The pattern of brain metabolism in chronic steno-occlusive cerebral artery disease

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Background: Dispersion of gray matter and white matter and abnormal hemodynamic changes are common in patients with chronic stenosis cerebral artery disease. It is not easy to capture these abnormal changes with conventional magnetic resonance imaging (MRI). Magnetic resonance spectroscopy (MRS) is useful for obtaining metabolic information in either preclinical or clinical applications. The aim of our study was to apply MRS to non-invasively investigate changes in brain metabolism in MRI-negative patients with chronic cerebral artery steno-occlusive disease.

Methods: We performed MRS examinations with 3.0T MRI on 34 patients with severe unilateral middle cerebral artery (MCA) stenosis or occlusion without parenchymal abnormalities. Additionally, N-acetylaspartic acid (NAA), creatine (Cr), choline (Cho), NAA/Cr, and Cho/Cr in the coronal, parenchymal, and thalamic regions of the affected brain and contralateral brain were determined. The mean concentrations of NAA, Cr, Cho, NAA/Cr, and Cho/Cr in the coronal region of the affected side were significantly lower than those in the opposite side (P<0.05), but there was no significant difference between the pectin nuclei on both sides. No metabolic changes were found at the ipsilateral thalamus.

Conclusions: In this study, we demonstrated that MRS could reveal metabolic changes and that the NAA, NAA/Cr, Cho, and Cho/Cr concentration might be used as indexes for evaluating neuronal damage in the chronic steno-occlusive cerebral artery disease, treatment strategies, and treatment effectiveness.

Keywords: Cerebral arterial steno-occlusive disease; magnetic resonance imaging (MRI); magnetic resonance spectroscopy (MRS)

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Introduction

Dispersion of gray matter and white matter and abnormal hemodynamic changes are common in patients with chronic stenosis cerebral artery disease (1,2). Due to insufficient collateral circulation through the circle of Willis, perfusion pressure in the occluded arterial region may drop below the lower limit of automatic regulation. Diffusion increases and decreases in regional cerebral blood flow (RCBF) occur when the maximally dilated arterial bed cannot maintain RCBF at normal levels (3). It is not easy to capture these
abnormal changes with conventional magnetic resonance imaging (MRI).

Magnetic resonance spectroscopy (MRS) is useful for obtaining metabolic information in either preclinical or clinical applications (4). In the MRS, metabolites determine chemical shifts [parts per million (ppm)], and each metabolite can be individually identified and quantified. The increase/decrease of several of these metabolites is indicative of a certain condition and, therefore, can be used to distinguish different pathological conditions. So far, MRS has been used in a variety of pathological conditions, such as cerebral ischemic injury, brain tumors, and multiple sclerosis. However, the study of MRS in chronic occlusive cerebrovascular disease is still limited. The purpose of this study was to use MRS to study the metabolic changes of gray matter and white matter in patients with chronic stenosis occlusive middle cerebral artery (MCA) disease. We present the following article in accordance with the MDAR reporting checklist (available at https://atm.amergroups.com/article/view/10.21037/atm-22-3993/rc).

### Methods

#### Participants

In this study, 34 patients were collected from outpatients and inpatients in Qilu Hospital of Shandong University with unilateral chronic steno-occlusive MCA disease (22 men, 12 women; age range, 28 to 65 years; mean age, 47 years) were included. Among them, 12 patients had dizziness and mild cognitive impairment (MCI) and 16 patients had transient ischemic attacks (TIA). The clinical symptoms and history of all participants are presented in Table 1. In the patient group, the normal-appearing gray and white matter or lacunar infarcts (<3 mm in diameter) were confirmed using the axial T2-weighted fluid-attenuated inversion recovery imaging (FLAIR). To evaluate the ischemic effects on the territory of ipsilateral (affected hemisphere) MCA, only patients with unilateral MI portion of MCA severe stenosis (stenosis >70%) or occlusion with or without ipsilateral internal carotid artery (ICA) stenosis or occlusion were enrolled in the present study. The exclusion criteria were as follows: grade 2 or 3 hypersignal in deep white matter or periventricular hypersignal on T2-weighted FLAIR, as described in previous study (5); and occlusion or stenosis of more than 30% of the MCAs in the contralateral (unaffected hemisphere). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of Qilu Hospital of Shandong University (No. 2021005) and informed consent was taken from all the patients.

