Chapter 4

Correlation of magnetization transfer ratio histogram parameters with neuropsychiatric systemic lupus erythematosus criteria and proton magnetic resonance spectroscopy

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ABSTRACT

Purpose

To investigate whether, in neuropsychiatric systemic lupus erythematosus (NPSLE) patients, magnetization transfer ratio (MTR) histogram parameters are related to neurochemical findings obtained using proton magnetic resonance spectroscopy (^{1}H-MRS) and to determine whether MTR histogram changes are linked to specific SLE and NPSLE characteristics.

Methods

Eighteen SLE patients (15 female, 3 male; mean ± SD age 42.8 ± 12.8 years), 34 NPSLE patients (32 female, 2 male; mean ± SD age 35.9 ± 12.2 years), and 15 healthy controls (14 female, 1 male; mean ± SD age 44.7 ± 9.6 years) underwent magnetization transfer imaging and ^{1}H-MRS. Whole-brain MTR histogram parameters were associated with ^{1}H-MRS metabolite ratios, certain SLE criteria, and neuropsychiatric syndromes.

Results

No differences were found in the MTR histogram parameters between SLE patients and NPSLE patients. NPSLE patients had a lower MTR histogram peak height than did the healthy controls. The MTR histogram peak height and the mean height were significantly associated with the *N*-acetylaspartate to creatinine ratio, suggesting neuronal dysfunction. Of all SLE criteria, renal dysfunction and arthritis were associated with MTR histogram parameters. After corrections for age, sex, and these SLE criteria, of the various neuropsychiatric syndromes only cognitive dysfunction was associated with the MTR histogram peak height.

Conclusion

The MTR peak height is lower in NPSLE patients than in healthy controls. MTR peak height reflects neuronal dysfunction, as detected by ^{1}H-MRS. Furthermore, the MTR peak height is associated with cognitive dysfunction but not with the other neuropsychiatric syndromes evaluated in our study.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease with a relapsing-remitting course and symptoms based on multiorgan involvement. (1) Up to 80% of SLE patients develop neurologic or psychiatric symptoms. (2) In 40% of the cases, neurologic or psychiatric symptoms are the consequence of secondary causes, such as infections, metabolic derangement based on damage to organs other than the brain due to SLE, or side effects of drug treatment. (3) In the remaining 60%, the symptoms are ascribed to primary SLE involvement in the brain, which is referred to as neuropsychiatric SLE (NPSLE).

The exact pathogenesis of NPSLE is still not known. Some symptoms are associated with thromboembolisms, ascribed to the presence of thrombogenic anticardiolipin antibodies (aCL) in NPSLE patients. These can lead to antiphospholipid syndrome, with increased coagulation and a high risk of thromboembolisms. Other symptoms are probably due to general vasculopathy or direct neuronal damage. Patients with primary NPSLE can have focal and diffuse symptoms. (4-6) Research has benefited from a detailed case-definition system, which groups together patients with the same neuropsychiatric syndromes, but in clinical practice, the diagnosis is generally still made per exclusionem. (7,8) Reports of the number of patients who develop neuropsychiatric syndromes vary greatly, depending on the population studied and the duration of the disease. (9-11) This variation is inherent to the large number and the heterogeneity of the neuropsychiatric syndromes that occur in SLE.

Using various imaging techniques to detect central nervous system involvement in NPSLE is a challenge. Despite overt clinical symptoms, conventional magnetic resonance images (MRIs) can appear normal. (11) Still, several studies have shown that the magnetization transfer ratio (MTR) can be used to detect cerebral changes in normal-appearing brain tissue of NPSLE patients. Bosma and coworkers found a significantly lower peak height of the MTR histogram of the whole brain in NPSLE patients compared with control subjects. (12) A recent study found selective damage in the gray matter of the brain in NPSLE patients. (13) In addition, it was shown that the decreased peak height of the MTR histograms may increase after the patient's clinical situation improves. (14) However, despite these findings, the underlying pathogenesis and the relationship to specific neuropsychiatric syndromes remain unknown.

This study had 2 objectives. First, we wanted to investigate whether MTR histogram changes are related to specific NPSLE characteristics. To do this, MTR histogram parameters were compared with individual SLE criteria and, if present, neuropsychiatric syndromes. Second, we wanted to determine whether any possible relationship between MTR histogram parameters and specific NPSLE characteristics is associated with neuronal dysfunction. To this end, MTR histogram parameters were compared with neurochemical findings obtained using proton magnetic resonance spectroscopy (^{1}H-MRS).

