Journal of Zhejiang University SCIENCE
ISSN 1009-3095
http://www.zju.edu.cn/jzus
E-mail: jzus@zju.edu.cn

MRS study on lentiform nucleus in idiopathic Parkinson's disease with unilateral symptoms

ZHENG Xu-ning (郑旭宁)[†1], ZHU Xiong-chao (朱雄超)[1], RUAN Ling-xiang (阮凌翔)[1], ZHANG Ling-ju (张玲菊)[1],Yuan Min (袁 敏)[1], SHANG De-sheng (商德胜)[1], LIU yang (柳 扬)[2]

([1]*The first affiliated hospital, College of medicine, Zhejiang University, Hangzhou 310003, China*)

([2]*Department of Neurology, University of Goettingen, Germany*)

[†]E-mail: zhengxn1@mail.hz.zj.cn

Received Nov. 1, 2002; revision accepted June 30, 2003

Abstract: Objective: To investigate changes in magnetic resonance spectroscopy (MRS) of lentiform nucleus during the early stage of Parkinson's disease. Methods: Twenty-five patients with idiopathic Parkinson disease with unilateral symptoms (IPDUS) and 25 healthy volunteers were enrolled in this study. MRS of the lentiform nucleus in each patient was taken and then concentrations of N-acetylaspartate (NAA), Creatine (Cr) and Choline (Cho) were calculated. Results: Compared to that in the control, NAA/ (Cho+Cr) was significantly lower in the lentiform nucleus contralateral to symptoms and even that in the ipsilateral side in IPDUS patients (all $P<0.05$); while there was no difference between the two sides in the healthy volunteer ($P>0.05$). The ratio of NAA/(Cho+Cr) ipsilateral to the sympatomatic side of the patient was also lower than that of the control ($P<0.05$). Conclusions: there might be some changes with MRS on the lentiform nucleus during the early stage of idiopathic Parkinson's disease with unilateral symptom. MRS may be one of the reliable methods for early or even sub-clinical diagnosis.

Key words: Idiopathic Parkinson's disease with unilateral symptom (IPDUS), Magnetic resonance spectroscopy, N-acetyaspartate, Creatine, Choline

Document code: A **CLC number:** R742.5

INTRODUCTION

Along with the coming of the aged society, the morbidity of Parkinson's disease is also raised. But there is lack of objective experimental diagnostic indexes for it during the early stage. Magnetic resonance spectroscopy (MRS) is a noninvasive technique for measuring the chemical compounds in the human body. ^{1}H MRS can be used to analyze many metabolites, such as N-acetyaspartate (NAA), Creatine (Cr), Choline (Cho) and so on. In Parkinson's disease, the concentration of these metabolites in the lentiform nucleus may change, along with the loss of neurons, detection of which helps to distinguish atypical syndromes from Parkinson's disease (Brooks, 2000). In the present study, MRS was used to analyze the basal ganglia of the patients with idiopathic Parkinson's disease with unilateral symptoms (IPDUS) and investigated the feasibility of MRS as an objective diagnostic index for Parkinson's disease.

MATERIALS AND METHODS

Materials

Twenty-five IPDUS patients [14 males and 11 females; 57.3±9.4 (45−74) years old; duration of

disease, 19.3±6.5 (9−30) months] with mild symptoms scoring only 8.7±3.4 points according to the modified Webster Rating scale were enrolled in this study. Twelve patients took dopaminergic drugs for more than one year, and 13 patients not (only one of them had taken Artane; the others had never taken any special drugs for Parkinson's disease besides dopaminergic drugs). All diagnosis accorded with the diagnostic criteria of Parkinson's disease, established by the first National Committee for the Extrapyramidal System: 1. There were at least two of the four typical symptoms and signs (static tremor, hypomotion, rigor and positional disorder); 2. There were no coincidental symptoms and signs which do not support the diagnosis of idiopathic Parkinson's disease, such as pyramidal signs, apraxia dysbusia, cerebellar symptoms, hysterical fremitus, paralysis of gaze, serious dysautonomia, and apparent dementia associated with mild extrapyramidal symptoms (National Extrapyramidal Session, 1986). All cases with coincidental pathological changes in brain MRI were excluded. Twenty-five healthy volunteers [15 males and 10 females 58.1±8.9 (46−71) years old] were enrolled in this study as control. There were no statistical differences between these two groups in the aspects of age and sex.

