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Regional Metabolic Changes using Proton Magnetic Resonance Spectroscopy in Patients with Amnestic Mild Cognitive Impairment

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Background: Amnestic mild cognitive impairment (aMCI) is thought to be a prodromal stage of Alzheimer disease (AD). It is very important to diagnose aMCI for early treatment. Magnetic resonance spectroscopy (MRS) is a non-invasive technique for measuring intracerebral metabolites for early detection of cognitive decline. We measured regional metabolic changes in aMCI and healthy control (HC) subjects to assess the disease progression by using ^{1}H-MRS. **Methods:** We studied 9 subjects who met the criteria for aMCI and 10 HC subjects. We measured the ratio of N-acetylaspartate (NAA), myo-inositol (mI), and choline (Cho) to creatine (Cr) in hippocampus and posterior cingulate gyrus. **Results:** There was a significant elevation of the mI/Cr ratio in the hippocampus ($p < 0.05$). However, there were no significant differences in NAA/Cr and Cho/Cr ratios in the left hippocampus and left posterior cingulated gyrus. Also, there was no significant difference in the mI/Cr ratio in the left posterior cingulated gyrus. **Conclusions:** Using ^{1}H-MRS, we revealed that there is a difference in metabolic state between patients with aMCI and health controls.

Key Words: *Mild cognitive impairment, ^{1}H-MRS, Dementia*

INTRODUCTION

Alzheimer disease (AD) is a common degenerative brain disease, characterized by progressive cognitive impairment that results in not only to somatic dysfunction but also social loss. It is known that the earlier AD is detected and treated, the better the prognosis [1, 2]. Amnestic mild cognitive impairment (aMCI), in particular is known to be more likely to develop into AD, as compared with the healthy controls [3, 4]. However, in the case of people who generally have a low level of education, it is difficult to diagnose aMCI through routine neuroimaging studies and neuropsychological tests. Therefore, there are many cases in which reliable and non-invasive examinations are recommended.

Magnetic resonance spectroscopy (MRS) is a non-invasive technique for measuring intracerebral metabolites. In patients with incipient dementia, the level of N-acetylaspartate (NAA) decreases but that of myoinositol (mI) increases [5-11]. The decrease in NAA level reflects the hypometabolism of neuronal mitochondria, and the increase in mI level reflects the increase in gliosis caused by inflammation. Several recent studies have reported that MCI is apt to develop into dementia when associated with a decrease in NAA level, and that such a change is observed before actual cognitive dysfunction oc-

curs [12-14]. However, with conventional MRS, quantification of absolute metabolite values gets more complex so the metabolite ratios to creatine are much more reliable than the absolute levels, as they can minimize systematic error [15]. We therefore measured and compared the ratio of each metabolite to creatine (Cr) level between the aMCI patients and HCs, hypothesizing that the Cr level, which is related to energy metabolism, is not easily affected by disease progress.

The purpose of this study is to determine the ratio of each metabolite to Cr in the hippocampus and the posterior cingulate gyrus, and to ascertain inter-group differences.

MATERIALS AND METHODS

1. Subjects

Patients with aMCI (n = 9) were recruited consecutively and prospectively for longitudinal studies of cognitive disturbances, between September 2009 and June 2010. All patients underwent neuroradiological testing in conjunction with the usual battery of blood screening tests in order to exclude treatable or other causes of cognitive impairment. The exclusion criteria were medical history of stroke or other major neurological disease, such as leukoaraiosis or intraparenchymal lesions; thyroid dysfunction; seizure; psychiatric disorders; and medical diseases that might cause MCI. aMCI diagnoses were made in accordance with the Peterson et al. [16]. Cognitively healthy controls (HCs; n = 10) were consecutively recruited individuals who attending health screenings in the outpatient clinics of participating institutions. The controls were also tested with the mini-mental status examination (MMSE) to exclude unknown cognitive disturbances, and all scored above 27 points.

