*Original Article*

Journal of Child Neurology
1-4

DOI: 10.1177/08830738221081141
journals.sagepub.com/home/jcn
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# Time to Transplant in X-Linked Adrenoleukodystrophy

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## Abstract

**Objectives:** Cerebral X-linked adrenoleukodystrophy (cALD) is an inflammatory demyelination of the brain that can lead to death unless treated by hematopoietic stem cell transplantation. Survival and improved outcomes for cerebral adrenoleukodystrophy are associated with hematopoietic stem cell transplantation at earliest evidence of disease on magnetic resonance imaging (MRI). Our goal was to determine average duration between diagnosis of cALD and hematopoietic stem cell transplantation.
**Methods:** This was a retrospective review of data of patients aged 18 years or younger, using a nationwide administrative health care database (Pediatric Health Information System), with an *International Classification of Diseases, Tenth Revision* (*ICD-10*) diagnosis of adrenoleukodystrophy. Time range was October 1, 2015, through June 30, 2021. We determined time to hematopoietic stem cell transplantation by duration between index brain MRI and a code for hematopoietic stem cell transplantation.
**Results:** We identified 27 patients with cerebral adrenoleukodystrophy. Total charges for the cohort was $53 million. Time to transplant averaged 97 days. For Hispanic patients, time to transplant was 117 days, compared with 80 days for White, non-Hispanic patients. Comparison of different hospitals showed significant variability in time to hematopoietic stem cell transplantation.
**Discussion:** We found that time to hematopoietic stem cell transplantation was >3 months for patients with cerebral adrenoleukodystrophy in the hospitals we evaluated. We noted differences in average time by race/ethnicity and by hospital. Our findings suggest opportunity to reduce time to transplant in cerebral adrenoleukodystrophy.

## Keywords

children, leukodystrophy, pediatric, brain, epidemiology

Date Received 24 November 2021; Received revised 12 January 2022; Accepted for publication 27 January 2022.

## Introduction

X-Linked adrenoleukodystrophy (ALD) is a progressive nervous system disease caused by mutations in the peroxisomal gene *ABCD1*.[1] Nearly 40% of boys with adrenoleukodystrophy will develop an inflammatory demyelination of the brain termed cerebral adrenoleukodystrophy, which results in death within a few years of onset. Hematopoietic stem cell transplant can treat cerebral adrenoleukodystrophy if initiated in early stages.[2,3] In contrast, later use of hematopoietic stem cell transplantation is associated with poor outcomes and lack of efficacy. Given the known association between performing hematopoietic stem cell transplantation at earliest stages of cerebral adrenoleukodystrophy and improved outcomes and higher survival, our goal was to evaluate national trends for the time duration between abnormal brain MRI indicating cerebral adrenoleukodystrophy and hematopoietic stem cell transplantation. We sought to understand whether there was a delay in hematopoietic stem cell transplantation, which has importance for cerebral adrenoleukodystrophy because of its progressive course.

## Methods

We conducted a retrospective review of all patients aged ≤18 years admitted to a Pediatric Health Information System (PHIS)-participating hospital with an *International Classification of Diseases, Tenth Revision* (*ICD-10*), diagnosis of X-linked adrenoleukodystrophy (E71.52x). Time range for the study was October 1, 2015, through June 30, 2021.

The PHIS administrative database has demographic information, diagnosis, and procedure codes from inpatient and emergency room encounters at 51 tertiary care children's hospitals in the United States.[4,5] Data from all PHIS sites were included for analysis, including hospitals that joined PHIS during the study time period. The *ICD* coding were used to create variables for brain MRI and for transplant (bone marrow transplant, umbilical cord blood transplant, hematopoietic stem cell transplant). Time to transplant was determined by time duration between the most recent preceding brain MRI, and a code for a transplant. Results were only included if the

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time duration was more than 2 weeks and less than 6 months. These time limits were based on assumptions that any transplant done in a <2-week time period would likely reflect that an outside (non-PHIS) MRI had been already performed so that a time duration could not be determined. Similarly, that a time duration longer than 6 months was unlikely to be an accurate report on time between concern for cerebral adrenoleukodystrophy and transplant (again, that an outside MRI had been performed that precipitated the transplant).

All analyses were two-sided, and $p < 0.05$ was considered statistically significant.

## Results

We identified 27 patients with cerebral adrenoleukodystrophy; 13 (48%) were Hispanic (*Table 1*). 21 (78%) of patients had been diagnosed with adrenoleukodystrophy prior to their index MRI. Average age at adrenoleukodystrophy diagnosis was 6.2 years; and average age at hematopoietic stem cell transplantation was 6.8 years. Total charges for the cohort was $53 million, nearly $2 million per patient.

