Brain study using magnetic resonance imaging and proton MR spectroscopy in pediatric onset systemic lupus erythematosus

M. Mortilla[1], M. Ermini[2], M. Nistri[3], G. Dal Pozzo[4], F. Falcini[2]

[1]Department of Radiology, A. Meyer Children's Hospital, Florence;
[2]Rheumatology Unit, Department of Pediatrics, University of Florence;
[3]Neuroradiology Unit, Trauma Center, Florence;
[4]Neuroradiology Unit, Department of Clinical Physiopathology, University of Florence, Italy

Abstract

Objective

The aim of the present study was to assess and monitor brain damage in patients with pediatric onset systemic lupus erythematosus (SLE) using non-invasive techniques such as magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopy (H-MRS).

Methods

Twenty-four SLE patients, both symptomatic or asymptomatic for central nervous system (CNS) involvement, and 20 controls were examined. Each individual underwent a diagnostic MRI using a 1.5 T Philips ACS-NT scanner including transverse T2-weighted (T2W) spin echo, transverse FLuid Attenuated Inversion Recovery (FLAIR), and sagittal T2W turbo spin echo 5 mm slices. In addition, single voxel proton MR spectroscopy localized on the supraventricular region was performed in all patients and controls. Patients were re-examined after one year.

Results

75% of SLE patients had clinical CNS involvement; 46% showed abnormal MRI (3 of them, in the absence of neurologic signs); 4 SLE patients showed N-acetylaspartate / Creatine (NAA/Cr) ratios significantly lower than the controls. Among 5 SLE patients examined at the onset of the disease, 1 had MRI alterations and another showed a decrease of NAA/Cr values. Three patients with relapses showed a correlation between the course of the disease and the NAA/Cr ratios.

Conclusion

MRI and H-MRS are non-invasive techniques that might be useful, in some cases, in detecting CNS involvement in SLE patients and monitoring the disease course and efficacy of pharmacological treatment.

Key words

Juvenile systemic lupus erythematosus, magnetic resonance imaging, magnetic resonance spectroscopy, brain.

Marzia Mortilla, MD; Neurologist and Radiologist; Marialisa Ermini, MD, Pediatrician, PhD in Pediatrics; Marco Nistri, MD, Radiologist; Giancarlo Dal Pozzo, MD, Associate Professor of Neuroradiology; Fernanda Falcini MD, Associate Professor of Pediatrics.

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Please address correspondence and reprint requests to: Marzia Mortilla, MD, Department of Radiology, A. Meyer Children's Hospital, Via Luca Giordano no. 13, 50132 Florence, Italy.
E-mail: m.mortilla@ao-meyer.toscana.it

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Introduction

Central nervous system (CNS) involvement occurs frequently in systemic lupus erythematosus (SLE) patients and represents the second cause of morbidity and mortality after renal disease (1-4). CNS lupus has been reported in 14-75% of individuals affected with pediatric onset SLE and may develop during any phase of the illness (1, 4-6). The most frequent neuropsychiatric symptoms are organic cerebral syndrome with memory deficits, psychosis, epilepsy, cerebro-vascular events, chorea and headache (2, 4, 7, 8).

Because of the wide variety of neuropsychiatric manifestations and the lack of reliable and specific diagnostic markers, CNS involvement in SLE patients is often difficult to evaluate. In order to achieve a better control of cerebral disease, it is important to detect brain damage early. However, to date no techniques have been identified that are capable of confirming the diagnosis of CNS involvement in SLE (11-15).

Brain MRI studies in SLE patients have shown CNS involvement including atrophy, irreversible and/or reversible areas of increased signal in both the grey and white matter on T2 weighted images ascribable to microinfarcts, cerebral venous thrombosis and venous infarct,and (more rarely) intracranial calcifications (9, 12, 16).

