Observational Study

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An isolated pontine infarct extending to the basal pontine surface has a higher abnormal ankle-brachial index

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Abstract

Patients with ischemic stroke and branch atheromatous disease (BAD) have worse neurological deficits and prognoses than those with small vessel occlusion (SVO). However, both disorders are forms of deep brain infarctions. This study aimed to investigate an MRI-based etiological classification for isolated pontine infarctions and assess differences in vascular risk factors and peripheral arterial disease among etiological subtypes. Consecutive data of patients admitted for acute ischemic stroke or transient ischemic attack between August 2016 and July 2019 were reviewed. Acute isolated pontine infarcts were classified into 3 groups: BAD, SVO, and large-artery atherosclerosis (LAA), according to basilar or vertebral artery steno-occlusion and the extent of the infarct lesion on the basal pontine surface as displayed on magnetic resonance imaging and angiography. Vascular risk factors, ankle-brachial index (ABI), and brachial-ankle pulse wave velocity were analyzed in the 3 groups. Among 64 enrolled patients, BAD was the most common cause of isolated pontine infarct. The BAD group had a higher frequency of abnormal ABI and hypertension than the SVO group. The BAD group had abnormal ABI and hyperlipidemia more frequently than the LAA group. No significant difference was found in diabetes or brachial-ankle pulse wave velocity incidence between the BAD and SVO groups. ABI and vascular risk factors in the BAD group were more similar to those in the LAA group than to those in the SVD group. This finding suggests that pontine lesions extending to the basal pontine surface have an atherosclerotic mechanism in BAD, requiring potent antiplatelet therapy for the secondary prevention of ischemic stroke.

Abbreviations: ABI = ankle-brachial index, BAD = branch atheromatous disease, baPWV = brachial-ankle pulse wave velocity, LAA = large-artery atherosclerosis, PAD = peripheral arterial diseases, SVO = small vessel occlusion.

Keywords: ankle-brachial index, atherosclerosis, branch atheromatous disease, pons, pontine infarct, small vessel occlusion

1. Introduction

Cerebral infarction, a pathological condition arising from the obstruction of cerebral blood vessels, manifests due to diverse etiological factors. Cerebral infarction is classified based on the etiology of cerebral blood vessel blockage, facilitating a targeted therapeutic approach tailored to the specific etiology of the cerebral infarction. One such classification system is the Trial of Org 10172 in the Acute Stroke Treatment classification system.[1] Small vessel occlusion (SVO)—lacunar cerebral infarction—is caused by occlusion of a perforating artery corresponding to a small cerebral blood vessel. The penetrating arteries mainly exist in the basal ganglia, corona radiata, thalamus, and pons. An isolated cerebral infarct lesion ≤ 20 mm in one of these areas without ≥ 50% stenosis or occlusion in the proximal artery of the perforating artery is classified as SVO. However, the mechanism by which the penetrating artery is stenotic or occluded remains unclear. The mechanisms discussed thus far include the theory that atherosclerosis may play a role even in small vessels, lipohyalinosis may cause SVO, and an atheromatous plaque at the orifice of the perforating artery that is thin such that it cannot be seen on cerebrovascular images can block the perforating artery (branch atheromatous disease, BAD).[2] Based on these mechanisms, strong antiplatelet agents and statins are emphasized to treat atherosclerosis, and safer antiplatelet agents are emphasized owing to the risk of cerebral hemorrhage due to lipohyalinosis. Therefore, determining the mechanism of lacunar infarction is crucial for treatment.

The pons is a region where perforating arteries exist, and the paramedian artery, which branches from the basilar artery, serves as a perforating artery. Pontine infarction due to large-artery atherosclerosis (LAA) is characterized by significant stenosis or occlusion of the basilar or vertebral arteries. The lesions of the pons infarction caused by BAD extend to

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the basal surface of the pons, and pontine infarct lesions due to SVO are confined to the middle part of the pons, discontinuously away from the basal surface of the pons.[3–7] BAD is a mild condition of LAA and is reportedly a mechanism of intracranial atherosclerotic disease.[7–9] During the acute stroke phase, early neurological deterioration occurs more frequently in BAD than in SVO, and the prognosis is worse.[10,11] Several studies have provided evidence suggesting that the lesion extended to the basal surface of the pons because of atherosclerosis-associated BAD.[12,13]

Cerebral and peripheral arterial diseases (PAD) share atherosclerosis as a common mechanism. PAD is broadly defined as stenosis or aneurysm of the aorta and its branch arteries but is generally defined as stenosis of the lower extremity arteries.[14,15] Approximately 10% of patients with cerebral artery disease have PAD.[16] Patients with cerebral infarction alongside PAD have more severe neurologic deficits and are more likely to have stroke recurrence than those without PAD.[17,18] This is consistent with the fact that cerebral infarction due to atherosclerosis has a worse prognosis than cerebral infarction caused by SVO.

