

The Physician's Guide to
Pompe Disease
(Glycogen Storage Disease, Type II;
Acid Maltase Deficiency)

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INTRODUCTION

POMPE DISEASE (GLYCOGEN STORAGE DISEASE, TYPE II; ACID MALTASE DEFICIENCY)



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 thirty. While she and her family continue to battle with the effects of her disease, they now have hope. In 2006, the Food and Drug Administration (FDA) approved an enzyme replacement therapy for Pompe disease.

The House family's story illustrates a common theme among patients with rare diseases. The family endured nearly a decade of frustration and followed many dead-ends before receiving an accurate diagnosis for Tiffany. This is an agonizing and costly experience for families, and it is imperative that these delays in diagnosis are prevented. Therefore, in 1995 the House family founded the Acid Maltase Deficiency Association (AMDA) to promote research and increase awareness of Pompe disease.

Tiffany House received her diagnosis just as promising new avenues of research were opening up. In 1999 she was able to participate in the first successful late-onset clinical trial with enzyme replacement therapy, which

was conducted at Erasmus University Medical Center in Rotterdam, the Netherlands. Without a proper diagnosis that would not have been possible for her.

This guide 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 AMDA are grateful for the interest of medical professionals in Pompe disease and other rare disorders.

What is Pompe Disease?

Pompe disease is an autosomal recessively inherited metabolic disorder that affects one of more than 40 lysosomal enzymes. Patients with Pompe disease have a total absence or partial deficiency of the lysosomal enzyme acid α -glucosidase (GAA) due to mutations in the GAA gene. As a result, the body is unable to breakdown lysosomal glycogen, which leads to massive glycogen accumulation and cellular dysfunction, with prominent involvement of cardiac, smooth, and skeletal muscle ^[1].

Pompe disease can present in infancy, childhood, adolescence or adulthood. In the most severe form – infantile-onset Pompe disease (IOPD) – newborns typically present within the first few months of life (always by one year) with significant muscular hypotonia (e.g. “floppy baby syndrome”), severe cardiomegaly and cardiomyopathy, failure to thrive, feeding difficulties, and progressive respiratory insufficiency. Without treatment, cardio-respiratory failure usually leads to death within the first two years of life ^[2].

Patients with late-onset Pompe disease (LOPD) present any time after 12 months of age, typically with a progressive, proximal skeletal myopathy and variable degrees of respiratory weakness, but little or no cardiac disease. Clinical heterogeneity is significant in LOPD, but in all cases, the disease is progressive and often leads to significant morbidity (e.g., wheelchair and ventilator dependency) and early mortality ^[4]. Patients with LOPD can present with signs and symptoms similar to many other neuromuscular conditions; however, early respiratory involvement with myopathy may help raise clinical suspicion of Pompe disease ^[3]. The initial symptoms of respiratory insufficiency include: headache at night or in the morning, sleeping difficulty, nausea, orthopnea, and exertional dyspnea. Respiratory muscle involvement eventually occurs in all cases ^[4].

Synonyms for Pompe Disease

glycogen storage disease type II (GSD II)

acid a-glucosidase deficiency (GAA)

acid maltase deficiency (AMD)

Incidence of Pompe Disease

Pompe disease occurs in all countries, populations, and ethnic groups around the world. The combined incidence is approximately 1 in 40,000, although the true prevalence of the disease is unknown, as many late-onset cases are under- or misdiagnosed ^[5].

Pathophysiology of Pompe Disease

Complete deficiency of the GAA enzyme (activity <1% of normal controls) leads to the severe infantile-onset form of the disease. GAA enzyme activity of 2% to 40% is associated with some residual enzyme function and a later disease onset ^[6]. However, Pompe disease is progressive in patients of all ages. The excessive accumulation of lysosomal glycogen disrupts cellular functions, causes cell damage, and leads to clinical manifestations such as proximal (greater than distal) myopathy and respiratory muscle weakness. Significant cardiac abnormalities – massive cardiomegaly and hypertrophic cardiomyopathy – are common only in the infantile-onset form of the disease.

