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Retrospective Study

Investigating the Relationship between Intracranial Atherosclerotic Plaque Remodeling and Diabetes Using High-Resolution Vessel Wall Imaging

Relationship between Atherosclerotic Plaque Remodeling and Diabetes

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Abstract

BACKGROUND

Intracranial atherosclerosis, a leading cause of stroke, involves arterial plaque formation. This study explores the link between plaque remodeling patterns and diabetes using high-resolution vessel wall imaging.

AIM

To investigate the factors of intracranial atherosclerotic remodelling patterns and the relationship between intracranial atherosclerotic remodelling and diabetes mellitus using high-resolution vessel wall imaging (HR-VWI).

METHODS

Ninety-four patients diagnosed with middle cerebral artery or basilar artery atherosclerosis were enrolled. Their basic clinical data were collected, and HR-VWI was performed. The vascular area at the plaque (VA_{MLN}) and normal reference vessel ($VA_{reference}$) were delineated and measured on image postprocessing software, and the

reconstruction index (RI) was calculated. According to the value of the reconstruction index, the patients were divided into a positive reconstruction group (PR group), intermediate remodelling group (IR group), negative reconstruction group (NR group), or positive reconstruction group (PR group) and nonpositive reconstruction group (N-PR group).

RESULTS

The PR group exhibited a higher prevalence of diabetes and serum cholesterol levels compared to the IR and NR groups [45.2%, 4.54 (4.16, 5.93) *vs* 25%, 4.80±1.22 and 16.4%, 4.14 (3.53, 4.75); respectively, P<0.05]. Diabetes incidence was also significantly greater in the PR group compared to the N-PR group (45.2% *vs* 17.5%, P<0.05). Furthermore, the PR group displayed elevated serum triglyceride and cholesterol levels compared to the N-PR group [1.64 (1.23, 2.33) and 4.54 (4.16, 5.93) *vs* 4.54 (4.16, 5.93) and 4.24 (3.53, 4.89), P<0.05]. Logistic regression analysis revealed diabetes mellitus as an independent influencing factor in plaque-positive remodeling [odds ratio (95% confidence interval): 3.718 (1.207-11.454), P<0.05].

CONCLUSION

HR-VWI can clearly show the morphology and signal characteristics of intracranial vascular walls and plaques. Intracranial atherosclerotic plaques in diabetic patients are more likely to show positive remodelling, suggesting poor plaque stability and a greater risk of stroke.

Key Words: High-resolution vessel wall imaging; Intracranial atherosclerosis; Vascular remodelling; MRI

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Core Tip: HR-VWI provides clear visualization of intracranial vascular walls and plaques. Diabetic patients with intracranial atherosclerotic plaques are more likely to display positive remodelling, indicating unstable plaques and a heightened risk of stroke. These findings contribute to the basis for preventing ischemic stroke.

INTRODUCTION

Intracranial atherosclerotic disease is one of the main causes of ischaemic stroke in the world, accounting for approximately 10% of transient ischaemic attacks and 30% - 50% of ischaemic strokes[1]. It is the most common factor among Asian people[2].The adaptive changes in the structure and function of blood vessels that can adapt to changes in the internal and external environment are called vascular remodelling, which is a common and important pathological mechanism in atherosclerotic diseases, and the remodelling mode of atherosclerotic plaques is closely related to the occurrence of stroke. Positive remodelling is an outward compensatory remodeling where the arterial wall grows outwards in an attempt to maintain a constant lumen diameter. For a long time, it was believed that the degree of stenosis can accurately reflect the risk of ischaemic stroke[3-5]. Previous studies have revealed that lesions without significant luminal stenosis can also lead to acute events[6, 7] as summarized in a recent meta-analysis study in which approximately 50% of acute/subacute ischemic events were due to this type of lesion[6]. Research[8, 9] has pointed out that the positive remodelling of plaques is more dangerous and more likely to cause acute ischaemic stroke.

