

Chapter 2

Detection of Change in CNS Involvement in Neuropsychiatric SLE: a Magnetization Transfer Study

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ABSTRACT

Purpose

To assess whether magnetization transfer imaging (MTI) parameters change during clinical changes in NPSLE patients.

Methods

Nineteen female patients (mean age = 37.5 years, range = 19-64) underwent MTI on at least two separate occasions (mean time between scans = 25.4 months, range = 5.4-52.3 months). Twenty-four pairs of scans of 19 patients were available. Each patient's clinical course was classified as improved, stable, or deteriorated. Whole-brain magnetization transfer ratio (MTR) histograms were generated. The peak height of these histograms was used as an estimate of parenchymal integrity. Based on the change in clinical status, paired examinations were grouped and tested for significant differences between the first and second examinations using paired-samples *t*-tests.

Results

Four patients clinically deteriorated, all patients showed a significant peak height decrease (mean decrease = 8.6%, $P = 0.02$), and in 14 patients with stable disease the peak height did not change significantly (mean increase = 0.4%). Six patients clinically improved, and all showed a significant relative peak height increase (mean increase = 12.0%, $P = 0.02$).

Conclusion

The peak height of whole-brain MTR histograms corresponds to changes in the clinical status of individual NPSLE patients. This suggests that MTI can be a valuable tool in the clinical assessment of such patients.

INTRODUCTION

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

Primary NPSLE is divided into focal and diffuse disease. Focal NPSLE is strongly associated with the occurrence of thrombo-embolic events. (4) Diffuse primary NPSLE is a group of neurologic, psychiatric and cognitive syndromes comprising aseptic meningitis, demyelination syndrome, seizures, cognitive dysfunction, headache, chorea, mood disturbances, myelopathy, cranial neuropathy, anxiety disorders, psychosis and disorientation. (5) Like most autoimmune diseases, the disease activity of NPSLE fluctuates. In most NPSLE patients with diffuse symptoms, such as headache, cognitive impairment, and coma, conventional diagnostic imaging and other clinical tests fail to provide an explanation for the clinical picture. Research has benefited from a detailed case-definition system, grouping patients with the same neuropsychiatric syndromes, but in clinical practice the diagnosis is generally still made per exclusionem. (6;7)

Magnetization transfer imaging (MTI) is an MRI technique that provides quantitative information. It can be used to detect the severity of cerebral involvement in several diseases. (8-11) Besides providing quantitative information on lesions that are visible on conventional MR images, MTI has proven to be more sensitive to the presence of disease than conventional MRI techniques in normal appearing brain tissue. (8-12) Still, MTI has not yet been applied to follow the clinical course of individual patients.

The aim of this study was to detect changes in cerebral involvement in NPSLE using MTI during changes in clinical status of the NPSLE patients. Clinical changes were defined as changes in disease activity of the 1999 ACR criteria for neuro-psychiatric syndromes in SLE as determined by an expert panel. (6)

METHODS

Subjects

The scientific and ethics review board of our institution approved this study and all patients gave informed consent after the nature of the procedure had been fully explained. Patients were selected from the patient files of the Department of Rheumatology of our

institution. Selection was based on the 1982 revised ACR criteria for the classification of SLE, and the availability of MTI studies on at least two separate occasions. (13) Based on clinical data from the patient files, a history of CNS involvement according to the 1999 American College of Rheumatology NPSLE case definitions was determined by an expert rheumatologist blinded to the MTI results. (6)

Nineteen patients were included in this study. At the time of the first MRI session they ranged in age from 19 to 64 years (mean age = 37.9 years). The mean disease duration of SLE in these 19 patients at the time of their first MRI examination was 8.2 years (0 months to 29 years), and neuropsychiatric symptoms had been diagnosed on average 3.2 years (0 months to 18 years) prior to the first MRI. Three patients underwent more than two MTI scans. These patients had a fluctuating clinical course over time. For these patients subsequent MRI scans were paired (two pairs for the patients with three subsequent measurements, and three pairs for the patient with four subsequent measurements). This yielded 24 pairs of observations in total. In the 24 pairs of observations the second MRI was performed on average after 24.9 months (range = 5.4-52.3 months).

The patients were classified as having active or inactive NPSLE at the time of MRI, and their neuropsychiatric status between the first and the second MRI sessions was classified as deteriorated, stable, or improved by the same observer (Table 1). None of the three classification groups included more than one paired analysis for the same patient. Two experienced raters performed classification independently, and in case of doubt or disagreement an experienced rheumatologist in NPSLE classified the patient independently as well, after which consensus was reached during a discussion between all raters to obtain a final classification. In addition, the experienced rheumatologist classified every fifth case as a quality control. There was disagreement between the two raters about two of the 24 scores. All three raters were blinded to the MTI results. Subsequently the paired measurements were divided into three groups: deteriorated, stable, and improved.

