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Original Article

Correlation between MRI features and CSF inflammatory factor levels in patients with infarction or TIA, assessed by contrast-enhanced high-resolution MRI

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Abstract: Objective: To explore the correlation between the time course of CE-T1WI plaque and the level of CSF inflammatory factors in patients with cerebral infarction or TIA assessed by contrast-enhanced high-resolution MRI. Methods: From August 2019 to December 2021, 136 patients with ischemic stroke-related neurological symptoms or suspected ischemic stroke in Gong'an County Hospital of Traditional Chinese Medicine were retrospectively analyzed, including 69 men and 67 women aged 45-80 years old, with an average age of 65.98±8.29. The study was divided into two groups: infarction group (patients with high DWI signal in the middle cerebral artery supply area, n=68) and TIA group (patients with ischemic neurologic symptoms but no relevant imaging findings, n=68). Patients with grade 1 or grade 2 image quality were included in the study after imaging with a 3.0T MRI device. Unenhanced MRI (T1WI and T2WI) and contrast-enhanced T1WI (CE+T1WI) plaque signals were compared between the two groups. The expression levels of TNF-α, IL-6, and IL-1β in CSF of the two groups were detected by ELISA. VA_{MLN}, LA_{MLN}, PA, stenosis rate, and reconstruction index were compared between the two groups. The SNR and CNR values on T1WI and CE+T1WI were compared. The expression levels of TNF-α, IL-6, and IL-1β detected by ELISA in cerebrospinal fluid of patients with CE-T1WI plaque enhancement were compared. Results: The expression levels of TNF-α, IL-6, and IL-1β in the cerebral infarction group were higher than those in the TIA group (P<0.05). Comparing the VA_{MLN}, LA_{MLN}, PA, stenosis rate and remodeling index of the two groups, the VA_{MLN}, PA, and remodeling index of the cerebral infarction group were higher than in the TIA group (P>0.05), and there was no significant difference in VA_{MLN} and stenosis rate between groups (P<0.05). Comparing the plaque SNR and CNR values on T1WI and CE+T1WI, the signal intensity, adjacent signal intensity, SNR, and CNR of carotid plaque on CE+T1WI were higher than those on T1WI (P>0.05). The expression levels of TNF-α, IL-6, and IL-1β in the moderate enhancement group were higher than those in the non-enhancement group, and the expression levels of TNF-α, IL-6 and IL-1β in the high enhancement group were higher than those in the moderate enhancement group (P<0.05). Conclusion: The temporal variation of CE-T1WI plaque was positively correlated with the level of cerebrospinal fluid inflammatory factors. High levels of inflammatory factors, positive remodeling, and significant enhancement were closely related to unstable plaque, which may increase the risk of stroke in patients with atherosclerosis.

Keywords: Atherosclerosis, contrast-enhanced high-resolution MRI, arterial plaque, cerebrospinal fluid, inflammatory factor

Introduction

Atherosclerosis is the root cause of most cardiovascular and cerebrovascular diseases [1]. Ischemic stroke mostly occurs in patients with carotid stenosis and vulnerable atherosclerotic plaque [2]. Identifying the risk of stroke in asymptomatic patients remains a clinical challenge. However, the invasive evaluation of plaque morphology is of limited value for detection of subclinical coronary atherosclerosis and prediction or prevention of subsequent acute cardiovascular events [3, 4]. Recently, magnetic resonance imaging (MRI) technology has reached high spatial resolution level, which enables visualization of plaque in large and static arteries, such as carotid artery and aorta [5, 6]. MRI evaluation of carotid atherosclerotic plaque can help identify patients with unstable plaques, which are prone to rupture and lead to