The presence of aCL and antiphospholipid syndrome was also determined to investigate their relationship to MTR histogram parameters.

METHODS

Patients

All 52 patients were recruited from the rheumatology department of our institution. SLE was diagnosed according to the American College of Rheumatology (ACR) criteria. (15) At least 4 of the 11 criteria had to be met before the diagnosis was made. Of these 52 patients, 18 (15 female, 3 male; mean ± SD age 42.8 ± 12.8 years) had no neuropsychiatric syndromes according to the ACR nomenclature system for neuropsychiatric syndromes. (7) The remaining 34 patients (32 female, 2 male; mean ± SD age 35.9 ± 12.2 years) were diagnosed as having NPSLE, according to the ACR nomenclature system for neuropsychiatric syndromes and the SLE criteria. (7,15) All patients were diagnosed and classified by an experienced rheumatologist (GMS-B). Fifteen healthy controls were recruited among colleagues, friends, and relatives (14 female, 1 male; mean ± SD age 44.7 ± 9.6 years).

Table 1 shows the characteristics of the patients. In the NPSLE group (n = 34), 52 neuropsychiatric syndromes were present: aseptic meningitis (n = 1), cerebrovascular disease (n = 14), headache (n = 6), mononeuropathy (n = 1), movement disorder (n = 2), myelopathy (n = 2), cranial neuropathy (n = 2), seizure disorder (n = 11), cognitive dysfunction (n = 7), mood disorder (n = 4), and psychosis (n = 2). Of the NPSLE patients, 7 took no antirheumatic drugs or anticoagulants, 14 took >1 medication, 21 took prednisone, 6 took phenprocoumon, 5 took cyclophosphamide, 8 took azathioprine, and 9 took calcium carbasalate. Of the SLE patients, 5 took no antirheumatic drugs or anticoagulants, 6 took >1 medication, 11 took prednisone, 3 took phenprocoumon, 2 took azathioprine, and 2 took calcium carbasalate. The groups were well matched with regard to age and sex.

Magentic Resonance Imaging (MRI/) magnetization transfer imaging (MTI)

All MRI scans were performed using an Intera 1.5T MR system (Philips, Best, The Netherlands) and were interpreted by a radiologist (BJE). Axial T1-weighted spin-echo imaging was performed on all subjects. Imaging was performed using a spin-echo sequence with an echo time (TE) of 20 msec, a repetition time (TR) of 600 msec, and a scanning time of 30 minutes. Sequences consisted of 22 axial slices with a 6-mm slice thickness, and a matrix of 256 × 256 pixels. MTI was performed using a 3-dimensional gradient-echo pulse sequence with a 106-msec TR, a 6-msec TE, and a flip angle of 12° (14), with a scanning time of 11 minutes 27 seconds. Two consecutive sets of axial images were acquired. The first set was performed in combination with a radiofrequency saturation pulse and

Table 1 Patient characteristics*

	Controls	SLE	NPSLE
N	15	18	34
Age (SD)	44.7 (9.6)	42.8(12.8)	35.9 (12.2)
♀ / ♂	14/1	15/3	32/2
SLE disease duration	-	4.1 (5.3)	10.6 (9.8)
NPSLE disease duration	-	-	4.1 (5.8)
Malar rash	-	4	7
Discoid Rash	-	4	12
Photosensitivity	-	9	10
Oral Ulcers	-	5	10
Arthritis	-	15	30
Serositis	-	7	18
Renal Disorder	-	6	15
Neurological disorder	-	0	-
Hematological disorder	-	8	17
Immunological disorder	-	17	33
Anti-nuclear antibody	-	17	32
AcL IgM	-	14	15†
AcL IgG	-	13	24†
Anti-Phospholipid Syndrome	-	4	8

* SLE = systemic lupus erythematosus; NPSLE = neuropsychiatric SLE

† Not available in 1 patient

the second set without. The saturation pulse consisted of a sinc-shaped radiofrequency pulse 1,100 Hz upfield of H_2O resonance. A matrix of 256 × 256 pixels with an acquisition percentage of 50% was used for 28 contiguous slices with a thickness of 5 mm. The field of view was 220 mm.

