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# MRI and 2D-CSI MR spectroscopy of the brain in the evaluation of patients with acute onset of neuropsychiatric systemic lupus erythematosus

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**Abstract** MRI and 2D-CSI spectroscopy were performed in eight patients with systemic lupus erythematosus who presented with acute onset of neuropsychiatric lupus (NP-SLE), and in seven normal controls to evaluate for differences in metabolic peaks and metabolic ratios between the two groups. Also, the interval change of the metabolic peaks and their ratios during treatment in the NP-SLE patient group was evaluated. Metabolic peaks for *N*-acetylaspartate (NAA), choline (Cho), creatine (Cr), and lactate/lipids (LL) and their ratios (NAA/Cr, NAA/Cho, Cho/Cr, LL/Cr) were determined at initial presentation and 3 and 6 months later. In the eight lupus patients compared to the seven normal controls, NAA/Cho ratios were lower at presentation (1.05 vs 1.25; $p = 0.004$) and decreased even further at the three month follow-up (0.92 vs 1.05; $p = 0.008$). In contrast, both Cho/Cr (1.42 vs 1.26; $p = 0.026$) and LL/Cr ratios (0.26 vs 0.19; $p = 0.002$) were higher in the lupus patients at presentation compared to the controls and did not significantly change at three and six months follow-up. The NAA/Cr ratios were lower in the lupus patients compared to the controls at presentation but the difference was not statistically significant. However, the mean NAA/Cr significantly decreased from the initial examination to the three month follow-up (1.42 vs 1.32; $p = 0.049$) but did not significantly change from the three to the six month follow-up examinations. The NAA/Cr, Cho/Cr, and NAA/Cho ratios varied significantly ($p < 0.05$, $p < 0.05$, $p < 0.05$, respectively) between the 17 different locations measured in the brain in all eight patients and seven controls. Both the NAA/Cr ratios and the Cho/Cr ratios were also significantly lower in the gray matter than in the white matter ($p < 0.0001$) in both patients and controls, whereas the LL/Cr and NAA/Cho ratios were not significantly different. In conclusion, 2D-CSI MR spectroscopy may be useful in the early detection of metabolic CNS changes in NP-SLE patients with acute onset of new neurological symptoms as well as in the follow-up after treatment to assess presence and changes in metabolic brain injury. However, although there are detectable differences between normal individuals and lupus patients it is currently unclear whether these relate to the acute episode. Future studies are needed comparing NP-SLE patients with active CNS involvement with those inactive disease.

**Keywords** NP-SLE · SLE · MRI · MRS · Spectroscopy · Brain

## Introduction

Neuropsychiatric systemic lupus erythematosus (NP-SLE) occurs in 25–70% of patients with lupus and is associated with increased morbidity and mortality [1]. The clinical manifestations of NP-SLE include psychosis, stroke, and epilepsy, in addition to more subtle symptoms such as headache and neurocognitive dysfunction [2]. Patients with concomitant antiphospholipid antibodies (APL-ab) are at additional risk for neuropsychiatric events. Lupus patients are also at increased risk for a wide range of CNS events related to immunosuppressive therapy, including infection and drug toxicity, hypercoagulability, and accelerated atherosclerosis.

CNS vasculitis and/or cerebritis represent a potentially severe form of NP-SLE and may present with seizures, movement disorders, altered consciousness, stroke, and coma [3]. While CNS inflammation is uncommon in SLE, the clinician nevertheless must entertain this diagnosis any time a lupus patient presents with CNS signs or symptoms. Although clinical assessment is the keystone in the diagnosis of NP-SLE, the diagnosis is often difficult and remains presumptive in some patients. MR imaging findings are variable and in some cases the MRI is unremarkable [4–9]. Recently it has been suggested that other modalities such as MR spectroscopy could be an additional tool in the evaluation of NP-SLE. MR spectroscopy is the only non-invasive technique routinely used in clinical practice and research that allows assessment of in vivo metabolism at the molecular level. Accordingly, MRS might be more sensitive in the early detection of brain injuries in NP-SLE. Such early detection of metabolic brain abnormalities and time interval change may impact clinical treatment, aid in monitoring therapy, and increase our knowledge about the nature of brain involvement in patients with SLE or active NP-SLE.

Some previous studies, mainly using single-voxel spectroscopy (SVS), have demonstrated a decrease in the *N*-acetyl-aspartate/creatine (NAA/Cr) ratio and an increase in choline/creatine (Cho/Cr) ratio in white matter (WM) and/or basal ganglia of NP-SLE patients compared to those of normal healthy volunteers [10–14]. These reports indicate that MR spectroscopy might be a helpful tool in the early detection and evaluation of CNS abnormalities in SLE patients. The use of 2D-CSI in the evaluation of NP-SLE patients has been very limited. Based on these previous reports, utilizing mainly SVS, we decided to evaluate the presence of CNS abnormalities and their interval change in NP-SLE patients with the acute onset of new neurological symptoms, as identified by MRI and 2D-CSI MR spectroscopy.

