The burden of inherited leukodystrophies in children

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J.L. Bonkowsky, MD,
  PhD
C. Nelson, MD
J.L. Kingston
F.M. Filloux, MD
M.B. Mundorff, MBA,
  MHSA
R. Srivastava, MD,
  FRCP(C), MPH

Address correspondence and
reprint requests to Dr. Josh
Bonkowsky, Division of Pediatric
Neurology, Department of
Pediatrics, University of Utah
Health Sciences Center, 295
Chipeta Way/Williams Building,
Salt Lake City, UT 84108
joshua.bonkowsky@hsc.utah.edu

ABSTRACT

Objectives: Leukodystrophies are diseases of the white matter for which data concerning clinical characteristics, incidence, disease burden, and description of outcomes are sparse. The purpose of our study was to determine the incidence and most common types of inherited leukodystrophies in a population, the mortality and time course of deaths, common neurologic features in patients, and health care costs associated with leukodystrophies.

Methods: We conducted a retrospective, hospital- and clinic-based surveillance of inherited leukodystrophies among children younger than 18 years presenting to a regional children's hospital. We enrolled children evaluated from January 1, 1999, through December 31, 2007; clinical information was obtained from medical records. We calculated incidence based on state birth rates.

Results: A total of 122 children with an inherited leukodystrophy were identified; 542 patients were excluded. A total of 49% had epilepsy, 43% required a gastrostomy tube, and 32% had a history of developmental regression. Mortality was 34%; average age at death was 8.2 years. No final diagnosis was reported in 51% of patients. The most common diagnoses were metachromatic leukodystrophy (8.2%), Pelizaeus-Merzbacher disease (7.4%), mitochondrial diseases (4.9%), and adrenoleukodystrophy (4.1%). Endocrine abnormalities and hypoplastic cerebellum were noted in significant portions of patients (15% and 14%). Average yearly per-patient medical costs were $22,579. Population incidence was 1 in 7,663 live births.

Conclusions: Inherited leukodystrophies are associated with substantial morbidity and mortality in children. Overall population incidence is higher than generally appreciated (1 in 7,663 live births). Most leukodystrophies remain undiagnosed, but a logical algorithm based on prevalence could aid testing. ***Neurology*® 2010;75:718–725**

GLOSSARY

EDW = Enterprise Data Warehouse; **IH** = Intermountain Healthcare.

Inherited leukodystrophies are diseases of the myelin, including abnormal myelin development, hypomyelination, or degeneration of myelin.[1,2] Leukodystrophies are distinguished from the more general term leukoencephalopathy, used to describe any disease of white matter, including also acquired or toxic diseases of white matter.[2] Recognition of leukodystrophies has been revolutionized by MRI technology, because of its increased sensitivity compared to CT, and because of its ability in some cases to reveal disease-specific features that can lead to a diagnosis.[3,4]

Disappointingly, however, in almost half of leukodystrophy patients a final diagnosis cannot be determined.[5] Treatment options for leukodystrophies are limited, and exist chiefly for X-linked adrenoleukodystrophy, metachromatic leukodystrophy, Krabbe disease, and some

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lysosomal diseases.[6-10] Characterization and treatment of leukodystrophies has been hampered by the failure to diagnose many patients, a lack of clinical outcomes data (such as morbidities and mortality), and no data on overall incidence or relative frequencies of different leukodystrophies. Incidence has been estimated in a very broad range, from 1:5,000 to 2:100,000 live births.[11]

The purpose of our study was to determine the incidence and most common types of inherited leukodystrophies in a population, the mortality and time course of deaths, common neurologic features in patients, and health care costs associated with leukodystrophies.

METHODS Additional details of the methods can be found in e-Methods on the *Neurology*® Web site at www.neurology.org.

Study design. We reviewed the medical records of all children who had been evaluated for a possible leukodystrophy between January 1, 1999, and December 31, 2007. Follow-up for outcomes was from January 1, 1999, through June 30, 2009. We attempted to identify all patients who presented with a leukodystrophy over the 9-year time period. We searched records of children using a computer-based screen of International Classification of Diseases, Ninth Revision, Clinical Modification codes from pediatric neurology clinic billing records and hospital discharge diagnoses. A total of 664 unique possible patients were identified; 20 charts could not be located (figure e-1). The authors reviewed all 644 charts to determine whether a patient met inclusion and exclusion criteria.

