POMPE DISEASE IN INFANTS AND CHILDREN

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Pompe disease, also referred to as *glycogen storage disease type II* and *acid maltase deficiency*, is a genetic muscle disorder caused by a deficiency of acid α-glucosidase (GAA, also referred to as *acid maltase*).[1] This enzyme defect results in lysosomal glycogen accumulation in multiple tissues and cell types, with cardiac, skeletal, and smooth muscle cells (Fig 1) the most seriously affected.

Clinically, Pompe disease encompasses a range of phenotypes. Infantile-onset Pompe disease is uniformly lethal. Affected infants present in the first few months of life with hypotonia, generalized muscle weakness, and a hypertrophic cardiomyopathy, followed by death from cardiorespiratory failure or respiratory infection, usually by 1 year of age.[1,2] Juvenile and adult-onset disease (late-onset forms) is characterized by a lack of severe cardiac involvement and a less severe short-term prognosis. Symptoms may start at any age and are related to progressive dysfunction of skeletal muscles. With disease progression, patients become confined to wheelchairs and require artificial ventilation. Respiratory failure is the cause of significant morbidity and mortality in this form of the disease. The age of death varies from early childhood to late adulthood, depending on the rate of disease progression and the extent of respiratory muscle involvement.

In addition to being a lysosomal storage disorder, Pompe disease is classified as a neuromuscular disease, a metabolic myopathy, and a glycogen storage disease (in fact, Pompe disease is the only glycogen storage disease that is also a lysosomal storage disorder). The infantile form is also considered a cardiac disorder because of the prominent cardiac involvement.

There is currently no treatment other than supportive care for Pompe disease. Drugs such as epinephrine and glucagon, which enhance cytosolic glycogen breakdown, have no therapeutic effect.[3] Therapies that alter the synthesis of glycogen, such as high-protein diets and alanine, can have transient clinical benefits in some patients[4-7] but do not reduce the glycogen accumulation. Early attempts at enzyme replacement therapy with unphosphorylated GAA from *Aspergillus niger* or human placenta did not alter the clinical course of affected infants.[8-11] Bone marrow transplantation has not been successful.[12] However, recent clinical trials of enzyme replacement have been promising,[13-16] and for the first time, there is hope for patients with this often fatal disease. Other important advances include a better understanding of enzyme synthesis and trafficking, extensive mutation analysis in patients with different forms of the disease, generation of animal models for preclinical studies to direct therapeutic endeavors, and development of viral vectors for gene transfer.[17]

With enzyme replacement therapy likely to become available in the near future and other therapies on the horizon, early disease recognition is increasingly important so that patients can receive prompt and appropriate therapy. In infants, this recognition will be critical, because the available window of treatment after diagnosis is extremely short.

HISTORY AND NOMENCLATURE

Pompe disease was first described by Dutch pathologist J. C. Pompe[18] in 1932. In 1963, it became the first disease to be classified as a lysosomal storage disorder, after the discovery by de Duve et al[19] of this cellular organelle and the linkage by Hers et al[20] of the basis of the disease to an inherited deficiency of an enzyme within the lysosome.

CK	Creatine kinase	MPS	Mucopolysaccharidosis
GAA	Acid α-glucosidase		

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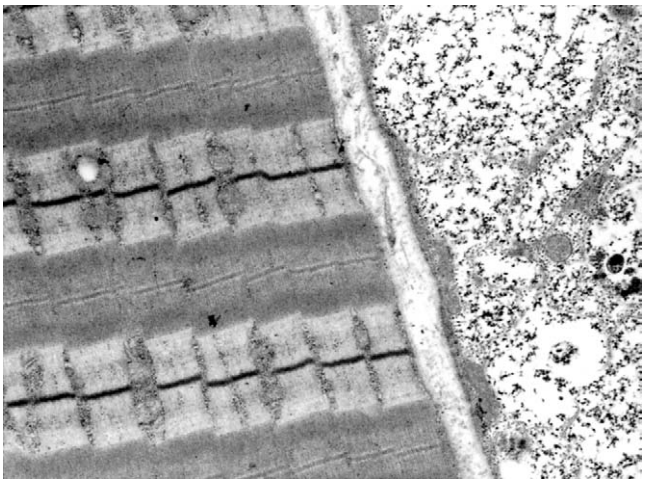

Fig 1. Glycogen deposition in muscle of a patient with Pompe disease. Electron micrograph. A normal fiber is on the left. The fiber on the right is replaced by glycogen. Original magnification ×4400.

