Second, owing to the retrospective design, patients with a poor condition that prevented LEUS examination were excluded. Finally, the severity of PAD was not quantitatively measured according to the stenosis degree.

Conclusion

Despite the limitations, our study has strength in showing the association between subclinical PAD, especially proximal PAD, and the functional outcome after stroke. Furthermore, the location of PAD was also demonstrated to be associated with the location of cerebral atherosclerosis in patients with stroke. LEUS may be helpful in the early diagnosis of PAD before an abnormal ABI appears, and further provides information about the location of PAD, which influences the functional outcome after ischemic stroke.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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