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Research Article

Clinical Features and Subtypes of Ischemic Stroke Associated with Peripheral Arterial Disease

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Abstract

Aim: The prognosis of patients with coronary artery disease or stroke accompanied by peripheral arterial disease (PAD) is poor. The purpose of this study was to investigate the subtypes and clinical features of stroke with and without PAD.

Methods: The ankle brachial index (ABI) was used to diagnose PAD in patients with acute ischemic stroke hospitalized from July 2014 to April 2015 in South Korea. The symptoms of PAD were surveyed using a questionnaire. Data collected included age, sex, hypertension, diabetes, hyperlipidemia, obesity, current smoking, old stroke history, National Institute of Health Stroke Scale score, atrial fibrillation, coronary arterial disease, and stroke subtypes.

Results: In total, 342 patients were enrolled, of whom 25 (7.3%) were diagnosed with PAD (ABI < 0.9); of these patients, four (18.7%) exhibited typical symptoms. Compared to patients without PAD, those with PAD had higher mean age (74.08 ± 9.97 vs. 65.07 ± 12, $p = 0.01$) and mean NIHSS score (7.24 ± 7.03 vs. 4.57 ± 5.42, $p = 0.02$). Moreover, patients with PAD exhibited atrial fibrillation (20% vs. 5.6%, odds ratio [OR] 4.19, 95% confidence interval [CI] 1.67 - 10.47, $p < 0.01$) and CAD (20% vs. 6.3%, OR 3.71, 95% CI 1.26 - 10.92, $p = 0.02$) more often than those without PAD. The subtypes of ischemic stroke were significantly different based on the presence of PAD (chi-square test, $p = 0.03$). In particular, compared to patients without PAD, those with PAD had a higher distribution of cardioembolism (38.9% vs. 18.0, OR 2.90, 95% CI 1.04 - 8.02, $p = 0.05$) and lower distribution of small vessel disease (16.7% vs. 43.9%, OR 0.25, 95% CI 0.07 - 0.91, $p = 0.02$). Of the 342 patients, 25 (7.3%) had only CAD and five (1.4%) had both CAD and PAD.

Conclusion: This study revealed that Korean patients with acute ischemic stroke have lower comorbidity with PAD and CAD compared with patients of other ethnicities. Moreover, patients with PAD were older and had severe neurologic deficits. Atrial fibrillation and CAD may be associated with comorbid PAD in acute stroke.

Keywords: *Ischemic Stroke; Peripheral Arterial Disease; Ankle Brachial Index*

Abbreviations

PAD: Peripheral Arterial Disease; ABI: Ankle Brachial Index; NIHSS: National Institute of Health Stroke Scale; CAD: Coronary Artery Disease; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; TOAST: Trial of Org 10172 in Acute Stroke Treatment; BMI: Body Mass Index

Introduction

In the peripheral arterial disease (PAD), the arteries of the extremities, especially the legs, are obstructed by arteriosclerosis or embolism, which may cause symptoms that include weakness, ulcer, and pain when walking. If the symptoms are severe, leg amputation may be considered. However, PAD is also a very common disease occurring in 3 - 10% of the general population [1]. Screening and diagnosis of

PAD can be made using noninvasive methods, such as measuring the ankle brachial index (ABI) or angiography using computed tomography (CT) or magnetic resonance imaging (MRI). However, definitive diagnosis requires invasive angiography [1,2]. Among the screening tests, ABI is often used because it is safe, less costly, and relatively accurate compared to other methods that are costly and associated with possible adverse effects [1,2,8].

Carotid stenosis is often found in cases involving PAD, and patients with PAD have a higher risk of cardiovascular disease. Moreover, it has also been reported that having one occlusive vascular disease increases the risk of comorbidity with two other vascular diseases [1,3,4]. Studies outside of Korea have reported that PAD is diagnosed in 10 - 51% of patients with stroke, and that those comorbid with PAD have higher mortality rate, incidence of cardiovascular disease, and recurrence of cerebrovascular disease than those without PAD [5,6]. Thus, diagnosis of PAD bears an important significance in patients with stroke.

