

EXTENDED REPORT

Proton magnetic resonance spectroscopy may predict future brain lesions in SLE patients: a functional multi-imaging approach and follow up

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Ann Rheum Dis 2005;64:1022-1027. doi: 10.1136/ard.2004.026773

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Accepted 15 December 2004
Published Online First 7 January 2005

Objective: To determine whether single photon emission tomography (SPECT) and magnetic resonance spectroscopy (^1H -MRS) can predict the appearance of new lesions in systemic lupus erythematosus (SLE), detectable by magnetic resonance imaging (MRI).

Methods: $^{99\text{Tc}^{\text{m}}}$ -HMPAO-SPECT, brain MRI, and ^1H -MRS were done in eight women with SLE (mean age 31.8 years; disease duration 5.5 years). NAA/Cho, NAA/Cre, and Cho/Cre ratios were assessed in hypoperfused and normoperfused areas detected by SPECT that were normal on MRI examination. Reference values were obtained in 20 normal healthy controls. In five patients, MRI was repeated four to six years after the first evaluation.

Results: Mean NAA/Cho and Cho/Cre ratios in hypoperfused and normoperfused frontal areas were, respectively, lower and higher than control. There were no differences in NAA/Cre ratios. Mean Cho/Cre ratios were increased in hypoperfused v normoperfused brain areas (mean (SD): 1.43 (0.27) v 1.00 (0.07); $p < 0.023$). NAA/Cre ratios were not altered (2.18 (0.30) v 1.99 (0.28); $p = 0.381$). Three of five patients who had a second MRI had new lesions in areas previously abnormal on MRS and SPECT but normal on first MRI. One patient with positive MRI, SPECT, and MRS showed an increase in the number of MRI lesions; one patient with negative MRI, SPECT, and MRS did not show any new lesions.

Conclusions: Abnormalities reflecting altered perfusion or neuronal-chemical changes can be demonstrated by functional imaging techniques even in the absence of morphological lesions detectable by MRI. The abnormal areas identified by SPECT and MRS may predict future parenchymal damage.

Central nervous system (CNS) involvement occurs in a large proportion of patients with systemic lupus erythematosus (SLE), depending on the population studied, the criteria for inclusion, the diagnostic methods used, and the length of the observation period.¹ The neuropsychiatric manifestations vary from overt neurological and psychiatric disorders to more subtle signs such as headache, mood disorders, and mild cognitive dysfunction.² Because of their low specificity, doubt has been raised as to whether these more subtle manifestations are part of the neuropsychiatric picture of SLE.³ To date the clinical assessment of neuropsychiatric systemic lupus erythematosus (NP-SLE) remains a major problem and often the diagnosis is only presumptive.⁴

Magnetic resonance imaging (MRI) is currently considered the standard technique for evaluating morphological brain abnormalities in NP-SLE.⁵ Nevertheless, as functional alterations such as hypoperfusion or metabolic impairment can precede anatomical lesions detectable by conventional MRI, other techniques including positron emission tomography (PET), single photon emission computed tomography (SPECT), and localised proton magnetic resonance spectroscopy (^1H -MRS) are now available and may be useful for evaluating brain involvement.⁶⁻¹⁰ ^1H -MRS has proved to be a valuable, non-invasive tool for detecting neuronal metabolic alterations.⁹⁻¹⁰ The proton spectra obtained from brain tissue show three main peaks arising from N-acetylaspartate (NAA), choline (Cho), and creatine (Cr). Altered metabolite ratios have been observed even in the absence of MRI lesions but up to now few studies have been carried out in SLE patients with and without overt neurological involvement.¹¹⁻¹⁵

In a previous preliminary study using a multi-imaging co-registration approach, we found a topographic correlation

between SPECT and metabolic abnormalities detected with ^1H -MRS in the absence of MRI lesions in two SLE patients.¹⁶ Our aim in the present report was to verify—in a further six patients with SLE but without clinical evidence of major CNS involvement—whether perfusion defects detected by SPECT in areas free of MRI abnormalities correspond to areas of neuronal metabolic impairment detected by ^1H -MRS and, if so, whether such alterations can predict the appearance of new lesions detectable by MRI.

