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Short Communication

Incidence of maple syrup urine disease, propionic acidemia, and methylmalonic aciduria from newborn screening data

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ABSTRACT

Incidence for the branched-chain intoxication-type disorders, maple syrup urine disease, propionic acidemia and methlymalonic aciduria is dependent on the population screened. Here newborn screening results from three world regions, state screening laboratories in the United States, a region in Germany and Kuwait provides new incidence numbers. Maple syrup urine disease incidence in the United States was calculated to be 1: 220219, in South-West Germany 1: 119573 (Germany nationwide 1:177978), and in Kuwait 1: 59426. Incidence of propionic acidemia alone is calculated to be 1: 242741 in the United States, 1: 284450 in South-West Germany (Germany nationwide 1:202617) and 1:59426 in Kuwait. Incidence of isolated methylmalonic aciduria alone is 1:69354 in the United States, 1:568901 in South-West Germany (Germany nationwide 1:159199) and 1: 19809 in Kuwait. In the United States several newborn screening laboratories combine their results for propionic acidemia and methylmalonic aciduria, and also include combined remethylation disorders in the respective category, resulting in an incidence of 1:50709. Combined evaluation of methylmalonic aciduria, propionic aciduria and combined remethylation disorders results in a similar incidence for Germany of 1:67539. This evaluation of newborn screening incidences reflects some population differences for three intoxication-type metabolic disorders. However, different sample sizes of the populations screened over different time periods, and differences in case definitions for methylmalonic acidurias have to be considered when interpreting these data.

1. Introduction

The intoxication-type branched chain inherited metabolic disorders, maple syrup urine disease, propionic acidemia and methylmalonic aciduria can be life-threatening if left untreated. Newborn screening (NBS) has been used to identify individuals with a number of inherited metabolic disorders with the goal that early treatment prior to symptoms will improve outcomes. Moreover, several studies have shown NBS improves outcomes [1–4]. NBS results also provide an opportunity to look at incidence across several populations which can be useful to understanding their differences, but also limited by the manner the information is reported. Here we look at incidences of three branched chain intoxication type disorders, maple syrup urine disease, propionic acidemia and methylmalonic aciduria based on newborn screening data from three different countries.

NBS has gone through continuous improvement and mild protocol changes ever since the addition of tandem-mass spectrometry (tandem-MS) techniques. These improvements have led to changes in cut-offs and data analysis to decrease false positives and increased sensitivity.

Maple syrup urine disease (MSUD, MIM #248600) is characterized by branched chain ketoacid dehydrogenase dysfunction resulting in elevations of the branched chain amino acids, leucine, isoleucine, and valine as well as the diagnostic marker alloisoleucine. Clinically, patients have elevation in leucine during metabolic stress which is thought to increase cerebral edema leading to an intoxication-like phenotype [5]. MSUD has an overall incidence proposed to be about 1:185,000. MSUD (classical and occasionally intermediate) is now able to be identified by the presence of elevated leucine [6,7] or leucine + (usually sum of leucine, isoleucine and alloisoleucine) using dried blood on filter paper cards. This technique is used for NBS alone in some locations. Other locals currently also incorporate ratios (i.e. leucine/phenylalanine and leucine/alanine) to improve accuracy [8]. There is an increase incidence in some populations due to founder effects, including those seen in the Mennonite population (incidence of as high as 1:358 in the Old Order Amish) [2,9], in the Galician population in Spain (1 in 52,541), [10] and in the Ashkenazi Jewish populations [11].

Propionic acidemia (PA, MIM #606054) is a disorder characterized by elevated propionic acid, 3-hydroxypropionate, methylcitrate and

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propionylcarnitine (C3) which often presents with metabolic acidosis and hyperammonemia [12,13]. It can be identified by elevated C3 on NBS. Some locales also have started to use C3 ratios (i.e. C3/C2 and C3/C16) to improve accuracy. True incidence in Europe is unknown [14]. Incidence in Western countries is estimated to be 1 in 50,000 to 1 in 500,000 [15]. In isolated areas much higher incidence is observed, for example certain tribes in Saudi Arabia have incidences as high as 1 in 2000 to 1 in 5000 [16] and certain Mennonite communities have higher incidence [17].

Methylmalonic aciduria (without homocystinuria, MMA, MIM #251000, #251100, #251110) is caused by three different enzyme deficiencies Methylmalonyl CoA mutase (MCM, MIM*609058; E.C. 5.4.99.2), Cobalamin A (MMAA;MIM *607481), or Cobalamin B (MMAB; MIM*607568; E.C. 2.5.1.17). MMA incidence in Europe is not well known [14]. However, in Western cultures the incidence is estimated to be 1 in 48,000 to 1 in 61,000 [18]. Elevation of C3 is seen on NBS.

