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Death Rates in the U.S. Due to Krabbe Disease and Related Leukodystrophy and Lysosomal Storage Diseases

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Leukodystrophies (LD) and lysosomal storage disorders (LSD) have generated increased interest recently as targets for newborn screening programs. Accurate epidemiological benchmarks are needed in the U.S. Age-specific mortality rates were estimated for Krabbe disease (KD) and nine related disorders. U.S. mortality records with E75.2 cause of death code during 1999–2004 were collected from 11 open record states. All E75.2 deaths in the United States were distributed into specific disease type based on proportions observed in these states. Yearly population sizes were obtained from the CDC and averaged. Mortality rates (per million individuals per year) by age group for the specific diseases were (for <5 or ≥ 5 years): Pelizaeus-Merzbacher (0.037/0.033); sudanophilic leukodystrophy (SLD) (0.037/0.004); Canavan (0.037/0.011), Alexander (0.147/0.022); Krabbe (0.994/0.007); metachromatic leukodystrophy (0.331/0.135); Fabry (0.000/0.124); Gaucher (0.221/0.073); Niemann–Pick (NP) (0.442/0.088); multiple sulfatase (0.000/0.004). This is the first report of mortality rates for the LD/LSD diseases in the U.S. Approximated birth prevalence rate for the early infantile Krabbe phenotype (onset 0–6 months) was based on the <5 year old mortality rate of one early infantile case per 244,000 births, which matches the 1 in 250,000 observed in the NYS newborn screening program as of 2011. It should be noted however that the NYS calculation refers only to the early infantile phenotype and does not include the majority of babies identified in the program with low GALC and two mutations who have remained clinically normal. It is presumed that most, if not all, will develop later onset forms of the disease, but this is by no means certain.

Key words: Krabbe disease; Fabry; Gaucher; Niemann–Pick; metachromatic leukodystrophy; leukodystrophy; lysosomal storage disorder; ICD-10 E75.2; mortality rate; death rate; infantile incidence; newborn screening

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INTRODUCTION

Krabbe disease (KD), otherwise known as globoid cell leukodystrophy, is a lysosomal storage disorder that is characterized by abnormally low levels of galactocerebrosidase (GALC) activity and by abnormalities in white matter in both the central and peripheral nervous systems. Low levels of GALC result in the impaired degradation of galactosylceramide and galactosphingosine (psychosine). The accumulation of these molecules is thought to lead to deficient myelination of axonal projections of neurons throughout the nervous systems of patients with KD. Reduced GALC activity is caused by one of many known mutations to the *GALC* gene. Although severe mutations to the gene (e.g., the 30 KB

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deletion found in 40–50% of alleles in Krabbe patients of European ancestry) show a strong association with disease phenotype, other mutations do not reliably predict disease severity [Wenger, 2011]. The disease is fatal and death occurs before the age of 5 in the vast majority of cases with symptom onset in early infancy [Duffner et al., 2009a].

KD is coded as E75.2 (Other sphingolipidosis) in the WHO ICD-10 classification system, along with related leukodystrophies (LD) and lysosomal storage disorders (LSD). The leukodystrophy types coded in this category include Krabbe, Pelizaeus-Merzbacher, Canavan, sudanophilic, metachromatic leukodystrophy, and myeloleukodystrophy. Alexander disease (AD) also is commonly reported using this code on death certificates. Lysosomal storage disorder types that are coded as E75.2 on death certificates include Fabry, Gaucher, Niemann–Pick (NP), KD, Farber's syndrome, sulfatase deficiency, and metachromatic leukodystrophy.

Adrenoleukodystrophy (E71.3), Tay-Sachs disease (E75.0), and Refsum's disease (G60.1) are excluded specifically [WHO, 2007]. Interest in several E75.2 diseases has increased in recent years as advances in treatment capabilities (e.g., enzymatic replacement therapies) have generated considerable interest in the prospect of newborn screening for select leukodystropies and LSD [Meikle et al., 2006; Hwu et al., 2010; Kemper et al., 2010; Marsden and Levy, 2010; Nakamura et al., 2011]. Potential treatments exist for some of these disorders, but they generally must be initiated as early in life as possible for maximal effectiveness. For example, evidence suggests that hematopoietic stem cell transplantation in patients with KD may be more effective if completed before the detection of clinical signs compared to transplantation after clinical signs are observed [Krivit et al., 1999]. It is anticipated that newborn enzymatic screening will offer the ability to diagnose affected cases early in life, thus improving treatment outcomes. A recently developed multiplex assay of the set of enzymes that, when deficient, cause five LSD [Gelb et al., 2006] is under consideration for use in newborn screening programs of several states. The targets of this assay include four E75.2 diseases: Fabry, Gaucher, Krabbe, and NP; and the developers of the assay are working to add a fifth, metachromatic leukodystrophy [Dr. Michael Gelb, personal communication]. Early detection can improve a child's life, but on the other hand, identification of certain diseases may yield unnecessary tests and treatments [Marcus, 2011].

