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Metabolic Changes in Patients with Parkinson's Disease after Stereotactic Neurosurgery by Follow-up 1H MR Spectroscopy

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Abstract Authors investigated neuronal changes of local cellular metabolism in the cerebral lesions of Parkinsonian symptomatic side between before and after stereotactic neurosurgery by follow-up 1H magnetic resonance spectroscopy (MRS). Patients with Parkinson's disease (PD) (n = 15) and age-matched normal controls (n = 15) underwent MRS examinations using a stimulated echo acquisition mode (STEAM) pulse sequence that provided 2x2x2 cm3 (8ml) volume of interest in the regions of substantia nigra, thalamus, and lentiform nucleus. Spectral parameters were 20 ms TE, 2000 ms TR, 128 averages, 2500 Hz spectral width, and 2048 data points. Raw data were processed by the SAGE data analysis package (GE Medical Systems). Peak areas of N-acetylaspartate (NAA), creatine (Cr), choline-containing compounds (Cho), inositols (Ins), and the sum (Glx) of glutamate and GABA were calculated by means of fitting the spectrum to a summation of Lorentzian curves using Marquardt algorithm. After blindly processed, we evaluated neuronal alterations of observable metabolite ratios between before and after stereotactic neurosurgery using Pearson product-moment analysis (SPSS, Ver. 6.0). A significant reduction of NAA/Cho ratio was observed in the cerebral lesion in substantia nigra of PD patient related to the symptomatic side after neurosurgery (P = 0.03). In thalamus, NAA/Cho ratio was also significantly decreased in the cerebral lesion including the electrode-surgical region (P = 0.03). A significant reduction of NAA/Cho ratio in lentiform nucleus was not oberved, but tended toward significant reduction after neurosurgery (P = 0.08). In particular, remarkable lactate signal was noted from the surgical thalamic lesions of 6 among 8 patients and internal segments of globus pallidus of 6 among 7 patients, respectively. Significant metabolic alterations of NAA/Cho ratio might reflect functional changes of neuropathological processes in the lesion of substantia nigra, thalamus, and lentiform nucleus, and could be a valuable finding for evaluation of Parkinson's disease after neurosurgery. Increase of lactate signals, being remarkable in surgical lesions, could be consistent with a common consequence of neurosurgical necrosis. Thus, 1H MRS could be a useful modality to evaluate the diagnostic and prognostic implications for Parkinsons disease after functional neurosurgery.

Key words: Parkinsons disease (PD); magnetic resonance spectroscopy (MRS)

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INTRODUCTION

Movement disorders are neurological dysfunctions that cause abnormal and involuntary movements and postures. Most movement disorders are associated with pathologic changes in basal ganglia, which lies in the base of the brain. Parkinsons disease (PD) is a neurological syndrome manifested by the combination of tremor of the arms and legs, stiffness and rigidity, loss of postural reflexes, and slowness of movement. Degeneration of the dopaminergic neurons of substantia nigra and their axon terminals in striatum (caudate nucleus and putamen), leading to a reduction of striatal dopamine is the pathological process of this disease. Deficiency of the neurotransmitter dopamine seems central in accounting for the attending motor symptoms. Most patients with PD are treated with a combination of levodopa and carbidopa. Levodopa is used to make dopamine, the principal neurotransmitter that is deficient in PD. Carbidopa is given to block some of the side effects that can occur from levodopa. However, this therapeutic methodology 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. For this reason, surgical therapy is largely responsible for the resurgence of functional neurosurgical procedures in the treatment of this disease.[1,2] Common neurosurgical procedures available for PD include pallidotomy and thalamotomy. They involve the ablation of certain areas of the brain believed to contribute to Parkinsonian symptoms. Especially, in the pallidotomy procedure, an internal segment of the globus pallidus, a structure deep within the brain, is surgically destroyed, resulting in improved motor functioning. Pallidotomy can significantly reduce rigidity, tremor and levodopa-induced dyskinesia, and can improve mobility in medically intractable PD.[3-5] Thalamotomy, in which a destructive lesion is made within the ventral intermediate nucleus (VIM) of the thalamus, was the surgery of choice for treating medically unresponsive Parkinsonian or essential tremor.[1,6,7]

