Pompe Disease: The Sphinx of Science

Stephanie Hiltscher

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Josh Cannon

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Abstract:

For nearly a century, scientists have been wandering a medical maze. The study of a fascinating disease classified as Glycogen Disease Type II (Pompe Disease), has mystified scientists around the world. Its current incurability, its ability to affect the entire body, and its unusual infantile onset set Pompe disease apart from other genetic disorders. Geneticists may predict a baby's likelihood of developing Pompe Disease and what kind of treatment would be in store for infantile onset. Myozyme, a type of enzyme replacement therapy, recently approved by the FDA in 2009, has lengthened the life of Pompe Disease patients; however, it involves weekly treatments not a lifelong cure.

Background:

Also known as Glycogen Storage Disease Type II, Pompe Disease takes 1 out of every 40,000 children's lives every year. Mainly debilitating the skeletal, cardiac, and nervous muscles (see figure 1), Pompe sufferers lack an essential gene due to one of many possible mutations. This gene codes for the enzyme Acid Alpha Glucosidase, discovered by Henri G. Hers in 1956. Acid Alpha Glucosidase is necessary for the breaking down of glycogen in the lysosomes, hence Pompe Disease's classification as the second glycogen storage disease (Harbers, 2007). Other glycogen storage diseases include Andersen disease, Cori disease, Forbes disease, Hers disease, McArdle disease, Tauri disease, von Gierke disease, and Liver phosphorylase deficiency (World Health Organization, 2006).

Discovered in 1932, Pompe disease, astounded scientists internationally. Johannes Pompe discovered a buildup of glycogen in the liver, cardiac, and skeletal tissues, but could not explain the effects of the disease he named, Pompe. His assistant, Christian Duve's discovery of lysosomes in 1955 revolutionized the understanding of glycogen storage diseases for decades to come. Although infantile onset is prominent, symptoms of Pompe Disease can present themselves in infancy, childhood, or even late adulthood (see figure 2). Pompe disease has been classified based on its victims' lack of the enzyme, acid alpha glucosidase. This vital enzyme

breaks down glycogen for proper storage in the lysosomes; hence Pompe Disease is also classified as a lysosomal or metabolic disorder (Harbers,2007).

Lysosomes. These sac-like organelles balance the pH of each and every cell in our bodies. Imagine a disease in which every fibrous muscle of your body begins to fail. Pompe disease is distinguished by the body's declining muscular function due to the absence of the enzyme, Acid Alpha Glucosidase. Over 70 mutations have been identified including C.525dert (34% Dutch, 9% of U.S.), Exon 18 deletion(25% infantile Dutch and Canadian, 5% of United States), and IVS1-13T>G (36-50% late onset cases) (Harbers, 2007).For infants, genetic testing for the lack of this vital gene is often too late; most die within a year of diagnosis.

Pompe knows no age boundaries or cultural divides. Because Pompe Disease is an autosomal recessive disorder, the disease may strike at any time with the combination of two recessive alleles from carrier parents. Heterogeneously allelic individuals may become patients of late onset Pompe disease (Leslie, & Tinkle, 2008).

Visible at a few months of age, Pompe victims develop similar phenotypic characteristics which include lacking muscle tone, especially in the facial structure and appendages. Failure to thrive, poor nutrition, respiratory concerns, hepatomegaly, and cardiac problems are all common manifestations of the infantile onset of Pompe disease. Physical exertion must remain minimal, commonly due to cardiomegaly, which is also the main cause of death for infantile onset of Pompe Disease. Hepatomegaly or enlargement of the liver is also a grave symptom (see figure 1 for signs and symptom

incidences). Once Pompe begins, it is only a matter of slowing the manifest symptoms and treating each one individually for longevity and the comfort of the patient.