acute arterial thrombosis [7]. Atherosclerosis is a systemic disease, which can lead to cerebral infarction or transient ischemic attack (TIA) when carotid or intracranial arteries are involved [8-10]. Carotid atherosclerosis is the most common cause of cerebrovascular ischemic events in Europe and America, while intracranial atherosclerosis is more common in Asians. In China, 33%-50% of patients with cerebral infarction and more than 50% of patients with TIA report symptomatic intracranial atherosclerotic stenosis, among which the middle cerebral artery is the most common involved vessel. Intracranial atherosclerotic stenosis can be evaluated by traditional angiography techniques, including digital subtraction angiography, computed tomography angiography, and magnetic resonance angiography (MRA) [11-13]. However, due to the small size of coronary arteries, heart and respiratory movement, and low contrast noise between coronary artery wall and surrounding structures, magnetic resonance imaging of coronary artery wall is still challenging. Incorporating carotid plaque stability into the graded management of ischemic events provides higher accuracy than evaluating endoluminal stenosis. Therefore, further understanding of the structure of the blood vessel wall may be valuable and clinically relevant. High resolution (HR) MRI is the only imaging method of intracranial vascular wall in vivo, and has become the focus of research on intracranial atherosclerotic stenosis [14]. With the introduction of T1 weighted imaging (T1WI) of carotid plaque, some researchers have reported that high intensity signal of the coronary artery on T1WI is related to vulnerable plaque morphology and increased risk for future cardiac events [15]. Although there are some limitations and problems to be solved, this new MR technique of coronary plaque imaging may affect the treatment strategy for atherosclerotic thrombosis, and explain the pathophysiologic mechanism of atherosclerotic thrombosis. Besides traditional risk factors, chronic "low-grade" inflammation is also related to the pathogenesis of atherosclerosis and cardiovascular diseases [16]. Inflammatory cells, including monocytes, produce many pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6. The purpose of this study was to evaluate the correlation between the time-course changes of middle cerebral artery plaque evaluated by CE high-resolution MRI, and the level of inflammatory factors in cerebrospinal fluid.

Experimental methods

General information

This is a retrospective study. From August 2019 to December 2021, 136 patients with neurologic symptoms related to ischemic stroke or suspected ischemic stroke were recruited in Gong'an County Hospital of Traditional Chinese Medicine, including 69 men and 67 women, with an average age of 66.0±8.3 years. Based on the flow of blood to the middle cerebral artery: patients were grouped into an infarction group (patients with high DWI signal in the blood supply area of middle cerebral artery, n=68) and TIA group (patients with ischemic neurological symptoms but no related imaging findings, n=68).

Admission criteria: MRA-detected middle cerebral artery stenosis; There was at least one risk factor for atherosclerosis, including smoking history, drinking history, diabetes history, hypertension history, and hyperlipidemia; No history of cardiovascular events or cardiac embolism.

Exclusion criteria: Patients with non-atherosclerotic vascular diseases, such as vasculitis, arterial dissection, perforating artery disease, and moyamoya disease.

Medical ethics: This study was approved by the ethics committee of Gong'an County Hospital of Traditional Chinese Medicine, and patients or their relatives had informed consent before MRI examination.

Main outcome indicators: Differences in Non-enhanced MRI (T1WI and T2WI) features between the TIA and stroke patients, enhanced T1WI (CE+T1WI) plaque signal, and SNR and CNR values of T1WI and CE+T1WI.

Secondary output indicators: The protein levels of TNF-α, IL-6, and IL-1β in cerebrospinal fluid were determined by ELISA.

Magnetic resonance imaging

Equipment and scanning sequence: 3.0T MRI equipment (Achieva, Philips Medical System, Best, Netherlands). Routine MRI scanning sequences of skull included cross-sectional fast

spin echo (FSE) sequences T1-weighted (T1W), T2-weighted (T2W), liquid attenuation inversion recovery and diffusion-weighted imaging. Contrast-enhanced MRA (CE-MRA) of cervical spine was performed with 16 craniocervical spiral tubes, using high-pressure syringe, contrast agent Gadopentetate Dimeglumine (GD-DTPA, Bayer Healthcare, Germany). The speed was 2.5 mL/s, and no breath-holding scanning (2D-BOLUSTRAK technique) was used to observe the time when the contrast agent reached the aortic arch. Then, a large dose of contrast agent was injected with 19 mL, and the average delay time was 13 s (11-19 s). Coronal high-resolution enhanced volume scanning (S2-3D Hi Res), with the following parameters: 3D fast field echo sequence, the shortest TR/TE 4.7 ms/1.79 ms, flip angle 270; The field of view was 320 mm × 320 mm, the reconstructed pixel was 0.45 mm × 0.45 mm × 0.49 mm, the reconstructed matrix was 704, the number of scanned slices was 150, the slice thickness was 1.0 mm, the overlap was 50%, the SENSE value was 2, and the scanning time was 1 min, 27 s.

