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Metabolic Abnormalities in Idiopathic Parkinson's Diseases with Unilateral Symptoms

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Abstract : Authors investigated whether there is a lateral effect of ^{1}H MRS observable metabolite ratios between the symptomatic and the nonsymptomatic side in the early stage of Parkinson's disease with unilateral symptom. Localized in vivo ^{1}H MR spectroscopy (MRS) was used to measure the metabolite levels in the symptomatic and the nonsymptomatic sides of the lentiform nucleus in Parkinson's disease with unilateral symptom (N=25). The metabolite ratios of NAA/Cr and Cho/Cr in the symptomatic side were compared with those in the nonsymptomatic side. Significant metabolic lateral effect of NAA/(Cho+Cr) ratio was established between the symptomatic and the nonsymptomatic side of lentiform nucleus in Parkinson's disease with unilateral symptom ($p<0.05$). The ratio of NAA/(Cho+Cr) homolateral to the sympatomatic side of the patient is also lower than that of the control ($P<0.05$). On the basis of NAA/Cr ratios of lentiform nucleus between the symptomatic and the nonsymptomatic side, the present ^{1}H MRS study shows a significant neuronal laterality in Parkinson's disease with unilateral symptom. In vivo ^{1}H MRS may provide a diagnostic marker for neuronal dysfunction in Parkinson's disease with unilateral symptom.

INTRODUCTION

Parkinson's disease is a progressive, relatively common neurodegenerative disorder of the extrapyramidal system leading to specific motor symptoms. Clinically, Parkinson's disease is characterized by akinesia, rigidity and tremor. Pathologically, the condition is characterized by neuronal cell loss and gliosis particularly involving the putamen, substantia nigra, pons, cerebellar cortex, inferior olives, and Onuf's nucleus.[1] Other Parkinsonian syndromes include

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additional degenerative alterations affecting other basal ganglia structures. The neuronal loss underlies the catastrophic decrease in the concentration of striatal dopamine where the axons of the involved neurons terminate. The clinical differential diagnosis between the Parkinsonian syndromes is often very difficult, particularly in the early stage.[2] Even magnetic resonance imaging (MRI) and positron emission tomography (PET) can fail to demonstrate specific changes in the Parkinsonian syndromes.[3]

Along with the aged society coming, the morbidity of Parkinson's disease is also raised. But there is lack of objective experimental diagnostic indexes for it during the early stage. MRS is one of the possible noninvasive techniques to measure the chemical compounds in human body. ^{1}H MRS can analyze a lot of metabolites, such as N-acetyaspartate (NAA), Creatine (Cr), Choline (Cho) and so on. In Parkinson's disease, the concentration of those metabolites in the lentiform nucleus may change, along with the loss of neurons, detection of which helps to discriminate atypical syndromes from Parkinson's disease.[4] In the present study, we would take MRS analysis on basal ganglia of the patients with idiopathic Parkinson's disease with unilateral symptoms and investigate the feasibility of MRS as an objective diagnostic index for Parkinson's disease.

MATERIALS AND METHODS

Subjects

During the period from June 2002 to April 2004, twenty-five patients with Parkinson's disease (14 males and 11 females; age range 45-72 years) that had restricted unilateral symptomatic manifestation and twenty-five healthy normal volunteers (10 males and 15 females; age range 35-70) were included. The symptomatic side was right in fifteen patients and left in ten patients. The symptomatic duration of the disease was 8 to 62 months. The early stage group (N=12) was defined with the symptomatic duration within less than 12 months. Each patient was diagnosed by neurologists as having Parkinson's disease using criteria of the United Kingdom Parkinson's Disease Society Brain Bank[5] and completed a questionnaire detailing patient history, symptoms, and medication. After complete description of the study to the subjects, written informed consent was obtained from each subject.

Normal control subjects were recruited from the Catholic University Medical Center

(CUMC) staff, residents, interns, and medical students. The volunteers were screened for medical and neurological illness and history of substance abuse. None of normal control subjects had a history of substance dependence or current abuse or a history of neurological disorders.

