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RESEARCH REPORT

Birth Prevalence of Fatty Acid β-Oxidation Disorders in Iberia

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Abstract Mitochondrial fatty acid β-oxidation disorders (FAOD) are main targets for newborn screening (NBS) programs, which are excellent data sources for accurate estimations of disease birth prevalence. Epidemiological data is of key importance for the understanding of the natural history of the disorders as well as to define more effective public health strategies. In order to estimate FAOD birth prevalence in Iberia, the authors collected data from six NBS programs from Portugal and Spain, encompassing the screening of more than 1.6 million newborns by tandem mass spectrometry (MS/MS), and compared it with available data from other populations. The participating NBS programs are responsible for the screening of about 46% of all Iberian newborns. Data reveals that Iberia has one of the highest FAOD prevalence in Europe (1:7,914) and that Portugal has the highest birth prevalence of FAOD reported so far (1:6,351), strongly influenced by the high prevalence of medium-chain acyl-CoA dehydrogenase deficiency (MCADD; 1:8,380), one of the highest ever reported. This is justified by the fact that more than 90% of Portuguese MCADD patients are of Gypsy origin, a community characterized by a high degree of consanguinity. From the comparative analysis of various populations with comparable data other differences emerge, which points to the existence of significant variations in FAOD prevalences among different populations, but without any clear European variation pattern. Considering that FAOD are one of the justifications for MS/MS NBS, the now estimated birth prevalences stress the need to screen all Iberian newborns for this group of inherited metabolic disorders.

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Introduction

Mitochondrial fatty acid β-oxidation is a key metabolic pathway to the provision of energy for the organism, particularly during periods of fasting and metabolic stress (Bartlett and Eaton 2004; Houten and Wanders 2010). To carry out the process, at least 25 enzymes and specific transport proteins are involved and defects in many of them are associated with human diseases (Kompare and Rizzo 2008; Houten and Wanders 2010).

Fatty acid oxidation defects (FAOD) are a group of inherited metabolic disorders that present heterogeneous clinical phenotypes mainly affecting heart, liver and skeletal

muscles (Kompare and Rizzo 2008). Some patients present the full spectrum and multisystemic disease, while others may stay asymptomatic and only exhibit hypoketotic hypoglycemia during illness or periods of rhabdomyolysis due to vigorous exercise (Wilcken 2010). Presumed pathophysiology of FAOD is supposed to rely mainly on inadequate energy supply, on the toxicity of accumulated metabolites or mutated proteins, and in some cases carnitine depletion. Pathophysiological threshold of some of these factors can be triggered by external factors like insufficient caloric intake, diet changes or infections (Olpin 2013).

Treatment options include avoiding fasting, which is in some cases complemented with carnitine, riboflavin or CoQ10 supplementation (Spiekerkoetter et al. 2010) and leads in most cases to favourable prognosis following diagnosis, being FAOD associated with high mortality/morbidity rates for those diagnosed later in a symptomatic phase (Baruteau et al. 2013). The effectiveness of available treatments for most of FAOD patients, the availability of high throughput adapted tests (acylcarnitine analysis on dried blood spots) and the advantages of an early intervention made this group of disorders main targets for Newborn Screening (NBS) programs worldwide (Lindner et al. 2010; Bennett et al. 2012; Baruteau et al. 2013).

NBS programs, besides being public health programs that allow on an early and positive intervention on affected newborns, are valuable data sources on the screened disorders. Since the introduction of FAOD in the screening panels of NBS programs, generated data has pointed to a significant increase in the disease incidence (Wilcken et al. 2007) that is now believed to be about 1:9,000, although some significant differences can be observed between different populations (Zytkovicz et al. 2001; Wilcken et al. 2003; Frazier et al. 2006; Kasper et al. 2010; Lindner et al. 2011; Lund et al. 2012). In the pre-NBS era, diagnosis was achieved mainly through organic acid analysis in the urine of symptomatic patients that resulted in a low detection rate, which together with the detection of potentially asymptomatic patients through NBS, justifies the observed difference (Sturm et al. 2012).