Interest in these diseases notwithstanding, there is a scarcity of concrete epidemiological information available about them. We found no reports on mortality rates for these diseases and true incidence and prevalence rates are not known. Epidemiological studies of LD and LSD have varied widely in terminology and reporting of methods used in calculating rates. It is often quoted that KD, for example, occurs in 1 in about 100,000–200,000 births in the U.S. [Suzuki et al., 1995; Wenger, 2011]. A rigorous empirical basis for this belief, however, has not been presented. Published papers that gave empirically based rates and that presented methods of calculation typically divided the number of newly diagnosed cases during a "diagnosis period" by the total number of births during the period of time from the first birth date to the last birth date of diagnosed cases. Rates are typically reported in units of 100,000 births. The key quantity of interest seems to be the proportion of affected cases at, or near birth, which is called birth prevalence [Rothman, 1986]. Reported values of this calculation in the LD/LSD literature have been referred to variably as birth prevalence [Poorthuis et al., 1999; Pinto et al., 2004; Poupetova et al., 2010], prevalence [Meikle et al., 1999] cumulative incidence [Heim et al., 1997], and incidence [Applegarth et al., 2000; Ozkara and Topcu, 2004]. Reported rates vary from 0.4 [Poupetova et al., 2010] to 1.35 [Poorthuis et al., 1999] per 100,000 births. No empirically based rates have been reported for the U.S.

The objectives of the current study are twofold: (1) To estimate age specific (<5, ≥5 years) mortality rates for KD and related leukodystrophy and lysosomal storage diseases in the U.S. from national mortality data and state death certificates; and (2) To compare Krabbe rates to those of the related diseases. We report on estimated type-specific mortality rates among individuals <5, ≥5, and over all ages for the 10 prominent types of LD/LSD that were coded as ICD-10 E75.2 from 1999 to 2004.

MATERIALS AND METHODS

KD has been reported as a cause of death on U.S. death certificates since 1999 under the ICD-10 code E75.2 along with related disorders that fall into two overlapping disease categories: LD and LSD. The E75.2 code includes KD and metachromatic leukodystrophy (MLD), which belong to both disease categories, along with four other leukodystrophy types; Pelizaeus-Merzbacher disease (PMD), sudanophilic leukodystrophy (SLD), Canavan disease (CD), AD; and four other LSD; Fabry (F), Gaucher (G), NP, multiple sulfatase deficiency (MSD). These 10 diseases formed a mutually exclusive and exhaustive categorization of E75.2 deaths of known specific and correctly coded types in 11 states[1] from which we obtained death certificates for 1999–2004. Farber's syndrome and myeloleukodystrophy were not observed in the state dataset. The National Center for Health Statistics (NCHS) "Mortality Multiple Cause File" for 1999–2004 was downloaded from the NCHS website. Specific cause of death within the E75.2 code is not indicated in these records. Thus, death certificates for decedents with an E75.2 cause of death code in the national file were collected from the 11 open-record states listed below to determine specific sub-type from literals that are written on the certificates. After permission was provided by each state, the NCHS provided a list of death certificate numbers in the national database that fell into the ICD-10 E75.2 category. Seven of the 11 states used this list to provide death certificates and 4 chose to scan the literals in their own database to select E75.2 cases. Of the 10 diseases studied, those with any of the 6 specific LD types or 6 LSD[2] listed as a cause of death were used to estimate the distribution of E75.2 deaths into 12 categories: the 10 specific disease types, an "unspecified disease type" category, and an "incorrectly classified" category. This distribution was then used to distribute cases of E75.2 in the national data files into these 12 categories. Population sizes were obtained from the CDC's Compressed Mortality File and averaged over the years 1999–2004 to determine a typical population size for three populations: <5 year olds, ≥5 year olds, and all ages. The distributed

[1]California, Connecticut, Kentucky, Massachusetts, Michigan, Minnesota, Montana, North Carolina, Ohio, Vermont, and Washington.
[2]KD and ML belong to both disease categories.

number of cases and average population sizes were used to calculate type-specific mortality rates by age category within each of the 10 disease types.

To determine incorrectly coded literals on the state death certificates, the WHO ICD-10 Version: 2010 query system [WHO, 2007] was used to determine the correct coding for each disease observed among the state literals. The WHO system returned no code for one observed disease (AD). In this case the Orphanet system was used to determine the correct code, which was E75.2. Examples of incorrectly coded certificates included those with literals indicating adrenoleukodystrophy which should have been coded as an E71.3. Also surfactant deficiency disorder was seen in the literals on some death certificates, which is believed to have been confused with sulfatase deficiency or SLD. This type of error is referred to below as incorrectly coded type (i.e., an error of commission). A second type of error occurred when a case that was missing in the national database was found by scanning the literals of state death certificates (i.e., error of omission). The number of errors of omission could be determined in four states (Kentucky, Montana, Ohio, and Vermont) that scanned literals to select death certificates with an indication of an E75.2 disease. If a literal indicating E75.2 was observed but the record was not present in the E75.2 portion of the NCHS database then the case was counted as an error of omission.

