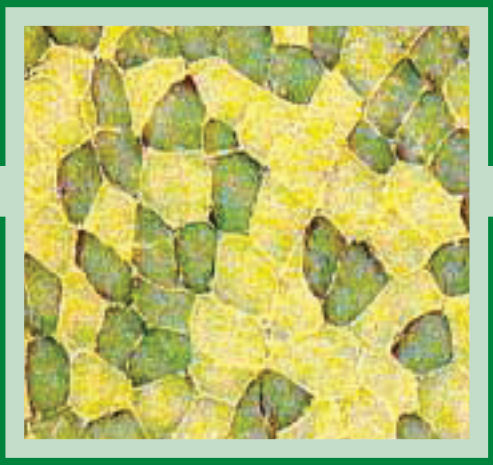

Late-Onset Pompe Disease

Presentation, Diagnosis, and Management

A CME Monograph

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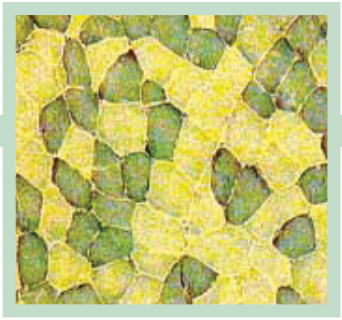

Late-Onset Pompe Disease:
Presentation, Diagnosis, and Management

A Continuing Medical Education Monograph

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Target Audience

This activity is designed for neuromuscular specialists, neurologists, physiatrists, pulmonologists, medical geneticists, and physicians with an interest in the diagnosis and management of Pompe disease.

Learning Objectives

At the conclusion of this activity, the participant should be able to

- Describe the epidemiology and pathophysiology of late-onset Pompe disease
- Recognize the clinical presentation of late-onset Pompe disease and describe the necessary baseline assessments
- Differentiate between the signs and symptoms of late-onset Pompe disease and those of other limb-girdle disorders
- Describe the tests available to neuromuscular specialists for diagnosing Pompe disease
- Discuss pharmacologic and nonpharmacologic strategies for the treatment of patients with late-onset Pompe disease
- Interpret and apply guidelines for the diagnosis and management of late-onset Pompe disease

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Introduction

Pompe disease, also known as acid maltase deficiency and glycogen storage disease type II, is a rare, progressive, autosomal recessive disorder that is often fatal. It was first described in 1932 by Dutch pathologist J.C. Pompe[1] and is characterized by a total or partial deficiency of acid α-glucosidase (GAA), an enzyme that hydrolyzes lysosomal glycogen. As a result of GAA enzyme deficiency, lysosomal glycogen accumulates in tissues of the body, which can lead to progressive debilitation, organ failure, and death.

Pompe disease is a disorder with a heterogeneous clinical presentation and multiple rates of progression (Table 1).[2-17] The infantile-onset form of the disease presents within the first few months of life.[3,8,9] This form is rapidly progressive and is characterized by marked cardiomyopathy, respiratory failure, and death within the first year of life.[2,7-9]

Late-onset Pompe disease (ie, juvenile- and adult-onset) can present as early as the age of 1 year to as late as the sixth decade of life. The late-onset form is associated with significant morbidity and is characterized by progressive skeletal muscle weakness and respiratory insufficiency that leads to respiratory failure and death.[3,11,18] Patients typically present with progressive proximal myopathy; however, respiratory involvement can be the primary presenting clinical feature. Patient age at death varies widely, with death occurring from childhood to late adulthood.[3,10]

The combined prevalence of all forms of Pompe disease is estimated to be 1 in 40,000,[19,20] with the disease affecting males and females equally.[3] Based on carrier frequencies of 3 common mutations found in the Dutch population, the estimated frequency of late-onset Pompe disease is 1 in 57,000.[19] The estimated frequency of infantile-onset Pompe disease is approximately 1 in 100,000; higher frequencies of the infantile-onset form have been reported in some populations, including African Americans (approximately 1 in 14,000) and persons with Chinese ancestry (1 in 50,000 to 1 in 40,000).[3] The accuracy of these estimations—and our knowledge about Pompe disease, in general—will improve with widespread screening for Pompe disease. Newborn screening programs for Pompe disease have recently been implemented in many countries worldwide, with the goal of improving early detection of Pompe disease; such programs have been established in Asia, Austria, Australia, the Netherlands, and parts of the United States.[21-25] For example, in a pilot newborn screening program in Taiwan that used a blood-based enzyme activity assay (ie, dried blood spot [DBS]), 132,538 infants were screened, and 4 infants with Pompe disease were found.[26] Based on the data in this study population, the prevalence of Pompe disease in infants was 1 in 33,333 (95% confidence interval, 1 in 12,048 to 1 in 100,000).

Disease Presentation and Course

By clinical definition, patients with late-onset Pompe disease present with symptoms at any time after the age of 12 months.[3,5,8] The late-onset form is heterogeneous, and a range of neuromuscular, musculoskeletal, respiratory, and cardiac symptoms are possible. Progressive myopathy is a common feature; muscle weakness is generally more pronounced in proximal muscles of the lower extremities, with lesser involvement of the distal muscles and upper extremities. The distribution of muscle pathology may be asymmetric or symmetric; the trunk, thigh, and pelvic girdle muscles are the groups most likely to be affected, and there may be selective involvement of specific muscle groups (eg, the paraspinal muscles and hip adductors).[18,27,28] Patients may report that they have difficulty walking, running, participating in sports, climbing stairs, rising from a chair, and rising from a recumbent position.[3,14,29] In children with late-onset Pompe disease, achievement of motor development milestones is often delayed.[5,8] Additionally, limb-girdle weakness, back pain, fatigue, and muscle cramps are often reported.[3,5,10-12,14,15] Table 1 lists some common musculoskeletal signs and symptoms.

Table 1. Comparison of Characteristics Associated With Infantile-Onset and Late-Onset Pompe Disease

Feature	Infantile-Onset Pompe Disease	Late-Onset Pompe Disease
Onset	First year of life (typically first few months of life)	>1 year to adulthood
GAA enzyme activity	Typically absent[2,3]	Some residual activity[5]
Cardiomyopathy	Present and often severe (eg, cardiac failure, disturbances of rhythm, cardiomegaly, cardiomyopathy)[2,3,7-9,15]	Typically not present[5]; some cases of WPW syndrome reported[17]
Common signs and symptoms at presentation	Hypotonia, profound muscle weakness, respiratory insufficiency/distress, respiratory infections, and feeding difficulties/failure to thrive are among the most common symptoms[2,7-9] Hepatomegaly[3,7,8,15] Macroglossia[2,3,7,8,15]	Musculoskeletal symptoms (eg, mobility problems, limb-girdle weakness, back pain, rigid spine syndrome, muscle cramps)[3,10-14] Respiratory symptoms (eg, frequent respiratory infections, respiratory distress or insufficiency, sleep-disordered breathing, oxygen desaturation when supine)[3,5,11,13,14] Gastrointestinal symptoms (eg, difficulties eating/swallowing, poor weight gain in children[5]
Rate of progression	Rapid	Widely variable, slower than for the infantile-onset form
Death	Typically occurs within the first year of life[2,5,7] Often caused by cardiorespiratory failure or respiratory infection[5,7]	Age of death varies—childhood to late adulthood[11] Respiratory failure is the most common cause of death[3,11] Death as a result of cerebral aneurysm has been reported[16]

Abbreviations: GAA, acid α-glucosidase; WPW, Wolff-Parkinson-White.

The natural course of late-onset Pompe disease varies widely, but the disease is progressive.[29,30] Typically, the first muscles affected are the hip adductors (ie, adductor magnus), hip abductors and extensors (ie, gluteal muscles), hip flexors (ie, psoas), the paraspinal muscles, the semimembranosus, the abdominal muscles, and the vastus medialis.[12,14,15,18,28] Weakness may also be noted in the scapular stabilizers and neck flexors and extensors.[14] Several studies have also reported weakening of the biceps, triceps, deltoid muscles, quadriceps, and tongue, as well as the disappearance of deep tendon reflexes as the disease advances.[3,14,18] As muscle weakness progresses, motor function decreases and patients often develop compensatory movement patterns and altered postural and positioning habits. Such alterations in movement and posturing can lead to a self-perpetuating cycle of secondary musculoskeletal impairments, including contracture and deformity. Furthermore, weakness and decreased motor function increase the risk of osteopenia or osteoporosis.[5,14] Finally, wheelchair use also tends to increase with the duration of the disease.[5,30]

Respiratory involvement, which is caused by weakness of the diaphragm and accessory muscles of respiration, is an important feature of late-onset Pompe disease. Progressive respiratory muscle weakness and impaired cough can lead to recurrent upper and lower respiratory tract infections. In some instances, respiratory insufficiency precedes the development of measurable muscle weakness. Sleep-disordered breathing, including the development of nocturnal hypoventilation and oxygen desaturation, may occur because of impaired respiratory muscle function in the supine position and alterations in respiratory control mechanisms during sleep.[3,5,10,12,13] Ultimately, the use of ventilatory support tends to increase with disease progression.[5,29,30] Although respiratory failure is often manageable with ventilatory assistance systems, respiratory failure is the most common cause of death in patients with the late-onset form of the disease.[3,10]

The clinical features of late-onset Pompe disease were recently examined in a prospective cohort study of 58 patients (the Late-Onset Pompe Observational Study [LOPOS]).[31] At the time of the initial diagnosis (ie, before study entry), the primary presenting symptom was proximal muscle weakness in the lower extremities in 54 of 58 patients (93.1%) and respiratory dysfunction in the remaining 4 patients. At the start of the study, all patients had proximal muscle weakness, and respiratory muscle weakness was noted in 89.7% of patients. Muscle weakness was greater in lower extremities than it was in upper extremities. All patients experienced a decline in proximal and respiratory muscle weakness over the 12-month study period, but patients with the lowest residual GAA enzyme activity levels and the most advanced disease progression had the greatest declines in muscle strength.

Although cardiac involvement is a prominent feature of infantile-onset Pompe disease, it is not well documented in patients with the late-onset form and is rarely reported in adults or children over the age of 2 years. Cardiac involvement predominantly manifests as ventricular dysfunction or arrhythmia in patients with late-onset Pompe disease.[32-34] Some cases of Wolff-Parkinson-White (WPW) syndrome have been documented.[17,35,36] Müller-Felber and colleagues[17] found WPW syndrome in 3 of 38 patients who were diagnosed with Pompe disease via genetic testing. For these 3 patients, the authors speculated that glycogen may have selectively accumulated in the cardiac conduction system, as it does in infantile-onset Pompe disease and other lysosomal storage disorders.[37-39] The lack of overt cardiac involvement in patients with late-onset Pompe disease is thought to be related to the presence of higher residual enzyme activity in these patients than in infants.

