ORIGINAL

Association between middle cerebral artery morphology and branch atheromatous disease

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Abstract : Introduction : Branch atheromatous disease (BAD) is a type of cerebral infarction caused by stenosis or occlusion at the entrance of the penetrating branch due to the presence of plaque. Despite its clinical significance, it is not clear how these plaques are formed. Focal geometrical characteristics are expected to be as important as vascular risk factors in the development of atherosclerosis. This study aimed to analyze the association between middle cerebral artery (MCA) geometric features and the onset of BAD. Shear stress results from the blood flow exerting force on the inner wall of the vessels and places with low wall shear stress may be prone to atherosclerosis. At the curvature of blood vessels, the shear stress is weak on the inside of the curve and plaque is likely to form. When this is applied to the MCA M1 segment, downward type M1 is likely to form plaques on the superior side. Because the lenticulostriate artery usually branches off from the superior side of the MCA M1 segment, in downward type M1, a plaque is likely to be formed at the entrance of the penetrating branch, and for that reason, BAD is likely to onset. Methods : We retrospectively reviewed hospitalized stroke patients with BAD and investigated the morphology of their MCA using magnetic resonance imaging. The M1 segment was classified as straight or curved. Additionally, we compared the difference between the symptomatic and the asymptomatic side. Data regarding patients' medical history were also collected. Results : A total of 56 patients with lenticulostriate artery infarctions and BAD were analyzed. On the symptomatic side, downward type M1 accounted for the largest proportion at 44%, whereas on the asymptomatic side, it was the lowest, at 16%. Conclusion : A downward type MCA may be associated with the onset of BAD and the morphological characteristics might affect the site of plaque formation. J. Med. Invest. 70 : 411-414, August, 2023

Keywords **:** *Branch atheromatous disease, shear stress, middle cerebral artery, morphology*

INTRODUCTION

Branch atheromatous disease (BAD), which accounts for 10.3%–10.8% of all cerebral infarctions (1, 2), is caused by stenosis or occlusion due to localized plaque formation at the entrance of the penetrating branch (3). Symptom exacerbation after hospitalization, such as progressive motor deficits, is seen in 17%–75% of patients with BAD (4). Thus, early diagnosis and treatment are crucial. Despite its clinical significance, it is not yet clear how plaques form at the entrance of the penetrating branch.

Studies on coronary arteries have shown that arterial geometric features such as curvature and bifurcation are associated with altered hemodynamic flow, plaque formation, and progression, as well as ischemic events (5). Moreover, plaques tend to form at segments opposite to flow dividers (6). The relationship between geometric features and plaque distribution of the middle cerebral artery (MCA) has been shown (7-9).

However, few have studied the relationship between vascular morphology and the development of cerebral infarction.

Considering the fact that BAD is caused by occlusion at the entrance of the penetrating branch, focal geometrical characteristics are expected to be as important as vascular risk factors in the development of atherosclerosis. In this study, we aimed to analyze the association between MCA geometric features and the onset of BAD using magnetic resonance imaging (MRI).

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MATERIALS AND METHODS

We retrospectively reviewed our single institutional database of hospitalized stroke patients between April 2016 and December 2020 and enrolled patients with BAD during the study period.

We diagnosed BAD by the following radiographic criteria. (a) infarcts with size more than 10 mm in diameter on axial slice and visible for 3 or more axial slices on diffusion-weighted images (DWI) of the lenticulostriate artery (LSA) area. (b) No $\geq$ 50% stenosis on the parent artery of the criminal vessel (corresponding middle cerebral artery), confirmed by magnetic resonance angiography (MRA) or computed tomography angiography (CTA). These are based on the diagnostic criteria widely used in past BAD studies (10, 11). BAD also develop in the pons, But in this study, only patients with cerebral infarction in the LSA area were included.

Patients were excluded if they had evidence of cardioembolism (atrial fibrillation, left atrial/ventricular thrombus identified by echocardiography, recent myocardial infarction within 1 month), $>$ 50% stenosis of the responsible parent artery (internal and external carotid artery, MCA), multiple cerebral infarctions in locations other than the LSA , and other determined etiologies (vasculitis, arterial dissection, Moyamoya disease, cancer-associated thrombosis, antiphospholipid antibody syndrome, etc.). We classified infarcts in the LSA area of 2 slices or less in axial diffusion-weighted images as lacunar and distinguished them from BAD. We classified infraction lies between the tip of the anterior horn and the top of the superior limb of the insular cleft in the coronal section of MRI diffusion weighted images as Long insular artery infraction, and distinguished them from BAD (12). Exacerbation of symptoms is defined as an increase in NIHSS score of 1 or more and no new cerebral infarction or intracranial hemorrhage on MRI.

