Research article

Vascular tortuosity is related to reduced thalamic volume after middle cerebral artery occlusion

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ABSTRACT

Objectives: The mechanisms underlying secondary brain injury in remote areas remains unclear. This study aimed to investigate the relationship between vascular tortuosity and thalamic volume. Methods: In this study, we retrospectively analyzed sixty-five patients with unilateral middle cerebral artery occlusion (MCAO) who underwent magnetic resonance angiography. We compared the vascular tortuosity in patients with MCAO and controls, and analyzed the relationship between vascular tortuosity and thalamic volume. Results: Compared with controls, the MCAO group exhibited a significantly smaller thalamus volume on the affected side (5874 ± 183 mm^3 vs. 5635 ± 383 mm^3, $p < 0.0001$). The vascular tortuosity of the posterior cerebral artery (PCA) was higher in the MCAO group than in the controls (82.8 ± 17.3 vs. 76.7 ± 17.3, $p = 0.040$). Logistic regression analysis revealed that PCA tortuosity was an independent risk factor for reduced thalamic volume after MCAO ($p = 0.034$). In the subgroup analysis, only the 4-7-day group was not statistically different in thalamic volume between the MCAO and control groups. In the MCAO group, patients older than 60 years and female patients had a more tortuous PCA. Conclusion: Reduced thalamic volume after MCAO was associated with a tortuous PCA. After MCAO, PCA tortuosity increased more significantly in patients aged >60 years and in female patients.

1. Introduction

Cerebral infarction accounts for 70% of all strokes and has recently become a leading cause of death in China [1]. Most survivors have permanent neurological dysfunction that reduces their ability to perform activities of daily living.

Cerebral infarction not only causes neuronal cell degeneration at ischemic sites but also leads to secondary brain injury in remote areas, such as the thalamus. In 1914, Von Monakow introduced the term 'diaschisis' to describe this phenomenon which he defined as the reduction of function, metabolism, and perfusion in brain areas distant from the cerebral lesion [2,3]. Although there is no obvious stenosis of the vertebrobasilar artery, neuronal loss [4,5], shrunken cytoplasm, and pyknotic nuclei [6] in the ipsilateral thalamus are still observed. Previous studies have shown that secondary brain injury of the thalamus may be related to oxidative stress, autophagy

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activation, axonal degeneration, neurotrophic disorders, and inflammatory responses [5–10]. Post-infarction transneuronal degeneration may also be a crucial mechanism [11]. A study by Tamura et al. [12] showed that the thalamus progressively shrinks after middle cerebral artery occlusion (MCAO). Kuchcinski et al. [13] found that, depending on the initial infarct location, iron accumulates in the ipsilateral thalamus after cerebral infarction. Reidler et al. [14] demonstrated that patients with middle cerebral artery (MCA) stroke had ipsilateral thalamic hypoperfusion. However, the mechanisms underlying secondary brain injury in remote areas remain poorly understood.

Previous studies have revealed that vascular tortuosity is associated with various diseases such as the development and metastasis of tumors [15,16], aneurysms [17], hypertension [18], and diabetes [19]. Some studies suggested that increased vascular tortuosity augments the distribution of flow disturbances and may increase the risk of atherosclerosis [20,21]. Tortuous blood vessels may cause damage to remote parts owing to slow blood flow, changes in intravascular hemodynamics, and the formation of microthrombi. To the best of our knowledge, few studies have focused on the relationship between vascular tortuosity and secondary brain injuries. Therefore, we compared the tortuosity between patients with MCAO and controls. We first confirmed that patients with MCAO infarction had a reduced thalamic volume and then explored the relationship between **reduced thalamic volume after** MCAO.

2. Materials and methods

2.1. Ethics approval

This study was conducted retrospectively using data obtained for clinical purposes. The Committee of Medical Ethics of the First Affiliated Hospital of Guangxi Medical University approved this study. The need for informed consent was waived because patient data were de-identified for our retrospective study.