Unlike coronary artery disease (CAD), ischemic stroke does not only involve one pathogenesis, but can be divided into different subtypes based on its pathogenesis [7]. Since the prevalence of PAD has been associated with the different stroke subtypes, identifying such differences would be helpful for a better understanding of stroke or PAD.

The objective of the present study was to investigate the percentage of patients with stroke comorbid with PAD and their symptoms using ABI. The study also investigated the differences in clinical characteristics, such as risk factors associated with PAD, clinical severity of stroke, and stroke subtypes. Moreover, the mutual ratio of patients with stroke diagnosed with CAD and PAD was also investigated.

Materials and Methods

Participants and data collection

The study population included adults, aged 20 years or older, who were admitted to Eulji University Hospital in South Korea for acute stroke during the period of between July 2014 and June 2015. The study included only patients who were admitted within 1 week from stroke onset and had acute ischemic lesion confirmed by brain CT or MRI. Moreover, patients with hemorrhagic stroke, critical condition, without ABI measurements due to other reasons, and patients who did not consent to the study were excluded.

The data of each patient were obtained from the prospective stroke patient data registry, and included demographic data, risk factors, stroke subtypes (Trial of Org 10172 in Acute Stroke Treatment [TOAST]), and severity of the neurological deficits (National Institute of Health Stroke Scale [NIHSS] score). Moreover, the comorbidity with CAD, previous history of PAD, and symptoms were also investigated.

The risk factors of the patients investigated were those mentioned in the 2007 Inter-Society Consensus for the Management of PAD (TASC II), and included the following: (1) age; (2) sex; (3) hypertension (patients with blood pressure ≥ 140/90 mmHg, prior diagnosis of hypertension, or currently on medication for hypertension); (4) diabetes (patients with fasting blood sugar ≥ 126 mg/dl, diagnosed with diabetes by oral glucose tolerance test, prior diagnosis of diabetes, or currently on medication for diabetes); (5) hyperlipidemia (patients with fasting total cholesterol ≥ 220 mg/dl or currently on medication for hyperlipidemia based on prior diagnosis); (6) obesity (body mass index [BMI] ≥ 25 kg/m2); and (7) smoking status at admission [1,3]. The NIHSS score was measured at admission, while stroke subtypes were categorized by TOAST classification [7].

History of stroke was defined as patients who had been diagnosed in the past with hemorrhagic or ischemic stroke, while history of PAD was defined as currently on medication for prior diagnosis. Atrial fibrillation was defined as currently on medication for prior diagnosis or diagnosis based on electrocardiography performed at admission. In addition, CAD was defined as patients with prior history of stent implantation or coronary bypass, currently on medication for diagnosis of angina pectoris or myocardial infarction, or patients diagnosed by coronary angiography performed based on the discovery of regional wall motion abnormality on echocardiogram at admission for stroke.

Definition of PAD and measurement methods

Similar to previous studies, patients with PAD were defined as those who were diagnosed with PAD in the past and underwent subsequent surgery or procedure for arterial obstruction and patients with ABI < 0.9 [1-3].

For the ABI test, each patient was allowed to rest for 5 minutes or more in the supine position prior to the test. Vasoguard version 8.021, Doppler 8 MHz was used to measure the systolic blood pressure from both left and right dorsalis pedis and posterior tibial arteries, and the highest blood pressure from the systolic blood pressure measurements was divided by the highest systolic blood pressure measured from the left and right upper arms to derive the left and right ABI values. The lowest ABI value was used as the ABI value for that patient [2]. In addition, a questionnaire survey was conducted on all patients to determine the symptoms of PAD.

Statistical analysis

All data analyses were performed using SPSS 15.0 for Windows. For comparison between the two groups based on patients with stroke with and without PAD, analysis was performed using the t-test or Mann-Whitney U test, depending on whether the continuous variable satisfied normality or not. Differences between two or more categorical variables were analyzed using the chi-square test, and Fisher's exact test when necessary. Moreover, various factors that may influence PAD were analyzed using multivariate analysis. All data were processed by two-sided test and the statistical significance was set at $p < 0.05$.

