Pompe disease
or
Glycogenosis type II

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Dr. Joanes Cassianus Pompe described **Pompe Disease or Glycogenosis type II** in 1932; a rare, chronic, and debilitating, often fatal neuromuscular disorder with autosomal recessive transmission. Frequency: 1/57,000 for the adult form and 1/138,000 for the infantile form. In Italy, about 300 people are estimated to be affected.

Deficiency of the lysosomal acid α-glucosidase (GAA) due to GAA gene mutation

↓

Accumulation of glycogen in lysosomes

↓

failure to dispose of glycogen, the energy reserve of the muscles

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glycogen is accumulated in the heart, skeletal muscles and liver

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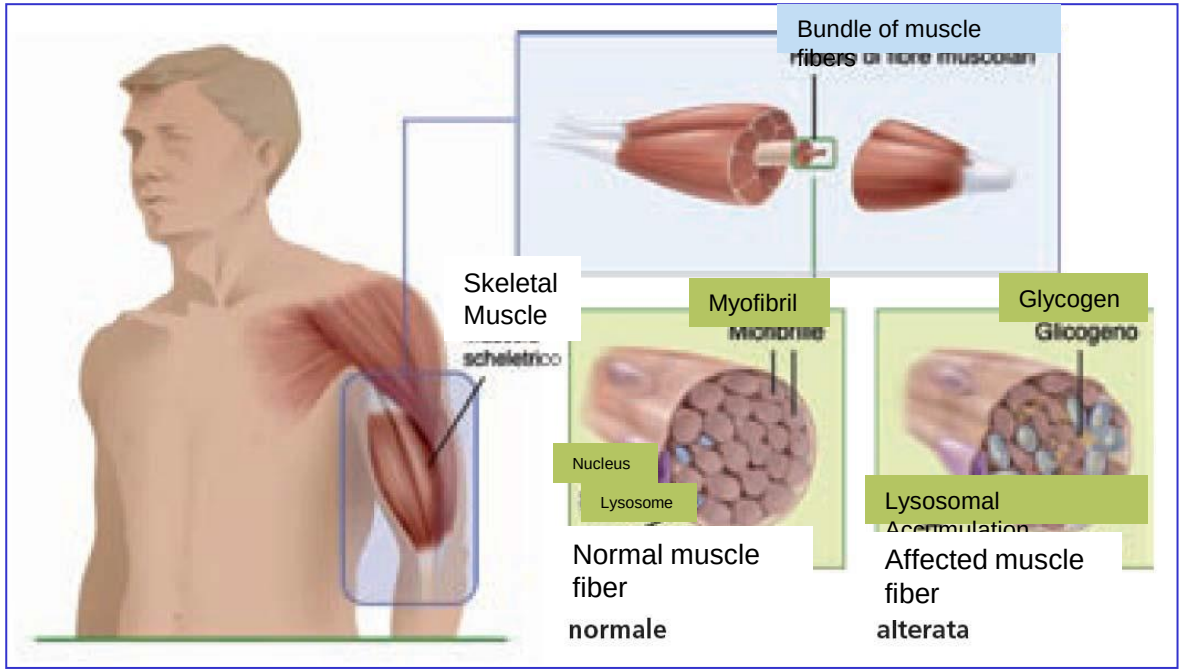

When too much glycogen is deposited in muscle cells, **the cells become damaged, and the muscles can no longer function correctly.**

progressive muscle weakness

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LABORATORY DIAGNOSIS

Non-specific laboratory parameters

↑ CK (Creatine kinase), LDH (Lactate dehydrogenase), AST (Aspartate transaminase), ALT (Alanine transaminase)

↑ Oligosaccharides in urine

↑ Accumulation of glycogen in the muscle

Specific tests

Biochemical → determination of acid glucosidase enzyme activity (GAA)

Enzyme activity can be determined in muscle (muscle biopsy), fibroblasts (skin biopsy) and purified lymphocytes

Molecular → GAA gene mutation analysis

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CLINICAL FORMS

based on age of symptoms onset

Classic infantile → Onset within 3 months of life

Non-classic infantile → Onset between the first and second year of life

Late onset → Onset after the first year of life

childhood adult

All patients affected by Pompe Disease are characterized by accumulation of glycogen in the muscles, which causes progressive muscle weakness. The spectrum of Pompe Disease is broad and ranges from the more severe classic infantile form to those with a more mitigated course with late onset. The severity of Pompe Disease depends on the age of symptoms onset, how much organ and muscle (skeletal, respiratory, and cardiac) are involved, and on the speed of disease progression.

