

THE NATIONAL ORGANIZATION FOR RARE DISORDERS (NORD)<sup>®</sup>

# THE PHYSICIAN'S GUIDE TO POMPE DISEASE



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Organization for  
Rare Disorders  
(NORD)<sup>®</sup>

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... out of the darkness,  
into the light...<sup>®</sup>

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Acid Maltase Deficiency Association.



Tiffany House today

For more information about NORD's programs and services, contact:

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Note: You can access information about more than 1,100 rare disorders through NORD's online Rare Disease Database at [www.rarediseases.org](http://www.rarediseases.org).

Cover photo: Tiffany House at age 12



## INTRODUCTION

In 1995 at the age of twelve, Tiffany House was diagnosed with Pompe Disease, a rare, progressive, metabolic disorder. At that time, her parents were told that there was no treatment or cure for Pompe Disease and that Tiffany probably would not live beyond her second decade.

Today, Tiffany is part of an investigational study and is receiving enzyme replacement therapy. While she and her family continue to battle with the effects of her disease, they are not without hope. It now seems possible that enzyme replacement may soon result in an approved therapy for this once untreatable disease.

The House family's story illustrates a common theme among patients with rare diseases. The family endured several years of frustration and followed many dead-end roads before receiving an accurate diagnosis for Tiffany. This is an anguishing and costly experience for families.

Tiffany House received her diagnosis just as a promising new avenue of research was opening up. She was able to participate in the first delayed onset clinical trial with enzyme replacement therapy, which was based in The Netherlands. Without a proper diagnosis that would not have been possible for her.

This booklet is part of a series on rare diseases provided by NORD, free of charge, to medical professionals in the hope of encouraging early recognition of rare diseases and the appropriate referral to sources of help. NORD and the Acid Maltase Deficiency Association are grateful for the interest of medical professionals in Pompe Disease and other rare diseases.

*If you would like additional copies of this booklet, please contact NORD, and we will be happy to send them to you.*

## WHAT IS POMPE DISEASE?

Pompe Disease is a hereditary metabolic disorder caused by the complete or partial deficiency of the enzyme, acid alpha-glucosidase (also known as lysosomal alpha-glucosidase or acid maltase). This enzyme deficiency causes excess amounts of glycogen to accumulate in the lysosomes of many cell types but predominantly in muscle cells. The resulting cellular damage manifests as muscle weakness and/or respiratory difficulty.

There are 49 rare genetic disorders known as Lysosomal Storage Diseases (LSD), and Pompe Disease is one of them. It is also classified as Glycogen Storage Disease Type II (GSD II).

### SYNONYMS

Acid Maltase Deficiency (AMD)  
Acid alpha-Glucosidase Deficiency  
Lysosomal alpha-Glucosidase Deficiency  
Glycogen Storage Disease Type II (GSD II)

*Entry # 232300 in McKusick's catalogue: Mendelian Inheritance in Man (OMIM):*

*Gene symbol: GAA (glucosidase-acid-alpha)*

## POMPE DISEASE IS CROSS CULTURAL

The disease occurs around the world in different countries, populations, and ethnic groups. The estimates of disease incidence vary by the study and by the country. In the United States and in The Netherlands, an incidence of 1 in 40,000 births is probably realistic. Males and females are affected in equal numbers.

## CAUSE OF POMPE DISEASE

This inborn error of metabolism is caused by a complete or partial deficiency of the enzyme **acid alpha-glucosidase** that normally breaks down the lysosomal glycogen into glucose. Glycogen, therefore, accumulates within the lysosomes of several tissues (mainly the muscles), interferes with cellular function, and causes cell damage. In the delayed onset form, typically, effects are seen in the skeletal and respiratory muscles of the patient. In the infantile form where the patient has a complete enzyme deficiency, glycogen also accumulates in the heart.

Pompe Disease is inherited as an autosomal recessive genetic trait. More than 100 different mutations in the acid alpha-glucosidase gene (GAA) have been identified in families with this disorder.

