Long-term Neurocognitive and Quality of Life Outcomes in Survivors of Pediatric Hematopoietic Cell Transplant

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Abstract

Background: Pediatric patients who undergo hematopoietic cell transplant (HCT) are at risk for neurocognitive impairments; however, long-term studies are lacking. Procedure: Eligible survivors (HCT at age <21y and [?]1y post-HCT) completed a 60-question survey of neurocognitive function and quality of life, which included the Childhood Cancer Survivor Study Neurocognitive Questionnaire (CCSS-NCQ) and the Neuro-Quality of Life Cognitive Function Short Form (Neuro-QoL). Baseline demographic and transplant characteristics were retrieved from the institutional research database. Analyses of risk factors included univariate comparisons and multivariable logistic regression. Results: Participants (n=199, 50.3% female, 53.3% acute leukemia, 87.9% allogeneic transplants) were surveyed at median age of 37.8 years (range 18-61) at survey and median 27.6 years (range 1-46) from transplant. On the CCSS-NCQ, 18.9-32.5% of survivors reported impairments (Z-score >1.28) in task efficiency, memory, emotional regulation, or organization, compared with expected 10% in the general population (all p<0.01). Certain co-morbidities were associated with impaired CCSS-NCQ scores. However, survivors reported average Neuro-QoL (T-score 49.6±0.7) compared with population normative value of 50 (p=0.52). In multivariable regression, impaired Neuro-QoL (T-score <40) was independently associated with hearing issues (OR 4.79, 95% CI 1.91-12.0), history of stroke or seizure (OR 5.22, 95% CI 1.73-15.7), and sleep disturbances (OR 6.90, 95% CI 2.53-18.9). Conclusions: Although long-term survivors of pediatric HCT reported higher rates of impairment in specific neurocognitive domains, cognitive quality of life was perceived as similar to the general population. Subsets of survivors with certain co-morbidities had substantially worse neurocognitive outcomes.

Introduction

Hematopoietic cell transplant (HCT) is increasingly performed as a potentially curative treatment for both malignant and non-malignant disorders. However, survivors are at higher risk for developing chronic health conditions, which contributes to increased morbidity and mortality compared with non-HCT cancer survivors and the general population.[1,2] Neurocognitive function is a broad category which encompasses memory, attention, concentration, planning, organization, and problem solving, among other abilities. Impairments in cognition can complicate the post-HCT course with substantial effects on both specific cognitive abilities as well as overall quality of life.[3] Survivors of pediatric HCT are at greater risk for neurocognitive toxicity due to treatment exposures during a developmentally vulnerable period. Despite this fact, few studies have described the late neurocognitive outcomes in pediatric HCT survivors.

In studies of pediatric cancer survivors regardless of transplant history, long-term survivors reported greater

neurocognitive impairments at an average of 2 decades following diagnosis compared with healthy siblings,[4,5] with more impairments noted in survivors of central nervous system (CNS) tumors and acute lymphoblastic leukemia (ALL) following direct CNS treatment or prophylaxis.[6,7] In these patients, survivors with neurocognitive deficits were less likely to attain educational milestones[8] or follow recommendations for general care.[9] Therefore, further studies of long-term neurocognitive function are needed specifically in pediatric HCT survivors to identify potential areas for intervention with the goal of improving patient function and quality of life.

Despite known or suspected risk factors, neurocognitive dysfunction may not become apparent until decades after HCT. The existing literature is limited by inconsistent definitions, heterogeneous testing methods, and short follow-up time.[3,10-13] Specifically among pediatric HCT survivors, there is a particular lack of data describing neurocognitive outcomes and functional impact beyond 5 years post-HCT.[14] Overall, the limited understanding of the incidence and characterization of neurocognitive dysfunction following HCT has been recognized as an important area deserving of further research.[15,16] In this study, we aim to address this gap in knowledge by characterizing the late neurocognitive outcomes in a cohort of long-term pediatric HCT survivors. We also examine the association between treatment variables and medical co-morbidities and neurocognitive dysfunction in this patient population.

