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Hospitalization Burden and Incidence of Krabbe Disease

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Abstract

Objective: The purpose of our study was to understand the healthcare burden and incidence of Krabbe disease (Krabbe).

Methods: Retrospective analysis of Krabbe patients identified October 1, 2015 through December 31, 2020, ages birth through age 3, evaluated in two national databases. We estimated point prevalence and incidence from year 2016 data.

Results: We identified 98 unique Krabbe patients with 736 visits including 260 were inpatient admissions. Total healthcare charges were $51.5 million dollars. We determined a point prevalence of 34 – 68 Krabbe patients in 2016 ages 0 – 3 years. This estimates a birth incidence of ~1 in 310,000 live births.

Keywords

pediatric; leukodystrophy; Krabbe disease; Globoid cell leukodystrophy; incidence

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INTRODUCTION

Krabbe disease (Krabbe) is a rare and deadly autosomal recessive leukodystrophy characterized by low levels of galactocerebrosidase, a lysosomal enzyme involved in myelin turnover.[1] The clinical phenotype of Krabbe is variable, and implementation of newborn screening (NBS) and development of therapy has been complicated by the rarity of Krabbe and difficulty in predicting disease course.[2–7] The only current treatment for Krabbe is hematopoietic stem cell transplant (HSCT), which is only effective if given prior to symptom onset.[5] However, over the past few years there has been a rapid progression in understanding disease pathophysiology, predicting severity, and developing new therapies for Krabbe including gene therapy.[8–11] These advances underscore the need for improved understanding of health care needs and prevalence of Krabbe.

A major challenge for Krabbe is that its rarity has made understanding its clinical burden and prevalence unclear. This is in part because data has primarily been available from a few specialty referral centers, which often specialize in HSCT. Further, understanding Krabbe prevalence has been challenging because NBS has only been implemented in eight states,[12] and because Krabbe has a complex disease penetrance that is affected by genetic mutation type and by levels of galactocerebrosidase and the toxic metabolite psychosine.[3,5,13,14] At this time, estimates of Krabbe range from 1 in 12,080 live births, based on incidence predictions from genomic allele frequency predictions;[15] to 1 in 394,000, from NBS performed in New York.[16] Incidence also varies in some racial and ethnic groups, ranging as high as 1 per 100 live births in the Druze people,[17] to as low as 2 in 1,000,0000 live births in Japan.[18]

Our objective was to use national data, focusing on hospitalization data, to understand Krabbe healthcare use and incidence, avoiding single center referral biases. This would provide insights on the burden of Krabbe health problems, and would further determine a range of Krabbe incidence in the U.S. This information can help guide development of preventative care guidelines for Krabbe patients; for determining numbers of Krabbe patients to expect from NBS efforts; and for efforts to effectively plan for developing and distributing therapies.

METHODS

Ethics Approval

This project using deidentified data was not considered human subjects research in accordance with the Common Rule (45CFR§46.102[f]) and was exempted by the Institutional Review Boards at the University of Utah and Intermountain Healthcare.

Study Design

We conducted a retrospective study of patients ≤ age 3 years with an International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis of Krabbe disease (E75.23); identified between October 1, 2015 through December 31, 2020; with a visit to a Pediatric Health Information System (PHIS) hospital; or identified in the Kids' Inpatient Database (KID).

The PHIS database has information from 49 children's hospitals in the U.S.[19] Hospitals are affiliated with the business alliance of Children's Hospital Association (Lenexa, Kansas). 37 hospitals had at least one Krabbe case identified. Patient information across multiple visits can be linked with a deidentified patient identity code. Data collected include patient and visit demographics such as age, gender, race, insurance type, type of visit, estimated total visit cost, length of stay, ICD coding and detailed charge information. The hospital visits included primarily inpatient admissions with additional visit types such as emergency department, observation, ambulatory surgery, clinic and other visit types where available. Race and ethnicity are collected as patient/family-reported answers to separate questions at registration: one for race and one for ethnicity. In 2016, PHIS represents 14% of all pediatric admissions excluding normal newborns and 84% of visits excluding normal newborns age 0–3 years at a children's hospital when compared to the KID database.