The nomenclature used to describe patients with Pompe disease is varied. As noted, the disease has several synonyms (Pompe disease, glycogen storage disease type II, acid maltase deficiency). In addition, because of overlapping signs and symptoms, there is currently no standard way to classify the different disease presentations. Because the first patient described by Pompe was an infant, some clinicians use the term *Pompe disease* for patients with the infantile presentation and refer to the later-onset forms (juvenile-onset and adult-onset) as *glycogen storage disease type II* or *acid maltase deficiency*. In addition, patients who present in infancy without severe cardiac manifestations are variously grouped with later-onset patients (who also lack significant cardiac involvement) or considered a subset of the infantile-onset group, referred to as *nontypical*, *nonclassic infantile-onset*, or *muscular variant*. Here we use the term *Pompe disease* to describe all patients with GAA deficiency, regardless of age of onset, because the enzyme deficiency is the underlying cause of the disease regardless of its manifestations. Although Pompe disease may best be described as having a spectrum of severity, in this review, we categorize the wide spectrum of presentations in Pompe disease into infantile-onset, presenting before age 1 year and associated with a very rapid course and very early death, and late-onset, presenting any time after age 1 year. The latter broad category includes both juvenile-onset and adult-onset patients.

INCIDENCE AND INHERITANCE

As with many rare genetic diseases, incidence data on Pompe disease are scattered and incomplete, with reported incidence ranging from one in 14,000 to one in 300,000, depending on the geographic area or ethnic group examined.[1] The infantile-onset form has an apparent higher incidence among African Americans and in southern China and Taiwan,[1] whereas the late-onset adult form has an apparent higher incidence in The Netherlands.[21] The combined incidence of all forms of Pompe disease is estimated to be 1:40,000.[1,21,22]

Table I. Acid-α-glucosidase activity in fibroblasts of patients with Pompe disease*

	Enzyme activity (% of normal)†
Infantile-onset (<12 mo)	<1%
Late-onset	
Children and juveniles	~1%–10%
Adults	~2%–40%

*Estimates from Hirschhorn and Reuser[1] and Chen and Amalfitano[2]
†Results of the enzyme assay can vary somewhat depending on the substrate used (4-methylumbelliferyl-α-D-glucopyranoside, maltose, or glycogen).

The gene has been localized to chromosome 17q25 and is designated GAA on the human gene map.[23] Pompe disease is inherited in an autosomal-recessive manner; thus, both parents of a child with the disease are carriers of a mutant gene. Siblings have a 25% chance of having the disease and a 50% chance of being carriers. More than 120 mutations in the GAA gene that give rise to Pompe disease have been identified and are cataloged by the Erasmus University Medical Center in Rotterdam (http://www.eur.nl/FGG/CH1/pompe/). The type of mutation is often a good predictor of clinical phenotype,[17] such as the leaky IVSI(–13T→G) splice-site mutation found in more than half of all late-onset Caucasian patients,[24] the Asp645Glu mutation found in most infantile-onset patients from Taiwan,[25] and the Arg854stop common nonsense mutation found in many African or African American infantile-onset patients.[26] However, genotype does not always match phenotype, suggesting the role of modifying genes.[27-31]

CLINICAL PRESENTATION

As a genetic disease, Pompe disease is present at birth and is progressive, regardless of when signs and symptoms become apparent. All presentations have a varying degree of myopathy but differ with respect to age at symptom onset, organ involvement, and rate of progression—factors that are determined in part by residual GAA activity and other genetic (eg, type of mutation, modifier genes) and environmental influences. In general, age of onset appears to correlate with residual GAA level, which tends to correlate inversely with disease severity (Table I); thus, in general, the later the onset, the higher the residual GAA level, and the better the prognosis.

Myopathy, prominent in the majority of affected infants and eventually in all affected children and adults, results in progressive muscle weakness in the trunk, lower limbs, and diaphragm.[1] Severe cardiomegaly and cardiomyopathy are prominent only in patients with the infantile-onset presentation. Tables II and III summarize the signs and symptoms that may indicate Pompe disease in infants and in children.