Methods

Participants

This study was approved by the Fred Hutchinson Cancer Research Center (FHCRC) Institutional Review Board. FHCRC maintains continuous follow-up of HCT survivors who consent to long-term follow-up via an annual patient-reported health survey, with the earliest transplant performed in 1971.[17,18] Patients underwent HCT for both malignant and non-malignant conditions, including immunodeficiencies and benign hematologic disorders. The following HCT survivors were eligible for this study: alive [?]1 year after HCT at FHCRC, age <21 years at time of transplant, current age [?]18 years at the time of survey, and available current mailing address. Baseline demographic characteristics (including age, sex, race and ethnicity, underlying diagnosis) and HCT details (including conditioning regimen, donor type, chronic graft versus host disease (cGVHD) status) were retrieved from the FHCRC research database. Additionally, pre-HCT cranial irradiation exposure was abstracted from the medical record.

Survey Instrument

All FHCRC HCT survivors consenting to long-term follow-up receive an annual survey consisting of 236 questions mailed on their transplant anniversary. The annual survey includes standardized questions on interval changes in health and presence of cGVHD or other health conditions. For this study, a 60-question supplementary module was added to the annual survey to collect information on neurocognitive function and perceived cognitive quality of life. This supplementary module included items from several validated self-reported survey measures. The Childhood Cancer Survivor Study Neurocognitive Questionnaire (CCSS-NCQ) is validated for use in adult survivors of childhood cancer and consists of 33 questions divided into 4 domains of emotional regulation, task efficiency, memory, and organization.[19] The factors of emotional regulation and organization are primarily measures of executive function, while task efficiency and memory address attention, processing speed, and both working and long-term memory.[20] The Neuro-Quality of Life Cognitive Function Short Form (Neuro-QoL) Version 2.0 is an 8-question self-reported measure addressing perceived difficulties in cognitive abilities, as well as application of these abilities to daily tasks reflecting cognitive quality of life.[21] The Patient-Reported Outcomes Measure Information System (PROMIS) Sleep Disturbance Short Form 4a is a 4-question survey to assess perception of sleep quality and restfulness.[22] An additional 3 questions were adapted from the National Health and Nutrition Examination Survey (NHANES) 2011 Audiometry Questionnaire to screen for hearing issues (6-point Likert scale), need for hearing aid, or presence of tinnitus (5-point Likert scale).[23] Finally, 6 questions were included to assess for neurologic conditions predicted to impact neurocognitive function, including previous stroke or transient ischemic attack and epilepsy or seizures. For this analysis, we used responses from surveys distributed from July 2018 to

June 2019 with all results collected by November 2019. During this time, initial non-responders were sent 2 follow-up survey requests for a total of 3 mailings.

Statistical Analysis

Patient-reported surveys were scored according to the scoring guides of the individual test developers, including methods for handling any missing data. The CCSS-NCQ was scored by calculating a total raw score for each of the 4 domains, then converted to a Z-score using a healthy comparison group as reference, with higher Z-scores corresponding to worse neurocognitive scores.[19] Responses for the Neuro-QoL were summed as total raw scores and converted to standardized T-scores with a mean score of 50 and a standard deviation of 10 using the general U.S. population as reference, with lower T-scores suggesting lower cognitive quality of life.[21] The PROMIS Sleep Short Form 4a was summed as a total raw score and then translated into a T-score with a mean of 50 and a standard deviation of 10 based on the general population, with higher T-scores signifying worse sleep quality.[22] Hearing issues were defined as self-reported moderate/severe hearing trouble or deafness, current use of hearing aid, or moderate/severe tinnitus.

Descriptive statistics including frequency distributions and medians and IQR (interquartile range) were calculated for demographic and treatment variables. Primary outcome variables, including individual CCSS-NCQ domain and Neuro-QoL scores, were further dichotomized into 2 groups based on perceived clinical impairment. Consistent with previous studies, impairment was defined as Z-score >1.28 for the CCSS-NCQ (corresponding to the worst 10^{th} percentile of scores based on healthy control age-adjusted norms)[19] and T-score <40 for the Neuro-QoL (corresponding to 1 SD below the standardized mean).[24]Scores were compared using chi-squared test for categorical variables and analysis of variance or t-tests as appropriate for continuous variables. To assess the potential influence of non-responders on the reported group averages, we also applied inverse probability sampling weights accounting for sex, age at HCT, and current age of the entire eligible population. Finally, the strength of the associations between certain clinical features and impairment on the CCSS-NCQ or Neuro-QoL were examined using multivariable logistic regression and reported as odds ratios (OR) with 95% confidence intervals (95% CI). The models for risk of neurocognitive impairment included dichotomized co-variates, defined as presence or absence of age <10 years at HCT, hearing issues, stroke/seizures, and sleep impairment adjusted for each other, as well as sex and current age. Other potential co-variates were examined but ultimately not included in the multivariable models. All analyses were completed using Stata (Version 16, StataCorp, College Station, TX).