1H Magnetic Resonance Spectroscopy (MRS) is a non-invasive technique that allows the concentration of a number of cerebral metabolites to be measured *in vivo*. 1H MRS at a short echo time (TE) is able to detect metabolites with short T2 relaxation times. The major metabolites detected are N-acetylaspartate (NAA), a marker for neuronal tissue, creatine/phosphocreatine (Cr), an indicator of energy status, and choline-containing compound (Cho), a metabolite involved in membrane synthesis and degradation (8, 9). There are also several other peaks present in the proton spectrum that can assigned to important metabolites, including myo-inositols (Ins), intracellular signal transduction, and GABA, glutamine and glutamate (Glx), the metabolism of neurotransmitters. Biochemical information may be obtained about local cellular metabolism by determining peak metabolite ratios of the neurochemicals detected in the spectra.[10] These metabolite ratios may have important implications regarding the neurological disorders, namely, neurodegenerative disorders such as Huntingtons disease and Alzheimers disease.[11,12]

Recently, *in vivo* 1H MRS studies have been also used in the study of Parkinsons

disease localized the volume of interests involving the putamen, globus-pallidus, lentiform nucleus (putamen and globus-pallidus), substantia nigra, and cerebella cortex.[13-15] Using this technique, neuronal metabolic changes within the local cerebral cellular metabolism in the lesions related to the symptom side have important diagnostic and prognostic implications for PD after functional neurosurgery. Therefore, the present study investigated alterations of observable metabolite ratios concerning the neuronal metabolic changes of the local cerebral metabolism in substantia nigra, thalamus, and lentiform nucleus related to the symptomatic side in PD. Especially, this study was based on the comparison of the metabolite ratios in the lesion of Parkinson's disease by follow-up 1H MRS between before and after functional neurosurgery.

MATERIALS AND METHOD

Subjects

During the period from January 1999 to December 2001, 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 2-15 years) treated with levodopa were included.

According to the stereotactic neurosurgical procedures utilized in the treatment of PD, the patients were classified into two groups, tremor-dominant group (n = 8) for thalamotomy, and bradykinesia and rigidity-dominant group (n = 7) for pallidotomy. Each patient was diagnosed with Parkinson's disease by neurologists using criteria of the United Kingdom Parkinson's Disease Society Brain Bank (16) 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.

Fifteen age-matched controls with mean age 54.8 years (7males and 10 females; age range 39-64 years) were also examined.

1H Magnetic Resonance Spectroscopy

In vivo 1H MRS studies were performed on a 1.5T MRI/MRS system (GE Signa Advantage, Version 4.8; GE Medical System, Milwaukee, WI) with a standard quadrature birdcage head coil. Localized single voxels (2x2x2 cm3; 8mL) centered on the volume of interested lesion in substantia nigra, thalamus, and lentiform nucleus were selected using the T2-weighted MR images (TR 2500 ms; TE 90 ms). The stimulated-echo acquisition mode (STEAM) (17, 18) 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 voxels in the lesion of substantia nigra, thalamus, and lentiform nucleus related to the clinical symptomatic side of each subject in both before and after neurosurgery. It took approximately 30 minutes per case, including the total acquisition time of 1H MR spectrum. 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).

After 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.[19]. Proton resonances in the spectra were assigned on the basis of prior assignments.[20] Resonance peak assignments of major *in vivo* 1H MRS observable metabolites were CH3 of NAA, 2.00 ppm; N-CH3 of Cr, 3.00 ppm; N-(CH3)3 of Cho, 3.20 ppm; -CH2 of Glu and GABA (Glx), 2.35, 2.25 ppm; H4 and H6 of Ins, 3.50 ppm. In order to obtain the relative metabolite ratios, Cr was used as a putative reference.[21] Results are expressed as meanSD of NAA/Cho, NAA/Cr, Cho/Cr, Glx/Cr, and Ins/Cr ratios.

Follow-up MRI/MRS studies in patient with PD were performed after about two weeks from stereotactic functional neurosurgery.

