Analysis of Cerebral Structural Changes in Systemic Lupus Erythematosus by Proton MR Spectroscopy

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PURPOSE: To determine whether cerebral atrophy in systemic lupus erythematosus is associated with decreased levels of the neuronal marker *N*-acetylaspartic acid. **METHODS:** Two groups of patients with systemic lupus erythematosus were studied, those with significant atrophy (n = 11) and those without significant atrophy (n = 10), using proton MR spectroscopy on a 1.5-T imaging unit. The solvent-suppressed, short-echo, volume-localized proton spectroscopy technique showed typical brain metabolites, including *N*-acetylaspartate, creatine/phosphocreatine, and choline-containing compounds. **RESULTS:** The *N*-acetylaspartate–to–creatine/phosphocreatine ratio was smaller in those patients with significant cerebral atrophy (1.68 ± 0.27) than in those patients with minimal or no atrophy (2.17 ± .30). The degree of atrophy was negatively correlated with the *N*-acetylaspartate–to–creatine/phosphocreatine ratio. The choline-to-creatine/phosphocreatine ratio was not significantly altered in systemic lupus erythematosus patients with atrophy. **CONCLUSION:** These data suggest that cerebral atrophy in systemic lupus erythematosus is associated with neuronal dropout (or damage), which results in decreased *N*-acetylaspartate ratios. A change in choline ratios is not implicated in the biochemical changes associated with cerebral atrophy. Proton MR spectroscopy may be useful in correlating brain metabolites with cerebral structural changes in patients with autoimmune diseases.

Index terms: Brain, atrophy; Brain, magnetic resonance; Brain, metabolism; Lupus erythematosus; Magnetic resonance, spectroscopy; Degenerative brain disease

AJNR Am J Neuroradiol 15:923–928, May 1994

Magnetic resonance (MR) imaging is frequently used to evaluate neuropsychiatric systemic lupus erythematosus (SLE). Typical findings noted on MR images include focal and diffuse high-intensity lesions, infarcts, hemorrhage, and atrophy (1–7). A large proportion of patients with SLE demonstrate diffuse and focal increases in white matter signal on T2-weighted MR images that are often associated with atrophy (1, 2, 6). The cause of cerebral atrophy in SLE is unclear but could be the cumulative effects of multiple white matter infarctions and neuronal loss secondary to diffuse inflammation, or the effects of corticosteroid therapy.

In the current study, we used volume-localized proton MR spectroscopy in vivo specifically to examine the brain biochemistry of SLE patients with or without cerebral atrophy to determine whether metabolic changes were associated with structural alterations on MR images.

Subjects and Methods

Twenty-one patients with SLE (ages 24 to 62 years) were studied, 11 patients with moderate to severe cerebral atrophy and 10 patients with no atrophy or mild atrophy on MR images. SLE was diagnosed according to the 1982 revised criteria as established by the American College of Rheumatology (8). Clinical data are included in Table 1.

MR images were obtained at 1.5 T using a head coil, multiplanar pulse sequences, and a field of view of 20 cm with the following acquisitions: T1-weighted sagittal sec-

Received March 9, 1993; accepted pending revision June 9; revision received August 27.

This work was supported by the Lupus Foundation of America and the State of New Mexico through a grant to the Center for Non-Invasive Diagnosis.

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AJNR 15:923–928, May 1994 0195-6108/94/1505–0923

TABLE 1: Clinical characteristics of the SLE study population

Patient	Age, y	SLE Criteria[a]	Disease Duration, y	Therapy
1	52	3,5,6,11	15	NSAID
2	34	7,8,10,11	11	Prednisone, azathioprine
3	17	5,6,9,10,11	2	Prednisone, hydroxychloroquine
4	24	1,5,9,11	7	None
5	46	3,5,7,9,11	11	Prednisone, NSAID
6	31	1,3,5,7,11	13	None
7	27	1,3,4,5,8,11	3	Prednisone, NSAID
8	37	3,4,5,6,8,11	10	Prednisone
9	65	8,9,10,11	2	Prednisone, cyclophosphamide
10	43	1,7,8,9	9	Prednisone, cyclophosphamide
11	59	3,5,9,10,11	18	Methotrexate
12	59	5,7,8,9	37	Prednisone, NSAID
13	45	3,4,5,11	7	Prednisone, NSAID
14	51	5,7,10,10	11	Prednisone, hydroxychloroquine
15	44	1,5,7,8,10,11	20	None
16	57	1,3,4,9,10,11	3	NSAID
17	56	1,4,9,10,11	1	NSAID
18	44	3,4,5,8,11	10	NSAID
19	42	1,3,4,5,8,10,11	2	Prednisone, hydroxychloroquine
20	23	1,3,4,8,10,11	2	Prednisone
21	26	3,4,5,8,9,10,11	4	Prednisone