METHODS

Between January 1995 and January 1997, $^{99\text{Tc}^{\text{m}}}$ -HMPAO-SPECT, brain MRI, and ^1H -MRS were undertaken in eight patients with their informed consent. The patients included the two we have described previously¹⁶ and fulfilled the 1982 American College of Rheumatology classification criteria for SLE.¹⁷ The mean age of the patients (all women) was 31.8 years (range 15 to 48), and the mean duration of disease was 5.5 years. Secondary antiphospholipid syndrome (SAPS) was identified using the Sapporo preliminary criteria.¹⁸ All patients underwent a neurological examination carried out by the same expert neurologist. Age, disease duration, clinical picture, and seroimmunological profile were recorded (table 1).

SPECT

Ten minutes after the intravenous injection of 925 MBq (25 mCi) of $^{99\text{Tc}^{\text{m}}}$ -HMPAO, brain SPECT was carried out with a rotating single head gamma camera system (Orbiter 7500,

Abbreviations: Cho, choline; Cr, creatine; MRS, magnetic resonance spectroscopy; NAA, N-acetylaspartate; NP-SLE, neuropsychiatric systemic lupus erythematosus; rCBF, regional cerebral blood flow; SLE, systemic lupus erythematosus; SPECT, single photon emission computed tomography

Table 1 Demographic, clinical, and laboratory data on eight patients with systemic lupus erythematosus

Case	Age (y)	Disease duration (months)	ANA*	aDNA†	aENA‡	LAC§	aCL¶	Symptoms	Clinical evaluation	Treatment**
1	33	120	+	Neg	Neg	Pos	IgG high titre	Headache	Negative	CIA, ASA, methylprednisolone
2	48	132	+	Neg	SSA	Neg	Neg	Asymptomatic	Negative	HCQ, ASA, methylprednisolone
3	20	24	+	Neg	RNP	Pos	IgG high titre	Asymptomatic	Hypereactive tendon reflexes	Warfarin, prednisone
4	15	48	+	1:160	Neg	Neg	Neg	Headache	Negative	HCQ, deflazacort
5	43	1	+	Neg	SSA/SSB	Neg	Neg	Asymptomatic	Negative	HCQ, prednisone
6	44	130	+	Neg	Neg	Neg	IgG high titre	Headache	Hypereactive tendon reflexes	Warfarin, prednisone
7	35	72	+	1:160	Neg	Neg	Neg	Asymptomatic	Hypereactive tendon reflexes	HCQ, CIA, methylprednisolone
8	17	1	+	1:80	SSA	Neg	Neg	Headache	Negative	HCQ, ASA, prednisone

Cases in bold are those with a secondary antiphospholipid syndrome.

*Detected by indirect immunofluorescence (IFI) using Hep-2 cells as substrate.

†Detected by IFI on *Chritidia luciliae*.

‡Detected by a double immunodiffusion (ID) method.

§Detected by kaolin clotting time, diluted Russell viper venom test.

¶Detected by a standardised enzyme linked immunosorbent assay method.

**At the time of instrumental evaluation.

aCL, anticardiolipin antibodies; aDNA, anti-dsDNA antibodies; ANA, antinuclear antibodies; ASA, aspirin; CFS, cyclophosphamide; CIA, ciclosporine A; aENA, anti-extractable nuclear antigen antibodies; HCQ, hydroxychloroquine; LAC, lupus anticoagulant; y, years.

Siemens, Erlangen, Germany), equipped with a high resolution collimator. $^{99}\text{Tc}^{\text{m}}$ -HMPAO was purchased from Amersham International (Amersham, UK), prepared according to the manufacturer's instructions and used within five minutes of labelling. Data were acquired in a 64×64 matrix over a 360° rotation at 6° intervals. The average radius of rotation was 20 cm. The spatial resolution of the system, expressed as FWHM (full width half maximum) at the centre of the field of view and at a depth of 20 cm from the camera crystal, was 17 mm. Approximately eight million counts were acquired. Data storage and reconstruction of transverse images were carried out using a computer system (micro Delta-Max Delta) coupled to the gamma camera on a 64×64 matrix. Neither scatter nor attenuation correction was made. Transaxial slices 2 pixels thick (pixel size = 6.2 mm) were reconstructed. The transaxial slices were normalised to the maximum pixel count and displayed on a colour scale with a lower threshold of 0%.

