



Stopping the
progression of ALD

Jean Kelley DIRECTOR

Statement of Jean Kelley and John Kelley, M.D.

SENATE BILL 465, AN ACT REQUIRING NEWBORN SCREENING FOR ADRENOLEUKODYSTROPHY

February 27, 2013

Senator Gerrataña, Representative Johnson, and Public Health Committee Members

Thank you for providing us with this opportunity to appear here today. We are honored to speak in support of this vital bill. We are especially excited at the possibility of making a change in the outcome of the lives of boys who have Adrenoleukodystrophy and their families. Early detection of Adrenoleukodystrophy will help avoid undue suffering and the enormous emotional and financial costs associated with the treatment and care of the full onset of the disease. That is possible now. We have a test that detects ALD from newborn blood spots.

Adrenoleukodystrophy, or ALD, is a life threatening disorder that often causes adrenal gland failure, as well as neurologic dysfunction, affecting the brain and/or spinal cord. ALD has 3 characteristics of phenotypes: adrenal insufficiency that all get at a very young age, cerebral demyelination in about 40% of the children which leads to death, and AMN as an adult if they live to that age. It is truly a parent's worst nightmare. We know. This was our experience with our warrior, Brian.

Brian was diagnosed with the cerebral demyelination form of ALD at the age of 6 after suffering a head injury. While sledding one day, Brian hit his head on a woodpile. At the Yale ER, a CAT Scan and follow up MRI led to Brian's diagnosis. Within 6 months of Brian's diagnosis he lost his mobility, speech, ability to eat and most of his vision. Since there was no newborn screening at the time of Brian's birth and although this is a X-linked hereditary disease, there were no red flags in our family. Had his condition been detected at birth, early intervention would likely have altered the outcome.

Despite his disabilities there is much Brian is able to do. In his very quiet way and with his tenacity to persevere, he has inspired us to move on and impact others in a positive way, such as this. Adoption of ALD newborn screening will be Brian's legacy so his many challenges in life were meant to help others and were not in vain.

Early detection is crucial. The missed diagnosis of newborns with ALD, will most importantly, result in the needless suffering and loss of lives. At best, ALD results in neurological impairment, developmental delays, long-term feeding issues, and costly therapies, all at huge costs to the health care system and tremendous emotional pain for the families of these precious children. Physicians, hospital administrators, and advocates clearly understand that early detection of newborn diseases and disorders saves lives and dramatically reduces health care costs and burdens associated with deferred diagnosis. Add to this, the very expensive cost of educating children with special needs as a result of the disease and the financial cost of ALD can easily run into the millions of dollars per child.

Newborn screening for ALD is a simple and cost-effective solution to these problems; a simple newborn screening, costs \$1.50 per child and would be part of the existing newborn screening panel. The savings—both in dollars and in needless suffering—are dramatic.

It is completely within our power to keep babies born with the potential for this devastating disease well, setting them up for a normal and healthy adulthood. Treatment is most effective if begun before symptoms of ALD appear. For this reason, it is vital that parents have the information so that they can make the best possible medical choices for their children. This one intervention could save lives.

We believe this testing should become a standard of care for all newborns, prior to discharge from the hospital. We urge you to leverage your leadership and expertise in public health to support this important bill. SB#465 will save lives and money. It is that simple. The time is right...there is an accepted method and treatments. Let's make this happen.

Screening Newborns for Adrenoleukodystrophy

Adrenoleukodystrophy

Adrenoleukodystrophy (ALD) is a life threatening disorder that often causes adrenal gland failure, as well as neurologic dysfunction affecting the spinal cord and/or brain.

The disease is passed down from parents to their children as an X-linked genetic trait.¹ It therefore affects mostly males, although some women who are carriers can have milder forms of the disease. It affects approximately 1 in 17,000 people from all races. The condition results in the buildup of very-long-chain fatty acids in the nervous system, adrenal gland, and testes, which disrupts normal activity. There are three major categories of disease:

- Childhood cerebral form -- appears in mid-childhood (at ages 4 - 8)
- Adrenomyelopathy -- occurs in men in their 20s or later in life
- Impaired adrenal gland function (called Addison disease or Addison-like phenotype) -- adrenal gland does not produce enough steroid hormones

Newborn Screening

Connecticut law requires newborns to be screened in the hospital for a number of diseases including cystic fibrosis, severe combined immunodeficiency, critical congenital heart disease, HIV, sickle cell and other tests that determine if the newborn has inborn metabolic or other disorders (Section 19a-55).

The Federal government is currently monitoring a study underway at the Mayo Clinic's Biochemical Genetics Laboratory to develop the best possible screening test using dried blood spots from anonymous newborns to test for ALD. We expect the results of this work could be completed and forwarded to the federal panel that will consider newborn screening protocols in May 2013. A larger study would then occur before a final recommendation is made to the Uniform Screening Panel in 2014.

ALD met all the criteria to be included in the uniform newborn screening panel and the initial preliminary results from the Mayo clinic were 12 positives out of 42,000 samples. Due to the extensive time this will take for each state to implement, too many children will be put at significant risk, many of them dying.

¹ www.nih.gov

The legislation we are seeking will add screening for Adrenoleukodystrophy to the existing newborn screening panel.

Life-saving Test

- *It is an inexpensive and sensitive screening test.
- *It is an opportunity to detect complications from the disease before there are symptoms.
- *There are treatments, which if given in the early phase, dramatically improve the outcome.
- *If treatment is delayed until the condition is apparent clinically, the outcome is much worse.
- *Up to this point, early, often life-saving treatment has been available only to those diagnosed because a relative suffered the disease.

Brian Kelley

Brian Kelley is a 24-year old, young man from Branford who was diagnosed with ALD at the age of 6. Unfortunately, Brian was already symptomatic. There were no red flags in his family. Had the newborn screening for ALD been in place at the time of Brian's birth, he would not be facing the great challenges he does today. With great courage and tenacity, Brian has taught much to many in his very quiet way for the past 18 years. We hope we can honor Brian by making a difference in the lives of others diagnosed with ALD.

Connecticut Facts

Connecticut Birth Rate: 37,708 per year

Price of test: \$1.50-2.00 per test

Cost per year to add ALD newborn screening: \$56,500-74,000

Mission Statement of the Connecticut Department of Public Health

To protect and improve the health and safety of the people of Connecticut by:

- *Assuring the conditions in which people can be healthy
- *Preventing disease, injury, and disability, and
- *Promoting the equal enjoyment of the highest attainable standard of health, which are a human right and a priority of the state

**The time is right.... there is an accepted method and treatments.
Let's make this happen.**

HAMLET M. HERNANDEZ
Superintendent

MARY PERARO, Ed.D.
Assistant Superintendent

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Chief Financial Officer



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Cost Estimate for 12 years of Brian's Education

Paraprofessional Salary-Gross Pay- \$21,254.00/ Extended School Year-\$2,360.00 per year

Transportation-School Year-\$45,974.00/ Extended School Year-\$5,080.00 per year

OT/PT Therapy-based on 3 hours a week-\$3,195.3/Extended School Year-\$1,065.12 per year

Assistive Technology Evaluation-\$20,000 (based on 12 years of education)

Computer Software/Hardware-\$15,000 (based on 12 years of education)

Wheelchair- (2) at \$30,000.00 (this is often a covered cost by insurance)

\$927,266 is the estimated total without the cost of the chairs.

Progress Made toward Universal Newborn Screening for X-linked adrenoleukodystrophy (ALD)

History and recent developments:

It was Hugo Moser's dream to identify boys with ALD early, at a time before Addison's disease and brain dysfunction occurred. In 2005 Hugo suggested to the national newborn screening committee that ALD be added to the list of disorders that would possibly benefit from newborn screening, however, at that time there was no test for ALD utilizing the sample collected on all newborns, the heel stick blood spot on filter paper.

