SHORT REPORT

Assessing "occult" cervical cord damage in patients with neuropsychiatric systemic lupus erythematosus using diffusion tensor MRI

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Background: Whereas focal and diffuse brain damage on conventional MRI is seen in patients with neuropsychiatric systemic lupus erythematosus (NSLE), the spinal cord seems to be rarely involved. Diffusion tensor (DT) MRI provides information on the patterns of tissue disruption of the central nervous system, which may go undetected by conventional MRI. **Objective:** To quantify the extent of otherwise "occult" injury of the cervical cord in NSLE, and to improve our understanding of its nature.

Subjects and methods: Conventional and DT MRI scans of the cervical cord and brain were acquired from 11 patients with NSLE and 10 healthy controls. Histograms of mean diffusivity (MD) and fractional anisotropy (FA) of the cervical cord and brain were analysed. Measures of cervical cord and brain atrophy and focal lesion loads were computed.

Results: Only one patient had a single focal lesion of the cord whereas all had multiple brain lesions on conventional MRI scans. Cord and brain volumes did not differ between patients and controls. Mean peak height of the cervical cord MD histogram ($p=0.0001$) and average brain FA ($p=0.001$) were significantly lower in patients than in controls. Average cord MD was correlated with average brain MD ($r=0.69$, $p=0.01$) and FA ($r=-0.81$, $p=0.002$).

Conclusion: DT MRI shows mild and otherwise "occult" cord damage in NSLE, which might be secondary to Wallerian degeneration of long tract fibres passing through damaged areas of the brain.

Systemic lupus erythematosus (SLE) frequently affects the central nervous system (CNS), leading to a condition which is termed neuropsychiatric SLE (NSLE).¹ Diffuse immune mediated tissue damage, focal ischaemic lesions and vasculitis are all potential pathological substrates underlying CNS dysfunction in NSLE. However, in contrast with other "diffuse" CNS disorders, cord damage seems to be a relatively rare feature of NSLE,² outside the context of acute myelitis.³

Diffusion tensor (DT) MRI provides quantitative indices of the structural and orientational features of the CNS tissues.⁴ The increased sensitivity of DT MRI over conventional MRI in detecting tissue changes associated with demyelinating⁴ and ischaemic vascular disease⁵ has prompted the use of DT MRI to define the actual extent of brain damage associated with NSLE.^{6–8} However, to date, no DT MRI study has investigated the features of NSLE pathology in the spinal cord. Using a DT MRI sequence tailored to cervical cord imaging,⁹ the present study was performed to assess the overall extent of otherwise "occult" damage of the cervical cord in patients with NSLE. We also assessed the correlation between the extent of such cord

damage with that present in the brain in an attempt to improve our understanding of its nature.

PATIENTS AND METHODS

We studied 11 consecutive patients (9 women and 2 men; mean age 51.2 (SD 15.7) years) who were diagnosed as having NSLE.^{10–11} Neuropsychiatric symptoms were epileptic seizures in 6 patients, cerebral ischaemia in 5 patients and cognitive impairment in 1 patient. Patients with a clinical history of ongoing or previous acute myelitis were excluded, as were those with signs of clinical activity in the past 3 months. Ten healthy volunteers (8 women and 2 men; mean age 52.2 (SD 13.2) years) with no history of neurological disorders and a normal neurological examination served as controls. All subjects gave written informed consent prior to study entry and the study design was approved by the local ethics committee.

Using a 1.5 Tesla system, the following pulse sequences were acquired from the cervical cord.

- (1) Fast short tau inversion recovery (TR = 2288, TE = 60, TI = 110, echo train length = 11, field of view (FOV) = 280×280 mm, matrix size = 264×512; geometry: eight, 3 mm thick sagittal slices, with 0.3 mm interslice gap).
- (2) Pulsed gradient, diffusion weighted (DW) sensitivity encoded (SENSE) single shot echo planar imaging (TR = 7000, TE = 100; FOV = 240×90 mm; matrix = 128×48; geometry: five, 4 mm thick sagittal slices). A detailed description of this sequence is given elsewhere.⁹
- (3) Sagittal three dimensional magnetisation prepared rapid acquisition gradient echo (MP-RAGE) (TR = 9.7, TE = 4, flip angle = 12°, slab thickness = 160 mm, FOV = 280×280 mm, number of partitions = 128).