If pontine infarction due to BAD occurs as a mechanism of atherosclerosis, more atherosclerotic comorbidities of pontine infarction are due to LAA than SVO, especially PAD. However, no study has been conducted to date. Thus, we hypothesized that PAD would be more common in patients with pontine infarction due to BAD than in those caused by SVO. This study aimed to determine whether patients with pontine infarction due to BAD had more PAD than those with pontine infarction caused by SVO after classifying patients with pontine infarction into 3 groups according to the shape of the infarction lesions: SVO, BAD, and LAA.

2. Methods

2.1. Study design and patients

The clinical and imaging data of patients consecutively admitted to Daegu Catholic University Medical Center within 1 week of symptom onset due to acute cerebral infarction or transient ischemic attack between August 2016 and July 2019 were retrospectively analyzed. Acute cerebral infarction was observed as high signal intensities on brain MR diffusion-weighted imaging. Transient ischemic attack was defined as cases with complete disappearance and improvement of stroke symptoms within 24 hours, regardless of brain MR diffusion-weighted imaging findings. The inclusion criterion for this study was an isolated single infarction lesion in the pons. Exclusion criteria were as follows: multiple cerebral infarct lesions, atrial fibrillation, failed ankle-brachial index (ABI), and not undergoing brain MR or CT angiography imaging. This study was approved by the institutional review board of our medical institution. The requirement for informed consent was waived owing to the retrospective nature of the study.

2.2. Brain image analysis and classification

For isolated pontine infarctions, we investigated whether there was only one high-intensity signal in the pons using brain MR diffusion-weighted imaging. The shape of the pons lesion was classified as follows: continuously centered on the basal surface of the pons and only in the middle of the pons, discontinuously away from the basal surface of the pons. Two doctors blinded to the patients' clinical information independently performed brain image analysis. In cases of disagreement, a third doctor (neuroradiologist) was consulted to reach a consensus.

Acute isolated pontine infarcts were classified into 3 groups: cases with ≥ 50% stenosis or occlusion in the basilar or vertebral artery (LAA), cases without stenosis or occlusion in the basilar or vertebral artery with lesions continuously extending to the basal surface of the pons (BAD), and middle lesions discontinuously separated from the basal surface of the pons without stenosis or occlusion in the basilar or vertebral artery (SVO) (Fig. 1).

2.3. ABI measurement

An examiner blinded to the patients' clinical information measured ABI during hospitalization using a VP 2000 (Colin Medical Technology, Komaki, Japan). After measuring the systolic blood pressure of the bilateral posterior tibial and brachial arteries, ABI was calculated by dividing the systolic blood pressure of the bilateral posterior tibial artery by the higher systolic blood pressure of the bilateral brachial artery. ABIs of ≤ 0.9 and ≥ 1.3 were considered abnormal. Furthermore, if either of the bilateral ABI values was abnormal in a patient, it indicated PAD. In addition to ABI, brachial-ankle pulse wave velocity (baPWV) was measured using the same device. Caffeine and smoking were prohibited for 3 hours prior to measuring the baPWV, and after resting for 10 minutes, the mean bilateral baPWV values were analyzed.

2.4. Vascular disease risk factors

This study investigated the risk factors for vascular diseases, including hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, and smoking history. The fasting low-density lipoprotein cholesterol, total cholesterol, and triglyceride levels measured after admission were analyzed. Hypertension was defined as a previous diagnosis of hypertension or receiving medication for hypertension. Diabetes mellitus was defined as having been previously diagnosed with diabetes mellitus, receiving diabetes medication, or having high blood glucose levels (fasting blood glucose ≥ 126 mg/dL or postprandial blood glucose ≥ 200 mg/dL) and an additional HbA1c test result of ≥ 6.5%. Hyperlipidemia was defined as a previous diagnosis of hyperlipidemia or the use of hyperlipidemia medication. Coronary artery disease was defined as angina, myocardial infarction, or coronary artery intervention history. Smoking status was defined as the current smoking status.

