Factors associated with loss of white matter anisotropy in post-treatment medulloblastoma survivors

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Introduction:

Radiation injury to the white matter is more severe in the maturing brain and with higher radiation dose (1). It is implicated as a cause of intellectual decline that occurs after treatment in medulloblatoma survivors (2). We have previously shown that anisotropy is reduced in the white matter of childhood medulloblastoma survivors after cranial irradiation and chemotherapy (3). We aim to evaluate the effects of age at cranial irradiation, time interval since irradiation and irradiation dose on white matter anisotropy in a cohort of childhood medulloblastoma survivors.

Methods:

Nineteen medulloblastoma survivors (13 male, 6 female, age range: 5 yrs to 18.6 yrs, median: 11 yrs) previously healthy prior to diagnosis were enrolled. All patients were treated with surgery, craniospinal irradiation (CSI) and chemotherapy. Total CSI dose was 23.4Gy (*n=3*), 30.6Gy (*n=6*), 36Gy (*n=8*) or 40Gy (*n=2*). Age at CSI ranged between 2.9 yrs to 17.4 yrs (median: 8 yrs) and time interval since CSI ranged between 0.5 yrs and 5.8 yrs (median: 1.6 yrs).

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=100ms, acquisition matrix=128x128, FOV =28cm, slice thickness= 5mm with 1.5mm gap, b factor=1200s/mm^2. Diffusion-sensitizing gradient encoding was applied in 25 directions. Fractional anisotropy (FA) maps were generated (FUNCTOOL, GE Medical Systems).

Thirty-one control subjects were imaged with the same protocol and divided into three sub-groups by age; >5 yrs-9 yrs (Group A, *n=12*), > 9 yrs-13 yrs (Group B, *n=12*), and >13 yrs-18 yrs (Group C, *n=7*) for analysis.

SPM99 (Wellcome Dept of Cognitive Neurology, Institute of Neurology, UK) was used for creating non-diffusion-weighted (b0) image template and its associated apriori probability maps. A SPM-template-base b0 image template was created for each age sub-group by first coregistering the b0 image to its own T1W images using mutual information co-registration. The T1W image was then spatially affine normalized to the pediatric T1W template CCHMC2_fp (Cincinnati Children's Hospital Medical Center, OH, USA). The same set of affine transformation parameters was applied to the in-register b0 images followed by smoothing with an 8mm-isotropic Gaussian filter to form a new pediatric b0 template. Each normalized b0 image was segmented to give probability maps of gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF). All probability maps of each tissue class in each age sub-group were averaged and then smoothed with an 8mm-isotropic Gaussian filter to form a set of apriori maps. Probability maps of GM, WM and CSF of each patient were obtained by partitioning the native b0 images. A high probability WM binary mask of each patient was created using the equation (i2>i1) & (i2>i3) & (i2>(1–i1–i2–i3)) in function ImCalc, where i1, i2 and i3 represent probability maps of GM, WM and CSF, respectively. The WM mask was then element-by-element multiplied to the in-register FA map to produce a WM FA map (Fig.1). This map was used to construct a histogram which was created using 0.5% of the maximum wide bins. Each bin was normalized by the total number of voxels contributing to the histogram of each subject so as to compensate for differences in brain size. The histogram-derived index, mean WM FA was computed for every patient and this was compared with mean WM FA values of control subjects in the respective 3 age sub-groups to evaluate the percentage deviation of FA in each patient.

Spearman's rank correlation was used to analyze the relationship between percentage reduction of WM FA and age at CSI, time interval since CSI and CSI dose. For analysis of CSI dose, patients were divided into 3 groups based on CSI dose; 23.4 Gy (Group I), 30.6 Gy (Group II), combined 36 Gy and 40Gy (Group III). This was followed by multivariate regression analysis to study the simultaneous influence of these factors on percentage reduction of WM FA.

Results:

Examination of the b0 image segmentation result confirmed that the three tissue classes were successfully partitioned by the SPM segmentation function in every patient and control subject. An example of a final WM FA map is depicted in Fig. 1.

Mean WM FA of the Group A, B and C control subjects was 0.298 ± 0.013, 0.316 ± 0.012, 0.323 ± 0.017 respectively. The mean percentage change in WM FA of the 19 patients compared to controls was -4.4% (sd = 7.6%).

Using Spearman's rank correlation, there were significant associations between percentage reduction of WM FA and age at CSI (Fig. 2, r=0.673, p=0.002) and CSI dose (Fig.3, r=-0.723, p=<0.001), but not with time interval since CSI. Multivariate regression analysis confirmed that both age at CSI and CSI dose correlated significantly with percentage reduction of WM FA (adjusted r^2=0.516, p=0.001).

The estimated equation was: Percentage reduction of WM FA = - 2.03 + 0.871 x age at CSI – 4.18 x CSI dose.

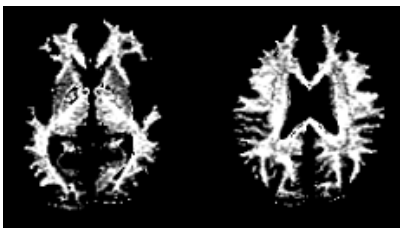

Fig.1: Segmented WM FA map

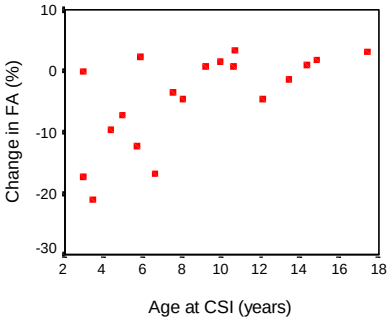

Fig.2: scatter plot showing % change in FA against Age at CSI in 19 medulloblastoma survivors

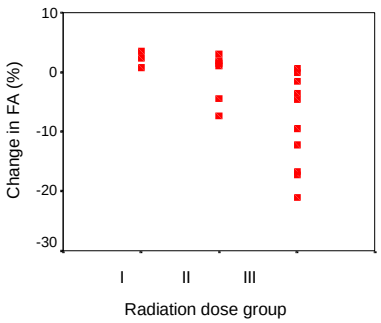

Fig.3: scatter plot showing % change in FA against radiation dose in 19 medulloblastoma survivors

Conclusion:

Both young age at CSI and larger CSI dose are significantly associated with increasing loss of WM anisotropy in medulloblastoma survivors. These findings are in agreement with known risk factors of radiation injury to white matter and suggest that DTI is a useful tool for monitoring treatment-induced white matter injury.

References:

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