RESEARCH ARTICLE

Post-transplant adaptive function in childhood cerebral adrenoleukodystrophy

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Abstract

Objective: Hematopoietic stem cell transplantation (HSCT) is the only treatment known to slow or halt inflammatory demyelination among boys with the cerebral form of X-linked adrenoleukodystrophy (cALD), a devastating childhood condition affecting the central nervous system. HSCT can lead to a range of adverse outcomes including fatality. Previous studies have examined the potential predictors of post-HSCT survival and neurologic functioning. However, little is known about patients' daily-life adaptive functional outcomes (i.e., ability to communicate, maintain social relationships, and independently execute tasks of daily living). The purpose of this retrospective cohort study was to identify which patient characteristics and treatment-related variables predict long-term adaptive function among the survivors of HSCT for cALD. **Methods**: We obtained caregiver ratings of adaptive functioning of 65 transplant survivors at an average of 4.6 years (range: 1.0–24.1 years) post-HSCT. Using linear regression with penalized maximum likelihood estimation, we modeled the relative contribution of pre-transplant neurocognitive test performance, MRI severity, transplant regimen, and length of time since transplant on patient adaptive functioning outcomes. **Results**: Higher radiographic disease severity and poorer performance on baseline neurocognitive tests requiring fine motor skills and visual perception were associated with inferior adaptive functioning after HSCT. Use of radiation during the transplant preparative regimen also predicted poorer adaptive outcomes. **Interpretation**: In addition to radiological disease severity, baseline neurocognitive test performance is associated with post-transplant adaptive functional outcomes. Neurocognitive measures may play an important role in prognostic counseling and post-transplant treatment planning for patients considering HSCT for cALD.

Introduction

Adrenoleukodystrophy (ALD) is an X-linked disorder of very long-chain fatty acid metabolism affecting 1 in 21,000 males.[1] One-third of boys with ALD will develop cerebral disease in childhood (cALD), with initial onset of symptoms around 3–10 years of age.[2] The childhood cerebral phenotype is characterized by white matter signal changes on brain magnetic resonance imaging (MRI), and progressive inflammatory demyelination manifesting with problems in vision, auditory processing, motor function and cognition. If untreated, cALD is nearly always fatal within several years of initial symptoms.[3]

In the early 1990s, allogeneic hematopoietic stem cell transplantation (HSCT) emerged as an effective therapy for cALD.[4,5] Although HSCT does not restore brain myelination or lost cognitive function, arrest in further demyelination after transplant is usually observed. Patients transplanted in the early stages of cerebral disease (also termed "standard risk" cALD and characterized by an MRI severity score <10 on the Loes scale[6]) typically have more favorable survival and neurological outcomes, although selective neurocognitive deficits are observed in

some patients.[4,7–9] Patients treated at a more advanced stage of demyelination ("higher risk") frequently experience serious, irreversible neurological complications after transplantation that may include seizures, blindness, speech problems, loss of continence, and restricted gross motor function and mobility.[10]

Most published studies reporting the effects of HSCT have focused on outcomes such as engraftment, survival, neurological function, or neurocognitive ability.[3] Although these metrics represent essential benchmarks for evaluating the success of intervention for cALD, recent publications have commented on the failure of these endpoints to fully characterize the experience of transplant survivors in terms of their quality of life or ability to actively and fully participate in their world (i.e., to independently handle life demands).[11,12] A more comprehensive understanding of the range of possible adaptive functional outcomes is needed to inform counseling for patients and families undergoing evaluation at transplant centers. Furthermore, although a robust association between pre-HSCT MRI severity score and post-HSCT endpoints has been observed across studies, little information is available as to whether other variables, such as pre-HSCT neurocognitive function or treatment regimen, may predict a transplant survivor's capacity for independent functioning in the years following HSCT. Such information can play a vital role when weighing the risks and benefits of HSCT and conveying concrete prognostic information to families. To address these gaps, we characterized adaptive functioning outcomes among a large cohort of boys who survived HSCT for cALD, and modeled the factors that were most associated with these outcomes.