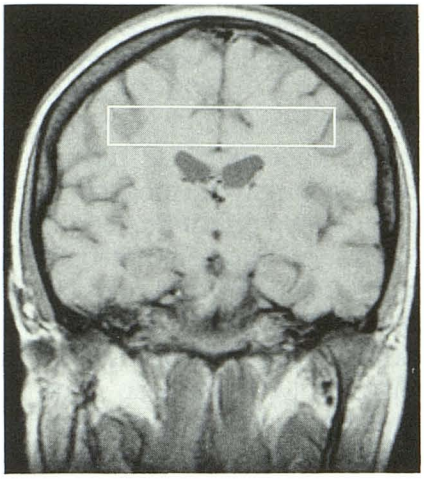
Note.—NSAID indicates nonsteroidal antiinflammatory drug.

[a] 1 indicates malar rash; 2, discoid rash; 3, photosensitivity; 4, oral ulcers; 5, arthritis; 6, serositis; 7, renal disorder; 8, neurologic disorder; 9, hematologic disorder; 10, immunologic disorder; 11, antinuclear antibody.

tions, 600/20 (repetition time/echo time); proton-density and T2-weighted coronal sections, 2000/20 and 2000/80; and proton-density and T2-weighted axial series, 2000/20 and 2000/80; section thickness was 5 mm with a 2.5-mm section gap number of excitations = 1 and a 256 × 192 acquisition matrix. Cerebral atrophy was defined as a generalized increase in the size of cortical sulci and ventricles on MR images and was graded with 0 indicating no atrophy; 1, mild atrophy; 2, moderate atrophy; and 3, severe atrophy. Scores were blindly assigned by a radiologist who did not have access to the spectroscopic data.

Localized proton MR spectroscopy was performed using solvent-suppressed, short-echo, volume-localized proton spectroscopy on a 1.5-T scanner (Signa, GE Medical Systems, Milwaukee, Wis) with conventional well-compensated gradient coils (9). Focal lesions apparent on T2-weighted images in white matter were intentionally avoided on the volume selected for spectroscopy to exclude artifacts induced by infarct, focal inflammation, or plaque.

Localization was achieved with preliminary standard localizing MR images obtained in the coronal plane and section selective field gradients defining a 2 × 2 × 10-cm^3 columnar region extending through both hemispheres superior to the ventricles. The solvent-suppressed, short-echo, volume-localized proton spectroscopy chemical shift imaging technique used 64 phase-encoding steps and a 64-cm field of view along the columnar dimension providing 10 2 × 2 × 1-cm^3 frames of a chemical shift image. Immediately before the acquisition of localized proton spectra of brain metabolites, the brain water proton signal was generally suppressed by applying frequency-selective radio-frequency pulses along the x, y, and z directions, each radio-frequency pulse followed by a 0.8-G/cm magnetic field gradient–dephasing pulse of duration 2 milliseconds (x), 4 milliseconds (y), and 2 milliseconds (z). The frequency-selective radio-frequency pulse was constructed with a 1-sine cycle and a duration of 80 milliseconds for an excitation bandwidth of 50 Hz (9). The typical water line width was 7 Hz. Data were then obtained at 1500/19 for the block of 8 × 64 acquisitions, treated with 1 Hz exponential broadening, multiplied by a shifted sine bell window, Fourier transformed, phase corrected, and represented in graphic form. The shifted sine bell in the second dimension was used to reduce Fourier bleed artifacts among adjacent voxels. Baseline was corrected to remove any direct current offset in the free induction decay. The last eighth of the