The M1 segment shape was classified as straight or curved, based on the coronal maximum intensity projection images of three-dimensional time-of-flight magnetic resonance angiography. We determined the direction of the M1 segment in which the curve opened. A line was drawn from the bifurcation points of M1 and anterior cerebral artery to the bifurcation points of M2 (shown in Fig. 1). If the vertex of the curve was above this line, then it was classified as upward type M1, and downward type if it was below. If there were no vertices, then it was classified as straight type. If the M1 had more than two angles (like the S-shaped), It was classified in the direction that is the largest angle with respect to A line.

And we investigated whether there was a shape difference between the MCA on the symptomatic and the asymptomatic side. The symptomatic side is the side that developed BAD, and the asymptomatic side is the MCA that did not develop BAD. As described in the discussion, we assumed that BAD is more likely to occur in the downward type M1, and compared the ratio of downward type M1 between the symptomatic side and the asymptomatic side. We also collected data regarding the medical history, such as hypertension, diabetes, dyslipidemia, smoking status, and atrial fibrillation of each patient.

Statistical Analysis

We analyzed the difference in the shape of the M1 segment between the symptomatic and asymptomatic sides. Univariate comparisons between categorical variables were performed using the $\chi 2$ test, Fisher's exact test, and unpaired t-test. All statistical tests were 2-sided with p values of < 0.05 used to denote significance.

RESULTS

A total of 846 patients with cerebral infarction were hospitalized during the study period. Among them, 56 patients (6%) had BAD in the LSA territories.

A total of 56 patients with BAD and LSA territory infarctions were included in this study. The M1 segment shapes are listed in Table 1. On the symptomatic side, downward type M1 accounted for the largest proportion at 44% and was the lowest on the asymptomatic side at 16%. On the other hand, on the asymptomatic side, the upward type was the most common (64%). Patient characteristics, stratified by each M1 shape are summarized in Table 2. The mean age, prevalence of male sex, hypertension, diabetes, dyslipidemia and smokers were not significantly different between the each groups.

DISCUSSION / CONCLUSION

In this study, we found that the M1 shape that led to BAD was more often the downward type than upward or straight.

BAD is caused by stenosis or occlusion at the entrance of the penetrating branch due to localized plaque formation. However, it is not clear how these plaques occur. Studies on coronary arteries have shown that geometric features such as curvature and bifurcation are associated with altered hemodynamic flow, plaque formation, and progression (5). In addition, the relationship

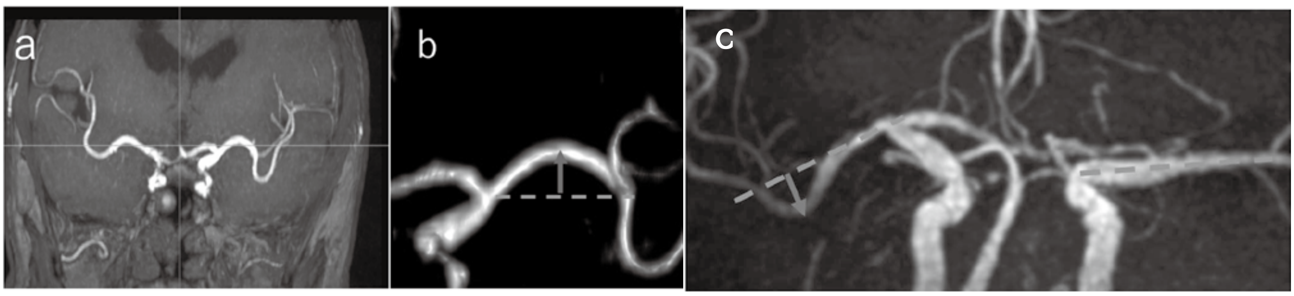

Fig 1.
a. M1 segment shape classification as straight or curved based on the coronal maximum intensity projection images of three-dimensional time-of-flight magnetic resonance angiography.
b. A line was drawn from the M1 origin to M2 bifurcation, and the vertices of the curves were evaluated based on whether they were above or below this line.
c. The right MCA is downward type, and the Left MCA is straight type.