In order to develop a newborn test for ALD Hugo and I contacted Walter Hubbard, Ph.D. at the Dept. of Clinical Pharmacology at Johns Hopkins. Walter is an expert in liquid chromatography tandem mass spectroscopy (LC/MSMS) of lipids and he was interested in helping us devise a test for ALD utilizing the newborn dried whole blood spot (DBS). We first used LC/MSMS to measure the total lipid C26 fatty acid content of the DBS and also the C26 content of other lipids such as ceramides and sphingomyelins, but found that the naturally high red blood cell C26 content interfered and gave many false positives. Finally in January of 2006, we determined that the C26 content of the lyso phosphatidylcholines (lyso PC) was 5 to 10 fold higher in whole venous blood spots from ALD patients when compared with controls. This finding was published in the *Molecular Genetics and Metabolism* in 2006. There was still much more work to be done to validate the assay. We contacted Walter Shaw at Avanti Lipids and paid for the custom synthesis of an authentic C26:0 lyso PC standard and a 4 deuterium labeled C26:0 lyso PC as an internal standard. With IRB permission, we obtained the newborn blood spots from known ALD patients born in the states of CA and MI. At the same time we also tested anonymous leftover newborn DBS from the States of MD, CA, the CDC and Costa Rica and found no positives. The ALD newborn DBS had a 5 to 15 fold increased C26:0 lyso PC with no overlap when compared with the anonymous newborn DBS. These findings were published in *Molecular Genetics and Metabolism* 2009. Since that time we have developed a high throughput LC/MSMS screening procedure and have published a combined extraction of the C26:0 lyso PC with that of the acyl carnitines. Recently together with the MD State Newborn Screening Lab, we have completed the screening of 5000 consented newborns born in 3 local Baltimore hospitals and did not find one positive, thus we believe that using our procedure the false positive rate will be low.

From the beginning of our interest in developing ALD newborn screening, our colleagues Drs. Piero Rinaldo, Silvia Tortorelli and Dieter Matern at the Mayo Clinic were very supportive of our initial efforts and made significant contributions to the design of our study and to our method of analysis. In addition at the newborn screening lab at the Mayo Clinic, they developed their own rapid high throughput method of LC/MSMS analysis of the newborn DBS for ALD and obtained funds to do 100,000 anonymous newborn DBS from the state of California. To date they have analyzed 60,000 and have found 20 positive samples. The plan is to confirm these positives by DNA sequencing of the ALD gene in these positive newborn DBS samples. Steven Steinberg, PhD and colleagues at the DNA Diagnostic Lab at Johns Hopkins will provide the DNA analyses. We expect to find that most of the positives, both males and females, will have a mutation in the ALD gene, but there may be a few positives from newborns with Zellweger spectrum disorders and these samples will be analyzed and confirmed by the Peroxisomal Lab at the Kennedy Krieger Institute.

In order to have ALD newborn screening confirmed for inclusion in the panel of disorders recommended for newborn screening nationally, Amber Salzman, PhD and Charlie Peters, MD prepared the nomination form for the inclusion of ALD. The nomination was reviewed and on September 13, 2012 Gerald Raymond, MD, Amber Salzman's 12 year old son, Spencer Barsh, 14 year old Taylor Kane, daughter of Jack Kane who died with ALD, and I testified before the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (HRSA) in Washington on behalf of many advocate organizations including: The Stop ALD Foundation, ALD/AMN Global Alliance, Be A Hero Become A Donor, Fight ALD, The Myelin Project, Run4ALD, ELA and the ULF. Unfortunately the HRSA Review Committee did not recommend inclusion of ALD in the Recommended Uniform Screening Panel at this time. The following quotes are from a letter from Joseph A. Bocchini Jr, MD, Chairperson of HRSA dated 10/1/12.

"The Committee recognizes ALD as a medically important disorder that deserves serious consideration, possessing a well-established case definition as well as screening, diagnostic, and treatment protocols. However, at this time the Committee has decided to not send the nomination forward to the external review group.

The Committee's decision is based primarily on the determination that sufficient prospective data is not yet available from the large pilot study presently underway at the Mayo Biochemical Genetics Laboratory (MBGL).

After the additional data from the MBGL study is made available to the Committee for evaluation, we encourage you to contact us to facilitate an expedited review. The Committee will then determine whether the new data provides sufficient support for the Committee to request a formal review of the scientific evidence by the external condition review group."

Based on the letter from HRSA we are proceeding with our plan to confirm the positive newborn DBS from the pilot study at Mayo. It is our hope that sufficient data will be available for the May 16th 2013 meeting of HRSA and that the Review Committee will accept the nomination that ALD newborn screening be forwarded to the external review group where it will take up to a year before the final recommendation of ALD to the Uniform Screening Panel.

Yesterday I forwarded 120 anonymous venous DBS from ALD, ALD heterozygotes, and Zellweger spectrum disorders from our collection of consented research samples to Silvia Tortorelli, MD at the Mayo Clinic so that the positive sample data collected by the Mayo Clinic can be augmented. We thank all the patients and their families for their willingness to provide samples for the ALD DBS screening data.

Ann Moser, January 9, 2013

NEWBORN SCREENING UNIFORM PANEL			
NOMINATION FORM FOR PROPOSED CONDITION			
Name of Proponent Charlie Peters, MD	Advocate Organizations: The Stop ALD Foundation; ALD/AMN Global Alliance, Be A Hero Become a Donor, Fight ALD, The Myclin Project, Run4ALD, ELA, ULF	Date May 4, 2012	
Condition	X-linked Adrenoleukodystrophy (ALD)		
Type of Disorder	Adrenal insufficiency and neurodegeneration		
Screening Method	High throughput screening assays and tandem mass spectrometry of dried blood spots		
Treatment strategy	Hormone replacement therapy for adrenal insufficiency, hematopoietic cell transplant (HCT) for cerebral demyelination		

CONDITION	Comment	Gene:	ABCD1	Locus:	Xq28	OMIM	300100
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*Note: Please reference each statement, listing references below (p.2)

Incidence	Determined by clinical identification. In the US, the estimated combined male and female frequency of ALD is 1:17,000 [1].
Timing of clinical onset	Distinct phenotypes exist with virtually all males developing adrenal insufficiency, some as early as 1 yr [2]. All phenotypes can occur in a kindred [1] with 31-35% of affected males having the demyelinating childhood cerebral form (CCER) [1] with typical onset between 4 and 8 yrs [1]. Boys develop normally until the onset of dementia and progressive neurologic deficits which lead to a vegetative state and death often within 3 yrs [1]. Forty to 46% of males with ALD present in mid-adulthood with slowly progressive paraparesis, sensory, and sphincter disturbances involving spinal cord long tracts (adrenomyeloneuropathy, AMN) [1]. At least 30% of men with AMN develop cerebral involvement that is similar to CCER [1]. Fifty per cent of heterozygous females develop overt neurologic disturbances resembling AMN, with a mean age of onset of 37 yrs [1].
Severity of disease	Untreated adrenal insufficiency can be fatal and untreated CCER is fatal. Earlier onset of CCER correlates with more severe, rapidly progressive clinical manifestations [3]. Boys with parieto-occipital lobe disease demonstrate visual and/or auditory processing abnormalities, impaired communication skills and gait disturbances, prior to death. The neuropsychological consequences have been described [1]. Boys with frontal lobe involvement have signs/symptoms similar to ADHD and are often misdiagnosed, prior to death. The extent of demyelination can be quantitated using the MRI severity score of Loes [4]. The presence of gadolinium contrast enhancement in areas of cerebral demyelination on brain MR imaging is highly positively predictive of clinically significant disease progression [3,5].
TEST	Comment
Screening test(s) to be used	Pilot 1: Analysis by tandem mass spectrometry with or without chromatographic separation of lyso-phosphatidyl choline (LPCs) species (C20 to C26) [6][13]. Pilot 2: Analysis of these compounds can be multiplexed with other analytes (e.g., acylcarnitines, lysosomal enzymes).
Modality of screening	Dried blood spots, the same specimen and collection modalities that are currently used for newborn screening tests
Clinical validation	<i>Pilot study 1:</i> 5,000 newborns completed by Kennedy Krieger Institute (KKI). <i>Pilot study 2:</i> 100,000 anonymous newborn specimens to be analyzed at Mayo Clinic for analytical validation (25,000 as of April 2012). <i>Clinical validation of the test (KKI):</i> 16/16 ALD newborn blood spots; 2/2 PBD (peroxisomal biogenesis disorders) newborn blood spots; 0/0 ALD carrier newborn blood spots; 105/105 ALD not newborn blood spots; 66/66 PBD not newborn blood spots; 95/118 ALD carrier not newborn blood spots [6]. <i>Clinical validation of the test (Mayo Clinic):</i> 20/20 ALD newborn blood spots; 2/2 PBD newborn blood spots; 3/5 ALD carrier newborn blood spots; 12/12 ALD non-newborn blood spots; 6/6 PBD non-newborn blood spots; 9/12 ALD carrier non-newborn blood spots [??].
Laboratory performance metrics	<i>Pilot study 1:</i> true positive cases: 0; false positive cases: 0.[14] <i>Pilot study 2:</i> true positive cases: to be determined (TBD) false positive cases: TBD (expected:<< 0.1%) [??].
Confirmatory testing	Analysis of very long-chain fatty acids in plasma by GC/MS: elevated in 99.9% of affected males and 85% of heterozygous females. Mutation analysis of the ABCD1 gene. In addition, the KKI Peroxisomal Diseases Laboratory has set up analyses of plasmalogens and peroxisomal bile acid intermediates on dried blood spots [??].
Potential harms of screening and testing	Patients affected with peroxisomal biogenesis disorders and 70-85% of ALD heterozygous females will be detected by this assay. Post analytical tools based on the R4S model are available to discriminate these cases from females affected with other peroxisomal disorders [??].