2.5. Statistical analysis

We compared ABI, baPWV, and vascular disease risk factors among the 3 groups classified using brain imaging into LAA, BAD, and SVO. We conducted 3 comparisons between BAD and SVO, BAD and LAA, and SVO and LAA. Categorical variables were analyzed using the chi-square or Fisher exact tests, whereas continuous variables were analyzed using the Student *t* test. Statistical analysis was performed using SPSS version 18.0 for Windows (SPSS Inc. Chicago, IL, USA), and statistical significance was set at $P < .05$.

3. Results

Between August 2016 and July 2019, 2176 patients were admitted for acute cerebral infarction or transient ischemic attack. Of these, 169 patients with isolated pontine infarction were included in the study. Subsequently, 65 patients with severe stroke symptoms or an inability to measure ABI during hospitalization, 23 with concomitant atrial fibrillation, and 17 without intracranial and extracranial angiography were excluded. Finally, 64 patients were included in the analysis.

3.1. Baseline characteristics according to stroke mechanism

The mean age was 69 ± 13.5 years, and males accounted for 59.4%. The most common stroke mechanism was BAD, followed by SVO and LAA; however, their frequencies were similar. Hypertension was most common in the BAD group (87%),

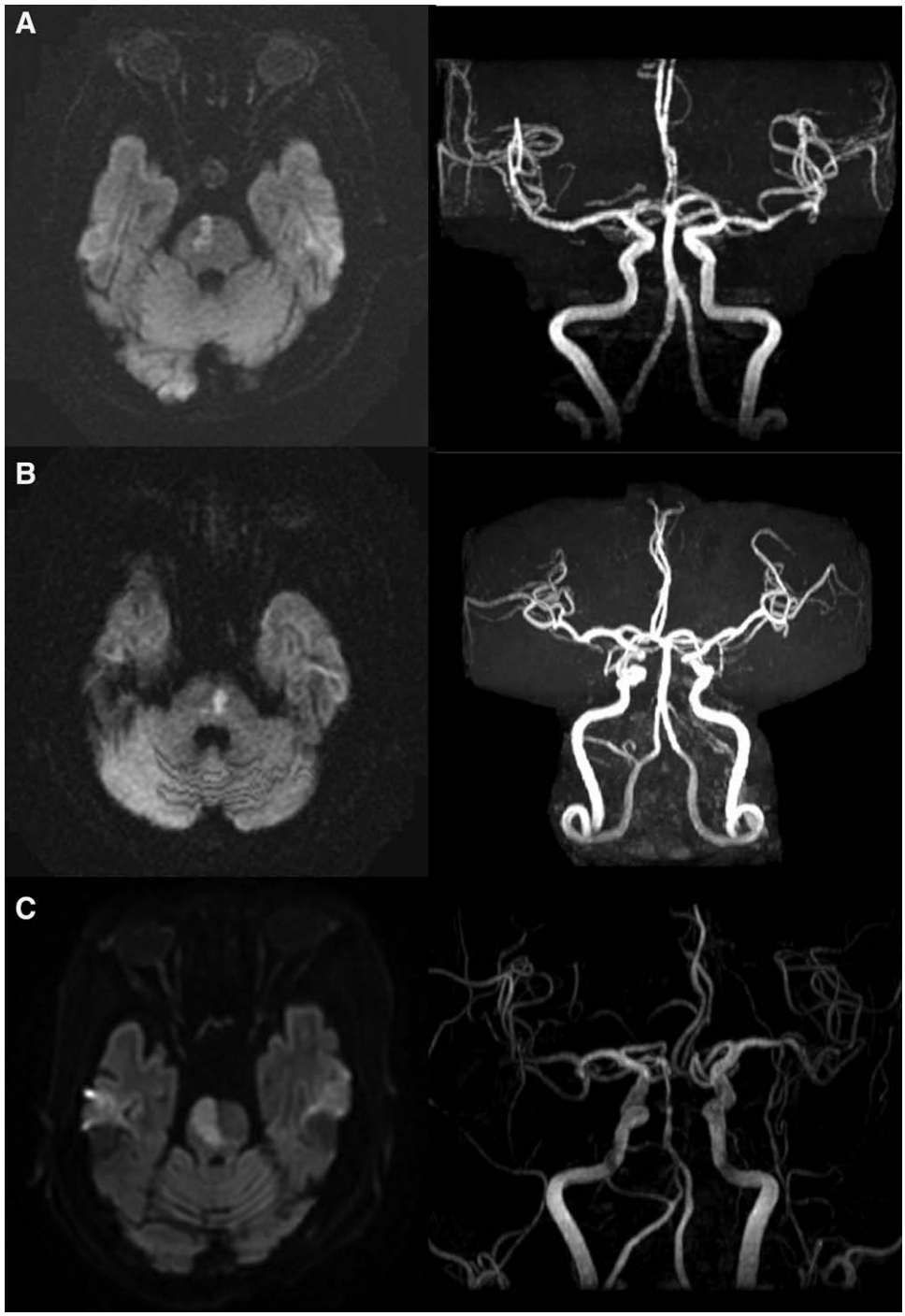

Figure 1. Typical images on MR diffusion-weighted images (DWI) and MR angiography (MRA) of the 3 groups. (A) MR DWI revealing a substantial infarct extending to the pontine basal surface with a normal basilar artery on MRA (BAD). (B) MR DWI showing a lacunar pontine infarction not extending to the basal pontine surface with a normal basilar artery on MRA (SVO). (C) MR DWI revealing a substantial infarct extending to the basal pontine surface with severe basilar artery stenosis on MRA (LAA).