The KID database is a national sample of inpatient pediatric data from all payers in the United States, developed by the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality (AHRQ).[20] Data is collected every three years, based on discharge codes, and weighted estimates were used to provide information on the estimated 6.3 million U.S. pediatric hospitalizations in 2016. Data are sampled from 4,200 U.S. community hospitals; normal newborns are sampled at a rate of 10%, while complicated newborns and other pediatric discharges (age 20 or less at admission) are sampled at a rate of 80% (https://www.hcup-us.ahrq.gov/kidoverview.jsp). Data available include primary and secondary diagnoses and procedures; patient demographics (e.g., sex, age, race, median income for ZIP Code); hospital characteristics (e.g., ownership, size, teaching status, Census division); expected payment source; total charges; and length of stay.

Uncomplicated births were defined as an ICD-10-CM principal or secondary diagnosis code of Z3800, Z3801, Z382, Z3830, Z3831, Z385, Z3861, Z3862, Z3863, Z3864, Z3865, Z3866, Z3868, Z3869, or Z388 and DRG 795.

Statistical Analysis

Estimation of the period prevalence for Krabbe in U.S. children ages 0–3 years for the interval from January 1, 2016-December 1, 2016 was conducted by combining information from several sources. The number of children born in the U.S. each year was obtained from CDC data published by the CDC.[21] The number of children with Krabbe during the interval was estimated using information from the PHIS and KID databases. To perform an estimation, we identified the number of US hospital admissions of children age 0–3 years with Krabbe in the KID database. To turn this into an estimate of the number of US Krabbe patients, we used PHIS to calculate the average number of inpatient admissions per Krabbe patient. We also considered the group of Krabbe patients that would not be identified in the KID database such as Krabbe patients who were not hospitalized during 2016 or Krabbe patients born in the relevant time frame but who had died before 2016. Because of the lack of data for this group, we assumed two extremes about the relative size of this group, specifically that there were no Krabbe patients not captured in KID and that KID represented only half of the Krabbe US patient population. Given the CDC birth numbers and the total of the above Krabbe patients, the period prevalence estimation would be a simple ratio.

Data Availability Statement

Data are included in this manuscript.

RESULTS

Krabbe Disease Numbers and Hospital Burden

For our analysis of Krabbe disease, we used two sources of hospital data: PHIS, which includes data from 49 children's hospitals; and KID, which uses sampling estimates derived from 4,200 hospitals. The PHIS data set includes complete records and each patient is uniquely identified; however, it is not comprehensive for all pediatric patients because it reports data from only children's hospitals, and from a subset (albeit majority) of children's hospitals. In contrast, the KID uses a sampling and estimation method to provide totals on hospitalizations, but does not have patients uniquely identified. Thus, KID, while more comprehensive and able to estimate the total number of Krabbe hospitalizations, does not report the unique number of patients who accounted for the hospitalizations.

In PHIS, we analyzed the number of unique patients with Krabbe, by year of birth (Table 1). Prior to 2015, Krabbe did not have a unique ICD code. However, in PHIS, a patient born prior to ICD-10-CM implementation in 2015 can be followed retroactively into prior years' data. Since life expectancy is often < 3 years for infantile or early onset Krabbe,[22] 2013 would be the first year in which Krabbe patient numbers might reflect a relative steady-state of patient numbers (Table 1).

We analyzed PHIS visit data for the Krabbe identified patient visits, with the earliest in October 2013 and the latest in December 2020, to evaluate Krabbe hospital utilization (Table 2). 37 hospitals reported at least one Krabbe patient visit (range 1– 83), with from 1 to 26 unique patients. During this slightly over 7 year time period, of 98 total Krabbe patients, 79 patients had 260 hospital admissions, with a median of 4 admissions per hospital. The most common visit type was an inpatient hospitalization (260), followed by clinic visits (189) and emergency department visits (153). There were 23 (28%) patients with an ICD or billing code for bone marrow or stem cell transplant.