NOMINATION OF CONDITION (page 2)

TREATMENT	Comment
Modality	Maintenance and stress-dosing adrenal hormone replacement therapy is the standard of care for primary adrenal insufficiency including that associated with ALD [2]. HCT is the only effective long-term treatment for CCER; however, to achieve optimal survival and clinical outcomes, HCT must occur prior to manifestations of symptoms [7-10]. Gene therapy experimental treatment has been shown to be safe and efficacious [11].
Urgency	It is imperative to implement by 3 months the following: (a) adrenocortical function testing to detect adrenal insufficiency and by 3 yrs (b) serial neuroimaging to detect the earliest evidence of demyelination [9,12]; therefore timely diagnosis is critical. The recommended evaluation for boys 3 to 15 yrs is comprehensive neurologic, neuropsychological, neuroradiologic, and adrenal function evaluations at diagnosis with serial monitoring at least every 6 months during the 1 st decade of life and annual monitoring in the 2 nd decade [9,12]. The goals are: (a) to detect cerebral disease early, prior to the development of neuropsychological and/or neurologic signs/symptoms, and (b) to identify adrenal insufficiency, a potentially life-threatening condition, and to treat it. Monitoring is essential and critical since phenotype cannot be predicted and there is no genotype-phenotype correlation. Early knowledge of an ALD diagnosis is critical for the treatment of a patient during the narrow therapeutic window [9].
Efficacy (Benefits)	Reports have described the initial success of HCT for a patient with CCER [7], long-term beneficial effects of HCT [8], and large international HCT experience [9]. By using this monitoring strategy (see above), timely and effective HCT can be achieved i.e., 95% 5-year survival, with excellent clinical outcomes compared to 54% survival for a similar group not treated by HCT [10]. Of note, boys in the untreated group progressed to a vegetative state and death. Survival for transplanted patients is 92% for boys with <u>early stage</u> brain disease compared with 45% at 5 years for patients with <u>late stage</u> disease [9]. Identification of ALD can lead to timely diagnosis of adrenal insufficiency and initiation of hormone replacement therapy [2]. A metabolic crisis due to unrecognized and consequently untreated adrenal insufficiency can be fatal or result in significant morbidity with long-term sequelae including profound, rapid neurologic deterioration in boys with CCER [2,9].
Availability	Adrenal hormone therapy is available to treat adrenal insufficiency. Due to volunteer bone marrow donor registries, umbilical cord blood banks, HLA-matched related donor(s) and autologous hematopoietic cells (HCs), a suitable source of therapeutic HCs is available for all patients [11,12]. This applies to patients with CCER as well [9,11].
Potential harms of treatment	Adrenal hormone therapy for adrenal insufficiency has no adverse effects but, rather, can be life-saving [2]. While HCT carries risk of morbidity (e.g., acute and chronic GVHD, cardiac, pulmonary, GI, skeletal and endocrine complications) and mortality, HCT safety is markedly enhanced when it is performed prior to clinical manifestations and at an early stage of disease in CCER patients [9,12].

KEY REFERENCES (Specific citations – limit to 15)

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3	Moser HW, Loes DJ, Melhern ER, et al. X-linked adrenoleukodystrophy: overview and prognosis as a function of age and brain magnetic resonance imaging abnormality. A study involving 372 patients. <i>Neuropediatrics</i> 2000;31:227-39.
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5	Melhern ER, Loes DJ, Georgiades CS, Raymond GV, Moser HW. X-linked adrenoleukodystrophy: the role of contrast-enhanced MR imaging in predicting disease progression. <i>AJNR Am J Neuroradiol</i> 2000;21:839-44.
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11	Cartier N, Hacein-Bay-Abina S, Bartholomae CC, et al. Hematopoietic stem cell gene therapy with a lentiviral vector in X-linked adrenoleukodystrophy. <i>Science</i> 2009;326:818-23.
12	Appelbaum FR, Forman SJ, Negrin RS, Blume KG, eds. <i>Thomas' Hematopoietic Cell Transplantation</i> . 4 th ed. Oxford: Wiley-Blackwell, 2004, chapters: 11-13, 15-17, 19, 21-23, 25, 27, 29, 30-31, 33, 34, 36-39, 46-48, 77, 80-108.

13	Sandlers Y, Moser AB, Hubbard WC, Kratz LE, Jones RO, Raymond GV. Combined extraction of acyl-carnitines and 26:0-lysophosphatidylcholine from dried blood spots; prospective newborn screening for X-linked adrenoleukodystrophy. Molec Genetics Metabol, 2012;105:416-420.
14	Statement from Kennedy Krieger

Submission Check list		Submit Nominations to:	
	Cover letter by proponent	Sara Copeland, MD Acting Chief, Genetics Services Branch Division of Services for Children with Special Health Needs Maternal and Child Health Bureau 5600 Fishes Lane, Room 18-A-19 Rockville, MD 20857 301-480-1312 - fax 301-443-1080 - phone	
	Nomination form		
	Copy of references listed on this form		
	Formal conflict of interest statement by proponent		
Contact information (proponent) Charlie Peters, MD <u>cjpeters1982@earthlink.net</u> (612) 760-6192			

Field Code



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Secretary's Advisory Committee on Heritable
Disorders in Newborns and Children
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October 1, 2012

Charles Peters, M.D.
48055 252nd Street
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Amber Salzman, Ph.D.
The Stop ALD Foundation
500 Jefferson Street, Suite 2000
Houston, Texas 77002-7371

Dear Drs. Peters and Salzman:

The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (Committee) appreciates your nomination of X-linked Adrenoleukodystrophy (ALD) for inclusion in the Recommended Uniform Screening Panel (RUSP) for state newborn screening programs. As part of the formal review process, the Nomination and Prioritization Committee conducted a preliminary review of the nomination package, and results were presented for discussion and a decision during the September 2012 Committee meeting. A copy of the presentation is enclosed.

The Committee recognizes ALD as a medically important disorder that deserves serious consideration, possessing a well-established case definition as well as screening, diagnostic, and treatment protocols. However, at this time, the Committee has decided to not send the nomination forward to the external condition review group.

The Committee's decision is based primarily on the determination that sufficient prospective data is not yet available from the large pilot study presently underway at the Mayo Biochemical Genetics Laboratory (MBGL).

After additional data from the MBGL study is made available to the Committee for evaluation, we encourage you to contact us to facilitate an expedited review. The Committee will then determine whether the new data provides sufficient support for the Committee to request a formal review of the scientific evidence by the external condition review group.

Please contact Lisa Vasquez (lvasquez@hrsa.gov) when you are prepared to submit any additional data or if you have any questions or concerns.