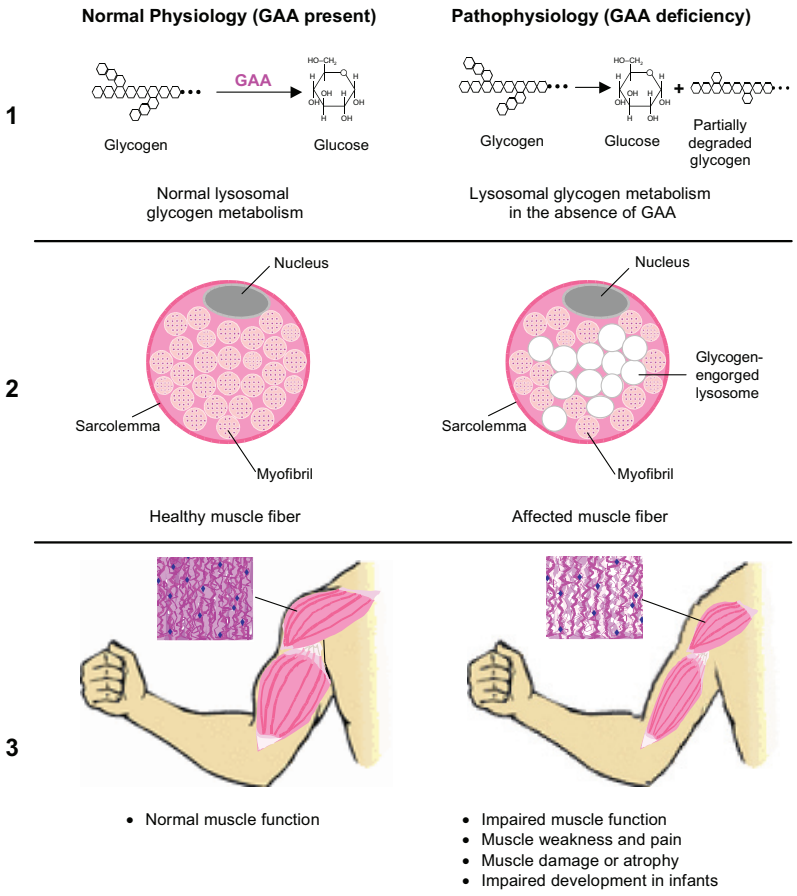
Pathophysiology

Pompe disease is caused by a deficiency of the GAA enzyme. The degree of deficiency varies, and some residual activity is typically present in children and adults with late-onset Pompe disease—from <1% to 40% residual enzyme activity.[3,31,40] The GAA gene is located on chromosome 17 (17q25.2-q25.3) and is highly polymorphic; more than 200 mutations have been identified to date.[41-43] The most common mutation found in late-onset patients is the c.-32-13T>G mutation, which is seen in one allele in approximately 60% of patients with late-onset Pompe disease.[42,44,45]

In late-onset Pompe disease, deficient GAA enzyme activity results in glycogen accumulation, primarily in muscle cells (Figure). It is believed that muscle weakness is caused when swollen, glycogen-filled lysosomes displace or distort myofibrils, thereby interrupting the contractile capacity of the muscle; however, other mechanisms may also have a role in the pathophysiological process, such as abnormal processing of the GAA enzyme and abnormal autophagy.[43,45-50] Additionally, it is thought that excessive glycogen accumulation leads to lysosomal enlargement, leakage, and eventually, rupture, which releases hydrolytic lysosomal enzymes that may further damage muscle.[47]

A recent study found that muscle from patients with Pompe disease (many of whom had the c.-32-13T>G mutation) contains relatively high amounts of the precursor forms of the GAA enzyme (ie, 110 kDa and 95 kDa) and very low or absent amounts of the mature/functional forms (ie, 76 kDa and 70 kDa). Under normal conditions, processing of the 110 kDa precursor GAA protein in the Golgi complex leads to the formation of a 95 kDa intermediate protein. After transportation to the lysosome, the intermediate protein is cleaved to a 76 kDa form, and then to a functional 70 kDa enzyme.[45] The abnormally high amounts of the precursor forms of the enzyme in patients with Pompe disease is postulated to be a result of incomplete processing, delayed transport, and incorrect targeting to lysosomes, all of which may cause excessive sialylation of mutant proteins in the Golgi.

The presence of excess GAA enzyme in intermediate forms in patients with late-onset Pompe disease appears to contribute to increased autophagy.[45] Autophagy is a catabolic process whereby a cell's own components are selectively degraded and recycled. Damaged organelles are sequestered in double-membrane vesicles called autophagosomes, which fuse with lysosomes and are degraded by lysosomal enzymes.[50] Under normal circumstances, basal levels of autophagy help maintain a balance between the synthesis and degradation of cellular products.[50] A GAA enzyme deficiency causes impaired glycogen digestion, which leads to local starvation and triggers an autophagic response.[49] Increased autophagy, along with a postulated failure of autophagosomes to fuse with lysosomes, leads to an accumulation of autophagic material and disruption of muscle architecture, which may be partially responsible for the muscle damage associated with Pompe disease.[48-50] Oxidative stress may also have a role in the increased autophagy associated with Pompe disease.[48,50]



Figure

Comparison of normal physiology to pathophysiology in Pompe disease. (1) Glycogen is composed of long chains of glucose with multiple side chains and is stored in lysosomes. During glycogen metabolism, glucose molecules are removed from the ends of glycogen by phosphorylase and by debranching enzymes in the cytosol. GAA, a lysosomal enzyme, is required to break the links between branched chains of glucose in the lysosome. In the absence of GAA, glycogen accumulates in the lysosome. (2) Glycogen accumulates in the lysosomes, causing them to swell and push the myofibrils to the periphery; glycogen also seeps out of the cell and into the extracellular space. (3) This accumulation of glycogen impairs muscle function and can cause muscle damage and wasting. Skeletal, smooth, and cardiac muscles are all affected by GAA enzyme deficiency. GAA indicates acid α-glucosidase.

Diagnosis

Pompe disease may be difficult to identify because patients can present with generic symptoms that are similar to those of other neuromuscular disorders. The differential diagnoses for late-onset Pompe disease are detailed in Table 2.[5,35,51-55] The presence of isolated respiratory weakness, muscle pain, lower back pain, rigid spine syndrome, myopathy, or exercise intolerance suggests that a diagnosis of Pompe disease should be considered if these symptoms cannot be conclusively attributed to another disorder. The diagnosis can be easily confirmed by testing for a reduction or absence of GAA enzyme activity or by testing for the presence of 2 GAA gene mutations.[5,56] On the basis of the current understanding of muscle pathophysiology in Pompe disease, early diagnosis—before the development of end-stage muscle disease—provides the best hope for therapeutic intervention.

Table 2. Conditions With Symptoms Similar to Those of Late-Onset Pompe Disease

Differential Diagnosis	Shared Signs and Symptoms
Motor neuron disease	
Spinal muscular atrophy[5]	Asymmetrical muscle weakness, voluntary muscle atrophy
Inflammatory myopathy	
Polymyositis, inclusion body myositis, or other inflammatory or nonspecific myopathies[5,35,51,52]	Unexplained muscle weakness
Myopathy	
Limb-girdle muscular dystrophy[5,51]	Progressive muscle weakness in the pelvis, legs, and shoulders
Becker or Duchenne muscular dystrophy[5,51,53]	Progressive proximal muscle weakness, respiratory impairment, difficulty walking, difficulty rising from a lying or sitting position, elevated creatine kinase levels
Other muscular dystrophies[53]	Muscle weakening, contractures, loss of mobility
Scapuloperoneal syndromes[5]	Progressive muscle weakness behind the knees and around the shoulder girdle
Rigid spine syndrome[5]	Spinal rigidity, lower back pain
Myasthenia gravis[5]	Generalized muscle weakness
Congenital myopathies[54]	Generalized proximal muscle weakness, hypotonia
Mitochondrial myopathies[5]	Hypotonia, hyporeflexia, hepatomegaly; some forms with hypertrophic cardiomyopathy, muscle weakness, elevated creatine kinase levels
Glycogen storage disease	
Type IIIa (debranching enzyme deficiency/ Cori or Forbes disease)	Hypotonia, hepatomegaly,[a] muscle weakness, elevated creatine kinase levels
Type IV (branching enzyme deficiency/ Andersen disease)	
Type V (muscle phosphorylase deficiency/ McArdle disease)	
Type VII (muscle phosphofructokinase deficiency/ Tarui disease)[5]	
Other	
Danon disease[5]	Hypertrophic cardiomyopathy, skeletal muscle myopathy, vacuolar glycogen storage
Rheumatoid arthritis[5,51]	Stiffness/pain upon exertion, progressive muscle weakness, respiratory impairment, difficulty walking

[a] Patients with Type V glycogen storage disease typically do not have hepatomegaly, but they have high creatine kinase levels and a high risk for rhabdomyolysis.

Neuromuscular Evaluations

Muscle strength is generally assessed by manual muscle testing; the Medical Research Council (MRC) scale is frequently used to quantify muscle strength[57] and may be supplemented with dynamometry in some settings. Kinematic assessment of a patient's movement reveals the use of compensatory movements associated with specific areas of weakness and areas at risk for contracture, deformity, and potential functional loss. Functional testing may include timed tests (eg, 6-minute walk, time to walk 10 meters, time to ascend 4 steps, time to achieve standing from sitting and supine positions), standardized tests of development (for children), and quality of life measures. Musculoskeletal evaluations should include assessments of posture, alignment, spinal abnormalities (ie, scoliosis, kyphosis, and lordosis), passive range of motion, and muscle extensibility.[5,14]

Electromyography (EMG) typically shows a myopathic pattern in affected muscles[5]; however, abnormal spontaneous activity (eg, fibrillation potentials, myotonic or myotoniclike discharges) and excessive irritability of muscle fibers may be noted.[8,12,13,15] Although myotonic potentials are observed by EMG, clinical myotonia is not seen.[8] Because of the possibility of asymmetric or uneven muscle involvement in patients with late-onset Pompe disease, multiple muscle groups should be examined.[15] It may be useful to assess the paraspinal muscles by EMG, as these muscles may show abnormal spontaneous activity despite a lack of such activity in the limbs. Although nerve conduction studies are conducted as part of a complete evaluation in patients suspected of having Pompe disease, sensory and motor nerve conduction tends to be normal.[12,13]

Evaluation of Respiratory Function

In patients with late-onset Pompe disease, both the diaphragm and intercostal muscles are often affected, and respiratory muscle weakness may be the predominant presenting feature. Thus, pulmonary function tests should be performed whether respiratory symptoms are present or not. Furthermore, because of the progressive nature of the disease, respiratory testing should be repeated regularly over the course of care. In order to detect early diaphragm weakness, standard pulmonary function tests should be performed with the patient in both seated and supine positions. A >10% decrease in forced vital capacity (FVC) measured while the patient is in a supine position, relative to a seated position, has been shown to correlate with diaphragm weakness.[58] Early respiratory dysfunction may also be identified by reductions in maximal inspiratory and expiratory pressures. Sleep studies, noninvasive tests of gas exchange, and arterial blood gas (ABG) measures may also be useful in determining respiratory dysfunction.