Results

Of 626 eligible pediatric HCT survivors surveyed, 199 participated (50.3% female) at a median age of 37.8 years (range 18-61) at survey and median 27.6 years (range 1-46) from transplant (Table 1). Of note, 59 (29.6%) of participants underwent transplant at age <10 years and 21 (10.6%) were transplanted at age <3 years. The majority underwent transplantation for malignant conditions, including 106 patients with acute leukemia (53.3%) and 20 with chronic leukemia (10.1%). Among non-malignant conditions, 44 patients (22.1%) received transplants for hematologic conditions, most commonly aplastic anemia. Nine patients (4.5%) received transplants for immunodeficiencies, histiocytic disorders, or other indications. Most (175/199 patients) initially received allogeneic transplants (87.9%) and a subset of 20 patients (10.1%) received multiple transplants. Across all transplants, 132 patients (66.3%) underwent conditioning with total body irradiation (TBI), with 123 (61.8%) receiving [?]1000cGy. Eighteen (9.0%) also received additional cranial irradiation prior to TBI (median 1200cGy, range 480-5400); 1 additional patient received cranial irradiation alone without TBI. The prevalence of moderate/severe hearing issues and history of stroke/seizures was 40/198 (20.2%) and 21/197 (10.7%), respectively. Compared with non-participants, participants were more likely to be female, currently older, and transplanted at an earlier age, but did not differ across other demographic or clinical characteristics (Supplemental Table S1).

On the CCSS-NCQ, 32.5% of survivors reported problems with task efficiency, 25.4% with memory, 21.8% with emotional regulation, and 18.9% with organization compared with an expected 10% in the general population (Table 2; all $p<0.01$). Results were similar after application of inverse probability weights, with

33.0% reporting impairment with task efficiency, 27.6% with memory, 22.6% with emotional regulation, and 18.4% with organization (Supplemental Table S2). In unweighted analysis, female survivors reported more issues with emotional regulation and memory relative to males. Race/ethnicity, current age, underlying diagnosis, year of transplant, number of transplants, or history of cGVHD were not associated with a significant difference in CCSS-NCQ scores. Characteristics associated with impairments in most or all CCSS-NCQ domains included hearing issues, history of stroke or seizure, and self-reported sleep disturbances. Survivors >25 years of age with less educational achievement also reported significantly worse scores in all domains (all$p<0.05$). Survivors who received cranial irradiation were more likely to report impaired scores in task efficiency and organization compared with survivors who did not receive any radiation or those treated with TBI alone ($p<0.05$). In multivariable regression analysis adjusted for sex and current age, hearing issues were independently associated with impaired task efficiency (OR 2.71, 95% CI 1.19-6.17) and organization (OR 3.39, 95% CI 1.38-8.32), while history of stroke or seizure was independently associated with impaired emotional regulation (OR 4.78, 95% CI 1.81-12.6) and memory (OR 3.98, 95% CI 1.46-10.8; Figure 1 and Supplemental Table S3). Sleep disturbances were associated with impairments across all CCSS-NCQ domains. Younger age at transplant was generally associated with increased risk of impairments in CCSS-NCQ domains, although estimates were not statistically significant in adjusted models. Additionally, results were essentially unchanged if models were further adjusted by radiation exposure.

Respondents reported average Neuro-QoL (49.6±0.7) compared with an expected mean score of 50 in the general population ($p=0.52$; Table 3). The proportion with impaired cognitive quality of life with T-score <40 was 19.1% compared with 16% expected in the general population sample ($p=0.23$).[21] These values were similar after accounting for inverse probability weights, with mean Neuro-QoL score of 49.2±0.7 and 20.5% impairment (Supplemental Table S2). In unweighted analysis, characteristics associated with lower Neuro-QoL scores included younger age (<10 years) at HCT, prior cranial irradiation, hearing issues, history of stroke or seizure, and sleep disturbances (all$p<0.05$). Sex, race/ethnicity, current age, underlying diagnosis, year of transplant, number of transplants, or history of cGVHD were not associated with a significant difference in Neuro-QoL scores. In survivors >25 years old, lower Neuro-QoL scores were associated with less educational achievement, defined as less than college completion ($p<0.01$). In multivariable regression analysis adjusted for sex and current age, impaired Neuro-QoL was independently associated with hearing issues (OR 4.79, 95% CI 1.91-12.0), history of stroke or seizure (OR 5.22, 95% CI 1.73-15.7), and sleep disturbances (OR 6.90, 95% CI 2.53-18.9; Figure 1 and Supplemental Table S3). Younger age (<10 years) at time of transplant was not significantly associated with impaired Neuro-QoL in multivariable analysis compared with age [?] 10 years (OR 1.63, 95% CI 0.64-4.16).