Typically taking place in the third decade of a person's life, late-onset Pompe disease is characterized by progressive muscle weakness in the legs and trunk, and is less severe than other types of onset. According to the National Institute of Health, some clinical manifestations of late-onset Pompe disease include, "respiratory insufficiency, exercise intolerance, exertional dyspnea, orthopnea, sleep apnea, hyperlordosis, Hepatomegaly, macroglossia, difficulty chewing and swallowing, decreased deep tendon reflexes, joint contractures, cardiac hypertrophy, and cardiac hypertrophy (childhood onset)". It has been known to appear in late childhood, adolescence, and adulthood. Adults may remember small signs beginning in childhood due to the fact that after the first year of life, late-onset of the disease may manifest itself (National Institute of Health, 2010). A cure for Pompe Disease has been nowhere to be found and treatments have been well under way for the last century.

In the incidence of the non-classic onset of Pompe disease, infants often experience trauma from respiratory distress and progressive muscular weakness. Non-classic onset usually involves infancy and early childhood and victims usually only live to experience the initial part of childhood. Serious heart conditions including cardiomegaly are generally not involved (National Institute of Health, 2010).

Testing:

Testing for specific genetic disorders can be a complex and lengthy process. A clinician's diagnosis alone is insufficient (Leslie, & Tinkle, 2008). Misdiagnosis often occurs. Some common misdiagnoses of Pompe victims include spinal muscular atrophy 1, Danon disease, endocardial fibroelastosis, carnitine uptake disorder, Glycogen Storage disease type III, Glycogen storage disease type IV, idiopathic hypertrophic cardiomyopathy, myocarditis, and mitochondrial and respiratory chain disorders (National Institute of Health, 2010). Inevitably, misdiagnosis leads to fatality.

In order to avoid misdiagnosing a patient, doctors do several tests including tests which are simply indicators. Indicating tests which point to Pompe disease include Serum creatine kinase (CK) concentration which is multiplied approximately three times higher than average in a classic-Pompe victim, and may present normal levels in an adult-onset patient. Urinary oligosaccharides have shown high amounts of glucose when testing patients with glycogen storage disorders (National Institute of Health, 2010). These indicator tests are cheaper and therefore the first baby steps to pinpointing the patient's diagnosis of Pompe disease.

To confirm a diagnosis of Pompe disease, doctors measure GAA enzyme activity using skin fibroblasts. Since 1985 scientists have been able to diagnosis the fetus using a chorionic villi biopsy on amniotic cells (Besançon, Castelnau, Nicolesco,, Dumez, & Poenaru, 1985). With complete deficiency of GAA production, infantile-onset is confirmed; with partial deficiency other types (non-classic and adult-onset) of Pompe

disease are suspected. A muscle biopsy has defined cases of the disease accurately by evaluating the “vacuoles of varying severity that stain positively with periodic acid-Schiff” (Leslie, & Tinkle, 2008). By scanning for all possible mutations for the GAA gene, the test is completely accurate (Shannon, 2007). It is highly recommended that following the diagnosis of one Pompe sufferer in the family, that all family members be tested using a molecular enzyme activity measure.

Treatment:

The age of onset seems to correlate with the speed of progression of Pompe disease. The alleviation of symptoms in the patient has been the most widely accepted treatment because there is no definite cure. Patients often hire a neurologist, cardiologist, and respiratory specialist to improve conditions temporarily. Pompe cannot be cured at present; however, scientists and doctors have been tirelessly working to relieve patients of a lifetime of weekly treatments. It is an extremely difficult and expensive lifestyle to keep up.

Currently the drug, Myozyme, which received FDA approval in 2006, is the most effective treatment for infantile onset of Pompe disease. But for this miracle treatment, there is a price to pay namely: $300,000 a year is not an unusual fee. Insurance companies have often refused to offer coverage for Pompe disease besides the treatment of manifest symptoms, because enzyme replacement therapy is a new innovation (Duke Medicine News and Communication, 2001).

