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Brain metabolism assessed via proton magnetic resonance spectroscopy in patients with amnestic or vascular mild cognitive impairment

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ABSTRACT

Background and objectives: To address the possible role of brain regional metabolic differences between different types of mild cognitive impairment (MCI).
Patients and methods: Brain regional metabolites in patients with amnestic mild cognitive impairment (A-MCI) and vascular mild cognitive impairment (V-MCI) were measured via proton magnetic resonance spectroscopy (^{1}H MRS) technique. Twenty-eight patients with A-MCI, 24 patients with V-MCI and 34 normal controls (NC) were tested by a battery of neuropsychological screens. All the subjects underwent the single voxel ^{1}H MRS with the regions of interest (ROIs) located in the left frontal lobe, left basal ganglia and left hippocampus.
Results: The A-MCI showed lower NAA/Cr ratio in the left hippocampus. There was a significant correlation between recent memory score and the NAA/Cr ratio. In V-MCI, NAA/Cr ratio in the left frontal lobe was positively correlated with the cognitive score evaluated with Cambridge Cognitive Examination-Chinese version (CAMCOG-C) and its subscores of orientation, praxi, language and language comprehension.
Conclusions: This study indicated that there are differences in metabolism related to brain regions between A-MCI and V-MCI, thus it may be concluded that ^{1}H MRS may be a useful tool to differentiate A-MCI and V-MCI.

1. Introduction

Mild cognitive impairment (MCI) has been described as a transitional state from normal aging to early dementia [1]. Increasing evidence suggests that MCI may be a heterogeneous condition comprised of various subtypes [2]. Recently, MCI has been classified into four subtypes according to the presence or absence of a memory disorder and the existence of affected cognitive domains: amnestic MCI-Single Domain (aMCI-SD), non-amnestic MCI-Single Domain (naMCI-SD), amnestic MCI-Multiple Domain (aMCI-MD) and non-amnestic MCI-Multiple Domain (naMCI-MD) [3]. Subjects with amnestic MCI may often develop Alzheimer's disease (AD), while individuals with non-amnestic MCI would progress to vascular dementia (VaD), frontotemporal dementia (FTD) and dementia with Lewy bodies (DLB), etc. However, this classification may not help us predict the conversion from MCI to dementia, and thus has limited help in medication choice. Another notion of etiological heterogeneity has been put forward in classifying MCI subtypes, as the identification of the etiology of specific MCI subtypes might be amenable to different medications. AD is preceded by amnestic MCI (A-MCI), while VaD especially subcortical ischemic vascular dementia (SIVD) is preceded by vascular MCI (V-MCI) [4]. As we all know, Alzheimer dementia (AD) and vascular dementia (VaD) are two of the most prevalent types of dementia. Because of their common occurrence, cost, and possible preventability, A-MCI or V-MCI, the prodromal of AD and VaD arouse great interest of clinicians and researchers.

Proton magnetic resonance spectroscopy (^{1}H MRS), a non-invasive technique, has been widely used to assay cerebral metabolites in many types of neurological diseases, such as mild

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cognitive impairment, dementia [5–7]. The primary metabolites detected by ^{1}H MRS include N-acetyl-aspartate (NAA), creatine (Cr), choline (Cho) and myo-inositol (MI). NAA is mainly contained in neuron and the reduction of NAA reflects the neuronal loss or dysfunction. Cr is an energy buffer in the brain, including creatine and phosphocreatine. As the internal reference, Cr is always stable in different pathophysiological conditions. As the sum of choline-containing compounds, Cho is involved in both synthesis and breakdown of phospholipid membranes. MI is a marker of glial cells. The concentration of MI is in accordance with the quantity of gliosis.

^{1}H MRS studies have shown that AD patients have significantly lower concentrations of NAA in bilateral hippocampi. While Binswanger's disease (BD) patients have remarkably lower levels of NAA in white matter, especially in anterior white matter [8]. Compared to that in AD, NAA is lower by 13% in frontal cortex and by 20% in the left parietal cortex in SIVD [9]. MI/Cr ratio is significantly higher in the midline of the occipital lobes in AD patients than that in VaD patients [10]. These results suggested that ^{1}H MRS may be useful in identifying AD from VaD. ^{1}H MRS studies have shown that AD patients had decreased NAA/Cr and increased MI/Cr ratio in the post cingulated gyrus and hippocampus. A-MCI patients also had a similar change [11]. van Zandvoort et al. showed that V-MCI patients had a declined NAA/Cr ratio in the centrum semiovale [12], but ^{1}H MRS-detectable neurochemical alterations in V-MCI is remained largely unknown. Also the metabolism difference between A-MCI and V-MCI has not been well investigated yet.

This study aimed to analyze the correlation between the cognitive impairment and ^{1}H MRS index through measuring the metabolites in patients with A-MCI or in those with V-MCI using single voxel ^{1}H MRS.