Statistics

Statistical analysis was performed using SPSS (SPSS for Windows, Version 6.0, SPSS Inc., Chicago, IL). The data were analyzed with paired-samples *t*-test for comparison between PD patients and age-matched controls, and between before and after the neurosurgery, where $P<0.05$ was considered significant to account for multiple comparisons. In particular, Pearson product-moment (bivariate) analysis performed a significance of metabolite ratios in lesion of substantia nigra, thalamus, and lentiform nucleus related to the clinical symptomatic side in PD between before and after the operative.

RESULTS

On MR images obtained after neurosurgery, the most common appearance of the electrode-surgical lesions was a moderate ring-enhancing surrounded by a halo of edema.

Tables 1, 2, and 3 show the results of mean metabolite ratios for age-matched controls compared with PD patients both before and after neurosurgery. No significant difference between metabolite ratio of age-matched controls and that of patients with PD before the operative was statistically established.

Substantia nigra

Compared with before neurosurgery, a significant reduction of NAA/Cho ratio was statistically observed in the cerebral lesion of substantia nigra related to the clinical symptomatic side in PD (1.79 0.76 versus 1.34 0.39, $P=0.03$). NAA/Cr ratio also tended

Table 1. Mean metabolite ratios for examining significant differences between before and after stereotactic functional neurosurgery in substantia nigra of Parkinson disease patients.

Metabolite Ratio	Control (N=15)*	Before (N=15)*	After (N=15)*	P Value
NAA/Cho	1.54±0.48	1.79±0.76	1.34±0.39	0.03}
NAA/Cr	1.55±0.49	1.70±0.47	1.39±0.34	0.06
Cho/Cr	1.02±0.24	1.04±0.33	1.11±0.39	0.51
Glx/Cr	0.64±0.16	0.72±0.30	0.62±0.23	0.37
Ins/Cr	0.70±0.29	0.92±0.29	0.79±0.24	0.11

Table 2. Mean metabolite ratios for examining significant differences between before and after stereotactic functional neurosurgery in thalamua of Parkinson disease patients.

Metabolite Ratio	Control (N=15)*	Before (N=15)*	After (N=15)*	P Value
NAA/Cho	1.86 ±0.50	1.54 ±0.29	1.27 ±0.32	0.03}
NAA/Cr	1.28 ±0.25	1.24 ±0.17	1.16 ±0.27	0.43
Cho/Cr	0.72 ±0.18	0.85 ±0.21	0.92 ±0.27	0.48
Glx/Cr	0.73 ±0.27	0.67 ±0.25	0.67 ±0.23	0.96
Ins/Cr	0.65 ±0.15	0.77 ±0.29	0.76 ±0.31	0.93

Table 3. Mean metabolite ratios for examining significant differences between before and after stereotactic functional neurosurgery in lentiform nucleus of Parkinson disease patients.

Metabolite Ratio	Control (N=15)*	Before (N=15)*	After (N=15)*	P Value
NAA/Cho	1.82 ±0.56	1.85± 0.56	1.44 ±0.55	0.08}
NAA/Cr	1.32 ±0.28	1.41 ±0.28	1.18 ±0.37	0.12
Cho/Cr	0.77 ±0.24	0.83± 0.29	0.91 ±0.55	0.64
Glx/Cr	0.80 ±0.27	0.69± 0.22	0.67 ±0.18	0.71
Ins/Cr	0.62 ±0.19	0.67± 0.29	0.55 ±0.17	0.15

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

*Ratios are given as the mean SD.

}Statistical significance determined by using the paired-samples *t*-tests for bilateral spectra in substantia nigra of PD patients, where $P<0.05$ was considered significant.

toward significant decrease in the identical cerebral lesion (1.70 0.47 versus 1.39 0.34, P=0.06). Except for the NAA/Cho ratio, no significant alterations of other metabolite ratios such as NAA/Cr, Cho/Cr, Ins/Cr, Glx/Cr, and Lac/Cr were established in substantia nigra at short TE.

Thalamus

Compared with before neurosurgery, NAA/Cho ratio was significantly decreased in the cerebral lesion of thalamus related to the clinical symptomatic side in PD (1.54 0.29 versus 1.27 0.32, P=0.03). In particular, remarkable Lac/Cr ratio was observed from the surgical lesion in thalamus of 6 among 8 patients after stereotactic thalamotomy (1.62 1.06). However, lactate signals could not be found in the identical lesion before.

