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Survival and Functional Outcomes in Boys with Cerebral Adrenoleukodystrophy with and without Hematopoietic Stem Cell Transplantation

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A B S T R A C T

Cerebral adrenoleukodystrophy (CALD) is a rapidly progressing, often fatal neurodegenerative disease caused by mutations in the *ABCD1* gene, resulting in deficiency of ALD protein. Clinical benefit has been reported following allogeneic hematopoietic stem cell transplantation (HSCT). We conducted a large multicenter retrospective chart review to characterize the natural history of CALD, to describe outcomes after HSCT, and to identify predictors of treatment outcomes. Major functional disabilities (MFDs) were identified as having the most significant impact on patients' abilities to function independently and were used to assess HSCT outcome. Neurologic function score (NFS) and Loes magnetic resonance imaging score were assessed. Data were collected on 72 patients with CALD who did not undergo HSCT (untreated cohort) and on 65 patients who underwent transplantation (HSCT cohort) at 5 clinical sites. Kaplan-Meier (KM) estimates of 5-year overall survival (OS) from the time of CALD diagnosis were 55% (95% confidence interval [CI], 42.2% to 65.7%) for the untreated cohort and 78% (95% CI, 64% to 86.6%) for the HSCT cohort overall ($P = .01$). KM estimates of 2-year MFD-free survival for patients with gadolinium-enhanced lesions (GdE^+) were 29% (95% CI, 11.7% to 48.2%) for untreated patients (n = 21). For patients who underwent HSCT with GdE^+ at baseline, with an NFS $\leq$1 and Loes score of 0.5 to $\leq$9 (n = 27), the 2-year MFD-free survival was 84% (95% CI, 62.3% to 93.6%). Mortality rates post-HSCT were 8% (5 of 65) at 100 days and 18% (12 of 65) at 1 year, with disease progression (44%; 7 of 16) and infection (31%; 5 of 16) listed as the most common causes of death. Adverse events post-HSCT included infection (29%; 19 of 65), acute grade II-IV graft-versus-host disease (GVHD) (31%; 18 of 58), and chronic GVHD (7%; 4 of 58). Eighteen percent of the patients (12 of 65) experienced engraftment failure after their first HSCT. Positive predictors of OS in the HSCT cohort may include donor-recipient HLA matching and lack of GVHD, and early disease treatment was predictive of MFD-free survival. GdE^+ status is a strong predictor of disease progression in untreated patients. This study confirms

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HSCT as an effective treatment for CALD when performed early. We propose survival without MFDs as a relevant treatment goal, rather than solely assessing OS as an indicator of treatment success.

INTRODUCTION

Adrenoleukodystrophy (ALD) is a rare X-linked peroxisomal metabolic disorder affecting approximately 1 in 17,000 births [1,2]. The disease results from mutations in the *ABCD1* gene, which encodes the peroxisomal membrane ALD protein (ALDP) [3]. ALDP deficiency leads to impaired transmembrane transport of very-long-chain fatty acids (VLCFAs) into peroxisomes, where they are degraded. Consequently, VLCFAs accumulate in plasma, brain, spinal cord, and adrenal glands of patients with ALD [4,5]. ALD phenotypes cannot be predicted based on VLCFA concentrations, genotype, or family history and can vary widely, ranging from adrenal insufficiency to fatal neurodegenerative disease [6].

Cerebral ALD (CALD) represents the most severe phenotype of the disease, characterized by progressive inflammatory demyelination in the brain. Approximately 40% of boys with ALD develop CALD [7], and most of these boys will die within a decade of diagnosis without treatment [8]. In early disease, symmetric contiguous white matter lesions can be observed on routine magnetic resonance imaging (MRI) before the onset of neurologic symptoms [9]. When present, gadolinium enhancement (GdE^+), a marker of active inflammation in the brain, is considered a critical predictive biomarker of rapidly progressive disease [10]. The extent of CALD MRI disease severity is typically graded using the Loes score (range, 0 to 34), which quantitates the regions of white matter involvement [11].

Untreated CALD tends to progress predictably [12]. Initially, boys often manifest behavioral or academic decline, which may be misdiagnosed as attention-deficit/hyperactivity disorder. Typically, the disease progresses to disabilities of visual/auditory dysfunction, gait abnormalities, episodes of incontinence, bulbar dysfunction, and seizures. Affected boys eventually develop major functional disabilities (MFDs), including loss of communication, cortical blindness, tube feeding dependence, total incontinence, wheelchair dependence, complete loss of voluntary movement, and ultimately death related to neurologic deterioration. Clinical symptoms of CALD can be graded using the Neurologic Function Score (NFS) [13], with a lower NFS indicating better neurologic function. Currently, allogeneic hematopoietic stem cell transplantation (HSCT) is the only therapy known to stabilize disease progression. Previous reports document favorable outcomes when HSCT is performed early in the course of disease, with better survival post-transplantation when performed in presymptomatic boys (NFS 0) [14,15].

Although HSCT is effective and outcomes are favorable when performed in early-stage CALD, it is associated with serious and sometimes fatal complications, including infection, graft-versus-host disease (GVHD), and graft failure or rejection [14-16]. The timely availability of a suitably histocompatible related or unrelated donor also remains a significant limitation of allogeneic HSCT, especially in boys of mixed ethnicity or with rare HLA haplotypes that are not well represented in donor registries.

Given these limitations, new treatments are needed. However, developing new treatment options for CALD necessitates a thorough understanding of its natural history and robust methods for objectively measuring key outcomes, including maintenance of neurologic functioning following treatment with HSCT. To address these needs, we retrospectively analyzed a large, multicenter CALD cohort, including both untreated and HSCT-treated boys. We propose survival without MFDs as a relevant treatment goal. We performed additional analyses to gain further insight into ongoing risks and determinants of successful outcomes after HSCT, identify appropriate populations for treatment, and define endpoints that could be useful for future clinical studies.

METHODS

Study Design

This was an international, multicenter, retrospective chart review of patients with CALD, regardless of treatment history. Data were collected from 5 study centers in the United States and France: University of Minnesota, Kennedy Krieger Institute, University of North Carolina, Duke University, and Hôpital St Vincent de Paul. The Institutional Review Board or Independent Ethics Committee of each study site approved this retrospective study, and the need for informed consent was waived.

