Newborn Screening for Lysosomal Storage Disorders CE

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ABSTRACT

Lysosomal storage disorders (LSDs) are a heterogeneous group of approximately 50 rare inherited metabolic conditions that result from enzyme deficiencies that interfere with lysosome function. Although often grouped together, there is great variability regarding age of onset, severity, treatment, and outcomes for each disorder and subtype. Currently, laboratory methods are available to test newborns for seven of these conditions. Although newborn screening programs remain state-based, each at a different phase of condition review and implementation, if newborn screening for LSDs has not yet been adopted by the state within which you practice, it likely will. Given the extremely low prevalence and limited provider familiarity with these conditions, this article provides an overview of LSDs and the seven conditions for which newborn screening is available. It offers information about each of the conditions including enzyme deficiency, mode of inheritance, incidence rates, types, clinical course, and available as well as potential treatment options. J Pediatr Health Care. (2018) *32*, 285-294.

KEY WORDS

Lysosomal storage disorder, lysosomal storage disease, lysosomal enzyme disorder, newborn screening

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OBJECTIVES

At the completion of this continuing education program, the participant will be able to:

1. Describe the pathophysiology of lysosomal storage disorders.
2. List the lysosomal storage disorders for which newborn screening is available and those included in the Recommended Uniform Screening Panel.
3. Discuss the differences and similarities between these conditions.
4. Explain current and potential future treatment options for lysosomal storage disorders.
5. Identify the mode of inheritance, clinical course, and available treatment options for at least two of the most common conditions.
6. Identify key (differentiating) features for at least two lysosomal storage disorders.

Newborn screening saves lives and through early, often presymptomatic detection, has reduced disease-associated morbidity. Since the introduction of tandem mass spectrometry to newborn screening almost two decades ago, newborn screening has continued to expand exponentially. Processes and panels vary from state to state and as technology advances, the conditions screened, diagnostic testing, and treatments have grown in complexity, challenging providers to keep pace. This article offers an overview of newborn screening and lysosomal storage diseases and describes each of the lysosomal storage diseases for which screening is available to familiarize providers with these rare conditions should they encounter a newborn or child who has a positive screening result.

NEWBORN SCREENING

Under the auspices of the Advisory Committee on Heritable Disorders in Newborns and Children (Committee), the Recommended Uniform Screening

Panel guides state-based newborn screening programs across the United States. Over the past several years, widespread adoption of filter paper screening for severe combined immunodeficiencies and pulse oximetry screening for critical congenital heart disease have been implemented. More recently, methodology to screen for seven lysosomal storage disorders and one peroxisomal disorder, X-linked adrenoleukodystrophy became available, prompting Committee review for panel inclusion. Of the conditions for which newborn screening methods are available, Pompe disease, mucopolysaccharoidosis type I disease (MPS I) and X-linked adrenoleukodystrophy (see Box) were reviewed by the Committee and met criteria for addition to the Recommended Uniform Screening Panel (U.S. Department of Health and Human Services, Advisory Committee on Heritable Disorders in Newborns and Children, 2016). Before inclusion in the Recommended Uniform Screening Panel, however, several states began screening and/or passed legislation to screen for one or more of the LSDs. In 2006, the New York State Newborn Screening Program paved the way when it added Krabbe disease to the state panel. As laboratory methods became more available, Illinois and Missouri followed by legislating ambitious LSD screening panels (Illinois Department of Public Health, n.d.; Missouri Department of Health & Senior Services, n.d.). Despite efforts for standardization, state-based newborn screening varies across the country. As such, states are at different phases of review and implementation of newborn screening for LSDs (Table 1), but the inevitability of expanded screening looms.

Despite efforts for standardization, state-based newborn screening varies across the country.

BOX. Overview of X-linked adrenoleukodystrophy

X-linked adrenoleukodystrophy (ALD) is a heterogeneous genetic condition of perixosomal fatty acid beta oxidation. It is the most common peroxisomal inborn error of metabolism, with an incidence between 1:20,000 and 1:50,000 (Bezman et al., 2001; GHR, 2013). Enzyme deficiency causes damage to nerve myelin sheaths, resulting in seizures. Because the condition is X-linked, it occurs most commonly in males. Heterozygote females, however, can develop neurologic symptoms of the milder form of disease, adrenomyeloneuropathy (AMN), later in life. Most patients present with severe cerebral disease in childhood. There is normal early development, followed by hyperactivity, and then rapid decline in cognition, behavior, vision, hearing, and motor function between ages 4 and 8 years. Although variable, patients typically progress to total disability within 2 years, and death follows at varying ages. Other forms of ALD range in severity and may include progressive paraparesis (AMN) and, less commonly, adrenal insufficiency (Addison only disease). Treatment for ALD is limited and primarily supportive. Dietary treatment may include restriction of very-long-chain fatty acids and, in asymptomatic patients, a combination of unsaturated fatty acids (Lorenzo's oil). For the cerebral form, allogenic hematopoietic stem cell transplantation is an option if detected early. It is not, however, recommended for individuals with severe neurologic and neuropsychologic dysfunction. Those with adrenal insufficiency respond to corticosteroids (Steinberg, Moser, & Raymond, 2015; NINDS, n.d.b).

Lysosomal Storage Disorders

LSDs are a heterogeneous group of inherited metabolic diseases. Depending on the source, more than 50 different LSDs have been identified. Although each is individually quite rare, the combined incidence rate for LSDs is 1:7,000 to 1:8,000 live births (Schneidereith, 2016). Most conditions are autosomal recessive, but several are X-linked. These generally progressive disorders result from a condition-specific enzyme deficiency that allows substances (lipids and carbohydrates) to accumulate in the lysosome (Figure). Symptoms result from the deposition of these metabolites in the cells of various organs, and disease severity depends on the rate and site of accumulation.

Although LSDs are categorized based on this similarity, they vary in severity, age of onset, treatment options, morbidity, and mortality (Schneidereith, 2016). Each of the LSDs for which newborn screening is available is discussed below. Table 2 provides a summary of the conditions for comparison, and Table 3 provides an overview of available and potential future treatment options.

Krabbe Disease

Krabbe disease is an autosomal recessive, progressive neurodegenerative leukodystrophy caused by a deficiency of the enzyme ß-galactosidase (galactocerebrosidase) that inhibits myelin production. Before the implementation of newborn screening, the disease incidence rate in the United States and Europe was estimated to be 1:100,000 (Wenger, 2011). Based on data from New York State Newborn Screening Program, Wasserstein et al. (2016) report an actual incidence of 1:394,000.

There are several types of Krabbe, including early infantile, late infantile, and later onset disease. Before information shared by the New York State Newborn Screening Program, 85% to 90% of diseased individuals were diagnosed with severe, infantile onset disease. Data compiled after 8 years of newborn screening in New York, however, suggests a much greater incidence of infants with later onset than early infantile disease. Interestingly, it is estimated that the percentages are almost completely reversed, with 90% of infants having later onset disease (Wasserstein et al., 2016).