Image Processing

All images were transferred to an offline Linux workstation. All MTR processing steps were performed using software from the Oxford University Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) software library (FSL). (16) The MTR sequence was split into separate data sets, those with (m_1) and those without (m_0) a saturation pulse. These were subsequently skull stripped using the brain extraction tool in FSL. (17) The data set without a saturation pulse (m_0) was subtracted from the data set with a saturation pulse (m_1) and then divided by the data set without a saturation pulse (m_0). The resulting image was then multiplied by 100 to produce the MTR map. To obtain segmented white and gray matter, the T1-weighted image was segmented using the FMRIB automated segmentation tool. (18) The T1-weighted image was subsequently registered to the m_0 data set using the FMRIB linear image registration tool (19), and the transformation matrix of this registration was saved. Consequently, this registration matrix was used to coregister the MTR map and the segmented brain parenchyma and

gray and white matter volume from the T1-weighted image segmentation so that the MTR map could be masked with these tissue maps. The resulting MTR maps of the brain parenchyma and gray and white matter were then eroded 2-dimensionally to reduce the partial-volume effects of cerebrospinal fluid (CSF) at the borders of the maps. The mean MTR was derived from these regions of interest (ROIs). In addition, histograms were created with a bin size of 0.01 and 100 bins. To reduce partial-volume effects, a threshold of 0.20 was used to remove any remaining voxels that might still be contaminated with CSF. (20) These histograms were finally normalized to the size of the ROI by dividing every histogram bin by the total number of voxels in the ROI. The peak height was derived from these histograms. (Appendix A,C)

^{1}H-MRS

Single-voxel ^{1}H-MRS was performed using a double spin-echo point-resolved spectroscopy sequence. The volume of interest was selected in the left centrum semiovale of each subject. When placing the voxel, gray matter and CSF were visually excluded to ensure the homogeneity of the selected tissue and the comparability of the selected voxel between different subjects. The dimensions of the selected volumes of interest were typically 40 mm anteroposterior, 15 mm left-right, and 10 mm caudocranial. (Appendix B) Measurement parameters were as follows: TR 2,000 msec, TE 136 msec, 2,048 time domain data points, spectral width 2,000 Hz, and 128 signals acquired. After zero-filling to 4,096 data points, exponential multiplication of 2 Hz, Fourier transformation, and linear baseline correction, *N*-acetylaspartate (NAA) (referenced at 2.0 ppm), the integrated area under the curve of choline peaks, and total creatinine peaks were quantified using integration software routines, which were provided by the manufacturer (Philips). The NAA:creatinine and choline:creatinine ratios were calculated using the obtained metabolites.

Statistical analysis

The mean values of the MTR histogram parameters in the controls, the SLE patients, and the NPSLE patients were calculated, and the significance of differences was determined using analysis of variance after Bonferroni correction. To study the influence of disease duration and sex, we performed a linear regression analysis on the MTR parameters. All subsequent analyses were corrected for disease duration and sex. To investigate the association between MTR histogram parameters and the neurochemical ratios derived from the ^{1}H-MRS, we performed a linear regression analysis of all subjects. To determine the association between SLE criteria and MTR histogram parameters, a linear regression analysis of each of the 11 SLE criteria was performed. To investigate the association between neuropsychiatric syndromes and MTR histogram parameters, we performed a linear regression analysis of every neuropsychiatric syndrome present in ≥5 patients. This

resulted in the analysis of cerebrovascular disease, headache, and cognitive dysfunction. To determine the influence of aCL on the MTR histogram parameters, a linear regression analysis was performed.

RESULTS

Table 2 shows the MTR histogram parameters of control subjects, SLE patients, and NPSLE patients. The peak height of the MTR histogram of the brain parenchyma was significantly lower in NPSLE patients compared with healthy controls. No significant differences in MTR histogram parameters were found between SLE patients and NPSLE patients. Figure 1 shows the average MTR histogram of the brain parenchyma for all 3 groups.