Patient Population

Patients met inclusion criteria if they were diagnosed with CALD (either by pathognomonic VLCFA concentrations or documented pathogenic mutation in the *ABCD1* gene) between the ages of 3 and 15 years, and demonstrated an ALD Loes MRI score [11] between 0.5 and 14.5, inclusive. Patients were grouped into 2 cohorts: HSCT (patients who had undergone 1 or more transplantations) and untreated (patients who never underwent HSCT). In the untreated cohort, data were collected for patients who had been diagnosed with CALD in 1990 or later; in the HSCT cohort, data were collected for patients who underwent HSCT in or after 2001. Patients were included if they had been followed for at least 2 years after diagnosis (untreated cohort) or after HSCT (HSCT cohort), or until death. For change from baseline analyses relative to the date of CALD diagnosis, baseline was defined as the value closest to the date of CALD diagnosis, using a window of 6 months before to 3 months after the diagnosis of CALD. For the HSCT cohort, baseline for assessment of change in patient status subsequent to transplantation was defined as the value closest to (but before) the time of HSCT. In the HSCT cohort at baseline, a "GdE^+ early disease" subset was identified by clinical characteristics considered to confer eligibility for HSCT by modern standards (NFS $\leq$1, a Loes score of 0.5 to $\leq$9, and GdE^+). A cohort of patients with advanced disease was defined as GdE^+, NFS $>$1, and Loes score $>$9.

For the HSCT cohort, details of the transplantation were recorded, including time from diagnosis of ALD and CALD to HSCT, source of hematopoietic stem cells (HSCs), donor relationship, donor-recipient HLA matching, and intensity of the HSCT preparative regimen. Donors were defined as related (sibling or parent) or unrelated (all others), and as matched (at relevant HLA alleles/antigens according to conventional matching practices within each stem cell source at the time of HSCT) or unmatched ($<$100% HLA match).

Efficacy Measurements

Loss of communication, cortical blindness, tube feeding dependence, total incontinence, wheelchair dependence, and complete loss of voluntary movement are critical deficits that result from CALD and are of particular clinical significance because they severely compromise a patient's ability to function independently. These were classified as MFDs.

The NFS was developed in 2000 to track the progression of clinical neurologic symptoms in patients with CALD [13] (Supplementary Table S1). It is a 25-point scale used to evaluate the severity of gross neurologic dysfunction by scoring 15 disabilities across multiple domains.

The NFS and the presence of MFDs were determined at the time of diagnosis and for follow-up time points, as available. Overall survival (OS) at 2 and 5 years and 2-year MFD-free survival were also assessed in the untreated and HSCT cohorts. Historical data on Loes MRI score, if available in the medical record, were used to assess the extent of demyelination as evaluated by MRI. Gadolinium enhancement of cerebral lesions was recorded as positive (GdE^+), negative (GdE^-), or unknown (NA) when relevant MRI data were available.

Safety Assessments

Safety outcomes assessed included incidence of serious adverse events, including those linked to the transplantation or preparatory regimen in the HSCT cohort, incidence of infections, use of concomitant medications for CALD, 100-day and 1-year mortality post-HSCT, and cause of death. Additional safety outcomes assessed in the HSCT cohort included incidence of graft failure,

incidence and grade of acute and chronic GVHD, as well as documentation of medications for GVHD prophylaxis and myeloablative medications used in the conditioning regimen. Graft failure after HSCT was defined by the investigator.

Statistical Analyses and Survival Analyses

For time to event data, the Kaplan-Meier (KM) method was used to estimate the 25th, 50th (median), and 75th percentiles of survival rates and the associated 2-sided 95% confidence intervals (CIs), as well as the 2-year and 5-year survival rates and the associated 2-sided 95% CIs. The number and percentage of censored observations and events were also recorded. The Cox proportional hazards model was used to identify univariate and multivariate predictors of MFD-free survival and OS in the HSCT cohort, with covariates including donor type, GVHD occurrence and severity, and stage of CALD before HSCT. Given the retrospective nature of the study, some desired data were missing. (See Supplementary Appendix for a description of imputation methods.) Patients with engraftment failure were not excluded from analyses of OS, MFD-free survival, change in Loes score, or change in NFS. Patients who experienced engraftment failure, lack of/inadequate chimerism, or death within 30 days post-transplantation were excluded from the analysis of GVHD.

RESULTS

Enrollment and Patient Demographics

Data were collected for 137 patients (72 in the untreated cohort and 65 in the HSCT cohort) seen at 5 clinical sites in the United States and France. The untreated and HSCT cohorts were chronologically distinct. Before 2001, HSCT had not been widely adopted as a treatment for CALD, and thus it was possible to collect clinical data on the natural history of the disease. After 2001, virtually all eligible boys with CALD underwent HSCT [8]. Demographic data, including age at diagnosis, ethnicity, clinical presentation, and duration of follow-up, were similar in the 2 groups (Table 1).

OS and MFD-Free Survival, Untreated Cohort

In the untreated cohort, median OS was 92 months (95% CI, 41 to 219 months) from the time of CALD diagnosis. The KM-estimated probabilities of OS at 2 and 5 years from diagnosis were 74% (95% CI, 62.5%–83.0%) and 55% (95% CI, 42.2%–65.7%), respectively. The KM-estimated MFD-free survival rate at 2 years from diagnosis was 48% (95% CI, 36.3%–59.6%) (Figure 1A).

GdE^+ status on diagnostic MRI was associated with less favorable outcomes. In untreated patients who were GdE^+ at baseline (n = 15), median OS was 34 months (95% CI, 14 to 119 months), with KM-estimated probabilities of 2- and 5-year OS of 64% (95% CI, 34.3% to 83.3%) and 36% (95% CI, 13.0% to 59.4%), respectively. KM estimates of OS and MFD-free survival were also lower for untreated patients who were GdE^+ at any time during the observation period (n = 21), with only 29% (95% CI, 11.7% to 48.2%) of such patients MFD-free at 2 years (Figure 1B). The observed MFD-free survival rate at 2 years was consistent with, but slightly lower than, the KM estimates. In untreated patients with GdE^+ at any time during the study period (n = 19), the observed month 24 MFD-free survival rate within 2 years of their first GdE^+ MRI was 21% (95% CI, 6.1% to 45.6%).

The majority of untreated subjects (48 of 72; 67%) had progressive disease resulting in MFD or death during the study period, with 91% of GdE^+ (at any time) patients (19 of 21) dying or experiencing an MFD. The occurrence of specific MFDs from the time of diagnosis of CALD in untreated patients who were GdE^+ at baseline is shown in Figure 2.