Patients were included if they were younger than 19 years at their initial presentation for evaluation of their symptoms that led to the diagnosis of leukodystrophy; if they had brain MRI findings showing abnormalities of white matter signal consistent with the diagnosis of a leukodystrophy; and if the MRI results were obtained prior to determination of an alternative diagnosis not typically considered a leukodystrophy (for example, Rett syndrome).

Patients were excluded from the study if they had a known (past medical history) or likely reason for their leukodystrophy.

Standard protocol approvals, registrations, and patient consents. The study was approved by the Institutional Review Boards of the University of Utah and Intermountain Healthcare. Written informed consent was obtained from patients (or their guardians) participating in the study for patients enrolled prospectively. Patients (and data) enrolled retrospectively had a waiver of consent (approved by the Institutional Review Boards).

Data collection and outcomes. Clinical, laboratory, and radiologic data were abstracted from the charts. Follow-up for outcomes ended on June 30, 2009. Data abstracted from Intermountain Healthcare's (IH) computerized database (Enterprise Data Warehouse [EDW]) included age and total hospitalization cost and charges.[12,13] Hypodontia was defined as absence of dentition by age 18 months, and/or agenesis of 4 or more teeth.[14,15]

Deaths were identified through the EDW and through state health death records (Utah State vital records) by cross-matching patients using a unique electronic patient identification number.

Table 1	Selected demographic characteristics of patients with leukodystrophy[a]
Characteristics	**Values**
Gender, n (%)	
Male	67 (55)
Female	55 (45)
Mean age at presentation, mo	35
Race, n (%)	
Caucasian	109 (89)
Hispanic	9 (7.4)
Native American	3 (2.5)
Unknown	1 (0.8)
Premature (<37 wk), n (%)	13 (11)

[a] Total n = 122.

The EDW incorporates data from the State of Utah Department of Vital Records, which identifies patient deaths occurring outside of IH facilities. This identification is done using a probabilistic matching algorithm. Deaths were also verified by examination of the patient medical record. Finally, we queried national death records (Social Security Database Index)[16] based on name and social security number.[17]

Incidence was determined using birth rates collected by the Centers for Disease Control and Prevention[18] using a global mean per 1,000 live births for the years 1995–2005.

Statistical and cost analyses. Descriptive statistics were used to characterize the study cohort. Two-tailed *p* values for odds ratios were calculated using Fisher exact test. The patients were matched by unique identifier numbers to a summary table from the IH EDW, where their hospital-based encounter data provided costs, dates of service, and type of encounter (inpatient, ambulatory, emergency).

RESULTS The identification of the study population is shown in figure e-1. We identified 664 patients with a possible leukodystrophy, of whom 122 patients met inclusion criteria (20 charts could not be found). Demographics of the 122 patients are displayed in table 1. Follow-up of the patients in the cohort ranged from 2.0 to 22.6 years, with a median follow-up of 9.2 years.

The average age at presentation to a physician for evaluation of an underlying neurologic complaint (most often developmental delay) of these patients was not until almost age 3 years (35 months) (table 2). Epilepsy was a common diagnosis (49% of patients) with a relatively early age at onset (4.0 years). Mortality was high at 34%, and average age at death was 8.2 years. The hospital and clinic costs of this cohort during the follow-up period were over $14 million, with an average yearly cost per patient of $22,579 (table 2).

A wide spectrum of MRI findings and clinical features was noted in the cohort (table 3). Contrast enhancement on MRI was found in 8 patients, but in 3

Table 2	Death, neurologic features, and costs in the leukodystrophy cohort[a]	
Outcomes		Values
Death, n (%)		42 (34)
Average age at death, y		8.2
Epilepsy, n (%)		60 (49)
Average age at onset, y		4.0
Developmental regression, n (%)		39 (32)
Feeding tube, n (%)		53 (43)
Costs		
Total cohort cost		$14,315,919
Average yearly cost/patient		$22,579

[a] Total number of patients was 122. Costs were calculated for the entire follow-up period (January 1, 1999–June 30, 2009).

