LSD WORKSHOP

WHAT EVERY PEDIATRICIAN SHOULD KNOW

Amal Al Tenaiji
Pediatric Metabolic Genetics
SKMC – Abu Dhabi

CASE

A 1 month old infant presents with difficulty feeding and respiratory distress.

Mom and dad give a history of a normal pregnancy and delivery.

No maternal diabetes, no perinatal complications.

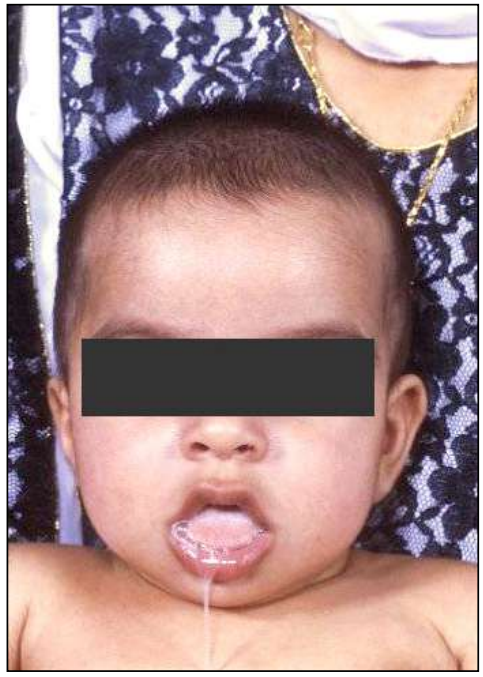
He has been a quiet baby, sleeping a lot

CASE

On physical exam he has failure to thrive, macroglossia, mild hypotonia, increased respiratory rate, slightly dusky in color and his cardiac exam revealed normal blood pressure with a gallop

He is not coarse in appearance

There is perhaps mild liver enlargement but no splenomegaly



What next?