The method used to calculate estimates of type specific mortality rates is presented in the Appendix.

RESULTS

There were 943 cases with E75.2 listed as the cause of death nationally from 1999–2004 (252 < 5 years of age, 691 ≥ 5 years). Of these deaths, 279 were among the death certificates obtained from the 11 open-record states. A complete accounting of these 279 cases is given in Table I. A specific cause of death was indicated in the literals of the death certificates of 230 of the 279. The remaining 49 deaths were of unspecified cause. Thirty-two of the 230 deaths with a specific cause indicated were incorrectly coded as E75.2, leaving 198 (71%) deaths in the 11-state sample that were correctly coded and fell into one of the 10 mutually exclusive and exhaustive specific LD/LSD categories. The most common leukodystrophy type was MLD (46 cases), followed by KD (29 cases). The most common LSD type was MLD, followed by NP (36 cases). The ranges of ages at death are given in Table I for specific disease types. As expected, there were no Fabry related deaths among children, and Krabbe and Canavan deaths occurred only in childhood. Deaths due to all other diseases spanned child and adult ages.

Table II shows the distribution of LD and LSD deaths as well as the distribution of all E75.2 deaths in the 11-state database. In <5 year olds, Krabbe makes up 63% of LD's, 50% of LSD's, and 44% of all E75.2 cases. In the greater than or equal to 5-year category, MLD makes up 64% of LD's, 31% of LSD's, and 27% of all E75.2 cases. When looking at all ages, MLD is the most common LD, LSD, and E75.2 at 46%, 27%, and 23% respectively. Death rates were calculated using the numbers in Table I and the distribution in the last column of each age category in Table II. See the Appendix for an example calculation.

Death rates are presented by each specific cause of death by age category (<5, ≥5), and overall ages, in Table III. As seen in this table, estimated death rates due to E75.2 leukodystrophy types were 1.583 and 0.212 per 1,000,000 individuals per year for <5 year olds and ≥5 year olds, respectively, and 0.309 overall. Calculated LD type specific death rates among children <5, ≥5, and all ages are listed in Table III. Figure 1 illustrates type-specific LD death rates and shows that KD is by far the most common type of E75.2 leukodystrophy among younger children (age < 5) while being rare among those who are older.

Also seen in Table III, estimated death rates due to E75.2 LSDs were 1.988 and 0.431 per 1,000,000 individuals per year for <5 year

TABLE I. Number of E75.2 Deaths by Specific Cause of Death and Age Category in the 11 State Database

Type of disease	Disorder	<5 years of age	≥5 years of age	All ages	Range of ages at death[a]
Pelizaeus-Merzbacher	LD[b]	1	9	10	4–66 years
Sudanophilic	LD	1	1	2	4 months to 40 years
Canavan	LD	1	3	4	1–12 years
Alexander	LD	4	6	10	1–48 years
Krabbe	LD and LSD[c]	27	2	29	2 months to 7 years
Metachromatic Leukodystrophy	LD and LSD	9	37	46	2–46 years
Fabry	LSD	0	34	34	26–90 years
Gaucher	LSD	6	20	26	7 months to 93 years
Niemann–Pick	LSD	12	24	36	10 months to 59 years
Multiple sulfatase deficiency	LSD	0	1	1	22 years
Total LD (known type)		43	58	101	
Total LSD (known type)		54	118	172	
Total E75.2 (known type)		61	137	198	2 months to 93 years
Unspecified type		15	34	49	
Incorrect E75.2 classification		7	25	32	
National number of E75.2		252	691	943	

[a]Age ranges among deaths in the 11 states from which we have death certificates. The age range in the national database was 1 month to 99 years.
[b]Leukodystrophy.
[c]Lysosomal storage disorder.

TABLE II. Distribution of E75.2 Deaths into Specific Cause of Death Categories by Age Group in the 11 State Database

		<5 years of age			≥5 years of age			All ages		
Type of disease	**Disorder**	**% LD**	**% LSD**	**% E75.2**	**% LD**	**% LSD**	**% E75.2**	**% LD**	**% LSD**	**% E75.2**
Pelizaeus-Merzbacher	LD[a]	2		2	16		7	10		5
Sudanophilic	LD	2		2	2		1	2		1
Canavan	LD	2		2	5		2	4		2
Alexander	LD	9		7	10		4	10		5
Krabbe	LD and LSD[b]	63	50	44	3	2	1	29	17	15
Metachromatic Leukodystrophy	LD and LSD	21	17	15	64	31	27	46	27	23
Fabry	LSD		0	0		29	25		20	17
Gaucher	LSD		11	10		17	15		15	13
Niemann–Pick	LSD		22	20		20	18		21	18
Multiple Sulfatase Deficiency	LSD		0	0		1	1		1	1
Total LD		99[c]			100			101[c]		
Total LSD			100			100			101[c]	
Total E75.2				102[c]			101[c]			100

[a]Leukodystrophy.
[b]Lysosomal storage disorder.
[c]Does not add to 100% due to rounding errors.

olds and ≥5 year olds, respectively, and 0.525 overall. Calculated LSD type-specific death rates among individuals <5, ≥5, and all ages are listed in Table III and illustrated in Figure 2.

