Directional diffusivity as an MR biomarker of axonal injury in leukodystrophy

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Introduction

The leukodystrophies (LD) comprise a set of central nervous system diseases in which the myelin sheath around axons has abnormal growth or abnormal maintenance with varying degress of secondary effects on axonal integrity[1-3]. The long term outcome for these diseases is progressive disability leading to severe cognitive decline and death[2-4]. There are no known cures, however there are promising drugs under development. Recently MRI directional diffusivity has been established as an MR biomarker for axonal and myelin injury, in which acute increases in radial diffusivity ($\lambda_\perp$) correspond to demyelination and decreases in axial diffusivity ($\lambda_\parallel$) correspond to axonal injury[5-8]. Commonly, patients with suspected LD and their family members present for MR imaging workup months before precise genetic testing results are available. Thus directional diffusivity measurements may serve as an MR biomarker to evaluate the degree of underlying axonal damage and thus provide important early diagnostic and prognostic information.

Materials and Methods

6 subjects (2M, 4F) with known or suspected LD presenting for clinical care at our institution were prospectively enrolled in a MR imaging trial. Diseases represented severe adrenoleukodystrophy (ALD) in a 9 yo boy; Alexander's disease in an 11 yo boy, and Pelizaeus-Merzbacher like-diesase (PMD) in a 28 yo woman. 2 known and 1 suspected carrier of PMD were also evaluated. 12 pediatric and 12 young adult controls were also scanned for comparison. Protocol was approved by the local institutional review board.

Image Acquisition

Imaging was performed on a 3 T TIM Trio (Siemens) using a 12 channel head coil. A single shot spin-echo echo EPI-technique was used for diffusion tensor (DTI) acquisition with the following parameters: 60 slices without gap, 2 mm isotropic voxels, , TR = 9900 msec, TE = 102 msec, 25 scaled *b*-values with *b*-max = 1400 sec/mm^2. A single DTI average was acquired with 4.5 min; DTI was then repeated up to 3 additional times, for a total of up to 20 min. of total DTI acquisition. A standard clinical brain MR protocol was obtained including MP-RAGE with 1mm isotropic resolution and TSE or BLADE T2 axial images.

Postprocessing and Data analysis

Multiple parameters were derived from the diffusion tensor measurements including ADC, scaled RA (sRA, defined as the standard deviation of the three eigenvalues normalized by the ADC divided by 1.4), axial diffusivity ($\lambda_\parallel = \lambda_1$), and radial diffusivity ($\lambda_\perp = \lambda_2 + \lambda_3/2$) off-line. Analysis was performed using ImageJ (NIH). Images were drawn on the anatomic (MPRAGE) scan. For a single slice, near the top of the lateral ventricles, a set of standard small white matter (WM) regions of interest (ROIs) in the corpus callosum, frontal and parietal lobes were generated. On the same slice, a large histogram was obtained for a region including subcortical white matter down to central grey matter (Fig.1). For those carriers with discrete lesions, additional regions of interest were obtained, centered on the white matter lesions with additional matched ROIs for the contralateral normal-appearing tissues. Similar measurements were made for age and gender matched controls.

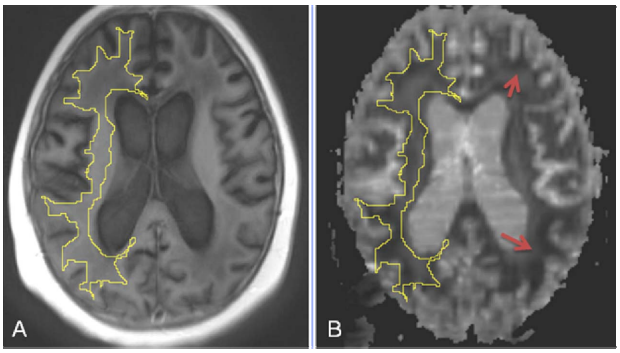

Figure 1. (A) Axial T1 (MPRAGE) in a patient with severe ALD. There is central atrophy, with enlargement of the lateral ventricles, and diffusely abnormal white matter. However, these conventional images suggest sparing of a rim of peripheral white matter. **(B)** Co-registered $\lambda_\parallel$map demonstrates a hypointense rim (arrows) within the area of normal-appearing white matter (NAWM), suggestive of severe axonal injury. The patient expired a few days after this scan was obtained

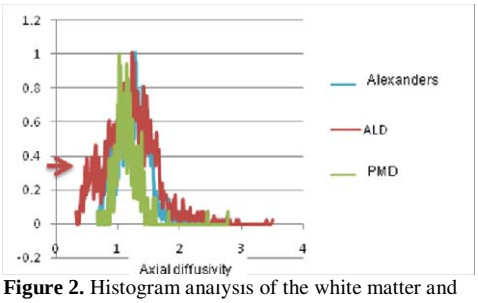

Figure 2. Histogram analysis of the white matter and central grey matter in 3 patients with leukodystrophy demonstrates a unique peak of low axial diffusivity in the ALD patient.

Results: Histogram analysis of the subjects with a clinical diagnosis of LD demonstrated large shifts of increased ADC and decreased sRA in all cases. Further analysis using an ROI-approach demonstrated that these findings were associated with the areas of abnormally T2-hyperintense WM. In the case of ALD, histogram analysis demonstrated an additional peak of low $\lambda_\parallel$ (Fig.2). ROI-analysis demonstrated that this peak corresponded to NAWM on conventional images but could be identified on $\lambda_\parallel$ maps (Fig.1). In Alexander's disease, areas of T2-hyperintense abnormal WM demonstrated significant ($p<0.05$) increased ADC and decreased sRA associated with both increased $\lambda_\perp$ and $\lambda_\parallel$. Areas of WM T2 abnormality in PMD and suspected PMD carriers demonstrated significant ($p<0.05$) increased ADC and $\lambda_\perp$,decreased sRA , but no significant alteration in $\lambda_\parallel$.

Discussions and conclusions: DTI evaluations of LD have previously demonstrated WM with elevated ADC and decreased sRA[9, 10]. Multiple mouse models of WM disease have recently demonstrated increases in $\lambda_\perp$ corresponding to demyelination and decreases in $\lambda_\parallel$ corresponding to axonal injury [5-8]. Here we report the first application of this analysis to human LD and demonstrate that disease with suspected severe ongoing axonal injury (ALD) has a marked decrease in $\lambda_\parallel$, chronic LD (Alexander's) does not. Interestingly, PMD, which is characterized histologically by myelin (rather than axonal) pathology demonstrates increases in $\lambda_\perp$in T2-hyperintense lesions of both subjects and gene carriers. This suggests that in patients presenting with a clinical diagnosis of LD but unconfirmed genetics, analysis of directional diffusivity may be helpful to discriminate between LD's on the basis of the degree of axonal injury suspected. In additional, screening of possible carriers for abnormal myelin may also be possible. Enrollment in this study is ongoing and further subjects will be required for full validation.

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