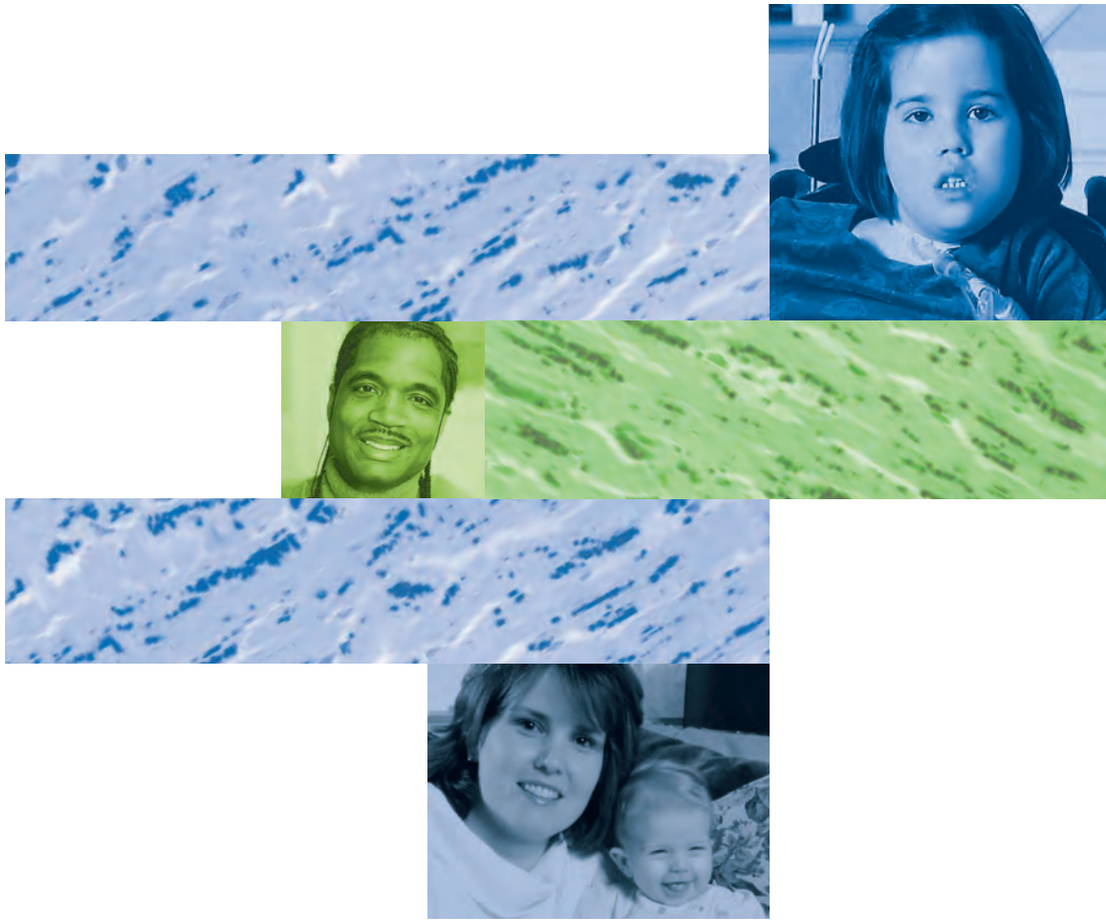
A PHYSICIAN'S GUIDE TO POMPE DISEASE



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Introduction

Pompe disease is a rare, progressive muscle disease that can often be fatal. This disorder comprises **a continuous spectrum of manifestations** caused by an inherited metabolic deficiency of the lysosomal enzyme, acid alpha-glucosidase (GAA).[1]

Pompe disease is a rare and heterogeneous condition. To help healthcare providers identify and understand this illness, this booklet will discuss the following aspects:

