ORIGINAL ARTICLE

Proton magnetic resonance spectroscopy and cognitive impairment in patients with ischemic white matter lesions

Ying Xing, Fang Fang, Xu Zhang, Ling Ling Hou, Zhao-shi Zheng, Mohamed Sheikhali
Department of Neurology, China-Japan Union Hospital, Ji Lin University, Changchun, China

Background: The purpose of this study is to investigate the relationship between the cognitive impairment and NAA/Cr and Cho/Cr ratios in the proton magnetic resonance spectroscopy (^{1}HMRS), and to assess the importance of ^{1}HMRS in the early diagnosis of cognitive impairment in patients with ischemic white matter lesions (WMLs). **Materials and Methods:** A total of 45 patients (23 males and 22 females) with the ischemic WML were divided into mild WML group (n = 15), moderate WML group (n = 15), and severe WML group (n = 15). A total of 15 healthy controls (8 males and 7 females) with no WML on magnetic resonance imaging were included. ^{1}HMRS focusing on the frontal lobe white matter around the anterior horn of the lateral ventricle and Montreal Cognitive Assessment (MoCA) were conducted. **Results:** Patients with more severe WML had lower MoCA scores. The NAA/Cr ratio in ^{1}HMRS was reduced in all the patients and was strongly correlated with the total MoCA scores (r = 0.845, P < 0.001). The Cho/Cr ratio in ^{1}HMRS was increased in mild and moderate patients, was negatively correlated with the total MoCA scores (r = 0.907, P < 0.001). The Cho/Cr ratio was reduced in the severe patients and was positively correlated with the total MoCA scores (r = 0.937, P < 0.001). In addition, NAA/Cr and Cho/Cr ratios in ^{1}HMRS were changed in patients with the mild WML whose total MoCA scores were similar to the controls. **Conclusion:** Our results suggest that NAA/Cr and Cho/Cr ratios in ^{1}HMRS are useful indicators for early diagnosis of ischemic WML and cognitive impairment in patients with ischemic WML.

Keywords: ^{1}HMRS, Cho/Cr ratio, cognitive impairment, ischemic white matter, montreal cognitive assessment, NAA/Cr ratio, white matter lesions

How to cite this article: Xing Y, Fang F, Zhang X, Hou LL, Zheng Z, Sheikhali M. Proton magnetic resonance spectroscopy and cognitive impairment in patients with ischemic white matter lesions. J Res Med Sci 2013;18:1061-6.

INTRODUCTION

Cerebral white matter lesions (WMLs) are commonly found in patients with cerebrovascular diseases such as atherosclerosis, hypertension, stroke, and brain infarction.[1-4] It has been reported that white matter ischemic lesions (WMILs) are caused by chronic ischemia resulting from long-term low cerebral blood perfusion due to atherosclerosis.[1,5-7] Ischemic WMLs are associated with clinical manifestations of cognitive impairment including reduced memory, processing speed, and executive functions.[8,9] Several studies have shown that the severity of WMLs is associated with the extent of cognitive impairment.[10-12] However, it remains unclear how WMLs lead to the cognitive impairment.

Magnetic resonance imaging (MRI) and computed tomography (CT) have been widely used for the detection of WMLs. WMLs appear as areas of hyperintensity on T_2-weighted MRI, and as areas of low attenuation on CT.[12,13] Ischemia or demyelination has been reported to underlie the cause of the radiological changes on CT and MRI.[2,7] Though CT and MRI can detect the morphological changes in the WMLs, they provide little information on the functional change in the WMLs, especially in the early stage of WML when no obvious morphological changes occur. Proton magnetic resonance spectroscopy (^{1}HMRS), which detects the abnormalities of tissue metabolism rather than anatomy, emerges as a useful technique for evaluating the extent and severity of the WML.[14] It has been reported that ^{1}HMRS can effectively distinguish WMLs in patients with subcortical arteriosclerotic encephalopathy from those in asymptomatic elderly.[15]

