Seminars in Perinatology 39 (2015) 206–216

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Newborn screening for lysosomal storage disorders

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ARTICLE INFO

Keywords:
Dried blood spots
Newborn screening
Tandem mass spectrometry
Immunoquantification
Lysosomal storage disorders

ABSTRACT

Every newborn in the U.S. is screened for at least 29 disorders, where evidence suggests that early detection is possible and beneficial. With new or improved treatment options and development of high-throughput screening tests, additional conditions have been proposed for inclusion in newborn screening programs. Among those are several lysosomal storage disorders that have been evaluated in limited pilot studies or that are already included in a few national or international newborn screening programs. These conditions include Pompe disease, Niemann–Pick type A/B disease, Fabry disease, Krabbe disease, Mucopolysaccharidoses types I and II, and Gaucher disease. Here, we review the current state of newborn screening for these lysosomal storage disorders.

Introduction

In the early 1960s, Guthrie[1] introduced population screening for phenylketonuria (PKU) by a bacterial inhibition assay for the detection of abnormally elevated concentrations of phenylalanine in blood collected from newborns by heel stick and dried onto special filter paper. Guthrie was prompted to pursue such testing because treatment for this otherwise devastating neurometabolic disorder had become available, and it had been shown that early initiation of treatment gave the best outcomes. Newborn screening (NBS) for PKU then developed into a broad public health prevention program aimed at identifying an increasing number of conditions for which early intervention can prevent premature mortality, morbidity, and disabilities.

From its beginning, NBS was a regional or state-based effort, which led to differences in the number of conditions included in each program. Differences were mostly based on local expertise and interests, or they were the result of political decisions, but typically they were not based on rigorous and comprehensive evaluations. State NBS program discrepancies became particularly apparent when tandem mass spectrometry (MS/MS) was adapted for screening in the 1990s. MS/MS allowed rapid and simultaneous analyses of amino acid and acylcarnitine profiles for the detection of more than 40 different inborn errors of amino acid, fatty acid, and organic acid metabolism.[2]

In order to harmonize NBS programs in the U.S. and in other countries, advisory committees were eventually created to advise the public health system on which conditions should uniformly be included in all NBS programs. In 2002, the US Health Resources and Services Administration of the Department of Health and Human Services (HHS) first contracted with the American College of Medical Genetics

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http://dx.doi.org/10.1053/j.semperi.2015.03.005
0146-0005/

[now American College of Medical Genetics and Genomics (ACMG)] to help with this effort. In 2004, it then initiated the first meeting of the Secretary of HHS's Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC).

In 2006, the ACMG contract yielded a report describing the work of a Newborn Screening Expert Group and documenting their recommendation that every U.S. newborn should be screened for at least 29 core conditions.[3] In acknowledgment of the fact that screening tests do not determine disease status—rather, they measure analytes that in many cases are not specific for a particular disease—the ACMG report included 25 additional conditions that are either of uncertain clinical significance or are untreatable, but on the basis of screening results, they may be identified in the differential diagnosis of the 29 core conditions. These recommendations were adopted by ACHDNC and ultimately by the HHS Secretary. The ACHDNC subsequently created both a mechanism to propose additional conditions for inclusion in the Recommended Uniform Screening Panel (RUSP) (available at: http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendedpanel/index.html; last accessed 09.03.15) and to evaluate proposed conditions through an independent external evidence review.

Since 2007, 12 conditions have been proposed for inclusion on the RUSP of which 8 were submitted for external evidence review. Seven reports have been completed to date that have resulted in a vote by the ACHDNC for their possible inclusion on the RUSP. Four conditions [severe combined immune deficiency (SCID), critical congenital heart disease (CCHD), Pompe disease, and Mucopolysaccharidosis type I (MPS I)] have received majority votes sufficient to prompt a recommendation to the HHS Secretary that they be added to the RUSP. To date, the Secretary has endorsed the addition of SCID, CCHD, and Pompe disease, and a decision is pending for MPS I (http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/nominatecondition/reviews/nominatedconditions.pdf; last accessed 09.03.15). In addition to Pompe disease and MPS I, other lysosomal storage diseases (LSDs) that have been nominated to the ACHDNC for addition to the RUSP include Krabbe disease, Niemann–Pick A and B diseases, and Fabry disease. Here, we review NBS for LSDs, with particular focus on the conditions that have been proposed officially for inclusion in the RUSP or have been included in the requirements of at least 1 U.S. NBS program.