Table 3	MRI and clinical characteristics of the leukodystrophy cohort[a]	
Diagnosis		No. (%)
Hypomyelination		57 (47)
Hypoplastic cerebellum		17 (14)
Cortical atrophy		42 (34)
Basal ganglia involvement		4 (3.3)
Corpus callosum abnormality		44 (36)
Contrast enhancement		8 (6.6)
Microcephaly		27 (22)
Macrocephaly		4 (3.3)
Endocrine abnormalities		18 (15)
Hypothyroid		7 (5.6)
Sex hormone axis		4 (3.3)
Growth hormone axis		4 (3.3)
Diabetes mellitus		3 (2.5)
Nystagmus		9 (7.4)
Hypodontia		3 (2.5)
Hypotonia		62 (51)
Spasticity		51 (42)
Hydrocephalus		7 (5.7)
Ventriculoperitoneal shunt		2 (1.6)
Home oxygen requirement		16 (13)
Roll by age 6 mo		30 (25)
Sit by age 1 y		35 (29)
Hold object by age 1 y		30 (25)
Walk ever		62 (51)
Visual track ever		88 (72)
Diagnoses of patients with endocrine abnormalities (n = 18)		
Unknown		9 (50)
Adrenoleukodystrophy		3 (17)
Metachromatic leukodystrophy		3 (17)
Chromosome microdeletion		2 (11)
FG syndrome		1 (6)

[a] Neurologic findings were reported as positive if they were ever present. The corpus callosum was defined as abnormal if it was thin or if it had disease involvement.

of them no final diagnosis was found. Similarly, a hypoplastic cerebellum was noted in 17 patients, of whom 8 remained undiagnosed. Abnormality of the corpus callosum (either atrophic/thin or with white matter disease involvement) was common, involving 36% of patients. Only 9 of the patients with a hypoplastic cerebellum had concordant involvement (atrophy) of the corpus callosum. CT was performed on 61 patients; calcifications were found in 2 patients, 1 of whom had the clinical diagnosis of leukoencephalopathy with cerebral calcifications and cysts (table 4). Lumbar puncture and CSF analysis was performed in 49 patients, none of whom had leukocytosis. The severity of the disease course is reflected in the developmental milestones achieved by the cohort; only 51% ever walked, and 28% did not achieve visual tracking.

Endocrine abnormalities were found in 15% of patients (table 3); in some cases this was associated with known leukodystrophies (such as adrenoleukodystrophy or chromosome microdeletion syndromes). However, half of the patients with endocrine abnormalities (9 of 18) remained undiagnosed.

The most common disease diagnoses were metachromatic leukodystrophy (8.2%), Pelizaeus-Merzbacher disease (7.4%), mitochondrial diseases (4.9%), and adrenoleukodystrophy (4.1%) (table 4). In male patients, the most common diagnosis was Pelizaeus-Merzbacher disease (13% of male patients). Of note, in our cohort more than half (51%) of patients did not have a final diagnosis. This may in part reflect the historical nature of the cohort, since evaluation of these patients was often performed before recognition of certain disease entity types (such as vanishing white matter disease), or before genetic testing was available (as for Alexander disease). Also, in 3 cases patients have been assigned likely diagnoses although definitive biochemical or genetic testing is not available (table 4; 4H syndrome, hereditary spastic paraparesis, leukoencephalopathy with cerebral calcifications and cysts[19]). Some familial clustering was noted: 3 families each had 2 patients with an unknown leukodystrophy, 1 family had 2 children with adrenoleukodystrophy, and 7 (of 10) patients with metachromatic leukodystrophy were from 2 families.

We also examined rates of epilepsy and death by age. The onset of epilepsy varied both by diagnosis and by age (figure 1A). Most patients who developed epilepsy did so in the first 2 years of life, of whom the largest proportion of patients never had a definitive