We hypothesize that patients with acute onset of NP-SLE have abnormal metabolic peaks and ratios compared with healthy individuals. We also postulate that these metabolic differences will change or normalize during treatment. To test this hypothesis, 11 patients with acute onset of neurological signs and symptoms suspected to be related to NP-SLE were examined serially with conventional MRI and MR spectroscopy at presentation, as well as three and six months later. For the purpose of comparison, seven healthy volunteers underwent one MRI and MRS examination.

## Material and methods

Eleven female patients, aged 35–59 years, mean 44.4 years, were included in this prospective study. Patients were included if they: (1) fulfilled the 1982 revised criteria for SLE set forth by the American Rheumatism Association [14] and (2) had new onset of neurological symptoms suspected to be related to their known SLE within a week prior to the initial examination. Three of the patients had associated Sjögren's disease with no

**Table 1** Patient demographics including diagnosis, duration of disease, and presence or absence of antiphospholipid antibodies (APL-Ab). Patients nos. 4, 7, and 10 were excluded from spectroscopy statistics as final clinical diagnosis did not confirm NP-SLE

| Patient no. | Gender | Age | Race[a] | Diagnosis | Duration[b] | APL+/APL−[c] |
|---|---|---|---|---|---|---|
| 1 | Female | 45 | W | SLE | 16 years | − |
| 2 | Female | 46 | W | SLE | 20 years | − |
| 3 | Female | 32 | W | SLE | 23 years | − |
| 4 | Female | 59 | AA | SLE | >5 years | + |
| 5 | Female | 44 | AA | SLE | >5 years | + |
| 6 | Female | 52 | W | SLE | 14 years | + |
| 7 | Female | 41 | W | SLE + Sjogren | 10 years | + |
| 8 | Female | 55 | W | SLE + Sjogren | >10 years | − |
| 9 | Female | 23 | As | SLE | 6 months | + |
| 10 | Female | 45 | AA | SLE | 19 years | − |
| 11 | Female | 46 | W | SLE + Sjogren | 13 years | + |

[a]AA, Afro-American; As, Asian; W, white.
[b]Duration of disease at the time of the initial MRI study.
[c]Presence of antiphospholipid antibodies (APL-Ab) (+/−).

clinical evidence of CNS involvement (Table 1). All patients underwent conventional MR of the brain and MR spectroscopy within 24 h of admission to the hospital. Follow-up examinations, including conventional MRI of the brain and MR spectroscopy, were performed three and six months after the initial study. All work that was related to this research was performed in accordance with our institutional review board and with the expressed informed consent of the participants.

The MR examinations were performed on a 1.5 T scanner (GE Medical Systems, Milwaukee, USA). The conventional MRI examination included: pre- and post-contrast enhanced axial and sagittal T1-weighted images, axial T2-weighted images with fat saturation, axial FLAIR and diffusion-weighted images, and post-contrast enhanced T1-weighted images in the coronal projection. Twenty milliliters of Gd-DTPA (Magnevist, Berlex Laboratories, USA) was intravenously injected before post-contrast enhanced images.

The MR images were evaluated for brain volume loss (none, mild, moderate, and severe), abnormal signal, abnormal contrast enhancement, abnormal diffusion, presence of hemorrhage or mineralization, and any additional abnormalities. Brain lesions were either classified as infarct-like (moderate to large-sized, roughly wedge-shaped areas of increased T2/FLAIR intensity, and/or encephalomalacia involving gray matter (GM) and WM) or WM lesions (further categorized as subcortical, deep, periventricular, punctuate, or patchy). Lesions were further characterized as to location and number. Serial imaging was evaluated to characterize lesions as stable, improving, or progressing. Diffusion-weighted images were examined for areas of restricted or increased diffusion, with ADC maps utilized. MR spectroscopy was performed as the last sequence in the examination and therefore performed after IV contrast administration in all patients. The MR spectroscopy consisted of 2D-CSI MR spectroscopy (2D-CSI) at the levels of basal ganglia and of the WM of centrum semiovale.

The following parameters were used for the 2D-CSI spectroscopy: PRESS sequence, TE/TR 144/1,000 ms, field of view (FOV) 16 cm, matrix $16 \times 16$, slice thickness 10–20 mm, acquisition one average, scan time 4.20 min. The volume of interest (VOI) was placed on non-angled contrast-enhanced axial T1-weighted or on non-angled FLAIR images. One VOI was placed at the level of the basal ganglia and a second VOI was placed in the periventricular WM superior to the ventricles (centrum semiovale). Multiple voxels within the VOI were systematically placed in GM, WM, and basal ganglia in both hemispheres of each of the eight patients and the seven normal controls. These multiple voxels were separately evaluated for both groups.

Out-of-field-of-view saturation bands were routinely placed in all MRS examinations. Automatic pre-scanning was performed twice before each spectroscopic scan to assure adequate water suppression and acceptable full-width half-maximum (FWHM) values.

In all cases, the data were transferred to independent workstation (Advantage Windows; GE Medical Systems) using Functool 2000 software (GE Medical Systems) for post-processing of the spectra. The spectra were analyzed for the signal intensity of the following metabolites: NAA, Cho, Cr, and presence of lactate/lipids (LL). The following ratios were calculated: NAA/Cr, Cho/Cr, NAA/Cho, and LL/Cr. The signal intensity was measured as the integration between the peak edges (surface under the peak), which were carefully selected by the author performing the spectra analysis to ensure that the whole peak was well defined. As long TE (144 ms) was used to collect the data, the baseline of the spectrum was fairly flat due to lack of macromolecule contamination, thus, the baseline of the spectrum was not subtracted from the peak integration. The mean signal to noise ratios (S/N) of creatine and choline was estimated as 15–20, the noise was defined as root-mean-square of the values between 0.5 and 1.0 ppm in the spectrum. No threshold was used in the calculations of the present data. For comparison of the MR spectroscopy findings seven healthy volunteers were examined with a limited conventional brain MRI including axial T1 and FLAIR images without contrast administration followed by MR spectroscopy using the same sequences as described above.

Clinical data for each patient was extracted via a focused search of our institution's computerized data record, including patient demographics (age, sex, and race), disease characteristics (primary and secondary diagnoses, duration of diagnosis, medications, presence of APL-ab, clinical symptoms, neurological diagnosis, pathologic diagnosis, therapy, and clinical course).

Summary demographics and clinical characteristics of the 11 patients entered in the study are presented in Table 1. Presenting symptoms for each patient were classified according to the 1999 American College of Rheumatology Nomenclature and Case Definitions for Neuropsychiatric Lupus Syndromes [3] and are summarized in Table 2.

## Statistical evaluation

Since the repeated measurements in each subject were performed in 17 identical anatomical locations and at (6 out of 8 patients) 3 different time points, we have used a linear mixed model to analyze the response variable assuming location is a random effect. We also assume that within each subject, the correlation between any two replicated responses is the same. ANOVA was used to evaluate for variations in metabolic ratios at different locations. The Student's $t$-test was used for each voxel location comparison. The level of significance was set to $p < 0.05$.

**Table 2** Clinical symptoms at time of presentation, medical treatment, interval change in clinical symptoms, and final diagnosis for this event of acute symptoms for the 11 SLE patients

| Patient no. | Clinical symptoms | Medical treatment | Interval change in symptoms | Final diagnosis |
|---|---|---|---|---|
| 1 | Dysphasia, blurred vision | Methylprednisolone, prednisone 40–20 mg | Improved | Unclear etiology most likely lupus cerebritis |
| 2 | Transient double vision | None | Improved | Ischemic event, lupus cerebritis |
| 3 | Acute left weakness | Methylprednisolone | Improved | Lupus cerebritis |
| 4 | Mental status decline, increased tremor | Multiple medications. No additional medication | Improved | Drug related symptoms |
| 5 | Cognitive dysfunction, history of seizures | None | Unchanged | Lupus cerebritis |
| 6 | Headache | Hydroxychloroquine, dehydroepiandosterone | Improved | Lupus cerebritis |
| 7 | Disorientation, headache | None | Unchanged | Dissociative fugue, conversion disorder |
| 8 | Increased tremor, tics, diplopia | Prednisone | Improved | Lupus cerebritis |
| 9 | Headache, nephritis | Cytophosphamide methylprednisolone | Improved | Lupus cerebritis |
| 10 | Syncope, headache, difficulties in finding words | Multiple medications. No additional medication | Improved | Orthostatics |
| 11 | Severe headache, meningitis | Methylprednisolone, prednisone | Improved | Lupus cerebritis |

## Results

Based on clinical criteria 8 out of the 11 SLE patients were classified as NP-SLE at the final diagnosis. Three patients were classified as having symptoms not related to NP-SLE (patients nos. 4, 7, and 10) as final diagnosis and therefore their results have been excluded from the final analysis. As this study concerns patients with acute onset of neuropsychiatric SLE, the results are dealing only with these eight patients and seven controls, except for Tables 1, 2, and 3, which present all the 11 SLE patients that entered the study.