In the same session, the following pulse sequences were used to image the brain.

- (1) Dual echo turbo spin echo (TSE) (TR = 3300, TE = 16/98, echo train length = 5).
- (2) Pulsed gradient DW echo planar imaging (inter-echo spacing = 0.8, TE = 123), with gradients applied in eight different directions.¹²

Abbreviations: CCA, cervical cord area; CNS, central nervous system; DT, diffusion tensor; DW, diffusion weighted; FA, fractional anisotropy; FOV, field of view; MD, mean diffusivity; MP-RAGE, magnetisation prepared rapid acquisition gradient echo; MT, magnetisation transfer; NBV, normalised brain volume; NSLE, neuropsychiatric systemic lupus erythematosus; SLE, systemic lupus erythematosus; TSE, turbo spin echo

Table 1 Mean values of cervical cord diffusion tensor MRI histogram derived metrics from 10 healthy subjects and 11 patients with neuropsychiatric systemic lupus erythematosus

	Healthy subjects	NSLE patients	p Value
Mean MD	1.21 (0.09)	1.36 (0.20)	NS
MD peak height	11.1 (1.70)	7.5 (1.13)	0.0001
Mean FA	0.42 (0.04)	0.37 (0.08)	NS
FA peak height	6.7 (1.84)	6.2 (1.65)	NS

FA, fractional anisotropy; MD, mean diffusivity; NSLE; neuropsychiatric systemic lupus erythematosus.
Values are mean (SD).
MD is expressed in $\text{mm}^2/\text{s} \times 10^{-3}$; FA is a dimensionless index. Normalised histogram peak heights are expressed in per cent units.

- (3) Sagittal three dimensional MP-RAGE (TR = 11.4, TE = 4.4, slab thickness = 160 mm, FOV = 256×256 mm, number of partitions = 160).

For TSE, 24 contiguous interleaved axial slices were acquired with a slice thickness of 5 mm, a matrix size of 256×256 and a FOV of 250×250 mm. For the DW scans, 10 axial slices of 5 mm thickness, a 128×128 matrix size and a 250×250 mm FOV were acquired, with the second last caudal slice positioned to match exactly the central slice of the TSE set.

MRI analysis was performed by two observers by consensus. Cervical cord hyperintense lesions were identified on the fast short tau inversion recovery scans. DT MRI data were reconstructed offline on a UNIX workstation (Sun Microsystems, Mountain View, California, USA).⁹ The images were then corrected for distortions introduced by the DW gradient pulses, and DT was calculated for each voxel. From the tensor matrix, cervical cord mean diffusivity (MD) and fractional anisotropy (FA) maps were derived.¹³ From these maps, the cord from C1 to C5 was segmented using a semiautomated technique.¹³ To reduce partial volume effects from the cerebrospinal fluid, only the central slice of the sagittal images was used for the production of normalised histograms of MD and FA values.¹³ For each histogram, the average MD and FA values and the histogram peak heights (ie, the proportion of pixels at the most common MD and FA values) were calculated.

MP-RAGE data were reformatted using the standard software available on the scanner. A set of five contiguous, 3 mm

thick axial slices was reconstructed using the centre of the C2–C3 disc as the caudal landmark. Then, a semiautomated technique was used to measure the average cross sectional cervical cord area (CCA).¹⁴

Hyperintense brain lesions were identified on proton density weighted images. Then, lesion volumes were measured using a segmentation technique based on local thresholding.¹² DW images were first corrected for distortions introduced by DW gradient pulses.¹² Then, the DT was calculated, MD and FA maps created and average MD/FA values from the whole brain parenchyma measured.¹² On MP-RAGE images, normalised brain volume (NBV) was measured using the cross sectional version of the Structural Image Evaluation of Normalised Atrophy software (SIENAX).¹⁵

An analysis of variance model was used to compare MRI derived measures from controls and patients. Analysis of DT MRI derived data was corrected for the subject's age, NBV and CCA, to account for the effect of aging and atrophy. After correction for preplanned group comparisons ($n = 9$), p values < 0.0056 were considered statistically significant. Univariate correlations were assessed using the Spearman Rank Correlation Coefficient.