We evaluated the most common reasons for hospitalization (Table 2), first by excluding what we deemed "intrinsic" diagnoses associated with Krabbe itself (Leukodystrophy; Lack of expected normal physiological development; Other disorders of psychological development; and Other sphingolipidoses). The five most common discharge diagnosis groupings (using ICD-10 Clinical Classifications Software Refined (CCSR) categories) were Epilepsy 220 visits (30%), 33 patients (34%); Esophageal disorders 104 (14%), 39 (40%); Fluid and electrolyte disorders 91 (12%), 45 (46%); Dysphagia 88 (12%), 32 (33%);); and Other gastrointestinal disorders 80 (11%), 34 (35%). The five most common procedure groupings were administration of nutritional and electrolytic substances 75 visits (10%), 39 patients (40%); Gastrostomy 47 (6%), 42 (43%); Mechanical ventilation 40 (5%), 15 (15%); Venous and arterial catheter placement 37 (5%), 30 (31)%; and Lumbar puncture 36 (5%), 33 (34%).

The common medications prescribed to the Krabbe patients (excluding acetaminophen and sodium chloride), were levetiracetam 120 visits (16%), 36 patients (37%); albuterol 115

(16%), 23 (23%); propofol 114 (15%), 61 (62%); baclofen 107 (15%), 39 (40%); and gabapentin 101 (14%), 39 (40%) (Table 2).

Using day of service for charges as a proxy for number of treatments or exams, the 98 Krabbe patients had 36 MRIs (21 (21%) patients); 92 CTs (58 (59%)); 158 EEGs (49 (50%); 106 EKGs (41 (42%)); and 927 nebulizer treatments (25 (26%)) (Table 2).

The total charges of 98 Krabbe patients in the 7+ year time period was $51.3 million dollars, or $526,274/patient (Table 3) with a median of $112,723 and IQR ($39,249-$662,470). This included 3,204 inpatient days; an average of 33 days/patient; 154 emergency department visits; $1.6 million charges for imaging; $7.8 million charges for lab; $13.5 million pharmacy charges; and $20.5 million room and nursing charges. The 23 Krabbe patients with HSCT had total charges of $30.3 million or $1.3 million per patient; with a median of $1.01 million and IQR ($436,000 to $1.7 million). For the 75 Krabbe patients without a transplant, total charges were $21.2 million or $282,629 per patient with a median of $67,151 and IQR ($22,667-$229,259).

Point Prevalence and Incidence

To estimate point prevalence and incidence, we used the year 2016. KID data is only available every three years and 2016 was the most recent completed data set at the time of our analysis; and prior to 2015 Krabbe was not uniquely coded by ICD-9 making it impossible to track Krabbe patients.

The PHIS data from 2016 had a total of 236,386 unique patients who had 234,783 hospital discharges (excluding births of uncomplicated newborn infants) (Table 4). There were 18 unique Krabbe patients, who had a total of 25 hospitalizations for an average of 1.39 hospitalizations per patient. Their average length of stay was 11.6 days.

In KID in 2016, there were 2,214,956 hospitalizations (excluding births of uncomplicated newborn infants), and 47 Krabbe hospitalizations. The Krabbe average length of stay was 12.2 days. We examined the hospitalizations in 2016, of children ages birth through age 3 years, with an ICD-10 diagnosis of Krabbe (E75.23). If the ratio of Krabbe hospitalizations to unique patients is the same in KID as it in PHIS, this would estimate that the 47 Krabbe hospitalizations were accounted for by 34 patients.

We estimate a range of 34–68 Krabbe patients in 2016 ages 0–3 years as a point prevalence. That is, the low end is derived from the KID and PHIS data, and the high end is derived assuming that half of children with Krabbe ages 0 – 3 years are not hospitalized or not otherwise recorded in any given year in the KID or PHIS databases. Children who were ages 0–3 years at the end of 2016 were born between 2013 and 2016. From 2013 – 2016, the U.S. had a total of 15,844,629 live births. Based on the midpoint of the point prevalence range, if the point prevalence is 51 patients with Krabbe, and encompassing birth years 2013 through 2016, this is a birth incidence of ~1 in 310,000 live births.