Sepsis workup (click to see results) >>

- Negative for infectious etiology

Arterial blood gas (click to see results) >>

- Metabolic acidosis with respiratory compensation
- O_2 saturation is 91%

Cranial ultrasound (click to see results) >>

- Normal

CPK (click to see results) >>

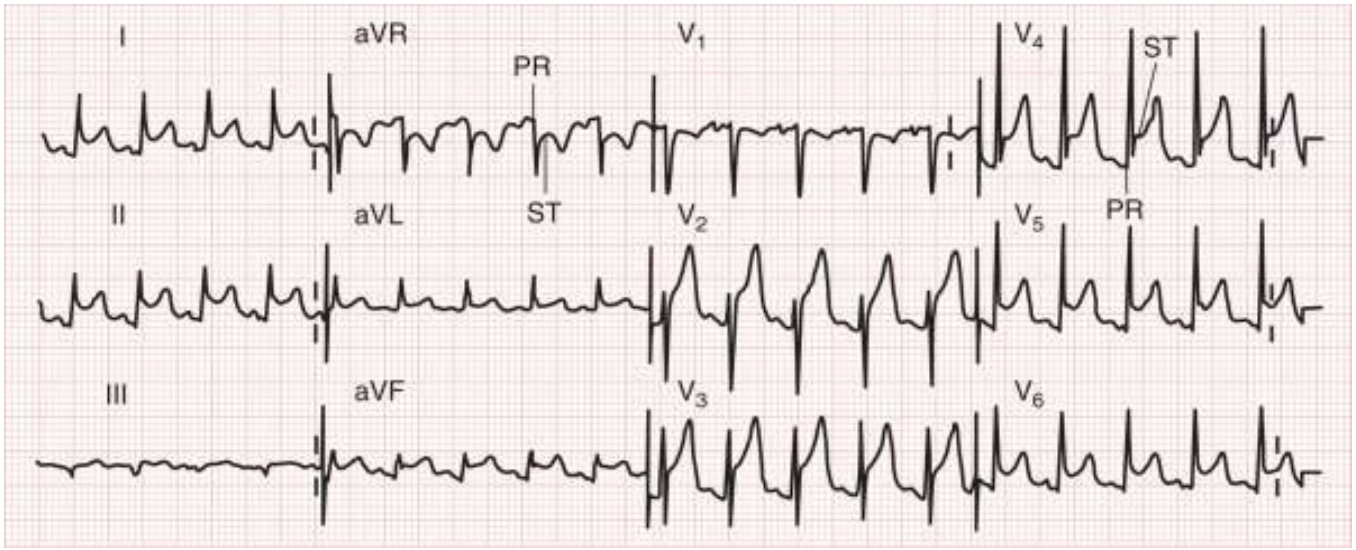
- Elevated – 879

CBC, lactate, pyruvate, NH_3, CO_2 (click to see results) >>

- Normal

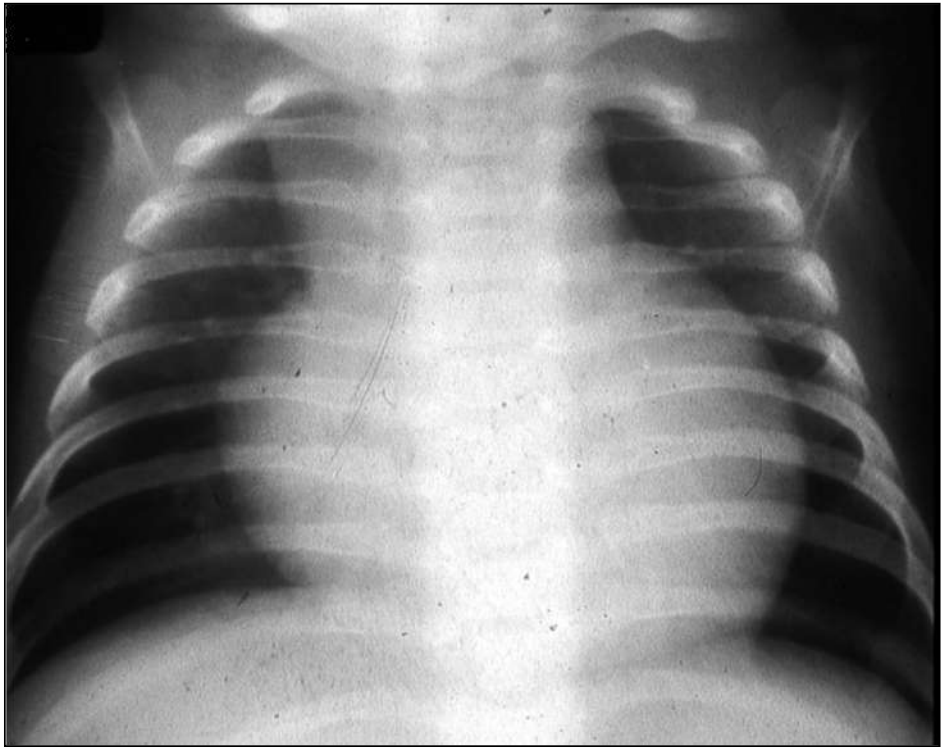
ECG (click to see results) >>

Left ventricular hypertrophy without arrhythmias

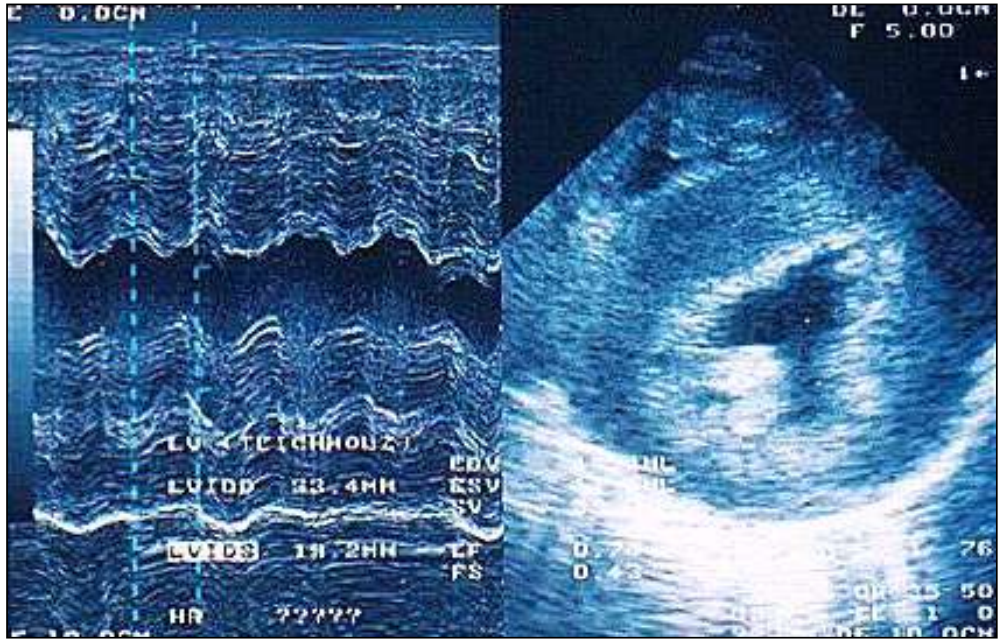


CXR (click to see results) >>

Cardiac enlargement, atelectasis interpreted as congestive heart failure



ECHO (click to see results) >>



Cardiac enlargement with increased wall thickness of both ventricles and interventricular septum, decreased ventricular cavity size

DIFFERENTIAL DIAGNOSIS?

Differential diagnosis:

1. Congenital heart disease
2. Metabolic disease:
    - Pompe disease
    - Respiratory chain defects
    - Fatty acid oxidation defects (e.g., mitochondrial trifunctional protein deficiency)
    - Congenital disorders of glycosylation

What additional testing do you order?

CASE

Diagnostic testing:

- Cultured skin fibroblasts or
- Newborn filter paper specimen

for lysosomal enzyme α-glucosidase activity

CASE

Alpha-Glucosidase activity(click to see results) >>

Deficiency of α-glucosidase, confirming a diagnosis of infantile-onset Pompe disease (GSD II)

CASE

Which ONE of the following is the most appropriate treatment for this child?

A. Hematopoietic stem cell transplantation
B. Enzyme replacement therapy (ERT) or substrate reduction therapy
