Correlation of The Characteristics of Symptomatic Intracranial Atherosclerotic Plaques with Stroke Types and Risk of Stroke Recurrence

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Research Article

Keywords: Intracranial atherosclerotic plaques, Acute ischemic stroke, Transient ischemic attack, Stroke recurrence, High-resolution vessel wall imaging

Posted Date: August 18th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-757545/v1>

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Abstract

Purpose

To explore the relationship of the characteristics of symptomatic intracranial atherosclerotic plaques (ICAP) with stroke types and risk of stroke recurrence.

Methods

Patients with symptomatic intracranial atherosclerotic stenosis were prospectively enrolled. The vessel stenosis degree, plaque shape, plaque thickness, plaque burden, and plaque enhancement degree of all patients were assessed using high-resolution magnetic resonance imaging and statistically analyzed.

Results

In total, 206 patients (mean age (64 ± 12) years; 141 males) were included in this study, 154 had acute ischemic stroke (AIS), 52 had transient ischemic attack (TIA), 124 had anterior circulation ischemic symptom (ACIS), and 82 had posterior circulation ischemic symptom (PCIS). AIS patients showed higher diastolic blood pressure ($t=-2.605$, $p=0.011$), total cholesterol ($t=-2.470$, $p=0.014$), apolipoprotein b ($z=-2.411$, $p=0.016$), apolipoprotein a/b ($t=-2.865$, $p=0.006$), LDL ($t=-2.424$, $p=0.016$), arteriosclerosis index ($z=-2.256$, $p=0.024$), stenosis degree ($t=-3.317$, $p<0.001$) but smaller luminal area at the plaque than TIA patients ($t=2.539$, $p=0.013$). In addition, 24 (13.6%) patients had stroke recurrence within 6 months. The proportion of patients with T1WI hyperintensity was higher in patients with recurrent stroke than in patients without recurrent stroke ($RR=2.592$ (1.091, 6.58), $\chi^2=4.892$, $p=0.034$). Patients with PCIS had greater plaque thickness ($t=-4.205$, $p<0.001$) and remaining luminal area ($z=-4.127$, $p<0.001$), significantly enhanced ICAP ($\chi^2=9.681$, $p=0.003$), more positive remodeling ($\chi^2=5.661$, $p=0.015$) and higher incidence of T1WI hyperintensity ($\chi^2=16.472$, $p<0.001$) than patients with ACIS. The prevalence of diabetes ($\chi^2=9.038$, $p=0.004$) in patients with PCIS is higher than that in patients with ACIS.

Conclusions

The degree of stenosis and the remaining luminal area of symptomatic ICAP are related to the type of stroke, and patients with T1WI hyperintense plaque had a higher risk of stroke recurrence within six months. Posterior circulation culprit plaque tends to have higher vulnerability, which may be related to metabolic factors secondary to diabetes.

Introduction

Intracranial atherosclerosis is a progressive pathological process that causes progressive luminal stenosis and insufficient brain perfusion ^[1]. Symptomatic intracranial atherosclerotic stenosis (sICAS),

including acute ischemic stroke (AIS) and transient ischemic attack (TIA), occurs in as high as 46.6% of Chinese populations and is related to the high risk of stroke recurrence^[2]. SAMMPRIS showed that although patients with severe sICAS received active medication treatment, 15% of these still had a recurrent stroke. Subgroup analysis showed that AIS patients had a higher risk of recurrence than TIA patients^[3–5], indicating that AIS and TIA patients should be subject to stratified management in clinics. Previous studies have shown that hypertension, diabetes, smoking, dyslipidemia, and vulnerable plaque are the risk factors of sICAS^[6, 7]. However, the differences of these risk factors in AIS and TIA and in anterior circulation ischemic symptom (ACIS) and posterior circulation ischemic symptom (PCIS) are still unclear. Early identification of the differences in risk factors is critical for developing standardized treatment.