To identify areas of abnormal perfusion, visual interpretation of SPECT images obtained in each patient was carried out twice in random order, according to Chang *et al*,¹⁹ evaluating agreement between two independent and experienced observers blind to the clinical picture. In case of divergence between the two observers a consensus was reached after discussion. Abnormal findings consisted of heterogeneous regional cerebral blood flow (rCBF) with regions of hypoperfusion or evident asymmetry on at least two consecutive slices detected by each of the two observers. Hypoperfused areas or asymmetry were assessed, comparing the amount and homogeneity of tracer uptake with adjacent or contralateral corresponding areas of the brain, or both. Conversely, normal findings included homogeneous rCBF in the grey matter of the cortex and basal ganglia without regions of hypoperfusion or visible asymmetry. This type of subjective evaluation has proved to be accurate for assessing both cerebral lupus and other diseases.^{16 19 20}

Magnetic resonance imaging

MRI was carried out using a conventional 1.5 Tesla whole body MR imaging Magnetom SP 4000 (Siemens), using a standard circular polarised head coil. We acquired T1 sequences (time of repetition (TR) 500 ms, time of echo (TE) 14 ms), T2 sequences (TR 2002 ms, TE 90 ms), weighted

images, and fluid attenuated inversion recovery (FLAIR) sequences (TR 8002 ms, TE 104 ms, inversion time (TI) 2000 ms, 6.0 mm thickness, 1.0 mm gap, 256×192 matrix).

^1H -Magnetic resonance spectroscopy

^1H -MR spectra were obtained using the same Siemens imager (1.5 Tesla whole body MR imaging Magnetom SP 4000, Siemens). A single voxel spin echo sequence with a TE of 135 ms and a TR of 2000 ms was used. Water suppression was achieved using three Gaussian shaped chemical shift selective pulses of 60 Hz width (CHESS technique). For mathematical eddy current compensation, the echo signal (six scans, two prescans) without water suppression was collected first. The final echo (obtained using 256 scans and water suppression) was first corrected for eddy current using the echo without suppression as the reference, then zero filled (from 1024 to 2048 data points), filtered using a Gaussian function (256 ms half width), and Fourier transformed. Finally, manual (zero and first order) phase correction and peak integrations of the real part of the spectrum were carried out. No baseline manipulation was done.

The neurometabolite spectra were obtained from different volumes of interest ($2 \times 2 \times 2$ cm) localised in abnormally and normally perfused regions on SPECT. MRI imaging data from the same areas were also collected.

Peak levels of signals from brain metabolites NAA, choline, and creatine were measured and values were expressed as NAA/Cho, Cho/Cre, and NAA/Cre ratios. The spectroscopic imaging acquisition data in the present study were reported as ratios because, at the time of data acquisition, absolute quantitation was not available for this spectroscopic imaging protocol. Data from healthy brain tissue in 20 normal subjects (obtained with the same machinery and protocol) were used as the referral cut off (see table 2 for reference values).

To minimise bias deriving from different positioning of voxels—as metabolite concentrations derived from ^1H -MRS examination may differ according to the brain region explored and the amount of grey/white matter—we selected only volumes of interest (VOI) with normal MRI signal, hypoperfused or normoperfused by SPECT, and located in similar brain regions. For this evaluation the frontal lobes

Table 2 Results of single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), and localised ¹H-magnetic resonance spectroscopy (¹H-MRS) carried out in eight patients with systemic lupus erythematosus

Case	Symptoms	Volume of interest	SPECT	MRI	¹ H-MRS		
					NAA/Cho	NAA/Cr	Cho/Cr
1	Headache	Right temporal	Hypoperfused	Normal	1.74	2.05	1.18
		Right frontal	Hypoperfused	Normal	1.25	2.21	1.77
		Left frontal	Normoperfused	Normal	2.13	2.32	1.09
2	Asymptomatic	Right frontal	Hypoperfused	Normal	1.43	1.97	1.38
		Left frontal	Hypoperfused	Normal	1.47	1.95	1.33
		Left occipital	Normoperfused	Normal	2.21	1.9	0.86
3	Asymptomatic	Left frontal	Hypoperfused	Normal	1.39	2.44	1.76
		Right frontal	Normoperfused	Normal	1.81	1.77	0.98
		Right occipital	Normoperfused	Normal	3.44	1.95	0.57
4	Headache	Right temporo-parietal	Hypoperfused	Normal	2.74	2.86	1.05
		Left temporo-parietal	Normoperfused	Normal	2.13	1.93	0.91
		Right frontal	Hypoperfused	Normal	2.17	2.65	1.22
5	Asymptomatic	Right parieto-occipital	Hypoperfused	Normal	2.93	1.97	0.67
		Left parieto-occipital	Normoperfused	Normal	2.79	2.09	0.75
		Left frontal	Hypoperfused	Abnormal	2.01	1.43	0.71
6	Headache	Right frontal	Normoperfused	Abnormal	3.32	2.87	0.87
		Right occipital	Normoperfused	Normal	3.26	1.96	0.6
		Right temporal	Hypoperfused	Abnormal	2.4	1.9	0.8
7	Asymptomatic	Right frontal	Hypoperfused	Normal	1.66	1.88	1.13
		Left occipital	Normoperfused	Normal	2.4	2.12	0.88
		Left frontal	Normoperfused	Normal	2.02	1.89	0.94
8	Headache	Right frontal-posterior	Normoperfused	Abnormal	2.04	2.27	1.12
		Right parieto-occipital	Hypoperfused	Abnormal	2.57	2.06	0.8
		Reference values for healthy tissue (frontal lobes) from 12 male and 8 female control subjects aged 25 to 65 years (mean (SD))				2.6 (0.5)	2.1 (0.5)