Previous studies[10-13] have found that there are specific vascular remodelling phenomena in the coronary and carotid arteries of diabetic patients. However, due to the deep location and small lumen of intracranial arteries and limitations of imaging techniques, the relationship between intracranial arterial remodelling and diabetes is still unclear. In recent years, with the development of magnetic resonance technology and the emergence of high-resolution vascular wall imaging, a clear and multidimensional display of the intracranial vascular wall has been achieved.

Therefore, in this study, HR-VWI was used to display the remodelling characteristics of bilateral middle cerebral arteries and basilar arteries and to explore the factors of intracranial vascular remodelling and its relationship with diabetes.

MATERIALS AND METHODS

Subjects

This is a retrospective study. Patients were collected from Shenzhen Second People's Hospital from December 2019 to March 2022. All patients met the following inclusion and exclusion criteria.

Inclusion Criteria:

The patient had a clinical preliminary diagnosis of ischaemic stroke or transient ischaemic attack in the corresponding blood supply areas of bilateral middle cerebral arteries or basilar arteries and had a diagnosis of cerebral atherosclerosis on CTA or MRA.

The patient had stable vital signs, was conscious, and had no obvious restlessness, and was expected to cooperate well with the HR-MRI examination.

Exclusion criteria:

Nonatherosclerotic vascular diseases, such as arteritis, moyamoya disease and dissection, are present;

The patient has contraindications for magnetic resonance examination (such as claustrophobia, cardiac pacemaker, nerve stimulator, drug pump, electronic cochlea, defibrillator, heart stent, artificial heart valve, metal clip after aneurysm surgery and other metal implants);

The image quality is degraded due to motion or flow artefacts and cannot be used for diagnosis;

The basic clinical data of the patients were collected and included sex, age, blood pressure, history of diabetes, total cholesterol, triglycerides, *etc.*

The study was approved by the local institutional review board.

MRI Protocol

All patient imaging tests were performed using a Siemens Prisma 3.0 T (Siemens, Germany) magnetic resonance scanner with a 32-channel head coil.

The scanning protocols comprised conventional brain and cerebrovascular imaging. Conventional brain imaging encompassed T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), fluid-attenuated inversion-recovery (FLAIR). Cerebrovascular imaging involved 3-dimensional time-of-flight MRA (3D TOF-MRA) and high-resolution vascular wall imaging technology, specifically the 3D-SPACE sequence for HR-VWI. The contrast medium was meglumine gadolinium pyrospermate (Gd-DTPA) and was given *via* a bolus in an elbow vein at an amount of 0.2 mL/kg body weight. The imaging parameters of these sequences were as follows: (1) T1WI: TR/TE: 2000/7.4 ms, FOV 220×220; slice thickness 5 mm, and slice number 20; (2) T2WI: TR/TE: 4000/117 ms, FOV 220×220; slice thickness 5 mm, and slice number 20; (3) FLAIR: TR/TE: 9000/81 ms, FOV 220×220; slice thickness 5 mm, and slice number 20; (4) 3D-TOF MRA: TR/TE: 21/3.4 ms, FOV 200×200; slice thickness 0.7 mm, and slice number 40; and (5) 3D-SPACE: sagittal imaging orientation, TR/TE: 900/14 ms, FOV 240×240; slice thickness 0.6 mm, and slice number 224.

MRI Image Analysis

The 3D SPACE data (DICOM format) were imported into an image postprocessing workstation (Siemens Syngo Via workstation), and all parameter measurements were performed on the platform.

The images were analysed in the workstation by two senior neuroimaging physicians jointly, without knowledge of patient information, and disagreements in conclusions were discussed and agreed upon.