A **mutation database** is accessible at:

**Web:** <http://www.pompecenter.nl>

## SPECTRUM OF CLINICAL SUBTYPES

Pompe Disease has an **infantile** form and a **delayed onset** form. The delayed onset form may be further broken down into a **childhood** form and a **juvenile/adult** form.

Severity and progression of the disease varies depending upon the age of onset and the degree of enzyme deficiency <sup>1,3</sup>.

## SYMPTOMS OF POMPE DISEASE

### INFANTILE FORM

Patients with the infantile form are the most severely affected. Although these infants usually appear normal at birth, the disease presents within the first two or three months of life with rapidly progressive muscle weakness, hypotonia, and hypertrophic cardiomyopathy. Many patients have a protruding tongue and a moderate enlargement of the liver. Infants appear "floppy" and are unable to move their arms and legs properly. The legs often lay in "frog-position" and feel firm on palpation (pseudo-hypertrophy). Feeding problems and respiratory difficulties, which are often combined with respiratory tract infections, are common. Major developmental milestones such as rolling-over, sitting, and standing are not achieved. The mental development is normal. Death typically occurs within the first year of life as a result of cardiorespiratory failure. The infantile form of Pompe Disease is characterized by a total lack of alpha-glucosidase activity and by a rapid build-up of glycogen in skeletal muscle and in the heart.

### Key Features

Early onset (within 6 months)  
Generalized muscle weakness

- Slipping through
- Axial hypotonia
- Head-lag

Hypertrophic cardiomyopathy  
Feeding problems

Respiratory difficulties  
Delayed motor milestones  
Rapidly progressive

#### **Additional Features**

Hepatomegaly (moderate)  
Macroglossia (often)

#### **DELAYED ONSET FORMS**

The time of presentation of the delayed onset form of Pompe Disease varies from the first to the seventh decade. Patients who develop symptoms early in life tend to be the more severely affected. Delayed onset patients have residual acid alpha-glucosidase activity. Glycogen build-up is not as rapid as in the infantile form, but the disease is progressive and can greatly affect the quality of life and decrease the lifespan of the affected person. The delayed onset form is subdivided into childhood and juvenile/adult subforms.

#### **Childhood Form**

Typically, the childhood form presents during infancy or early childhood as a myopathy. Motor milestones may be delayed, and some symptoms may resemble muscular dystrophy. Cardiac enlargement, which is a main characteristic of the infantile form, is infrequent in this form. The extent of organ involvement is variable. This form of the disease progresses more slowly than the infantile form. Progressive weakness, swallowing difficulty, severe respiratory failure, and shortened life expectancy are the pattern of this form.

#### **Key Features**

Onset within first 3 years of life  
Delayed motor milestones  
Swallowing difficulty  
Respiratory failure (frequent respiratory tract infections)  
Severely progressive  
Muscle weakness

- Mostly proximal
- Lower limbs more affected than upper limbs

#### **Additional Features**

Cardiomegaly (infrequent)  
Muscles feel firm on palpation

#### **Juvenile/Adult Form**

The juvenile/adult form presents between the first and seventh decades as a slowly progressive myopathic limb-girdle syndrome or with symptoms of respiratory insufficiency. The pattern of limb-girdle muscle weakness exhibited is similar to that found in other chronic muscle disorders. Development of scoliosis as well as contractures may occur in juvenile patients. This form of the disorder is slowly progressive without cardiac involvement, and life expectancy varies from shortened to normal. Approximately one-third of the adult cases present with respiratory failure. The initial symptoms of respiratory insufficiency include: headache at night or upon awakening, sleeping difficulty, nausea, orthopnea, and exertional dyspnea. Respiratory muscle involvement eventually occurs in all cases, and respiratory failure is the usual cause of death.

#### **Key Features**

Onset between 1st and 7th decades  
Waddling gait  
Gower sign  
Slowly progressive  
Muscle weakness

- Mostly proximal
- Lower limbs more affected than upper limbs
- Paraspinal muscles often involved

Respiratory difficulties  
(often combined with respiratory tract infections)

- Obstructive sleep apnea
- Exertional dyspnea
- Morning headache

#### **Additional Features**

Swallowing difficulty  
Urinary incontinence may occur  
Scoliosis may occur

## DIFFERENTIAL DIAGNOSIS

Pompe Disease in infants may be misdiagnosed as Werdnig-Hoffman disease (progressive spinal muscular atrophy) or progressive muscular dystrophy. In older children and adults Pompe Disease may be misdiagnosed as polymyositis.