Laboratory Tests

Nonspecific tests for muscle disease

Several blood tests may be useful in evaluating patients for Pompe disease. Creatine kinase (CK) levels are elevated (1.5-15 times the upper limit of normal)[59] in most patients with late-onset Pompe disease, although some patients with this disorder may have CK levels within the normal range.[59] One study found that CK levels were elevated in patients who were eventually diagnosed with Pompe disease, despite the absence of symptoms or histological indicators of the disease.[60] Although CK is considered a sensitive marker for muscle disease in general, it is nonspecific for Pompe disease.[5] Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) levels are also commonly elevated, reflecting enzyme release from muscle.[2,10]

Urine testing may be useful in evaluating patients who may have Pompe disease. Elevated urine levels of the hexose tetrasaccharide Glcα1-6Glcα1-4Glcα1-4Glc (urine Hex4) often are seen in patients with Pompe disease.[5] Elevated Hex4 level is a marker for Pompe disease; however, like CK, Hex4 is nonspecific, and elevated levels are also associated with other glycogen storage diseases and other muscle disorders.[5] Urine Hex4 has been found to be useful for monitoring the response to enzyme replacement therapy (ERT) in infants and is currently being evaluated in adults.

Tissue obtained by biopsy of affected muscle typically shows vacuolar myopathy with excessive glycogen accumulation and increased acid phosphatase staining. Vacuoles containing glycogen stain positive with the periodic acid–Schiff (PAS) stain, which is the standard histological procedure for evaluating muscle glycogen. Although in the majority of biopsies muscle histopathology is clearly identifiable, some biopsies from patients with Pompe disease reveal normal or near-normal results.[18] Thus, confirmatory testing is required, either via GAA enzyme activity assays or mutation analysis.[5]

Specific tests for Pompe disease

Historically, muscle tissue histology has served neuromuscular specialists as the primary tool for the diagnosis of patients who present with a myopathy. However, the diagnostic value of biopsy tissue histology in Pompe disease may be limited because of the heterogeneity of muscle involvement and the uneven distribution of affected muscle fibers. Thus, if there is strong clinical suspicion of Pompe disease, a finding of normal muscle histology should not exclude this diagnosis. The definitive diagnostic tests for Pompe disease include GAA enzyme activity assay (which can be measured by using a variety of methods in a number of tissues, including blood, skin, and muscle) and mutation analysis.[5,8,56,61-63]

Blood-based GAA enzyme activity assays

Until recently, blood-based assays have been seen as unreliable for the diagnosis of Pompe disease because of false-negative results associated with the activity of nonlysosomal enzymes such as maltase-glucoamylase (MGA), which can mask GAA enzyme deficiency.[62] Contemporary assays that use acarbose for competitive inhibition of MGA have eliminated this confounding factor, making the blood-based GAA enzyme activity assay a simple, reliable, minimally invasive, inexpensive method for identifying Pompe disease.[61] Blood-based assays use whole blood, DBS, isolated lymphocytes, or mixed leukocytes. The DBS assay of GAA enzyme activity has several advantages over other methods. This assay has been reported to have sensitivity between 90% and 100% and specificity of >99%.[24,64-66] Additionally, blood can be collected by standard blood spotting on filter paper (with the use of appropriate cautions to prevent false-positive results) and then conveniently shipped to the testing laboratory. Alternatively, blood can be collected in an EDTA tube via standard blood draw techniques and shipped to the testing laboratory for spotting, which may be the preferred method for those who are unfamiliar with the collection of blood samples on filter paper.[61] Laboratories offering DBS testing for Pompe disease at the time this monograph was prepared are listed in Table 3.[67-72]

The GAA enzyme activity test can also be performed in isolated lymphocytes or mixed leukocytes.[62,63,73] However, it is important to note that certain procedures should be followed to minimize contamination by polymorphonuclear cells when leukocytes or lymphocytes are isolated for GAA enzyme activity testing. Compared with skin- and muscle-based testing, testing in leukocytes, lymphocytes, or whole blood is advantageous in that the blood draw is minimally invasive.[56] However, the amount of blood required to obtain an adequate number of lymphocytes for testing is greater than the amount of blood needed for DBS testing. Although blood-based testing is reliable, a second test (eg, enzyme activity from another blood assay or in another tissue, as discussed below) or genotyping is recommended to support the diagnosis of Pompe disease.

Table 3. Laboratories Offering Dried Blood Spot Testing for Pompe Disease [a]

Location	Laboratory
United States	Duke University Medical Center[67] Glycogen Storage Disease Laboratory Research Triangle Park, NC
	Children's Hospital and Regional Medical Center[68] Department of Laboratories Seattle, WA
	Emory University School of Medicine, Department of Human Genetics[69] Emory Biochemical Genetics Laboratory Atlanta, GA
	Genzyme Genetics[70] Reproductive/Genetics Client Services Santa Fe, NM
South Australia	Women's and Children's Hospital[71] National Referral Laboratory North Adelaide
Belgium	Laboratory for Metabolic Diseases[72] Gent

[a] Other locations may also offer dried blood spot testing for acid α-glucosidase enzyme activity.

Tissue-based GAA enzyme activity assays

Measurement of GAA enzyme activity can be readily performed from tissues such as cultured skin fibroblasts and biopsied muscle. An advantage of measuring GAA enzyme activity in fibroblasts or muscle is the ability to determine the percentage of residual GAA enzyme activity. Muscle biopsy tissue can also be used for histological assessment of morphology, measurement of glycogen content, and assessment of areas of glycogen storage in muscle fibers. However, data showing the absence and inconsistency of histological changes in muscle biopsies support the use of blood- or tissue-based GAA enzyme activity testing to formally diagnose patients.[45,74] Furthermore, cultured fibroblasts can take 4 to 6 weeks to grow, which can substantially delay diagnosis.[5] Compared with measurement of GAA enzyme activity in skin fibroblasts, measurement of GAA enzyme activity in muscle tissue yields faster results.[8]

GAA gene mutation/sequence analysis

Mutation analysis is important for the identification of carriers when a familial mutation is known and in cases of ambiguous GAA enzyme activity test results.[5] In patients with high residual levels of GAA, mutation analysis of the GAA gene may be needed to confirm the diagnosis.[5] Although more than 200 mutations are known to cause Pompe disease, few of these mutations have been characterized. Some gene mutations have been correlated with certain phenotypes, but other factors, including modifier genes and environmental influences, can also affect phenotypes in patients with Pompe disease.[44,75] Further investigation into the nature of the GAA gene mutation and the clinical phenotypes may reveal other, as yet undetermined, genetic or exogenous factors that modulate disease severity and the rate of disease progression.[32,44]

Management

Guidelines published by the American College of Medical Genetics (ACMG) for the management of patients with Pompe disease stress the importance of coordinated care involving a multidisciplinary team of individuals from a variety of specialties.[5] A physician who has experience in treating patients with Pompe disease should lead the multidisciplinary team and coordinate the contributions of its members. The main roles of the care coordinator are to identify and organize patient needs and to refer the patient to the appropriate specialists (Table 4). Many specialties, including neuromuscular and pulmonary specialists, geneticists, and speech, occupational, and physical therapists, provide essential care for and assessment of patients with Pompe disease.

Once a diagnosis is confirmed, the patient and family members should be thoroughly educated about the expected outcomes of the disease and the potential challenges the patient may face. The patient and the family must be informed about treatment options and about available sources of information and support (see Appendix). One source, the Muscular Dystrophy Association, sponsors clinics that specifically cater to the needs of patients with muscle diseases (including Pompe disease) and has extensive resources, that can be valuable for both patients and their families, related to the challenges of living with a neuromuscular condition.

Until recently, no specific treatment for Pompe disease was available, and disease management consisted of supportive care alone. Respiratory, nutritional, and physical therapies and the use of assistive devices have provided some benefits to patients. Small studies of albuterol,[76] branched-chain amino acids,[76] high-protein diets (some combined with an exercise regimen),[77-79] and alanine[80,81] have shown that these treatments have some potential to reduce respiratory and skeletal muscle loss in some patients. However, results from these reports are variable, and there are no definitive results regarding the effectiveness of these interventions. Other treatments such as epinephrine and glucagon,[82] bone marrow transplantation,[83] and heart transplantation[5] have not been shown to be useful, although experience with these approaches has been limited.

