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Neurocognitive Trajectory of Boys Who Received a Hematopoietic Stem Cell Transplant at an Early Stage of Childhood Cerebral Adrenoleukodystrophy

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IMPORTANCE Untreated childhood cerebral adrenoleukodystrophy (cALD) is a fatal disease associated with progressive cerebral demyelination and rapid, devastating neurologic decline. The standard of care to enhance long-term survival and stabilize cerebral disease is a hematopoietic stem cell transplant (HSCT). Neurologic outcomes are better when HSCT occurs at an earlier stage of cALD, yet there is limited understanding of the neurocognitive trajectory of patients who undergo HSCT.

OBJECTIVES To characterize neurocognitive outcomes of boys with cALD and early-stage cerebral disease who were treated with an allogeneic HSCT and to identify disease- and treatment-related factors associated with long-term functioning.

DESIGN, SETTING, AND PARTICIPANTS Baseline and follow-up neurocognitive test performance was analyzed for all boys with cALD who received an HSCT at the University of Minnesota between January 1, 1991, and October 20, 2014, and who had a pretransplant magnetic resonance imaging (MRI) severity score of less than 10 (scale range, 0-34; higher scores indicate greater severity).

MAIN OUTCOMES AND MEASURES Longitudinal neurocognitive test performance in 4 domains (verbal comprehension, perceptual [visual] reasoning, working memory, and processing speed) were the primary outcome measures. Secondary analysis at the most recent evaluation also included measures of sustained attention, verbal memory, visual-motor integration, and fine motor function.

RESULTS Among the 62 boys in this study (mean [SD] age at transplant, 8.37 [2.80] years; range, 4-16 years), there was a significant association of pretransplant MRI severity and baseline verbal comprehension (r = −0.340; P = .008), perceptual reasoning (r = −0.419; P = .001), and processing speed (r = −0.285; P = .03) scores. Higher pretransplant MRI severity scores were also associated with a steeper decline in neurocognitive functioning during the 5-year follow-up period. Twenty-two of 33 patients (67%) with available long-term follow-up neurocognitive testing had severe impairment in at least 1 neurocognitive domain at the most recent evaluation.

CONCLUSIONS AND RELEVANCE Boys with cALD who have greater than minimal cerebral disease detected on MRI scans at the time of an HSCT are at risk for severe, persistent neurocognitive deficits. These findings motivate further exploration of methods of detecting cerebral disease prior to development of lesions observable on MRI scans, an endeavor that may be facilitated by newborn screening for adrenoleukodystrophy. These findings may serve a benchmark role in evaluating the efficacy of novel interventions for cALD.

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Supplemental content

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Adrenoleukodystrophy (ALD) is an X-linked disorder caused by alterations in the *ABCD1* gene (OMIM 300371). Adrenoleukodystrophy occurs in approximately 1 in 20 000 males[1] and primarily affects the adrenal cortex and central nervous system. The most severe form, childhood cerebral ALD (cALD), affects about one-third of boys with ALD and is characterized by progressive inflammatory demyelination, causing deterioration to a vegetative state or death within a few years of clinical onset. Boys with cALD may initially present with attention and impulse control problems, behavioral and personality changes, visual impairment, auditory processing problems, and/or seizures.[2] The disease can be detected via radiography prior to acute clinical symptoms; therefore, it is recommended that boys with known ALD (identified via an affected family member or other diagnostic or screening method) undergo routine surveillance with magnetic resonance imaging (MRI).[3,4] Despite significant efforts, no current method is able to determine which boys with ALD will develop childhood cerebral disease, and investigations have failed to detect any reliable correlation between genotype and phenotype.[5]

