



Neurometabolic Improvement in Parkinson's Disease after Stereotactic Functional Neurosurgery by Follow-up MR Spectroscopy

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Abstract : PURPOSE - To investigate neurometabolism from the brain destructive lesions and striatal putamen-pallidus regions to the clinically worst side in patients with Parkinson's disease after stereotactic functional neurosurgery. METHODS - Using proton magnetic resonance spectroscopy (^1H MRS), fifteen patients (7 males and 8 females; mean age 56.5 years; age range 43-67 years) with Parkinson's disease (PD) were studied to measure N-acetylaspartate (NAA), creatine (Cr), choline-containing compounds (Cho) and lactate (Lac) levels on the neurosurgical lesions of thalamus, globus pallidus and striatal putamen-pallidus regions in a brain. RESULTS - Brain destructive lesion and striatal putamen-pallidus region in PD compared with controls were highly and significantly related to NAA/Cho ratios reduction, respectively ($P = 0.002$, $P = 0.04$), but showed no difference from the same regions of PD prior to neurosurgery ($P = 0.06$, $P = 0.77$). Increased lactate peaks at 1.3 ppm were present in all the cerebral lesions, and these resonances were confirmed at a long TE = 136 ms, indicating that these signals distinguished from lipids. CONCLUSIONS - Our results suggest that NAA/Cho ratios may provide as a neurometabolite marker for neurochemical changes in brain surgical lesion, and the ratios might be related to functional change of neuropathophysiological status in the striatal putamen-pallidus region of PD. Increase of lactate signals, being remarkable in surgical lesions, could be consistent with a common consequence of surgical necrosis. Therefore, MR spectroscopy could be a sensitive diagnostic tool in monitoring neurometabolic changes in PD with neurosurgical treatment.

Key words: Parkinson's disease (PD); Stereotactic functional neurosurgery; Neurometabolism; Proton magnetic resonance spectroscopy (^1H MRS).

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INTRODUCTION

Idiopathic Parkinson's disease (PD) is a progressive neurodegenerative disease of the extrapyramidal system that is clinically characterized by akinesia, rigidity, and tremor. The pathological process of PD involves the degeneration of dopaminergic neurons in the substantia nigra and their axon terminals in striatum, leading to a reduction of striatal dopamine. Deficiency of the neurotransmitter dopamine seems central in accounting for the attending motor symptoms. Levodopa treatment is very effective initially, but after long-term therapy with this drug, there is often a shortening of efficacy and closely dose-related motor fluctuations.

Recently, there has been increasing interest in the stereotactic functional neurosurgery of PD.¹⁻⁵ This interest has been prompted by recognition of the limitations of pharmacotherapy (i.e., levodopa) for PD, and introduction of MR imaging and the use of microelectrode recording techniques have improved the safety and accuracy of surgical treatment. Deep-brain electrical stimulation lesioning (or disruption) of a ventral intermediate nucleus of the thalamus (thalamotomy) or an internal segment of the globus pallidus (pallidotomy) represents a treatment for PD patient whose symptoms are not well-controlled by the drug therapy. These neurosurgical procedures are associated with a striking improvement obtained with surgical lesions in contralateral akinesia, rigidity, and tremor.⁶⁻⁸

Proton magnetic resonance spectroscopy (¹H MRS) has been used in the study of PD localized the volume of interests involving putamen, globus pallidus, substantia nigra and cerebellar cortex.⁹⁻¹² The issues of these studies were to evaluate the role of N-acetylaspartate (NAA)/choline-containing compound (Cho) ratios in relation to monitoring the striatal effects of levodopa or dopamine therapy in PD, or whether there was a significant correlation between neurometabolite ratios and the clinical assessment in PD. To our knowledge, no previous studies have been performed evaluation for neurometabolic changes in the basal ganglia structures of PD with stereotactic functional treatment, although MRI findings were reported to evaluate the temporal evolution and appearance of a radiosurgery lesion and the clinical response in PD undergoing radiosurgical treatments.¹³ Biochemical information about local cellular neurometabolism within the basal ganglia may have important implications concerning neuropathophysiological status in relation to a clinically striking improvement in PD. Therefore, the purpose of present study is to investigate whether there are significant neurometabolic changes in brain destructive lesion to the most clinically affected side in PD, and whether there are neurometabolite markers to indicate a functional change of striatal putamen-pallidus region after neurosurgical thalamotomy or pallidotomy.