Image analysis and post-processing

The image quality was divided into three grades: cases with grade 1 and grade 2 image quality were included in this study. In the classification standard, Grade 1 was a high-definition image without motion artifacts, Grade 2 was an image that is unclear and had slight motion artifacts but can still be used for diagnosis, and Grade 3 was an image with poor quality, obvious motion artifacts and blurred blood vessels. Images were sent to Advantage Workstation 4.5 for post-processing (GE Medical Systems). Multiplane reconstruction of the image along the middle cerebral artery path. Observe the enhancement degree of middle cerebral artery plaque. The vessel area (VA) and lumen area (LA) were measured manually at the maximum lumen stenosis (MLN) site and the reference site. The reference site was defined as the segment with no lesion or minimal lesion at the proximal or distal end of the stenosis. Vascular-blood interface and vascular-cerebrospinal fluid interface were used to track LA and VA respectively. The average of the near-end and far-end values were taken as reference LA and VA. The WAll area (wa) was calculated as (VA-LA) and the PAtch area (PA) was estimated as (WAMLN-WA reference). The stenosis degree was calculated as (1-LA_{MLN}/LA reference) × 100%. The VAN was the vessel area of the largest lumen stenosis, the VA_{MLN} was defined as the lumen area of the largest lumen stenosis, the VA reference was defined as the vessel area of the reference site, and the LA reference was defined as the lumen area of the reference site. The reconstruction index was calculated as VA_{MLN}/VArefer × 100%. Reconstruction index greater than or equal to 1.05 was positive reconstruction, and reconstruction index less than or equal to 0.95 was negative reconstruction. However, if the reconstruction index was less than 0.95 and less than 1.05, it was regarded as no reconstruction to measure the plaque signal intensity (SI) before and after enhancement, and calculate (SIpre × SIpost)/SIpre as the enhancement percentage. SIpre and SIpost were defined as the slight enhancement of plaque signal intensity before and after enhancement, which was defined as an enhancement percentage of less than 10%, moderate: 10%-50%, or higher than 50%.

ELISA

① Coating process (pay attention to setting blank control and negative control): Dilute the used antigen with coating diluent to appropriate concentration (generally, the required antigen coating amount is 20-200 per well μg), add 100 antigen per well μL. Set at 37°C for 4 h, or 4°C for 24 h; Discard the liquid in the hole (to avoid evaporation, the plate should be covered or placed flat in a metal wet box with wet gauze at the bottom). ② Close the enzyme-labelled reaction hole: 5% calf serum is sealed at 37°C for 40 min. When sealing, fill the reaction holes with the sealing solution and remove the bubbles in the holes. After sealing, wash the holes with the washing solution three times, each time for 3 min. Washing method: Absorb the reaction liquid in the hole, fill the plate hole with the washing liquid, place it for 2 min, shake it slightly, absorb the liquid in the hole, pour out the liquid and pat it dry on the absorbent paper. Washing times 3 times. ③ Add the sample to be tested (establish appropriate concentration gradient): The dilution ratio of 1:50-1:400 is generally used for the test, and the larger dilution volume shall be used for the test. Generally, the sample absorption is more than 20 μL. Add the diluted sample into the enzyme-labelled

Table 1. Statistics of baseline data (s)

Item	TIA group	Cerebral infarction group	T/χ^2 value	*P* value
n	68	68		
Gender			1.134	0.378
Male	35	34		
Female	33	34		
Age (years)	65.32±8.76	66.14±8.79	0.897	0.597
BMI (kg/m^2)	24.23±3.18	24.76±3.19	1.026	0.561
Smoking at present	28 (41.18%)	29 (42.65%)	0.964	0.694
Drinking at present	15 (22.06%)	16 (23.53%)	0.857	0.562
Diabetes	16 (23.53%)	15 (22.06%)	0.697	0.187
Hypertension	49 (72.06%)	50 (73.53%)	1.112	0.347
Hyperlipemia	50 (73.53%)	51 (75.00%)	1.078	0.225
Family history of stroke	2 (2.94%)	13 (19.12%)	1.943	0.078

Note: TIA: Transient ischemic attack; BMI: body mass index. T value is the statistical value of t test; χ^2 value is the statistical value of chi-square test.