2. Patients and methods

2.1. Patients

Twenty-eight patients with A-MCI and 24 patients with V-MCI were recruited from our department of Neurology in the First Hospital of Anhui Medical University. Thirty-four normal controls (NC) were from the health examination clinic. All the subjects were right-handed. This study was approved by the ethics committee of Anhui Medical University and the written informed consent participation in the study is available from all subjects.

Patients with A-MCI and V-MCI were identified from historical and clinical presentations, a battery of neuropsychological screens and the brain MRI. The neuropsychological screens included Mini-Mental State Examination (MMSE), Cambridge Cognitive Examination-Chinese version (CAMCOG-C) [13], Clinical Dementia Rating (CDR) score and Geriatric Depression Scale (GDS). The criteria for A-MCI followed the guidelines proposed by Petersen et al. [1]: subjective memory complaints confirmed by close relatives, impaired memory function for age and education level, intact activities of daily living, preserved general cognitive function, and absence of cerebrovascular disease and dementia. V-MCI was established according to the criteria modified form Giovanni et al.'s study [14]: cognitive impairment for age and education, progression, patchy areas of low attenuation or diffuse symmetrical areas of low attenuation with ill defined margins extending to the centrum semiovale plus at least one lacunar infarct, presence of a history of neurological signs such as hemiparesis, lower facial weakness, Babinski sign and sensory deficit. We excluded structural abnormalities that may predict dementia, such as cerebral hemorrhages, cortical or subcortical non-lacunar territorial infarcts and watershed infarcts, specific causes of white matter lesions (e.g. multiple sclerosis, brain irradiation), subdural hematoma, normal pressure hydrocephalus, addictions, severe depression and other psychiatric diseases, etc.

2.2. MRI and ^{1}H MRS

All the subjects underwent MRI and ^{1}H MRS studies on a 3.0-T-scanner (Signa; GE Medical Systems, Milwaukee, WI). A brain MRI was performed in all the participants as a part of initial assessment. ^{1}H MRS was performed with the automated single voxel ^{1}H MRS package: Proton Brain Examination/Single Voxel (PROBE/SV). T2 weighted images in cross-section and coronal plane were obtained for localizing the ^{1}H MRS voxel. The regions of interest (ROIs) were located in the left frontal lobe, left basal ganglia and left hippocampus (typical size, 20 mm × 20 mm × 20 mm) (see Fig. 1). Point resolve spectroscopy (PRESS) pulse sequence was used for the examinations. Repetition time of 1500 ms, echo time of 30 ms in the left frontal lobe as well as in the left basal ganglia , and 35 ms in the left hippocampus were employed. Satisfactory spectra were consisted of 192 acquisitions in average. The prescan program of PROBE completed automated localized shim, selective water signal inversion, transmitter and receiver gains adjustment. Metabolite ratios using Cr as internal reference were automatically calculated at the end of each PROBE-SV acquisition.

2.3. Statistical analysis

All the data were analyzed by SPSS 13.0 for windows. We applied the Chi-squared test among the three groups to test the qualitative data. For the quantitative data, one-way ANOVA test would be used if satisfied homogeneity of variance, otherwise non-parametric tests would be chosen. We further compared each other between the groups employing Dunnett and SNK tests if the ANOVA test below 0.05 level. Correlation analysis was performed with the Pearson moment correlation for ^{1}H MRS index and cognitive scores. The significant level of all tests set at $P < 0.05$ and two-sided.

3. Results

There was no significant difference among the groups in age, gender and education years. The prevalence of hypertension was significantly higher in the A-MCI as well as in the V-MCI groups than that in the control group (Table 1).

The MMSE and CAMCOG-C scores in A-MCI and V-MCI were significantly lower in comparison with that in NC ($P < 0.01$). The scores of CAMCOG-C subscales including orientation, language, language comprehension, language expression and attention were lower in A-MCI group as well as in V-MCI group ($P < 0.05$). It was noteworthy that the recent memory function was significantly impaired in A-MCI group in comparison with that in NC group ($P < 0.01$) and in V-MCI group ($P < 0.01$). In V-MCI group, the praxis function score was significantly decreased compared to NC ($P < 0.05$) and to A-MCI ($P < 0.05$) (Table 2).

Table 1
Demographic and prevalence of vascular risk factors in three groups.

	A-MCI ($n = 28$)	V-MCI ($n = 24$)	NC ($n = 34$)	P value
Male/female	17/11	20/4	20/14	0.113
Age (years)	72.36 ± 6.97	73.46 ± 5.66	71.03 ± 6.10	0.345
Education (years)	10.93 ± 3.70	11.88 ± 3.28	11.06 ± 4.36	0.638
Hypertension	21 (75.00%)[a]	20 (83.30%)[a]	14 (41.20%)	0.001
Hyperlipemia	6 (21.40%)	4 (16.70%)	2 (5.90%)	0.168
Diabetes mellitus	6 (21.40%)	6 (25.00%)	2(5.90%)	0.078
Smoking	2 (7.10%)	6 (25.00%)	6 (17.60%)	0.190
Alcoholism	0 (0.00%)	2 (8.30%)	0 (0.00%)	0.073

[a] A-MCI vs. NC or V-MCI vs. NC, $P < 0.017$.