C. Supportive therapy only

CASE

- **Enzyme replacement therapy with supportive therapy**
  - Alpha glucosidase (Myozyme) administered IV 20-40 mg/kg/dose every 1-2 weeks
  - ERT is considered medically urgent in this disorder where congestive heart failure is present
  - 24 hour Holter monitoring is recommended because of life-threatening risk of arrhythmias

CASE

- **Infusion reactions are common with development of IgG antibodies. The development of IgE antibodies are less common but associated with anaphylactic reactions**
- **Treatment of infusion reactions includes:**
  - Slowing the infusion rate
  - Antipyretics
  - Antihistamines
  - Glucosteroids

CASE

ERT is begun. At 9 months of age in clinic, you find:

- Mild macroglossia
- Continued mild respiratory issues, requires CPAP at night
- Improved muscle tone, child is sitting
- Normal social interaction

CXR - normal heart size

EKG - mild left ventricular hypertrophy

Labs:

- Continued elevation of CPK
- Renal function normal despite prior cardiac compromise

CASE

Plan:

- Continued ERT
- Begin physical therapy
- Optimize nutrition including feeding tube prn

NOTE: At this point it is clinically clear that the skeletal muscle has a relative resistance to ERT compared to cardiac muscle. This is why it is essential that children begin ERT before they become ventilator-dependent

CASE

At 30 months of age, examination of the child shows:

- Mild hypotonia without macroglossia
- Failure to thrive, with improving growth velocity
- No respiratory distress

The patients is not yet walking but is attempting to pull to a stand, and is speaking in 4-word sentences

