Diffusion Tensor Imaging of Therapy Induced Leukoencephalopathy in Children Treated for Acute Lymphoblastic Leukemia

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PURPOSE: Pediatric patients treated for Acute Lymphoblastic Leukemia (ALL) have an increased chance of survival [1], but remain subject to increased cognitive impairments secondary to disease and treatment [2,3]. Imaging studies of ALL patients reveal a subset of patients which develop T2-hyperintensities in white matter (WM), or leukoencephalopathy (LE), during therapy. The impact of these imaging changes on long-term neurocognitive deficits is actively under investigation. The goal of this study was to evaluate differences between patients with and without LE using diffusion tensor imaging (DTI) metrics to identify patients with more intense WM injury due to ALL therapy.

PATIENTS AND METHODS: Patients at least one year of age enrolled on an institutional IRB-approved ALL treatment protocol were eligible for the study. Imaging was performed at week 7 of consolidation, which occurs after the final intravenous high dose methotrexate administration. Twenty-six patients with normal appearing studies were selected to age match 26 subjects with conventional imaging evidence of LE. This resulted in 52 age matched patients included on the study, ranging in age from 1.2 to 19 years of age at evaluation.

MR imaging was performed on a 3T whole-body system (Siemens Medical Systems, Iselin, NJ). DTI was acquired using bipolar diffusion-encoding gradients to reduce gradient-induced eddy currents that cause image distortion and degradation. All images were acquired as forty 3 mm thick contiguous sections with whole-head coverage and a 128 square matrix using a double spin echo EPI pulse sequence (TR/TE = 10/100 ms, b=1000 ms). Thirteen images, one in which b=0 and the others in which b=1000 s/mm^2, are used to calculate the diffusion tensor for each voxel. For the b=1000 images, the diffusion gradients were applied along non-collinear, non-coplanar directions in space. The set of images were acquired four times. Once the tensors have been calculated, Eigen values were derived and used to calculate fractional anisotropy (FA), apparent diffusion coefficient (ADC), as well as axial and radial diffusivity maps.

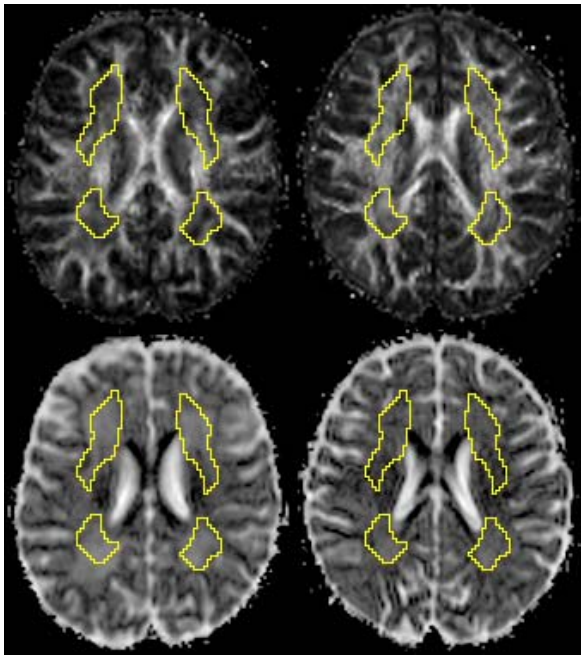
Calculated DTI maps were registered to the ICBM average 152 T2 atlas aligned in Talairach space found in SPM2, resampled to a 1mm isotropic resolution. A voxel-based analysis had been previously performed to identify regions where T2 weighted hyperintensities commonly occurred in patients who developed treatment induced LE [4]. The previously defined cluster was used as a region of interest (ROI) for the present study. Mean values for the ROI were extracted and statistical tests were performed to evaluate the differences in age and DTI metrics between the LE and normal appearing cohorts.

RESULTS: Independent samples T-tests revealed no significant difference in age between the two groups of patients as expected. Even with this small sample, there was a significant drop in the FA and a corresponding significant rise in radial diffusivity (**Table 1, Figure 1)**. ADC values were also significantly elevated in the LE group, and the axial diffusivity trended in a higher direction. In addition to the difference in mean values, the standard deviations of the measures in the LE group are approximately double the normal appearing patients.

Table 1. Comparisons of DTI metrics for 52 age matched patients treated for ALL.

	Normal Patients	LE Patients	P Value
Age	6.58 ± 4.23	6.55 ± 4.35	0.974
FA	0.37 ± 0.03	0.31 ± 0.07	< 0.001
ADC	0.47 ± 0.06	0.54 ± 0.10	0.005
Axial Diff	0.66 ± 0.08	0.70 ± 0.11	0.064
Radial Diff	0.38 ± 0.05	0.45 ± 0.10	0.001

Figure 1. A 5.6 yr old patient with LE (left) and an age matched 5.8 yr old normal appearing patient (right). FA (top) and radial diffusivity (bottom) are overlaid with the VBA cluster in yellow.



CONCLUSIONS: Preliminary results show the feasibility of using the registered DTI maps with the previously defined ROI. Reduced FA along with the elevated radial diffusivity suggests that patients treated for ALL undergo an inflammatory / demyelinating process. The impact of this process on the long-term neurocognitive performance is under active investigation.

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