Best Practice & Research Clinical Endocrinology & Metabolism xxx (2014) 1–13

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

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Epidemiology and diagnosis of lysosomal storage disorders; challenges of screening

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Keywords:
lysosomal storage disorders
epidemiology
diagnosis
newborn screening
high-risk screening
carrier screening

The lysosomal storage disorders (LSDs) are a group of genetic disorders resulting from defective lysosomal metabolism and subsequent accumulation of substrates. Patients present with a large phenotypic spectrum of disease manifestations that are generally not specific for LSDs, leading to considerable diagnostic delay and missed cases. Introduction of new disease modifying therapies for LSDs has made early diagnosis a priority. Increased awareness, but particularly the introduction of screening programs allow for early diagnosis and timely initiation of treatment. This review will provide insight into the epidemiology and diagnostic process for LSDs. In addition, challenges for carrier screening, high-risk screening and newborn population screening for LSDs are discussed.

Introduction

The lysosomal storage disorders (LSDs) comprise a heterogenic group of more than 50 genetic disorders caused by progressive accumulation of specific substrates due to deficiency of hydrolytic

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http://dx.doi.org/10.1016/j.beem.2014.08.004
1521-690X/

Please cite this article in press as: Kingma SDK, et al., Epidemiology and diagnosis of lysosomal storage disorders; challenges of screening, Best Practice & Research Clinical Endocrinology & Metabolism (2014), http://dx.doi.org/10.1016/j.beem.2014.08.004

enzymes, non-enzymatic lysosomal proteins or non-lysosomal proteins involved in lysosomal biogenesis [1]. A wide range of disease manifestations can occur, including hydrops foetalis, neurocognitive decline, dysmorphia, hepatosplenomegaly and musculoskeletal abnormalities. Most LSDs are characterized by a broad phenotypic spectrum and may present from very early in life to late in adulthood. Due to the rarity of the diseases and the heterogeneity of disease manifestations, which are generally not specific for LSDs, lengthy diagnostic delays and missed cases are common [2]. In this review, epidemiological studies that studied a large panel of LSDs, current diagnostic workup of patients suspected of LSDs and subsequent challenges for implementation of screening are discussed.

Epidemiology

Information about the incidence of LSDs is relatively limited. The results of the 6 largest epidemiological studies that studied birth prevalences of a relatively large panel of LSDs are presented in Table 1. Birth prevalences of the neuronal ceroid lipofuscinoses (NCLs) and female Fabry carriers were only studied in some reports, and were therefore not included in this table. Combined birth prevalences of LSDs range from 7.5 per 100,000 in British Columbia to 23.5 per 100,000 live births in the United Arab Emirates (UAE) with the sphingolipidoses as the most prevalent group, followed by the mucopolysaccharidoses (MPSs) [3,4].

Social isolation, immigration and epidemiology

When discussing introduction of screening programs for LSDs, reliable epidemiological data are essential, as birth prevalences may differ considerably per population group. Striking differences in birth prevalences between countries can be observed (Table 1) and these can, indeed, at least partially be explained by differences in immigration patterns or isolation, for instance due to geographical, lingual, ethnic or religious preferences or customs. For example, in persons from Ashkenazi Jewish ancestry, strikingly high prevalences of several genetic diseases occur, including some LSDs, which has led to the introduction of highly successful screening programs [5]. The remarkable high birth prevalences of MPS VI, GM1 gangliosidosis and fucosidosis in the UAE are another example and primarily due to ethnic isolation and founder effects, which is illustrated by the observations that 95% of genotyped patients were homozygous for their LSD causing mutation and that, indeed, most patients were from the same tribes or blood-related [4]. Birth prevalences for most of the LSDs are comparable between British Columbia, the Czech Republic, Australia and The Netherlands, with MPS I, Gaucher disease and metachromatic leukodystrophy (MLD) as the most prevalent LSDs (mean birth prevalences around 1/100,000 live births) [3,6–8]. The population of British Columbia and Australia are primarily of European and particularly British origin [3,7], suggesting a cause for the similarity in birth prevalences of LSDs. However, the increasing immigration rates from different countries and ethnic groups to Western countries, is likely to change the birth prevalences of genetic diseases, including LSDs, in the near future [9].

Clinical awareness and epidemiology

Extensive investigations in a region or population group and increased awareness may have major influences on epidemiological data in rare diseases, as only a few extra diagnosed cases may have a considerable effect on calculated birth prevalences. This is suggested to be a partial explanation for the high birth prevalences observed in Northern Portugal, as other regions of Portugal were excluded from most of the epidemiological analysis [6,10].

However, birth prevalences reported in published epidemiological studies all date from before the start of newborn screening (NBS) pilot studies and likely underestimate the true prevalences of many of the LSDs. Indeed, NBS (pilot) studies done in Hungary, Austria, Taiwan, Italy and the States of New York and Washington, reported on average 5–80 times higher birth prevalences than previously reported [11–19]. The increase is primarily due to recognition of more attenuated and/or later-onset forms of the diseases, as demonstrated by Spada et al., who reported that 10 out of 11 Fabry patients diagnosed by a NBS pilot study in a part of Italy were of the late-onset type [18].

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