whereas hyperlipidemia was similar between the BAD and SVO groups (87% and 81.8%, respectively) (Table 1). An abnormal ABI was most common in patients with BAD (47.8%) (Table 2).

3.2. Comparison between BAD and SVO

Compared to those with SVO, patients with BAD had a higher prevalence of hypertension (87% vs 54.5%, $P = .023$) and abnormal ABI (47.8% vs 4.5%, $P = .002$). Additionally, patients with BAD had a higher prevalence of diabetes ($P = .088$), total cholesterol, and low-density lipoprotein cholesterol ($P = .069$ and $P = .067$, respectively) than those with SVO. No significant differences were observed in age, sex, hyperlipidemia, triglycerides, coronary artery disease, smoking, or baPWV between the groups.

3.3. Comparison between BAD and LAA

Patients with BAD had more hyperlipidemia (87% vs 47.4%, $P = .008$) and an abnormal ABI (47.8% vs 15.8%, $P = .048$) than those with LAA. No differences were observed in other

Table 1

Basic characteristics and vascular risk factors in the 3 stroke mechanisms.

	SVO (n = 22)	BAD (n = 23)	LAA (n = 19)	BAD vs SVO *P* value	BAD vs LAA *P*-value	SVO vs LAA *P* value
Age, yr	67.8 ± 13.2	70.0 ± 12.5	69.2 ± 15.4	.580	.854	.766
Male, %	13 (59.1)	14 (60.9)	11 (57.9)	.903	.845	.938
Hypertension, %	12 (54.5)	20 (87.0)	14 (73.7)	.023	.433	.205
Diabetes, %	6 (27.3)	12 (52.2)	7 (36.8)	.088	.320	.511
Hyperlipidemia, %	18 (81.8)	20 (87.0)	9 (47.4)	.699	.008	.026
Total cholesterol, mg/dL	164.2 ± 43.5	183.8 ± 24.5	173.6 ± 38.0	.069	.302	.469
LDL cholesterol, mg/dL	105.5 ± 40.6	125.2 ± 29.1	119.4 ± 37.7	.067	.576	.265
Triglyceride, mg/dL	123.4 ± 98.3	130.4 ± 59.3	113.2 ± 46.9	.773	.311	.682
Coronary disease, %	2 (9.1)	2 (8.7)	1 (5.3)	1.000	1.000	1.000
Smoking, %	7 (31.8)	5 (21.7)	5 (26.3)	.445	.729	.699

BAD = branch atheromatous disease, LAA = large-artery atherosclerosis, SVO = small-vessel occlusion.

Table 2

Comparison of ankle-brachial index and brachial-ankle pulse wave velocity by stroke etiology.