Methods

Participants

Records from the prospectively maintained program database indicated that 137 boys with cALD between ages 4 and 16 years underwent allogeneic HSCT at the University of Minnesota Blood and Marrow Transplant Center prior to April 2016. Following transplantation, 31 boys (23%) in this cohort died within the first year. Among the 106 surviving patients, a valid parent/caregiver adaptive function rating from ≥1 year post-HSCT was available for 65 patients (61% of the surviving boys). These ratings were obtained either as part of routine neuropsychological follow-up at our institution ($n = 56$) or as part of a clinical research study on HSCT outcomes ($n = 9$). Written informed consent to participate in this clinical outcomes research was obtained from parents/guardians. Adaptive outcomes for each patient were determined

from the most recent assessment available. Outcomes data were collected from evaluations that occurred between August 1994 and April 2017.

Pre-transplant MRI

Boys in the study cohort underwent brain MRI at an average of 1.1 months (SD, 1.3 months) prior to HSCT. Each baseline study was reviewed by a board-certified neuroradiologist (D.N.) and characterized according to the extent of white matter signal abnormality and atrophy using a 0–34 point severity scale developed by Loes et al.[6] Higher scores denote more extensive cALD, with a pre-HSCT threshold of 10 or more points indicating "higher risk" disease status.[8]

Pre-transplant neurocognitive evaluation

Following institutional protocol, patients underwent comprehensive neurocognitive evaluation at an average of 2.0 months (SD, 1.4 months) prior to transplant. Scores in six neurocognitive domains were widely available across the pre-HSCT assessments. Four domains (verbal comprehension, perceptual reasoning, working memory, and processing speed) were assessed using the age-appropriate version of the Wechsler Intelligence Scales.[13–17] Using a method previously described,[9] prorating procedures were used to standardize these four constructs across multiple versions of the Wechsler Scales. A fifth domain, fine motor dexterity, was evaluated using the average of scores obtained from three trials (dominant hand, non-dominant hand and both hands) of the Purdue Pegboard Test.[18] This task requires the examinee to grasp metal pegs and place them into a series of small holes as rapidly as possible. The Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI), a task requiring the examinee to copy a series of increasingly complex geometric shapes with paper and pencil, was used to evaluate visual perception and visual-motor function.[19]

Hematopoietic stem cell transplantation

All boys were treated on IRB-approved HSCT protocols. Patients underwent preparative regimens comprising chemotherapy with or without irradiation prior to blood stem cell graft infusion. These regimens varied based upon institutional standards at the time of HSCT. Nine patients (14%) in the study cohort required second transplantation due to failed engraftment with first HSCT. Eight boys (12%) were only exposed to reduced intensity preparative regimens, while 57 (88%) had exposure to at least one myeloablative regimen. The majority of patients

undergoing myeloablative regimens were conditioned with a busulfan-based strategy. In an earlier transplant era, high-dose total body irradiation (TBI) regimens were used in 14 (22%) patients. Regarding blood stem cell source, nearly all patients (97%) received either bone marrow or umbilical cord blood (UCB); 2 (3%) patients received blood stem cell grafts harvested via peripheral blood leukocytopheresis (PBSC). Patients with more advanced cALD tended to be more likely to receive UCB, a graft source more readily available than bone marrow or PBSC from volunteer donor registries.

Adaptive function outcome measure

The Vineland Adaptive Behavior Scales (VABS)[20] is a widely used, norm-referenced parent/caregiver report measure that evaluates an individual's degree of competence and independence in daily life within three domains: Communication, Daily Living Skills, and Socialization. A fourth domain, Motor Skills, was available for patients who were <7 years old when the VABS was administered ($n = 3$). These domain scores are combined to form an overall Adaptive Behavior Composite (VABS-ABC) score. Domain and composite scores have a mean of 100 and a standard deviation of 15. There is empirical evidence of high reliability and validity of this instrument in the general population as well as among individuals with significant cognitive impairment.[21] The VABS was first published in 1984; a second edition containing a normative update and revisions to scale items was published in 2005.[22] Eleven patients (17%) in this study were assessed using the first edition. Fifty-five patients (83%) were rated using the second edition, which can be administered as an interview or in a questionnaire format.