The primary sources of the ^{1}HMRS signals in normal brain are N-acetyl aspartate (NAA), choline (Cho), creatine (Cr). NAA is found in neurons and axonal process, and is reduced in ischemia, multiple sclerosis, and degenerative diseases, suggesting neuronal death or injury.[16,17] Cho has been reported to be elevated in demyelinating diseases and ischemia.[18,19] In this study, we investigated the cognitive impairment in 45 patients with the ischemic WMLs and measured the NAA/Cr and

Address for correspondence: Dr. Ying Xing, Department of Neurology, China-Japan Union Hospital, Ji Lin University, No.126 Xian Tai Avenue, Changchun, 130033, China. E-mail: yingxing1234@hotmail.com
Received: 21-11-2012; **Revised:** 10-07-2013; **Accepted:** 01-10-2013

Cho/Cr changes, using ^{1}HMRS. The purpose of this study was to study the relationship between cognitive impairment and NAA/Cr and Cho/Cr ratios in ^{1}HMRS, and to assess the importance of ^{1}HMRS in the early diagnosis of cognitive impairment in patients with ischemic WMLs.

MATERIALS AND METHODS

Subjects

The study was approved by the Medical Ethics Committee of the Medical University and all subjects gave their informed consent. This prospective case-control study included 45 patients (23 males and 22 females) who were diagnosed clinically with WMILs from January 2011-March, 2012 at our department. A total of 15 healthy controls (8 males and 7 females) with no WMLs on MRI were included. This study only included patients with WMLs who were diagnosed with brain ischemic diseases including brain infarction, chronic cerebral circulation insufficiency, and subcortical arteriosclerotic encephalopathy. We excluded patients with WMLs, who were associated with infection, poisoning, metabolic diseases, and neurodegenerative diseases. In addition, the patients with disturbance of consciousness, delirium, and mental illness were excluded. We also excluded the patients who did not undergo MRI, ^{1}H-MRS, and neuropsychological test (MoCA) due to aphasia, hearing impairment, visual impairment, and motor and sensory disorders.

All patients underwent MRI and the severity of WMLs was scored based on T_2-weighted MRI images according to the report by Wahlund *et al*.,[13]. The WML was defined as hyperintensity >5 mm on T_2-weighted images. Patients with WMIL were categorized into three groups according to the severity of WMLs. For patients with mild WMLs (Group A, $n = 15$), a single lesion was observed on MRI. For patients with moderate WMLs (Group B, $n = 15$), confluence of lesions were found on MRI. For patients with severe WML (Group C, $n = 15$), diffuse involvement of the entire regions were identified on MRI.[13] For controls (Groups D, $n = 15$), no WMLs were found on MRI. The clinical data of these patients and controls are shown in Table 1. Patient age, gender, and education level did not differ significantly among the four groups.

The MoCA for testing cognitive impairment

The MoCA was administered by a well-trained neurologist in 10-15 min to all groups on the days of their first visit to the hospital. The MoCA is a 30-point test, including visuospatial executive function assessed by a clock-drawing test (5 points), naming task (3 points), language skills assessed by verbal fluency test (3 points), attention (6 points), short memory recall (5 points), abstract thinking (2 points), and orientation (6 points). One point was added for subjects with less than 12 years in education. The total score of 26 points or above was considered normal. All patients were assessed by MoCA under the same conditions.

^{1}HMRS detection of NAA/Cr and Cho/Cr

Subjects underwent magnetic resonance spectroscopy (MRS) on the following day after MoCA was administered. The MRS was performed in all patients using a 3.0-T Sigma CV/I MRI device (GE, USA) and a circular polarized head coil. All patients had T_1-weighted imaging (T_1WI) and T_2-weighted imaging () in the axial, sagittal, and coronal planes. The hyperintense lesions with a diameter of >5mm were selected for both T_2WI and ^{1}HMRS. Axial magnetic resonance (MR) images with maximum lesions were used for ^{1}HMRS positioning. A voxel of 15 × 15 ×15 mm was selected in the frontal lobe white matter around the anterior horn of the lateral ventricle as the regions of interest (ROI). MR spectra were acquired using point resolved echo spectroscopy (repetition time 2000 ms and echo time 35 ms). The acquired data were transferred to the workstation and automatically processed with GE-specific software (Functionaltool 2000) for water suppression, Fourier transform, baseline correction, and phase correction. The areas under the metabolic peaks of Cho, Cr, and NAA were automatically calculated at each ROI at the same time. The metabolite ratios (Cho/Cr and NAA/Cr) were calculated based on the areas under the metabolic peaks of Cho, Cr, and NAA to improve the signal to noise ratio. All data were evaluated by a neuroradiologist blinded to the patient's clinical information.