Cho, choline; Cr, creatine; NAA, N-acetylaspartate.

were chosen, as the reference values from the control subjects were obtained in these areas.

Neurometabolite mean ratios were then compared. ¹H-MRS data were entered and processed in a one dimensional MR software package as previously reported.¹⁶ In each patient all three imaging examinations were obtained within 48 hours using the following sequence: SPECT, MRI, ¹H-MRS. SPECT and MRI image analyses were first separately undertaken by two expert radiologists and then jointly after multimodal co-registration of the acquired volumes (done with statistical parametric mapping software using the "maximisation of mutual information" technique). Finally, a follow up re-evaluation was carried out in five patients in whom an MRI analysis was repeated between four and six years after the first instrumental evaluation (between January 2001 and December 2003).

Owing to the small number of observations, statistical analysis were carried out using the non-parametric Mann-Whitney U test, defining a probability (p) value <0.05 as statistically significant.

RESULTS

At the time of the first investigation all eight patients had stable and inactive SLE (as judged by the European

consensus lupus activity measure (ECLAM) scoring); four patients complained only of mild neurological manifestations such as tension headache, while the other four were completely asymptomatic. Neurological examination was negative except for mildly increased tendon reflexes (in two asymptomatic patients and one patient with headache). Demographic data, laboratory data, and ongoing treatment of each patient are summarised in table 1.

SPECT scan and MRI findings

Multiple perfusion defects on SPECT were detected in all eight patients, with a total of 12 hypoperfused areas: 25% were localised in the temporal regions, 59% in the frontal regions, and 16% in parieto-occipital regions. Three patients (two with headache and one asymptomatic) had abnormal MRI findings; the MRI changes appeared as one or more small (<1 cm) areas of increased signal intensity on T2 weighted and FLAIR acquisition in the white matter of the frontal, temporal, and parieto-occipital lobes. All the other patients (two with headache and three asymptomatic) had normal MRI findings. MRI was normal in nine of the 12 areas shown to be hypoperfused by SPECT and in nine of 11 normoperfused areas, giving a total of 18 normal MRI areas with different perfusion patterns on SPECT.

Table 3 Results of magnetic resonance imaging carried out in five patients between four and six years after the first instrumental evaluation

Case	Symptoms on initial evaluation	MRI	SPECT	MRS	Follow up MRI	Symptoms at follow up
2	Asymptomatic	Negative	Positive	Positive	Positive	Headache, cognitive dysfunction
3	Asymptomatic	Negative	Positive	Positive	Positive	Asymptomatic
4	Headache	Negative	Positive	Positive	Positive	Worsened headache, cognitive dysfunction
5	Asymptomatic	Negative	Negative	Negative	Negative	Asymptomatic
6	Headache	Positive	Positive	Positive	Positive with new lesions	Worsened headache, cognitive dysfunction

MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; SPECT, single photon emission computed tomography.

Correlation of SPECT findings with ¹H-MRS and neuropsychiatric manifestations

For this evaluation we selected only results of SPECT, MRI, and ¹H-MRS obtained from the frontal lobes, corresponding to a total of nine voxels (detected in six of eight patients) that were hypoperfused or normoperfused on SPECT and normal on MRI.

When comparing neurometabolite ratios of the patients with the reference controls, the mean NAA/Cho ratios in both hypoperfused and normoperfused frontal areas were reduced (hypoperfused *v* control: $p < 0.0001$; normoperfused *v* control: $p = 0.002$), while mean Cho/Cre ratios both in hypoperfused and normoperfused frontal areas were higher than in the controls (hypoperfused *v* control: $p = 0.001$; normoperfused *v* control: $p = 0.01$); there were no differences in the NAA/Cre ratios between the groups.