Clinical heterogeneity depends on the heterogeneity of mutations in the GAA gene located on chromosome 17q23

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CLASSICAL INFANTILE POMPE DISEASE

Infantile-onset Pompe disease is the most aggressive and fatal form of the disease.

- Onset within 3 months of life
- Cardiomegaly and cardiomyopathy
- Hypotonia *(like a "rag doll", not able to lift the head)*
- Muscle weakness
- Respiratory failure
- Delay in motor milestones or loss of acquired milestones
- Reduction in gag reflex
- Suction and swallowing deficiency
- Hepatomegaly
- Absent GAA activity
- Mental development does not appear to be impaired by disease
- Rapidly progressive and fatal form within 1-2 years of life due to cardio-respiratory failure unless receiving recombinant enzyme replacement therapy (Myozyme)

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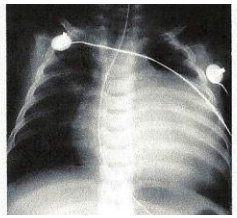
Infantile form: possible clinical signs and symptoms

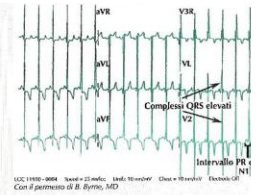
The pediatrician should always consider Pompe Disease if the infant has (suspected or confirmed) hypertrophic cardiomegaly and/or generalized hypotonia and muscle weakness (child resembling a “rag doll”).[1]

Cardiomegaly



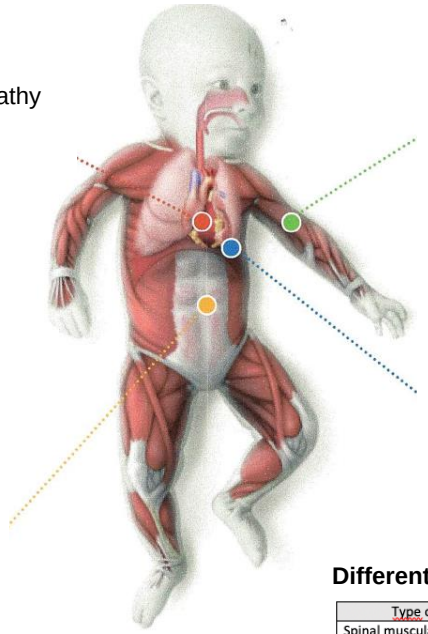
Infant with Pompe Disease

Electrocardiogram



Heart

- Hypertrophic cardiomyopathy
- Arrhythmias
- Cardiorespiratory failure



Gastrointestinal

- Hepatomegaly
- Macroglossia
- Swallowing difficulties

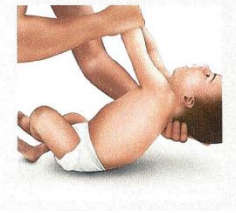
Laboratory parameters

- Elevated ALT/AST
- Elevated CK

Skeletal muscles

- Severe and progressive hypotonia (“rag doll”)
- Delay in the achievment or regression of motor milestones achieved

Severe, progressive hypotonia “rag doll”



Respiration

- Progressive involvement of respiratory muscles
- Recurrent respiratory infections

Differential diagnosis[1]

