Journal of the Korean Radiological Society 1996 : 34(6) : 711~716

^{1}H MR Spectroscopy in Parkinson's Disease and Progressive Supranuclear Palsy : Preliminary Study[1]

Kee Hyun Chang, M.D., Beom Seok Jeon, M.D.[2], In Chan Song, M.S.[3,4], Dong Sung Kim, B.S., Kwan Hong Min, B.S., Moon Hee Han, M.D. Sa. -Ouk Kang, Ph.D.[4], Byoung Goo Min, Ph.D.[3], Man Chung Han, M.D.

Purpose : To determine whether ^{1}H magnetic resonance spectroscopy (MRS) is useful in differentiating idiopathic Parkinson's disease (IPD) from progressive supranuclear palsy (PSP), based on metabolite ratios.

Materials and Methods : Using a 1.5 T MR Unit, single voxel ^{1}H MRS using STEAM with a TR of 2000 ms and a TE of 135 ms was performed in seven PD and eight PSP patients. Five age-matched volunteers(mean age, 63 years) and another five younger healthy volunteers(mean age, 30 years) were studied as normal controls. The regions of interest were the putamen and pallidum, with a size of $2 \times 2 \times 2$ cm. After measuring the spectral intensities of each metabolite (N-acetylaspartate=NAA, choline =Cho, creatine=Cr and lactate), relative peak height ratios of NAA/Cr, Cho/Cr and NAA/Cho, and lactate levels among four groups were compared.

Results : NAA/Cho and NAA/Cr ratios were statistically lower in the PSP group than the IPD group (1.21 ± 0.26 versus 1.45 ± 0.20, and 1.26 ± 0.23 versus 1.38 ± 0.19, respectively : $p<0.05$). NAA/Cho and NAA/Cr ratios were significantly lower in age-matched controls than in younger normal controls (1.39 ± 0.21 versus 1.76 ± 0.15, and 1.36 ± 0.13 versus 1.79 ± 0.17, respectively : $p<0.05$). However, NAA/Cho and NAA/Cr ratios between age-matched controls and IPD were not significantly different ($p>0.05$). Cho/Cr ratios were not different among four groups. Lactate was not detected in any patients.

Conclusion : NAA/Cho and NAA/Cr ratios in the corpus striatum were significantly lower in the PSP group than in the age-matched control and IPD groups. These results suggest that loss of neuron cells in the corpus striatum is more prominent in PSP than in IPD, and that NAA/Cho and NAA/Cr ratios may help in differential diagnosis of IPD and PSP.

Index Words : Magnetic resonance(MR), spectroscopy
Brain, atrophy
Brain, diseases

INTRODUCTION

Parkinsonism is a clinical syndrome with rest tremor, bradykinesia, rigidity, freezing and loss of postural reflexes as cardinal features. It is generally classified into idiopathic Parkinson's disease (IPD), symptomatic or secondary parkinsonism and Parkinson-plus syndrome. IPD is the most common cause of parkinsonism, and the main pathology lies in the substantia nigra pars compacta (SNpc). Severe depletion of dopaminergic neurons in the SNpc and subsequent nigrostriatal dopaminergic denervation are responsible for parkinsonian symptoms. Dopaminergic replacement and dopamine receptor agonists are highly effective. Symptomatic parkinsonism is caused by known disease processes such as infarcts in the basal ganglia, or biochemical blockade of the nigrostriatal system by neuroleptics. It can be correctly diagnosed by clinical information and neuroimaging studies (1). Parkinson-plus syndrome includes a var-

[1]Department of Diagnostic Radiology, Seoul National University
[2]Department of Neurology, Seoul National University
[3]Department of Biomedical Engineering, College of Medicine, Seoul National University
[4]Department of Lab. of Biophysics, Department of Microbiology, College of Exact Sciences, Seoul National University
Received November 23, 1995 ; Accepted January 3, 1996
This study was supported in part by Clinical Research Fund of Seoul National University Hospital (1994)
Address reprint requests to : Kee Hyun Chang, M.D., Department of Diagnostic Radiology, Seoul National University, Seoul Korea.