For descriptive purposes, the degree of impairment on the VABS was defined as follows: scores above or within 1 SD of the population mean (not impaired), between −1 SD and −2 SD (below average), and less than or equal to −2 SD (severely impaired).

Statistical analysis

Baseline MRI severity scores and neurocognitive evaluation results for all patients who received HSCT at the University of Minnesota (including those who died or were lost to follow-up) are presented in Table 1. Patients who died within one year of HSCT presented with the highest MRI severity and lowest performance on neuropsychological testing at the pre-HSCT evaluation. Among the patients who survived but did not participate in adaptive function evaluation at ≥1 year post-HSCT, greater effects of cALD disease were evident on baseline

Table 1. Baseline MRI severity and neurocognitive test scores for all patients with cALD ($n = 137$) who underwent HSCT at University of Minnesota prior to April 2016.

	Patients who were deceased by 1 year post-HSCT ($n = 31$)	HSCT survivors lost to follow-up ($n = 41$)	HSCT survivors with 1+ year follow-up ($n = 65$)
	Mean (SD)	Mean (SD)	Mean (SD)
MRI Severity Score (0–34)	11.88 (4.47)	10.26 (4.65)	7.52 (5.02)
Neurocognitive measures[1]			
Wechsler scales			
Verbal comprehension	88.85 (17.82)	89.63 (16.17)	94.98 (14.01)
Perceptual reasoning	72.88 (26.57)	80.78 (18.03)	91.65 (18.42)
Working memory	82.04 (16.40)	86.87 (11.43)	88.53 (13.82)
Processing speed	65.08 (16.33)	72.71 (18.53)	83.48 (19.33)
Purdue pegboard			
Fine motor dexterity	61.98 (25.02)	66.10 (26.38)	75.76 (24.54)
Beery-Buktenica VMI			
Visual-motor integration	78.65 (16.87)	80.97 (17.12)	85.45 (15.38)

[1]Neurocognitive measures are represented in Standard Scores, with normative population mean of 100 and SD of 15.

evaluation than among the survivors who received follow-up neurocognitive evaluations.

For the 65 surviving patients who comprised the study cohort, we examined pre-HSCT neurocognitive measures, transplant characteristics, and adaptive behavior outcomes relative to baseline MRI severity score (standard vs. higher risk) and in aggregate (Table 2). A linear regression model to predict long-term functioning as measured by the VABS-ABC score was performed using R version 3.0.2.[23] Eleven pre-specified independent variables were considered and retained in the final model. One additional variable, VABS version (I or II), was not expected to be predictive, but we included it in a second model to verify that the two versions had similar mean scores, which was confirmed (partial $R^2 = 0.01$). Five of the pre-transplant neurocognitive tests had some missing values (3–15%) which were assumed to be missing at random. These were imputed using predictive mean matching.[24] The primary analysis was performed using multiple imputation with the R rms[25] and Hmisc[26] packages. Final estimates were pooled across five imputed data sets and standard errors adjusted for imputation.

A linear regression model was fit for 11 predictors. Pre-transplant MRI severity and years from HSCT to VABS assessment were allowed to have non-linear effects, using three-knot restricted cubic splines. However, the

Table 2. Study cohort characteristics.