Table 4	Diagnoses in the leukodystrophy cohort (total n = 122), arranged by diagnosis and by brain MRI features
Diagnosis	No. (%)
Leukodystrophy cohort diagnoses[a]	
No diagnosis	62 (51)
Metachromatic leukodystrophy	10 (8.2)
Pelizaeus-Merzbacher disease	9 (7.4)
Mitochondrial	6 (4.9)
Adrenoleukodystrophy	5 (4.1)
Vanishing white matter disease	3 (2.4)
Krabbe disease	2 (1.6)
Alexander disease	2 (1.6)
Tay-Sachs disease	2 (1.6)
Hurler syndrome	2 (1.6)
Neuronal ceroid lipofuscinosis	2 (1.6)
Diagnoses arranged by MRI features[b]	
Hypomyelination (n = 57)	
Unknown	32
Pelizaeus-Merzbacher disease	8
Metachromatic leukodystrophy	4
Multifocal (n = 22)	
Unknown	11
Mitochondrial	3
Metachromatic leukodystrophy	3
Vacuolating (n = 6)	
Unknown	4
Contrast enhancement (n = 8)	
Unknown	3
Metachromatic leukodystrophy	2
Basal ganglia involvement (n = 4)	
Mitochondrial	3
Hypoplastic cerebellum (n = 17)	
Unknown	8
Abnormal corpus callosum (n = 44)	
Unknown	29
Vanishing white matter disease	2
Metachromatic leukodystrophy	2
Pelizaeus-Merzbacher disease	2

[a] One patient each: Canavan disease, 18q− syndrome, 2q24.3 syndrome, 4H syndrome, Cockayne syndrome, FG syndrome, Gaucher disease, glutaric acidemia type I, leukoencephalopathy with cerebral calcifications and cysts, megaloencephalic leukodystrophy, neuronal intranuclear hyaline inclusion disease, non-Langerhans cell histiocytosis, oculodentodigital dysplasia syndrome, hereditary spastic paraparesis, Refsum disease, Rett syndrome, Acyl-CoA dehydrogenase deficiency (short chain).
[b] The diagnoses are listed in descending frequency (diagnoses are only listed if more than 1 patient was affected).

diagnosis. Mortality showed a trimodal pattern, with elevated rates in the first 2 years of life, around age 8 years, and after age 14 years (figure 1B). Disease severity was also reflected in the high rates (32%) of developmental regression (table 2).

To determine whether there were features that could predict mortality, we evaluated odds ratios for the risk of death for different clinical characteristics (table 3). We found that failure to achieve developmental milestones was associated with an increased risk for death, most significantly for inability to roll by age 6 months and inability to walk ever. The odds ratios (and 95% confidence intervals and p values) were as follows: require feeding tube 3.3 (1.5–7.0, $p = 0.0024$); failure to roll by 6 months 3.4 (1.2–9.6, $p = 0.030$); failure to sit independently by 1 year 1.6 (0.65–4.0, $p = 0.30$); failure to hold object by 1 year 2.6 (0.96–6.9, $p = 0.080$); failure to walk ever 3.5 (1.6–7.8, $p = 0.0021$); and failure to feed self by 1 year 1.9 (0.63–5.5, $p = 0.31$). However, epilepsy was not associated with an increased risk for death in this cohort (odds ratio 0.59; 95% confidence interval 0.27–1.2, $p = 0.19$).

The variability in disease severity was also reflected by the cost data (figure 1C). Many patients had low total medical costs; roughly 50% of patients had total costs (for the duration of the study period) less than $30,000. However, about 10% of patients had costs greater than $500,000 per patient. Of the 6 patients with highest costs (greater than $500,000), 2 had bone marrow transplantation. However, 5 other patients in the leukodystrophy cohort had bone marrow transplantation and were not among the highest cost patients.

In order to calculate a population incidence, we used Utah births years 1995–2005, during which time the average live birth rate in Utah was 46,580/year.[18] Prior to 1995, and after 2005, there were significantly fewer cases per year (1–2) in our database. This was likely due to underascertainment for cases prior to 1995; after 2005, this may have been due to the average age at presentation (age 35 months), making it likely that patients would not yet have presented. There were 66 patients with leukodystrophy in the cohort born in Utah during this time period. Therefore, the incidence of leukodystrophies is 1:7,663 live births.