- Nomenclature
- Inheritance
- Epidemiology
- Pathophysiology
- Clinical phenotypes
- Presentation, signs, and symptoms
- Diagnosis
- Management
- Investigational approaches

Pompe disease is named after Dr. J. C. Pompe, who first described this condition in 1932. The lysosomal accumulation of glycogen, which results from a deficiency in the lysosomal enzyme GAA, supports classification of Pompe disease as a lysosomal storage disease. Abnormal glycogen accumulation also accounts for its classification as a glycogen storage disease. Prominent muscle wasting seen in Pompe disease accounts for its classification as a neuromuscular/metabolic muscle disease.[1] In the literature, Pompe disease is also referred to as[1,2]:

- Glycogen storage disease type II
- Glycogenosis, type II
- Acid maltase deficiency

Inheritance of Pompe Disease

Pompe disease is an autosomal recessive disorder occurring equally among females and males (Figure 1). Carriers of Pompe disease are heterozygous, with 1 normal and 1 abnormal copy of the GAA gene. These copies are called alleles. Children of 2 carriers may[1]:

- Receive 2 abnormal alleles and present with Pompe disease (25%)
- Receive 2 normal alleles and neither present with nor carry the disease (25%)
- Receive 1 normal and 1 abnormal allele and be carriers (50%)

Almost 150 different mutations (ie, 150 mutant alleles) to the GAA gene, which is found on chromosome 17, have been identified.*[3,4] Although some of the mutations occur with certain frequency in the general population or in particular ethnic groups, most of them have been identified in individual patients.[3]

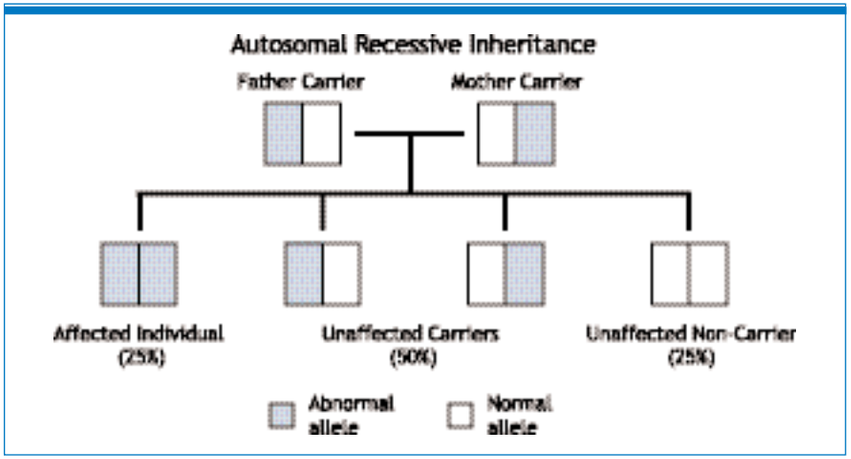

Figure 1. Pompe disease has an autosomal recessive mode of inheritance.

* Available at: http://www2.eur.nl/fgg/ch1/pompe/mutations.html

Pompe Disease: A Continuum of Clinical Phenotypes

A broad classification of Pompe patients divides them in 2 categories: infantile-onset (including classical and non-classical presentations) and late-onset (juvenile and adult) patients. The variability in the underlying enzymatic defect, however, makes this disorder heterogeneous in age at onset, rate of progression, and extent of organ involvement in patients.[1] Pompe disease is therefore better understood when considered as a continuous spectrum of pathology (Figure 2).[1,5,6]

Infantile-onset disease (patients with symptom onset at < 12 months of age) generally progresses much more rapidly than late-onset disease and typically proves fatal, usually within the first year of life. A subset of patients with infantile-onset Pompe disease has been described by Slonim et al.[7] The clinical course of these patients was characterized by a slower progression of cardiomyopathy and longer survival, generally developing respiratory failure between 1 and 2 years of age. Although several of these patients die before 1 year of age, others may survive beyond 2 years.