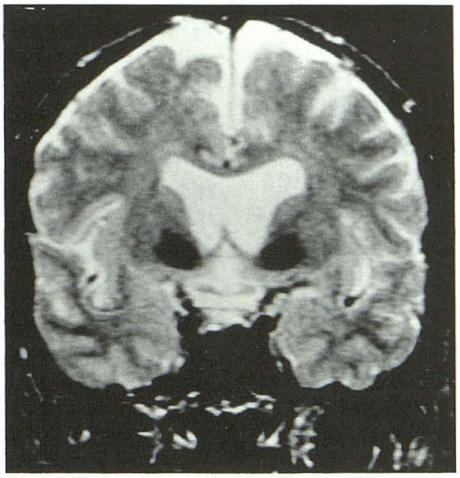


Fig. 1. Coronal proton-density image (2000/20) with a typical frame for proton spectroscopy defined by a 2 × 2 × 8-cm^3 rectangular volume extending across both hemispheres.

Fig. 2. T2-weighted coronal image (2000/80) from an SLE patient with moderate to severe cerebral atrophy.

TABLE 2: Results of proton MR and MR spectroscopy in SLE patient population

Patient	MR Findings	Atrophy Rating[a]	NAA/(Cr + PCr)[b]
1	Mild atrophy, few SFL	1	2.04
2	Multiple SFL, mild atrophy	1	1.87
3	Normal	0	2.37
4	Mild atrophy	1	2.27
5	Normal	0	2.40
6	Mild atrophy	1	1.85
7	Moderate atrophy, increased signal	2	1.97
8	Severe atrophy, increased signal	3	1.72
9	Severe atrophy, increased signal	3	1.72
10	Severe atrophy, multiple SFL, increased signal	3	1.45
11	Moderate atrophy, increased signal	2	1.89
12	Mild atrophy, sinusitis, increased signal	1	2.00
13	Moderate atrophy, SFL, increased signal	2	1.67
14	Mild atrophy, multiple SFL, increased signal	1	1.92
15	Severe atrophy, multiple SFL, left occipital and parietal infarcts, increased signal	3	1.75
16	Moderate atrophy, increased signal	2	1.47
17	Moderate atrophy, increased signal	2	1.18
18	Moderate atrophy, increased signal, prior left-sided stroke, SFL	2	1.50
19	Normal	0	2.83
20	Mild atrophy, SFL	1	2.13
21	Severe atrophy, increased signal, SFL	3	2.13

Note.—SFL indicates a small focal lesion of increased signal on T2-weighted images.

[a] 0 indicates normal; 1, mild; 2, moderate; and 3, severe.

[b] NAA/(Cr + PCr) indicates *N*-acetylaspartate/(creatine/phosphocreatine) ratio for a 2 x 2 x 8-cm^3 volume of parietal brain parenchyma.

free induction decay was used to calculate the average of the data points, which was subtracted from each of the points in the free induction decay.

Peak areas were integrated and metabolic concentrations expressed as metabolite concentration ratios which equaled: area of metabolite resonance/area of creatine resonance (= Cr+Pr).

Peak areas of N-acetyl aspartate (NAA), choline esters, and creatine plus phosphocreatine (Cr+PCr) were determined for each 2 × 2 × 1-cm^3 volume. Limits for integration for the individual resonance peaks were NAA (1.8 to 2.2 ppm), Cr+PCr (2.8 to 3.15 ppm), and choline (3.1 to 3.55 ppm). The most external 2 × 2 × 1-cm^3 volume was excluded from analysis to minimize contamination by scalp lipid and susceptibility artifacts from skull. The spectral values for the eight interior volumes were averaged to provide a mean value for each metabolite ratio for a composite 2 × 2 × 8-cm^3 volume (Fig 1). These are the values reported in Table 2 and Figure 3. The mean values, standard deviations, classical *t* test comparisons, and linear regression analysis were performed with the statistical computer software package ICS Version 1.1. (PWS Publishers, Boston, Mass). All data are expressed as mean ± SD. Satherwaite's approximation was used to correct the *t* test for abnormal variations in the populations.