reaction hole, and add at least two holes for each sample, with each hole of 100 μL. Place it at 37°C for 40-60 min. Wash the holes with washing solution for 3 times, each time for 3 min. ④ Add enzyme-labelled antibody: Enzyme-labelled antibody: according to the reference working dilution provided by the enzyme conjugate supplier 37°C, 30-60 min, shorter than 30 min, the result is often unstable. Add 100 μL for each hole. Wash as before. ⑤ Add the substrate solution (used and prepared): TMB - hydrogen peroxide urea solution is preferred, and OPD - hydrogen peroxide substrate solution system is next. Substrate addition: 100 μL per hole. Place it in the dark at 37°C for 3-5 minutes, and add the termination solution to develop color. ⑥ Termination reaction: Add termination solution 50 μL per hole Stop the reaction and measure the experimental results within 20 minutes. ⑦ Result judgment: The wavelength of 492 nm is used after the OPD color development, and the wavelength of 450 nm is required for the TMB reaction product detection. The blank hole system must be zeroed first during the detection. It is expressed by the ratio (P/N) of the absorption value of the test sample hole to the average value of the test hole of a group of negative samples. When the P/N is greater than 2, it is used as the effective value of the antibody.

Statistical analysis

All data in this study were processed with SPSS20.0 statistical analysis software (IBM, USA). The measurement data were expressed by "mean ± standard deviation" ($\bar{x}$±s), the inter-group comparison was performed by one-way ANOVA or repeated measurement ANOVA, and the inter-group pairwise comparison was performed by LSD-t test. Counted data were expressed in percentage (%), and the inter-group comparison was conducted using χ^2 Analysis. The correlation between CE-T1WI plaque enhancement and CSF TNF-α, IL-6, and IL-1β expression levels was analyzed by Pearson correlation analysis. *P*<0.05 was considered a significant difference.

Results

Baseline data statistics

General clinical data of patients in the TIA group showed that the ratio of males to females was 35:33, the average age was 65.3±8.8, and the average BMI was 24.23±3.18 kg/m^2. In the recent five years, there were 28 cases of smoking, 15 cases of drinking, 16 cases of diabetes, 49 cases of hypertension, 50 cases of hyperlipidemia, and 2 cases of family history of stroke. The male to female ratio in the cerebral infarction group was 34:34, with an average age of 66.14±8.79 and an average BMI of 24.76±3.19 kg/m^2. In the recent five years, there were 29 cases of smoking, 16 cases of drinking, 15 cases of diabetes, 50 cases of hypertension, 51 cases of hyperlipidemia, and 13 cases of family history of stroke. Family history of stroke in the cerebral infarction group was higher than in the TIA group (*P*<0.05). There was no significant difference in sex, age, BMI, smoking history, drinking history, diabetes history, hypertension, or hyperlipidemia between the two groups (all *P*>0.05, **Table 1**).

Comparison of plaque signal of non-enhanced MRI between the two groups

Comparing the non-enhanced MRI plaque signals between the two groups, the proportion of patients with low signal, equal signal, and high signal on TIWI and T2WI in cerebral infarction group had no difference with the TIA group (*P*>0.05, **Tables 2**, **3**).

Table 2. Comparison of plaque signal of T1-weighted imaging between the two groups

Group	n	TIWI		
		Low signal	Equal signal	High signal
TIA group	68	2 (2.94%)	35 (51.47%)	31 (45.59%)
Cerebral infarction group	68	2 (2.94%)	36 (52.94%)	30 (44.12%)
T value		1.126	0.564	1.133
P value		0.748	0.654	0.398

Note: TIA: Transient ischemic attack; T1WI: T1-weighted imaging. t value is the statistical value of t test; χ^2 value is the statistical value of chi-square test.

Table 3. Comparison of plaque signal of T2-weighted imaging between the two groups

Group	n	T2WI		
		Low signal	Equal signal	High signal
TIA group	68	23 (33.82%)	11 (16.18%)	34 (50.00%)
Cerebral infarction group	68	22 (32.35%)	14 (20.59%)	32 (47.06%)
T value		5.327	1.024	6.495
P value		0.005	0.854	0.013

Note: TIA: Transient ischemic attack; T2WI: T2-weighted imaging. T value is the statistical value of t test; χ^2 value is the statistical value of chi-square test.

Comparison of plaque signal of CE+T1WI between the two groups

The plaque signals of CE+T1WI between the two groups were compared. The proportion of patients with cerebral infarction who had no enhancement or moderate enhancement on CE+T1WI was lower than that of the TIA group, and the proportion of patients with high enhancement was higher than that of the TIA group (*P*<0.05, **Table 4**).

