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Usefulness of proton magnetic resonance spectroscopy in differentiating parkinsonian syndromes

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Abstract Proton magnetic resonance spectroscopy (^{1}H-MRS) was performed in patients with a clinical diagnosis of idiopathic Parkinson's disease (IPD), multiple system atrophy (MSA) or progressive supranuclear palsy (PSP) in order to assess metabolic differences between the three groups of patients. Single-volume ^{1}H-MRS, localized to the lentiform nucleus, was carried out in 19 IPD patients, 14 MSA patients, 11 PSP patients and 12 age-matched healthy subjects. The signals of *N*-acetylaspartate (NAA), choline-containing compounds (Cho) and creatine-phosphocreatine (Cr) were evaluated as peak area ratios. The NAA/Cho peak ratio was significantly reduced in MSA and in PSP patients compared to IPD patients and to controls. The NAA/Cr peak ratio was significantly reduced in MSA, in PSP and in IPD patients compared to controls, but only in MSA compared to IPD patients. The NAA reduction in the basal ganglia of MSA and PSP patients may reflect a neuronal loss or damage. Single-volume ^{1}H-MRS may be a useful tool in differentiating MSA and PSP from IPD patients.

Key words Proton spectroscopy • Parkinsonian syndromes

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Introduction

Parkinsonian syndromes can be classified into two major categories: idiopathic Parkinson's disease (IPD) and atypical parkinsonian disorders (APD). APD patients are those in which the parkinsonism evolves rapidly, responds poorly or transiently to L-dopa therapy and has other associated features such as supranuclear gaze palsy, early falls and postural instability, early autonomic failure, and pyramidal or cerebellar signs [1-4]. The two most common atypical parkinsonian disorders are progressive supranuclear palsy (PSP) and multiple system atrophy (MSA). The clinical differentiation of these patients is generally possible when all the signs are present. Nevertheless various clinicopathological studies have evidenced that a misdiagnosis in life is frequent. Approximately one-quarter of patients diagnosed as having IPD during life have another neuropathological diagnosis postmortem [5, 6]. As there is no diagnostic test for MSA, an early recognition of the disease may be particularly difficult [7]. Furthermore, neuropathologically confirmed cases of PSP have been clinically confused with IPD, MSA, corticobasal degeneration, Lewy body dementia and Alzheimer's disease [8, 9]. In recent studies, attempts have been made to recognize clinical predictors useful for a correct diagnosis in the early stage of APD, but the results are not quite satisfactory [1, 7, 8]. Even powerful diagnostic tools such as magnetic resonance imaging (MRI) [10] and positron emission tomography (PET) [11, 12] can fail to demonstrate specific changes.

Proton magnetic resonance spectroscopy (^{1}H-MRS) is a technique that allows the presence and concentration of certain brain metabolites to be measured in vivo. ^{1}H-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*-acetylaspartate (NAA), an aminoacid present in the brain almost exclusively in neurons and in their processes [13-17]. The signal at 3.0 ppm is from creatine-

phosphocreatine (Cr) compounds, which are involved in energy metabolism and are relatively stable in ^{1}H-MRS [15, 16]. Choline-containing compounds (Cho), at 3.2 ppm, are linked to membrane metabolism [15, 16]. Lactate (Lac) signal at 1.33 ppm usually represents an index of anaerobic metabolism [17, 18]. Metabolic information can be quantitated because the acquired signal integral is proportional to the concentration of the signal-producing metabolite [17]. In the last few years we have obtained interesting results from single-volume ^{1}H-MRS carried out in patients with different neurologic disorders such as ischemic stroke, multiple sclerosis, AIDS-related and HIV-related syndromes, blepharospasm and parkinsonism [19-24]. The majority of ^{1}H-MRS studies in parkinsonian syndromes have shown similar metabolic patterns in the lentiform nucleus of IPD patients when compared to control subjects [25-30], although a slight, but not significant NAA level reduction has been reported in IPD patients [23-25]. Nevertheless, a significant reduction of this metabolite has been found when IPD patients with motor fluctuations [31] and drug-naive IPD patients were compared with a group of treated patients and with a control group [32]. On the contrary a significant NAA decrease has been evidenced in PSP [23, 29, 33] and MSA patients [24, 26] as compared to controls. This result suggests a neuronal loss in basal ganglia of these patients in agreement with neuropathologic studies [3, 34, 35]. Nevertheless in these previous studies no significant difference between APD and IPD was found, limiting therefore the diagnostic utility of ^{1}H-MRS.