A hematopoietic stem cell transplant (HSCT) is the only treatment documented to enhance long-term survival for boys with cALD.[6,7] Among boys who undergo an HSCT during early-stage cerebral disease (henceforth termed *standard risk cALD* and defined as having a pretransplant MRI severity score of <10), neurologic and neurocognitive outcomes have been described as generally favorable.[8-10] However, our collective clinical experience indicated that some patients with standard risk cALD have significant, persistent learning and academic challenges, difficulties with reasoning and judgment, and limited functional independence in the years following HSCT. Equipped with the largest single-institution cohort of patients with cALD who underwent a transplant, we sought to delineate the neurocognitive trajectory of patients who were treated with an HSCT at an early stage of disease. The goals of our study included identifying disease- and treatment-associated risk factors for neurocognitive impairment, providing an updated benchmark description of outcomes of standard risk cALD after HSCT, and informing transplant-related and prognostic counseling.

Key Points

Question What factors are associated with the neurocognitive trajectory of patients with childhood cerebral adrenoleukodystrophy (cALD) undergoing a hematopoietic stem cell transplant in early-stage cerebral disease?

Findings In this cohort study of neurocognitive assessments from 62 boys with cALD, higher baseline magnetic resonance imaging (MRI) severity scores were associated with greater neurocognitive decline after a transplant. Despite expedient intervention after detection of early cerebral disease on MRI scans, most boys with cALD exhibited clinically significant neurocognitive deficits at long-term follow-up.

Meaning Patients with cALD who have greater than minimal evidence of cerebral disease on MRI scans at the time of a hematopoietic stem cell transplant are at risk for severe, persistent neurocognitive impairment.

Methods

Study Population

A total of 139 patients with cALD who underwent an allogeneic HSCT at the University of Minnesota between January 1, 1991, and October 20, 2014, were identified after query of the prospectively maintained University of Minnesota Blood and Marrow Transplant Database. The pretransplant brain MRI scans for all 139 patients were reviewed by a board-certified neuroradiologist (D.N.) and scored using the scoring method of Loes et al,[11] a 34-point severity scale in which higher scores represent more extensive disease. A total of 65 patients met the study inclusion criterion of a pretransplant MRI severity score less than 10 (71 patients had an MRI severity score ≥10, and 3 had insufficient MRI data for determining the severity score). Within this group, 63 patients underwent neuropsychological testing prior to transplant. Data were excluded for 1 patient with preexisting intellectual disability not associated with cALD. The remaining patients constituted a cohort of 62 patients with standard risk cALD who had participated in neuropsychological assessment. A diagram depicting the selection of the study population is found in eFigure 1 in the Supplement. Neuropsychological evaluations, both at baseline and following HSCT, were performed following written parental consent for participation in transplant studies that were approved by the University of Minnesota Institutional Review Board.

MRI Pattern

Forty-eight of the 62 patients (77%) included in our analyses had the most common parietal-occipital dominant pattern of cerebral disease; 8 patients (13%) had a frontal dominant pattern; the remaining 6 patients (10%) had equal disease in the parieto-occipital and frontal white matter or another atypical variant.

Hematopoietic Stem Cell Transplant

Patients underwent a transplant at a mean (SD) age of 8.37 (2.80) years (range, 4.0-16.1 years). All boys were administered myeloablative transplant conditioning. Although all HSCTs were performed within a single institution, exact regimens varied across time. Forty-six patients (74%) received busulfan-based conditioning without radiotherapy; 16 patients (26%) underwent high-dose total-body irradiation (TBI)-based regimens. Two patients (3%) received a second transplant after a failed initial engraftment; in both patients, nonmyeloablative regimens were administered for the subsequent HSCT. Donor allograft selection followed existing institutional protocols. Thirty-seven patients (60%) received bone marrow grafts from related or unrelated donors, whereas 24 patients (39%) received umbilical cord blood grafts from unrelated individuals. One patient received a peripheral blood stem cell graft from an unrelated donor. Supportive care regimens, including prophylaxis for graft-vs-host disease,

