American Journal of Alzheimer's Disease & Other Dementias®
2016, Vol. 31(5) 422-429

DOI: 10.1177/1533317515628052
aja.sagepub.com
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Hydrogen Proton Magnetic Resonance Spectroscopy in Multidomain Amnestic Mild Cognitive Impairment and Vascular Cognitive Impairment Without Dementia

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Abstract

To investigate the value of hydrogen proton magnet resonance spectroscopy (^{1}H-MRS) in the differential diagnosis of multiple-domain amnestic mild cognitive impairment (M-aMCI) and vascular cognitive impairment with no dementia (VCIND); ^{1}H-MRS was performed in patients with M-aMCI and VCIND. The level was determined for *N*-acetylaspartate (NAA), glutamate (Glu), inositol (ml), choline (Cho), and creatine (Cr). Compared with the normal control group, the NAA–Cr ratio in all regions studied was significantly lower in the M-aMCI and VCIND groups. The Glu–Cr ratio in the posterior cingulate gyrus of the M-aMCI group was significantly lower than in the VCIND. The ml–Cr ratio in the frontal white matter of the VCIND was significantly higher than in the M-aMCI group. In the white matter adjacent to the lateral ventricles, the Cho–Cr ratio was significantly higher in the VCIND than the M-aMCI. Our results suggested ^{1}H-MRS is an effective method in the differential diagnosis of M-aMCI and VCIND.

Keywords

multi-domain amnestic mild cognitive impairment, vascular cognitive impairment without dementia, Alzheimer's disease, magnet resonance spectroscopy

Introduction

Amnestic mild cognitive impairment (aMCI) is a transitional stage between normal aging and Alzheimer's disease (AD), with a risk for AD conversion of up to 10% per year, whereas the risk for AD conversion from normal aging was approximately 1% to 2% per year.[1] Amnestic mild cognitive impairment includes the following 2 subtypes: single-domain aMCI (S-aMCI) and multiple-domain aMCI (M-aMCI). Single-domain aMCI mainly has memory impairment, whereas M-aMCI has memory impairment and functional impairments in language, execution, attention, or other cognitive domains[2] and a higher AD conversion rate than S-aMCI.[3] Vascular cognitive impairment with no dementia (VCIND) is a prodromal stage of vascular dementia (VD). Wentzel et al[4] showed that approximately 50% of patients with VCIND converted to VD within 5 years. Previous studies have concluded that VCIND mainly affects executive functional disorder, but recent research has confirmed that VCIND is often accompanied by multiregional cognitive impairments in memory, attention, and visuospatial ability.[5]

Compared with patients experiencing impairment in a single cognitive function, clinical manifestations of patients with M-aMCI or VCIND vary more broadly and have a worse prognosis.[6] Therefore, early and definitive diagnosis may effectively guide the clinical therapy and the prognosis of patients having M-aMCI or VCIND. However, solely relying on clinical manifestations, neuropsychological testing, and routine imaging cannot effectively differentiate between M-aMCI and VCIND. This study used hydrogen proton magnet resonance spectroscopy (^{1}H-MRS) to determine the features of metabolic change in patients with M-aMCI and VCIND in different brain regions using imaging to provide a better understanding between M-aMCI and VCIND and a clinical basis for early diagnosis of either disease.

Materials and Methods

Research Participants

Thirty-eight patients with M-aMCI and 44 patients with VCIND from the Suzhou Hospital affiliated to Nanjing

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This article was accepted under the editorship of the former Editor-in-Chief, Carol F. Lippa.

Table 1. Characteristics of Patients in M-aMCI, VCIND and NC Groups.

	M-aMCI	VCIND	NC	Test Value	P
Gender (M/F)	38 (22/16)	44 (27/17)	30 (17/13)	5.273	.05
Age, years	68.32 ± 6.13	70.46 ± 6.77	70.74 ± 6.58	4.152	.05
Education, years	9.6 ± 2.3	8.7 ± 3.1	9.1 ± 3.3	1.663	.05

Abbreviations: M-aMCI, multiple-domain amnestic mild cognitive impairment; NC, normal cognitive; VCIND, vascular cognitive impairment with no dementia.

Medical University were randomly selected from July 2011 to June 2014, and 30 age-matched healthy elderly population served as normal controls in this study (see Table 1 for age, gender, and education level). All tested participants underwent epidemiological investigation, neuropsychological testing, and conventional radiographic examination to exclude patients with severe depression, schizophrenia, and other mental disorders. All tested participants were right-handed and signed a written informed consent form that had been approved by the ethics committee of Nanjing Medical University.