2.2. Study subjects

We retrospectively analyzed patients with unilateral MCAO who underwent magnetic resonance angiography (MRA) by two neuroradiologists at the First Affiliated Hospital of Guangxi Medical University between February 2015 and April 2021. Patients were included according to the following criteria: 1) age >18 years; 2) MCA ischemia caused by the occlusion of M1 and/or M2 of the MCA;
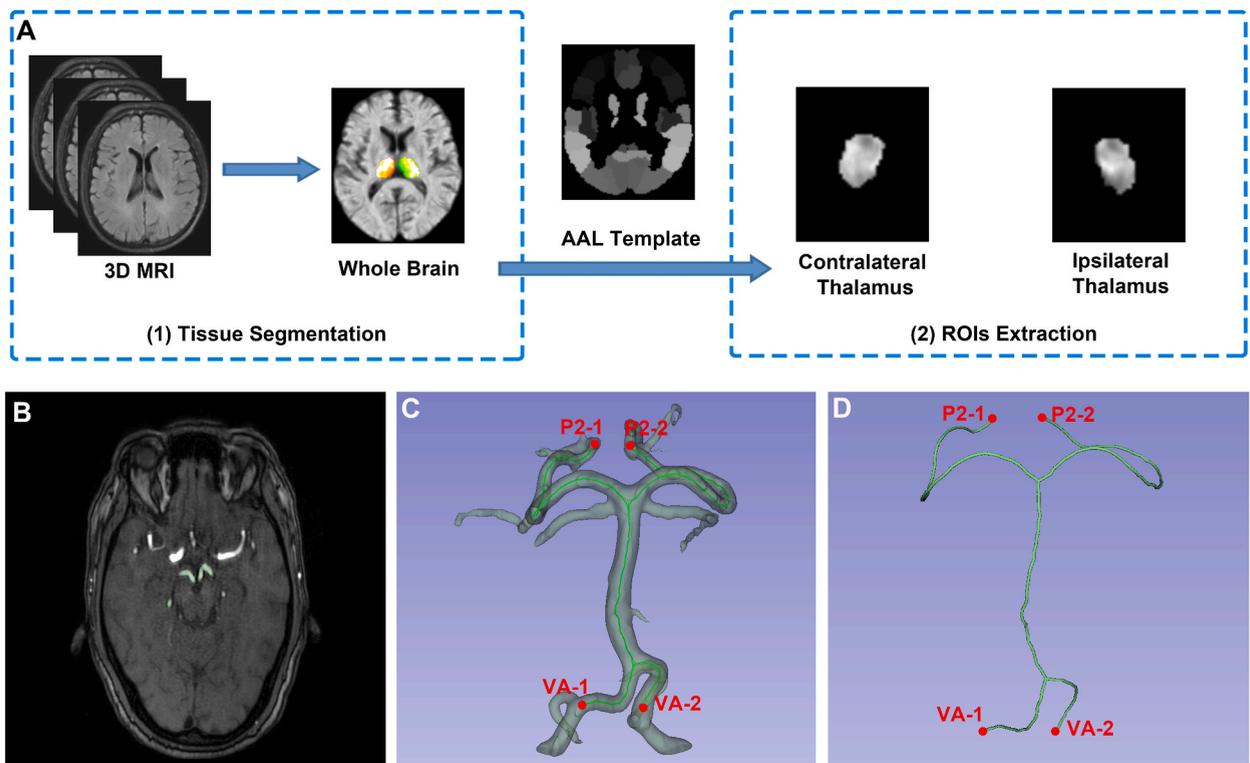

Fig. 1. (A) Process of bilateral thalamus segmentation. Anatomical Automatic Labeling (AAL) as a template for the brain segmentation. The bilateral thalamus was extracted as a region of interest and its volume was calculated. The process of blood vessel centerline extraction is depicted in (B), (C), and (D). (B) Magnetic resonance angiography (MRA) original image. (C) 3D reconstruction of bilateral posterior cerebral artery and basilar artery, point VA-1 and VA-2 were located at V4 segments of the bilateral vertebral artery, point P2-1 and P2-2 were located at the end of P2 of the PCA. (D) The extracted centerline.; VA, vertebral artery; PCA, posterior cerebral artery.

3) vertebrobasilar system without vascular stenosis; 4) adequate quality of MRI and MRA; and 5) MRI performed at least 72 h after cerebral infarction. Patients were excluded according to the following criteria: 1) MCAO caused by embolism, tumor, trauma, inflammation, immune factors, or congenital malformation; 2) history of thalamic lesions; and 3) bilateral MCA stenosis or occlusion. Controls was selected from people who presented for other disorders, did not have organic neurological diseases, and had normal MRA.