	Full cohort (n = 65)	MRI severity <10 "standard risk" (n = 42)	MRI severity ≥ 10 "higher risk" (n = 23)
Pre-HSCT baseline variables			
	Mean (SD)	**Mean (SD)**	**Mean (SD)**
MRI Severity Score (0–34)	7.52 (5.02)	4.36 (2.68)	13.28 (2.44)
Neurocognitive measures[1]			
Wechsler scales			
Verbal comprehension	94.98 (14.01)	97.57 (14.04)	89.81 (12.74)
Perceptual reasoning	91.65 (18.42)	98.93 (16.45)	78.35 (14.02)
Working memory	88.53 (13.82)	91.27 (14.75)	84.41 (11.39)
Processing speed	83.48 (19.33)	91.97 (17.11)	67.71 (11.99)
Purdue pegboard			
Fine motor dexterity	75.76 (24.54)	88.24 (16.83)	53.08 (19.69)
Beery-Buktenica VMI			
Visual-motor integration	85.45 (15.38)	90.23 (13.83)	75.90 (14.07)
Treatment variables			
	Mean (SD)	**Mean (SD)**	**Mean (SD)**
Age at transplant, years	8.51 (2.51)	7.96 (2.63)	9.50 (1.95)
	N (%)	**N (%)**	**N (%)**
Graft source			
Bone marrow	37 (57%)	26 (62%)	11 (48%)
Umbilical cord blood	27 (42%)	15 (36%)	12 (52%)
Peripheral blood	1 (2%)	1 (2%)	–
Total body irradiation	14 (22%)	9 (21%)	5 (22%)
Post-HSCT adaptive behavior assessment			
	N (%)	**N (%)**	**N (%)**
VABS version I	11 (17%)	10 (24%)	1 (4%)
VABS version II	54 (83%)	32 (76%)	22 (96%)
	Mean (SD)	**Mean (SD)**	**Mean (SD)**
Years since transplant	4.55 (4.44)	4.59 (3.91)	4.46 (5.36)
VABS sub-domain scores[1]			
Communication	73.83 (24.85)	80.19 (23.19)	62.22 (24.00)
Daily living skills	76.30 (28.92)	87.90 (26.29)	55.61 (20.98)
Socialization	77.85 (24.61)	84.76 (22.26)	65.22 (24.10)
VABS total[1]			
Adaptive behavior composite	74.59 (25.61)	83.00 (23.54)	59.22 (22.20)

[1]Neurocognitive and adaptive behavior measures are represented in Standard Scores, with normative population mean of 100 and SD of 15.

non-linear effects were negligible. Because the number of variables was high relative to the number of observations, penalized maximum likelihood estimation was used to reduce overfitting. This algorithm shrinks (penalizes) large coefficients toward zero, resulting in estimates that are more likely to be close to the true parameter values.[27] Coefficient estimates and predicted values for individual patients are presented based on this pre-specified, penalized model.

Results

Adaptive outcomes

Caregiver ratings of long-term adaptive function were obtained at an average of 4.5 years (SD 4.4, range: 1.0–24.1 years) after transplant. Mean chronological age at this follow-up was 13.1 years (SD 5.0). Among this cohort of HSCT survivors, 22 patients (34%) were rated as having no impairment in adaptive functioning based on the VABS-ABC, 16 patients (25%) scored below average, and 27 patients (42%) were severely impaired.

Length of time of the VABS rating since transplant was similar across the standard risk and higher risk cALD subgroups (Table 2). Consistent with previous research,[9] patients with standard risk cALD performed better on neurocognitive testing at the pre-HSCT evaluation than higher risk patients. Individuals who had standard risk status before HSCT also demonstrated less impaired overall adaptive functioning in the years after transplant. When comparing across domains, patients in the higher risk group showed more impaired long-term functioning in the Daily Living Skills domain, which reflects ability to complete tasks to care for self and others in the home

Table 3. Patients with cALD in the "higher risk" category (pre-transplant MRI severity score ≥10) who were able to independently complete each activity of daily living on a consistent basis at most recent follow-up (*n* = 23; mean age 14.0 years, SD, 5.6 years).

Activity	*n* (%)
Communication/literacy	
Tells about experiences in simple sentences	16 (70)
Follows simple instructions	14 (61)
(e.g., "bring me the book," "close the door")	
Reads at least 10 words	9 (39)
Prints or writes own first and last name	8 (35)
Daily living skills	
Uses toilet independently	15 (65)
Drinks from cup or glass without spilling	14 (61)
Walks without wheelchair or assistance	11 (48)
Bathes/showers without assistance	8 (35)
Makes telephone calls to others	6 (26)
Socialization	
Shows affection toward familiar people	19 (83)
Meets with friends regularly	5 (22)
Initiates conversation on topics of interest to others	2 (9)

and community settings, relative to Communication and Socialization domains. In contrast, the Daily Living Skills domain was relatively strong in the post-HSCT period among those who underwent HCST with standard risk cALD.