MATERIALS AND METHOD

Subjects

During the period from August 2001 to May 2003, patients with Parkinson's disease were recruited from the Neurologic Clinics at Kangnam St. Mary's Hospital. Fifteen patients with Parkinson's disease of mean age 56.5 years (7 males and 8 females; age range 43-67 years) and mean disease duration 7.7 years (range 4-13 years) underwent stereotactic functional neurosurgery (Leksell, Model G). Patients usually sought treatment when pharmacotherapy became ineffective or the slowly progressive disability resulting from their severe symptoms interfered with activities of daily living (especially feeding, dressing and hand-writing).

According to the neurosurgical procedures utilized in the treatment of PD, five patients with tremor-dominant PD underwent MR-guided stereotactic functional thalamotomy, and ten patients with bradykinesia and rigidity-dominant PD underwent MR-guided stereotactic functional pallidotomy. Thalamotomy, in which a destructive lesion is made within the ventral intermediate nucleus of the thalamus (TH_{vim}), is the surgery of choice for treating medically essential tremor. Pallidotomy is the surgical lesioning of an internal segment of the globus pallidus (GPi), situated near the thalamus. Electrical stimulation through implanted deep-brain electrodes was then performed as a reversible and adjustable treatment method. Although the mechanism through which electrical stimulation acts is not understood, the striking improvement in the clinical effects obtained with surgical lesions. Each patient was diagnosed with Parkinson's disease by neurologists using criteria of the United Kingdom Parkinson's Disease Society Brain Bank¹⁴ 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 patients and controls. Further clinical assessments of PD patients are shown in Table 1.

Fifteen age-matched controls with mean age 54.8 years (6 males and 9 females; age range 39-64 years) were also examined. None of the subjects in the control group had neurologic disease or structural lesions involving the basal ganglia.

MR Imaging

All MR imaging examinations were performed on a clinical 1.5 T imaging unit (GE Signa Advantage, Version 4.8; GE Medical System, Milwaukee, WI) with a standard quadrature birdcage head coil. T2-weighted MR images (TR 2500 ms; TE 90 ms) obtained in each patient prior to neurosurgery, and all patients also underwent additional routine MR studies after approximately 2 weeks from stereotactic neurosurgery treatment. The images of the PD patients showed a mild focal hyperintensity surrounding edema in the expected location after thalamotomy or pallidotomy. The lesion presumably represents electrical neurosurgical necrosis, and this pattern of edema in the surgical area was seen in all PD patients.

Table 1. Clinical details of fifteen Parkinson's disease patients with severe symptoms

Patient no.	Age (yr)	Duration (yr)	Asymmetry	Signs	Therapy
1	56	6	Rt > Lt	TR, BK, R	TM
2	61	8	Lt > Rt	TR, R	
3	62	13	Lt > Rt	TR, BK, R	
4	62	6	Rt > Lt	TR, BK	
5	54	5	Rt > Lt	TR, BK	
6	57	8	Lt > Rt	R, BK	PD
7	59	7	Rt > Lt	R, BK, TR	
8	67	13	Rt > Lt	R, BK	
9	58	7	Lt > Rt		
10	64	10	Lt > Rt		
11	59	6	Lt > Rt		
12	59	9	Lt > Rt		
13	43	4	Lt > Rt		
14	49	6	Rt > Lt		
15	54	7	Lt > Rt		

Note. Lt = left; Rt = right; BK = Bradykinesia; R = rigidity; TR = tremor; TM = thalamotomy; PD = pallidotomy.