iety of neurodegenerative disorders with parkinsonian features as a part of the broad neurological manifestation. Progressive supranuclear palsy (PSP) is the most common Parkinson-plus syndrome (2). The pathology of PSP is much more widespread in distribution than that of IPD, and is characterized by neuronal loss and gliosis in the globus pallidus, putamen, subthalamic nucleus, red nucleus, dentate nucleus, and in the periaqueductal gray and tectum of the brainstem (3). L-dopa and dopamine receptor agonists are ineffective and the course is much more aggressive, with a fatal outcome in five to eight years (4, 5). Unresponsiveness to L-dopa and dopamine receptor agonists is thought to be due to loss of receptor neurons in the striatum (6). The diagnosis usually depends on characteristic clinical features. It is, however, often difficult to differentiate IPD from Parkinson-plus syndrome such as PSP by clinical criteria and neuroimaging studies (2, 7). As both IPD and Parkinson-plus syndrome are degenerative diseases without a specific known cause, there are no definite biochemical and neurophysiological tests to make a differential diagnosis, though recent advances in imaging studies have made some progress in these diseases. There may be increased iron deposition in the SNpc, demonstrable by MR imaging in IPD (8). However, clinical application to individual cases is limited because of the wide overlap with the normal population (9). In PSP, brainstem atrophy and decreased signal in the putamen may be seen, but are not sensitive or specific (10). In IPD, a fluorodopa PET scan shows a decreased uptake of fluorodopa in the striatum with an anterior-posterior down-sloping and a greater decrease in the gradient, putamen, whereas in PSP it shows a decreased uptake of fluorodopa in the whole putamen. (11). Most importantly, the basic question of L-dopa responsiveness or intactness of receptor neurons is not addressed.

Differences in the distribution of striatal pathologic lesions between IPD and PSP might be reflected by a difference in metabolites detectable on ^{1}H magnetic resonance spectroscopy (MRS), thus contributing to a better understanding and diagnosis of parkinsonism. The pathologic findings lead to the hypothesis that cerebral metabolites such as N-acetylaspartate (NAA), choline (Cho), and creatine compounds (Cr), which can be measured by *in vivo* ^{1}H MRS in the striatum may be more prominently decreased in PSP than in IPD. The purpose of this study is to determine whether the spectral intensities of the metabolites in the striatum as measured by single voxel ^{1}H MRS demonstrate any differences between IPD and PSP.

MATERIALS and METHODS

Seven patients with IPD (four men and three women, 53 —68 years ; mean 60 years) and eight patients with PSP (six men and two women, 61 —75 years ; mean 68 years) were examined with *in vivo* single voxel ^{1}H MRS. The diagnosis of IPD followed the criteria of Core Assessment Program for Intracerebral Transplantation (12). IPD duration was 3 —10 years and patients were moderately to severely affected (Hoehn-Yahr scale : 2.5 —4). The criteria for PSP followed those of Golbe *et al* (5). Duration of the disease was 1 —8 years and the Hoehn-Yahr scale was 3 —5. In both groups of patients, MR imaging normal other than nonspecific findings such as diffuse brain atrophy or low signal intensity in the putamen on T2-weighted images. Three patients with PSP had multiple small foci of high intensity in the periventricular white matter on T2-weighted images. Five age-matched (two men and three women, 59 —73 years ; mean 63 years) and five younger (five men, 27 —32 years ; mean 30 years) control subjects were also studied.