In the present study we performed single-volume ^{1}H-MRS localized to lentiform nucleus to assess NAA, Cr and Cho striatal levels in three groups of patients: (a) IPD patients, (b) MSA patients, and (c) PSP patients. Our purpose was to evaluate if proton spectroscopy could detect metabolic difference between these patients.

Patients and methods

During the period December 1994 - July 1998 we studied 3 groups of patients recruited from the Movement Disorder Centre of the Neurology Clinic, University of Bari.

Group A comprised 19 IPD patients. Mean age was 57.7 ± 10.5 years, with a mean disease duration of 3.8 ± 1.7 years (range 1-6). Two patients were drug naive, ten patients were taking L-dopa treatment, five assumed ropinirole, and the remaining two cases were taking L-dopa in combination with ropinirole. Other concomitant medications in L-dopa-treated patients included: L-deprenyl (two patients) and anticholinergics (two patients). All treated patients had a good or sufficient response to the therapy. Mean Hoehn and Yahr stage was 1.9 (range 1-3).

Group B included 14 MSA patients (from A to N as indicated in Table 1) with a mean age of 60.1 ± 6.7 years. Mean disease duration was 3.2 ± 1.3 years (range 1-6). At the MRS study, patients A, C, D, E, H, J, K, and N had been classified as possible MSA, whereas patients B, F, G, I, L and M as probable MSA. This clinical differentiation was based on Quinn's criteria [36]. All patients from group B showed a sporadic adult onset of no or poorly L-dopa-responsive parkinsonism with marked akinesia and rapid progression of the disease. None had pyramidal signs, and only patients K and L had cerebellar signs. Severe symptoms of autonomic failure (i.e. urinary incontinence, urinary retention, fecal incontinence, syncope) were present in patients A, B, F, G, H, I, J,

Table 1 Clinical outcome of patients with multiple system atrophy (group B)

Patients	Age (years)	Sex	Diagnosis at examination	Clinical outcome	New signs
A	64	M	Possible SND	Probable SND	Autonomic signs
B	57	M	Probable SND	Death	—
C	58	M	Possible SND	PSP	Downward gaze palsy
D	60	M	Possible SND	Probable SND	Autonomic signs
E	60	M	Possible SND	Possible SND	—
F	60	M	Probable SND	Probable SND	—
G	55	M	Probable SND	Probable SND	—
H	50	M	Possible SND	Possible SND	—
I	46	M	Probable SND	Probable SND	—
J	63	F	Possible SND	Probable SND	Autonomic signs
K	65	F	Possible OPCA	Possible OPCA	—
L	65	M	Probable OPCA	Probable OPCA	—
M	67	M	Probable SND	Probable SND	—
N	71	F	Possible SND	Possible SND	—

SND, striatonigral disease; *PSP*, progressive supranuclear palsy; *OPCA*, olivopontocerebellar atrophy

L and M at time of examination. Therefore, according to clinical data, patients A, B, C, D, E, F, G, H, I, J, M and N had been diagnosed as having the striatonigral variety (SND) and patients K and L has having the olivopontocerebellar atrophy variety (OPCA) of MSA.

Group C included 11 PSP patients (from O to Y, as indicated in Table 2) with a mean age of 68.9 ± 4.3 years and mean disease duration of 4.9 ± 1.7 years (range 2-7). The diagnosis of PSP was made according to Golbe et al.'s criteria [37], namely age at onset > 40 years, rapid progression of the disease, bradykinesia, supranuclear gaze palsy (voluntary downgaze less than 15 degrees and preserved oculocephalic reflexes), 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. A clinical follow-up was planned in all patients who underwent the spectroscopic examination.

The control group comprised 12 healthy age-matched (mean age 59.7 ± 8.5 years) subjects. Structural MRI images of the brain were reported by an experienced neuroradiologist who was unaware of the clinical diagnosis. In all cases MRI findings were in agreement with clinical diagnosis. Those patients judged unable to comply with the examination protocol were excluded. In no case was sedation performed. Informed consent was obtained from patients and the experimental protocol was approved by the Ethics Committee of the Neurology Department, University of Bari.

