Magnetic resonance imaging and proton magnetic resonance spectroscopy in neuro-Behçet's disease

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Abstract

Objective

Neuro-Behçet's disease (NBD) is one of the most serious complications of Behçet's disease (BD). Proton magnetic resonance spectroscopy (^{1}H MRS) has been proved to be useful in detecting neuro-metabolic abnormalities in various diseases affecting the brain. In this study, we attempted to characterize the magnetic resonance imaging (MRI) findings in Korean patients with NBD and then examined the usefulness of ^{1}HMRS in evaluating the MRI-negative brain area of NBD patients.

Methods

We performed brain MRI in 18 BD patients with neurologic symptoms and signs. Seven NBD patients without thalamic lesions and 8 healthy controls underwent brain ^{1}HMRS, in which an 8 ml voxel was placed in the left thalamus and the N-acetylaspartate (NAA)/creatine (Cr) ratio was measured.

Results

Fourteen of 18 BD patients were diagnosed as having NBD and 12 NBD patients (86%) had brain lesions on MRI. Most lesions were of high signal intensity on T2-weighted images and located in the midbrain, pons, basal ganglia, and white matter. On ^{1}HMRS, the thalamic area without gross abnormalities on MRI showed a significantly lower NAA/Cr ratio in NBD patients compared to healthy controls (1.07 ± 0.08 versus 1.54 ± 0.27, $P < 0.01$). In 2 NBD patients, the NAA/Cr ratios, monitored serially, were normalized along with clinical improvement 6 months after treatment with prednisolone and immune suppressive agents.

Conclusion

MRI is a very sensitive diagnostic method for NBD, and ^{1}HMRS may be useful for the early detection and follow-up of MRI-negative NBD.

Key words

Neuro-Behçet's disease, magnetic resonance imaging, magnetic resonance spectroscopy.

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Introduction

Behçet's disease (BD) is a systemic inflammatory disorder characterized by recurrent oral and/or genital ulceration and uveits. Other clinical features include skin lesions, vascular thrombosis, intestinal ulceration, arthritis, and central nervous system (CNS) involvement (1). Among these CNS involvement, which is known as neuro-Behçet's disease (NBD), is one of the most serious complications and has been reported to occur in 4–49% of BD patients (2–5). NBD shows various symptoms and signs including pyramidal signs, mental behavioral changes, hemiparesis, sphincteric disturbance, headache, aseptic meningitis, meningoencephalitis, dementia, etc. It is generally diagnosed based on neurologic manifestations and abnormal findings on brain MRI. Although MRI is known to be the most sensitive diagnostic test for NBD (6–8), some BD patients with neuro-psychiatric symptoms do not have abnormal MR images, and thus other diagnostic methods are required (9).

Proton magnetic resonance spectroscopy (1H MRS) is a new, non-invasive method for the evaluation of metabolite *in vivo* and has been proved to be useful for detecting neuro-metabolic abnormalities in various diseases affecting the brain including brain tumors, strokes, schizophrenia, and systemic lupus erythematosus (SLE) involving CNS (10-14). 1H MRS detects brain metabolites such as N-acetylaspartic acid (NAA), choline (Cho), creatine (Cr), glutamate, gammabutyric acid (GABA), lactate, and lipid. In particular, NAAdepletion is reported to be associated with neuronal damage and thus has been used as a sensitive marker for neuronal cell loss associated with CNS vasculitis (10-12). For example, Chinn et al. (12) reported a decrease in the NAA/Cr ratio in SLE patients without brain lesions on MRI. It has also been documented that normal-appearing brain tissue in patients with minor neuro-psychiatric lupus is characterized by the loss of the neuronal marker NAAon 1H MRS (15).

In the present study, we investigated the MRI findings in 18 Korean BD patients with neurologic symptoms and signs, and examined the usefulness of 1H MRS in studying the MRI-negative brain area of NBD patients. In addition, we serially monitored the 1H MRS in two NBD patients 6 months after treatment with prednisolone plus immunosuppressive agents.