DISCUSSION

We present national data on Krabbe disease, with analysis of the largest single-study cohort of 98 patients. In just a seven+ year period, we show a significant burden of 736 visits and over $51 million in healthcare charges. Krabbe has a rapid progression of disability and an average life span of less than 3 years in the absence of treatment.[22] Reflecting disease severity, we observed frequent and prolonged hospitalizations, with each patient having on average 2.6 hospitalizations with a length of about 33 patient days, and frequent testing including EEGs and MRIs. The most common medications and procedures, including for epilepsy, spasticity, and feeding intolerance, match previous analysis of Krabbe patient medical problems.[23–25]

This project was performed through analysis of two large national administrative databases, PHIS and KID. PHIS includes data from a large number of children's hospitals (49) and each patient can be uniquely followed; however, it is largely based on in-patient hospitalization data, and does not include all hospitals or all children's hospitals. KID uses a sampling approach; thus, while representing all hospitalizations, it can not follow unique patients.

Current literature suggest that HSCT is indicated in pre-symptomatic Krabbe patients, including both early infantile and late infantile types.[5,26–28] Our data show the high costs and burden of medical care for Krabbe, which are greater in HSCT patients. This demonstrates high healthcare utilization for HSCT Krabbe patients. This suggests that on-going tracking of short- and long-term outcomes for HSCT (or other therapies) is important to gauge effectiveness of transplant and to consider standardized guidelines for determination of candidacy for transplant. Compared to other leukodystrophy patients, Krabbe patients have higher charges $526,000/patient versus $131,000,[29] even if HSCT patients were excluded ($282,000 for non-HSCT Krabbe patients). Cystic fibrosis, another chronic disease, had even lower charges of ~$29,000/patient.[30]

By determining numbers of Krabbe patients represented in the KID and PHIS databases, we were also able to estimate a birth incidence of 1 in 310,000 live births, which is similar to the rate observed from newborn screening in New York State, of 1 in 394,000 live births.[16] However, because these estimated incidences are based on newborn screening levels of galactocerebrosidase and psychosine; or through symptomatic presentation of patients; a still unresolved issue is whether milder cases of Krabbe could be present in the population, with either later onset of symptoms or with incomplete penetrance.[3,15]

The point prevalence estimation relied on several influential assumptions. More complex point prevalence estimation approaches were considered, including a Bayesian model to propagate uncertainty associated with various inputs and to allow for the inclusion of prior information. However, the Bayesian model still employed strong assumptions, and the statistical complexity was deemed unmerited given the continued dependence on such assumptions. The lack of information on how many children with Krabbe do not have hospitalizations in a given year is a persistent limitation.

Additional limitations of this study are that it was derived from administrative data, and was a retrospective study. A few centers accounted for the majority of patients, which could skew evaluation of practice patterns and approaches to care. We expect our data is incomplete and not all Krabbe patients are accounted for; for example, significant underdiagnosis of Krabbe (and other leukodystrophies) has been noted in racial and ethnic minority groups.[31] Other studies have reported on the impact of Krabbe on quality of life,[32] which our study did not address. Strengths include the large sample size; the use of national data that was not limited to a single or few referral centers; and ability to estimate point prevalence and incidence.

In conclusion, Krabbe patients have high healthcare costs, reflecting a significant disease burden and need for medical treatments and hospitalizations. Treatments to reduce hospitalizations and morbidities, including for seizures and feeding difficulties, could have major impacts for improving Krabbe patient care and reducing costs. Future efforts could work on developing preventative care guidelines for Krabbe. For example, by determining which antiepileptic medications are most effective in Krabbe patients, this could reduce the number of hospitalizations related to seizures.

