Proton magnetic resonance spectroscopy in Parkinson's disease and progressive supranuclear palsy

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Abstract

Objectives—Proton magnetic resonance spectroscopy (¹H-MRS) localised to the lentiform nucleus, was carried out in eight patients with idiopathic Parkinson's disease and five patients with progressive supranuclear palsy. The aim of the study was to assess the concentration of N-acetyl-aspartate (NAA), creatine and phosphocreatine (Cr), and choline containing compounds (Cho) in the putamen and globus pallidus of these patients.

Methods—Peak ratios obtained from patients were compared with those from nine healthy age matched controls.

Results—NAA/Cho and NAA/Cr ratios were reduced significantly in patients with progressive supranuclear palsy.

Conclusion—These results suggest an NAA deficit, due to neuronal loss, in the lentiform nucleus of these patients. ¹H-MRS is a non-invasive technique that can provide useful information concerning striatal neuronal loss in the basal ganglia of patients with parkinsonian syndromes.

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The pathology of idiopathic Parkinson's disease is characterised by degenerative changes in the pars compacta of the substantia nigra, leading to a reduction of striatal dopamine. Other parkinsonian syndromes include additional degenerative changes affecting other basal ganglia structures. In progressive supranuclear palsy, neuronal loss involves the globus pallidus, subthalamic nucleus, dentate nucleus, substantia nigra, and other mesencephalic nuclei.¹ In the striatonigral variety of multiple system atrophy the areas chiefly affected are the putamen, subthalamic nucleus, substantia nigra, pontine nuclei, inferior olives, and cerebellar cortex.² The clinical differential diagnosis between these parkinsonian syndromes is often very difficult, particularly in the early stage. Even MRI and PET can fail to demonstrate specific changes in these patients.³⁻⁶

Proton magnetic resonance spectroscopy (¹H-MRS) is a recently developed non-invasive technique that allows the presence and concentration of certain brain metabolites to be measured in vivo. ¹H-MRS at a long echo time (TE) of 135 ms detects metabolites with

long T2 relaxation times. The signal at 2.0 ppm is primarily from N-acetyl-aspartate (NAA), an amino acid present in the brain almost exclusively in neurons and in their processes⁷⁻¹⁰; the signal at 3.0 ppm is from creatine and phosphocreatine (Cr) compounds, which are involved in membrane biosynthesis and breakdown^{7,8}; and the signal at 3.2 ppm is from choline containing compounds (Cho), which are cell membrane constituents.^{7,8} The lactate (lac) signal at 1.33 ppm is usually an index of anaerobic metabolism.^{8,11} ¹H-MRS has been utilised, measuring areas underlying spectral peaks, in different neurological disorders—namely, tumours,^{12,13} stroke,¹⁴⁻¹⁶ multiple sclerosis,^{17,18} AIDS and HIV related disorders,^{19,20} and neurodegenerative disorders such as Huntington's disease and Alzheimer's disease.^{21,22}

Recently this technique has also been used in the study of parkinsonian disorders, localising the volume of interest to the basal ganglia.²³⁻²⁷ In particular, Holshouser and coworkers, in a large series, did not find any significant difference between patients with idiopathic Parkinson's disease and normal subjects.²⁶ On the other hand a significant reduction in the NAA/Cr ratio in the lentiform nucleus was found by Davie *et al* in patients with the striatonigral atrophy variety of multiple system atrophy and also, to a lesser degree, in patients with the olivopontocerebellar atrophy variety.²³ Other parkinsonian syndromes such as idiopathic Parkinson's disease have not yet been examined with this technique.

In this study we performed ¹H-MRS, localised to the lentiform nucleus, in two groups of patients: (1) patients with idiopathic Parkinson's disease, (2) patients with progressive supranuclear palsy, to assess NAA, Cr, and Cho striatal levels.