Type of disease	Disease	Shared symptoms
Spinal muscular arthrophy	Acute Werdnig-Hoffmann disease	Severe hypotonia
Muscular dystrophies	Congenital muscular dystrophies (Duchenne-Becker, Emery-Dreyfuss, girdle dystrophy)	Hypotonia, cardiomyopathy
Congenital myopathies	Nemaline myopathy, fiber type disproportion, central core	Hypotonia, cardiomyopathy
Hereditary metabolic diseases	Glycogenosis, mitochondrial diseases Peroxisomal disorders Congenital disorders of glycosylation	Cardiomegaly, myopathy, elevated CK, hepatomegaly Hypotonia, hepatomegaly Hepatopathy, cardiomyopathy, hypotonia
Congenital heart diseases	Idiopathic hypertrophic cardiomyopathy, myocarditis, endocardial fibroelastosis	Cardiomegaly, heart failure, difficulty in eating
Lysosomal storage diseases	Danon disease	Cardiomegaly, myopathy, accumulation of glycogen in vacuoles
Others	Hypothyroidism	Cardiomegaly, myopathy, accumulation of glycogen in vacuoles

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NON-CLASSIC INFANTILE POMPE DISEASE

- Onset between the first and second year of life
- Slower progression than classic form
- Muscle weakness
- Motor disorders
- Reduction in weight gain
- Slowdown in motor milestones
- Absent or mild cardiac involvement
- First symptom of the disease is muscle involvement
- Muscle weakness can cause severe respiratory problems
- If untreated, the prognosis for this form of the disease is more variable with death in early childhood

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ADULT POMPE DISEASE

- Slow progression and milder clinical expression allowing for long survival
- Involvement of skeletal muscles (predominant) in lower limbs, pelvic girdle and shoulder girdle
- Absent or mild cardiac involvement
- Respiratory muscle and diaphragm impairment
- Hypotonia, Progressive Hyposthenia
- Wide variability in onset age and clinical presentation
- Signs and symptoms common to many other acquired/congenital conditions (e.g., polymyositis, muscular dystrophy)
- Progressive muscle weakness that can lead to inability to walk and respiratory failure
- Can lead to death due to pulmonary or cardiac complications

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THERAPY

Glycogenosis type II requires a multidisciplinary approach

- Pharmacotherapy
- Nutrition
- Physical exercise
- Cardiac treatment
- Ventilatory assistance

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PHARMACOTHERAPY

- Enzyme replacement therapy (ERT) with recombinant alpha-1,4-acid glucosidase, rhGAA (MYOZYME) infused intravenously has been available in Italy since 2006.
- Myozyme replaces the absent or insufficient enzyme
- Increases survival in the Classic form, especially ventilator-free survival, and improves cardiac function
- The effects on skeletal muscle are not so evident: it is not able to intervene where irreversible cellular damage correlated with autophagy has set in
- Fewer data are reported regarding ERT in adults, with encouraging results in cases where therapy is undertaken early
- Administration: the recommended dose is 20 mg/kg/dose every 15 days
- Treatment with Myozyme is not a cure for Pompe disease, it does not correct the genetic defect

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NUTRITION

- At the metabolic level, in muscle cells, glycogen accumulates in lysosomes and an excessive consumption of protein occurs as an alternative source of energy

- Proteolysis causing protein depletion contributes to muscle damage

- The purpose of the diet is to maintain an adequate caloric intake and compensate for the increased protein catabolism

- The rationale is to supply amino acids as a substrate for protein synthesis

- Studies prove protein-rich diets can slow disease progression

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PHYSICAL EXERCISE

- Reduce glycogen storage and increase the use of fat as an energy source
- Maintain muscle tone and trophism

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VENTILATORY SUPPORT THERAPY

- In cases of significant respiratory deficiency, positive pressure non-invasive ventilation (NIV) is used

- In more compromised patients (with impaired swallowing and risk of chronic aspiration, with significant expectoration deficiency, or with a need for ventilation >20h) invasive mechanical ventilation via tracheostomy may be required.

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ORO-FACIAL FEATURES

- Macroglossia
- Low and forward tongue posture
- Hypotonia of facial muscles
- Lip incompetence and no lip seal
- Backward head posture
- Oral breathing
- Suction and swallowing deficiency
- Difficulty in eating and accumulation of secretions in the oral cavity
- Class III skeletal malocclusion
- Negative overjet
- Ogival palate
- Concave profile
- Hyperdivergent growth

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