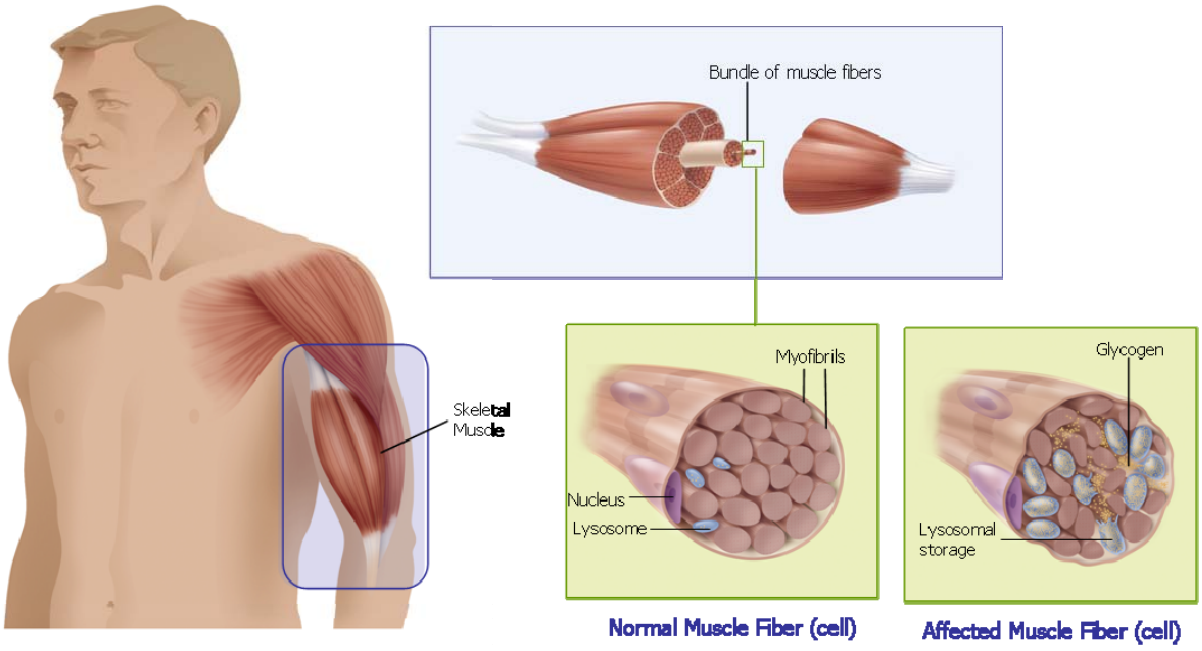
THE SIGNS AND SYMPTOMS OF POMPE DISEASE

Pompe disease is a rare progressive disorder that is genetically inherited or passed on to children when both parents have a defective gene. People diagnosed with Pompe disease do not have enough of an enzyme called **acid alpha-glucosidase (GAA),** or **acid maltase.** This enzyme is needed to break down **glycogen,** a form of sugar stored in muscle cells. When too much glycogen builds up in the muscle cells, the cells become damaged and the muscles cannot function properly. Because the enzyme is found in a part of the cell called the **lysosome,** Pompe disease is often referred to as a **lysosomal storage disorder.** Since the material stored is glycogen Pompe disease is also referred to as a glycogen storage disease (GSD), and since Pompe disease also affects the muscles, it is also called a **neuromuscular disorder.** Even though symptoms of Pompe disease may appear at any time from infancy through adulthood, patients receive the diagnoses of either infantile or late-onset Pompe disease.



Muscle cells (or fibers) are grouped in bundles. Each cell is made up of bands of myofibrils. Glycogen starts to build up in a part of the muscle cell called the lysosome. This causes the lysosomes to expand until they take up so much space that the muscle cell is damaged. Glycogen may also leak out of the cells and cause more damage to the muscle cells.

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Q: How does the severity of Pompe disease relate to the age at which symptoms first appear?