Thus, except for NAA/Cho and Lac/Cr ratio, no significant alterations of other metabolite ratios such as NAA/Cr, Ins/Cr, and Glx/Cr were established in thalamus at short TE.

Lentiform nucleus

Compared with before neurosurgery, a significant reduction of NAA/Cho ratio was not statistically observed in the cerebral lesion of lentiform nucleus related to the clinical symptomatic side in PD, but tended toward significant decrease after (1.85 0.56 versus 1.44 0.55, P=0.08). In addition, remarkable Lac/Cr ratio was measured from the surgical lesion centered on the part of globus pallidus of 6 among 7 patients after stereotactic pallidotomy (1.22 1.31). Therefore, except for Lac/Cr ratio, no significant alterations of metabolite ratios such as NAA/Cho, NAA/Cr, Cho/Cr, Ins/Cr, and Glx/Cr were established in lentiform nucleus at short TE.

DISCUSSION

In recent years, there has been increasingly interested in the stereotactic functional neurosurgical treatment, thalamotomy or pallidotomy, of movement disorders.[1,2] This interest has been prompted by recognition of the limitations of pharmacotherapy (i.e., levodopa or carbidopa) for PD and other movement disorders, improvements in neuro-imaging, and development of more sophisticated stereotactic electrode-neurosurgical techniques. Also, there has been increasing interest in the stereotactic neurosurgical treatment (radiosurgical pallidotomy or thalamotomy) with the Gamma Knife in movement disorderes.[22] Thalamotomy is currently used exclusively for tremor, whereas surgery on the internal segment of the globus pallidus is being studied for the treatment of all features of Parkinsonism, as well as drug-induced dyskinesias. Interventions at the ventral intermediate nucleus of the thalamus provide approximately 80 percent reductions in contralateral arm tremor.[6,7] Pallidotomy is associated with a striking improvement in levodopa-induced dyskinesias (an improvement of 80 percent or more in contralateral drug-induced

dyskinesias) and approximately a 30 percent improvement in total motor scores, with significant reductions in contralateral akinesia, rigidity, and tremor.[23-25]

In this present study, PD patients were classified into two groups based on symptoms, tremor-dominant group for thalamotomy, and bradykinesia and rigidity-dominant group for pallidotomy, according to the functional neurosurgical procedures utilized in the treatment. On MR images obtained after treatment, the most common appearance of the electrode-surgical lesion was a moderate ring-enhancing surrounded by a halo of edema. This appearance presumably represents a moderate area of surgery necrosis surrounded by electrode-surgical induced vasogenic edema. This appearance was noted in all patients.

Lactate signals could not be detected in the cerebral lesion of substantia nigra, thalamus, and lentiform nucleus in PD prior to the operative. This findings 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.[13,15] After neurosurgery, however, remarkable Lac/Cr ratios were observed from the surgical lesions in thalamus and internal segment of globus pallidus related to the clinical symptomatic side of PD. This lactate signal was noted in 6 both 8 patients with thalamotomy and 7 patients with pallidotomy, respectively. Therefore, the presence of lactate generally could be consistent with a common consequence of neurosurgery necrosis caused by vasogenic edema in the electrode-surgical lesion of PD.

Substantia nigra

Compared with before neurosurgery, a significant reduction (34%) of NAA/Cho ratio was observed in the cerebral lesion of substantia nigra related to the clinical symptomatic side in PD after the treatment. Both NAA/Cr and Cho/Cr ratios were not significantly different, but the former tended toward significant decrease in the identical cerebral lesion. Then, NAA/Cr ratio was measured moderate neuronal reduction (18%), and Cho/Cr ratio approximately showed slight increase (7%) in the same lesion related to the clinical symptomatic side in PD after neurosurgery.

