Voxelwise MT Analysis Shows Less Pronounced Brain Tissue Damage in Benign MS than in Early Relapsing MS

M. Battaglini[1], M. L. Stromillo[1], M. L. Bartolozzi[2], V. Zipoli[3], B. Goretti[3], L. Guidi[2], E. Portaccio[3], A. Giorgio[1], A. Federico[1], M. P. Amato[3], N. De Stefano[1]

[1]Department of Neurology and Neurological Sciences, University of Siena, Siena, Italy, [2]Unit of Neurology, Empoli Hospital, Empoli, Italy, [3]Department of Neurology, University of Florence, Florence, Italy

Introduction

The course of the disease in Multiple Sclerosis (MS) is characterised by a wide range of rates of progression. The mildest form of MS that is clinically apparent has been labelled "benign" multiple sclerosis (B-MS)[1]. The ability to predict the subsequent clinical course of MS either clinically or paraclinically would be invaluable, considerably adding to the accuracy and quality of prognostic information provided for patients and leading to the most appropriate selection of patients for therapeutic interventions. Indeed, the trend to start disease modifying therapy early in the course of multiple sclerosis makes it important to understand the substrates leading to disability. MR measures such as magnetization transfer (MT) ratio (MTr) can provide specific estimate of tissue damage that has been shown to be predictive of clinical and pathological evolution in MS. Thus, MTr may be a useful tool to identify differences between patients with a benign course of the disease and those with a typical relapsing remitting form (relapsing remitting MS, RR-MS).

Methods

We acquired conventional MRI and MT imaging from a cohort of 50 patients with B-MS (defined as having EDSS ≤3 and disease duration ≥15 years) and 50 RR-MS patients selected to have similar disability (EDSS ≤3), but with very short disease duration (≤3 years). In each subject, we measured T2-weighted (T2-W) MRI white matter (WM) lesion volumes (LV), lesional-MTr, perilesional MTr, normal-appearing WM MTr (NAWM-MTr) and cortical-MTr. For the analysis of MT data, we used here a fully automated procedure (De Stefano N *et al.*, Ann Neurol, in press). Briefly, saturated (Sat) images were registered to No-Sat images using a registration method previously described[2]. The brain was extracted from both Sat and No-Sat images and MT ratio (MTr) images were then calculated using the formula MTr = 100 * (No-Sat –Sat)/No-Sat[3]. The extracted No-Sat images were then segmented into different tissue types [grey matter (GM), WM and cerebrospinal fluid (CSF)] using a previously described segmentation method [2], thresholding the resulting probabilistic tissue-class images to retain voxels where the tissue-class probability was equal to or greater than p=0.75. This gives fairly conservative GM and WM binary images which were applied to the MTr image to produce GM-MTr and WM-MTr images. To select identical brain regions in each subject, standard space WM and GM masks were automatically applied in native space to the WM-MTr and GM-MTr images by using the MNI152-to-native brain space transformation derived during registration. For a conservative measurement of the WM-MTr, we used a thresholded (up to the 60% of the intensity) standard space WM mask, made on the MNI152 average normal brain (McConnell Brain Imaging Centre, Montreal Neurological Institute). For selective MTr measurement of neocortical brain regions, a standard space mask (made on the MNI152 average normal brain and including ventricles, deep GM, cerebellum and brain stem) was used to separate segmented GM-MTr into neocortical and non-neocortical tissues. To avoid contamination of image noise, all voxels of the neocortical regions with values <10% of the grey matter- MTr (GM-MTr) mean value were excluded. Voxel fully inside the lesions and those around the lesions (obtained by using one non-binary morphological dilatation - of one voxel in each dimension - of the lesion mask) were masked out from the MTr image and assessed separately.

The non-parametric Mann-Whitney test was used for comparisons of the two groups of MS patients. Values of MTr for RR-MS and B-MS patients were compared to those of control group of healthy subjects. As the two groups were not age-matched, before statistical comparisons MR data were corrected for by using a z-score transformation relative to an age-matched normal control group for each patient group. After z-score transformation, differences between patient and normal control groups were assessed using analysis of variance (ANOVA) followed by pair-wise post-hoc comparison using Tukey's HSD procedure to account for multiple comparisons. Data were considered significant at the 0.05 level.

Results

B-MS patients were significantly older than the RR MS [median age: B-MS 49 years (range 34-69) *vs.* RR-MS 30 years (range 19-45), p <0.001)]. Mean T2-W LV was significantly higher in B-MS than in RR-MS (13.2±12 cm^3 *vs.* 6.5±12 cm^3, p<0.001). After correction for common effects of age, B-MS patients showed values of lesional-MTr and perilesional-MTr significantly lower than healthy subjects (p<0.0001), but significantly higher than RR-MS patients (p<0.0001). In addition, B-MS values of NAWM-MTr and cortical-MTr were significantly higher than those of the RR-MS patients (p<0.0001 and p<0.01, respectively). Also, similar results were confirmed when only patients with higher T2-W LV (>10 cm^3) were selected from both groups (B-MS: n=24, RR-MS: n=10) (see Figure). No difference in NAWM-MTr and cortical-MTr was observed between B-MS and control group.

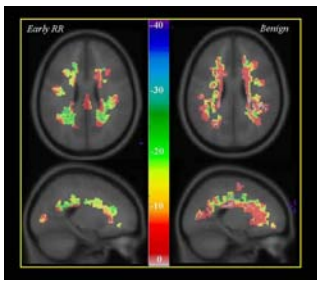

Figure. Example of the fully automatic MTr analysis in two MS patients with high LV (>10 cm3) who have either an early RR-MS (*left*) or a benign course of the disease (*right*). The colour overlay created on top of the MNI152 standard brain represents the lesional-MTr masks of the two patients. Colour coding shows the z-score deviations from the WM-MTr values of the normal controls. Note that lesional-MTr is lower in RR-MS than in the B-MS despite the latter has much higher lesion load.

Conclusions

Results of the present study clearly demonstrate that, despite the presence of significantly more WM lesions and much longer disease duration, focal and diffuse structural brain damage as measured by MTr is significantly less pronounced in B-MS than in a cohort of RR-MS at their earliest disease stages. This might be possibly due to more effective repair mechanisms to demyelination in patients with B-MS than in RR-MS. On this basis, the use of MTr might be helpful in differentiating patients with benign form of MS from those with a typical disabling course of the disease.

References

1. Hawkins SA, McDonnell GV.1999;67(2):148-52.
2. Smith SM, Jenkinson M, Woolrich MW, et al. NeuroImage 2004;23 Suppl 1:S208-19.:S208-S219
3. Pike GB, De Stefano N, Narayanan S, et al Radiology 2000;215:824-830.