Thank you for your nomination of ALD for inclusion in the RUSP for state newborn screening programs.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Joseph A. Bocchini Jr.", written in dark ink.

Joseph A. Bocchini Jr., M.D.
Chairperson

Enclosure:

SACHDNC Nomination and Prioritization Workgroup Presentation: ALD

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September 12, 2012

Re: Newborn Screening for Adrenoleukodystrophy

To Whom It May Concern:

We submit this letter at the request of Mrs. Elisa Seeger, mother of Aiden Seeger who died from X-linked adrenoleukodystrophy (ALD) at the age of 7 years. It is our understanding that Mrs. Seeger is working towards the inclusion of ALD in the New York state newborn screening program. We applaud her efforts and, by submission of this letter, state our full support to achieving this aim.

We comprise the Blood and Marrow Transplantation team with a focus on ALD at the University of Minnesota. Our institution has a long history of treating children with life-threatening, inherited metabolic disorders which are amenable to blood stem cell therapy. We have performed over 135 blood stem cell transplants for boys with adrenoleukodystrophy (ALD).

ALD is a life-threatening disorder that often causes adrenal gland failure, as well as neurologic dysfunction, affecting the spinal cord and/or brain. In its most devastating form, children develop rapidly progressing brain disease. Currently, no prevention for this form of ALD has been identified. In addition, no "cure" for the cerebral form of ALD has been discovered. However, blood or marrow transplantation is effective in arresting progression of this otherwise fatal disease. To achieve the best outcomes, transplantation needs to be performed at the earliest onset of brain involvement.

Unfortunately, many boys with ALD go un-diagnosed until significant symptoms of cerebral disease have developed. For these boys, survival and neurologic outcomes after blood stem cell transplantation are inferior. In some cases, transplant is not feasible due to very advanced disease, and all that the families can do is care for these boys as best they can as they deteriorate neurologically, and eventually die.

Therefore, early diagnosis of ALD followed by routine, serial brain MRI screening has the potential to dramatically impact treatment options for affected boys with ALD. The critical aspect in achieving optimal outcomes is a means of detection of the disease before it results in too much damage to the brain. In this circumstance, ALD is an excellent candidate for making a difference in this devastating disorder.

We unequivocally support Mrs. Seeger's charge to include adrenoleukodystrophy in the New York State screening program.

Sincerely,



Paul Orchard, MD
Director, Metabolic Transplant Program
University of Minnesota
Pediatric Blood and Marrow Transplantation



Jakub Tolar, MD, PhD
Albert D. and Eva J. Corniea Chair
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Troy Lund, MD, PhD
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blood

2011 118: 1971-1978
Prepublished online May 17, 2011;
doi:10.1182/blood-2011-01-329235

Outcomes after allogeneic hematopoietic cell transplantation for childhood cerebral adrenoleukodystrophy: the largest single-institution cohort report

Weston P. Miller, Steven M. Rothman, David Nascene, Teresa Kivisto, Todd E. DeFor, Richard S. Ziegler, Julie Eisengart, Kara Leiser, Gerald Raymond, Troy C. Lund, Jakub Tolar and Paul J. Orchard

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Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published weekly by the American Society of Hematology, 2021 L St, NW, Suite 900, Washington DC 20036.
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Outcomes after allogeneic hematopoietic cell transplantation for childhood cerebral adrenoleukodystrophy: the largest single-institution cohort report

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Cerebral adrenoleukodystrophy (cALD) remains a devastating neurodegenerative disease; only allogeneic hematopoietic cell transplantation (HCT) has been shown to provide long-term disease stabilization and survival. Sixty boys undergoing HCT for cALD from 2000 to 2009 were analyzed. The median age at HCT was 8.7 years; conditioning regimens and allograft sources varied. At HCT, 50% demonstrated a Loes radiographic severity score ≥ 10 , and 62% showed clinical

evidence of neurologic dysfunction. A total of 78% (n = 47) are alive at a median 3.7 years after HCT. The estimate of 5-year survival for boys with Loes score < 10 at HCT was 89%, whereas that for boys with Loes score ≥ 10 was 60% (P = .03). The 5-year survival estimate for boys absent of clinical cerebral disease at HCT was 91%, whereas that for boys with neurologic dysfunction was 66% (P = .08). The cumulative incidence of transplantation-related mortality at day 100 was 8%. Post-

transplantation progression of neurologic dysfunction depended significantly on the pre-HCT Loes score and clinical neurologic status. We describe the largest single-institution analysis of survival and neurologic function outcomes after HCT in cALD. These trials were registered at www.clinicaltrials.gov as #NCT00176904, #NCT00668564, and #NCT00383448. (Blood. 2011;118(7):1971-1978)

Introduction

Adrenoleukodystrophy (ALD) is an X-linked disorder affecting approximately 1 in 21 000 males.¹ Characterized by supra-normal ratios of saturated very long chain fatty acids (VLCFAs) to shorter-chain fatty acid species in tissues and circulating plasma, ALD results from dysfunction of the peroxisomal membrane-bound adrenoleukodystrophy protein.²⁻⁴ Adrenoleukodystrophy protein, coded by the *ABCD1* gene at Xq28, participates in the transport of cytosolic VLCFA into the peroxisome for homeostatic β -oxidation.⁵ Although disease phenotype varies, the common pathophysiologic denominator is the disruption of normal cell membrane structure and function by abnormal VLCFA levels and/or an autoinflammatory response elicited by these perturbations.⁶ More than 500 unique mutations in *ABCD1* have been associated with ALD.⁷ However, a lack of correlation between genotype and phenotype renders precise prediction of disease in an affected individual impossible, even within familial cohorts.⁸

Approximately 80% of ALD patients develop neurologic involvement. Up to 25% of these demonstrate a long axonopathy of the spinal cord. Termed adrenomyeloneuropathy, onset is typically in the third decade and is characterized by slowly progressive paraparesis.⁹ The most severe clinical manifestation of ALD, however, is the cerebral variant (cALD). With a median presentation at 7 years of age, childhood-onset cALD features rapid and profound neurologic decline resulting from demyelination within the cerebral white matter.^{9,10} Characteristic leukodystrophic changes

on brain magnetic resonance imaging (MRI) typically precede clinically evident cerebral disease.¹¹ Early signs and symptoms include hyperactivity with decreased attentiveness, emotional regression, visual field disturbances, fine motor deficits, and declining school performance. Eventually, affected patients experience profound cognitive, visual, auditory, language, and motor decline with ensuing death.^{5,10} Timely diagnosis is of utmost importance, as it has been well established that intervention in advanced cALD results in inferior outcomes.¹²

To date, only allogeneic hematopoietic cell transplantation (HCT) has been definitively shown to significantly enhance long-term survival and disease stabilization in cALD.¹³ Although transplantation-mediated correction of inherited metabolic disorders resulting from soluble enzyme defects has been shown feasible because of the principle of enzymatic "cross correction,"¹⁴ the mechanism of action of transplantation in cALD, a disease of a defective peroxisomal membrane-bound protein, remains unclear. Although murine models for ALD exist, mice do not demonstrate the neuroinflammatory cerebral variant of the disease, making preclinical studies for the efficacy and mechanism of intervention with HCT challenging.¹⁵ Based on evidence that oxidative stress and oxidative damage contribute to central nervous system (CNS) and non-nervous tissue pathophysiology in ALD,¹⁶ Tolar et al demonstrated improved survival using adjunct *N*-acetyl-L-cysteine (NAC) therapy in boys undergoing transplantation for advanced cerebral disease.¹⁷

Submitted January 21, 2011; accepted April 29, 2011. Prepublished online as *Blood* First Edition paper, May 17, 2011; DOI 10.1182/blood-2011-01-329235.

An Inside *Blood* analysis of this article appears at the front of this issue.