The MRI and MRS scans were performed using a 3.0T MR scanner with a quadrature birdcage head coil (GE SIGNA EXITE II3T MRI, General Electric Company, the US) and maximal gradient strength of 45 mT/m. The scanning protocol was as follows: T1-weighted transverse spin-echo sequence [repetition time (TR), 550 ms; echo time (TE), 9 ms; the number of excitations (NEX), 2]; T2-weighted transverse fast spin-echo sequence (TR, 4,600 ms; TE, 102 ms; NEX, 2); and T2-weighted FLAIR transverse fast spin-echo sequence (TR, 7,500 ms; TE, 120 ms; NEX, 2). The sections were 5 mm thick, and the matrix was 256×192. T2-weighted sagittal fast spin-echo sequence (TR, 4,600 ms; TE, 102 ms; NEX, 2; section thickness, 3 mm), axial diffusion-weighted imaging (DWI) echo-planar sequence (TR, 5,000 ms; TE, 66.5 ms; NEX, 4; section thickness, 5 mm, b=1,000 s/mm²), and 3 dimensional (3D)-time-of-flight magnetic resonance angiography (3D-TOF-MRA) (TR, 3.2 ms; TE, 22.5 ms; NEX, 1; section thickness, 1 mm). Specifically, we applied multi-voxel 1H-MRS with point-resolved spectroscopy sequence (PRESS) combined with outer volume suppression [field of vision (FOV), 240×240 mm; TR, 1,500 ms; TE, 135 ms; NEX, 1; flip angle, 90; NEX, 4; section thickness,12 mm; nominal voxel size of 10×10×12 mm; scan time, 5.6 min]. All spectra were pre-scanned using automated software on the GE SIGNA EXITE II3T MRI software 4.2, which adjusted radiofrequency (RF), transmission power, water suppression pulse power, and magnetic field uniformity.

### Table 1 Clinical symptoms and history of thirty-four patients

| Symptoms and history | Dizziness and MCI | TIA | HBP | DM | HBP and DM | RA | SLE | No related history and symptoms |
|----------------------|-------------------|-----|-----|----|------------|----|-----|-------------------------------|
| Number of patients   | 12                | 16  | 14  | 8  | 3          | 3  | 2   | 6                             |
| Duration             | >1 W              | <1 W| >3 Y| >3 Y| >3 Y       | <1 Y| >6 M| N/A                           |

*, N/A. MCI, mild cognitive impairment; TIA, transient ischemic attack; HBP, high blood pressure; DM, diabetes mellitus; RA, rheumatic arthritis; SLE, systemic lupus erythematosus; W, week; Y, year; M, month.
Measurements

Two experienced neuroradiologists assessed the brain parenchymal signals on conventional MRI, DWI, and cerebral artery stenosis or occlusion on magnetic resonance angiography (MRA) or digital subtraction angiography (DSA). A consensus was reached by discussion. The volume of interest (VOI) with a voxel size of 2 cm³ was established by the PRESS volume selection gradients, which was located at the ipsilateral and contralateral corona radiata, lenticular nucleus, and thalamus. Automatic data analysis software (General Electric Medical Systems, Milwaukee, WI, USA) was used to measure the area of major peaks, including N-acetylaspartic acid (NAA), creatine (Cr), choline (Cho), lactic acid (Lac), NAA/Cr, and Cho/Cr values. To avoid confounding factors, lacunar infarcts were excluded in the region of interest (ROI). A reference database was established by collecting NAA, Cr, Cho, NAA/Cr, and Cho/Cr values of the bilateral corona radiata, lenticular nucleus, and thalamus. A P value <0.05 was considered statistically significant.