Six of the eight patients underwent all three examinations and therefore completed the study. Two patients underwent two of the examinations but declined to participate in the final follow-up examination six months after the initial study. In these eight patients, the cause of their acute symptoms was confirmed as lupus with CNS involvement. In the remaining three patients who are not included into the proper study of NP-SLE, the likely etiology of their symptoms was believed to be drug-related (patient no. 4), orthostatic (patient no. 10), and dissociative fugue/conversion disorder (patient no. 7) (Table 2).

Four of the eight patients were antiphosolipid antibody positive (APL-ab+) and four were negative (APL-ab−) (Table 1). Six of the eight patients (75%) had major neuropsychiatric symptoms such as cognitive problems, weakness, visual problems, and meningismus. Two of the eight included patients had associated diagnosis of Sjögren's disease, the third patient (no. 7) (Table 1) with the clinical history of Sjögren's disease belonged to the three excluded patients. Two patients (25%) had headache and/or mild cognitive complaints such as difficulties in concentration, memory, or word finding as the only problem at time of the initial study. Morphological brain abnormalities were seen in five of the six patients with major neuropsychiatric symptoms and in both patients with minor neuropsychiatric symptoms on conventional MRI. Six patients had some medical treatment for SLE, most commonly prednisone prior to the initial study. After the initial admission, four patients were treated with additional medication: methylprednisolone (four patients), prednisone (two patients), and cyclophosphamide (one patient). The remaining patient received no additional medication. Seven of the eight NP-SLE patients (88%) had a clinical response/improvement to therapy whereas one patient did not improve (Table 2).

### MR imaging of the brain

Imaging findings are summarized in Table 3. Seven of the eight patients (86%) had abnormal findings on MR imaging. The most common findings were scattered

**Table 3** Findings at the MRI of the brain in each of the 11 SLE patients entering the study at the different examinations

| Patient no. | Initial study at time of presentation of symptoms | Three month follow-up | Six month follow-up |
|---|---|---|---|
| 1 | Normal | Normal | Normal |
| 2 | Scattered bilateral nonspecific WM foci, mild brain volume loss | Unchanged | Unchanged |
| 3 | Signal alterations in WM and GM, moderate brain volume loss | New areas of increased signal in left frontal lobe | Unchanged |
| 4 | Patchy T2-signal abnormalities in bilateral periventricular WM, abnormal DWI in the left basal ganglia, mild brain volume loss, old infarcts | NA | NA |
| 5 | Scattered foci of increased T2 signal in bilateral WM | Unchanged | NA |
| 6 | Old infarct left frontal lobe, multiple scattered areas of increased T2 signal, mild brain volume loss | Unchanged | Unchanged |
| 7 | Mild brain volume loss | NA | NA |
| 8 | Diffuse subcortical and periventricular WM- and brainstem signal abnormality, general loss of brain volume | Unchanged | Unchanged |
| 9 | Patchy areas of increased T2 signal in the WM of both hemispheres, petechial hemorrhage | Normal | NA |
| 10 | Scattered foci of increased T2 signal in bilateral WM, small meningioma | Unchanged | NA |
| 11 | Scattered foci of increased T2 signal in bilateral WM, meningeal enhancement | Unchanged | Interval resolution of meningeal enhancement |

single or multiple foci or patchy areas of increased signal on T2-weighted or FLAIR images in the deep and periventricular WM, with no pathological contrast enhancement (Fig. 1). Other abnormal findings included increased signal on diffusion-weighted images (DWI-images), volume loss or brain atrophy, old infarctions, encephalomalacia, and meningeal enhancement. Incidental note was made of small meningiomas in two patients.

## MR spectroscopy

The mean NAA/Cr, Ch/Cr, NAA/Cho, and LL/Cr ratios and their ranges for the eight NP-SLE patients and for the seven controls are given in Table 4.

The NAA/Cho ratios were significantly lower ($p = 0.004$), the Cho/Cr ratios significantly higher ($p = 0.026$), and the LL/Cr ratios were significantly higher ($p = 0.002$) in the eight NP-SLE patients compared with those in the seven normal healthy volunteers.

The NAA/Cr ratios were lower in the NP-SLE patients than in the controls but the difference was not statistically significant: the estimated expected difference of NAA/Cr between patients and controls is 0.13 ($p = 0.14$). The estimated expected difference of NAA/Cho is 0.22 ($p = 0.004$), the estimated expected difference of Cho/Cr is 0.13 ($p = 0.026$), and the estimated expected difference of LL/Cr is 0.04 ($p = 0.002$), respectively (Table 4, Fig. 2).

There were significant changes over time in the NAA/Cr and NAA/Cho ratios in the eight NP-SLE patients. The mean (calculated from all 17 measured voxels in each patient) NAA/Cr ratio varied with time: it significantly decreased from the initial examination to the three month follow-up by 0.10 ($p = 0.049$), then insignificantly increased from the three to the six month follow-up examinations. The mean NAA/Cho ratio significantly decreased from the initial examination to the three month follow-up by 0.13 ($p = 0.008$), then insignificantly increased from the three to the six months follow-up examinations. No significant interval differences in the mean Cho/Cr, and the mean LL/Cr ratios were found (Fig. 3).