Whereas magnetic resonance imaging (MRI) is an anatomic imaging modality, proton magnetic resonance spectroscopy (H-MRS) is the only technique in clinical medicine that provides non-invasive access to living chemistry *in situ*. This technique shows 4 major resonances corresponding to different metabolites: N-acetylaspartate (NAA), which can be considered a neuronal marker; Choline (Cho) including choline-containing phospholipids that are released during active myelin breakdown; Creatine (Cr), which has a constant concentration throughout the brain and tends to be resistant to change in all but the most severe destructive lesions (therefore it is suitable for use as an internal standard against which the resonance intensities of NAA and Cho can be normalized); and lactate (LA), which is the end product of glycolysis and accumulates when oxidative metabolism cannot meet energy requirements. Recently brain H-MRS has been performed in adult SLE with encouraging results (16).

The non-invasive techniques of MRI and H-MRS were used in the present study to detect CNS involvement in clinically symptomatic and asymptomatic pediatric onset SLE patients.

Patients and methods

Twenty-four patients with pediatric onset SLE (19F and 5M aged 8 to 27 yrs; mean age 15.4 ± 4.4 yrs) underwent MRI and H-MRS. In all patients the onset of SLE occurred before the age of 15 yrs (mean age at the onset 9.9 ± 4 yrs) (Table I). SLE was diagnosed according to the 1982 revised criteria as established by the American College of Rheumatology (17). Twenty healthy age- and sex-matched individuals were studied as controls. Informed consent was obtained for all the subjects from their parents.

The mean duration of the disease in SLE patients was 4.7 ± 5.4 yrs (range 1 month to 22 yrs). Five out of 24 patients were examined at the onset of the disease. All SLE patients had a complete physical examination, routine hematologic and chemistry determinations, and serologic tests. Disease activity was assessed using the SLE Disease Activity Index (SLEDAI) (20) by an experienced pediatric rheumatologist on the day of the MRI and H-MRS evaluations. Disease with a score >10 was defined as active (18). The scores are shown in Table I.

Eighteen out of the 24 SLE patients had clinical evidence or a history of CNS involvement that was considered to be SLE-related, as other causes had been excluded. Eight out of 18 SLE patients showed minor symptoms while 10 had both minor and major symptoms according to How *et al.* (19) and the DSM IV criteria (20). At the time of the examinations or before, 17 SLE patients were receiving corticosteroids plus hydroxychloroquine, 2 patients were receiving hydroxychloroquine, and 5 patients examined at the disease onset had not yet received any therapy.

MR analysis

All subjects underwent diagnostic MRI and H-MRS with a 1.5T apparatus (Philips ACS-NT, Best, The Netherlands).

The standard MRI exam included: transverse double spin-echo T2 weighted sequence (TR 2300 ms, TE 20/90 ms, 250 mm field of view (FOV), 80% rectangular FOV (RFOV), 5 mm slice thickness); transverse Fluid Attenuated Inversion Recovery (FLAIR) sequence (TR 9000 ms, TE 150 ms, TI 2600 ms, 250 mm FOV, 80% RFOV, 5 mm slice thickness); and sagittal turbo T2 weighted sequence (TR 3000 ms, TE 120 ms, 250mm FOV, 85% RFOV, 5 mm slice thickness). When the MRI exam showed alterations, a transverse T1 weighted sequence was also performed (TR 500 ms, TE 20 ms, 250mm FOV, 80% RFOV, 5 mm slice thickness).

For proton MR-Spectroscopy a single voxel of 70 x 50 x 20 mm was acquired using the PRESS technique (24) (TR 2000ms, TE 272ms). The volume of interest (VOI) was positioned parallel to the anterior commissure – posterior commissure line and centred just above the corpus callosum; this position was chosen in order to include in the VOI principally white matter (Fig. 1).

Before the acquisition of the localized proton MR of brain metabolites, the brain water proton signal was suppressed. The total duration of the MRI and H-MRS examinations was 40 minutes.