High-resolution vessel wall imaging (HR-VWI) is currently an important diagnostic technique for assessing atherosclerosis. It can not only accurately assess the degree of vascular luminal stenosis but also provide the size and composition information of intracranial atherosclerotic plaque (ICAP), including the detection of intra-plaque hemorrhage, plaque enhancement, vascular wall remodeling, and plaque distribution, etc., with extremely high repeatability^[8, 9]. In previous studies, ICAP features based on HR-VWI, including positive remodeling, intraplaque hemorrhage, and plaque enhancement, have been identified as markers of future stroke risks^[10–12]. In this study, we focused on the relationship between plaque characteristics and stroke types in sICAS patients undergoing HR-VWI examination and followed up the patients to assess the differences in clinical risk factors and ICAP characteristics between patients with and without recurrent stroke, with the hope to identify novel intervention targets to develop more standardized secondary prevention strategies for ischemic stroke and TIA to reduce stroke recurrence.

Materials And Methods

Research subjects

This is a single-center prospective cohort study. Consecutive inpatients of the Department of Neurology from February 2020 to December 2020 due to suspected sICAS, including TIA or AIS were enrolled if they met the following criteria: (1) HR-VWI performed within 2 weeks of symptom onset; and (2) the culprit vessel had at least 1 intracranial atherosclerotic plaque identified on HR-VWI. Patients were excluded if they had (1) non-atherosclerotic vascular disease, such as vascular malformation or intracranial aneurysm; (2) ipsilateral extracranial artery stenosis $\geq 50\%$, and intracranial large vascular occlusion; (3) potential cardiogenic embolism, such as atrial fibrillation; and (4) incomplete clinical information or poor imaging quality. All research protocols were approved by the Ethics Committee and conducted following the relevant guidelines and regulations. Written informed consent was obtained from patients or their legal guardians.

Clinical index collection

The demographic data, atherosclerosis risk factors, blood pressure at admission, and laboratory test results during hospitalization were collected from all patients. A history of diabetes was defined as previous use of blood sugar lowering drugs or insulin. Past or current smokers were defined as having a smoking history. Total cholesterol ≥ 5.18 mmol/L or triglycerides ≥ 1.7 mmol/L was defined as hyperlipidemia. Arteriosclerosis index was defined as (total cholesterol-HDL)/HDL. All patients received the best treatment according to the latest guidelines. The recurrence of AIS or TIA and their correlation with the same area were determined based on the newly developed neurological deficits and the presence of new infarct lesion confirmed by DWI at the time of recurrence. When no imaging examination was performed for a suspected recurrence event, the duration of recurrence and characteristics of the newly developed neurological deficits were used to determine the outcome event by the followers^[13].

HR-VWI image acquisition

HR-VWI images were acquired using the German Siemens Verio 3.0 T MR imaging system. In addition to the conventional MRI and MRA scanning sequence, 3D-T1-SPACE sequence was scanned before and after injecting the contrast agent with the following parameters: TR= 700 ms, TE= 12 ms, FOV =200 ×200 ×40mm³, voxel size= 0.8× 0.8 ×0.7 mm³ and scanning time= 7 min 16 s. Gadoteric acid was used as the contrast agent at a dose of 0.1 mmol/kg, and the enhanced images were collected at 8 min after injection. The scanning range included the complete presentation of the intracranial segment of the internal carotid artery, M1 and M2 segments of the middle cerebral artery, A1 and A2 segments of the anterior cerebral artery, P1 and P2 segments of the posterior cerebral artery, V4 segment of the vertebral artery, and the basilar artery.

Image analysis and evaluation

All images were analyzed by two neuroradiologists with 5 years and 15 years of experience, respectively, and the consensus was reached after consultation when they disagreed. The quality of each image was scored with 1 for poor quality, 2 for acceptable, and 3 for good. Only images with a score of 2 or above were used in the study. Images were processed using the MMWP Siemens Erlangen workstation. The location of the vascular stenosis was determined on the obtained TOF-MRA image, and the location of the ICAP was then determined using the 3D-T1-SPACE sequence in combination with the sagittal, coronal, and axial images, that is, the location of eccentric stenosis in the lumen or the site with locally thickened vascular wall. The two evaluators jointly determined the culprit plaque based on the clinical manifestations. When multiple plaques existed in the same vascular area, the one that caused the most severe stenosis was defined as the culprit plaque.