There was a significant variation between the 17 locations measured in the brain for three of the four ratios NAA/Cr, Cho/Cr, and NAA/Cho ($p < 0.05$, $p < 0.05$, and $p < 0.05$, respectively) but not for LL/Cr ($p = 0.87$) (ANOVA method). These differences in ratios depending on the anatomic location were seen in all eight patients and seven controls.

When comparing gray and WM, the NAA/Cr ratios were significantly lower in the GM than in the WM (estimated expected difference (0.28, $p < 0.0001$), and the Cho/Cr ratios were also significantly lower in GM than that in WM (estimated expected difference (0.16, $p < 0.0001$), in both patients and controls. The LL/Cr and NAA/Cho ratios were not significantly different in the GM compared to the WM in either group, ($p = 0.12$, $p = 0.97$, respectively).

There were no differences in any of the four spectroscopic variables between patients with major vs minor symptoms, between those who were APL-ab+ and those who were APL-ab−, or patients who had brain lesions on their conventional MRI compared with those who had no lesions.

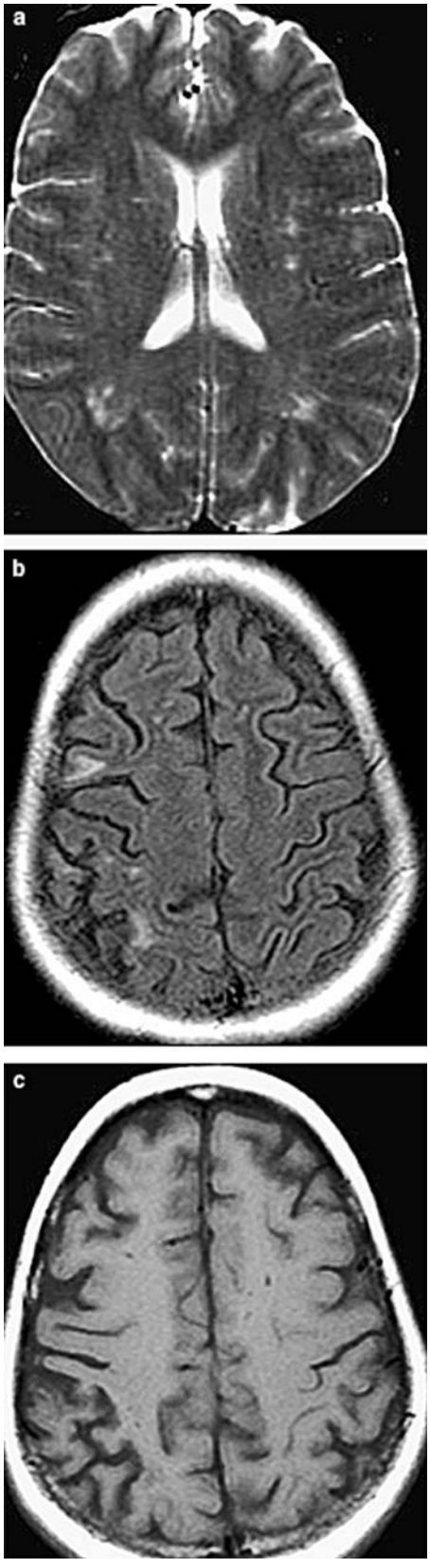


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**Fig. 1** Axial T2-weighted (**a**), FLAIR (**b**), and T1-weighted images (**c**) in a SLE patient with new symptomatology suspicious of brain involvement. Scattered confluent and punctuate areas of increased signal on T2-weighted and FLAIR images as well as an old ischemic changes in left parietal lobe. General brain volume loss and old ischemic changes are also present (**c**)

## Discussion

Our study in a limited number of patients differs from most of the previous studies not only in the spectroscopic technique used (2D-CSI) but also in patient selection, in the time for initial MR scanning, and in the inclusion of follow-up studies. We obtained the brain MR spectroscopy studies shortly after the initial clinical presentation and then followed six patients over a six-month period and two patients over three months. This is in contrast to previous reports that have mainly focused on NP-SLE patients with major or minor symptoms regardless of when the MR study was performed with respect to initial symptoms [10, 12, 15] or on SLE patients without any acute neuropsychiatric symptoms [13, 14]. These differences may account for some of the discrepancies between our results and those of others. Some previous reports, utilizing predominantly SVS spectroscopy in the evaluation of NP-SLE, have demonstrated a decrease in the NAA/Cr ratio and an increase in Cho/Cr ratio in the periventricular WM and basal ganglia [10, 12]. Such a decline in NAA has been suggested to be a sign of neuronal loss, whereas an increase in the choline compounds was assumed to be a sign of increased metabolic turnover/activity [10].