Statistical analysis

Analyses were performed using SPSS 17.0. All values were presented as mean and standard deviation. Categorical data were compared with chi-square analysis. One-way analysis of variance was used to compare the differences in the patient's age among groups. Analysis of covariance was used to compare differences in the MoCA scores among Groups A-D adjusted for age, sex, and education level. The Student-Newman-Keuls test was used to adjust for multiple pairwise comparisons. The Pearson correlation analysis was

Table 1: Clinical characteristics of patients with white matter ischemic lesions and controls

Groups	A ($n = 15$)	B ($n = 15$)	C ($n = 15$)	D ($n = 15$)	*P* value
Age (years)	62.67±7.650	61.33±6.779	64.07±8.388	57.6±7.971	0.1331*
Male (%)	8 (53.33)	8 (53.33)	7 (46.67)	8 (53.33)	0.9776#
Education level (% with less than 12 years in education)	8 (53.33)	9 (60.00)	7 (46.67)	8 (53.33)	0.9110#

*One-way analysis of variance (ANOVA); #Chi-square test

applied to assess the relationship between MoCA score and the ratios of Cho/Cr and NAA/Cr. Probability values less than 0.05 were considered statistically significant.

RESULTS

The MoCA in WMIL patients

The MoCA scores were normally distributed, except the scores in memory, languages, and abstract thinking in Groups A and D, and the scores in naming tasks in Groups A, B, and D. The total MoCA scores decreased with the increased severity of the WMIL. Analysis of covariance was used to compare differences in the MoCA scores among Groups A-D adjusted for age, sex, and education level. The Student-Newman-Keuls test was used to adjust for multiple pairwise comparisons. We first checked the assumption of linear regression of the data and found that the covariates exhibited linear associations with the MoCA scores. We further tested the collinearity of the covariates (age, sex, and education levels) and found no covariates were multicollinear in each group. We also checked whether the association between MoCA scores and the covariates (age, sex, and education levels) were similar among groups. Results showed that there were no significant interaction between group and covariates in any items of the MoCA socres [Table 2], indicating that the assumption of homogeneity of regression slopes was satisfied. After adjusted by age, sex, and education levels, the total MoCA score in the Groups B and C, but not the Group A, was significantly decreased compared with that in the control group [Table 3]. However, the MoCA score in the memory recall was significantly lower in the Group A compared with that in the control group ($P < 0.05$), suggesting that the damage in the memory occurred at the early stage of the ischemic WML. In addition, the MoCA score in each tested item was significantly lower in the Groups B and C than that in the control group ($P < 0.05$). These data suggested that the attention and orientation were damaged at the late stage of the ischemic WML.

Table 2: Results of testing the assumption of homogeneity of regression slopes

Groups	Homogeneity of regression slopes		
	Education vs. age	Sex vs. age	Group vs. age
Visuospatial functions	0.9167	0.4144	0.5477
Naming task	0.7021	0.7929	0.8079
Memory recall	0.1511	0.1285	0.1644
Attention	0.0921	0.5665	0.5006
Language skills	0.7296	0.2808	0.1757
Abstract thinking	0.0887	0.2844	0.6426
orientation	0.1212	0.1492	0.3061
Total MoCA scores	0.1159	0.3241	0.0688

MoCA = Montreal Cognitive Assessment

Measurement of NAA/Cr and Cho/Cr with ^{1}HMRS

Figure 1 shows representative MRI images and ^{1}HMRS images from WMIL patients and healthy controls. The white matter around the anterior horn of the lateral ventricle was selected as ROI. The NAA/Cr ratio was significantly lower in the Groups A, B and C compared with that in the control [$P < 0.05$, Figure 2]. The Cho/Cr ratio was significantly higher in the Groups A and B, but was significantly lower in the Group C compared with that in the control [$P < 0.05$, Figure 2]. Group C exhibited the lowest NAA/Cr and Cho/Cr ratios [Figure 2].