	SVO	BAD	LAA	BAD vs SVO *P* value	BAD vs LAA *P* value	SVO vs LAA *P* value
Abnormal ABI, %	1 (4.5)	11 (47.8)	3 (15.8)	.002	.048	.321
Mean baPWV, cm/s	2070.1 ± 481.4	2150.4 ± 559.9	2093.1 ± 480.7	.609	.727	.879

ABI = ankle-brachial index, BAD = branch atheromatous disease, baPWV = brachial-ankle pulse wave velocity, LAA = large artery atherosclerosis, SVO = small vessel occlusion.

vascular risk factors, such as hypertension, diabetes, coronary artery disease, smoking, or baPWV, between the 2 groups.

3.4. Comparison between SVO and LAA

The prevalence of hyperlipidemia was higher in patients with SVO than in those with LAA (81.8% vs 47.4%, $P = .026$). No differences existed in ABI, baPWV, or other vascular risk factors between the 2 groups.

4. Discussion

Cerebral infarctions in the deep brain, which is supplied by the perforating artery, were first classified into 4 categories by Caplan in 1989: when the perforating artery itself is occluded due to atherosclerosis or lipohyalinosis; when embolism from the proximal artery stenosis or occlusion of the perforating artery causes a borderzone infarct due to artery-to-artery embolism or hemodynamic mechanisms; cardiogenic embolism; and when the orifice of the perforating artery is occluded due to atherosclerosis, obstructing blood flow through the perforating artery.[2] Of these 4 mechanisms, the first corresponds to SVO, the second to LAA, and the fourth to BAD. Therefore, SVO partially includes the mechanism of atherosclerosis, whereas BAD and LAA are mainly influenced by atherosclerosis. Thus, pontine infarction caused by BAD is between the mechanisms of SVO and LAA but is closer to the mechanism of LAA and is likely to be accompanied by the atherosclerotic vascular disease observed in LAA.

This study investigated whether pontine infarction due to BAD accompanies PAD, which is suggestive of atherosclerosis, more frequently than SVO pontine infarction. The main finding was that an abnormal ABI was more frequent in BAD than in SVO pontine infarction. This result is consistent with another study indicating that risk factors for vascular disease, such as hemoglobin A1c, are more prevalent in BAD pontine infarction than in SVO.[13] In another study comparing BAD, SVO, and LAA pontine infarction, white matter lesions on brain MRI, which are characteristic of SVO, were significantly more frequent in SVO than in BAD and LAA.[12] These results and those of our study provide evidence that the BAD mechanism is more likely due to atherosclerosis than lipohyalinosis. Thus, the secondary prevention strategies for stroke due to atherosclerosis in BAD and lipohyalinosis in SVO may differ.

The frequency of the 3 mechanisms was the highest in BAD, consistent with other studies.[12] Hypertension was not consistently higher in BAD than in SVO. Diabetes mellitus was consistently more prevalent in BAD than in SVO.[12,13] Total cholesterol and low-density lipoprotein cholesterol level were higher in BAD than in SVO, consistent with LAA pathogenesis. However, hyperlipidemia was more prevalent in the BAD and SVO groups than in the LAA group, and abnormal ABI was more prevalent in the BAD group than in the LAA group. This may include mechanisms unrelated to atherosclerosis, such as vertebral artery hypoplasia or dissection, which are difficult to distinguish on routine MR angiographic images. This is consistent with the findings of other studies showing that vascular risk factors are more commonly associated with BAD than with LAA.[12,13]

This retrospective study had a small sample size, with many patients who met the exclusion criteria. In addition, since the results were from a single tertiary care hospital, it may not be generalizable. A limitation of this study is that several patients had severe symptoms of cerebral infarction or were unstable, and ABI could not be measured during hospitalization. Additionally, arterial dissection and hypoplasia in the basilar and vertebral arteries were not completely excluded using conventional MR angiographic imaging. Further research using high resolution MRI is warranted to identify arterial dissection and hypoplasia.

In conclusion, this study results reveal that pontine infarction due to BAD is more frequently associated with PAD than pontine infarction due to SVO, suggesting that atherosclerosis may be more crucial in the pathological mechanism of BAD than lipohyalinosis. This finding suggests that pontine lesions extending to the basal pontine surface have an atherosclerotic mechanism in BAD, requiring potent antiplatelet therapy for the secondary prevention of ischemic stroke.

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