Methods

Patients and controls first underwent MR imaging using 1.5 T tesla Signa horizon Lx superconducting MRI system (GE, USA) with a standard 27-cm-diameter quadrature head coil, to exclude coincidental pathological changes such as multisystemic atrophy and lacunar conditions. 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 the bilateral lentiform nucleus (Iranzo *et al.*, 1999). Each spectrum was acquired from a volume measuring 20×20×20 mm^3. *TR*/*TE*=1800/288 msec, *NEX*=4, total scan times=128. Because of the small size of the regions with affected myelin on T2-weighted images, no spectra in the abnormal white matter could be recorded exclusively.

On ADW WIN 3.1 graph station and with analysing software (Version 8.3.1), data processing consisted of zero-filling (2058 points), gaussian filtering (2 Hz), Fourier transformation, zero-order phase correction, and manual baseline correction. The spectra were referenced to Creatine (3.04×10^6). The signals from myo-inositol (Ins) and Glycine (Gly), Choline (Cho), Creatine and phosphocreatine (tCr), and N-acetylaspartate (NAA) were integrated. The final data represented the concentration of each metabolite. The data and images were managed by two veteran MR doctors simultaneously, eliminating windage of the sampling sites and defining the stability of the spectrums.

Statistical methods

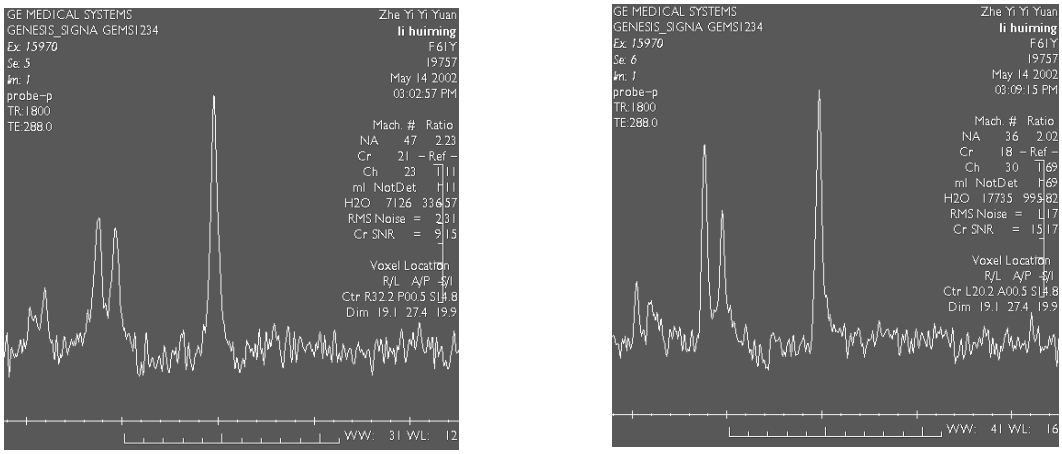
All the data were expressed with mean±standard deviation ($x\pm s$), and the independent sample t test was carried out by SPSS 10.0 software package.

RESULTS

Typical MRS of idiopathic Parkinson's disease with unilateral symptoms is shown in Fig.1 of the typical asymmetric spectra between the bilateral lentiform nucleus in the same patient (symptoms on the right limbs). The highest three peaks from right to left side in Fig.1a and Fig.1b are NAA, Cr and Cho, respectively.