Symptoms and Signs

The clinical spectrum of Pompe disease is continuous and broad. In the severe, infantile onset cases, signs and symptoms usually present within the first months of life. In many late-onset patients, symptoms may not develop (or be brought to clinical attention) for several years or decades. Initial signs and symptoms in children and adults may be subtle (such as having difficulty rising from a chair or climbing stairs, or morning headaches and fatigue), but the severity of symptoms and the rate of progression will vary from person to person. Disease expression is modified by the age of onset, underlying genetic mutations, and as-of-yet unknown genetic and environmental interactions. Table 1 presents clinical symptoms typical of infantile versus late-onset Pompe disease. Given the clinical heterogeneity of Pompe disease, (particularly in the late onset form) not all patients will have all signs and symptoms.

Table 1. Signs and Symptoms of Pompe Disease

Infantile Onset Pompe Disease (onset < 1 yr.)	Late Onset Pompe Disease (onset >1 yr. to 7th decade)
<ul style="list-style-type: none"> • Absent or delayed motor milestones • Severe hypotonia • Cardiomegaly and cardiomyopathy • Feeding and swallowing difficulties • Respiratory dysfunction • Hepatomegaly (moderate) • Failure to thrive • Macroglossia • Hearing deficit 	<p>Limb-girdle weakness</p> <ul style="list-style-type: none"> • Waddling gait • Gower sign • Trendelenburg sign <p>Muscle weakness</p> <ul style="list-style-type: none"> • Mostly proximal • Lower limbs more affected than upper limbs • Paraspinal and neck muscles often involved <p>Respiratory difficulties (often combined with respiratory tract infections)</p> <ul style="list-style-type: none"> • Sleep apnea / sleep-disordered breathing • Exertional dyspnea • Morning headache <p>Additional Features</p> <ul style="list-style-type: none"> • Fatigue • Delayed milestones (in children affected early) • Scoliosis (extra risk in puberty) • Contractures (extra risk in childhood) • Scapular winging (often) • Ptosis (often) • Macroglossia • Difficulty chewing/swallowing • Muscle cramps • Diarrhea • Left ventricular hypertrophy (occasional, mild, and sometimes transient)

Causes

Pompe disease is inherited in an autosomal recessive manner, which means that affected individuals must have two abnormal copies of the GAA gene (one on each chromosome 17 at 17q25.2-25.3). Two carrier parents have a 25% chance (1 in 4) of having an affected child with each pregnancy. If a person with Pompe disease has children (with an unaffected spouse), all of his or her children will be asymptomatic carriers. At present, more than 300 different pathogenic sequence variations have been identified in the GAA gene, many belonging to only one family. However, some individuals are homozygous for a pseudodeficiency allele [c.1726 G>A (p. Gly576Ser)] (relatively common in the Asian population), which can complicate diagnostic confirmation; yet, more sensitive assays using dried blood spots have been developed to distinguish the pseudodeficiency alleles from disease-causing mutations^[7].

Differential Diagnoses

Pompe disease can masquerade as several other neuromuscular disorders due to overlapping signs and symptoms. Several differential diagnoses are briefly described below ^[8].

Infantile-onset Pompe disease

- Werdnig-Hoffman disease (spinal muscular atrophy I): hypotonia, feeding difficulties, progressive proximal muscle weakness, but no cardiac involvement. Autosomal recessive.
- Danon disease: hypotonia, hypertrophic cardiomyopathy, and myopathy from excessive glycogen storage due to a mutation in lysosome-associated membrane protein 2 (LAMP2). Primarily affects males. X-linked.
- Glycogen storage disease IIIa: hypotonia, cardiomegaly muscle weakness, elevated creatine kinase (CK), non-ketotic hypoglycemia* with more dramatic liver involvement than usually seen in Pompe disease. Autosomal recessive.
- Glycogen storage disease type IV: hypotonia, cardiomegaly, muscle weakness, elevated CK, with more dramatic liver involvement than usually seen in Pompe disease. Autosomal recessive.
- Endocardial fibroelastosis: respiratory and feeding difficulties, cardiomegaly, and heart failure without significant muscle weakness. May be viral or familial with X-linked, autosomal dominant, or autosomal recessive inheritance.

Late-onset Pompe disease

- Facioscapulohumeral muscular dystrophy (FSHD): slowly progressive, asymmetric muscle weakness usually starting in the face and progressing to the shoulder girdle, abdominal, and leg muscles. Autosomal dominant.
- Polymyositis: progressive, symmetric, unexplained muscle weakness.
- Limb-girdle muscular dystrophy: progressive muscle weakness in the legs, pelvis and shoulders, but sparing the truncal muscles.
- Duchenne-Becker muscular dystrophy: progressive proximal muscle weakness, respiratory insufficiency, and difficulty ambulating. Primarily affects males. X-linked.
- Glycogen storage disease type V (McArdle disease): elevated CK and muscle cramping with exertion. Autosomal recessive.

