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Quality of life among boys with adrenoleukodystrophy following hematopoietic stem cell transplant

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ABSTRACT
Hematopoietic stem cell transplant (HSCT) is the only accepted treatment capable of halting the progression of X-linked cerebral adrenoleukodystrophy (CALD). While survival and neurological outcomes have been described, there is little information regarding the quality of life (QoL) of transplanted patients with CALD. This analysis is a cross-sectional study of QoL in 16 males diagnosed with CALD who underwent HSCT at a single institution. Each child or parent proxy completed subscales from the Neuro-QoL and the PROMIS Pediatric Profile Instrument representing physical, mental, and social health domains. Descriptive statistics summarized the demographic characteristics and QoL subscale T-scores, Spearman Rho correlations identified the relationships among the variables, and Mann-Whitney tests examined group differences between those with pre-HSCT Loes scores <10 and those with pre-HSCT Loes scores ≥10. The median age of respondents at the time of transplant was 8 years at HSCT (5–14) with a median of 5 years since HSCT (0.5–11). Scores from the selected QoL subscales were similar to healthy peers, though those with pre-HSCT Loes scores ≥10 had lower mobility, upper extremity function, peer interaction, and higher scores for anxiety. Although HSCT has the capability of halting progression of CALD, those with pre-HSCT Loes scores ≥10 after HSCT are at risk for poor QoL. Longitudinal monitoring is necessary to further appreciate the factors affecting QoL among boys with CALD after HSCT, and how this may be improved.

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Hematopoietic stem cell transplant; bone marrow transplant; childhood adrenoleukodystrophy; cerebral adrenoleukodystrophy quality of life

Adrenoleukodystrophy (ALD) is an X-linked, metabolic disease of the peroxisome resulting in accumulation of very long chain fatty acids. ALD is caused by hundreds of described mutations in the ABCD1 gene and affects 1 in every 21,000 males. Approximately 35% of boys with ALD develop neuroinflammation, which results in progressive, lethal cerebral demyelination of the brain, termed childhood cerebral ALD (CALD) (Berger & Gärtner, 2006). There is no genotypic predictor of the childhood CALD phenotype, and even within affected kinships individual patients have
unpredictable clinical courses. If untreated, virtually all patients with CALD will become symptomatic (Bezman et al., 2001; Miller et al., 2011). Childhood CALD has a median symptom onset of seven years of age. Clinically silent but radiographically evident white matter disease can be detected by standard brain MRI and often precedes symptoms by several years. As CALD expands to affect more cerebral white matter, symptoms present initially as hyperactivity and inattention but progress to visual, auditory, motor, and cognitive decline before eventual death (Berger & Gärtner, 2006; Mahmood, Dubey, Moser, & Moser, 2005; H. Moser, Dubey, & Fatemi, 2004).

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only proven treatment for halting the progression of childhood CALD (Kato, 2007; H. W. Moser et al., 2004; Peters & Steward, 2003). After HSCT, some children with CALD achieve neurologic stabilization and remain asymptomatic, especially those that are transplanted with minimal radiographically evident, but clinically silent disease. Ideally, the transplant is performed promptly following detection of white matter disease on MRI and before CALD has progressed to symptomatic phases. Importantly, not all boys will benefit, particularly those with advanced cerebral disease. Those with symptomatic, higher cerebral disease burden at the time of transplant are more likely to have life-long difficulties related to the neurological deterioration that occurred prior to stabilization (Miller et al., 2011). There is interest in an approach to use autologous transplantation for CALD, using gene therapy techniques to restore expression of the ABCD1 gene in the patient’s own cells, but this is not readily available.

HSCT involves infusion of healthy hematopoietic stem cells typically from an HLA-similar donor following the recipient’s preparative regimen of intensive chemotherapy and, in some instances, radiotherapy (Bevans, Mitchell, & Marden, 2008). Currently, HSCT is the accepted treatment-of-last-resort for children diagnosed with one of approximately eight blood malignancies or over 20 nonmalignant diseases. This latter category may be further divided into five disease subgroups including hemoglobinopathies, metabolic storage disorders, bone marrow failure, immune deficiency, and unique rare disease (Pulsipher et al., 2010). Metabolic storage disease results from genetic abnormalities affecting lysosomal enzymes or peroxismomal function (Boelens, Prasad, Tolar, Wynn, & Peters, 2010). The decision to undergo HSCT for metabolic disease can be complex and is typically based on a variety of factors including the severity of the disease, the rate of progression, the child’s age, the availability of a suitable donor, and consideration of alternative therapies (Boelens et al., 2010).