Results

Cerebral atrophy of various degrees was present in 18 of the study patients (Fig 2 and Table 2). Diffusely abnormal white matter signal was

TABLE 3: Brain metabolite ratios of SLE patients with varying degrees of cerebral atrophy

	None to Mild Atrophy (n = 10)	Moderate to Severe Atrophy (n = 11)	*P* Value
Choline	0.83 (0.21)	0.80 (0.14)	.708
NAA	2.17 (0.30)	1.68 (0.27)	.001

Note.—Ratio of metabolite peak intensity to that of creatine plus phosphocreatine.

closely associated with varying degrees of cerebral atrophy (Table 2).

Table 3 compares MR spectra from SLE patients with moderate to severe cerebral atrophy to those from patients with no or mild atrophy. These spectra represent predominately white matter. There were no significant differences in the measured metabolite ratios except for a decrease in the NAA/(Cr+PCr) ratio ($P = .001$). The latter differences are more significant when the groups were separated into no, mild, moderate, and severe atrophy (Fig 3). The degree of atrophy was negatively correlated with the NAA/(Cr+PCr) ratio ($r = .679$, $r^2 = .462$, $P < .001$). Representative spectra are shown in Figures 4A and 4B.

Discussion

Neurologic complications affect a large portion of patients with SLE. Cranial neuropathy, peripheral neuropathy, stroke, seizure, organic brain syndrome, and movement disorder are the most common, although affective disorders can also represent neurologic involvement (1–6, 10–18). Lesions similar to those of multiple sclerosis have also been reported (16–18). MR has been used extensively to evaluate neuropsychiatric SLE and seems to be more sensitive than computed tomography (2). Typical lesions noted on MR include labile areas of focally increased signal on T2-weighted images (focal edema), diffuse and focal fixed lesions of increased signal on T2-weighted images, infarct, hemorrhage, atrophy, and chronic sinusitis. Generalized cerebral atrophy is a common finding of unclear significance (3, 19–21). However, because many patients with SLE suffer memory and intellectual impairment with long-term disease, the finding of atrophy may have important functional correlates.

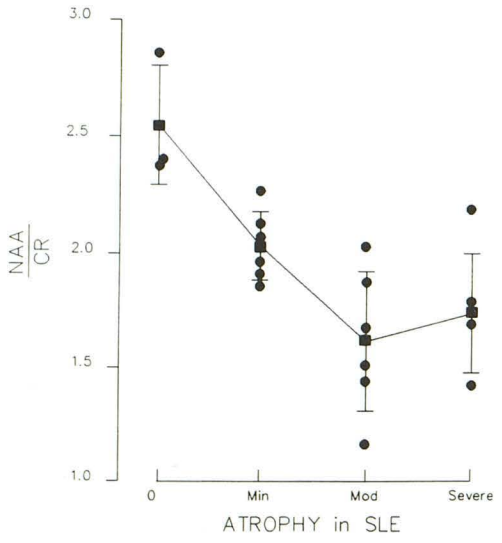


Fig. 3. Inverse relationship between the degree of cerebral atrophy and the NAA/Cr ratio.