All ^{1}H MRS measurements were performed on a 1.5 T MR unit (Magnetom SP, Siemens, Erlangen, Germany) using a standard CP head coil and spectroscopy package. In every patient the MR spectra were obtained from both the right and left striata with a voxel size of $2 \times 2 \times 2$ cm, using STEAM sequence (TR=2000 ms, TE=135 ms, 128 scans). First, a set of three T2-weighted orthogonal axial, coronal and saggital images of the brain was acquired using the turbo spin echo technique, and an image at the level of the basal ganglia in each plane was chosen as a reference for voxel location. The voxel included primarily the basal ganglia, encompassing both the putamen and globus pallidus (Fig. 1). Approximately 10 —20% of the voxel volume was estimated to be outside the striatum. Field homogeneity was shimmed to give a localized water-proton spectral line width of 4 —8 Hz before data acquisition. Following the zero-filling of raw data to 4096 points, exponential line broadening (center : 0 ms, half time :

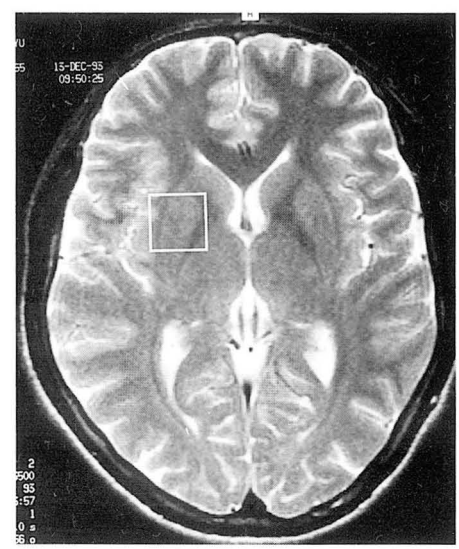

Fig. 1. T2-weighted MR image in a normal younger control subject showing a voxel of $2 \times 2 \times 2$ cm in the right corpus striatum

150 ms) was applied before Fourier transformation. The spectra were phased manually and second-order baseline was corrected. After measurement of the peak heights of the metabolites' resonances including NAA, Cho and Cr, the relative peak height ratios of NAA/Cho, NAA/Cr, and Cho/Cr were calculated and compared among four groups. A peak of lactate (1.34 ppm) or lipid in the 0.9 to 1.3 ppm region, if present, was then selected. MR spectral data were analysed by one of the authors (I. C. S.) blinded to the clinical diagnosis. The student unpaired t-test was used for statistical analysis.

RESULTS

In all patients spectra were obtained unevent- fully, taking approximately one hour per patient. All the spectra were of acceptable quality, even though some showed poor baseline correction, and were included in the data for subsequent analysis. In all subjects, ^{1}H MR spectra demonstrated peak resonances of three metabolites of NAA, Cho and Cr. The spectra from younger and age-matched control subjects and from patients of IPD and PSP are shown in Fig. 2. Table 1 shows a comparison of mean values of NAA/Cho, NAA/Cr, and Cho/Cr ratios in all control subjects and patients with IPD and PSP.

Mean values of NAA/Cho and NAA/Cr ratios in the elderly age-matched control subjects were lower than those in the younger control subjects, respectively (1. 39 $\pm$ 0.21 versus 1.76 $\pm$ 0. 15 for NAA/Cho, $p<0.05$; 1. 36 $\pm$ 0.13 versus 1.79 $\pm$ 0.17 for NAA/Cr, $p<0.05$). However, the mean values of NAA/Cho and NAA/Cr ratios were not different between age-ma- tched control subjects and IDP (1.39 $\pm$ 0.21 versus 1.45 $\pm$ 0.20 for NAA/Cho, $p>0.05$; 1.36 $\pm$ 0.13 versus 1.38 $\pm$ 0.19 for NAA/Cr, $p>0.05$). Mean values for NAA/Cho and NAA/Cr in PSP patients were lower than those of patients with IPD (1.21 $\pm$ 0.26 versus 1.45 $\pm$ 0.20 for NAA/Cho, $p<0.05$; 1.26 $\pm$ 0.23 versus 1.38 $\pm$ 0.19 for NAA/Cr, $p<0.05$), even though the spectral pattern of a given patient with PSP appeared to be not significantly different from that of age- matched controls and IPD patients, as in Fig. 2. Mean values of NAA/Cho and NAA/Cr ratios tended to be slightly higher in the left striatum than in the right one, but were not statistically significant. There was no difference between sexes.

