REGIONAL EVALUATION OF WHITE MATTER INJURY IN CHILDREN TREATED WITH CRANIAL-SPINAL RADIATION FOR MEDULLOBLASTOMAS

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Introduction and Purpose. Cranial-spinal radiation (CSR) therapy is a critical procedure for effective control of medulloblastomas in children. Unfortunately, this procedure is also associated with significant neuro-toxicity that is hallmarked by damage to the brain's white matter. One of the fundamental challenges we face is to delineate the white matter regions that are most affected by CSR therapy in this population. Identifying white matter regions most sensitive to CSR injury is crucial in providing information that can help in making the best treatment choice for individual patients - whether that is delaying CSR therapy until cortex or white matter matures further or delineating areas of the brain to be avoided in treatment planning. Importantly, no one has yet investigated the relationship between the biophysical properties of white matter and the regional sensitivity to CSR in the developing brain. Our goal in this study was to determine which white matter regions are most affected by CSR in children treated for medulloblastomas.. In order to do this we compared regional values of white matter integrity in both areas of the posterior fossa and cerebral regions. We then compared regional white matter integrity in healthy children versus children who received CSR for medulloblastomas. We also examined the relation between regional radiation dose and white matter values.

Subjects and Methods. ***Subjects***. We recruited 16 children diagnosed with medulloblastomas and treated with CSR (F(7), mean age = 12.28 SD=3.37). These children received standard treatment for medulloblastomas which included a whole-brain radiation dose (range 2340-3600 cGy) with a boost to the posterior fossa (range 5400-5580 cGy). Dose-maps depicting regional radiation dispersion for these children are depicted in Figure 1. We also recruited 24 healthy control subjects (F(12), mean age = 10.62 SD=2.76). All participants were recruited from The Hospital for Sick Children in Toronto, The BC Children's Hospital, in Vancouver, and The Alberta Children's Hospital in Calgary, collectively. MRI measurements were performed at the three hospitals using a 1.5T scanner.. The scanning protocol included a 3D-T1 FSPGR gradient echo, inversion recovery-prepared sequence (IR time = 400ms; TE/TR = 4.2/10.056ms; 116-124 contiguous axial slices; NEX = 1; 256 x 192 matrix, interpolated to 256 x 256; FOV = 24 x 24cm; rbw = 162.734kHz; slice thickness = 1.5mm) and a diffusion-weighted sequence (single shot spin echo DTI sequence with an EPI readout: 25-31 directions; b = 1000s/mm^2; TE/TR = 85.5/15000ms; 45-50 contiguous axial slices; NEX = 1; 128 x 128 matrix, interpolated to 256 x 256; FOV = 24 x 24cm; rbw = 1953.12kHz; slice thickness = 3mm. ***Regional White Matter***. First, each subjects' T1 scan was classified into cerebrospinal fluid, gray matter, and white matter using an automatic tissue segmentation algorithm[4]. Second, white matter segmentations were subdivided into compartments using an anatomically-based template modified from Kabani et al[5] which consisted of eight cerebral (bilateral frontal, parietal, temporal, and occipital) and four posterior fossa (pons, vermis, and bilateral cerebellar) regions. Third, the regional template was then applied to the T1 of all subjects via affine transformation. Fourth, individual T1 scans were registered to DTI acquisition space with a combination of linear and non-linear automatic transformation algorithms in order to delineate the white matter compartments within this space (Figure 2). Finally, measures of white matter integrity [Mean Diffusivity (MD), Fractional Anistropy (FA), Axial Diffusivity (AD), and Radial Diffusivity (RD) were calculated for each white matter compartment. ***Statistical Comparisons.*** We first controlled for hospital site, and ran univariate analyses for age and sex across all subjects to verify that our samples fit normal distribution parameters. We then ran a MANCOVA for the independent variables (group) and dependent variables (MD, FA, AD1, and RD) controlling for hospital (site) to determine whether there were significant differences between groups within regions. Post-hoc ANCOVAs determined which specific measures of white matter integrity were significantly different within each region of interest.