Table 2 Mean MTR histogram parameters

	Healthy controls	SLE patients	NPSLE patients
Parenchyma Peak height†	135.6 ± 10.8	131.8 ± 13.8	125.1 ± 14.7*
Parenchyma mean	0.350 ± 0.006	0.346 ± 0.005	0.348 ± 0.010
White matter peak height†	182.4 ± 13.8	185.0 ± 16.5	177.3 ± 18.2
White matter mean	0.363 ± 0.006	0.361 ± 0.006	0.364 ± 0.011
Gray Matter peak height†	106.3 ± 19.5	101.8 ± 19.7	97.0 ± 20.0
Gray matter mean	0.336 ± 0.009	0.333 ± 0.008	0.333 ± 0.011

Values are the mean ± SD. MTR = magnetization transfer ratio; SLE = systemic lupus erythematosus; NPSLE = neuropsychiatric SLE.

† Peak height values were multiplied by 1,000 for readability.

* $P < 0.05$ versus healthy controls

Table 3 shows the association between the neurochemical ratios derived from the ^{1}H-MRS spectra and the MTR histogram parameters for all groups combined. The NAA/Cre ratio was significantly associated with peak height of the parenchyma, the white and the gray matter. In addition, it was associated with the mean MTR of the gray matter, but not with mean MTR of the parenchyma or the white matter. The Cho/Cre ratio did not show any significant correlation with any of MTR parameters.

The results of the linear regression analysis of the SLE criteria and the MTR histogram parameters were corrected for disease duration and sex. Only arthritis and renal disorder had an influence on MTR histogram parameters, and these SLE criteria were taken into account in the analyses of the association between the MTR histogram parameters and neuropsychiatric syndromes. Arthritis was associated with a higher mean MTR of the brain parenchyma ($\beta = 0.450$, $R = 0.610$, $P < 0.001$) and the white matter ($\beta = 0.390$, $R = 0.440$, $P < 0.01$). Renal disorder was associated with a lower peak height of the MTR histogram of the brain parenchyma ($\beta = -0.341$, $R = 0.510$, $P < 0.01$), the white matter ($\beta = -0.264$, $R = 0.478$, $P < 0.05$), and the gray matter ($\beta = -0.264$, $R = 0.591$, $P < 0.05$).

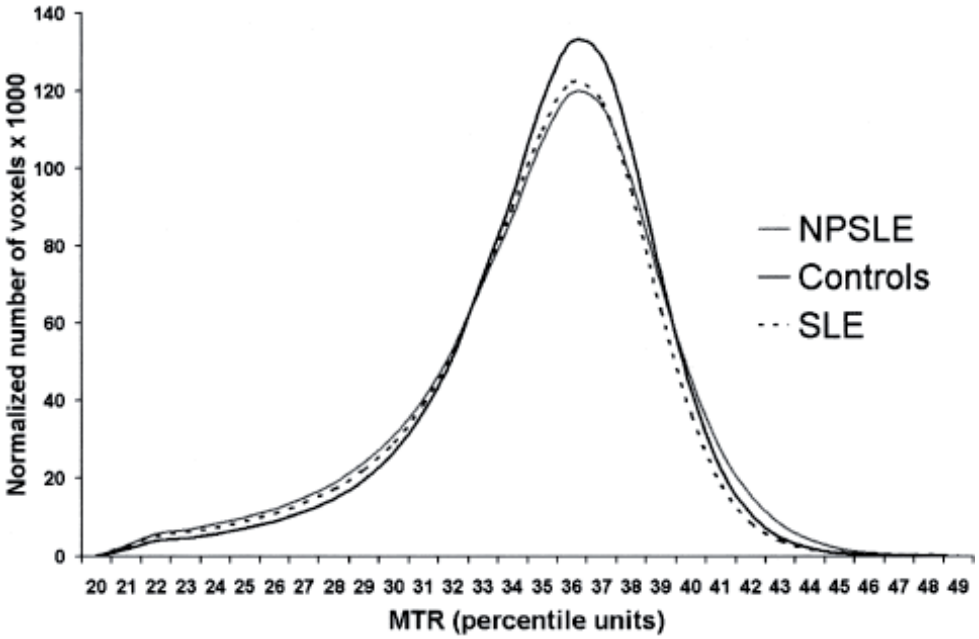

Figure 1 .Average peak height of the magnetization transfer ratio (MTR) histogram of the parenchyma of the brain, normalized to the number of voxels in the histogram, for each study group. NPSLE = neuropsychiatric systemic lupus erythematosus.

