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Newborn Screening of Lysosomal Storage Diseases, Including Mucopolysaccharidoses

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Tandem mass spectrometry and other new technologies for the multiplex and quantitative analysis of dried blood spots have emerged as powerful techniques for the early screening and assessment of newborns for lysosomal storage diseases (LSDs). Screening newborns for these diseases is important, since treatment options, including enzyme replacement therapy or hematopoietic transplantation, are available for some LSDs, such as infant-onset Pompe disease, Fabry disease, some types of mucopolysaccharidoses (MPSs), and Krabbe disease. For these diseases, early initiation of treatment, before symptoms worsen, often leads to better clinical outcomes. Several problems, however, are associated with newborn screening for LSDs, including the development of accurate test methods to reduce low false-positive rates and treatment guidelines for late-onset or mild disease variants, the high costs associated with multiplex assays, and ethical issues. In this review, we discuss the history, current status, and ethical problems associated with the newborn screening for LSDs, including MPSs.

Keywords: Newborn screening, Lysosomal storage disease, Mucopolysacchariodis

Introduction

A newborn screening test is the first test performed in most babies. Over the last half century, there has been technological development in newborn screening, and it is now possible to screen for various rare diseases, including lysosomal storage diseases (LSDs). In this review, we discuss the history, current status, and ethical problems associated with newborn screening for LSDs, including mucopolysaccharidoses (MPSs).

History of Newborn Screening Tests

In the early 1960s, the US physician and microbiologist, Robert Guthrie, developed an assay for the presymptomatic identification of phenylketonuria, an inborn error of amino acid metabolism that causes irreversible neurological damage unless treatment is initiated within the first few weeks of life. The assay is a simple and inexpensive bacterial inhibition assay that detects abnormally elevated concentrations of phenylalanine in blood collected from newborns using heel stick and dried on filter paper[1]. By identifying an affected newborn, the family can adopt the necessary restrictive diet before symptom onset, which would provide their child with a better chance to live a healthy life. Until the early 1990s, a few other diseases were added, "one at a time," to newborn screening programs. Congenital hypothyroidism screening was initially performed using a radioimmunoassay, and later replaced by an immunoassay[2]. Congenital adrenal hyperplasia screening was also conducted using an immunoassay[3]. In the 1990s, the introduction of tandem mass spectrometry (MS/MS) into the metabolic screening laboratory changed the paradigm of analyzing one analyte per disorder. Now, with a single sample and a 2–3 min analysis of a small dried blood spot (DBS), MS/MS allows the determination of the multiple analytes that are characteristic of several (>40) metabolic disorders[4-6].

LSDs are a group of diseases caused by the dysfunction of lysosomes, the cellular organelles responsible for the degradation of intracellular waste materials. Although individual LSDs are rare, their combined incidence has been estimated at 1 per 7,700 live

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births in Australia[7]. The analysis of stored materials often serves as a screening test for the presence of LSDs[8]. Several LSDs, including MPS type I (MPS I), Fabry disease, Pompe disease, and Krabbe disease, were also considered for inclusion in newborn screening panels by the American College of Medical Genetics Newborn Screening Expert Group because of the increasing availability of treatment options, including enzyme replacement therapy (ERT)[9,10] and bone marrow transplantation[11], both of which appear to be particularly effective when initiated early in life[12-14].

