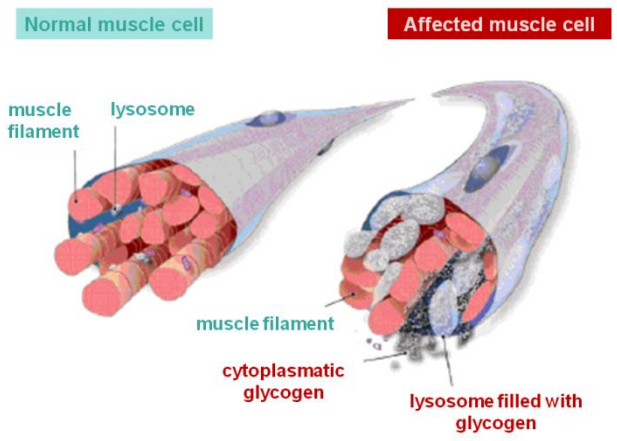
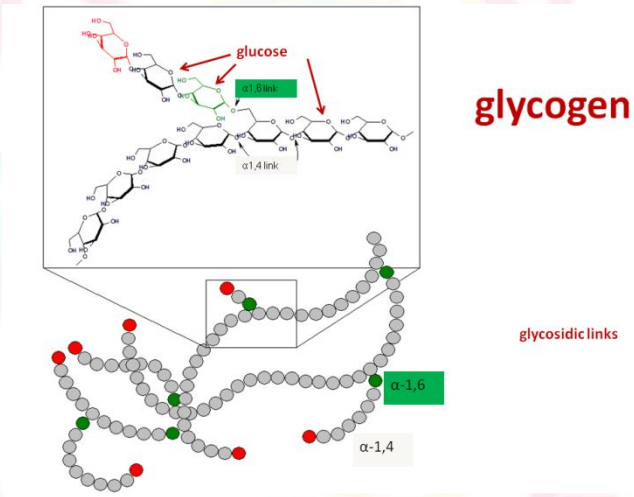
POMPE DISEASE OR TYPE II GLYCOGENOSIS

WHAT IS POMPE DISEASE?

Pompe disease or glycogen storage disease type II is a **metabolic disorder caused by the storage of glycogen in multiple tissues**, mainly muscle, causing progressive heart respiratory and motor failure. It is due to **deficiency of the lysosomal enzyme acid α-glucosidase or acid maltase**. It was described by the Dutch pathologist J.C.Pompe in 1932 in a 7-month-old girl with severe muscle weakness, whose autopsy showed a massive accumulation of glycogen in body tissues.



WHAT IS GLYCOGEN?

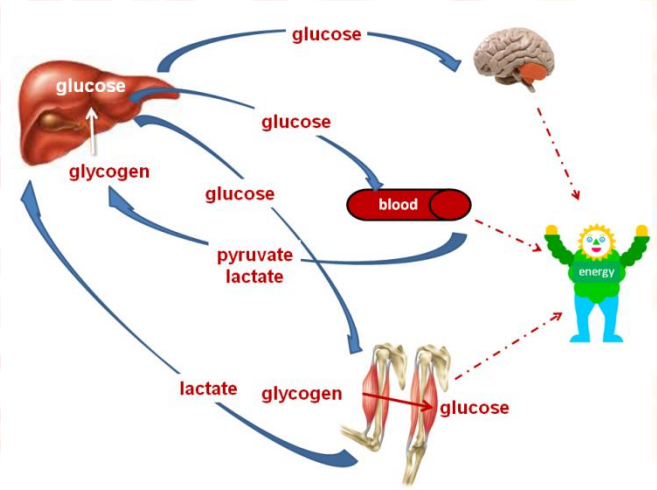


It is a polymer consisting of **highly branched glucose** chains. Its mission is to release glucose when the body needs it, that is, when the body requires the energy provided by glucose degradation.

Glycogen is abundantly stored in the **liver** and, to a lesser extent, in the **skeletal muscle** and other tissues.

The **glycogen stored in the muscle**, once converted into glucose, is used to provide the muscle fibers the energy they need to contract.

By contrast, **liver glycogen** is converted into glucose by **glycogenolysis**, and it is released to keep the blood glucose, being used for all tissues.



WHAT IS THE ACID A-GLUCOSIDASE?