Labs show continued to show mild elevation of CPK

CXR shows normal heart size and EKG normal

JOANNES POMPE

Dutch pathologist

Published first description of the disease in 1932

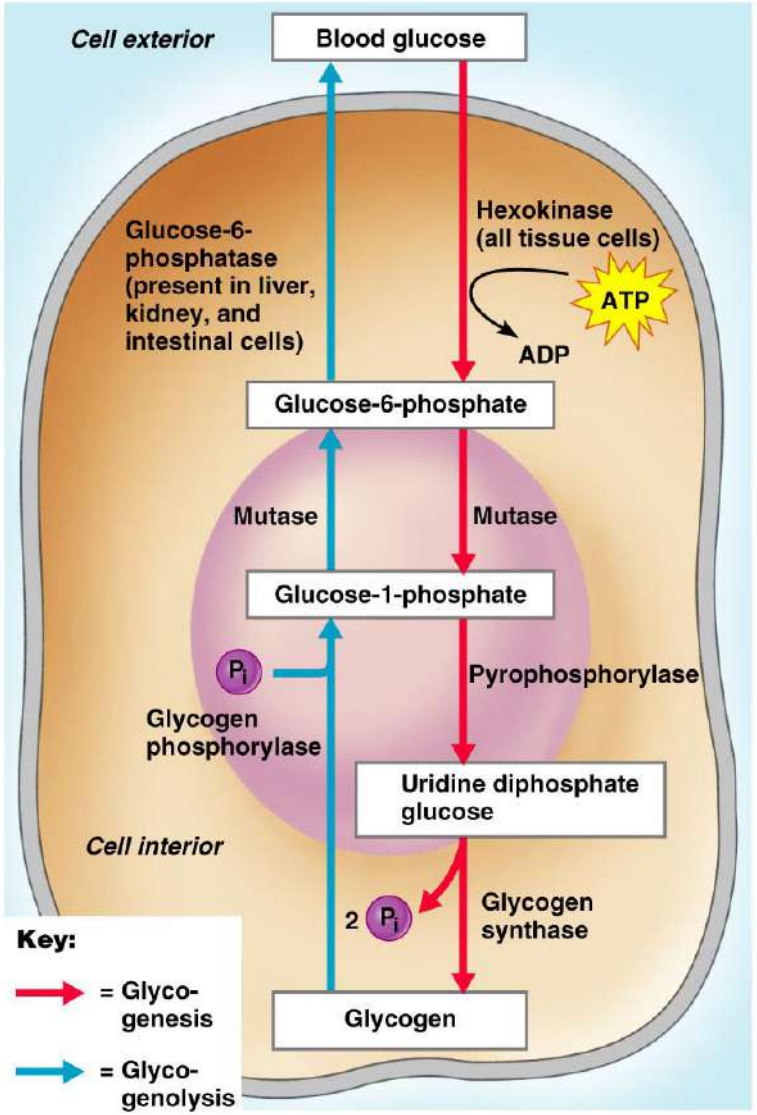
Identified it as a glycogen storage disease