## ROUTINE LABORATORY TESTS

The following abnormalities are found:

- Serum CK (frequently elevated)
- ASAT/ALAT/LDH (frequently elevated)
- Oligosaccharides in urine (frequent in infantile form; infrequent in adult form)

## BIOCHEMICAL DIAGNOSIS

The ultimate diagnosis should be based on the finding of acid alpha-glucosidase deficiency in suitable cells and/or tissues (see below) or on the finding of proven pathogenic mutations in both copies of the acid alpha-glucosidase gene (mutant alleles) if enzyme assay cannot be performed.

**Fibroblast cultures** established from skin biopsies are the preferable material for measuring the acid alpha-glucosidase activity because the activity of this cell type is relatively high (under confluent culture conditions).

When expressed as a percentage of the average normal value, the acid alpha-glucosidase activity of affected individuals is routinely:

Infantile form:	< 2 %
Childhood form:	1 - 5 %
Juvenile/Adult forms:	5 -25 %
Carriers:	25-75 %

The acid alpha-glucosidase activity assay performed on **muscle biopsy** specimens is less sensitive and less suitable for the detection of low levels of residual acid alpha-glucosidase activity, but it can be used for diagnostic purposes.

*(The use of 4-methylumbelliferyl-alpha-D-glucopyranoside, as an artificial substrate, provides a sensitive and convenient method for assay of fibroblasts as well as muscle biopsy specimens, but the substrates maltose or glycogen can be used as well).*

**Leukocytes** are often used as a primary cell source for diagnostic purposes, but the results are error-prone.

*(4-Methylumbelliferyl-alpha-D-glucopyranoside cannot be used for this cell type due to interfering neutral alpha-glucosidase activities. Glycogen as substrate bears the problem that statistically 1 in 16 (Caucasian) individuals carries an acid alpha-glucosidase pseudodeficiency allele with low activity for glycogen. As a consequence, acid alpha-glucosidase deficiency in leukocytes needs to be confirmed by repeating the assay on fibroblasts or by mutation analysis with DNA extracted from the leukocytes).*

## MUSCLE PATHOLOGY

If a **muscle biopsy** is taken, it may reveal the following abnormalities:

### ROUTINE HE STAINING:

- "Lace-work pattern" in infantile, childhood, and advanced stages of juvenile/adult forms of Pompe Disease due to (large) vacuoles disrupting the regular architecture of the contractile elements.
- Vacuolar myopathy in juvenile/adult forms of Pompe Disease, but the morphology may appear normal.

**PAS STAINING** – after fixation with glutaraldehyde and GMA embedding:

- Strong PAS positive (diastase sensitive) staining of most muscle fibers in infantile Pompe Disease
- PAS positive staining of vacuoles in delayed onset forms of Pompe Disease, **but the PAS staining may not be evident in all muscle groups and/or bundles.**

### ACID PHOSPHATASE STAINING:

- The vacuoles in affected muscle fibers usually have elevated acid phosphatase activity.

## A DIAGNOSTIC PROTOCOL

Ausems et al. have formulated a diagnostic protocol for juvenile and adult patients presenting with a slowly progressive limb-girdle weakness or a respiratory insufficiency. This protocol postpones the taking of a muscle biopsy and starts with the measurement of serum CK activity. When the CK activity is elevated, Pompe Disease needs to be considered. If fibroblasts are not available, the acid alpha-glucosidase activity in leukocytes can be measured (with glycogen as substrate). When a deficiency of acid alpha-glucosidase is found, it needs to be confirmed or rejected by assay of acid alpha-glucosidase activity on fibroblasts **in which case a muscle biopsy is not required for the diagnosis of Pompe Disease.**

## PRENATAL DIAGNOSIS, CARRIER DETECTION AND GENETIC COUNSELING

Prenatal diagnosis is available for pregnancies at risk for Pompe Disease. The preferred method is assay of uncultured chorionic villi for acid alpha-glucosidase activity using the artificial substrate. Chorionic villus sampling can be performed as early as 12 weeks gestation, and diagnosis can be

determined within one day after sampling. Cultured amniotic fluid cells can also be used for prenatal diagnosis, but enzyme activity is lower in amniocytes than in chorionic villi, and results are generally not available until later in pregnancy (e.g. 19th week).