Diagnostic Standard

Diagnosis of M-aMCI was revised primarily based on the criteria of Petersen et al.[7] (1) Patients complained about memory loss, which was corroborated by their family members. (2) In addition to memory dysfunction, objective evidence existed for cognitive impairment in one or more of the following functions: language, executive function, and calculation (consistent with a Mini-Mental State Evaluation [MMSE] score of 24-27; a Clinical Dementia Rating [CDR] score of 0.5; and a Montreal Cognitive Assessment [MoCA] score of 23-26). However, the patients did not meet the diagnostic criteria of dementia according to the *Diagnostic and Statistical Manual of Mental Disorder IV*. (3) The daily activities were not affected (ie, the activity of daily living [ADL] score below 22).

Diagnoses of VCIND were revised according to the VCIND criteria[8] proposed by National Institute of Neurological Disorders and Stroke-Canadian Stroke Network (NINDS-CSN). (1) Patients had impairment of executive function, which was confirmed by their family members. (2) Patients also had other cognitive impairments (eg, memory loss). (3) However, the cognitive impairments did not meet the diagnostic criteria for NINDS. The MoCA score was 23 to 26, and the CDR score was 0.5. (4) The daily activities were not affected, with an ADL score below 22. (5) Cerebrovascular disease was considered to be a risk factor for or a cause of cognitive impairment and confirmed by corresponding focal neurological signs or imaging data, with a Hachinski Ischemic Score (HIS) of above 7.

Tested participants in the normal cognitive (NC) function group had no clinical cognitive dysfunction and an uneventful neurological history, as well as had normal scores of MMSE, CDR, and MoCA.

Neuropsychological Evaluation

All tested participants underwent neuropsychological assessments by senior neurologist to examine their cognitive function using MMSE, ADL, CDR, MoCA, and HIS.

Hydrogen Proton Magnet Resonance Spectroscopy

All tested participants were examined using a Siemens MAGNETOM Aera 3.0T magnetic resonance imaging (MRI) scanner, and image capture was performed using a 24-channel standard quadrature head coil. All tested participants first underwent conventional scanning sequences of T_1WI, T_2WI, and fluid attenuation inversion recovery, followed by using point-resolved spatially localized spectroscopy for 3-dimensional single-voxel ^{1}H-MRS, with scanning parameters: repetition time/echo time = 2200/45 ms, rotation angle of 90°, field of vision 180 × 240 × 60 mm, incentive number of 200, and each voxel size of 0.8 × 0.8 × 1.0 cm. The regions of interest in the left hippocampus, the posterior cingulate gyrus, the frontal white matter, and the white matter adjacent to the lateral ventricles were selected (Figure 1) and oriented in 3 directions (ie, cross-sectional, coronal, and sagittal sections) to avoid impact from the skull, blood vessels, fat tissue, or cerebrospinal fluid, with the setting of automatic shimming, water suppression, and full width at half-maximum less than 15 Hz. After scanning was completed, raw data were transferred to workstations to obtain the spectrum of original phase diagram via a Fourier transformation. The baseline calibration and the phase correction were automatically completed by the MRI software. The area under the peaks for *N*-acetylaspartate (NAA), glutamate (Glu), inositol (mI), choline (Cho), and creatine (Cr) were measured to calculate the ratio differences of NAA–Cr, Glu–Cr, mI–Cr, and Cho–Cr.

Statistical Analysis

SPSS for Windows 17.0 software was used for statistical analysis of measured data. Data were presented using mean ± standard deviation ($\bar{x} \pm s$). Qualitative data were analyzed using χ^2 test, whereas quantitative data were measured using 1-way analysis of variance. Pairwise comparisons between groups were measured using Fisher least significant difference test. $P < .05$ was considered as statistically significant difference.

Results

1. Comparison of clinical features in M-aMCI, VCIND, and NC groups (Table 1).

The age, education level, and gender were homogeneously distributed in the test participants of the 3 groups, with no significant difference between groups ($P > .05$).