Table 1
Demographic and Other Baseline Characteristics

Parameter/Statistic	Untreated (n = 72)	HSCT (n = 65)	*P* Value*
Age at ALD diagnosis, yr, median (range)	7.0 (0-15)	7.0 (0-13)	N/A
Age at CALD diagnosis, yr, median (range)	8.0 (2-15)	8.0 (1-13)	.2393
Year of HSCT, n	N/A	1997–2004: 31 2005–2010: 34	N/A
Race, n (%)			
White	51 (70.8)	42 (64.6)	.4364
Black or African American	6 (8.3)	2 (3.1)	
Asian	5 (6.9)	2 (3.1)	
Other†	1 (1.4)	2 (3.1)	
Unknown/not reported	8 (11.1)	17 (26.2)	
Clinical presentation, n (%)‡			N/A
Signs and symptoms	42 (58.3)	38 (58.5)	
Family history	26 (36.1)	28 (43.1)	
Adrenal insufficiency	33 (45.8)	41 (63.1)	
Deaths during follow-up period, n (%)	40 (55.6)	16 (24.6)	.0002
Duration of follow-up after confirmed CALD diagnosis, mo, median (range)§	52 (.20-259)	54 (4.8-125)	.8015
Positive gadolinium enhancement, n (%)‖	21 (29.2)	45 (69.2)	N/A
Baseline Loes score¶			
≤9	39 (60.9)	40 (69.0)	.3540
>9	25 (39.1)	18 (31.0)	
Baseline NFS¶			
≤1	24 (47.1)	42 (75.0)	.0030
>1	27 (52.9)	14 (25.0)	
MFDs at baseline¶			
0	38 (74.5)	54 (98.2)	.0004
1	8 (15.7)	1 (1.8)	
≥2	5 (9.8)	0	

N/A indicates not applicable.
The majority of patients in the untreated cohort were diagnosed with CALD before 2000, whereas the majority of patients in the HSCT cohort were diagnosed with CALD after 2000, reflecting the increased acceptance of HSCT for CALD.

* *P* values are based on a median 2-sample test (SAS PROC NPAR1WAY) for median tests and the chi-square or Fisher's exact test for categorical variables.

† Patients with "other" or with more than 1 race checked were included under Other.

‡ More than 1 category may apply.

§ Measured from confirmed CALD to last evaluation date/date of death.

‖ For the untreated cohort, gadolinium is defined as a positive result at any time during the observation period. For the HSCT cohort, gadolinium positivity is defined based on the last gadolinium scan before HSCT.

¶ Baseline was a diagnosis of CALD for the untreated cohort and a diagnosis of CALD before allogeneic HSC infusion for the HSCT cohort.

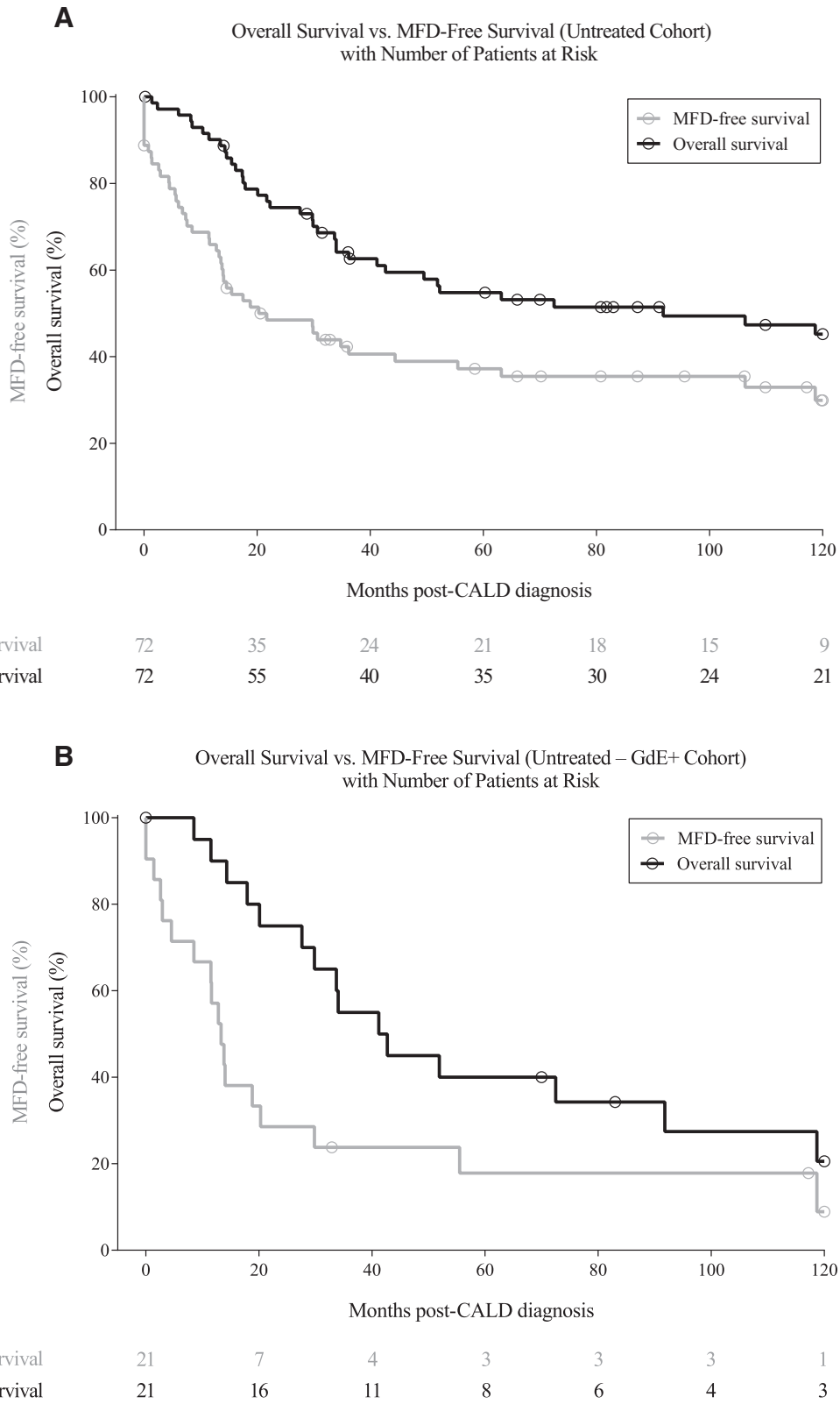

Figure 1. OS and MFD-free survival in all untreated patients (A) and in untreated patients who were positive for gadolinium enhancement at any time during the study (B).

