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Pompe Disease

History/Pathogenesis

Clinical manifestations

IOPD&LOPD DX/Diagnosis



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Tehran / Oct 8 2026



Presentation Objectives

- To understand the pathophysiology and clinical spectrum of Pompe disease .
- To differentiate between Infantile-Onset Pompe Disease (IOPD) and Late-Onset Pompe Disease (LOPD) in terms of presentation, and natural history .
- Differential diagnosis of IOPD and LOPD .
- To review the diagnostic algorithm, including the critical role of newborn screening and enzyme testing.

Pompe Disease / History

- In 1932 the Dutch pathologist **Johannes Cassianus Pompe** reported a girl who suddenly died from an idiopathic myocardial hypertrophy at seven months of age with massive cardiomegaly and vacuolar storage of glycogen .
- In this family a number of patients had died of cardiac disease in early infancy.



Dr. Joahnnes Cassianus Pompe (1901-1945)
Utrecht, The Netherlands
14 April, 1945 Overveen / world war II

What is Pompe disease?

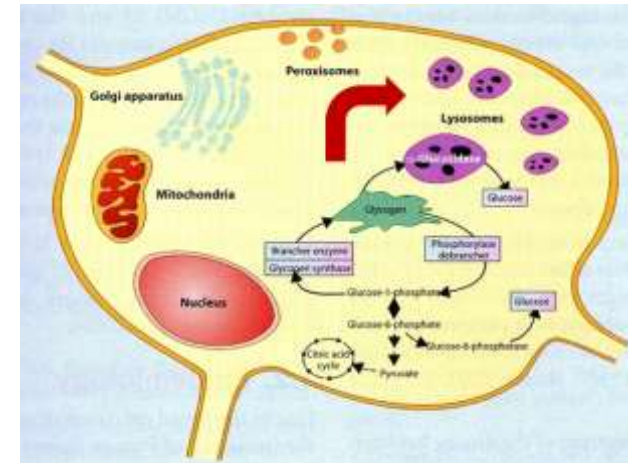
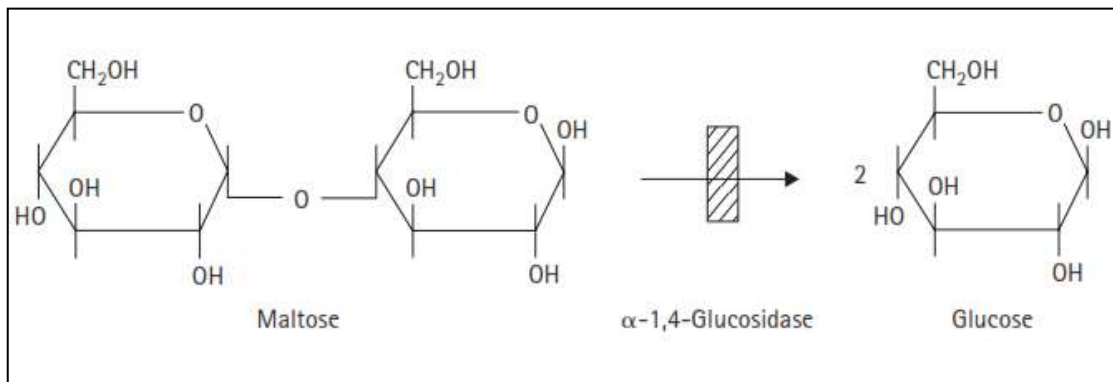
- Pompe disease or glycogenosis type II (GSD II) has been referred to as **Generalized Glycogenosis** because the defect is present in all cells.
- Clinical expression is most prominently manifested in the heart, and therefore the disease has been considered as **Cardiac Glycogenosis**.
- Of the various GSD , only type II is a **Lysosomal disorder** .

What is Pompe disease?

Disorder	Enzyme Defect	Inheritance	Clinical Features
Type I (von Gierke's disease)	Glucose-6-phosphate	Autosomal recessive	No neuromuscular signs or symptoms
Type II (Pompe disease)	Acid α -1,4-glucosidase	Autosomal recessive	Infancy: hypotonia and generalized weakness Childhood/adult: progressive weakness and ventilatory failure
Type III (Cori-Forbes disease)	Debrancher (amylo-1,6-glucosidase)	Autosomal recessive	Infancy: hypotonia and generalized weakness Childhood/adult: proximal or distal weakness, spasticity, dementia, and incontinence
Type IV (Anderson disease)	Brancher (amylo-1,4-1,6-transglucosidase)	Autosomal recessive	Infancy: hypotonia and generalized weakness Childhood/adult: proximal or distal weakness
Type V (McArdle disease)	Myophosphorylase	Autosomal recessive	Infancy: rare weakness Childhood/adult: exercise intolerance, and rare weakness
Type VI	Liver phosphorylase	Autosomal recessive	No muscle involvement
Type VII (Tarui disease)	Phosphofructokinase (PFK)	Autosomal recessive	Childhood: exercise intolerance and rare weakness
Type VIII	Phosphorylase b kinase (PBK)	Autosomal recessive and X-linked	Infancy to adult: exercise intolerance and rare weakness
Type IX	Phosphoglycerate kinase (PGK)	X-linked	Childhood: exercise intolerance, rare weakness, hemolytic anemia, mental retardation, and seizures
Type X	Phosphoglycerate mutase (PGAM)	Autosomal recessive	Childhood-adult: exercise intolerance
Type XI	Lactate dehydrogenase	Autosomal recessive	Childhood-adult: exercise intolerance
Type XII	Aldolase	Autosomal recessive	Infancy-childhood: exercise intolerance and weakness
Type XIII	Triosephosphate isomerase	Autosomal recessive	Infancy: hypotonia, generalized weakness, and mental retardation
Type XIV	β -Enolase	Autosomal recessive	Childhood-adult: exercise intolerance

What causes Pompe disease?

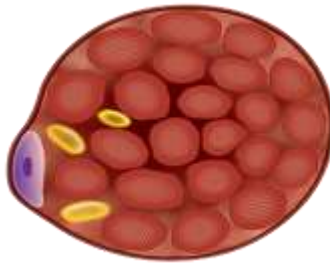
- Pompe disease is a LSD resulting from a deficiency of the enzyme acid α -glucosidase (GAA), that is active against maltose and other oligosaccharides, as well as glycogen, and the product is free-glucose .
- It is associated with progressive accumulation of glycogen within the lysosomes of cells, most notably in skeletal muscle and heart.



What causes Pompe disease?

While the exact process by which muscle damage occurs is still unknown, it has been hypothesized that the progressive accumulation of glycogen leads to ultrastructural damage and autophagic buildup.