Usually, late-onset disease (patients with symptom onset at > 12 months of age) correlates with slower progression and a lower rate of cardiac involvement.[1] Muscle weakness, motor deficit, and respiratory complications are common and dominant symptoms observed in both infantile- and late-onset Pompe disease.[1,2] However, while juvenile and adult patients die from respiratory failure, cardiorespiratory failure is the most common cause of death among infants.

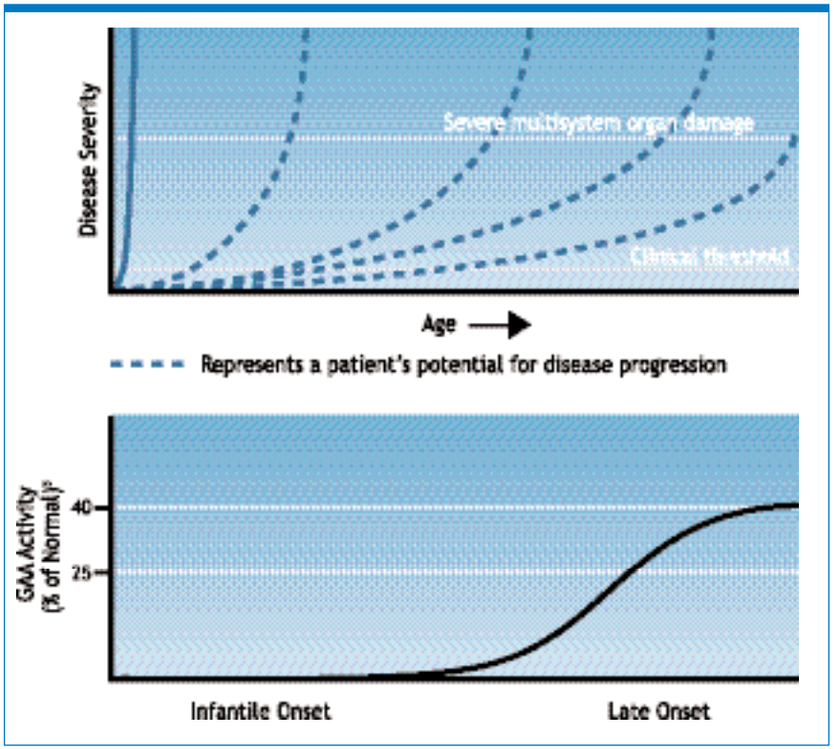

Figure 2. Clinical phenotypes of Pompe disease encompass a continuous spectrum in which severity generally correlates inversely with age of onset. Most patients with infantile-onset disease have undetectable to minimal GAA activity, leading to massive glycogen accumulation and rapid and aggressive progression in skeletal muscle and in several organ systems (heart, liver). In contrast, late-onset patients tend to have limited, but detectable, residual GAA activity; in these cases, organ damage is less pronounced and disease progression is slower.

Epidemiology of Pompe Disease

Conducting epidemiologic studies on Pompe disease is difficult due to its rarity and the limited sources of information available. As a result, epidemiologic data are scarce and somewhat variable.

Incidence

Genetic mutation frequency studies conducted in the Dutch population have obtained reliable estimates of the incidence of both infantile-onset and late-onset forms of Pompe disease by calculating the frequency of known GAA mutations (Table 1).[1,8]

Table 1. Epidemiologic Data Disclose the Rarity of Pompe Disease[1,8]

Pompe Disease Type	Incidence per Births (95% CI)
Infantile onset	1/138,000 (1/43,000 to 1/536,000)
Late onset	1/57,000 (1/27,000 to 1/128,000)
All Pompe	1/40,000 (1/18,000 to 1/100,000)

CI = confidence interval.