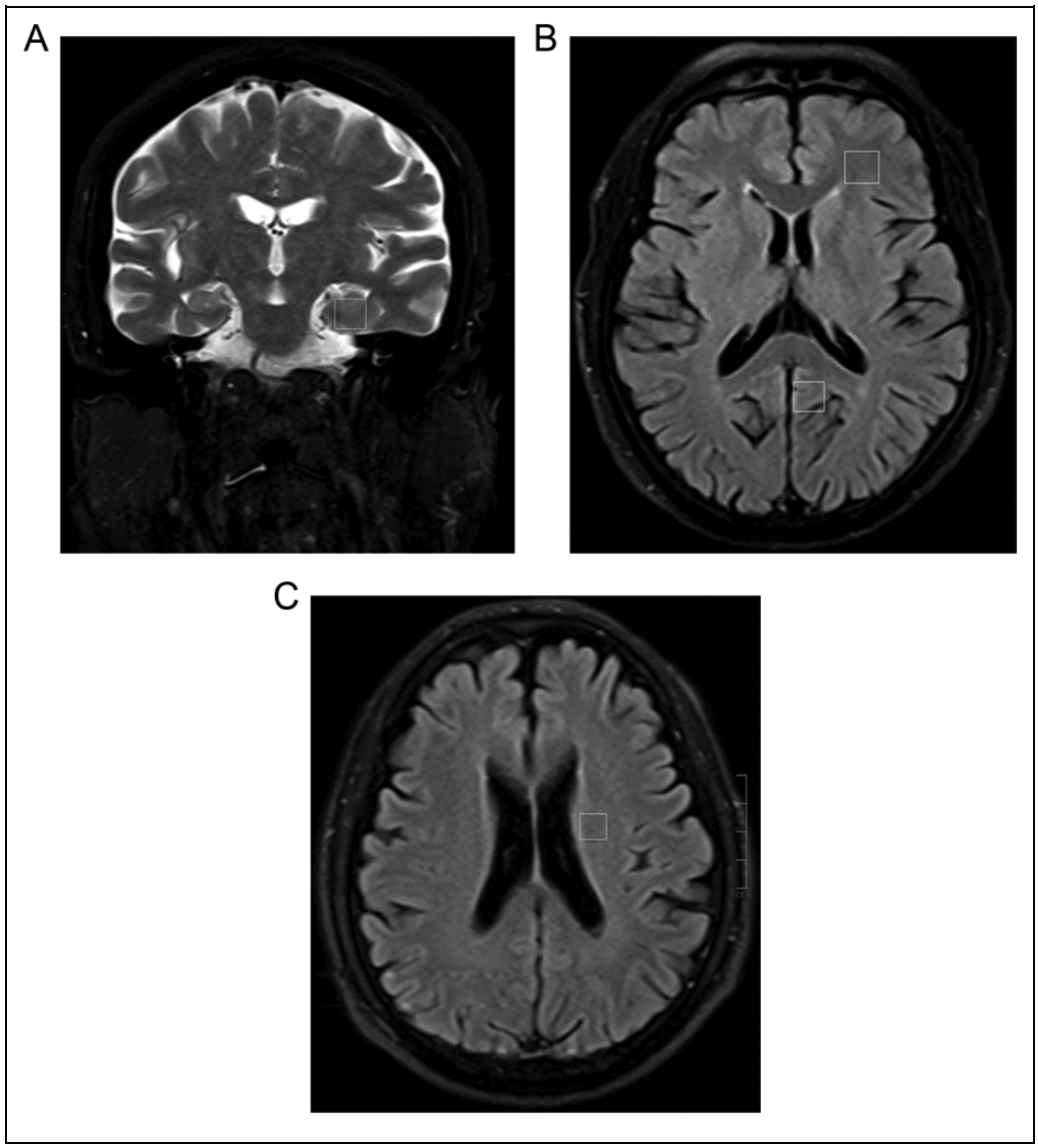

Figure 1. Localized proton magnet resonance spectroscopy (MRS) of patient: (A) hippocampus (HIP); (B) white matter of the frontal lobe (FLWM) and posterior cingulate gyrus (PCG); (C) white matter adjacent to the lateral ventricles (WMALV). Region of interest (ROI) sizes were approximately 0.8 × 0.8 × 1.0 cm.

Table 2. The Neuropsychological Feature of the M-aMCI, VCIND, and NC Groups.