Over the past 30 years, modifications in the field of HSCT have led to decreases in the morbidity and mortality of patients with nonmalignant and malignant disease. Identification of well-matched donors at human leukocyte antigen (HLA) loci are necessary as a source of hematopoietic stem cells capable of differentiating into all cellular components of the blood (Baron, Storb, & Little, 2003; Szilvassy, 2003). Approximately 4,500 children ages 0–17 years received HSCT between 2010 and 2013 compared to approximately 2,200 between 2002 and 2005 (Program, 2013). Estimates project that the total population of HSCT survivors who received transplants prior to 18 years of age will approach 64,000 by the year 2030 (Majhail et al., 2013). This growing population is at risk for health concerns that may be distinct from their peers. More than 80% of childhood HSCT survivors have at least one chronic condition, 60% have two or more chronic conditions, and 25% have a severe or life-threatening chronic condition following HSCT (Armenian et al., 2011).
HSCT involves significant risk including psychological, cognitive, and physical effects from the preparative chemotherapy and potential adverse late effects from the transplant including infertility, organ toxicity, neurocognitive changes, and graft versus host disease (GVHD) (Barrera, Boyd-Pringle, Sumbler, & Saunders, 2000; Bevans et al., 2008; Pulsipher et al., 2010). Immediate effects observed following transplant include negative physical symptoms associated with the preparative regimen. These physical manifestations include mucositis pain and gastroparesis resulting in nausea, vomiting, diarrhea, dependence on blood transfusions and antimicrobial therapy; and life-threatening complications from infection and GVHD (Chung, Lyckholm, & Smith, 2009; Pulsipher et al., 2010).

These stressors increase risk for poor adjustment and psychosocial function (Barrera, Atenafu, & Pinto, 2009). Anxiety is highest at the time of HSCT while anger and sadness emerge as anxiety declines (Phipps, Dunavant, Garvie, Lensing, & Rai, 2002). Adolescents demonstrate higher levels of discomfort and distress following HSCT compared to younger children (Phipps, Dunavant, Lensing, & Rai, 2002). Though long-term survivors of HSCT describe generally good QoL ratings, psychosocial implications of HSCT among survivors reaching adulthood include increased levels of anxiety and distress as well as perceived vulnerability (Felder-Puig et al., 1999). While QoL testing shows steady increases throughout the first year following HSCT, control-matched levels are not reached for up to 3 years following transplant (Clarke, Eiser, & Skinner, 2008). School-aged and younger children report higher QoL than adolescents, particularly in physical and emotional dimensions (Phipps et al., 2002).

Previous work among childhood HSCT survivors regardless of underlying disease demonstrates that children who undergo allogeneic HSCT have lower QoL than children who undergo autologous HSCT (Parsons et al., 2005; Rodday, Terrin, Parsons, Journeys to Recovery, & Study, 2013). Understanding quality of life (QoL) after HSCT is critical as the number of patients with CALD surviving HSCT grows. To date, QoL in childhood CALD patients following HSCT has not been robustly described. The World Health Organization (WHO) first defined QoL as “individuals’ perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns.” (Group, 1995). Ferrell’s QoL conceptual model further details four domains of QoL: physical, psychological, social, and spiritual well-being (Ferrell et al., 1992). Consequences of HSCT include lower immunity and decreased physical conditioning; changes in coping, hope, and religious beliefs; and altered appearance, relationships, and routines. Ferrell’s framework for HSCT survivors increases awareness about how HSCT impacts recipients’ daily lives and aids in the creation of instruments to evaluate QoL after HSCT (Ferrell et al., 1992).

Despite the importance of better understanding outcomes in this extremely vulnerable population, examination of QoL following HSCT for children with CALD remains unstudied. The primary aim of this descriptive, cross-sectional pilot study is to explore QoL among male survivors following HSCT for childhood CALD at the University of Minnesota Children’s Hospital. The secondary aim is to understand factors that are associated with QoL after HSCT for CALD, specifically: (A) to understand the effect on QoL of the child’s age at survey, time since HSCT, and pre-HSCT Loes score; and (B) to analyze the association among different aspects of QoL for these boys. It was
hypothesized that regardless of the child’s age or time from HSCT, boys with pre-HSCT Loes scores <10 would have higher mental, physical, and social QoL scores than those with Loes scores ≥10. Furthermore, it was hypothesized that peer interaction and the QoL domains of physical health, mental health, and social health would be inversely correlated with anxiety, anger, stigma, and depression; positive correlations would be observed for those variables with mobility and upper extremity function. A generalized understanding of the body of knowledge on the general QoL variables assessed following HSCT lays the foundation for a more specific approach in evaluating QoL in this unique population.