It is seen in Figures 1 and 2 that deaths due to both leukodystrophy and LSD of the E75.2 types generally had higher rates of occurrence in the younger age group. In Table I, however, we see that more E75.2 deaths occurred among those who are ≥5 years old. This phenomenon is explained by the fact that the population size of individuals who are ≥5 was approximately 13.7 times that of those <5. Overall rates, which are weighted averages of the age specific rates with weights equal to population size, therefore, are closer to the rates in the ≥5 year old population.

DISCUSSION

This is the first paper to our knowledge that provides mortality rates for type specific leukodystrophy or lysosomal storage diseases in the U.S. It is based on national death certificates which do not include specific cause of death and state death certificates from 11 states on which literals indicate the specific cause. It is well known that errors exist in coding/diagnosis reported on death certificates. We adjusted for errors that were identifiable. Some errors were identified on state death certificates when literals indicated that the E75.2 code was incorrectly assigned. For example, adrenoleukodystrophy was sometimes coded as an E75.2 when it should have been

TABLE III. Rates of E75.2 Deaths by Specific Cause of Death and Age Category Per Year Per 1,000,000 People

Type of disease	**Disorder**	**<5 years of age**	**≥5 years of age**	**All ages**
Pelizaeus-Merzbacher	LD[a]	0.037	0.033	0.031
Sudanophilic	LD	0.037	0.004	0.006
Canavan	LD	0.037	0.011	0.012
Alexander	LD	0.147	0.022	0.031
Krabbe	LD and LSD[b]	0.994	0.007	0.089
Metachromatic leukodystrophy	LD and LSD	0.331	0.135	0.140
Fabry	LSD	0.000	0.124	0.104
Gaucher	LSD	0.221	0.073	0.079
Niemann–Pick	LSD	0.442	0.088	0.110
Multiple sulfatase deficiency	LSD	0.000	0.004	0.003
Total LD		1.583	0.212	0.309
Total LSD		1.988	0.431	0.525
Total E75.2		2.246	0.501	0.605

[a]Leukodystrophy.
[b]Lysosomal storage disorder.

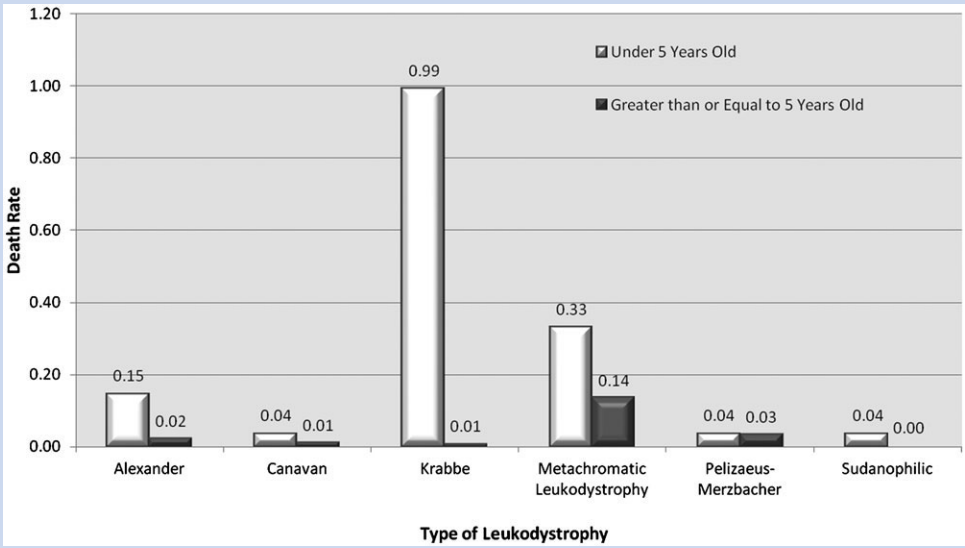

FIG. 1. Leukodystrophy death rates in the U.S. per 1 million people, per year, by leukodystrophy type and age category. This figure illustrates type-specific LD death rates and shows that Krabbe disease is by far the most common type of E75.2 leukodystrophy among younger children (age $<$ 5) while being rare among those who are older. MLD is by far the most common among individuals greater than or equal to 5 years of age.