During enzyme replacement therapy, scientists at Duke University noticed that rhGAA (recombinant human acid alpha-glucosidase) antibodies were present in the

patients being treated. As a result of cross-reacting immunologic material with rhGAA, this caused the enzyme replacement therapy to be entirely ineffective. When Methotrexate was added to the patient's prescription every week, the antibodies against recombinant human acid alpha glucosidase declined to an "undetectable level". Since then, recombinant human acid alpha-glucosidase enzyme replacement therapy has remarkably improved muscular debilitation of Pompe disease in infants, reduced heart size, and helped regulate cardiac functions (Kishnani, 2009). Because of its vitriolic side effects, gene therapy for Pompe disease has been debated for the past decade. Dr. Y.T. Chen head of the division of medical genetics in Pediatrics at Duke University Medical Center said, "We have been working toward this for quite some time, and this is a major milestone in our efforts to develop a treatment for this fatal disease" (Duke Medicine News and Communication, 2001). Although controversial, enzyme replacement therapy is by far the greatest hope for those and their families who suffer from Pompe disease.

Conclusion:

The perplexity of Pompe disease and other genetic lysosomal disorders has baffled scientists for centuries, however, with greater knowledge of the glycogen storage diseases and increased government funding, in time the questions will be answered. With mastery of enzyme replacement therapy with recombinant human GAA, and the engineering of a GAA generating pill, Pompe patients' will live with increasing comfort and longer lives. Continued dedication of leading scientists and health

education will lead to the disappearance of such devastating, hereditary diseases like Pompe disease.

Appendix:

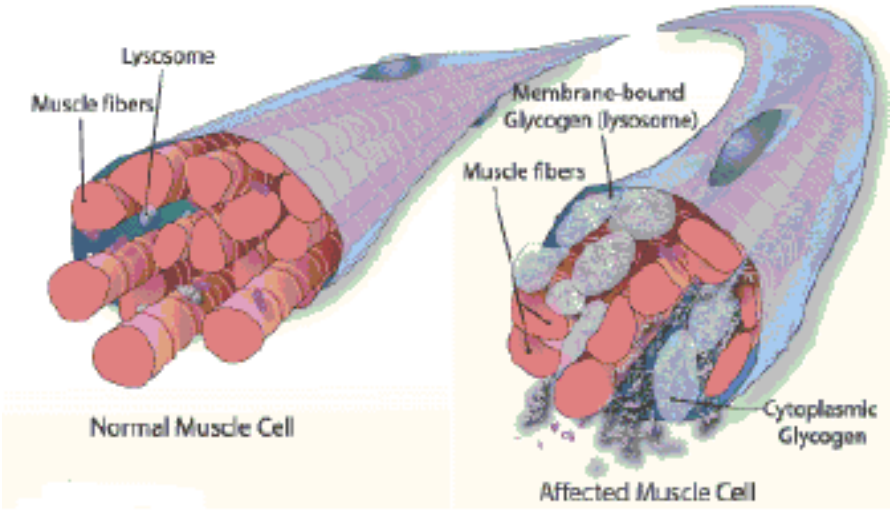

Figure 1, damage of Pompe to muscle cells

Signs/Symptoms	Incidence
Hypotonia/muscle weakness	52-96%
Cardiomegaly	92-100%
Hepatomegaly	29-90%
Left ventricular hypertrophy	83-100%
Cardiomyopathy	88%
Respiratory distress	41-78%
Murmur	46-75%
Macroglossia (enlarged tongue)	29-62%
Feeding difficulties	57%
Failure to thrive	53%
Absent deep tendon reflexes	33-35%

Normal cognition	95%

Figure 2, Common signs of Pompe disease (National Institute of Health, 2010) 2006).

Population	Incidence
African American	1:14,000
Netherlands	1:40,000 combined, 1:138,000 infantile onset, 1:57,000 adult onset
United States	1:40,000 combined
South China/Taiwan	1:50,000
Caucasian	1:100,000 infantile onset, 1:60,000 late onset
Australia	1:145,000
Portugal	1:600,000

Figure 3, Incidence of Pompe disease in different cultures. (Leslie, & Tinkle, 2008) .

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