MR Imaging protocol

All MRI scans were carried out on a Philips Gyroscan Intera ACS-NT 1.5T MR scanner (Philips Medical Systems, Best, The Netherlands). Transaxial proton-density (TR/TE: 2500/30 ms), T₂-weighted (TR/TE: 2500/120ms) and FLAIR (TR/TI/TE: 8000ms/2000ms/120ms) were acquired with the following parameters: field of view 220mm, matrix 256x256, 22 6mm slices with 0.6mm slice gap. MTI was performed using a 3D gradient-echo pulse sequence with a TE/TR of 6/106 ms and a flip angle of 12°(14), resulting in proton density contrast in the absence of MT saturation pulses. An MTI study comprised two consecutive sets of axial images, the first with and the second without a radio frequency saturation pulse (sinc-shaped, 1100 Hz upfield of H₂O resonance).

Table 1. Patient characteristics and MTR peak height change.

Pt	Age	NP syndrome*	1 st Peak height	2 nd Peak height	Peak height change	Clinical Change
1	38	CVD, seizures, CD	97.04	91.35	-5.87%	deteriorated
2	29	CVD	116.19	121.51	4.58%	stable
3	33	chorea	99.81	127.37	27.61%	improved
4	64	CD	101.07	114.53	13.31%	improved
5	41	headache, CD, chorea	94.64	101.16	6.90%	improved
6	27	seizures	133.05	123.28	-7.34%	stable
7	19	psychosis	100.70	105.91	5.18%	improved
8	34	cranial neuropathy, myelitis	122.48	111.30	-9.12%	deteriorated
8	35	transversa, demyelinating	111.30	127.17	14.25%	improved
8	35	syndrome	127.17	120.40	-5.32%	stable
9	25	seizures	91.60	82.62	-9.80%	stable
10	27	mononeuropathy	116.74	120.55	3.27%	stable
11	41	mononeuropathy	110.46	111.22	0.69%	stable
12	36	CVD, CD	108.99	110.80	1.66%	stable
13	59	headache, CD plexopathy	109.37	111.92	2.33%	stable
14	26	myelitis transversa	110.81	116.55	5.18%	stable
15	32	CVD, cogn dysf	94.23	91.90	-2.47%	stable
16	41	CD	104.56	115.13	10.11%	stable
17	26	seizures	122.42	122.06	-0.29%	stable
18	54	CD, mood disorder	120.60	121.14	0.44%	stable
18	55		121.14	105.34	-13.04%	deteriorated
18	57		105.34	110.50	4.90%	improved
19	36	CVD, headache, seizures	126.14	118.17	-6.31%	deteriorated
19	39		118.17	121.18	2.55%	stable

* According to the ACR nomenclature and case definitions for neuropsychiatric lupus syndromes (6). Age was defined as age at the first MRI scan.

§ CVD = cerebrovascular disease

CD = cognitive dysfunction

Twenty-eight contiguous 5mm slices were acquired with a field of view of 220mm and a matrix of 256x256 (acquisition percentage 50%). Scanning time for MTI was 11 minutes and 27 seconds; total scanning time for the entire MRI examination was \pm 21 minutes.

Image processing

An experienced neuro-radiologist analyzed conventional MRI sequences for the presence of abnormalities. MTI data were transferred to an offline workstation and segmented using SNIPER as described previously. (15) [figure 1] MTR histograms, normalized for tissue volume, were generated for the whole brain and for the normal appearing brain tissue. From these MTR histograms the peak height was calculated. (12;16;17) The peak height of these histograms was used as measure of cerebral lesion load. (17)

