Pompe's Glycogen Storage Disease

Synonyms: glycogen storage disease type II; acid maltase deficiency

Pompe's disease is a glycogen storage disorder. Deficiency of the lysosomal enzyme alpha-1,4-glucosidase (acid maltase) leads to the accumulation of glycogen in many tissues:

- The clinical spectrum is continuous and broad and three major forms are recognised: infantile, juvenile and adult-onset.[1]
- In the infantile form, accumulation of glycogen in cardiac muscle leads to cardiac failure.
- Accumulation may also occur in the liver, which results in hepatomegaly and elevation of hepatic enzymes.
- Glycogen accumulation in muscle and peripheral nerves causes hypotonia and weakness.
- Glycogen deposition in blood vessels may result in intracranial aneurysms.

Epidemiology

- The overall prevalence has been estimated at 1 in 40,000, with 1 in 138,000 for the infantile form and 1 in 57,000 for the adult form.[2]
- 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.[3]
- Infantile and adult forms are inherited as autosomal recessive conditions. The gene has been traced to chromosome 17.[4]

Presentation

- Presentation later in life is associated with a less severe form of disease.
- There is a continuous spectrum between the classic infantile and adult forms.
- The infantile form presents in the first six months of life (typically at between 4-8 weeks) with weakness, hypotonia, respiratory distress, feeding difficulties and heart failure.
- The juvenile form presents later in childhood with delayed motor development, muscle weakness and hypotonia.
- The adult form usually presents as skeletal and respiratory muscle weakness. The typical age of presentation is 20-40 years. There may be limb-girdle weakness and weakness of respiratory muscles.[5]

Signs

- Infantile form:
  - Cardiomegaly and congestive heart failure.
  - Generalised hypotonia, absent or reduced reflexes.
  - Enlarged tongue, enlarged liver.
  - Reflexes may be depressed or absent because of glycogen accumulation in spinal motor neurons.
  - Alertness may be impaired.

- Adult form:
  - Weakness may affect only specific muscle groups, eg upper arms, and may be asymmetrical.
  - Limb-girdle weakness is common and respiratory muscle involvement may be prominent.[6]

Differential diagnosis

- Other glycogen storage disorders.
- Muscular dystrophy: Duchenne muscular dystrophy (or less severe muscular dystrophies for older-onset disease).

Investigations

- Serum creatine kinase and aspartate aminotransferase are elevated.[7]
- Definitive diagnosis is made by the measurement of acid alpha-glucosidase activity in cultured skin fibroblasts or peripheral blood lymphocytes.[4]
- Intracranial aneurysms may be shown on angiography or magnetic resonance angiography.
- Echocardiogram to assess heart size and degree of left ventricular hypertrophy.
- ECG: short PR interval and elevated QRS complexes in the infantile form.
Electromyography (EMG) shows a myopathic pattern and also often shows pseudomyotonic discharges, fibrillation potentials and positive waves.\[1\]

Muscle biopsy for the evaluation of differential diagnosis of muscle weakness.

Management

**Enzyme replacement therapy:**
- Enzyme replacement therapy has been shown to be very effective and substantially improves the prospects for patients.\[8\]
  - Alglucosidase alfa (Myozyme®), an enzyme produced by recombinant DNA technology, is licensed for long-term replacement therapy in Pompe's disease.\[8\] Myozyme® is available by referral to an expert centre.\[9\]
  - Paediatric centres in England: Addenbrooke's (Cambridge), Birmingham Children’s Hospital, Great Ormond Street Hospital, Willink (Royal Manchester Children’s Hospital).

- Alglucosidase alfa therapy has been shown to improve cardiac and skeletal muscle function.\[10, 11\] Therapy has been shown to achieve significant reductions in the risk of death and invasive ventilation among treated patients.\[1\]

- 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.\[12\]
- 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.\[13\]

Complications

- 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

- Without enzyme replacement therapy, the infantile form is usually fatal, with most deaths occurring within one year of birth.\[14\]
- Later clinical onset usually corresponds with more benign symptoms and disease course.
- The adult form is not necessarily fatal, but complications, such as rupture of an aneurysm or respiratory failure, may cause significant morbidity and mortality.

Further reading & references

1. Ibrahim J et al; Genetics of Glycogen-Storage Disease Type II (Pompe Disease), Medscape, Jul 2011
4. Glycogen Storage Disease II, Online Mendelian Inheritance in Man (OMIM)
8. British National Formulary
9. Pompe Pages, Association for Glycogen Storage Disease UK

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