**Methods & materials**

This pilot study used a descriptive, cross-sectional approach to measure QoL following HSCT for treatment of CALD. Eligible survivors of HSCT for CALD at the University of Minnesota Medical Center were invited to participate. Patients were considered for inclusion if at the time of consent they were <25 years old, ≥180 days post-HSCT, had demonstrated stable donor engraftment at most-recent assessment, and were proficient in English. Approximately 180 days after HSCT the majority of patients are recovered from HSCT, no longer require immune suppressive medications, and have resumed their normal daily activities.

After approval from the University of Minnesota Institutional Review Board, the principal investigator (PI) obtained names of potential participants from the University of Minnesota HSCT database. Nine of the 75 males identified did not meet eligibility criteria; five were more than 21 years of age and four were deceased. The remaining 66 children and their parents received a mailing, which included an invitation letter with instructions, consent and assent forms, questionnaire, and a pre-paid addressed return envelope. Instructions guided families how to complete and return the consent and questionnaire. The family received a second mailing if there was no response within 1 month. For questions the child could not answer independently, the parent was instructed to read the questions to the child, or if needed, served as proxy for the child. If the respondent did not want to answer a question or was unable to answer the question, the respondent was instructed to leave the answer blank.

Participants completed a total of seven subscales selected from the Neuro-QoL and the PROMIS Pediatric Profile Instrument to measure physical, mental, and social QoL domains. Five selected Neuro-QoL short-form subscales were used instead of the full instrument in order to minimize participant burden. Two subscales from the PROMIS were selected to measure physical QoL because short-form subscales measuring physical QoL are not available for the Neuro-QoL instrument. Both the Neuro-QoL and PROMIS showed similar QoL ratings for child self-report and parent proxy measures (Bertisch et al., 2017).

Neuro-QoL is a series of self-report question banks that assesses health-related QoL in children with neurological diseases. Selected subscales from the Neuro-QoL included applied cognition-general concerns, pediatric social relations-interaction with peers, pediatric depression, pediatric anxiety, and pediatric anger. Each form asked the child to select a response based on recollection of the past 7 days. Responses range from “never” to “always” on a five-point Likert scale with higher responses corresponding to
higher levels of each subscale trait (Lai et al., 2012). Subscales are scored by converting raw scores into standardized T-scores with a mean of 50 and a standard deviation of 10 based on the United Status general population (National Institute of Neurological Disorders and Stroke (NINDS), 2015). A higher T-score equals presence of more of the concept measured. Before converting raw scores to T-scores, subscales were reviewed for missing values. Raw scores were imputed if 1 response was missing from the subscale. If there were two or more missed responses for a subscale, the score was not included in the analysis. As with previous literature (Lai et al., 2012, 2015), internal consistency for all respondents with the Neuro-QoL in this study was high across all domains (Cronbach’s alpha values: anxiety = 0.91, anger = 0.94, peer relations = 0.98, cognition = 0.90, depression = 0.94, stigma = 0.85).

Physical health was measured by the subscales of upper extremity function and physical mobility, which were selected from the PROMIS Pediatric Profile Instrument. Responses range from “not able to do” to “with no trouble” on a five-point Likert scale with higher scores indicating higher physical ability for each item. The PROMIS Pediatric Profile Instrument subscales are scored by converting the raw score into a standardized T-score distribution with a mean of 50 and a standard deviation of 10 based on the United Status general population (DeWitt et al., 2011; National Institute of Neurological Disorders and Stroke (NINDS), 2015). A higher T-score represents more of the concept measured. Prior to scoring, subscales were reviewed for missing values. Raw scores were imputed if 1 response was missing from the subscale but not included in the analysis if two or more responses were missing from a subscale. Similar to previous work (DeWitt et al., 2011; Hinds et al., 2013), respondent internal consistency was high (Cronbach’s alpha values: 0.98 for mobility and 0.97 for upper extremity function).

Basic demographic data were collected from the medical record including child’s ethnicity, transplant graft source, and child’s age at HSCT. Pre-HSCT CALD radiographic cerebral disease severity was measured by Loes score. The Loes score is an MRI-based measure of the extent of demyelination in patients with CALD, higher scores representing more severe disease (Loes et al., 1994). It is known that children with CALD with a Loes score >10 at the time of HSCT have inferior long-term survival compared to boys with lower Loes scores (Miller et al., 2011). All Loes scores were prospectively assigned by a single pediatric neuro-radiologist with expertise in Loes MRI scoring.