DISCUSSION This study presents novel data concerning inherited leukodystrophies. First, the overall incidence is 1 in 7,663 live births. Second, mortality is 34%, with an average age at death of 8.2 years. Third, the most common determined diagnoses were metachromatic leukodystrophy, Pelizaeus-Merzbacher disease, and mitochondrial diseases. Among male patients, Pelizaeus-Merzbacher disease was the most common diagnosis. Finally, inherited leukodystrophies

Figure 1 Leukodystrophy cohort epilepsy, deaths, and costs
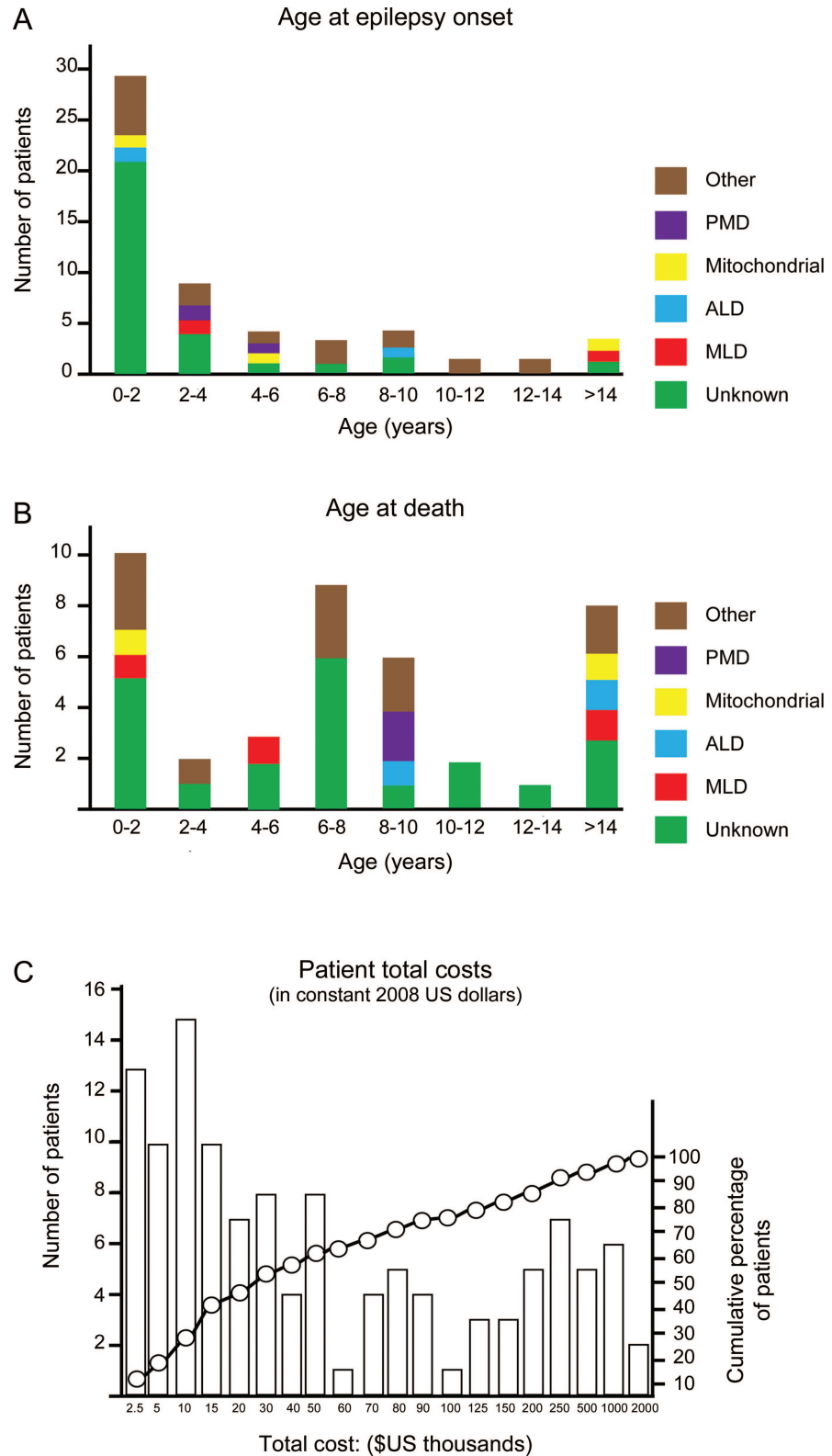
Number of new epilepsy cases (A) and deaths (B) shown by age. Vertical axis: number of cases. Underlying diagnosis is color-coded, key to right of graphs. (C) Total costs per patient, in thousands of dollars. Cumulative percentage of patients represented is indicated by solid line. ALD = adrenoleukodystrophy; MLD = mitochondrial disease; PMD = Pelizaeus-Merzbacher disease.

impose significant financial burdens, with average per patient per year costs of $22,579.

