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Newborn screening for six lysosomal storage disorders in a cohort of Mexican patients: Three-year findings from a screening program in a closed Mexican health system

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ABSTRACT

Objective: To evaluate the results of a lysosomal newborn screening (NBS) program in a cohort of 20,018 Mexican patients over the course of 3 years in a closed Mexican Health System (Petróleos Mexicanos [PEMEX] Health Services).
Study design: Using dried blood spots (DBS), we performed a multiplex tandem mass spectrometry enzymatic assay for six lysosomal storage disorders (LSDs) including Pompe disease, Fabry disease, Gaucher disease, mucopolysaccharidosis type I (MPS-I), Niemann–Pick type A/B, and Krabbe disease. Screen-positive cases were confirmed using leukocyte enzymatic activity and DNA molecular analysis.
Results: From July 2012 to April 2016, 20,018 patients were screened; 20 patients were confirmed to have an LSD phenotype (99.9 in 100,000 newborns). Final distributions include 11 Pompe disease, five Fabry disease, two MPS-I, and two Niemann–Pick type A/B patients. We did not find any Gaucher or Krabbe patients. A final frequency of 1 in 1001 LSD newborn phenotypes was established.
Discussion: NBS is a major public health achievement that has decreased the morbidity and mortality of inborn errors of metabolism. The introduction of NBS for LSD presents new challenges. This is the first multiplex Latin–American study of six LSDs detected through NBS.

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1. Introduction

Lysosomal storage disorders (LSDs) constitute a diverse group of over 50 inherited metabolic disorders, with a collective incidence of 1 in 7000 to 9000 live births, due to a reduction or lack of lysosomal enzymes, transport proteins, or impaired lysosomal enzyme biogenesis [1–3]. Progressive accumulation of metabolic precursors within the lysosomes result in cellular dysfunction and multiple organ damage [4, 5]. Recently, LSDs have been recognized as diseases that could greatly benefit from newborn screening (NBS). Currently, LSDs NBS programs have been developed for Pompe disease, Fabry disease, Gaucher disease, mucopolysaccharidosis type I (MPS-I), Niemann–Pick type A/B, and Krabbe disease (Table 1).

Mexico's health system is fragmented into seven different health care providers that serve the population according to the employer's compulsory contributors and unemployed social security providers [6]. For instance, PEMEX (Petróleos Mexicanos Oil Company) Health Services covers oil company workers and their families, accounting for approximately 1%–1.5% of the entire Mexican population. PEMEX Health System's NBS program was established in 2005, and aims to detect inborn errors of metabolism (amino acid disorders, organic acidemias, etc.), monogenic disorders (inherited hemoglobin disorders, cystic fibrosis, congenital adrenal hyperplasia) [7], and NBS for hearing

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Table 1
Summary of data published worldwide between 2006 and 2016 of the six LSDs that were screened as positive in NBS programs.

LSD	Birth prevalence[a]	Positives	Newborns tested	Study, year (location)
Fabry	32.34	12	37,104[b]	Spada et al., 2006 (Italy) [10]
	42.44	73	171,977	Hwu et al., 2009 (Taiwan) [11]
	40.89	45	110,027[b]	Lin et al., 2009 (Taiwan) [12]
	23.61	5	21,170	Inoue et al., 2009 (Japan) [13]
	0	0	3403	Paciotti et al., 2012 (Umbria, Italy) [14]
	29.98	12	40,024	Wittman et al., 2012 (Hungary) [15]
	25.90	9	34,736	Mechtler et al., 2012 (Austria) [16]
	14.69	16	108,905	Scott et al., 2013 (Washington, United States) [17]
	33.37	64	191,767	Liao et al., 2014 (Taiwan) [17]
	32.04	14	43,701	Hopkins et al., 2015 (Missouri, United States) [19]
	18.60	8	43,000	Elliott et al., 2016 (Washington, United States) [9]
	24.97	5	20,018	Present study
Pompe	1.41	6	206,088	Chien et al., 2008 (Taiwan) [28]
	0	0	3403	Paciotti et al., 2012 (Umbria, Italy) [14]
	84.95	34	40,024	Wittmann et al., 2012 (Hungary) [15]
	11.51	4	34,736	Mechtler et al., 2012 (Austria) [16]
	15.24	17	111,504	Scott et al., 2013 (Washington, United States) [17]
	8.34	16	191,786	Liao et al., 2014 (Taiwan) [18]
	11.44	5	43,701	Hopkins et al., 2015 (Missouri, United States) [19]
	4.65	2	43,000	Elliott et al., 2016 (Washington, United States) [9]
	54.95	11	20,018	Present study
MPS-I	8.44	9	106,526	Scott et al., 2013 (Washington, United States) [17]
	5.66	2	35,285	Lin et al., 2013 (Taiwan) [39]
	0	0	60,473	Liao et al., 2014 (Taiwan) [18]
	2.28	1	43,701	Hopkins et al., 2015 (Missouri, United States) [19]
	13.95	6	43,000	Elliott et al., 2016 (Washington, United States) [9]
	9.99	2	20,018	Present study
NPA/B	0	0	3403	Paciotti et al., 2012 (Umbria, Italy) [14]
	5	2	40,024	Wittman et al., 2012 (Hungary) [15]
	0	0	34,736	Mechtler et al., 2012 (Austria) [16]
	11.4	5	43,000	Elliott et al., 2016 (Washington, United States) [9]
	9.99	2	20,018	Present study
Krabbe	4.55	25	550,000	Duffner et al., 2009 (New York, United States) [40]
	25.58	11	43,000	Elliott et al., 2016 (Washington, United States) [9]
	0	0	20,018	Present study
Gaucher	29.38	1	3403	Paciotti et al., 2012 (Umbria, Italy) [13]
	24.98	10	40,024	Wittmann et al., 2012 (Hungary) [15]
	5.76	2	34,736	Mechtler et al., 2012 (Austria) [16]
	2.96	3	101,104	Liao et al., 2014 (Taiwan) [18]
	0	0	43,701	Hopkins et al., 2015 (Missouri, United States) [19]
	6.98	3	43,000	Elliott et al., 2016 (Washington, United States) [9]
	0	0	20,018	Present study