Results

A total of 414 patients with stroke were identified during the study period. Among the 72 excluded patients, 1 was younger than 20 years, 37 could not be analyzed due to severe symptoms, and 34 refused to perform the ABI measurement. Of those, 342 patients were included (mean age, 65.73 ± 12.73 years; 191 male (55.8%), 151 female (44.2%); with hypertension, 249 (72.8%); with diabetes, 110 (32.2); with hyperlipidemia, 50 (14.6%); with obesity 107 (31.3%); smoker, 82 (24%); with CHD, 25 (7.3%); with atrial fibrillation, 40 (11.7%); prior stroke, 62(18.1%); mean NIHSS score, 4.76 ± 5.59 points). Table 1 summarized their general characteristics.

	Number (n = 342)	Percent (%)
Age	65.73 12.73	
Male/Female	191/151	55.8/44.2
Hypertension	249	72.8
Diabetes	110	32.2
Hyperlipidemia	50	14.6
Obesity	107	31.3
Smoking	82	24
Coronary artery disease	25	7.3
Atrial fibrillation	40	11.7
Prior stroke	62	18.1
NIHSS	4.76 5.59	
TOAST		
Small vessel	86	25.1
Large artery	80	23.4
Cardioembolism	41	12.0
Other	9	2.6
Undetermined	75	21.9

Table 1: *Baseline characteristics of patients with acute ischemic stroke.*

NIHSS: National Institute of Health Stroke Scale; TOAST: Trial of Org 10172 in Acute Stroke Treatment.

Out of the 342 patients, 7.3% (n = 25) were diagnosed with PAD and an ABI < 0.9. Among them, 16% (n = 4) had been diagnosed previously with PAD, while 84% (n = 21) were newly diagnosed with PAD based on the ABI measurement. The PAD symptoms were confirmed by a questionnaire survey in 16% (n = 4).

The group of patients with PAD, as compared with the group without PAD, showed higher mean age (74.08 ± 9.97 vs. 65.07 ± 12.70 years, p = 0.01) and mean NIHSS score (7.24 ± 7.03 vs. 4.57 ± 5.42, p = 0.02). Furthermore, significant differences were also found in atrial fibrillation (20% vs. 5.6%, OR 4.19, p < 0.01) and CAD (20% vs. 6.3%, OR 3.71, p = 0.02) between the two patient groups.

As shown in table 1, the stroke subtypes based on TOAST classification consisted of small vessel occlusion (29.2%, n = 84), large artery atherosclerosis (27.4%, n = 79), cardioembolism (14.2%, n = 41), and other determined and undetermined patients (29.5%, n = 84). The results also indicated a significant association between PAD and the occurrence of the three stroke subtypes, namely small vessel occlusion, large artery atherosclerosis, and cardioembolism (p = 0.03). In particular, the PAD group exhibited a higher percentage of cardioembolism (38.9% vs. 18.0%, OR 2.90, p = 0.05) and lower percentage of small vessel occlusion (16.7% vs. 43.9%, OR 0.25, p = 0.02; Table 2).

