

### POMPE DISEASE

Pompe disease is named after Johannes C. Pompe, a Dutch doctor who first described the disorder in 1932 in an infant patient. The disease is rare affecting around 1:40,000. Pompe Disease is also referred to as acid maltase deficiency (AMD) or glycogen storage disease type II (GSDII) and is an autosomal recessive disorder. The symptoms are caused by a deficiency of the lysosomal enzyme acid- $\alpha$ -glucosidase (GAA). Because this enzyme is missing or not working properly glycogen located in the lysosomes cannot be broken down. The swollen lysosomes interfere with the correct workings of the muscles and can rupture causing damage. Skeletal, cardiac, and smooth muscle tissue are most prominently involved.

**Glycogen** – a string of sugars which are stored in the body and used for energy

**Lysosomal** – found in the ‘mini stomach’ of a cell in which unwanted things are destroyed.

**Enzyme** – proteins which make our body’s chemical reactions work

### DISEASE PROGRESSION

All people with Pompe disease share the same general disease course which is due to the continuous buildup of damage in various tissues over time. The severity varies dependent on the amount of active GAA present. People with an enzyme amount closer to normal usually present with a more slowly progressive late-onset form. Very low amounts or absence are associated with the more severe rapidly progressive infantile form. Ultimately left untreated this damage leads to progressive debilitation, organ failure and/or death.

Babies with *infantile Pompe disease* present in the first few months of life with a **hypertrophic cardiomyopathy**, generalized muscle weakness and **hypotonia**, followed by death from cardiorespiratory failure usually by 1 year.

**Hypertrophic Cardiomyopathy** – thickening of a specific heart muscle which can lead to cardiac arrest

**Hypotonia** – “floppy muscles” associated with reduced strength

*Late-onset Pompe disease* can present at any age and is characterized by a lack of severe (typically absence of) cardiac involvement and the progression rate is slower. Symptoms are related to progressive skeletal muscle dysfunction. Lower limbs and spinal muscles closest to the body’s trunk are usually affected first, followed by involvement of the diaphragm and accessory muscles of breathing. As the muscle weakness worsens, patients often become wheelchair users and may require assisted ventilation. Respiratory failure is usually the cause of significant morbidity and mortality in this form of the disease. The age of death varies from early childhood to late adulthood.

### Heart

Heart function monitoring is required to be sure the condition is managed properly. This also indicates progression and how the patient is responding to interventions. Use of anaesthesia especially in infants should be done with extreme caution and with experienced pediatric/cardiac anesthesiologists.

### Lungs

As Pompe disease progresses, the muscles weaken leading to low lung volumes, an impaired cough, blood gas abnormalities, and sleep-disordered breathing. These changes are similar to those seen in any patient with an underlying neuromuscular weakness, such as Duchenne muscular dystrophy and spinal muscle atrophy. Patients with Pompe disease are also at an increased risk for aspiration pneumonia.

Impaired cough results in retained secretions and an inability to clear both the normal volume of lung secretions as well as those associated with acute infections, thereby predisposing the patient to developing collapsed lungs and pneumonia.

As respiratory muscle weakness progresses exhalation of carbon dioxide becomes difficult and levels of oxygen in the blood decrease. This usually develops first while asleep, because of the mechanical disadvantage of the supine position and the effect of sleep on respiratory control mechanisms.

Immunizations should be kept up to date and patients and household members should receive the influenza vaccine during influenza season.

### Nutrition and Feeding

People with Pompe disease have feeding and swallowing difficulties and often fail to thrive. In infantile Pompe disease, contributing factors include facial hypotonia, unusually large tongue and/or tongue weakness, poor oral range of motion with extremely limited tongue elevation and decreased ability to achieve tongue cupping and lip seal for sucking.

There is also difficulty with saliva management and people may swallow less leading to pooling of secretions and drooling. Vocal quality is often noted to be “wet” indicating pooling of secretions at the level of the vocal cords, correlating with increasing respiratory complications which could be secondary to aspiration events. In patients with late onset Pompe disease, fatigue of jaw muscles with difficulty swallowing a bolus and chewing food is often a first complaint and this often results in an inadequate intake of total calories, vitamins, and minerals leading to endogenous muscle protein breakdown.