The spectra acquired were processed using standard software (Philips). Results were expressed as ratio to creatine. Thus the 3 main metabolite ratios of N-acetylaspartate/creatine (NAA/Cr), N-acetyl aspartate/choline (NAA/Cho) and choline/creatine (Cho/Cr) were assessed.

Statistical analysis

All H-MRS data were expressed as mean ± SD. Comparison between controls and SLE patients were performed using the Student's t-test. P values less than 0.05 were considered significant. Metabolite ratios were considered abnormal if they were more than two standard deviations outside the mean values of the controls.

Table I. Clinical data for the SLE patients.

Patients	Sex/age	Duration of disease (years/months)	SLEDAI*	Neuropsychiatric symptoms in the patient history
1	M/27	22 yrs.	10	-
2	F/17	11 mos.	6	Headache
3	F/11	1 yr./3 mos.	0	Headache
4	F/15	3 yrs./5 mos.	4	-
5	F/15	2 yrs./5 mos.	0	Headache
6	F/17	3 yrs.	12	Headache/Anorexia
7	M/11	5 yrs./3 mos.	4	-
8	F/15	6 yrs.	4	-
9	F/25	16 yrs.	0	Headache/Loss of memory/Depression
10	F/16	5 yrs.	10	-
11	F/9	4 mos.	12	Headache
12	M/10	1 yr./8 mos.	10	Headache/Seizures
13	F/13	1 moK	14	Headache/Loss of memory
14	F/14	5 yrs./3 mos.	16	Headache/Numbness
15	M/10	3 yrs.	16	Loss of consciousness/vertigo
16	M/12	1 mo.	10	Headache
17	F/18	4 yrs.	8	Headache/Depression
18	F/18	12 yrs.	4	Chorea/Psychosis/TIA
19	F/14	8 yrs.	8	Headache
20	F/17	2 mo.	14	Headache
21	F/18	5 yrs.	2	Headache
22	F/19	7 yrs.	1	Headache/Depression
23	F/13	7 mos.	10	-
24	F/14	1 mo.	10	Headache/Loss of memory

* Scores were calculated on the day of MR exams.

Results

All of the images and spectra obtained were suitable for analysis. MRI sequences were chosen in order to detect the typical brain abnormalities present in SLE patients. The FLAIR sequence cancels the signal from liquor, thus allowing a better detection of the lesions in the surrounding white matter, so it was specifically useful in discriminating small and focal white matter lesions from enlarged vascular spaces. Eleven out of 24 SLE patients had an abnormal MRI consisting of: brain atrophy (n = 3), focal white matter abnormalities (n = 5) or both alterations

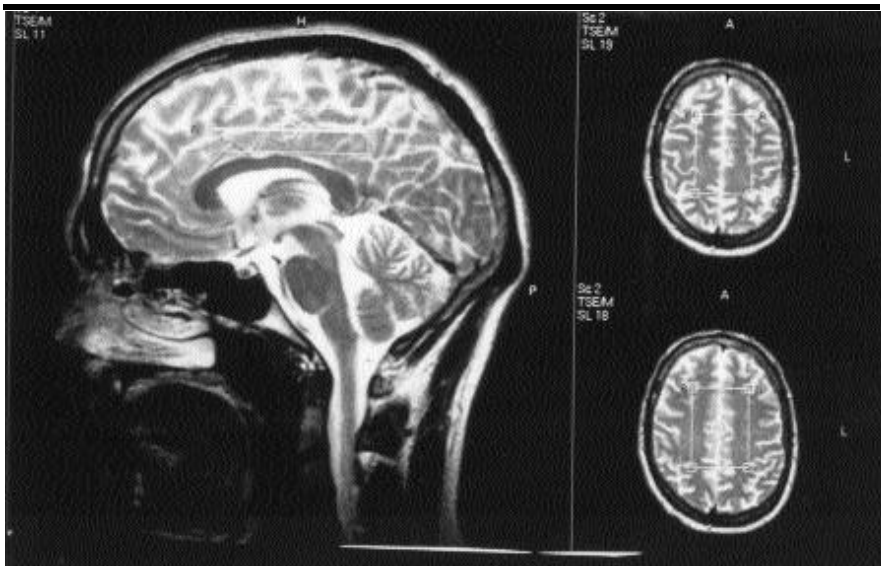

Fig. 1. VOI of 70 x 50 x 20 mm including mainly supraventricular white matter. Single voxel obtained by the PRESS technique (TR 2000 ms, TE 272 ms).