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Hearing/auditory processing problems	1
Aphasia/apraxia	1
Loss of communication	3
Vision impairment/fields cut	1
Cortical blindness	2
Swallowing difficulty	2
Tube feeding	2
Running difficulties/hyperreflexia	1
Walking difficulties/spasticity/spastic gait (no assistance)	1
Spastic gait (needs assistance)	2
Wheelchair required	2
No voluntary movement	3
Episodes of urinary or fecal incontinuity	1
Total urinary or fecal incontinuity	2
Nonfebrile seizures	1
Possible Total	25

Figure 1. NFS used to evaluate gross clinical neurologic status for the cohort at pre-HCT and post-HCT time points. Note that a score of "0" denotes absence of clinical signs of cerebral disease. Maximal signs within a domain score the total of all grades within that domain. For example, 3 indicates a patient with total urinary or fecal incontinuity; 1, the sum of episodes of incontinuity; and 2, total incontinuity.

First successfully performed for cALD in 1988, HCT in this disease has been increasingly explored over the past 2 decades.^{12,19-28} In 2004, Peters described 94 boys treated with HCT at 43 international transplant centers, documenting a clear role for HCT in early cALD.¹² This was confirmed on Mahmood's demonstration of superior post-HCT survival compared with nontransplanted historical controls.¹³ Still, the ability to accurately anticipate the benefit of HCT with respect to both survival and neurologic function has remained elusive. The primary goal for undertaking this current analysis was to describe survival, post-HCT disease progression/neurologic function, and the factors that may predict these in a large, recent cohort of boys undergoing HCT for cALD at a single institution. To our knowledge, this is the largest such cohort reported to date.

Methods

Cohort selection

Characteristics of (and outcomes for) 60 consecutive boys undergoing HCT at the University of Minnesota between January 1, 2000 and August 13, 2009 were reviewed. In accordance with the Declaration of Helsinki and following the provision of informed consent by patients or guardians, all members of the cohort were treated on University of Minnesota Blood and Marrow Transplant (BMT) Program Protocols approved by the University Institutional Review Board. Both (1) a diagnosis of ALD based on abnormal plasma VLCFA profile findings and (2) the presence of active cerebral disease evidenced by characteristic white matter signal changes on brain MRI were required for enrollment on all treatment protocols.

Conditioning

Conditioning regimens varied and were dependent on institutional, disease-specific protocols available at the time of HCT. Early patients underwent cyclophosphamide (Cy)/total body irradiation (TBI)-based myeloablative conditioning (n = 16, 27%); this was supplanted by a busulfan (Bu)/Cy-based regimen (n = 28, 46% of all transplants) to eliminate CNS irradiation. Beginning in 2006, boys with advanced disease defined by radiographic and clinical criteria were treated with reduced-intensity conditioning (RIC; alemtuzumab, clofarabine, melphalan, 200 cGy TBI; n = 16, 27%), whereas boys with minimal cerebral disease continued to receive a Bu/Cy-based full

preparative regimen. Peri-HCT NAC therapy (70 mg/kg intravenously every 6 hours, from the start of the preparative regimen through day 100) was administered to all boys beginning in 2005.

Supportive care

Acute graft-versus-host disease (aGVHD) prophylaxis was either mycophenolate mofetil/cyclosporine A-based, cyclosporine A/methylprednisolone-based, or, for some recipients of matched related donor grafts, cyclosporine A/methotrexate-based. Infectious disease prophylaxis, growth factor administration, and blood product support were per University of Minnesota BMT Program standard of care guidelines. All patients administered Bu received levetiracetam or phenytoin-based seizure prophylaxis; patients with a history of seizures before HCT were maintained on their respective antiepileptic therapy.

Allograft selection

Donor selection was per University of Minnesota BMT Program algorithms for allograft identification; however, patients with advanced or rapidly progressive cerebral disease who did not have a suitable related donor were considered for umbilical cord blood graft preferentially given the need for expeditious intervention at the discretion of the treating physician. All male umbilical cord blood units or male sibling donors were excluded of *ABCD1* mutation hemizygosity using VLCFA analysis. Related female donors (n = 7) were screened for familial *ABCD1* mutation, although heterozygote carrier status (n = 2) did not exclude the donor as the allograft source. Umbilical cord blood units were typed at intermediate resolution for human leukocyte antigen (HLA)-A and -B, and at allele level for HLA-DRB1; unrelated marrow donors were typed at allele level for HLA-A, -B, -C, and -DRB1.

Data acquisition

Patient-related characteristics and HCT outcomes were obtained from the University of Minnesota BMT Program Database; additional clinical information was obtained from retrospective review of medical records. Radiographic severity of cerebral involvement was determined per the scoring system described by Loes et al²⁹; MRI Loes scores were assigned at 3 time points (baseline pre-HCT, 1 year [9-15 months] after HCT, and most recent) for each subject based on availability by a single pediatric neuroradiologist (D.N.). Clinical neurologic dysfunction severity was determined per the Neurologic Function Score (NFS) scale reported by

Moser et al³⁰ (Figure 1); retrospective assignment of NFS by review of pediatric neurology records was performed at 3 time points as available (baseline pre-HCT, 1 year [9-15 months] after HCT, and most recent) for each subject by one of 2 investigators (S.M.R. and W.P.M.). Neuropsychometric assessment was performed at baseline and, as possible, at various post-HCT time points. Normalized measures of Verbal Intelligence Quotient (VIQ), Performance IQ (PIQ), and Full-Scale IQ (FSIQ) were generated from age and clinically appropriate assessment tools: Wechsler Primary Preschool Scale of Intelligence (3rd ed),³¹ the Wechsler Intelligence Scale for Children (4th ed),³² the Wechsler Abbreviated Scale of Intelligence,³³ or the Wechsler Adult Intelligence Scale (3rd ed).³⁴ Donor hematopoietic chimerism status was assessed at various post-HCT time points on the nonlymphocytic fraction of separated nucleated peripheral blood cells per University of Minnesota BMT Program standard method at the time of acquisition.

Statistical analysis

We compared patient characteristics by Loes score (< 10 vs ≥ 10) using the general Wilcoxon test for continuous factors and the χ^2 test or Fisher exact test for categorical factors where appropriate. Survival was compared by Kaplan-Meier estimation, and comparisons were completed by the log-rank test.³⁵ Although we were somewhat limited by patient numbers, Cox regression was used to look for independent predictors of survival.³⁶ All factors were tested for proportional hazards. The factors evaluated included: baseline Loes score (< 10 vs ≥ 10), baseline NFS (0 vs 1 vs > 1), age at HCT (< 10 years vs ≥ 10 years), time-dependent onset of grade II-IV aGVHD, year of HCT, NAC therapy (yes vs no), donor type (sibling vs unrelated donor), and time from ALD diagnosis to HCT (< 1 year vs ≥ 1 year). When analyzing the effect of donor hematopoietic chimerism on survival, only patients surviving to the point of chimerism evaluation were included for analysis. Cumulative incidence was used to estimate the endpoints of hematopoietic recovery and platelet recovery treating nonengraftment deaths as a competing risk.³⁷ Comparison of the continuous change of Loes score and NFS was made with the Wilcoxon test (for 2 categories) and Kruskal-Wallis test (for multiple categories) among evaluable patients. The analysis of Loes score and NFS excluded patients with autorecovery or primary graft failure. Comparison of factors using donor hematopoietic chimerism as an outcome on day 100, day 180, and most recent available time point was performed by the χ^2 test or Fisher exact test when appropriate. All *P* values were 2-sided. Stated interquartile ranges report the maximum value in the lowest quartile to the minimum value in the highest quartile. Analyses were performed using SAS Version 9.2 (SAS Institute), and R Version 2.4 statistical software. The University of Minnesota Institutional Review Board approved this retrospective analysis.

Results

Patient characteristics

Patient and HCT-related characteristics of the cohort are summarized in Table 1. Stratification of demographic and disease characteristics by Loes score (< 10 vs ≥ 10) at the time of HCT appears in Table 2.

Hematopoietic recovery and aGVHD

Across the entire cohort, neutrophil recovery (peripheral absolute neutrophil count ≥ 500/ μ L for 3 consecutive days) occurred at a median of day 15 (range, days 8-41); platelet recovery (peripheral platelet count ≥ 50 × 10³/ μ L and transfusion independent for ≥ 7 days) occurred at a median of day 40 (range, days 15-146). The cumulative incidence of grade II-IV aGVHD was 18% (95% confidence interval [CI], 9%-27%).