Patients and methods

Eighteen BD patients with neurologic symptoms and signs were included in this study, comprising 11 men and 7 women (mean age 38.6 ± 7.6 years, mean disease duration 34.4 ± 25.5 months). After carefully describing the study to the subjects, written informed consent was obtained from each. All patients fulfilled the criteria of the International Study Group for BD (1). We performed brain MRI in all patients and ^{1}H MRS in 7 BD patients (5 men and 2 women, mean age 38.1 ± 10.6 years). In addition ^{1}H MRS was carried out in 8 healthy controls (4 men and 4 women, mean age 38.4 ± 8.6 months). The normal control subjects were being screened for medical and psychiatric illness and history of substance abuse. None of these control subjects had a history of substance dependence or current abuse or a history of neurologic disorders.

Both MRI and ^{1}H MRS were performed using the 1.5 T MRI/MRS system (GE SIGNA Advantage version 4.8). The conventional spin echo (SE) pulse sequence with TE 20ms and TR 400ms was employed to obtain the T1-weighted MR images. The fast spin echo (FSE) pulse sequence with TE 90ms and TR 2500ms was employed to obtain the T2-weighted MR images. As for ^{1}H MRS, a 2 x 2 x 2 cm^3 (8 ml) voxel was placed in the left thalamus on a T2-weighted MR image (Fig. 1A). The [1]H-spectrum was obtained from the voxel using the stimulated echo acquisition mode (STEAM) sequence with water suppression by a chemical-shift selective saturation (CHESS) RF pulse. The spectral parameter was 20 ms TE, 2000 ms TR, 128 averages, 2500 Hz signal width, and 2048 data point. A shimming procedure focused on the water signal was performed to obtain the uniform and homogeneous
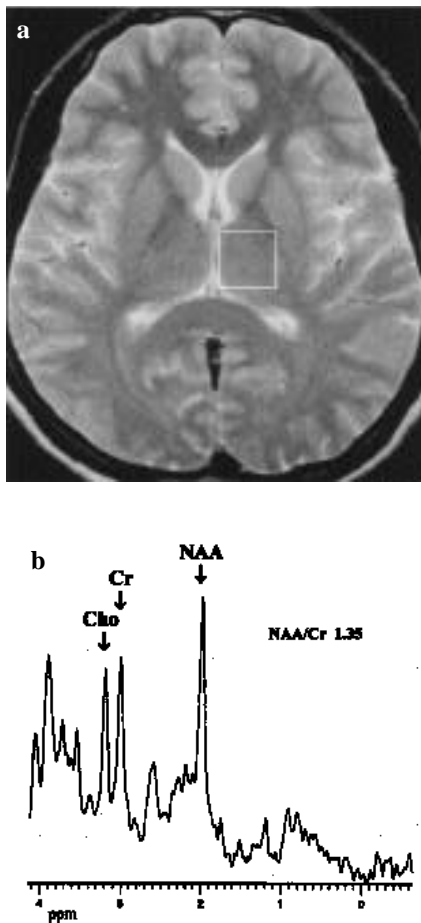
Fig. 1. (**a**) Axial T2-weighted MR image (2,500/90) shows an example of 8 ml voxel placement in the left thalamus. (**b**) ^{1}H MRS spectral pattern in a healthy control.

magnetic field. The typical water line width (full width at half maximum) was 3-4 Hz. Special attention was given to locating the water signal frequency to maximize the water suppression. An exponential line broadening of 0.5 Hz was applied.

Time domain data were converted to frequency domain by Fourier transformation. Frequency domain spectra were phased by hand, with the use of frequency-independent phase corrections only. Phased absorption spectra are reported directly without baseline correction or resolution enhancement. Raw data were processed by the SAGE data analysis package (GE Medical Systems). The 3 principal peaks were derived from the spectra; NAA at 2.00 parts per million (ppm), Cho at 3.2 ppm, and Cr at 3.0 ppm (Fig. 1B). The peak area of NAA, Cr, or Cho was cal-culated by fitting the spectrum to a summation of Lorentzian curves using a Marquardt algorithm. The results were expressed as a ratio of areas under the peaks of NAA and Cr, the NAA/Cr ratio.

All data were expressed as mean ± standard deviations (SD). Statistical analysis was done using the SPSS statistical package (SPSS Inc., Chicago, Illinois) and the Mann-Whitney test was performed for comparison of NAA/Cr ratio between NBD patients and healthy controls. Statistical significance was defined as $p < 0.05$.

