Pompe Disease

Literature Review and Case Series

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KEYWORDS

- Metabolic myopathy • Hypotonia • Autosomal recessive
- Enzyme replacement therapy • Newborn screening
- Lysosomal glycogen storage disease

KEY POINTS

- Pompe disease, also known as type II glycogenosis, is a progressive autosomal recessive glycogen storage disease caused by deficiency of lysosomal acid-α-glucosidase (GAA) primarily in skeletal and cardiac muscle with age of onset ranging from infancy through adulthood. Extramuscular phenotypes are also recognized.
- Recognized clinical presentations of Pompe disease include infantile (with/without cardiomyopathy) and late-onset (childhood, juvenile, and adult) forms. In addition to cardiomyopathy in the classic infantile form, musculoskeletal signs and symptoms are the most frequent.
- Excessive lysosomal glycogen storage and defects in autophagy are the main determinants of pathogenesis of Pompe disease.
- Diagnosis of symptomatic individuals, as well as screening in healthy newborns, is now possible by demonstrating low GAA enzyme activity in dried blood samples complemented by DNA mutation analysis.
- Diagnostic gaps in patients with Pompe disease across the disease spectrum continue.

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- In our cohort of patients, 3 with infantile and 9 with late-onset Pompe disease, we identified 4 novel, potentially pathogenic *GAA* mutations and 1 pregnancy that was complicated by prenatal exposure to recombinant human GAA (rhGAA) and spontaneous miscarriage.
- In addition to supportive therapy, rhGAA enzyme replacement therapy is now available. Oral chaperone therapy, modified rhGAA, autophagy suppression, and gene transfer represent potentially promising novel therapies that are being tested in clinical research trials.

INTRODUCTION

Pompe disease (GSD II) is an autosomal recessive disorder caused by deficiency of the lysosomal enzyme acid-α-glucosidase (GAA; EC 3.2.1.20), leading to generalized accumulation of lysosomal glycogen, especially in the heart, skeletal and smooth muscle, and the nervous system. Pompe disease was first described in a 7-month-old girl with severe muscle weakness who also had hypertrophic cardiomyopathy and generalized glycogen accumulation in various tissues throughout the body.[1] Bischoff[2] and Putschar[3] also independently described the disease in the same year. Hers[4] identified alpha-glucosidase deficiency and localized the GAA enzyme activity to the lysosomes of liver, heart, and muscle tissues of 5 infants with classic Pompe disease and was the first to recognize impaired autophagy. Pompe disease is generally classified based on the age of onset as infantile (IOPD) when it presents during the first year of life, and late onset (LOPD) when it presents afterward. Childhood, juvenile, and adult-onset Pompe disease are examples of the late-onset form. IOPD associated with cardiomyopathy is referred to as classic Pompe disease and, in the absence of cardiomyopathy, as nonclassic Pompe disease.[5–7] Similar to other lysosomal storage disorders, Pompe disease clinically presents as a continuum in its age of onset and multisystem involvement. The role of autophagy in the pathogenesis of Pompe disease, especially the late-onset form, has increasingly become evident and may be clinically relevant. Autophagy (self-eating) is a highly complex, ubiquitously expressed, and evolutionarily conserved lysosomal degradative process, which is controlled by a multigene network (http://autophagy.lu/index.html). Its main function is to recycle obsolete cellular constituents and eliminate damaged organelles and protein aggregates. It involves dynamic membrane rearrangement for sequestration of cytoplasm and its delivery into the vacuole/lysosome. Basal autophagy plays a role in cellular development and differentiation,[8] innate and adaptive immunity,[9] and is induced in response to various stress conditions, such as nutrient limitation, heat, and oxidative stress. Ammonia derived from the deamination of glutamine via glutaminolysis supports basal autophagy and protects cells from tumor necrosis factor alpha–induced cell death.[10] As a result, basic metabolites are released into the cytoplasm for new synthesis or as sources for energy. Autophagy also is implicated in a wide range of disorders, such as neurodegeneration, cancer, and aging, and now various lysosomal storage diseases, especially Pompe disease.[11–14]

Clinically, infants with classic Pompe disease typically present during the first few weeks of life with hypotonia, progressive weakness, macroglossia, hepatomegaly, and hypertrophic cardiomyopathy. With this typical clinical presentation, diagnosis is usually straightforward. The natural history of IOPD is that most of these infants die by their first birthday. On the other hand, the diagnosis of Pompe disease in older children and adults can be more challenging, as these patients generally present with slowly progressive limb girdle–type weakness and respiratory insufficiency without significant