The image quality was first evaluated to exclude cases with poor image quality that could not meet the diagnosis. By CRP or MPR reconstruction, the most stenotic site of the lumen at the plaque was selected as the target site in the transverse axis perpendicular to the vessel alignment, and the reference site was selected at the normal segment proximal to the target site (if the proximal reference site was not available, the

adjacent distal site was used). The images of the narrowest site of the lumen and the reference site were magnified to 300%, and the vascular boundaries were manually traced by using the drawing tool according to the specific morphology of the narrowed vessel to obtain the vascular area at the narrowest point of the vessel (VA_{MLN}) and the vascular area of the reference vessel ($VA_{reference}$), as shown in Figure 1. Then, the remodelling index was calculated according to the formula: remodelling index (RI) = $VA_{MLN}/VA_{reference}$. Based on the values of the remodelling index, the plaque remodelling pattern was classified as follows: RI>1.05 for positive remodelling (PR), $0.95 < RI \leq 1.05$ for intermediate remodelling (IR), and $RI \leq 0.95$ for negative remodelling (IR).

Statistical Analysis

All data were analysed by using the SPSS26.0 package (Chicago, IL, USA). Variables underwent normality testing *via* the Kolmogorov-Smirnov test. Quantitative data are expressed as mean ± standard deviation ($\chi \pm s$), while non-normally distributed data are presented as median with interquartile range. Independent sample t-tests were employed for normally distributed and homogenous variance quantitative data comparisons; otherwise, the Mann-Whitney U test was used.

Categorical values were summarized by counts and percentages. The chi-square test (or Fisher's exact test when appropriate) was applied for categorical data comparisons. Multivariate logistic regression was conducted to identify independent factors associated with plaque-positive remodeling. Statistical significance was defined as $P < 0.05$.

RESULTS

According to the inclusion criteria, we collected 113 cases, but 13 cases were excluded due to quality reasons, and 6 cases were also excluded which diagnostic as arteritis or arterial dissection. Finally, a total of 94 patients were enrolled in this study

(Figure 2), and they had an age range of 29 to 82 years and a mean age of 55.56 ± 12.168 years. Among them, there were 65 males, with an age range of 29 to 82 years, and the average age was 52.72 ± 11.905 years. There were 29 female patients, with an age range of 31 to 82 years, and the average age was 61.93 ± 10.347 years. There were 31 patients in the positive remodelling group (PR group), 8 patients in the intermediate remodelling group (IR group), and 55 patients in the negative remodelling group (NR group), in which the intermediate remodelling group (IR group) and negative remodelling group (NR group) was merged into the nonpositive remodelling group (N-PR group) with a total of 63 patients.

Comparison of clinical data between the PR group, IR group and NR group

The univariate analysis showed that there were statistically significant differences in the prevalence of diabetes and serum cholesterol levels among the three groups [14 (45.2%) and 4.54 (4.16,5.93) *vs* 2 (25%) and 4.80±1.22 *vs* 9 (16.4%) and 4.14 (3.53,4.75); respectively, $P<0.05$]. There was no significant difference in age, sex, hypertension history or triglycerides among the three groups. See Table 1 for the comparison of clinical data characteristics between the three groups of patients.

Comparison of clinical data between the PR group and the N-PR group

The univariate analysis showed that there were significant differences in the prevalence of diabetes, triglycerides and cholesterol between the two groups. The number of patients with diabetes in the PR group was greater than that in the N-PR group [14 (45.2%) *vs* 11 (17.5%), $P<0.05$]. Compared with the N-PR group, the patients in the PR group had higher serum triglyceride and cholesterol values [1.64 (1.23,2.33) and 4.54 (4.16,5.93) *vs* 1.55 (1.06,1.67) and 4.24 (3.53,4.89); respectively, $P<0.05$]. There was no significant difference in age, sex or hypertension history between the PR group and the N-PR group. See Table 2 for the comparison of clinical data characteristics and Figure 3 Figure 4 for the comparison of image features between the two groups of patients.

Analysis of independent factors associated with plaque-positive remodelling

The indicators that had statistical significance in the univariate analysis and that may affect the vascular remodelling pattern, including age, sex, diabetes, hypertension and triglycerides, were included in the binary logistic regression analysis to explore the important factors affecting the remodelling pattern.

