Diffusional Kurtosis Imaging of Gray Matter in Patients with Multiple Sclerosis

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Introduction: Multiple Sclerosis (MS) is an inflammatory, demyelinating disease of the CNS with involvement of neurons and axons[1]. Although pathological studies have shown early involvement of gray matter (GM) structures in the disease[2], GM lesions are difficult to detect with conventional MRI. Quantitative MRI metrics derived from diffusion tensor imaging (DTI) such as fractional anisotropy (FA) and mean diffusivity (MD) are useful to assess subtle pathology in normal-appearing white matter (NAWM),[3] and there is increasing evidence that they are sensitive to tissue damage in the normal-appearing GM (NAGM) of patients with MS[4]. However, DTI might be of limited utility in GM because of highly isotropic diffusion properties of this tissue. Diffusional kurtosis imaging (DKI) is a new MRI method that allows the non-Gaussianity of water diffusion to be quantified[5,6] A directionally averaged kurtosis coefficient - mean kurtosis (MK) - a unitless parameter, has been shown to be sensitive to structural changes in isotropic tissue such as GM[7]. MK can be regarded as an index of tissue microstructural complexity with increased values pointing to a higher order tissue organization. The aims of this study were to investigate GM abnormalities in MS patients using MK and DTI measures (MD and FA) and to investigate the association among GM MK, white matter injury and conventional MRI measures of tissue burden.

Material and methods: Twenty-nine patients with relapsing-remitting MS (mean age 39 ± 9, range 27-61 yrs; mean disease duration 3.6 ± 4.2, range 1-14 yrs; median expanded disability status scale (EDSS): 2.0, range 0-5) and 14 healthy controls (mean age 38 ± 12, range 26-60 yrs) underwent MRI on a 3T whole body imager (Siemens Medical Solutions, Erlangen, Germany). Approval for this study was obtained from the Institutional Board of Research Associates of New York University Medical Center and informed consent was obtained from all subjects. The MRI protocol included the following sequences: axial T2 TSE, 3D T1 MPRAGE, and twice-refocused-spin-echo (TRSE) diffusion sequence for DKI. The DKI parameters were: 30 diffusion encoding directions, 3 b values for each direction (0, 1000, 2000 s/mm^2), TR: 3700 ms, TE: 96 ms, 2 averages, FOV: 222 × 222 mm^2, matrix size: 82×82, slice thickness 2.7 mm, 28 oblique axial slices. Both DTI and DKI parametric maps were calculated from a single dataset using an in-house developed software Diffusional Kurtosis Estimator (DKE) running on Matlab 7 (**Figure 1**). Lesion, NAWM with lesions, NAWM without lesions and NAGM masks were obtained from T2 images and applied to the quantitative maps. Then, the mean MK, MD and FA of lesions, NAGM, NAWM with lesions and NAWM without lesions were measured using histogram analysis. Normalized brain volume (NBV), GM volume (GMV), and WM volume (WMV) were assessed on MPRAGE images using SIENAX. T2-W and T1-W lesion volumes (T2LV and T1LV) were measured using a semiautomatic segmentation technique based on local thresholding (Jim version 3, Xinapse Systems)

Results: In GM, a significant decrease of MK (0.70 vs. 0.73; p=0.009) and FA (0.13 vs. 0.14; p=0.014) and increase of MD (1.18 vs. 1.10 mm^2/s*10^{-3}, p=0.009) was found in patients compared to controls. In NAWM with lesions and NAWM without lesions, FA was lower (0.28 vs. 0.30; p<0.001), whereas MD and MK did not show a significant difference when patients were compared to controls. No correlation was found among GM MK, GM MD and GM FA. GMV and WMV showed a negative correlation with GM MD (r=-0.3, p=0.045; r=-0.3, p=0.007) but not with GM MK and GM FA (p=0.1). T2LV and T1LV were correlated with GM MD (r=0.7, p<0.001, r=0.73, p<0.001) but not with GM MK and GM FA (p=0.1). NAWM FA was correlated with GM MD (r=-0.3, p=0.015) and GM FA (r=-0.3, p=0.04) but not with GM MK (p=0.1). Lesion MD was correlated with GM MK (r=-0.4, p=0.011) and GM MD (r=0.5, p=0.002). Lesion MK was correlated with GM MK (r=0.6, p<0.001) and GM MD (r=-0.4, p=0.016).

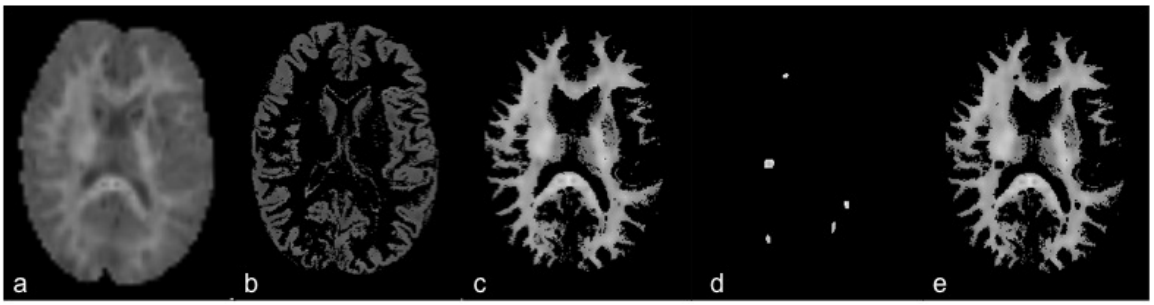

Figure 1: Selected whole-brain MK map from one MS patient (a), corresponding grey matter MK map (b) and normal-appearing white matter with lesions MK map (c) lesions MK map (d) normal-appearing white matter without lesions MK map (e)

Conclusion: Our study suggests that DKI can provide information about brain tissue microstructure which is complementary to that DTI-derived metrics, especially with respect to highly isotropic tissue such as GM. The GM abnormalities are, at least in part, associated with the severity of intrinsic lesion damage rather than with lesion volume.

References: 1) Trapp BD *et al*., N Engl J Med 1998. **2**) Peterson JW *et al.,* Ann Neurol 2001. **3**) Werring DJ *et al.,* Mult. Scler 2001. ***4)*** Rovaris M *et al., J. Neurol 2008.* **5**) Jensen J *et al*., MRM 2005. ***6)*** Lu H *et al*., , NMR in biomedicine 2006. 7) Falangola MF et al., JMRI 2008.

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