^{1}H MR spectroscopy

All localized, water-suppressed *in vivo* ^{1}H MRS studies were performed on 1.5 T MRI/MRS system (GE Signa Advantage, version 4.8; GE Medical System, Milwaukee, Wisconsin) using a stimulated echo acquisition mode (STEAM) pulse sequence.[6] A single voxel technique with a 1.5x1.5x1.5 cm^3 (3.375 ml) voxel was used. MRS was performed using the STEAM sequence (1800/20; mixing time, 10 milliseconds) to collect spectra from voxels containing the putamen and globus pallidus on bilateral lentiform nucleus.[7]

^{1}H MR spectra were obtained both from total four voxels in the right and left side of SN and PG from each subject. It took approximately 1.5 hour per case, including the total acquisition time of ^{1}H MR spectrum. Spectral parameters were: 20 ms TE, 2000 ms TR, 128 averages, 2500 Hz spectral width, 2048 data points. All of the *in vivo* ^{1}H MR spectra were acquired with use of the standard bird-cage quadrature head coil (GE Medical Systems, Milwaukee, Wisconsin) that produces a uniform RF field (63.86 MHz). Raw data were transferred to a Sun SPARC station *IPC* (Sun Microsystems, Mountain View, California) and processed by the SAGE data analysis package (GE Medical Systems, Milwaukee, Wisconsin).

The shimming procedure focused on the water signal was performed to obtain the uniform and homogeneous magnetic field. Typical water line width (full width at half maximum) was 3-4 Hz. Special attention was given to locating the water signal frequency to maximize the water suppression. An exponential line broadening of 0.5 Hz was applied. Time domain data were converted to frequency domain by Fourier transformation. Frequency domain spectra were phased by hand, with use of frequency-independent phase corrections only. Phased absorption spectra are reported directly without baseline correction or resolution enhancement. Frequency domain signals were fitted to Lorentzian lineshapes using a Marquardt algorithm.[8] Proton resonances in the spectra obtained from brain tissues were assigned on the basis of prior assignments.[9] Resonance peak assignments of major ^{1}H MRS observable metabolites were CH_3 of NAA, 2.00 ppm; N-CH_3 of Cr, 3.00 ppm; N-$(CH_3)_3$ of Cho, 3.20 ppm; γ-CH_2 of Glu, 2.35 ppm

H4 and H6 of Ins, 3.50 ppm. To obtain the relative metabolite ratios, Cr was used as a putative reference.[10] The metabolite ratios of NAA/Cr and Cho/Cr in SN and PG were compared for the symptomatic and contralateral side. After subdividing into two groups according to their symptom duration, we evaluated whether there was specific correlation between their laterality and clinical stage.

Statistics

Statistical analysis was performed using SPSS (SPSS for Windows, Version 6.0, SPSS Inc. Chicago, Illinois). The data were analyzed with paired-samples t tests, where $p<0.05$ was considered significant to account for multiple comparisons.

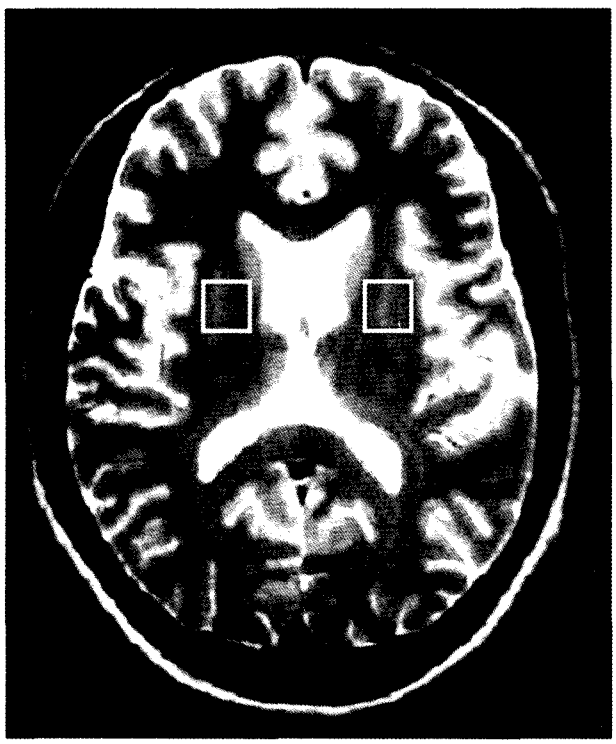


Fig. 1. Typical T2-weighted axial MR images in Parkinson's disease with unilateral symptom. The right and the left voxels of basal ganglia are selected for localized *in vivo* ^{1}H MRS.

