Moderated by: Sakina Butt

1 Ototoxicity and Cognitive Outcomes among Children Treated for Brain Tumors in Infancy

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Objective: Treatment of childhood central nervous system (CNS) tumors can lead to sensorineural hearing loss (SNHL), with prior research indicating associations between SNHL and cognitive difficulties. Infants (0-3 years) treated for CNS tumors are at particular risk for neurocognitive deficits due to increased vulnerability of the developing brain and missed developmental opportunities secondary to prolonged treatment. This study expands upon existing research by examining the association between treatment-related SNHL and later neurocognitive outcomes among infants.
Participants and Methods: Serial audiology and neurocognitive assessments were conducted as part of a prospective, multisite, longitudinal trial (SJYC07). Children with newly diagnosed CNS tumors were treated with chemotherapy, with or without focal proton or photon radiation therapy (RT). SNHL was dichotomized based on hearing in the better ear as present versus not present (Chang grade ≥1a vs. <1a). Neurocognitive assessments included intellectual functioning (IQ), and parent ratings of executive functioning and behavioral functioning. Demographic and clinical variables investigated included: sex, age at diagnosis (years), treatment type (chemotherapy only vs. chemotherapy + RT), risk group (low vs. intermediate vs. high), and socioeconomic status (SES, continuous). Logistic regression models were used to identify factors associated with SNHL. Change point longitudinal models were used to examine the effect of each covariate individually and the potential impact of SNHL on trajectories of neurocognitive outcomes.
Results: Of 135 patients (median age at diagnosis= 1.5 years), 67% had mild-to-severe SNHL as defined by Chang grade ≥1a at last follow-up. SNHL occurred early after treatment with a 1-year cumulative incidence 63.0% ± 4.3%. SNHL was associated with age at diagnosis ($p < .001$) but not sex, treatment exposure or study risk arm ($p > .10$). At pre-treatment baseline, IQ was associated with age at diagnosis (older age= higher IQ) and SES (higher SES= higher IQ) with a change in the trajectory of IQ after SNHL (stable prior to SNHL and declined 1.46 points/year after SNHL), which was impacted by tumor location (patients with supratentorial tumors stable prior to SNHL and declined 2.84 points/year after SNHL; whereas, patients with infratentorial tumors increased 1.93 points/year prior to SNHL and were stable after SNHL). At pre-treatment baseline, adaptive functioning was associated with age at diagnosis (older age= higher skills) with a change in adaptive functioning after SNHL that varied by age. There was a change in trajectory of attention problems (stable before SNHL and worsening 1.39 points/year after SNHL). SNHL was not associated with parent report of emerging executive functioning.
Conclusions: Children with brain tumors experience SNHL and cognitive difficulties early in treatment that can worsen over time. Younger age at diagnosis is associated with greater risk for SNHL and cognitive difficulties. Analyses of the time course between the emergence of SNHL and cognitive late effects suggests even mild SNHL is associated with a clinically signficant decline in IQ and attention problems. These findings have notable implications with respect to refining monitoring guidelines, informing modifications to treatment, advocating for interventions, and helping educate parents, teachers, and providers about the significant impact of mild SNHL.

Categories: Acquired Brain Injury (TBI/Cerebrovascular Injury & Disease - Child)
Keyword 1: cancer
Keyword 2: neuro-oncology
Keyword 3: quality of life
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2 Cognitive Sparing in Proton Versus Photon Radiotherapy for Pediatric Brain

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Tumor Associated with White Matter Integrity

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Objective: Radiotherapy for pediatric brain tumor is associated with reduced white matter structural integrity and neurocognitive decline. Superior cognitive outcomes have been reported following proton radiotherapy (PRT) compared to conventional photon radiotherapy (XRT), presumably due to sparing of healthy brain tissue. This study examined long-term white matter change and neuropsychological performance in pediatric brain tumor survivors treated with XRT vs. PRT.
Participants and Methods: Pediatric brain tumor survivors treated with either XRT (n = 10) or PRT (n = 12) underwent neuropsychological testing and diffusion weighted imaging > 7 years following radiotherapy. A healthy control group (n = 23) was also recruited. Groups had similar demographic characteristics, except for handedness (p = .01), mean years of age at testing (XRT = 21.7, PRT = 16.9, Control = 15.5; p = .01), and mean years since radiation (XRT = 14.7, PRT = 8.9, p < .001). Age and handedness were selected as covariates; analyses were not adjusted for time since radiation due to redundancy with treatment group (i.e., standard of care transitioned from XRT to PRT in 2007). Participants completed age-appropriate versions of the Weschler Intelligence Scales (WAIS-IV/WISC-IV/WISC-V) and the Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI and Motor Coordination subtests). Tractography was conducted using automated fiber quantification (AFQ), and fractional anisotropy (FA) was extracted from 12 tracts of interest. Linear mixed models were used to summarize group differences in FA, with tracts nested within subjects. Neuropsychological performance and tract-level FA were compared between groups using analysis of covariance (ANCOVA). Pearson correlation was used to examine associations between cognitive functioning and tract-level FA.
Results: Across all tracts, FA was significantly lower in the XRT group than the PRT group ($t(514) = -2.58$, $p = .01$), but did not differ between PRT and Control groups ($t(514) = .65$, $p = .51$). For individual tracts, FA differed significantly between treatment groups (XRT < PRT) in the left inferior fronto-occipital fasciculus (IFOF), right IFOF, left inferior longitudinal fasciculus (ILF) and right uncinate (all $t < -2.05$, all $p < .05$). No significant differences in FA were found between PRT and Control participants for any tract. All neuropsychological scores were significantly lower for XRT than PRT patients (all $p < .03$), while PRT and Control groups performed similarly on these measures (all $p > .19$). Cognitive functioning was most consistently associated with FA of the corpus callosum major forceps (4/7 domains; all $r > .33$, all $p < .04$) and the left ILF (4/7 domains; all $r > .37$, all $p < .02$).
Conclusions: Both white matter integrity and neuropsychological performance were generally reduced in patients with a history of XRT, but not in those who received PRT. The PRT group was similar to healthy control participants with respect to both FA and cognitive scores, suggesting improved long-term outcomes compared to patients receiving XRT. This exploratory study is the first to provide direct support for white matter integrity as a mechanism of cognitive sparing in PRT. Future work with larger samples is necessary to replicate these findings.

Categories: Cancer
Keyword 1: brain tumor
Keyword 2: radiotherapy
Keyword 3: pediatric neuropsychology
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3 Predicting Neuropsychological Late Effects in Pediatric Brain Tumor

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