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# Early changes in white matter predict intellectual outcome in children treated for posterior fossa tumors☆

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ABSTRACT

*Purpose:* Prospective and longitudinal neuroimaging studies of posterior fossa tumors are scarce. Here we evaluate the early changes in white matter and intellectual outcome up to 3 years after diagnosis.

*Patients and methods:* Twenty-two children with posterior fossa tumors and 24 similarly-aged healthy children participated. Patients included: (a) 12 individuals who received surgery, cranial-spinal radiation (CSR), and focal radiation to the tumor bed (CSR group) and (b) 10 individuals who received local therapy, either surgery only or surgery and focal radiation to the tumor bed (Local group). Diffusion tensor imaging (DTI) and intelligence measures were obtained an average of 3 months after diagnosis and then at 12, 24, and 36 months later. DTI tractography and voxel-wise approaches were employed. The Neurological Predictor Scale was used to summarize the type and amount of treatment for PF tumor patients. Linear mixed modelling was used to evaluate group differences at baseline and changes over time in DTI metrics for both the specific white matter tracts and voxel-wise, as well as for intelligence measures.

*Results:* Based on tractography, patients treated with CSR had significantly higher Axial and Mean diffusivity in the cortical-spinal tracts (CST) 3 month after diagnosis – particularly on the right side, $p < .003$, compared to healthy children. Mean diffusivity in right CST decreased over time in this group of patients, $p = .001$. No differences compared to controls were evident in specific tracts for the Local group, $p > .10$. Voxel-wise analyses revealed multiple areas of white matter compromise in both patients groups. Notably, both patient groups had lower scores on intelligence measures compared to the Control group: The CSR group displayed lower performance 3 months following diagnosis, $ps < 0.001$, and their performance remained stable over time $ps > 0.10$, whereas the Local group displayed no differences at 3 months, $ps > 0.10$, but their performance declined over time, $ps < 0.01$. At baseline, higher MD in right CST predicted lower Perceptual Reasoning scores across all participants, $p = .001$. Furthermore, lower FA in left IFOF at baseline predicted decline in Processing Speed over time, $p = .001$. In patients, more aggressive treatment protocols and presence of mutism were related to lower performance on intelligence measures at baseline, $ps < 0.04$.

*Conclusions:* Children treated with CSR displayed diffuse white matter compromise and poor intellectual outcome shortly after radiation treatment. There was evidence of subsequent growth of white matter structure, but stable intellectual insult. Conversely, in children treated with either surgery only or surgery and focal radiation to the tumor bed we observed less compromise of white matter early following treatment and no intellectual insult compared to healthy children. However, declines in intellectual function were evident for these children, though their performance remained within the average normative range. Overall, results suggest that early intervention is necessary to circumvent these deficits.

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## 1. Introduction

Pediatric brain tumors are most frequently located in the posterior fossa (PF), including medulloblastoma, ependymoma, and astrocytoma (Pollack, 1994). With advances in therapy, survival rates have increased dramatically, but these tumors and their treatment can lead to injury to white matter as well as poor intellectual outcome (Lassaletta et al., 2015; Mabbott et al., 2006; Reddick et al., 2005; Riggs et al., 2014; Rueckriegel et al., 2010; Scantlebury et al., 2016). Cranial-spinal radiation (CSR) is related to white matter insult and cognitive impairment (Copeland et al., 1999; Hoppe-Hirsch et al., 1995; Reddick et al., 1998). Previous studies show that younger age at diagnosis and larger radiation dose and field consistently predict the poorest outcomes (Chapman et al., 1995; Grill et al., 1999; Khong et al., 2003; Moxon-Emre et al., 2014; Mulhern et al., 1998; Silber et al., 1992). However, the time course of when these deficits appear is less clear, including whether it starts immediately following a diagnosis of PF tumor or several years after treatment completion. This knowledge is crucial for monitoring the emergence of and potentially mitigating the impact of these adverse effects, including informing the implementation of neurorehabilitation strategies.

In most longitudinal studies, relatively intact intellectual function is observed immediately after acute stages of diagnosis and treatment, along with subsequent decline with increasing time from diagnosis (Copeland et al., 1999; Mulhern et al., 1998) (Mulhern et al., 2005; Palmer et al., 2001; Radcliffe et al., 1994; Ris et al., 2001). However, some studies show immediate deficit, stability over time, or even improvement in cognition according to each patient's trajectory (Kun and Mulhern Jr., 1983; Moxon-Emre et al., 2014; Moxon-Emre et al., 2016b). The majority of studies have focused on children treated with CSR and have not included children treated with local therapies or healthy control children.

Similarly, there is some evidence of decreased white matter organization and volume with increased time from treatment (Glass et al., 2017; Palmer et al., 2002; Reddick et al., 2000). However, the majority of imaging studies are retrospective, cross sectional, and conducted many years following diagnosis. Only recent studies have focused on changes in white matter immediately following diagnosis and treatment; these studies provide emerging evidence that there is the presence of early insult in white matter (Glass et al., 2017; Nieman et al., 2015; Perreault et al., 2014).