Demographic and clinical data of each patient were collected using an electronic medical record system at our institution. Patients' anamnesis, such as hypertension, smoking, diabetes mellitus, history of coronary artery disease, and hyperlipidemia, were also recorded. Hypertension was defined as the use of antihypertensive medication or a blood pressure >140/90 mmHg. Diabetes mellitus was defined as the use of diabetes mellitus medication, fasting blood glucose >126 mg/dL, or 2-h plasma glucose >200 mg/dL. Hyperlipidemia was defined as the use of any lipid-lowering agent, low-density lipoprotein cholesterol level >130 mg/dL, or total cholesterol level >220 mg/dL. Smoking was defined as continuous or cumulative smoking of at least one cigarette per day for more than 6 months. History of coronary artery disease was defined as previously diagnosed coronary heart disease.

2.3. Imaging protocol

MRA and T2 and T1-weighted imaging (T2WI/T1WI) were performed using a 3.0-T scanner (Philips, Achieva, Netherlands). The imaging parameters were TR/TE = 3000/80 ms (T2WI), TR/TE = 2000/20 ms (T1WI), flip angle 120°, matrix 256 × 168, slice thickness 6 mm, and slice number 18. The TOF-MRA parameters were TR = 21 ms, TE = 3.4 ms, FoV = 332 × 176 mm, matrix = 320 × 75, FA = 18°, and 24 contiguous axial sections with 5-mm thickness.

2.4. MRI preprocessing

All original MR images were segmented using the CAT12 (dbm.neuro.uni-jena.de/cat/) toolkit running on MATLAB (The Math-Works Inc., Natick, MA, USA; Fig. 1A). CAT12 is based on SPM12 (fil.ion.ucl.ac.uk/spm/) and was developed by Dr. Christian Gaser and Dr. Robert Dahnke at the Department of Psychiatry and Neurology, Jena University Hospital, Germany. The 'Segment Data' module was used to segment the tissue. This step, mainly via Dartel registration, registers all 3D MR images into the Montreal Neurological Institute (MNI) space (MNI152 T1 1.5 mm brain) to achieve spatial standardization. Finally, we removed the skull tissue from each MR image, obtaining an MR image with 121 × 145 × 121 voxels. Subsequently, we used Anatomical Automatic Labeling (AAL) for brain segmentation. According to the AAL template provided by the MNI, we divided the whole brain into 90 regions and calculated the volumes of the left and right thalamus.

2.5. Measurement of tortuosity

Vascular tortuosity was measured using a 3D image analysis tool (Slicer 4.11.0; open-source software, www.slicer.org; Fig. 1). First, 3D TOF-MRA images (.nii format) were imported, and, if necessary, the transforms module was used to align the sagittal midline of the brain with the Y-axis. As no contrast agent was used to obtain the MRA images, oversampling the image before performing 3D reconstruction of blood vessels by the segment editor module was used to help obtain a better reconstruction effect. After reconstructing the 3D model of the blood vessel, the vascular modeling toolkit module was used to extract the centerline. Vascular tortuosity was measured in the basilar artery (BA) and bilateral posterior cerebral artery (PCA) of both the patients with MCAO and controls. For the BA, tortuosity was measured from the vertebrobasilar junction to the origin of the PCA. For the PCA, tortuosity was measured from the origin of the PCA to the P2 endpoint (Fig. 1C). Tortuosity was calculated using the following formula: [(curve length/straight length −1) × 100] [22]. Here, the curve length is the actual length of the curve, and the straight length is the length of the straight line between the start and end points of the curve.

2.6. Statistical analysis

IBM SPSS Statistics 22 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Continuous variables were expressed as mean ± standard deviation (SD) or median ± interquartile range (QR) The Mann–Whitney test was used when data lacked normal distribution, and the Student's t-test was applied when data were normally distributed. Categorical variables were expressed as frequencies and percentages, and the chi-square test or Fisher's exact test were used to determine correlations. In addition, the correlation between various factors, including vascular tortuosity and secondary brain injury of the thalamus, was investigated using a logistic regression analysis. As there was no difference in the length and tortuosity of the bilateral PCA in the control group, we combined the data of the bilateral PCA in the control group and compared it with the lesioned side of the MCAO group. Results were considered statistically significant at $p < 0.05$.

3. Results

3.1. Demographic and clinical characteristics

A total of 65 patients with MCAO (37 left and 28 right MCAO) and 65 age- and sex-matched controls were included in our retrospective analysis. A flowchart of the recruitment process is shown in Fig. 2. Table 1 lists the characteristics of the patients with MCAO and the controls. Except for hypertension ($p < 0.0001$), the risk factors for cerebral infarction showed no differences between

the two groups.