MR Spectroscopy

In vivo ^1H MRS studies were performed at localized single voxels (8mL) centered on the region of interest of THvm or GPi and striatal putamen-pallidus related to the clinical symptomatic side in PD both before and after stereotactic neurosurgical treatment. The stimulated-echo acquisition mode (STEAM)^{15,16} was used with TR 2000 ms, TE 20 ms, data points of 2048, spectral bandwidth of 2500 Hz, and acquisition averages of 128. The shim procedure was performed for optimizing the magnetic field homogeneity over the entire volume of interest detected by the receiver coil and focused on the water signal. After auto-prescan, typical line width (full width at half maximum; FWHM) was usually 3 to 4 Hz. ^1H MRS spectra were obtained from the regions of interest within the basal ganglia of each subject both before and after functional neurosurgery. Raw data were transferred to a Sun SPARC station IPC (Sun Micro System, Mountains View, CA) and processed by SAGE data

analysis package (GE Medical System, Milwaukee, WI).

Data were postprocessed using zerofilling to 4K, apodization filtering to improve either SNR or resolution and/or reduce truncation artifacts. Fourier transformation and zero order phase correction, phased absorption spectra were obtained directly with baseline corrections or resolution enhancement. Peak areas were obtained from the spectra by employing the Marquardt algorithm to fit a series of Lorentzian lines.¹⁷ Proton resonances in the spectra were assigned on the basis of prior assignments.¹⁸ Resonance peak assignments of major *in vivo* ¹H MRS observable neurometabolites were NAA of 2.00 ppm; Cr of 3.00 ppm; Cho of 3.20 ppm; Glu and GABA (Glx) of 2.35, 2.25 ppm; Ins of 3.50 ppm; Lactate of 1.30 ppm. Estimation of the absolute levels of these neurometabolites was customarily expressed by the peak integral of the corresponding resonances relative to that of Cr as a reference.¹⁹ Results were expressed as mean±SD of NAA/Cho, NAA/Cr, Cho/Cr, Glx/Cr, Ins/Cr, and Lac/Cr ratios as previously described.

To confirm lactate signal, distinguishing them from liquids, water-suppressed a point resolved spectroscopy (PRESS) sequence with a long TE, 136 ms was used to obtain localized spectra from surgical lesioning in PD.

Statistics

Statistical analysis was performed using SPSS (SPSS for Windows, Version 6.0, SPSS Inc., Chicago, IL). The data were analyzed with student's paired-samples *t*-test for comparison of neurometabolite ratios between PD patients and age-matched controls both before and after stereotactic neurosurgical treatment, where at the *P* < 0.05 level, the two means are significantly different.

RESULTS

MR images obtained approximately 2 weeks after thalamotomy or pallidotomy treatment showed the mildly hyperintense surgical lesion surrounded by extensive edema. Fig. 1 shows typical T2-weighted axial MR image (A) and corresponding spectrum (B) in brain surgical destructive lesion of thalamus nucleus of Parkinson's disease patients with neurosurgical thalamotomy treatment, selected for *in vivo* ¹H MRS. And, Fig. 2 shows typical T2-weighted axial MR image (A) and corresponding spectrum (B) in brain surgical destructive lesion of putamen-pallidus of Parkinson's disease patients with neurosurgical thalamotomy treatment, selected for *in vivo* ¹H MRS. The typical spectra obtained from the destructive lesion and striatal putamen-pallidus region to the clinical symptomatic side in PD.