The examination protocol was the same used in our previous studies [23, 24]. MRI and ^{1}H-MRS were carried out with a whole body 1.5 T iron-shielded system (Magnetom 63 SP, Siemens, Erlangen, Germany) using a standard circularly polarized head coil. The imaging protocol consisted of sagittal T_1-weighted spin echo (repetition time (TR), 600 ms; echo time (TE), 15 ms) and coronal and transverse T_2-weighted (TR, 2200 ms; TE, 80 ms) sequences in order to obtain the best resolution of basal ganglia. The slice thickness was 5 mm and the matrix was 256x256. MRS was carried out after global shimming, performed with a standard, non-selective shimming sequence. The cubic volume of interest (VOI) ranged from 3.4 ml to 8 ml and was localized to the lentiform nucleus. The positioning was guided by anatomic landmarks and great care was taken in order to include the largest volume of the structure in the center of the VOI (Fig. 1). This was done on both sides when possible. Local shimming within the selected VOI 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 radio frequency pulse [38]. The proton spectra were acquired by means of a double spin echo sequence with TE = 135 ms, TR = 1500 ms; and 256 or 512 acquisitions, depending on the size of VOI (necessary to obtain 1 spectrum). The total examination time for MRI and MRS was generally 60-90 min. 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; however it was not used for the measurement of peak areas. Post-procedure processing was always performed by the same investigator (D.M.M.) 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, and Lac at 1.33 ppm [39]. The selection of a long TE (135 ms) minimizes 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, 7.35 Hz). It is difficult to measure absolute values with our technique; therefore, results are obtained in terms of ratios of metabolite signals. Ratios between areas underlying metabolite spectral peaks (NAA/Cho, NAA/Cr, Cho/Cr) have therefore been utilized.

Statistical analysis was performed using the Kruskal-Wallis one-way ANOVA for non-parametric data and post hoc analysis was conducted using Dun's multiple comparison test.

Table 2 Clinical outcome of patients with progressive supranuclear palsy (group C)

Patients	Age	Sex	Diagnosis at examination	Clinical outcome
O	75	F	PSP	Worsened
P	68	F	PSP	Death
Q	72	F	PSP	Death
R	72	F	PSP	Worsened
S	68	F	PSP	Worsened
T	66	F	PSP	Worsened
U	64	F	PSP	Worsened
V	70	F	PSP	Worsened
W	68	M	PSP	Worsened
X	61	M	PSP	Worsened
Y	74	F	PSP	Worsened

PSP, progressive supranuclear palsy

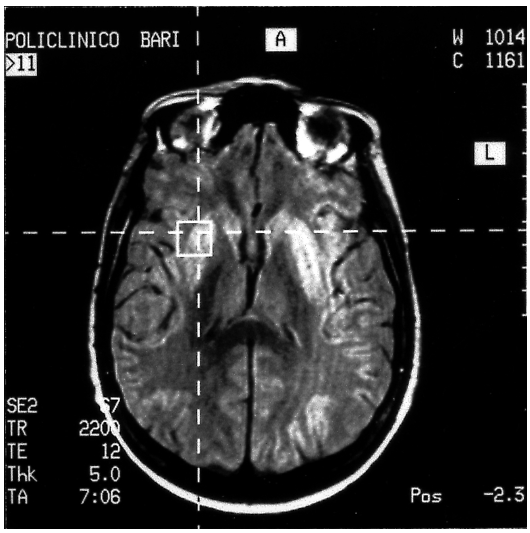

Fig. 1 Axial section of the brain of an idiopathic Parkinson's disease subject showing the cubic volume of interest (15 mm^3) centred on the right lentiform nucleus

Results

[1]H-MRS data

We obtained 35 [1]H-MRS spectra from the 19 IPD patients, 27 from the 14 MSA patients, 18 from the 11 PSP patients and 18 from the 12 control subjects. Examples of spectra are shown in Fig. 2. In all cases the spectra quality allowed the assessment of metabolite peaks. The means (± SD) of peak ratios are reported in Table 3. Analysis of peak ratios did not show any significant difference between the left and right sides in any of the groups.