Methods and subjects

MRI and ¹H-MRS were carried out with a whole body 1.5 T iron shielded system (Magnetom Siemens) using a standard circularly polarised head coil. The imaging protocol consisted of sagittal T1 weighted spin echo sequences (TR 600 ms and TE 15 ms) and coronal and transverse T2 weighted sequences (TR 2200 ms and TE 80 ms) to obtain the best resolution of basal ganglia. Slice thickness was 5 mm and the matrix 256 × 256. After global shimming, performed with a standard non-selective shimming sequence, a volume of interest of 3.4 ml was localised to the lentiform nucleus; this was done on both sides whenever

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Figure 1 T2 weighted spin echo (TR 2200 ms TE 80 ms) coronal image from a control subject showing the spectroscopic volume of interest centred on the left putamen and globus pallidus.

possible (fig 1). Local shimming within the selected volume of interest was required to obtain a spectral width of half maximum of the water proton peak of 3–6 Hz. The water proton signal was suppressed by a preceding chemical shift selective radiofrequency pulse.²⁸ The proton spectra were acquired by means of a double spin echo sequence with TE 135 ms, TR 1500 ms, and 512 acquisitions. The total examination time for MRI and MRS was generally 60–90 minutes. The signals in the time domain were multiplied by a half Gaussian function with a half width of 256 ms and by a factor of 100. After Fourier transformation and zero order phase correction the areas under the peaks were obtained by numerical integration. Baseline correction was performed for the purpose of presentation. Postprocessing was always performed by the same investigator, who was unaware of the clinical diagnosis. Resonances were assigned as follows: Cho at 3.2 ppm, Cr at 3.0 ppm, NAA at 2.0 ppm, lac at 1.33 ppm.²⁹ The selection of a long TE (135 ms) minimises potential signal contamination by lipids which

have a very short T2, and also allows acquisition of a signal from lactate methyl groups in antiphase condition doublet (spin-spin coupling constant (J) 7.35 Hz).

It is difficult to measure absolute values with our technique; therefore, the results are obtained in terms of ratios of metabolite signals. Ratios between areas underlying metabolite spectral peaks (NAA/Cho, NAA/Cr, Cho/Cr) have been utilised.

During the period December 1994–November 1995 we studied three groups of patients. Group A comprised eight patients with idiopathic Parkinson's disease, mean (SD) age 60.0 (7.8) years, mean disease duration 7 (range 4–12) years. All patients were taking levodopa (mean daily dosage: 275, range 150–400 mg). Mean Hoehn and Yahr stage was 2. Group B comprised five patients with progressive supranuclear palsy with a mean age of 71.4 (3.3) years. The diagnosis of progressive supranuclear palsy was made according to the criteria of Golbe *et al*³⁰: age at onset > 40 years; rapid progression of the disease, bradykinesia, gaze palsy, and at least three of the following symptoms: dysarthria, dysphagia, axial rigidity with hyperextended neck, no or mild tremor, frequent falls, and pyramidal signs. None of these patients had cerebellar or autonomic signs or evidence of polyneuropathy. Mean duration of disease was 5 (1.87) (range 3–8) years.

All patients from groups A and B were seen regularly as outpatients at the movement disorder clinic of the Institute of Neurology, University of Bari. The control group comprised nine healthy age matched (mean age 63.4 (8.9) years) subjects. Structural MRI images were studied by an experienced neuro-radiologist. Brain MRI findings were in agreement with the clinical diagnoses.

Patients judged unable to comply with the examination protocol were excluded. Informed consent was obtained from patients or their immediate relatives and the experimental protocol was approved by the ethics committee of the Neurology Department of the University of Bari.

Statistical analysis was performed with the Mann-Whitney *U* test.

Results

Fifteen spectra were obtained from the eight patients with idiopathic Parkinson's disease, seven from the five patients with progressive supranuclear palsy, and 13 from the nine control subjects. Figure 2 gives samples of the spectra. In all these instances, the quality of the spectra allowed the assessment of metabolite peaks. In some patients, abnormal peaks in the lipid zone (0.5–1.6 ppm) were detected. However, they did not interfere with the measurement of NAA, Cho, and Cr peak areas.

The means (SD) of peak area ratios were: idiopathic Parkinson's disease group: NAA/Cho 1.89 (0.76), NAA/Cr 1.89 (0.79), Cho/Cr 1.03 (0.22); progressive supranuclear palsy group: NAA/Cho 1.27 (0.25), NAA/Cr 1.33 (0.06), Cho/Cr 1.08 (0.20); control

¹H-MRS data

	NAA/Cho	NAA/Cr	Cho/Cr
IPD patients (8)	1.89 (0.76)	1.89 (0.79)	1.03 (0.22)
PSP patients (5)	1.27 (0.25)**	1.33 (0.06)††	1.08 (0.20)
Controls	1.97 (0.59)**	1.88 (0.52)††	0.97 (0.15)

NAA/Cho = N-acetyl-aspartate/choline; NAA/Cr = N-acetyl-aspartate/creatine; Cho/Cr = choline/creatine; IPD = idiopathic Parkinson's disease; PSP = progressive supranuclear palsy.