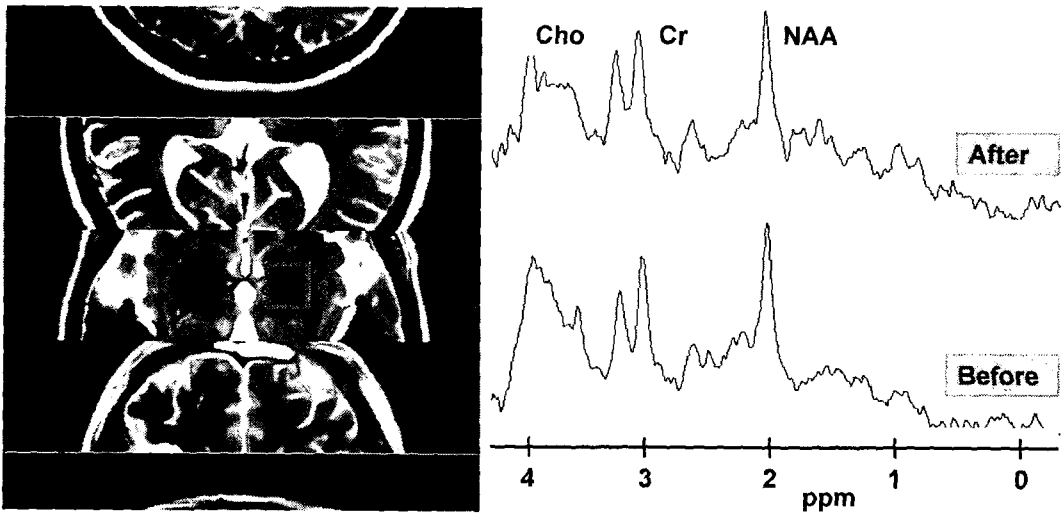


Fig. 1. Typical T2-weighted axial MR image (A) and corresponding spectrum (B) in brain surgical destructive lesion of thalamus nucleus of Parkinson's disease patients with neurosurgical thalamotomy treatment, selected for *in vivo* ^1H MRS.

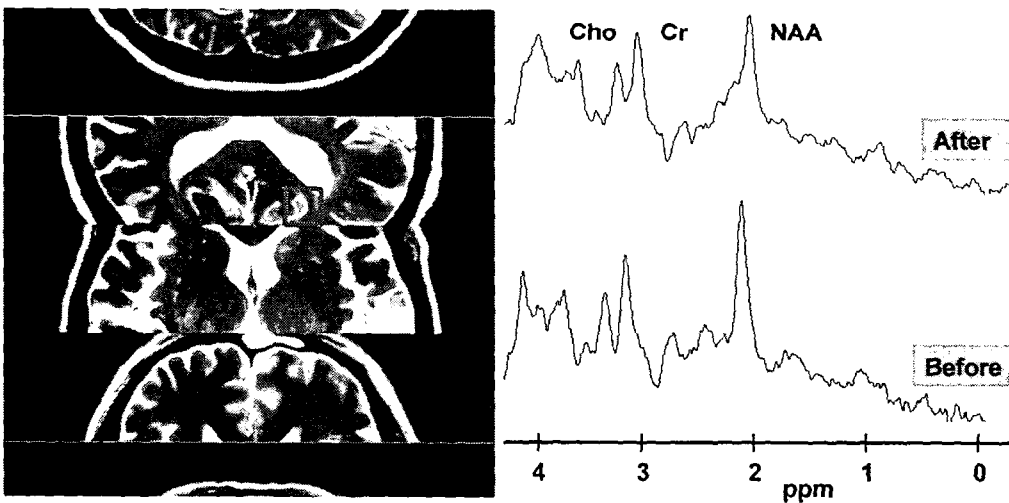


Fig. 2. Typical T2-weighted axial MR image (A) and corresponding spectrum (B) in brain surgical destructive lesion of putamen-pallidus of Parkinson's disease patients with neurosurgical thalamotomy treatment, selected for *in vivo* ^1H MRS.

Table 2. Mean metabolite ratios from a part of thalamus region to the most affected clinically in PD patients compared with age-matched controls both before and after stereotatic functional neurosurgery.

Metabolite Ratio	Control (n = 15)*	Before (n = 15)*	After (n = 15)*	P ¹ Value	P ² Value
NAA/Cho	1.86 ± 0.48	1.54 ± 0.29	1.27 ± 0.32	0.06	0.002 [†]
NAA/Cr	1.28 ± 0.25	1.24 ± 0.17	1.16 ± 0.27	0.67	0.31
Cho/Cr	0.72 ± 0.18	0.85 ± 0.21	0.92 ± 0.27	0.14	0.07
Glx/Cr	0.73 ± 0.27	0.67 ± 0.25	0.67 ± 0.23	0.58	0.59
Ins/Cr	0.65 ± 0.15	0.77 ± 0.29	0.76 ± 0.31	0.28	0.34
Lac/Cr			1.62 ± 1.06		

Note. NAA = N-acetylaspartate, Cr = creatine, Cho = choline-containing compounds, Glx = sum of the GABA and Glutamate, Ins = myo-inositol, Lac = lactate.