Since April 2006, ERT has been a treatment option for all patients with Pompe disease. Intravenous administration of recombinant human acid α-glucosidase (rhGAA; alglucosidase alfa) is used to replace the deficient enzyme in patients who have Pompe disease. Enzyme replacement therapy has the potential to significantly alter the course of both early- and late-onset Pompe disease. Studies of rhGAA have shown that ERT improves muscle strength, pulmonary function, and other disease symptoms in many patients.[40,84-87]

Coordinated Care of Patients With Pompe Disease

Roles of the neuromuscular specialist

The neuromuscular specialist is a critical member of any multidisciplinary team that provides care for patients with Pompe disease.[5] This specialist often serves as care coordinator throughout the course of a patient's illness. Neuromuscular specialists, including neurologists and physiatrists (along with geneticists), are more likely than other physicians to confirm the diagnosis of late-onset Pompe disease. These physicians are involved in diagnostic testing, periodic assessment of motor and functional capacities, and identification of the patient's need for assistive or adaptive equipment. As is standard for all neuromuscular disorders, routine periodic evaluation should include assessments of range of motion, strength, functional ability, pain, and quality of life. A detailed list of the relevant motor and functional assessments that may be necessary is found in the ACMG guidelines for the management of Pompe disease.[5]

Communication between neuromuscular specialists and other members of the management team is critical. The results of assessments performed by neuromuscular specialists should be shared with physical, occupational, and speech therapists, so that programs can be coordinated to promote maximal function and minimize secondary complications. In cooperation with these rehabilitation therapists and with orthopedists, neuromuscular specialists direct the prevention and management of the physical complications often experienced by patients with muscle disease. Because of the risk for scoliosis and joint contractures, which can further limit movement, patients should have regular examinations of the spine and major joints. Contracture and deformity are managed through optimization of alignment and positioning, development of stretching or exercise programs for structures that are at risk, and the use of adaptive equipment (eg, adapted seating systems for strollers and wheelchairs, adapted car seats, supportive standing devices) or orthotic interventions (eg, ankle-foot orthoses, thigh binders, knee extension splints).[5,14] Patients with Pompe disease may benefit from bracing, depending on distribution of weakness, gait problems, and joint stability. In addition, interventions may be needed to prevent osteopenia or osteoporosis (eg, weight-bearing activities).[5,14]

A recent uncontrolled prospective study of the benefit of submaximal exercise and optimal nutrition for patients with late-onset Pompe disease found that plateau or improvement of motor status was achieved in all 22 patients who adhered to the exercise and nutrition program.[88] The program included exercise at 60% to 65% of maximal oxygen consumption or heart rate, a perceived rate of exertion described as mildly difficult (according to the Borg Scale), and a high protein/low carbohydrate diet. Motor deterioration continued in 8 patients who did not adhere to the exercise and nutrition program. Data from studies of other neuromuscular disorders[89-91] support the recommendation of a submaximal strengthening program for patients with Pompe disease.[5,14] Patients with late-onset Pompe disease may benefit from aerobic exercises designed to improve endurance and mobility; however, patients should be advised not to exercise to exhaustion because of the risk of further muscle damage.[5,14,78,89,90] Early intervention with gentle, low-impact aerobic exercise such as walking, swimming, and stationary bicycling may improve muscle efficiency and lessen fatigue. In addition to improving physical functioning, aerobic exercise is beneficial in fighting depression, maintaining ideal body weight, and improving pain tolerance. Monitoring of cardiopulmonary response to exercise is recommended, especially when an exercise program is introduced or changed.[5,14,90]

Roles of the pulmonologist

Because of the high prevalence of respiratory complications in patients with Pompe disease, pulmonologists are important members of the multidisciplinary team, and they may manage the care of patients.[5] Respiratory system involvement may be overlooked in patients with Pompe disease because overt respiratory symptoms may be absent. In addition, exercise-induced symptoms may be difficult to elicit because physical activity may be limited by skeletal muscle weakness. Respiratory complications, such as repeated episodes of tracheobronchitis and pneumonia, may present as the primary clinical feature. As respiratory muscle weakness progresses, chronic respiratory failure with CO_2 retention and hypoxemia develops. Thus, pulmonologists may aid in the diagnosis of Pompe disease, assess patients' respiratory status, and provide supportive treatment to improve and maintain respiratory function. In the clinical setting, evaluations of shortness of breath, cough, and airway clearance are performed. Objective assessments of pulmonary function are typically obtained by measurements of FVC, maximal inspiratory and expiratory pressures, peak cough flow, and gas exchange (noninvasively assessed by pulse oximetry, capnography, and/or serum bicarbonate levels). Additional measurements such as forced expiratory volume in 1 second and negative inspiratory pressure

may be clinically indicated for some patients. Chest radiographs are used to determine the presence of atelectasis or pneumonia. Because of the progressive nature of respiratory involvement in Pompe disease, pulmonary assessments should be completed at the time of diagnosis and repeated on a regular basis.

As respiratory muscle weakness progresses, patients often require increased assistance to maintain sufficient gas exchange and ventilatory function. Respiratory and pulmonary function is managed through promotion of appropriate positioning (ie, seated and supine), use of pulmonary hygiene and airway clearance techniques (eg, chest physical therapy, cough assist devices, appropriate exercise), inspiratory muscle training, and maintenance of rib cage mobility.[14] Supportive care with noninvasive or invasive positive airway pressure ventilation should be prescribed on the basis of the underlying ventilatory abnormality (eg, hypoxemia, obstructive sleep apnea, hypoventilation). Options for noninvasive ventilatory intervention include intermittent positive airway pressure ventilation by mouth (which can be used during wakefulness) or bilevel positive airway pressure (the preferred initial treatment for nocturnal hypoventilation); proper use of noninvasive ventilatory support can prevent the need for tracheostomy. As respiratory muscle weakness progresses, there is an increased tendency for hypoventilation to persist during both wakefulness and sleep; consequently, tracheostomy with invasive mechanical ventilation may be required. However, some pulmonologists strongly advocate optimizing the use of noninvasive techniques without resorting to tracheostomy.[92] Finally, pulmonologists should aggressively manage any pulmonary infections that develop in patients with Pompe disease.

Polysomnography is a useful tool for assessing the presence and severity of respiratory dysfunction that occurs with sleep. Sleep-disordered breathing, a condition of dysfunctional ventilation during sleep, is a complication that can be present in the absence of significant skeletal muscle weakness. Ventilatory abnormalities such as hypoxemia, obstructive sleep apnea, and sustained hypoventilation can be present and are treated as appropriate. Although hypoxemia is always present in sleep-disordered breathing, treatment should target the underlying respiratory disorder before supplemental oxygen is given. Supplemental oxygen can be used if other methods do not fully correct the hypoxia. For patients with obstructive sleep apnea, treatment can be limited to continuous positive airway pressure (nasal); more aggressive intervention, such as nocturnal noninvasive positive pressure ventilation (ie, bilevel ventilation), should be used only in patients with nocturnal hypoventilation.[93] In patients who receive supplemental oxygen, close monitoring of arterial carbon dioxide levels is necessary to ensure that oxygen-induced hypercapnia does not develop.

Roles of the geneticist or metabolic specialist

Geneticists can have several roles in diagnosing and managing Pompe disease, such as conducting confirmatory diagnostic testing, serving as care coordinators, and providing genetic counseling for patients and their families.[5] Pompe disease is an autosomal recessive disorder; de novo mutation rates are low, and asymptomatic parents of an affected individual are assumed to be carriers. Mutation analysis is also used to identify extended family members who may be carriers. In genetic counseling, a 3-generation pedigree from the consultand or proband should be obtained. During prenatal diagnostic testing, either an enzyme activity test in uncultured chorionic villus samples or a mutation analysis is performed; mutation analysis is the preferred method when both mutations are known.[5] Because genotype and phenotype correlate in some cases,[44] geneticists and metabolic specialists may also educate patients about the effects of polymorphisms or specific mutations on clinical outcomes, as applicable.

Roles of the physical therapist

Physical therapists are important members of the multidisciplinary team who are active in many aspects of assessment and intervention, including managing musculoskeletal system symptoms and optimizing patient strength and endurance while preventing overexertion.[14] Physical therapists also coordinate the use of adaptive equipment and assistive technology to maximize functional independence. Pompe disease is characterized by a self-perpetuating cycle of progressive muscle weakness and decreased motor function that leads to compensatory movements and posturing that can result in secondary musculoskeletal impairments and additional functional losses.[5,14] Physical therapists provide evaluations and interventions for many aspects of motor, musculoskeletal, and cardiorespiratory function in order to prevent, slow, halt, or reverse this cycle in each individual patient and to preserve as much motor and physiological function as possible (Table 4).[14] Physical therapy interventions are designed to optimize biomechanical

advantage for movement, allow for strengthening and practice of new skills and/or functional movements within physiological limits, and assist in optimizing pulmonary and cardiorespiratory functions. Such interventions aim to prevent disuse atrophy, optimize strength and endurance, prevent contracture and deformity, conserve energy, and minimize fatigue. In children, physical therapy promotes the attainment of motor skills.[14] Detailed guidelines for physical therapy in the management of Pompe disease have been published.[5,14]

***Table 4. Multidisciplinary Management of Pompe Disease*[5]**

Specialty	Possible Roles
Musculoskeletal and functional rehabilitation (neuromuscular specialties, physiatry, developmental pediatrics, physical therapy, occupational therapy, speech therapy)	Assessment of musculoskeletal function, strength, disability, pain, and health-related quality of life Monitoring of cardiorespiratory status as related to position and activity Screening for osteopenia and osteoporosis Evaluation of x-rays for scoliosis, hip stability, and long bone integrity Enhancement of muscle function through appropriate, monitored exercise regimens (eg, submaximal and aerobic exercises) Prevention/minimization of deformity and contractures through stretching, positioning, orthotic interventions, splinting, and use of seating systems and supported standing Addition of assistive devices (eg, canes, walkers, wheelchairs) to optimize function Education of patients and family members Optimization of communication Maximizing independence in activities of daily living
Neurology	Motor and functional testing Performance of electromyography and nerve conduction studies Evaluation of hearing, including behavioral assessment, auditory evoked potentials, otoacoustic emissions, and tympanometry
Pulmonology	Assessment of respiratory status, pulmonary function, and gas exchange Evaluation of chest x-rays Collection of polysomnography data Maximization of airway clearance Treatment of ventilatory abnormalities with supplemental oxygen and/or noninvasive positive pressure ventilation Management of pulmonary infections
Gastroenterology	Assessment of swallowing via videofluoroscope Evaluation of gastric reflux Assessment of laryngeal penetration and aspiration
Nutrition	Monitoring of growth parameters Dietary counseling for adequate nutrition (with a focus on BMI in adults)
Cardiology	Evaluation of chest x-rays, echocardiograms, and ECGs Monitoring for arrhythmias
Genetics	Genetic counseling for parents of children with Pompe disease and for adults with Pompe disease Construction of 3-generation pedigree from consultand or proband Prenatal diagnostic testing
Surgery/anesthesia	Intensive monitoring during surgical procedures Use of anesthetics that are appropriate to the patient's condition Avoidance of intubation when possible
General medical	Prevention and aggressive management of infections Routine immunizations (eg, influenza, pneumococcal) for patients and household members Education of patients/caregivers on appropriate use of over-the-counter and other concomitant medications

Abbreviations: BMI, body mass index; ECG, electrocardiogram.

Schedule of Assessments

Table 5 presents the schedule of assessments and monitoring that is recommended by the Pompe Registry,[94] a program initiated with the goals of enhancing understanding of Pompe disease, assisting medical professionals with optimization of patient care, collecting information to characterize the Pompe disease patient population, and evaluating the safety and effectiveness of treatments for Pompe disease. Because the Pompe Registry schedule of assessments is consensus based, it may change as a greater understanding of Pompe disease is achieved. Several members of the multidisciplinary team may conduct periodic assessments; however, the care coordinator should track these assessments and communicate the results to other members of the management team as needed.