NBS programs have facilitated the expansion of epidemiological knowledge of screened disorders, with clear advantages over prevalence estimations calculated based on diagnosis of symptomatic cases. The present work incorporates population data derived from the use of tandem mass spectrometry by Iberian NBS programs and has the aim to obtain up-to-date estimates of birth prevalence of FAOD in Iberia and compare it with those of other reported population-based studies.

The increased knowledge on epidemiology is useful for a better understanding of the natural history of the disorders, so that we can define better treatments and public health strategies.

Material and Methods

Study Design

The present study includes data from the metabolic screening by tandem mass spectrometry of 1,672,286 Iberian newborns (812,902 Portuguese and 859,384 Spanish) (Table 1). Data was collected from six NBS programs, the Portuguese one and five from Spain (Galicia, Murcia, Western Andalucia, Eastern Andalucia and Aragón/La Rioja) during several years. All participating programs are well-implemented public health programs that virtually screen all newborns from their regions. All together, the regions covered by participating NBS programs represent about 46.2% of all annual births in Iberia.

Patient Detection

FAO detection criteria applied in the participating NBS programs are identical (all according to the best-accepted practices) and present similar levels of ascertainment. The panel of FAOD screened in the different programs is similar with exception of the Portuguese that doesn't screen for short-chain acyl-CoA dehydrogenase deficiency. After the initial suspicion of FAOD, based on the acylcarnitine profile, all diagnoses were confirmed by molecular and/or enzymatic approaches.

Statistical Analysis

FAOD birth prevalence in Iberia was determined by dividing the number of diagnosed patients by the total number of newborns screened. The calculation of the confidence interval of the prevalence was calculated using Wilson's score method.

Results and Discussion

Accurate assessment of the birth prevalence of screened disorders requires analysis of test results from a birth cohort representative of a geographic population. In this work, data from well-defined Iberian populations was used to assess the birth prevalence of FAOD in this European region.

Analysing the variation of FAOD prevalence within Iberian populations, what clearly emerges is that the prevalence of FAOD in Portugal (1/6,351) is the double of that observed in Spain (1/12,104). If we compare it excluding SCADD (not screened in Portugal), the difference is even bigger (1/6,351 versus 1/14,817). Undoubtedly, MCADD is the major contributor for this difference; nevertheless, all other FAOD present in Portugal higher

Table 1 Number of FAOD detected in the participating Iberian NBS programs and estimated birth prevalences, as well as in other NBS programs with available data reported