When comparing neurometabolite ratios in hypoperfused versus normoperfused areas, the mean NAA/Cho ratios were lower (but not significantly so) in the hypoperfused than in the normoperfused areas (mean (SD) values, 1.56 (0.32) *v* 1.98 (0.16); $p = 0.166$); conversely, mean Cho/Cre ratios were significantly increased in hypoperfused compared with normoperfused areas (1.43 (0.27) *v* 1.00 (0.07); $p < 0.023$); no significant differences were detected in the NAA/Cre ratios (2.18 (0.30) *v* 1.99 (0.28); $p = 0.381$).

Follow up

Five patients underwent a new MRI after four to six years from baseline evaluation (two of the others refused to repeat the analysis and one was lost to follow up). Three of the five had new MRI lesions in areas with previously abnormal ¹H-MRS and hypoperfusion on SPECT but negative on MRI examination. One patient with positive MRI, SPECT, and MRS had an increase in the number of MRI lesions and one patient with negative MRI, SPECT, and MRS did not have any new lesions (table 3). All the new MRI lesions showed anatomical correspondence with the previously detected abnormal ¹H-MRS and SPECT areas.

DISCUSSION

CNS involvement is an important complication of SLE, clinical signs and symptoms occurring in a large proportion of patients, depending on the sensitivity of the criteria applied.¹ Owing to the lack of effective imaging methods, accurate diagnosis and assessment of disease activity and severity is usually difficult, particularly in those patients with minor and less specific clinical signs. As a result of the poor diagnostic accuracy, it is not surprising that the pathogenic mechanisms responsible for the different neuropsychiatric disorders and types of brain damage remain undefined in a large proportion of patients.^{21–22}

In order to improve the diagnostic value and to gain a better understanding of the pathophysiological mechanisms responsible for damage, it may be useful to link morphological imaging techniques (in particular MRI) with functional techniques such as SPECT and ¹H-MRS.

MRI is currently considered the neuroimaging method of choice for morphological brain evaluation in NP-SLE, being capable of detecting a large proportion of the brain lesions, which are mainly represented by small punctate focal lesions in the white matter.²³ Although MRI appears sensitive for detecting abnormalities in patients with major clinical manifestations such as focal neurological defects, seizures, and cerebrovascular disease, its sensitivity is very low in patients with diffuse neuropsychiatric disturbances such as headache, cognitive dysfunction, affective disorders, or confusional states.^{24–27} In these patients functional (perfusion or metabolic) alterations could play a role in revealing abnormalities that would remain undetected by conventional

MRI. Furthermore the interpretation of small punctate hyperintense MRI lesions which are often observed even in normal subjects is still debated, as is the normal MRI found in patients with overt NP-SLE. In these cases coupling morphological and functional imaging techniques may be helpful.

Because of the increasing evidence that mechanisms of NP-SLE are mainly related to microangiopathic vascular involvement,²⁸ determination of cerebral blood flow as an indicator of early CNS involvement seems promising. SPECT scanning provides information on regional brain perfusion which is closely linked to cerebral metabolism. SPECT has revealed abnormalities in regional distribution of the radiotracer not only in patients with definite CNS disease, but also in most patients without clinically apparent CNS disease.^{29–30} In a study that assessed the relation between perfusion abnormalities, clinical manifestations, MRI, and EEG, it was observed that up to 35% of SPECT alterations (and in the present study 73%) did not correspond to MRI abnormalities.¹⁶ The hypotheses proposed to explain these discrepancies may be summarised as either a false positive SPECT (the presence of deep MRI lesions resulting in a mild to moderate reduction in HMPAO uptake in the projection area (diaschisis)), or a very early stage of neurological involvement, or both.