A: All patients with Pompe disease share the same general disease course, namely the steady buildup of glycogen in muscle tissues leading to progressive muscle weakness. The broad spectrum of Pompe disease has the classic infantile onset at the severe end of the spectrum and the late onset at the other side of the spectrum. The severity of Pompe disease varies by age of onset, organ involvement and severity of muscular involvement (skeletal, respiratory, cardiac), and rate of progression.

In an attempt towards establishing a uniform terminology, Pompe disease is classified as follows:

- Classic Infantile Pompe disease
- Nonclassic Infantile Pompe Disease
- Late-Onset Pompe disease

Q: What are the signs and symptoms of classic and non-classic infantile Pompe disease?

A: Classic Infantile Pompe disease: This is a more aggressive and life-threatening form of the disease, and usually appears during the first 6 months of life. Extreme muscle weakness (myopathy) is the most noticeable sign. Babies with Pompe disease have poor muscle tone (hypotonia), look "floppy" and cannot hold up their heads. They typically are slow to acquire motor skills; they may lose previously acquired motor skills. They may never achieve the ability to sit up, crawl or stand. The muscle weakness progresses rapidly. Breathing, sucking, and swallowing become extremely difficult. The heart enlarges (cardiomegaly), the liver enlarges (hepatomegaly), and the tongue becomes enlarged (macroglossia). Affected infants may also fail to gain weight and fail to grow at the expected rate (failure to thrive) and have breathing problems. Increasing weakness of the heart muscle leads to heart and respiratory failure. If untreated, this form of Pompe disease leads to death in the first year of life. This represents the most severe form of the disease.

Mental development does not seem to be affected.

Nonclassic Infantile Pompe Disease: Usually appears by one year of age. It is characterized by delayed motor skills (such as rolling over and sitting up), and progressive muscle weakness. The heart may be abnormally large (cardiomegaly), which may result in heart failure similar to the most severely affected infants; the rate of progression may not be as rapid…. Some have minimal to no cardiac involvement, with early muscle involvement as the primary presenting feature The muscle weakness can lead to serious breathing problems, and if untreated, children with this form of Pompe disease can live into early childhood.

Q: What are the signs and symptoms of late-onset Pompe disease?

A: Late-onset Pompe disease may not become apparent until later in childhood, adolescence, or adulthood. Some present as early as the first year of life. Late-onset Pompe disease is usually milder than the infantile forms of this disorder and is less likely to involve the heart. Most individuals with late-onset Pompe disease experience progressive muscle weakness, especially in the legs and the trunk, including the muscles that control breathing.

The first symptom is often a weakness of the legs or hips, which causes a swaying gait or waddle. People may have muscle aches and frequent falls. Babies may not learn to crawl, stand, walk, or meet other developmental milestones. As children get older they often develop a curvature of the spine: Lordosis (swayback), kyphosis (hunchback), or scoliosis (curved from side to side) that continues into adulthood.

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Children with Pompe disease may have trouble keeping up with other children their age when they do physical activities. Adults may tire easily or get winded after exercising or climbing stairs. Some have low back pain. Enlargement of the heart or liver, a classic symptom of infantile onset Pompe disease, is rarely seen in late-onset Pompe disease. As muscle weakness increases, patients often start to use wheelchairs and may require assisted ventilation. To learn more about assisted ventilation refer to the brochure titled Breathing Problems in Pompe Disease.

Pompe disease affects one of the most important muscles that we use for breathing - the diaphragm. The diaphragm is located just below the lungs and heart and separates the chest from the abdomen. As the diaphragm gets weaker, breathing becomes more difficult, especially while sleeping. Morning headaches and daytime sleepiness can result. In some cases, diaphragmatic weakness may be evident before any other significant weakness is noted

It is important to remember that everyone has disease progression at a different rate and some children and adults have milder symptoms than others. Adult-onset Pompe disease can present as late as the second to sixth decade of life.

Q: Is fatigue an important feature of late-onset Pompe disease?