3.2. Secondary brain injury of the thalamus

The thalamic volume in the MCAO group was markedly smaller than that in the control group ($p < 0.0001$; Table 1). In the MCAO group, the volume of the thalamus on the affected side was smaller than that on the contralateral side (5635 ± 383 mm^3 versus 5754 ± 226 mm^3, $p = 0.033$). In addition to changes in thalamic volume, the ipsilateral thalamus showed spot or plaque-like hypointensity in the T2WI sequence (Fig. 3).

3.3. Length and tortuosity analysis

The tortuosity of the PCA could only be measured in 50 of the 65 patients with MCAO (76.9%) and 56 of the 65 controls (86.2%). The remaining vessels could not be measured because the PCA was supplied by the anterior circulation. The vascular tortuosity of the BA could be measured in all participants in both groups.

There was no difference in the length of the PCA between the affected side and the contralateral side in the MCAO group (61.5 ± 7.6 mm versus 60.2 ± 6.4 mm, $p = 0.367$), but the length of PCA on the affected side in the MCAO group was longer than that in the control group ($p = 0.004$). Further, there was no statistically significant difference in bilateral PCA length in the control group (56.6 ± 7.0 mm versus 59.2 ± 6.8 mm, $p = 0.057$). BA length was similar in the MCAO and control groups ($p = 0.488$).

There was no significant difference in the tortuosity between the left and right PCA in the control group (74.9 ± 17.9 versus 78.5 ± 16.8, $p = 0.273$). The vascular tortuosity of the PCA on the affected side of the MCAO group was higher than that on the contralateral side (82.8 ± 17.3 versus 75.5 ± 16.9, $p = 0.036$) and that in the control group (82.8 ± 17.3 versus 76.7 ± 17.3, $p = 0.040$). The tortuosity of the BA was not significantly different between the MCAO and control groups ($p = 0.120$).

The logistic regression analysis (Table 2) results demonstrated that hypertension (OR 2.659; 95% CI, 1.156–6.120; $p = 0.021$) and the PCA tortuosity on the affected side (OR 1.025; 95% CI, 1.002–1.048; $p = 0.034$) were independent risk factors for reduced thalamic volume after MCAO. Moreover, adjusted for sex and age (OR 1.029; 95% CI, 1.004–1.055; $p = 0.020$) and risk factors for cerebral infarction (OR 1.024; 95% CI, 1.000–1.049; $p = 0.048$), the PCA tortuosity on the affected side was still an independent risk factor for reduced thalamic volume after MCAO.

3.4. Subgroup analysis according to disease course

Patients in the MCAO group were divided into six groups according to the disease course. The numbers of patients in each group were as follows: six in the 4-7-day group, eleven in the 7-14-day group, ten in the 14-30-day group, and nine in the 31-90-day group. Fourteen patients had a disease duration of greater than 90 days, but less than 1 year, and sixteen patients had a disease course of more than 1 year. The thalamic volumes on the affected side in the all patient groups (except for the 4-7-day group) with MCAO were smaller than those on the contralateral side and significantly smaller than those of the control group. The PCA tortuosity on the affected side
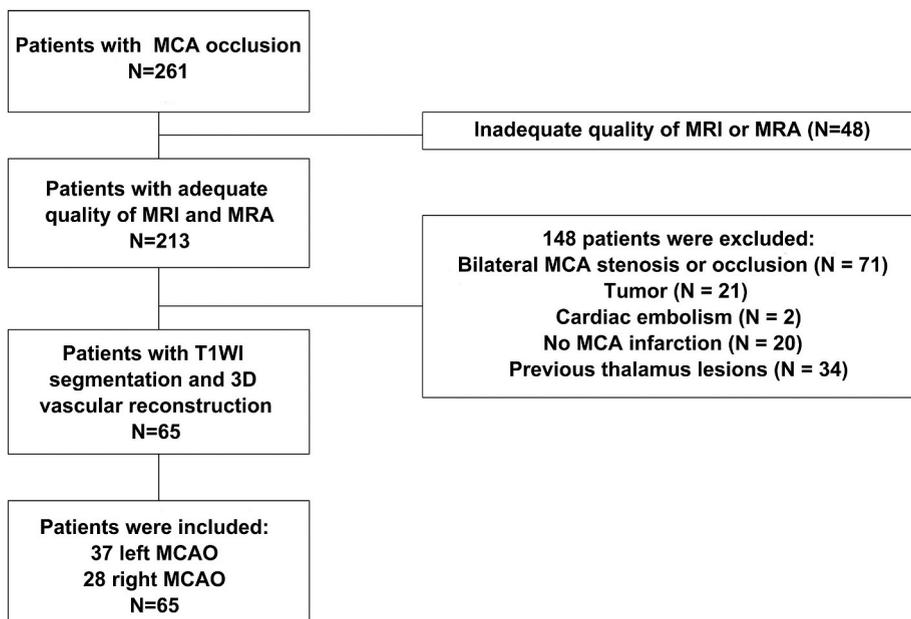

Fig. 2. The flowchart of patient recruitment. MCAO, Middle Cerebral Artery Occlusion; MCA, Middle Cerebral Artery.