Compared with the control, in the patients with IPDUS, the NAA and the ratio of NAA/Cho+Cr in the lentiform nucleus contralateral to the symptomatic limbs, and only the ratio of NAA/Cho+Cr in the ipsilateral side, were significantly lower (all $P<0.05$). Between the lentiform nucleus on both sides in the same patients, there was also a significant decline of NAA/Cho+Cr ratio opposite to the symptoms ($P<0.05$). However, no difference in the NAA/Cho+Cr ratio was found between the two sides in the healthy cases, detailed in Table 1.

There was no significant difference in various metabolites, except NAA/Cho+Cr of the lentiform nucleus contralateral to the symptomatic limbs between IPDUS patients who had and those who had not taken dopaminergic drugs. Detailed in Table 2.



(a) (b)

Fig.1 Typical MRS of idiopathic ParRinson's disease with unilateral symptoms

(a) right lentiform nucleus; (b) left lentiform nucleus

Table 1 MRS of the lentiform nucleus in the patients with Parkinson's disease with unilateral symptoms and the control

		NAA	Cho	Cr	NAA/(Cho+Cr)
IPDUS (*n*=25)	Lentiform nucleus contralateral to the symptoms	24.36±7.47*	18.56±5.98**	13.89±4.87	0.75±0.22$^{\oplus\Delta}$
	Ipsilateral lentiform nucleus	27.32±8.73	15.32±6.12	13.64±4.21	0.94±0.26*
Control (*n*=25)	Left	30.52±10.13	13.96±5.19	13.31±4.13	1.11±0.28
	Right	31.12±9.65	14.02±4.89	13.17±4.72	1.14±0.26

Compared with the related values of left and right sides in control;

$^{*}P<0.05$, $^{**}P<0.01$, $^{\Delta}P<0.001$, $^{\oplus}$compared with the ipsilateral lentiform nucleus in the same patients, $P<0.05$

Table 2 Influence of taking dopaminergic drugs on MRS

		NAA	Cho	Cr	A/Cho+Cr
Patients taking dopaminergic drugs (*n*=16)	Lentiform nucleus contralateral to the symptoms	25.86±8.29	17.33±5.18	13.07±4.92	0.85±0.21*
	Ipsilateral lentiform nucleus	28.60±9.12	15.78±6.56	13.98±4.75	0.95±0.29
Patients taking no dopaminergic drugs (*n*=9)	Lentiform nucleus contralateral to the symptoms	22.73±6.64	19.98±6.39	14.93±4.65	0.64±0.23
	Ipsilateral lentiform nucleus	26.34±7.47	14.91±5.42	13.26±3.79	0.93±0.21

* Compared with the related values in non-dopaminergic drugs taking group, $P<0.05$

DISCUSSION

The main pathological changes of Parkinson's disease are loss of dopaminergic (DA) neurons and the appearance of Lewy body in the nigra-striatum system. 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 diagnosis such as multiple system atrophy and progressive supranuclear palsy in life is crucial. Early diagnosis of Parkinson's disease is even more difficult. But the prognosis will be better if the patients receive accurate early di-