Table 1. Neurocognitive Outcome Measures

Domain(s)	Score	Measure
Verbal comprehension; perceptual (visual) reasoning; working memory; processing speed	Standard score	Wechsler Preschool and Primary Scale of Intelligence (various editions)[12-14]; Wechsler Intelligence Scale for Children (various editions)[15-18]; Wechsler Adult Intelligence Scale (various editions)[19,20]
Verbal learning and memory	T score (composite)	California Verbal Learning Test, Children's version[21]
Sustained attention	Standard score (omissions, variability)	Test of Variables of Attention[22]
Fine motor dexterity	Standard score (3-trial mean)	Purdue Pegboard Test[23]
Visual-motor ability	Standard score	Beery-Buktenica Developmental Test of Visual-Motor Integration[24]

antimicrobial therapy, and blood product transfusion support, were per existing institutional guidelines.

Neuropsychological Evaluation

Patients received longitudinal follow-up by the neuropsychology service as part of the standard pretransplant and posttransplant protocol for cALD. Annual evaluations typically occurred within 1 to 2 months of the HSCT anniversary. Composite scores in the following 4 domains were obtained from age-appropriate versions of the Wechsler Intelligence Scales: verbal comprehension, perceptual (visual) reasoning, working memory, and processing speed. These domains target more specific circuitry than a single global cognitive measure (eg, full-scale IQ) and are thus better positioned to detect emergence of selective neurocognitive deficits in patients with cALD. Prorating procedures were used to harmonize these 4 constructs across multiple editions of the Wechsler scales (eAppendix in the Supplement). Consistent with previously published research studying outcomes of cALD,[6] patients who could not complete an attempted neurocognitive measure owing to disability from disease progression (eg, visual loss, severe auditory or speech impairment) were assigned the lowest possible standard score for that measure. Verbal comprehension domain scores were excluded for 3 children who did not speak English; other subscales for these same patients were administered via interpreter.

To examine long-term outcomes across a wider range of functions, the most recent neurocognitive data from all patients assessed at a 2-year posttransplant evaluation or later (n = 33) were analyzed for the 4 aforementioned domains as well as for verbal learning and memory, sustained attention, fine motor dexterity, and visual-motor integration (**Table 1**).[12-24] Level of impairment was defined according to the following rubric: scores above or within 1 SD of the population mean (no impairment), between -1 SD and -2 SD (below average), and less than or equal to -2 SD (severe impairment).

Statistical Analysis

Pearson correlation coefficients were calculated to describe the association between pretransplant MRI severity scores and baseline neurocognitive test performance. To test the hypothesis that the trajectory of neurocognitive abilities would differ based on baseline disease- and treatment-associated variables, a multivariable linear mixed model was fit separately for each of the 4 primary neurocognitive domains. All assessments administered just prior to HSCT through 5 years after HSCT were included as dependent variables. Independent variables were prespecified and included pretransplant MRI severity score, age at HSCT, time (in years) relative to HSCT, and the interaction of time with MRI severity, age at HSCT, and treatment (TBI, bone marrow graft without TBI, or umbilical cord blood graft without TBI). Only an interaction effect, but not a main effect, was included for treatment since treatment is not associated with baseline score. Random participant intercept and slope effects were included to account for the correlation of repeated measurements from the same patient, with variance components covariance structure. All tests were 2-tailed. Analysis was performed with SAS, version 9.3 (SAS Institute Inc).

Results

Baseline

At baseline evaluation, neurocognitive functioning was better in patients with lower MRI severity scores (eFigure 2 in the Supplement). There was a significant association of pretransplant MRI severity and baseline verbal comprehension (r = -0.340; P = .008), perceptual reasoning (r = -0.419; P = .001), and processing speed (r = -0.285; P = .03) scores.

Neurocognitive Trajectory

Linear mixed models fitted for the 4 neurocognitive domains were constructed using 812 observations from 62 patients. Patients with higher pretransplant MRI severity scores performed more poorly on neurocognitive measures during the 5-year period and showed a more dramatic decline over time in verbal comprehension, perceptual reasoning, and processing speed abilities (**Table 2**). Several patients who received TBI demonstrated especially severe declines, particularly in the domain of working memory, although this group size was small (n = 16) and thus confidence intervals are wide for the longitudinal effect of TBI. There were no conclusive trends regarding the effect of age at time of HSCT, but older patients remained slightly more stable on average after HSCT.