Discussion

Our study demonstrated that pediatric HCT survivors reported higher impairments in specific CCSS-NCQ neurocognitive domains of emotional regulation, task efficiency, memory, and organization but average cognitive quality of life compared with general population norms at a median of 27 years post-transplant. Despite reported problems with specific cognitive abilities, reassuringly these problems were not perceived to have significant consequences on daily life as reflected on the Neuro-QoL. This could represent adaption to cognitive difficulties over time or an adjustment in expectations. These results reflect the long-term follow-up period of our patient population, in contrast with a shorter-term study in pediatric HCT survivors that described largely stable intelligence and academic achievement through 5 years post-HCT.[12] Given the limited studies of late neurocognitive effects among pediatric HCT survivors, some comparisons can be drawn from CCSS studies of childhood cancer survivors at a similar follow-up interval.[4,9,25] In a report from the CCSS featuring over 6,000 survivors (mean age 32 years), a lower percentage (12.5-22.4%) reported impairments in the CCSS-NCQ domains.[9] Although not directly comparable, this suggests that pediatric HCT survivors may be more likely to report neurocognitive impairments compared with general pediatric cancer survivors.

Various treatment characteristics and exposures have been explored in terms of their association with neurocognitive dysfunction. Previous literature has suggested that younger age at time of cancer diagnosis or HCT is a risk factor for worse neurocognitive function.[4,14,15] While a cohort study of pediatric HCT survivors

initially demonstrated overall stability in cognitive functioning at 5 years post-HCT,[12] a follow-up study with an expanded cohort showed that patients <3 years at time of transplant may be particularly susceptible to the cognitive impact of TBI, with lower IQ (16 points on average) at 5 years post-HCT compared with those who did not receive TBI.[26] In our study, younger age <10 years at time of HCT was suggestive of worse outcomes after multivariable analysis, although the study may have been underpowered to detect a statistically significant association. Additionally, the sample size was too small to draw any conclusions in the cohort <3 years at time of HCT. As above, radiation exposures such as TBI and cranial irradiation have been associated with neurocognitive dysfunction.[3,11] While we did not find a difference between non-irradiated survivors versus those who underwent TBI only, those who received pre-HCT cranial irradiation were more likely to report worse neurocognitive function. In our cohort, survivors treated with cranial irradiation reported impairments in the CCSS-NCQ domains comparable to childhood CNS tumor survivors,[8,27,28] as well as pediatric ALL survivors treated with cranial irradiation, with significant late cognitive deficits detected at a median follow-up of 28.5 years after treatment.[29]

Subsets of pediatric HCT survivors were more likely to have impaired neurocognitive function, including those with hearing conditions (moderate to severe hearing loss or more bothersome tinnitus), history of stroke or seizures, or sleep disturbances. The association of poor long-term neurocognitive outcomes in survivors with a higher burden of chronic health conditions is unsurprising, given previous studies.[25] Specifically for long-term pediatric cancer survivors, hearing and visual deficits have been associated with impaired emotional regulation and organization,[4] while history of stroke is associated with worse health-related quality of life and neurocognitive function, particularly task efficiency and memory.[30] Lastly, we found that self-reported sleep disturbances were significantly associated with greater impairments in all CCSS-NCQ domains and worse cognitive quality of life. Given the cross-sectional nature of our study, we were unable to determine if sleep issues had a causal effect on neurocognitive function. However, pediatric cancer survivors who reported greater fatigue and poorer sleep quality have also exhibited greater impairments in all CCSS-NCQ domains.[31] Studies of pediatric cancer survivors have reported a greater burden of sleep disturbances and fatigue compared with non-cancer controls.[6,32] Additional research to better characterize the sleep disorders experienced by our patients may help determine specific targets for intervention.