These findings may indicate moderately reduced NAA, slightly increased Cho, and unaffected Cr levels in the lesion of substantia nigra. Cr peak is relatively stable in interpreting many pathological MR spectra and has been used as an internal standard in previous study on basal ganglia.[21] NAA is an amino acid confined in the brain only to neurons, and usually considered as a marker of neuronal integrity.[26] Thus, there might be neuronal metabolic alteration to tend toward significant reduction in NAA level upon MRS examination, and that NAA may provide as a prominent marker for neuronal metabolic change in PD after neurosurgery. In addition, when compared with age-matched controls, we observed the neuronal loss in at least one between before and after neurosurgery. Slight neuronal accumulation (10%) was measured in the lesion in substantia nigra related to the clinical symptomatic side before neurosurgery, while slight neuronal loss (10 %) was found in the same lesion after neurosurgery.

Changes of Cho in 1H MR spectrum reflect variations of the concentration and physiochemical state of choline-containing compounds, which are abundant in all cell synthesis and degradation.[27] Compared with age-matched controls, slight neuronal increase of Cho/Cr ratio was observed in the identical cerebral lesion both before and after neurosurgery. Slight neuronal laterality (2%) of choline metabolism was measured in the lesion in substantia nigra before neurosurgery and slightly more increased neuronal laterality (9%) was also found in the same lesion after neurosurgery. Thus, a slight increase of Cho/Cr ratio may indicate some membrane alternation or possible functional change of Cho metabolism in the cerebral lesion of substantia nigra related to the clinical symptomatic side.

Therefore, significant metabolic alterations of NAA/Cho ratio caused by contrastive changes between NAA/Cr and Cho/Cr ratio might reflect functional changes of neuropathological processes in the lesion of substantia nigra, and that NAA/Cho may provide as a marker for neuronal metabolic change in PD after functional neurosurgery.

Except for the NAA/Cho ratio, no significant alterations of other metabolite ratios such as NAA/Cr, Cho/Cr, Ins/Cr, Glx/Cr, and Lac/Cr were established in substantia nigra at short TE.

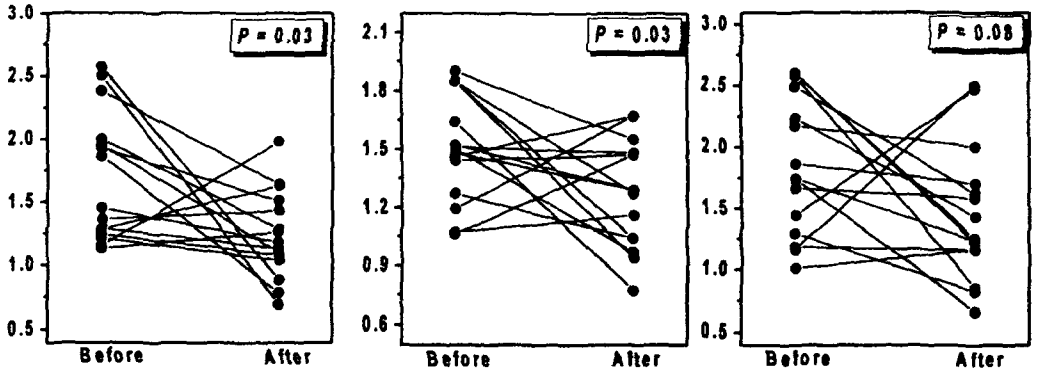

Fig.1 (a) Fig.1 (b) Fig. 1 (c)

Fig. 1. Comparision of NAA/Cho ratios obtained from the cerebral lesion in substantia nigra (A), thalamus (B), and lentiform nucleus (C) of Parkinsons disease between before and after functional neurosurgery.

Thalamus

A significant reduction (20%) of NAA/Cho ratio was statistically observed in the cerebral lesion of thalamus related to the clinical symptomatic side in PD after neurosurgery. Both NAA/Cr and Cho/Cr ratios were not significantly different in the identical cerebral lesion of thalamus in PD. However, NAA/Cr ratio was observed slight neuronal decrease (7 %), and Cho/Cr ratio showed slight increase (8 %) in the lesion of thalamus related to the clinical symptomatic side in PD after neurosurgery.