The **acid α-glucosidase** (also called α-1,4-glucosidase or acid maltase) is an **enzyme that hydrolyzes (breaks) glycogen to produce glucose in the cell lysosome**, ie, in acidic medium (hence its name).

WHAT IS THE CELL LYSOSOME?

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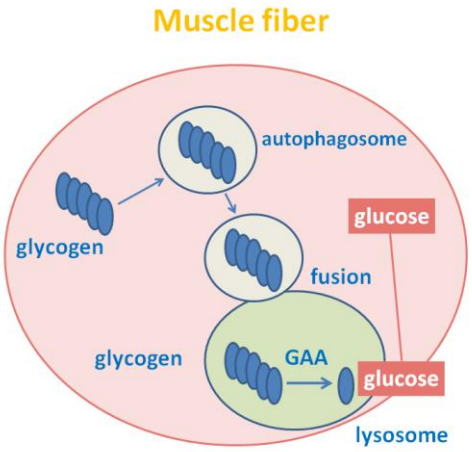
HOW DOES GLYCOGEN ENTER IN THE CELL LYSOSOME?

Glycogen is a large molecule, a polymer formed by a large number of glucose molecules (20,000 to 30,000), so it does not easily pass through cell membranes. It

goes into the lysosome at least in part by autophagy, although the exact process is not jet exactly known.

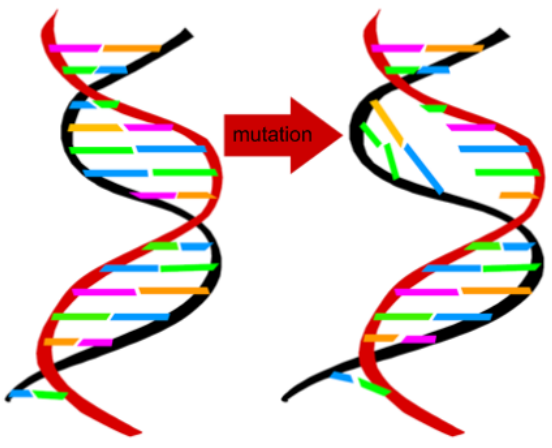


WHAT IS AUTOPHAGY?

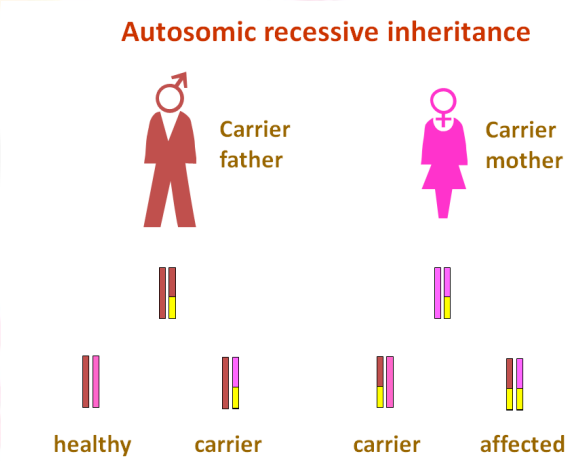
It is an **intracellular catabolic pathway that delivers aged proteins and damaged organelles to lysosomes for degradation and recycling**. Its function is to provide energy and amino acids to maintain cell function under conditions of starvation. It also performs a cleaning function, liberating the cell of misfolded proteins, protein aggregates and worn organelles, which could interfere with metabolic processes, providing a kind of recycling, the **physiological cell renewal**. It is an essential process in which many recently known proteins are involved and whose suppression is lethal to the cell.

WHY DOES POMPE DISEASE OCCUR?

The α-glucosidase enzyme is genetically determined (encoded). Its deficiency is caused by mutations (stable and heritable changes) in the GAA gene coding for the enzyme protein.



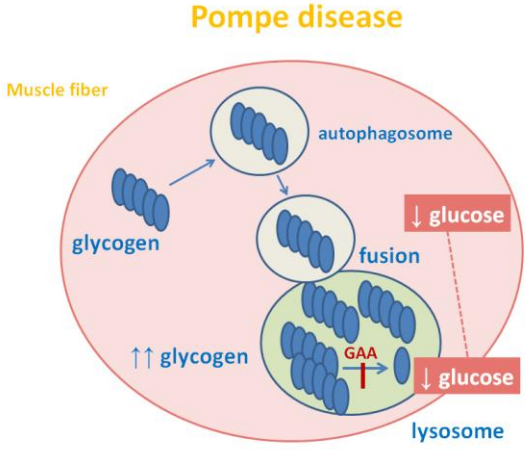
Pompe GSD is inherited as an **autosomal recessive disease**, ie, parents are carriers of mutations in the GAA gene, but do not suffer the effects of acid α-glucosidase deficiency. If both parents transmit the gene mutation to the child, he/she will suffer a Pompe disease.