For pediatric HCT survivors over the age of 25 years at the time of survey completion, greater impairments in all CCSS-NCQ domains and worse Neuro-QoL scores were associated with less educational achievement (defined as less than college education). Our findings are similar to other studies showing that childhood cancer survivors with neurocognitive deficits are less likely to attain educational milestones, obtain employment, or live independently.[3,4] These results may be time-dependent, as differences in educational achievement may not be fully appreciated until an extended time interval after HCT. This highlights the importance of early referrals for resources or interventions to potentially mitigate HCT treatment effects. The Children's Oncology Group's Long-Term Follow-Up guidelines recommends routine formal neuropsychological evaluation for patients at risk for late neurocognitive deficits, including those who receive any cranial irradiation (including TBI) or specific chemotherapy agents commonly used during HCT, including intrathecal methotrexate, high-dose intravenous methotrexate and/or cytarabine.[33] While previous pediatric HCT reviews[3,15] have suggested the implementation of similar routine screening, further studies will be needed to study if earlier testing and intervention improves long-term outcomes.

Our study benefited from a very long average follow-up duration, greatly exceeding that of other studies of neurocognitive outcomes among pediatric HCT survivors. Additionally, our study also featured one of the largest samples examining neurocognitive outcomes in this patient population. However, there were several limitations to this study. Our study was conducted at a single center and limited by lower response rate; thus, our results may not be fully representative of the overall population of pediatric HCT survivors. Non-responders were more likely to be younger and male; however, when inverse probability weighting was applied to represent the entire cohort, we did not find a meaningful difference in our results. It is unclear how potential response bias would have influenced these results, as those with lower function or quality of life may have been both less likely to respond or possibly more likely to participate given the nature of the survey. Lastly, while our study was based on self-reported measures with no objective neurocognitive testing,

many components of cognition can only be captured by patient self-report and we relied on well-validated surveys which enabled comparisons with the general population.

Conclusion

Our study found that pediatric HCT survivors surveyed at a median of 27 years post-transplant reported higher frequencies of impairments in the domains of emotional regulation, task efficiency, memory, and organization but similar cognitive quality of life compared with the general population. Subsets of survivors with certain neurologic co-morbidities were at higher risk for worse neurocognitive outcomes, which may influence monitoring and counseling for post-HCT survivorship care. Sleep intervention and early referral for educational and rehabilitation services may offer possible avenues to mitigate HCT-related treatment effects on later life achievements.

Conflict of Interest Statement

None of the authors have conflicts of interest to declare.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

All of the authors have contributed to the manuscript in significant ways and have reviewed and agreed upon its content.

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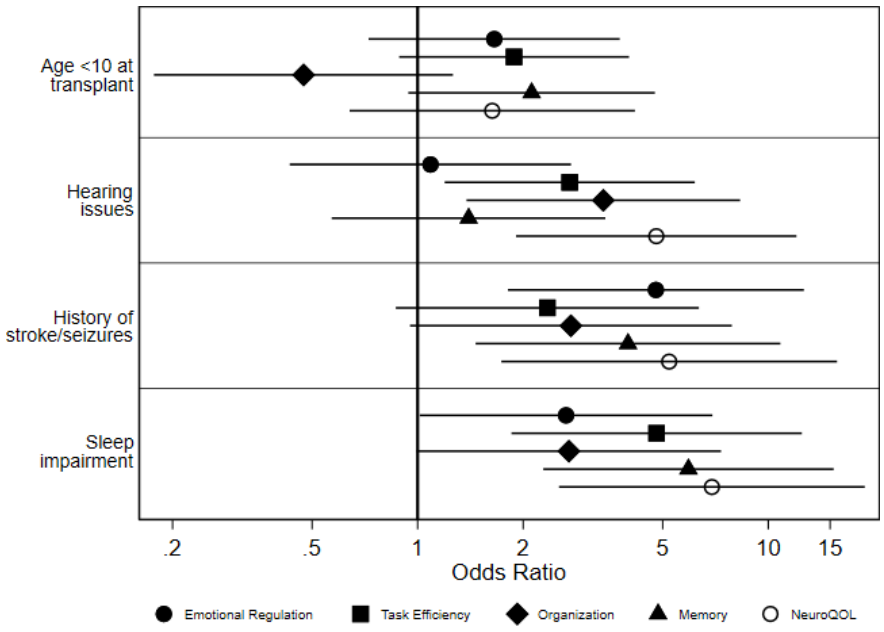
Figure Legend



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