	PAD (+) N (%)	PAD (-) N (%)	p-value (OR, 95% CI)
Age (years)	74.08 ± 9.97	65.07 ± 12.70	0.01*
Old age (≥ 80 years)	7 (28.0)	35 (11.0)	0.02 (3.13, 1.22 - 8.03)
Male	14 (56.0)	177 (55.8)	0.987 (1.00, 0.44 - 2.28)
Hypertension	19 (76.0)	230 (74.6)	0.709 (1.19, 0.46 - 3.09)
Diabetes	11 (44.0)	99 (31.2)	0.188 (1.73, 0.75 - 3.94)
Hyperlipidemia	5 (20)	45 (14.2)	0.38** (1.51, 0.54 - 4.23)
Obesity	19 (76.0)	215 (68.0)	0.40 (1.48, 0.57 - 3.83)
Smoking	6 (24.0)	76 (24.0)	0.99 (1.00, 0.38 - 2.59)
Old stroke	7 (18.0)	55 (17.4)	0.18** (1.85, 0.73 - 4.64)
NIHSS	7.24 ± 7.03	4.57 ± 5.42	p = 0.02*
NIHSS (≥ 13)	7 (28.0)	39 (12.3)	0.03** (2.77, 1.08 - 7.06)
Coronary artery disease	5 (20.0)	20 (6.3)	0.02** (3.71, 1.26 - 10.92)
Atrial fibrillation	8 (32.0)	32 (10.1)	< 0.01** (4.19, 1.67 - 10.47)
TOAST +			0.03**
Small vessel	3 (16.7)	83 (43.9)	0.02
No small vessel	15 (83.7)	106 (56.1)	(0.25, 0.07 - 0.91)
Large artery	8 (10)	72 (38.1)	0.59
No large artery	10 (55.6)	117 (61.9)	(1.30, 0.49 - 3.44)
Cardioembolism	7 (38.9)	34 (18.0)	0.05**
No cardioembolism	11 (61.1)	155 (82.0)	(2.90, 1.04 - 8.02)

Table 2: *Comparison of the clinical characteristics between patients with and without PAD.*

**Data are expressed as mean ± standard deviation*

***Fisher's exact test.*

+Transient ischemic attack, others, and undetermined groups are excluded in TOAST classification analysis. Data were analyzed by chi - square test.

NIHSS: National Institute of Health Stroke Scale; PAD: Peripheral Arterial Disease; TOAST: Trial of Org 10172 in Acute Stroke Treatment.

Risk factors with high probability of comorbidity with PAD were adjusted for old age (≥ 80 years), male sex, hypertension, diabetes, hyperlipidemia, atrial fibrillation, obesity, smoking, CAD, moderate to severe neurological deficits (NIHSS ≥ 13 points), and TOAST classification by multivariate analysis. Based on the results, only old age (OR 3.18, $p = 0.03$) and atrial fibrillation (OR 9.12, $p = 0.04$) showed significant differences. Finally, among all patients with stroke, 7.3% (n = 25) had CAD and 7.3% (n = 25) had PAD, while 1.4% (n = 5) had both CAD and PAD.

Discussion

In the present study, the percentage of patients with stroke diagnosed with PAD was 7.3%, which was slightly lower than that of 10% reported in the REACH registry [4]. Not only the REACH registry but also other studies outside of Korea have reported that comorbidity of PAD among patients with stroke typically ranged between 18.1% and 33%, with some reporting up to 51% [3-5,11].

It is believed that such discrepancies are due to differences in ethnic and cultural factors, errors because of not measuring ABI in some patients, and problems with the ABI measurement method. With respect to the ethnic and cultural differences, studies conducted in Western countries have reported the prevalence of PAD to be 3 - 10% among the general population and 15 - 20% among patients aged 70 years or older [1]. In Korea, some studies have reported a prevalence of 1.8 - 4.4% among the general population [7,8], which is 4 - 5 times lower than the prevalence of PAD reported outside of Korea. One study from Taiwan, which shares ethnic similarities with Korea, reported an 18.1% comorbidity rate of PAD among patients with stroke, which was the lowest rate so far reported [11]. Therefore, it can be surmised that in Korea, because the prevalence of PAD itself is low among the general population, the comorbidity rate of PAD among patients with stroke was also low.

