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Newborn Screening + Enzyme Replacement Therapy = Improved Lysosomal Storage Disorder: Outcomes in Infantile-Onset Pompe Disease

Exactly 50 years after the introduction of newborn screening and 8 years after approval of an enzyme replacement therapy (ERT) for Pompe disease (alglucosidase-alfa, Myozyme), Chien et al demonstrate in this issue of *The Journal* the long-term beneficial effects in 10 patients with infantile-onset Pompe disease detected by newborn screening and begun on treatment at a mean of 16 days of age. After an average (median) of 63 months of every-other-week intravenously infused recombinant human acid α-glucosidase, all patients were ambulatory and none required mechanical ventilation. This powerful combination of early detection by routine newborn screen blood spots and access to storage-reducing ERT has demonstrated for the first time the utility and feasibility of intervening as early as possible in the progressive form of Pompe typically characterized by infantile death of cardiomyopathy if left untreated.

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With the availability of an effective ERT for acid α-glucosidase deficiency, a major remaining barrier to treatment of this rare autosomally inherited lysosomal storage disorder was early detection. Patients with infantile-onset Pompe disease are typically diagnosed symptomatically with left ventricular hypertrophy (mean age at diagnosis: 4.7 months) and die without ERT in infancy of cardiac insufficiency (mean age of death: 8.7 months).[1] Addition of Pompe disease to the newborn screening panel would allow complete ascertainment of patients prior to catastrophic illness.

Chien et al began screening newborn infants for Pompe disease in Taiwan in 2005 and identified 10 classic patients, all with cross-reacting immunologic material (CRIM+).[2] Patients with CRIM+ have decreased immunologic reactions to ERT and have a more favorable prognosis than patients with CRIM−, while still classically affected with cardiomyopathy. Patients were started on ERT immediately after diagnosis. All patients had left ventricular hypertrophy at diagnosis, which resolved in almost all patients by age 6 months. Survival was 100% at a mean age of 61 months with all patients free of mechanical ventilation. The efficacy of ERT was less complete in motor function, with some patients developing proximal muscle and ankle weakness, but all patients could walk fast or run at the end of the study. Additionally, mild cognitive impairment was observed in some patients and brain magnetic resonance imaging had white matter abnormalities in the majority of patients.

The dramatic benefit of early ascertainment of patients with Pompe has begun to be applied to other lysosomal storage disorders for which there is an effective therapy. In a recent issue of *The Journal*, Hopkins et al[3] reported the first

CRIM	Cross-reacting immunologic material
ERT	Enzyme replacement therapy
MPS I	Mucopolysaccharidosis type I

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6 months of a newborn screening pilot program at the Missouri State Public Health Laboratory for Pompe disease, Fabry disease, Gaucher disease, and mucopolysaccharidosis type I (MPS I) using dried blood spots and a digital microfluidics enzyme detection system. The system demonstrated acceptably low false positives, and no missed cases were identified. After screening 43 700 newborn dried blood spots, 27 cases were confirmed with 1 of the 4 lysosomal storage disorders with incidence rates higher than previously reported for Pompe disease, Gaucher disease, and MPS I. Other states have begun newborn screening programs for lysosomal storage disorders, notably New York State, which began screening for Krabbe disease in 2006. Bone marrow transplantation in infancy is the only known effective treatment for this severe neuronopathic disease. Outcomes of the Krabbe screening program have not yet been formally reported but early reports suggest that even infants transplanted at 1 month of age have some neuronopathic sequelae. Illinois has begun to screen for Pompe disease, Krabbe, MPS I, Gaucher disease, Fabry disease, and Niemann-Pick disease, and a few other states are considering similar screening programs.

Newborn screening for lysosomal storage disorders raises a number of difficult issues for which there are no simple solutions. The incidence of affected patients appears to be significantly more frequent in the Missouri pilot than expected leading to the concern that some patients who were enzymatically deficient may have mild or late-onset disease. Lysosomal storage disorders are highly clinically variable between patients, and mutation analysis does not adequately predict phenotype in many cases. The timing of ERT therapy initiation and dosing are open questions in many lysosomal storage disorders as little data exist to demonstrate optimal efficacy in pre-symptomatic patients. For neuronopathic lysosomal storage disorders, such as MPS I and Krabbe disease, bone marrow transplant is the only proven effective therapy for the neurologic sequelae. Optimal outcomes are seen in patients who receive a transplant prior to symptom onset, raising the concern about transplanting infants who may have mild or adult-onset disease. Much will be learned by the few states screening for these lysosomal storage disorders, bringing to an end the era when there were no options for treatment of these progressive storage disorders. ■

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Maternal Cigarette Smoking and Congenital Heart Defects

Congenital heart defects (CHDs) are of public health concern because they affect approximately 1% of newborns,[1-3] are a leading cause of infant mortality,[4] and often result in increased use and costs of health services among affected children, adolescents, and adults.[5] In recent decades, epidemiologic research has made notable progress in the identification of modifiable risk factors for some CHDs (eg, congenital rubella infection, use of certain medications, and pregestational diabetes).[6] For most CHDs, however, the causes remain unknown. In this issue of *The Journal*, Sullivan et al[7] describe results of a population-based study in which they assessed the possible association of maternal periconceptional cigarette smoking and the occurrence of CHDs among live births by linking self-reports of cigarette smoking on birth certificates with records of children with CHD (ie, cases) identified from birth certificates and a statewide hospital discharge registry. The authors examined 19 specific CHD phenotypes and observed associations between maternal cigarette smoking during the first trimester of pregnancy and 3 phenotypes: pulmonary valve anomalies, pulmonary artery anomalies, and isolated secundum type of atrial septal defects. They also observed a suggestion of a dose-response relationship between maternal cigarette smoking and the risk of CHDs examined as a group. These findings are of interest because they highlight: (1) methodologic issues common to studies of associations of maternal cigarette smoking, a prevalent and modifiable exposure, with specific CHD phenotypes in the offspring; (2)

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CHD	Congenital heart defect

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