The results showed that diabetes was an independent feature of plaque-positive remodelling [odds ratio (95% confidence interval): 3.718 (1.207-11.454), $P<0.05$]. There was no significant correlation between hypertension, triglycerides, sex and age and positive remodelling of plaque ($P>0.05$). The independent factor analysis of patient characteristics and plaque-positive remodelling is shown in Table 3.

DISCUSSION

In our study, we used high-resolution vessel wall imaging to explore the remodelling patterns of the responsible plaques of intracranial arteries and their influencing factors in patients with ischaemic stroke or transient ischaemic attack. This proved that high-resolution vessel wall imaging can noninvasively and accurately show the morphological characteristics and signal characteristics of intracranial artery plaques and can be used as an effective means to evaluate the vessel walls of intracranial atherosclerosis patients. The results showed that the prevalence of diabetes was higher in the group with positive remodelling of intracranial responsible plaques, and diabetes was an independent factor affecting the positive remodelling of plaques, which revealed that hyperglycaemia might promote the formation of positive remodelling of plaques.

An increasing number of studies have proven that arterial remodelling is an important pathological mechanism commonly present in atherosclerotic diseases. Arterial remodelling can occur in coronary arteries, renal arteries, femoral arteries, carotid arteries, *etc.* However, different arteries have different abilities and methods of remodelling. Arterial remodelling includes both positive remodelling (arterial dilation)

and negative remodelling (artery constriction). Positive remodelling is outward compensatory remodelling, in which the arterial wall grows outwards in an attempt to maintain a constant lumen diameter, while negative remodelling is defined as local contraction of vessel size[14].

Previous studies have often evaluated the severity of intracranial atherosclerotic plaques or the probability of ischaemic stroke by the degree or number of vascular stenoses. In recent years, studies have shown that the stability of the plaque itself is an important factor affecting the occurrence of stroke[15]. Intracranial atherosclerosis should be evaluated not only according to the degree of lumen stenosis but also according to the characteristics of the vascular wall. Plaques that do not cause lumen stenosis can also lead to stroke. The pattern of plaque remodelling is closely related to plaque instability. Positive remodelling of arteries is more dangerous than negative remodelling and is more likely to cause acute ischaemic stroke[16, 17].

In diabetes, vascular remodelling can be caused by irritation of the vascular wall due to hyperglycaemia, insulin resistance, endothelial cell dysfunction, nonenzymatic glycosylation, and other factors. Wasese *et al*[13] examined 557 plaques of common carotid arteries and internal carotid arteries and found that the carotid artery plaques in diabetic patients showed more positive remodelling than those in nondiabetic patients. Terashima et al.[12] also found that positive remodelling in the coronary artery is associated with diabetes. The results of our study also indicated that the positive remodelling of intracranial arterial plaques was related to diabetes, and the prevalence of diabetes in the positive remodelling group was higher than that in the nonpositive remodelling group. Moreover, our study also shows that diabetes is an independent factor in the positive remodelling of intracranial plaques. It is suggested that hyperglycaemia may promote the formation of plaque-positive remodelling. Pathological studies have confirmed that positively remodelled plaques have a large lipid core and accumulate macrophages and inflammatory cells[18, 19]. We speculate that hyperglycaemia may promote severe vascular wall inflammatory infiltration or the formation of a lipid core, thus increasing the risk of plaque rupture. This helps prompt

clinicians to early intervene regarding blood glucose management in diabetic patients to prevent the occurrence of stroke.

Contrary to the results of our study, Zhang *et al*[16] found that the remodelling pattern of the middle cerebral artery was not associated with diabetes. We consider that the possible reason why their study, which included asymptomatic patients with suspected middle cerebral atherosclerosis, differed from ours is related to the different inclusion criteria of patients.