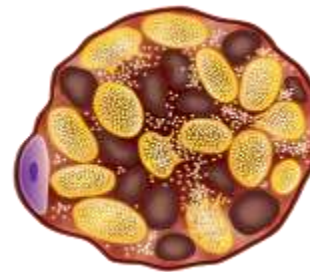
Disease progression



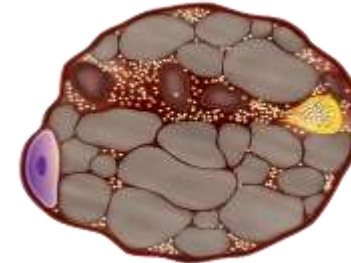
- In early stage disease, cells contain small, glycogen-filled lysosomes, which increase in size and number over time
- Clinical symptoms may not yet be evident



- As the disease progresses, glycogen accumulates and lysosomes expand
- Muscle dysfunction may be present
- Mild / moderate myopathy is now present



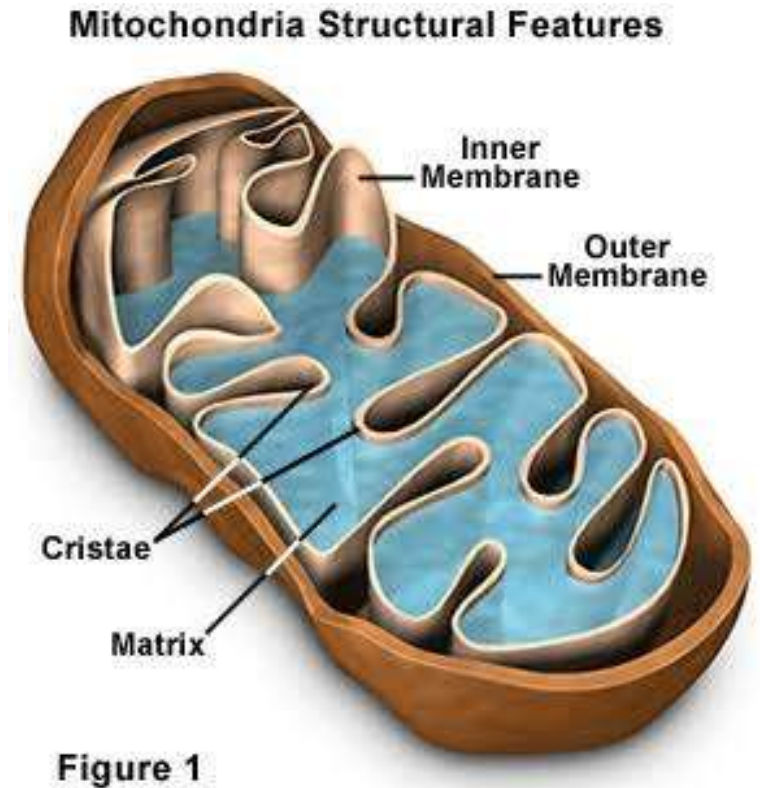
- Lysosomes begin to rupture, allowing glycogen to enter the cytoplasm
- Muscle damage may begin
- Severe myopathy is now present



- In the advanced stage of disease, most glycogen is now cytoplasmic
- Muscle tissue has undergone extensive ultrastructural damage
- Severe myopathy and fibril loss has occurred, and muscle function is impaired

What causes Pompe disease?

- Beyond lysosomal pathology, mitochondrial dysfunction is increasingly recognized as a central mechanism in disease complications.
- Glycogen accumulation disrupts autophagic flux, impairing the clearance of damaged mitochondria (mitophagy), leading to oxidative stress and bioenergetic failure.
- This contributes to disease severity and explains why current ERTs, which do not cross the blood-brain barrier (BBB), fail to address neurological decline .



Pompe disease (GSD II)

- Type II glycogenosis is inherited in an **autosomal recessive** fashion.
- Consanguinity has been observed and although occurs in all ethnic groups, prevalence is high in **Taiwan and South China** .
- The gene has been localized to **chromosome 17q21-25** .
- The gene has been cloned and the sequence of the cDNA determined, It **contains 20 exons** and is approximately 20 kb.
- Mutations have been defined in patients with different phenotypes.
- Currently, **more than 560 mutations** spread throughout *GAA* gene have been reported. (Simona Taverna, AGING 2020, Vol. 12, No. 15)

How many people have Pompe disease?

- As with many rare diseases, it is difficult to know exactly how many people are actually affected.
- Based on studies conducted in the Dutch population and in New York City, it is estimated that Pompe disease occurs in **1 in 40,000 live births worldwide**.
- It is estimated that there are between **5,000** and **10,000** people around the world living with the symptoms of Pompe disease.
- Pompe disease affects both men and women equally .



Pompe Disease Subtype	Incidence (95% CI)
Infantile-onset	1/138,000 (1/43,000-1/536,000)
Late-onset	1/57,000 (1/27,000-1/128,000)
Overall incidence*	1/40,000 (1/17,000-1/100,000)

The spectrum of Pompe disease

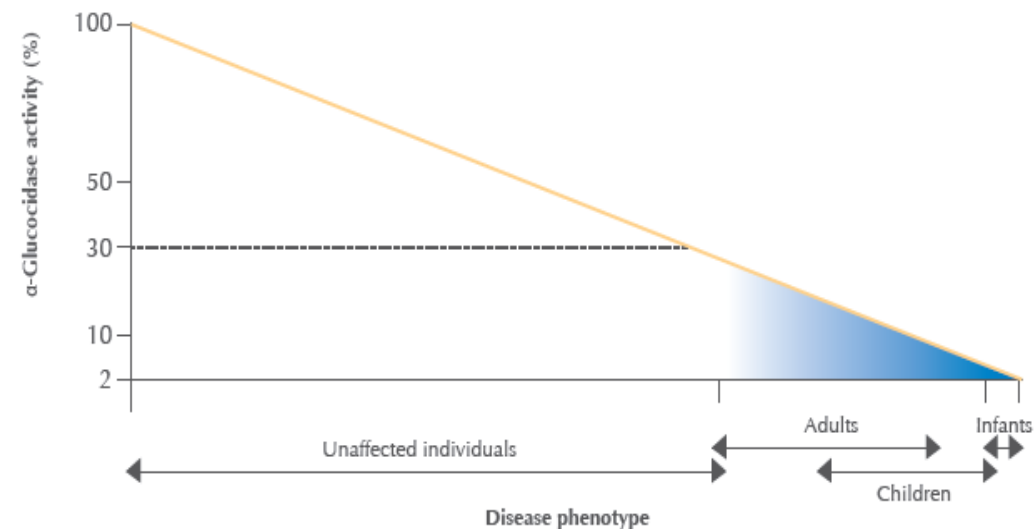
Mutations of the gene coding for **acid α –glucosidase** is associated with a large spectrum of clinical symptoms, ranging from severe sickness characterized by hypertrophic cardiomyopathy and marked muscle weakness to a gradually progressing myopathy and respiratory insufficiency with adult onset .

The spectrum of Pompe disease

Phenotypic variation (severity and rate of disease progression) may be related to residual GAA activity .

- Typically, infants with little to no detectable enzyme activity (<1%) have a rapid and uniformly fatal disease course
- Children and adults with low to moderate GAA activity (2-30%) generally have a less rapid and more variable disease course

Disease phenotype related to residual enzyme level



Introduction & Pathophysiology

- **Definition:** Pompe disease (PD) is a rare, autosomal recessive, neuromuscular disorder .
- **Genetic Basis:** Caused by mutations in the *GAA* gene on chromosome 17q21-25, leading to a deficiency in the lysosomal enzyme acid alpha-glucosidase (GAA) .
- **Pathophysiology:** Deficiency of GAA results in the pathological accumulation of glycogen in lysosomes, primarily in cardiac, skeletal, and smooth muscle tissues, as well as the central nervous system .
- Beyond lysosomal pathology, mitochondrial dysfunction is increasingly recognized as a central mechanism in disease complications.
- **Spectrum:** The severity of the disease is inversely correlated with the level of residual GAA enzyme activity

Classification and Clinical Forms

- The clinical continuum is broadly classified into two main phenotypes:
- **Infantile-Onset Pompe Disease (IOPD)**
 - **Classic IOPD:** Presents within the first few months of life. Nearly absent GAA activity (<1%) .
 - **Non-classic IOPD:** Presents within the first year, less severe cardiac involvement .
- **Late-Onset Pompe Disease (LOPD)**
 - Can present in childhood (juvenile), adolescence, or adulthood .
 - Patients have some residual GAA activity (2-40% of normal)



Pompe disease in infants

The term **infantile onset** incorporates those patients who display symptoms before 1 year of age , who have an average life expectancy of less than 1 year due to severe cardiac hypertrophy and generalized skeletal muscle weakness .