The degree of luminal stenosis was evaluated according to the Warfarin-Aspirin Symptomatic Intracranial Disease Study^[14]. The plaque burden was defined as 1 minus the ratio of the remaining luminal area to the vascular wall area ×100%^[15]. The remodeling index was defined as the ratio of the vascular wall area at the most severe stenosis to the reference vascular wall area. The remodeling index of ≥ 1.05 , 0.95–1.05, and ≤ 0.95 was considered as positive remodeling, no remodeling, and negative remodeling,

respectively ^[16]. The increase of vascular wall thickness involving $\geq 50\%$ of arterial wall circumference was defined as centripetal, otherwise as eccentric. Plaque T1WI signal intensity greater than 150% of the adjacent muscle signal intensity was defined as T1WI hyperintensity ^[17]. The plaque signal intensity after enhancement less than the signal intensity of the pituitary stalk was defined as a mild enhancement. The enhancement degree equal to or greater than the signal intensity of the pituitary stalk was defined as a significant enhancement ^[18].

Statistical analysis

SPSS 21.0 software was used for statistical analysis of data. A p value < 0.05 was considered statistically significant. The Shapiro-Wilk test was used to evaluate whether the data conformed to the normal distribution. Variables conforming to the normal distribution were presented as the mean $\pm$ standard deviation, variables with skewed distribution were presented as the median and interquartile range, and the categorical data were presented as the count and percentage. T test or Mann-Whitney test was used according to the normality test results. The comparison of categorical variables was performed by chi-square test or Fisher's exact test. Variables with a p value < 0.1 were included in the binary logistic regression analysis.

Results

1. Patients' general information

A total of 206 patients were enrolled, of which 68.4% (141/206) were male; 52 (25.2%) had TIA, and 154 (74.8%) had AIS. A flow diagram summarizing the exclusion information is shown in Fig. 1. The previous statin use rate was lower in AIS patients than in TIA patients ($\chi^2=7.688$, $p = 0.009$). Diastolic blood pressure ($t=-2.605$, $p = 0.011$), total cholesterol ($t=-2.470$, $p = 0.014$), apolipoprotein b ($z=-2.411$, $p = 0.016$), apolipoprotein a/b ($t=-2.865$, $p = 0.006$), LDL ($t=-2.424$, $p = 0.016$) level, and arteriosclerosis index ($z=-2.256$, $p = 0.024$) were significantly higher in AIS patients than in TIA patients. There was no statistically significant difference between the plaque thickness and the plaque burden between TIA patients and AIS patients. AIS patients had significantly smaller remaining luminal area at the stenosis ($t = 2.539$, $p = 0.013$) and significantly higher stenosis degree ($t=-3.317$, $p < 0.001$) than TIA patients. All patients' clinical data are shown in Table 1.

Table 1
Comparison of clinical data and plaque characteristics between TIA and AIS group

