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Cerebral metabolic changes in neurologically presymptomatic patients undergoing haemodialysis: in vivo proton MR spectroscopic findings

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Abstract *Objective:* To prospectively investigate and detect early cerebral metabolic changes in patients with end-stage renal disease (ESRD) by using in vivo proton MR spectroscopy (MRS). *Methods:* We enrolled 32 patients with ESRD and 32 healthy controls between the ages of 26 and 50 years. Short echo time single-voxel proton MRS was acquired from volumes of interest (VOIs) located in the frontal grey and white matter, temporal white matter and basal ganglia. The choline/phospatidylcholine (Cho), *myo*-inositol (mI), *N*-acetylaspartate (NAA) and total creatine (tCr) peaks were measured and the metabolic ratios with respect to tCr were calculated. *Results:* In the ESRD group, significant elevations of the Cho/tCr and mI/tCr ratios were observed for the frontal grey matter, frontal white matter, temporal white matter and basal ganglia as compared with controls. There was no significant difference in the NAA/tCr ratios at all VOIs between the ESRD patients and the healthy controls. *Conclusions:* Proton MRS is a useful and non-invasive imaging tool for the detection of early cerebral metabolic changes in neurologically presymptomatic ESRD patients.

Keywords End-stage renal disease · Magnetic resonance spectroscopy · Haemodialysis · Cognitive deficit · Magnetic resonance imaging

Introduction

Haemodialysis is commonly used to treat patients with end-stage renal disease (ESRD). Patients who undergo chronic haemodialysis often present with neurological complications such as white matter changes, cerebral atrophy, dialysis dementia, hypertensive encephalopathy, haemorrhagic stroke, osmotic myelinolysis and

opportunistic infections [1–4]. In order to improve the morbidity and mortality of these patients, early diagnosis and prevention of these complications is an important issue.

CT and MRI are the most frequently used imaging modalities for the clinical evaluation of neurological complications in these ESRD patients. CT can be used to assess neurological complications, such as intracranial haemorrhage and cerebral infarction. MRI is a sensitive imaging tool for the neurological evaluation of ESRD patients [1]. The conventional imaging methods of MRI, including T1-weighted, T2-weighted and FLAIR techniques can be used to detect white matter changes, haemorrhage, cerebral atrophy and hypertensive encephalopathy. Furthermore, various new MRI techniques are applied to aid in the diagnostic value, such as diffusion MRI and proton MR spectroscopy (^{1}H-MRS). Diffusion MRI can be used to detect early white matter changes in ESRD patients [5]. Also, proton MRS is a non-invasive imaging tool that can be used in the assessment of cerebral metabolic alternations. As ESRD patients often present with various neurological complications, proton MRS may be of benefit in detecting the early cerebral metabolic changes in ESRD patients. However, as there are limited reports regarding this particular application, we aim to prospectively investigate the early cerebral metabolic changes in ESRD patients undergoing haemodialysis by using in vivo proton MRS.

Materials and methods

Subjects

Our institutional review board approved this prospective study, and all participants provided informed consent. A total of 33 patients with ESRD (17 female and 16 male) and 32 healthy volunteers (17 female and 15 male) were enrolled. The ESRD patients received regular haemodialysis three times per week at our hospital. All subjects were required to be 50 years of age or younger. Subjects were excluded if they had a history of diabetes, alcoholism, drug abuse or major neurological disorder (i.e. severe head injury, stroke, epilepsy, mental retardation, congenital neurological deficits or intracranial tumours). All subjects underwent magnetic resonance (MR) imaging and were required to complete cognitive testing and personal information questionnaires regarding gender, age, health status and level of education, on the same day as the MR examination. The cognitive abilities screening instrument (CASI) was used for cognitive testing [6]. The CASI included a broad range of cognitive domains and required approximately 30 min to complete. One male subject was excluded due to abnormal findings on conventional T2-weighted and diffusion-weighted images.

MR imaging and MR spectroscopy

All experiments were carried out at 1.5 T on a clinical whole-body MR system (Signa Excite; GE Medical Systems, Milwaukee, USA) with a standard head coil. Single-voxel ^{1}H-MRS data were acquired by using a PRESS sequence with TE=35 ms, TR=1,500 ms, spectral width=2,500 Hz, 2,048 data points and 128 imaging averages. Water suppression was achieved by three chemical shift selective (CHESS) pulses before the PRESS; the bandwidth of each CHESS pulse was 60 Hz. For phase correction of metabolite spectra, a total of 16 additional acquisitions were collected without water suppression in the sequence. The MR data acquisition time for each item of MRS data was 3 min 42 s.