Another reason for these discrepancies may be due to the patients with no ABI measurements in the present study, which may influence the results. Indeed, there were 71 patients without ABI measurements in the present study, because they were being treated in the intensive care unit, died due to severe symptoms during the acute phase, or did not consent to the ABI measurement. When the groups with and without ABI measurements were compared, we found that old age (≥ 80 years), obesity, atrial fibrillation, and moderate to severe neurological deficits (NIHSS ≥ 13 points) were significantly higher in the group without ABI, which also was associated with cardioembolism among TOAST classifications (Table 3). These results indicate that ABI measurements could not be performed in many of the older patients who suffered from stroke due to cardioembolism and had severe stroke symptoms. As shown in table 2, these factors are very similar to the factors that were common in the patient group with PAD. Therefore, we assumed that if ABI had been measured in all the included patients, the comorbidity rate of PAD would have been slightly higher.

	ABI Test (+) N (%)	**ABI Test (-) N (%)**	**P value (OR, 95% CI)**
Old age (> 80 years)	42 (12.3)	21 (29.2)	< 0.01 (2.94, 1.61 - 5.37)
Male	191 (55.8)	40 (55.6)	0.96 (0.98, 0.59 - 1.64)
Hypertension	249 (72.8)	52 (72.2)	0.91 (0.97, 0.55 - 1.71)
Diabetes	110 (32.2)	33 (33.3)	0.84 (1.05, 0.61 - 1.81)
Hyperlipidemia	50 (14.6)	13 (18.1)	0.46** (1.28, 0.65 - 2.51)
Obesity	234 (68.6)	15 (20.0)	< 0.01 (0.12, 0.06 - 0.22)
Smoking	82 (24.0)	18 (25.0)	0.85 (1.05, 0.58 - 1.90)
Old stroke	62 (18.1)	21 (29.2)	0.03 (1.86, 1.04 - 3.31)
NIHSS (≥ 13)	36 (10.5)	30 (41.7)	< 0.01 (6.07, 3.39 - 10.86)
Coronary artery disease	25 (7.3)	10 (13.9)	0.06 (2.04, 0.93 - 4.47)
Atrial fibrillation	40 (11.7)	19 (26.4)	0.01 (2.70, 1.45 - 5.02)
TOAST+			< 0.01**
Small vessel	86 (41.5)	8 (17.8)	
Large artery	80 (38.6)	12 (26.7)	
Cardioembolism	41 (19.8)	25 (55.6)	

Table 3: *Comparison of the clinical characteristics of patients with and without ABI test.*

**Data are expressed as mean ± standard deviation*

***Fisher's exact test.*

+Transient ischemic attack, others, and undetermined groups are excluded in TOAST classification analysis. Data were analyzed by chi - square test.

ABI: Ankle Brachial Index; NIHSS: National Institute of Health Stroke Scale; PAD: Peripheral Arterial Disease; TOAST: Trial of Org 10172 in Acute Stroke Treatment.

The final factor that may have influenced the prevalence of PAD in our patients was problems with the ABI measurement method. Indeed, the ABI results may vary depending on the testing equipment used or the proficiency level of the evaluator. Therefore, each study may produce different results, which is a limitation in many studies that use ABI to evaluate PAD.

As shown in table 2, there were significant differences in age, atrial fibrillation, CAD, and NIHSS score between patients with and without PAD. Compared with patients without PAD, the mean age was approximately 9 years higher, and the association with old age (≥ 80 years), CAD, and atrial fibrillation was 3-, 3.5-, and 4-fold higher in patients with PAD. Similarly, the mean NIHSS score was higher by approximately 2.7 points, while moderate to severe neurological deficits (NIHSS ≥ 13 points) showed a higher association by 2 - 3 folds in patients with PAD.

Since older age showed higher prevalence of PAD, it may be a relevant factor that increased the comorbidity rate of PAD in patients with stroke. Moreover, patients with severe neurological deficits showing high comorbidity with PAD were reported in other foreign studies [1,3,4]. A significantly high prevalence of CAD was observed in patients with stroke and PAD, which may be due to a common mechanism of arteriosclerosis between CAD and PAD.

