The Effect of Systemic Chemotherapy on White Matter Tracts Involved with Cognition in Children with NF1-Associated Optic Pathway Gliomas

Peter MK de Blank[1], Michael J Fisher[2], Timothy PL Roberts[2], and Jeffrey I Berman[2]
[1]*UH Case Medical Center, Cleveland, OH, United States,* [2]*The Children's Hospital of Philadelphia, PA, United States*

Introduction: Low grade gliomas are the most common brain tumor in children. Brain tumor therapies, including surgery, cranial radiation and high-intensity chemotherapy, have been associated with decreases in white matter integrity as measured by DTI[1]. Decreased FA and increased diffusivity in corpus callosum and cerebello-thalamo-cortical tracts correlate with cognitive deficits in childhood brain tumor survivors.[2-4]

Children with neurofibromatosis type 1 (NF1) are predisposed to low grade gliomas and are commonly treated with low-intensity carboplatin-based chemotherapy regimens thought to have little or no late cognitive effects. However, children with NF1 often suffer from attention and learning difficulties that may obscure cognitive deficits caused by tumor therapies. The effect of low-intensity chemotherapy on white matter integrity, separate from surgery or cranial radiation, has never been investigated. This study uses diffusion MR to examine cerebello-thalamic tracts associated with working memory[4], and corpus callosum associated with processing speed[2,3] and IQ.[1]

Methods: In a database of children (<18 years) with NF1 and associated low grade glioma of the optic pathway, we identified 12 subjects who did not receive chemotherapy and 12 age-matched (±1 year) controls who did receive chemotherapy due to tumor progression. All subjects were free of tumor involvement outside the optic pathway, and no subjects had received radiation, surgical resection or biopsy. All low intensity chemotherapy-exposed subjects received carboplatin-based regimens, 4 subjects also received vinblastine, 2 received thioguanine/procarbazine/lomustine/vincristine and 1 received bevacizumab with irinotecan.

All MR examinations were performed at 3T on either a Trio, Skyra or Verio (Siemens; Erlangen, Germany). Diffusion MR was acquired with an echo planar pulse sequence with 128 x 128 matrix, in-plane voxel size of 2 x 2mm, diffusion weighting of b=1000 s/mm^2, and full brain coverage with no gap between slices. Examinations were acquired with 30 gradient directions and 2mm slice thickness, except for 9 examinations which were acquired with 20 diffusion gradient directions and 2.5mm slice thickness. On the Trio, TE was 91-93ms, with TR of 7.3-11.6 s and bandwidth of 1395Hz/pixel. On the Skyra, TE was 84ms, with TR of 9.4-9.6 s and bandwidth of 1565Hz/pixel. On the Verio, TE was 91-104ms, with TR of 9.4-14 s and bandwidth of 1395Hz/pixel.

To trace fibers in the cerebello-thalamic tracts, a starting region of interest was placed around the dentate nucleus of the cerebellum and a target region on the inferior aspect of the thalamus on b=0s/mm^2 echo planar images. Thalamo-cortical tracts were identified between regions of interest placed around the superior aspect of the thalamus and the dorsolateral prefrontal cortex. Tracts in the corpus callosum were identified by regions of interest on either side of the mid-sagittal image. Deterministic streamline fiber tracking with fiber assignment by continuous fiber tracking algorithm was used with minimum FA value of 0.15 and maximum turning angle of 70º for cerebello-thalamo-cortical tracts, and a minimum FA value of 0.25 and maximum turning angle of 80º for corpus callosum tracts. (Figure 1) White matter tracts were assessed for number of fiber trajectories, tract volume, tract density (number of trajectories/tract volume), FA, mean diffusivity (MD) and radial diffusivity (RD). Left and right thalamo-cortical and cerebello-thalamic tract measures were averaged.