**P < 0.01 (Mann-Whitney); ††P < 0.01 *v* controls (Mann-Whitney).

Figure 2 ^1H -MRS spectra obtained from a control subject (top) and from two different patients, one with idiopathic Parkinson's disease (middle) and one with progressive supranuclear palsy (bottom); NAA/Cho and NAA/Cr ratios are decreased in patients with progressive supranuclear palsy.

group: NAA/Cho 1.97 (0.59), NAA/Cr 1.88 (0.52), Cho/Cr 0.97 (0.15) (table).

Analysis of peak ratios did not show any significant differences between the left and the right side in any of the groups.

Statistical analysis disclosed a significant reduction of NAA/Cho and NAA/Cr ratios in patients with progressive supranuclear palsy compared with controls ($P < 0.008$ in both cases).

Discussion

In this study ^1H -MRS did not show any significant difference between patients with idiopathic Parkinson's disease and control subjects. This result is in agreement with previous reports.²³⁻²⁶ The NAA/Cho and NAA/Cr ratios were significantly reduced in patients with progressive supranuclear palsy compared with control subjects. A similar result was found by Davie *et al* in patients with multiple system atrophy.²³ In our study we compared peak area ratios; this type of relative quantitation is currently a common way of expressing spectral information.⁸ The reduction of NAA/Cho and NAA/Cr ratios seems more likely due to a selective reduction of NAA level; in fact, the Cr peak is relatively stable and has been used as an internal standard in a previous study on basal ganglia;^{7,23} up to now it has been found to be reduced only in neoplastic and infectious diseases, or in association with a large reduction of NAA and Cho levels, in severe ischaemic lesions.^{7,16} Davie *et al* reported in patients with multiple system atrophy a reduction of the Cho/Cr ratio, due to a Cho deficit.²³ In our study, no patient group showed any significant difference in the Cho/Cr ratio compared with controls. We hypothesise that in patients with progressive supranuclear palsy the reduction of NAA/Cho and NAA/Cr peak ratios could be due to a selective decrease in NAA levels, rather than to a contemporary increase of Cho and Cr levels. The reduction of NAA is also supported by the role of this metabolite, which is an amino acid confined in the brain only to neurons, and therefore usually considered as a marker of neuronal integrity.^{7,8} Thus in different types of neurological disease, the NAA deficit has been shown to be related to the extent of neuronal loss.^{7,9} In this study the reduction of NAA/Cr and NAA/Cho ratios was significant in patients with progressive supranuclear palsy, in whom neuronal loss involves the putamen and globus pallidus. Normal ^1H -MRS data suggest a diagnosis of idiopathic Parkinson's disease, whereas low striatal levels of NAA could suggest a diagnosis of multiple system atrophy or progressive supranuclear palsy. This technique could therefore be useful for differentiating between these different clinical conditions in vivo. In fact 5% to 22% of patients diagnosed in life as having idiopathic Parkinson's disease show postmortem pathological findings of multiple system atrophy or progressive supranuclear palsy.^{5,23,31}

The technique allowed us to detect lac as a

doublet at 1.33 ppm. Lac peaks in our study were difficult to recognise because of the presence, in some patients, of wide base peaks between 0.5 and 1.6 ppm, of uncertain interpretation. These peaks, when present, did not interfere with the measurement of the three main metabolite peaks. These additional wide base peaks could be related to acyl chains of phospholipids and triglycerides. Usually these lipid compounds are absent in the brain, but can be detected in peroxisomal disorders.⁸ The presence of these lipid peaks could be related to lipofuscin storage in basal ganglia.^{25,32}

In conclusion, the significant reduction of NAA/Cr and NAA/Cho in the lentiform nucleus of patients with progressive supranuclear palsy seems to confirm in vivo the neuronal loss occurring in the globus pallidus of these patients. Further studies, in larger series, are necessary to better define the utility of ¹H-MRS in this field. ¹H-MRS may be a useful tool for the diagnosis and the pathogenetic interpretation of parkinsonian neurodegenerative disorders.

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