	M-aMCI	VCIND	NC	*F*	*P*
MMSE	25.49 ± 1.08[a]	25.13 ± 1.51[a]	29.54 ± 2.01	58.841	<.05
MoCA	24.28 ± 1.23[a]	24.75 ± 1.17[a]	28.94 ± 3.52	38.695	<.05
HIS	2.92 ± 0.39	9.32 ± 0.73[a,b]	3.03 ± 0.25	249.383	<.05

Abbreviations: HIS, Hachinski Ischemic Score; M-aMCI, multiple-domain amnestic mild cognitive impairment; MMSE, Mini-Mental State Evaluation; MoCA, Montreal Cognitive Assessment; NC, normal cognitive; VCIND, vascular cognitive impairment with no dementia.
[a]$P < .05$ versus NC group.
[b]$P < .05$ versus M-aMCI group.

2. Comparing the neuropsychological test results in M-aMCI, VCIND, and NC groups (Table 2).

Univariate analysis of variance showed statistically significant differences in MMSE, MoCA, and HIS scores among the tested participants of the 3 groups ($P < .05$), whereas the ADL scores were not significantly different between the 3 groups ($P > .05$). The MMSE and MoCA scores in the M-aMCI and VCIND groups were significantly lower than in the NC group

Table 3. The ratio of NAA–Cr From M-aMCI, VCIND, and NC Groups.

Group	HIP	PCG	FLWM	PAWM
NC	1.19 ± 0.21	1.22 ± 0.25	1.21 ± 0.18	1.21 ± 0.24
M-aMCI	1.12 ± 0.08[a]	1.09 ± 0.09[a]	1.08 ± 0.12[a]	1.09 ± 0.11[a]
VCIND	1.10 ± 0.11[a]	1.12 ± 0.15[a]	1.11 ± 0.10[a]	1.08 ± 0.13[a]
F	8.194	7.772	11.236	9.815
P	.05	.05	.05	.05

Abbreviations: Cr, creatine; FLWM, white matter of the frontal lobe; HIP, hippocampus; M-aMCI, multiple-domain amnestic mild cognitive impairment; NAA, *N*-acetylaspartate; NC, normal cognitive; PAWN, white matter adjacent to the lateral ventricles; PCG, posterior cingulate gyrus; VCIND, vascular cognitive impairment with no dementia.
[a]$P < .05$ versus NC.

Table 4. The Ratio of Glu–Cr From M-aMCI, VCIND, and NC Groups.

Group	HIP	PCG	FLWM	PAWM
NC	0.41 ± 0.05	0.40 ± 0.05	0.39 ± 0.03	0.39 ± 0.04
M-aMCI	0.39 ± 0.05	0.31 ± 0.02[a,b]	0.40 ± 0.03	0.39 ± 0.04
VCIND	0.38 ± 0.04	0.42 ± 0.05	0.41 ± 0.04	0.41 ± 0.03
F	0.512	7.418	0.843	0.626
P	.05	.05	.05	.05

Abbreviations: Cr, creatine; FLWM, white matter of the frontal lobe; Glu, glutamate; HIP, hippocampus; M-aMCI, multiple-domain amnestic mild cognitive impairment; NC, normal cognitive; PAWN, white matter adjacent to the lateral ventricles; PCG, posterior cingulate gyrus; VCIND, vascular cognitive impairment with no dementia.
[a]$P < .05$ versus NC.
[b]$P < .05$ versus VCIND.

Table 5. The Ratio of mI–Cr from M-aMCI, VCIND, and NC Groups.

Group	HIP	PCG	FLWM	PAWM
NC	0.46 ± 0.05	0.42 ± 0.05	0.43 ± 0.06	0.45 ± 0.04
M-aMCI	0.69 ± 0.09[a,b]	0.71 ± 0.08	0.40 ± 0.04	0.39 ± 0.04
VCIND	0.49 ± 0.04	0.44 ± 0.05	0.61 ± 0.07[a,c]	0.42 ± 0.03
F	2.672	5.491	4.463	0.774
P	.05	.05	.05	.05

Abbreviations: Cr, creatine; FLWM, white matter of the frontal lobe; HIP, hippocampus; M-aMCI, multiple-domain amnestic mild cognitive impairment; mI, inositol; NC, normal cognitive; PAWN, white matter adjacent to the lateral ventricles; PCG, posterior cingulate gyrus; VCIND, vascular cognitive impairment with no dementia.
[a]$P < .05$ versus NC.
[b]$P < .05$ versus VCIND.
[c]$P < .05$ versus M-aMCI.

Table 6. The Ratio of Cho–Cr From M-aMCI, VCIND, and NC Groups.