All analyses were completed using IBM SPSS Statistic (version 23.0). To appropriately describe the small sample, median, minimum, and maximum were used to summarize the T-scores for each subscale. Spearman’s rho correlations assessed the associations of QoL subscale T-scores with the demographic characteristics of age at survey, time since HSCT, and pre-HSCT Loes score, as well as the extent of the associations among the subscale scores. Mann-Whitney tests were used to test for differences in age, time since HSCT, and QoL with the males with pre-HSCT Loes scores <10 and males with pre-HSCT Loes scores ≥10. Statistical significance was determined by $p < .05$. Given that this was a pilot, descriptive study, no $a$ priori statistical powering for hypothesis testing was conducted nor were there any corrections to the alpha for multiple tests. The magnitude of the effect sizes (group differences and correlations) was the primary focus.
Results

Of 66 eligible males, 18 completed the study. Seven were unable to be reached because of inaccurate contact information. The remainder of eligible males did not respond to mail inquiries for the study. Data from two participants were discarded from analysis for lack of stable donor engraftment. Demographic characteristics of the 16 who were included in the analysis are presented in Table 1. Respondents were a median age of 8 years at HSCT (min = 5, max = 14), 14.5 years of age at survey (min = 8, max = 20) and were a median of 5 years since HSCT (min = 0.5, max = 11). Graft source was HLA-matched sibling donor marrow for 6 participants and unrelated umbilical cord blood for the remaining 10. The median pre-HSCT Loes MRI score for all participants was 6.8. Nine had pre-HSCT Loes scores <10 and seven had Loes scores ≥10. There were no statistically significant differences in the ages at HSCT or at survey, years since HSCT, ethnicity, or HSCT source between participants with Loes scores <10 and Loes scores ≥10 (p > .05). Neither were any statistically significant demographic differences observed in age at HSCT, years since HSCT, ethnicity, and pre-HSCT between those who responded to the mail questionnaires (n = 18) and those that did not (n = 48, p > .10).

QoL among boys with CALD after HSCT

Descriptive summaries of the QoL subscale scores are reported in Table 2. While the median T-score for each of the QoL subscales for all participants were within one standard deviation of the sample of healthy US children used in the development of the PROMIS and Neuro-QoL (National Institute of Neurological Disorders and Stroke (NINDS), 2015), there was

Table 1. Descriptive statistical summaries of child characteristics following HSCT for CALD (n = 16).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at HSCT (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall, n = 16</td>
<td>8</td>
<td>5</td>
<td>14</td>
<td>.125</td>
</tr>
<tr>
<td>Loes &lt;10, n = 9</td>
<td>8</td>
<td>5</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Loes ≥10, n = 7</td>
<td>9</td>
<td>8</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td><strong>Age at survey (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall, n = 16</td>
<td>15</td>
<td>8</td>
<td>20</td>
<td>.522</td>
</tr>
<tr>
<td>Loes &lt;10, n = 9</td>
<td>15</td>
<td>8</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Loes ≥10, n = 7</td>
<td>14</td>
<td>10</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td><strong>Time since HSCT (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall, n = 16</td>
<td>5</td>
<td>0.5</td>
<td>11</td>
<td>.122</td>
</tr>
<tr>
<td>Loes &lt;10, n = 9</td>
<td>7</td>
<td>0.5</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Loes ≥10, n = 7</td>
<td>2</td>
<td>0.5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td><strong>Loes Score (pre-HSCT)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>7</td>
<td>2</td>
<td>18</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Loes &lt;10, n = 9</td>
<td>4</td>
<td>2</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Loes ≥10, n = 7</td>
<td>15</td>
<td>10</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td><strong>Overall N(%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>13 (81%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>3 (19%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSCT source</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cord blood</td>
<td>9 (56.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matched sibling</td>
<td>7 (43.8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
considerable variability in the scores. This variation is partially explained by the differences between the subgroups of boys with pre-HSCT Loes scores <10 and boys with Loes scores ≥10. Compared to those with pre-HSCT Loes scores <10, those with Loes scores ≥10 had lower median scores for mobility (28.4 vs. 58.5, \(p = .001\)), peer interaction (38.1 vs. 59.1, \(p = .009\)), upper extremity function (23.5 vs. 56.7, \(p = <.001\)) and higher scores for depression (44.3 vs. 58.1, \(p = .017\)) and anxiety (47.7 vs. 60.4, \(p = .032\)) (Table 2).