For demonstration purposes, predicted values were estimated based on this model for a typical 8-year-old boy with cALD who received a bone marrow graft following a TBI-sparing conditioning regimen (**Table 3**). For a hypothetical boy with an MRI severity score of 2 who underwent a transplant, the predicted scores during the 5-year period remain relatively stable across all cognitive domains, ranging from no change in standard score to a loss of 9 points. In contrast, if the hypothetical boy had an MRI severity score of 7, the predicted scores suggest a high risk for significant long-term neurocognitive deficits. In this scenario, performance was estimated to worsen in all domains by 5 years after transplant, ranging from an average decrease of 7 standard score points (working memory) to a decrease of 39 standard score points (processing speed). Although neurocognitive scores of pa-

Table 2. Coefficients From Linear Mixed Models to Estimate Neurocognitive Test Scores in 4 Domains[a]

Variable	Coefficient (95% CI)			
	Verbal Comprehension	Perceptual Reasoning	Working Memory	Processing Speed
Intercept	109.9 (94.7 to 125.2)	117.2 (102.7 to 131.7)	97.2 (83.0 to 111.4)	104.4 (89.9 to 119.0)
Time	−2.0 (−7.3 to 3.4)	−5.9 (−13.7 to 2.0)	−1.1 (−8.1 to 5.9)	−4.0 (−13.0 to 4.9)
Pre-HSCT MRI severity	−1.9 (−3.5 to −0.2)	−2.7 (−4.2 to −1.1)	−1.6 (−3.1 to −0.1)	−1.9 (−3.5 to −0.4)
Pre-HSCT MRI severity × time	−0.7 (−1.4 to −0.1)	−1.0 (−1.9 to −0.2)	−0.2 (−1.0 to 0.5)	−1.2 (−2.2 to −0.2)
Age	−0.8 (−2.6 to 0.9)	−1.3 (−2.8 to 0.3)	0.0 (−1.5 to 1.6)	−0.8 (−2.4 to 0.8)
Age × time	0.3 (−0.4 to 0.9)	1.0 (0.1 to 1.9)	0.2 (−0.6 to 0.9)	0.6 (−0.5 to 1.6)
TBI × time	−1.4 (−5.4 to 2.7)	−5.5 (−11.6 to 0.6)	−6.1 (−11.0 to −1.3)	−2.1 (−8.7 to 4.4)
UCB × time	1.8 (−1.7 to 5.2)	0.2 (−4.8 to 5.3)	−0.3 (−4.8 to 4.2)	3.4 (−2.1 to 8.9)

Abbreviations: HSCT, hematopoietic stem cell transplant; MRI, magnetic resonance imaging; TBI, total-body irradiation; UCB, umbilical cord blood.

[a] Reference group is bone marrow graft without TBI and all continuous variables set equal to zero. Coefficients estimate change in expected outcome per unit of each continuous variable. Time is years since HSCT.

Table 3. Predicted Values on Neurocognitive Testing Based on Model Coefficients for a Hypothetical 8-Year-Old Boy With Cerebral Adrenoleukodystrophy Undergoing HSCT Without TBI

Time Since HSCT, y	Predicted Score (80% Prediction Limit)			
	Verbal Comprehension	Perceptual Reasoning	Working Memory	Processing Speed
Pre-HSCT MRI Score of 2				
0	99 (78-121)	102 (81-122)	94 (76-112)	95 (75-114)
1	98 (76-120)	102 (80-124)	94 (75-113)	93 (72-113)[a]
5	93 (61-125)	102 (58-146)	93 (62-124)	86 (45-126)
Pre-HSCT MRI Score of 7				
0	90 (68-112)	88 (68-109)	86 (68-104)	85 (65-104)
1	85 (63-107)	83 (61-105)	85 (66-103)	77 (56-98)
5	65 (32-97)	63 (18-107)	79 (47-110)	46 (5-87)

Abbreviations: HSCT, hematopoietic stem cell transplant; MRI, magnetic resonance imaging; TBI, total-body irradiation.