Mean values of Cho/Cr ratios were not significantly different among the four groups. A resonance peak of lactate or lipid was not detected in any subjects examined.

DISCUSSION

Morphological neuroimaging studies such as CT and MR imaging are of limited value in distinguishing the

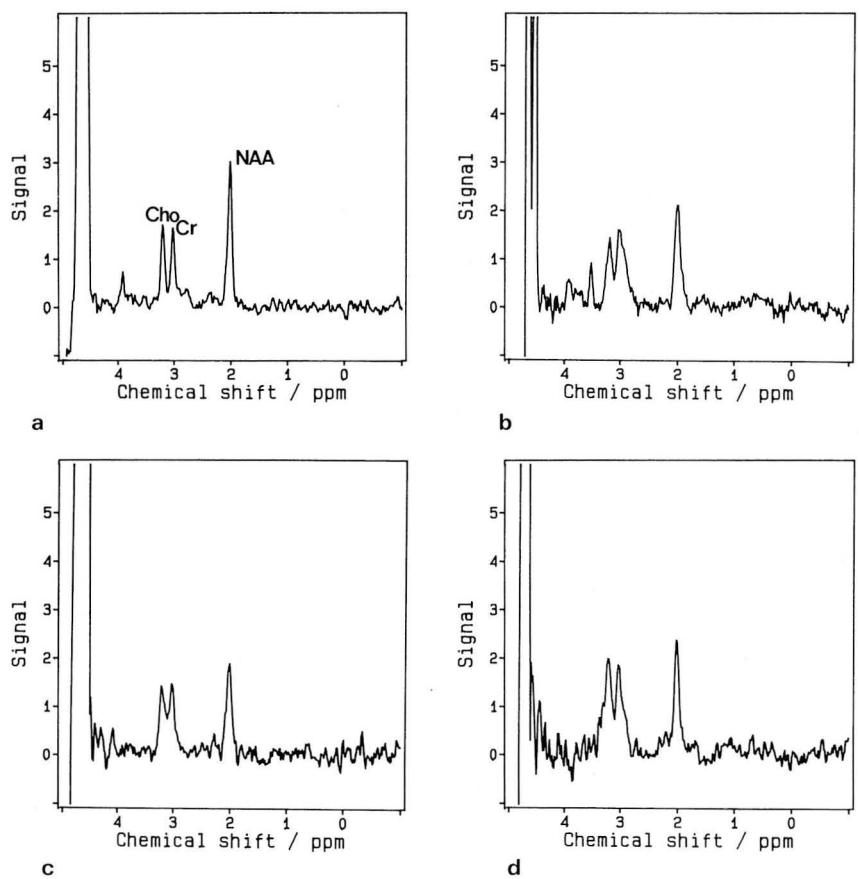

Fig. 2. *In vivo* ^{1}H MR spectra obtained on a 1.5 T MR unit using a STEAM sequence with a TR of 2000 ms and a TE of 135 ms for a younger healthy control (a), an elderly age-matched control (b), a patient with IPD (c) and a patient with PSP (d).
NAA/Cho and NAA/Cr ratios of (a) are higher than those of (b), (c) and (d). Although mean NAA/Cho and NAA/Cr ratios of PSP groups are statistically lower than those of IPD group, the metabolite ratios in (b) appear to be similar to those of (c) and (d).