* Ratios are given as the mean ± SD. P¹ and P² are significant level between PD before and after, and age-matched controls.

[†] Statistical significance determined by using the student's paired-samples *t*-tests for PD patients compared with controls, where P < 0.05 was considered significant.

Table 3. Mean metabolite ratios from striatal putamen-pallidus region related to the clinical symptomatic side in PD patients compared with age-matched controls both before and after stereotatic functional neurosurgery.

Metabolite Ratio	Control (n = 15)*	Before (n = 15)*	After (n = 15)*	P ¹ Value	P ² Value
NAA/Cho	1.92 ± 0.56	1.85 ± 0.56	1.44 ± 0.55	0.77	0.04 [†]
NAA/Cr	1.36 ± 0.28	1.41 ± 0.28	1.18 ± 0.37	0.68	0.24
Cho/Cr	0.75 ± 0.24	0.83 ± 0.29	0.92 ± 0.55	0.51	0.44
Glx/Cr	0.80 ± 0.27	0.69 ± 0.22	0.67 ± 0.18	0.21	0.09
Ins/Cr	0.62 ± 0.19	0.67 ± 0.29	0.55 ± 0.17	0.83	0.24

Note. * Ratios are given as the mean ± SD, and P¹ and P² are significant level between PD before and after, and age-matched controls.

[†] Statistical significance determined by using the student's paired-samples *t*-tests for PD patients compared with controls, where P < 0.05 was considered significant.

Tables 2 and 3 show the results of mean neurometabolite ratios for PD compared with age-matched controls. The patient data includes spectra acquired from patients both before and after neurosurgical treatment. Especially, no significant difference between any of neurometabolite ratios of PD prior to neurosurgery and those of controls was statistically established.

Mean NAA/Cho ratios from brain destructive lesion to the most affected side clinically in PD were highly and significantly reduced compared with controls ($P = 0.002$), but did not reach statistical significance before thalamotomy or pallidotomy treatment ($P = 0.06$). There was a lower but nonsignificant NAA/Cr ratio from the brain lesion in PD compared with controls both before and after ($P = 0.67$, $P = 0.31$). The mean Cho/Cr ratios did not also differ significantly in PD and controls both after and before, but tended toward significant increase from the surgical destructive lesion in PD after ($P = 0.14$, $P = 0.07$).

Increased Lac/Cr ratios in all PD patients were observed from the neurosurgical lesion surrounded by focal hyperintense edema (1.62 ± 1.06). Moreover, these resonances were confirmed at a long TE value, indicating that these signals distinguished from lipids. However, lactate signal was not found in the patient group prior to neurosurgery and the control group. In addition, no significant alterations of other neurometabolite ratios such as Ins/Cr and Glx/Cr were established.

After neurosurgical thalamotomy or pallidotomy, the mean NAA/Cho ratios from brain striatal putamen-pallidus region to the most clinically worst side in PD showed significantly lower value compared with controls ($P=0.04$), although no differences in NAA/Cho ratios between PD and controls were not significant before ($P=0.77$). There was no significant difference of NAA/Cr ratios from striatal putamen-pallidus region in PD compared with controls both before and after ($P=0.68$, $P=0.24$). Also, the mean Cho/Cr ratios from PD and controls did not show any statistical significance both before and after ($P=0.51$, $P=0.44$).

Lac/Cr ratio was measured from striatal putamen-pallidus region in PD and age-matched controls both before and after neurosurgical treatment. In addition, no significant alterations of other neurometabolite ratios such as Ins/Cr and Glx/Cr were established.