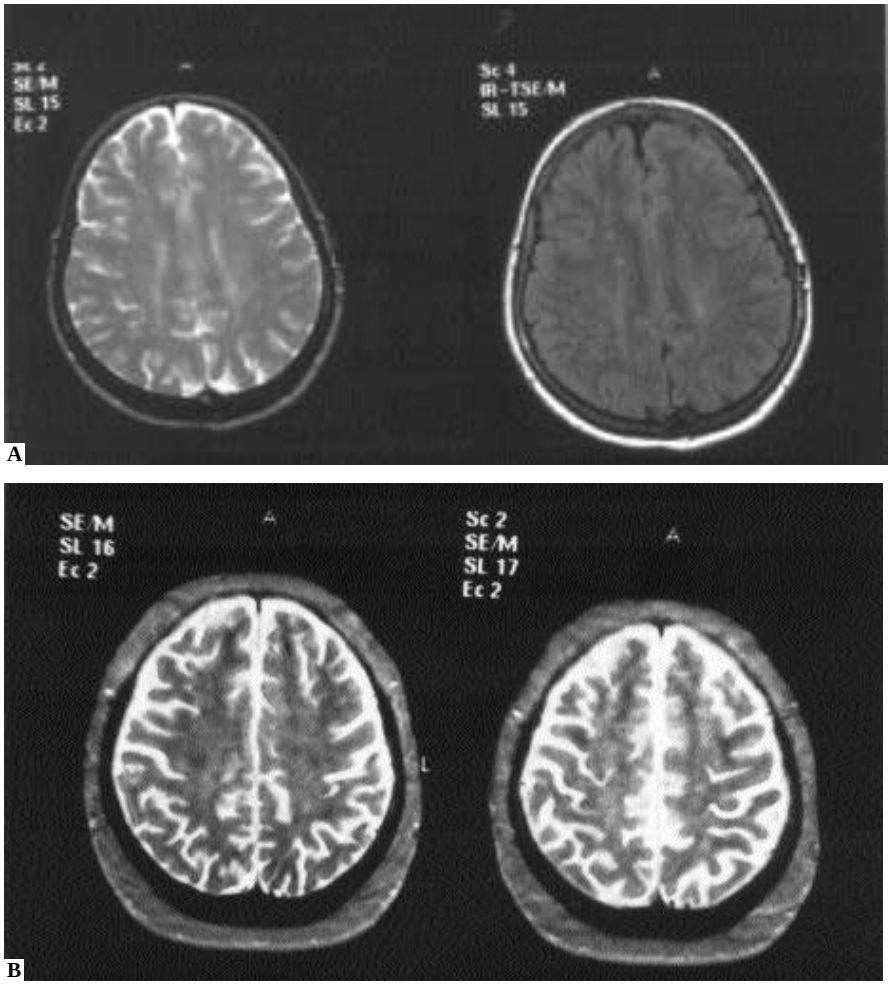

Fig. 2. (**A**) VP, a 20-year-old girl with a history of chorea, psychosis and TIA. Supraventricular microinfarcts shown in a transverse spin echo T2w sequence (TR 230 ms,TE 90 ms, FOV 250 mm, 5 mm thickness) and a transverse FLAIR sequence (TR 9000 ms,TE 150 ms,TI 2660 ms,FOV 250 mm, 5 mm thickness). (**B**) RJ, a 14-year-old girl with headache and numbness. Transverse spin echo T2w sequence (TR 230 ms, TE 90 ms, FOV 250 mm, 5 mm thickness) shows diffuse cortical atrophy.