Table 1

Comparison between patients with middle cerebral artery occlusion and age- and gender-matched controls.

	MCAO (N = 65)	Controls (N = 65)	p Value
Age, y	62.7 ± 4.8	63.9 ± 13.3	0.518
Women	65.2 ± 14.6	65.0 ± 4.9	0.952
Men	63.3 ± 12.8	61.7 ± 4.5	0.434
Male	46 (70.8)	45 (69.2)	0.848
Hypertension	38 (58.5)	15 (23.1)	<0.0001
Diabetes mellitus	15 (23.1)	5 (7.7)	0.117
Hyperlipidemia	12 (18.5)	21 (32.3)	0.170
Coronary heart disease	1 (1.5)	3 (4.6)	0.365
Smoking	18 (27.7)	13 (20.0)	0.303
Vascular tortuosity			
PCA	82.8 ± 17.3[#]	76.7 ± 17.3[*]	0.040
BA	6.6 (7.2)	6.0 (5.3)	0.120
Vascular length, mm			
PCA	61.5 ± 7.6[#]	57.9 ± 67.0[*]	0.004
BA	28.4 ± 7.4	29.2 ± 5.9	0.488
Thalamic volume	5635 ± 383	5874 ± 183	<0.0001

Results are expressed as number (% column), mean [SD], or median [QR]. Tortuosity was calculated using the following formula: [(curve length/straight length −1) × 100]. MCAO, Middle Cerebral Artery Occlusion; PCA, Posterior Cerebral Artery; BA, Basilar Artery. # Lesion-side data; * combined data from bilateral PCA.
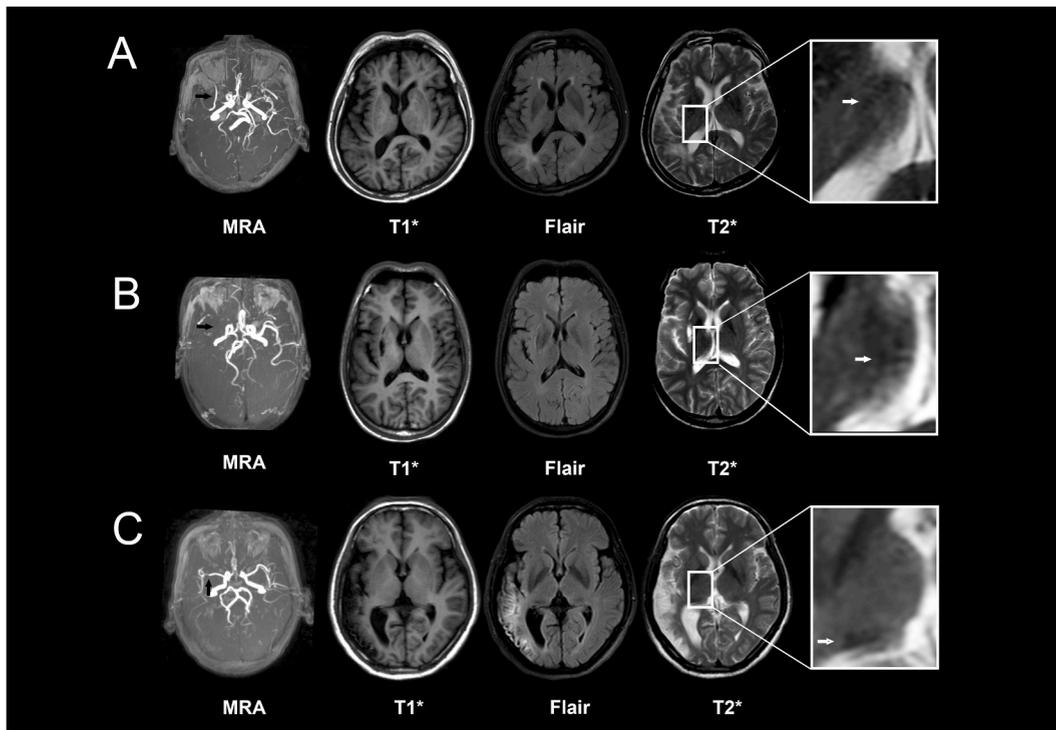

Fig. 3. Exemplary MRI sequences of the ipsilateral thalamus after unilateral middle cerebral artery occlusion. The men aged 40 (A), 73 (B), and 49 (C) were diagnosed with chronic cerebral infarction caused by the occlusion of M1 or/and M2 of the MCA (black arrow), with no thalamus infarction on T1 and FLAIR sequences, but hypointensity (white arrow) in the ipsilateral thalamus on T2 sequences.

was higher than that of the contralateral side in all MCAO subgroups, but the difference was not statistically significant (Fig. 4).

