PATTERNS OF BRAIN DAMAGE IN PATIENTS AT PRESENTATION WITH CLINICALLY ISOLATED SYNDROMES SUGGESTIVE OF MS: A MULTIPARAMETRIC MR STUDY

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Introduction

Conflicting results have been obtained when using MR-based techniques to investigate the characteristics of brain tissue damage occurring outside MRI-visible lesions in patients at presentation with clinically isolated syndrome (CIS) suggestive of multiple sclerosis (MS). Diffusion tensor (DT) MRI has the potential to elucidate *in vivo* many characteristics of tissue microstructure inaccessible to other MR techniques (1). ^{1}H-MRS can be used to measure whole brain *N*-acetylaspartate (WBNAA), whose decrease is considered a marker of neuronal loss and/or dysfunction in MS patients (2). The present study was performed to investigate the patterns of brain damage in CIS patients using a multiparametric MR approach and to assess whether they may predict the short-term evolution of the disease according to MRI-based consensus criteria for MS diagnosis (3).

Patients and Methods

Forty-six patients with CIS were studied within three months from the onset of the neurological manifestations and at least 15 days after the termination of steroid treatment, if any. Using a 1.5 T magnet, the following scans of the brain were acquired: 1) dual-echo turbo spin echo (SE) (TR/TE/NEX=3300/16-98/1; number of slices: 24, contiguous, 5-mm thick); 2) pulsed-gradient spin–echo (PGSE) echo-planar (inter-echo spacing = 0.8, TE = 123; number of slices: 10, contiguous, 5-mm thick), with diffusion gradients applied in nine non-collinear directions; 3) ^{1}H-MRS pulse sequence based on a four-step cycle of non-selective 180° inversion pulses to obtain WBNAA measurement; 4) T1-weighted SE (TR/TE/NEX=768/15/2; number of slices: 24, contiguous, 5-mm thick), 5 minutes after the injection of 0.1 mmol/kg of gadolinium-DTPA. The duration and maximum amplitude of the diffusion gradients were 25 msec and 21mT m^{-1}, giving a maximum b factor in each direction of 1044 s mm^{-2}. The same scans were obtained in 22 age-matched healthy subjects. In CIS patients, dual-echo and post-contrast T1-weighted scans were also repeated 3 and 12 months after the first scanning session, to assess the presence of temporal disease dissemination (3). A local thresholding technique was used for MS lesion segmentation and brain total lesion volumes (LV) were measured. Mean diffusivity (MD) and fractional anisotropy (FA) maps of the normal appearing brain tissue were created by superimposing the lesion outlines and nulling out the corresponding regions. Normal-appearing white matter (NAWM) and grey matter (NAGM) were segmented using a technique based on statistical parametric mapping (SPM). NAWM and NAGM MD and FA histograms were produced and analyzed as previously described (4). Normalized brain volumes (NBV) were calculated using a fully-automated technique (SIENA) (5). Absolute WBNAA amounts (in mmoles - mM) were calculated using a phantom replacement method and were then corrected for individual subjects' brain volumes (2).

Results

Paraclinical evidence of spatial disease dissemination (3) was present at study entry for all CIS patients, based either on MRI findings in isolation (36 patients) or on the combination of MRI and cerebrospinal fluid findings (10 patients). At follow-up MRI, 28 patients also showed MRI evidence of disease dissemination in time, thus fulfilling criteria for a diagnosis of MS (3). The Table reports the MR characteristics of the study subjects. When compared to healthy controls, CIS patients showed an increase of average NAWM MD ($p<0.01$), a decrease of average NAWM FA ($p<0.001$) and a reduction of average WBNAA concentration ($p<0.001$). DT MRI changes in the NAWM were significantly correlated with T2 LV (r values ranged from 0.46 to 0.56). No significant differences in conventional, DT MRI or ^{1}H-MRS characteristics were found between CIS patients with paraclinical evidence of disease dissemination in time and those without.

Conclusions

NAWM damage associated with axonal loss/dysfunction occurs at a very early stage in patients at presentation with CIS. Long-term studies are needed to clarify whether these findings may have a prognostic value for the subsequent development of established MS.

	CIS patients	Healthy controls
T2 LV (ml)	4.2 (3.9)	-
NBV (ml)	1627.5	1630.5
Average NAGM MD	0.99 (0.04)	0.98 (0.04)
Average NAWM MD	0.82 (0.03)	0.80 (0.02)
Average lesion MD	0.98 (0.09)	-
Average NAGM FA	0.13 (0.007)	0.13 (0.006)
Average NAWM FA	0.28 (0.02)	0.30 (0.01)
Average lesion FA	0.28 (0.04)	-
WBNAA (mM)	12.7 (2.0)	16.1 (2.0)

Values are mean (SD). PH = Peak Height

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