***Table 5. Minimum Recommended Schedule of Assessments for Patients With Pompe Disease*[94]**

	All Patients	Patients Aged <5 Years			Patients Aged ≥5 Years		
Assessment	**Upon Enrollment[a]**	**Every 3 Months**	**Every 6 Months**	**Every 12 Months**	**Every 3 Months**	**Every 6 Months**	**Every 12 Months**
General diagnosis							
Demographics	•						
Diagnosis (enzyme assay, DNA analysis)	•						
General patient monitoring[b]							
Medical history	•						
Clinical follow-up			•			•	
Pregnancy (applies to females of childbearing potential)	•					•	
Physical examination							
Height/weight/infant head circumference[c]	•	•	•				•
Blood pressure/body temperature	•	•					•
Laboratory tests[d]							
Blood tests	•		•				•
Urine tests	•		•				•
Clinical assessments							
Chest x-ray	•		•				•
Electrocardiogram	•		•				•
Echocardiogram	•		•				•
Audiometry examination	•			•			•
Visual screening[e]	•			•			•
Cognitive/development assessments[f]	•			•			
Pulmonary function tests/gas exchange/ polysomnography	•		•				•
Motor assessments[g]	•		•			•	
Quality of life/health outcomes							
SF-36v2™ Health Survey[h]	•						•
Rotterdam 9-Item Handicap Scale[h]	•					•	
Fatigue Severity Scale[h]	•					•	

Table 5. Minimum Recommended Schedule of Assessments for Patients With Pompe Disease[94] (cont'd)

Assessment	All Patients	Patients Aged <5 Years			Patients Aged ≥5 Years		
	Upon Enrollment[a]	Every 3 Months	Every 6 Months	Every 12 Months	Every 3 Months	Every 6 Months	Every 12 Months
Patients receiving ERT							
Upon ERT initiation	In addition to the initial assessments made upon Pompe Registry enrollment, there should also be documentation of these assessments at the time of ERT initiation						
Ongoing ERT administration	ERT information, including dose and frequency, should be collected (at a minimum) at first infusion and every 6 months thereafter and when a change in the ERT regimen has occurred						
Antibody testing	Antibody testing according to the following schedule is recommended • Serum sample before first ERT infusion • Serum sample every 3 months thereafter						
Adverse event reporting	It is highly recommended there be ongoing/continuous monitoring with reporting of adverse events through the manufacturer's Pharmacovigilance Department[i]						

[a] Refers to enrollment in the Pompe Registry.
[b] General monitoring assessments include development/neurology, ear/nose/throat, respiratory, cardiovascular, gastrointestinal tract, renal, hepatic, and musculoskeletal assessments, as appropriate.
[c] For patients ≤2 years of age, conduct height/weight/infant head circumference examination every 3 months. For patients 2-5 years of age, conduct only height/weight examination every 6 months.
[d] Blood and urine tests should include
1) Aspartate aminotransferase, alanine aminotransferase, serum albumin, prothrombin time, partial thromboplastin time, and factor VII (as appropriate for all patients and for patients with hepatic involvement)
2) Serum creatinine, urine creatinine, urine protein, and estimated glomerular filtration rate (as appropriate for all patients and for patients with renal involvement)
3) Lactate dehydrogenase, creatine kinase (CK), urine Hex4, and CK cardiac isozyme fraction for all patients.
[e] The appropriate visual screening assessment applied should be based on the patient's age (0-2 years, 3 years, or 4+ years).
[f] Cognitive/development assessments: Denver Developmental Screening Test II (0-2 years), modified Leiter International Performance Scale–Revised beginning when patient is >2 years.
[g] As appropriate, include assessment of motor milestones and motor functional activities, Medical Research Council scale, Walton and Gardner-Medwin scale, arm and leg functional tests, musculoskeletal assessments, and timed functional tests including the 6-minute walk test and measures of disability such as the Functional Independence Measure, Functional Independence Measure for Children (ie, WeeFIM), or Pompe Pediatric Evaluation of Disability Inventory. Since patients with Pompe disease are at increased risk for osteopenia, screening should include dual-energy x-ray absorptiometry and radiographic and orthopedic assessments.
[h] SF-36v2™ Health Survey, Rotterdam 9-Item Handicap Scale, and Fatigue Severity Scale should be completed by adult patients (18 years and older) simultaneously on an annual basis; in addition, the Rotterdam 9-Item Handicap Scale, and Fatigue Severity Scale should be completed by adult patients (18 years and older) simultaneously on a semiannual basis.
[i] See safety section (2.0) of the Pompe Disease Registry Protocol for specific reporting guidelines and instructions.
Abbreviation: ERT, enzyme replacement therapy.
Adapted with permission from Pompe Registry.[94]

Enzyme Replacement Therapy

The efficacy of ERT was initially demonstrated in studies using quail[95] and in mouse models of Pompe disease.[95-98] Subsequently, phase 1 and 2 clinical studies that investigated the use of rhGAA purified from transgenic rabbit milk[99,100] or rhGAA derived from Chinese hamster ovary cells[101,102] demonstrated improvements in overall survival, cardiac function, tissue morphology, skeletal muscle function, left ventricular mass index, and growth in patients with infantile-onset Pompe disease.

Clinical trials in infantile-onset Pompe disease

Results from 2 clinical trials of alglucosidase alfa demonstrated the benefits of early ERT in patients with infantile-onset Pompe disease. The results of the first trial,[84] a pivotal study of infants <7 months old at the start of ERT (n=18), and the second trial,[103] a study of children 6 to 42 months of age at the start of ERT (n=21), showed that these infants experienced a significant response to ERT, including a duration of survival that was longer than the duration of survival in an untreated natural history cohort.[84,103] In the natural history cohort, all but 1 patient died within the first 18 months of life (n=61).[84] In contrast, 15 of 18 patients from the first trial who received ERT and 16 of 21 patients from the second trial who received ERT were still alive after 18 months, and 15 of 18 and 10 of 16, respectively, were free of invasive ventilatory support. Patients who received ERT also demonstrated significant improvements in left ventricular hypertrophy, physical growth, motor and cognitive development, and duration of ventilator-free survival.

Clinical trials in late-onset Pompe disease

Studies of ERT in children and adults with Pompe disease have also demonstrated the effectiveness of alglucosidase alfa for late-onset patients. In an open-label study, 5 patients with late-onset Pompe disease were treated with 20 mg/kg of rhGAA every other week.[104] After 6 months of ERT, clinically meaningful increases in FVC (3 patients) and the distance walked in 6 minutes (3 patients) were noted. In another study, 3 patients (aged 11, 16, and 32 years) with late-onset Pompe disease were treated with rhGAA isolated from rabbit milk (10-20 mg/kg per week for 3 years).[105] All patients were using wheelchairs, and 2 patients were dependent on ventilators when they began ERT. Muscle strength improved in 2 patients during ERT. One patient was able to abandon his wheelchair after 73 weeks of treatment and had a normal age-related increase in FVC during treatment. Additionally, the patient's muscle morphology was nearly normal after 43 weeks of ERT. Muscle fibers of the other 2 patients remained variably affected by the disease. All 3 patients had improvements in quality of life and decreases in CK, ALT, AST, and LDH levels. In a follow-up study, these patients were observed for another 5 years of ERT. The 2 patients who remained wheelchair and ventilator dependent became more independent in their daily activities and quality of life improved. The third patient had substantial improvements in muscle strength, regained the ability to walk, and eventually reached normal strength and functioning values.[85]

In another open-label study, 18 juvenile and adult patients with severe late-onset Pompe disease were assessed after at least 6 months of treatment with alglucosidase alfa (duration of treatment ranged from 8 months to 6.3 years).[87] All 18 patients used wheelchairs and required ventilator support at the time of ERT initiation. Motor function improved in 72% of patients, and there was no decline in muscle strength or tone between baseline and the 6-month assessment. Ten patients experienced improved respiratory function, and most patients (15 of 16) reported improvements in their quality of life since starting ERT.

The Late-Onset Treatment Study (LOTS)

Additional clinical trials of alglucosidase alfa that have included patients with late-onset Pompe disease are ongoing or have recently been completed.[106-108] One of these was a randomized, double-blind, placebo-controlled investigation of the benefits of ERT in patients with late-onset Pompe disease.[40] This study evaluated the safety and efficacy of alglucosidase alfa in children and adults with late-onset Pompe disease; 90 patients at 8 sites in the United States and Europe were enrolled. All study patients showed evidence of disease progression before beginning treatment: 34.4% of patients required the use of nocturnal ventilatory support and 43.3% of patients used assistive walking devices. Patients who required invasive ventilation or who were unable to do the 6-minute walk test (6MWT) were excluded from the study. Study patients received either alglucosidase alfa (20 mg/kg every 2 weeks) or a placebo for 18 months. Overall, ERT patients showed marked improvements on both primary study end points: 6MWT distance and percent predicted FVC. Patients who received alglucosidase alfa had a mean increase in distance walked of approximately 30 meters, whereas patients who received a placebo did not show any improvement from baseline (p=0.03). Additionally, the percent predicted FVC at 18 months increased by 1% in patients treated with alglucosidase alfa, indicating stabilization of respiratory function. In contrast, percent predicted FVC progressively declined by approximately 2% in the placebo group (p=0.0019).

Safety and tolerability

Alglucosidase alfa is administered via intravenous infusion and is generally well tolerated. The standard dosage of ERT is 20 mg/kg alglucosidase alfa every 2 weeks, and infusions should be administered initially over approximately 4 hours.[103,105] The most commonly reported treatment-emergent adverse events in clinical studies were fever, rash, vomiting, cough, pneumonia, otitis media, upper respiratory tract infection, gastroenteritis, diarrhea, and decreased oxygen saturation.[103]

Immunogenicity may be a concern with the use of ERT, as it is with administration of any biological agent.[103] Findings from 34 of 38 infants (89.5%) tested in clinical trials of alglucosidase alfa were positive for immunoglobulin G (IgG) antibodies to the drug. Patients with sustained high anti–alglucosidase alfa antibody titers may develop a decreased response to the drug.[103] The formation of IgG antibodies occurred most often within the first 3 months of exposure,[103] and most patients showed a downward trend in antibody formation or they developed tolerance. Furthermore, the presence of IgG antibodies after treatment was not associated with an increased risk of anaphylactic reactions.