Results

The neurologic symptoms and signs of BD patients are summarized in Table I. Among 18 patients with BD, 4 patients were not diagnosed as having NBD. Patient 1 had migraine and patient 3 had tension headache. Patients 11 and 15 had vague symptoms which responded to conventional treatment. Although patients 3, 11, and 15 had dot-like scattered lesions on brain MRI, they seemed to be of no clinical significance for their age.

We made a diagnosis of NBD in 14 BD patients. Nine patients (patients 2, 4, 6, 7, 8, 9, 13, 14, and 17) showed neurologic symptoms and signs suggesting pyramidal tract or cranial nerve involvement which are the most characteristic manifestation of NBD. Patient 5 showed only seizure, which has been reported to be a very uncommon symptom for NBD (4). However, MRI showed lesions on basal ganglia, which should not have been present at his age of 21. Furthermore, they disappeared on follow-up MRI after immunosuppressive treatment, along with improvement of his seizure activity. Patient 18 also showed improvement of her seizure activity after immunosuppressive treatment, which made it plausible that she had NBD in spite of a normal MRI. In patient 10, a spinal tap revealed leukocytosis and his brain MRI showed a pontine lesion. Patient 12 exhibited only isolated headache which is not sufficient for the diagnosis of NBD and midbrain lesion could be of no clinical importance at her age of 43. However, her severe headache which did not respond to conventional medication, improved after the administration of azathioprine and we could not find any other possible explanations than NBD. Patient 16 was also diagnosed as having NBD based on his response to immunosuppressant in spite of his vague neurologic symptoms. Furthermore, patients 12 and 16 experienced exacerbation of their neurologic symptoms and signs in conjunction with an aggravation of oral ulceration and skin lesions, which made the diagnosis of NBD more likely.

In 14 patients with NBD, the most frequent symptom was headache (57%) followed by memory impairment (50%), dysarthria (43%), hemiparesis (21%), seizure (21%), meningitis (21%), diplopia (14%), dizziness (14%), difficulty in urinating (14%), paraplegia (14%), enuresis (7%), depression (7%), tremor (7%), upper extremity weakness (7%), visual impairment (7%), and gait disturbance (7%). Eleven patients had more than 2 manifestations and 3 patients had only one (Table I).

Twelve of the 14 patients (86%) had single or multiple brain lesions on MRI. Most of the lesions appeared as high signals on T2-weighted images and were usually small, dot-like, and scattered. Confluent patchy lesions were also found (Fig. 2). The location of the lesions was as follows: midbrain in 6 patients (43%), pons in 6 (43%), basal ganglia in 6 (43%), white matter in 3 (21%), thalamus in 2 (14%), cerebellum in 1 (7%), and spinal cord in 1 (7%) (Table I). Atrophic changes of the cerebellum and brainstem were found in 3 patients (patients 2, 7, and 9).

Seven NBD patients without thalamic lesions and 8 healthy controls underwent ^{1}H MRS (Table I). Because we wished to determine whether ^{1}H MRS could sensitively detect functional and metabolic abnormalities in the brain of NBD patients, a 2 x 2 x 2 cm[3] (8 ml) voxel was placed in the left thalamus where no abnormal finding was detected on MRI. Among 7 NBD patients, two (patients 4, and 18) showed no brain lesion on MRI despite definite neurologic symptoms such as dysarthria, memory impairment, tremor, and seizure (Table I). We selected the thala-

Table I. Neurologic manifestations, site of brain lesions, and treatment of patients with Behçet's disease (BD).