Statistical analysis

Metabolite concentration of the ipsilateral and contralateral corona radiata, lenticular nucleus, and thalamus were analyzed using the software SPSS 13.0 (IBM Corp., Chicago, IL, USA). We used 2-tailed paired t-tests to compare the mean values for NAA, Cr, Cho, NAA/Cr, and Cho/Cr at the ipsilateral and contralateral corona radiata, lenticular nucleus, and thalamus. A P value <0.05 was considered statistically significant.

Results

In this study, MRA and/or DSA showed unilateral M1 portion of MCA severe stenosis (≥70% diameter reduction) in 11 patients (32.35%), and unilateral M1 portion of MCA occlusion in 25 patients (73.53%). On MRA or DSA, a few distal branches of the ipsilateral MCA were demonstrated. Conventional MRI confirmed normal brain parenchyma in 19 patients and subcortical lacunar infarcts (<3 mm in diameter) in 17 patients.

The present study showed that mean NAA values were significantly lower across all regions, but Cho and Cho/Cr were significantly higher at the contralateral corona radiata and lentiform nucleus (P<0.05). Mean Cr and NAA/Cr values were significantly lower at the ipsilateral corona radiata than the contralateral corona radiata (P<0.05), but no differences were observed at the bilateral lenticular nucleus. Mean NAA, Cr, Cho, NAA/Cr, and Cho/Cr values showed no significant differences at the ipsilateral and contralateral thalamus (Figure 1). No patient showed Lac peaks at the bilateral corona radiata, lenticular nucleus, and thalamus. All statistical results regarding these metabolites concentration are presented in Table 2 and Figures 2,3.

Discussion

The corona radiata is the farthest white matter perfusion area of the cortical branch of the MCA and the anterior cerebral artery (ACA), and the deep watershed of the distal parenchyma through the small artery. The central putamen and lateral segment of the globus pallidus of the lenticular nucleus and the lateral posterior thalamic nucleus of the thalamus are supplied by the central branches of the MCA (6,7). Tsuchida et al. showed that carotid artery occlusion disease leads to ischemic changes in gray matter and white matter due to hemodynamic impairment, and that the oval center may be at least as susceptible to ischemic changes due to MCA occlusion as the cortical gray matter (8). Positron emission tomography (PET) has been widely used to evaluate oxygen metabolism in brain tissue and is suitable for evaluating oxygen metabolism in gray matter (9). By contrast, MRI of white matter can be performed easily (8). Using MRI, we evaluated the corona radiata, lenticular nucleus, and thalamus of patients with unilateral chronic steno-occlusive MCA disease. In order to apply accurate spectra at the ipsilateral radiographic crown, an ROI was placed at the level of the lateral ventricle body, thus avoiding perfusion of the white matter region at the farthest end of the cortical branch of the ACA. We excluded the evaluation of metabolism at the cortical gray matter using MRS as it is thin and easily contaminated by cerebrospinal fluid (CSF).

Since the MRS parameters are affected by age, individual, magnetic field homogeneity, and temperature, we used the hemispheric ratios to determine the relationship between MRS measurements. The use of hemispherical ratios exploits the fundamental symmetry of the brain to improve sensitivity in identifying local diseases (10). Previous study has focused on metabolic diffusion, hemodynamics, and pathological changes in patients with unilateral stenosis occlusive carotid artery disease, but the hemodynamic status of the contralateral cerebral hemisphere in severe carotid artery stenosis cannot be assumed to be normal due to the possibility of interhemispheric shunt (11). To prevent the spectroscopy of ipsilateral hemisphere from...
Figure 1 A 65-year-old man with a left MCA occlusion. (A,B) T2-weighted imaging showed a normal signal in the cerebral parenchyma. ROIs were placed on the symmetric corona radiata, lentiform nucleus, and thalamus as shown on the T2-weighted imaging by the indicated rectangle. (C) MRA showed an M1 portion of the left MCA occlusion and a few distal branches (arrow). (D) MRS showed a normal Cho, NAA, and Cr peak at the contralateral corona radiata. (E) The Cho peak increased, whereas the NAA and Cr peak decreased at ipsilateral corona radiata. (F) MRS showed a normal Cho, NAA, and Cr peak at the contralateral lenticular nucleus. (G) The Cho peak increased slightly, the NAA peak slightly decreased, but there was no significant change in the Cr peak at the ipsilateral lenticular nucleus. (H,I) MRS showed similar Cho, Cr, and NAA peaks at the bilateral thalamus. MCA, middle cerebral artery; ROI, region of interest; MRA, magnetic resonance angiography; MRS, magnetic resonance spectroscopy; Cho, choline; NAA, N-acetylaspartic acid; Cr, creatine.
Table 2 Comparison of metabolites at bilateral corona radiata, lenticular nucleus, and thalamus in unilateral chronic steno-occlusive middle cerebral artery disease