In order to aid in prognostic counseling when considering HSCT for patients with higher risk cALD, outcomes with regard to post-transplant function for several benchmark life activities are presented in Table 3. Outcomes for this subgroup were obtained at an average age of 14.0 years (SD, 5.6; range: 9.4–35.9 years). Approximately one-third of patients with higher risk status who survived transplant had difficulty with basic communication (comprehending simple instructions and expressing themselves verbally), and almost two-thirds were unable to complete basic reading or writing tasks. About half of these boys and young men had significant mobility limitations (i.e., were unable to walk unassisted), and many needed assistance for activities such as toileting and bathing/showering. The majority of survivors of HSCT with higher risk cALD were able to show affection toward others, but most individuals did not consistently engage in social activities such as regularly meeting with friends, making telephone calls, and initiating conversations about shared interests.

Predictors of adaptive function

Radiological, neuropsychological, and treatment-related variables all demonstrated a reliable association with adaptive function outcomes of transplant survivors (Table 4). Performance on the Purdue Pegboard Test at

pre-transplant evaluation predicted the largest amount of variance in functional outcomes. Based on the penalized model, a decrease of four-points on this measure of fine motor dexterity prior to transplant predicted a one-point loss in overall adaptive function (VABS-ABC) after transplant, keeping other variables constant. MRI severity scores were a similarly robust predictor of VABS outcomes. Each 1-unit increase in pre-transplant MRI severity score estimated a decline of one-point on the VABS-ABC. The combined influence of these two predictors on VABS outcomes is depicted in Figure 1. Notably, patients with MRI severity scores >11 or Purdue Pegboard Scores <70 invariably had below average or severely impaired long-term adaptive function outcomes.

Additional variables predicted small amounts of variability within the model. The binary treatment-related variables had a reliable association with outcomes, with use of TBI predicting a 9.41 point drop in VABS-ABC scores and umbilical cord blood being associated with a 6.25 point increase in VABS outcomes, holding other variables constant. Other pre-HSCT neurocognitive measures, including tasks of visual reasoning and visual-motor integration (VMI) predicted small amounts of variability in the functional outcomes of surviving patients.

Table 4. Linear regression model predicting post-transplant parent/caregiver ratings on the Vineland Adaptive Behavior Composite among 65 surviving patients of HSCT for cALD.

Variable	Coefficient	Lower 95% CL	Upper 95% CL
Purdue pegboard test	0.25	0.05	0.44
Pre-transplant MRI severity score	−1.00	−1.95	−0.06
Total body irradiation (0 = no; 1 = yes)	−9.41	−18.67	−0.15
Graft source (0 = marrow; 1 = UCB)	6.25	−1.70	14.20
Perceptual reasoning index (Wechsler)	0.18	−0.09	0.44
Beery VMI	0.18	−0.14	0.49
Age at transplant (years)	−0.52	−2.15	1.12
Working memory (Wechsler)	−0.10	−0.41	0.22
Processing speed (Wechsler)	0.03	−0.22	0.29
Years since transplant	0.02	−0.93	0.97
Verbal comprehension index (Wechsler)	0.02	−0.28	0.32

Coefficients represent the expected absolute change in long-term Vineland composite score associated with a one unit increase in the given variable. Variables are sorted by decreasing partial R^2, that is, the proportion of outcome variance explained by each variable, accounting for all other variables in the model. The intercept of this model is 40, with the reference values being 0 for all continuous variables and no TBI or UCB. Adjusted R^2 is 0.48, meaning this set of variables explains approximately half the outcome variance. CL, confidence limit.