A: Fatigue is a frequently experienced symptom in adults with Pompe disease and may have a disabling impact on the lives of patients. Until recently, fatigue in Pompe disease did not receive much attention and was not structurally assessed. Fatigue is widespread among both mildly and severely affected adult patients with Pompe disease. The Fatigue Severity Scale (FSS) appears a useful tool in assessing fatigue in Pompe disease. The FSS is designed to differentiate fatigue from clinical depression, since both share some of the same symptoms. The FSS consists of answering a short questionnaire that requires the subject to rate his or her own level of fatigue.

Besides symptoms related to weakness of the skeletal and respiratory muscles, non-motor problems such as fatigue can also have a deep and disabling impact on the patients' lives. Fatigue is difficult to define, as it is often a non-specific and subjective complaint. Two suggested definitions are 'extreme and persistent tiredness, weakness or exhaustion mental, physical or both' and 'difficulty in initiation of or sustaining voluntary activities'. Although fatigue is a frequent symptom in many chronic disorders, it has received little attention in Pompe disease and was only sporadically reported.
For the best possible treatment of fatigue it is important to know why it is so notably present in Pompe disease. In a recent review the contribution of 'central' and 'peripheral' components to fatigue in neurological disorders has been discussed. In Pompe disease, a peripheral cause of fatigue, resulting from muscle weakness, is perhaps the most likely explanation. Especially relevant with respect to fatigue in Pompe disease is weakness of the respiratory muscles. Respiratory insufficiency may lead to fragmented sleep, which in turn may lead to daytime sleepiness and fatigue.

Fatigue is highly prevalent among adult patients with Pompe disease. It is present in both mildly and severely affected patients and is independent of disease duration. The FSS appears a useful tool for the assessment of fatigue in adult patients with Pompe disease. Further research is needed to unravel the pathophysiological mechanism and to identify targets for fatigue management.

Q: Are pain and fatigue features of late-onset Pompe disease?

A: Although pain and fatigue are not specific for Pompe disease, they can have a strong impact on patients´ lives. Data from the IPA- Erasmus MC Pompe Survey showed that 76% of the participating patients suffered from fatigue and that 46% experienced pain 'often' or 'always' in one or more areas of the body, mostly in the upper arms and legs.

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Not much further research has been performed on pain in Pompe disease, while fatigue in adult patients was studied in more detail using the Fatigue Severity Scale (FSS). It turned out that fatigue was not only present among severely affected patients, but also among patients who were still mildly affected by the disease and had limited other complaints. It is important to note that fatigue is also an important first symptom among adult patients with Pompe disease.

To identify the best possible treatment of fatigue one first needs to know why it is such an important symptom in Pompe disease. In a recent review it is discussed that fatigue in Pompe disease is most likely caused by muscle weakness, leading to increased muscle fatigability. However, patient do also experience a more generalized sense of fatigue, possible initiated by feedback mechanisms from the brain to prevent excessive physical strain. As little is known about the cause of fatigue in Pompe disease, further research on this topic is needed.

Especially relevant with respect to fatigue in Pompe disease is weakness of the respiratory muscles. Respiratory insufficiency may lead to fragmented sleep, which in turn may lead to daytime sleepiness and fatigue. Pulmonary function testing in sitting and supine position is therefore indicated in patients with excessive fatigue, as well as a sleep study (polysomnography) to detect whether nightly hypoventilation or other sleep disorders could cause the present symptoms of fatigue.

Q: Why does it sometimes take so long to get the right diagnosis?

A: Pompe disease is very rare, affecting about 1 in 40,000 people. The infantile form of the disease may be easier to recognize because the unique symptoms point toward a specific diagnosis.

Recognizing Pompe disease can be challenging as signs and symptoms may be diverse and shared with those of other disorders, such as Werdnig-Hoffmann disease, Polymyositis, Becker / Duchene muscular dystrophy, or limb-girdle muscular dystrophy. Diagnostic delays have been reported to average 7 years in older children and adults. A diagnosis of Pompe disease can be confirmed by measuring acid alpha-glucosidase (GAA) enzyme activity. It is now possible to accurately measure GAA activity in dried blood spots, mixed leukocytes, and lymphocytes

Q: What health problems may occur with Pompe disease?