- Glycogen storage disease type VI: hypotonia, hepatomegaly, muscle weakness, hypoglycemia* and elevated CK. Autosomal recessive.

*Patients with Pompe disease do not present with hypoglycemia or other metabolic decompensations characteristic of other glycogen storage disorders^[9].

Diagnosis

Enzymatic and Molecular Diagnosis

Blood-based assays of GAA enzyme activity (via whole blood or dried blood spots) are a reliable and convenient method for diagnosing and screening patients for Pompe disease and should be used as a first-tier tests^[10, 11].

Diagnosis based on a blood-based assay must be confirmed by another method, preferably GAA gene sequencing, or by a separate blood or tissue sample^[12]. Skin and muscle biopsies may be used, but are not necessary, and can take weeks to process, thereby delaying the initiation of treatment. Pros and cons for various enzymatic and molecular diagnostic methods are outlined in Table 2 below.

Table 2. Enzymatic and molecular diagnostic methods

Sample Type (collection)	Turn-around	Utility/Comments
Blood (whole or dried blood spot)	2-10 d	<ul style="list-style-type: none"> • Is minimally invasive • Has rapid turnaround time and is inexpensive • Whole blood or dried blood spot can be shipped, as sample submitted will be tested as a dried blood spot • Assay employed may use acarbose to remove interference by an α-glucosidase isoenzyme • May preclude the need for more invasive tests (skin or muscle biopsy)
Lymphocytes (blood draw)	7-10 d	<ul style="list-style-type: none"> • May preclude the need for invasive skin or muscle biopsy sample • Has rapid turnaround time
Fibroblasts (skin biopsy)	4-6 wk	<ul style="list-style-type: none"> • May preclude the need for invasive muscle biopsy sample • Requires 4-6 wk of cell culture • If culture is not successful, results will be delayed
Muscle tissue (muscle biopsy)	1-4 wk	<ul style="list-style-type: none"> • Is invasive and can require general anesthesia* • Does not require cell culture • Sample must be frozen in liquid nitrogen and shipped on dry ice

* Anesthesia is not recommended unless absolutely necessary for patients with Pompe disease due to reduced cardiovascular return and underlying respiratory insufficiency^[8].

Routine Laboratory Tests

As part of the diagnostic work-up, laboratory tests may be suggestive of Pompe disease if they reveal elevated levels of biochemical markers related to pathologic processes and muscular degeneration. However, it is important to note that normal laboratory levels do not rule out a diagnosis of Pompe disease or the need for the GAA enzyme assay.

- Serum CK (often elevated)
- aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) / lactate dehydrogenase (LDH) (all often elevated)
- Oligosaccharides (Glc4) in urine (often elevated in IOPD; less so in LOPD)

Muscle Pathology

The proximal muscle weakness commonly observed in Pompe disease can be indicative of a number of other, more common muscle diseases, so biopsies are frequently carried out at an early stage. However, unlike the obvious infantile-onset pathology, normal muscle glycogen is reported in up to 20% of children and adults with Pompe disease, who exhibit widely variable degrees of glycogen accumulation and vacuolar myopathy [13]. For that reason, a positive result for vacuolar myopathy on a muscle biopsy can confirm the diagnosis of Pompe disease, but a negative result cannot rule out the diagnosis.

Routine hematoxylin and eosin staining

- “Lace-work pattern” in infantile, childhood and advanced stages of juvenile/adult Pompe disease due to vacuolar inclusions in the muscle fibers.
- Vacuolar myopathy in juvenile/adult Pompe disease, but can be difficult to detect.

Periodic acid-Schiff staining (after fixation with glutaraldehyde and GMA embedding)

- Strong PAS positive (diastase-resistant) staining of muscle fibers in infantile Pompe disease.
- PAS positive inclusions in other forms of Pompe disease, but not necessarily present in all muscle fibers, or all muscle bundles.

Acid phosphatase staining

- Fibers with elevated activity are almost always encountered.

Carrier Testing, Prenatal Diagnosis, and Genetic Counseling

All affected families should be advised to consult a genetic counselor. Genetic counselors will provide families with information on the mode of inheritance, risks to other family members, and can discuss the natural history, treatment, and available support and advocacy resources.