Post-HSCT Vineland Adaptive Behavior Outcomes

- ● No impairment (> 85)
- ▲ Below average function (71-85)
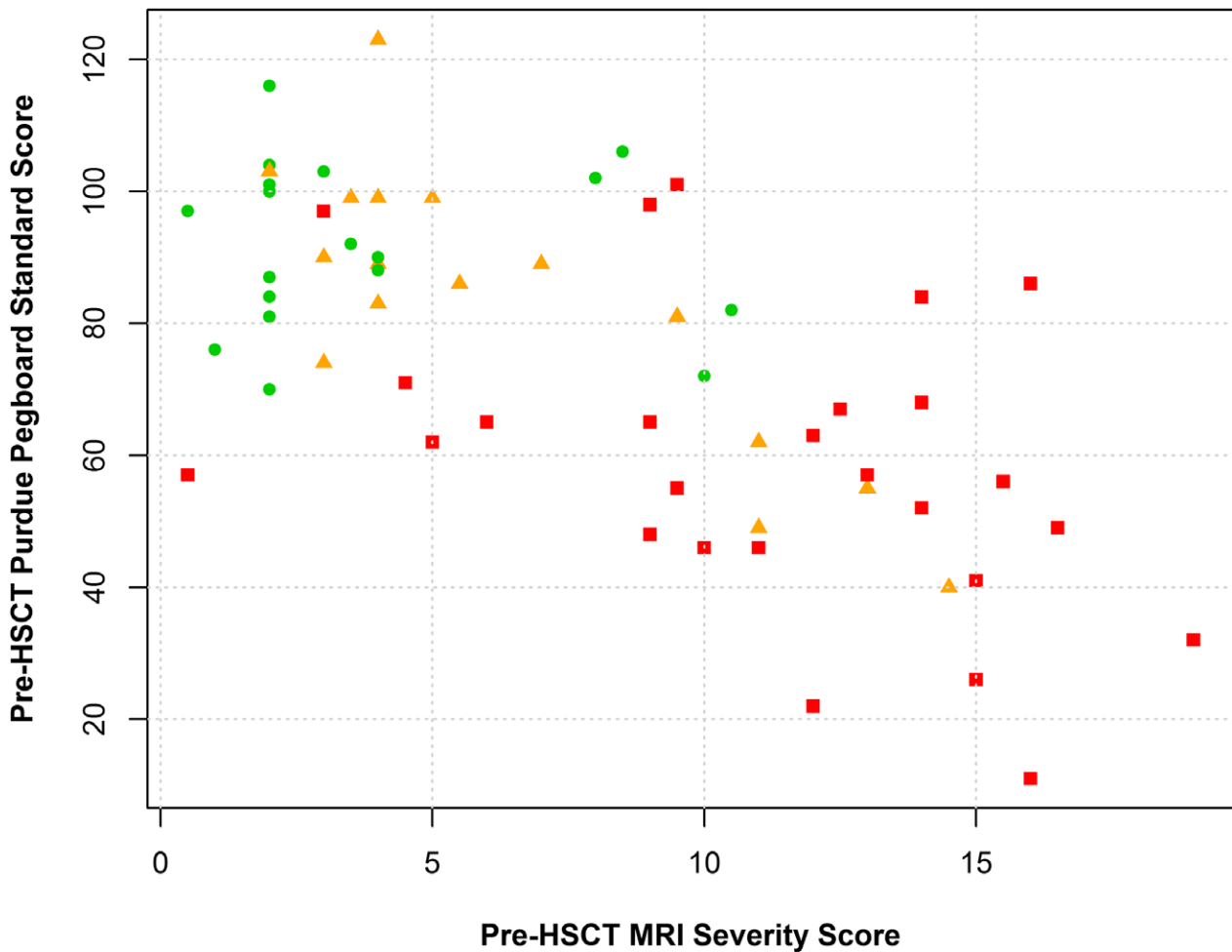- ■ Severely impaired (≤ 70)

Figure 1. Adaptive behavior outcomes in survivors of hematopoietic stem cell transplantation for cALD, plotted according to pre-transplant MRI severity and pre-transplant evaluation of fine motor speed and dexterity.

Table 5 presents predicted adaptive functioning scores based on several pre-specified hypothetical combinations of the two strongest predictors, MRI severity score and Purdue Pegboard Test scores.