Table 1. Mean Values of Metabolite Ratios in Striata in Control Subjects and Patients with IPD and PSP

mean(SD)

	NAA/Cr*	Cho/Cr	NAA/Cho**
Younger control			
Left(n=5)	1.85(0.12)	1.18(0.09)	1.59(0.19)
Right(n=5)	1.73(0.21)	1.14(0.20)	1.56(0.36)
Total(10/5)	1.79(0.17)	1.16(0.15)	1.57(0.27)
Age-matched control			
Left(n=5)	1.41(0.11)	1.03(0.23)	1.40(0.21)
Right(n=4)	1.31(0.15)	0.96(0.07)	1.38(0.24)
Total(9/5)	1.36(0.13)	0.99(0.17)	1.39(0.21)
IPD			
Left(n=7)	1.41(0.19)	0.94(0.07)	1.50(0.14)
Right(n=7)	1.36(0.20)	0.99(0.21)	1.40(0.24)
Total(14/7)	1.38(0.19)	0.96(0.15)	1.45(0.20)
PSP			
Left(n=10)	1.33(0.29)	1.09(0.21)	1.24(0.24)
Right(n=10)	1.19(0.13)	1.07(0.32)	1.18(0.29)
Total(20/10)	1.26(0.23)	1.08(0.26)	1.21(0.26)

STEAM sequence (TR/TE = 2000/135 ms) is used for all spectra. *$p<0.006$ for PSP vs. IPD **$p<0.003$ for PSP vs. IPD
The values are based on the peak heights of resonances. Student unpaired t-test is used for the statistical analysis.
IPD=idiopathic parkinson's disease PSP=progressive supranuclear palsy

neurodegenerative causes of parkinsonism and often show no abnormality. Parkinson-plus syndromes may show low signal intensity in the putamen and SNpc on T2-weighted MR images, indicating iron deposit (7, 8, 10). Such a low striatal signal, however, can also be seen in many elderly normal subjects (9). The presence of atrophy of the brainstem, cerebrum, and cerebellum may help distinguish IPD from Parkinson-plus syndrome, but is neither specific nor sensitive (10).

Clinical *in vivo* ^{1}H MRS shows promise as a tool to improve diagnostic accuracy under these conditions. A few investigations of ^{1}H MRS spectral findings have been reported (13—15). In a study by Heerschap *et al* (13), mean values of NAA/Cho and NAA/Cr ratios measured in the striatum of IPD were not significantly different from those of normal controls, as in the present study. Recently, there has been a multicenter study reporting ^{1}H MR spectra measured in the striatum of IPD patients (15) ; in that study, the combining data from all ages demonstrated no significant difference of NAA/Cho and NAA/Cr ratios between normal control subjects and IPD patients, whereas considering those in elderly age-matched patients, there was a significant decrease of NAA/Cho ratios in IPD patients compared to normal controls. These are not consistent with the results of the present study. In a study by Bowen *et al* (14), in which the metabolites were measured in the occipital lobes, NAA/Cho and NAA/Cr ratios of IPD patients were not significantly different from those of normal controls. However, the lactate/NAA ratio was described as elevated in IPD patients. Inhibition of mitochondrial electron transport and concomitant increase in free radical generation due to defects in oxidative pho- sphorylation have been suggested as a pathogenesis of dopaminergic cell loss in IPD. Bowen *et al* (14) interpreted a significant increase of the lactate/NAA ratio in the occipital lobes of IPD patients as a consequence of impairment of oxidative phosphorylation. However, in the present study we did not observe an increase of lactate in the basal ganglia in either the control or parkinsonian patients. No detection of lactate signal in the present study might be due to use of the STEAM sequence with a TE of 135 ms, in which J-modulation of lactate reduces its signal intensity. However, other group also did not observe increased lactate levels in a recent ^{1}H MRS study on IPD patients (15). Further investigations are needed for the detection of lactate signal in IPD patients.

In our present study, the mean values of NAA/Cr and NAA/Cho ratios of the elderly age-matched control subjects and the patients with IPD and PSP are slightly lower than those of the published data (13, 15). The difference is probably caused by differing measurement parameters including repetition time, echo time, pulse sequence (double spin echo or STEAM), and post-processing including calculation of peak areas versus peak heights.