[a] Example calculation to derive the estimated values from linear mixed model coefficients: estimated processing speed score 1 year after HSCT for an 8-year-old boy with an MRI severity score of 2 who received bone marrow graft without TBI is 104.4 − 4.0 × 1 − 1.9 × 2 − 1.2 × 2 × 1 − 0.8 × 8 + 0.6 × 8 × 1 = 93.

tients with higher pretransplant MRI severity scores decreased more, on average, there was substantial variation among individual trajectories, as evidenced by the wide prediction intervals for each measure.

Figure 1 depicts the individual neurocognitive trajectories of boys with cALD with lower (0.5-4.0; median split) and higher (4.5-9.5) pretransplant MRI severity scores in the domain of processing speed. This domain, which reflects motivational and fine motor demands as well as rapid processing, was particularly vulnerable to baseline cALD MRI severity score and treatment effects based on our models. Individual trajectories for the other 3 neurocognitive domains are available in eFigure 3 in the Supplement.

Long-term Neurocognitive Function

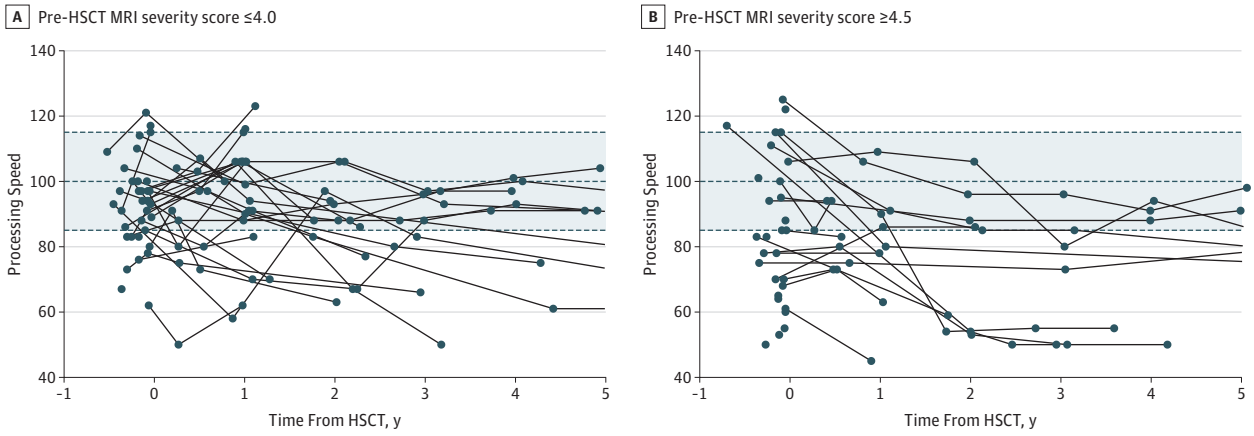
Long-term follow-up results of neurocognitive testing were available for 33 patients. Data were obtained from the patients' most recent evaluation at a median of 4.2 years (range, 1.8-25.4 years) after transplant. When considering frequency of neurocognitive impairment among the sample, 22 of the boys (67%) had a severe impairment in at least 1 domain. Nine patients (27%) demonstrated only mild impairment (below average performance) in 1 or more domains. Only 2 patients (6%) performed within or above the average range on all tasks at long-term follow-up; both of these patients had a pretransplant MRI severity score of 2.