A PUZZLE

Glycogen storage disease

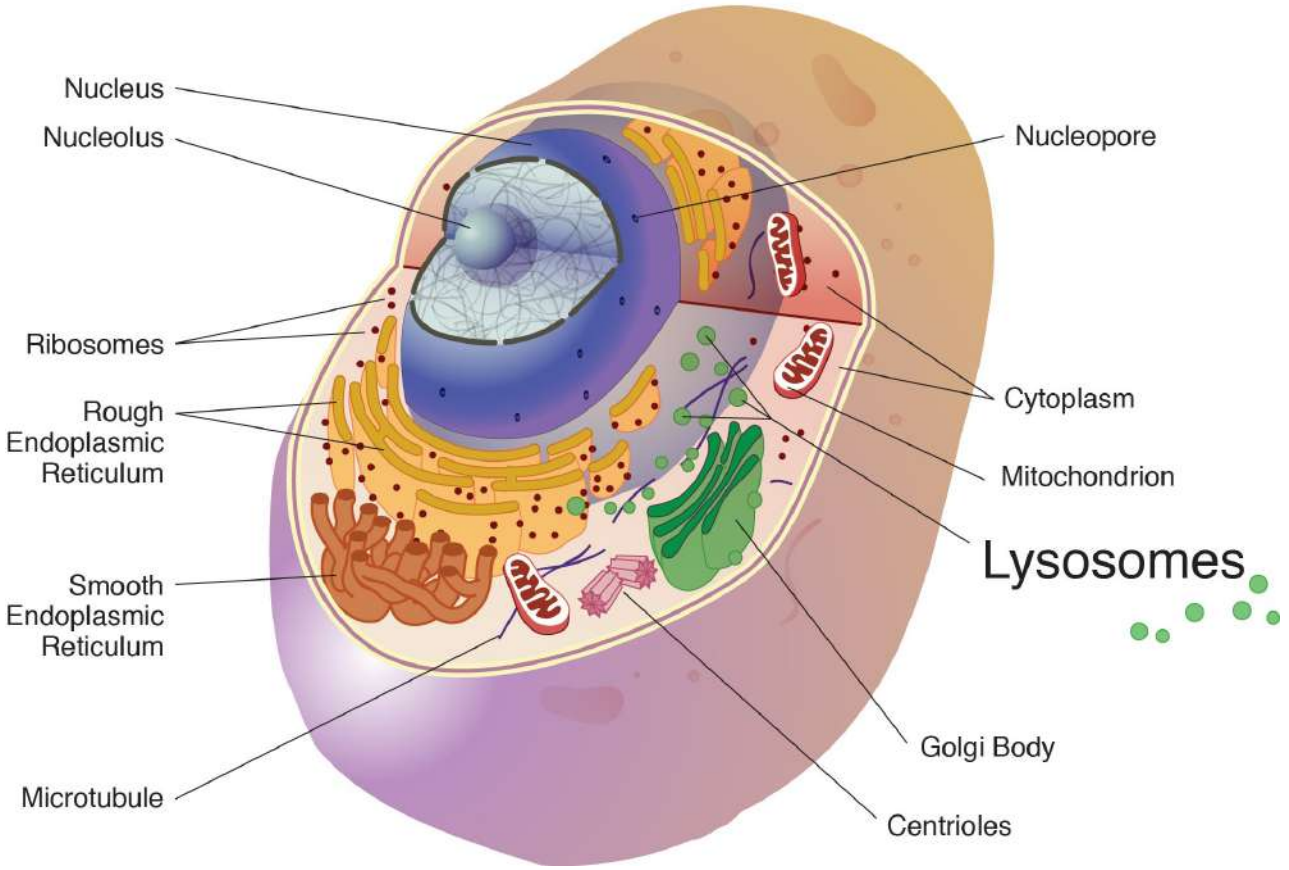
But

Normal glycogen metabolism enzymes present



LYSOSOMES

- Membrane-enclosed organelles
- Contain enzymes – acid hydrolases
- Functional in the acidic PH inside the lysosome
- Degrade intracellular material



HENRI-GERY HERS

Co-worker of de Duve

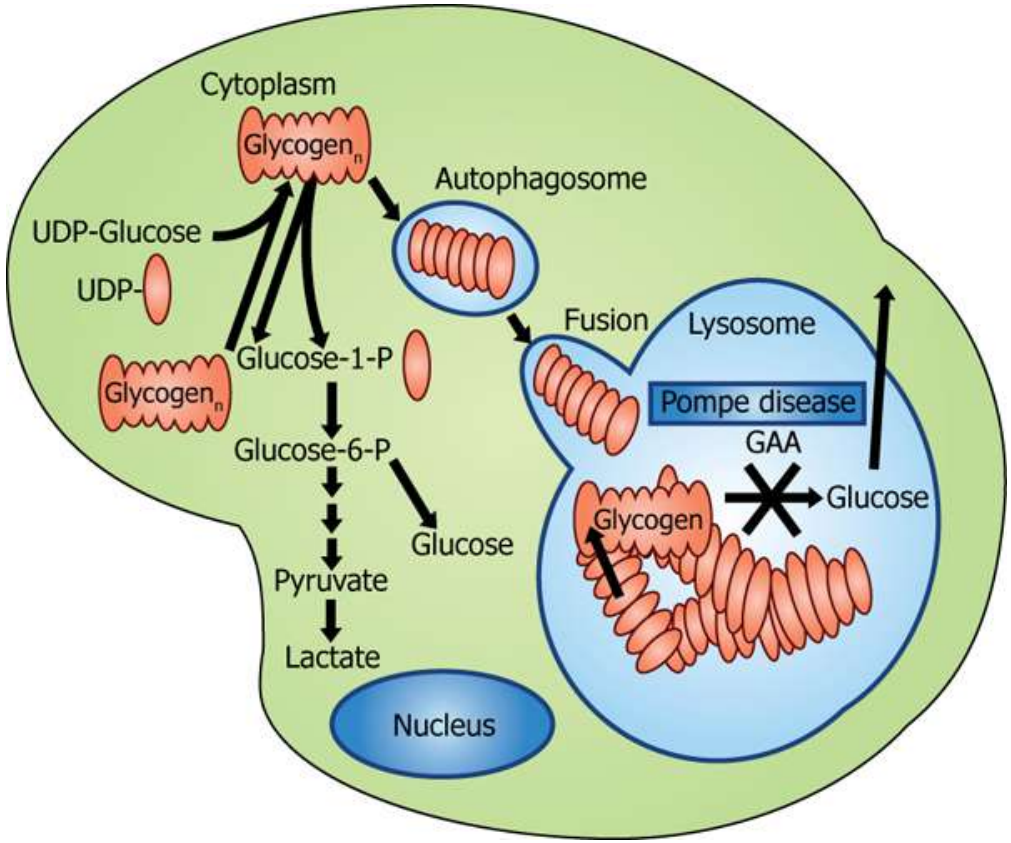
Interested in glycogen storage disease

Alpha-glucosidase deficiency

A lysosomal enzyme

Lysosomal Storage Disease concept - 1965

ALPHA-GLUCOSIDASE



POMPE DISEASE

Glycogen Storage Disease Type II

Deficiency of the lysosomal enzyme: acid α-glucosidase

Very rare disease (1 in 40,000)