Index	TIA group (n = 52)	AIS group (n = 154)	<i>P</i> value
Male [(n, (%))]	29 (55.8)	112(72.7)	0.023
Age (year)	63.61 ± 1.84	63.97 ± 0.93	0.870
Systolic blood pressure (mmHg)	135.40 ± 3.10	146 ± 1.77	0.085
Diastolic blood pressure (mmHg)	80.37 ± 2.03	85.44 ± 1.41	0.011
Smoking history [(n, (%))]	12 (23.1)	43(27.5)	0.588
History of diabetes [n, (%))]	15 (28.8)	53(34.4)	0.499
History of statin usage [n, (%)]	15 (28.8)	19(12.3)	0.009
Fasting blood glucose(mmol/L)	5.21 (4.90, 5.94)	5.60(5.05,7.28)	0.082
Glycated hemoglobin(%)	5.90 (5.60, 6.73)	6.20(5.70,7.40)	0.390
hs-CRP (mg/L)	0.15 (0.03, 1.01)	0.51(0.05,2.23)	0.233
Triglycerides (mmol/L)	1.25 (0.91, 2.57)	1.91(0.98,2.29)	0.228
Total cholesterol (mmol/L)	3.78 ± 0.20	4.16 ± 0.12	0.014
Apolipoprotein B (mmol/L)	0.72 (0.54, 0.89)	0.82 (0.66, 1.01)	0.016
Apolipoprotein A/B	1.74 ± 0.15	1.40 ± 0.05	0.006
LDL (mmol/L)	2.25 ± 0.17	2.60 ± 0.10	0.016
Arteriosclerosis index	2.00 (1.39, 3.13)	2.53 (1.90, 3.07)	0.024
Lipoprotein phospholipase a2 (mmol/L)	290.50 (195.00, 482.25)	317.00(245.00, 487.50)	0.054
Brain natriuretic peptide (mmol/L)	153.00 (49.40, 192.50)	97.00 (41.60, 282.40)	0.934
Cystatin C (mmol/L)	0.86 ± 0.06	0.88 ± 0.03	0.864
plaque thickness (mm)	1.64 ± 0.08	1.52 ± 0.03	0.155
Remaining luminal area (mm ²)	5.21 ± 0.46	3.06 ± 0.18	0.013
Degree of stenosis	0.43 ± 0.02	0.53 ± 0.07	< 0.001
Plaque burden	0.71 ± 0.01	0.73 ± 0.01	0.287
significant enhancement [n, (%)]	22 (42.3)	78 (50.6)	0.337
Centripetal distribution [n, (%)]	13 (25.0)	53 (34.4)	0.233

Index	TIA group (n = 52)	AIS group (n = 154)	<i>P</i> value
Positive remodeling [n, (%)]	32 (61.5)	90 (58.4)	0.746
T1WI hyperintensity [n, (%)]	13 (25.0)	50 (32.5)	0.385

Table 2
Clinical data and plaque characteristics of patients with and without recurrent stroke

Index	without recurrent stroke (n = 176)	with recurrent stroke (n = 24)	Univariate analysis <i>P</i> value	binary logistic regression <i>P</i> value(95% CI)
Male [n (%)]	53 (30.1)	10 (41.7)	0.348	0.775 (0.456,2.872)
Age (year)	63.87 ± 12.04	64.17 ± 11.47	0.875	0.944 (0.966,1.038)
Obesity [n (%)]	5 (6.9)	1 (7.1)	0.979	
Smoking history [n (%)]	52 (29.5)	2 (8.3)	0.047	0.064 (0.049,1.090)
History of diabetes [n (%)]	56 (31.8)	10 (41.7)	0.360	
Hyperlipidemia [n (%)]	72(40.9)	8 (33.3)	0.515	
Hb1AC ≥ 7% [n (%)]	45(27.8)	9 (40.9)	0.218	
plaque thickness (mm)	1.55 ± 0.03	1.59 ± 0.08	0.645	
Remaining luminal area (mm ²)	4.36 ± 0.21	3.60 ± 0.34	0.062	
Degree of stenosis	0.52 ± 0.06	0.47 ± 0.03	0.771	
Plaque burden	0.72 ± 0.01	0.75 ± 0.02	0.237	
significant enhancement [n, (%)]	85 (48.3)	12 (50.0)	1.000	
Centripetal distribution [n, (%)]	54 (30.7)	10 (41.7)	0.351	
Positive remodeling [n (%)]	107 (60.8)	12 (50.0)	0.377	
T1WI hyperintensity [n (%)]	49 (27.8)	12 (50.0)	0.034	0.040 (1.044,6.188)

