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Brief Communication

The incidence of urea cycle disorders

Marshall L. Summar [a,*], Stefan Koelker [b], Debra Freedenberg [c], Cynthia Le Mons [d], Johannes Haberle [e], Hye-Seung Lee [f], Brian Kirmse [a], The European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD) [e], and The Members of the Urea Cycle Disorders Consortium (UCDC) [f]

[a] Division of Genetics and Metabolism, Children's National Medical Center, 111 Michigan Ave. NW, Washington DC 20008, USA
[b] University Children's Hospital, Dept. of General Pediatrics, Division of Inherited Metabolic Diseases, Im Neuenheimer Feld 430, D-69120 Heidelberg, Germany
[c] Texas Department of State Health Services, 1100 W 49th Street — Mail code 1918, Austin, TX 78756, USA
[d] National Urea Cycle Disorders Foundation, 75 South Grand Avenue, Pasadena, CA 91105, USA
[e] Division of Metabolism, University Children's Hospital, Steinwiesstrasse 75, CH-8032 Zürich, Switzerland
[f] Data Management and Coordinating Center, University of South Florida, Tampa, FL, USA

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ABSTRACT

A key question for urea cycle disorders is their incidence. In the United States two UCDs, argininosuccinic synthetase and lyase deficiency, are currently detected by newborn screening. We used newborn screening data on over 6 million births and data from the large US and European longitudinal registries to determine how common these conditions are. The incidence for the United States is predicted to be 1 urea cycle disorder patient for every 35,000 births presenting about 113 new patients per year across all age groups.

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1. Introduction

A commonly asked question about almost all rare inborn errors of metabolism is: "How common is it?". Most publications and web pages will provide an estimate that can range by orders of magnitude. With the advent of accountable care organizations, development and marketing of new treatments, and the creation of national registries and longitudinal studies, this question requires a more accurate answer. Urea cycle disorders (UCDs) present a particular challenge since only two of the eight conditions, argininosuccinate synthetase (ASSD; or citrullinemia type 1) and lyase deficiency (ASLD) are reliably detected and reported by tandem mass spectroscopy based newborn screening in the United States [1]. The large natural history studies, i.e. the NIH sponsored Urea Cycle Disorders Consortium (UCDC) and the European Registry and Network for Intoxication Type Metabolic Diseases (E IMD) both give an idea of the proportions for the different conditions but cannot be presumed to have enrolled all available patients [2]. We used a combination of data from US newborn screening programs and the ratios of individual conditions from the natural history studies to calculate an incidence for UCDs. Using those same datasets we were also able to estimate the number of UCD related patients that should present each year and the number with hyperammonemia in the United States.

2. Material and methods

We obtained open published data from the annual newborn screening (NBS) reports from the states of Texas (Dr. Freedenberg), New York (New York State Department of Health, Albany NY), Michigan (Michigan Newborn Screening Program, Michigan Department of Community Health), California, Massachusetts, North Carolina, and Wisconsin (2011 Annual Report to Congress, Health and Human Services, Secretary's Advisory Committee on Heritable Disorders in Newborns and Children Committee Report) during periods where newborn screening was performed for ASSD and ASLD. To determine the ratios of ASSD and ASLD to the other UCDs we used data from the UCDC as a longitudinal registry generally corresponding to the same time frame as the newborn screening data (2004 present). UCDC data include asymptomatic and symptomatic patients distributed

* Corresponding author at: Division of Genetics and Metabolism, Children's National Medical Center, Suite 4800, 111 Michigan Ave. NW, Washington DC 20008, USA.
E-mail addresses: msummar@childrensnational.org (M.L. Summar), Stefan.Koelker@med.uni-heidelberg.de (S. Koelker), debra.freedenberg@dshs.state.tx.us (D. Freedenberg), Cindy@nucdf.org (C. Le Mons).
URL's: http://www.e-imd.org/en/index.phtml (E-IMD), http://rarediseasesnetwork.epi.usf.edu/ucdc/ (UCDC).

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across the United States. Data from the E IMD, and the National Urea Cycle Disorders Foundation (NUCDF) were used to check if the UCDC data were representative. E IMD data were not used to calculate the incidence since population differences in newborn screening candi dates exist between the two entities and it is still in a rapid patient enrollment phase. Data from the UCDC were used to determine the pro portion of patients who were symptomatic in the newborn period and the proportion of all patients who were symptomatic across the age spectrum of patients. UCDC data were also used to calculate the esti mated incidences for the individual enzyme defects. Numbers were rounded to the nearest thousand for presentation.