Discussion

A magnitude of evidence points to the success of HSCT as a life-saving procedure that can prevent rapid cognitive deterioration among boys with cALD in the early stages of cerebral disease. By comparison, clinical decision-making and prognostic counseling for boys in more advanced stages of disease remains a greater challenge, as the relative benefits and risks of transplantation can be less clear. This study identifies potential parameters that can be used to predict long-term functional outcomes among transplant survivors. Previous studies found that post-transplant neurological and neurocognitive outcomes in boys with cALD were associated with key variables evaluated in the pre-transplant assessment. In particular, the association between MRI severity with disease progression and neurological/neurocognitive outcomes is

Table 5. Predicted adaptive functioning outcomes for a set of hypothetical patients with a pre-selected series of pre-transplant MRI severity and Purdue Pegboard Test scores.

Pre-HSCT MRI severity score	Pre-HSCT purdue pegboard test score	Predicted Post-HSCT vineland score	Lower 80% PL	Upper 80% PL
2	100	87	62	112
2	70	80	55	104
2	55	76[1]	51	101
5	100	84	59	108
5	70	76	52	101
5	55	73[1]	48	98
10	100	78	54	103
10	70	71	46	96
10	55	67	43	92
15	100	73[1]	47	98
15	70	65	40	90
15	55	62	36	87

The table shows model-estimated predicted values for a pre-selected series of scores. Other variables were set to their median value, and no TBI or UCB. PL, prediction limit.

[1]These combinations of MRI severity and purdue pegboard test scores were not common; therefore model fit is unknown for these predicted outcomes.

well-established.[10,28,29] In addition, previous studies reported that boys scoring <80 on the Wechsler Performance IQ scale (a subscale available on older versions of this measure, which assessed visual reasoning and processing speed) at the time of HSCT were at greater risk for worsening neurological status after transplant.[7,8] These reports underscored the importance of initiating intervention as early as possible upon detection of active cerebral disease.

This study builds on previous research by examining the relative influence of several different neurocognitive tests, as well as MRI severity and treatment variables, in terms of predicting long-term adaptive functional outcomes. Relative to earlier studies, the current analysis found that subdomains of the Wechsler scales predicted only a small amount of variance in long-term functional (VABS-ABC) outcomes when controlling for other neurocognitive and treatment variables. In our model, the strongest predictors of post-HSCT adaptive functioning were a boy's MRI severity score prior to transplant and his performance on a test of fine motor dexterity (Purdue Pegboard Test). These two predictors had sizeable independent associations with likelihood of impaired long-term adaptive functioning (Fig 1). The Purdue Pegboard Test requires a combination of visual acuity, rapid processing, and fine motor accuracy. Thus, individuals who are experiencing progressive cortical vision loss, slowing of cognitive functioning, and/or

significant motor impairment would be expected to score poorly on this test. Given that these capacities are susceptible to cALD disease progression, this test may therefore be a sensitive marker of neural integrity in untreated boys with cALD. Additional neuropsychological measures with visual or motor components, including visual-spatial reasoning tests from the Wechsler scales and visual-motor integration (VMI) abilities, also predicted small amounts of variance in the model. Thus, our results highlight the potentially important predictive role of baseline neurocognitive testing to help guide transplant centers in estimating likely adaptive functioning outcomes for patients with cALD.

Consistent with studies showing an association between the use of radiation within the conditioning regimen (a procedure which is not commonly used in modern transplant protocols for nonmalignant disease indications), and neurocognitive outcome,[9,30,31] our study found that the use of TBI also predicted greater impairments in adaptive functioning after transplant. A small association between UCB grafts and higher VABS-ABC scores was observed. The use of cryopreserved UCB, an immediately-available graft source, has grown in modern HSCT. Thus, this association may reflect the effects of more current and improved transplant care and regimens, as well as more rapid time to transplantation among individuals receiving UCB grafts.

Research investigating "real-world" functioning and life quality among transplant survivors with cALD has been notably lacking.[11,12] Measures of adaptive functioning, such as the VABS, quantify key attributes of how a person interacts with their world and have demonstrated associations with life satisfaction in a variety of clinical populations.[32,33] Adaptive function is also an important correlate of academic achievement and employment/income independence.[34,35] Given this tangible significance for patients and families, adaptive functioning is of great importance to medical teams and caregivers facing difficult treatment-related decisions. These considerations are often especially difficult for boys in the "higher risk" cALD category, as these patients are over-represented among the patients who die of HSCT complications and those who are unlikely to participate in follow-up evaluation (Table 1). Our data indicate that boys with higher risk cALD who do survive HSCT are at great risk for severe, permanent impairments that will impact quality of life. Analysis of the VABS outcomes for the 23 boys with higher risk cALD indicates that at an average age of 14 years (and, for most patients, several years after HSCT), over half of transplant survivors were unable to ambulate independently, read 10 words, write their name, make phone calls, or bathe without assistance. Few were meeting with friends regularly or initiating reciprocal conversations, thus limiting their capacity for