| Metabolites | Corona radiata | Lenticular nucleus | Thalamus |
|-------------|----------------|------------------|----------|
|             | C   | I   | P value | C   | I   | P value | C   | I   | P value |
| Cho         | 94,740±11,312 | 104,268±16,909 | 0.01     | 73,778±5,969 | 76,769±5,872 | 0.04     | 75,011±6,623 | 76,750±6,927 | 0.29     |
| Cr          | 84,393±10,422 | 78,541±7,910   | 0.01     | 73,611±4,567 | 72,613±4,611 | 0.37     | 71,930±4,626 | 71,163±4,510 | 0.49     |
| NAA         | 182,814±27,980| 160,711±38,941 | 0.01     | 134,227±9,975| 128,671±2,027| 0.04     | 130,842±13,004| 128,037±12,361| 0.37     |
| NAA/Cr      | 2.35±0.44     | 1.92±0.48      | < 0.01   | 1.83±0.18     | 1.78±0.20    | 0.26     | 1.83±0.20     | 1.80±0.19    | 0.67     |
| Cho/Cr      | 1.20±0.19     | 1.31±0.25      | 0.04     | 1.83±0.17     | 1.68±0.19    | 0.02     | 1.05±0.12     | 1.09±0.12    | 0.18     |

*, data are the mean ± SD. C, contralateral; I, ipsilateral; Cho, choline; NAA, N-acetyl-aspartate; Cr, creatine.

Figure 2 Comparison of metabolites at the bilateral corona radiata, lenticular nucleus, and thalamus in the unilateral MCA steno-occlusive disease. The Y-axis represents the signal intensity. MCA, middle cerebral artery; ICR, ipsilateral corona radiata; CCR, contralateral corona radiata; IT, ipsilateral thalamus; CT, contralateral thalamus; ILN, ipsilateral lenticular nucleus; CLN, contralateral lenticular nucleus; Cho, choline; Cr, creatine; NAA, N-acetyl-aspartate.

Figure 3 Comparison of metabolism ratio at the bilateral corona radiata lenticular nucleus and thalamus in the unilateral MCA steno-occlusive disease. The Y-axis represents the ratio of the signal intensity. MCA, middle cerebral artery; ICR, ipsilateral corona radiata; CCR, contralateral corona radiata; IT, ipsilateral thalamus; CT, contralateral thalamus; ILN, ipsilateral lenticular nucleus; CLN, contralateral lenticular nucleus; NAA, N-acetyl-aspartate; Cr, creatine; Cho, choline.
being affected by perfusion through the anterior and posterior communicating artery, patients with unilateral M1 portion of MCA severe stenosis or occlusion were enrolled in the present study. Thus, hemodynamic status in the contralateral hemisphere can be assumed as normal, given the shunting of blood in the bilateral MCA territory through the anterior and posterior communicating artery is excluded.

In the present study, NAA was decreased at the ipsilateral corona radiata and lenticular nucleus (putamen) while NAA/Cr was decreased at the ipsilateral corona radiata. The level of amino acid NAA can be used as an index of neuronal viability in cerebral tissue. It can be depleted during the long duration of mitochondrial dysfunction in infarcted areas but will return to normal levels if nerve cell degeneration necrosis is prevented after timely treatment during the short duration of mitochondrial dysfunction (12,13). The reduction of NAA in ischemic stroke may be due to inhibition of NAA synthesis, accelerated catabolism of NAA, and further metabolism of NAA-related derivatives into the blood (14,15). Our findings suggested that neuronal damage (death and/or dysfunction) occurred at the ipsilateral corona radiata and lenticular nucleus (putamen). Notably, the NAA result was inconsistent with the NAA/Cr at the ipsilateral corona radiata and lenticular nucleus (putamen) in our studies, which might be caused by changes of Cr in the territory supplied by steno-occlusive MCA or caused by measurement error. This issue needs to be verified in future.