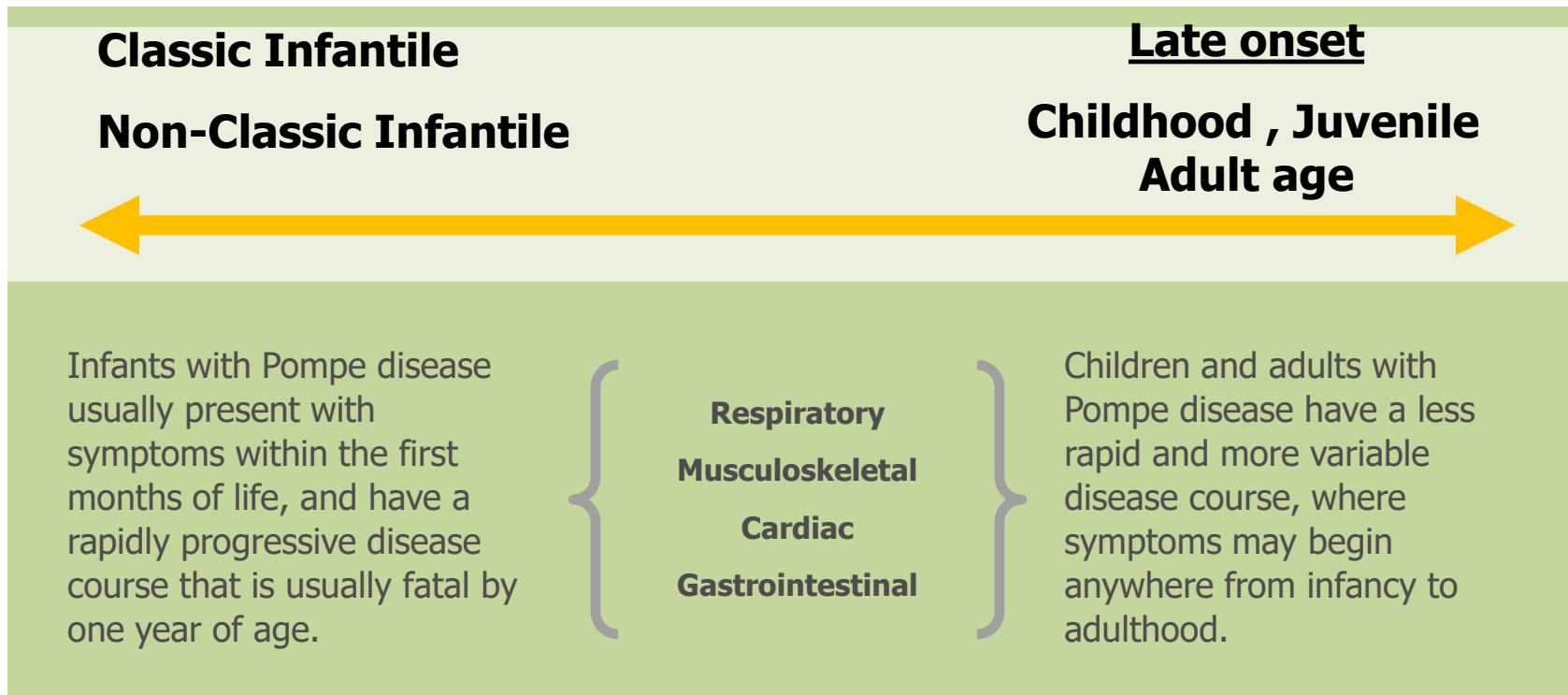
Pompe disease in infants

- 1 -**Classic infantile**: patients as originally described by JC Pompe, in 1932 who exhibit rapidly progressive disease characterized by prominent cardiomegaly, hepatomegaly, weakness and hypotonia, and death due to cardiorespiratory failure in the first year.
- 2 -**Nonclassic infantile**: patients with the infantile variant form with slower progression and less severe cardiomyopathy but presenting in the first year of life as described originally by Hers and, more recently, by Slonim et al.



Clinical Spectrum

Differences in disease presentation are observed among infants, children and adults. Patients typically present with symptoms that manifest in **four organ systems: respiratory, musculoskeletal, cardiac, and gastrointestinal.**



Classic Infantile Pompe Disease

- Patient with classic infantile PD usually come to attention during their first two months of life with marked muscular hypotonia together with a rapidly progressing muscular weakness .
- Muscle weakness and motor delay are the presenting manifestation in **40% of cases** .
- It is manifested by **marked hypotonia** and **weakness associated with diminished or absent deep tendon reflexes.**
- The clinical picture may be suggestive of SMA .
- Muscle mass is normal, but the muscles may feel hard.

Classic Infantile Pompe Disease



Classic Infantile Pompe Disease

- Poor feeding and failure to thrive may be early complaints, but cyanosis and attacks of dyspnea begin promptly, and there is rapid progression to intractable cardiac failure.
- **Early cardiac problems** such as myocardial insufficiency or cardiac arrhythmia are seen in **15-20%** of patients .
- Physical examination reveals signs of cardiac failure and the hallmark feature, cardiomegaly.
- Significant cardiac murmurs are not usually present .

Classic Infantile Pompe Disease

- **Hepatomegaly** may be seen once cardiac failure begins, but it does not result from massive storage of glycogen in the liver.
- **Feeding difficulties** are the first manifestation in **50%** of cases and leading to Failure to thrive .
- Most infants requiring nursing via gastric tube .
- **Respiratory problems** combined with frequent respiratory infections are the first symptoms in **30-40%** of patients .

Classic Infantile Pompe Disease



Classic Infantile Pompe Disease

- Classically the tongue is enlarged.
- **Macroglossia** is caused by infiltration of the muscle fibers of the tongue with glycogen, but macroglossia is noted in **fewer than 50 % of** patients.
- A protuberant tongue with failure to thrive, hypotonia, a protuberant abdomen and possibly an umbilical hernia may suggest a diagnosis of hypothyroidism or Down syndrome.