coded as E71.3. Cases of surfactant deficiency were seen in the literals on some death certificates and were coded incorrectly as E75.2. The percentage of identified incorrectly coded state death certificates (11.5%, over all ages; 8.4%, $<$5 year olds; 12.8%, $\geq$5 year olds) was used to adjust for similar coding errors nationally. A second type of error for which we adjusted occurred because some cases that should have been reported as an E75.2 may have been misclassified into an incorrect ICD-10 code. Four states provided death certificates that were selected by them based on the observance of an E75.2 disease in the literals. There were 24% (11/46) more cases identified by these states over all ages than were observed in the national database. This percentage was 16% among $<$5 year olds and 30% among $\geq$5 year olds. Thus, mortality rates were multiplied by 1.32 ($=1/(1-0.24)$), 1.19 ($=1/(1-0.16)$), 1.43

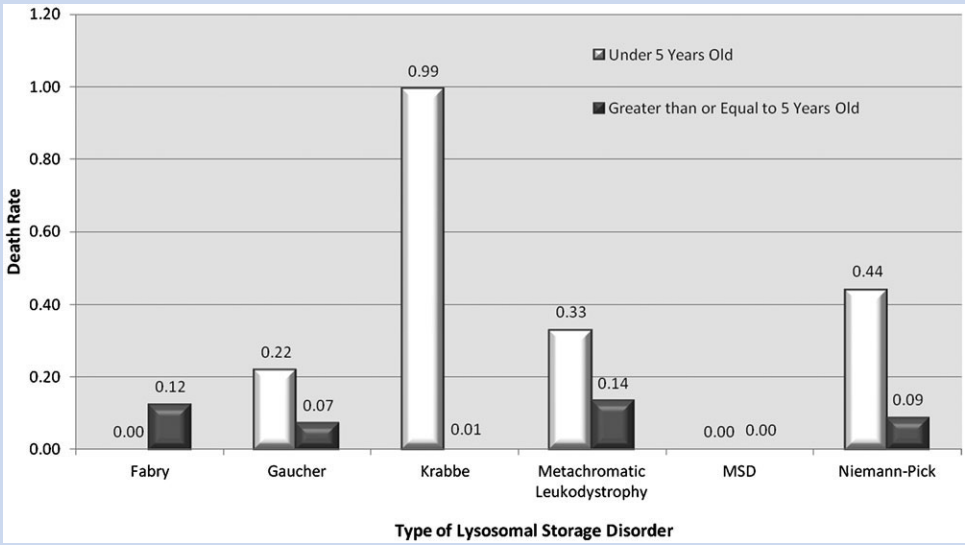

FIG. 2. Lysosomal storage disorder death rates in the U.S. per 1 million people, per year, by LSD and age category. This figure illustrates type-specific LSD death rates and shows that Krabbe disease is by far the most common type of E75.2 LSD among younger children (age $<$ 5) and MLD is the most common among individuals greater than or equal to 5 years of age.

(=1/(1 − 0.30)) to adjust for this type of error for all ages, <5 year olds, and ≥5 year olds, respectively. These adjustments minimize the effects of errors to the extent possible. However, other errors may have occurred for which we could not adjust. Some patients may not be diagnosed properly. For example, a case of Metachromatic leukodystrophy may have been misdiagnosed as cerebral palsy and reported as such in the literals. Some cases may be undiagnosed even at the time of death. The frequencies of such diagnosis errors and of potentially counter-balancing errors due to misdiagnoses of other diseases as LD or LSD were impossible to determine. If not balanced, it seems that these errors would lean toward underestimation of mortality rates, but it is impossible to know the direction or magnitude of the impact of diagnostic errors.

For some of these diseases the estimated mortality rates for children younger than 5 years are expected to approximate the prevalence of early infantile onset cases among births. KD, for example, is highly lethal with short survival times in its early infantile (EIKD) form. Late infantile (LIKD) and later onset (LOKD) cases survive longer. Most children with EIKD die by the age of 5 [Duffner et al., 2009a]. There are, however, deaths prior to age 5 among LIKD (7–12 months) and LOKD (13+ months) cases as well as cases of survival in EIKD patients beyond 5 years. From the Hunter's Hope Krabbe Family Database [Duffner et al., 2009a], 10.5% of EIKD cases die after age 5, while 72.4% of LIKD cases and 20.4% of LOKD cases die before age 5. This sample included patients with symptom onset between 0 and 5 years of age [P. Duffner, personal communication]. In this database there were 81 EIKD patients, 22 LIKD patients, and 11 LOKD patients. Therefore it is estimated that 72.5 EIKD cases, 15.9 LIKD cases, and 2.2 LOKD cases were expected to die before age 5 in the Hunter's Hope Database. Thus, 80% (i.e., 72.5/90.6) of all Krabbe deaths prior to age 5 occurred among EIKD patients and the approximate incidence of KD in the first 6 months of life is 0.80 (i.e., 0.80 × 0.994) cases per million births per year. Similarly, 36% of all Krabbe deaths after age 5 are EIKD.