Our estimation of a Krabbe incidence of 1 in 310,679 births suggests that each year in the United States, there will be 12 births of children at-risk for symptomatic Krabbe. However the low incidence highlights that costs of implementation and screening could be a barrier for individual states, and raises a question as to whether coordinated national-level screening should be considered. Our data suggest opportunity to reduce healthcare costs and improve the lives of Krabbe patients and their families.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significance:

Krabbe disease patients had over $51 million in health care charges and hundreds of hospitalizations. Estimated prevalence and birth incidence is similar to rates observed from newborn screening. Our findings show the tremendous health impacts of Krabbe disease, and provide guidance for efforts in screening and treatment planning.

Table 1.

Birth year and unique Krabbe patients in PHIS; patient demographics.

Birth Year	N Patients	N Receiving HSCT	% with HSCT codes
2020	5	0	0%
2019	13	4	31%
2018	18	6	33%
2017	13	1	8%
2016	17	5	29%
2015	14	3	21%
2014	12	3	25%
2013	5	0	0%
2012	1	1	100%

* Other Demographics based on first visit			
Gender	**N Patients**	**N Receiving HSCT**	**% with HSCT codes**
Male	53	15	28%
Female	45	8	18%
Race/Ethnicity Grouping			
White Non-hispanic	45	12	27%
Other	18	3	17%
White Hispanic	16	3	19%
Missing	9	3	33%
Black	7	2	29%
Asian	3	0	0%
Primary Payer Grouping			
Government	46	12	26%
Other	13	1	8%
Private	35	10	29%
Self Pay	4	0	0%
First visit age in years			
0	72	17	24%
1	12	1	8%
2	7	3	43%
3	7	2	29%

Table 2.

PHIS hospital data for Krabbe use, 10/2013 −12/2020. Data is from 37 children's hospitals. Abbreviations: DRG, diagnosis related group; GERD, gastroesophageal reflux disease; ICU, intensive care unit; KD, Krabbe disease. Full results in Supplemental Data 1.

Number of KD visits total (mean, median, range)	736 (20, 9, 1–83)	
Number of KD patients total (mean, median, range)	98 (3, 2, 1–26)	
Visit type/characteristics	*N (%)*	
Inpatient	260 (35%)	
Emergency department	154 (21%)	
Ambulatory surgery	46 (6%)	
Observation unit	46 (6%)	
Clinic visit	189 (26%)	
Other	41 (6%)	
In Hospital Death	7 (7%)	
ICU stay	32 (33%)	
of those in ICU, Days	21.2 days (1–134)	
Diagnosis *	*Visits N (%)*	*Patients N (%)*
Epilepsy; convulsions	220 (30%)	33 (34%)
Esophageal disorders	104 (14%)	39 (40%)
Fluid and electrolyte disorders	91 (12%)	45 (46%)
Dysphagia	88 (12%)	32 (33%)
Other specified and unspecified gastrointestinal disorders	80 (11%)	34 (35%)
Procedures **	*Visits N (%)*	*Patients N (%)*
Administration of nutritional and electrolytic substances	75 (10%)	39 (40%)
Gastrostomy	47 (6%)	42 (43%)
Mechanical ventilation	40 (5%)	15 (15%)
Venous and arterial catheter placement	37 (5%)	30 (31%)
Lumbar puncture	36 (5%)	33 (34%)
Most common medications ^	*Visits N (%)*	*Patients N (%)*
Levetiracetam	120 (16%)	36 (37%)
Albuterol	115 (16%)	23 (23%)
Propofol	114 (15%)	61 (62%)
Baclofen	107 (15%)	39 (40%)
Gabapentin	101 (14%)	39 (40%)
Other Conditions	*Visits N (%)*	*Patients N (%)*
Gastrostomy	285 (39%)	58 (59%)
Feeding difficulties	130 (18%)	46 (47%)
Epilepsy	220 (30%)	33 (34%)
GERD	103 (14%)	39 (40%)
Failure to thrive	72 (10%)	44 (45%)
Developmental Delays	103 (18%)	39 (40%)