Patient	Age/Sex	BD duration	Neurologic manifestations	Site of lesions on MRI	MRS	Treatment*
1	45 (yrs) /F	84 (months)	Headache	None		Analgesics
2	36/M	42	Headache, hemiparesis	Pons, cerebellum	Done	MP
3	42/F	5	Headache	Midbrain		Analgesics
4	56/F	36	Dysarthria, memory impairment, tremor	None	Done	Oral CYC
5	21/M	24	Seizure	Basal ganglia	Done	AZP
6	25/F	12	Dysarthria, headache, seizure, upper extremity weakness	Pons, basal ganglia		CYC pulse, MP
7	33/M	50	Aseptic meningitis, diplopia, enuresis, headache, memory impairmemt, paraplegia	Midbrain, basal ganglia, white matter, upper spinal cord atrophy	Done	MP
8	39/F	9	Dysarthria, memory impairment	Basal ganglia		Cyclosporin
9	41/M	1	Depression, dysarthria, hemiparesis	Pons, midbrain, thalamus, cerebellum, white matter		Oral CYC, MP
10	36/M	96	Aseptic meningitis, headache	Pons		Cyclosporin, AZP
11	37/F	16	Dizziness, headache	Thalamus		Analgesics
12	43/M	28	Headache	Midbrain		AZP
13	35/M	36	Hemiparesis	Pons, midbrain		Chlorambucil, MP
14	38/M	17	Aseptic meningitis, dysarthria, gait disturbance, headache, memory impairment, urination difficulty	Basal ganglia	Done	Chlorambucil
15	41/M	24	Dizziness, headache, memory impairment	White matter		Analgesics
16	44/M	43	Dizziness, headache, memory impairment, visual impairment	Pons, midbrain	Done	AZP
17	43/M	48	Diplopia, dysarthria, gait disturbance, headache, memory impairment, urination difficulty	Midbrain, thalamus, basal ganglia, white matter		MP
18	39/F	48	Memory impairment, seizure	None	Done	AZP

*All patients have been taking colchicine and low-dose prednisolone (7.5 mg/day). MP: methylprednisolone, AZP: azathioprine, CYC: cyclophosphamide.

mic area for ^{1}H MRS because the thalamus is reported to be one of the most frequently affected structures in NBD (8). In the analysis of MRS findings in this area, we observed that the NAA/Cr ratio was significantly lower in NBD patients compared to healthy controls (1.07 ± 0.08 versus 1.54 ± 0.27, $P< 0.01$) (Fig. 3).

We treated 14 NBD patients using immunosuppressive drugs such as methylprednisolone, azathioprine, cyclosporin, chlorambucil, and cyclophosphamide (Table I). The neurologic symptoms and signs described in Table I at least partially improved 2 or 3 months later in all patients. Of note, we administered oral cyclophosphamide and azathioprine to 2 patients (patients 4 and 18 respectively) despite the absence of any gross abnormality on MRI because their ^{1}H MRS showed a low NAA/Cr ratio (1.12 and 1.09 respectively) compared to the normal range at our hospital (1.2 ~ 1.7). Patient 4 had been tak-

ing propranolol, trihexyphenidyl, and bromocriptine for slurred speech and a resting tremor in the left hand without improvement. We stopped the above drugs to make a differential diagnosis with Parkinson's disease, but there was no aggravation of the neurologic symptoms, which made Parkinson's disease less likely. Even though brain MRI was negative, the patient was suffering from active oral ulcer and erythema nodosum at the time of evaluation. Therefore we attempted high dose prednisolone (> 30 mg/day) and oral cyclophosphamide 50 mg/day based on the MRS data, which resulted in a dramatic improvement of the neurologic symptoms 6 months later. In patient 18, EEG and brain MRI were normal despite seizures, so we administered prednisolone 15 mg plus azathioprine 75 mg after the ^{1}H MRS evaluation.

We serially monitored the ^{1}H MRS in two NBD patients (patients 4 and 16) 6 months after treatment with predni-

solone plus immunosuppressants such as cyclophosphamide and cyclosporine. As shown in Figures 4 and 5, the NAA/Cr ratio increased to a normal value, along with a marked improvement of neurologic symptoms after treatment with prednisolone plus immunosuppressants (from 1.12 to 1.45, from 0.95 to 1.50, respectively) (Figs. 4 and 5).