The frontal grey and white matter, temporal white matter and basal ganglia were examined in each subject (Fig. 1). The voxel size was $2\times2\times2$ cm^3 for the frontal white and grey matter and temporal white matter and $1.5\times2.5\times2$ cm^3 for the basal ganglia. The voxel locations were carefully chosen to ensure that voxels were placed in normal-appearing brain regions.

Choline/phospatidylcholine (Cho), *myo*-inositol (mI), *N*-acetylaspartate (NAA) and total creatine (tCr) were quantified using linear combination of model spectra (LCModel), which is an automated, user-independent curve-fitting software for quantification of cerebral metabolites from MR spectra. Estimated uncertainties by Cramer–Rao lower bounds (CRLB) served as the main guidelines for judging the spectra of metabolite concentrations. Spectra with a full width at half maximum (FWHM) greater than 0.070 ppm were not included in the study. Only metabolite spectra with LCModel estimated uncertainty below 15% standard deviation (SD) of the evaluated concentrations and spectra with a signal to noise ratio (SNR) above 3 were included in this study. The NAA/tCr, Cho/tCr and mI/tCr ratios were calculated for further statistical analyses.

Statistic analyses

A *t* test was used to compare the difference in continuous variables between the two groups. A chi-squared test was used to test the difference in the nominal variable, gender, between the two groups. We use the statistical software package SPSS 12.0.0 (SPSS, Chicago, Ill) in the data analysis. *P* values less than 0.05 (two-tailed) were considered statistically significant.

Results

Description of study subjects

Demographic characteristics of the study population are shown in Table 1. The mean age of the ESRD patients was