OS and MFD-Free Survival, HSCT Cohort

Details of transplantation for the HSCT cohort are presented in Table 2. The median age at the time of transplantation (8 years; range, 2 to 18 years) was the same as that at CALD diagnosis, reflecting the short time between diagnosis and transplantation (median, 4.3 months). KM estimates of OS at 2 and 5 years from HSCT (n = 65) were 82% (95% CI, 69.8% to 89.1%) and 74% (95% CI, 59.3% to 83.6%), respectively. MFD-free

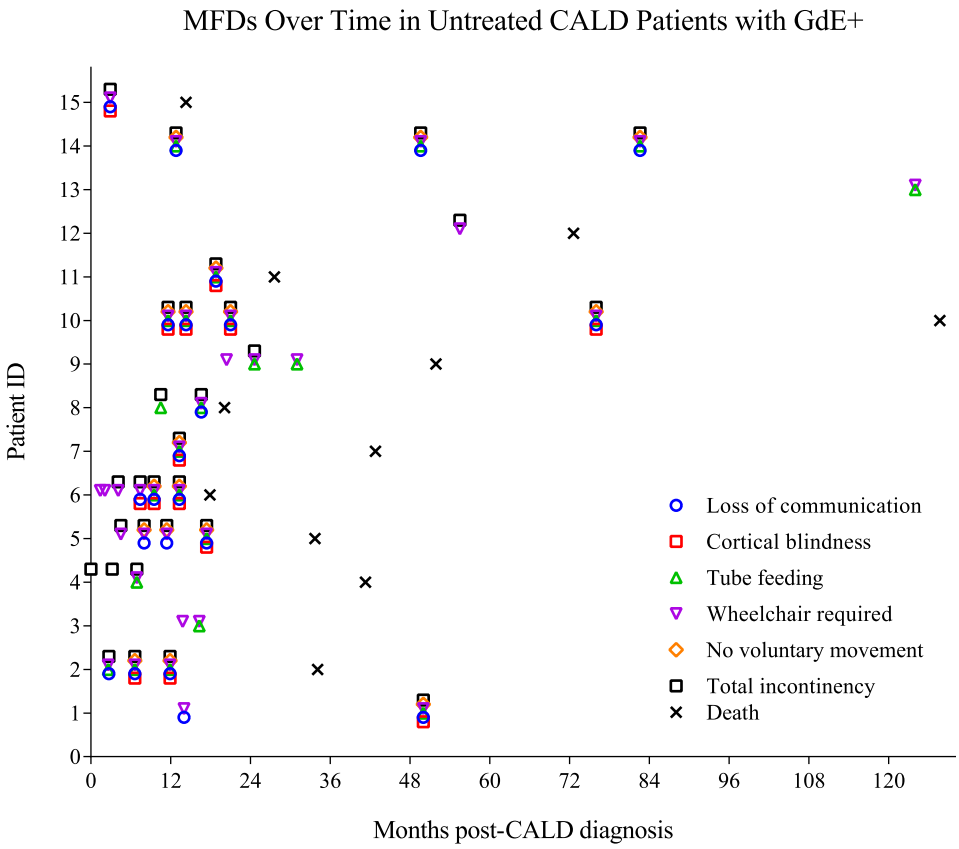

Figure 2. Occurrence of major functional disabilities in patients with untreated CALD who were GdE$^+$ at baseline. The occurrence of individual MFDs over time and death are plotted for each patient.

Table 2
Allogeneic HSCT Parameters (N = 65)

Parameter/Statistic	Value
Age at allogeneic HSCT, yr, median (range)	8.0 (2-18)
Time from CALD diagnosis to allogeneic HSCT, mo, median (range)	4.3 (0.4-73.0)
Stem cell source, n (%)	
Bone marrow	31 (47.7)
Umbilical cord	31 (47.7)
G-CSF-mobilized peripheral blood	2 (3.1)
Donor HLA match, n (%)*	
HLA-matched related	13 (20.0)
HLA-mismatched related	5 (7.7)
HLA-matched unrelated	13 (20.0)
HLA-mismatched unrelated	32 (49.2)
Preparative/conditioning regimen, n (%)	
Myeloablative	53 (81.5)
Reduced intensity	12 (18.5)
Cell dose	
Bone marrow	
CD34$^+$ cells, $\times 10^6$/kg, median (range)	5.45 (.40-18.7)
Total nucleated cells, $\times 10^7$/kg, median (range)	33.05 (.80-91.7)
Umbilical cord	
CD34$^+$ cells, $\times 10^6$/kg, median (range)	.26 (.10-14.5)
Total nucleated cells, $\times 10^7$)/kg, median (range)	6.50 (2.5-147.3)
Time to recovery from HSC infusion, d, median (range)†	
Neutrophil recovery	18 (9-173)
Platelet recovery	46 (12-228)

G-CSF indicates granulocyte-colony stimulating factor.
*HLA mismatch defined as any graft that was not 6/6 matched for umbilical cord blood, 8/8 matched for bone marrow, or 10/10 matched for peripheral blood stem cells.
†Defined as the first day of 3 consecutive days of a neutrophil count $\geq .50 \times 10^9$/L and platelet count of 50×10^9/L.

survival was 56% (95% CI, 41.8% to 67.3%) at 2 years and 44% (95% CI, 29.6% to 58.0%) at 5 years post-HSCT. Fewer deaths were reported for the HSCT cohort than for the untreated cohort (16 of 65 [25%] versus 40 of 72 [56%]).

The stage of disease pretreatment impacted MFD-free survival in the HSCT cohort. Although KM estimates of OS in patients with advanced disease (NFS >1 and Loes score >9; n = 10) were 90% (95% CI, 47.3% to 98.5%) at 2 years and 5 years from CALD diagnosis (Figure 3A), MFD-free survival was 20% (95% CI, 3.1% to 47.5%) and 10% (95% CI, .6% to 35.8%) at these respective time points. In contrast, for boys who underwent HSCT in earlier stages of CALD (NFS ≤1 and Loes score .5 to 9), KM estimates of OS at both 2 and 5 years from CALD diagnosis were 94% (95% CI, 78.5% to 98.5%), and MFD-free survival was 91% (95% CI, 73.5% to 96.9%) and 76% (95% CI, 53.1% to 88.9%), respectively (Figure 3B).

In patients who were GdE$^+$ pre-HSCT and underwent GdE assessment post-transplantation (n = 43), GdE$^+$ status resolved within 4 months after HSCT (median time to resolution, 3.4 months) in 40 patients (93%). Contrast enhancement resolved following HSCT in all patients who were GdE$^+$ with NFS ≤1 and Loes score .5 to 9 (n = 27) at baseline, and they remained GdE$^-$ during the remainder of the observation period. KM-estimated 2-year MFD-free survival was 84% (95%CI, 62.3% to 93.6%) in this cohort of early GdE$^+$ HSCT-treated patients (n = 27).