Discussion

NBD is one of the most serious complications of BD, and early diagnosis is crucial to prevent permanent neurologic damage (2-5). NBD is usually diagnosed by the combination of neurologic manifestations and findings on brain MRI, which has been reported to be the best diagnostic method for NBD, with a sensitivity of 76% to 81% (7, 8). In NBD, brain lesions are usually located in the brainstem, basal ganglia, thalamus, and white matter. In particular, pontine involvement is reported to be characteristic in these regions (6-8, 16).
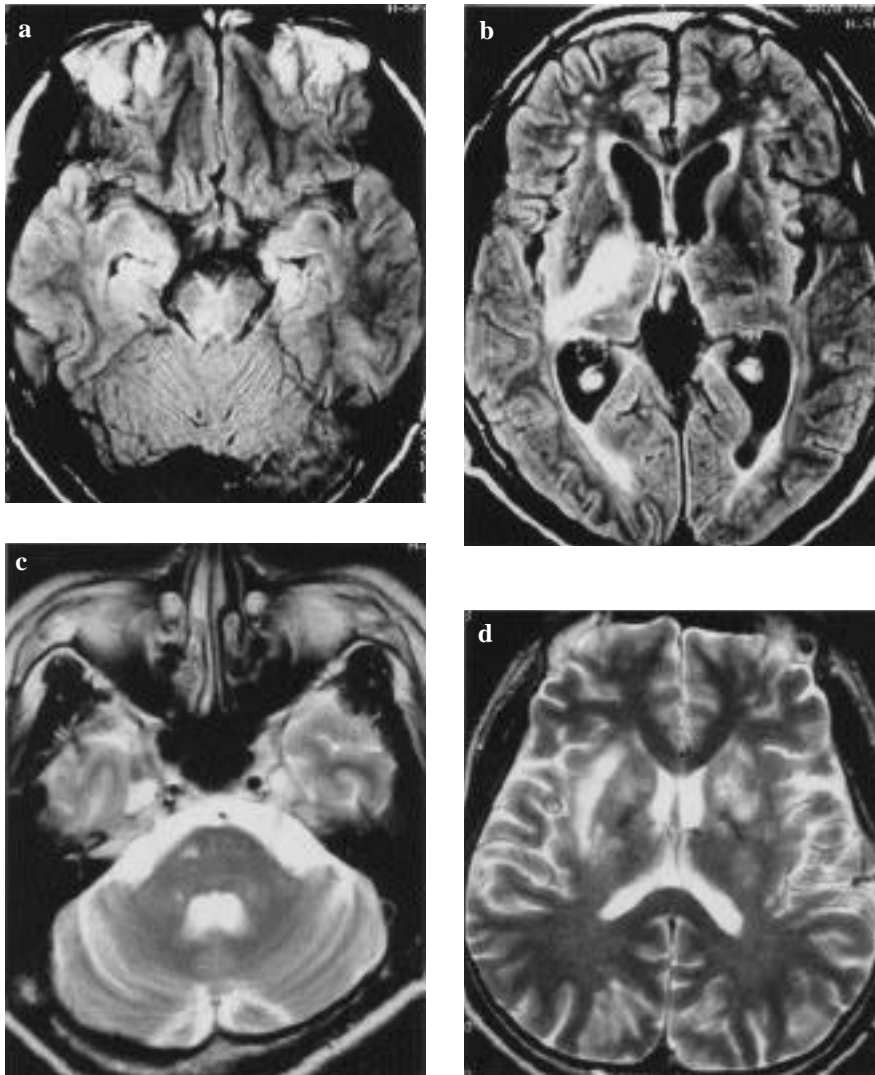
Fig. 2. Axial T2-weighted images in patients with neuro-Behçet's disease showing involvement of the midbrain in patient 7 (**a**), the internal capsule and thalamus in patient 9 (**b**), the pons in patient 13 (**c**), and the basal ganglia in patient 17 (**d**).

Fig. 3. NAA/Cr ratio in patients with neuro-Behçet's disease (NBD) and in healthy controls (HC). Bars denote mean values.

Fig. 4. ^{1}H MRS in patient 4 before (**A**) and 6 months after (**B**) treatment with prednisolone plus cyclophosphamide, showing normalization of the NAA/Cr ratio from 1.12 to 1.45

In the present study, we found that 12 (86%) of 14 NBD patients had brain lesions on MRI, which was comparable to previous studies (7, 8). Also the brainstem was the most frequently involved site (71%), with midbrain involvement (43%) as frequent as pontine involvement (43%), as has been reported earlier (6-8, 16).