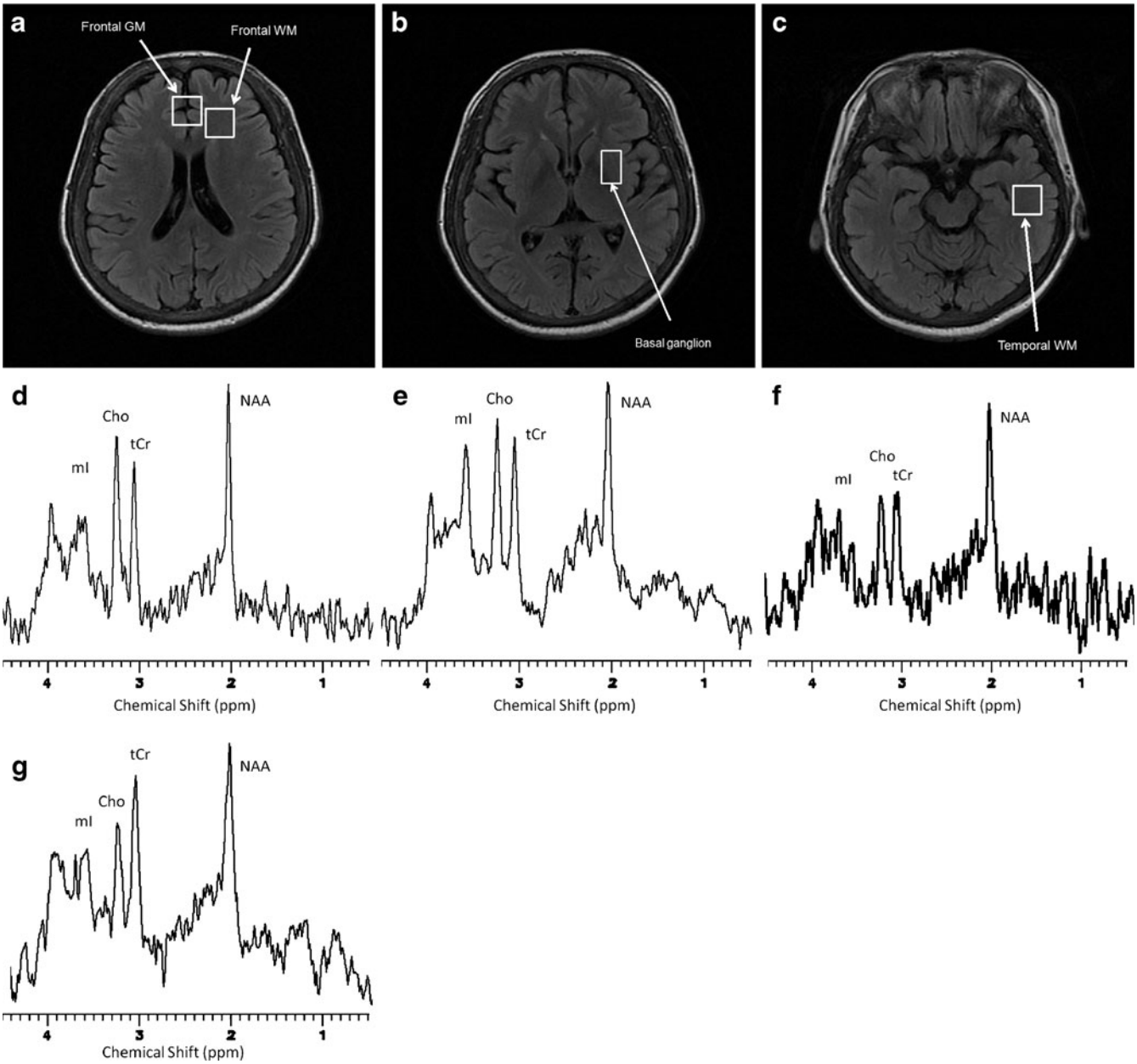

Fig. 1 FLAIR images and MR spectra in a 34-year-old male patient with end-stage renal disease. The MR images show VOIs in **a** the frontal white and grey matter, **b** the basal ganglia and **c** the temporal white matter; the MR spectra in each location are also shown in **d** the frontal white matter, **e** the frontal grey matter, **f** the basal ganglia and **g** the temporal white matter

39.72 years (range 26–50 years; SD 8.09 years) and the mean age of the healthy volunteers was 38.91 years (range 26–49 years; SD 7.26 years). There were no significant differences in gender ($p=1.000$) or age ($p=0.674$) between the patients with ESRD undergoing haemodialysis and the healthy volunteers. The duration of dialysis for the patient group was 6.25±3.96 years (mean ± SD) compared with no dialysis in the control group. There was also no significant difference in the CASI between the ESRD patients (93.98± 8.65) and the healthy controls (96.50±3.55).

MR spectroscopy

A comparison between our ESRD patients who underwent haemodialysis and the controls is summarised in Table 2. Significant elevations in the Cho/tCr ratios of the ESRD group were observed for the frontal grey matter ($p=0.005$), frontal white matter ($p=0.002$), temporal white matter ($p<0.001$) and basal ganglia ($p<0.001$) compared with the healthy control group. The mI/tCr ratios for ESRD patients who underwent haemodialysis were also significantly

Table 1 Demographic characteristics of the study population

Characteristics	Mean ± SD or *n*		*p* value
	HD	Control	
Number	32	32	
Gender (female/male)	17/15	17/15	
Age (years)	39.72±8.09 (26–50)	38.91±7.26 (26–49)	0.674
Male	38.07±7.41 (26–49)	38.07±6.96 (26–49)	1
Female	41.18±8.60 (29–50)	39.65±7.64 (28–49)	0.587
HD duration (years)	6.25±3.96		
CASI	93.98±8.65	96.50±3.55	0.177

HD haemodialysis, *CASI* cognitive abilities screening instrument (cognitive function test)

higher compared with the control group in the frontal grey matter ($p=0.001$), frontal white matter ($p<0.001$), temporal white matter ($p<0.001$) and basal ganglia ($p=0.005$). There was no significant difference in the NAA/tCr ratio between the ESRD patients and the healthy controls for all VOIs.

Discussion

Proton MR spectroscopy is a powerful imaging tool that has been used to assess a variety of intracranial pathological processes such as demyelinating lesions [7], tumours [8–10], multiple sclerosis [11, 12] and Alzheimer's disease [13–16]. In order to detect early neurological changes in patients with ESRD, we evaluated the cerebral chemistry and metabolic changes by using proton MR spectroscopy. In our protocol, we studied only subjects who were 50 years of age or younger to minimise the effect of aging, because aging itself can cause cerebral metabolic changes [17–19]. We found significant elevations in the Cho/tCr and mI/tCr ratios of patients with ESRD compared with controls; however, there was no significant difference in the NAA/tCr ratio.

Elevation in the Cho/tCr ratio may be due to significant osmolytic changes in the brains of dialysis patients. In their study, Geissler et al. reported an elevation of the Cho/tCr ratio that was limited only to the grey matter [20]. However, in our study, a significant elevation of the Cho/tCr ratio was observed not only for grey matter but also

Table 2 Metabolite ratios mI/tCr, Cho/tCr and NAA/tCr at each VOI for ESRD patients and control groups

Metabolic ratios/VOI	HD (*n*=32)	Control (*n*=32)	*p* value
mI/tCr			
Temporal WM	1.07±0.20	0.90±0.18	<0.001*
Frontal GM	1.15±0.20	0.96±0.25	0.001*
Frontal WM	1.08±0.20	0.90±0.15	<0.001*
Basal ganglia	0.85±0.23	0.68±0.23	0.005*
Cho/tCr			
Temporal WM	0.29±0.04	0.25±0.04	<0.001*
Frontal GM	0.33±0.06	0.29±0.04	0.005*
Frontal WM	0.37±0.07	0.32±0.04	0.002*
Basal ganglia	0.33±0.07	0.26±0.03	<0.001*
NAA/tCr			
Temporal WM	1.40±0.18	1.46±0.22	0.224
Frontal GM	1.46±0.17	1.44±0.16	0.658
Frontal WM	1.65±0.20	1.73±0.24	0.140
Basal ganglia	1.44±0.18	1.38±0.23	0.222

Data are expressed as mean ± SD
WM white matter, *GM* grey matter
*$p<0.05$ indicates a significant difference

white matter. Similar elevations in the Cho/tCr ratio for both grey and white matter of ESRD patients were observed by Sasaki et al. [21]. White matter changes were also observed in patients with ESRD in the periventricular and subcortical white matter in other previous MR studies [1, 22, 23]. Therefore, these reports suggest that ESRD patients undergoing haemodialysis may experience neurological changes involving both the grey and white matter.

NAA is thought to be a neuronal marker as it is found primarily in neurons [24]. A decreased NAA/tCr ratio has been noted for a variety of diseases, such as Alzheimer's disease, brain tumours, multiple sclerosis and brain infarction [11, 13–15, 25, 26] and may be related to neuronal cell damage or neurodegeneration. Geissler et al. found a decreased NAA/tCr ratio for ESRD patients [20]. However, another report by Michaelis et al. revealed no significant difference in the NAA/tCr ratio [27]. In our study, there was no significant difference in the NAA/tCr ratio between ESRD patients and healthy controls. Several previous studies, however, revealed a significant decrease in the NAA/tCr ratio for subjects who demonstrated normal aging of the human brain [17, 19]. Therefore, normal brain aging may be an important cause of cerebral metabolic changes and may account for the discrepancy between our results and these previous studies, as all of our patients were 50 years of age or younger with essentially normal brain MRIs.

Previous studies of MRS in ESRD patients revealed a significant elevation of mI, which is a major osmolyte in the brain [28]. Elevation of the mI/tCr ratio may be related to the osmolytic changes seen in dialysis patients. However, it was also reported that glial cells may be the source of the mI peak [20]. Therefore, the significant elevation of the mI/tCr ratio for ESRD patients may be related to either osmolytic changes associated with haemodialysis or gliosis.

We studied all four cerebral locations, including frontal grey and white matter, temporal white matter and basal ganglia, and found similar metabolic changes: specifically, significant elevations of the Cho/tCr and mI/tCr ratios and no significant differences in the NAA/tCr ratios. This suggests that the effect of end-stage renal disease and haemodialysis on the central nervous system may be diffuse.

Our study has several limitations. The small sample size was necessitated by the desire to choose young patients with ESRD; therefore, we only included 32 patients and 32 healthy controls and this may limit the power of our results. Furthermore, we were unable to demonstrate a relationship between the duration of dialysis and the serum metabolic level. Most of the patients in our study had relatively short haemodialysis durations because of their young age. In addition, the cerebral metabolic changes may have been secondary either to the uraemic status of the patient or to a haemodialysis effect, and the explicit relationship is still unclear. A larger follow-up study may provide more information concerning the relationship between dialysis duration and the cerebral metabolic changes.

In summary, proton magnetic resonance spectroscopy is a useful and non-invasive imaging tool for the detection of early cerebral metabolic changes in presymptomatic ESRD patients on dialysis, which may be of benefit in improving the quality of life in these patients.

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