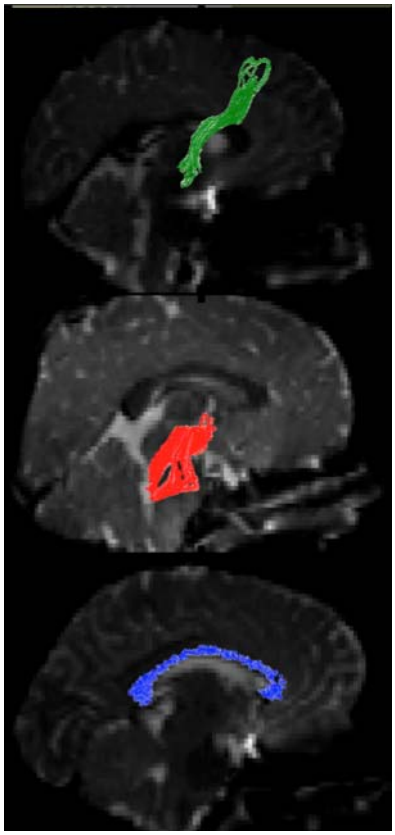

Figure 1: Thalamocortical (green), Cerebellothalamic (red) and corpus callosum (blue) tracts superimposed on the sagittal B0 image

Measure	Glioma with chemotherapy (n=12)	Glioma without therapy (n=12)	p value
Corpus Callosum			
FA	*0.654±0.037*	*0.703±0.034*	*0.013*
RD (x10^{-4}mm^2/s)	4.93±0.56	4.44±0.41	0.065
MD (x10^{-4}mm^2/s)	8.90±0.6	8.83±0.27	0.759
Cerebello-Thalamic Tracts			
FA	*0.484±0.041*	*0.528±0.048*	*0.030*
RD (x10^{-4}mm^2/s)	6.29±0.52	5.90±0.66	0.190
MD (x10^{-4}mm^2/s)	8.84±0.42	8.75±0.55	0.696
Thalamo-Cortical Tracts			
FA	0.459±0.049	0.469±0.042	0.565
RD (x10^{-4}mm^2/s)	6.27±0.93	6.06±0.55	0.496
MD (x10^{-4}mm^2/s)	8.60±0.88	8.46±0.48	0.637

Paired t-test was used to compare means of subject characteristics and DTI parameters between age-matched controls. A multivariable linear regression was used to compared FA between groups, covarying for age and number of gradient directions.

Results: Subjects with and without exposure to chemotherapy did not differ in mean age (7.5±3.3 vs. 7.7±3.0, p=0.87), gender (58% male vs. 33% male, p=0.22), or number of diffusion gradient directions (75% 20 dir vs 58%, p=0.39). There was no difference in tract volume measured. Group differences in FA were found in cerebello-thalamic tracts as well as corpus callosum tracts (Table), and the effect of chemotherapy on FA remained after adjusting for age and number of gradient directions (cerebello-thalamic: -0.036±0.017, p=0.048; corpus callosum: -0.045±0.015, p=0.007). In two subjects with diffusion imaging before and after chemotherapy, FA decreased in cerebello-thalamic tracts and corpus callosum over 1 year (Figure 2).

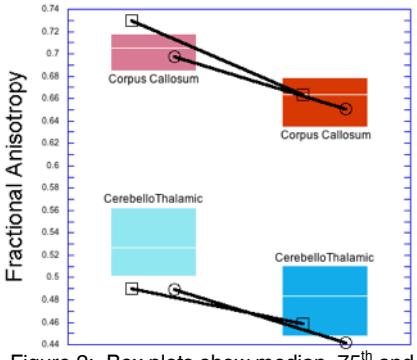

Figure 2: Box plots show median, 75th and 25th percentile of FA in cerebello-thalamic tracts and corpus callosum. Lines (box and circle) represent FA in two subjects who had DTI measurements one year apart, before and after chemotherapy.

Discussion: Previous studies have been unable to isolate the effect of systemic low-intensity chemotherapy on white matter tracts, distinct from other therapies (surgery, cranial radiation and intrathecal chemotherapy). Most prior studies in cancer survivors use diffusion imaging approaches that examine the whole brain, sacrificing tract specificity for sensitivity to diffuse changes in white matter integrity. We have shown that tracts and white matter regions previously shown to be associated with cognitive deficits have significantly lower FA in subjects with NF1 exposed to chemotherapy. Elevations in RD and MD in the chemotherapy group demonstrated a non-significant trend. Individuals with NF1 frequently have cognitive and behavioral problems and may be more susceptible to chemotherapy-induced changes in white matter. Further study is needed to examine the degree of cognitive deficit and its association with FA in patients with NF1 exposed to low-intensity chemotherapy.

References: **1.** Khong PL, et al. *J clin onc.* 2006. **2.** Aukema EJ, et al. *Intl journ of radiation oncology, biology, physics.* 2009. **3.** Palmer SL, et al. *Neuro-oncology.* 2012. **4.** Law N, et al. *NeuroImage.* 2011.