(n = 1) and corpus callosum atrophy (n = 2) (Fig. 2). Three patients with abnormal MRI had no history of neuropsychiatric symptoms. Five patients, all with a history of neuropsychiatric symptoms, were examined at the disease onset. Only one of them showed atrophy on the standard MRI exam; the others were normal. The overall spectroscopic data at the first examination did not demonstrate statistically significant differences between SLE patients and controls (p = 0.3) (Table II). Only 4 patients out of 24 had an NAA/Cr ratio lower than 2 SD (2 of them had no MRI alterations); in one the disease was just at its onset with a normal MRI, but the other 3 had severe systemic involvement, 2 of them with no clinical evidence of CNS damage. The MRI and H-MRS results are summarized in Table III.

The patient with the lowest NAA/Cr value (NAA/Cr 2.1) was an 8-year-old girl examined at the onset of her disease, who presented with recurrent severe headache attacks and a negative MRI. The girl was re-examined after 4 months of oral corticosteroid treatment; her MRI was still normal while a partial recovery of NAA levels was detected (NAA/Cr 2.4) (Fig. 3). Another patient with a history of chorea and psychosis underwent a second MRI and H-MRS exam 5 months after the first observation, during a recrudescence of the chorea. The second MRI exam was unchanged compared to the first, but the NAA/Cr ratio was lower than previously (NAA/Cr 2.3 vs 2.5).

No alterations in Cho/Cr and no abnormal metabolites (in particular lactate) were detected in the SLE patients.

After one year 23/24 SLE patients were re-examined. Twenty-two MRI were unchanged while one patient showed an abnormal MRI that was previously normal. She presented headache and episodes of vertigo at our first observation, when she was taking steroids and hydroxychloroquine. At the second MR examination she was still on the same therapy but no neuropsychiatric symptoms were present.

The overall H-MRS data showed a significant decrease in the NAA/Cr ratios (p = 0.002) (Table IV).

Table II. H-MRS data at the first examination.

	NAA/Cr*	Cho/Cr	NAA/Cho
SLE patients	2.50 ± 0.3	1.20 ± 0.2	2.05 ± 0.2
Controls	2.58 ± 0.15	1.27 ± 0.05	1.98 ± 0.1

*SLE patients vs controls p = 0.3

Discussion

To our knowledge this is the first H-MRS study in patients with pediatric onset SLE. The main epidemiological and clinical features of our SLE population are comparable to those reported in the literature (25, 26); CNS involvement (including minor neuropsychiatric symptoms) was present in 75% of the patients (2-4,6,15). The MRI alterations detected in our patients were similar to data previously reported (12, 17, 27, 28).

We found abnormal MRI in 11 patients (46%) and 3 of them were asymptomatic for neurological manifestations. This suggests that MRI might be useful in detecting asymptomatic CNS involvement in some cases, but on the other hand 10 patients with neuropsychiatric symptoms presented a normal MRI. A previous study of neurologically symptomatic adult SLE patients

Table III. Clinical and MRI data at the first examination.

Patients with SLE	SNC involvement	MRI	NAA/Cr
2	+	+	=
9	+	+	=
15	+	+	=
22	+	+	=
16*	+	+	=
18	+	-	=
12	+	+	=
14	+	+	<<
20*	+	-	=
5	+	-	=
6	+	-	=
17	+	-	=
21	+	-	=
11*	+	-	<<
13*	+	-	=
24*	+	-	=
3	+	-	=
19	+	-	=
1	-	+	<<
4	-	+	=
7	-	+	=
8	-	-	=
10	-	-	<<
23	-	-	=

* At the onset of the disease; << 2 SD below the mean value of controls.

with a negative MRI reported alterations in the apparently normal grey and white matter, probably due to cerebral oedema, using non-routine techniques such as T2 relaxation time measurements (29). We regularly use FLAIR sequencing to study white matter abnormalities (e.g. microinfarcts) since they are better highlighted after the suppression of liquor signal. The presence of microinfarcts in SLE patients suggests a small vessel disorder. Although the pathogenesis of the disease has not yet been clarified, histopathologic studies in SLE patients have shown cerebral cortical multifocal microinfarcts associated with microvascular damage and rarely, vasculitis (6, 9, 10).