DISCUSSION

The establishment of a model of Parkinsonism through the administration of MPTP to nonhuman primates (i.e., monkeys) has provided important insights into new therapeutic strategies.^{20,21} A typical Parkinsonian syndrome develops in the animals characterized by dopaminergic cell loss in the substantia nigra and striking abnormalities in the spontaneous activity and sensorimotor responses of neurons in the basal ganglia.²² The striatum receives inputs from the sensorimotor cortex. Direct and indirect pathways from the striatum go to the GPi and the pars reticulata of the substantia nigra and have opposing effects on movement in the normal, non-dopamine deficient state. In Parkinson's disease, dysfunction

of these pathways is thought to lead to excessive inhibition and effectively, to a shutdown of the thalamic nuclei that receive their outflow. The excessive thalamic inhibition leads to suppression of the cortical motor system, possibly resulting in akinesia, rigidity, and tremor that characterize the clinical disorder.²³ The putamen is thus the main striatal component of the motor circuitry between the cerebral cortex, basal ganglia, and thalamus. Therefore, the stereotactic functional neurosurgical procedures, thalamotomy or pallidotomy, may be associated with an increased activation of premotor cortexes in a more nearly normal state, and thus, may result in the striking improvement of clinical effects obtained with surgical lesions in parkinsonism.^{1,2} For this reason, it is important to examine a more understanding of neuropathophysiological status in surgical destructive lesion and striatal putamen-pallidus region of PD with the treatment by ¹H MRS.

Proton MR spectroscopy techniques have been also used to evaluate important proton neurometabolites in localized the volume of interest to the basal ganglia of PD.¹⁰⁻¹² To our knowledge, this is the first study concerning in neurometabolic changes of brain surgical destructive lesion and striatal putamen-pallidus region related to the clinical symptomatic side in PD with functional treatment.

The results of this study indicate that NAA/Cho ratios from surgical disrupted lesion and striatal putamen-pallidus region are significantly reduced in patients with PD compared with age-matched controls but not prior to neurosurgery. This reflects that MRS may be sensitive enough to detect functional change of neuropathophysiological status in PD with neurosurgical treatment.

A significant reduction (32 %) of NAA/Cho ratio was observed from brain surgical lesion to the clinical symptomatic side in PD compared with controls. Although NAA/Cr ratio was lower than normal controls, it did not show any significant difference, and Cho/Cr ratio tended toward significant increase from the brain lesion in PD compared with controls. In our quantitative analysis of the data from all patients and controls, the estimation of the absolute levels of neurometabolites was expressed by the peak integral of the corresponding resonances relative to Cr as a reference. The Cr peak was relatively considered to have the most consistent level under various physiological and pathological conditions, and has been also utilized as an internal standard in the previous study on basal ganglia.¹⁹ Thus, our MRS findings may interpret carefully that both NAA and Cho are affected by surgical lesioning process during brain-deep electrical stimulation, and it is likely this combination that allows the significant difference to be detected. NAA is an amino acid confined in the brain only to neurons and axons, and usually considered as a marker of neuronal integrity.²⁴⁻²⁹ Usually, decreased NAA has been associated with injury and neuronal death in both animal and human studies.^{27, 28, 30-33} The Cho signal reflects phospholipid metabolites and may represent neuronal membrane integrity, which may be altered in membrane synthesis and degradation.^{34, 35} Hence, the reduced NAA/Cr ratios may reflect a slight neuronal loss (10 %), and elevated Cho/Cr ratios (28 %) may indicate considerable membrane alterations or possible functional change of Cho metabolism in brain destructive lesion. Therefore,

significance of NAA/Cho ratios may be caused by contrastive changes between NAA/Cr and Cho/Cr ratios. There might be neurometabolite alterations to reflect highly reduction in NAA/Cho level upon MRS examination, and that NAA/Cho ratios may provide a neurometabolite marker in neurochemical changes of the brain surgical destructive lesion in PD.