We further studied the correlation of MoCA scores with the NAA/Cr and Cho/Cr ratios in patients with the ischemic WML. The NAA/Cr ratio was strongly correlated with the total MoCA scores ($r = 0.845$, $P < 0.001$) [Figure 3a]. The Cho/Cr ratio in the mild and moderate WMIL patients was negatively correlated ($r = 0.907$, $P < 0.001$) [Figure 3b), and the Cho/Cr ratio in the severe patients was positively correlated with the total MoCA scores ($r = 0.937$, $P < 0.001$) [Figure 3c].

DISCUSSION

In this study, we investigated the correlation between cognitive impairment and NAA/Cr and Cho/Cr ratios in the ^{1}HMRS in patients with ischemic WML. We found that the patients with more severe WML had a lower MoCA score, suggesting that these patients exhibited more severe

Table 3: The MoCA scores in WMIL groups and control groups adjusted by age, sex, and education level

Groups	A (mild WMIL)	B (moderate WMIL)	C (severe WMIL)	D (control)	*P* value
Visuospatial functions	4.73±0.46	3.40±0.91**	2.53±0.52***	4.73±0.46	<.0001
Naming task	3.00±0.00	2.33±0.49**	1.93±0.80***	3.00±0.00	<.0001
Memory recall	3.93±0.59*	3.20±0.78**	2.67±0.72***	4.93±0.26	<.0001
Attention	5.63±0.63	5.20±0.68**	3.20±0.94***	5.67±0.49	<.0001
Language skills	3.00±0.00	2.47±0.52**	2.13±0.52***	3.00±0.00	<.0001
Abstract thinking	2.00±0.00	1.87±0.35**	1.93±0.26***	2.33±0.49	0.0419
orientation	5.80±0.41	5.40±0.98**	4.93±0.96***	5.87±0.35	0.0017
Total MoCA scores	28.13±1.41	23.93±2.69**	19.33±3.40***	29.53±0.64	<.0001

Analysis of covariance was performed to compare differences among Groups A-D after adjustment for age, sex, and education level. The Student-Newman-Keuls test was used to adjust for multiple pairwise comparisons.*$P < 0.05$ Group A versus control; **$P < 0.05$ Group B versus control; ***$P < 0.05$ Group C versus control. MoCA = Montreal Cognitive Assessment; WMIL = white matter ischemic lesion