Survival and engraftment

Forty-seven patients (78%) are alive at a median post-HCT follow-up of 3.7 years (range, 0.7-9.6 years). Causes of death were

Table 1. Patient demographics and HCT characteristics

Factor	No. (%)
Total cALD cohort	60 (100)
Reason for diagnosis	
Family history	17 (28)
Signs/symptoms	37 (62)
Unknown	6 (10)
Months from diagnosis* to HCT	
Median (range), (IQR)	5.1 (0.7-123), (2.7-25.4)
Location of cerebral disease at HCT	
Predominant frontal	8 (13)
Predominant parieto-occipital	49 (82)
Mixed	3 (5)
Loes score at HCT	
< 10	30 (50)
≥ 10	30 (50)
NFS at HCT	
0	23 (38)
1	17 (29)
≥ 2	20 (33)
Adrenal insufficiency before HCT	
Yes	43 (72)
No	10 (17)
Unknown	7 (12)
Age at HCT, y	
Median (range), (IQR)	8.7 (4-23.3), (7-10.1)
Year of HCT	
2000-2005	28 (47)
2006-2009	32 (53)
Donor type	
Related marrow	18 (30)
Unrelated marrow	10 (17)
Unrelated UCB (single)	12 (20)
Unrelated UCB (double)	20 (33)
HLA compatibility	
Matched	27 (45)
Mismatched	33 (55)
Preparative regimen	
Bu/Cy-based	28 (46)
Cy/TBI-based	16 (27)
RIC	16 (27)
Peri-HCT NAC therapy	
Yes	34 (57)
No	26 (43)

Male-related marrow donors (n = 11) were excluded of disease by plasma VLCFA profile testing; female-related marrow donors (n = 7) were tested for carrier status by *ABCD1* gene analysis: 4 indicates wild-type; 2, heterozygote carrier; and 1, unknown status.

IQR indicates interquartile range; and UCB, umbilical cord blood.

*Diagnosis is defined as the first positive plasma VLCFA profile.

disease progression in 5 (38% of deaths), graft failure in 3 (23%), infection in 2 (15%), and in 1 (8%) each of hemorrhage, aGVHD, and hemolytic anemia. The estimated probability of survival at 5 years is 75% (95% CI, 64%-88%; Figure 2). The cumulative incidence of transplantation-related mortality by day 100 across the entire cohort was 8% (95% CI, 1%-15%).

Survival for the cohort varied significantly with the Loes score at the time of HCT (Figure 3). The probability of 5-year survival for patients with a baseline Loes score < 10 was 89% (95% CI, 70%-96%), whereas that for patients with a baseline Loes score ≥ 10 was 60% (95% CI, 34%-78%; *P* = .03). A trend toward increased survival was observed in those without clinically evident gross neurologic disease at the time of HCT: the probability of 5-year survival for patients with a baseline NFS = 0 was 91% (95% CI, 69%-98%), whereas that for patients with a baseline NFS

Table 2. Patient demographics and disease characteristics stratified by Loes score at the time of HCT

Characteristic	Loes score < 10	Loes score ≥ 10	P
Age at diagnosis, y			< .01
Median (range)	5.2 (0-14.3)	8.4 (2.5-22.3)	
Time from ALD diagnosis* to HCT, y			< .01
Median (range)	1.4 (0-10.1)	0.2 (0-10.3)	
Cerebral disease at HCT			.66
Predominant frontal	3 (10%)	5 (17%)	
Predominant parieto-occipital	25 (83%)	22 (73%)	
Mixed	2 (7%)	3 (10%)	
Cerebral disease at diagnosis*			.06
Yes	16 (53%)	21 (70%)	
No	12 (40%)	5 (17%)	
Unknown	2 (7%)	4 (13%)	
NFS at HCT			< .01
0	20 (67%)	3 (10%)	
1	9 (30%)	8 (27%)	
≥ 2	1 (3%)	19 (63%)	
Neuropsychometric indices, median (range)			
Verbal IQ at HCT	89 (50-121)	88 (59-117)	.33
Performance IQ at HCT	96 (61-131)	77 (45-100)	< .01
Full Scale IQ at HCT	91 (45-124)	75 (51-103)	< .01
Treatment with NAC			.80
Yes	15 (50%)	19 (63%)	
No	15 (50%)	11 (37%)	

*Diagnosis is defined as the first positive plasma VLCFA profile.

≥ 1 was 66% (95% CI, 46%-81%; $P = .08$). No significant difference in survival was noted for the following pre-HCT factors: graft source, year of HCT, age at HCT, cytomegalovirus serostatus, conditioning regimen, reason for initial ALD diagnosis (family history vs signs/symptoms), time from initial diagnosis of ALD to HCT, presence of adrenal insufficiency, predominant location of cerebral demyelination (frontal vs parieto-occipital), PIQ, VIQ, or FSIQ. Notably, survival among patients with a pre-HCT Loes score < 10 and who received a related allograft ($n = 8$) is 100%. Furthermore, among all patients with a pre-HCT Loes score ≥ 10, significantly greater survival was observed among those who received NAC in the peri-HCT period (Figure 3). The degree of donor chimerism at day 100 correlated significantly with estimated 5-year survival (94% survival if > 80% donor engraftment vs 69% survival if ≤ 80% donor engraftment; $P = .02$). Multivariate analysis of the predictors of survival confirmed pre-HCT Loes score as a strong determinant (relative risk of death for Loes score ≥ 10 of 9.2 [95% CI, 1.7-49.4] compared with Loes score < 10, $P < .01$).

Among patients alive at day 100, 49 (82%) had evaluable donor chimerism data. The probability of demonstrating more

than 80% donor engraftment at that time point was 73% (95% CI, 61%-85%). Achieving full donor chimerism (> 80%) at day 100 depended significantly on preparative regimen (Bu/Cy 96%, Cy/TBI 69%, RIC 38%; $P < .01$), but not graft source.

Neurologic outcomes and disease progression

Progression of cerebral disease after HCT for the cohort, as well as the factors that impacted it, was evaluated by analysis of change in disease state using 3 assessment tools: (1) Loes score, (2) NFS (Figure 1), and (3) neuropsychometric testing.

We defined post-HCT radiographic progression of cerebral involvement (Δ Loes) as the difference between a subject's most recent evaluable post-HCT Loes score and his baseline Loes score at the time of HCT. Pre-HCT factors that significantly impacted Δ Loes included baseline Loes score and PIQ (Table 3). A trend toward greater radiographic progression was seen for those with pre-HCT clinically evident cerebral disease (baseline NFS ≥ 1). The following factors did not significantly affect Δ Loes: conditioning regimen, age at HCT, NAC exposure, pre-HCT VIQ, and pre-HCT FSIQ. Additionally, post-HCT donor chimerism levels did not significantly correlate with radiographic progression.

Similarly, we described post-HCT clinical progression of cerebral disease (Δ NFS) as the difference between a subject's most recent evaluable post-HCT NFS and his baseline NFS at the time of HCT. Pre-HCT factors that significantly impacted Δ NFS included baseline Loes score, NFS, PIQ, and FSIQ (Table 4). Furthermore, Δ NFS correlated significantly with post-HCT donor chimerism levels at day 60. The following factors did not significantly affect Δ NFS: age at HCT, NAC exposure, or pre-HCT VIQ.

Assessment of neuropsychometric outcomes for the cohort was limited by attrition and, in some instances, the inability to capture equivalent outcome measures secondary to markedly decreased subject neurologic functioning. However, for the subset of this cohort, which (1) demonstrated minimal cerebral disease at the time of HCT (defined by both baseline Loes score < 10 and NFS ≤ 1) and (2) experienced minimal change in gross neurologic function after transplantation

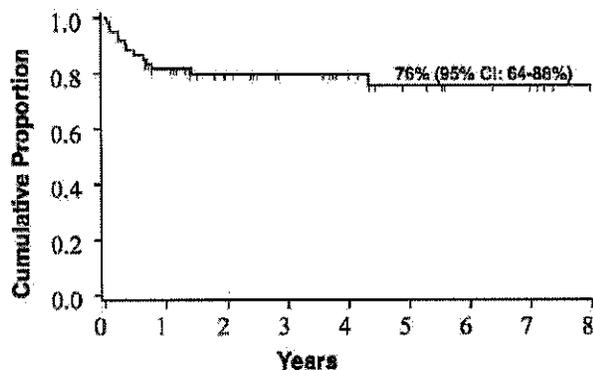


Figure 2. Probability of survival after HCT for the entire cohort of boys with c-ALD ($n = 60$).