There is a dearth of prospective longitudinal studies examining the trajectory of white matter change in children with PF tumors and relating such changes to cognitive function. Furthermore, previous longitudinal imaging studies have not examined changes in white matter for both specific tracts and in a voxel-wise manner, nor have they included children treated with CSR, those treated with local therapy, and healthy children. A comprehensive approach to evaluating white matter across multiple groups is critical to determine the areas of white matter most affected by disease or treatment. Here we evaluate changes in white matter and intellectual outcome in children treated for PF tumors in the first 3 years after diagnosis, compared to healthy children. Our specific research objectives are to: 1) evaluate differences between patients and controls in white matter microstructure (using tractography and voxel-wise methods) and in intelligence scores close to diagnosis and over time, and 2) examine whether white matter indices or clinical information predict cognitive outcomes. We hypothesize that declines over time in white matter metrics and intellectual outcome will be observed in children with brain tumors, and this decline will be greatest in children treated with CSR.

## 2. Methods

### 2.1. Participants

Following REB approval at each site, 61 participants were recruited from 3 pediatric hospitals in Canada between 2007 and 2011 (The Hospital for Sick Children, Alberta Children's Hospital, and British Columbia Children's Hospital). Fifteen children ($n = 6$ healthy control; $n = 9$ brain tumor) were excluded due to having only one data point or poor imaging quality. The final cohort included 22 children diagnosed with PF tumors and 24 similarly-aged healthy children (Control group). Patients were placed into 2 groups. The first patient group (CSR group) included 12 patients who received surgery, CSR, and focal radiation to the tumor bed:(2 patients on the St. Jude Medulloblastoma (SJMB) -96 protocol (Gajjar et al., 2006); 10 patients on SJMB-03 protocol (Green et al., 2015). The second patient group (Local group) included 10 patients who received local therapy, including surgery only ($n = 7$) or surgery and focal radiation to the tumor bed ($n = 3$). Demographic details are provided in Table 1. The 3 groups did not differ for sex, $\chi^2$ (2) = 0.25, $p = .884$, handedness, $\chi^2$ (2) = 0.23, $p = .893$, or age at first testing, $F(2, 43) = 0.47$, $p = .631$. Parent education was significantly higher in the Control group compared to the CSR and Local group (mother's education: $F(2, 40) = 7.40$, $p = .002$; father's education: $F(2, 40) = 6.05$, $p = .005$). Medical information is provided in Table 2.There were 17 children diagnosed with PF tumors at The Hospital for Sick Children within the same time frame and who did not participate in our study; those patients had similar diagnostic and treatment information to those included in the current study.

**Table 1**
Demographic information for all groups.

| Variable | Control group ($n = 24$) | Local group ($n = 10$) | CSR group ($n = 12$) |
|---|---|---|---|
| Sex (male: female) | 12: 12 | 5: 5 | 7: 5 |
| Handedness (left: right) | 3: 21 | 1: 9 | 2: 10 |
| Age at first testing (years) | | | |
| Mean (SD) | 10.51 (2.55) | 9.88 (3.65) | 9.59 (2.66) |
| Range | 5.81–14.93 | 6.01–16.07 | 6.27–15.41 |
| Mother's education (years)* | | | |
| Mean (SD) | 19.04 (4.81) | 14.30 (3.30) | 14.00 (2.60) |
| Range | 12–30 | 7–18 | 11–18 |
| Father's education (years)* | | | |
| Mean (SD) | 18.17 (3.81) | 14.50 (1.90) | 14.67 (3.24) |
| Range | 12–25 | 12–17 | 10–20 |

* Indicates significantly higher values for the Control group in comparison to the brain tumor groups ($p < .05$).

### 2.2. Study design

Patients completed baseline cognitive testing and MRI scans approximately 3 months after diagnosis (i.e., during or immediately after radiation for those receiving this therapy) and then 12, 24, and 36 months later; the Control group completed testing at corresponding intervals. All participants (except one at the first time point) completed cognitive testing and MRI scans on the same day across all time points. Children were included in the analyses if they had participated for at least 2 time points (median of 3 assessments per participant, total = 127).

### 2.3. Image acquisition and processing

MRI scans were obtained on a 1.5 T GE Signa Excite LX scanner with an 8-channel head coil at The Hospital for Sick Children (SickKids) or 1.5 T Siemens Avanto scanners with a 12-channel head coil at Alberta Children's Hospital (ACH) or British Columbia Children's Hospital (BCCH). An axial 3D-T1 anatomical scan using a rapid acquisition gradient echo sequence with inversion recovery preparation and a diffusion tensor imaging (DTI) scan using echo-planar imaging with a single-shot spin echo sequence were acquired. Imaging signal-to-noise ratios differed between the GE (SickKids) and Siemens (ACH and BCCH) scanners for our cohort (Law et al., 2011). Consequently, scanner type