HSCT is associated with improvement in MFD-free survival at 2 years from CALD diagnosis (24% [n = 21 GdE$^+$ at any time] for the untreated cohort versus 60% [n = 45 GdE$^+$ before HSCT] for the HSCT cohort; P = .0083) (Figure 4). Comparisons of 2-year MFD-free survival rates for HSCT-treated versus untreated subjects with early disease and GdE$^+$ at baseline

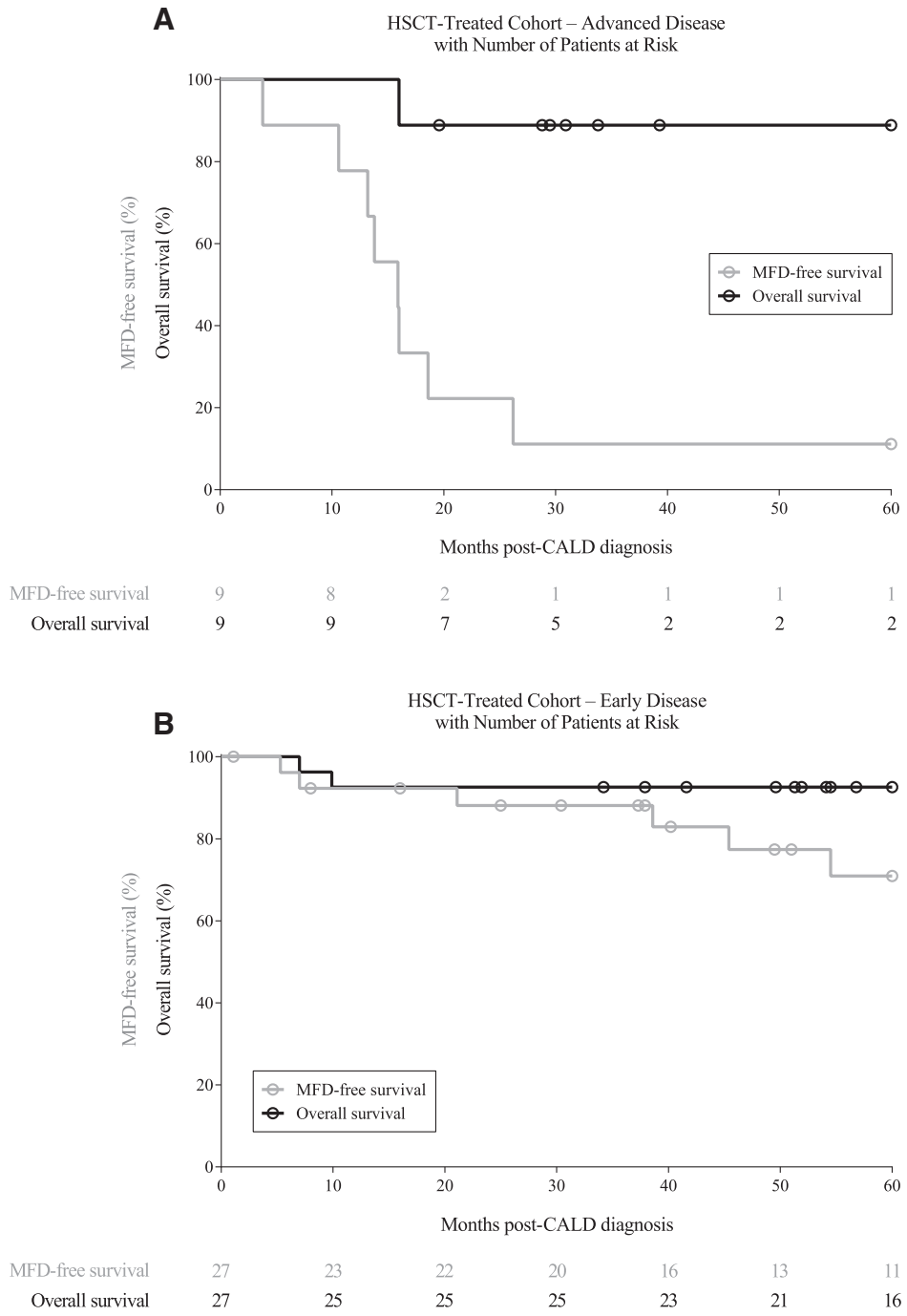

Figure 3. OS and MFD-free survival following HSCT in GdE+ patients with early or advanced disease. (A) Patients with advanced disease (NFS >1, Loes score >9, and GdE$^+$ at baseline). (B) Patients with early disease (NFS ≤1, Loes score .50 to 9, and GdE$^+$ at baseline).

(n = 1) or at any time (n = 3) were not done because of limited numbers.

However, in untreated patients with GdE$^+$ at any time during the study period, the observed month 24 MFD-free survival rate within 2 years of their first GdE$^+$ MRI (n = 19) was 21% (95% CI, 6.1% to 45.6%).

Survival and MFD-Free Survival by Donor Type and HLA Status, HSCT Cohort

Estimated survival after HSCT was analyzed by donor type and HLA status. Twenty percent of the patients (13 of 65) had an HLA-matched, related donor. (ALD carrier status of related female donors was not captured.) In the majority of patients (46 of 65; 71%), the donor was unrelated. For approximately one-half of the patients (32 of 65; 49%), the donor type (including both bone marrow and umbilical cord blood sources) was unrelated and HLA-mismatched. The proportion of deaths was highest among patients with an HLA-mismatched unrelated donor (12 of 32; 37.5%; P = .041) compared with patients with other types of donors.