NBD is mainly a disease of the motor compartment of the CNS, frequently accompanied by mental behavioral changes. The clinical symptoms and signs of NBD include pyramidal signs, mental behavioral changes, hemiparesis, sphincteric disturbance, headache, aseptic meningitis, meningoencephalitis, dementia, etc. (16). Major manifestations in our NBD patients were headache, memory impairment, dysarthria, hemiparesis, pyramidal signs, and meningitis, which is consistent with a previous report (16). In our study, seizure was present in 3 patients (21%), which was more frequent than in a previous report (4).

One of our NBD patients (patient 12) had isolated headache. Unless accompanied by other neurologic manifestations, headache has not been considered to be of clinical importance (3, 4). Furthermore, her midbrain lesion on MRI could be of no clinical importance in her age of 43. However, her severe headache, which did not show any response to conventional medication, improved after administrati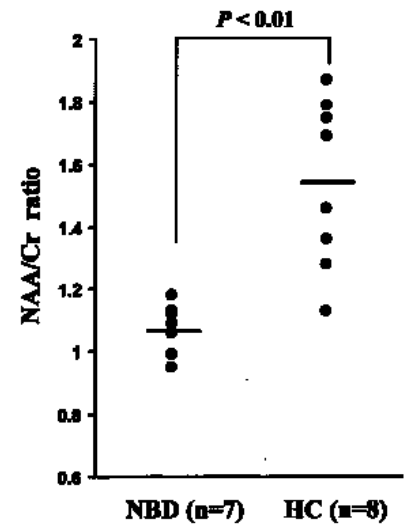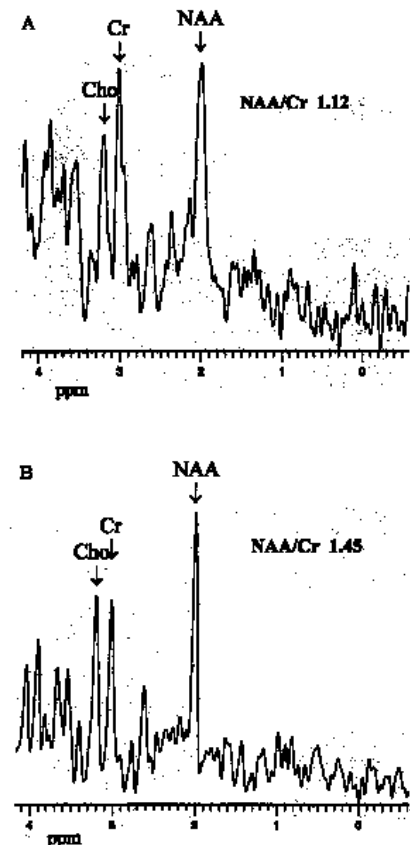on of azathioprine and we could not find any other possible explanation for her condition than NBD. This suggests that cases of headache in BD patients, if
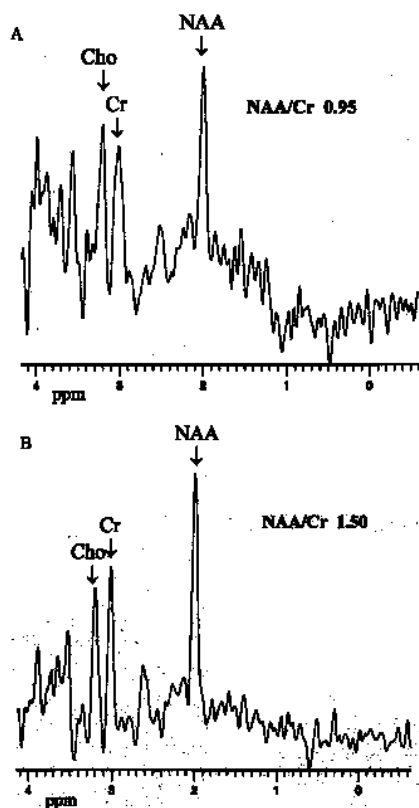
Fig. 5. ¹H MRS in patient 16 before (**A**) and 6 months after (**B**) treatment with prednisolone plus azathioprine, showing a dramatic increase in the NAA/Cr ratio from 0.95 to 1.50 after treatment.