Among the 13 subjects with normal MRI we found 2 patients with clinical evidence of CNS involvement and significantly decreased NAA/Cr ratios. Among the 5 SLE patients with neuropsychiatric symptoms examined at disease onset, one showed an abnormal MRI and another one had a decreased NAA/Cr ratio. This girl, as noted above, underwent a follow-up that clearly showed an increase in NAA/Cr resonance intensity as well as a clinical improvement after corticosteroid therapy. Three other patients were re-examined during relapses of the disease and they all showed a significant decrease of NAA/Cr ratio. These data support the hypothesis that NAA/Cr seems to correlate with clinical manifestations of SLE as it has been described for other diseases (e.g. multiple sclerosis).

The overall data at one-year follow up showed a significant decrease of NAA/Cr ratios indicating that the progression of the disease implies a worsening of CNS involvement.

One patient with abnormal MRI at baseline and no neuropsychiatric symptoms, showed an unchanged MRI at the follow-up and a significant decrease of the NAA resonance intensity (NAA/Cr = 2.63 at baseline and 2.1 at follow-up) (Fig. 4). Three months before the second examination he stopped corticosteroid therapy and 2 months after the follow-up he developed psychosis. This case suggests that H-MRS may help in monitoring cerebral involvement and the efficacy of therapy. The girl who showed an abnormal MRI after the 1-year follow-up had a low NAA/Cr ratio at the first observation but a normal H-MRS data at the second examination, concordantly with the disappearance of neuropsychiatric symptoms. Although our data suggest that MRI and H-MRS may be useful in some cases for the early detection of CNS damage, with H-MRS seeming to better correlate with the clinical manifestations of neuropsychiatric SLE than MRI, further data needs to be acquired in order to confirm this.

In our study we did not discover any evidence of a correlation between MRI and/or H-MRS and sero-immunological findings (data not shown) as previously reported (16). Even when the patients were divided into 2 subgroups, one with minor symptoms (headache) and one with more significant CNS involvement, no correlation with the MRI or H-MRS data was found. Furthermore, there was no correlation ($p > 0.5$) between the MRI and H-MRS data and the SLEDAI score.

Sibbitt *et al.* (30) suggested a close association between decreased NAA/Cr and cerebral atrophy. This aspect could imply a permanent anatomic alteration associated with neuronal dropout. We detected atrophy in 4 patients. One of them was examined at disease onset before any corticosteroid therapy. This case supports the hypothesis that atrophy might represent a specific feature of the disease rather than a unique complication of the treatment, although it is widely recognized that patients treated with corticosteroids for a long period present atrophy and low NAA/Cr ratios because of a catabolic effect of corticosteroids on the brain.

Recently Brooks *et al*. (31) studied focal and generalized brain abnormalities in SLE patients using MR spectroscopic imaging (MRSI). They demonstrated that MRSI findings are consistent with widespread neuronal injury and demyelination, but not with anaerobic metabolism. Lactate is elevated in acute stroke and is supposed to also be increased in SLE, since the main MRI features are stroke-like lesions. Our data, as well as those from Brooks *et al*., did not show the presence of lactate in SLE patients, even in those with acute neurological signs, although Sibbit *et al.* (30) suggested a correlation. The decreased NAA/Cr ratio indicates