These results are consistent with similar estimates derived from a US-based study population. Other studies have also shown that incidence may vary across ethnic groups, with the highest incidence of infantile-onset disease occurring in African-American and Chinese populations.[1]

Pathophysiology of Pompe Disease

Glycogen, the basic form of glucose storage in cells, is abundantly present in muscle and liver tissue. When glucose is needed, glycogen is hydrolyzed via complex enzymatic pathways in the cytoplasm. During times of cellular turnover, glycogen is taken up by the lysosome and broken down into glucose that can be excreted and recycled. GAA is responsible for metabolizing lysosomal glycogen, but in Pompe disease, this process is impaired due to the deficiency in GAA activity (Figure 3).[1,3] As a result, glycogen accumulates within the lysosomes. Glycogen metabolism in the cytoplasm, however, is not directly affected, because it does not depend on GAA. Glucose levels do not fall, because they are maintained by other pathways (eg, the cytoplasmic glycogen-debranching pathway).[9]

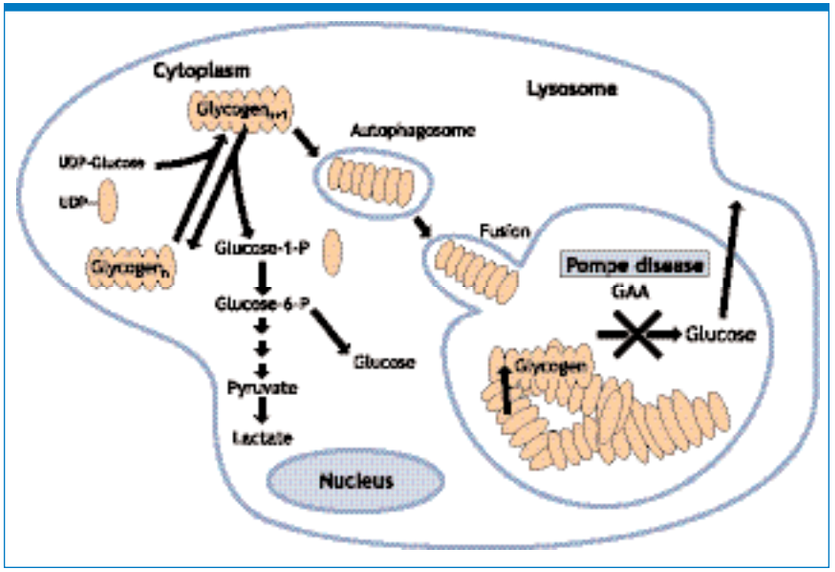

Figure 3. Impaired lysosomal glycogen degradation in Pompe disease.[10]

The deficiency of GAA results in the accumulation of glycogen within lysosomes. This accumulation leads to lysosomal distention, with glycogen dispersion into the cytoplasm, cellular damage, and eventual organ dysfunction. As the disease advances in muscle cells, healthy myofibrils are damaged and replaced by glycogen, and muscle function is gradually impaired (Figure 4).[3] In patients with Pompe disease, lysosomal glycogen accumulation occurs mostly in cardiac and skeletal muscle cells, but can be found in all cells and tissues including leukocytes, smooth muscles, liver, and kidneys.[1,3] In addition, significant lysosomal glycogen accumulation has been observed in cardiac muscle cells in infants with Pompe disease.[1,3]