Classic Infantile Pompe Disease

Macroglossia



Classic Infantile Pompe Disease

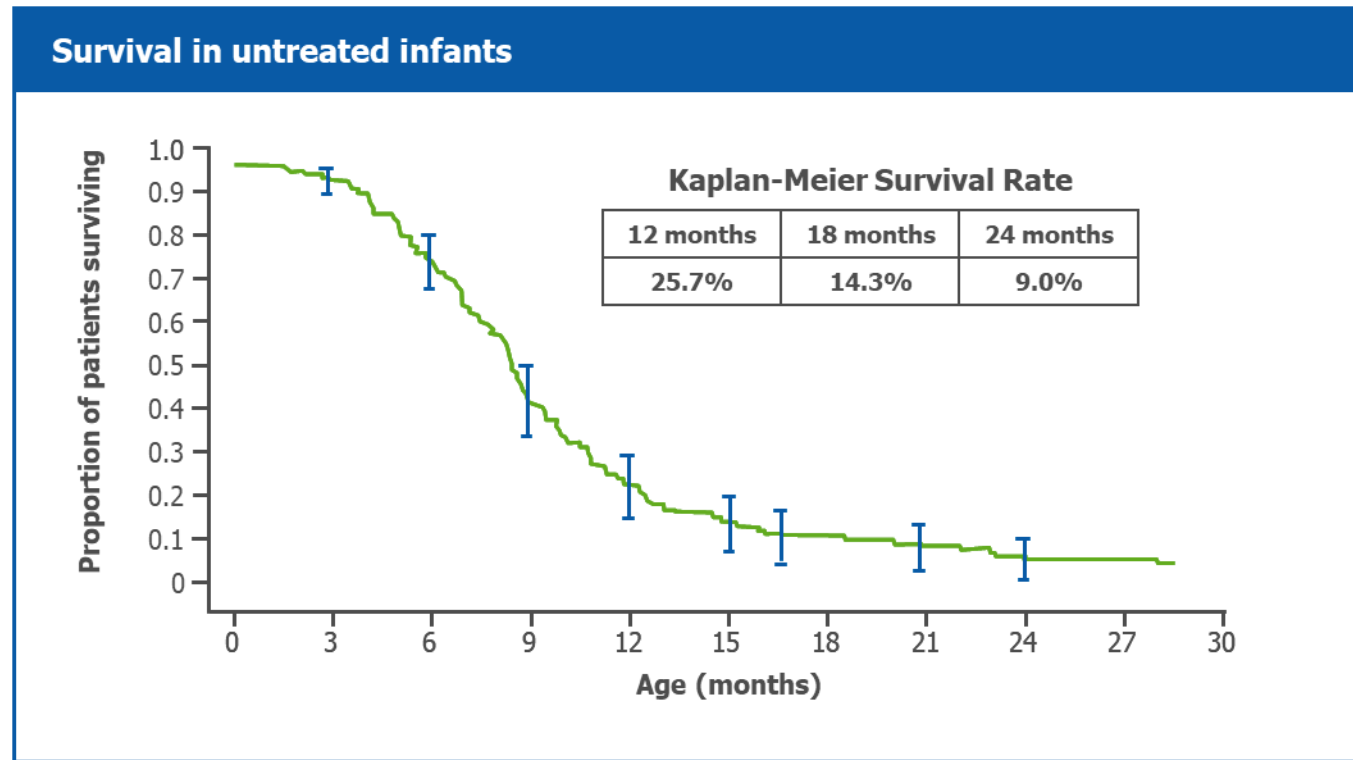
- **Hearing deficits** have been reported in several lysosomal storage diseases, including Fabry disease, Gaucher disease and MPS .
- Hearing loss has been recognized as an important cause of morbidity in infants with pome disease (Classic Infantile PD) .
- Glycogen storage in the cells of the organ of corti is the main cause of the hearing impairment .

Classic Infantile Pompe Disease

- Patient with classic infantile PD usually come to attention during their first two months of life .
- The cardinal features are :
 - Severe cardiomyopathy
 - Muscle weakness
- Death within the first year of life is the usual course in this disease (median age of 6 - 7.7 months).

Course for untreated infants

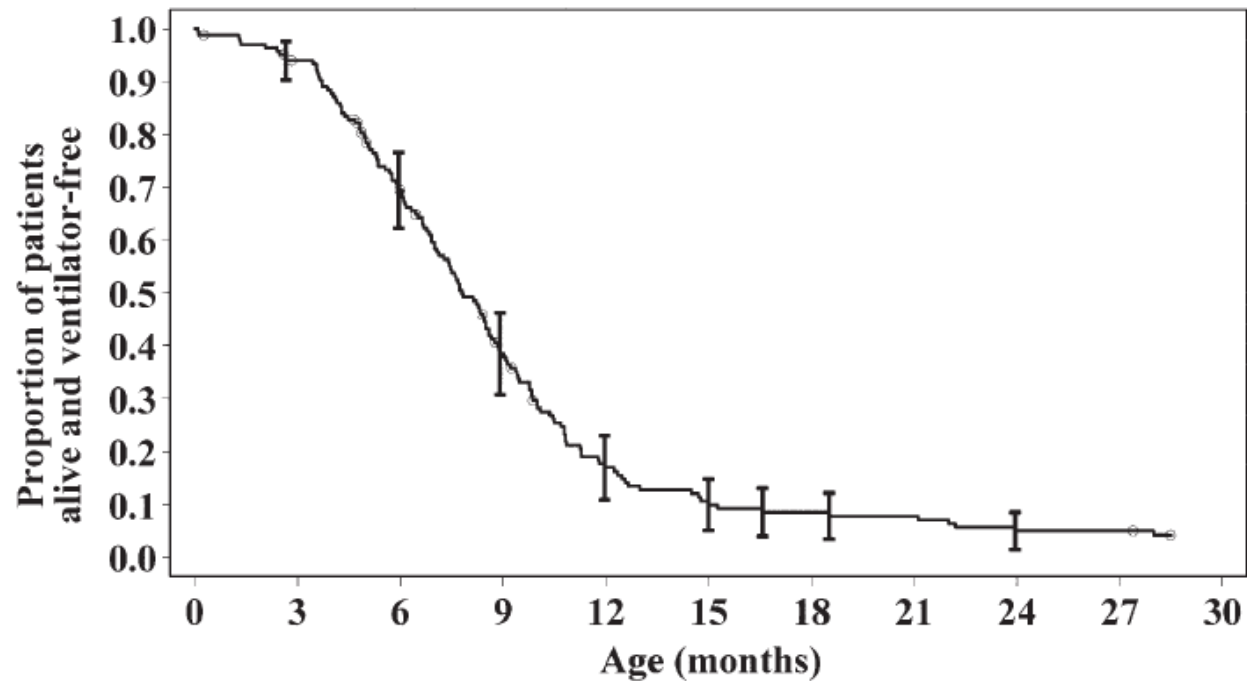
Infants presenting with signs within the first year of life typically have poor prognoses and **a rapidly progressive fatal disease course.**



The **Kaplan-Meier (KM) method** is used to analyze 'time-to-event' data.

Course for untreated infants

Kaplan-Meier analysis of ventilator-free survival time since birth in patients with infantile-onset Pompe disease. Bars represent 95% confidence intervals



Non-Classic Infantile Pompe Disease

Onset of Disease

In the Non-Classic or milder form of infantile PD the onset of symptoms is later (50% were not presented until 4-11 months in contrast to onset between 1-3 months in the majority of cases and at latest at 4 months in classic infantile) .

Non-Classic Infantile Pompe Disease

Cardiomegaly

All infants with the classic form, but none with the mild form, developed relevant cardiomegaly during the first sixth months of life, although both groups of infants had the typical EKG alterations (short P-R intervals and large QRS complexes) .

Non-Classic Infantile Pompe Disease

Macroglossia/Hepatomegaly

Macroglossia and hepatomegaly are not as pronounced as in children with classic infantile Pompe Disease .



Non-Classic Infantile Pompe Disease

Feeding and swallowing dysfunction

- In all infants with PD disturbances in feeding and swallowing result in an insufficient caloric supply and FTT .
- In patients with the classic form, these problems are difficult to overcome, even by gastric tube feeding, on the other hand, supplementary alimentation via a gastrostomy tube in patients with the non-classic form may improve both weight gain and body length .