Group	HIP	PCG	FLWM	PAWM
NC	0.92 ± 0.05	0.94 ± 0.05	1.06 ± 0.09	1.02 ± 0.05
M-aMCI	0.95 ± 0.06	0.92 ± 0.06	1.05 ± 0.06	0.99 ± 0.04
VCIND	0.99 ± 0.04	0.94 ± 0.05	1.03 ± 0.06	1.12 ± 0.11[a,b]
F	0.651	0.349	0.720	7.813
P	.05	.05	.05	.05

Abbreviations: Cho, choline; Cr, creatine; FLWM, white matter of the frontal lobe; HIP, hippocampus; M-aMCI, multiple-domain amnestic mild cognitive impairment; NC, normal cognitive; PAWN, white matter adjacent to the lateral ventricles; PCG, posterior cingulate gyrus; VCIND, vascular cognitive impairment with no dementia.
[a]$P < .05$ versus NC.
[b]$P < .05$ versus M-aMCI.

($P < .05$ and $P < .05$, respectively). No statistically significant differences in the MMSE and MoCA scores were found between the M-aMCI and VCIND groups ($P > .05$). The HIS score in the VCIND group was significantly higher than in the M-aMCI and NC groups ($P < .05$), whereas no significant difference in the HIS score was found between the M-aMCI and NC groups ($P > .05$).

3. Comparing the results of ^{1}H-MRS in M-aMCI, VCIND, and NC groups (Tables 3–6).

The NAA–Cr ratios in the left hippocampus, the posterior cingulate gyrus, the frontal white matter, and the white matter adjacent to the lateral ventricles in the M-aMCI and VCIND groups were significantly lower than in the NC group ($P < .05$ and $P < .05$, respectively). No significant difference in NAA–Cr was found between the M-aMCI and VCIND groups in any of the brain regions studied ($P > .05$).

Results of ^{1}H-MRS showed that the Glu–Cr ratio in the left lateral posterior cingulate gyrus of the M-aMCI group was significantly lower than in the VCIND and NC groups ($P < .05$ and $P < .05$, respectively), and no significant difference in Glu–Cr was found between the VCIND and NC groups ($P > .05$; Figure 2). In the left hippocampus, frontal white matter, and white matter adjacent to the lateral ventricles, no significant difference in Glu–Cr was found between the 3 groups ($P > .05$).

The mI–Cr ratios in the left hippocampus and posterior cingulate gyrus in the M-aMCI group were significantly higher than those in the VCIND and NC groups ($P < .05$). No significant difference in the mI–Cr ratio was found between the VCIND and NC groups ($P > .05$). In the region of the left lateral posterior cingulate gyrus, the mI–Cr ratio in the VCIND group was significantly higher than in the M-aMCI and NC groups ($P < .05$; Figure 3). In the white matter adjacent to the lateral ventricles, no significant difference in the mI–Cr ratio was found between the 3 groups ($P > .05$).

No significant difference in Cho–Cr ratio in the left hippocampus, cingulate gyrus, and frontal white matter was found between the M-aMCI and VCIND groups ($P > .05$); in the white matter adjacent to the lateral ventricle, the ratio was significantly higher in the VCIND group than in the M-aMCI and NC groups ($P < .05$; Figure 4).

Discussion

Pathological features of M-aMCI are amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs) in the hippocampus and