Prior to this work, an accurate estimation of the incidence of leukodystrophies has been lacking. A study from Sweden determined the prevalence of progressive childhood encephalopathy at 0.6:1,000 live births (1 in 1,666),[20] but this study was not specific for leukodystrophies, did not include nonprogressive diseases, and was performed prior to widespread use of MRI. The leukodystrophy incidence in Germany was estimated at 2:100,000 live births,[11] but was likely an underestimation as it was a multicenter study and included a more limited set of diseases. Interestingly, our data would suggest a much lower rate of adrenoleukodystrophy (closer to 1:186,902 live births) than had previously been estimated.[21] Reasons for this discrepancy are not clear; possible reasons include lower rates of adrenoleukodystrophy in the Utah population, missed cases in our cohort, or that prior work was based upon data from a tertiary referral center.[21]

Our incidence of 1:7,663 live births is likely an underestimation. This is because of the historical nature of this cohort (a time period during which brain MRI became part of the standard workup for evaluating patients with seizures or developmental delay, so earlier leukodystrophy cases could have been missed), because we did not reexamine patients with previously assigned diagnoses (such as multiple sclerosis), and because some patients with known leukodystrophies were excluded (because our inclusion criteria required a MRI). Nevertheless, this provides a substantively improved estimation of the incidence of inherited leukodystrophies.

Another key issue in leukodystrophy clinical care has been attempts to design rational testing strategies. Because leukodystrophies commonly present before clinical and radiologic features are obvious or reach their final disease-specific type, strategies for diagnosis based on MRI criteria are limited.[4,5] MRI-based diagnostic approaches also have not been tested for their sensitivity and specificity, and will likely be dependent on skilled MRI interpretation. Current MRI-based algorithms require that the patient be older than 2 years, but many patients present before this age, and the need to initiate therapies in the future will require early diagnosis. The complexity and limitations of an MRI-based diagnostic strategy is highlighted by our data. Specifically, we found that multiple different diagnoses may be encompassed within any given single MRI category (for example, the category of hypomyelination) (table 4). Other novel approaches, using proteomics[22] or whole-genome sequencing,[23,24] so far have had limited application.

Our finding of high mortality rates in the first 2 years of life underscores the necessity of developing improved methods for diagnosis. This is especially important because currently half of these patients are not diagnosed (figure 1). Further, because some treatments (such as bone marrow therapy) are most successful when initiated in the presymptomatic stage,[6-10] early diagnosis is critical. However, early diagnosis of patients may be complicated by situations in which a patient has enzymatic or genetic evidence of a disease, but in which the natural history of progression (e.g., whether or not a patient actually will become symptomatic) of the disease is unknown.[25] We did find that failure to achieve developmental milestones was associated with increased risk of death. This could be predicted at an early age, by the failure to roll over by age 6 months. Of note, these findings are similar to other cohorts of children with neurologic impairment.[26]

Our identification of the most common diseases presenting in this cohort suggests a logical testing strategy. Patients presenting with a leukodystrophy should be tested for metachromatic leukodystrophy and mitochondrial disease, and male patients should be tested for Pelizaeus-Merzbacher disease and X-linked adrenoleukodystrophy. These 4 disease categories account for 25.4% of the inherited leukodystrophies in our cohort. With improved recognition and testing, it will be interesting to see whether diseases such as vanishing white matter disease are encountered more frequently. It is also unknown whether some diseases may account for a larger proportion of cases but are not tested for because of atypical imaging or clinical presentations. For example, atypical subtypes of Alexander disease are now recognized.[27]

An unexpected finding was that epilepsy was more widespread than is commonly expected for white matter diseases (in 49% of patients). Further, the onset of seizures was at a relatively young age (average 4.0 years, with the largest proportion of cases presenting before age 2 years), which is only 1 year after the average age at presentation.