Patients with Pompe disease are at increased risk for aspiration (food going into the lungs).

### Osteopenia and osteoporosis

Osteopenia and osteoporosis have recently been recognized as complications of Pompe disease. Osteopenia has been seen in patients with Pompe disease as young as 4 months of age, which could be attributed to chronic immobilization and weakness, but osteopenia has also been identified in patients with Pompe disease with good motor strength and nutrition and needs to be further studied.

### DIAGNOSIS

Due to the rarity of the condition and the range of symptom presentation it can be difficult to diagnose. Tests used to rule out other conditions and clarify what may be happening for the individual include; Chest x-rays , Electrocardiogram , Echocardiogram , muscle function, milestones met, lung capacity, sleep studies, enzyme creatine kinase levels and muscle biopsy. Once Pompe is suspected the diagnosis can be confirmed via a blood test measuring GAA. Levels of <1% up to 40% usually identifies Pompe Disease. Tests can also be performed on skin or muscle tissue.

Mutation Analysis (looking at the gene to see the precise error) can also be used to confirm a diagnosis and to test other family members if indicated.

### GENETICS

Pompe Disease is an inherited disease caused by a defect in the gene which tells the body how to make GAA. We each have two copies of this gene in each cell. To be affected with the condition both copies need to be defective. As the chances that the defect is new are extremely low it is assumed that that both parents have each passed on one defective copy to their offspring. This specific type of inheritance is called *recessive*. Each parent’s functional gene is sufficient to avoid symptoms. This is called being a *carrier*. Two carrier parents have a ¼ chance in each pregnancy of having a child affected with the condition.

Genetic counseling is available to families who have had a diagnosis of Pompe Disease. This service provides information, helps families understand inheritance patterns and what this means in their family, as well as enabling people to make more informed family-planning decisions.

### MANAGEMENT

Pompe disease is a multi-system disorder and is best managed by a multidisciplinary team led by a physician with experience managing this disorder. Ideally, team members should include a metabolic disease specialist/biochemical geneticist in addition to the specialists dictated by the disease manifestations, which might include a cardiologist, pulmonologist, neurologist, neuromuscular specialist, intensivist, orthopedist, respiratory therapist, physical therapist, occupational therapist, otolaryngologist, speech therapist, audiologist, genetic counselor, and a metabolic dietitian.

### TREATMENT

Enzyme Replacement Therapy (ERT)

This is delivering the missing enzyme to the tissue that requires it. Allowing the glycogen to be broken down and therefore reducing the impact of the buildup in the tissues. Several clinical trials involving patients with infantile-onset Pompe disease have shown that ERT significantly prolongs survival, shrinks heart size and improves cardiac and skeletal muscle function. In the vast majority of cases cardiac response appears to be good, irrespective of the stage of the disease at the start of ERT. Skeletal muscle response has been more variable than cardiac muscle response. The best skeletal muscle response has been noted in patients treated early, prior to severe skeletal

muscle damage. There are several patients with infantile-onset Pompe disease on ERT who are walking, a milestone that would not have been achieved without ERT.

MYOZYME (alglucosidase alfa) is a lysosomal glycogen-specific enzyme indicated for use in patients with Pompe disease (GAA deficiency). MYOZYME has been shown to improve ventilator-free survival in patients with infantile-onset Pompe disease as compared to an untreated historical control, whereas use of MYOZYME in patients with other forms of Pompe disease has not been adequately studied to assure safety and efficacy. This is not currently funded in New Zealand.

#### Gene Therapy

This treats the condition by correcting the defective gene. The functioning version is delivered direct to the cells. Studies in mice with Pompe Disease using viruses as delivery agents have had some success. There is not currently a treatment available using this method.

#### RESOURCES

Support Group Lysosomal Diseases NZ <http://www.ldnz.org.nz/>

<http://www.ncbi.nlm.nih.gov/books/NBK1261/>

<http://ghr.nlm.nih.gov/condition/pompe-disease>

<http://www.pompe.com/>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3110959/>