¹H-MRS is a technique that provides non-invasive access to “live chemistry” *in situ*. This technique shows four major spectra corresponding to different metabolites: N-acetylaspartate, which can be considered a marker of neuronal integrity; choline, including choline containing phospholipids that are released during active myelin breakdown; creatine, which has a constant concentration throughout the brain and tends to be resistant to change in all but the most severely destructive lesions (therefore is suitable for use as an internal standard against which the resonance intensities of NAA and choline can be normalised); and lactate (Lac), which is the end product of glycolysis and accumulates when oxidative metabolism cannot meet energy requirements.¹⁵ Brain ¹H-MRS has been carried out in SLE patients with encouraging results.^{12–15–31} Concerning single metabolites, previous quantitative studies have shown that NAA is substantially reduced both in patients with active NP-SLE and in SLE patients with a past history of NP-SLE. This suggests that it is most probably a measure of NP-SLE severity and outcome rather than of NP-SLE activity.^{32–34} The choline peak is usually increased in NP-SLE and has been related to disease activity or reactive brain inflammation.^{32–34} With regard to lactate, although ischaemia has been implicated in NP-SLE, a definite peak of this metabolite has not been observed, suggesting that in anything but overt stroke extensive anaerobic metabolism is not a fundamental characteristic of NP-SLE.^{35–37} In the present study a lactate peak was not detected in any patient.

Results obtained from ¹H-MRS studies carried out on patients with NP-SLE have shown the ability of this technique to detect neurochemical brain abnormalities—even in normal MRI areas—or to reveal an organic substrate in patients with neurocognitive disorders. It has also been proposed that it quantifies the severity of cerebral damage.

At present, the value of this tool is not in a diagnostic phase, but it may contribute to shedding light on the interpretation, quantification, and qualitative characterisation of brain damage (atrophic, demyelinating, gliotic, ischaemic, inflammatory) and in monitoring cerebral involvement and the efficacy of treatment. Thus ¹H-MRS could be useful in follow up for outcome studies, prognosis estimates, or disability determination in patients with SLE.^{9–16}

The information provided by different diagnostic tools such as SPECT, MRI, and ¹H-MRS make it reasonable and

potentially useful to apply them in the same patient. In this study all eight patients—four with subtle symptoms and four without any complaints—had MRI, SPECT, and $^1\text{H-MRS}$. While SPECT revealed the presence of hypoperfused areas in both symptomatic and asymptomatic patients and in all cases with positive anticardiolipin antibodies or lupus anticoagulant or both, only three cases (two suffering from headache and one asymptomatic) had an abnormal MRI.

Co-registration of SPECT, MRI, and $^1\text{H-MRS}$ has shown that $^1\text{H-MRS}$ can identify metabolic abnormalities in brain areas with reduced blood perfusion detected by SPECT but free of MRI abnormalities. In our patients, the major component of neurometabolic abnormalities seemed to be an increased in choline rather than a reduction in the NAA peak, as commonly reported by other investigators.^{32–35} However, the patients examined in this report are quite different as they did not suffer from overt major NP-SLE manifestations. The significance of our findings in this kind of patient remains to be elucidated. Interestingly, the majority of neurometabolically impaired areas were located in the frontal regions. Similar findings have been reported by others.¹²

Although the precise meaning of these metabolic abnormalities remains to be determined, their localisation in areas of reduced cerebral blood flow suggests that they could represent an early sign of neuronal injury in SLE patients, even in the presence of normal brain MRI. If so, $^1\text{H-MRS}$ could be a sensitive measure of neuronal damage; this would corroborate the hypothesis that cerebral hypoperfusion detected by SPECT in areas with normal MRI appearances should not to be regarded as a false positive result but could represent a very early manifestation of CNS involvement.

Some interesting preliminary information comes from the follow up study of the patients who had a further MRI some years later. Three of them showed new MRI lesions in areas previously positive to $^1\text{H-MRS}$ and SPECT and negative on MRI examination. One patient with positive MRI, SPECT and $^1\text{H-MRS}$ showed an increase in the number of MRI lesions while one patient with negative MRI, SPECT, and $^1\text{H-MRS}$ did not show any new lesions (table 3).

If confirmed, these data suggest that pathological areas examined using functional imaging could be at risk of future parenchymal damage. This could be of great importance in elucidating some of the discrepancies between clinical and “traditional” imaging pictures and for prognostic assessment.^{1–38} Thus a careful functional imaging evaluation may contribute to the detection of early or subclinical CNS involvement in the course of the disease, and could be useful in assessing prognosis, offering a window of opportunity to start appropriate treatment and prevent irreversible damage.

Conclusion

Our study shows that, in both mild symptomatic and asymptomatic SLE patients, abnormalities of perfusion or neuronal-chemical changes can be demonstrated by functional imaging techniques even in the absence of morphological lesions. The abnormal areas identified by both SPECT and $^1\text{H-MRS}$ may not represent benign lesions or false positive findings, but may be predictive of future parenchymal damage, as suggested by Axford *et al.*¹⁴ Owing to the limited number of patients included, larger prospective follow up studies are needed.

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