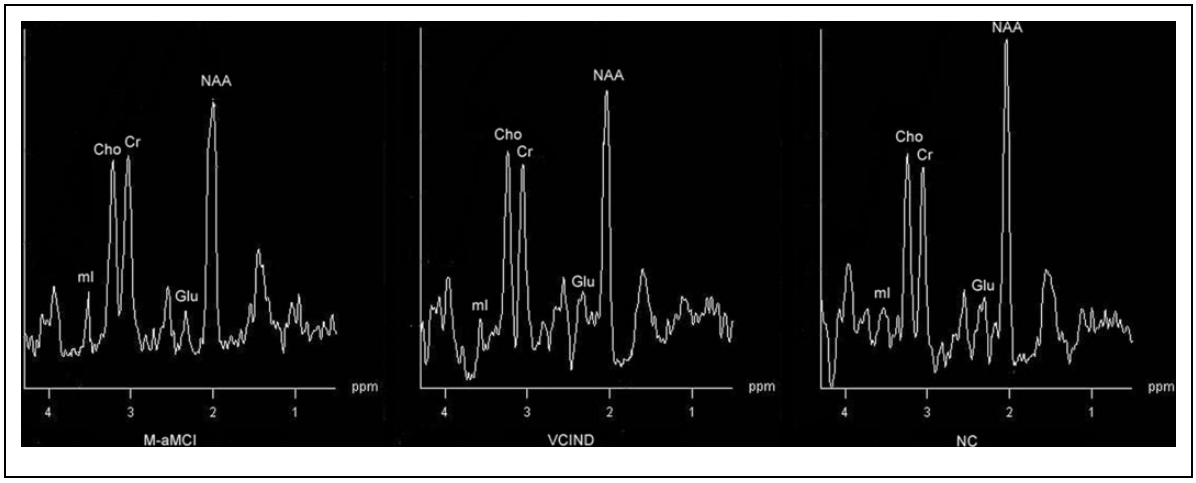

Figure 2. Spectra from the left lateral posterior cingulate gyrus: glutamate (Glu) level of the multiple-domain amnestic mild cognitive impairment (M-aMCI) group was significantly lower than in the vascular cognitive impairment with no dementia (VCIND) and normal cognitive (NC) groups.

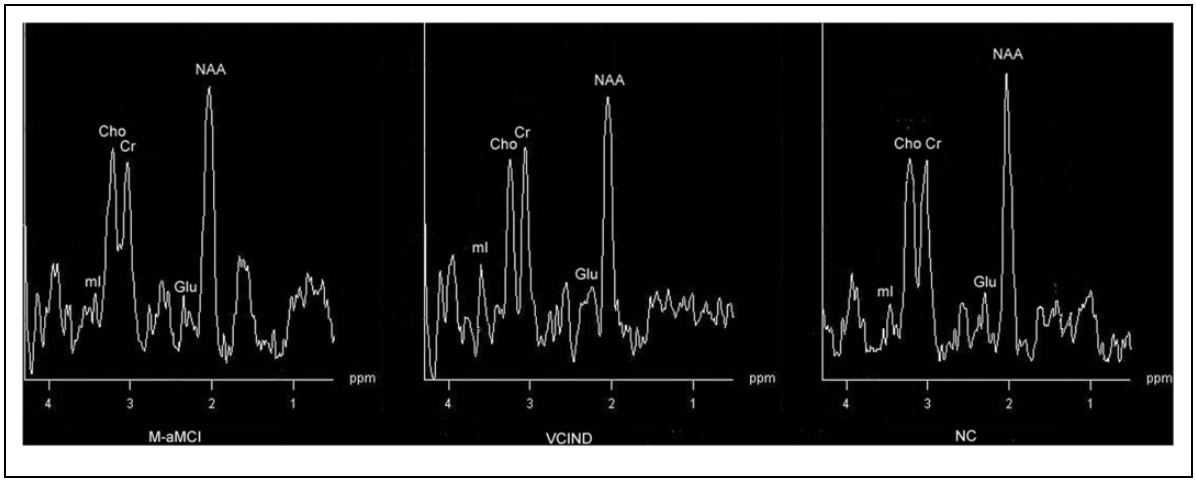

Figure 3. Spectra from the left lateral frontal white matter: inositol (mI) level of the vascular cognitive impairment with no dementia (VCIND) group was higher than those in the multiple-domain amnestic mild cognitive impairment (M-aMCI) and normal cognitive (NC) groups.

entorhinal area, whereas the histopathological feature of VCIND is subcortical ischemic vascular disease with small vessel disease. Differences in the pathological basis between M-aMCI and VCIND lead to the development of different types of dementia.[9] Initially, aMCI was considered to show memory impairment only and no other cognitive dysfunctions.[10] However, later studies showed that many patients showed impairment in memory, executive function, and information-processing capacity compared with normal elderly participants, that is, cognitive dysfunction was seen in multiple brain regions.[11,12] Similarly, although VCIND shows prominent impairment of executive function, it shares common features with M-aMCI that include memory loss and other areas of cognitive impairment.[6] Even with imaging, some VCIND caused by undetected cerebrovascular disease (eg, low perfusion and incomplete infarction) may appear to be negative on MRI examination. Patients with M-aMCI often have cerebrovascular disease (eg, lacunar infarction and leukoaraiosis) as a comorbidity. Thus, although neuropsychological assessment and conventional neuroimaging are important strategies for the diagnosis of different types of cognitive dysfunction, in practice, M-aMCI and VCIND are difficult to distinguish clinically.