Comparison of TNF-α, IL-6, and IL-1β expression levels in cerebrospinal fluid between the two groups

The expression levels of TNF-α, IL-6, and IL-1β in cerebrospinal fluid of the two groups were detected by ELISA. Expression levels of TNF-α, IL-6, and IL-1β in the cerebral infarction group were higher than those in the TIA group (*P*< 0.05) (**Table 5**).

Comparison of stenosis rate and remodeling index between the two groups

The vessel wall and lumen can be clearly seen in the axial (A) and oblique (C) positions of CE-T1WI. After proper enlargement of the visual field, the blood vessel area (B) of the reference site, the blood vessel area of the largest stenosis site and the lumen area (D) on the sagittal plane were measured. Comparing the VA_{MLN}, LA_{MLN}, PA, stenosis rate and remodeling index of the two groups, the VA_{MLN}, PA, and remodeling index of the cerebral infarction group were higher than those of the TIA group (*P*>0.05), and there was no statistical difference in VA_{MLN} and stenosis rate between groups (*P*<0.05, **Figure 1**; **Table 6**).

SNR and CNR of plaque on T1WI and CE+T1WI

Comparing the plaque SNR and CNR values on T1WI and CE+T1WI, the signal intensity, adjacent signal intensity, SNR, and CNR of carotid plaque on CE+T1WI were higher than those on T1WI (P>0.05, **Table 7**).

Comparison of expression levels of TNF-α, IL-6, and IL-1β in cerebrospinal fluid of patients with enhanced degree of CE-T1WI plaque

Comparing the expression levels of TNF-α, IL-6, and IL-1β in cerebrospinal fluid of patients with CE-T1WI plaque enhancement degree, the expression levels of TNF-α, IL-6, and IL-1β in the moderate enhancement group were higher than those in non-enhancement group, and the expression levels of TNF-α, IL-6, and IL-1β in the high enhancement group were higher than those in the moderate enhancement group (*P*<0.05, **Table 8**).

CE-T1WI plaque enhancement and the expression level of CSF TNF-α, IL-6, and IL-1β: CE-T1WI plaque enhancement and the expression level of CSF showed high consistency and positive correlation among the detection levels of TNF-α, IL-6, and IL-1β, as shown in **Table 9**.

Discussion

Intracranial atherosclerotic stenosis is an important cause of ischemic stroke and TIA. It usually occurs in the middle artery and basilar

Table 4. Comparison of plaque signal of CE+T1WI between the two groups

Group	n	CE+T1WI		
		No reinforcement	Medium strengthening	High reinforcement
TIA group	68	47 (69.12%)	17 (25.00%)	4 (5.88%)
Cerebral infarction group	68	8 (11.76%)	9 (13.24%)	51 (75.00%)
T value		15.334	16.268	11.175
P value		<0.001	<0.001	<0.001

Note: TIA: Transient ischemic attack; CE-T1WI: contrast-enhanced T1-weighted imaging. T value is the value of t test; χ^2 value is the value of chi-square test.

Table 5. Comparison of expression levels of TNF-α, IL-6, and IL-1β in cerebrospinal fluid between the two groups (pg/mL, s)

Group	n	TNF-α	IL-6	IL-1β
TIA group	68	226.32±25.64	155.33±15.32	187.32±26.57
Cerebral infarction group	68	925.33±56.37	678.32±1.16	798.32±45.87
T value		15.634	22.567	26.854
P value		<0.001	<0.001	<0.001

Note: TIA: Transient ischemic attack; TNF-α: tumor necrosis factor-α; IL-6: interleukin-6; IL-1β: interleukin-1β. T value is the value of t test; χ^2 value is the value of chi-square test.