The preferred method of prenatal diagnosis for pregnancies at risk for juvenile/adult onset Pompe Disease is DNA analysis for the previously documented familial mutations in the acid alpha-glucosidase gene (GAA). The enzyme assay does not allow accurate distinction between affected and carrier status for this form of the disorder. Prenatal diagnosis for adult onset conditions is strongly discouraged by the American College of Medical Genetics.

Carrier testing for all forms of Pompe Disease requires DNA analysis. The enzyme assay is not an accurate test to distinguish carriers.

Before genetic testing is initiated, the patient should be advised to consult with a genetic counselor.

## TREATMENT OF POMPE DISEASE

Standard therapy, currently, is symptomatic and supportive, but there are promising investigational therapies under review.

## SUPPORTIVE TREATMENT

Due to the very severe and rapidly progressive nature of infantile Pompe Disease, the course of this form of the disease cannot be changed substantially by supportive treatment only.

There are reports suggesting that a subset of patients with delayed onset forms of Pompe Disease may benefit from a high-protein diet or from L-alanine supplementation<sup>64</sup>. The purpose of the dietary intervention is to prevent excessive muscle protein turnover and catabolism. Respiratory support during the night or periods of the day, or during respiratory tract infections, improves the quality of life. Continuous ventilation via tracheostomy may be required in an advanced stage of the disease. Moderate daily exercise is advised if the condition allows. Attention has to be given to the potential development of scoliosis and contractures; corrective intervention may be required.

## INVESTIGATIONAL THERAPIES

The therapeutic interventions that have been considered for Pompe Disease include:

- Bone marrow transplantation
- Gene therapy
- Enzyme replacement therapy

### BONE MARROW TRANSPLANTATION

Bone marrow transplantation has been investigated in humans and cattle with Pompe Disease in the hope that it would provide a permanent source of enzyme. However, the results to date have been disappointing.

### GENE THERAPY

Pilot studies have demonstrated the feasibility in principle of gene therapy as a permanent, internal source of the missing enzyme, but many obstacles remain to be overcome before clinical application becomes a reality.

### ENZYME REPLACEMENT THERAPY

In January 1999, the first clinical study of the safety and efficacy of recombinant human alpha-glucosidase from rabbit's milk started at the Sophia Children's Hospital in Rotterdam, The Netherlands. Four infants received treatment in an infantile clinical trial and three juveniles received treatment in a delayed onset clinical trial<sup>65</sup>.

In May another clinical study began at Duke University in North Carolina in which recombinant human alpha-glucosidase from Chinese hamster ovary cells was tested. Three infantile patients participated in the Duke University trial<sup>66</sup>.

Currently, there are eight sites at which patients with Pompe Disease receive enzyme replacement therapy, experimentally, with the aim of testing the methods' safety and efficacy. The recombinant human acid alpha-glucosidase used in these studies is currently supplied by Genzyme Corporation of Cambridge, Massachusetts. Genzyme plans to launch expanded clinical trials at additional sites in 2003 and hopes to have an approved product available for marketing in the United States and Europe in 2005.

**Genzyme Corporation**  
One Kendall Square  
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Telephone: (617) 252-7605

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## RESOURCES

### AMDA

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### OTHER WEB SITES OF INTEREST MAY BE FOUND AT:

<http://www.amda-pompe.org/other.htm>

*This booklet was produced by the Acid Maltase Deficiency Association and the National Organization for Rare Disorders.*



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The **Pompe Center** was established to generate, collect, and forward relevant information that is important for the understanding of Pompe Disease from a molecular, clinical, and therapeutic aspect.

**The Pompe Center**

Erasmus MC  
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