Although atrial fibrillation does affect peripheral arteries, it involves the obstruction of the peripheral arteries by embolism in the atrium. Thus, atrial fibrillation is closely linked to acute peripheral obstructive disease [1]. In contrast, ABI measures arterial stenosis caused by arteriosclerosis; thus, PAD and atrial fibrillation diagnosed using ABI may be somewhat irrelevant. However, other studies have also reported significant differences in atrial fibrillation between the between the PAD and non-PAD groups [11]. which is in line with the present findings.

Previous studies have reported an association between arteriosclerosis and atrial fibrillation [12,13,15], including common risk factors, such as hypertension, diabetes, metabolic disorder, and cigarettes [12,13]. Based on these previous findings, it becomes plausible that atrial fibrillation and PAD may also be associated to a certain degree. However, we did not observe significant differences between the two groups in the other risk factors of arteriosclerosis. Moreover, when the data were adjusted for various factors, only old age and atrial fibrillation showed a significant association. The results also confirmed that PAD was more associated with atrial fibrillation than with CAD (Table 2). Thus, there may be a direct link between atrial fibrillation and PAD, in addition to sharing risk factors for arteriosclerosis. However, there are to date no reports on this topic, and additional future studies are deemed necessary.

Regarding the three stroke subtypes, our results indicated that patients with PAD had a lower rate of small vessel occlusion and a significantly higher rate of cardioembolism. These results may be caused by the higher number of patients with CAD and atrial fibrillation in the PAD group. Previous studies conducted outside of Korea reported that the group with PAD had significantly higher rates of large artery atherosclerosis, cardioembolism, and undetermined causes [11], which is slightly different from our present findings. In the present study, when comparisons were made based on TOAST classification, other causes and underdetermined causes were excluded from the analysis. The group with other causes consisted of patients with stroke occurring from various causes, such as vasculitis and arterial dissection. The undetermined group consisted of patients who had 2 or more causes of stroke or patients in which the stroke subtype could not be identified because of the lack of the required tests. Therefore, including these two groups would have very little significance on the objective of the present study, which was to analyze the associations between causes of stroke and PAD. Accordingly, these two groups were excluded from the analysis. However, the high number of patients in these two subgroups (84, 24%) may be one of the study's limitations.

Among all the included patients with stroke, 25 (7.3%) had CAD and five (1.4%) had both CAD and PAD. These results were much lower than those reported in the REACH study (36% and 6%, respectively), which is in line with the lower PAD prevalence. In comparison with previous findings from Western studies, the prevalence of CAD in our study is different. In 2007, the incidence of myocardial infarction in Korea was 91.8 per 100,000 persons, whereas 565,000 persons per year suffered from myocardial infarction in the USA. According to various reports, CAD occurs in 400 - 1,250 per 100,000 each year, depending on ethnicity and sex [14,16]. This large difference in prevalence based on ethnicity reflects the difference in prevalence of CAD in stroke patients.

As mentioned earlier, one of the study's limitations is the exclusion of the two patient groups with other or undetermined causes of stroke, which consisted of 84 patients, from the analysis. However, since the number of patients with PAD was only 25, many of the items would not satisfy the minimum frequency requirement for statistical analysis if the patients with other or undetermined causes of stroke would be included, which would compromise the reliability of the statistics. Furthermore, since the objective of the present study was to use TOAST classification to surmise the associations between the causes of stroke and PAD, including patients with stroke of undetermined cause in the analysis would be meaningless. Indeed, by excluding these two subgroups to simplify the statistical analysis, the present study unexpectedly found a certain degree of association between cardioembolism and PAD.

Conclusion

In conclusion, the present study revealed that Korean patients with acute ischemic stroke exhibited a lower co-morbidity with PAD and CAD compared with patients of other ethnicities. Furthermore, patients with PAD were older and had severe neurologic deficits, while atrial fibrillation and CAD may also be associated with comorbid PAD in acute stroke. Acute cerebral infarction patients with PAD should be evaluation for coronary artery disease and arterial fibrillation. Additional prospective studies are needed to determine the mechanisms responsible for this association and incremental risk for atrial fibrillation and CAD associated with PAD among individuals with acute ischemic stroke.

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Conflict of Interest

None declared.

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