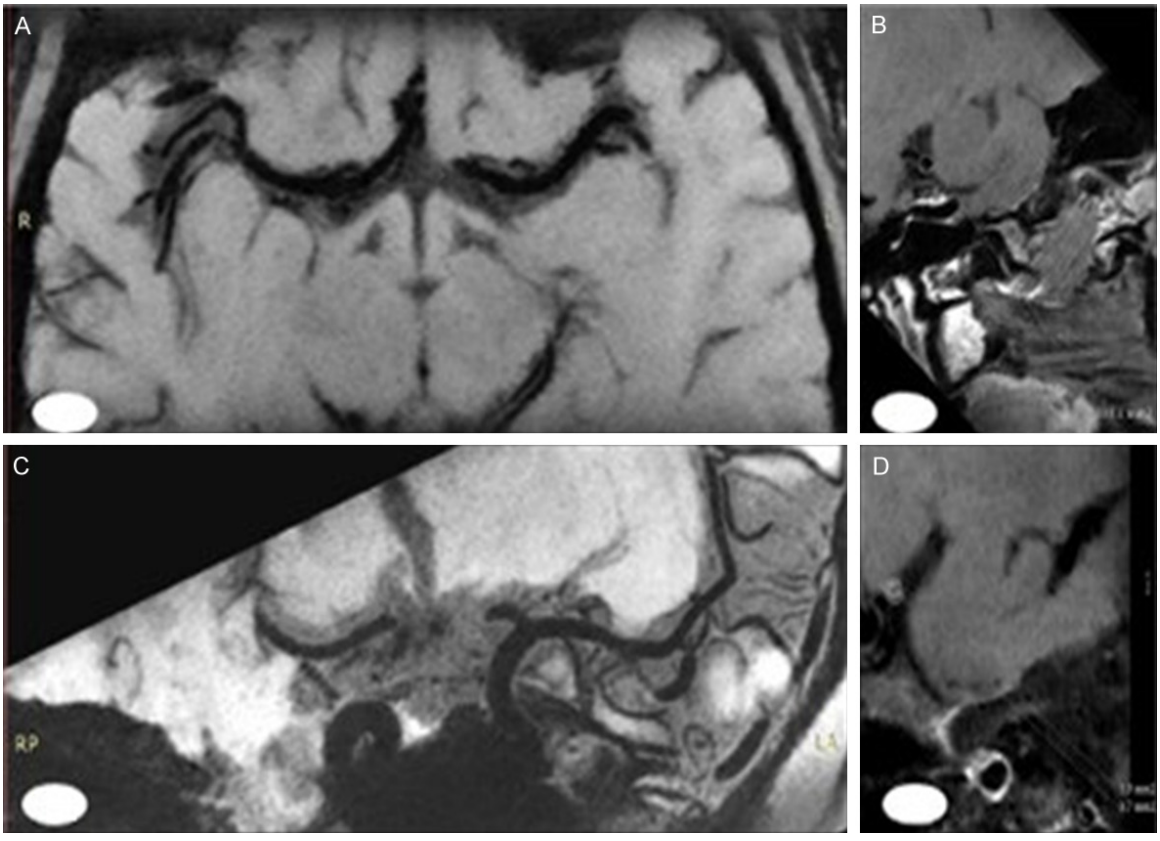

Figure 1. CE-T1WI multiplanar reconstruction. A: The vascular wall and lumen can be clearly seen in the axial direction of CE-T1WI; B: Vascular area; C: The oblique position of CE-T1WI can clearly see the vessel wall and lumen; D: The vascular area and the lumen area on the sagittal plane of the largest stenosis. CE-T1WI: contrast-enhanced T1-weighted imaging.

Table 6. Comparison of stenosis rate and remodeling index between the two groups (pg/mL, s)

Group	VA_{MLN} (mm^2)	LA_{MLN} (mm^2)	PA (mm^2)	Stenosis rate	Reconstruction index
TIA group	7.11±0.48	2.70±0.56	3.05±0.27	0.65±0.32	0.84±0.12
Cerebral infarction group	8.83±0.67	2.66±0.34	3.84±0.25	0.68±0.33	1.15±0.21
T value	13.524	0.186	5.231	0.856	12.235
P value	<0.001	0.537	0.013	0.489	<0.001

Note: TIA: Transient ischemic attack; VA_{MLN}: vessel area at lesion level; LA_{MLN}: lumen area at lesion level; PA: Patch area. T value is the value of t test; χ^2 value is the value of chi-square test.