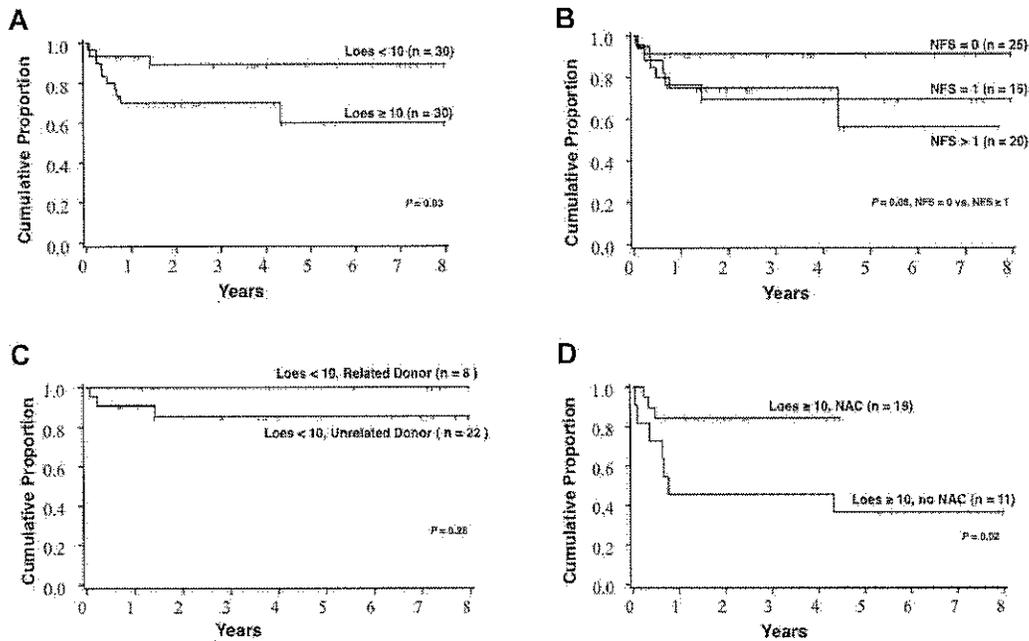


Figure 3. Survival estimates after HCT based on various patient and HCT characteristics. (A) All patients in the cohort stratified by Loes score at the time of HCT. (B) All patients in the cohort stratified by the NFS at the time of HCT. (C) Patients with Loes score < 10 at the time of HCT stratified by donor type. (D) Patients with Loes score ≥ 10 at the time of HCT stratified by NAC treatment.

(Δ NFS ≤ 2 at the most recent evaluation), neurocognitive changes at 1 year after HCT were evaluable. For this group ($n = 10$), the median change in VIQ was -3 (range, 12 to -27 ; interquartile range, 7 to -17); the median change in PIQ was -10 (range, 9 to -31 ; interquartile range, -5 to -16); the median change in FSIQ was -7.5 (range, 7 to -36 ; interquartile range, -4 to -21).

Discussion

We report the largest single-institution experience of allogeneic HCT for patients with cALD. This analysis was performed with the intent of evaluating survival and radiographic and neurologic function outcomes of these patients, which we think will serve a critical role in evaluating the efficacy of novel interventions for this disease.

The estimate of survival at 5 years after HCT for the entire cohort was 76% (95% CI, 64%-88%). Survival differed significantly based on radiographic severity of cerebral disease (Loes

score) at the time of HCT. For boys with a baseline Loes score < 10, survival at 5 years was estimated at 89%, whereas for those with advanced radiographic disease (Loes score ≥ 10), 5-year survival was estimated at only 60% ($P = .03$). A trend toward superior survival was seen in boys with no baseline clinical evidence of cerebral disease, defined by a NFS of "0." Estimate of 5-year survival for this clinically silent group was 91%, whereas that for boys with clinically evident brain disease (NFS ≥ 1) was 66% ($P = .08$). Although limited by the cohort size, we performed multivariate analysis in an effort to identify independent predictors of survival; this confirmed pre-HCT Loes score as a powerful determinant. Transplantation-related mortality by day 100 across the entire cohort was 8% (95% CI, 1%-15%). Although the numbers were limited, we found that all boys with limited cerebral disease at the time of HCT receiving a related allograft (sibling marrow) remain alive at the time of this analysis. Although survival outcomes across the entire cohort are favorable, a clear stratification exists based on the burden of cerebral disease at the time of HCT.

Although survival is clearly a salient measure for evaluating the efficacy of HCT in cALD, an assessment of both post-HCT

Table 3. Change in Loes score after HCT stratified by patient characteristics at the time of HCT

Factor	No. at HCT	No. (%) evaluable for most recent Loes score	Time after HCT to most recent Loes, y, median (range)	Change in Loes score, IQR, median (range)	P
Overall	60				
Loes score at HCT					
< 6	16	16 (100)	2.2 (0.5-8.5)	1 (-1 to 13), (0-3.5)	.03
≥ 6	44	38 (86)	1.5 (0.2-7.7)	3 (0-13), (2-5.5)	
NFS at HCT					
0	23	20 (87)	1.8 (0.5-8.5)	2.25 (-1 to 10), (0-4)	.09
≥ 1	37	25 (69)	1.5 (0.2-6.3)	3 (0-13), (1-6.5)	
Performance IQ at HCT					
≥ 80	29	24 (83)	3.1 (0.3-8.5)	2 (-1 to 10), (0-4.5)	.05
< 80	22	15 (68)	1 (0.2-5.2)	3 (0-13), (3-6.5)	

IQR indicates interquartile range.

Table 4. Change in NFS after HCT stratified by patient characteristics

Factor	No. at HCT	No. (%) evaluable for most recent NFS	Time to most recent NFS, y, median (range)	Change in NFS, IQR, median (range)	P
Overall	60				
Loes score at HCT					< .01
< 10	30	26 (87)	2.9 (0.2-8.3)	0 (-1 to 20), (0-1)	
≥ 10	30	18 (60)	2.1 (0.8-6.6)	7.5 (0-23), (4-19)	
NFS at HCT					< .01
0	23	20 (87)	2.2 (0.2-8.3)	0 (0-8), (0-0)	
≥ 1	37	24 (65)	2.3 (0.8-7.2)	7 (-1 to 23), (1-17.5)	
Performance IQ at HCT					< .01
≥ 80	29	23 (79)	3.1 (0.5-8.5)	0 (-1 to 22), (0-1)	
< 80	22	16 (73)	1 (0.2-5.2)	8 (0-23), (3-17.5)	
Full Scale IQ at HCT					< .01
≥ 80	26	20 (77)	3.5 (0.5-8.5)	0 (-1 to 12), (0-1)	
< 80	20	14 (70)	1 (0.2-5.2)	11 (0-23), (2-20)	
Donor chimerism at day 60					< .01
> 80%	30	29 (97)	3.1 (0.2-8.5)	0 (-1 to 20), (0-7)	
≤ 80%	19	16 (84)	0.5 (0.2-2)	8 (0-23), (6-20.5)	

IQR indicates interquartile range.

neurologic function status and the pre-HCT factors that can predict it is highly desirable in this neurodegenerative disorder. Therefore, we aimed to describe disease progression after transplantation as an outcome for this cohort by analyzing changes over time in radiographic (Loes score), gross neurologic function (NFS), and neurocognitive (standardized neuropsychometric testing) measures. We observed that baseline Loes score and PIQ were significantly associated with the degree of radiographic progression. In addition, progression of clinical neurologic dysfunction as measured by the NFS scale depends significantly on baseline Loes score, NFS, PIQ, and FSIQ. Interestingly, different predictors of radiographic and clinical progression were identified for the cohort, suggesting that post-HCT cerebral radiographic and neurologic clinical status does not entirely correlate in this disease. Although they provide a more nuanced evaluation of neurocognitive functioning, the use of neuropsychometric measures (FSIQ, PIQ, and VIQ) in the post-HCT setting as quantifiers of disease burden was challenging for those patients whose cALD status precluded accurate measure (eg, visual dysfunction because of occipital disease). Within the subset of less advanced patients for whom post-HCT neuropsychometric measures were obtainable and in whom minimal gross neurologic change (Δ NFS) was observed after HCT, changes in VIQ, PIQ, and FSIQ over time were relatively modest. Not surprisingly, these data suggest that more extensive cerebral disease at the time of HCT correlates with greater progression of cerebral disease after transplantation. Such neurologic function outcomes data are critical to shaping important decision-making when parents and clinicians are considering HCT for boys with advanced cerebral disease and may prove important in developing alternative therapies for this population.