Table 3 Association between MTR histogram parameters and the 1H-MRS neurochemical ratio

	β (R)
Parenchyma peak height	0.284 (0.498)†
Parenchyma mean	-‡
White matter peak height	0.406 (0.536)§
White matter mean	-‡
Gray matter peak height	0.392 (0.606)§
Gray matter mean	0.298 (0.558) †

(NAA:creatinine) in all study groups (n = 67 subjects)*

* MTR = magnetization transfer ratio; 1H-MRS = proton magnetic resonance spectroscopy; NAA = N-acetylaspartate.

† $P < 0.05$ by linear regression analysis, corrected for disease duration and sex.

‡ Association was not significant.

§ $P < 0.005$ by linear regression analysis, corrected for disease duration and sex.

The linear regression analysis of the neuropsychiatric syndromes present in ≥5 patients and the MTR histogram parameters showed that only cognitive dysfunction was significantly associated with MTR histogram parameters. These results were corrected not only for disease duration and sex, but also for arthritis and renal disorder to remove the influence of these systemic disease symptoms on the MTR histogram parameters. Cognitive dysfunction was significantly associated with a lower peak height of the MTR histogram

of the brain parenchyma (β = -0.435, R = 0.664, $P < 0.001$), the white matter (β = -0.445, R = 0.647, $P < 0.001$), and the gray matter (β = -0.306, R = 0.663, $P < 0.01$).

Analysis of the influence of aCL did not reveal any significant influence of these antibodies on the MTR histogram parameters after correction for disease duration and sex.

DISCUSSION

The most important findings of this study were, first, that the MTR peak height of the brain parenchyma was decreased in NPSLE patients compared with healthy controls. Second, the lower peak height of the MTR histogram of the brain parenchyma was significantly associated with lower NAA:creatinine ratios after correction for disease duration and sex, suggesting neuronal dysfunction. Third, the lower MTR peak height of the brain parenchyma was associated with cognitive dysfunction but not with cerebrovascular disease, seizures, or headache, after correction for disease duration, sex, and SLE criteria.

Additional findings were as follows. First, analysis of the MTR histogram parameters and the neurochemical ratios revealed that a lower peak height of the white and the gray matter as well as a lower mean MTR value of the brain parenchyma and the gray matter were also significantly associated with lower NAA:creatinine ratios, indicating neuronal (i.e., axonal) dysfunction. Second, analysis of the SLE criteria revealed that arthritis was associated with higher mean MTR values in the brain parenchyma and white matter. In addition, renal disorder was associated with a lower peak height of the MTR histogram of the brain parenchyma and white and gray matter. Third, analysis of neuropsychiatric syndromes and the MTR histogram parameters revealed that a lower MTR peak height of the white matter was associated with cognitive dysfunction but not with cerebrovascular disease, seizures, or headache, after correction for age, sex, and SLE criteria. Finally, analysis of the relationship between MTR histogram parameters and the presence of aCL revealed no significant associations.

The lower peak height of the MTR histogram in NPSLE patients compared with healthy controls is consistent with previous studies. (12) Our data show similar, although not significant, trends for selective lowering of the peak height in the gray matter compared with those in the study by Steens et al. (13) Quantitative analysis of average diffusion coefficient (ADC) maps in SLE patients has also revealed subtle damage not detected by conventional MRI. (21,22) Further study of the relationship between quantitative MTR and ADC analysis could help elucidate the underlying cause of these findings.

This is the first study to associate SLE criteria with neuroimaging findings. We found that arthritis was significantly associated with higher mean MTR of the brain parenchyma and the white matter. A possible explanation for this could be the early phase of Wallerian degeneration (23) or the influence of specific antirheumatic drugs on the mean

MTR values. Although we did not correct for the influence of medication, due to the large variation in dosage and duration of the medication, Steens et al (24) showed that antirheumatic drugs did not have an influence on quantitative neuroimaging parameters or ^{1}H-MRS metabolite ratios. In our study, the NPSLE patients generally took more medication than the SLE patients. This is probably due to the fact that neuropsychiatric involvement is detected later in the disease process or during flares, when more medication is prescribed.