In accordance with previous reports [10–12, 14] our results demonstrate a significant decrease ($p = 0.004$) in NAA/Cho ratios and a significant increase ($p = 0.026$) in the Cho/Cr ratios in NP-SLE patients compared with those in normal healthy volunteers. However, unlike that in other reports, the expected decrease in NAA/Cr ratio in our patients compared with controls was not significant ($p = 0.14$) at time of presentation.

In our study, however, the lower NAA/Cr ratios in NP-SLE patients decreased significantly in the interval between the initial- and the 3 months follow-up studies ($p = 0.049$) and remained decreased at the six months follow-up study. To our knowledge no data from statistically relevant number of patients followed over time and demonstrating decline in NAA/Cr over time have been presented; our findings are in agreement with the only previous SVS study in which two patients were followed over 27 and 23 months, respectively [11]. Our findings of decline in NAA as a marker of neuronal damage support the theory of diffuse permanent neuronal loss in NP-SLE patients regardless of the clinically apparent severity of disease [11]. Our findings

**Table 4** Metabolic ratios at the initial examination in individual voxels in the white matter of the NP-SLE patients with clinical diagnosis of lupus cerebritis and normal controls, respectively

| Metabolic ratios | Patients ($n = 8$) mean (range) | Controls ($n = 7$) mean (range) | $p$-values of differences between the groups |
|---|---|---|---|
| NAA/Cr | 1.42 (0.48–2.49) | 1.54 (0.50–2.72) | n.s. |
| Cho/Cr | 1.42 (0.33–2.77) | 1.26 (0.66–1.97) | $p < 0.026$ |
| NAA/Cho | 1.05 (0.35–3.86) | 1.25 (0.41–2.70) | $p < 0.004$ |
| LL/Cr | 0.26 (0.05–1.97) | 0.19 (0.03–0.67) | $p < 0.002$ |

of interval significant decrease in the NAA/Cr ratios between the first and second examination and the insignificant difference between the second and third examination may suggest that this decline will continue or remain permanent regardless of medical treatment. These findings support the assumption that neuronal damage, seen as decline in NAA, might be complete and not reversible even if the patient receives the appropriate treatment. As with NAA/Cr ratios, the initially significantly decreased NAA/Cho ratios (compared to normal individuals) decreased significantly within the initial 3 month interval ($p = 0.008$) and insignificantly changed from the three-month to the six-month study.

In accordance with previous studies [10, 11] the mean Cho/Cr ratios were significantly increased in the eight NP-SLE patients compared to the normal controls at the time of presentation and remained increased over time.

Unlike those in other studies, our patients had significantly increased LL/Cr ratios ($p < 0.002$) at the initial examination compared to the controls. The LL/Cr ratios showed a slight tendency to further increase over time, but this change was not statistically significant (Fig. 1). In one study it was suggested that the abnormal findings seen in the brain of NP-SLE patients are not related to hypoxic/anaerobic events but rather indicate a host response to injury, such as an inflammatory reaction, membrane activation, or demyelination [12]. The integrity of such a theory is questioned by findings of abnormal levels of lactate in the brain at 1.3 ppm, presenting as an inverted lactate peak at TE of 144 ms, in our NP-SLE patients at the initial study. Our findings are suggestive of a partly anaerobic metabolism in NP-SLE patients, at least at the time of the patients' acute symptoms. Our findings are in contrast to a previous study in which no lactate was found in acute NP-SLE patients with major symptoms but rather presence of macro lipids at 1.3 ppm [12]. To our knowledge interval follow-up and demonstration of the presence of abnormal levels of brain lactate/lipids have not yet been demonstrated. Our findings may indicate the possibility of partial and focal anaerobic metabolism associated with hypoxia as underlying patho-physiological mechanism in the acute stage. This may, however, not necessarily contradict a host response to injury as etiology suggested by others [12] in patients with active neuropsychiatric symptoms that might resolve after/during treatment. Further support for the possibility of such an anaerobic metabolism in the acute stage of NP-SLE might be found in the known absence of lactate in SLE patients who had no active neuropsychiatric symptoms, as previously reported by others [13].

In the present study the range of the metabolic ratios in the individual voxels were large as can be seen from Table 4. The random error of metabolic ratios was estimated as less then 10%, which could account partially for the large range of the values tabulated. Other possible system errors may result from the RF pulse excitation profile, which are shifted according to the metabolic frequency. Therefore, it is likely that signal intensity ratios between two metabolites with larger chemical shift difference were overestimated or underestimated. Also the different locations in the brain from which these voxels within the VOI have been chosen, for example anterior frontal lobe vs posterior parietal lobe, might partly explain the large ranges.