In vivo, the Cho signal predominantly consisted of glycerophosphocholine and phosphocholine, which is a precursor of acetylcholine (16). Elevated Cho suggests increased cell membrane turnover or destruction in invasive brain tumors and demyelinating diseases (17). In a patient with acute MCA stroke, the increase in Cho signal intensity preceded the change in signal intensity shown on T2-weighted MRI. In addition, Cho/Cr values were increased in the subacute and chronic stages after stroke compared with healthy controls (18,19). Garnett et al. found that Cho/Cr was proportional to the severity of traumatic brain injury in normal-looking white matter (20). The above-mentioned studies indicated that Cho and Cho/Cr were sensitive metabolic indexes in evaluating chronic cerebral ischemia/injury. In our study, the increase of Cho and Cho/Cr indicated that nerve cell membrane damage and/or glial cells loss may occur at the ipsilateral corona radiata and lenticular nucleus (putamen) as chronic ischemia that had not yet developed into apparent morphologic changes.

The single peak at 3.0 ppm of Cr in 1H spectrum represents Cr and its phosphorylated form of phosphocreatine (PCr). They were found in high concentrations of metabolically active tissues that require sudden bursts of energy, including the brain, muscles, and heart. Polymerase chain reaction (PCR) can quickly donate its phosphate group to ADP, which can be converted into Cr to regenerate adenosine triphosphate (ATP) rapidly. Under healthy conditions, Cr is thought to vary less throughout the brain than other 1H-MRS metabolites. Therefore, it is the most common denominator for expressing the metabolite ratio of 1H (21). The results of Cr studies in brain ischemic diseases are contradictory (22). In addition, Rumpel et al. suggested that neuronal cells and glial cells loss or death after cerebral infarction would result in a decrease of Cr (23). In the present study, Cr reduced at the ipsilateral corona radiata, but there were no significant changes at the ipsilateral lenticular nucleus. Thus, our findings suggested that neuronal cells or glial cells might be lost at the ipsilateral corona radiata but not at the ipsilateral lenticular nucleus. These results, however, need to be verified in future studies with increased sample size.

As the end product of anaerobic glycolysis consumption, Lac is generally considered a marker of hypoxia and/or ischemia (24). The Lac levels elevated persistently in infarcted brain parenchyma for weeks, which is associated with inflammatory macrophages (25-27). No patient showed a Lac peak in this study.

In the present study, metabolic changes of NAA, Cr, Cho, and Lac were not found at the ipsilateral thalamus. The thalamus blood is supplied by branches of the ICA, posterior communicating artery, and the posterior cerebral artery (6,7), so there are no metabolic changes in the ipsilateral thalamus with sufficient hemodynamics in patients with unilateral chronic steno-occlusive of M1 port of MCA disease.

In conclusion, MRS may be a sensitive tool depicting metabolism changes in chronic steno-occlusive cerebral artery disease without evidence of brain abnormalities by conventional MRI. The NAA, NAA/Cr, Cho, and Cho/Cr may be used to evaluate neuronal damage, treatment strategies, and treatment effectiveness in the chronic steno-occlusive cerebral artery disease.

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**Footnote**

**Reporting Checklist:** The authors have completed the MDAR reporting checklist. Available at [https://atm.amegroups.com/article/view/10.21037/atm-22-3993/rc](https://atm.amegroups.com/article/view/10.21037/atm-22-3993/rc)

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**Conflicts of Interest:** All authors have completed the ICMJE uniform disclosure form (available at [https://atm.amegroups.com/article/view/10.21037/atm-22-3993/coif](https://atm.amegroups.com/article/view/10.21037/atm-22-3993/coif)). The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of Qilu Hospital of Shandong University (No. 2021005) and informed consent was taken from all the patients.

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