Hydrogen proton magnet resonance spectroscopy is the only imaging technique to study metabolic changes in living tissue noninvasively with good reproducibility and stability. Changes in metabolite levels precede the structural changes in the brain that define the pathological changes in dementia and are widely used in basic and clinical research in dementia.[13-16] Currently, ^{1}H-MRS studies are mostly conducted in aMCI but rarely reported in VCIND. In addition, in such studies, the tested participants were mainly diagnosed with s-aMCI or VCIND.[17-19] Studies on the early differential diagnosis of M-aMCI and VCIND have been rarely reported.

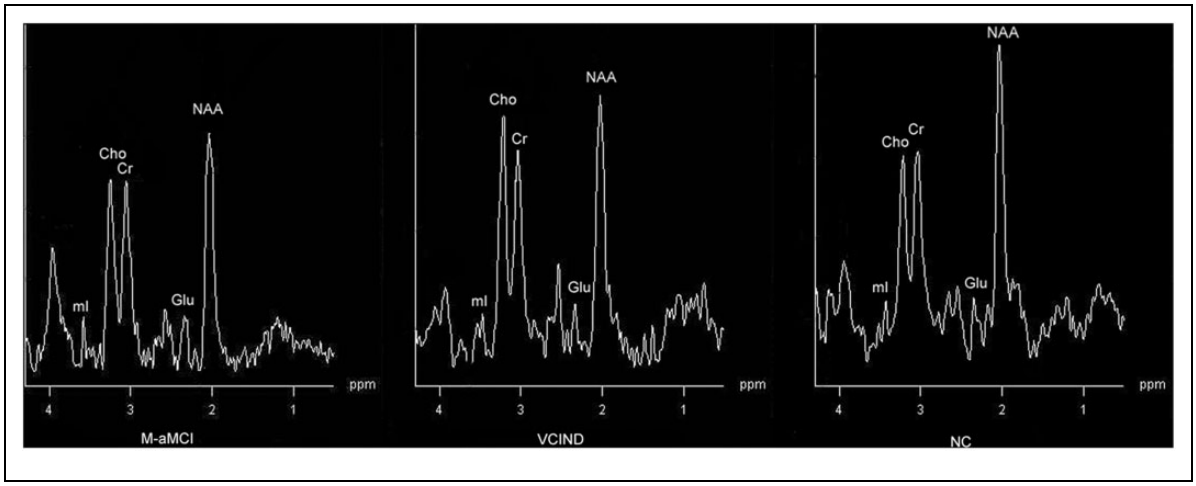

Figure 4. Spectra from the white matter adjacent to the left lateral ventricles: choline (Cho) level of the vascular cognitive impairment with no dementia (VCIND) group was significantly higher than those in the M-aMCI and NC groups.

N-acetylaspartate, a neuronal cell-specific marker, has been frequently used as a metabolic indicator in studies of cognitive impairment and dementia. Many studies confirmed a significant reduction in NAA levels in multiple brain regions of patients with MCI, AD, and VD.[20-25] Zhu et al[26] found that there were differences in NAA–Cr related to brain regions between different types of MCI. Kattapong et al[27] also reported that the NAA–Cr and NAA–Cho ratios in the subcortical white matter of patients with VD were significantly reduced compared with patients with AD. In this study, we detected similar changes in NAA levels between patients with M-aMCI and VCIND. Although the NAA levels in multiple brain regions of patients with M-aMCI and VCIND were significantly lower than those in normal elderly participants, suggesting a reduction in neuronal function or demyelination, no significant regional difference in the NAA–Cr ratio was found between M-aMCI and VCIND, suggesting that NAA may lack specificity when differentiating between M-aMCI and VCIND.