Region	Screened newborns	Fatty acid β-oxidation disorders															
Iberia		SCADD		MCADD		VLCADD		LCHADD		MADD		CPT1		CPT2		CUD		Overall
Portugal	812,902	Not screened		97	1/8,380	8	1/101,613	7	1/116,129	3	1/270,967	2	1/406,451	3	1/270,967	8	1/101,613	1/6,351
Galicia	278,371	5	1/55,674	14	1/19,884	0	0	3	1/92,790	0	0	0	0	0	0	0	0	1/12,653
Múrcia	124,942	1	1/124,942	3	1/41,647	0	0	2	1/62,471	1	1/124,942	0	0	0	0	1	1/124,942	1/15,618
Western Andalucia	272,462	3	1/90,981	15	1/18,196	0	0	0	0	1	1/272,462	1	1/272,462	0	0	1	1/272,462	1/12,997
Aragón/La Rioja	54,901	1	1/54,901	3	1/18,300	0	0	0	0	0	0	0	0	0	0	0	0	1/13,725
Eastern Andalucia	128,228	3	1/42,743	8	1/16,029	0	0	0	0	0	0	0	0	3	1/42,743	2	1/60,114	1/8,014
Overall	1,672,286	13	1/66,106	140	1/11,945	8	1/209,036	12	1/139,357	5	1/334,457	3	1/557,429	6	1/278,714	11	1/139,357	1/7.914
		(95% CI: 1/113, 111–1/ 38,634)		(95% CI: 1/14,093–1/ 10,122)		(95% CI: 1/ 415,522–1/ 105,923)		(95% CI: 1/ 243,603–1/ 79,720)		(95% CI: 1/ 783, 014–1/ 142,860)		(95% CI: 1/1,639, 060–1/ 189,576)		(95% CI: 1/608, 135–1/ 127,737)		(95% CI: 1/272, 250–1/ 84,891)		(95% CI: 1/9, 054–1/6,916)
Austria (Kasper et al. 2010)	622,489	1/155,622		1/24,900		1/88,927		1/69,165		1/311,245		0		0		1/311,245		1/12,704
Germany (Lindner et al. 2011)	583,555[a]/ 1,084,195[b]	1/64,839[a]		1/14,0808[b]		1/180,699[b]		1/216,839[b]		1/194,517[a]		1/1,084,195[b]		1/1,084,195[b]		1/194,518[a]		1/9,198
Denmark (Lund et al. 2012)	190,287[a]/ 504,049[b]/ 363,538[c]	1/190,287[a]		1/9,164[b]		1/168,016[b]		1/168,016[b]		0[c]		1/363,538[c]		0[c]		1/100,810[b]		1/7,691
Italy[d]	640,707	1/27,857		1/22,882		1/45,765		1/640,707		0		1/640,707		1/640,707		1/128,141		1/8,777
Greece (Loukas et al. 2010)	45,000	0		1/45,000		0		0		0		0		0		0		1/45,000
Switzerland (Rhead 2006)	57,000			1/11,500														
UK (Oerton et al. 2011)	1,500,000			1/10,204														
Belgium(Bodamer and Pollitt 2005)	120,000			1/15,000														
Netherlands (Derks et al. 2008)	182,850			1/9,624														
USA																		
New England (Zytkovicz et al. 2001)	164,000	1/32,800		1/16,400		1/164,000		0		0		0		1/164,000		0		1/9,647
North Carolina (Frazier et al. 2006)	944,078	1/118,010		1/12,933		1/78,673		1/314,693		0		0		1/472,039		0		1/9,633
California (Feuchtbaum et al. 2006; Gallant et al. 2012)	353,894[a]/ 2,632,058[b]	1/34,632[b]		1/27,223[a]		1/353,894[a]		1/353,894[a]		1/176,947[a]		0		0		0		1/13,002
Michigan[e]	708,257	1/16,097		1/13,620		1/88,532		1/708,257		1/354,129		0		1/708,257		1/354,129		1/6,439
Western USA (Merritt et al. 2014)	2,802,504					1/53,894												
New York (Arnold et al. 2010)	±1,501,022			1/24,210														
Japan (Bodamer and Pollitt 2005)	102,000			1/51,000														
Saudi Arabia (Al-Hassnan et al. 2010)	237,812			1/18,293														
Australia (Wilcken et al. 2003)	362,000	1/72,400		1/21,294		1/120,667		0		0		0		0		1/120,667		1/12,929

[a-c] refer to the number of screened newborns in a given population

[d] Data from Italy was extracted from national NBS reports from 2006 to 2012 (available on http://www.simmesn.it/it/documents/rt_screening/index.html; Accessed on December 2013)

[e] Data from the Michigan NBS program was extracted from program reports from 2006 to 2011 (available on www-michigan.gov/mdch/0,1607,7-132-2942_2950-233593-,00.html, accessed on September 2013). *CI* confidence interval, calculated using Wilson's score method

birth prevalence than in Spain. In Portugal, the prevalence of MCADD (1:8,380: 95% CI; 1:10,221 to 1:6,869) is higher than in any Spanish region and than in any other country with available data reported so far (Table 1). This high prevalence of MCADD can be justified by the fact that the great majority of the patients are of Gypsy origin (over 90%, and all homozygous for the most common mutation c.985 A>G), a community characterised by high inbreeding and where the high occurrence of genetic diseases, namely MCADD is known (Martinez et al. 1998; Kalaydjieva et al. 2001). The same is observed in Spain but to a less extent. This bias in the ethnical distribution of MCADD patients represents a significant difference in MCADD epidemiology in Iberia, namely Portugal, in comparison with other European countries where patients are almost exclusively of non-Gypsy origin (Khalid et al. 2008). This particular characteristic of Portuguese Gypsy community is the main justification for the observed birth prevalence of FAOD in Portugal, the highest among countries with available comparable data. These results are in disagreement with a pre-NBS assumption that there was in Europe a north-to-south gradient in the incident of MCADD (Tanaka et al. 1997).

