Occult Disease in Gray and White Matter Differ between Subtypes of MS by Diffusion MR Histograms

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Introduction

The phenotypical subtypes of multiple sclerosis (MS) are considered to be a series of syndromes that have heterogeneous pathogenetic mechanisms, clinical and therapeutic implications. While this phenotypical classification has historically been based on clinical and demographic criteria, it remains subject to wide variability. This variability in patient stratification can have serious implications in the study-designs and therapeutic outcomes in natural history and clinical MS trials. Hence recent attention has been focused on establishing consensus definitions to distinguish these various clinical subtypes more effectively. (1,2)

Previous reports have shown some correlation of focal lesions (3-6) and whole brain diffusion histograms to disease subtype (7). The objectives of our study were to a) assess the predictive significance of segmented quantitative diffusion MR techniques in differentiating between the relapsing-remitting (RRMS) and secondary progressive (SPMS) subtypes; and b) evaluate the role of MR as a possible adjunct to clinical criteria in distinguishing the various subtypes.

Methods

Eighteen patients with clinically definite MS (14 RRMS and 4 SPMS) and 10 age- and sex-matched normal controls underwent MR at 1.5T using: a) Dual-echo FSE T2-weighted and FLAIR oblique-axials, b) and single-shot diffusion-weighted spin echo EPI for full diffusion tensor data. Diffusion was measured in 6 non-collinear directions with 4 averages; 2 images with no diffusion weighting (b=0s/mm²) and inversion recovery images for CSF nulling (TI~2100ms) were acquired with b=0s/mm².

Images were segmented into white matter (WM), gray matter (GM) and CSF based on FSE using a previously described method. Lesions were shown on FLAIR using automatic segmentation, classifying [intensity >2 x SD of total brain intensity] as lesion, followed by manual editing. Segmentation results were transferred to MTR maps. For correction of geometric distortions on EPI, b=0 images were unwarped with respect to FSE images using AIR. Unwarping parameters were then applied to apparent diffusion coefficient (ADC) and FA (fractional anisotropy) maps.

Pixel-by-pixel histograms for NAWM and NAGM of ADC and FA were normalized; mean, peak heights, peak locations, and individual quartile analyses were assessed with t-tests (significance <0.05), comparing patients to controls and RRMS to SPMS patients.

Results

A) MS Patients vs. Normal Controls: FA histograms of both the NAWM and NAGM were significantly shifted to lower values in all patients (n=18, RRMS + SPMS) when compared with controls (p <= 0.05) [Fig. 1].

B) RRMS Patients vs. SPMS Patients: FA histograms for RRMS patients (n=14) of NAWM and NAGM of ADC and FA were normalized; mean, peak heights, peak locations, and individual quartile analyses were assessed with t-tests (significance <0.05), comparing patients to controls and RRMS to SPMS patients.

Discussion

Our data suggests that occult disease in both NAWM and NAGM exists in MS patients. Furthermore, it appears that the important distinction between clinical subtypes of MS may be apparent on quantitative diffusion data. Regardless of the precise microstructural changes responsible for ADC or FA alterations in NAWM and NAGM of MS patients, the study indicates that MR diffusion histogram analysis may be a useful quantitative method for evaluating total disease burden and may prove to be clinically useful in following the progression of disease.

References