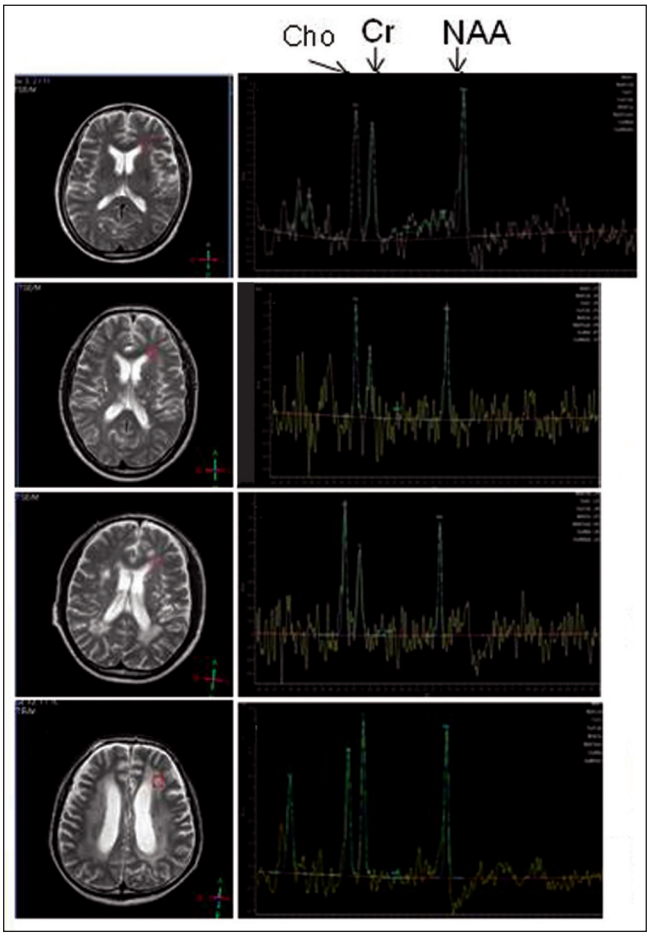

Figure 1: Representative magnetic resonance images (a, c, e, and g) and proton magnetic resonance spectroscopy images (b, d, f, and h) from control (a and b), and patients with mild (c and d), moderate (e and f), and severe (g and h) ischemic white matter lesion. A voxel of 15 × 15 × 15 mm was selected in the frontal lobe white matter around the anterior horn of the lateral ventricle as regions of interest indicated by red square (a, c, e, and g). The metabolic peaks of choline (Cho), creatine (Cr), and N-acetyl aspartate (NAA) are indicated by arrows (b, d, f, and h)

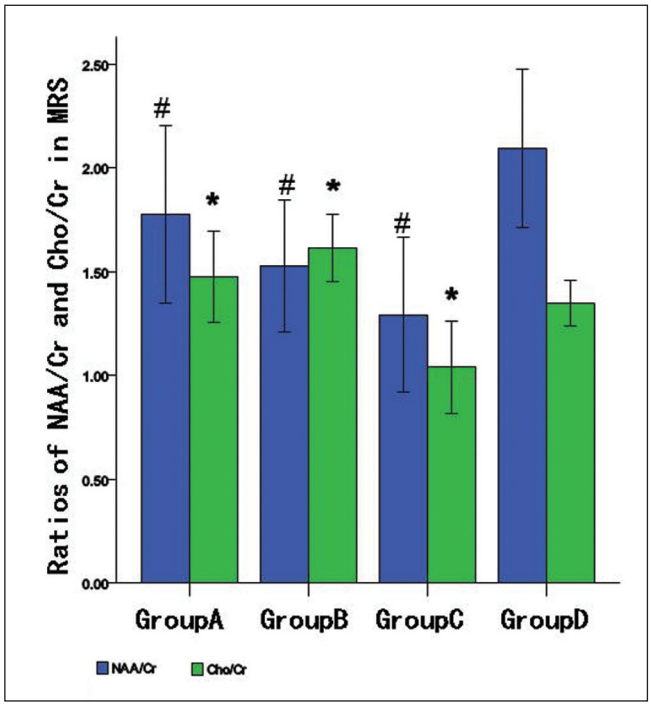

Figure 2: The N-acetyl aspartate (NAA)/ creatine (Cr) ratio and the choline (Cho)/ Cr ratio in patients with mild (Group A), moderate (Group B), and severe (Group C) ischemic white matter lesion, and controls (Group D). *n* = 15. For the Cho/Cr ratio,**P* < 0.05 versus controls; for the NAA/Cr ratio, #*P* < 0.05 versus controls

cognitive impairment. A reduction in the NAA/Cr ratio in ^{1}HMRS was found in the patients with ischemic WML as compared with the controls, suggesting that the NAA/Cr ratio in ^{1}HMRS was a good indicator for detecting WML. We also found an increase in the Cho/Cr ratio in mild and moderate patients, and a reduction in the Cho/Cr ratio in the severe patients, suggesting that Cho was elevated at the early stage of ischemic WML, but was decreased at the late stage of ischemic WML when irreversible damages occurred in the brain so that the cells lost their ability to repair the damages. Furthermore, we found that the NAA/Cr ratio was strongly correlated with the total MoCA scores, and that the Cho/Cr ratio in the mild and moderate WMIL patients was negatively correlated, and the Cho/Cr ratio in the severe patients was positively correlated with the total MoCA scores.