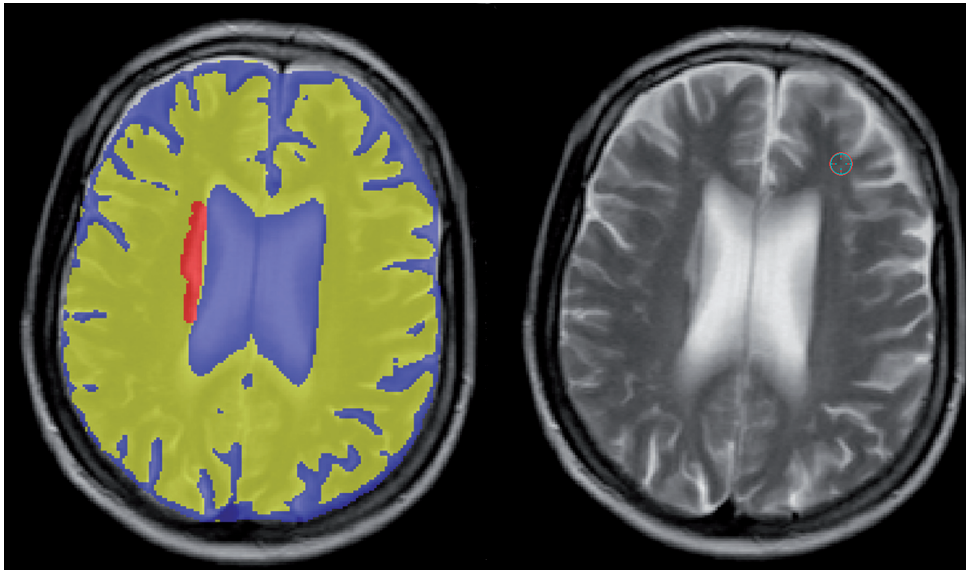


Figure 1. Original axial T2 weighted image (left) and SNIPER segmentation (right), showing segmentation of the intracranial compartment (mask), brain parenchyma (yellow), CSF (blue) and lesions (red).

Statistics

Statistical analysis was performed with commercially available software (SPSS version 11.5 for windows; SPSS, Chicago, Ill). Within the deteriorated, the stable and the improved group a paired samples *t*-test was performed to test for significant differences between the first and the second MTR peak height measurement.

RESULTS

None of the NPSLE patients had major abnormalities on conventional MRI.

Four of the 24 pairs of observations that were made in our 19 patients were classified as deteriorated. In all clinically deteriorated patients the MTR peak height decreased between the first and second scans. On average this decrease was 8.6% ($P = 0.02$, range = -13.0% to -5.9%) in this group. [figure 2]

Fourteen patients were classified as stable disease. In this group an average increase in peak height of 0.4% ($p=0.79$) was observed between the first and second scan (range -9.8% to 10.1%). [figure 2]

Six patients were classified as improved. In all clinically improved patients the MTR peak height increased between the first and second scan. On average this group showed a relative increase in peak height of 12.0% ($p=0.02$) on average (range 4.9% to 27.6%). [figure 2] A typical improved case is shown in figure 3.

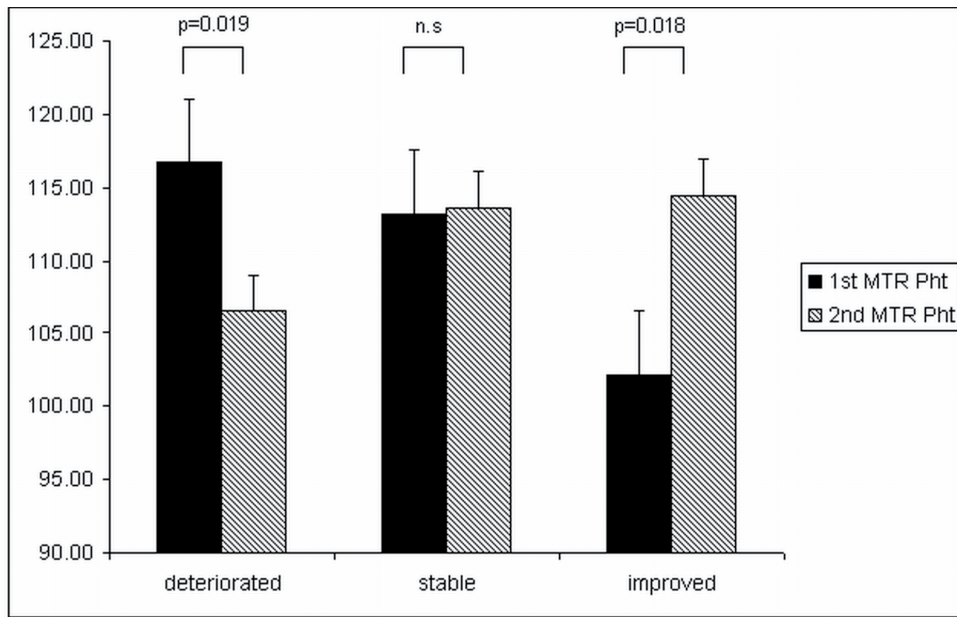


Figure 2 Mean MTR peak height and standard error of the first and the second scan per clinically classified patient group (deteriorated, stable and improved).