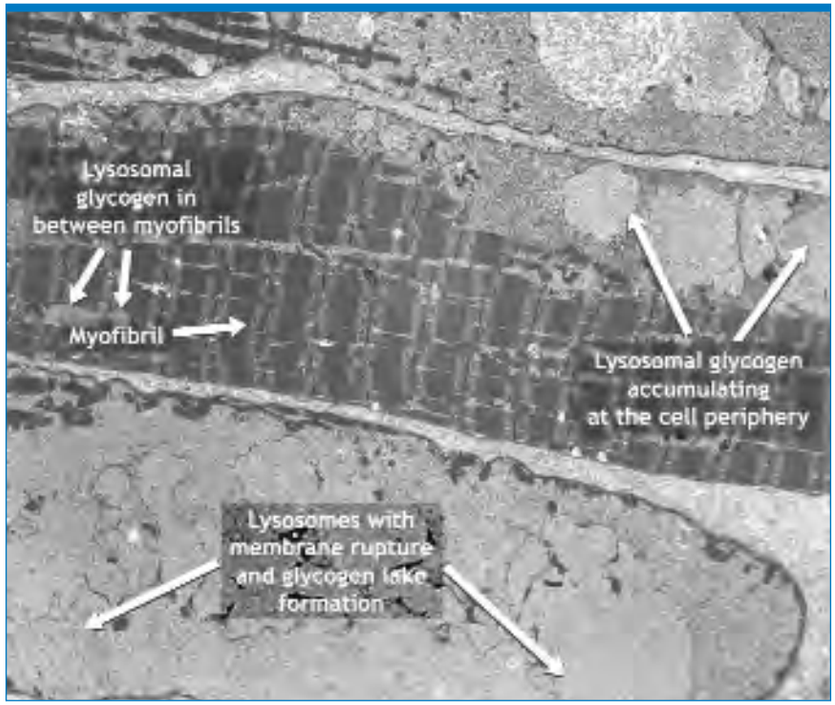

Figure 4. Electronmicrograph of muscle cell from a Pompe disease patient.[10]
Photo courtesy of Genzyme Corporation, data on file.

Presentation of Infantile-Onset Pompe Disease

Symptoms commonly observed in patients with infantile-onset Pompe disease include clinical manifestations related to 4 organ systems (Table 2).[1,2,11]

Table 2. Prominent Symptoms in Infants With Pompe Disease[1,11,12]

Musculoskeletal	• Progressive muscle weakness • Profound hypotonia • Floppiness • Head lag • Failure to achieve motor milestones • Macroglossia
Pulmonary	• Progressive respiratory weakening • Frequent respiratory infections • Death due to cardiorespiratory failure
Gastrointestinal	• Difficulty feeding • Failure to thrive • Hepatomegaly
Cardiac	• Striking and progressive cardiomegaly • Cardiomyopathy • Heart failure

Key Presenting Manifestations

Common initial clinical signs that should prompt physicians to consider Pompe disease as a likely diagnosis in infants include[1]:

- Head lag ("floppy baby" appearance, Figure 5)
- Frog-like posture of the legs
- Failure to achieve motor milestones
- Cardiomegaly is typically visible in chest x-rays (Figure 6). Electrocardiograms may show shortened PR intervals and large QRS complexes (Figure 7). Echocardiograms may show reduced ventricular volume leading to the eventual obstruction of left ventricular outflow

Figure 5. Photograph of an infant with characteristic "floppy-baby" appearance.[10]
Photo courtesy of Genzyme Corporation, data on file.

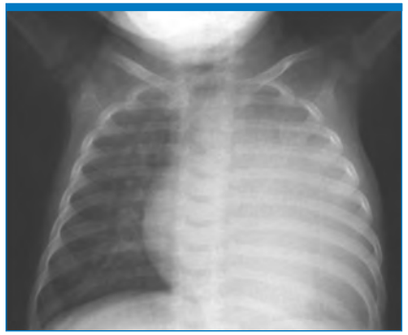

Figure 6. Chest x-ray of an infant with Pompe disease showing cardiomegaly.
With permission from B. Byrne, MD.

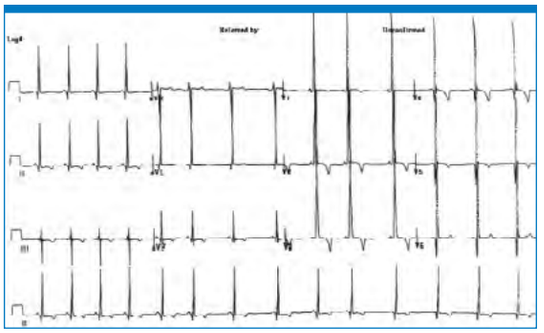

Figure 7. EKG from an infant with Pompe disease showing short PR intervals and tall QRS complexes.[13]
From: Wahbeh GT, Moodie DS. *Clin Pediatr (Phila).* 2001;40:615-619. Reproduced with permission.