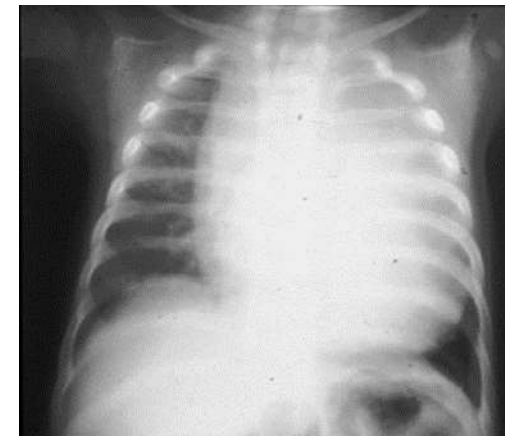
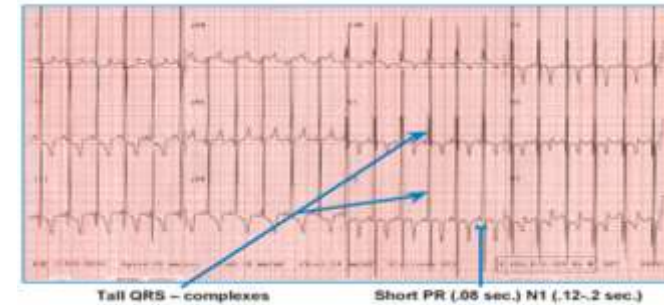
Non-Classic Infantile Pompe Disease

Survival

- Children suffering from the non-classic form of PD usually survive longer, because their cardiac performance remains stable .
- In fact, these children can survive for many years, albeit with continuing ventilatory support .

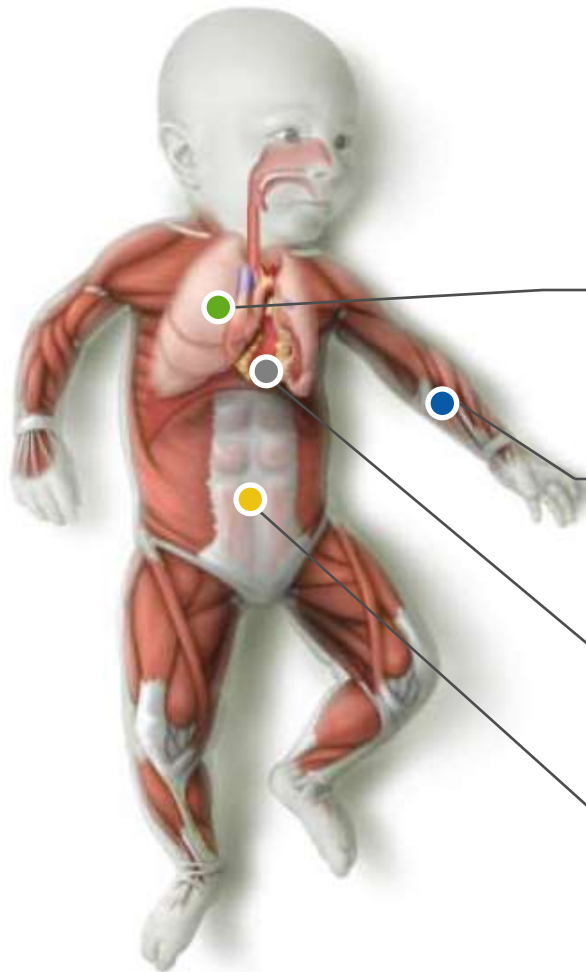
Major Symptoms of IOPD

Major symptoms of Pompe disease in infants	
Muscles	Digestive (GI) Tract
■ Severe muscle weakness ■ “Floppiness” due to loss of muscle tone ■ Head lag — when you try to pull the baby up to a sitting position by grasping the hands or arms, the head drops back ■ Frog-like position of legs ■ Failure to meet developmental milestones such as rolling over, sitting up, crawling, and walking — or loss of milestones	■ Feeding problems that occur as it becomes harder to breathe, suck, or swallow ■ Failure to thrive or gain weight as rapidly as other babies the same age ■ Enlarged liver ■ GI discomfort: vomiting, regurgitation ■ Enlarged tongue
Lungs	Heart
■ Difficulty breathing ■ Frequent respiratory infections ■ Respiratory failure	■ Enlarged heart ■ Heart failure ■ Heart rhythm changes



Kishnani PS, et al. Genet Med 2006;8:267-288.
Gilbert-Barness E. Ann Clin Lab Sci 2004; 34:15-34.
Roe CR, Ding J. New York, New York: McGraw-Hill; 2001.

Recognizing Infantile Pompe disease



Infants typically present with severe cardiac involvement and profound muscle weakness

Respiratory

- Progressive respiratory muscle involvement
- Frequent respiratory infections
- Sleep-disordered breathing

Musculoskeletal

- Progressive muscle weakness
- Profound hypotonia / head lag / “floppy baby”
- Delayed motor milestones

Cardiac

- Cardiomegaly
- Progressive cardiomyopathy

Gastrointestinal

- Macroglossia
- Feeding difficulties
- Failure to thrive / poor weight gain
- Hepatomegaly

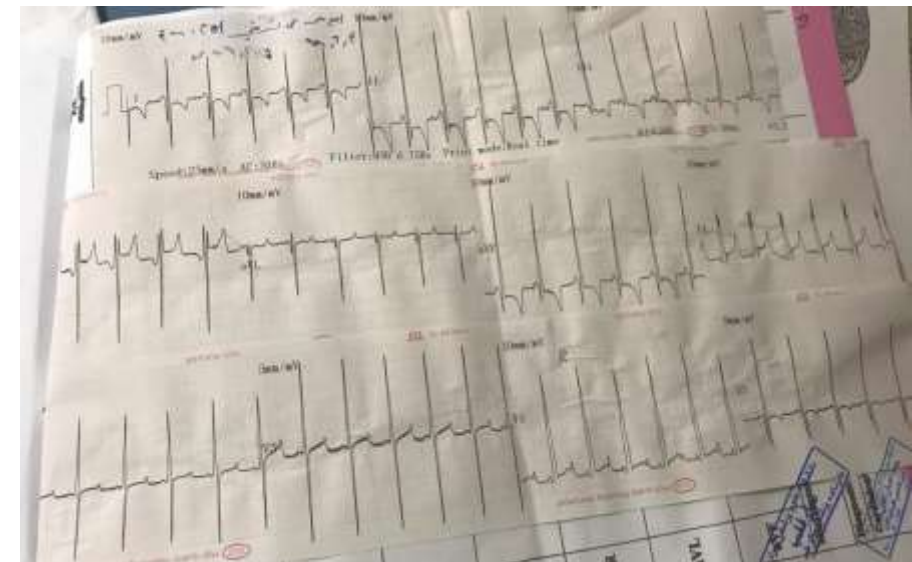
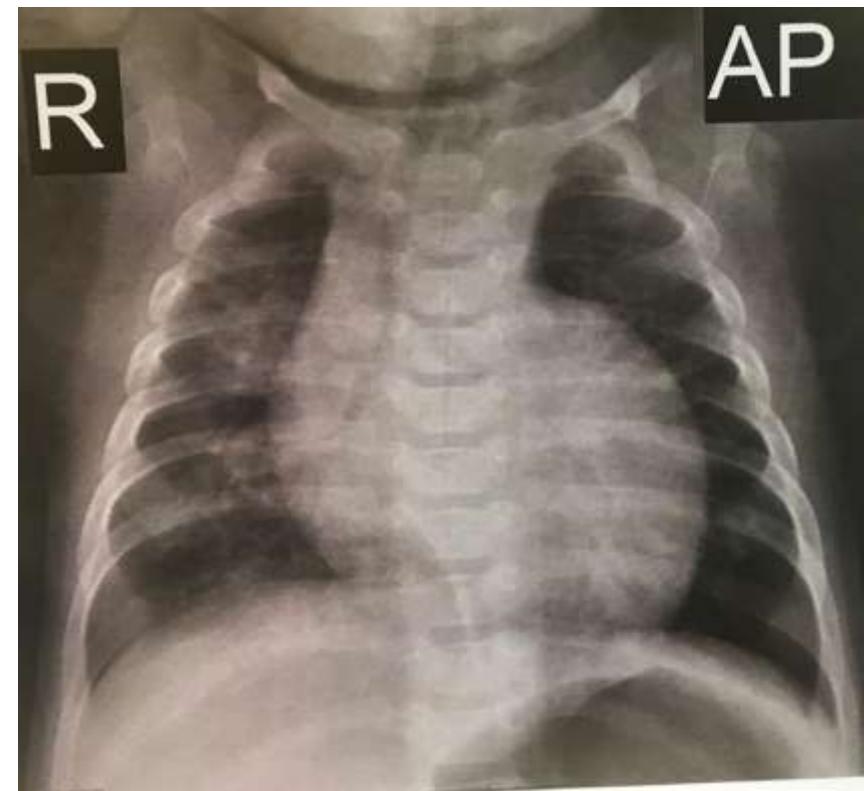
The patient presenting here is a 4.5 month-old boy,
first was referred here with :