WHAT DOES IN ACID A-GLUCOSIDASE DEFICIENCY HAPPEN?

Glycogen that reaches the lysosome from the cell cytoplasm, cannot properly be hydrolyzed to glucose due to acid α-glucosidase deficiency and it accumulates in the lysosome causing its breakage thereof.

The exact process by which muscle function is affected is unknown, but in the initial stage small vacuoles accumulate in the muscle fibers. Lysosomes are enlarged and fused and interfere the structure of the muscle fiber (muscle cells) and also waste material surrounded by membranes (autophagosomes), and aberrant mitochondria accumulate, so it is believed that **autophagy is also impaired in this disease**.



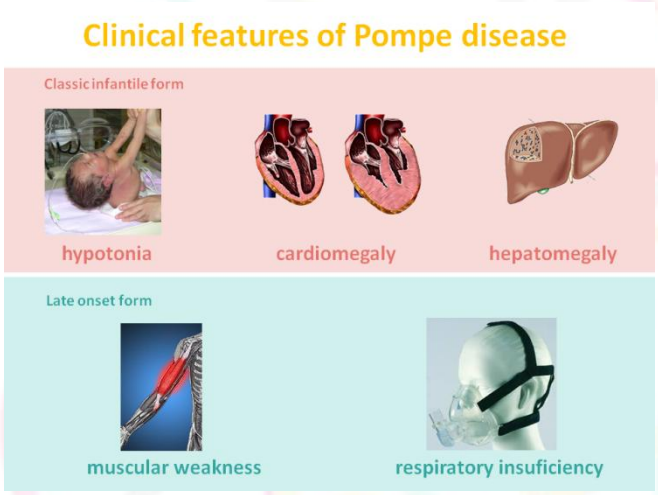
If the enzyme deficiency is complete, and accumulation occurs prenatally and muscle fibers are damaged by the massive accumulation of glycogen. If the enzyme deficiency is partial or not so severe, the disease occurs

later and less severely, which determines the clinical heterogeneity of the disease.

WHICH ARE THE CLINICAL FEATURES OF POMPE DISEASE?

It is a neuromuscular disease that presents with a variable range of age of onset, organ involvement and degree of myopathy (muscle involvement). It basically classifies in childhood and late onset forms. The severity varies depending on the age of onset, rate of progression of organ involvement and muscle involvement.

The **infantile form** presents in the first year of life, average age around 2 months. In this form there are patients with more severe classic infantile variant, characterized by cardiomegaly (increased heart size), generalized muscle weakness, hypotonia, hepatomegaly (enlarged liver), respiratory failure before the age of one. Some patients show milder or atypical variants in which skeletal muscle is the only tissue affected.



The **late-onset form** occurs after the first year of life, and **infantile, juvenile and adult forms** are distinguished by age of onset, and severity, closely related to the residual enzymatic activity of α-glucosidase (<1% in the infantile form, up to 10% in juvenile and <40% but more than 10% in the adult form). It is characterized by the involvement of skeletal muscles, which causes **progressive muscle weakness and respiratory failure**. Weakness is preceded by myalgia (muscle pain) and muscle cramps. In children, delayed motor development is present. In adults there is a proximal muscle weakness, increased in the muscles of the pelvic girdle, with difficulty in climbing stairs, running or getting up from the chair. Chewing and swallowing are sometimes difficult.