Newborn screening for lysosomal storage disorders (LSDs)

Several LSDs including MPS I, Fabry disease, Pompe disease, and Krabbe disease were considered by the ACMG Newborn Screening Expert Group.[3] Despite the increasing availability of treatment options such as enzyme replacement therapy (ERT) and bone marrow transplantation, both of which were shown to lead to better outcomes when initiated early in life,[4,5] none of the LSDs were recommended for inclusion in NBS, because at that time, there was no proven high-throughput screening test available. Since then, several screening tests not only have been proposed but have been applied to population screening either in pilot studies or in state-mandated screening. Moreover, additional therapeutic approaches such as chemical chaperone therapy, substrate reduction therapy, gene therapy, and stop codon read-through are in use in clinical trials, furthering interest in NBS for LSDs.[5–7]

An additional argument for inclusion of at least some LSDs in NBS has been the relative prevalence of these conditions, which for most conditions has been shown to be more frequent than previously expected. For example, pilot NBS studies for Fabry disease in Italy and in Taiwan revealed surprisingly high incidences (approximately 1:3100 and 1:1250 male newborns, respectively[8,9]). These incidences are significantly higher than the prevalence of some screened conditions such as phenylketonuria (ca. 1:12,000 live births).

Newborn screening assays for LSDs

The first assay describing the identification of LSDs using dried blood spots (DBS), the traditional NBS sample, was an immunoquantification assay for lysosome-associated membrane protein (LAMP-1) developed by Hopwood and colleagues.[10] Lysosomes typically accumulate in LSDs, and it was expected that LAMP-1, as a marker of lysosomal abundance, would also accumulate in LSDs. However, subsequent studies have found no significant differences in LAMP-1 concentrations in leftover NBS samples from patients with several targeted LSDs, with the exception of mucolipidosis II/III and Fabry disease.[11]

Hopwood's group then pursued a more direct approach with their immunoquantification method. This method directly targets the enzymes that are deficient in LSDs under the premise that in most LSDs, pathogenic mutations cause decreased amounts of protein.[12–14] Furthermore, they also developed a multiplex assay of 11 proteins, taking advantage of microbead array technology.[15] Their goal was to enable positive identification of 11 different conditions by fluorometric quantification of enzyme concentrations in DBS. This approach enabled the correct identification of most conditions except for cases of Pompe and Gaucher diseases, which were not consistently detected. Better results were obtained in a further expansion of this assay by inclusion of 3 additional proteins (alpha-*N*-acetylglucosaminidase, CD45, and chitotriosidase) and using samples from patients whose samples were collected beyond the newborn period.[16] This assay, modified to allow additional detection of patients with Friedreich ataxia and Wilson disease, is currently being evaluated in a large prospective NBS study in our laboratory.[17]

Between 2001 and 2004, Chamoles et al. were the first to develop DBS-based activity assays for several lysosomal enzymes, including alpha-galactosidase A,[18] alpha-L-iduronidase,[19] alpha-glucocerebrosidase, acid sphingomyelinase,[20] and acid-glucosidase.[21] These fluorometric assays used commercially available fluorogenic (4-methylumbelliferone) substrates and were adopted for NBS pilot studies, usually with small modifications, of Fabry disease and/or Pompe disease in Italy, Taiwan, and Japan.[8,9,22–25] In Taiwan, 2 NBS laboratories implemented a fluorometric assay for routine screening for Pompe disease but one switched to MS/MS in 2010.[25,26] The switch to MS/MS was possible because, in collaboration