Dose and Volume Effects of Radiation on White Matter in Children Treated for Medulloblastoma

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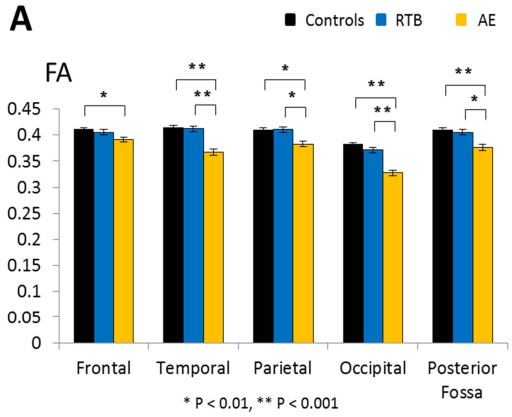
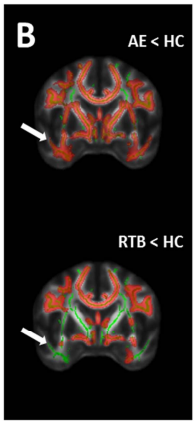
Target Audience: This study will be most relevant to scientists and clinicians interested in understanding the vulnerability of white matter to insult during childhood.

Purpose: Patients with medulloblastoma (MB) are treated with a combination of surgery, craniospinal radiation (CSR) with a boost to the tumor site, and chemotherapy. It is widely accepted that CSR damages white matter (WM), but much less is known about the mediating effects of specific doses and boost volumes. To address this issue, the goal of the present study was to compare the impact of treatment with the least intensive therapy (i.e. reduced dose CSR and a boost restricted to the tumor bed (TB)) on WM microstructure, to treatments with higher CSR doses and/or larger boost volumes.

Methods: MRI obtained at the Hospital for Sick Children (Toronto, Ontario) for 34 patients treated for MB and 38 healthy age-matched children. The patient group was separated into those treated with 1) reduced dose CSR + TB (RTB group; n = 17) and 2) 'all other treatments/all else', comprised of: standard dose CSR + posterior fossa (PF) boost, reduced dose CSR + PF boost and standard dose CSR + TB (AE group; n = 17). Diffusion tensor imaging (DTI) was used to assess fractional anisotropy (FA), mean, axial and radial diffusivities (MD/AD/RD), measures thought to reflect WM microstructure. MRI was performed using either a GE LX 1.5T MRI scanner with an 8-channel head coil or a Siemens 3T whole-body MRI scanner (Trio Tim syngo MR B17 system) with a 12-channel head coil. The GE LX 1.5T MRI 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 = 240 x 240mm, rbw = 162.734kHz, slice thickness = 1.5mm) and a diffusion-weighted single shot spin echo DTI sequence with EPI readout (25-31 directions, b = 1000s/mm2, TE/TR = 85.5/15000ms, 45-50 contiguous axial slices, NEX = 1, 128 x 128 matrix interpolated to 256 x 256, FOV = 240 x 240mm, rbw = 1953.12kHz, slice thickness = 3mm). The Siemens 3T MRI protocol utilized a T1 AX 3D MPRAGE Grappa 2 protocol (TE/TR = 3.91/2300ms, 160 contiguous axial slices, flip angle = 9°, 256 x 224 matrix, voxel size = 1mm ISO, FOV = 256 x 224mm) and diffusion-weighted single shot spin echo DTI sequence with EPI readout (30 directions, b = 1000s/mm2, TE/TR = 90/9000ms, 70 contiguous axial slices, flip angle = 9°, voxel size = 2mm ISO, 122 x 122 matrix interpolated to 244 x 244, FOV = 244 x 244mm). First, regional WM differences were examined between groups, using multivariate analysis of variance (MANOVA). Then, to acquire more specific spatial localization, whole brain voxel-based analyses were conducted.





Results: *Regional WM analyses*: AE differed considerably from both controls and RTB in many brain regions. Relative to controls, AE had lower FA and greater RD across all regions (ps<0.05) (FA: Fig A). Relative to RTB, AE had lower FA in temporal, parietal, occipital and PF regions (ps<0.005), and greater RD in temporal and occipital regions (ps<0.005) (FA: Fig A). Notably, FA did not differ between controls and RTB in any brain region, but RD was greater in the PF (ps<0.05). Post-hoc analyses conducted between patient groups, controlling for treatment-specific factors, revealed that relative to RTB, AE had lower FA (p=0.05) and greater RD (p=0.04) in the temporal lobe. *Voxel-based analyses:* There were many voxels throughout the brain where both AE and RTB had lower FA and greater RD than controls (ps<0.05) (FA: Fig B. Arrows indicate areas where AE differed from controls, but where RTB did not). Critically, AE had many voxels with lower FA and greater RD than RTB (ps<0.05), but none where the reverse was true. Overlaying voxels that differed between AE and RTB onto dosimetry maps provided visual confirmation that these differences localized primarily to brain regions encompassed by the PF boost, but not the TB boost (i.e. the temporal lobes).

Discussion & Conclusion: Relative to controls, patients treated with higher doses and/or larger boost volumes (i.e. AE) show more compromised WM than patients than patients treated with reduced dose CSR and a TB boost (i.e. RTB), particularly in brain regions encompassed by the PF boost. These findings suggest the PF boost is more detrimental to WM than the TB boost, and when taken together with previous reports showing preserved intellectual functioning with RTB treatment, suggest the PF boost should be avoided whenever possible.

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