Since mortality rates among <5 year olds were calculated based on a 5-year age range (0–5 years of age), estimates of the number of deaths prior to age 5 due to EIKD per million births can be calculated approximately as 3.98 (= 5 × 0.994 × 0.80) = number of years in the 0–5-year age category × Krabbe mortality rate among 0–5 year olds per year per million × the proportion of deaths prior to age 5 that are EIKD). Similarly, the number of deaths after age 5 due to EIKD was calculated approximately as 0.09 (= 35 × 0.007 × 0.36 = number of years in the 5–40-year age category × Krabbe mortality rate among ≥5 year olds per year per million × the proportion of deaths after age 5 that are EIKD, where 35 is the maximum number of years of survival past age 5 observed in the Hunter's Hope database [Duffner et al., 2009a]). Thus, the total number of deaths due to Krabbe among 1 million births is approximated as 4.07 = 3.98 + 0.09, or 0.41/100,000 births (i.e., 1 case per 244,000 births). This is our estimate of birth prevalence of early infantile KD (i.e., rate of symptom onset in the first 6 months of life). This rate provides a means for calculating the expected number of cases to be observed per year by a newborn screening program.

The data required to make similar translations of mortality rates among 0–5 year olds to approximate incidence rates in the first 6 months of life are not available for other E75.2 diseases. However, there is some evidence that it may be reasonable to assume for NP and AD that approximately 100% of deaths among 0–5 year olds are NP type A and infantile Alexander cases, respectively. If so, then the incidence of infantile NP and AD in infancy are approximately the corresponding mortality rates among 0–5 year olds. For example, NP type A typically leads to death by age three, while other forms of NP typically survive beyond age 5 [Patterson et al., 2001; Schuchman, 2007]. Thus, the mortality rate among less than 5 year olds (0.442 each year per million children) is expected to be directly proportional to the birth prevalence of NP type A. In AD non-infantile cases atypically result in death before age 5, while not all infantile cases result in death before age 5 [Flint and Brenner, 2011]. Assuming that these types of atypical cases are balanced in number, the mortality rate reported herein (0.147 each year per million children) is proportional to the approximate incidence of AD in the first year of life. Under this balance assumption, the birth prevalence of NP type A is 0.22/100,000 or 1 case per about 455,000 births. The approximated birth prevalence for infantile AD under this assumption is 0.07/100,000 or approximately 1 case per about 1.3 million births. These rates can serve as reasonable approximations to incidence of infantile forms of NP type A and AD until information becomes available about the frequencies of death before age 5 among non-infantile cases and death after age 5 among infantile cases.

Our estimated birth prevalence rate of KD of 1 per 244,000 births was confirmed by the newborn screening experience in New York State (NYS). During the first 4 years of screening for KD, 1 million babies were screened [Marcus, 2011] and four were affected by the early infantile form of Krabbe [Duffner et al., 2011]. Therefore, the observed prevalence was 1 case per 250,000 births, matching closely to the 1 per 244,000 approximated above from national and state death certificate data and previously reported data from Hunter's Hope Krabbe Disease database [Duffner et al., 2009a]. The four babies were identified as having early infantile KD and were considered for hematopoietic cell transplantation based on the NYS scoring system [Duffner, personal communication]. The scoring system is 2 points for a positive MRI, 2 points for increased spinal fluid protein, 2 points for abnormal neurologic examination, 1 point for abnormal BAER, VER or NCV, and a 30 KB homozygous deletion is 4 points [Duffner et al., 2009b].

It would appear that the approximation in this paper that 1 in every 244,000 births is affected by early infantile KD is notably less than previously reported rates in the literature, that is, 1/100,000–1/200,000. It is not clear however that these rates can be compared to ours, as the diagnostic criteria, choice of denominator populations, and proper/precise interpretation of the commonly reported rates are unclear. More information about methods used in these reports is needed to resolve the differences. The fact that independently calculated estimates of incidence of early infantile KD from our mortality rates and from the NYS newborn screening experience are consistent is comforting. However (if anything) both underestimate the overall incidence of KD as later onset phenotypes are not included in the estimates. This is a particular issue with the NYS data as the majority of children with low GALC and two mutations are currently asymptomatic. It is assumed that many if not all will eventually develop clinical signs/symptoms of the later onset

phenotypes. This, however, is by no means certain, and will only be answered with long term follow-up.

No empirically based estimates of mortality rates for specific LD or LSD types have been reported for the U.S. population. Those presented in this paper and their translation to approximate birth prevalence rates (when possible), therefore, provide new and valuable benchmark information to states considering the inclusion of tests for specific LSDs or LDs in their newborn screening programs, and will also prove useful for evaluating the effectiveness of therapeutic interventions.

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APPENDIX: METHODS FOR CALCULATING RATES

The method used to calculate estimates of type specific mortality rates is presented below.

Notation

Capital letters will be used to denote quantities from the national death records database and corresponding lowercase letters denote the same quantity from the 11-State database. Let

D = number of death certificates with the E75.2 code in any field in the national database for 1999–2004;
d = number of death certificates with the E75.2 code in any field in the 11-state database for 1999–2004;
N_t = population size in year t; and
T = number of years of deaths included in the study (e.g., $T = 6$ in the current study, 1999–2004).