- ▶ hypotonia
- ▶ shallow breathing, tachypnea
- ▶ delayed motor development
- ▶ poor weight gain



Regarding the clinical presentation some Para clinic studies were done for the patient :

- ▶ **Ammonia ,lactate** :NL ,CPK:663
- ▶ **HPLC**:NL
- ▶ **TFT**:NL
- ▶ **Homocysteine** :NL
- ▶ **EDX**: irritable myopathic process of proximal and distal muscles with profound myotonic discharges
- ▶ **EEG**:NL
- ▶ **BRAIN SONOGRAPHY** :NL
- ▶ **CXR , ECG and cardiology consult**



Clinical Presentation of IOPD: The "Classic" Picture

- **Key Presentations (within first few months):**
 - **Neuromuscular:** Severe hypotonia ("floppy baby"), generalized muscle weakness, hyporeflexia/areflexia, and motor developmental delay .
 - **Cardiac:** Severe, rapidly progressive hypertrophic cardiomyopathy, cardiomegaly, cardiac failure, and arrhythmias (e.g., short PR interval, high QRS voltage on ECG) .
 - **Respiratory:** Respiratory distress, tachypnea, recurrent infections, and respiratory failure due to muscle weakness .
 - **Gastrointestinal/Nutritional:** Feeding difficulties, failure to thrive, and macroglossia .
 - **Other:** Hearing impairment, impaired vision, white matter abnormalities on brain MRI .
- **Natural History:** Without treatment, death from cardiorespiratory failure typically occurs within the first year of life

Classic Infantile PD-Differential Diagnosis

The classic infantile form of PD with muscular **hypotonia** , **muscle weakness** and **cardiomyopathy** does not seem to be very challenging for differential diagnosis and always consider PD with this triad .

Differential diagnosis of infantile-onset Pompe disease

Differential diagnosis	Shared signs and symptoms
Acute Werdnig-Hoffman disease (Spinal Muscular Atrophy I)	Hypotonia, progressive proximal myopathy, absent reflexes
Hypothyroidism	Hypotonia, macroglossia
Endocardial fibroelastosis	Breathlessness, feeding difficulties, cardiomegaly, heart failure
Myocarditis	Cardiomegaly
Congenital muscular dystrophy	Severe hypotonia and muscle weakness
Glycogen storage diseases: IIIa (Debrancher deficiency/ Cori or Forbes disease and, IV (Branching enzyme deficiency/Anderson disease)	Cardiomegaly, myopathy, elevated creatine kinase (CK)
Mitochondrial/respiratory chain disorders	Hepatomegaly, muscle weakness, cardiomegaly, elevated creatine kinase (CK)
Danon disease	Cardiomegaly, cardiomyopathy, myopathy, vacuolar glycogen storage
Idiopathic hypertrophic cardiomyopathy	Biventricular hypertrophy
Peroxisomal disorders	Hypotonia, hepatomegaly



Pompe disease in children and adults

late-onset form includes :

- 1- **Childhood, juvenile**, or muscular variant that is a heterogeneous group usually presenting later than infancy and typically not including severe cardiomyopathy.
- 2- **Adult-onset** form characterized by a slowly progressive myopathy predominantly involving skeletal muscle that can present as late as the second to sixth decade of life.

Pompe disease in children and adults

- Children and adults with low to moderate GAA activity (2-30%) generally have a less rapid and more variable disease course .
- Thus, LOPD children are not uncommonly misdiagnosed with Duchenne or some other form of limb-girdle muscular dystrophy.
- Rarely, acid maltase deficiency presents with rigidity of the spine.

Pompe disease in children and adults

- Unlike the infantile-onset acid maltase deficiency, cardiomegaly, hepatomegaly, and macroglossia are uncommon.
- Motor milestones may be delayed.
- Weakness is slowly progressive and involves proximal greater than distal muscles in the legs and arms.
- Children often have hypertrophy of the calf muscles, a waddling gait, and significant lumbar lordosis and demonstrate a Gower maneuver to arise from the floor.

Major Symptoms of LOPD

Major symptoms of Pompe disease in children and adults

Muscles

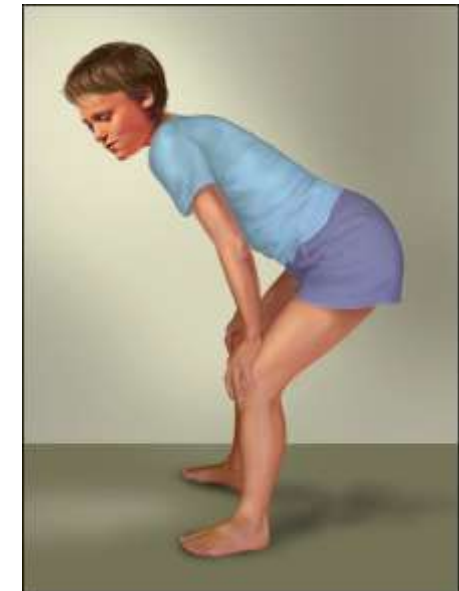
- Progressive muscle weakness in the legs and hips
- Difficulty climbing stairs, running, or getting up from a chair
- Walking with swaying hips or a waddle
- Frequent trips and falls (loss of balance)
- Gradual loss of motor milestones that have been achieved, such as walking, running, or jumping (children)
- Low back pain
- Scoliosis (curvature of the spine)

Lungs

- Difficulty breathing, especially after exertion or when lying on your back
- Morning headaches, daytime sleepiness, shortness of breath and other signs of respiratory insufficiency
- Frequent respiratory infections, such as bronchitis and pneumonia

Digestive (GI) Tract

- Difficulty gaining or maintaining weight
- Problems chewing and/or swallowing



Natural history of Non Classic late -onset Pompe Disease

The natural history of late-onset (childhood, juvenile, and adult) Pompe disease without ERT is characterized by onset of symptoms after 1 year of age, less severe to no cardiac involvement, slower progression, and significant heterogeneity of symptoms, with symptoms primarily related to progressive dysfunction of skeletal and respiratory muscles.