KM-estimated 2-year OS and MFD-free survival rates by donor relationship and HLA status are shown in Table 3. The KM-estimated 2-year OS rate was 92% (95% CI, 56.6% to 98.9%) among patients with an HLA-matched related donor (n = 13) and 72% (95% CI, 52.9% to 84.3%) among those with an HLA-mismatched unrelated donor (n = 32). Patients with a

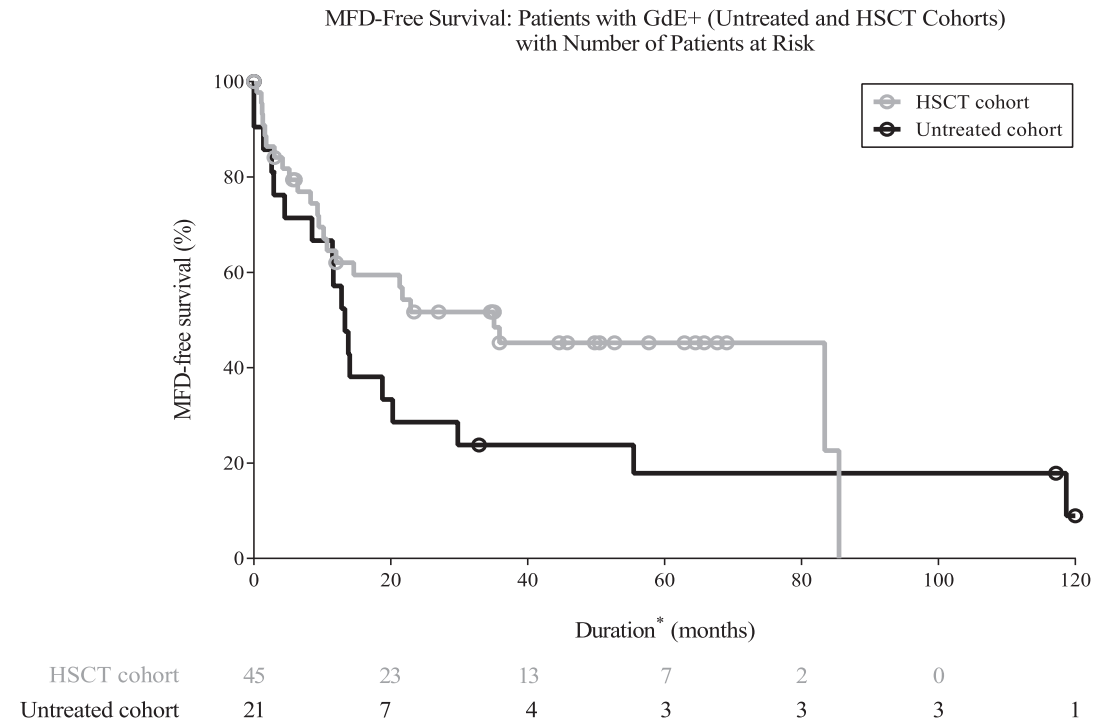

Figure 4. MFD-free survival in untreated and HSCT-treated GdE$^+$ patients *Duration is relative to CALD diagnosis (untreated cohort) or to HSCT (HSCT cohort).

Table 3
Kaplan-Meier Estimated Overall Survival and MFD-free Survival from Time of Allogeneic HSCT by Donor Relationship and HLA Status

Parameter/Statistic	HLA-Matched Related*	HLA-Matched Unrelated	HLA-Mismatched Related	HLA-Mismatched Unrelated
Allo-HSCT Cohort, n	13	13	5	5
OS at 2 yr post-HSCT, % (95% CI)	92 (56.6-98.9)	92 (56.6-98.9)	80 (20.4-96.9)	72 (52.9-84.3)
MFD-free survival at 2 yr post-HSCT, % (95% CI)	69 (37.3-87.2)	82 (44.4-95.3)	40 (1.1-82.9)	38 (20.9-55.2)
GdE$^+$, NFS ≤1, and Loes ≥0.5 to ≤9 at baseline, n	5	9	1	10
OS at 2 yr post-HSCT, % (95% CI)	100 (100-100)	100 (100-100)	100 (100-100)	80 (40.9-94.6)
MFD-free survival at 2 yr post-HSCT, % (95% CI)	100 (100-100)	86 (33.4-97.9)	100 (100-100)	67 (28.2-87.8)

* Related includes both sibling and parent donors.

mismatched unrelated donor had the lowest KM-estimated 2-year MFD-free survival (P = .010 comparison of mismatched unrelated versus all others). A similar pattern was observed in patients with GdE$^+$ early disease; patients with a mismatched unrelated donor (n = 10) had a lower KM-estimated 2-year, MFD-free survival rate (67%; 95% CI, 28.2% to 87.8%) compared with patients with all other types of donors, but the difference was not statistically significant (P = .409). The 2-year MFD-free survival in this cohort (GdE$^+$ with early disease) was 76% in recipients of grafts of all types exclusive of HLA-matched related donors.

In univariate analysis, transplants from mismatched unrelated donors (both marrow and cord blood) were observed to have lower OS and MFD-free survival compared with other donor types (OS hazard ratio [HR], 3.1 [95% CI, .99 to 9.57], P = .052; MFD-free survival HR, 2.5 [95% CI, 1.21 to 5.11], P = .013). This effect was further emphasized with univariate analysis indicating a protective effect of receiving a graft from a matched donor compared with a mismatched donor (OS HR, .29 [95% CI, .08 to 1.02], P = .054; MFD-free survival HR, .39 [95% CI, .18 to .83], P = .014). Recipients of mismatched unrelated grafts had lower MFD-free survival compared with recipients of with matched unrelated donor grafts (HR, 3.9; 95% CI, 1.17 to 3.32; P = .027).

Neurologic and Radiologic Outcomes Following HSCT in GdE$^+$ Patients with Early Disease

Analysis of evaluable patients with GdE$^+$ early disease showed that the majority (70%; 16 of 23) had a change of ≤3 NFS points and an absolute NFS ≤4 at 2 years (±6 months) following HSCT (Figure 5A). In patients with a baseline NFS of 0, 1, and >1 (n = 27, 11, and 12, respectively), the median change in NFS was 0, .7, and 3.3, respectively, at the last evaluable time point through 5 years post-treatment.

Slightly more than one-half (54%; 13 of 24) of the patients with GdE$^+$ early disease had a Loes score change of ≤5 points or an absolute Loes score of ≤9 at 2 years (±6 months) post-HSCT (Figure 5B). In patients with baseline Loes scores of <5, 5 to 10, and > 10 (n = 20, 21, and 14, respectively), the median change in score was .4, 1.4, and 3.8, respectively, at the last time point through 5 years post-treatment. For context, changes in NFS and Loes scores in untreated patients over time are shown in Supplementary Figure S1.

These data demonstrate that HSCT was generally associated with disease stabilization, as measured by NFS and Loes score, and that less severe disease at time of transplantation is associated with less neurologic and radiographic progression. After an initial period of decline in the post-HSCT period, NFS and Loes score stabilized within 18 months in most subjects.

