DTI Evaluation of White Matter integrity in Long Term Survivors of Pediatric Low Grade Gliomas

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Introduction and Purpose: Low-grade gliomas are the most prevalent type of brain tumor in children. Around 90 to 95% of patients with pediatric low-grade gliomas (PLGG) will survive their disease, however due to either the effects of the tumor or the treatment required to control it, the survivors may experience functional disability and cognitive sequelae (1,2). Understanding the reasons for variability in outcome is important for approaches directed at limiting treatment-related sequelae. White matter compromise has been shown to predict cognitive outcome in pediatric brain tumor patients with other pathologies but as yet white matter integrity following treatment for PLGG has not been examined. Diffusion Tensor Imaging (DTI) can be used to characterize the biological tissue properties of normal and damaged brain white matter (3). In this study, we used DTI MRI to investigate differences in white matter integrity between long-term PLGG survivors and healthy controls.

Subjects and Methods: Fourteen PLGG patients (mean age = 15.61; SD = 2.45) and 9 healthy control children (mean age = 12.88; SD = 1.67) participated in the study. With respect to tumor location, 7 patients had optic pathway tumors, 5 had combined midline tumors, and 2 had posterior fossa tumors. With respect to treatment, 2 patients went through gross total surgery; the rest of patients had either biopsy or subtotal resection. A single patient received radiation therapy. The remaining were treated with chemotherapy or monitored without adjunct therapy. Diffusion tensor imaging was acquired on a GE LX 1.5T MRI scanner using 31 non-collinear directions of diffusion sensitization with an echo planar readout (b-value = 1000 s/mm^2, TE / TR= 84.6 / 15000 ms, FOV = 240 mm, matrix = 128 × 128, number of slices = 45 ~ 50, slice thickness = 3 mm thick). Tract based spatial statistics (TBSS) were used to examine voxel-wise differences in white matter integrity between PLGG patients and healthy controls. Data sets were imported into FSL software (FMRIB software library, v4.1) to calculate the fractional anisotropy (FA) map, then non-linearly aligned to standard space (FMRIB58_FA) and a mean FA skeleton map was created for all 23 subjects. TFCE (threshold-free cluster enhancement) was adopted to find "clusters" of voxels where FA differed between PLGG patients and healthy controls. Voxels were considered significantly different between patients and controls at $p < 0.01$. Group means for FA were calculated across all significant clusters.

Results: FA was significantly lower in PLGG patients versus healthy controls in multiple areas (Figure 1). The PLGG group mean in these areas was 0.422 (SD = 0.023) and the control group mean was 0.473 (SD = 0.014). Areas of significant differences included right occipital WM, left occipital WM, corpus callosum splenium, and the brain stem. Cluster locations within these regions are detailed in Table 1.

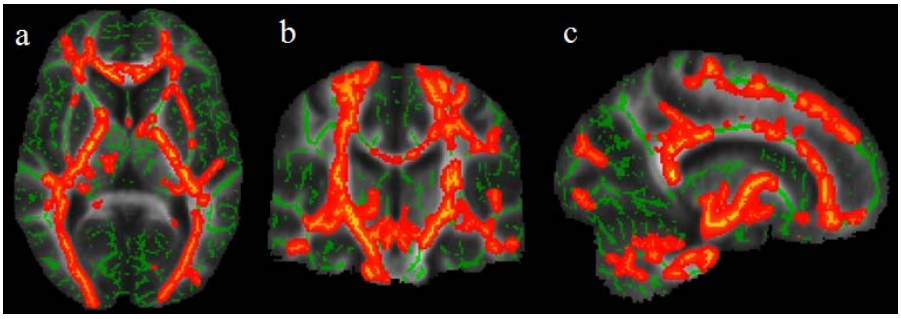

Figure 1. Regions of skeleton with significantly reduced FA for PLGG patients versus controls (red-yellow), overlaid on the standard map FMRIB58_FA in axial (a), coronal (b) and saggital (c). Skeleton width has been expended for emphasis. Green areas represent the mean FA skeleton.

Cluster location	MNI 152 coordinates (X, Y, Z)
Right occipital white matter	25, -70, 1
Left occipital white matter	23, 78, 1
Corpus callosum splenium	-1, 24, 23
Brain stem	-4, -38, -29

Table 1. Clusters showing significant differences between PLGG patients and controls

Conclusions: Despite being a heterogeneous sample, our patients with PLGG had significantly lower FA compared to a younger healthy control sample. These findings provide evidence of significant white matter compromise in patients with PLGG. Notably, only a single patient received radiation therapy. Consequently, it is likely other factors lead to white matter compromise in these PLGG patients. We will further examine medical and treatment related factors that may result in compromise, and relate our findings to neuro-cognitive outcomes as we acquire a larger sample of participants.

References: [1]. Aarsen et al (2006) Cancer, 106, 396-402 [2]. Benesch et al (2006) J Neurooncol, 78,199-205 [3]. Mabbott et al (2008) Neuropsychology, 22,159-68