Infantile Onset

Infants with Pompe disease have virtually no GAA activity and present in the first few months of life with feeding

Table II. Signs and symptoms of Pompe disease in infants

Rapidly progressive and profound muscle weakness (~96% of infants)
Floppy baby appearance
Calf muscles feel firm on palpation
Axial hypotonia
Head lag
Laxity of facial muscles
Infant slips through when grasped under the arms
Areflexia (in late stages of disease)
Cardiomegaly and cardiomyopathy and/or cardiac failure (~95% of infants)
Moderate hepatomegaly (~82% of infants)
Macroglossia (~62% of infants)
Feeding difficulties (difficulty sucking and swallowing) and poor weight gain
Frequent respiratory infections
Respiratory distress or insufficiency with increased work of breathing
Delayed motor milestones
Markedly elevated CK
Rapidly progressive disease course

problems, poor weight gain, respiratory difficulties frequently complicated by pulmonary infection, or delayed motor milestones. Most infants have a profound, generalized muscle weakness. Despite this, the muscles generally feel firm, even hypertrophic, but the infant is unable to hold up the head or move normally, resulting in floppiness and head lag (Fig 2). More than half of the infants also have macroglossia, moderate hepatomegaly, or both. Other cardinal features apparent with laboratory investigation include cardiomegaly and markedly elevated plasma creatine kinase (CK).[32] Glycogen accumulation is found in cardiac, skeletal, and smooth muscle tissue; in the liver; and in the central nervous system in the anterior horn cells and motor neurons of brainstem.

Infantile-onset Pompe disease results in very early demise, particularly for those infants (the majority) with significant cardiac manifestations before 6 months of age. These classic or typical infants present in the first few months of life and rarely survive beyond their first birthday. A subset of infants, referred to by Slonim et al[33] as "atypical," present a few months later and have less severe cardiomyopathy and a somewhat better prognosis, with survival to age 2 years. These infants are sometimes misdiagnosed with Werdnig-Hoffmann disease or a congenital muscular dystrophy.

Cardiomegaly and Cardiomyopathy

Most infants with Pompe disease develop massive and progressive cardiomegaly before 6 months of age (Fig 3). Glycogen accumulation in cardiac muscle causes thickening of the walls of both ventricles and interventricular septum, resulting in a hypertrophic cardiomyopathy, which progresses to a dilated cardiomyopathy. Increasing left ventricular thickness can also lead to obstruction of the left ventricular outflow tract. At autopsy, the heart can be as much as three times its normal size (Fig 4), commonly with endocardial fibroelastosis. Electrocardiographic findings are striking, revealing a shortened PR interval often accompanied by large QRS complexes, a feature that can differentiate Pompe disease from other causes of cardiac disease in infants.

Infants with the atypical infantile form of Pompe disease develop left ventricular hypertrophy after age 6 months but without outflow obstruction, allowing more normal cardiac function.[33]

Table III. Signs and symptoms of late-onset Pompe disease in children (age 1 year and older)*

Progressive muscular weakness (all patients)
Predominantly proximal
Delayed motor milestones
Lower limbs affected more than upper
Calf muscle hypertrophy
Involvement of paraspinal muscles (older children)
Gower sign
Hypotonia
Decreased deep tendon reflexes
Swallowing difficulty
Respiratory problems
Frequent respiratory infections
Respiratory insufficiency or failure
Exertional dyspnea
Obstructive sleep apnea
Orthopnea
Exercise intolerance
Elevated CK
Moderate hepatomegaly (~29%)
Cardiomegaly and cardiomyopathy (less severe than in infantile-onset ~4%)
Macroglossia (infrequent)
Morning headache
Somnolence
Waddling gait
Lower back pain
Decreased deep tendon reflexes
Lordosis, kyphosis, and/or scoliosis
Normal intelligence

*Late-onset Pompe disease is very heterogeneous; the absence of one or many of these clinical indicators does not rule out the possibility of the disease.

Late Onset

Late-onset Pompe disease can present any time from the toddler years to adulthood. Virtually all children who present after age 2 years have no significant cardiac manifestations, slower progression of muscle disease, and a less severe prognosis than infantile-onset cases. Late-onset Pompe disease, particularly in adults, can pose a diagnostic dilemma.