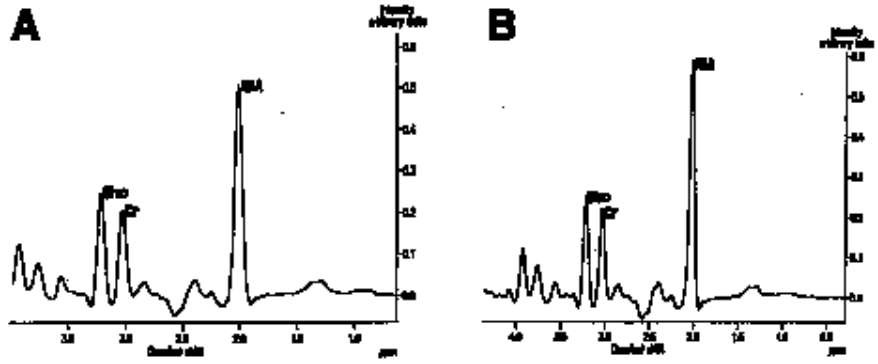

Fig. 3. (**A**) Spectrum obtained from an 8-year-old girl (PRESS, TR 2000 ms,TE 272 ms) who at disease onset showed a normal MRI and decreased NAA/Cr ratio; (**B**) spectrum for the same patient 4 months after corticosteroid treatment showing a return to normality of the NAA/Cr ratio.

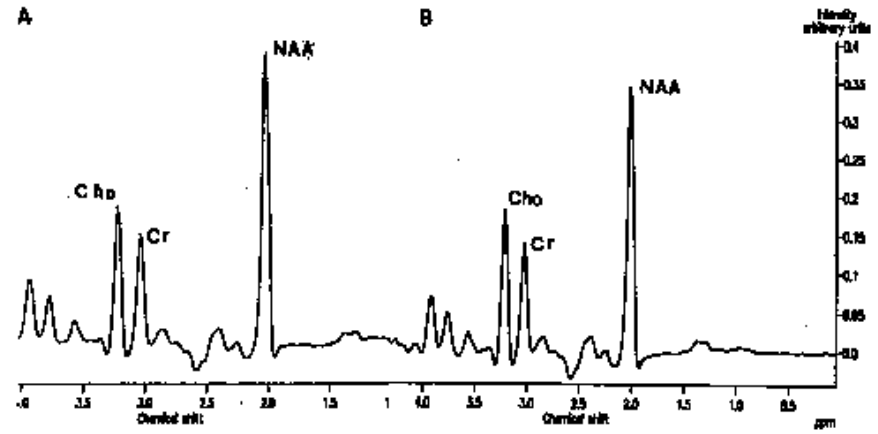

Fig. 4. (**A**) Spectrum from CM (VOI 70 x 50 x 20 mm, PRESS, TR 2000 ms,TE 272 ms) a 15-year-old boy with abnormal MRI at baseline and normal spectrum. (**B**) The same patient at follow-up,showing a significant decrease in NAA resonance intensity despite an unmodified MRI.

Table IV. H-MRS data at one year follow-up.

	NAA/Cr*	Cho/Cr	NAA/Cho
SLE patients	2.44 ± 0.15	1.22 ± 0.09	2.075 ± 0.14
Controls	2.58 ± 0.15	1.27 ± 0.05	1.98 ± 0.1

*SLE patients vs controls p = 0.002.

a neuronal injury or loss that is not confined to the lesions but is also present in normal appearing white matter. This finding was confirmed by our study because the lesions were small in relation to the VOI studied and sometimes no lesions were included in the VOI.

In addition, reversibility of the decrease in NAA levels found during the follow-up examinations in patients who underwent corticosteroid therapy after relapses of the disease suggests that the pathologic process of SLE does not always lead to neuronal death, but can also be the expression of a partially reversible neuro-axonal dysfunction.

In conclusion MRI and H-MRS may be useful non-invasive tools in detecting some cases of early CNS involvement in SLE even though these techniques are not specific for the diagnosis of active neurological disease. Additional data are required to support our results for patients at the onset of the disease to be followed over the years.

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