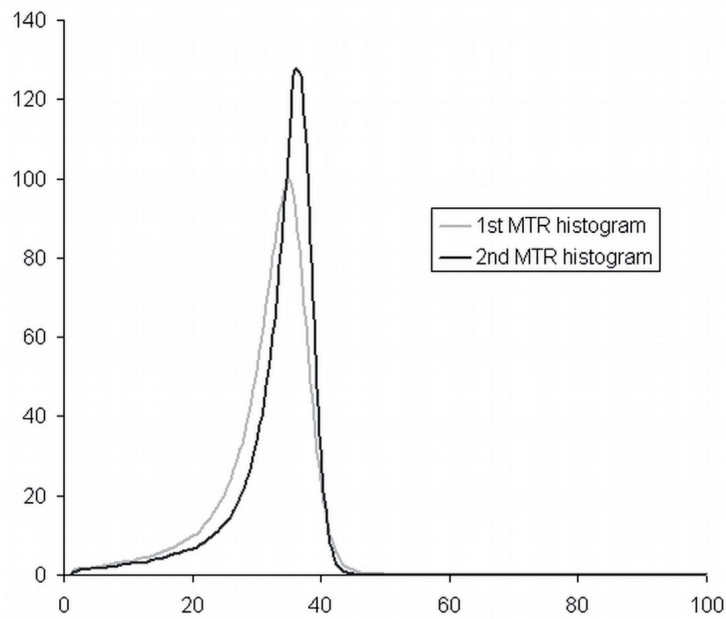


Figure 3. Reversible peak height lowering in patient 3. [Table 1.]
 Two histograms of patient 3: during the 1st histogram patient 3 suffers from chorea and is classified as acute active; at the time of the 2nd histogram, almost 6 months later, the chorea is not active.

DISCUSSION

This study shows that changes in clinical status of individual NPSLE patients correspond with changes in MTR peak height. In addition, our results demonstrate that brain involvement in NPSLE patients, as detected by MTI, is at least partly reversible.

MTI was recently applied in NPSLE patients in several studies with a cross sectional design. (12;16) In these studies, NPSLE patients without visible abnormalities on conventional MR sequences had a lower MTR peak height compared to SLE patients without neuropsychiatric symptoms and healthy controls. (12;16;17) Furthermore, these cross-sectional studies found correlations between MTR peak height and psychiatric, neurologic, and cognitive functioning, suggesting that the MTR peak height is clinically relevant. (17) The present study is the first study to evaluate whether MTI can also be used to substantiate the clinical course in individual NPSLE patients. The findings that MTR peak height decreases in patients who deteriorate and that MTR peak height increases in patients who improve, suggests that MTI is indeed a valuable objective measure to follow the clinical course in NPSLE. Other techniques, such as diffusion-weighted and tensor imaging may be able to provide such information, and similar studies with these techniques could be of interest.

In relapsing-remitting MS, another fluctuating autoimmune disease of the CNS, progressive lowering of the MTR peak height occurs over time despite short term oscillation of MTI parameters during flares and remissions. (18) This gradual decrease of MTR peak height could represent an accumulation of cerebral damage. The question whether this accumulation is also present in NPSLE cannot be answered in this study due to the limited observation period in our patients. However, a cross sectional correlation between NPSLE duration and MTR peak height has not been found. (17)

The nature of the pathophysiological substrate of the reversible MTR change in NPSLE patients is unclear. Reversible changes of integrity of parenchyma probably consist of edema. Neuronal loss would not show such a degree of reversibility and neuronal apoptosis is not a common finding in postmortem studies of NPSLE. Conversely, general vasculopathy, is often found diffusely throughout the brain. (19-23) Although our patients did not show major abnormalities on the conventional images, vascular damage to larger vessels cannot be excluded. (24;25) Inflammation influences the vessel walls and permits extravasation of fluid and inflammatory mediators into the brain tissue. This leads to inflammatory brain edema, in which inflammatory mediators cause cellular swelling. Therefore, the reversible damage measured by MTI possibly represents general inflammatory brain edema, (both cytotoxic and vasogenic). (26)

A limitation of this study is that changes in activity of the neuropsychiatric syndromes are hard to quantify without the availability of validated clinical assessment scores. Patients with pronounced clinical improvement or deterioration are likely to be correctly

classified as such. However, patients with more subtle changes in clinical status are more prone to incorrect classification as “clinically stable”. In addition the number of patients in this study is small and larger studies are needed to confirm our findings. A further source of potential misclassification is the inclusion in the ACR case definition system of peripheral neuropathies such as patients 10 and 11. Still, the clinical course in both NPSLE patients did not change, and consequently neither did the MTI peak height.

In conclusion, the increase in MTR peak height during clinical improvement in NPSLE patients suggests that the MTR peak height reflects, at least in part, reversible damage. Although these findings are non-specific (possibly reflecting different pathological mechanisms) and do not show an increased specificity, the sensitivity for CNS involvement is improved. This study suggests that in addition to neuropsychological and neurological evaluations, MTI can be a valuable tool for assessing cerebral involvement in NPSLE patients.

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