Table 7. SNR and CNR values of plaque on T1WI and CE+T1WI (s)

Index	Carotid plaque signal intensity	Adjacent signal strength	Carotid plaque SNR	Carotid plaque CNR
T1WI	515.85±56.87	403.22±87.56	30.74±6.55	6.07±2.21
CE+T1WI	986.32±55.64	692.38±75.43	59.34±3.46	22.34±3.24
T value	13.564	15.267	18.526	16.334
P value	<0.001	<0.001	<0.001	<0.001

Note: SNR: Signal-to-noise ratio; CNR: contrast to noise ratio; T1WI: T1-weighted imaging; CE-T1WI: contrast-enhanced T1-weighted imaging. T value is the value of t test; χ^2 value is the value of chi-square test.

Table 8. Comparison of expression levels of TNF-α, IL-6, and IL-1β in cerebrospinal fluid of patients with CE-T1WI plaque enhancement degrees (pg/mL, s)

Group	n	TNF-α	IL-6	IL-1β
No reinforcement	55	204.33±25.34	125.46±32.54	142.37±26.45
Medium strengthening	26	533.42±56.38	343.53±45.26	432.34±34.75
High reinforcement	55	987.25±34.21	725.33±58.36	893.26±47.16
T value	-	13.264	15.289	14.327
P value	-	<0.001	<0.001	<0.001

Note: CE-T1WI: contrast-enhanced T1-weighted imaging; TNF-α: tumor necrosis factor-α; IL-6: interleukin-6; IL-1β: interleukin-1β. T value is the value of t test; χ^2 value is the value of chi-square test.

Table 9. Correlation between CE-T1WI plaque enhancement and expression levels of TNF-α, IL-6, and IL-1β in CSF

Group	TNF-α	IL-6	IL-1β
No reinforcement	*r*=0.84, *P*<0.05	*r*=0.90, *P*<0.05	*r*=0.89, *P*<0.05
Medium strengthening	*r*=0.85, *P*<0.05	*r*=0.79, *P*<0.05	*r*=0.93, *P*<0.05
High reinforcement	*r*=0.94, *P*<0.05	*r*=0.93, *P*<0.05	*r*=0.88, *P*<0.05

artery. Because the middle cerebral artery is the most vulnerable artery and supplies most areas of the brain, the incidence of ischemic stroke in the areas supplied by the middle cerebral artery is high. Clinical treatment of ischemic stroke mainly depends on the degree of vascular stenosis. However, ischemic events may still occur in patients with mild or moderate stenosis after drug treatment [17, 18]. Therefore, it seems valuable for neurologists to study the stability of plaques. Compared to traditional imaging methods, HR-MRI has unique advantages in visualization of blood vessel wall and plaque details and has been successfully applied to carotid atherosclerosis [19, 20]. Similarly, we used 3.0T MRI scanner to study the stroke mechanism of middle atherosclerotic stenosis. The signal-to-noise ratio and resolution of this study were acceptable.

The results of this study suggested that there was no significant difference in the proportion of patients with low signal intensity, equal signal intensity, and high signal intensity on TIWI and T2WI between infarction group and TIA group, indicating that the degree of vascular stenosis was not the decisive factor for cerebral infarction. The remodeling index and PA of diseased vessels in the infarction group were higher than those in the TIA group. The middle cerebral artery in stroke patients was mostly positive remodeling, while the middle cerebral artery in TIA patients was mostly negative remodeling. Arterial dilatation may be a physiologic compensatory reaction to ensure blood supply in the early stage of atherosclerotic stenosis and ischemia. Because positive remodeling can maintain vascular patency or relieve

ischemic symptoms for a certain period of time, the stroke risk of these patients may be underestimated if only the degree of arterial stenosis is assessed. A study showed that the plaque burden of middle cerebral artery with positive remodeling is greater. The results are similar to our research. Another study reported that compared with patients without positive remodeling, patients with positive remodeling were more likely to have microembolization and larger VA and WA at MLN. These pathologic changes may be due to the repeated repair of ruptured plaques and the increase in blood deposited in dilated blood vessels stimulated by the remodeling mode. High biologic activity will lead to instability and vulnerability of plaque. Previous studies reported that patients with positive coronary artery remodeling showed higher levels of low-density lipoprotein, C-reactive protein, and homocysteine, which were related to advanced atherosclerosis and unstable plaque. Positive remodeling of middle cerebral artery was also reported in this study. In addition, unstable plaques mostly have ulcers and bleeding, which can fall off under repeated flushing of blood flow. Other authors describe intra-plaque hemorrhage as an independent risk factor for ischemic stroke, which plays an important role in the progression of plaque-related events. These common risk factors may explain the prevalence of ischemic stroke in the infarction group.