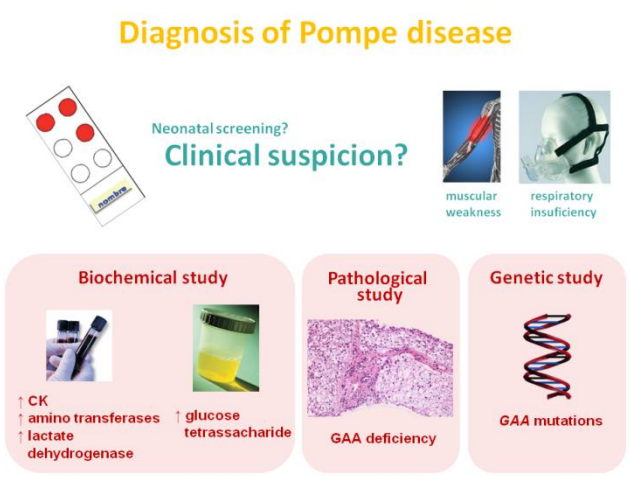
Respiratory complications are often serious. Clinical implications and respiratory failure are the leading cause of morbidity and mortality. The progression of muscle symptoms causes respiratory insufficiency and some patients need a wheelchair and assisted ventilation.

HOW IS POMPE DISEASE DIAGNOSED?

Early diagnosis is vital, because since 2006 there is a specific treatment that can change the clinical course of the disease. Neonatal screening is performed only in some countries (Taiwan, Austria and some U.S. states), so that, in general, clinical suspicion is basic, and it is more difficult in later forms because of the clinical heterogeneity. At present, some pharmaceutical companies offer the genetic study for free to neurologist, in case of patients with strong clinical suspicion.

The **clinical evaluation** should include an assessment of muscle strength and gait, as well as spirometry, electrophysiological examination (electromyogram) and imaging tests.

The basic **biochemical changes** include elevated creatine kinase, lactate dehydrogenase and aminotranferases, which are sensitive but nonspecific indicators. The elevation of urinary glucose tetrasaccharide, added to the clinical suspicion, supports the diagnosis of Pompe disease, but it can also be high in other muscle glycogenosis.

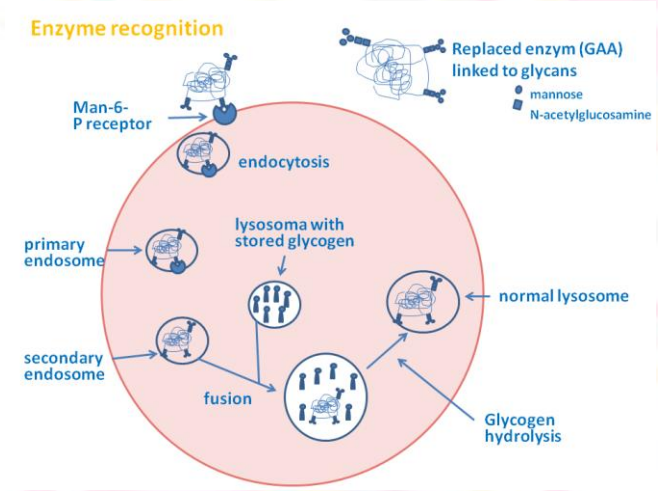


Muscle biopsy shows a vacuolar myopathy with glycogen storage.

The analysis of **acid α-glucosidase activity** in lymphocytes is essential for the confirmation of the defect as well as the **genetic studies** of mutations in the ***GAA* gene** that allows genetic counseling and prenatal diagnosis, if required.

IS THERE A TREATMENT FOR POMPE DISEASE?

Since 2006, when the European Medicines Agency approved the **enzyme replacement therapy**, late onset Pompe disease has changed its clinical course. **Alpha-Alglucosidase** infusions were performed with the recombinant form of human acid α-glucosidase. Such treatment can stop or slow the progression of the disease. It has been effective even in children with the classic phenotype with rapid progress, reducing the hypertrophic cardiomyopathy. In adults, several published studies showed the benefit of motor and respiratory function and muscle strength. The benefit is greater when the enzyme replacement therapy is started in an early stage and in patients whose baseline clinical condition is best preserved.



Gene therapy is being investigated in mouse animal models. Also the administration of chaperones with enzyme replacement therapy is studied. All of them may be future therapeutic options.

Support treatments are important, such as enhancing muscle function with physical therapy and aids and corrections to avoid or minimize musculoskeletal impairment, and even orthotic or surgical measures if needed.

Patients' nutrition should be optimized with high protein content (25-30% of total calories) and reduced carbohydrate intake, adding vitamin and mineral supplements. To treat dysphagia (see measures for dysphagia) thickening of food should be used and exercises should be performed to improve swallowing.

Pompe disease is a neuromuscular disorder that can be serious if not diagnosed. Early diagnosis and treatment has changed the course of the disease in many patients, especially for late onset forms and this, together with supportive therapies, can improve the quality of life of patients.

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