Table 3
Clinical data and plaque characteristics of patients with ACIS and PCIS

Index	ACIS (n = 124)	PCIS (n = 82)	P value
Male [n (%)]	83 (66.9)	56 (68.3)	0.880
Smoking history [n (%)]	30 (24.4)	25 (30.5)	0.338
History of diabetes [n (%)]	31 (25.0)	37 (45.1)	0.004
Stroke Recurrence [n (%)]	13 (10.7)	11 (13.9)	0.512
Plaque thickness (mm)	1.45 ± 0.03	1.71 ± 0.06	< 0.001
Remaining luminal area (mm ²)	3.30 (2.13, 4.70)	4.70 (2.95, 6.70)	< 0.001
Degree of stenosis	0.46 ± 0.01	0.45 ± 0.01	0.328
Plaque burden	0.72 ± 0.01	0.74 ± 0.01	0.161
significant enhancement [n, (%)]	49 (39.5)	51 (62.2)	0.002
Centripetal distribution [n, (%)]	35 (28.2)	31 (37.8)	0.171
Positive remodeling [n (%)]	65 (52.4)	57 (69.5)	0.020
T1 hyperintensity [n (%)]	28 (22.6)	35 (42.7)	0.003

2. Clinical data and plaque characteristics of patients with and without recurrent stroke

All patients were followed up for 6 months. Among them, 24 (13.6%) patients had stroke recurrence. According to the occurrence of recurrent stroke, patients were divided into recurrence and non-recurrence groups and compared. The results showed that patients with recurrent stroke had a significantly higher proportion of T1WI hyperintensity (RR = 2.592 (95%CI, 1.091, 6.58), $\chi^2=4.892$, $p = 0.034$) than patients without recurrent stroke. Binary logistic regression analysis showed that T1WI hyperintensity (OR = 2.542, $p = 0.040$) were independently related to stroke recurrence within 6 months. In addition, patients with recurrent stroke had greater culprit plaque thickness and burden and smaller remaining luminal area than patients without recurrent stroke, although the differences were not statistically significant.

3. Clinical data and plaque characteristics of patients with ACIS and PCIS

Among these patients, 124 (60.2%) had ACIS and 82 (59.8%) had PCIS. posterior circulation ICAP tended to have a significantly greater plaque thickness ($t=-4.205$, $p<0.001$) and remaining luminal area ($z=-4.127$, $p<0.001$) than anterior circulation ICAP while the difference in the degree of luminal stenosis was not statistically different. Moreover, the incidences of significant enhancement ($\chi^2=9.681$, $p=0.003$), positive remodeling ($\chi^2=5.661$, $p=0.015$), and T1 hyperintensity ($\chi^2=16.472$, $p<0.001$) were significantly higher in patients with PCIS than in patients with ACIS, while the difference in the plaque distribution was not significantly different. The prevalence of diabetes ($\chi^2=9.038$, $p=0.004$) in patients with PCIS is higher than that in patients with ACIS.

Discussion

In this study, we included 206 patients with symptomatic ICAP and collected their clinical data and HR-VWI image information. Alexander et al.^[19] found that the misdiagnosis rate of cerebrovascular disease events during the first visit to the emergency department was approximately 9%. Especially, patients with mild symptoms and non-specific or transient symptoms were at higher risk of misdiagnosis. These patients were often misdiagnosed with TIA. Therefore, they were subjected to delayed treatments or had a poor prognosis. All these observations suggest that there might be some shortcomings in the management of patients based only on the results of diffusion-weighted imaging examinations in clinical work. We diagnosed the patients based on their clinically localized symptoms and HR-VWI. The results showed that AIS patients had higher diastolic blood pressure and blood lipid level than TIA patients. Moreover, HR-VWI showed that AIS patients had higher stenosis degrees and smaller remaining luminal areas at the plaque than TIA patients. Feng et al.^[13] showed that patients with sICAS caused by a mixed mechanism of arterial-arterial embolism and low perfusion distal to stenosis were more likely to have a history of dyslipidemia and hypertension, consistent with our results. Dyslipidemia might increase the risk of vulnerable plaque rupture and arterial-arterial embolism^[20]. The luminal stenosis caused by ICAP was negatively correlated with the distal perfusion status, and the blood flow acceleration caused by the reduction of the remaining luminal area could also increase the risk of ICAP rupture^[21, 22]. Therefore, we speculated that the degree of luminal stenosis and the remaining luminal area might be related to the stroke type of sICAS. We also found that previous use of statins had a certain protective effect on the occurrence of AIS, consistent with the results of Chung et al.^[23].