These findings may also indicate slightly reduced NAA, slightly increased Cho, and unaffected Cr levels in the lesion of thalamus. When compared with age-matched controls, we observed the neuronal loss both before and after neurosurgery. Slight neuronal loss (3%) was measured in the thalamic lesion before neurosurgery, and slightly more decreased neuronal loss (9%) was found in the same lesion after neurosurgery. In addition, we observed a considerable increase of Cho/Cr ratio in the thalamic lesion related to the clinical symptomatic side in PD both before and after neurosurgery. Moderate neuronal laterality (18 %) of choline metabolism was measured in the thalamic lesion before neurosurgery and significant neuronal laterality (28 %) was also found in the identical thalamic lesion after neurosurgery. Thus, a significant increase of Cho/Cr ratio may indicate some membrane alternation or possible functional change of Cho metabolism in thalamus after stereotactic thalamotomy.

A significant metabolic alteration of NAA/Cho ratio caused by contrastive changes between NAA/Cr and Cho/Cr ratio might reflect functional changes of neuropathological processes in the lesion of thalamus. Thus, NAA/Cho ratio may provide as a marker for neuronal metabolic change in thalamus of PD after functional neurosurgery. In detail, when compared with age-matched controls, we found a significant reduction (46%) of NAA/Cho ratio in the thalamic lesion including local edema occured after thalamotomy ($P=0.02$). Except for the NAA/Cho ratio, no significant alterations of other metabolite ratios such as NAA/Cr, Cho/Cr, Ins/Cr, and Glx/Cr ratios were established in thalamus at short TE.

Lentiform nucleus

NAA/Cho ratio statistically tended toward significant reduction (22%) in the cerebral lesion of lentiform nucleus related to the clinical symptomatic side in PD after neurosurgery. NAA/Cr and Cho/Cr ratio were not significantly different in the identical cerebral lesion in PD. NAA/Cr ratio showed moderate neuronal reduction (16 %), and Cho/Cr ratio showed slight increase (10 %) in the identical lesion of lentiform nucleus related to the clinical symptomatic side in PD after neurosurgery.

These findings may indicate moderately decrease NAA and slightly increased Cho, and unaffected Cr levels in the lesion of lentiform nucleus. When compared with age-matched controls, we observed the neuronal loss in at least one between before and after neurosurgery. Slight neuronal accumulation (7%) was measured in the lesion in lentiform

nucleus before neurosurgery, while moderate neuronal loss (11%) was found in the same lesion after neurosurgery.

Compared with age-matched controls, we observed increase of Cho/Cr ratio in the lesion both before and after neurosurgery. Slight neuronal laterality (8%) was measured in the lesion in lentiform nucleus before neurosurgery, and moderate neuronal laterality (18%) was also found in the same lesion after neurosurgery. Thus, increasing tendency of Cho/Cr ratio may indicate some membrane alternation or possible functional change of Cho metabolism in lentiform nucleus.

Therefore, considerable metabolic alterations of NAA/Cho ratio caused by contrastive change between NAA/Cr and Cho/Cr ratio might reflect functional changes of neuropathological processes in the lesion of lentiform nucleus. And, NAA/Cho may provide as a marker for neuronal metabolic change in lentiform nucleus of PD after functional neurosurgery. No significant alterations of metabolite ratios such as NAA/Cho, NAA/Cr, Cho/Cr, Ins/Cr, and Glx/Cr ratios were established in lentiform nucleus at short TE.

CONCLUSIONS

After neurosurgery, the values of NAA/Cr ratio showed generally lower level in the lesion of substantia nigra, thalamus, and lentiform nucleus, while those of Cho/Cr ratio observed higher level in the same lesion of Parkinsons disease. Metabolic alterations of NAA/Cho ratio caused by contrastive change between NAA/Cr and Cho/Cr ratio might reflect functional changes of neuropathological processes in the lesion of Parkinsonian symptomatic side, and could be a valuable finding for evaluation of Parkinsons disease. Thus, NAA/Cho ratio may provide as a marker for neuronal metabolic change in Parkinsons disease after stereotactic neurosurgery. Increase of lactate signals, being remarkable in surgical lesions, could be consistent with a common consequence of surgical necrosis induced by vasogenic edema. Therefore, 1H MRS could be a useful modality to evaluate the diagnostic and prognostic implications for Parkinson disease after fucntional neurosurgery.

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