Subscripts then indicate sub-populations defined by age (Y = younger age, i.e., Age < 5; O = older age, i.e., Age ≥ 5) or disease type (e.g., D_{Yc} = the number of deaths in the national database among children <5 years old due to disease type c, where c represents KD for Krabbe, MLD for metachromatic leukodystrophy, etc., through U for unspecified type, and EC for an error of commission. We use a subscript of EO to denote a case that was missing in the national database, but was found by scanning the literals of a state's death certificate (i.e., error of omission). If there is no Y or O subscript, then all ages are included (e.g., D_c = the number of deaths in the national database due to disease type c). D_{EC} and D_c are not observed in the national database, but can be estimated from the data in the national and state databases. These estimated quantities are denoted by D_{EC}^* and D_c^*. From these basic quantities, we calculate

N = the average of the N_t over the years t = 1999, 2000, . . ., 2004;
$p_{EC} = d_{EC}/d$ (the proportion of deaths that were incorrectly coded as E75.2 on a state death certificate);
p_{EO} = the proportion of cases in the four state database (i.e., the database of death certificates from the four states that selected death certificates by scanning literals for indications of E75.2 diseases) that were not reported in the national database, that is the proportion of errors of omission;
$D_{EC}^* = D \times p_{EC}$ (the expected, i.e., estimated number of deaths in the national database that were incorrectly coded as E75.2);
$d_{known} = d - d_U - d_{EC}$ (the number of deaths in the 11-state database with specifically known and correctly coded cause of death in the E75.2 category);
$p_c = d_c/(\text{sum of } d_c)$, where the sum of d_c is taken over the values of c that correspond to specific LD or LSD types (i.e., c = KD, MLD, PMD, SLD, CD, AD, F, G, NP, MSD). That is, p_c = proportion of disease type c among deaths with specific disease type coded correctly and is an estimate of the probability that a specifically and correctly coded death falls in disease category c;
$D_c^* = \{[D - (d_{known} + D_{EC}^*)] \times [1/(1 - p_{EO})]\} \times p_c + d_c$ (the expected number of deaths due to disease type c from 1999–2004); and
$R_c = [(D_c^*/T)/N] \times 1{,}000{,}000$ (expected number of deaths due to disease type c per year per 1,000,000 individuals in the typical population in any given year).

By applying these calculations to the same quantities for sub-populations, we can obtain estimated mortality rates by age group (<5 and ≥ 5 years). The formulas are:

$R_{Yc} = [(D_{Yc}^*/T)/N_Y] \times 1{,}000{,}000$ (the expected number of deaths due to disease type c per 1,000,000 children <5 years old per year); and
$R_{Oc} = [(D_{Oc}^*/T)/N_O] \times 1{,}000{,}000$ (the expected number of deaths due to disease type c per 1,000,000 individuals ≥ 5 years old per year).

Example Calculation

The above methods are illustrated below for future researchers who wish to use them in similar settings. We use the above formulas to calculate the KD death rate for children less than 5 years old:

$D = 252$;
$d_c = 27$;
N_t = 19,135,544; 19,175,798; 19,369,341; 19,609,147; 19,769,279; 20,071,268;
$T = 6$;
N = 19,521,730 (average N_t for children < 5 years of age, t = 1, 2, . . ., 6.);
$p_{EC} = 7/83 = 0.084$;

$p_{EO} = 3/19 = 0.16$;
$D_{EC}^{*} = 252 \times 0.084 = 21.17$;
$d_{known} = 83 - 15 - 7 = 61$;
$p_c = 27/61 = 0.443$;
$D_c^{*} = \{[252 - (61 + 21.17)] \times [1/(1 - 0.16)]\} \times 0.443 + 27 = 116.53$; and
$R_{Yc} = [(116.53/6)/19{,}521{,}730] \times 1{,}000{,}000 = 0.994$.

The N_t, $t = 1, 2, \ldots, 6$, for individuals ≥ 5 years of age were 259,904,624; 262,246,108; 265,427,546; 268,759,559; 271,041,510; 273,584,136; with $N = 266{,}827{,}247$. Over all ages N was 286,348,977.

REFERENCES

Applegarth DA, Toone JR, Lowry RB. 2000. Incidence of inborn errors of metabolism in British Columbia, 1969–1996. Pediatrics 105: e10.

Duffner PK, Jalal K, Carter RL. 2009a. The Hunter's Hope Krabbe family database. Pediatr Neurol 40:13–18.

Duffner PK, Caggana M, Orsini JJ, Wenger DA, Patterson MC, Crosley CJ, Kurtzberg J, Georgianne AL, Escolar ML, Adams DJ, Andriola MR, Aron AM, Ciafaloni E, Djukic A, Erbe RW, Galvin-Parton P, Helton LE, Kolodny EH, Kosofsky BE, Kronn DF, Kwon JM, Levy PA, Miller-Horn J, Naidich TP, Pellegrino JE, Provenzale JM, Rothman SJ, Wasserstein MP. 2009b. Newborn screening for Krabbe disease: The New York state model. Pediatr Neurol 40:245–252.