Although some studies have shown that [20] hypertension is related to damage to structural and functional cerebrovascular health and can promote an increase in the thickness of the middle layer of intracranial arteries, plaque and stenosis, the relationship between intracranial plaque remodelling and hypertension is still controversial. Guo R et al.[21] found that there was no statistically significant difference in blood pressure indicators of the basilar artery between the PR group and the N-PR group, which was consistent with the results of this study, indicating that hypertension did not necessarily promote the positive remodelling of plaques. In addition to the basilar artery, our study also included the middle cerebral artery, both of which are prone to the development of intracranial plaques. However, Zhang D *et al*[16] studied arterial plaques in the middle cerebral in patients with atherosclerosis and found that the PR group had a higher prevalence of hypertension than the N-PR group, but his study only included patients with moderate or severe MCA stenosis (n = 33) and did not include patients with mild MCA stenosis (stenosis degree<30%). Our study also included patients with mild stenosis, and our study had a larger sample size (n = 67) and more types.

There are still some deficiencies in this study. First, the sample size in this study was small, and there was a lack of pathological controls. Therefore, future research needs to further expand the sample size and obtain pathological samples as much as possible. Second, the parameters of the blood vessel wall and plaque were evaluated manually, and measurement error is inevitable. In addition, we did not conduct a

follow-up study to evaluate whether the treatment effect of the PR group was better than that of the non-PR group, which will be explored in further studies in the future.

CONCLUSION

In conclusion, HR-VWI can clearly show the morphology and signal characteristics of intracranial vascular canal walls and plaques. Patients with diabetes mellitus are more likely to experience positive remodelling of intracranial atherosclerotic plaques, suggesting poor plaque stability and a greater risk of stroke, and the results of this study may provide a basis for the prevention of ischaemic stroke and may help reducing the incidence and severity of ischaemic stroke by predicting dangerous plaques.

ARTICLE HIGHLIGHTS

Research background

Intracranial atherosclerosis, a leading cause of stroke, involves arterial plaque formation.

Research motivation

This study explores the link between plaque remodeling patterns and diabetes using high-resolution vessel wall imaging.

Research objectives

To investigate the factors of intracranial atherosclerotic remodelling patterns and the relationship between intracranial atherosclerotic remodelling and diabetes mellitus using high-resolution vessel wall imaging (HR-VWI).

Research methods

Ninety-four patients diagnosed with middle cerebral artery or basilar artery atherosclerosis were enrolled. Their basic clinical data were collected, and HR-VWI was

performed. The vascular area at the plaque (VA_{MLN}) and normal reference vessel ($VA_{reference}$) were delineated and measured on image postprocessing software, and the reconstruction index (RI) was calculated. According to the value of the reconstruction index, the patients were divided into a positive reconstruction group (PR group), intermediate remodelling group (IR group), negative reconstruction group (NR group), or positive reconstruction group (PR group) and nonpositive reconstruction group (N-PR group).

Research results

The PR group exhibited a higher prevalence of diabetes and serum cholesterol levels compared to the IR and NR groups [45.2%, 4.54 (4.16, 5.93) *vs* 25%, 4.80±1.22 and 16.4%, 4.14 (3.53, 4.75); respectively, P<0.05]. Diabetes incidence was also significantly greater in the PR group compared to the N-PR group (45.2% *vs* 17.5%, P<0.05). Furthermore, the PR group displayed elevated serum triglyceride and cholesterol levels compared to the N-PR group [1.64 (1.23, 2.33) and 4.54 (4.16, 5.93) *vs* 4.54 (4.16, 5.93) and 4.24 (3.53, 4.89), P<0.05]. Logistic regression analysis revealed diabetes mellitus as an independent influencing factor in plaque-positive remodeling [odds ratio (95% confidence interval): 3.718 (1.207-11.454), P<0.05].

Research conclusions

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Research perspectives

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Second, the parameters of the blood vessel wall and plaque were evaluated manually, and measurement error is inevitable. In addition, we did not conduct a follow-up study to evaluate whether the treatment effect of the PR group was better than that of the non-PR group, which will be explored in further studies in the future.

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