Ethical Problems Associated with Newborn Screening for LSDs

In 1968, the World Health Organization (WHO) commissioned a report on screening by Wilson and Jungner entitled, *Principles and Practice of Screening for Disease*, which has since become a public health classic. After about 40 years, several adaptations have been made to the classic criteria, and several new criteria have emerged[15]. Platform technologies (e.g., MS/MS) that allow the identification of numerous conditions from a single sample challenge the traditional Wilson and Jungner criteria because they simultaneously identify many conditions and variants. Some of these conditions may actually be benign, such as short-chain acyl-coenzyme A dehydrogenase deficiency, especially in certain populations. For other conditions, asymptomatic adults are diagnosed after their children are identified as having abnormal analytes during newborn screenings (e.g., 3-methylcrotonyl coenzyme A carboxylase deficiency), whereas some other conditions may not present until adulthood (e.g., citrullinemia or arginosuccinate lyase deficiency). Some conditions may be detected for which there is a lack of evidence regarding the benefits of current treatment modalities (e.g., very long chain acyl-CoA dehydrogenase deficiency). Informing parents of tentative or ambiguous findings raises ethical and psychosocial concerns[16,17]. Waisbren et al. reported that false-positive findings in new screening tests generate anxiety among parents. This is reflected by their children being twice as likely to have emergency department visits or hospitalizations as children with normal screening test results. False-positive screening test results may also place families at risk for increased stress and parent-child dysfunction[18].

In the case of LSDs, there are also several ethical and policy issues regarding the necessity of newborn screening. Ross argued that three LSDs, including Pompe disease, Fabry disease, and Krabbe disease, fail to fulfill the critical criteria enumerated in the classic WHO report, and are not ready to be included in routine newborn screening programs[16]. There were some major problems associated with newborn screening for Pompe disease. First, the Taiwan pilot program had high rates of false-positive results. Second, many infants were identified as having late-onset disease. Third, ERT may be much less effective in those who are cross-reactive immunologic material-negative and develop antibodies to ERT. Fourth, the efficacy of ERT in late-onset Pompe disease was not well-established. In the case of Fabry disease, there were additional major problems, similar to those for Pompe disease. First, current screening methodologies do not identify many female heterozygotes and do not distinguish between classic and late-onset disease. Second, screening during infancy has been questioned because late-onset presentations are much more common than the classic form, and professional statements discourage or proscribe testing children for adult-onset conditions. Third, there are no guidelines for when to initiate treatment. Dimmock et al. also argued that data from a New York program suggest that newborn screening for infantile-onset Krabbe disease should be abandoned, pending the development of improved screening or therapies shown to confer both survival and quality-of-life benefits rather than supportive care. The results of these experiences suggest that research efforts should focus on improving presymptomatic treatment outcomes in children, identified by newborn screening, prior to the deployment of mandatory presymptomatic screening[19-21].

Newborn Screening for MPSs

MPSs are a group of inherited metabolic diseases caused by defects in the lysosomal hydrolytic enzymes needed to break down glycosaminoglycans (GAGs)[22]. The overall incidence of MPS is >1 per 25,000 live births[23]. However, the incidence of each of the different forms of MPS varies. Eleven enzyme deficiencies have been identified, to date, and some of the MPS types have been further divided into subtypes, according to the enzyme defect involved and the type of GAG eliminated in the urine (chondroitin sulfate, dermatan sulfate [DS], heparan sulfate [HS], keratan sulfate [KS], and/or hyaluronic acid)[24]. Treatment of MPS has advanced significantly in recent years with the use of ERT and hematopoietic stem cell transplantation to prevent or treat disease progression[25-28]. These treatment breakthroughs may have important impacts on disease prognosis and quality-of-life for many patients. Given the progressive nature of MPSs and the importance of early diagnosis, providing the various specialists who come into contact with these patients with information and tools that enable them to consider MPS in the differential diagnosis is