Confirmation of Pompe Disease in Members of Affected Families

Carrier testing in all forms of Pompe disease requires DNA analysis because GAA enzyme activity in fibroblasts, muscle, or peripheral blood is unreliable due to overlap in residual enzyme activity levels between carriers and the general population^[8]. Informed consent will be requested for all individuals who decide to undergo molecular genetic testing.

If a mutation (or mutations) is identified, prenatal diagnosis can be performed via chorionic villi sampling (at 10 to 12 weeks gestation) or amniocentesis (at 15 to 18 weeks gestation). GAA activity can also be measured in uncultured chorionic villi or amniocytes, but molecular testing is the preferred method when familial mutations are known^[14]. Pre-implantation genetic diagnosis (PGD) may also be available to families when familial mutations have been identified. Prenatal testing cannot, however, predict the age of onset, clinical course, or degree of disability^[8].

Due to the availability and efficacy of treatment, plus technological advances that have made high-throughput screening of dried blood spots feasible, Taiwan, the US, and several other countries have included Pompe disease in pilot studies of expanded newborn screening (NBS) panels^[15-18]. To date, NBS for Pompe disease has not been adopted, although in the coming years this remains a possibility.

Treatment

In 2006, enzyme replacement therapy (ERT) for Pompe disease (Myozyme®) was approved in the USA, Europe, and Canada, with subsequent approval in countries around the world. (In the US, Myozyme® is for patients younger than 8 years, and Lumizyme® is for patients older than 8 years of age. Genzyme Corp., Cambridge, MA). In all patients, enzyme replacement therapy is recommended every two weeks via intravenous administration of recombinant human acid a-glucosidase at a dose of 20 mg/kg body weight.

ERT for infantile-onset Pompe disease

Data from clinical trials has shown that treatment with Myozyme – particularly when initiated prior to irreversible muscle damage^[19,20] – markedly extends survival and invasive ventilation-free survival, improves cardiomyopathy, and makes it possible for many infants and children with Pompe disease to attain developmental milestones and levels of function never before possible, including walking and running^[20-22].

A subset of infantile-onset patients – approximately 20% – lack cross-reactive immunologic material (CRIM-). Because they produce no endogenous GAA enzyme, they develop high levels of IgG antibodies to exogenous enzyme, which renders ERT ineffective^[20,23]. Compared to CRIM+ patients, CRIM- patients seroconvert quickly (~ 4 weeks), regress in motor milestones, and decline clinically, culminating in invasive ventilation and death^[24,25]. However, immunomodulation protocols that prevent or eliminate immune responses to rhGAA allow CRIM- patients to reap the benefits of ERT. Tolerance has been induced prophylactically with simultaneous initiation of ERT (using a short rituximab with methotrexate regimen, as well as other combinations, thereby avoiding prolonged immune suppression). Therefore, knowing CRIM status as quickly as possible is of utmost importance for improving outcomes^[26].

Emerging phenotype of infantile-onset Pompe disease on long-term ERT

The first cohort of infantile Pompe patients treated with long-term ERT is now entering adolescence^[27], and a new phenotype is emerging that is distinct from untreated historical controls, as well as from late-onset Pompe disease. Dysphagia, speech disorders^[28], increased susceptibility to fractures^[29], deterioration of specific muscles in the neck, hip and foot^[27], hearing loss^[30], and arrhythmias following anesthesia^[31] have since received clinical attention in this cohort of patients. With their continued survival, the long-term nature of the disease, new management challenges, and potential new interventions are only now being explored.

ERT for late-onset Pompe disease

In patients with LOPD, clinical trial data and several recent studies have shown that ERT improves motor function (usually measured by the 6-minute walk test) and stabilizes or slightly improves respiratory function (usually measured by percent predicted forced vital capacity; FVC)^[32-34]. The benefits of ERT have been further reported in long-term, open label studies that showed

that alglucosidase alfa treatment stabilizes the progressive natural course of Pompe disease in many adult patients within a 36 month follow-up period^[35]. These results have also been corroborated in a 4-year study of Pompe patients, which is the largest cohort of late-onset patients undergoing ERT to date^[36]. In contrast to stabilization, pulmonary and muscle function progressively, relentlessly decline in untreated LOPD patients^[4].

Supportive Regimens

Management of Pompe disease includes a combination of disease-specific treatment and supportive regimens. Because patients with Pompe disease can have a wide range of clinical manifestations and functional impairment, they are best followed by a multidisciplinary team.