In some of the undiagnosed patients we found MRI (contrast enhancement, cerebellar atrophy) or clinical features (endocrine abnormalities) that were relatively distinguishing, suggesting the possibility for uncovering novel subtypes of leukodystrophies. In addition, the relatively high rate of endocrine abnormalities, including hypothyroidism, sex hormone and growth hormone axis abnormalities, and diabetes, suggests that patients with leukodystrophies should have baseline endocrine screening performed.

The patients with leukodystrophy are severely affected by their disease: almost half required feeding tubes, and just over half were ever able to walk inde-

pendently. This severity of neurologic impairment is reflected in the high health care costs. The total cohort cost over a time period of 10.5 years was $14 million, with an average per year per patient cost of $22,579, not including outpatient therapies. A small proportion of patients (about 10%) accounted for a disproportionate share of the costs, with average per patient costs of >$500,000. Interestingly, half of these patients (those with costs >$500,000) had metachromatic leukodystrophy, and the other half of these patients did not have a final diagnosis. Further, a third of this high-cost cohort died during the study time period. The requirement for bone marrow transplantation is not alone sufficient to account for the high costs incurred by some patients, as only 2 of the 6 patients with the highest costs had bone marrow transplants.

Strengths of this study include the large cohort size and the extended follow-up (over 10 years). Our inclusion criteria evaluated for all patients initially presenting with a leukodystrophy, since we used MRI findings as our chief inclusion criterion. This led to the inclusion of some patients not historically considered leukodystrophy patients, as in mitochondrial disease or Rett syndrome. However, this representation of the spectrum of leukodystrophy more accurately reflects the actual clinical cases encountered in practice.

Also, we had the ability to comprehensively track and identify patients for subsequent outcomes because a significant majority of pediatric patients in Utah are cared for by the same health care system, which maintains records in an electronic format. Further, the study hospital is the sole tertiary care pediatric hospital in Utah, and receives referrals from neighboring states. We were also able to track patients by their referrals to the pediatric neurology clinic (there is only one other pediatric neurologist in Utah), as well as evaluate for any deaths through 3 separate sources (the IH database, Utah vital statistics records, and the Social Security Database Index).

There are several limitations to this study. First, data were collected retrospectively. This affected determination of diagnoses since some tests, such as for Alexander disease or for mutations in the *MCT8/SLC16A2* gene,[28,29] were only available partway through the study time period. Second, we excluded some patients with definitive or likely leukodystrophies (e.g., positive test result for metachromatic leukodystrophy) who did not have a MRI. Third, patients diagnosed with multiple sclerosis and other disorders were not further evaluated to determine whether an erroneous diagnosis had been given. Therefore, it is probable that we have underascertained the true incidence of inherited leukodystro-

phies. Finally, this cohort of patients with leukodystrophy has an ethnic background which is predominantly northern European. The relative prevalence of leukodystrophies may be affected by the population makeup or founder effects. It will be important for future studies to determine rates of leukodystrophies in other populations (such as African or Asian).

AUTHOR CONTRIBUTIONS

J.L.B. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. J.L.B., C.N., F.M.F., R.S., M.B.M., and J.L.K. participated in data collection; J.L.B., C.N., M.B.M., and R.S. were involved in data and statistical analysis; and all authors participated in manuscript drafting and revisions.

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DISCLOSURE

REFERENCES

1. Berger J, Moser HW, Forss-Petter S. Leukodystrophies: recent developments in genetics, molecular biology, pathogenesis and treatment. Curr Opin Neurol 2001;14:305–312.
2. Kaye EM. Update on genetic disorders affecting white matter. Pediatr Neurol 2001;24:11–24.
3. Miller DH, Robb SA, Ormerod IE, et al. Magnetic resonance imaging of inflammatory and demyelinating white-matter diseases of childhood. Dev Med Child Neurol 1990;32:97–107.
4. Schiffmann R, van der Knaap MS. An MRI-based approach to the diagnosis of white matter disorders. Neurology 2009;72:750–759.
5. van der Knaap MS, Breiter SN, Hart AAM, Valk J. Defining and categorizing leukoencephalopathies of unknown origin: MR imaging approach. Radiology 1999;213:121–133.
6. Biffi A, Lucchini G, Rovelli A, Sessa M. Metachromatic leukodystrophy: an overview of current and prospective treatments. Bone Marrow Transplant 2008;(suppl 2):S2–S6.
7. Cartier N, Aubourg P. Hematopoietic stem cell gene therapy in Hurler syndrome, globoid cell leukodystrophy, metachromatic leukodystrophy and X-adrenoleukodystrophy. Curr Opin Mol Ther 2008;10:471–478.
8. Escolar ML, Poe MD, Provenzale JM, et al. Transplantation of umbilical-cord blood in babies with infantile Krabbe's disease. N Engl J Med 2005;352:2069–2081.
9. Mahmood A, Raymond GV, Dubey P, Peters C, Moser HW. Survival analysis of haematopoietic cell transplantation for childhood cerebral X-linked adrenoleukodystrophy: a comparison study. Lancet Neurol 2007;6:687–692.
10. Orchard PJ, Tolar J. Transplant outcomes in leukodystrophies. Semin Hematol 2010;47:70–78.