Serious hypersensitivity reactions, including anaphylactic reactions, have been reported during alglucosidase alfa infusion; hypersensitivity reactions were reported in 8 of 280 patients (3%) treated with alglucosidase alfa in clinical trials and expanded access programs.[103] In clinical trials and expanded access programs, 38 of 280 patients (14%) treated with alglucosidase alfa developed infusion reactions that involved at least 2 of 3 body systems (ie, cutaneous, respiratory, and/or cardiovascular systems).[103]

Response to ERT is variable within the body, and several factors have been suggested as contributors to this variability.[96,101,102,109] Some of these factors are patient age at start of ERT, the number of mannose 6-phosphate receptors (alglucosidase alfa binds to these receptors) in heart muscle versus skeletal muscle, the extent of underlying pathology (ie, muscle and lysosomal damage), the ERT dose as it relates to tissue delivery, and neutralizing antibody formation.[25] Additionally, type II (fast-twitch) muscle fibers appear to be more resistant to ERT than type I (slow-twitch) muscle fibers are.[49,96,109] Proposed reasons for this differential response include (1) differences between the fiber types in distribution and organization of their lysosomes, (2) lower levels of proteins involved in receptor-mediated endocytosis and lysosomal enzyme trafficking in type II fibers than in type I fibers, and (3) increased autophagic buildup in type II fibers, which results in diversion of rhGAA from the lysosomes.[48,49]

One additional factor should be considered regarding initiation of ERT: generally, ERT should begin as soon as possible after the diagnosis of Pompe disease is confirmed and if clinical symptoms are present. Some studies suggest that therapeutic intervention with ERT should start early in the disease course in order to maximize a patient's response to treatment. Patients who have already sustained extensive, irreversible muscle damage may have a variable or limited response to ERT.[9,84,86,110-113] Further studies of ERT will help clarify any issues surrounding efficacy.

Other Emerging Therapies

Progress continues in the development of other potential therapies for Pompe disease. Human tissue and animal studies have investigated gene therapy using a variety of vectors for delivery, including recombinant adeno-associated viruses (AAVs),[114-120] retroviruses,[121] and adenoviruses.[122-126] Results of studies in animal models of Pompe disease have suggested that gene therapy can restore GAA enzyme activity in skeletal and heart muscle and that the expression of the GAA gene in muscle or the secretion of GAA by the liver may ameliorate the glycogen storage abnormality.[114,115,118-120,122-126] In studies using cells from humans with Pompe disease, gene therapy has led to increased GAA enzyme activity and attenuation of the glycogen storage abnormality.[118,121-123] Additionally, studies of administration of an AAV vector in an animal model showed that immune tolerance to human GAA could be induced, resulting in nearly complete clearance of accumulated glycogen from skeletal muscle.[127,128] Furthermore, AAV vector–mediated gene therapy has the potential to prevent the development of antibodies to rhGAA and to enhance ERT in patients who have developed antibodies to rhGAA.[128] The results of gene therapy studies and preclinical work suggest that a curative therapy for Pompe disease may be possible in the future.

Another form of therapy that is in development is the use of chemical chaperones. Chaperones are low molecular weight chemicals that restore protein function by rescuing misfolded or unstable proteins from a cell's own degradation mechanisms.[129,130] These agents could potentially be used for treating patients with Pompe disease who produce some GAA. In vitro studies on the use of chaperones have been conducted by using cultured fibroblasts from patients with Pompe disease,[129,130] but clinical study data in humans are not available at this time, and the clinical usefulness of this therapy remains undetermined.

Case Studies

18-Year-Old Man With Muscle Weakness

The patient was an 18-year-old man from Manila, Philippines, who was diagnosed with Pompe disease at the age of 13. The diagnosis of Pompe disease was made on the basis of (1) muscle biopsy, which revealed storage of glycogen within lysosomes and the presence of vacuoles that stained positive for glycogen, and (2) reduction of GAA enzyme activity to approximately 25% of normal in cultured skin fibroblasts. The patient stated that he was in his usual state of health but that his exercise tolerance was limited by muscle weakness. He had no complaint of shortness of breath either on exertion or at rest.

Medical History

The patient and his family first noted symptoms of disease when the patient was about 10 years old. The patient's initial problems included inability to perform physical activities or to participate in sports at school. Symptoms progressed over the next few years, and the patient developed difficulty standing and climbing stairs. More recently, his weakness has progressed further, and he can now ambulate for only a few steps. In addition, weakness is now evident in his upper extremities, and he has difficulty lifting his arms to comb his hair and brush his teeth.

In the past year, the patient has also noted the onset of pulmonary symptoms, including several episodes of bronchitis that were treated with oral antibiotics. Approximately 4 months before the evaluation, the patient was diagnosed with pneumonia, for which he was hospitalized and treated with intravenous antibiotics. The patient did not require intubation with mechanical ventilation or noninvasive ventilation during these illnesses.

Physical Examination

Upon initial evaluation at the time of his hospital admission, the patient was awake and alert. There was significant weakness in the proximal muscles of the lower extremities, and his movement was severely limited; the patient was able to walk only 2 or 3 steps and required a wheelchair. He was able to speak, but dyspnea and cyanosis of the lips and fingertips were evident. Shallow respirations were noted, with a respiratory rate ranging from 20 to 25 breaths per minute. Arterial oxygen saturation, determined by pulse oximetry, was 80% while the patient breathed ambient air. Respiratory examination revealed crackles heard at the base of both lungs. His blood pressure, heart rate, and body temperature were normal.

Laboratory and Clinical Findings

Laboratory evaluation at the time of the patient's admission to the hospital revealed a normal white blood cell count and normal hemoglobin concentration. Blood electrolytes and renal function were within normal limits, with the exception of an increased bicarbonate concentration of 36 mEq/L. Arterial blood gas analysis revealed low partial pressure of oxygen (Po_2) and elevated partial pressure of carbon dioxide (Pco_2; Box 1a).

Box 1a. Arterial Blood Gas Analysis (breathing ambient air)

Parameter	Measured Value
pH	7.32
Pco_2	66 mm Hg
HCO_3	36 mEq/L
Po_2	49 mm Hg
O_2 saturation	80%

Box 1b. Evaluation of Pulmonary Function			
Parameter	**Measured Value**	**Predicted Normal**	**% of Predicted**
Vital capacity (upright)	0.4 L	4.3 L	9
Maximum inspiratory pressure	–15 cm H_2O	–133 cm H_2O	11
Maximum expiratory pressure	+15 cm H_2O	+250 cm H_2O	6
Maximum voluntary ventilation	14.9 L/min	149 L/min	10

Pulmonary function tests showed severe respiratory dysfunction (Box 1b). Chest radiography revealed submaximal inspiration with elevation of both hemidiaphragms. Multiple areas of linear atelectasis were noted at both lung bases. These findings were interpreted as evidence for severe diaphragmatic weakness with associated basilar atelectasis. There were no clinical or radiographic findings suggestive of acute pneumonia.

Course of Treatment and Clinical Outcomes

Pulmonary evaluation revealed chronic respiratory failure. Treatment with supplemental oxygen was immediately administered at the minimum flow rate required to achieve an arterial oxygen saturation of 90%. Noninvasive positive pressure ventilation (ie, bilevel ventilation) delivered via a nasal mask was started on the first hospital day. Ventilator parameters were set with the goals of augmenting the tidal volume and facilitating CO_2 excretion; expiratory pressure was set at the minimum pressure available on the ventilator (3 cm H_2O), and the inspiratory pressure was set at 14 cm H_2O. Ventilation was initially applied continuously to achieve a sustained reduction in arterial Pco_2 (Box 1c). Once a reduction in serum bicarbonate concentration was noted on the electrolyte panel, ventilation was rapidly weaned to nocturnal use only.

Box 1c. Follow-up ABG Analysis During Wakefulness (obtained on hospital Day 5 with the patient breathing spontaneously)	
Parameter	**Measured Value**
pH	7.33
Pco_2	49 mm Hg
HCO_3	26 mEq/L
Po_2	65 mm Hg
O_2 saturation	91%

Abbreviation: ABG, arterial blood gas.

The patient was discharged from the hospital after 6 days of treatment. He was instructed to use bilevel ventilation during sleep. Specific therapy for Pompe disease, such as ERT, was not available at the time that this patient was hospitalized. Therefore, no medications were prescribed, but the patient was instructed to return to his primary physician in Manila, where additional supportive treatments could be prescribed as medically indicated.

One year after hospitalization, the patient's ABG values remained unchanged, and his vital capacity had increased from 0.4 to 1.34 L. Subsequently, the patient has continued to use nocturnal maintenance ventilation. He was placed on nutritional and exercise therapy by his doctors in Manila. Reevaluation of the patient 1 year after this hospitalization revealed that the patient's muscle strength had improved and that he was able to ambulate with crutches.

Discussion

Chronic respiratory failure can be overlooked in patients with neuromuscular diseases such as Pompe disease. Progressive respiratory muscle weakness and impaired cough can lead to recurrent upper and lower respiratory tract infections, which often precede the development of chronic respiratory failure. As was the case with this patient, specific respiratory symptoms are frequently absent. In addition, exercise-induced symptoms may be difficult to elicit

because physical activity and ambulation may be limited by muscle weakness. Although careful examination revealed rapid shallow breathing in this patient, impaired respiration may be missed if the patient is not specifically observed in the supine position during the examination. Because of these considerations, the ACMG recommends annual evaluation of pulmonary function (or as clinically indicated) in all patients with late-onset Pompe disease.

In patients with late-onset Pompe disease, diaphragm weakness is often an early sign of the disease, and respiratory failure can be identified by an elevated blood bicarbonate concentration (a marker of renal compensation for carbon dioxide retention) on routine electrolyte evaluation. This finding should always prompt pulmonary function evaluation, which may include ABG analysis. In the present case, arterial Pco_2 and serum bicarbonate concentration were elevated, confirming the presence of chronic respiratory failure. Severe respiratory muscle weakness with reduction in vital capacity was also noted during the pulmonary function evaluation. Thus, initiation of noninvasive ventilatory support was associated with a rapid decrease in both arterial Pco_2 and bicarbonate concentration, highlighting the effectiveness of this treatment modality.

Optimal management of respiratory dysfunction in chronic neuromuscular disease may result in significant improvement in clinical and functional status. In the present case, ventilation could be tapered to nocturnal use only, with sustained reduction of arterial Pco_2. Additionally, the patient demonstrated improved muscular function over time, and he was eventually able to ambulate with crutches. Potential mechanisms for these improvements included resolution of respiratory failure with improved oxygenation, ventilation, and nutritional and exercise therapies. However, the relative importance of these factors will likely vary between patients.

In summary, this case report highlights several aspects related to the respiratory impairment that occurs in patients with late-onset Pompe disease: (1) the patient presented with chronic respiratory failure in the absence of specific symptoms and, notably, with no subjective report of dyspnea; (2) respiratory failure occurred despite some ability to ambulate; (3) patients with Pompe disease can be supported with the use of oxygen and/or noninvasive ventilation; and (4) dramatic clinical improvement can be seen with supportive respiratory therapy.