### QoL correlational analysis

Correlations among the QoL subscales and with the pre-HSCT Loes scores are summarized in Table 3. The strongest statistically significant positive correlations among the domains were of anxiety with depression (.89, \(p < .001\)) and mobility with upper extremity function (.89, \(p < .001\)). The strongest statistically significant inverse correlation was between anxiety and peer interaction (−.88, \(p < .001\)). Pre-HSCT Loes scores demonstrated statistically significant inverse correlations with peer interaction (\(r_s = -.53, p = .043\)), mobility (\(r_s = -.65, p = .007\)) and upper extremity function (\(r_s = -.74, p = .001\)). Age at time of HSCT was positively associated with the QoL depression score (\(r_s = .53, p = .041\)). No other statistically significant
prior the use of HSCT, no treatments were successful in preventing progression of CALD long term (H. W. Moser, Raymond, & Dubey, 2005). Current research describes survival outcomes (Gassas et al., 2011; Miller et al., 2011) following HSCT for CALD but fails to describe QoL for these children, an important consideration for families both deciding to undergo and preparing for life after the child’s HSCT. This study is the first to describe QoL for survivors of HSCT for CALD.

QoL scores for measured domains of physical, mental, and social health for this sample of children with CALD at a median of 5 years after HSCT is similar to healthy peers. It is known that survival post-HSCT is more likely for children with Loes scores less than 10 (Miller et al., 2011). This study also suggests that boys with pre-HSCT Loes scores <10 experienced QoL similar to healthy children and higher than those with Loes scores ≥10. These findings provide further rationale for the general international recommendation to identify cerebral disease as early as possible in boys known to have ALD. This is currently best achieved through monitoring serial MRI, and pursuing HSCT at the onset of radiographic white matter disease when CALD is still clinically silent (Boelens et al., 2010). Though pre-HSCT Loes score ≥10 may be a risk factor for lower QoL post transplant, it is important to note that the group of males with Loes scores ≥10 was only a median of 2 years from HSCT. Previous literature shows QoL for children after HSCT improves over time and reaches the level of a control healthy population after approximately 3 years (Felder-Puig et al., 2006; Liu et al., 2016). No other demographics including child’s age at HSCT, child’s age at survey, or years since HSCT were significantly correlated to QoL subscales.

Children with pre-HSCT Loes scores ≥10 experienced lower mobility and upper extremity function compared to those with Loes scores <10; furthermore, collective function among this group was >1 standard deviation below average for the test’s

Table 3. Correlations among the QoL subscales (n = 16).

<table>
<thead>
<tr>
<th></th>
<th>Anger</th>
<th>Anxiety</th>
<th>Cognition</th>
<th>Depression</th>
<th>Mobility</th>
<th>Peer interaction</th>
<th>Stigma</th>
<th>Upper extremity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anger</td>
<td>–</td>
<td>.44</td>
<td>−.74</td>
<td>.63</td>
<td>−.53</td>
<td>−.46</td>
<td>−.05</td>
<td>−.35</td>
</tr>
<tr>
<td>Anxiety</td>
<td>–</td>
<td>–</td>
<td>−.61</td>
<td>.89</td>
<td>−.77</td>
<td>−.88</td>
<td>.57</td>
<td>−.45</td>
</tr>
<tr>
<td>Cognition</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>−.60</td>
<td>.47</td>
<td>.56</td>
<td>−.31</td>
<td>.20</td>
</tr>
<tr>
<td>Depression</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>21</td>
<td>−.78</td>
<td>.21</td>
<td>−.52</td>
</tr>
<tr>
<td>Mobility</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>.83</td>
<td>−.14</td>
<td>.89</td>
</tr>
<tr>
<td>Peer interaction</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>−.27</td>
<td>.61</td>
</tr>
<tr>
<td>Stigma</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>.04</td>
</tr>
<tr>
<td>Upper extremity</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Spearman’s rho correlation values in the cells are r (p-value).
normative population of healthy children. Physical limitations after HSCT are not unique to children with CALD. Physical function impairment was also observed in diverse samples of pediatric HSCT survivors with hematological and oncological disease (Armenian et al., 2011; Barrera & Atanafu, 2008; Liu et al., 2016). Aside from neurological impairment caused by CALD, most children following HSCT are at risk for avascular necrosis, decreased bone density, and pulmonary disease secondary to the preparative conditioning, which may also contribute to impaired physical function (Chow et al., 2016). Long term, approximately 10% of childhood survivors of HSCT have physical activity restrictions for routine daily activity and personal cares, and this is also associated with emotional and social performance (Ness et al., 2005).