Time to hematopoietic stem cell transplantation averaged 97 days following index MRI (*Table 2*). Time to transplant was similar for patients who had or had not been diagnosed prior to their index MRI with adrenoleukodystrophy. For Hispanic patients, time to transplant was 117 days, compared to 80 days for White patients. Comparison of different PHIS hospitals showed significant variability in time to hematopoietic stem cell transplantation (Figure 1).

## Conclusions

Our work shows that average time to hematopoietic stem cell transplantation was over 3 months for cerebral adrenoleukodystrophy. In addition, although not reaching statistical significance, we noted longer times to hematopoietic stem cell transplantation in Hispanic boys. We also found a wide variability in time to hematopoietic stem cell transplantation at different hospitals, ranging from a month to 6 months. A single-center study from Germany showed a similar duration between diagnosis and transplant of 3 months for cerebral adrenoleukodystrophy.[6]

The American Society for Blood and Marrow Transplantation (ASBMT) suggests autologous and allogeneic hematopoietic stem cell transplantation for treatment of cerebral adrenoleukodystrophy.[7] In general, time to hematopoietic stem cell transplantation for all conditions is dependent upon the matching process and finding a donor, and has been estimated at ~ 3 months.[8]

A strength of this study was the use of nation-wide data from PHIS for evaluation of cerebral adrenoleukodystrophy, including from the most recent 6 years. Interestingly, most of the hospitals only did hematopoietic stem cell transplantation for 1 or 2 patients. For the hospital with the most volume, the time range showed the greatest variability. Another interesting point is that we observed a larger proportion of Hispanic patients (48%), whereas the PHIS hospital patient population coverage is approximately 28%.[9] There are several possible explanations for this observation which warrant further study.

Limitations for this work are its use of retrospective data. PHIS does not have results including radiology results, thus limiting certainty that the MRI selected as the index was the abnormal MRI prompting hematopoietic stem cell transplantation. However, if another outside MRI was the index, then the time lag would be even greater. Thus if anything our time duration is an underestimate of the total time. Outcomes data, such as mortality or degree of neurological impairment post–hematopoietic stem cell transplantation, were not available. Future studies to evaluate outcomes and correlation to duration to transplant would be of interest. Because of inherent limitations of the PHIS database, it was also not possible to determine which patients were already followed prospectively with a known adrenoleukodystrophy diagnosis, versus patients with a new diagnosis. This difference (known patient vs new diagnosis) could impact timing between MRI and hematopoietic stem cell transplantation.

Since data from some centers is not included in the PHIS database, our findings represent only a portion of hematopoietic stem

**Table 1.** Selected Demographic Characteristics (N = 27 Individuals).

| Group | n (%) |
|---|---|
| Male | 27 (100) |
| Race | |
| White | 11 (41) |
| Hispanic | 13 (48) |
| Black | 2 (7) |
| Multiracial | 1 (4) |
| Private insurance | 9 (33) |
| Government insurance | 17 (63) |
| Other insurance | 1 (4) |
| Preceding diagnosis of ALD | 21 (78) |
| Age at ALD diagnosis, y, mean (range) | 6.2 (0.3-13.9) |
| Age at HSCT, y, mean (range) | 6.8 (0.3-15.7) |
| Charges, total | $53,943,561 |
| Charges, average | $1,997,910 |

Abbreviations: ALD, adrenoleukodystrophy; HSCT, hematopoietic stem cell transplantation.

**Table 2.** Outcomes (N = 27 Individuals).[a]

| Characteristic | Days (mean, median) | *P* value |
|---|---|---|
| Days between MRI and HSCT (overall) | 97, 88 | |
| Days between MRI and HSCT (preceding diagnosis of ALD) | 98, 90 | |
| Days between MRI and HSCT (no preceding diagnosis of ALD) | 95, 82 | |
| Days for Hispanic patient | 117, 127 | |
| Days for White patient | 80, 76 | .076 |

Abbreviations: ALD, adrenoleukodystrophy; HSCT, hematopoietic stem cell transplantation; MRI, magnetic resonance imaging.
[a]Unpaired *t* test calculated for 2-tailed *P* value.