Differential Diagnoses

Signs and symptoms of infantile-onset Pompe disease may be confused with other conditions.[1] Differential diagnoses include[1,14]:

- Spinal muscular atrophy I
- Danon disease
- Endocardial fibroelastosis
- Carnitine deficiency

Natural History

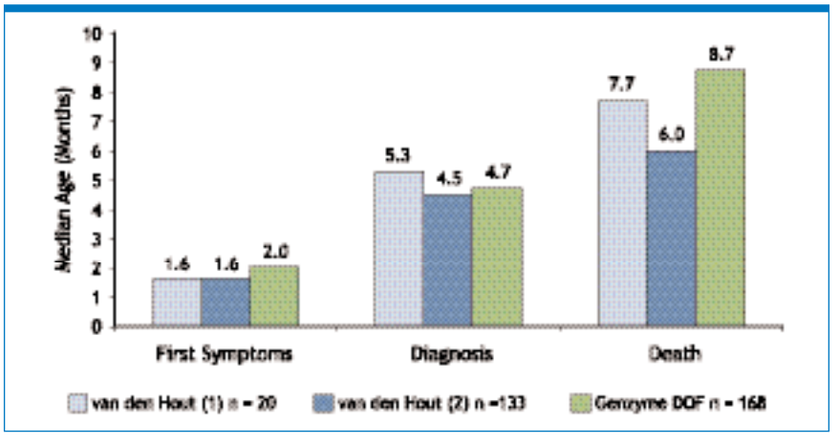

Figure 8. Milestones in the natural history of classical infantile-onset Pompe disease. This consistent pattern of progression from initial symptoms to death has been observed across several studies. Overall survival rates range from 5% to 22% at 12 months and from 0% to 12% at 18 months.[10,12]

Presentation of Late-Onset Pompe Disease

Symptoms commonly observed in patients with late-onset Pompe disease include clinical manifestations related to a number of organ systems (Table 3, Figures 9-11).[1,2]

Table 3. Prominent Symptoms in Adults With Pompe Disease[1,2]

Musculoskeletal	• Progressive proximal muscle weakness (esp. trunk and lower limbs) • Gait abnormalities • Lower back pain • Reduced deep tendon reflexes	• Difficulty climbing stairs • Scapular winging • Delayed motor milestones • Lordosis/scoliosis
Pulmonary	• Respiratory failure/ insufficiency • Orthopnea	• Sleep apnea • Exertional dyspnea • Respiratory infections
Other	• Daytime somnolence	• Headache

Key Presenting Manifestations

A recent survey collected data directly from 210 self-reporting patients with late-onset Pompe disease, age 2.6 to 81 years. According to responses, there are 2 predominant categories of initial symptoms[15]:

- Deficits in mobility, such as difficulty climbing stairs or running (majority of patients)
- Breathing insufficiency (a common early complaint in a minority of patients, 15%)

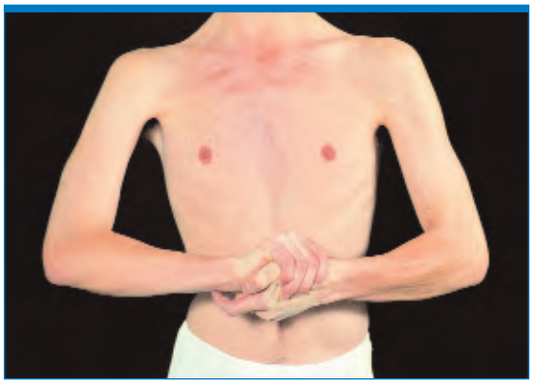

Figure 9. Photograph of a patient with proximal weakness since childhood showing atrophy of the upper arms and pectoral muscles.