2. MRI and ^{1}H-MRS

MRI and ^{1}H-MRS were performed on all subjects, with the use of 1.5-tesla apparatus (Signa HDxt; General Electric Medical Systems, Milwaukee, WI) and single voxel ^{1}H-MRS was performed in an automated point resolved spectroscopy (PRESS) sequence (repetition time/echo time = 2,000/35 ms). As shown in Figure 1, the voxels of interest (VOIs) for ^{1}H-MRS were assigned to 2 areas in the brain: the left hippocampus and left posterior cingulated gyrus. The VOI was placed along the long axis of the hippocampus; sagittal images were obtained, followed by T2-weighted coronal images perpendicular to the long axis of the hippocampus, with a slice thickness of 20 mm. This region was chosen because spectroscopically detectable alterations in its neurochemical composition, corresponding with the severity of cognitive dysfunction, are well documented in cognitive disorders [17].

3. Statistical analysis

Results are represented as mean ± standard deviation. Statistical analyses were performed using SPSS® Ver. 12.0 for Windows. Group differences in each metabolite concentrations and metabolic ratio were analyzed by nonparametric analysis. Multivariate analysis was conducted to determine the independent risk factors of cognitive impairment adjusted for age and education. Statistical significance was considered at $p < 0.05$.

RESULTS

The demographic characteristics of the study subjects are shown in Table 1. As predicted, the 2 groups exhibited significant differences in age and the mean scores of MMSE ($p <$

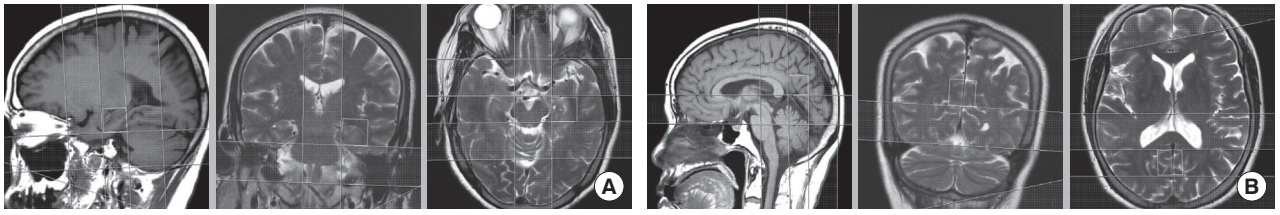

Fig. 1. Locations of VOIs for ^{1}H-MRS : left hippocampus (A); left PCG (B). In the PCG, VOIs were located in paramedian positions.

Table 1. Clinical characteristics of patients with aMCI and HCs

	aMCI (n = 9)	Controls (n = 10)	*p* value
Age (yr)	67.1 ± 8.7	66.3 ± 4.1	0.029
Male/Female	2/7	3/7	0.925
Education (yr)	6.6 ± 3.6	7.4 ± 4.7	0.407
MMSE	24.1 ± 2.8	27.0 ± 1.4	0.023

aMCI, amnestic mild cognitive impairment; HCs, healthy controls; MMSE, mini-mental statue examination.

0.05). However, there were no significant differences in gender or level of education.

Using ^{1}H-MRS, the absolute concentrations and the ratios of NAA/Cr, mI/Cr, and Cho/Cr were obtained. The concentrations of metabolites are presented in Table 2 as mean ± SD (mmol/L).

The NAA concentratons was lower in aMCI group in the hippocampus and posterior cinguate gyrus ($p < 0.05$). The mI/Cr ratio was significantly higher in the hippocampus of the aMCI group ($p < 0.05$) and showed statistical tendency after adjustment for age and education level. The 2 groups did not show a significant difference in the ratio of NAA/Cr and Cho/Cr in the hippocampus. In the posterior cingulate gyrus, the 2 groups did not show a significant difference in the absolute concentrations of metabolites or the ratios of NAA/Cr, mI/Cr and Cho/Cr.

DISCUSSION

This study showed that aMCI patients have a higher mI/Cr ratio than those of HC subjects in the hippocampus. MRS is to used to conduct in vivo analyses of metabolites and metabolic conditions, without invasive procedures such as biopsy, which facilitate the quantitative and qualitative analyses of NAA, Cho, Cr, mI, and lactate.

