Evaluation of Cerebrocerebellar Pathway Integrity in Pediatric Posterior Fossa Tumor Patients with Cerebellar Mutism Syndrome

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Introduction and Purpose: Cerebellar mutism syndrome (CMS) has been documented in up to 25% of patients who undergo resection of posterior fossa (PF) tumors. CMS can present with diminished speech output, abnormalities in speech or dysarthria, hypotonia, ataxia, emotional lability, and affective disturbances. Recovery is usually incomplete and residual difficulties in speech, language, and cognitive function may persist. While the cerebellum is involved in many of the CMS symptoms it is not known whether CMS is related to damage of the major afferent or efferent white matter pathways connecting the cerebellum with cerebral regions (i.e. cerebrocerebellar pathways). We used diffusion tensor imaging (DTI) and probabilistic tractography to generate maps of fibre connectivity between cerebellar and frontal regions. We also measured differences in white matter organization between patients with PF tumors who displayed CMS, patients with PF tumors who did not show CMS, and healthy controls. Our goal was to investigate the relation between CMS and the structural integrity of afferents/efferents connecting the cerebellum with cortical areas.

Methods: Twelve children with PF tumors (2 astrocytoma, 1 ganglioglioma, 8 medulloblastoma, 1 germinoma) and CMS, 29 children with PF tumors (8 astrocytoma, 1 choroid plexus papilloma, 5 ependymoma, 15 medulloblastoma) but without CMS, and 26 healthy control children participated in this study. Of the 30 patients in which site of tumor was available, tumor location was primarily midline, right cerebellar hemisphere, or left cerebellar hemisphere in 8, 2, and 0 of patients with CMS and in 19, 0, and 1 of patients without CMS, respectively. MRI measurements were performed at the Hospital for Sick Children, British Columbia Children's Hospital or Alberta Children's Hospital. The scanning protocol included a 3D-T1 FSPGR gradient echo, inversion recovery-prepared sequence and a diffusion-weighted sequence. Probabilistic tractography was used to delineate the dominant white matter pathways from each cerebellar hemisphere to the contralateral cerebral cortex (via the contralateral thalamus). Seed and waypoint masks included either the left or right dorsolateral prefrontal cortex (DLPFC) as a seed mask, either the left or right thalamic region as the first waypoint mask, and either the right or left cerebellar hemispheric white matter as the second waypoint mask. Each tract obtained was segmented into anatomical compartments (i.e. frontal, mid, pons, and cerebellum) in order to evaluate regional DTI indices. Means and standard deviations for anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were calculated for the whole tract as well as each anatomic compartment. Multivariate analyses were used to evaluate group differences in all DTI indices for each tract.

Results: Bilateral tracts connecting the cerebellum with frontal cortical areas (i.e. DLPFC) via thalamic nuclei were delineated in all participants (see Figure 1 for an example). Multivariate analyses revealed significant group differences in the integrity of the tract connecting the right cerebellar hemisphere with the left DLPFC via the left thalamic region ($p = .008$). Univariate analyses showed significant differences in FA ($p = .034$), MD ($p = .001$), AD ($p = .008$), and RD ($p < .001$). Post-hoc comparisons (see Table 1 for means) revealed the following significant differences: between the mutism group and controls for FA ($p = .039$), MD ($p = .006$), and RD ($p = .001$); and between the mutism group and the no mutism group for MD ($p = .001$), AD ($p = .007$), and RD ($p = .001$). No group differences were found for integrity of the tract connecting the left cerebellar hemisphere with the right DLPFC. Tracts were separated into anatomical compartments (i.e. frontal, mid, pons, cerebellum) to examine any local damage to the pathway. Group differences were localized to more posterior regions, including the left mid region for MD ($p = .023$); the left pons region for FA ($p = .028$), MD ($p = .005$), AD ($p = .016$), and RD ($p = .006$); and the right cerebellar region for MD ($p = .005$) and RD ($p = .017$).

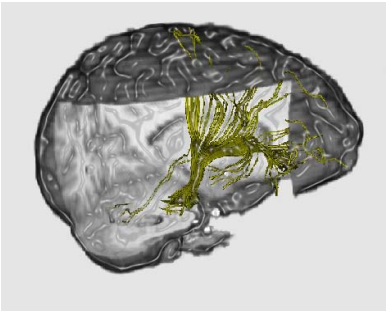

Figure 1: The cerebrocerebellar tract connecting the right DLPFC with the left cerebellar hemisphere via the right thalamic region.

Table 1. Means and standard deviations for DTI indices within the bilateral cerebrocerebellar tracts for patients presenting with CMS, patients without CMS, and healthy controls.

	Right Cerebellum-Left Frontal				Left Cerebellum-Right Frontal			
Group	FA	MD	AD	RD	FA	MD	AD	RD
CMS Patients	.456899 (.033693)	.000823 (.000055)	.001249 (.000087)	.000609 (.000049)	.478575 (.032940)	.000763 (.000047)	.001190 (.000084)	.000550 (.000040)
Non-CMS Patients	.473394 (.039279)	.000767 (.000039)	.001194 (.000078)	.000554 (.000039)	.477743 (.035211)	.000764 (.000065)	.001154 (.000222)	.000551 (.000057)
Controls	.476838 (.018114)	.000771 (.000047)	.001199 (.000077)	.000557 (.000037)	.479524 (.025373)	.000742 (.000039)	.001160 (.000059)	.000533 (.000036)

Conclusion: We show that patients presenting with CMS following treatment show greater damage to the cerebrocerebellar white matter tract connecting the right cerebellar hemisphere with left frontal areas via the left thalamus than patients that do not present with CMS or healthy controls. Furthermore, the more posterior regions of this tract showed greater damage/deterioration in the CMS patient group relative to the two other groups. The specific insult to mid, pons, and cerebellar portions of this pathway is evidence that resections of PF tumors may be associated with an interruption of cerebellar-cortical communication resulting in problems in the coordination and processing of speech, language, and emotion. Notably, we found that the pathway connecting the right cerebellar hemisphere with left frontal regions was selectively damaged in patients with CMS. Left frontal regions are important in mediating speech production and expressive language. Hence, we provide evidence that the cerebrocerebellar pathway connecting the cerebellum with areas of the brain important for speech production and expressive language is disrupted in children treated for PF tumors who show CMS.