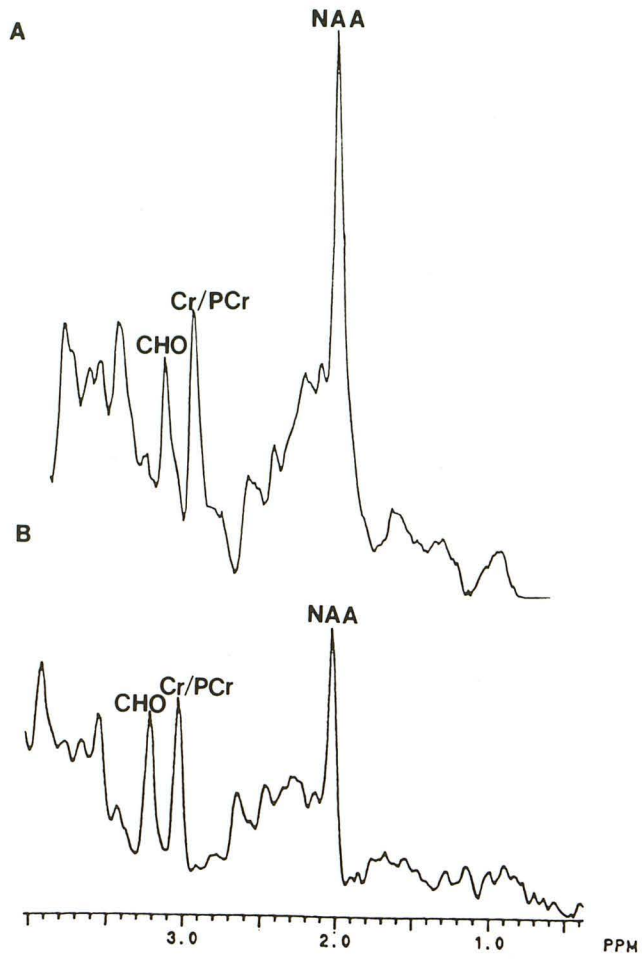


Fig. 4. Proton MR spectra of SLE white matter frames by solvent-suppressed, short-echo, volume-localized proton spectroscopy.

A, Spectrum from a 2 × 2 × 1-cm^3 volume demonstrating typical brain metabolites, including resonances from NAA, choline esters (CHO), and creatine/phosphocreatine (Cr/PCr).

B, Decrease in the NAA resonance relative to A. Creatine and choline resonances are not significantly different between the two spectra.

In this study, the presence of a diffuse increase in white matter MR signal intensity was closely associated with cerebral atrophy. Postulated causes of periventricular hyperintensity include deep white matter infarction, the presence of reactive astrocytes, or loss of blood-brain barrier integrity with consequent edema and suffusion of hydrophilic molecules such as albumin and IgG (22). Similar microscopic pathologic changes have been reported in the postmortem studies of patients with SLE, and it is not surprising that a

generalized increase in white matter signal might be present in SLE patients with long-standing disease (10, 20).

The cause of cerebral atrophy in SLE is unclear, but SLE has been attributed both to neuronal dropout (or damage) secondary to microinfarctions and to the use of corticosteroids (4, 23). Corticosteroids have been associated with apparent cerebral atrophy, but these changes are reversible and do not appear to be associated with permanent intellectual impairment (24, 25). The atrophy associated with corticosteroids may be related to shifts in intracerebral water or to catabolic effects on lipid metabolism, especially on the myelin in white matter. Corticosteroid-induced atrophylike changes cannot be entirely excluded in the present series of patients, because 13 of the study patients were receiving corticosteroids. However, 5 of the patients demonstrated atrophy without therapy with corticosteroids, indicating that other processes were most likely responsible for the observed anatomic changes in these patients.

In the present study, we compared cerebral metabolite ratios in SLE patients with various degrees of atrophy using a combination of MR imaging and proton MR spectroscopy. The NAA/(Cr+PCr) ratio was lower in those patients with significant atrophy than in those patients with relatively normal brain volumes ($P < .001$). These data suggest that atrophy in patients with SLE is caused by neuronal and axonal dropout or damage, which results in a relative decrease in NAA (26–31). A decrease in the NAA/(Cr+PCr) ratio has been reported in areas of chronic stroke, focal lesions, inflammatory brain disease, and viral encephalitis, and probably represents a relative decrease in the proportion of surviving neuronal cells (32–35). Similar areas of ischemic injury in SLE may be reflected behaviorally by permanent intellectual impairment or affective changes even in the absence of disease activity (10, 20, 33, 36).

Volume-localized proton MR spectroscopy may have a wider application to the analysis of structural lesions present on standard cranial MR images in the autoimmune diseases. It is unclear whether the observed biochemical changes associated with atrophy are irreversible or are influenced by disease activity. However, the close association of decreased NAA with cerebral atrophy in SLE implies permanent anatomic alterations associated with neuronal dropout.

Acknowledgment

We gratefully acknowledge the assistance of Joanne Migneault, Associate to the Director, for her invaluable assistance in preparation of the manuscript.

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