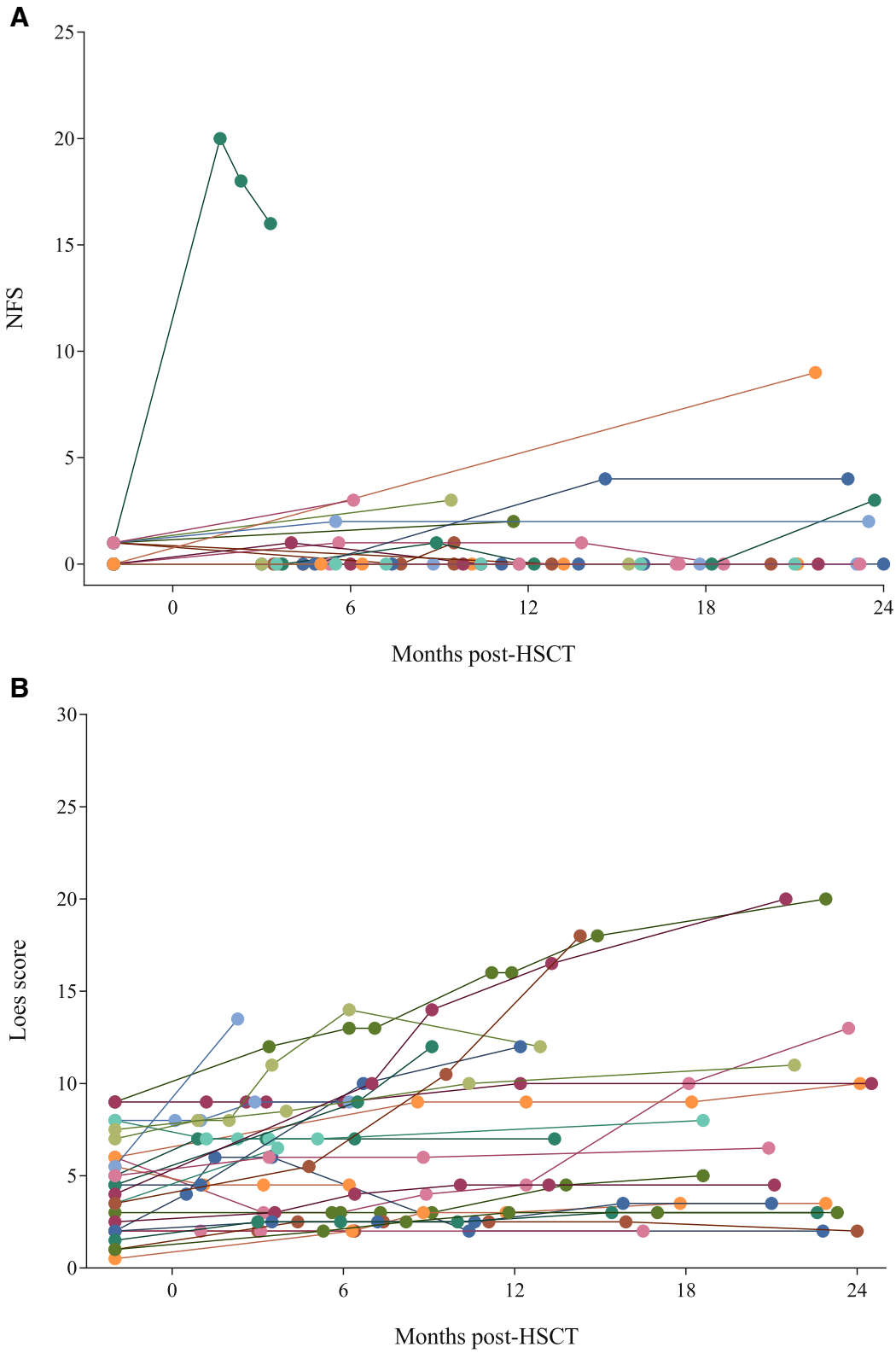

Figure 5. Neurologic and radiologic findings in the 2 years after HSCT in patients with GdE$^+$ early disease (Loes score .50 to 9, NFS ≤1, and GdE$^+$). (A) Change in NFS from baseline over time. (B) Change in Loes score from baseline over time (n = 27).

Causes of Morbidity and Mortality

In the untreated cohort, 40 deaths were reported during the data collection period after diagnosis of CALD, with underlying disease progression reported as the primary cause of death in 31 of 40 patients (78%). Among the 3 remaining patients in whom a cause of death was reported, the primary cause of death was aspiration, pneumonia, and seizure in 1 patient each. The incidence of serious infections in the untreated cohort was low (7%).

Data on mortality, engraftment failure, and rate of GVHD by donor source in the HSCT cohort are presented in Table 4. A total of 16 deaths (25%) were reported in the HSCT cohort during the data collection period. The 100-day and 1-year mortality rates post-transplantation were 8% (5 of 65) and 18% (12 of 65), respectively. Among the 16 patients in whom a primary cause of death was reported, death was from ALD progression in 7, infection in 5, multisystem organ failure in 1, respiratory failure in 1, GVHD in 1, and bronchiolitis obliterans with chronic GVHD in 1. Given the need for immunosuppressive therapy after HSCT, serious infections were common (29%; 19 of 65).

The overall incidence of graft failure was 18% (12 of 65) and was highest among patients who received cells from a mismatched unrelated donor (Supplementary Table S2). Of the 12 patients with graft failure, 10 had received full myeloablative conditioning and the other 2 had received reduced-intensity conditioning. Of these 12 patients, 4 died before engraftment, 1 engrafted with <10% donor cells, 1 had eventual (delayed) ≥10% donor cell engraftment, 1 had successful engraftment of subsequent autologous back-up cells, and 5 had successful engraftment of >89% donor cells after an additional HSCT.

In the entire HSCT cohort, either acute GVHD or chronic GVHD (all grades) were reported in 45% (26 of 58) and 21% (12 of 58) of patients, respectively. Severe or life-threatening acute GVHD occurred in 10% (6 of 58). Chronic GVHD was considered severe or life-threatening in 5% (3 of 58).

The effect of GVHD and donor chimerism on disease progression, as measured by change in NFS from baseline and MFD-free survival at 24 months, are summarized in Supplementary Tables S3 and S4.

DISCUSSION

This is the first multicenter analysis of survival and functional outcomes in patients with CALD in more than 10 years, and considering the rarity of this disease, it includes a large number of patients. The findings reported here provide additional insight into symptom progression in patients with untreated CALD and the benefits and risks of HSCT intervention, especially in early, presymptomatic cerebral disease.

A hallmark of inflammatory disease in CALD is the presence of a compromised blood-brain barrier behind the leading edge of demyelinating lesions, as evidenced by gadolinium enhancement on brain MRI. GdE^+ represents a clinically important radiographic biomarker of active neuroinflammatory disease and signals a poor prognosis in untreated patients. As it reflects cerebral inflammation, GdE^+ is a strong predictor of the future development of MFDs. Patients in the untreated cohort with GdE^+ MRI experienced the most rapid progression of disease, had more MFDs, and had a higher mortality rate due to disease progression.