Through a 6-month follow-up of the enrolled patients, we found that the baseline HR-VWI images of patients with recurrent stroke were more likely to have T1WI hyperintensity. T1WI hyperintensity often represents intraplaque hemorrhage, which is currently a more recognized feature of vulnerable plaque and is significantly related to the downstream ischemic events^[24, 25]. A recent meta-analysis of 1,542 subjects and a total of 1,750 plaques showed that plaque enhancement, positive remodeling, T1WI hyperintensity, and surface irregularities were significantly related to the downstream ischemic events. In all subgroups, plaque enhancement was significantly associated with downstream ischemic events^[26]. However, in this study, no significant difference was found in enhancement degree between patients with and without recurrent stroke. This discrepancy might be because that the enhancement degree in this

study was defined as classification data rather than quantitative data, leading to the loss of significance. Moreover, patients were followed up for 6 months, which is relatively short.

Edlow et al. ^[27] found that the incidence of DWI-negative acute ischemic stroke was 6.8%, and five times higher in patients with PCIS than in patients with ACIS. This suggests that the pathogenesis might be different between patients with PCIS and ACIS. Our study included 82 patients with PCIS. After comparing the clinical data and culprit plaque conditions of patients with PCIS, we found that more patients with PCIS had a history of diabetes. In addition, patients with PCIS had thicker plaques and a higher enhancement degree than patients with ACIS. Moreover, the posterior circulation plaques were prone to T1WI hyperintensity and positive remodeling. Studies have shown that poor blood sugar control might play an important role in the occurrence and development of plaques in patients with AIS or TIA. Compared with non-diabetic patients, diabetic patients had a significantly higher incidence of plaque enhancement, longer maximum plaque length, greater maximum plaque wall thickness, and increased luminal stenosis degree ^[28–30]. Therefore, we speculated that the appearance of the vulnerable characteristics of the posterior circulation culprit plaque might be related to the metabolic factors of secondary diabetes.

Our research has certain limitations. First, the sample size was relatively small, especially the number of patients with recurrent stroke, which may lead to certain statistical bias. Second, the follow-up time was relatively short, and these patients need to be followed up for a longer period in the future. Third, ICAP features based on HR-MRI may not reflect the true characteristics of intracranial plaques because of its limited resolution. In addition, some data were manually measured, which might have some deviation. With the subsequent application of artificial intelligence software, our results will become more accurate.

Conclusions

The degree of stenosis at the symptomatic intracranial atherosclerotic plaque and the remaining luminal area were related to the type of stroke, and the risk of stroke recurrence was increased within six months in patients with plaque T1WI hyperintensity. Posterior circulation culprit plaque tends to have higher vulnerability, which may be related to metabolic factors secondary to diabetes.

Declarations

Ethics approval and consent to participate

The study was approved by our institutional review board at The second Affiliated Hospital of Nantong University with waiver of informed consent.

Consent for publication

Not applicable.

Availability of data and material:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests

Funding:

Nantong City Science and Technology Project, MS12020041; Nantong City Science and Technology Project, MS12020041; Nantong City Science and Technology Project, MS12020041; Nantong City Science and Technology Project, MS12020041

Authors' contributions:

LZ and TW conceived the experiments. XZ prepared the materials and laboratory. KR and HJ wrote the main manuscript text and ZZ prepared figures. All authors reviewed the manuscript.

Acknowledgements

Not applicable.

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Figures

Figure 1

Flow diagram of study identification

Figure 2

Example case of a patient with 3 days of weakness in the right limb. DWI showed hyperintense in the left basal ganglia, TOF-MRA showed lumen stenosis in the M1 segment of the left middle cerebral artery. HR-VWI find a eccentric plaque, which showed TIWI hyperintense and significantly enhanced.