At several years after transplant, patients with standard risk cALD most frequently demonstrated impairments on tests assessing processing speed, sustained attention, and visual-motor integration. In each of these domains, more than 33% of patients with standard risk cALD exhibited severe impairments at the most recent evaluation. Patients with higher pretransplant MRI severity scores had a higher frequency of severe neurocognitive impairments (**Figure 2**). Furthermore, pretransplant MRI severity scores correlated with the percentage of neurocognitive tasks (across all 8 domains) in which a patient was severely impaired (r = 0.531; P = .001), signifying more pervasive impairment. On average, patients with lower pretransplant MRI severity scores (0.5-4.0; median split) had severe impairments on 17% of the measures. In contrast, patients with higher MRI severity scores (4.5-9.5) were severely impaired with regard to nearly half (48%) of the neurocognitive tasks.

Discussion

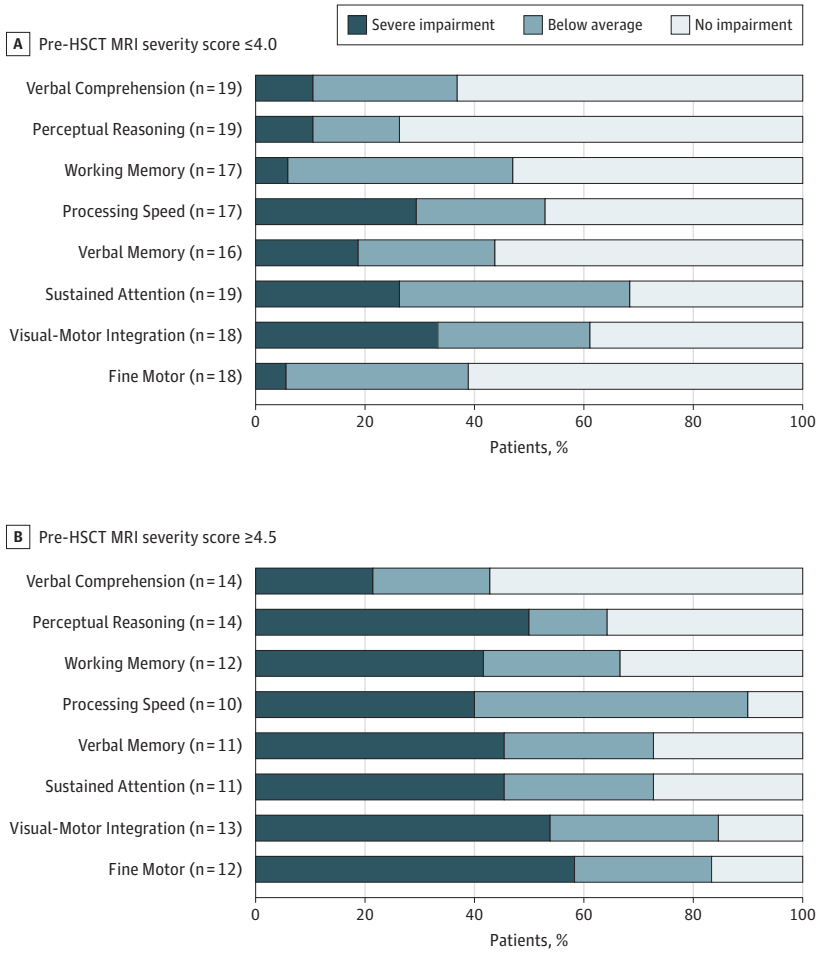
We present the first study, to our knowledge, to delineate persistent long-term neurocognitive deficits following HSCT in boys

Figure 1. Individual Neurocognitive Trajectories on a Standardized Measure of Processing Speed After Hematopoietic Stem Cell Transplant (HSCT) of 62 Patients With Childhood Cerebral Adrenoleukodystrophy



A, Patients with a pretransplant magnetic resonance imaging (MRI) severity score ≤4.0. B, Patients with a pretransplant MRI severity score ≥4.5. The shaded region depicts age-typical performance (normative mean [SD], 100 [15]). The horizontal line at 100 depicts the normative population mean, and the upper and lower limits of the shaded region represent +1 and −1 SD of the normative mean.