RESULTS

Fig. 1 shows the typical T2-weighted axial MR images in Parkinson's disease with unilateral symptom including the right and the left voxels of basal ganglia for localized *in vivo* ^{1}H MRS. No apparent morphologic abnormalities in Parkinson's disease are observed (Fig. 1). Fig. 2 shows the typical right and left asymmetric spectra between the bilateral lentiform nucleus in the same patient.

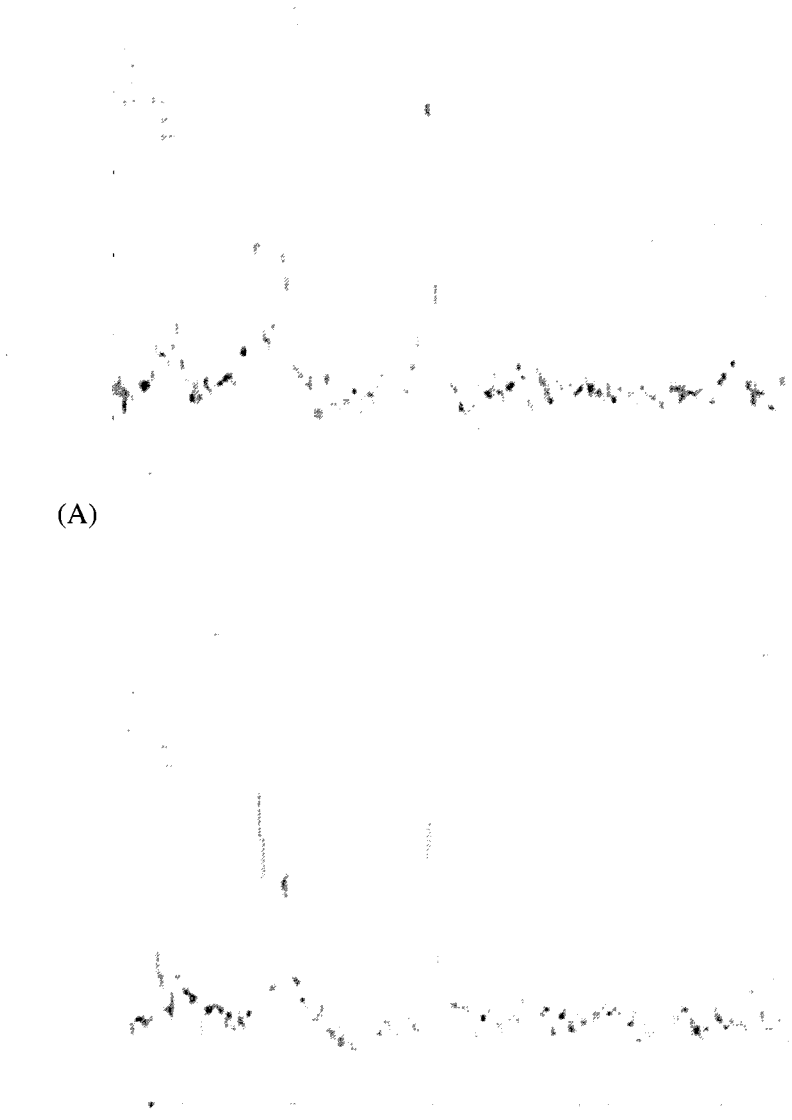
The ratio of NAA/(Cho+Cr) in lentiform nucleus contralateral to the symptomatic limbs and only the ratio of NAA/(Cho+Cr) in the homolateral side in Parkinson's disease with unilateral symptom were significantly lower than those of the normal healthy control. ($P<0.05$) There was also a significant decrease of the ratio of NAA/(Cho+Cr) opposite to the symptoms between the lentiform nucleus on the both sides in the same patients. ($P<0.05$) However, no difference in the ratio of NAA/(Cho+Cr) had been found between the two sides in the healthy volunteers.