[a] The total number of patients screened as positive was estimated to be 1 in 100,000 newborns.
[b] Male newborns screened. LSD – lysosomal storage disorder; MPS-I – mucopolysaccharidosis type I; NPA/B – Niemann–Pick type A/B.

disorders. In the present article, we report the results from the PEMEX Health System LSDs NBS program.

2. Methods

2.1. Patient sample

Six different LSDs were added to the PEMEX NBS program, including Fabry disease (acid α-galactosidase [GLA] deficiency), Pompe disease (acid α-glucosidase [GAA] deficiency), Gaucher disease (acid β-glucosidase [GBA] deficiency), Krabbe disease (galactosylceramide β-galactosidase [GALC] deficiency), Niemann–Pick type A/B (acid sphingomyelinase [ASM] deficiency), and mucopolysaccharidosis type I (MPS-I; α-L-iduronidase [IDUA] deficiency). Samples were collected at the general, regional, and central PEMEX hospitals located in the states of Tamaulipas, Veracruz, Tabasco, Campeche, Nuevo León, Hidalgo, Oaxaca, and Guanajuato, as well as of Mexico City. Genomi-k SAPI de C.V. (Monterrey, Nuevo León, Mexico) provided the sample pickup, storage, handling, and results reporting of the dried blood spots (DBS). PerkinElmer Genetics Laboratories (Bridgeville, PA, USA) performed the DBS analysis.

DBS were taken by venipuncture within the first 24–48 h of life; the samples were then placed on filter paper. The protocol consisted of obtaining a first sample, with which tandem mass spectrometry (MS/MS) was performed; however, if enzymatic activity was reported below the cutoff value, a second sample was requested. After a second abnormal result, the patient was referred to the Department of Genetics, Hospital Central Sur de Alta Especialidad, PEMEX, Mexico City, to perform clinical examination, leukocyte enzyme activity and molecular analysis, in order to confirm LSDs deficiency status. A false-positive result was considered after the second abnormal result if the leukocyte enzyme activity was also negative. All specimens collected from premature or sick infants were retested to exclude false-positive or false-negative results.

2.2. Tandem mass spectrometry, leukocyte activity, and molecular analysis

Quantitative measurements of lysosomal enzyme activity for Krabbe, Pompe, Niemann–Pick type A/B, Gaucher, Fabry, and MPS-I diseases were carried out by using MS/MS; described by Gelb, et al. [8,9]. Cutoffs were set at following levels: GLA, 0.52 μmol/L/h; GAA, 2.10 μmol/L/h; GBA, 1.45 μmol/L/h; GALC, 0.40 μmol/L/h; ASM, 0.75 μmol/L/h; and IDUA, 1.08 μmol/L/h. According to PerkinElmer Genetics Laboratories (Bridgeville, PA, USA), they used a validation approach that processed known positives and presumed negatives. The evaluation of the data resulted in the reported cutoffs.

Leukocyte lysosomal enzyme testing was performed either by radiometry (for Niemann–Pick type A/B disease and Krabbe disease) or by fluorometry using commercially available synthetic 4-methylumbelliferone

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