In this study, the frontal lobe white matter around the anterior horn of the lateral ventricle was selected as ROI. The white matter in this location mediates the subcortical and frontal cortical structures in the brain circuits involving in executive function, memory, and social behavior. It is known that the WML are associated with cognitive impairment related with the subcortical/frontal cortical brain systems.[8,9,12,20-22] It has been reported that damages to the white matter around the lateral ventricle can lead to cognitive impairment[21] and are associated with a high risk of dementia.[22] In this study, we found that the MoCA scores decreased with the increased severity of the WML, and the impairment in the cognitive domains was also associated with the severity of WML. Patients with mild WML only exhibited impairment in the memory, patients with moderate WML presented with cognitive impairments in the visuospatial executive function, language skills, and naming task, and patients with severe WML had cognitive impairments in all items tested. The cognitive impairment in the visuospatial executive function in patients with moderate and severe ischemic WML is possibly associated with the chronic ischemia-induced damages to the frontal cortical/subcortical structures that mediate the visuospatial executive function.[23,24] In addition, the memory impairment is possibly associated with the dysfunction of prefrontal cortex caused by ischemia-induced WMLs.[25]

NAA, a neuronal marker, is reduced due to neuronal death or injury.[16,17,26,27] Cho, rich in the glial cells, is elevated due to the gliosis and demyelination.[18,19] In this study, we found that the NAA/Cr ratio in ^{1}HMRS was significantly lower,

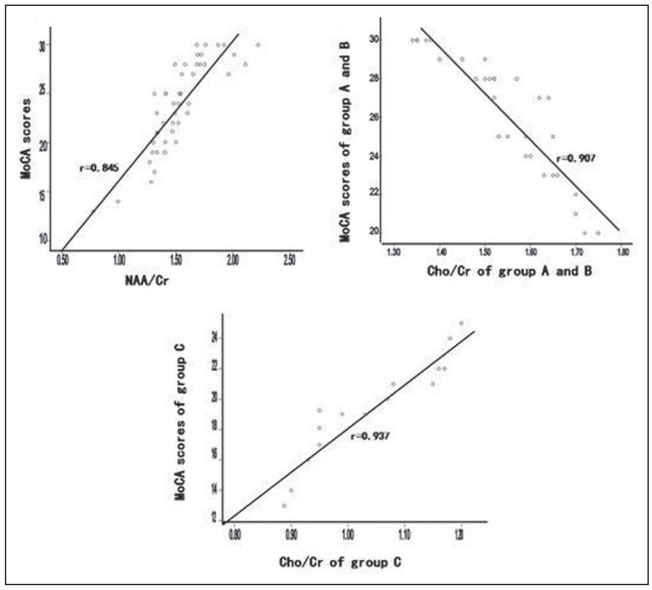

Figure 3: Correlation of Montreal Cognitive Assessment with the N-acetyl aspartate (NAA)/ creatine (Cr) ratio in all patients with ischemic white matter lesion (WML) and the choline (Cho)/Cr ratio in patients with mild and moderate (Groups A and B) and severe (Group C) ischemic WML. A. The NAA/Cr ratio in all patients with ischemic WML was correlated with the total MoCA scores. r = 0.845, P < 0.001. B. The Cho/Cr ratio in the mild and moderate white matter ischemic patients was negatively correlated. r = 0.907, P < 0.001. C. The Cho/Cr ratio in the severe patients was positively correlated with the total MoCA scores. R = 0.937, P < 0.001

and the Cho/Cr ratio in ^{1}HMRS was significantly higher in patients with mild and moderate ischemic WML than that in controls, suggesting that neuronal death and injury, gliosis, and demyelination occurred after ischemic WML. We also found that NAA/Cr ration was decreased with the increase in the severity of WML, suggesting that NAA/Cr ratio was a good indicator for detecting the severity of the WML. In addition, NAA/Cr and Cho/Cr ratios were significantly changed in patients with mild WML, who did not exhibit significantly difference in the total MoCA scores, suggesting that NAA/Cr and Cho/Cr ratios in ^{1}HMRS can be used to early detect the WML.