DISCUSSION

Neuroimaging modalities such as CT and MRI are of limited value in distinguishing the neurodegenerative causes of Parkinson's disease and often show no apparent morphologic abnormalities like in our study (Fig. 1). Although Parkinson's disease may show hypointensity in the putamen on T2-weighted MR images due to iron (or other paramagnetic) deposition, such an hypointense signal is nonspecific and/or indistinguishable from those seen in many elderly normal subjects.[11]

In vivo ^{1}H MRS is a noninvasive approach to measuring important proton metabolites in patient with Parkinson's disease. Several MRS investigations of the brain in patients suffering from Parkinson's disease were recently reported.[12] No significant difference of the NAA/Cr ratio in patients with Parkinson's disease was reported in most studies[13] while Holshouser and coworkers were able to demonstrate a decreased NAA/Cho ratio in an older subset of their patients.[14] All of these MRS studies were based on the comparison of metabolic ratios between normal controls and patients with Parkinson's disease. And, without clinical classification of laterality these studies included the combined cases with bilateral and unilateral

symptoms. Thus, we investigated the definite metabolic differentiation concerning the symptomatic neurochemistry in patients with Parkinson's disease.



(A)

(B)

Fig. 2. Typical (A) right and (B) left asymmetric spectra between the bilateral lentiform nucleus in the same patient.

The traditional diagnosis of Parkinson's disease depends on the clinical menifestations and diagnostic therapy of dopamine, without a certain objective experimental index. The latest data showed that the rate of mis-diagnosis of Parkinson's disease is about eighty percent, the differentiation of IPD from alternative diaganosis such as multiple system atrophy and progressive supranuclear palsy in life is crucial. Early diagnosis of Parkinson's disease is even more difficult. Pathological changes of nigra and striatum are related to the Parkinson's disease. The putamen and globus pallidus is the key structure for the neurotransmiter of dopamine. Frost found by PET technique that the dopamine transporter in the basal ganglia (especially in the putamen), had been significantly reduced in the in the early stage of Parkinson's disease.[15] In addition, PET scan showed that uptake of ^{18}F-dopa decreased in the heel of putamen, where the neurons received the projective fibers from the ventrolateral neurons in the compact parts of the nigra, which also suggested serious deletion of neurons in this area.[16] Water-suppressed proton magnetic resonance spectroscopy can provide information on the relative concentrations of intermediary metabolites in a small volume of cerebral tissue. The metabolite of largest concentration seen with MRS is N-acetylaspartate, which is found principally in neurones and their processes. The creatine peak is taken as a marker of energy status and that for choline as an indicator of membrane synthesis and degradation. In our experiments, compared with the control there were significant decline of the ratio of NAA/(Cho+Cr) in the lentiform nucleus contralateral to the symptoms in the patients. And we also found the ratio of NAA/(Cho+Cr) was significantly different between bilateral lentiform nucleus in the same patients with unilateral symptoms. The decrease of the ratio mainly came from the decrease of NAA and increase of Cho. Those results suggested that a higher rate of neuron loss and membrane degradation might have occurred in patients, especially in the lentiform nucleus contralateral to the sympatomatic side, rather than those age-paired old healthy people. In those patients who had not taken dopaminergic drugs, similar changes of NAA/(Cho+Cr) occurred on the lentiform nucleus contralateral to symptoms. But whether dopaminergic drugs could protect the neurons from degeneration or not needs further investigation.[17] In addition, there was also significant difference in the ratio of NAA/(Cho+Cr) in the homolateral lentiform nucleus between the IPDUS patients and control, which suggested there might be also loss of neurons in the basal ganglia without any symptoms on the contralateral limbs. It might help to explain why the clinical symptoms of patients would develop from unilateral to bilateral sides for a certain period

of time.

In conclusion, the present study suggests that localized, water-suppressed *in vivo* ^{1}H MRS may be a useful modality for the clinical evaluations and aid in better understanding the neuropathologic process in patients with Parkinson's disease on the basis of the variation of metabolite ratio, particularly NAA/Cr.

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