meaningful relationships beyond family members. Finally, even for patients with standard risk disease, our model predicts greater long-term functional impairment with increasing radiographic disease and declining neuromotor ability (Table 5).

Limitations of this study include the lack of data pertaining to the perspectives of the patients themselves. We employed a well-validated parent/caregiver rating scale to assess function, since self-report measures can have limited feasibility and validity when assessing patients with significant cognitive and sensory impairments. Sensory impairments will also impact scores on caregiver report measures of daily function, as adapting to loss of vision or auditory processing abilities takes time (i.e., a patient may eventually learn new modes of adaptation such as braille or sign, but this process can take many years). Furthermore, although several predictors were reliably associated with long-term functional outcomes, about half of the variance in these outcomes remains unexplained by this model. Due to the wide interval of years during which our data were collected (1994–2017), a variety of advances in medical treatment for patients undergoing HSCT (e.g., better antimicrobials; better donor options; improved prevention, recognition and treatment of graft-versus-host disease; increased ability to precisely deliver chemotherapy with individual-patient pharmacokinetic monitoring and dose alteration) may have contributed to variation in outcomes among patients in our cohort. Finally, even with improved ability to predict long-term outcomes, the acceptability of various levels of adaptive impairment to different families is likely to be wide-ranging.

Notably, the length of time between HSCT and the post-HSCT assessment was not predictive of outcomes when accounting for the baseline assessments and treatment-related variables. This finding suggests that although some patients' abilities may improve over time as they explore new modes of adaptation, other patients may experience a worsening of function relative to the general population. Rather than reflecting a true "loss" of skills, this worsening of functioning may indicate a failure to gain new skills at a similar rate as peers. Generally, our data suggest that the most dramatic changes in adaptive skills may be occurring prior to transplantation or within the first year after HSCT, and are highly related to the severity of cALD disease, as measured based on both observable white matter changes (MRI) and functional changes (neurocognitive testing). Given that we were only able to measure adaptive outcomes among the engrafted survivors of HSCT, combined with established literature showing better survival rates for patients with less advanced disease, our estimates of the impact of these variables may underestimate the influence of the pre-HSCT variables on patient adaptive function. Indeed, data from our baseline evaluations confirm that the patients who died were more likely to have presented for treatment with more advanced cALD. Scores on the relevant neurocognitive scales also tended to reflect worse pre-HSCT functioning in surviving patients for whom follow-up adaptive outcomes were unavailable.

Conclusion

As a previous analysis has associated superior longitudinal cognition with transplantation that is performed in the very early stages of cALD,[9] so does this study predict incrementally better long-term adaptive functioning with treatment in an earlier disease state. Recently, ALD was added to the recommended uniform screening panel for public newborn screening by the US Secretary of Health and Human Services, and a growing number of states are participating. This study's findings reinforce the importance of close monitoring of all boys with identified ALD, with urgent and expeditious HSCT upon detection of cALD. For regions of the world where newborn screening is not yet available, boys will continue to present for evaluation in later stages of disease. The current data have implications for practitioners seeking to estimate risk for functional impairment after transplant. They indicate that in addition to MRI severity, neurocognitive tests involving fine motor function, visual perception, and/or visual reasoning may aid in prognostic counseling regarding daily life functioning after transplant.

Acknowledgments

Author Contributions

E.I.P., E.M., and W.M. conceptualized the study and developed the study design with R.S. All authors participated in the acquisition and analysis of data. The initial draft of the manuscript and figures were completed by E.I.P., R.S. and W.M., and was critically reviewed and edited by all authors.

Conflicts of Interest

Nothing to report.

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