refractory to conventional therapy, should raise the suspicion of NBD and immune suppression should be attempted. Regarding the role of MRI in BD patients with isolated headache, Wechsler *et al.* (8) reported that they did not find any brain lesions in 7 such patients with isolated headaches, while Tali *et al.* found brain lesions in 4 of 5 BD patients with isolated headache (7). Histopathologically, BD is mainly characterized by inflammatory vasculitis in all types of blood vessels including the artery, arteriole, vein, and venule (17-19). In NBD, small venule vasculitis is the predominant pathology, which includes disseminated meningoencephalitis with perivascular cell infiltration, infarct with small necrotic areas the surrounding blood vessels, hemorrhage, loss of myelinated fibers, and gliosis (8,16,20). Most brain lesions in NBD seem to reflect the sum of the aforementioned vasculitic changes and thus are of high signal intensity on T2-weighted images of MRI. How-

ever, despite its high sensitivity, MRI may be normal in some BD patients with definite neurologic manifestations. In this regard, other methods including multi-modality evoked potential (21), brain single photon emission tomography (SPECT) (22), and brain MRS have been tried for the accurate diagnosis of NBD.

Brain ¹H MRS is a non-invasive method for the quantitative measurement of brain metabolites including NAA, Cho, Cr, glutamate, GABA, lactate, and lipid (10-12). In particular, the NAA peak is sensitively decreased in conditions accompanied by neuronal damage such as stroke and thus has been used as a marker for neuronal cell loss (10-12). ¹H MRS has also been employed for the evaluation of neuro-metabolic abnormalities in some rheumatic diseases. In neuro-psychiatric lupus, the NAA peak was markedly decreased in cases with cerebral atrophy or chronic stroke (10-13). As for BD, Nüssel *et al.* (23) found a reduction of the NAA/Cr ratio within the acute lesions, which were evident on MRI in 3 patients with NBD. However, whether ¹H MRS has the ability to reflect functional abnormalities in MRI-negative NBD patients has not been reported yet.

In this study, we obtained spectra from the thalamus of NBD patients without thalamic lesions on MRI to examine whether ¹H MRS can detect neuro-metabolic abnormalities in the MRI-negative brain area. In the analysis of MRS findings in this area, we observed that NBD patients had a significantly lower NAA/Cr ratio compared to healthy controls. This suggests that metabolic abnormalities might be present in the normal-looking area of the brain in NBD patients. Chinn *et al.* (12) reported a decrease of the NAA/Cr ratio in SLE patients without brain lesions on MRI. Moreover, it has been reported that normal-appearing brain tissue in patients with minor neuro-psychiatric lupus is characterized by loss of the neuronal marker NAA on ¹H MRS (15). Therefore our data, together with previous reports (12,15), suggest that ¹H MRS might be a very sensitive tool for the detection of NBD and could be useful for the early verification of the

onset of NBD.

In terms of neuro-metabolic abnormalities in BD patients with normal MRI imaging, Markus *et al.* (9) reported a patient with NBD suffering from headaches and personality changes, in whom the brain MRI was normal but regional cerebral blood flow imaging using SPECT showed extensive perfusion deficits. Additionally, Otte *et al.* (24) demonstrated significant hypometabolism in the parieto-occipital region in neuro-psychiatric SLE patients without brain lesions on MRI, and normalization of metabolism after treatment determined by positron emission tomography (PET), another method useful for the evaluation of brain functional abnormalities (24). In the present study, we also found normalization of the NAA/Cr ratio in the follow-up ¹H MRS, along with clinical improvement after treatment with prednisolone plus immunosuppressive agents. This suggests that ¹H MRS could be useful not only for the early detection but also for the follow-up of NBD.

In conclusion, brain MRI is a very sensitive method for the diagnosis of NBD. However, metabolic abnormalities, particularly hypometabolic states, may be present in the brain of NBD patients even in the absence of gross abnormalities on brain MRI. In these patients, ¹H MRS could be useful for the early detection and follow-up of NBD. However, our study is preliminary and larger studies are needed in order to clarify both the ¹H MRS findings in NBD and the effects of treatment on ¹H MRS.

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