Residual GAA activity (in skin fibroblasts) can be as much as 10% of normal in patients who present in childhood or adolescence, and as much as 40% of normal in patients who present in adulthood (Table I). Primary manifestations and

Fig 2. Hypotonia and head lag in patient with infantile-onset Pompe disease. Note the profound hypotonia and head lag in this 7-month-old girl. Reprinted with permission from The McGraw-Hill Co.[51]

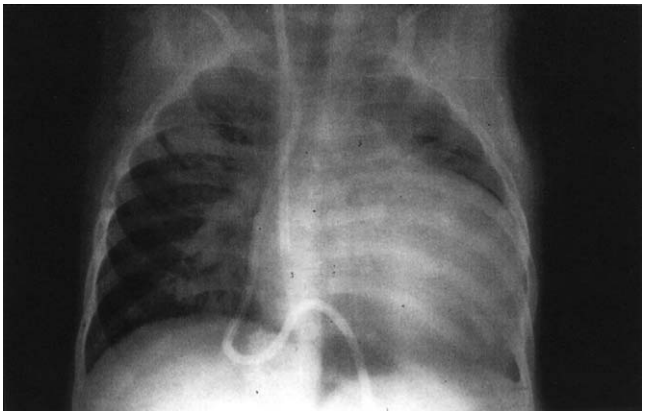

Fig 3. Cardiac hypertrophy in infantile-onset Pompe disease. This chest film is from a 5-month-old boy with infantile-onset Pompe disease. The massive heart dominates the film with a cardiothoracic ratio of 0.65.

organ involvement vary, but patients with late-onset Pompe disease experience slowly progressing muscle weakness. Proximal muscles (trunk and proximal muscles in lower limbs) are usually affected first, followed by involvement of the diaphragm and other muscles that aid in respiration, leading to pulmonary insufficiency and sleep-disordered breathing. Weakness of hip muscles leads to trouble walking. Toddlers can present with delayed motor milestones. Lordosis or kyphosis/scoliosis are common in older children. Possible differential diagnoses (Table III) include muscular dystrophy, polymyositis, spinal muscular atrophy, scapuloperoneal syndromes, rigid spine syndrome,[34] obstructive sleep apnea, and Danon disease.[35]

The disease can also present in adulthood, with onset from the 2nd to the 6th decade. However, many patients who are diagnosed as adults recall symptoms of Pompe disease in childhood, such as some degree of easy fatigability, exertional dyspnea, or both. In adults, the predominant symptom is slowly progressing proximal muscle weakness in lower extremities with truncal involvement, respiratory insufficiency, or both.[36] Not all muscles are equally affected, even in the same area. Deep tendon reflexes disappear as the disease progresses. Approximately one third of all adult cases present as respiratory failure.

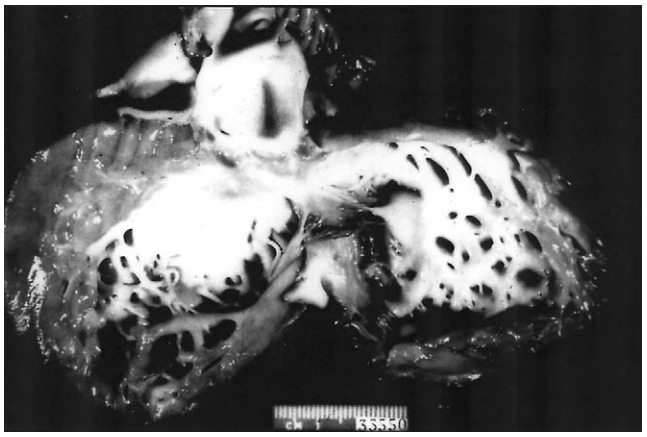

Fig 4. Heart at autopsy of 5-month-old girl with infantile-onset Pompe disease. The heart is greatly enlarged with thickened ventricles because of extensive glycogen deposition. There is some endocardial thickening. Reprinted with permission from The McGraw-Hill Co.[4]

DIAGNOSIS

Infantile-onset Pompe disease is usually recognized because of the unique and acute constellation of findings. However, precious time can be lost between onset of symptoms and consideration of a diagnosis of Pompe disease. Most infants survive only a few months beyond their diagnosis.[15,37] Because the disease progresses so rapidly, it is imperative that pediatricians and pediatric specialists become aware of possible signs and symptoms of Pompe disease and how to establish a differential diagnosis so that these infants can receive available therapy as soon as possible.

In older children, symptoms are more subtle and attenuated, and diagnosis can be delayed for years. Ausems et al[32] have proposed an algorithm involving CK measurement for diagnosis of Pompe disease in adults that may be a valuable screening tool appropriate for infants as well. Table IV lists some diagnoses often considered in the differential diagnosis of both infantile-onset and late-onset Pompe disease.

Although the laboratory findings described here are important in establishing a differential diagnosis, GAA assay in muscle or skin fibroblasts remains the gold standard because it can render a definitive diagnosis of Pompe disease. Several diagnostic procedures that do not require tissue biopsy are in development, including measuring glucose oligosaccharides or the total concentration of GAA protein (precursor and mature forms) in urine, plasma, or blood spots.[38-40]

Once Pompe disease is diagnosed, testing of all family members and consultation with a professional geneticist should be encouraged. Carriers are most reliably identified through mutation analysis.

Blood Chemistry

Blood tests in infants and children should include a serum CK examination as an early step to determine whether more invasive testing is warranted, because CK elevation is a sensitive although very nonspecific marker for Pompe disease.[32] The greatest elevation is usually found in infantile-onset patients (as high as 2000 UI/L).[32] Approximately 95% of late-onset patients have an elevated CK[32]; however, some adults with Pompe disease may have CK levels within the normal reference range. Serum enzymes such as aspartate aminotransferase, alanine aminotransferase, or lactate dehydrogenase may be elevated and may reflect enzymes released from muscle.[41]

Patients with Pompe disease, unlike patients with other forms of the glycogen storage diseases, have glycogen storage in the lysosomes and therefore do not typically display abnormalities of glucose metabolism such as hypoglycemia and other metabolic abnormalities. In addition, their responses to epinephrine and glucagon administration are normal.

Electromyography

Electromyography generally reveals a myopathic pattern in all patients with Pompe disease, although some muscles may appear normal in late-onset patients. Other common findings may include pseudomyotonic discharges (myotonic discharges without clinical myotonia), fibrillation poten tials, positive sharp waves, and excess electrical irritability. Conduction times for motor and sensory nerves are usually normal.[1,42,43]

Chest Imaging Studies

In many cases, a chest radiograph showing massive cardiomegaly provides the first clue that an infant may have Pompe disease. Beyond that, both echocardiography and electrocardiography are important tools in establishing a differential diagnosis of Pompe disease in infants and in determining the degree of cardiac involvement. Late-onset patients rarely ever display hypertrophy of the heart.

In infantile-onset patients, echocardiography may reveal thickening of both ventricles or the intraventricular septum or left ventricular outflow tract obstruction, whereas electrocardiography typically shows a shortening of the PR interval as well as very tall and broad QRS complexes. Late-onset patients (adult-onset presentation) have normal patterns.

Acid α-glucosidase Assay

Once a constellation of symptoms and laboratory findings suggestive of Pompe disease is noted, the confirmatory step is a GAA enzyme assay. This assay is usually performed in muscle or cultured skin fibroblasts by using maltose, glycogen, or 4-methylumbelliferyl-α-D-glucopyranoside as a substrate. The skin fibroblast assay is usually preferred because the skin biopsy procedure is less invasive and cell lines can be maintained for future use. However, a muscle biopsy can yield faster results and can provide additional information about glycogen content and site of glycogen storage within and outside the lysosomes of muscle cells. A major limitation of a muscle biopsy in late adult-onset patients is the variable pathology and glycogen accumulation in different muscles and within muscle fibers; thus, muscle histology and glycogen content can vary depending on the site of biopsy. In adults, skin biopsy can also be challenging when GAA activity is in the low normal range; in these situations, clinical correlation is necessary.

Measurement of GAA activity in whole leukocytes is not reliable because of the presence of several neutral maltases, which may have residual activity at an acid pH. Thus, patients affected with Pompe disease have been reported to have only mildly reduced or near-normal GAA activity from measurements performed in whole leukocytes.[44] Use of peripheral blood mononuclear cells is preferred to whole leukocytes for screening but does not provide an accurate quantitative measure of enzyme activity.[45]

Table IV. Possible misdiagnoses for Pompe disease

Infantile onset
Werdnig-Hoffmann disease
Hypothyroidism
Benign congenital hypotonia
Endocardial fibroelastosis
Myocarditis
Krabbe disease
Congenital muscular dystrophy
Peroxisomal disorders
Respiratory chain disorders
Late onset
Polymyositis
Limb-girdle muscular dystrophy
Muscular dystrophy, Becker type
Scapuloperoneal syndromes
Rigid spine syndrome
Myasthenia gravis
Familial dysautonomia
Danon disease

Prenatal Diagnosis

The preferred method of prenatal diagnosis is direct enzyme analysis of uncultured chorionic villus cells. Amniocentesis is also possible, but enzyme levels are lower in normal cultured amniotic cells than in direct chorionic villi, and results are not available until later in the pregnancy. Given the possibility of maternal cell contamination, an experienced clinician should oversee the direct enzyme assay in uncultured chorionic villus cells. If the family mutation has been identified, mutation analysis can also be performed on cells obtained by either chorionic villus sampling or amniocentesis.

DISEASE MANAGEMENT

Like all lysosomal storage disorders, Pompe disease is best managed with a multidisciplinary treatment team

coordinated by a physician with experience treating this rare disorder. Team members should include a professional geneticist (who may be the treating physician) in addition to the specialists dictated by the disease manifestations, who may include a cardiologist, neurologist, pulmonologist, respiratory therapist, physical therapist, occupational therapist, speech therapist, and metabolic dietitian.

All specialists involved in the care of an infant or child with Pompe should have an understanding of the disease, its broad manifestations, and its special challenges, including the psychological effect of this devastating disease on patients and families. Organizations that provide information, networking, and support for Pompe families are listed in the Appendix.

Currently, treatment options for Pompe disease are limited to supportive or palliative care. However, treatments that address the underlying cause of the disease are in development, most notably enzyme replacement therapy, which is in clinical trials, and gene therapy,[45] which is still in preclinical stages. Bone marrow transplantation has not been found to be effective because of poor enzyme penetration in muscle tissue[1]; however, newer methods involving mesenchymal stem cell transplantation could be more successful.[2]

Supportive Therapy

Supportive therapy greatly improves the quality of life for patients with Pompe disease and can minimize complications of the disease; however, it does not alter the disease course.

Respiratory Support

Infants and some children with Pompe disease have a severely weakened diaphragm and intercostal muscles and may require mechanical ventilation to reduce or eliminate the work of breathing. Infantile-onset patients often have a left lower lobe collapse because of compression of the left mainstem bronchus by the massively enlarged heart. Depending on the patient and the degree and type of respiratory difficulty, a noninvasive method such as bilevel ventilation or continuous positive airway pressure or an invasive method involving intubation can be used. Patients on prolonged mechanical ventilation may require tracheostomy. Pompe patients do not have obstructive airway disease; thus, therapies designed to expand the airways such as bronchodilators should be used with caution, especially because such drugs can affect the heart.

Weakness of the diaphragm in addition to weak abdominal and intercostal muscles also make it difficult for Pompe patients to cough, which increases their susceptibility to infection and aspiration. For infantile-onset patients, frequent oral or deep nasal suction and chest physical therapy are helpful. Where possible, caregivers can help patients cough by providing manual assistance. Alternatively, pulmonary airway clearance can be assisted by the use of mechanical insufflation-exsufflation.

Anesthesia Risks

Patients with Pompe disease, particularly infants, present a significant anesthetic risk because of respiratory muscle weakness and the pathophysiology of the hypertrophic cardiomyopathy.[46] General anesthesia should be performed only when absolutely necessary and only by anesthesiologists who have experience with these weak and seriously ill infants. During any sedation or general anesthesia of these infants, it is essential to ensure that coronary perfusion is maintained at all times. Intravenous ketamine 0.5 mg/kg titrated to sedative effect and supplemented with safe doses of surgically administered local anesthesia without epinephrine has been used to anesthetize these critically ill infants for minor procedures.[46,47]

The noncompliant thickened ventricular wall makes maintaining stroke volume and cardiac output dependent on the meticulous attention to appropriate intravascular volume and a high coronary perfusion pressure. Too much volume replacement will result in pulmonary edema, and underfilled ventricles may exhibit increased left ventricular outflow tract obstruction and diminished coronary perfusion. Infants with Pompe disease do not tolerate a lower diastolic blood pressure than their normal baseline. Therefore, maintaining an adequate systemic vascular resistance is equally important. Baseline heart rates should be maintained, because the thickened ventricular wall prevents increases in stroke volume and cardiac output should a bradycardia develop. These patients also do not tolerate high airway pressures associated with positive pressure ventilation, which may occur if overventilation decreases the intravascular heart filling pressures.

Infants whose echocardiograms show left ventricular outflow tract obstruction during ventricular systole are at greater risk for decreased coronary perfusion during general anesthesia. In such cases, use of an intra-arterial catheter for beat-to-beat blood pressure monitoring during a general anesthetic or even during sedation should be considered. These infants may also require postoperative monitoring in an intensive care unit if myocardial ischemia is associated with an extensive cardiomyopathy.

Treatment of Cardiomyopathy

Cardiomyopathy in patients with Pompe disease should be treated cautiously and by a pediatric cardiologist who has experience with the disease. Each patient's care must be individualized and based on the stage of disease, because inappropriate use of the standard drugs used to treat cardiomyopathy can be very detrimental. Infants with Pompe disease in the earlier phases of the disease generally present with severe ventricular hypertrophy with or without left ventricular outflow tract obstruction. Left ventricular systolic function is normal or even hyperdynamic. Such patients anecdotally may benefit from the use of beta blockers if they have significant outflow tract obstruction. In this situation, the use of digoxin, other inotropes, diuretics, and afterload-reducing agents such as angiotensin converting enzyme inhibitors may exacerbate the left ventricular outflow tract obstruction. These agents, however, are generally used in the later phases of the disease, when the ventricle becomes dilated with poor systolic function.

Dietary Therapy

A high-protein, low-carbohydrate diet or, alternatively, a diet rich in L-alanine has shown benefit in some but not all patients with late-onset Pompe disease.[4-6] Controlled studies of this treatment have not been performed. Patients who are extremely weak—especially infants—may require tube feeding. The early initiation of tube feeding in infants can greatly improve nutritional status as well as prevent aspiration of food.

Physical Therapy

Early intervention by occupational, physical, and speech therapists with experience in Pompe disease is paramount for infants with Pompe disease. Late-onset patients with lost mobility because of weakened muscles may benefit from a customized exercise or physical therapy program. Intervention is designed to optimize and preserve motor functions and functional independence and prevent or minimize secondary complications of the disease.[48] Adaptive equipment and assistive technologies such as motorized wheel chairs, computer access, canes, walkers, and orthoses to maximize gait efficiency can be of benefit.

Enzyme Replacement Therapy

Enzyme replacement therapy for Pompe disease is intended to address directly the underlying metabolic defect via intravenous infusions of recombinant human GAA to provide the missing enzyme. The discovery of cell-surface receptors that can mediate the delivery of lysosomal enzymes to target tissues has made enzyme replacement therapy possible for several lysosomal storage disorders. Such therapy is now commercially available for Gaucher disease, Fabry disease, and mucopolysaccharidosis (MPS) type I (Hurler/Scheie disease) and is in clinical trials for Pompe disease, MPS II (Hunter disease), MPS VI (Maroteaux-Lamy), and Niemann-Pick disease.

Pompe disease is an attractive candidate for enzyme replacement therapy for several reasons. First, patients with residual enzyme levels have a markedly improved outcome with minimal cardiac disease and increased lifespan in comparison with the infants who lack GAA activity. Second, Pompe disease does not appear to have a significant neurologic component, and thus, the inability of infused enzyme to cross the blood–brain barrier is less of a concern than for some other lysosomal storage disorders. However, because glycogen accumulates in nervous tissues in infantile-onset disease, enzyme replacement treatment that prolongs survival in affected infants may unmask later neurologic manifestations. The natural course of late-onset Pompe disease suggests that this is unlikely in this population. Finally, like patients with Gaucher disease, a high proportion of patients with Pompe disease (including 50% of infantile-onset cases)[15] have enough residual enzyme to reduce the likelihood of an immunologic reaction to exogenous enzyme. Such reactions have interfered with factor VIII treatment efficacy in patients with severe hemophilia. However, despite seroconversion rates of 12%[49] and 88%,[50] respectively, for patients with Gaucher and Fabry diseases treated with enzyme replacement therapy, efficacy of therapy has not been compromised.

Three recent open-label clinical trials involving a total of 15 infants[14-16] with classic infantile-onset Pompe disease (hypertrophic cardiomyopathy, severe GAA deficiency) show that enzyme replacement can decrease cardiomegaly, improve cardiac and skeletal muscle function, and prolong survival. Several additional trials are currently in progress.

The first study involved four infants treated with weekly infusions of recombinant human GAA purified from transgenic rabbit's milk.[13,14] Left ventricular mass index decreased markedly, GAA activity in muscle was normalized, and cardiac and motor function improved. In a parallel phase I/II trial, three infants received twice-weekly infusions of recombinant human GAA manufactured in a Chinese hamster ovary cell line.[15] Heart size decreased and cardiac function remained normal, and glycogen deposits in skeletal muscle decreased markedly in one patient. All infants in both studies survived past the critical age of 1 year.[14,15]

Preliminary results after 1 year of enzyme replacement therapy have been published from a third open-label phase II study of Chinese hamster ovary cell-derived recombinant human GAA involving eight infants with infantile-onset Pompe disease and cardiomegaly and cardiomyopathy by age 6 months.[16] Three infants died of complications of their disease. Four of the five surviving infants are ventilator-free. All five infants have shown motor improvement; three are now ambulatory with normal motor development, whereas the remaining two have shown modest motor improvement. After $\geq$12 months of treatment, all five have a markedly decreased left ventricular mass index and normal Bayley mental development index.

Overall, these preliminary results in infants suggest that the earlier enzyme replacement therapy is begun, the better the response. Other factors that could also affect outcome include stage of disease, genotype or presence of modifying genes or both, extent of muscle damage at start of therapy, and the immunologic status of the patient. The suggestion that early treatment in infantile-onset Pompe disease might be most beneficial, in addition to the fact that symptoms and diagnosis are made only months before death, raises the possibility that newborn screening may be valuable if the treatments are proven efficacious.

CONCLUSIONS AND FUTURE DIRECTIONS

Pompe disease is a progressive genetic disorder that encompasses a wide spectrum of phenotypes and presentations. The outlook for patients with this uncommon but devastating disease has become much more hopeful, with many babies on enzyme replacement therapy showing clinical improvement and surviving well past their first birthday. Additional larger-scale trials in infants are needed to establish the extent of long-term benefit (including neurological), the

optimal dosing protocol, and the effect of other factors on outcome of therapy. Trials of enzyme replacement therapy in children and adults with late-onset Pompe disease are also essential.

With enzyme replacement therapy likely to be available in the near future and other disease-specific therapies such as gene therapy in development, recognition and medical management of Pompe disease has assumed new importance. Thus, pediatricians and pediatric specialists need to be alert to the signs and symptoms of this life-threatening disease so that patients can be recognized early and treated as soon as possible. If further trials in infants confirm the clinical benefit of enzyme replacement therapy and the importance of its early initiation, some form of neonatal screening for Pompe disease may prove valuable.

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APPENDIX

Web Sites for Organizations and Support Groups for Patients With Pompe Disease and Families

Acid Maltase Deficiency Association (AMDA): http://www.amda-pompe.org

Association for Glycogen Storage Disease: http://www.agsdus.org

Muscular Dystrophy Association (MDA): http://www.mdausa.org

National Organization for Rare Disorders (NORD): http://www.rarediseases.org

United Pompe Foundation: http://www.unitedpompe.com

Association for Glycogen Storage Disease, United Kingdom: http://www.agsd.org.uk/home

Children Living with Inherited Metabolic Diseases (CLIMB):
http://www.climb.org.uk

Glycogen Storage Disease Network (GSDNet): http://www.pompe.org.uk/agsdnet.html

Helping Hands. . .Loving Hearts Foundation: http://www.hhlh.org

International Pompe Association (IPA): http://worldpompe.org

Ongoing and forthcoming clinical trials: http://www.clinicaltrials.gov

Pompe Center at Erasmus University in the Netherlands: http://www.pompecenter.nl