Tracheostomy	44 (6%)	2 (2%)
	Visits N (%)	*Patients N (%)*
MRI, brain	31 (4%)	21 (21%)
CT, brain	80 (11%)	58 (59%)
Ultrasound, brain	10 (1%)	10 (10%)
EEG	99 (13%)	49 (50%)
EKG	70 (10%)	41 (42%)
Nebulizer treatment	107 (15%)	25 (26%)
Top DRGs for Inpatient, Observation or Emergency Department Visits (98 patients, 460 visits)		
	Visits N (%)	Patients N Visits (%)
DRG - Description		
Seizure	50 (11%)	20 (20%)
Degen nerv syst dis X MS	48 (10%)	35 (36%)
Upper resp tract infect	30 (7%)	16 (16%)
Malnut/fail thrive/oth	22 (5%)	17 (17%)
Digestive system dx NEC	22 (5%)	14 (14%)

* Top five most common diagnoses. Excluding KD, Leukodystrophy, Lack of expected normal physiological development, Other disorders of psychological development, Other sphingolipidoses.

** Top five most common procedures using CCSR ICD procedure coding groupings from HCUP AHRQ.

^ Top five most common medications, excluding acetaminophen and sodium chloride.

Table 3.

PHIS hospital data for Krabbe charges analysis, 10/2013–12/2020. Data is from 37 children's hospitals; total number of Krabbe patients = 98. Charges adjusted for inflation to 2020 U.S. dollar amounts. Avg, average per patient.

	Overall	HSCT	No HSCT
Patients, number	98	23	75
Visits, number (avg)	736	186 (8.1)	550 (7.3)
Inpatient admissions (avg)	260	56 (2.4)	204 (2.7)
Total inpatient days (avg)	3204	1448 (63)	1756 (23.4)
Emergency department visits (avg)	154	21 (0.91)	133 (1.8)
Total charges (avg)	$51,574,837	$30,377,637 (1,320,767)	$21,197,200 (282,629)
Clinical charges (avg)	$ 7,454,482	$3,130,993 (136,130)	$4,323,489 (57,647)
Imaging charges (avg)	$1,687,041	$671,086 (29,177)	$1,015,955 (13,546)
Lab charges (avg)	$ 7,889,662	$5,764,864 (250,646)	$2,124,798 (28,331)
Room and nursing charges (avg)	$20,501,615	$9,006,995 (391,608)	$ 11,494,620 (153,262)
Pharmacy charges (avg)	$13,549,180	$11,675,448 (507,628)	$1,873,733 (24,983)
Supply charges (avg)	$492,534	$128,238 (5,576)	$364,295 (4,857)
Total charges/patient			
Mean	$526,274	$1,320,767	$282,629
Min	$9	$14,570	$9
Q1	$39,249	$ 436,000	$22,667
Median	$112,723	$1,074,831	$67,151
Q3	$662,470	$1,753,430	$229,259
Max	$4,528,709	$4,528,709	$3,908,669
Inpatient days/patient			
Mean	33	63	23
Min	0	0	0
Q1	2	26	2
Median	10	59	6
Q3	54	84	22
Max	265	164	265

Table 4:

Selected demographics of Krabbe cohort in KID or PHIS databases, year 2016, for Krabbe patients age 0–3. N, number of patients.

KID		N Visits (95% CI)
	Overall	4,580,421 (4,430,769–4,730,073)
	Exclude uncomplicated births	2,214,956 (2,118,820–2,311,092)
	Overall, Exclude uncomplicated births, KD	47 (27–68)
	Overall, children's hospitals	288,518 (227,605–349,431)
	Overall, children's hospital, exclude uncomplicated births	280,186 (221,921–338,451)
	Overall, children's hospital, exclude uncomplicated births, KD	26 (6–46)
PHIS		N Visits
	Overall, children's hospitals	289,525
	Overall, children's hospital, exclude uncomplicated births	234,783
	Overall, children's hospital, exclude uncomplicated births, KD	25
		N Patients
	Overall, children's hospital, exclude uncomplicated births, KD	18