From a psychological perspective, this study found an inverse association between anger, depression, and anxiety with mobility and cognitive function among boys with CALD after HSCT. Depression symptoms were more prevalent the older children were at time of HSCT. Similarly, previous longitudinal work following children after HSCT has identified that emotional QoL improves more quickly in younger children who undergo HSCT (Barrera, Atanafu, & Hancock, 2009). While some studies have reported normal emotional function after HSCT (Liu et al., 2016), others have described increased risk for anxiety and mood disorders long term after a child’s HSCT (Chang et al., 2012). Due to these risks, the Children’s Oncology Group HSCT survivor guidelines recommend annual psychosocial assessment to monitor for mental health difficulties (Chow et al., 2016). Similar approaches may be useful in this population.

The correlations between the QoL subscales demonstrate the complex interaction between social function and the children’s mental and physical health. The more the children exhibited mobility and mental difficulties, the more they experienced difficulty interacting with peers. This could be explained in part by previous research showing some children experience physical or emotional challenges requiring special education after HSCT (Ness et al., 2005). Children after HSCT are more likely to have frequent school absence or be held back an academic year (Liu et al., 2016), further limiting opportunity for peer interaction. Even children without CALD who return to school after HSCT initially struggle to return to academic coursework and extracurricular activities (Felder-Puig et al., 1999). The added neurological dysfunction experienced by boys with CALD likely heightens these challenges. Interestingly, despite the decreased ability for children with CALD after HSCT to experience normal peer relationship, children did not find the disease caused social stigma.

This study was limited by the cross-sectional design, small sample size, and great variation in time since HSCT. Due to the continued decline and ultimate death of boys with CALD who do not undergo HSCT, a control group comparison of boys with progressing CALD that do not undergo HSCT is not possible. The frequency of parent-proxy needed to complete the QoL surveys is not known for this sample and validity of parent-proxy for the Neuro-QoL is not described. The study was the first to use the relatively new QoL instrument, Neuro-QoL, among children with CALD. While the Neuro-QoL is designed to measure the unique challenges that are experienced by children with a neurological condition, it is difficult to compare QoL for children with CALD to children undergoing HSCT for other conditions.

Despite these limitations, this was the first study to measure QoL among children with CALD after HSCT. The study provides further support for early HSCT among clinically asymptomatic boys with early stages of MRI-evident CALD. This study shows
that physical, emotional, and social QoL is improved when HSCT occurs early at the onset of demyelination rather than waiting until brain demyelination worsens.

Future research should employ longitudinal designs to better understand how QoL changes over time, beginning with a pre-HSCT assessment of QoL. This approach will enable researchers to identify the time points when interventions are needed to support this unique patient population. Those with pre-HSCT Loes scores ≥10 are the most vulnerable to poor QoL. Further research is needed to understand the unique physical, emotional, and social needs of this group. For example, impaired mobility and difficulty interacting with peers after HSCT may be improved by supportive modalities. This in turn may improve peer interaction and alleviate symptoms of anger, depression, and anxiety. Further investigation is needed to understand the needs of boys as they transition back into schools and communities after HSCT. Finally, most boys at time of our survey were in adolescence, therefore, long-term research is needed to understand the health and long-term QoL of these children as they enter adulthood.

This study demonstrates the need for anticipatory guidance and education for boys and their families as they decide to undergo HSCT. It is important to educate families not only about survival following HSCT but also the potential physical, emotional, and social challenges encountered by transplant survivors. Health providers should support and guide families in learning to care for the child with CALD post-HSCT, particularly among boys with pre-HSCT scores ≥10. There is a need for care coordination between the HSCT center, the child’s school, and the primary care provider after HSCT to facilitate resources and ongoing support for the child and family.

In summary, pre-HSCT Loes scores ≥10 appears to be a risk factor for lower physical, mental, and social QoL. Though ongoing research and interventions are needed to support all childhood survivors following HSCT, this study suggests that QoL may be specifically enhanced in the ALD population by early biochemical diagnosis followed by careful radiographic surveillance and prompt HSCT consultation at the first sign of cerebral disease. This is essential for not only increased survival but also to preserving QoL among this population.

Disclosure statement

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