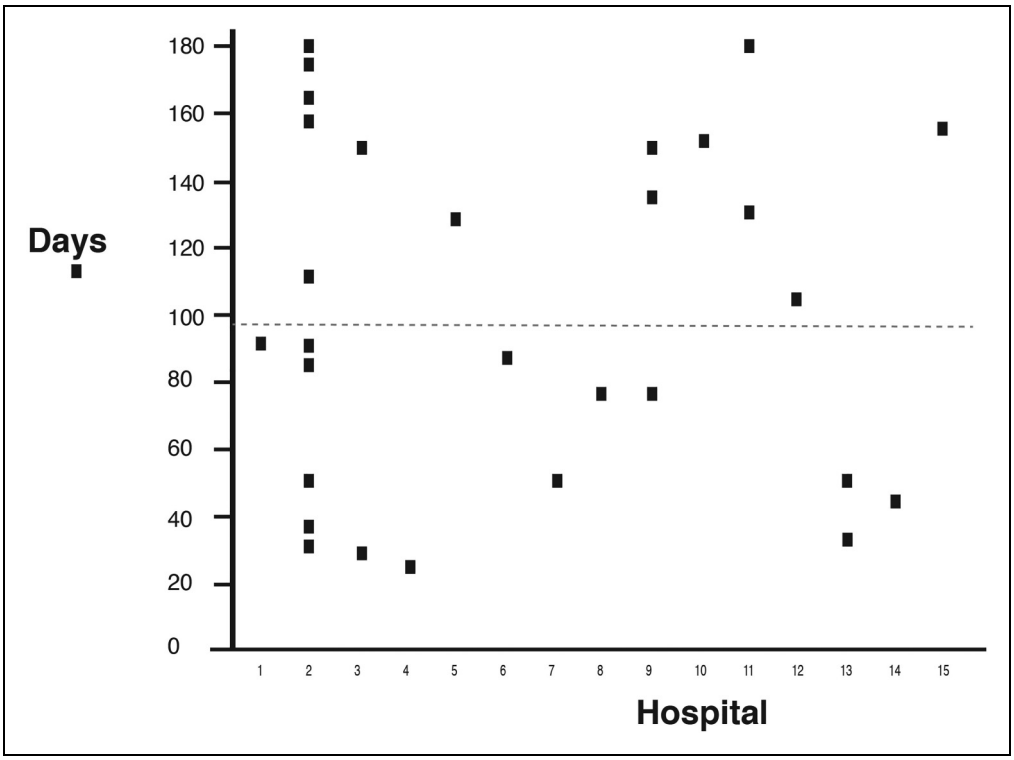


**Figure 1.** Hospital and time to hematopoietic stem cell transplantation (HSCT). *y* axis: time to transplant (days); *x* axis: Pediatric Health Information System (PHIS) hospital (coded). Dashed line indicates overall average time.

cell transplantation performed for cerebral adrenoleukodystrophy. For example, in a 2-year time period (2018-2019), 12 transplants for adrenoleukodystrophy were reported at the University of Minnesota, which is not part of PHIS.[10] National tracking, reporting, and metrics of details for hematopoietic stem cell transplantation in cerebral adrenoleukodystrophy (and other leukodystrophies) would be helpful for assessing opportunities to improve outcomes or reduce potential disparities.

In conclusion, we found that the time to hematopoietic stem cell transplantation for cerebral adrenoleukodystrophy was >3 months. Our findings suggest an opportunity to reduce time to hematopoietic stem cell transplantation in cerebral adrenoleukodystrophy, which could help with improving outcomes. We recommend considerations for shortening the time to hematopoietic stem cell transplantation: typing known adrenoleukodystrophy patients at time of first diagnosis; facilitating communication between the transplant team and the leukodystrophy specialist, to ensure that urgency of transplant is considered in timing of admission for transplant; improving efficiency in the process leading to hematopoietic stem cell transplantation such as shortening the time of HLA typing; and tracking time to hematopoietic stem cell transplantation to permit opportunities for ongoing quality improvement. These recommendations could be used at all centers and would not be unduly burdensome to providers or to patients and family, could help reduce time to transplant, and could serve as a model for other leukodystrophies in which expeditious hematopoietic stem cell transplantation or genetic therapies are indicated.

## Acknowledgments

We thank E. Mallack for discussion of work.

## Author Contributions

Both authors contributed to and edited drafts of the manuscript and read and approved the final manuscript.

## Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: J. L. Bonkowsky is a consultant for Autobahn Therapeutics, Bluebird Bio, Calico, Denali Therapeutics, Neurogene, and Passage Bio; serves on the Board of Directors of wFluidx; holds stock options in Orchard Therapeutics; receives royalties from Manson Publishing; and his spouse receives royalties from BioMerieux and receives research support from NIH NINDS (5U54NS115052) and the European Leukodystrophy Association. J. Wilkes reports no disclosures.

## Ethical Approval

This study was approved by the Institutional Review Board of the Child Health Corporation.

## Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Institutes of Health (grant number U54 NS115052).

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