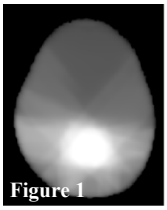
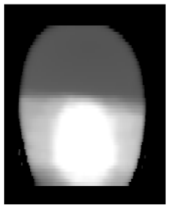
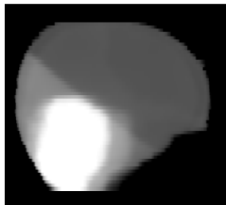


Figure 1





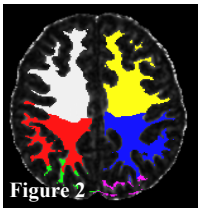


Figure 2

Table 1

		Right Hemisphere				Left Hemisphere			
		MD	FA	AD	RD	MD	FA	AD	RD
		M 10^{-4}	M	M 10^{-3}	M 10^{-4}	M 10^{-4}	M	M 10^{-3}	M 10^{-4}
Frontal	Control	7.73	0.384506	1.098	6.11	7.74	0.381601	1.097	6.13
	Radiation	7.7	0.376938	1.085	6.12	7.71	0.37575	1.087	6.14
Parietal	Control	7.47	0.385451	1.069	5.86	7.37	0.387489	1.056	5.78
	Radiation	7.55	0.376188	1.072	5.97	7.52	0.374062	1.066	5.96
Occipital	Control	7.66	**0.359026**	**1.076**	**6.11**	7.56	**0.360232**	**1.064**	**6.02**
	Radiation	7.77	**0.317563**	**1.046**	**6.42**	7.71	**0.314062**	**1.035**	**6.39**
Temporal	Control	7.92	**0.38926**	1.14	**6.18**	7.94	**0.393797**	1.148	**6.17**
	Radiation	8.03	**0.370438**	1.135	**6.37**	8.1	**0.3715**	1.147	**6.42**
Cerebellum	Control	**6.84**	**0.381176**	0.975	**5.38**	**6.83**	**0.372912**	0.966	**5.41**
	Radiation	**7.53**	**0.332**	1.014	**6.22**	**7.39**	**0.329438**	0.995	**6.11**
Vermis	Control	**8.09**	**0.374286**	1.145	**6.41**				
	Radiation	**8.86**	**0.332125**	1.191	**7.33**				
Pons	Control	8.26	0.439623	1.222	6.28				
	Radiation	8.27	0.428813	1.211	6.35				

Regions in which values of white matter integrity were significantly different between groups are indicated in red font ($p < 0.05$).

Results. Univariate analyses revealed that there were no significant differences for age or sex between the two groups ($p > 0.05$). For the MANCOVA, there was a significant effect of group on white matter integrity for bilateral occipital, temporal, and cerebellum as well as vermis. A post-hoc ANCOVA determined which measures of white matter integrity were significantly different in the patient compared to the healthy controls as detailed in Table 1. All values that were significantly different represented a *decrease* in white matter integrity in the patient sample relative to controls. These regional decreases in white matter integrity corresponded to the relative regional dose of radiation that each patient received. The 'dose map' in Figure 1 depicts the dispersion of radiation in patients with medulloblastomas. Each patient received a dose of radiation across the brain with a boost to the posterior fossa. This dose map reveals a significantly greater dose of radiation in the regions of, and surrounding, the posterior fossa and relatively lower dose of radiation in the anterior regions.

Conclusions. In this study, we provide evidence that white matter damage is regionally specific in children treated with CSR. These regional sensitivities are likely due to regional differences in radiation dose. Generally, in patients, the areas with the lowest white matter integrity were localized to posterior cerebral regions and regions of the posterior fossa. These regions coincide with those that received the highest doses of radiation during the treatment phase. These findings suggest that radiation directly caused white matter injury in a dose-dependent manner. Moreover, FA and RD values were most affected. This finding is significant as RD values have proven to be a sensitive measure of myelin degeneration[6] Our evidence therefore suggests that it may be the myelin sheath that surrounds the axons that is most affected in our patient group. Future studies will address these possibilities.

Our study is a novel investigation of regional values of white matter integrity in children treated with CSR for medulloblastomas. Our findings may serve as an index of how dose gradient relates to white matter injury when considering treatment in this clinical population.

References

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