It is the second most common cause of muscle glycogenosis (after GSD V)

Metabolic myopathy

Glycogen accumulation leads to muscle tissue damage → functional impairment → permanent disability

Characterized by: cardiac, skeletal and smooth muscle involvement

POMPE: DISEASE SPECTRUM

Continuum of disease severity

Early onset – INFANTILE –

- Individuals with onset before age 12 months with cardiomyopathy

Late onset – CHILDHOOD/JUVENILE/ADULT –

- Individuals with onset before age 12 months without cardiomyopathy;
- All individuals with onset after age 12 months

Rate of Clinical Deterioration

Rapid

With hypertrophic cardiomyopathy

Slower

Without hypertrophic cardiomyopathy

Disease Duration

Short

(death in 1st year of life)

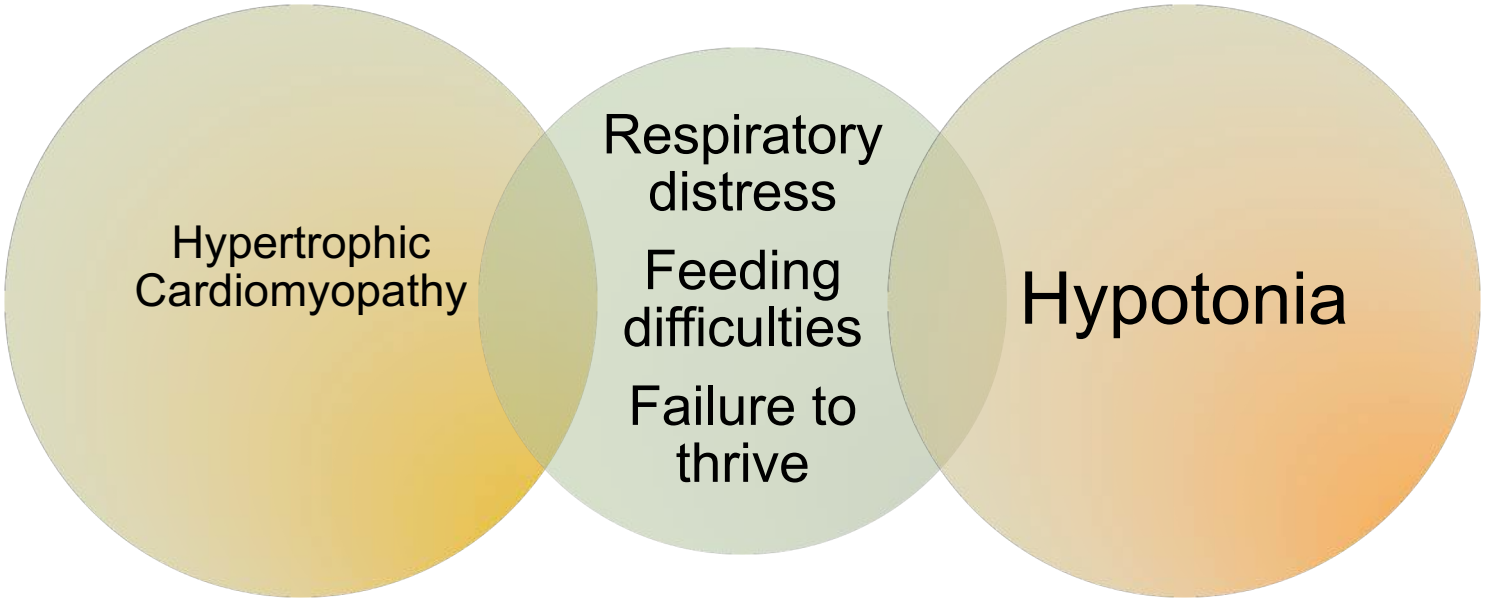
Longer

(with significant morbidity)