Although HSCT is clearly effective in stabilizing disease progression, it is most effective when undertaken early in the course of cerebral disease. Results from this and other studies [8,14] suggest that patients with early disease may be characterized as having a Loes score between .5 and 9 and an NFS ≤1. Outcomes following HSCT in this subset of patients are clearly more favorable than those in patients with more advanced disease (NFS >1, Loes score >9).

The life-threatening nature of untreated CALD and relative lack of clinical benefit from HSCT for patients with late-stage disease emphasize the need for early diagnosis of CALD, which may be achieved through the wider adoption of newborn screening for ALD. It is estimated that approximately 50% of boys with CALD are diagnosed too late to allow for effective treatment with HSCT. Importantly, in February 2016, the US Department of Health and Human Services recommended that screening for ALD be added to routine newborn screening [17]. To date, a limited number of states have implemented the recommendation. Newborn screening detects ALD at birth, allowing boys at risk for CALD to be monitored and identified before the onset of symptoms by screening MRI, increasing their chance of undergoing HSCT in time to stabilize disease with good residual function.

The early stages of CALD can be detected by scheduled brain MRIs in boys diagnosed with ALD, before the onset of symptoms [9]. Currently, which boys with ALD will go on to develop CALD cannot be predicted based on genotype, family history, or any other parameter. Monitoring of all boys with ALD age 12 months to 13 years is recommended. Present recommendations are evolving, but begin at 12 to 18 months, with MRI every 6 to 12 months to detect early signs of cerebral involvement [6]. After age 13 years, the incidence of CALD decreases, and annual MRI scanning is recommended. A new-onset GdE^+ white matter lesion on MRI is an indication for immediate HSCT. A recent analysis of neurocognitive outcomes in boys with very early CALD who underwent HSCT support the importance of vigilant MRI surveillance and readiness to proceed to treatment in boys who are known to have the biochemical defect of ALD and show evidence of cerebral disease. This study has demonstrated that sustained and severe

Table 4
Mortality, Engraftment Failure, and GVHD by Donor Source

Parameter	Related Donor, BM/PBSCs*	Unrelated Donor, BM/PBSCs	Unrelated Cord Blood	All Sources†
Allo-HSCT cohort, n	19	14	31	65
Mortality, n (%)				
100 d	1 (5.3)	0	4 (12.9)	5 (7.7)
1 yr	2 (10.5)	3 (21.4)	7 (22.6)	12 (18.5)
Graft failure	2 (10.5)	4 (28.6)	6 (19.4)	12 (18.5)
GVHD eligible population, n‡	18	12	27	58
Acute GVHD, n (%)				
Grade II-IV	3 (16.7)	4 (33.3)	11 (40.7)	18 (31.0)
Grade III-IV	1 (5.6)	2 (16.7)	3 (11.1)	6 (10.3)
Chronic GVHD, n (%)				
Grade II-IV	2 (11.1)	1 (8.3)	1 (3.7)	4 (6.9)
Grade III-IV	2 (11.1)	0	1 (3.7)	3 (5.2)

BM indicates bone marrow; PBSCs, peripheral blood stem cells.
* Related includes both sibling and parent donors.
† Donor source was unknown for 1 subject.
‡ Patients were excluded for GVHD analysis owing to engraftment failure, lack of/inadequate chimerism, or death within 30 days post-transplantation.

neurocognitive and processing issues can be identified even in those with relatively low Loes scores post-transplantation [18].

Given that individuals with CALD suffer significant neurologic impairment and functional disability, OS alone is an inadequate measure to assess CALD treatment outcomes. Using an MFD-focused assessment provides a more robust measure of post-transplantation outcomes. Prevention of MFDs provides important clinical benefits by significantly reducing the burden on patients' families and healthcare resources. We suggest that assessment of MFD-free survival (as opposed to survival alone) in both untreated patients and HSCT recipients is an effective and useful way to characterize functional outcomes. The NFS provides supportive evidence of treatment outcomes. Consistent with previous reports, both NFS and Loes scores were stabilized within approximately 18 months of HSCT in most patients. Favorable MFD-free survival rates were observed in GdE^+ patients with early disease who underwent HSCT. The majority of these patients demonstrated limited changes in NFS and Loes scores as of the last available data point in the study period.

While providing clinical benefit, HSCT is not without risks, which are increased with the use of HLA-mismatched and unrelated donors. In this study, the 100-day and 1-year mortality rates were 8% and 18%, respectively. Graft failure occurred in 18% of patients. Serious infections, including those due to opportunistic pathogens, were common (29%). Although improvements in treatments and supportive care have been implemented since the time of this study, graft failure, infection, and GVHD remain significant threats to successful outcomes following HSCT, particularly in the setting of HLA-mismatched unrelated donors [19]. To address this unmet need, transplantation with genetically corrected autologous hematopoietic stem cells (HSCs) [20] is currently being investigated in boys with early cerebral disease [21]. Early results are encouraging and suggest that autologous ex vivo gene therapy may be a promising alternative to allogeneic HSCT, but additional follow-up is necessary to assess the duration of response and long-term safety.

This study has several limitations. Given the retrospective nature, data were often incomplete with regard to efficacy (all functional outcomes over time) or safety. In addition, natural history data on CALD became scarce after the implementation of HSCT in the early 2000s, and thus the years of comparison between untreated and allo-HSCT-treated boys differ by more than 10 years. The majority of patients in the untreated cohort were diagnosed with CALD before 2000, whereas the majority of patients in the HSCT cohort were diagnosed with CALD after 2000, reflecting the increased acceptance of HSCT for CALD. In addition, it is possible that improvements in supportive care practices over the last decade may have contributed to longer survival, although this likely would not improve MFD, which is driven by the disease process. Boys in the untreated cohort were particularly underrepresented in some analyses, simply owing to the scarcity of these data. It is also important to note that many of the patients in this study were also included in a large, single-institution cohort study at the University of Minnesota that evaluated outcomes of HSCT in boys with CALD [14].

Limitations notwithstanding, the results of this study confirm the importance of early diagnosis and treatment of CALD. They also highlight the importance of GdE^+ status in predicting disease progression. Despite clear evidence that HSCT can halt the progression of CALD, the morbidity and mortality associated with this procedure demonstrate the need to identify patients earlier in the course of disease and the need for safer therapies, particularly for patients without the option of an HLA-matched donor. The data also suggest that 2-year MFD-free survival is a useful clinical outcome for evaluating the efficacy of treatments for CALD.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2018.09.036.

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