Characterizing the role of diabetes mellitus on neurocognitive outcomes in childhood cancer survivors: A report from the Childhood Cancer Survivor Study

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Background: Diabetes mellitus (DM) is associated with neurocognitive impairment in non-cancer populations. We examined associations between DM and neurocognitive impairment in survivors cross-sectionally and longitudinally, accounting for cardiovascular disease (CVD) and treatment exposures.

Methods: Survivors (Mean[SD] age=32.9[7.9] years; 50.2% female) with (N=615) and without DM (N=15,581) reported on neurocognition and chronic conditions. Treatment exposures were abstracted from medical charts. DM and CVD were graded according to CTCAE (grade≥2 and grade≥3, respectively). Models were adjusted for variables selected through elastic-net. Multivariable logistic regressions determined the association of DM with neurocognitive impairment. Path analysis explored effects of treatment exposures through DM and CVD on neurocognitive impairment. Multivariable linear regressions examined predictors of neurocognitive decline (i.e., change in z-scores) between baseline and follow-up (min-max: 1.5-19.6 years) in survivors with DM.

Results: Survivors with DM had increased risk of neurocognitive impairment relative to survivors without DM (task completion unadjusted rates of impairment: 37.5% vs. 25.9%, multivariable model-derived odds ratio[OR], 95 confidence limits[CI]=1.5, 1.2-9; emotional regulation: 16.9% vs. 11.5%, OR=1.4, CI=1.1-2.0; and organization: 18.4% vs. 13.1%, OR=1.5, CI=1.1-2.0). In path analyses, CVD was directly associated with impairment (task completion: Standard Estimate [SE]=0.23; emotion regulation: SE=0.10; memory: SE=0.17; organization: SE=0.12, all p<.001) but did not mediate DM on neurocognition. Cranial radiation was directly associated with impairment (task completion: SE =0.19; emotion regulation: SE=0.07; memory: SE=0.17; organization: SE=0.04, all p<0.01) and was mediated by DM on neurocognition (task completion: SE=0.02; emotion regulation: SE=0.02; memory: SE=0.01; organization: SE=0.02, all p<0.01). In survivors with DM, grade≥3 CVD—but not DM duration/severity—was associated with decline in task completion and organization (Estimate=0.44, and Estimate=0.27, respectively, both p<0.05).

Conclusion: Survivors with DM are at increased risk of neurocognitive impairment, underscoring the importance of DM screening and prevention. Preventing/managing CVD in survivors with DM could mitigate risk of neurocognitive decline.