Our data showing that NAA/Cr and NAA/Cho ratios were lower in older than in younger controls suggest that neuronal cells in the striatum of healthy subjects decrease with aging. This is consistent with the diffuse brain atrophy with the aging process. To our knowledge, there has been no report in the literature that NAA/Cr and NAA/Cho ratios are lower in PSP than in

IPD patients. That result in the present study is in agreement with the hypothesis that there is more loss of neuronal cells in the striatum of PSP patients. Decreased NAA/Cho and NAA/Cr ratios in PSP might be due to decreased NAA or alternatively due to increased Cho and Cr. Absolute quantitation of the metabolites would resolve the question. However, the age difference between IPD and PSP (mean ages : 60 and 68) may also contribute to the difference, and will need to be further pursued.

In conclusion, mean values of NAA/Cho and NAA/Cr ratios in the striatum were lower in PSP than in the age-matched controls and IPD, whereas those rations were not different between the age-matched controls and IPD. These results support the hypothesis that there is more loss of neuronal cells in the striatum in PSP than in IPD. Thus, ^{1}H MRS measurement of NAA, Cho and Cr, and their ratios may be of help in differentiating PSP from IPD.

REFERENCES

1. Fahn S. *Parkinsonism.* In : Rowland LP Ed. *Merritt's Textbook of Neurology*. 9th Ed. Baltimore ; Wiiliams & Wilkins. **1995** : 713-730
2. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease - A clinico-pathological study of 100 cases. *J Neurol Neurosug Psychiatry* **1992** ; 55 : 181-184.
3. Steele JC, Richardson JC, Olszewski J. Progressive supranuclear palsy : a heterogeneous degeneration involving the brainstem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia and dementia. *Arch Neurol* **1964** ; 10 : 333-359.
4. Golbe LI, Davis PH, Schoenberg BS, et al. Prevalence and natural history of progressive supranuclear palsy. *Neurology* **1988** ; 38 : 1031-1034.
5. Maher ER, Lees AJ. The clinical features and natural history of Steele-Richardson-Olszewski disease (progressive supranuclear palsy). *Neurology* **1986** ; 36 : 1005-1008.
6. Young AB. Progressive supranuclear palsy : postmortem chemical analysis. *Ann Neurol* **1985** ; 18 : 521-522.
7. Drayer BP, Olanow W, Burger P, et al. Parkinson plus syndrome : diagnosis using high field MR imaging of brain iron. *Radiology* **1989** ; 159 : 493-498.
8. Stern MB, Braffman BH, Skolnick BE, et al. Magnetic resonance imaging in Parkinson's disease and parkinsonian syndromes. *Neurology* **1989** ; 39 : 1524-1526.
9. Drayer BP. Imaging of the aging brain : part I. normal findings. *Radiology* **1988** ; 166 : 785-796.
10. Savoiardo M, Strada L, Girotti F, et al. MR imaging in progressive supranuclear palsy and Shy-Drager syndrome. *J Comput Assist Tomogr* **1989** ; 13 : 555-560.
11. Brooks DJ, Ibanez V, Sawle G, et al. Differing patterns of stiatal 18F fluorodopa uptake in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. *Ann Neurol* **1990** ; 28 : 547-555.
12. Langston JW, Widner H, Goetz CG, Brooks D, Fahn S, Freeman T, Watts R. Core assessment program for intracerebral transplantation(CAPIT). *Mov Disord* **1992** ; 7 : 2-13.
13. Heerschap A, Zijlmans JCM, Koster A, Boogert HJ, Thijssen HOM, Horstink HWIM. Proton MR spectroscopy of the striatum in patients with Parkinson's disease. *Abstract Book SMRM,* 11th Annual Meeting, Berlin, **1992** ; 1949
14. Bowen BC, Block RE, Snachez-Ramos J, et al. Proton MR spectroscopy of the brain in 14 patients with Parkinson disease. *AJNR* **1995** ; 16 : 61-68
15. Holshouser BA, Komu M, Moller HE, et al. Localized proton NMR spectroscopy in the striatum of patients with idiopathic Parkinson's disease : A multicenter pilot study. *Magn Reson Med* **1995** ; 33 ; 589-594