Renal disorder was significantly associated with lower MTR peak height in all ROIs. This could be an epiphenomenon; for instance, antibody-immune complex deposition occurs simultaneously in the renal vasculature and in the cerebral (micro) vasculature. (25,26) Alternatively, renal dysfunction might lead to hypertension and subsequently to some form of (vasogenic) edema in the brain. In summary, these associations between SLE criteria and MTR histogram parameters suggest that these criteria either have a direct effect on the structural integrity of the brain or have an indirect effect through the effects of medication used to treat these conditions.

The finding that not all neuropsychiatric syndromes are associated with MTR histogram parameters after correction for the presence of SLE criteria is inherent to the greater heterogeneity of the syndromes. In our study, 7 of 34 NPSLE patients had cognitive dysfunction. Consequently, little difference between the average histograms of the brain parenchyma in the NPSLE and the SLE groups was seen (Figure 1). This suggests that different pathogenic pathways result in distinct pathology, which is expressed as a variety of clinical symptoms. (6) The fact that cognitive dysfunction is specifically associated with a lower MTR peak height is consistent with results of a previous study of associations between cognitive dysfunction and MTR peak height by Bosma et al. (20) Accordingly, we found that a lower MTR histogram peak height was significantly associated with a lower NAA:creatinine ratio after correction for disease duration and sex. This suggests that MTR histogram peak height reflects neuronal dysfunction, damage, or loss. (27) Although previous studies have investigated MRS and MTR changes in SLE and NPSLE, these studies did not associate specific SLE and NPSLE characteristics with changes in the absolute metabolite concentrations or metabolite ratios or MTR histogram parameters. (14, 27-29) Our data unequivocally show that a decrease in MTR peak height is associated with neuronal dysfunction, damage, or loss and subsequent cognitive dysfunction.

Finally, after correction for disease duration and sex, we did not find any significant association between aCL and the MTR histogram parameters. Anticardiolipin antibodies are thrombogenic and are associated with the occurrence of thromboembolic events in SLE. In addition, we did not detect any large increases in lactate, a sign of anaerobic metabolism, consistent with previous ^{1}H-MRS studies. (30) These findings suggest that other pathogenic mechanisms besides ischemia, caused by vasculitis or thrombosis, are also responsible for the neuropsychiatric involvement in at least some of the SLE

patients. A possible pathogenic pathway is direct neuronal damage and dysfunction by antibodies, as was suggested by recent findings in mouse models of NPSLE. (31-33) However, the absence of lactate does not preclude ischemia as a pathogenic mechanism, and subtle microvascular ischemia could also explain our findings. Platelet-, leukocyte-, or vasculopathy-related thromboembolic events might still be responsible for neuropsychiatric involvement through edema or extravasation of neurotoxic molecules. Therefore, the neuronal dysfunction detected by MTR histogram peak height could be due to direct neuronal damage, subtle microvascular ischemia, or both.

A limitation of this study is the small number of patients per syndrome; this is inherent to the heterogeneity and large number of possible neuropsychiatric syndromes in SLE. This also prohibits definite conclusions about the relationship between neuropsychiatric syndromes and MRI findings. Another limitation is the fact that we do not have quantitative clinical data, but only dichotomized data on whether a certain syndrome is present or not. Furthermore, despite a threshold and eroding the segmentation in 2 dimensions, partial-volume effects are still present in our MTR data. No erosion was performed in the Z direction, since this would result in a very small residual area that is no longer representative of the segmented tissue type.

Finally, a limitation could be the fact that the MTR histogram parameters were not derived from the same area as the voxel of interest of the ^{1}H-MRS. However, we chose to compare published and well-established methods and thus compared histograms of the whole brain and white and gray matter instead of MTR parameters from the voxel of interest in the left centrum semiovale. MTR histogram analysis of a small ROI like the spectroscopy voxel is not common practice and would dramatically lower the number of voxels per histogram bin. This would increase the standard deviation of the histogram parameters and lower the robustness compared with whole-brain analysis, especially of the peak height, which has proven in the past to be the most clinically valuable parameter in NPSLE. (14)

In conclusion, MTR peak height reflects neuronal dysfunction, damage, or loss, as detected by ^{1}H-MRS. Furthermore, MTR peak height is associated with cognitive dysfunction but not with other neuropsychiatric syndromes seen in our study. Previous results from MTR histogram studies should be reconsidered and are possibly only valid in patients with cognitive dysfunction.

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