CNR value can be used as an MRI index of plaque vulnerability. A study showed that the neointimal area of rabbit femoral artery atherosclerosis model was significantly stronger than that of fibrotic connective tissue and undamaged artery after administration of contrast agent. Enhanced MRI showed that the CNR of femoral artery plaque was increased. Our results showed that there was a positive correlation between CNR increase and MRI enhancement.

An increase of endothelial cell permeability and extracellular matrix volume caused by inflammation also leads to a significant enhancement of plaque. CE is closely related to the stability and vulnerability of intracranial atherosclerotic plaques and can be used as an alternative marker to predict the risk of stroke [21-23]. Hemorrhage in new blood vessels and plaques contributes to the progression of atherosclerotic plaques. Compared to asymptomatic patients, atherosclerotic plaques in symptomatic patients have obvious neovascularization [24, 25]. Metalloproteinases can promote angiogenesis, induce the proliferation and migration of macrophages and smooth muscle cells, and degrade extracellular matrix, thus increasing the risk of plaque rupture and hemorrhage in the plaque [26, 27]. In one study, in contrast-enhanced MRI, the signal enhancement of human carotid atherosclerotic plaque in symptomatic patients was significantly higher than that in asymptomatic patients. TNF-α and IL-6 are key participants in vascular inflammation under atherosclerosis. The increase in these cytokines is related to the incidence of heart failure, insulin resistance, dyslipidemia, and obesity. Both TNF-α and IL-6 can predict the current and future mortality of CVD and cardiovascular diseases. TNF-α is related to the increase of intima-media thickness of the common carotid artery. These cytokines are related to the pathogenesis of atherosclerosis. TNF-α is released by inflammatory leukocytes, vascular endothelial cells, and smooth muscle cells. TNF-α promotes the endothelial expression of cell adhesion molecules, thus promoting leukocytes to enter and pass through the blood vessel wall. IL-6 is also a key pro-inflammatory cytokine, and can also increase the production of liver C-reactive protein, which is an independent risk factor for atherosclerosis [28]. IL-6 can induce endothelial dysfunction and is related to CVD, cerebrovascular events, and peripheral atherosclerosis. A study showed that coronary artery stenosis (>50% or >70%) and Gensini severity score were related to the levels of serum pro-inflammatory cytokines and other inflammatory markers. Research of TNF-α and IL-6 in the pathogenesis of atherosclerosis and vascular diseases is mostly based on non-invasive methods [29, 30]. Epidemiological studies, previous studies have revealed the relationship between signal changes and pathologic components of plaque in HR-MRI examination of carotid and cerebral arteries. However, the correlation between the temporal change in plaque and the level of inflammatory factors in cerebrospinal fluid has not been clearly explained. In this study, the expression levels of TNF-α, IL-6, and IL-1β in the cerebral infarction group were higher than those in the TIA group. The expression levels of TNF-α, IL-6, and IL-1β in the enhanced group were higher than those in the

non-enhanced group, and the expression levels of TNF-α, IL-6, and IL-1β in the highly enhanced group were higher than those in the moderately enhanced group.

This research has some limitations. First, we mainly focused on the correlation between the time course change of middle cerebral artery plaque and the level of inflammatory factors in cerebrospinal fluid. The images mainly refer to other related coronary artery and carotid artery studies, without pathologic confirmation, so the reliability of the results may be reduced to some extent. The pathologic mechanism of enhancement needs to be further verified. Second, T1WI sequence takes a long time to scan, which may introduce motion artifacts in the image. Third, we could not identify the special components of small plaques by T1WI, and could only observe the enhancement of plaques globally.

To sum up, CE-T1WI can be used to characterize the wall of the middle cerebral artery and atherosclerotic plaque. The time course change of CE-T1WI plaque is positively correlated with the level of inflammatory factors in cerebrospinal fluid. For patients with intracranial atherosclerosis, it is not enough to evaluate only the degree of vascular stenosis, but more important to evaluate the stability of plaque to explore the mechanism of stroke. High levels of inflammatory factors, positive remodeling and significant enhancement are closely related to unstable plaque, which may increase the risk of stroke in patients with atherosclerosis. The evaluation of time course change in the plaque should be included in the graded management of ischemic events.

Disclosure of conflict of interest

None.

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