3.5. The relationship between age, sex, and PCA tortuosity

In the MCAO group, the PCA tortuosity of patients aged >60 years was higher than that of patients aged ≤60 years ($p = 0.010$) and that of patients in the control group with the same age ($p = 0.024$). We obtained similar results for patients aged ≤60 years and controls ($p = 0.531$). There was no significant difference in BA tortuosity between the MCAO group and the control group (Fig. 5).

In the MCAO group, the PCA tortuosity of women was higher than that of men ($p = 0.001$), but there was no significant difference in

Table 2

Independent factors associated with secondary brain injury of the thalamus after the occlusion of the lateral middle cerebral artery.

	Crude OR (95% CI)	p Value	Adjusted OR (95% CI)	p Value
Hypertension	2.659 (1.156–6.120)	0.021		
Diabetes mellitus	2.524 (0.711–8.957)	0.152		
Hyperlipidemia	0.588 (0.240–1.441)	0.246		
Coronary heart disease	0.367 (0.037–3.649)	0.393		
Smoking	1.553 (0.553–4.243)	0.413		
Tortuosity of PCA	1.025 (1.002–1.048)	0.034	1.029 (1.004–1.055)[1]	0.020
			1.024 (1.000–1.049)[2]	0.048

CI, confidence interval; OR, odds ratio; PCA, Posterior Cerebral Artery. OR represents the OR value after adjustment for sex and age, and OR[2] represents the OR value after adjustment for risk factors for cerebral infarction.
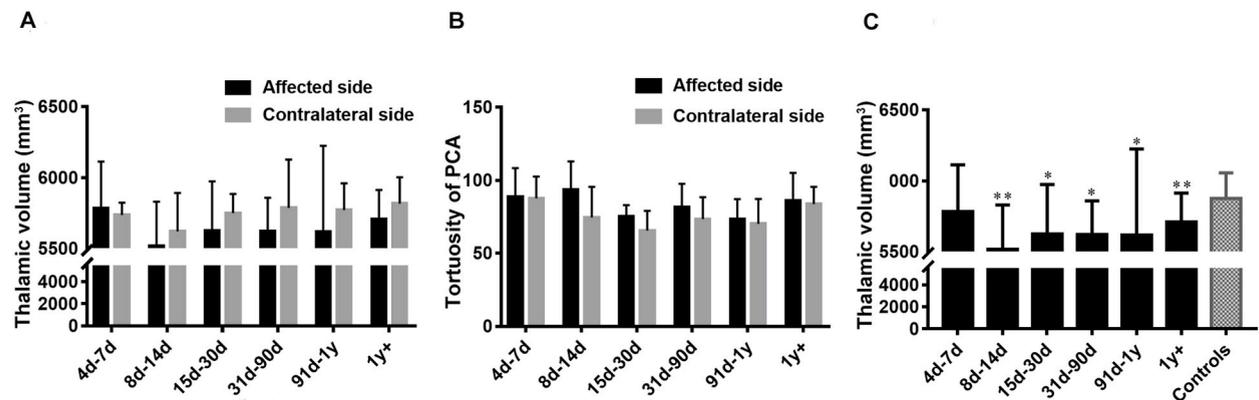

Fig. 4. Thalamic volume (A) and the tortuosity of the posterior cerebral artery (PCA; B) on the affected and contralateral sides in middle cerebral artery occlusion (MCAO) patients. (C) Thalamic volume of patients with MCAO and age- and gender-matched controls. *$p < 0.05$, **$p < 0.01$. d = Day. y = Year.

PCA tortuosity between male and female patients in the control group. There was a statistically significant difference in BA tortuosity between men in the MCAO group and in the control group (Fig. 5).