The NAA/Cho and NAA/Cr peak ratios showed significant group differences ($p < 0.0001$). The MSA and PSP groups reported a significant NAA/Cho peak ratio reduction compared to controls ($p < 0.001$ in both) and to IPD patients ($p < 0.001$ and $p < 0.05$, respectively). The NAA/Cr peak ratio was significantly reduced in MSA and in PSP patients compared to controls ($p < 0.001$ in both), and in MSA patients compared to IPD patients ($p < 0.01$). Also, the NAA/Cr peak ratio showed slight but significant reduction in IPD patients compared to controls ($p < 0.05$).

The [1]H-MRS data and statistical significance are illustrated in Fig. 3.

Table 3 [1]H-MRS results

		Mean peak ratio (SD)		
Group	Diagnosis	NAA/Cho	NAA/Cr	Cho/Cr
A	IPD	1.82 ± 0.42	1.65 ± 0.41	0.92 ± 0.17
B	MSA	1.39 ± 0.31	1.32 ± 0.30	0.97 ± 0.20
C	PSP	1.45 ± 0.28	1.40 ± 0.17	0.99 ± 0.18
Control		2.02 ± 0.43	1.86 ± 0.29	0.94 ± 0.15

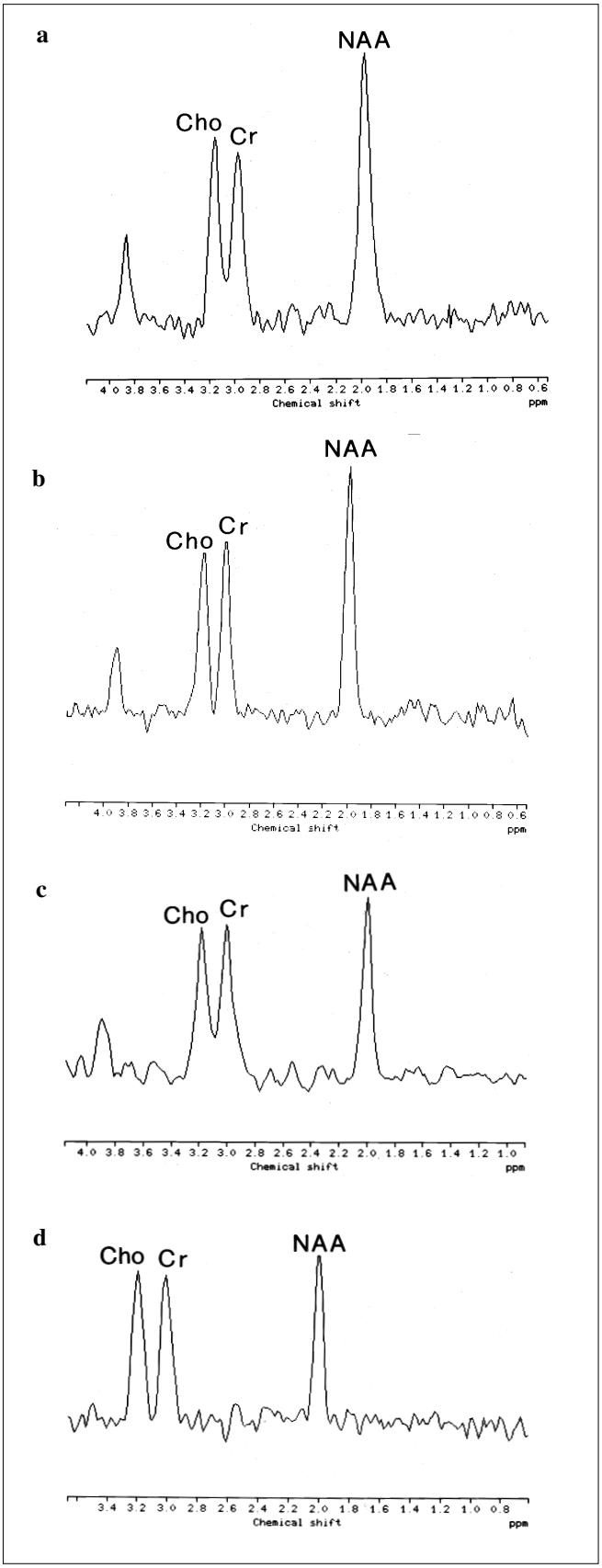

Fig. 2a-d *[1]H-MRS spectra showing Cho, Cr and NAA peaks.* **a** Control subject. **b** IPD patient. **c** MSA patient. **d** PSP patient. NAA/Cho and NAA/Cr ratios are markedly decreased in MSA and PSP patients