The role of NAC in enhancing survival post-HCT for boys with ALD has been previously demonstrated by our group¹⁷; thereafter, all patients with cALD undergoing transplantation at the University of Minnesota have received NAC in the peri-HCT period. Our current analysis reveals a subset of patients with radiographically advanced cALD (baseline Loes score ≥ 10) for whom NAC therapy continues to demonstrate clear survival advantage. Furthermore, a trend toward improved survival at 1 year with NAC therapy was also seen in analysis of the entire cohort (data not shown), although a larger population will be required to better assess these differences as outcomes in the lower-risk population have historically been very encouraging. In this present analysis, we could not

demonstrate that NAC treatment benefits after HCT neurologic function. This may in part be because severely affected boys who were previously transplanted without adjunct NAC therapy did not survive to allow evaluation of neurologic function. Data from our analysis continue to support the use of NAC in the peri-HCT period for cALD, particularly in boys with advanced disease.

Beginning in 2006, and partly in response to previously reported unfavorable post-HCT outcomes for boys with advanced cALD,¹² all patients with advanced cerebral disease (Loes score ≥ 10 or clinically evident neurologic dysfunction) in this cohort were prepared for HCT with RIC in an effort to minimize neurotoxicity from chemoradiation. Although estimates of survival at 1 year for this RIC-treated patient subset (81%; 95% CI, 52%-94%) appear encouraging, further longitudinal analysis is necessary. Still, neurologic function outcomes (a median change in NFS of 14 at a median post-HCT follow-up of 1.5 years) of the population with advanced cerebral disease at the time of HCT are disappointing. The ability to identify patients who may have acceptable post-HCT outcomes within this advanced disease group is critical for the families and clinicians involved in the decision to perform transplantation, even as non-HCT alternatives are lacking. Clearly, novel strategies and therapies are warranted for these patients.

One such novel approach is gene correction therapy. Cartier et al¹⁸ recently reported 2 boys with cALD for whom no appropriately HLA-matched allograft could be procured. After myeloablative chemotherapy, these patients underwent rescue with lentiviral-mediated genetically corrected autologous CD34⁺ cells. Both patients were reported alive at ≥ 2 years after autologous hematopoietic stem cell rescue, although longitudinal analysis and experience with additional patients will be critical for determination of efficacy.¹⁸

We investigated whether the degree of donor chimerism after HCT correlated with survival and neurologic function outcomes. Statistically significant associations between incomplete donor engraftment and both survival and change in neurologic function over time (Δ NFS) were observed. However, caution must be used in interpreting these data as the overwhelming number of patients who demonstrated incomplete donor chimerism received RIC, itself an indicator of the patient's advanced pre-HCT cerebral disease. Still, an intriguing question that presently remains undressed is the importance of donor hematopoietic engraftment in both survival and neurologic function outcomes in cALD. In part,

this question is driven by uncertainty about the mechanism of “correction” that allo-HCT provides for this disorder involving a peroxisomal membrane-bound protein. It is possible that wild-type, donor-derived hematopoietic cells migrating into the CNS milieu may alter the pathophysiologic VLCFA content, dampen the neuroinflammatory response, provide stabilization of oligodendrocytes, or some combination of these factors. Ongoing analysis of the RIC subset within this cohort may yet elucidate whether a “threshold” proportion of donor-derived cells is necessary for disease stabilization. Such revelations may be important in addressing questions, such as the appropriateness of using female carrier siblings as allograft donors as well as the necessary levels of genetically corrected hematopoiesis when using gene correction therapies. Of note, 5 boys in the cohort demonstrating primary graft failure but stable overall clinical status underwent subsequent transplantations.

Previously, Peters et al analyzed the largest reported cohort of boys undergoing HCT for cALD.¹² In their multicenter, international analysis, the estimated probability of survival at 5 years was 56% (95% CI, 44%-68%). In contrast, the probability of OS at 5 years in our single-institutional cohort was 76% (95% CI, 64-88%). Reported transplantation-related mortality between the 2 cohorts was similar. Differences in survival outcomes for this more modern group may reflect improvements in supportive care, differences in allograft source and matching, and changes in treatment bias (ie, denial of transplantation to the most severely affected cALD patients) over time. Indeed, the cohort reported by Peters et al¹² demonstrated a higher relative percentage of subjects with markers of advanced cerebral involvement (high Loes score and presence of neurologic signs/symptoms at the time of HCT); however, a limitation inherent to its multicenter nature was the difficulty in capturing consistent data reflecting the pre-HCT disease status by radiographic and clinical markers. Interestingly, although we used a more extensive neurologic function scoring system than that reported for the Peters et al cohort¹² in an effort to identify more subtle clinical neurologic predictors of post-HCT performance, our data show that even modest scores on the NFS scale anticipate survival and function outcome.

In conclusion, this single-institution, retrospective analysis of HCT for cALD represents the largest of its kind. Our outcomes continue to demonstrate efficacy of transplantation for this otherwise rapidly fatal childhood neuro-degenerative disease. Our current institutional practice reflects this experience. For patients without cerebral disease at the time of ALD diagnosis, we recommend serial neurologic, neuropsychometric and radiographic (brain MRI) testing with expeditious allo-HCT at the earliest evidence of active cerebral disease (gadolinium-enhancing leukodys-

trophic changes on MRI). Choice of preparative regimen (myeloablative vs nonmyeloablative) is dependent on the extent of cerebral disease, with patients demonstrating extensive involvement undergoing RIC HCT. We define high-risk disease as patients with an MRI Loes score ≥ 10 or clinical evidence of cerebral involvement; such definitions are often challenging and are made with the collective input of pediatric BMT physicians, pediatric neurologists, pediatric neuro-psychologists and pediatric neuro-radiologists. Our current myeloablative regimen is non-TBI containing in an effort to spare CNS radiation toxicity, and our RIC protocol utilizes preparative agents with minimal CNS toxicity profiles. For patients with rapidly-progressing, very severe cerebral disease with marked clinical dysfunction, careful consideration from the medical team and patient guardians regarding the appropriateness of HCT is paramount. Survival and neurologic function outcomes remain remarkably favorable for patients with limited cerebral disease at the time of HCT. Although modifications in the transplantation regimen, such as reduced-intensity conditioning and the use of NAC, may result in improved survival outcomes for advanced patients, concern for their neurologic function post-HCT remains. Novel treatment strategies are necessary and warranted in this latter population. As autologous hematopoietic stem cell gene correction and other interventions for cALD are explored, this analysis may serve a critical role in the evaluation of efficacy. Finally, our data highlight the need for both early cALD diagnosis and timely transplantation in the newly diagnosed if outcomes are to be maximized.

Acknowledgments

This work was supported in part by the Children's Cancer Research Fund and the Minnesota Medical Foundation.

Authorship

Contribution: W.P.M., P.J.O., J.T., and S.M.R. conceived the study and wrote the manuscript; D.N., T.K., R.S.Z., J.E., and K.L. collected data and assisted in data analysis; T.E.D. provided statistical support; and T.C.L. and G.R. provided data analysis and critical manuscript review.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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