Hirschhorn R. Glycogen storage disease type II: acid alpha-glucosidase (acid maltase) deficiency. In: *The Metabolic and Molecular Bases of Inherited Disease*. 8th ed. ©2001. Reproduced with permission of The McGraw-Hill Companies.

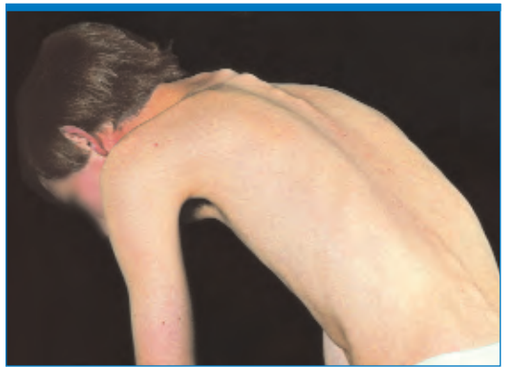

Figure 10. Photograph of the same patient as in Figure 9, showing his paraspinal muscles.

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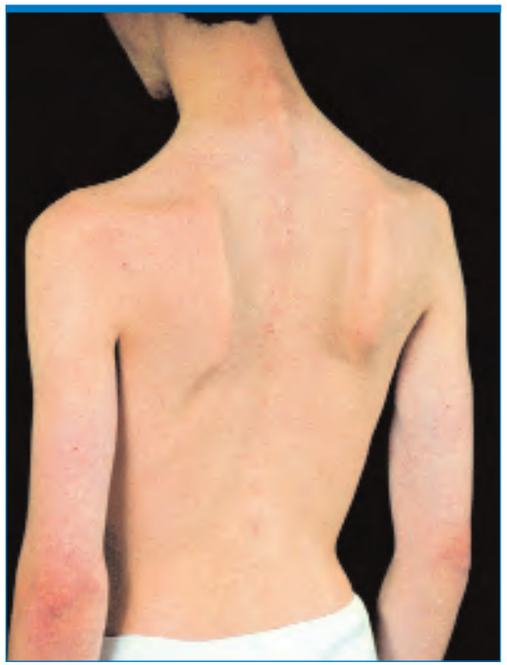

Figure 11. Same patient as in Figures 9 and 10, showing scapular winging.

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Differential Diagnoses

Signs and symptoms of late-onset Pompe disease may be confused with other conditions[1]:

- Limb girdle muscular dystrophy
- Becker/Duchenne muscular dystrophy
- Polymyositis
- Rheumatoid arthritis
- Glycogen storage disease III

Natural History

For adult patients with late-onset Pompe disease, initial manifestations of symptoms have been reported at mean ages of 30 to 36.3 years. Time to diagnosis ranged from 4.7 to 5.1 years, while 10.7 and 11.3 to 15 years passed from first symptoms to required wheelchair and ventilator, respectively (Figure 12).[10,11,13,15,16] In a small study of patients with juvenile-onset Pompe disease, the mean age at which symptoms were first observed was 5.1 years. The mean time until diagnosis was 2.4 months.[16]