In this study, we found that the NAA/Cr ratio was strongly correlated in WML, the Cho/Cr ratio in the mild and moderate WML patients was negatively correlated, and the Cho/Cr ratio in the severe patients was positively correlated with the total MoCA scores, suggesting that the NAA/Cr and Cho/Cr ratios in the ^{1}HMRS were good indicators for cognitive impairment in patients with ischemic WML. Frisoni *et al.*,[28] have reported that only patients with the severe WML exhibit clinically relevant cognitive impairment. Patients with the WML are often identified when moderate or severe cognitive impairment, even dementia, occurs, thus missing the best opportunity for early diagnosis and treatment. Our study shows that the NAA/Cr and Cho/Cr ratios in ^{1}HMRS can identify patients with mild WML, and are correlated with the cognitive impairment, suggesting that NAA/Cr and Cho/Cr ratios in ^{1}HMRS are good indicators for early diagnosis of WML.

The limitation of the study is that the group of patients were small (n = 15 for each group). Despite the relative small numbers of subjects, the results showed significant differences in the MoCA score in each tested items between Groups B and C patients and controls, and in the MoCA score in memory recall between Group A patients and controls. In addition, we found that the NAA/Cr ratio and the Cho/Cr ratio in ^{1}HMRS were correlated with the total MoCA scores in patients with ischemic WML. Our findings suggest that NAA/Cr and Cho/Cr ratios in ^{1}HMRS are useful indicators for early diagnosis of ischemic WML. Further studies with a large sample size are clearly needed to confirm and extend the study.

In summary, we find that the NAA/Cr ratio and the Cho/Cr ratio in ^{1}HMRS are correlated with the total MoCA scores in patients with ischemic WML. Our results suggest that the NAA/Cr and Cho/Cr ratios in ^{1}HMRS are useful indicators for early diagnosis of WML. ^{1}HMRS in combination with MRI and MoCA will be useful in the detection of the severe degrees of the WML, and in the study of cognitive impairment in the patients with the ischemic WML.

REFERENCES

1. Bots ML, van Swieten JC, Breteler MM, de Jong PT, van Gijn J, Hofman A, *et al*. Cerebral white matter lesions and atherosclerosis in the Rotterdam Study. Lancet 1993;341:1232-7.
2. Markus HS, Lythgoe DJ, Ostegaard L, O'Sullivan M, Williams SC. Reduced cerebral blood flow in white matter in ischaemic leukoaraiosis demonstrated using quantitative exogenous contrast based perfusion MRI. J Neurol Neurosurg Psychiatry 2000;69:48-53.
3. Gerdes VE, Kwa VI, ten Cate H, Brandjes DP, Buller HR, Stam J. Amsterdam Vascular Medicine Group. Cerebral white matter lesions predict both ischemic strokes and myocardial infarctions in patients with established atherosclerotic disease. Atherosclerosis 2006;186:166-72.
4. Kobayashi S, Maki T, Kunimoto M. Clinical symptoms of bilateral anterior cerebral artery territory infarction. J Clin Neurosci 2011;18:218-22.
5. Akiguchi I, Tomimoto H, Wakita H, Kawamoto Y, Matsuo A, Ohnishi K, *et al*. Topographical and cytopathological lesion analysis of the white matter in Binswanger's disease brains. Acta Neuropathol 2004;107:563-70.
6. Okeda R, Murayama S, Sawabe M, Kuroiwa T. Pathology of the cerebral artery in Binswanger's disease in the aged: Observation by serial sections and morphometry of the cerebral arteries. Neuropathology 2004;24:21-9.
7. Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis: A review. Stroke 1997;28:652-9.
8. Breteler MM, van Swieten JC, Bots ML, Grobbee DE, Claus JJ, van den Hout JH, *et al*. Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: The Rotterdam Study. Neurology 1994;44:1246-52.