Having a concentration of about 1mM, lactate is not usually seen in the spectra of normal brain. Lactate has been detected in patients with stroke,³⁶⁻³⁸ some brain tumors, hypoxia, anoxia, and mitochondrial encephalopathies.³⁹⁻⁴¹ It has been observed to increase in the epileptic focus immediately following a seizure.⁴² Recently, there was a report of increased cerebral lactate derived from occipital lobe in PD patients.⁹ In our results, however, lactate signal was not found from brain thalamus or globus pallidus region in the patient group prior to neurosurgery and the control group. This finding is also consistent with several investigations, which no lactate was observed in substantia nigra, thalamus, globus pallidus, and the striatum in a large number of PD patients.¹⁰⁻¹²

On MR images obtained about 2 weeks after thalamotomy or pallidotomy, the most common appearance of the surgical lesion showed a mild hyperintensity surrounded by a halo of edema. This appearance presumably represents a tissue necrosis due to electrical stimulation-induced vasogenic edema. Remarkable Lac/Cr ratio was observed from focal hyperintense edema in the brain lesion to the most affected side clinically in PD. This lactate signal was also confirmed through its typical structure by using a long TE sequence. Therefore, the presence of lactate could be generally consistent with a common consequence of neurosurgical necrosis caused by vasogenic edema. This finding would occur from the destructive tissue regardless of etiology, and are not surprising response to cellular necrosis.

Using ¹H MRS, the previous studies found that NAA/Cho ratio from cerebral striatum was significantly reduced in untreated PD but not in levodopa-treated PD patients compared with age-matched controls.¹⁰⁻¹² They did not observe significant differences of other neurometabolite ratios such as NAA/Cr and Cho/Cr ratios in untreated and levodopa-treated PD. Therefore, NAA/Cho ratio was normal in levodopa-treated PD. And, we suggest that NAA/Cho ratio may be affected by levodopa treatment and provide a reversible marker of neuronal dysfunction in the striatum. In addition, other studies with positron emission tomography (PET) have also shown that the reversal of akinesia with dopaminergic drugs (i.e., levodopa) is associated with an increase in the activity of the abnormally depressed supplementary motor and premotor cortex,⁴³ areas involved in the initiation of movement. Our observation supported that NAA/Cho ratio from striatal putamen-pallidus region did not be statistically significant in levodopa-treated PD prior to neurosurgery and age-matched controls, and there were no differences comparing NAA/Cr and Cho/Cr ratios from the region spectra obtained.

After neurosurgical thalamotomy or pallidotomy, however, NAA/Cho ratio from striatal putamen-pallidus region to the clinical symptomatic side in PD statistically showed a significant reduction (25%) from age-matched controls, while NAA/Cr and Cho/Cr ratios

were not significantly different. As the Cr peak was considered to have relatively stable level under various pathophysiological conditions, NAA/Cho ratio may interpret cautiously that the combinative changes of both NAA and Cho allows likely the significant difference to be detected. Hence, reduced NAA/Cr and elevated Cho/Cr ratios may reflect a slight neuronal loss (13 %) and possible alterations of Cho metabolism (23%), which might indicate functional change in the striatal putamen-pallidus region of PD. Significant NAA/Cho ratio caused by contrastive changes between NAA/Cr and Cho/Cr ratios may provide as a neurometabolite marker in neurochemical changes, and this ratio might indicate functional change of neuropathophysiological status associated with the striking improvement of clinical effects obtained with surgical lesioning in PD. Therefore, our present result suggests that NAA/Cho ratios may be a valuable criterion for evaluation of PD because the ratios may be related to the brain surgical lesion and striatal putamen-pallidus region to the most affected clinically. MR spectroscopy may be a more sensitive diagnostic tool in monitoring significant neurometabolic changes in patients with PD.

CONCLUSION

Our results suggest that NAA/Cho ratio may provide a neurometabolite marker for neurochemical changes in the brain destructive lesion to the clinical symptomatic side of PD, and could be a valuable finding for evaluation of PD with stereotactic functional treatment. Moreover, significantly reduced NAA/Cho ratio might be related to functional change in striatal putamen-pallidus region of PD after neurosurgery. Increase of lactate signal, being remarkable in surgical lesions, could be consistent with a common consequence of surgical necrosis induced by vasogenic edema. Therefore, these all findings support that proton MRS could be a useful modality to evaluate the diagnostic implications for PD.

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