3. Results

Published NBS data from the states listed covered 6,077,736 births covering years from 2001 to 2012 for different states. In this cohort, there were 52 patients listed as having a confirmed diagnosis of ASSD or ASLD initially detected by NBS. The findings were consistent across this wide geographical sample. The incidence of ASSD and ASLD from this cohort is 1 in 117,000 newborns. Data from the UCDC longitudinal study of 590 patients (after 8 years of patient enrollment) showed that ASSD represented 14% and ASLD 16% of patients combining for a total of 30%. Data from the E IMD sample of 224 patients (after 2 years of patient enrollment) showed a combined 30.5% and the NUCDF's 661 patients 31% for ASSD and ASLD combined. The UCDC and NUCDF regis tries contained data on all eight conditions, i.e. ASSD and ASLD as well as inherited deficiencies of: carbamyl phosphate synthetase I, ornithine transcarbamylase, N acetyl glutamate synthase, mitochondrial orni thine transporter 1, arginase, and citrin. E IMD collects data for all urea cycle disorders except for citrin deficiency. Table 1 shows the rela tive frequencies of the individual diseases.

Using the UCDC's 30% as the fraction of patients with ASSD and ASLD in the UCD population the incidence for all UCDs should can be estimat ed by multiplying the incidence of ASSD and ASLD patients in the new born screening cohort with the ratio of ASSD and ASLD to all urea cycle disorders, i.e. approx. 3:3. This gives an estimated cumulated incidence for all UCDs of 1 in 35,000. Table 1 shows estimates of the incidence for the individual disorders based on this overall incidence.

Using an incidence of 1 in 35,000 and a birth rate of 3,954,000 (US Census Bureau, 2011) live births per year in the US and of 5,229,813 live births in EU member states (Eurostat, as of 2011) an average of 113 new UCD patients with urea cycle disorders per year in the US and assuming that the same incidence is also found in Europe 149 new patients in EU member states can be expected. In the UCDC natural history study 26% of patients were symptomatic in the newborn period and 69% of all patients had symptoms at some point. This should result in a minimum of 30 newborns with hyperammonemia per year in the US.

Table 1
Distribution by group and estimated overall incidence.

	UCDC	E-IMD*	NUCDF	Incidence based on UCDC and newborn screening
All UCDs	590	224	661	1:/35,000
NAGS	3 (0.5%)	2 (1%)	6 (1%)	<1:2,000,000
CPSI	16 (2.7%)	10 (4.5%)	53 (8%)	1:1,300,000
OTC	363 (62%)	133 (59%)	377 (57%)	1:56,500
ASS	83 (14%)	43 (19%)	86 (13%)	1:/250,000
ASL	93 (16%)	26 (11.5%)	119 (18%)	1:218,750
ARG	22 (3%)	4 (2%)	14 (2%)	1:950,000
Citrin	2 (<1%)	n/a	0	<1:2,000,000
HHH	8 (1%)	6 (3%)	6 (1%)	<1:2,000,000

4. Discussion

The study places the estimated incidence of urea cycle disorders at 1 in 35,000 live births in the US or about 113 new patients per year. As suming that the same incidence is found in Europe, 149 new patients are to be expected in EU member states. These calculations would be af fected by the sensitivity of NBS for ASSD and ASLD. These analytes are reasonably robust in NBS and the data was consistent across the differ ent states (data not shown). Dr. Freedenberg called all of the metabolic disease centers in the state of Texas to query about any ASSD or ASLD patients who might have been missed by NBS but were determined clinically during the period reported; none were found. The calculation would also be affected if there were a particular disease segment of the UCD community not enrolled in any of the natural history studies or the NUCDF. Given these caveats the overall incidence should provide a reli able working number in planning for these patients and diseases.

The issue of prevalence is more complex and the UCDC and E IMD registries will be of some help in the future. Over the 8 years of enrollment of the UCDC there have been 6 deaths of 590 enrolled patients (1%). During this time there should have been 900 patients born with UCDs. There are most likely patients who passed away without diagnosis or before being enrolled (although the UCDC does capture deaths at the centers). Assuming the death rate is as high as 10% one would still expect more than 800 patients in the population with urea cycle disorders from this time period not accounting for births in prior years. Prevalence data in EU member states cannot yet be estimated based on available data, since E IMD is still in the lin ear phase of patient enrollment (with about 9 10 newly registered UCD patients per month).

This data will require further refinement but provide a sound basis for the disease incidence in the United States. Furthermore, this effort represents the importance of data collection in both the NBS programs and natural history registries.

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