9. Baloh RW, Yue Q, Socotch TM, Jacobson KM. White matter lesions and disequilibrium in older people. I. Case-control comparison. Arch Neurol 1995;52:970-4.
10. Kuller LH. Risk factors for dementia in the Cardiovascular Health Study cognition study. Rev Neurol 2003;37:122-6.
11. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003;348:1215-22.
12. Kim JH, Hwang KJ, Kim JH, Lee YH, Rhee HY, Park KC. Regional white matter hyperintensities in normal aging, single domain amnestic mild cognitive impairment, and mild Alzheimer's disease. J Clin Neurosci 2011;18:1101-6.
13. Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjogren M, *et al*. European Task Force on Age-Related White Matter Changes. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke 2001;32:1318-22.
14. Li C, Ling X, Liu S, Xu A, Zhang Y, Xing S, *et al*. Abnormalities of magnetic resonance spectroscopy and diffusion tensor imaging are correlated with executive dysfunction in patients with ischemic leukoaraiosis. J Clin Neurosci 2012;19:718-22.
15. Brooks WM, Wesley MH, Kodituwakku PW, Garry PJ, Rosenberg GA. 1H-MRS differentiates white matter hyperintensities in subcortical arteriosclerotic encephalopathy from those in normal elderly. Stroke 1997;28:1940-3.
16. Ross B, Bluml S. Magnetic resonance spectroscopy of the human brain. Anat Rec 2001;265:54-84.
17. Ramli N, Rahmat K, Azmi K, Chong HT. The past, present and future of imaging in multiple sclerosis. J Clin Neurosci 2010;17:422-7.
18. Hayashi T, Kumabe T, Jokura H, Fujihara K, Shiga Y, Watanabe M, *et al*. Inflammatory demyelinating disease mimicking malignant glioma. J Nucl Med 2003;44:565-9.
19. Karaszewski B, Thomas RG, Chappell FM, Armitage PA, Carpenter TK, Lymer GK, *et al*. Brain choline concentration. Early quantitative marker of ischemia and infarct expansion? Neurology 2010;75:850-6.
20. Murata T, Kimura H, Omori M, Kado H, Kosaka H, Iidaka T, *et al*. MRI white matter hyperintensities, (1)H-MR spectroscopy and cognitive function in geriatric depression: A comparison of early- and late-onset cases. Int J Geriatr Psychiatry 2001;16:1129-35.
21. Gold G, Kovari E, Herrmann FR, Canuto A, Hof PR, Michel JP, *et al.* Cognitive consequences of thalamic, basal ganglia, and deep white matter lacunes in brain aging and dementia. Stroke 2005;36:1184-8.
22. Prins ND, van Dijk EJ, den Heijer T, Vermeer SE, Koudstaal PJ, Oudkerk M, *et al*. Cerebral white matter lesions and the risk of dementia. Arch Neurol 2004;61:1531-4.
23. Roman GC, Erkinjuntti T, Wallin A, Pantoni L, Chui HC. Subcortical ischaemic vascular dementia. Lancet Neurol 2002;1:426-36.
24. Tekin S, Cummings JL. Frontal-subcortical neuronal circuits and clinical neuropsychiatry: An update. J Psychosom Res 2002;53: 647-54.
25. Nordahl CW, Ranganath C, Yonelinas AP, Decarli C, Fletcher E, Jagust WJ. White matter changes compromise prefrontal cortex function in healthy elderly individuals. J Cogn Neurosci 2006;18:418-29.
26. Frederick BD, Lyoo IK, Satlin A, Ahn KH, Kim MJ, Yurgelun-Todd DA, *et al*. *In vivo* proton magnetic resonance spectroscopy of the temporal lobe in Alzheimer's disease. Prog Neuropsychopharmacol Biol Psychiatry 2004;28:1313-22.
27. Schuff N, Capizzano AA, Du AT, Amend DL, O'Neill J, Norman D, *et al*. Different patterns of N-acetylaspartate loss in subcortical ischemic vascular dementia and AD. Neurology 2003;61:358-64.
28. Frisoni GB, Galluzzi S, Pantoni L, Filippi M. The effect of white matter lesions on cognition in the elderly--small but detectable. Nat Clin Pract Neurol 2007;3:620-7.

Source of Support: This work is supported by Research Project of Jilin Province Health Department (No. 2012Z112), **Conflict of Interest:** None declared.