Cobalamin (B12) is required for MCM function and so dysfunction in its processing both due to underlying functioning issues and/or due to diminished quantity can sometimes be found by NBS. The metabolic disorders, Cobalamin C and D deficiency can also result in positive screening for MMA using C3 as a primary marker. These are usually coupled with elevations in total homocysteine but often times homocysteine or methionine (which is low in these disorders) are not routinely included in newborn screening strategies.

We recognize that incidence of metabolic disorders are impacted by ascertation bias, population frequencies, and screening methods and so set out to use publicly available newborn screen data to determine whether we could calculate the incidence of MSUD, MMA, and PA for several populations. We found that there is most certainly a difference in incidence across populations and so it is best to recognize the risk within the population treated. We also notice that different systems report the data differently, complicating the calculations for incidences.

2. Material and methods

Newborn screening results from three different countries, the United States (US), Germany, and Kuwait were collected and analyzed. Each of these countries has a different reporting structure with more or less additional information available about diagnosis as well as differences in definition of positive results.

Online reporting data was queried from the US data base from 1991 to 2000 for positive newborn screens (defined as diagnosed with the disease in question) and compared to the on-line reported birth rates per US state. Some states do not publish their data; this includes Virginia, Maryland, Pennsylvania, etc. We were able to identify reports from California (2001–2006), Kansas (2010), Massachusetts (2001–2006), Michigan (2007–2013), New Jersey (2010 − 2013), New York (2004–2014), North Carolina (2001–2006), Washington (2009–2013) and Wisconsin (2001–2006). In addition, National Summary data from reports from 1991 to 2000 were also used. All these states use a tandem-MS, blood filter paper card approach.

In the US, different states have different approaches to reporting, different cut-offs and differences in whether ratios are used. In addition, the reports differ in that some states report PA and MMA together (due to marker C3 being in common, e.g. Michigan and New York) and other states report PA and MMA separately (e.g. Washington, California, Kansas, Wisconsin, North Carolina and Massachusetts). Different states use different approaches to identifying positive screens and this has also changed over the time surveyed. Most states in this composite analysis screen at 24–48 h of life. Determining which state used which cut-off and other ratios when is beyond the scope of this paper. False positive test results are not available for all states in these databases and so it is beyond the scope of this report as well.

A similar data extraction was made for positive newborn screens in the Heidelberg screening laboratory, performing newborn screening for the area of South-West Germany (currently about 135,000 newborns screened per year). Newborn screening Heidelberg implemented tandem-MS based newborn screening using blood filter paper cards in the course of a pilot study in the course of the year 1998 and therefore provided screening data for this region for MSUD from 1998 to 2014. From 2002 on tandem-MS screening was recommended for the whole of Germany. In 2005 a binding national screening panel under the use of tandem-MS was implemented for the whole county in Germany, which mandates screening for 12 metabolic disorders including MSUD, but no longer PA, MMA, or combined remethylation disorders (due to their low incidence in the German population). Therefore data on PA and MMA are provided for 1998–2004 only. Incidences for all conditions are provided with reference to the number of children screened for these conditions. In addition data from the national screening reports covering all of Germany are provided for the period of 2000–2014 (data on MSUD for all years except 2003, for PA and MMA for the years 2000–2002 and 2004) (reports from 2004 on are available from: http://www.screening-dgns.de/reports.php). The numbers reported for Germany include the cases found in South-West Germany for the respective years.

Calculations for Kuwait are based on published results from 2015 based on their initial experience of using a tandem-MS approach on blood filter paper cards. There are a number of private clinics and hospitals in Kuwait and these institutions are not obligated to report their findings. These results are limited to only the deliveries outside these private clinics and may not reflect the population at large.

3. Results

Incidences here were determined based on available data from public and from private databases.

3.1. Incidence from newborn screening in the United States

We found the US incidence of MSUD is lower (Table 1) than the incidence cited in The Metabolic & Molecular Bases of Inherited Disease [5]. PA is about as rare as expected given the various estimates (Table 1) and MMA both with and without cobalamin remethylation disorders are close to the cited incidences.

3.2. Incidence from newborn screening in Germany and Kuwait

German incidence for PA is close to that reported in the US data, but the incidence of MMA is much lower (Table 2). It is unclear whether this is a population difference or due to some ethnic variations. If the remethylation disorders are included, the incidence is closer to the US data.

Kuwait has low numbers of individuals screened and identified with disorders (Table 3). As a result, these estimates may not reflect the actual population incidence. This analysis shows higher incidence for all three branched-chain intoxication type disorders than the US and Germany.

Table 1
Overall summary table from US data. Solo refers to only that diagnosis included in these numbers.

Disorder screened	Number found with disorder	Number of births	Incidence
Maple Syrup Urine Disease	91	21,141,094	1/220,219
Propionic acidemia (solo)	12	2,912,901	1/242,741
Methylmalonic aciduria (solo)	42	2,912,901	1/69,354
MMA and PA together (and includes cobalamins)	147	7,544,243	1/50,709