Respiratory support

This is one of the most important aspects of Pompe management, as most patients have some degree of respiratory compromise and respiratory failure is the most common cause of death in children and adults with the disease^[13]. Physical therapy may help to strengthen respiratory muscles and airway secretion clearance can be optimized through assistive cough, chest percussion and suctioning. Close monitoring for the early signs of infection is critical. Further interventions include non-invasive or invasive ventilatory support for weakened diaphragm and intercostal muscles.

Physiotherapy

Pompe disease causes progressive muscular degeneration resulting in weakness and physical disability. Therefore, stabilizing or improving physical ability it is one of the aims of Pompe management. Physiotherapy, in conjunction with ERT, can help to alleviate or prevent secondary complications, such as reduced bone mineral density and contractures.

Occupational therapy

Patients may eventually need the assistance of mobility devices to remain independent. In the earlier stages of the disease, canes and walkers may suffice, but in advanced disease, patients may become non-ambulatory and require the use of wheelchairs.

Nutrition

Pompe disease can weaken muscles used for chewing and swallowing food. As a result, many people with Pompe disease have trouble gaining

and/or maintaining weight. Patients are routinely given guidance on balanced, high-calorie diets, as well as on strategies to change the size and texture of food to make it easier to eat and to reduce the risk of aspiration. Nasogastric or nasoenteric tube feeding may be called for if patients are at high risk for aspiration. Permanent tube placement in the abdomen may also be required. However, in general, tube feeding is more common in infantile-onset patients due to severe muscle weakness, ventilator dependency, and macroglossia.

Orthopedic support and interventions

As in a number of neuromuscular disorders, patients with Pompe disease may experience contractures, scapular winging, and truncal weakness due to muscle wasting and reduced muscle use. Spinal deformity, particularly scoliosis, can also affect pulmonary function and may cause discomfort while sitting. If severe, orthopedic braces or surgical intervention may be necessary to alleviate pain and/or disability^[37].

Speech therapy

Speech may be affected due to facial and tongue muscle weakness and macroglossia (particularly in infants). Bulbar muscle weakness affects speech intelligibility and therefore social communication. Early referral to a speech therapist may help to improve articulation and speech.

Additional assessments

Audiology assessments (particularly for children) and sleep studies are also often warranted in the management of Pompe disease. droplet in adipocytes.

Investigative Therapies

Several modifications to the recombinant human acid α -glucosidase that is presently used for enzyme replacement therapy are currently being explored. For example, carbohydrate side chains are being modified to improve uptake by muscle cells (neoGAA; an activity of Genzyme Corporation). Likewise, another effort to improve uptake involves the addition of peptide tags to rhGAA side chains (BMN 701; an activity of BioMarin Pharmaceuticals Inc.). Small molecule therapies to enhance the function of patient's residual, endogenous acid α -glucosidase, as well as to stabilize the intravenously administered form of rhGAA are also currently in

development (chaperones; AT2220, an activity of Amicus Therapeutics, Inc.). Numerous studies are currently in progress related to Pompe disease. For an overview of current clinical trials, visit www.clinicaltrials.gov.

Gene Therapy

Gene therapy remains an exciting option and progress continues. Gene therapy in Pompe disease is directed toward restoring the acid α -glucosidase production and activity in crucial tissues like the diaphragm in order to improve respiratory capacity. Other gene therapy efforts seek to restore the body's ability to produce acid α -glucosidase by transducing the functional GAA gene in liver cells in vivo, or in bone marrow stem cells ex vivo followed by stem cell transplantation.

NORD does not endorse or recommend any particular studies.

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Resources

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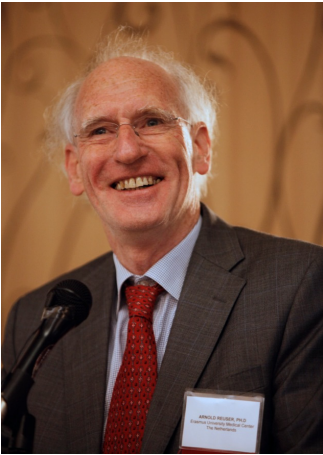
View the list of Acid Maltase Deficiency Association scientific advisors here:

<http://www.amda-pompe.org/index.php/main/research/>

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Contact NORD at orphan@rarediseases.org.

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