4. Discussion

In our retrospective study, the thalamic volume on the affected side of the MCAO group was smaller than that of the age- and sex-matched controls. In addition, focal hypointensity of the ipsilateral thalamus in patients with MCAO was identified on T2WI sequences which we interpreted as secondary thalamic neurodegeneration following MCAO. We also observed that the tortuosity of the PCA in the MCAO group was higher than that in the control group. Logistic regression analysis revealed that tortuosity of the PCA was independently associated with reduced thalamic volume after MCAO after adjustment for other confounding factors. To the best of our knowledge, this is the first study showing that tortuosity of PCA is associated with reduced thalamic volume after MCAO.

Our results, which are consistent with previous studies, indicate that the volume of the thalamus is reduced after MCAO due to neuronal degeneration and apoptosis [4,12,23]. Reduction in thalamic volume is an important manifestation of secondary damage after stroke; thus, our results suggest that secondary damage to the thalamus occurred in the MCAO group. Further, hypointensity of the ipsilateral thalamus on T2WI sequences, which is considered to be a manifestation of iron accumulation, is in concordance with previous research results [13,24]. However, it should be noted that the OR for PCA tortuosity was only 1.025, which suggests that PCA tortuosity may be associated with secondary thalamic damage, but that it may not a major clinical risk factor.

A previous study [25] investigated hemodynamic changes caused by increased vessel tortuosity that led to drops in blood flow and chronic ischemia of distal brain tissue. There are three possible reasons for the increased risk of reduced thalamic volume after MCAO. First, thalamic perfusion is reduced after MCAO [14,26]. Second, the blood flow in straight vessels tends to be laminar, arterial bends can cause irregular blood flow [20,27], and the complex disturbed flow may increase the possibility of microthrombosis. Third, increased vascular tortuosity may weaken the arterial wall by increasing the susceptibility to atherosclerosis, and previous studies have shown that increasing vascular tortuosity increases the total area of vascular walls exposed to low and oscillatory wall shear stress (WSS) [20] and increases LDL surface concentrations [28]. Low and oscillatory WSS has been demonstrated to be associated with atherosclerosis [29–31]. In conclusion, MCAO breaks the hemodynamic balance of the entire intracranial system, leading to a possible increase in the vascular tortuosity of the PCA and eventually increasing the risk of reduced thalamic volume after MCAO.

In this study, patients with MCAO were divided into six groups according to the duration of the disease course. We found that the thalamus shrank seven days after cerebral infarction. Animal experiments have shown that massive terminal degeneration and calcium
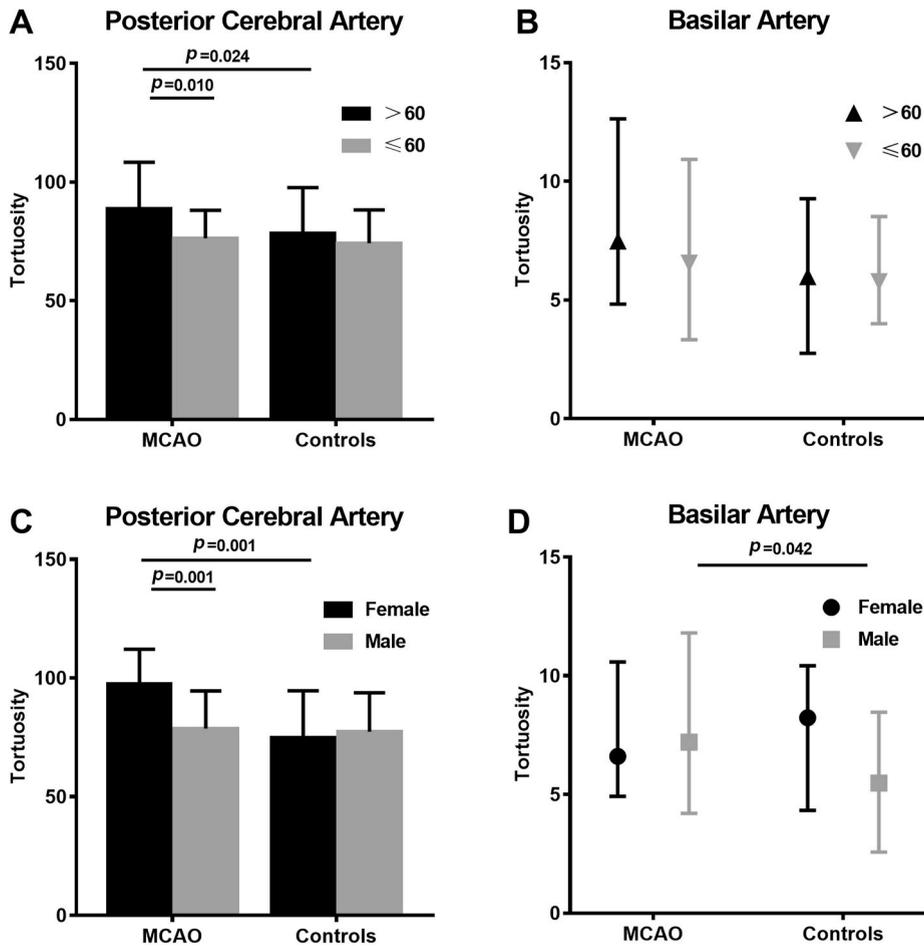
Fig. 5. Tortuosity of the posterior cerebral artery (PCA; A, C) and basilar artery (BA; B, D) in patients with middle cerebral artery occlusion (MCAO) and age- and gender-matched controls.