The role of mI in the brain as a glial marker has been proposed, mI levels are elevated by inflammatory gliosis [5-11]. Previous studies reported that mI increased in MCI patients compared to the healthy subjects, and it was regarded as a marker for the disconnection between the limbic area and other cortices [18]. In this study, the mI/Cr ratio in the hippocampus was significantly higher in aMCI patients, but intergroup differences were not observed in relation to the mI/Cr ratio in the posterior cingulate gyrus. We postulated that these results depend upon the progress of the disease. Glial proliferation may be an early change in AD, preceding significant neuronal loss or mitochondrial dysfunction [19, 20]. Specifically, an inflammation occurs in the hippocampus in the early stages and may gradually spread to the cerebral cortex via the posterior cingulate gyrus. It is consistent that aMCI is considered to be the prodromal stage of AD, which results in energy failure and synaptic dysfunction of cells from the primary limbic area, such as the hippocampus and proceeds to the associated limbic area such as the posterior cingulate gyrus, eventually spreading to the parietotemporal area [21, 22]. But, because of study size limitation, mI/Cr ratio showed statistical tendency after adjustment for age and education level.

Table 2. Regional metabolites from patients with aMCI and of HCs

Metabolites	Group	LH	LPC
NAA	HC	48.0 ± 5.88	90.0 ± 6.86
	aMCI	40.58 ± 6.57*	78.33 ± 9.08*
NAA/Cr	HC	1.19 ± 0.11	1.43 ± 0.09
	aMCI	1.22 ± 0.23	1.37 ± 0.09
MI	HC	33.08 ± 3.91	43.0 ± 4.49
	aMCI	34.85 ± 4.72	45.08 ± 17.43
MI/Cr	HC	0.87 ± 0.1	0.63 ± 0.05
	aMCI	1.01 ± 0.15*	1.01 ± 0.68
Cho	HC	39.23 ± 6.43	36.46 ± 4.84
	aMCI	31.44 ± 4.53*	33.83 ± 4.89
Cho/Cr	HC	0.96 ± 0.10	0.57 ± 0.05
	aMCI	0.90 ± 0.08	0.70 ± 0.26

*$p < 0.05$, Data are given as the mean ± SD.
aMCI, amnestic mild cognitive impairment; HCs, healthy controls; LH, left hippocampus; LPC, left posterior cingulate gyrus; NAA, N-acetylaspratate ; mI, myoinositol; Cr, Creatine ; Cho, Choline.

According to previous studies, the NAA levels in the hippocampus and the posterior cingulate gyrus were lower in MCI patients, which implied mitochondrial dysfunction of the hippocampus and posterior cingulate gyrus [23, 24]. In this study, the NAA levels in the hippocampus and the posterior cingulate gyrus were also lower in aMCI patients. However, significant inter-group differences were not observed in relation to the NAA/Cr ratios in the hippocampus and the posterior cingulate gyrus. This study is a small size, and also, MRS is sensitive to artifacts in the magnetic field and partial volume effect in areas near osseous structures and cerebral ventricles [15]. This is why we did not find any predictive val-

ues in the hippocampus, although this area is theoretically involved MCI or very early in AD.

Concerning Cho and Cr concentrations in AD and aMCI, previous studies showed that free choline increased due to hippocampal cholinergic loss and thus intrahippocampal choline increased, Cr and phosphocreatine concentrations were variable in patients with early dementia, and this normally occurs as the diseases progress. But, these results are not consistent and are not considered to be clinically significant [25-27].

A limitation of our study is that there may have been a selection bias and small size because single hospital study, and therefore our findings cannot be confidently generalized to other groups or populations without further research and we should be cautious against statistically over-interpretation. Nevertheless, we showed that the mI/Cr ratio in the hippocampus was significantly higher in the aMCI group, which is consistent with the results of a previous large-scale study on intrahippocampal metabolites [12, 18].

In conclusion, our results suggest that ^{1}H-MRS is expected to be a useful, non-invasive, early diagnostic method in patients with cognitive decline.

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