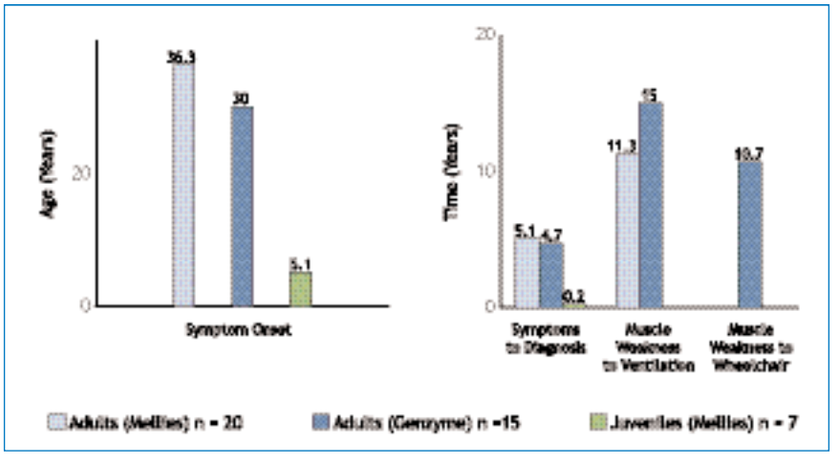

Figure 12. Late-onset Pompe disease: natural history. Data from 2 prospective studies.[10,16]

Diagnosis of Pompe Disease

GAA Activity Assays

Measurement of GAA activity in one of several different tissue specimens is used to confirm a diagnosis of Pompe disease.[1,17-19]

- Muscle biopsy requires an invasive procedure but usually provides reliable results. False-negative results may occur due to inaccuracies in the biopsy technique or sampling errors.
- Cultured skin fibroblasts is the source for reliable, sensitive, and less invasive enzymatic assays. Results, however, are obtained only after a several-week interval.
- Lymphocytes supply a ready assay source, but their use can result in false negatives due to contamination with granulocytes and/or other sources of neutral glucosidases.
- Dried blood spots could provide a simple, non-invasive source for screening of GAA activity. Several technologies based on this source have been developed that can be applied for newborn screening. Their validation as tools to perform confirmatory diagnosis is, however, still pending.

In addition to these tests, assaying GAA activity in cultured amniotic cells or chorionic villus biopsies allows prenatal diagnosis in families with a history of Pompe disease.[1]

Histological Examination of Muscle Biopsy

New methods are being developed to evaluate histological glycogen load in tissues from patients with Pompe disease (Figure 13).[20]

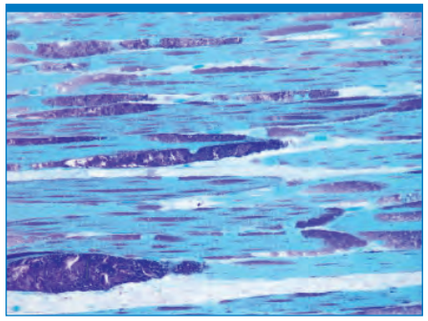

Figure 13. High-resolution light microscopy (HRLM) of human Pompe quadriceps. Tissue is embedded in epon and stained with PAS and Richardson's stain. Glycogen appears purple. (Photograph reprinted with permission of the authors from: Lynch et al. *J Histochem Cytochem.* 2005;53:63-73.[20])

Pompe Disease Management

Supportive care strategies can improve quality of life, but cannot alter the disease course.[1] Due to the multisystemic aspect of the disease, Pompe patients require multidisciplinary management by a team of specialists (Figure 14). Awareness of the manifestations, challenges, and psychological effects of Pompe disease on patients and families is crucial for its optimal management.

Figure 14. Multidisciplinary management of Pompe disease.

Investigational Approaches

Enzyme Replacement Therapy (ERT) is intended to replace the deficient enzyme that causes Pompe disease. Successful preclinical work with ERT has prompted further investigation of this approach. Clinical studies are ongoing to assess the safety and efficacy of ERT.[1]

Gene Therapy is in the early stages of preclinical investigation and takes a genetic approach to correcting Pompe disease. It aims to circumvent the inborn genetic mutation at the root of Pompe disease by introducing a working copy of the GAA gene into the tissues, in most cases via a modified virus. Gene therapy has been studied using both ex vivo and in vivo approaches. However, there are some safety concerns associated with this approach in other diseases, and there are currently no approved gene therapies.[1]

More information on clinical trials can be found at www.clinicaltrials.gov

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