Persistent Distal White Matter Microstructural Changes Caused by New Lesions at the Earliest Stage of Multiple Sclerosis

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Introduction: The role of lesions in permanent axonal loss is unknown in Multiple Sclerosis (MS) and the existence of a global axonopathy or microscopic inflammatory processes cannot be excluded, even early in the disease. Previous reports have presented evidence for abnormal white matter that is normal appearing (NAWM). The origin of these abnormalities is unknown though there has been indirect evidence linking these to the presence of visible lesions. However, this evidence is largely circumstantial due to a lack of direct anatomical link between the lesions and the NAWM, due to the complication of large lesion loads in MS patients, and also due to the lack of longitudinal studies to study this effect. We have studied patients with clinically isolated syndromes suggestive of MS longitudinally with diffusion tensor MRI (DTI). DTI fiber tracking allows delineation of lesions with connected white matter and the longitudinal studies in CIS patients provide a measure of the effects of lesions on NAWM when the lesion load is low and early in the disease course.

Methods: Twenty-five patients with CIS were studied longitudinally over 24 months (at 3 to 6 month intervals) with diffusion tensor MRI. New lesions were defined as those with contrast enhancement on T1-weighted MRI volumes and/or those with new or decreasing lesion volume on T2-weighted images. DTI fiber tracking was performed with seeded points within the new lesion regions using in-house software based on the FACT algorithm. The distal normal appearing white matter in the corpus callosum connected to the lesions was delineated and defined as the NAWM connected region for that lesion. DTI metrics of fractional anisotropy (FA), mean diffusivity (Dav), and the major (Ev1) and minor (EvT = (Ev2 + Ev3)/2) diffusion eigenvalues were determined within the lesion and the connected distal normal appearing corpus callosum regions (NACC). The lesion region was defined at the earliest time point. Fiber tracking and quantification was performed at each time point using the registered lesion regions of interest. The diffusion metrics within the lesions and connected NACC regions were compared before and after the appearance of the lesion.

Results: Thirty new lesions were defined. In the new lesions, the FA decreased and the mean and all diffusivities (Dav, Ev1, EvT) increased dramatically at the appearance of the lesion. The connected distal NACC also showed decreased FA and increased mean and transverse diffusivities (paired t-tests $p < 0.05$) concurrent with the appearance of the visible lesions. These changes within the NACC remained over the next 2 years after the appearance of the visible lesion. The Figure shows the values of the DTI metrics relative to their value at the time of the appearance of the new lesion.

Discussion: We have demonstrated changes in the NAWM connected to lesions that occur concurrent with the appearance of these lesions. Furthermore, the abnormalities to the NAWM persist for at least 1 year beyond the appearance of the lesion. Abnormality of the NAWM in CIS has been previously reported. However until now, these abnormalities have not been directly linked to the appearance of new lesions. Since our time resolution is coarse, we could not detect changes in the lesion region before the appearance of the visible lesion and any changes in the connected distal NACC may occur as much as 3 months or more after the appearance of the lesion. These effects could therefore be due to Wallerian degeneration as a consequence of the axonal injury due to the lesion. Nonetheless, the rapid appearance of these abnormalities in the distal aspects of tracts injured by the lesions may suggest other than degenerative effects.

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