Associations between chemotherapy exposures, chronic conditions and neurocognitive impairments in pediatric ALL survivors treated with chemotherapy only vary with sex: A Report from the Childhood Cancer Survivor Study (CCSS)

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Background/Purpose: Prior research has identified neurocognitive impairments after treatment for childhood ALL with chemotherapy only; however, little is known about risk modifiers such as sex and chronic health conditions.

Methods: ALL survivors treated with chemotherapy only (N=1221; 55% female) and 728 siblings (56% female) in the CCSS study completed the Neurocognitive Questionnaire (CCSS-NCQ) to assess task efficiency, emotional regulation, organization, and memory. Cognitive impairments were defined as Z-scores ≥ 1.28, corresponding to the 90^{th} percentile of the sibling sample. Chemotherapy exposures were abstracted from medical records. Chronic health conditions were graded according to Common Terminology Criteria for Adverse Events v4.03. Multivariable logistic regression models compared survivors and siblings to identify associations with neurocognitive impairment, stratified by sex and adjusted for age at NCQ assessment and race.

Results: Female survivors had a higher prevalence of neurocognitive impairments related to task efficiency (adjusted proportion 20.9%) and memory (27.6%) compared to siblings (12.7% and 17.7% respectively), with adjusted odds ratio (OR) 1.8 (95% confidence interval [CI] 1.2 - 2.8) and 1.8 (95% CI 1.3 - 2.5), respectively. Male survivors endorsed more impairments related to task efficiency than did siblings (17.0% vs 11.8%; OR 1.5, 95% CI: 1.0 - 2.3), but not for memory. Chemotherapy exposures were not significantly associated with neurocognitive impairments, except for dexamethasone, which was associated with increased risk of memory impairments in males (OR = 2.1, 95% CI 1.2 – 4.0). Having a grade 2-4 neurological chronic condition increased the risk of all types of neurocognitive problems in both female and male ALL survivors. In males, grade 2-4 pulmonary conditions were associated with increased risk of impaired task efficiency (OR 5.0, 95% CI 1.4 – 17.1) compared to those with < grade 2. In females, grade 2-4 endocrine conditions were associated with increased risk for impaired task efficiency (OR 2.4, 95% CI 1.3 – 4.3), organization (OR 2.1, 95% CI 1.0 – 4.1) and memory (OR 2.3, 95% CI 1.4 – 4.1).

Conclusions: Significant variation in risk for neurocognitive impairments based on sex was identified, highlighting the need to investigate sex-related differences in pathophysiology and monitoring of survivors. Further evaluation of risk modifiers of neurocognitive impairments after childhood ALL is important to effectively address these problems.