SCADD prevalence in Iberia reflects its birth prevalence only in Spain, since this FAOD is not screened in Portugal. It has a prevalence of 1:66,106 in line with other available data for Europe, with exception of Italy where this FAOD seems to be significantly more prevalent.

VLCADD presented a birth prevalence of 1:209,036 in our cohort. Its prevalence in Iberia doesn't present significant differences from what is reported to other European populations, with exception of Italy where it presents a prevalence of 1:45,765. Indeed in this country, and in comparison with the other southern countries, Portugal and Spain, and besides an overall similar birth prevalence of FAOD, there are some differences in individual FAOD. Besides the differences in SCADD and VLCADD it is also clear that there is a lower birth prevalence of MCADD in Italy comparing to Portugal and Spain.

For LCHADD Iberia has a prevalence of 1:139,357, similar to that of Germany and Denmark, but less than in Austria. Concerning CUD, Iberia presents a birth prevalence of 1/139,357 in line with available data from other European populations. Comparing available data from Europe, the USA and Australia, it seems that CUD is less prevalent in the USA.

The analysis of the birth prevalence of MADD, CPT1 and CPT2 encompasses some difficulties due to their low frequency, requiring higher numbers of screened newborns in order to get more accurate prevalence estimations.

In Iberia, and influenced by Portuguese population data, MCADD has a birth prevalence of 1: 11,945 one of the highest reported in European countries, alongside with UK, Denmark and the Netherlands. This is higher than those observed, for example, in Austria (1/24,900) or Germany (1/14,080) as well as in the USA or Australia (Table 1).

Iberia presents birth prevalence for FAOD of 1:7,914 one of the highest in Europe, only comparable with Denmark and Michigan-USA. MCADD is the most prevalent FAOD in our cohort (66.3%), being followed by SCADD (12.0%), CUD and LCHADD (5.7%), VLCADD (3.8%), CPT 2 (2.8%), MADD (2.4%) and finally CPT 1 (1.4%) (values corrected for the number of screened newborns). Comparing our data with those from the world collaborative NBS project – Region4genetics (McHugh et al. 2011), what emerges is a higher proportion of MCADD (66.3% versus 56.3%) and lower contribution of SCADD (12.0% versus 15.7%) and VLCADD (3.8% versus 12.2%), for the total number of FAOD patients.

In conclusion, Portugal has the highest birth prevalence of FAOD reported, estimated based on NBS data. Iberian as a whole presents a birth prevalence of FAOD in agreement with available data from other Caucasian populations, but exhibiting one of the highest values reported. As FAOD are one of the main justifications for MS/MS screening in Caucasian populations, the birth prevalence now estimated stresses the need to screen all Iberian newborns for this group of disorders.

Synopsis

Data on the birth prevalence of fatty acid β-oxidation disorders in Iberia is reported for the first time, highlighting the high birth prevalence of this group of metabolic disorders in this European region. From the comparative analysis of various populations with comparable data differences emerge, which points to the existence of significant variations in FAOD prevalences among different populations.

Compliance with Ethics Guidelines

Conflict of Interest

Hugo Rocha, Daisy Castiñeiras, Carmen Delgado, José Egea, Raquel Yahyaoui, Yolanda González, Manuel Conde, Inmaculada González, Inmaculada Rueda, Luis Rello, Laura Vilarinho and José Cocho declare that they have no conflict of interest.

Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Details of the Contributions of Individual Authors

Hugo Rocha: Conception, design and drafting of the article. Daisy Castiñeiras: Analysis and interpretation of data from Galicia. Carmen Delgado: Analysis and interpretation of data from Western Andalucia. José Egea: Analysis and interpretation of data from Murcia. Raquel Yahyaoui: Analysis and interpretation of data from Eastern Andalucia. Yolanda González: Analysis and interpretation of data from Aragón/La Rioja. Manuel Conde: Analysis and interpretation of data from Western Andalucia. Inmaculada González: Analysis and interpretation of data from Murcia. Inmaculada Rueda: Analysis and interpretation of data from Eastern Andalucia. Luis Rello: Analysis and interpretation of data from Aragón/La Rioja. Laura Vilarinho: Analysis and interpretation of data from Portugal and critical review of the article for important intellectual content. José Cocho: Conception, design and critical review of the article.

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