Common signs and symptoms in children and adults with Pompe disease

Children and adults experience steady degeneration of respiratory and skeletal muscles

Respiratory

- Respiratory failure / insufficiency
- Diaphragm weakness
- Sleep-disordered breathing
- Orthopnea
- Dyspnea

Musculoskeletal

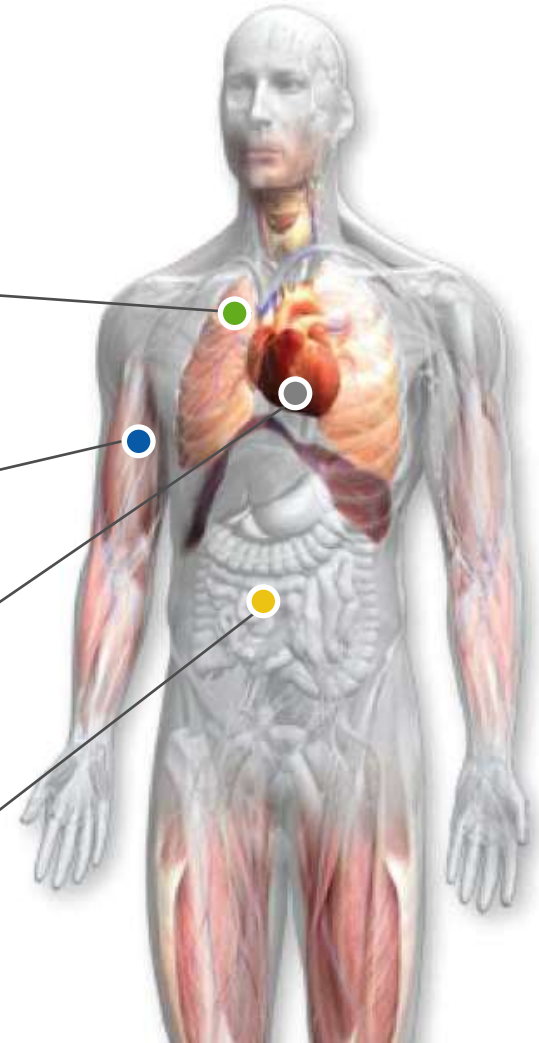
- Limb-girdle muscle weakness
- Muscle pain
- Frequent falls
- Gait abnormalities
- Difficulty walking, climbing stairs
- Scoliosis / scapular winging

Cardiac

- Less common among adults

Gastrointestinal

- Difficulty chewing / jaw muscle fatigue
- Poor weight gain / maintenance
- Swallowing difficulties / weak tongue
- Gastroesophageal reflux



Late-onset Pompe Disease

Differential Diagnosis

The non-specificity of symptoms and overlap of symptoms with more common neuromuscular and genetic disorders, combined with its rarity, can result in a low index of suspicion for Pompe disease, particularly for children and adults.

Late-onset Pompe Disease

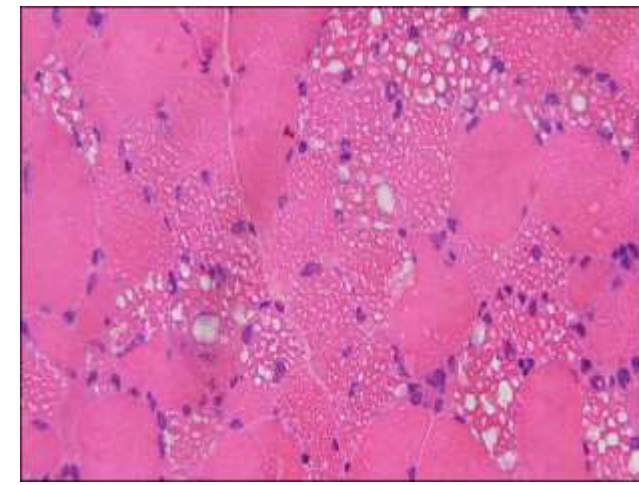
Differential Diagnosis

- The differential diagnosis for Pompe disease includes a broad range of myopathies, motor neuron, and neuromuscular junction disorders .
- Pompe disease should be considered as part of the differential diagnosis for all children and adults **presenting with limb-girdle muscle weakness and respiratory insufficiency** .

Disorder Type	Diagnoses
Dystrophies	▪ Limb-girdle muscular dystrophy ▪ Duchenne/Becker muscular dystrophy ▪ Myofibrillar myopathy ▪ Myotonic dystrophy type 2 ▪ Danon disease
Inflammatory myopathies	▪ Polymyositis ▪ Inclusion body myositis
Other metabolic myopathies	▪ Mitochondrial myopathy ▪ McArdle disease
Motor neuron disorders	▪ Spinal muscular atrophy ▪ Amyotrophic lateral sclerosis (ALS) ▪ Kennedy disease
NM junction disorders	▪ Myasthenia gravis ▪ Congenital myasthenic syndromes

The patient is a 5 Y.O. boy that admitted in Children's Medical Center with respiratory distress and muscle weakness.

- ✓ Frequent drop from onset of walking
- ✓ Waddling gait
- ✓ Difficulty in sitting to standing
- ✓ Motor developmental regression
- ✓ Frequent respiratory infection



- ✓ Failure to thrive(Wt:12kg)
- ✓ Mild hepatomegaly
- ✓ DTR: ↓(generalized)
- ✓ Muscle bulk : ↓
- ✓ Force : ↓(4/5)
- ✓ Hypotonia
- ✓ Severe proximal weakness(esp. in pelvis)
- ✓ **AST: 580, ALT: 135, ALKP:167**
- ✓ **CPK: 430** (39-308)
- ✓ LDH: 1724

- ✓ Abnormal EMG, normal NCS, due to the increased insertional activities on needle EMG.
- ✓ **CRDs and myotonic** discharges were so prominent.

- ✓ Severe vacuolar myopathy with glycogen excess compatible with glycogen storage myopathy
- ✓ Recommended: acid maltase enzyme study

Alpha- glucosidase at pH 3.8:
0.70 (1.5-10 nmol/spot21h)



Clinical Presentation of LOPD: The "Insidious" Course

- **Key Presentations (appearing after 1 year of age):**
 - **Musculoskeletal:** Slowly progressive proximal muscle weakness (pelvic > shoulder girdle), gait disturbances (waddling), difficulty climbing stairs, and Gowers' sign .
 - **Respiratory:** Diaphragmatic weakness leading to respiratory insufficiency, orthopnea, sleep-disordered breathing, and exertional dyspnea, which can be the presenting feature .
 - **Other:** Exercise intolerance, fatigue, myalgia, scoliosis, and lordosis .
- **Key Differences from IOPD:** Cardiac involvement is typically rare. Diagnosis is often delayed due to the insidious and nonspecific nature of symptoms

Pompe Disease Diagnosis

History and Physical Exams

- In PD, as well as in most other conditions, **patient history and physical examinations** are the two most important steps toward diagnosis .
- The classic infantile form can be diagnosed quite easily thanks to its characteristic and acute clinical presentation .