A: The progressive muscle weakness and breathing problems caused by Pompe disease can increase the risk for respiratory infections, sleep apnea (pauses in breathing while asleep), and difficulty in swallowing (dysphagia), as well as scoliosis, contractures (muscle tightness), and lower back pain. To learn more about the health problems caused by Pompe disease, refer the brochure titled Common Medical Concerns.

Q: Is there a cure for Pompe disease?

A: While we do not yet have a cure for Pompe disease, there is an effective treatment called Myozyme that is commercially available in many countries worldwide. Myozyme is marketed inside the United States (US) as both Myozyme (160L) and Lumizyme (4000L).

The name change from Myozyme to Lumizyme was based on the US Food and Drug Administration (FDA) determination that the Myozyme produced in the larger scale (4000L) possessed slightly different biochemical characteristics than the original Myozyme produced in the smaller scale (160L), and should therefore be classified as a different drug with a different name. The Pompe Connection brochures will refer to both Myozyme and Lumizyme as just Myozyme.

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Researchers are also studying other ways to slow the progression of symptoms or cure the disease. For more on these approaches, see the brochure titled Medical Progress in Pompe Disease). Supportive therapies are also available to help manage the symptoms of the disease. Such therapies may bring comfort and relief and help people live their lives as fully as possible.

Where to Learn More:

These sources can answer more of your questions about Pompe disease:

- The International Pompe Association (IPA) is a global federation of Pompe disease patient groups. The IPA helps patients, family members, and healthcare providers from around the world share their experiences and knowledge across continents and cultures. To find the contact for your country, visit the IPA Web site at www.worldpompe.org

- Understanding Pompe Disease is a free booklet that gives a good introduction to Pompe disease. It is available on Genzyme's Pompe Community Website at www.pompe.com.

- The Physicians Guide to Pompe Disease can be ordered from the National Organization for Rare Disorders (NORD) at www.rarediseases.org/programs/pompe_brochure.html.

- American College of Medical Genetics (ACMG) Practical Guideline: Pompe Disease Diagnosis and Management Guideline 2006. Vol. 8. No. 5. The *ACMG guidelines were designed as an educational resource for physicians and other health care providers.*

- Genetics Home Reference: Your Guide to Understanding Genetic Conditions http://ghr.nlm.nih.gov/gene/GAA.

- Center for Lysosomal and Metabolic Diseases Erasmus MC University Medical Center www.erasmusmc.nl/.

- Acid Maltase Deficiency Association (AMDA): The AMDA was formed to assist in funding research and to promote public awareness of Acid Maltase Deficiency, also known as Pompe's Disease. Visit the website www.amda-pompe.org.

- The Genzyme Corporation's Pompe Community website offers the Pompe community comprehensive information on the disease, as well as resources and support to help manage the challenges it may bring www.pompe.com.

- Medical Centers Specializing in Neuromuscular Disorders:
  To locate medical centers that specialize in treating neuromuscular disorders, contact the Neuromuscular disorders (NMD) association for your country.
  - In the United States, contact the Muscular Dystrophy Association (MDA) at www.mdausa.org/clinics.
  - In Europe, contact the European (EAMDA) at Web site www.eamda.net.
  - In other continents, visit the World Alliance of Neuromuscular Disorder Associations (WANDA) at Web site www.wandaweb.org and click on Your Country.

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- GSDNet: Join the GSDNet Listserv to exchange emails with people around the world living with Pompe disease. To subscribe to GSDNet by email:
  "To" Line: Type the following onto the "To" Line: listserv@listserv.icors.org
  "CC" Line: Leave the CC line blank
  "Subject" Line: Leave the subject line blank.
  Email Message: Type the following message into the body of the email: Subscribe GSDNet <add your name>

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