Perhaps the most important role of imaging in NP-SLE is deducing the etiology of acute focal stroke-like neurological deficits. The differential diagnoses vary and accurate assessment is of crucial importance as the treatment for these alternative diagnoses differs. One of the parameters involved in the differential diagnostic process is the presence of APL-Ab [16–18]. There remains some controversy regarding the relation between the presence of antiphosolipid antibodies and MRS findings in SLE patients. In the present study we found no differences in the metabolic ratios between APL-Ab positive and negative patients, possibly because of the small number of patients. Similarly, no differences were found in a previous study [15], while another study found significant differences in metabolic ratios between APL-Ab positive-and APL-ab negative patients [19].

Conventional MR imaging has been used extensively in the evaluation of neuropsychiatric SLE (NP-SLE) and has proven to be more sensitive than CT [8]. The most common findings seen with conventional MR imaging include areas of increased signal in various locations of the WM on T2-weighted imaging, infarction, and atrophy. In the present study such morphological brain abnormalities were present in 10 of the 11 SLE patients (90%) entering the study with acute onset of symptoms suspected to be related to NP-SLE, and 7 out of 8 patients (86%) who had the final clinical diagnosis of NP-SLE. This is markedly higher than the 60–70% seen in a recent previous report [5, 14]. In our study seven of the eight patients with major- and all three

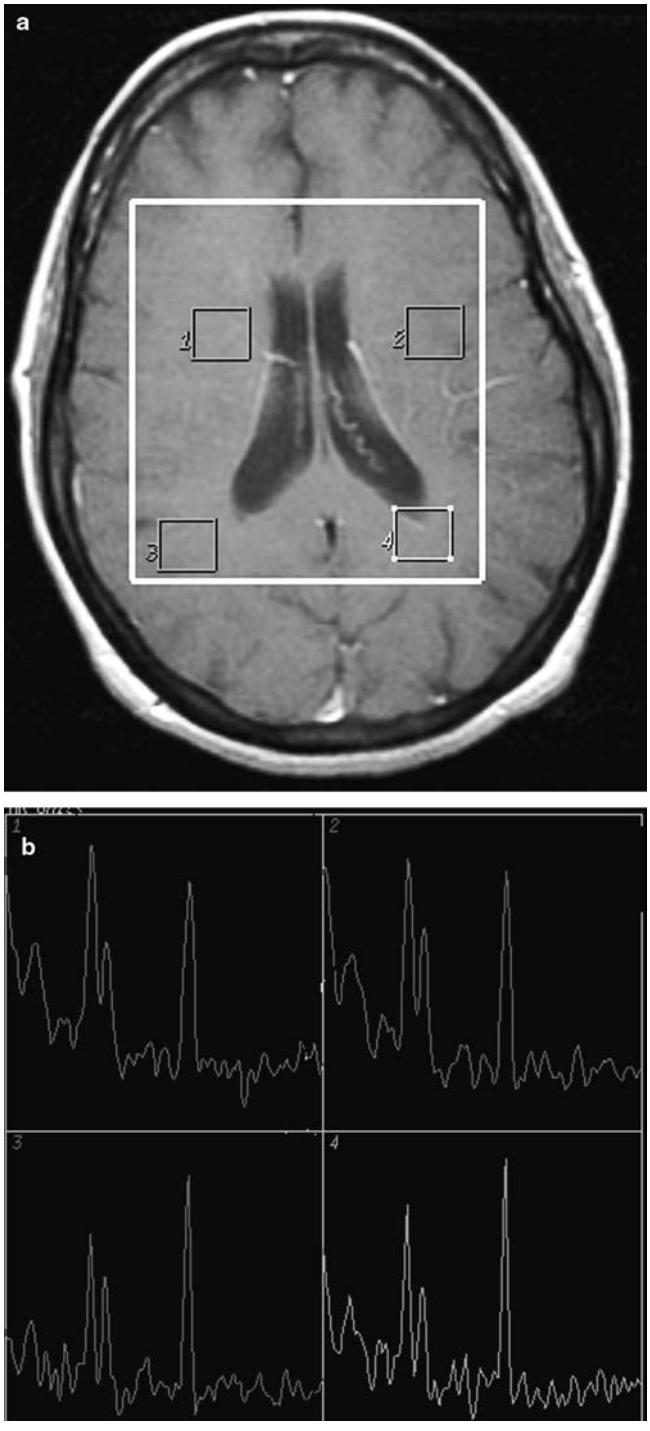


**Fig. 2** A 2D-CSI spectroscopy with the VOI located in the periventricular white matter (**a**). Decrease in the NAA peak and slight elevation of the choline peak with a decreased mean NAA/Cr ratio and increased mean Cho/Cr ratio, and presence of a small inverted lactate peak at 1.33 ppm, suggestive of neuronal damage and increased metabolic turnover (**b**)

patients with minor neuropsychiatric symptoms had morphological MR abnormalities that were rather non-specific and consisted mainly of scattered areas of increased signal on FLAIR and T2-weighted images and brain volume loss, thus correlating less with the severity of clinical signs and symptoms than previously suggested by others [10].