Creatine Kinase activity

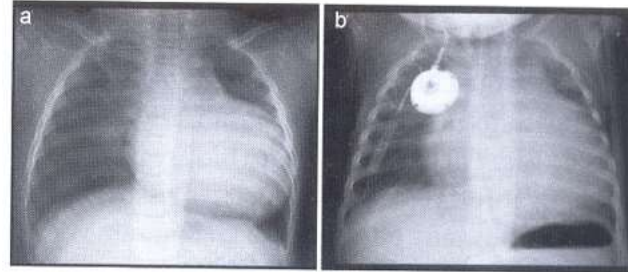
- In patients presenting with muscle weakness, **Creatine Kinase (CK)** activity in the serum should always be analysed.
- Elevation of CK in PD is a very sensitive, but not specific and its rate of elevation correlate with the severity of the disease.
- Other laboratory parameters with elevated levels in PD are **ALT, AST and LDH** .



IOPD Diagnosis

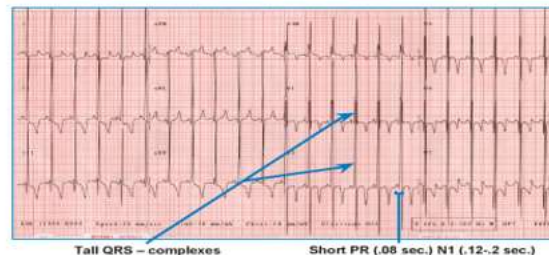
X-ray Examinations

- When cardiomegaly is diagnosed in infancy , infantile PD needs to be considered .
- Chest X-rays is often indicated when the patients show breathing problems .



Cardiac function Exams

- Electrocardiographic and Echocardiographic examinations in patients with Classic infantile PD can give important information on the degree of cardiac involvement .
- Cardiac involvement in an infant with muscular hypotonia and weakness can suggest PD in differential diagnosis .
- The electrocardiogram may show very **large QRS complexes** in all leads and a **short PR interval** .



Pompe Disease Diagnosis

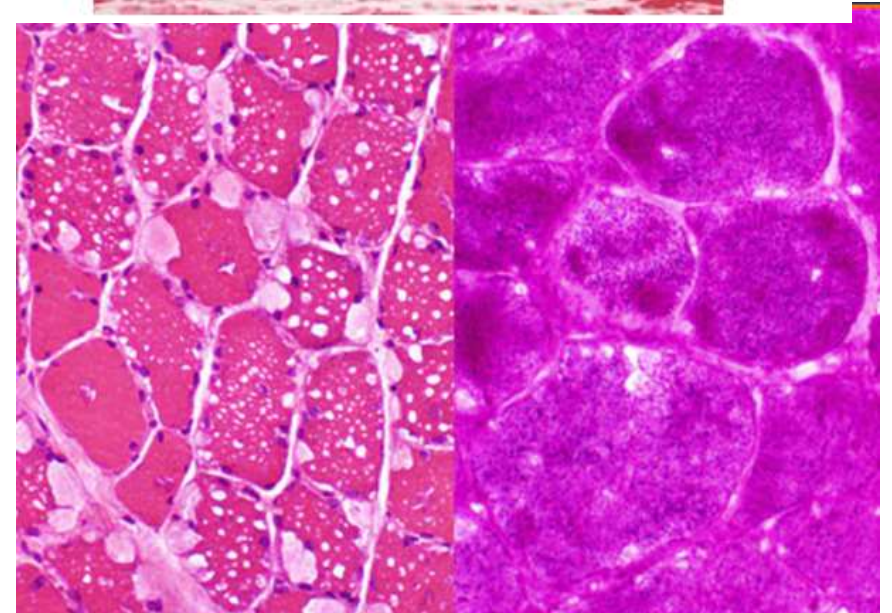
Electromyographic examination

- Motor and sensory nerve conduction studies (NCS) are normal.
- Electromyography (EMG) reveals **increased insertional and spontaneous activity in the form of fibrillation potentials, positive sharp waves, complex repetitive discharges, and even myotonic discharges.**
- In mild forms of the disease, these irritative discharges may be evident only in the paraspinal muscles.
- Motor unit action potentials (MUAPs) are **myopathic** in appearance and recruit early.

Muscle biopsy

- Muscle biopsy is an important step in the diagnosis of PD .
- Glycogen will accumulate in clinically affected muscles and result in a histopathologic picture of **vacuolar myopathy** .
- In the classic infantile form nearly all muscle fibres will show big vacuoles , but in the childhood and adult forms, these are apparent in only 25–75% of fibers in clinically affected muscles and may be absent in clinically unaffected muscle groups.
- When present, the vacuoles react strongly to periodic acid Schiff (PAS) .

Periodic acid Schiff (PAS)-stained longitudinal section of muscle



Left, hematoxylin and eosin stain showing vacuolated muscle fibers.
Right, periodic acid-Schiff (PAS) increased glycogen

Pompe Disease Diagnosis

- Blood tests , imaging procedures and specific techniques for the examination or organ function can support the suspected diagnosis .
- The diagnosis can be verified by measuring the **decreased enzyme activity of acid α - glucosidase** , or as it is a genetic disorder, by identifying the respective **mutation** in the acid α - glucosidase gene (GAA) .

- Like many other genetic diseases, PD can be diagnosed by verification of the respective mutation in the gene for the acid α -glucosidase (GAA) .
- It must be stated that mutation analysis does not replace the assessment of acid α -glucosidase, since it is not as reliable as the latter concerning evaluation of enzyme activity .

Measurement of Enzyme Activity

- More recently **dried blood spot (DBS)** enzyme assay developed .
- DBS is easy to collect, stable, highly specific and avoids need for muscle biopsy .
- DBS results provide enzyme activity ranges presented for normal, heterozygotes and affected individuals .
- DBS is being adopted rapidly around the world because of its speed (result within days), reliability and convenience, making it an ideal first line test for patients with suspected Pompe disease .



Diagnostic Pathway

- **1- Newborn Screening (NBS):** Increasingly adopted, allowing for early presymptomatic diagnosis, which is critical for optimal outcomes in IOPD .
- **2- Enzyme Activity Assay:** The first-line diagnostic test.
 - **Dried Blood Spot (DBS):** Widely used for screening .
 - **Leukocytes/Fibroblasts:** More sensitive and specific test for confirmation of diagnosis .
- **3- Genetic Testing:** Identifies biallelic pathogenic variants in the *GAA* gene to confirm the diagnosis and provide information for genetic counseling
- **4- Adjunctive Tests:**
 - **Biochemical:** Elevated Creatine Kinase (CK), Urinary Hex4 (glucotetrasaccharide) .
 - **Cardiac:** Echocardiogram and ECG (for IOPD) .
 - **Other:** Muscle MRI, electromyography (EMG), and pulmonary function tests (for LOPD)

Newborn screening: evolution and implementation

- Early diagnosis is crucial for initiating ERT before irreversible muscle damage occurs.
- Traditional newborn screening (NBS) utilizing heel-prick dried blood spots (DBS) faces logistical challenges, particularly with early hospital discharge.
- Cheah et al validated umbilical cord blood (UCB) as a viable alternative.



Thank you For your Attention