essential[29,30]. According to Hayes et al., most families of individuals with MPS and adults with MPS believe that newborn screening for MPSs should be implemented even if there is no cure or effective treatment. The most common reason cited was that an early diagnosis might avoid a delay in diagnosis and the associated distress caused by the delayed diagnosis[31]. However, concerns have been expressed because multiplex MS/MS screening assays, including those for MPSs and other LSDs, are expensive and have high false-positive rates[8]. GAG levels rise in all MPS patients; therefore, direct GAG measurements can be valuable screening tests. Currently, DS and HS might serve as biomarkers for newborn screening[32,33]. Disaccharides from DS, HS, and KS can be digested by chondroitinase B, heparitinase, and keratanase, respectively, and the digested products can be analyzed by MS/MS. Serum heparin cofactor II-thrombin complex, which is a GAG-regulated serpin-protease complex, has recently been identified as a promising biomarker for both newborn screening and monitoring of treatment outcomes in selected MPS types[34]. Second-tier tests, using enzymatic activity analyses and the original DBS, can increase the specificity of the screening test. Over the last few years, enzyme substrates from which the end products can be analyzed using liquid chromatography-MS/MS have also been developed. Recently, substrates for detection of MPS II, MPS IVA, and MPS VI have reported[35-38].

Status of Newborn LSD Screening Programs

In most countries, newborn screening for LSDs is not mandatory. Between 2008 and 2013, Lin et al. conducted a pilot newborn screening program for MPS I. As part of their screening program, α-iduronidase (IDUA) activity was measured in DBSs from 35,285 newborns using a fluorometric assay. Two subjects were identified as having deficient leukocyte IDUA activity that was confirmed by molecular DNA analyses. The incidence of MPS I in Taiwan, estimated from the same study, is about 1 per 17,643 live births. In 2013, the Missouri State Public Health Laboratory began screening for Pompe disease, Fabry disease, Gaucher disease, and MPS I on all DBS specimens collected in the state[39]. During the first 6 months of this pilot study, 43,701 specimens were screened, and 27 newborns were identified as having an LSD genotype (Pompe disease [n=8], Gaucher disease [1], Fabry disease [15], MPS I [3]). A cohort study of 20,018 patients, in Mexico, was conducted over 3 years within the closed Mexican Health System (Petróleos Mexicanos Health Services)[40]. DBS multiplex MS/MS enzymatic assays were conducted for six LSDs, including Pompe disease, Fabry disease, Gaucher disease, MPS I, Niemann–Pick type A/B, and Krabbe disease. Screen-positive cases were confirmed using leukocyte enzymatic activity and DNA molecular analyses. As a result, 20 patients were confirmed to have an LSD phenotype (99.9 per 100,000 newborns), including Pompe disease [n=11], Fabry disease [5], MPS-I [2], and Niemann–Pick type A/B [2] patients.

For other types of MPSs, a few pilot newborn screening studies have been conducted. Ruijter et al. explored the use of a fluorometric assay that could be used for high-throughput analysis of iduronate-2-sulfatase activity in 1,426 DBSs from newborns in the Netherlands[41]. Kubaski et al. reported newborn screening for MPSs involving the measurement of GAGs using MS/MS[33]. This pilot study analyzed 2,862 DBSs from normal newborns and 14 DBSs from newborns with MPS (MPS I, n=7; MPS II, 2; MPS III, 5). In Taiwan, a newborn screening program for MPS I, MPS II, and MPS VI has been conducted since August 2015. A total of 93,063 infants were included in the screening program through the end of December 2016; three infants with MPS I and one with MPS II were identified[42].

Conclusions

LSDs, including MPS, are relatively rare and the severity and the time to presentation of symptoms differ according to the type; thus, a diagnosis is often delayed. Recently, as treatment methods, including ERT, have been developed, early diagnosis of these diseases has become important. As a result, the introduction of newborn screening tests is actively being considered. Several pilot studies have shown that the prevalence of LSDs is actually higher than previously anticipated, supporting the importance of neonatal screening. In addition, neonatal screening is particularly important for diseases such as infant-onset Pompe disease, MPS I, and MPS II, for which ERT should be implemented early, before symptoms worsen, to maximize the individual's prognosis. However, several problems currently hinder broad adoption of these screening tests, including the development of accurate testing methods to reduce low false-positive rates and treatment guidelines for late-onset or mild disease variants, the high cost of multiplex assays, and ethical issues.

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