Many experts believe that the levels of the mI metabolites may the first to change in the brains of patients with aMCI or AD.[28,29] In the early stage of aMCI or AD, the mI–Cr ratio increases, and this change is associated with a decline in cognitive function. However, the value of mI as a specific marker for cognitive impairment or dementia remains controversial. In the study of Liu et al,[18] increased mI in the right posterior cingulate gyrus of patients with aMCI was observed. Walecki et al[30] evaluated a group of patients with aMCI who eventually developed AD using ^{1}H-MRS and showed no significant change in the mI–Cr ratio of the medial temporal lobe. Kantarci et al[31] showed that the mI–Cr ratio in the posterior cingulate gyrus of patients with S-aMCI was significantly higher than in the control group, but no change was observed in patients with M-aMCI. In contrast, Waldman et al[32] showed no abnormal change in the mI–Cr ratio in the brain of patients with VD. In this study, we demonstrated that the mI–Cr ratio increased abnormally in the hippocampus and the posterior cingulate gyrus of patients with M-aMCI and in the frontal white matter of patients with VCIND, suggesting that mI may be a marker differentiating the features of M-aMCI and VCIND. Although increases in mI concentration reflect a certain proliferation and activation of glial cells or microglial cells,[33] the pathological mechanism associated with the metabolic change in mI in the brain of patients with M-aMCI and VCIND remains unclear. Our analysis of increased mI levels in the hippocampus and posterior cingulate gyrus of patients with M-aMCI may be associated with the changes in pathological characteristic in these brain regions (eg, Aβ protein or NFT), whereas the increased mI levels in the frontal white matter of patients with VCIND may be associated with the first functional damage in the frontal lobe.

Glutamate is the main excitatory neurotransmitter in the brain and is closely related to neuronal survival and formation of synapses[34] involved in regulating learning, memory, and cognition in the cortex. Glutamate homeostasis relies on the functional integrity of neurons and glial cells[35]; therefore, the level of change in Glu can reflect functional or pathological changes in neurons and glial cells. However, compared with metabolites such as NAA, mI, and Cho, less attention has been paid to Glu studies of cognitive impairment and dementia. This may be due to the difficulties in detecting Glu in <1.5T MRI. Currently, only a few studies such as that by Rupsingh et al[36] and Fayed et al[37] have shown that the Glu–Cr ratio in the hippocampus of patients with AD was significantly reduced compared with the normal controls, but no significant changes were found in patients with MCI. Hattori et al[38] reported that Glu reduction only occurred in the cortex but not in the white matter of patients with AD. With the clinical application of 3.0T MRI, the detection of metabolic changes in Glu in the brain of patients with M-aMCI and VCIND has become feasible. Our study suggests that the Glu–Cr ratio in patients with M-aMCI is first reduced in the posterior cingulate gyrus, indicating that the change in Glu level in this region may be an effective indicator to distinguish between M-aMCI and VCIND. This result also suggests that the posterior cingulate

gyrus may play an important role in the neuropsychological process of learning and memory.

Choline is involved in the formation and metabolism of cell membranes and myelin. Its role as a marker for cognitive impairment and dementia remains unclear and contradictory. A study by Kantarci et al[17] reported that patients with aMCI who developed AD showed a significantly increased Cho–Cr ratio. Walecki et al[30] reported a decreased Cho–Cr ratio in the temporal lobe of patients with aMCI. In this study, the Cho–Cr ratio in the white matter adjacent to the lateral ventricle in the VCIND group was significantly higher than in the M-aMCI and NC groups, suggesting that patients with VCIND having subcortical ischemic vascular disease have excessive destruction in the myelin of white matter adjacent to the lateral ventricles.

Although the degree of cognitive impairment in M-aMCI and VCIND has not (yet) reached the diagnostic criteria for dementia, studies have confirmed that the pathological changes are similar in dementia and M-aMCI and VCIND. Thus, the concepts of M-aMCI and VCIND were proposed to improve the diagnosis of AD and VD. However, the reasons for regional differences in brain metabolism in patients with M-aMCI and VCIND remain unclear. We speculate that they may be associated with the 2 different patterns of cognitive impairment between M-aMCI and VCIND. The cognitive impairment of VCIND belongs to ''the frontal–subcortical'' pattern.[6] The frontal white matter and white matter adjacent to the lateral ventricles are key regions for the implementation dysfunction, whereas the cognitive impairment of patients with M-aMCI belongs to ''temporal lobe–neocortex'' pattern.[39] Hence, the main clinical manifestation is a decrease in memory capacity and the metabolic changes mainly in the hippocampus and cingulate gyrus.

In conclusion, our study showed that one of the most important markers of ^{1}H-MRS, that is, the change in NAA levels, lacked specificity to differentiate between M-aMCI and VCIND. The levels of mI, Glu, and Cho were significantly different in different brain regions, suggesting that ^{1}H-MRS is an effective method to differentiate between M-aMCI and VCIND.

Acknowledgments

The authors thank Dr Jun Wang for contributing to the statistical analysis. They also thank Mr Sunxing Zhang for the English revision.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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