Accelerated Cognitive Decline in Adult Survivors of Pediatric Central Nervous System (CNS) Tumors: A Report from the Childhood Cancer Survivor Study (CCSS)

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Abstract: (2600/2600-character limit)

Background: Survivors of pediatric CNS tumors may be at elevated risk for accelerated cognitive decline as they age through adulthood relative to the general population, which may be an early risk factor for dementia.

Methods: Longitudinal analysis of 512 CNS tumor survivors (52.3% female, mean [SD] 30.6 [7.1] years at T1) and 232 siblings (57.8% female, mean [SD] 34.2 [8.4] years at T1) from the CCSS was conducted using the Neurocognitive Questionnaire (NCQ) to assess task efficiency, emotional regulation, organization and memory at two timepoints separated by a mean of 11.6 [0.7] years. Impairment in each NCQ domain was defined as a score ≥ 90th percentile of the CCSS sibling distribution at each survey, with decline defined as moving from unimpaired at T1 to impaired at T2. Treatment exposures were abstracted from medical records. Chronic health conditions were self-reported at T1 and graded according to CTCAE v4.3. Relative risk of decline for group, treatment and chronic condition predictors was estimated using generalized linear models with robust variance estimates. Mediation analysis examined direct effects of treatments and mediating effects of chronic conditions. All models were adjusted for age, sex, and race.

Results: At T1, survivors demonstrated higher frequency of impaired memory (24.5% vs. 6.5%, p<0.001), emotional regulation (14.3 % vs. 5.6%, p<0.001), task efficiency (43.3% vs. 13.8%, p<0.001) and organization (17.7% vs. 10.8%, p=0.015) than siblings. Among those unimpaired at T1, more survivors vs. siblings declined in memory (34.7% vs. 7.8; RR 4.2, 95% CI 2.6-6.9), emotional regulation (15.5% vs. 5.0%; RR 2.8, 95% CI 1.5-5.3), task efficiency (22.7% vs. 7.0%; RR 2.9, 95% CI 1.7-5.2), and organization (14.5% vs. 2.9%; RR 4.9, 95% CI 2.1-11.0) by T2. Decline in survivor memory was associated with exposure to craniospinal irradiation (RR 1.9, 95% CI 1.3-2.8) and focal irradiation (RR 1.6, 95% CI 1.1-2.3) compared with no radiation, and exposure to Ara-C (RR 1.7, 95% CI 1.0-2.8) and cyclophosphamide (RR 1.7, 95% CI 1.01-2.8). Independent of therapy, serious/disabling or life-threatening cardiopulmonary conditions at T1 predicted future decline in memory (RR 1.5, 95% CI 1.02-2.2) and organization (RR 2.0, 95% CI 1.1-3.6), with the presence of 2 or more cardiopulmonary conditions associated with even higher risk (memory RR 2.6, 95% CI 2.0-3.1; organization RR 3.4, 95% CI 1.1-10.5). Chronic conditions did not mediate associations between treatment exposures and cognitive decline.

Conclusions: CNS tumor survivors are at elevated risk for impairment and accelerated cognitive decline compared to siblings. Cranial radiation, Ara-C, cyclophosphamide, and cardiopulmonary morbidity are risk

factors for decline. Survivors with these exposures/conditions may benefit from interventions to prevent additional future cognitive decline.