37-Year-Old Woman With Respiratory Insufficiency

The patient was a 37-year-old woman with Pompe disease who was referred for pulmonary evaluation. At the time the patient was referred, she could ambulate but used a cane. The patient was recently started on infusions of alglucosidase alfa.

Medical History

The patient was healthy until, at age 32, she started to notice muscle weakness when rising from a seated to a standing position, when walking or running, and when climbing stairs. Approximately 4 to 5 years passed before a neurologist accurately diagnosed the patient with Pompe disease. The patient had no respiratory symptoms when at rest or with exertion; however, she had a history of frequent respiratory infections.

The patient reported that she slept for 8 hours each night and rarely awakened. Occasionally, she woke up with a headache in the morning that usually resolved spontaneously after approximately 30 to 60 minutes.

Physical Examination

At the time of the initial evaluation, the patient was awake and alert and was not experiencing respiratory distress. Her respiratory rate was 20 breaths per minute, and her arterial oxygen saturation was 99% while breathing ambient air. Her blood pressure was 127/78 mm Hg and her heart rate was 79 beats per minute. She was able to speak full sentences comfortably. Lung examination revealed symmetrical chest expansion with clear breath sounds. Her cough strength was mildly to moderately reduced. Muscle weakness was noted in the patient's lower extremities; hip flexion and extension were rated at 4 to 4+ strength on the Medical Research Council (MRC) scale. The patient was able to ambulate slowly for several minutes, and she intermittently required the use of a cane.

Laboratory and Clinical Findings

Chest radiography revealed normal lung volumes without infiltrates. The results of ABG analysis (Box 2a) showed that arterial Pco_2 and bicarbonate concentrations were at the upper limit of normal. The patient was able to ambulate without the use of assistive devices and walked 393 meters during the 6MWT. The patient's upright vital capacity was within normal limits (89% of predicted), but her supine vital capacity was 66% of predicted, indicating diaphragm weakness (Box 2b).

Box 2a. Arterial Blood Gas Analysis (breathing ambient air)

Parameter	Measured Value
pH	7.42
Pco_2	45 mm Hg
HCO_3	29 mEq/L
Po_2	95 mm Hg
O_2 saturation	96%

Box 2b. Evaluation of Pulmonary Function

Parameter	Measured Value	Predicted Normal	% of Predicted
Vital capacity			
Upright	3.74 L	4.2 L	89
Supine	2.77 L	4.2 L	66
Change from upright to supine position	26%	<10%	
Maximum inspiratory pressure	–50 cm H_2O	–85 cm H_2O	59
Maximum expiratory pressure	+60 cm H_2O	+150 cm H_2O	40
Maximum voluntary ventilation	86.1 L/min	109 L/min	79

Subsequently, in the 2.5-year period between the diagnosis of Pompe disease and the initiation of ERT, the patient's upright vital capacity declined to 77% of predicted, her supine vital capacity declined to 54% of predicted, and her 6MWT distance decreased to 291 meters.

Course of Treatment and Clinical Outcomes

The patient began receiving infusions of alglucosidase alfa (20 mg/kg every other week). Follow-up data to assess the efficacy of ERT are not yet available.

Discussion

Late-onset Pompe disease is characterized by progressive respiratory muscle weakness that leads to reduced lung volumes and impaired cough. A feature that distinguishes Pompe disease from other neuromuscular disorders is the early and prominent involvement of the diaphragm, which occasionally leads to respiratory failure despite preserved ability to ambulate. Diaphragmatic weakness may be identified by a decrease in vital capacity when the patient moves from an upright to a supine position; a ≥10% decrease in vital capacity indicates diaphragmatic weakness, whereas a >30% decrease indicates severe weakness. In the case of this patient, upright vital capacity was normal, but a 26% decrease in capacity was noted when she was in the supine position. These findings highlight the need to consider the nature of respiratory muscle involvement when patients with Pompe disease are evaluated. Respiratory muscle weakness was confirmed in this patient by additional specific testing that revealed significant reductions in both inspiratory and expiratory muscle strength.

Sleep-disordered breathing is a complication that occurs frequently in patients with Pompe disease and in patients with other neuromuscular diseases. First, hypoventilation during sleep is often present in patients with Pompe disease because of the mechanical disadvantage of the supine position and because of the effect of sleep on respiratory control mechanisms. Second, decreases in upper airway tone may lead to obstructive respiratory events and may further compromise ventilation. Lastly, muscle weakness may impair the ability to compensate for obstructive sleep apnea (if present), which can lead to worsened hypercapnia and hypoxemia. If sleep-disordered breathing goes untreated, progression to cor pulmonale with cardiorespiratory failure and altered blood gas values during wakefulness may occur. In the case of patients with Pompe disease, the presence of diaphragmatic weakness may be predictive of hypoventilation during sleep and of the development of chronic respiratory failure during wakefulness.

In accord with the previous considerations, all patients with Pompe disease should be asked about the quality of their sleep to aid in the diagnosis of sleep-disordered breathing and nocturnal hypoventilation. Nocturnal hypoventilation may be difficult to identify because patients may snore or experience daytime sleepiness, which is common with obstructive sleep apnea syndrome. Therefore, specific questions should be asked about the presence of morning headaches that may be the result of acute episodes of hypoventilation and acidosis during sleep. In the case of this particular patient, morning headaches were intermittently noted; ABG analysis revealed borderline elevations of arterial Pco_2 and serum bicarbonate levels, which suggested that development of respiratory failure may have been imminent.

Nocturnal polysomnography is the preferred method for objective evaluation of sleep-disordered breathing in patients with late-onset Pompe disease. In addition, screening for hypercapnia should be performed by evaluation of either serum bicarbonate level or end-tidal Pco_2. Polysomnography should be performed at the time of the initial diagnosis of Pompe disease and should be repeated if the clinical condition becomes suggestive of sleep-disordered breathing. Sleep studies that gather only pulse oximetry and/or capnography data may provide an insufficient assessment of sleep-disordered breathing, although positive results may indicate nocturnal hypoxia or hypoventilation. Treatment should be based on the specific types of respiratory events identified during polysomnography. Although continuous positive airway pressure may be adequate for treatment of obstructive sleep apnea, nocturnal hypoventilation due to muscle weakness typically requires noninvasive bilevel ventilation.

In conclusion, this case report highlights several aspects related to the respiratory impairment that occurs in patients with late-onset Pompe disease: (1) routine evaluation of respiratory muscle function should include assessment of diaphragmatic function; (2) diaphragmatic weakness may precede and contribute to the development of chronic respiratory failure; (3) all patients should undergo clinical evaluation for sleep-disordered breathing, which should include both a targeted history and polysomnography; and (4) all patients should undergo screening for hypercapnia, with measurement of either serum bicarbonate level or end-tidal Pco_2.

62-Year-Old Woman With Muscle Weakness

This 62-year-old Caucasian woman was diagnosed with Pompe disease at the age of 39 years.[131] She had a history of muscle weakness and fatigue that, in retrospect, she believes first emerged when she was 27 years old. She was referred for pulmonary evaluation at the age of 56 years because of increasing problems with arousal from sleep and poor sleep patterns and because of an abnormal lung examination.

Medical History

At the age of 39 years, the patient began experiencing symptoms of chronic pain, muscle tenderness, and migrating arthralgias. This symptomatology led to a suspicion of ankylosing spondylitis; consequently, the patient was referred to a rheumatologist. An elevated eosinophil count was noted, and a punch muscle biopsy was performed to rule out polymyositis. The punch biopsy sample showed normal histochemistry, but vacuolar storage disease was seen, with glycogen deposits in both the lysosomes and cytoplasm. A needle EMG showed myopathic changes, and a diagnosis of Pompe disease was strongly suspected. The diagnosis was confirmed with the finding of deficient GAA enzyme activity in skin fibroblasts. At that time, the patient was unable to rise from a squat and had trouble getting out of a deep car seat. Additionally, a car accident when she was 15 years of age had resulted in chronic temporomandibular joint problems.

After being diagnosed with Pompe disease, the patient became severely depressed. Over the next 20 years, she accumulated additional diagnoses of fibromyalgia, gastroesophageal reflux disease, tennis elbow (from repetitive stress injury at work), osteoporosis, osteoarthritis, and decreased lung function. She began using a walker at age 51 because of repetitive falls and inability to achieve adequate support from a straight cane. Over time, the patient became sedentary and gained weight, reaching a weight of 222 pounds at the age of 54 years. At the age of 56 years, she had surgeries to replace her left knee and to correct a right ulnar fracture. Signs of osteoporosis were also seen, as indicated by vertebral compression fractures at T11 and L4. Bilevel ventilation was prescribed for overnight use, but was not well tolerated.

By the age of 58, the patient experienced a drop in oxygen saturation to approximately 85% while awake in the supine position, and she subsequently required continuous oxygen (2 L/min) via a nasal cannula during both the day and night. A year later, she was using a power scooter for mobility and had difficulty chewing because of weakened muscles of mastication.[131]

Laboratory and Clinical Findings

The results of pulmonary function tests are shown in Box 3a. The patient had no symptoms of overt respiratory insufficiency (eg, dyspnea), snoring, daytime hypersomnolence, or obstructive sleep apnea. Further examination revealed low lung volumes and bibasilar atelectasis on chest radiograph (right greater than left).

Box 3a. Pulmonary Function Improvements With ERT

Test	Baseline, 2-4 Years Before ERT (% of predicted)	After 18 Months of ERT (% of predicted)
Forced vital capacity	36	45
Forced expiratory volume in 1 s	39	47
Peak expiratory flow	…	63
Total lung capacity	46	45
Residual volume	…	50

Abbreviation: ERT, enzyme replacement therapy.

Course of Treatment and Clinical Outcomes

The patient began ERT (20 mg/kg every 2 weeks) at the age of 61 years. She participated in physical therapy, including aquatics, 1 or 2 times per week. She has reported that she is experiencing steady improvement and is more enthusiastic about participation in physical activities. In the past, her ability to exercise was limited by substantial fatigue.

Standard clinical assessments have been repeated every 6 months, with additional assessments, as needed, for specific issues. Evaluations of gross motor function have included impairment level measurements such as manual muscle testing, strength testing with dynamometry, timed functional tests, and the Gross Motor Function Measure (Box 3b), as tolerated. Additionally, the Functional Independence Measure (Box 3c) has been used to assess disability. Complete strength testing (using manual muscle testing) was generally not possible because the patient fatigued easily, but increased strength was noted in hip flexion and knee extension (Box 3d). The patient's tolerance for specific testing has also increased (ie, without the patient becoming fatigued).