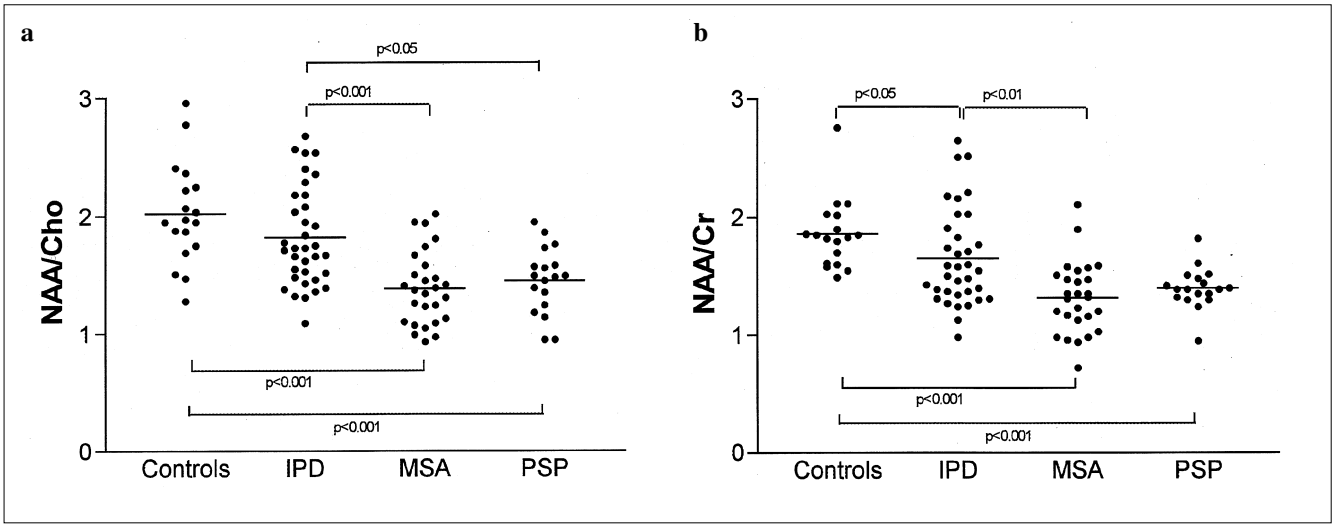

Fig. 3a,b [1]H-MRS metabolite peak ratios. **a** NAA/Cho ratios. **b** NAA/Cr peak ratios. Data are shown for healthy subjects (*Controls*, n = 12; spectra = 18), and for patients with idiopathic Parkinson's disease (*IPD*, n = 19; spectra = 35), multiple system atrophy (*MSA*, n = 14; spectra = 27), and progressive supranuclear palsy (*PSP*, n = 11; spectra = 18). Mean values are indicated by horizontal lines. Statistic significance with post hoc Dunn's multiple comparison test

Clinical outcome

Clinical outcomes of MSA and PSP patients are reported in Tables 1 and 2. All patients underwent a clinical follow-up. The mean time (± SD) from [1]H-MRS examination to clinical follow-up was 2.08 ± 0.93 years (range, 5.37 months to 3.53 years) in IPD patients, 1.69 ± 0.85 years (range, 2.1 months to 2.61 years) in MSA patients, and 1.72 ± 0.80) years (range, 3.03 months to 2.93 years) in PSP patients. In the IPD group all patients were still living at follow-up and clinical diagnosis was confirmed. Mean Hoehn and Yahr stage was 2.61 ± 0.90, indicating a slow progression of the disease. To evaluate MSA and PSP patients we considered the appearance of new clinical signs, disease progression and death. In the MSA group, all the patients had marked disease progression. Of the 8 patients classified as possible MSA at time of the study, patient C was redefined as affected by PSP for the appearance of a downgaze palsy, while patients A, D and J were reclassified as probable MSA. Patient B died without pathological examination and the remaining patients were all severely disabled. In the PSP group the clinical diagnosis was confirmed in all patients at follow-up. Patients P and Q died without pathological examination and all the remaining patients were severely disabled.