Figure 2. Frequency of Impairments Across 8 Neurocognitive Domains at Most Recent Follow-up of 33 Boys With Standard Risk Childhood Cerebral Adrenoleukodystrophy



A, Pre–hematopoietic stem cell transplant (HSCT) magnetic resonance imaging (MRI) severity score ≤4.0. B, Pre-HSCT MRI severity score ≥4.5.

with standard risk cALD. Our retrospective analysis of all boys with standard risk cALD who underwent a transplant at the University of Minnesota estimated the association of disease- and treatment-related factors with neurocognitive trajectory. This analysis expands on earlier reports documenting that posttransplant neurocognitive functioning is associated with the extent of pretransplant white matter disease detected by radiography[6,9] by showing a collectively high risk for neurocognitive impairment even among patients traditionally expected to have a favorable prognosis (ie, those treated with HSCT at an early stage of disease). Despite broadly satisfactory neurologic outcomes, only 1 in 3 patients in this cohort did not have a severe impairment in at least 1 of the evaluated neurocognitive domains at the most recent follow-up evaluation. Pretransplant MRI severity scores were not only associated with baseline neurocognitive functioning but were also associated with performance trajectories after transplant. Our model demonstrated a dramatic effect of pretransplant MRI severity scores on estimated 1- and 5-year neurocognitive test scores of patients with standard risk cALD. Furthermore, long-term impairments were more pervasive across domains in boys with higher pretransplant MRI severity scores. This finding implies that an HSCT or another novel intervention should be conducted urgently after detection of active cerebral disease in boys with ALD. Rapid intervention appears to be essential for preservation of neurocognitive functions.

Demyelinating disease in cALD follows a fairly predictable pattern,[25] typically originating in the splenium of the corpus callosum and spreading into contiguous parietal-occipital regions of the brain in approximately 85% of patients. In rarer cases, the initial lesion begins in the anterior portion of the corpus callosum and spreads to the frontal lobes or exhibits a balanced or atypical progression of disease. Aligned with this disease process, we observed that patients with cALD typically showed the most severe effects in neurocognitive functions that require visual perception, rapid processing, or coordination among multiple brain regions (eg, processing speed, attention, or visual-motor integration). In contrast, domains such as verbal comprehension and reasoning were more robust to brain insult, presumably because this knowledge is acquired slowly through repetition and practice and can be recalled through activation of a vast network. Nevertheless, some boys demonstrated downstream effects among even these functions over time. Although it is known that an HSCT can prevent further myelin loss,[26] our data provide little evidence that neurocognitive abilities that are lost are routinely regained after a transplant. Rather, functions compromised by the original white matter injury (eg, processing speed or attention span) may interfere with acquisition of new knowledge or development of crucial skills over time. In these patients, failure to make age-typical neurocognitive gains may result in the appearance of neurocognitive worsening.

Although longitudinal worsening in neurocognitive functioning was evident in some patients with standard risk cALD, there was wide variability in the extent of deficits and stability of function over time (Figure 1 and eFigure 3 in the Supplement). On average, adolescent patients were more stable and less likely to show rapid decline after a transplant than were boys who developed cerebral disease earlier in childhood. This finding suggests the possibility that having more fully developed white matter tracts prior to disease onset could blunt the effect of cALD. More important, for patients who did experience a significant decline in functioning during the follow-up period, neurocognitive worsening was generally not considered reflective of a continued active disease process. Among patients with standard risk cALD who underwent an uncomplicated HSCT, eventual posttransplant stabilization in the extent of white matter disease detected on MRI scans is usual.[9,10] Furthermore, the rapid deterioration into a vegetative state or death that occurs for most patients with cALD who do not undergo a transplant[10,27] occurred for only 2 patients (3%) in our cohort. Therefore, apparent neurocognitive worsening in these patients is likely better explained by the cumulative effects of treatment-related risk factors combined with the initial inflammatory demyelinating brain injury that can damage mechanisms important for amassing neurocognitive skills, leading to slower developmental progress.