accumulation appears in the thalamus within three days after MCAO, but no neuronal changes were observed [5]. Seven days after infarction, the cytoplasm of thalamic neurons and the number of neurons were reduced [5,32]. Changes in submicroscopic structural [5], decreases in enzymatic activity [33] and accumulation of calcium [34] may have appeared in a few hours or days after cerebral infarction, but obvious changes in thalamic volume were only visible one week after cerebral infarction [12,23,35]. In all subgroups, the vascular tortuosity of the PCA on the affected side was higher than that on the contralateral side, but the difference was not statistically significant, potentially due to the limited sample size.

Further, the subgroup analysis revealed that PCA tortuosity of patients aged >60 years was higher than that of patients aged ≤60 years. This difference was statistically significant in MCAO group. It has been reported that vascular tortuosity increases with age [36], which, may be related to increased vascular vulnerability, slow blood flow, and compensatory dilation of the proximal vessels. Similarly, Zhang et al. [37] found that patients aged >60 years had an increased risk of developing vertebrobasilar tortuosity. Our results mirror those of previous studies showing that older patients have higher vascular tortuosity. Rots [38] and Bracher [39] found that vascular tortuosity increases after hypoxia, which might explain why we only observed a significant difference in the MCAO group.

Bullitt et al. [36] showed that the average radius of healthy male volunteers was significant higher than that of female volunteers, meanwhile, PCA tortuosity was also higher in men than in women, but not statistically significant. Interestingly, in our study, the PCA tortuosity of women was significantly higher than that of men in the MCAO group, and significant differences in PCA tortuosity between the MCAO group and controls were only observed in female patients. This indicates that the PCA tortuosity of women in the MCAO group increased more easily than that of men. One possible reason is that the average age of the female patients in the MCAO group, who were mostly postmenopausal women, was 63 years. Previous studies have concluded that the tortuosity of the coronary artery increases in postmenopausal women, it may be raleted to age-related increase in sclerostin secretion [40]. It is known that estrogen has an anti-atherosclerotic effect [41], estrogen deficiency may cause greater increases in vessel length and tortuosity [42]. So all of these reasons may cause the vascular vulnerability of postmenopausal women increases, and the resistance to vascular remodeling weakens. Therefore, the blood vessels of the women in the MCAO group may have been more vulnerable and prone to

increase in tortuosity, and this difference may have mainly occurred after MCAO.

The current study has several limitations. First, owing to its retrospective design, we were unable to determine whether the increased tortuosity of the PCA occurred before or after cerebral infarction. Second, the number of patients in our study was small, and the results of the subgroup analysis were underpowered. Third, we only calculated one index of vascular tortuosity. This index is less sensitive to dense and low-amplitude bending [43]. Calculating multiple vascular tortuosity indices or computing fluid dynamics may be better for exploring the relationship between vascular tortuosity and secondary brain injury of the thalamus in terms of hemodynamics.

5. Conclusion

In the present study, the vascular tortuosity of the PCA in the MCAO group was higher than that in the controls, and the vascular tortuosity of the PCA was an independent risk factor for reduced thalamic volume after the occlusion of the lateral MCA. While our results provide new insight into the causes of secondary brain injury in the thalamus, further research with a larger sample is needed.

Author contribution statement

Wenxin Wei: Performed the experiments; Analyzed and interpreted the data; Wrote the paper. Huan Lao: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data. Yafu Tan, Shushu Liang, Ziming Ye: Performed the experiments. Chao Qin, Yanyan Tang: Conceived and designed the experiments; Wrote the paper.

Data availability statement

The authors are unable or have chosen not to specify which data has been used.

Declaration of interest's statement

The authors declare no competing interests.

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