Table 1. M1 segment shape classification.

	symptomatic side	asymptomatic side	*p*-value
Downward type	25 (44%)	9 (16%)	0.001
Upward type	20 (35%)	36 (64%)	0.004
Straight type	11 (19%)	11 (19%)	1

between MCA geometric features and plaque distribution has been reported in some studies (7-9). Shear stress is the result of the force that blood flow exerts on the inner walls of blood vessels. In locations where the shear stress is strong, there is antithrombotic action and plaques are hard to form. In contrast, low shear stress may initiate the process of atherosclerosis through endothelial dysfunction and secondary inflammation (13). At the curvature of blood vessels, the shear stress is exerted strongly on the outside of the curve and plaques are difficult to form, whereas on the inside, this stress is weak and plaques are more likely to form (14, 15). When this is applied to the MCA M1 segment, inferior side plaques are more likely to form in upward type M1, while superior side plaques are more likely to form in downward type M1. A previous study that investigated the relationship between MCA geometric features and plaque distribution supported this finding (6).

Considering the reason for the result of this study that most of the MCA that caused BAD were downward type, because the LSA usually branches off from the superior side of the MCA M1 segment (16), in downward type M1, a plaque is likely to be formed at the entrance of the penetrating branch (9), and for that reason, BAD is likely to onset in downward type MCA in this study (shown in Fig. 2).

A previous report has shown among the healthy population, the curved MCA is the most common and the straight type is the least (17). However, it is not yet clear what factors affect the formation of the M1 shape. In this study, the prevalence of hypertension, diabetes, and dyslipidemia was not significantly different between the groups, whereas smoking was more prevalent among those with a downward type M1. Smoking causes vascular endothelial injuries, which lead to functional and structural alterations (18). Endothelial dysfunction may cause abnormal contraction and dilation, resulting in the flexion of blood vessels.

Our study had several limitations. Firstly, the retrospective design could introduce a systematic selection bias, thus it cannot be used to prove causality. Moreover, the morphology of the MCA was only evaluated in two dimensions on the coronal side. However, because the actual MCA runs in three dimensions, including the axial side, it is necessary to evaluate them for increased accuracy. However, this is very complicated and difficult to apply to clinical practice. Therefore, a simpler and more practical evaluation method was used in this study.

In conclusion, we found that downward type MCA may be associated with the onset of BAD and that the morphological characteristics might affect the site of plaque formation.

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Table 2. Patient characteristics stratified by downward vs. non-downward type.

	Downward type (n = 25)	Upward type (n = 20)	Straight type (n = 11)	*p*-value
Male, n (%)	21 (84)	16 (80)	10 (90)	0.92
Age (mean ± SD) years	70.6 ± 13.6	73.4 ± 10.3	71.0 ± 9.5	0.93
Hypertension, n (%)	21 (84)	15 (75)	10 (90)	0.96
Dyslipidemia, n (%)	15 (60)	10 (50)	7 (63)	0.99
Diabetes, n (%)	9 (36)	8 (40)	3 (27)	0.99
Smoker, n (%)	15 (60)	11 (55)	4 (40)	0.98

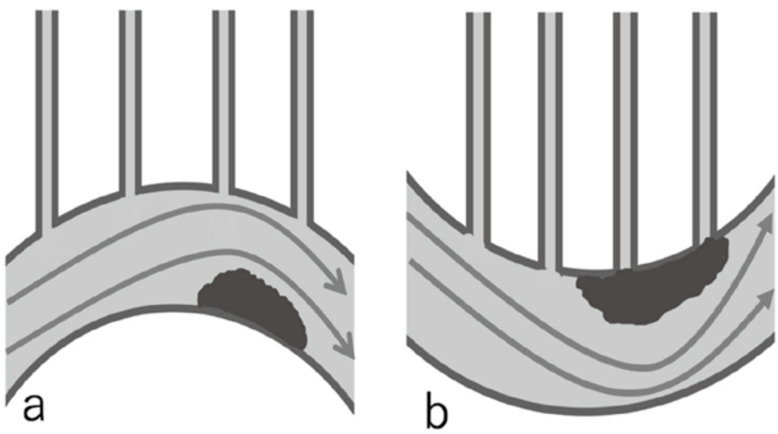

Fig 2.
a. Upward type M1 is more likely to form plaques on the inferior side of the blood vessel.
b. Downward type M1 is more likely to form plaques on the superior side of the blood vessel and block the entrance of the penetrating branch.

AUTHOR CONTRIBUTIONS

Sayori Hanasiro and Kenichi Suzuki conceived the idea of the study. Masaru Yanagihashi and Takehisa Hirayama developed the statistical analysis plan. Junpei Nagasawa draft the original manuscript. Osamu Kano and Masaaki Hori supervised the conduct of this study.

All authors reviewed the manuscript draft and revised critically on intellectual content. All authors approved the final version of the manuscript to be published.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author upon reasonable request.

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the ethics committee of Toho University Omori Medical Center (M20187) and was conducted according to the Declaration of Helsinki and current legal regulations in Japan. The potential participants were given the opportunity to decline to be further enrolled in the study (opt-out).

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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