agnosis and treatment. In the DATATOP program (deprenyl 10 mg/d+vitamine E2000IU/d), 800 patients with Parkinson's disease were treated at the early stage. They found that this kind of therapy could postpone the time for them to take dopaminergic drugs, which had been widely accepted by most scholars (Ronald, 1990). Pathological changes of nigra and striatum are related to Parkinson's disease. The putamen and globus pallidus comprise the key structure for the neurotransmiter of dopamine. Frost found by PET technique that the dopamine transporter (DAT) in the basal ganglia (especially in the putamen), had been significantly reduced in the early stage of Parkinson's disease (Frost *et al.*, 1993). Bernheimer *et al*.(1973) considered that the clinical symptoms would not appear until the concentration of dopamine in putamen decreased to eighty percent, which provided the possibility and time for early or subclinical diagnosis. In addition, PET scan showed that uptake of ^{18}F-dopa decreased in the putamen heel, 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 (Otsuka *et al.*, 1996). Water-suppressed proton magnetic resonance spectroscopy (MRS) 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 (NAA), which is found principally in neurons and their processes. The Creatine (Cr) peak is taken as a marker of energy status and that for Choline (Cho) as an indicator of membrane synthesis and degradation. In our experiments, compared with the control, there was significant decline of the NAA and NAA/Cho+Cr ratio in the lentiform nucleus contralateral to the symptoms in the patients with IPDUS. And we also found the NAA/Cho+Cr ratio was significantly different between bilateral lentiform nucleus in the same patients with unilateral symptoms, which was in accord with the previous report (Choe *et al.*, 1998). The decrease of the ratio was mainly due to 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 IPDUS, especially in the lentiform nucleus contralateral to the sympatomatic side, rather than in old healthy people. In 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 (Ellis *et al.*, 1997). In addition, between IPDUS patients and the control, there was also significant difference in the NAA/Cho+Cr ratio in the ipsilateral lentiform nucleus, which suggested there might also be loss of neurons in the basal ganglia without any symptoms on the contralateral limbs. It might help to explain why the clinical symptoms of IPDUS would develop from unilateral to bilateral sides for a certain period of time.

Our study led us to conclude that there are prominent changes of MRS in the lentiform nucleus in Parkinson's disease. ^{1}H-MRS is a useful tool for early or sub-clinical diagnosis of Parkinson's disease.

References

Bernheimer, H., Birkmayer, W., Hornykiewicz, O., Jellinger, K., Seitelberger, F., 1973. Brain dopamine and the syndromes of Parkinson and Huntington. Clinical, morphological and neurochemical correlations. *J Neurol Sci*., **20**(4):415-455.

Brooks, D.J., 2000. Morphological and functional imaging studies on the diagnosis and progression of Parkinson's disease. *J Neurol*, **247**(2):II11-8.

Choe, B.Y., Park, J.W., Lee, K.S., Son, B.C., Kim, M.C., Kim, B.S., Suh, T.S., Lee, H.K., Shinn, K.S., 1998. Neuronal laterality in Parkinson's disease with unilateral symptom by in vivo 1H magnetic resonance spectroscopy. *Invest Radiol.,* **33**(8):450-455.

Ellis, C.M., Lemmens, G., Williams, S.C., Simmons, A., Dawson, J., Leigh, P.N., Chaudhuri, K.R., 1997. Chan -ges in putamen N-acetylaspartate and Choline ratios in untreated and levodopa-treated Parkinson's disease: a proton magnetic resonance spectroscopy study. *Neurology*., **49**(2):438-444.

Frost, J.J., Rosier, A.J., Reich, S.G., Smith, J.S., Ehlers, M.D., Snyder, S.H., Ravert, H.T., Dannals, R.F., 1993. Positron emission tomographic imagine of the dopamine transporter with 11C-win 35 428 reveals marked declines mild Parkinson's disease. *Ann Neurol*, **34**: 423-431.

Iranzo, A., Moreno, A., Pujol, J., Marti-Fabregas, J., Domingo, P., Molet, J., Ris, J., Cadafalch, J., 1999. Proton magnetic resonance spectroscopy pattern of progressive

multifocal leukoencephalopathy in AIDS. *J Neurol Neurosurg Psychiatry*. **66**(4):520-523.

National Extrapyramidal Session, 1986. The diagnosis criteria and differential diagnosis of Parkinson's disease and Parkinson's syndromes . *Chin J Neurol Psychiatry*, **19**(5):256(in Chinese).

Otsuka, M., Ichiya, Y., Kuwabara, Y., 1996. Differences in the reduced ^{18}F-dopa uptakes of the caudate and putamen in Parkinson's disease: correlations with the three main symptoms. *J Neurol Sci*, **136**:169-173.

Ronald, F., 1990. Therapy of Parkinson's Disease. Marcel Dekker Inc, New York, p.95-120.