Diffusion-tensor MR imaging in the evaluation of treatment-induced neurotoxicity in medulloblastoma survivors

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Synopsis:
We use DTI to evaluate treatment-induced neurotoxicity in medulloblastoma survivors. Fractional anisotropy (FA) of supratentorial white matter (WM) in thirteen medulloblastoma survivors was measured and compared to healthy age-matched controls. Reduction in FA was compared with deterioration in school performance. FA of patients was reduced compared to controls and this was statistically significant in the parietal WM and corona radiata (p=0.011 and p=0.040 respectively). FA reduction was more severe in children with moderate/severe, compared to those with mild deterioration in school performance (60.6% and 19.9% respectively, p=0.041). DTI, using FA, is useful in the detection and monitoring of treatment-induced neurotoxicity.

Introduction:
We propose the use of diffusion tensor MR imaging (DTI) to evaluate treatment-induced white matter (WM) injury in childhood medulloblastoma survivors. This injury results in deterioration of cognitive function (memory, intelligence and attention), which is prevalent and severely impacts upon quality of life (1,2). We aim to test the hypothesis that loss of anisotropy occurs in the white matter after cranial irradiation and chemotherapy, and to determine if FA can be used as an index for evaluation of treatment-induced neurotoxicity.

Methods:
Medulloblastoma survivors previously healthy prior to diagnosis were enrolled. All patients were treated with surgery, cranial irradiation and chemotherapy. MRI was performed using a Signa 1.5 Tesla imager (GE Medical Systems, Milwaukee, WI, USA) with a standard head coil. DTI was performed using single-shot spin-echo echo-planar imaging with TR=10000ms, TE=minimum, acquisition matrix=128 x 128 and field of view =28cm. Using a slice thickness of 5mm with a 1.5mm gap, images were acquired through the entire brain (approximately 18 images). Diffusion-sensitizing gradient encoding was applied in 25 directions by using a diffusion-weighted factor b=1200s/mm². FA maps were generated (FUNCTOOL, GE Medical Systems).

Voxel-based comparison between the patient and control groups was performed with SPM99 (Wellcome Dept of Cognitive Neurology, Institute of Neurology, UK). A SPM-template-space non-diffusion-weighted (b0) image template was created, spatially normalized to the pediatric T1W template CCHMC2_fp (Cincinnati Children’s Hospital Medical Center, OH, USA) and smoothed with an 8mm-isotropic Gaussian kernel. Each FA map was first co-registered to its own b0 image using mutual information co-registration so that the same set of 12-parameter resulting from the affine transformation of b0 image to the new b0 template can be adopted. Non-linear warp was not used in the spatial normalization process to avoid regional distortions of the image. A WM mask was created for each subject by segmenting the b0 image with the paediatric a priori data provided by CCHMC. The mask was then used to mask out areas of FA map leaving WM areas of the FA maps for analyses. The WM FA maps were smoothed with a 12mm-isotropic Gaussian filter to improve the signal-to-noise ratio. 2-sample-t test was used for detection of statistical significance (p<0.05, or T>1.71 with degree of freedom=24). Contrasts (1 –1) and (–1 1) were employed for the detection of positive and negative activations.

We also measured FA of selected supratentorial WM sites (frontal periventricular WM, parietal periventricular WM and corona radiata) by placing regions-of-interest (ROI). ROIs of similar size were placed on identical sites as far possible in the healthy age-matched controls. FA (sum of frontal and parietal WM and corona radiata FA) was compared with age at treatment, time interval after treatment and intellectual outcome (deterioration of school performance). Deterioration of school performance was graded into mild (subtle changes in learning capacity, doing well in normal school), moderate (either in the remedial class in normal school or admitted to a special school) and severe (unable to attend school). Two-tailed paired t-test was used for detection of statistical significance (p<0.05).

Results:
13 medulloblastoma survivors (age range 3 yrs – 18 yrs, mean 11.7 yrs) were evaluated. Patients were between 3 yrs and 17 yrs of age at treatment (mean: 8.2 yrs) and time-interval between treatment and MR imaging ranged between 1 yr –11 yrs (mean: 3.7 yrs). Deterioration in school performance was mild in five patients, moderate in seven patients and severe in one patient. For statistical analysis, we combined the moderate and severe group into one group.

Voxel-based comparison showed areas of activation in the periventricular WM, especially parietal WM, and corona radiata (Fig.1). Using ROIs, mean FA of patients was reduced in all sites compared to controls, with a reduction of between 15.6% and 19.2%. The reduction was statistically significant in the parietal WM and corona radiata (p=0.011 and p=0.040 respectively) (Table 1).

FA reduction of the groups ≤ 5 years (n=5) and > 5 years of age (n=8) at treatment was 61.1% and 34.8% respectively and FA reduction in the group with < 5 years (n=8) and ≥ 5 years interval (n=5) since treatment was 35.4% and 60.3% respectively. These differences were however, not statistically significant using t-tests (p=0.214 and 0.241 respectively). Comparing school performance, FA reduction of those with mild deterioration (n=5) and those with moderate/severe deterioration (n=8) was 19.9% and 60.6 % respectively.

Table 1: FA in WM sites of 13 patients and controls

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<th>FWM</th>
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<tbody>
<tr>
<td>FA</td>
<td>0.24 (0.07)</td>
<td>0.31 (0.07)</td>
<td>0.40 (0.09)</td>
<td>0.28 (0.06)</td>
<td>0.38 (0.06)</td>
<td>0.47 (0.08)</td>
<td>15.1</td>
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<td>0.088</td>
<td>0.011</td>
<td>0.040</td>
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Conclusion:
Loss of anisotropy occurs in the periventricular white matter of post-treatment medulloblastoma survivors and this loss is significantly greater in those with poor intellectual outcome. DTI is therefore useful in detection and monitoring of treatment-induced neurotoxicity. Early recognition and accurate quantification are important for successful neuropsychological intervention and modification of drug regimen, and in the future, to assess the effectiveness of drugs that may prevent injury to normal brain tissue.

References: