Pompe's glycogen storage disease

Synonyms: glycogen storage disease type II; acid maltase deficiency

What is Pompe's glycogen storage disorder?[1]

Pompe disease is a glycogen storage disorder. It is a severe metabolic myopathy, caused by mutations in the gene coding for the enzyme alpha-1,4-glucosidase (GAA), which breaks down glycogen in the lysosomes.

Once in the lysosome, glycogen can escape following complete degradation by GAA in the form of glucose. A deficiency of the enzyme leads to lysosomal accumulation of glycogen in multiple tissues, but cardiac and skeletal muscles are most severely affected.

Pompe disease affects people of all ages with varying degrees of severity. The most severe form (classic infantile onset Pompe disease) presents before 12 months of age, and the less devastating late-onset Pompe disease presents after 12 months of age.

Pompe's glycogen storage disorder epidemiology

- Pompe's disease is an autosomal recessive disorder.[2]
- The estimated frequency of the disease is often cited as 1 in 40,000 live births, but newborn screening has revealed a much higher frequency.[3]
- Pompe's disease has an estimated frequency of 1 in 40,000 in African-American, 1 in 50,000 in Chinese, 1 in 40,000 in Dutch, and 1 in 146,000 in Australian populations.[4]
- Infantile and adult forms are inherited as autosomal recessive conditions. The gene has been traced to chromosome 17.[5]

Pompe's glycogen storage disorder symptoms (Presentation)[1]

Classic infantile onset Pompe disease

Presents before 12 months of age with rapidly progressive hypertrophic cardiomyopathy, left ventricular outflow obstruction, hypotonia and muscle weakness, respiratory distress, and progressive loss of independent ventilation. Breathing difficulties, feeding problems, and macroglossia are common manifestations.

Motor development is significantly delayed, and major developmental milestones, such as the ability to roll over, sit, or stand, are often not achieved. Only a small percentage of untreated patients survive beyond 1 year of age. The main cause of death is cardiac and respiratory failure.

Some present with similar clinical presentations during the first year of life but less severe cardiomyopathy (and absence of left ventricular outflow obstruction). This is called non-classic infantile onset Pompe disease. Atypical infantile onset Pompe disease is sometimes used to describe presentation within the first year of life without cardiomyopathy.

Late-onset Pompe disease

Presents at any time after 12 months of age, usually without significant cardiac involvement.

It often presents with the symptoms of proximal limb-girdle myopathy. The progression of the symptoms is relatively slow but ultimately leads to profound muscle weakness and wasting, wheelchair dependency, and respiratory failure due to the involvement of the diaphragm.
A history of “not being able to keep up with others” during physical activities may help clinical diagnosis in teenagers or adults.

Other symptoms may include dysarthria and dysphagia, osteoporosis, scoliosis, sleep apnoea, neuropathy, hearing loss, impaired gastric function, urinary tract and anal sphincter involvement, and pain and fatigue, as well as a risk of cardiac arrhythmia and cerebral and intracranial aneurysms.

Differential diagnosis[1]

Rare diseases presenting with cardiomyopathy, hypotonia, and myopathy in infancy, eg Werdnig-Hoffman disease, Danon disease, glycogenoses types III and IV, nemaline myopathy, myofibrillar myopathy, and mitochondrial myopathies. Newborn screening eliminates the need for differential diagnosis in infantile onset Pompe's disease as clinical findings plus a decreased enzyme activity are sufficient to confirm the diagnosis.

The diseases that may resemble late onset Pompe's disease include limb-girdle muscle dystrophy, Duchenne muscular dystrophy and Becker muscular dystrophy, facioscapulohumeral muscular dystrophy, scapuloperoneal syndromes, rigid spine syndrome, myasthaenia gravis, polymyositis, fibromyalgia, chronic fatigue syndrome, and glycogenoses types V and VI.

Investigations[1]

- Serum creatinine kinase activity is elevated, but a normal CK value in late-onset Pompe's disease does not exclude the diagnosis. Other enzymes, such as aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH), are often elevated
- Most have elevated urinary glucose tetrasaccharide (Glc4) levels which are higher in infants than in adults. This test can be useful for supporting the diagnosis and for monitoring the effects of enzyme replacement therapy.
- Chest X-rays reveal massive cardiomegaly in infantile onset Pompe disease.
- ECG shows a short P-R interval, tall QRS complexes, and increased QT dispersions.
- Echo reveals increased left ventricular wall thickness and mass with or without left ventricular outflow tract obstruction.
- Lung function tests.
- MRI can help to evaluate the extent and localisation of muscle changes in patients with late onset Pompe disease. MRI can also help identify the site for a muscle biopsy.

- Muscle biopsies show vacuolar myopathy, the extent of which usually correlates with the severity of clinical symptoms. The value of muscle biopsies in adult patients is limited because different muscle groups, and even fibres within the same muscle group, exhibit variable pathology.
- The diagnosis can be established by deficiency of GAA enzyme activity, which can be measured in blood, dried blood spots, cultured skin fibroblasts, or in a muscle biopsy. In classic IOPD, the enzyme activity is absent or almost absent (below 1%). Low levels of residual activity, up to approximately 30% of normal, are usually measurable in all other clinical forms.
- GAA mutation analysis is used to confirm the diagnosis but also to assess the genotype-phenotype correlation, to identify carriers within families, and to provide genetic counselling.[2]

Pompe's glycogens storage disease treatment and management[6]

The management requires an extensive multidisciplinary team to address the multisystem manifestations, including cardiology, respiratory, speech and language (swallowing), physiotherapy/neurology, genetics and metabolic physicians. Many patients require mobility support and many need non-invasive respiratory support.

Disease-modifying treatments using enzyme replacement therapy are now common in clinical use. Studies have confirmed the efficacy of this treatment ameliorating the natural history of infantile-onset and late-onset Pompe's diseases. However, current enzyme replacement therapy is not curative.

- Enzyme replacement therapy:
    - Enzyme replacement therapy has been shown to be very effective and substantially improves the prospects for patients. [4]
    - Alglucosidase alfa (Myozyme®), an enzyme produced by recombinant DNA technology, is licensed for long-term replacement therapy in Pompe's disease. [7]
    - Cipaglucosidase alfa (CIPA) plus miglustat is recommended by the National Institute for Health and Care Excellence (NICE) as an option for treating late-onset Pompe disease in adults. [8]
- Treatment of cardiac failure and respiratory failure may be required.
- Diet therapy may provide temporary improvement but does not alter the disease course: a high-protein, low-carbohydrate diet may be beneficial.
- Physiotherapy and occupational therapy may be required.
- Genetic counselling and prenatal diagnosis: chorionic villus sampling and amniocentesis can be used to determine enzyme activity in a fetus.
- Gene therapy remains a potentially effective treatment for the future. [1]

Complications [1]

- In the infantile form, cardiomegaly and congestive heart failure lead to death.
- Cardiomegaly with progressive obstruction to left ventricular outflow is a major cause of mortality.
- Aspiration pneumonia; weakness of ventilatory muscles increases the risk of pneumonia.
- The adult form manifests with dystrophy and respiratory muscle weakness.

- In the adult form, intracranial aneurysms present the greatest complication.
- Liver failure may occur.

Prognosis[1]

- Without enzyme replacement therapy, the infantile form is usually fatal, with most deaths occurring within one year of birth.
- However, early diagnosis and management has been shown to improve outcomes.[6]
- Later clinical onset usually corresponds with more benign symptoms and disease course.
- The late onset form is not necessarily fatal, but complications, such as rupture of an aneurysm or respiratory failure, may cause significant morbidity and mortality.

Further reading

- Pompe Pages, Association for Glycogen Storage Disease UK
- Salabarria SM, Nair J, Clement N, et al; Advancements in AAV-mediated Gene Therapy for Pompe Disease. J Neuromuscul Dis. 2020;7(1):15-31. doi: 10.3233/JND-190426.

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Originally Published: 20/11/2023	Next review date: 22/09/2023	Document ID: doc_2633

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