Journal of the Korean Radiological Society 1996 ; 34(6) : 711~716

대 한 방 사 선 의 학 회 지 1996 ; 34(6) : 711~716

파킨슨병과 진행성 핵상마비에서의 ^{1}H자기공명분광법 : 예비 연구[1]

[1]서울대학교 의과대학 방사선과학교실, [2]신경학교실
[3]서울대학교 의과대학 의공학교실, [4]자연과학대학 미생물학과 생물물리학실

장기현 · 전범석[2] · 송인찬[3,4] · 김동성 · 민관홍 · 한문희 · 강사욱[4] · 민병구[3] · 한만청

목 적 : ^{1}H자기공명분광법 (^{1}H MR Spectroscopy, MRS)에 의해 측정된 대사물질의 상대적 농도비가 특발성 파킨슨병 (idiopathic Parkinson's disease)과 진행성 핵상마비(progressive supranuclear palsy)를 감별하는데 유용한 가를 알고자 하였다.

대상 및 방법 : 1.5 T 자기공명영상기에서 7명의 특발성 파킨슨병 환자와 8명의 진행성 핵상마비 환자를 대상으로 STEAM 시퀀스 (TR/TE=2000/135 ms)를 사용하여 ^{1}H MRS를 시행하였다. 환자군과 동일한 나이대에 속하는 5명 (평균 연령 : 63세)과 건강한 청년 5명(평균 연령 : 30세)을 정상 대조군으로서 동일한 ^{1}H MRS를 시행하였다. 측정 대상 부위는 피각 (putamen)과 담창구 (globus pallidus)를 포함하는 기저핵으로서 그 크기는 2×2×2cm이었다. 각 대사물질 (N-acetyl aspartate=NAA, choline=Cho, creatine=Cr, lactate)의 스펙트럼을 측정한 후, 이들 최고치의 농도비 즉, NAA/Cr, NAA/Cho, Cho/Cr 및 lactate의 상대적 스펙트럼 최고치를 4 군간에 비교, 평가하였다.

결 과 : NAA/Cho 및 NAA/Cr 비가 파킨슨병 환자군보다 진행성 핵상마비 환자군에 있어서 통계적으로 유의하게 낮았다 (1.21 ± 0.26 대 1.45 ± 0.20 및 1.26 ± 0.23 대 1.38 ± 0.19, $p<0.05$). 또한, 환자군과 동일한 나이대에 속하는 정상군이 건강한 청년군보다 NAA/Cho 및 NAA/Cr 비가 통계적으로 유의하게 낮았다 (1.39 ± 0.21 대 1.76 ± 0.15 및 1.36 ± 0.13 대 1.79 ± 0.17, $p<0.05$). 그러나, 파킨슨병 환자군과 그와 동일한 나이대에 속하는 정상군간의 NAA/Cho 및 NAA/Cr 비의 차이는 통계적으로 유의하지 않았다 ($p>0.05$). Cho/Cr 비는 4개의 군에서 통계적으로 유의하게 차이가 없었다. Lactate는 모든 대상에서 관찰되지 않았다.

결 론 : 기저핵에서의 NAA/Cho 및 NAA/Cr 비가 파킨슨병 환자와 그와 동일한 나이대의 정상군보다 진행성 핵상마비 환자군에서 통계적으로 더 유의하게 낮았다. 이러한 결과는 기저핵에서의 신경세포의 손실이 파킨슨병 환자군보다 진행성 핵상마비 환자군에 있어서 더 크다는 것을 시사한다. 그러므로, NAA/Cho 및 NAA/Cr 비는 파킨슨병과 진행성 핵상마비의 감별에 도움을 줄 수 있을 것으로 생각한다.