Duffner PK, Barczykowski A, Jalal K, Yan L, Kay DM, Carter RL. 2011. Early infantile Krabbe disease: Results of the world-wide Krabbe registry. Pediatr Neurol 45:141–148.

Flint D, Brenner M. 2011. Alexander disease. In: Raymond GV, Eichler F, Fatemi A, Naidu S, editors. Leukodystrophies. London: Mac Keith Press. pp 90–105.

Gelb MH, Turecek F, Scott CR, Chamoles NA. 2006. Direct multiplex assay of enzymes in dried bloodspots by tandem mass spectrometry for the newborn screening of lysosomal storage disorders. J Inherit Metab Dis 29:397–404.

Heim P, Claussen M, Hoffmann B, Conzelmann E, Gärtner J, Harzer K, Hunneman DH, Köhler W, Kurlemann G, Kohlschütter A. 1997. Leukodystrophy incidence in Germany. Am J Med Genet 71:475–478.

Hwu W, Chien Y, Lee N. 2010. Newborn screening for neuropathic lysosomal storage disorders. J Inherit Metab Dis 33:381–386.

Kemper AR, Knapp AA, Green NS, Comeau AM, Metterville DR, Perrin JM. 2010. Weighing the evidence for newborn screening for early-infantile Krabbe disease. Genet Med 12:539–543.

Krivit W, Aubourg P, Shapiro E, Peters C. 1999. Bone marrow transplantation for globoid cell leukodystrophy, adrenoleukodystrophy, metachromatic leukodystrophy, and Hurler syndrome. Curr Opin Hematol 6:377–382.

Marcus A. New tests for newborns, and dilemmas for parent. Wall St J http://online.wsj.com/article/SB10001424053111904233404576462194284199496.html Published July 26, 2011. Accessed July 29, 2011.

Marsden D, Levy H. 2010. Newborn screening of lysosomal storage disorders. Clin Chem 56:1071–1079.

Meikle PJ, Hopwood JJ, Clague AE, Carey WF. 1999. Prevalence of lysosomal storage disorders. JAMA 281:249–254.

Meikle PJ, Grasby DJ, Dean CJ, Lang DL, Bockmann M, Whittle AM, Fietz MJ, Simonsen H, Fuller M, Brooks DA, Hopwood JJ. 2006. Newborn screening for lysosomal storage disorders. Mol Genet Metab 88:307–314.

Nakamura K, Hattori K, Endo F. 2011. Newborn screening for lysosomal storage disorders. Am J Med Genet Part C 157C:63–71.

Ozkara HA, Topcu M. 2004. Sphingolipidoses in Turkey. Brain Dev 26: 363–366.

Patterson MC, Vanier MT, Suzuki K, Morris JA, Carstea E, Neufeld EB, Blanchette-Mackie JE, Pentchev PG. 2001. Niemann–Pick disease type C: A lipid trafficking disorder. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic and molecular bases of inherited disease. New York: McGraw-Hill. pp 3611–3633.

Pinto R, Caseiro C, Lemos M, Lopes L, Fontes A, Ribeiro H, Pinto E, Silva E, Rocha S, Marcão A, Ribeiro I, Lacerda L, Ribeiro G, Amaral O, Sá Miranda MC. 2004. Prevalence of lysosomal storage diseases in Portugal. Eur J Hum Genet 12:87–92.

Poorthuis BJ, Wevers RA, Kleijer WJ, Groener JE, de Jong JG, van Weely S, Niezen-Koning KE, van Diggelen OP. 1999. The frequency of lysosomal storage diseases in The Netherlands. Hum Genet 105:151–156.

Poupetova H, Ledvinova J, Berna L, Dvorakova L, Kozich V, Elleder M. 2010. The birth prevalence of lysosomal storage disorders in the Czech Republic: Comparison with data in different populations. J Inherit Metab Dis 33:387–396.

Rothman KJ. 1986. Modern epidemiology. Boston: Little Brown.

Schuchman EH. 2007. The pathogenesis and treatment of acid sphingomyelinase-deficient Niemann–Pick disease. J Inherit Metab Dis 30:654–663.

Suzuki K, Suzuki Y, Suzuki K. 1995. Galactosylceramide lipidosis: Globoid cell leukodystrophy (Krabbe disease). In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic and molecular bases of inherited disease. New York: McGraw-Hill. pp 2671–2692.

Wenger DA. 2011. Krabbe disease (globoid cell leukodystrophy). In: Raymond GV, Eichler F, Fatemi A, Naidu S, editors. Leukodystrophies. London: Mac Keith Press. pp 90–105.

World Health Organization. International statistical classification of diseases and related health problems, 10th revision, 2007. Available from http://apps.who.int/classifications/apps/icd/icd10online/. Accessed May 30, 2011.