11. Heim P, Claussen M, Hoffmann B, et al. Leukodystrophy incidence in Germany. Am J Med Genet 1997;71:475–1478.

12. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients: excess length of stay, extra costs, and attributable mortality. JAMA 1997;277:301–306.

13. Harbarth S, Burke JP, Lloyd JF, Evans RS, Pestotnik SL, Samore MH. Clinical and economic outcomes of conventional amphotericin B-associated nephrotoxicity. Clin Infect Dis 2002;35:e120–e127.

14. Suri L, Gagari E, Vastardis H. Delayed tooth eruption: pathogenesis, diagnosis, and treatment: a literature review. Am J Orthod Dentofacial Orthop 2004;126:432–445.

15. De Coster PJ, Marks LA, Martens LC, Huysseune A. Dental agenesis: genetic and clinical perspectives. J Oral Pathol Med 2009;38:1–17.

16. Hill ME, Rosenwaike I. The Social Security Agency's Death Master File: the completeness of death reporting at older ages. Soc Sec Bull 2002;64:45–51.

17. Search Social Security Death Index. In: GenealogyBank. com. Available at: http://www.genealogybank.com/gbnk/ ssdi/?kbid=9064&m=9. Accessed September 15, 2009.

18. Utah Vital Statistics. In: Utah Department of Health. Available at: http://health.utah.gov/vitalrecords/vitalstatistics/ DataYear/2007Data.htm. Accessed September 10, 2009.

19. Nagae-Poetscher LM, Bibat G, Philappart M, et al. Leukoencephalopathy, cerebral calcifications, and cysts: new observations. Neurology 2004;62:1206–1209.

20. Uvebrant P, Lanneskog K, Hagberg B. The epidemiology of progressive encephalopathies in childhood: I: live birth prevalence in west Sweden. Neuropediatrics 1992;23:209–211.

21. Bezman L, Moser AB, Raymond GV, et al. Adrenoleukodystrophy: incidence, new mutation rate, and results of extended family screening. Ann Neurol 2001;49:512–517.

22. Vanderver A, Hathout Y, Maletkovic J, et al. Sensitivity and specificity of decreased CSF asialotransferrin for eIF2B-related disorder. Neurology 2008;70:2226–2232.

23. Lupski JR, Reid JG, Gonzaga-Jauregui C, et al. Whole-genome sequencing in a patient with Charcot-Marie-Tooth neuropathy. N Engl J Med Epub 2010 Mar 10.

24. Roach JC, Glusman G, Smit AF, et al. Analysis of genetic inheritance in a family quartet by whole-genome sequencing. Science Epub 2010 Mar 10.

25. Duffner PK, Jalal K, Carter RL. The Hunter's Hope Krabbe Family Database. Pediatr Neurol 2009;40:13–18.

26. Eyman RK, Grossman HJ, Chaney RH, Call TL. The life expectancy of profoundly handicapped people with mental retardation. N Engl J Med 1990;323:584–589.

27. Van der Knaap MS, Ramesh V, Schiffmann R, et al. Alexander disease. Neurology 2006;66:494–498.

28. Holden KR, Zuñiga OF, May MM, et al. X-linked MCT8 gene mutations: characterization of the pediatric neurologic phenotype. J Child Neurol 2005;20:852–857.

29. Vaurs-Barrière C, Deville M, Sarret C, et al. Pelizaeus-Merzbacher-like disease presentation of MCT8 mutated male subjects. Ann Neurol 2009;65:114–118.

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