Discussion

Recently, [1]H-MRS has been carried out in patients affected with parkinsonism to assess whether this technique is useful in improving diagnostic specificity and whether it can provide information regarding pathophysiology [23-26, 29, 30, 33]. The results of these studies have evidenced different metabolic patterns in IPD and APD. In MSA and PSP patients, the most remarkable result is the reduction of NAA levels in the lentiform nucleus consistent with the neuronal loss occurring in this region [23, 24, 26, 29, 30]. This information has not been confirmed with pathology in the published data; nevertheless [1]H-MRS results are in agreement with previous neuropathological and PET studies [11, 12, 40]. To our knowledge, the [1]H-MRS studies to date reported in the literature have shown a metabolic pattern of NAA reduction in MSA and PSP patients when compared to healthy, age-matched subjects. In the present study, for the first time, a statistically significant difference has been obtained even in comparison with IPD patients. To date, the validity of NAA as a marker of neuronal viability has been widely accepted [13, 14]. The considerable decrease of NAA in the striatum of APD patients suggests the occurrence of neuronal loss or degeneration. This finding agrees with the neuropathological features of MSA and PSP in which pronounced damage of basal ganglia is present [34, 40]. We have followed for a relatively long period of time all patients in order to confirm the initial diagnosis. This observation has validated the homogeneity of the three groups of subjects. In no case patients diagnosed as having IPD presented a progression of disease similar to that observed in the atypical parkinsonian disorders. In the MSA and PSP groups, the evolution of the disease was invariably worse because all patients of these groups became more severely disabled or died during the follow-up period. Unfortunately in no one of the dead patients a postmortem examination has been performed; however clinical data seem to be in agreement with spectroscopic results. Another interesting result of the pre-

sent study arises from the clinical outcome analysis. All the probable MSA patients showed a marked progression of the disease. Eight patients were diagnosed as possible MSA at the ^{1}H-MRS examination time. Three of these patients were reclassified as probable MSA at follow-up; low NAA/Cho and NAA/Cr ratios were present in each of these subjects. This observation suggests that spectroscopic examination may show a pattern of NAA reduction even in patients with an incomplete clinical picture.

In previous studies we had found an insignificant reduction of NAA/Cho and NAA/Cr ratios in IPD patients compared to healthy subjects [23, 24]. The present study, carried out in a larger series of patients, shows a significant reduction of NAA/Cr ratios in the IPD group. We have not obtained any correlation between NAA levels and duration or severity of the disease. Most of patients were taking antiparkinsonian drugs, including L-dopa therapy, but no correlation with dosage or duration of treatment has been found. None of the IPD patients had developed clinical signs of APD at the follow-up, confirming that the clinical diagnosis was correct. We hypothesize that in a subgroup of IPD patients some degree of striatal neuronal damage may be present; nevertheless we are unable to identify it. The severity of this damage could reflect different stages of the disease. We would undertake a new study in a larger series of patients in different stages of the disease to investigate this aspect.

The most remarkable result of this study is the confirmation of a significant reduction of NAA/Cho and NAA/Cr ratios in basal ganglia of MSA and PSP patients in comparison to IPD patients as well as to controls. Our results are clearly related to the groups of patients. The overlapping of ratio values make it difficult to recognize differences in individual patients. Although the specificity of proton spectroscopy is far from being sufficient, it may be possible in the near future, examining a larger number of patients, to improve the capability of this method in distinguishing patients with different diseases.

In summary we conclude that single-volume ^{1}H-MRS can help in differentiating MSA and PSP from IPD patients. This technique seems to be a useful investigative tool for parkinsonian syndromes.