RESULTS

No abnormalities were seen on MRI from healthy controls. Multiple brain lesions were found in all patients, while a single small cord lesion was identified at the C5 level in only one patient. Mean brain T2 lesion volume was 6.5 (SD 6.4) ml. Mean NBV and CCA were 1538.2 (SD 0.8) ml and 82.5 (4.8) mm^2 for healthy controls, and 1471.0 (SD 100.3) ml and 82.5 (8.9) mm^2 for patients with NSLE.

Cervical cord MD peak height was lower in patients than in controls (table 1). Average brain FA was lower in patients than in controls (mean 0.19 (SD 0.02) vs 0.23 (0.01); $p = 0.001$). Average brain MD did not differ between the two groups (mean 1.01 (SD 0.11) $\text{mm}^2/\text{s} \times 10^{-3}$ vs 0.93 (0.06) $\text{mm}^2/\text{s} \times 10^{-3}$).

Significant correlations were found between average cord MD and both average brain MD ($r = 0.69$, $p = 0.01$) and FA ($r = -0.81$, $p = 0.002$) (fig 1).

The results did not change when the patient with a macroscopic cord lesion was excluded from the analysis (data not shown).

DISCUSSION

The main result of this study is that otherwise “occult” cervical cord damage is present in patients with NSLE, but its severity is only mild. That the peak height of cervical cord MD histograms was significantly lower in patients than in controls, whereas they had similar average cord MD values, implies that fewer cervical cord pixels had normal MD values in patients, but such a change was not enough to affect the overall tissue MD. Interestingly, our patients did not show any change in their cervical cord anisotropy features. This indicates that the orientational properties of the cord tissue were maintained, despite the presence of pixels with increased MD, thus suggesting demyelination as the most likely substrate of the observed change. Axonal loss and reactive gliosis would, in fact, cause loss of alignment of nerve fibres with a consequent decrease in FA. This pattern of cervical cord damage has the potential to contribute to the work-up of patients with NSLE in the case of a differential diagnosis with multiple sclerosis, which can result in undistinguishable brain conventional MRI findings but which may in turn lead to significant and diffuse disruption of cord tissue integrity, as has been shown by magnetisation transfer (MT)¹⁶ and DT MRI¹³ studies.

Compared with controls, our patients also had significantly lower brain average FA values. This change may reflect loss of

Figure 1 Scatterplot of average cord mean diffusivity (MD) and average brain fractional anisotropy (FA) values from 11 patients with neuropsychiatric systemic lupus erythematosus.

alignment of the nerve fibres, which in turn is likely to be the result of diffuse axonal pathology. This agrees with MT MRI^{17–20} and magnetic resonance spectroscopy²¹ studies of NSLE. The mismatch between MD and FA findings in the brain may be secondary to glial proliferation, which would lead to a “pseudonormalisation” of MD values, but which would reduce FA as glial cells do not have the same anisotropic morphology as the tissue they replace.

Another important issue is whether the observed cord abnormalities result from intrinsic cord damage or are secondary to Wallerian degeneration of long fibre tracts passing through diseased brain areas. Although this study can only partially answer this question, it is likely that Wallerian degeneration may play an important role given the strong correlation found between brain and cord diffusivity features. This speculation is also supported by the presence of a reduced MD peak height of the cervical cord in patients with NSLE without any FA change, as it has been shown that Wallerian degeneration first occurs in the axonal membranes and myelin sheaths, thus causing MD changes (through increased diffusivity in the directions transverse to the involved fibres) but only minor or no changes to the measured FA.²² Moreover, the results of an MT MRI study of patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)²³ also suggest that cord fibres may be damaged by Wallerian degeneration in diffuse ischaemic diseases of the brain.

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