Possibly because of small number of patients (seven vs one, and six vs two, respectively) our study was not able to demonstrate any differences in spectroscopic parameters between patients with or without MRI brain lesions, or between those with major or minor neuropsychiatric symptoms.

One limitation of this study is the fact that two of the eight patients had associated Sjögren's disease. It is known that patients with Sjögren's disease may have signal abnormalities on brain MRI [20], and therefore, potentially, the findings in these two patients could be the result of Sjögren's disease rather then NP-SLE. However, the clinical work-up of these two patients—both with longstanding but mild form of Sjögren's disease without any prior evidence of CNS involvement—did not indicate any activity that could be related to Sjögren's disease at the time of the study. Therefore, we assume that the findings seen on conventional MRI and MRS in these two patients were related to the NP-SLE activity.

There are potential benefits with the use of 2D-CSI in the work-up of NP-SLE patients. The CNS involvement in NP-SLE can be diffuse and maximum metabolic abnormalities may not necessarily be present in areas that produce the dominant clinical symptoms or show the presence of abnormal MRI findings. 2D-CSI spectroscopy enables to coverage of larger areas of the brain to include both the areas of signal abnormalities or infarcts as well as areas that appear normal on the conventional MR images. By using 2D-CSI spectroscopy, different areas in the same VOI can be evaluated, such as GM, WM, as well as anterior and posterior parts of the brain. The use of standard locations for the placement of the VOI—at the level of the basal ganglia and in the WM of centrum semiovale—covers similar areas that were examined in previous studies using SVS with VOI in basal ganglia [10, 12, 17], frontal WM [12, 14], peritrigonal WM [10], and parieto-occipital WM [14]. The evaluation of the separate voxels within the VOI in the 2D-CSI examination can be easily done by using software provided by manufacturer or more advanced spectroscopy evaluation programs such as, for example, LC-model [21].

The potential benefit of using MRS instead of, of in addition to the conventional MRI in the follow-up of NP-SLE patients is the possibility to early detection of metabolic CNS changes, prior to the appearance of signal

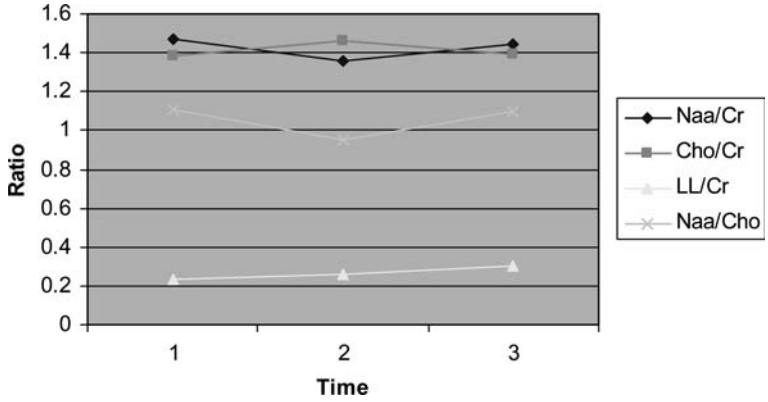


**Fig. 3** The plot demonstrates the interval change over time of the mean NAA/Cr, Cho/Cr, NAA/Cho, and LL/Cr ratios in the eight NP-SLE patients. The mean NAA/Cho and NAA/Cr ratios had significantly decreased at the 3 month follow-up ($p = 0.008$, $p = 0.049$, respectively). In contrast, both Cho/Cr and LL/Cr ratios were higher in the lupus patients at the initial study compared to the controls ($p = 0.026$, $p = 0.002$, respectively) and did not significantly change at three and six months follow-up

changes, if any, on the conventional MRI. In the later course of the disease MRS would then likely be a valuable tool for monitoring the success or failure of the therapy.

We conclude that our study has demonstrated that 2D-CSI MR spectroscopy may be useful in the early detection of metabolic CNS changes in NP-SLE patients with acute onset of new neurological symptoms. MRS might also be useful in the follow-up after treatment to assess presence of, and changes in, metabolic brain injury. However, larger longitudinal-studies including comparison with NP-SLE patients that have inactive disease as well as SLE patients without any CNS involvement, are needed to define the specificity of MRS as a clinically useful marker of brain disturbances in NP-SLE and SLE patients.

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