Sommario *Abbiamo esaminato con risonanza magnetica spettroscopica protonica a volume singolo pazienti con diagnosi clinica di morbo di Parkinson idiopatico (IPD), di atrofia multisistemica (MSA) e di paralisi sopranucleare progressiva (PSP) allo scopo di individuare differenze metaboliche nei tre gruppi. L'esame è stato eseguito, posizionando il volume di interesse sul nucleo lenitiforme, in 19 pazienti con IPD, 14 con MSA, 11 con PSP e in 12 controlli sani. I segnali corrispondenti ad N-acetilaspartato (NAA), composti contenenti colina (Cho) e creatina-fosfocreatina (Cr) sono stati valutati con i rapporti tra le aree sottostanti i picchi. Il rapporto NAA/Cho era significativamente ridotto nei pazienti con MSA e PSP rispetto ai pazienti con IPD ed ai controlli sani. Il rapporto NAA/Cr era significativamente ridotto nei pazienti con MSA, PSP e IPD rispetto ai controlli, ma solo nei pazienti con MSA rispetto ai pazienti con IPD. La probabile riduzione di NAA nei gangli della base di pazienti con MSA e PSP può riflettere una perdita o un danno neuronale. La risonanza magnetica spettroscopica protonica a volume singolo può configurarsi quale utile strumento per differenziare pazienti con MSA e PSP da pazienti con IPD.*

References

1. Colosimo C, Albanese A, Hughes AJ et al (1995) Some specific clinical features differentiate multiple system atrophy (striatonigral variety) from Parkinson's disease. Arch Neurol 52:294-298
2. Quinn N (1995) Parkinsonism - recognition and differential diagnosis. BMJ 310:447-452
3. Wenning GK, Ben-Shlomo Y, Magalhaes M et al (1995) Clinicopathological study of 35 cases of multiple system atrophy. J Neurol Neurosurg Psychiatry 58:160-166
4. Litvan I, Agid Y, Jankovic J et al (1996) Accuracy of clinical criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome). Neurology 46:922-930
5. Rajput AH, Rozdilsky B, Rajput A (1991) Accuracy of clinical diagnosis in parkinsonism - a prospective study. Can J Neurol Sci 18:275-278
6. Hughes AJ, Daniel SE, Kilford L et al (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 55:181-184
7. Albanese A, Colosimo C, Bentivoglio AR et al (1995) Multiple system atrophy presenting as parkinsonism: clinical features and diagnostic criteria. J Neurol Neurosurg Psychiatry 59:144-151
8. Litvan I, Mangone CA, McKee A et al (1996) Natural history of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) and clinical predictors of survival: a clinicopathological study. J Neurol Neurosurg Psychiatry 61:615-620
9. Kaye JA (1998) Diagnostic challenges in dementia. Neurology 51:S45
10. Savoiardo M, Girotti F, Strada L et al (1994) Magnetic resonance imaging in progressive supranuclear palsy and other parkinsonian disorders. J Neural Transm 42[Suppl]:93-110
11. Brooks DJ (1994) PET studies in progressive supranuclear palsy. J Neural Transm 42[Suppl]:119-134
12. Burn DJ, Sawle GV, Brooks DJ (1994) Differential diagnosis of Parkinson's disease, multiple system atrophy, and Steele-Richardson-Olszewski syndrome: discriminant analysis of striatal ^{18}F-dopa PET data. J Neurol Neurosurg Psychiatry 57:278-228
13. Nadler JV, Cooper JR (1972) N-Acetyl-L-aspartic acid content of human neural tumours and bovine peripheral nervous tissues. J Neurochem 19:213-219