Box 3b. Gross Motor Function Measure		
Dimension	**Baseline (3 years before ERT)**	**After 18 Months of ERT**
Lying and rolling	0% (unable to tolerate supine position without oxygen desaturation)	35% (able to tolerate supine position for testing without oxygen desaturation; O_2 level maintained at 96%-98%)
	Unable to tolerate prone position because of back pain	Unable to tolerate prone position because of back pain
Sitting	47%	60%
Crawling and kneeling	Unable to tolerate because of knee replacement	Unable to tolerate because of knee replacement
Standing	31%	38%
Walking, running, and jumping (without assistive devices)	0%	17%
Total gross motor functioning	15.6%	30%
Abbreviation: ERT, enzyme replacement therapy.		

Box 3c. Functional Independence Measure and Dynamometry		
Measure	**Baseline (before ERT)**	**After 12 Months of ERT**
Functional Independence Measure	73 (out of 126)	116 (out of 126)
Grip and lateral pinch strength (measured by dynamometry)		
Grip (average of 3 trials on each side)	37	36
Lateral pinch (average of 3 trials on each side)	10	10
Abbreviation: ERT, enzyme replacement therapy.		

Box 3d. Improvements in Strength Testing With ERT		
Function (MRC Score)	**Baseline (21 months before ERT)**	**After 12 Months of ERT**
Hip flexion	0 (no range of movement; patient could not tolerate supine position for testing with gravity minimized)	2+ (bilaterally; approximately 50% of the expected range for antigravity in seated position)
Knee extension	3 (right side) 3+ (left side)	4 (bilaterally)
Abbreviations: ERT, enzyme replacement therapy; MRC, Medical Research Council.		

Numerous changes have been seen in functional test results, as shown in Box 3e. Before starting ERT, the patient used a motorized scooter for mobility, was unable to stand without hand support, was unable to take steps without the use of a walker, and had been unable to climb stairs for many years. After receiving ERT for 6 months, the patient regained her ability to stand without hand support. Additionally, she was able to ascend and descend several stairs with the use of 2 railings. Eighteen months after starting ERT, the patient was able to take independent, sequential steps without hand support, stand independently without hand support, stand on one foot for 6 seconds, and ascend and descend stairs (maximum of 6 standard 7-inch steps, while holding 2 railings). By 24 months after ERT initiation, the patient had continued to experience gains in motor function: she was able to walk short distances without the aid of a walker and was able to climb a full flight of stairs by using 2 railings for support.[131]

Box 3e. Functional Improvements With ERT			
Measure	**Baseline (before ERT)**	**After 6 Months of ERT**	**After 18 Months of ERT**
Standing	With hand support alone	Stand without support for 34 s	Stand without support for 3.5 min
Walking – assisted (ie, with a walker)	30 ft in 20 s	30 ft in 14 s	30 ft in 10 s
Walking – independent (ie, without a walker)	Unable to walk without assistance	Unable to walk without assistance	16 steps
Climbing stairs (using handrails)	Unable to climb stairs	4 steps (6-in high) in 15.75 s	4 steps (7-in high) in 11.75 s
Abbreviation: ERT, enzyme replacement therapy.			

Since the start of ERT, results of pulmonary function studies have revealed marked improvements (Box 3a). For the first time in more than 4 years, the patient was able to tolerate supine positioning and maintained an oxygen saturation of 98% while supine. She remained on oxygen (2 L/min) at night because of her inability to tolerate bilevel ventilation, but she was eventually able to discontinue supplemental oxygen at night.[131]

Discussion

This patient has shown substantial improvements in gross motor and pulmonary function status since she began ERT—in spite of her advanced age, the longevity and previously progressive nature of her symptoms, and her state of physical impairment. She now displays a notable difference in her affect and describes her energy level as improved, and she states that she feels "more like getting up and going places." This case strongly highlights the potential for clinically significant gains in older patients with late-onset Pompe disease, even in patients with long-standing, clinically advanced symptoms.

11-Year-Old Boy With Severe Respiratory Dysfunction

This ambulatory 11-year-old boy has a history of extensive respiratory dysfunction and mild motor difficulties. Pulmonary dysfunction was first noted when the patient was an infant, and it was his predominant clinical symptom when he was diagnosed with Pompe disease at the age of 10 years. Pompe disease was suspected because of lower extremity skeletal muscle weakness that presented and had progressed since the patient was 8 years old. He was referred for assessment because of the new diagnosis of Pompe disease and for initiation of ERT.

Medical History

The patient's birth was full-term and otherwise normal. He had a tonsillectomy and adenoidectomy at the age of 1 year because of recurrent infections. His history of pulmonary and respiratory symptoms began early with dyspnea, and he had symptoms of asthma in childhood including chest pain, shortness of breath, and cough with wheezing during heavy play. At the age of 4.5 years, he started snoring, and apnea with resuscitative gasping during sleep was noted. His daytime symptoms included sleepiness and inattention. Polysomnography was performed, and the results were suggestive of obstructive sleep apnea. He began using nocturnal bilevel ventilation at 5 years of age. The lack of obesity or other physical explanation for the obstructive sleep apnea led to repeated adenoidectomies to correct tissue regrowth after the tonsillectomy. Results from a follow-up polysomnography at the age of 6 years were normal, and bilevel ventilation was discontinued, but it was reinitiated when an increase in daytime sleepiness was reported. The patient also continued to experience frequent respiratory infections. A history of chronic daytime headaches was considered to be secondary to obstructive sleep apnea, but the headaches did not improve with nocturnal bilevel ventilation.

The patient experienced a general deterioration in his lower extremity muscle strength at about the age of 8 years. Furthermore, the patient had notable intermittent weight loss that was associated with difficulty in swallowing.

Laboratory and Clinical Findings

When the patient was initially referred, he presented with skeletal muscle weakness that was somewhat subtle, as he compensated fairly well functionally (Box 4). He walked and ran independently, including running up and down stairs, and was independent in all positions and in transitions between them. However, he reported fatigue and an inability to keep up with his peers when running. Weakness was greater proximally than distally, and greater in scapular musculature than in pelvic girdle musculature. He walked with a bilateral heel-toe gait without obvious gait deviations, except for slightly excessive spinal extension at the lumbar level, accompanied by thoracic kyphosis and scapular winging. Upon manual muscle testing, proximal weakness was evident around the pelvic girdle, with hip abductors and hip adductors showing grades of 3+, and hip extensors and flexors showing grades of 4 to 4+ with the MRC scoring system. Atrophy was noted in rotator cuff musculature, with scapular winging more than protraction, which suggested greater functional weakness in the rhomboid muscle and trapezoid muscle than in the serratus anterior muscle. Grip and lateral pinch strength, as measured by dynamometry, were within the reference range for the patient's age and gender. Mild hypoextensibility was present in ankle plantar flexors and hamstrings.

Course of Treatment and Clinical Outcomes

The patient participates in physical therapy in the school setting, occupational therapy, and aquatic therapy. He uses noninvasive bilevel ventilation at night. He started ERT (20 mg/kg every 2 weeks) at age 11 years, but he has not yet been seen for follow-up.

Box 4. Initial Assessments of Physical Function

Function	Result (before ERT)
Supine to standing	5 s
Walking	30 ft in 6 s
Running	30 ft in 3 s
Climbing stairs	4 steps (7-in high) in 1.75 s

Abbreviation: ERT, enzyme replacement therapy.

Discussion

This case report demonstrates that respiratory involvement can be greater than skeletal muscle involvement at presentation, with muscle involvement identified only upon detailed testing. Thus, increased awareness of the common respiratory symptoms that are encountered in patients with late-onset Pompe is essential, particularly when respiratory symptoms are accompanied by only subtle signs of muscle weakness (eg, scapular and pelvic girdle muscle weakness). Increased awareness of this presentation is also important for earlier diagnosis and for consideration of ERT to prevent disease progression, particularly early on, when treatment may be most successful in maintaining a patient's strength over time.

Conclusions

Late-onset Pompe disease is a rare, progressive, autosomal recessive disorder that affects children and adults of all ages. This disease is characterized by complete or partial deficiency of the enzyme GAA, resulting in lysosomal glycogen accumulation in many tissues of the body, which then leads to progressive debilitation, organ failure, and death. Disease progression and symptomatology are highly variable between individuals, which complicates diagnosis of Pompe disease. However, recent advances in diagnostic technologies (eg, blood-based enzyme assays) have made the diagnosis of Pompe disease easier and more expeditious.

Until recently, no specific treatments for Pompe disease were available, and patients were treated with palliative care only. Multidisciplinary care and the use of ERT have substantially altered outcomes for many patients with Pompe disease. These patients have experienced improvements in muscle strength, pulmonary function, and other disease symptoms. Furthermore, early diagnosis has become increasingly important with the advent of ERT for the treatment of Pompe disease, as patients who begin ERT sooner in the course of the disease have a better chance for substantial improvements than do patients who begin treatment later.

There is more to be learned about Pompe disease, and future studies should address issues surrounding diagnosis, disease progression, and therapeutic interventions. The natural history of Pompe disease in late-onset patients will continue to change as we learn more about clinical presentations and responses to therapies. Coordinated care and optimal treatment strategies have the potential to increase survival and improve the quality of life for patients with Pompe disease.

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Appendix

Sources of information and support for patients with Pompe disease and for their families

Acid Maltase Deficiency Association
www.amda-pompe.org
PO Box 700248
San Antonio, TX 78270-0248
Phone: 210-494-6144

Association for Glycogen Storage Disease
www.agsdus.org
PO Box 896
Durant, IA 52747
Phone: 563-785-6038

Helping Hands, Loving Hearts Foundation
www.hhlh.org
1630 N Lawrence Court
Wichita, KS 67206
Phone: 316-687-6058

International Pompe Association
www.worldpompe.org
Lt Gen van Heutszlaan 6
3743 JN Baarn
The Netherlands
Phone: 00-31-35-5480461

Muscular Dystrophy Association
www.mdausa.org
3300 E Sunrise Drive
Tucson, AZ 85718
Phone: 1-800-FIGHT-MD (344-4863)

National Organization for Rare Disorders
www.rarediseases.org
55 Kenosia Avenue
PO Box 1968
Danbury, CT 06813-1968
Phone: 203-744-0100

United Pompe Foundation
www.unitedpompe.com
5100 N Sixth Street #119
Fresno, CA 93710
Phone: 559-227-1898

Notes

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