The estimates of neurocognitive deficits that we report may be conservative. First, our models did not capture the extent of neurocognitive worsening in the few patients who died of complications or disease progression. Second, participation in neurocognitive evaluation can be distressing for families and patients who have experienced significant functional declines, which may have led to avoidance of follow-up testing. Finally, the domains of neurocognitive functioning analyzed here do not encompass the full range of disease burden, which, in our clinical experience, can have significant psychosocial and mental health effects following a transplant.

The effect of treatment-associated variables, including allograft source and use of TBI conditioning, were also examined in this investigation. No clear association between the source of the graft (bone marrow vs umbilical cord blood) and neurocognitive trajectory was detected. Consistent with literature describing the effects of TBI among patients treated for pediatric malignant neoplasms,[28,29] our analysis presents preliminary evidence that neuropsychological functions such as working memory may be vulnerable to high-dose TBI, the use of which is less frequent in more modern protocols. All our patients receiving TBI underwent a transplant early in the study period, so this variable could hypothetically be confounded with some other treatment practice or historical factor. In general, existing studies of cognitive late effects are equivocal regarding the neurotoxicity of HSCT in school-aged children,[30,31] although chemotherapy is known to have subtle effects on specific neurocognitive functions.[32] One study identified processing speed and memory as neurocognitive areas of vulnerability to HSCT.[33] Agents commonly used for prevention or treatment of graft-vs-host disease are also an established cause of central nervous system toxicity and, therefore, may enhance risk among survivors of HSCT.[34,35] Furthermore, these findings must be tempered with the fact that some patients will die of transplant-related complications (8% of our sample). Thus, an allogeneic transplant with patients in an active disease state has significant risks even in the best of circumstances. Patient counseling and assessment of the risk to benefit ratio for transplant should be considered in light of the data presented here, which suggest variable neurocognitive outcomes even among patients with standard risk cALD.

Limitations

This study has some limitations. Inherent in the study of rare diseases is the problem of small sample sizes, limiting the number of variables that can be included when modeling outcomes. Factors such as small variations in conditioning regimens (other than TBI) or differences in cerebral disease variant could have contributed to the posttransplant trajectory of boys with cALD. A retransplant (n = 2) or a transplant from a relative with carrier status (n = 1) may have also affected the time course to arrest inflammatory demyelinating disease in a small number of our patients. Another limitation is that our model of neurocognitive outcomes was linear, which followed the trend of the available data. Had more patients had a longer follow-up interval, we may have been able to quantify whether performance eventually stabilized on longitudinal neurocognitive testing.

Conclusions

An expeditious transplant at the earliest detection of active cerebral disease is essential for preservation of cognitive functioning in patients with cALD. Our observations demonstrate that when greater than minimal active disease is detectable on MRI scans, boys are at risk for persistent and pervasive neurocognitive challenges affecting their potential productivity, independence, and quality of life. Given this finding, the scientific community is urgently tasked to discover strategies for the reliable and accurate detection of very early cerebral disease. Newer neuroimaging techniques, such as high-field magnetic resonance spectroscopy or diffusion tensor imaging, hold promise.[36,37] There is evidence that additional screening methods or biomarkers (such as measures of immune dysfunction, inflammation, and oxidative stress[38-40]; electrophysiological measures[41]; or neuropsychological assessment of subtle functional changes[42,43]) have potential value in assisting with detection of emerging cALD. The recent inclusion of ALD in newborn screening in several states will identify, prior to the emergence of clinical symptoms, significantly more patients with ALD than previously possible. These screening programs present a unique opportunity to intensify efforts to expand monitoring options and explore novel interventions that will optimize patient outcomes.

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Drafting of the manuscript: Pierpont, Eisengart, Raymond, Ziegler, Orchard, Miller.
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