14. Birken DL, Oldendorf WH (1989) N-acetyl-aspartic acid: a literature review of a compound prominent in ^{1}H-NMR spectroscopic studies of brain. Neurosci Biobehav Rev 13:23-31
15. Miller BL (1991) A review of chemical issues in ^{1}H-NMR spectroscopy: N-acetyl-L-aspartate, creatine and choline. NMR Biomed 4:47-52
16. Frahm J, Michaelis T, Merboldt KD et al (1991) On the N-acetyl methyl resonance in localized ^{1}H-NMR spectra of human brain in vivo. NMR Biomed 4:201-204
17. Vion-Dury J, Meyerhoff DJ, Cozzone PJ et al (1994) What might be the impact on neurology of the analysis of brain metabolism by in vivo magnetic resonance spectroscopy? J Neurology 241:354-371
18. Veech RL (1991) The metabolism of lactate. NMR Biomed 4:53-58
19. Federico F, Simone IL, Lucivero V et al (1998) Prognostic value of proton magnetic resonance spectroscopy in ischemic stroke. Arch Neurol 55:489-494
20. Simone IL, Federico F, Trojano M et al (1996) High resolution proton MR spectroscopy of cerebrospinal fluid in MS patients. Comparison with biochemical changes in demyelinating plaques. J Neurol Sci 144:182-190
21. Simone IL, Federico F, Tortorella C et al (1998) Localised ^{1}H-MR spectroscopy for metabolic characterisation of diffuse and focal brain lesions in patients infected with HIV. J Neurol Neurosurg Psychiatry 64:516-523
22. Federico F, Simone IL, Lucivero V et al (1998) Proton magnetic resonance spectroscopy in primary blepharospasm. Neurology 51:892-895
23. Federico F, Simone IL, Lucivero V et al (1997) Proton magnetic resonance spectroscopy in Parkinson's disease and progressive supranuclear palsy. J Neurol Neurosurg Psychiatry 62:239-242
24. Federico F, Simone IL, Lucivero V et al (1997) Proton magnetic resonance spectroscopy in Parkinson's disease and atypical parkinsonian disorders. Mov Disord 12:903-909
25. Holshouser BA, Komu M, Möller HE et al (1995) Localized proton NMR spectroscopy in the striatum of patients with idiopathic Parkinson's disease: a multicentre pilot study. Magn Reson Med 33:589-594
26. Davie CA, Wenning GK, Barker GJ et al (1995) Differentiation of multiple system atrophy from idiopathic Parkinson's disease using proton magnetic resonance spectroscopy. Ann Neurol 37:204-210
27. Bowen BC, Block RE, Sanchez-Ramos J et al (1995) Proton MR spectroscopy of the brain in 14 patients with Parkinson disease. Am J Neuroradiol 16:61-68
28. Davie CA, Pirtosek Z, Barker GJ et al (1995) Magnetic resonance spectroscopic study of parkinsonism related to boxing. J Neurol Neurosurg Psychiatry 58:688-691
29. Tedeschi G, Litvan I, Bonavita S et al (1997) Proton magnetic resonance spectroscopic imaging in progressive supranuclear palsy, Parkinson's disease and corticobasal degeneration. Brain 120:1541-1552
30. Clarke CE, Lowry M, Horsman A (1997) Unchanged basal ganglia N-acetylaspartate and glutamate in idiopathic Parkinson's disease measured by proton magnetic resonance spectroscopy. Mov Disord 12:297-301
31. Chaudhuri KR, Lemmens G, Williams SCR et al (1996) Proton magnetic resonance spectroscopy in untreated and levodopa treated Parkinson's disease patients with motor oscillations. Neurology 46:A457
32. Ellis CM, Lemmens G, Williams SCR et al (1997) Changes in putamen N-acetylaspartate and choline ratios in untreated and levodopa-treated Parkinson's disease: a proton magnetic resonance spectroscopy study. Neurology 49:438-444
33. Davie CA, Barker GJ, Machado C et al (1997) Proton magnetic resonance spectroscopy in Steele-Richardson-Olszewski syndrome. Mov Disord 12:767-771
34. Jellinger KA (1995) Neurodegenerative disorders with extrapyramidal features - a neuropathological overview. J Neural Transm 46[Suppl]:33-57
35. Golbe LI, Davis PH (1988) Progressive supranuclear palsy. In: Jankovic J, Tolosa E (eds) Parkinson's disease and movement disorders. Urban & Schwarzenberg, Baltimore Munich, pp 121-130
36. Quinn N (1994) Multiple system atrophy. In: Marsden CD, Fahn S (eds) Movement disorders. Butterworths, London, pp 262-281
37. Golbe LI, Davis PH, Schonberg BS et al (1988) Prevalence and natural history of progressive supranuclear palsy. Neurology 8:1031-1034
38. Michaelis T, Merboldt KD, Hanicke W et al (1991) On the identification of cerebral metabolites in localized ^{1}H-NMR spectra of human brain in vivo. NMR Biomed 4:47-52
39. Frahm J, Bruhn H, Gyngell ML et al (1989) Localized H-NMR spectroscopy in different regions of the human brain in vivo: relaxation times and concentrations of cerebral metabolites. Magn Reson Med 11:47-63
40. Lantos PL (1994) The neuropathology of progressive supranuclear palsy. J Neural Transm 42[Suppl]:137-152