IOPD

May be apparent in the early neonatal period

More often recognized - median age of 4 months



COMMON FINDINGS AT PRESENTATION OF IOPD

Hypotonia/muscle weakness	52%-96%
Cardiomegaly	92%-100%
Hepatomegaly	29%-90%
Left ventricular hypertrophy	83%-100%
Cardiomyopathy	88%
Respiratory distress	41%-78%
Murmur	46%-75%
Enlarged tongue (macroglossia)	29%-62%
Feeding difficulties	57%
Failure to thrive	53%
Absent deep tendon reflexes	33%-35%
Normal cognition	95%

IOPD

Hearing loss is common, possibly reflecting cochlear or conductive pathology or both

Without treatment, the cardiomegaly and hypertrophic cardiomyopathy progress to left ventricular outflow obstruction.

Enlargement of the heart can also result in diminished lung volume, atelectasis, and sometimes bronchial compression.

Progressive deposition of glycogen results in conduction defects as seen by shortening of the PR interval on ECG.

In untreated infants, death commonly occurs in the first two years of life from cardiopulmonary insufficiency

LOPD

Manifests at various ages with:

- muscle weakness
- respiratory insufficiency

Disease progression is predicted by the age of onset

- progression is more rapid if symptoms are evident in childhood

COMMON FINDINGS AT PRESENTATION OF LOPD

Progressive proximal muscle weakness (95%)

Respiratory insufficiency

Exercise intolerance Exertional dyspnea

Orthopnea Sleep apnea

Hyperlordosis and/or scoliosis

Hepatomegaly (childhood and juvenile onset)

Macroglossia (childhood onset)

Difficulty chewing and swallowing

GI symptoms, including irritable bowel- like symptoms

Chronic pain

Increased respiratory infections

Decreased deep tendon reflexes

Gower sign

Joint contractures

CARDIAC COMPLICATIONS- LOPD

Do not typically include cardiac complications, however some adults with late-onset disease have **arteriopathy**:

- dilation of the ascending thoracic aorta
- ectasia of the basilar and internal carotid arteries which may be associated with clinical signs, such as transient ischemic attacks, ischemic stroke and third nerve paralysis

SKELETAL MUSCLE - LOPD

Progression of skeletal muscle involvement is **slower** than in the infantile forms; yet **progressive** and eventually involves the diaphragm and accessory respiratory muscles.

Affected individuals often become wheelchair users because of lower limb weakness.

Respiratory failure causes the major morbidity and mortality.

Male gender, severity of skeletal muscle weakness, and duration of disease are all risk factors for severe respiratory insufficiency [van der Beek et al 2011].

DIAGNOSIS
ELECTROPHYSIOLOGIC STUDIES

Myopathy can be documented by electromyography (EMG) in all forms of **Pompe** disease although some muscles may appear normal.

In adults, needle EMG of the paraspinal muscles may be required to demonstrate abnormalities.

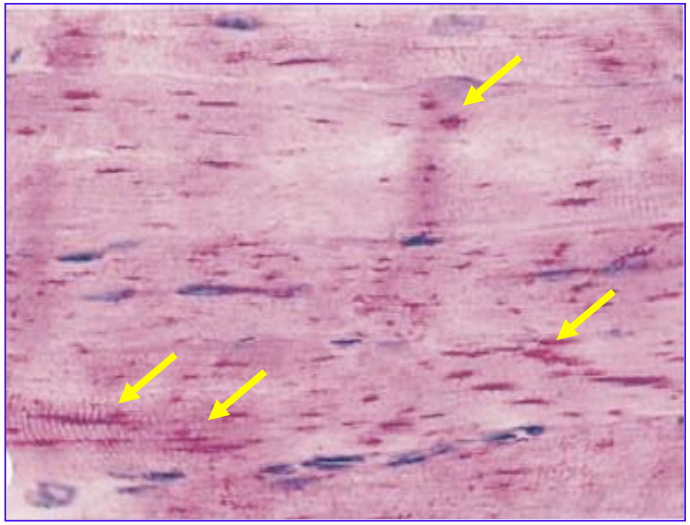
Nerve conduction velocity studies are normal for both motor and sensory nerves, particularly at the time of diagnosis in IOPD and in LOPD.

DIAGNOSIS
MUSCLE BIOPSY

In **Pompe** disease glycogen storage may be observed in the lysosomes of muscle cells as **vacuoles** of varying severity that **stain positively with periodic acid-Schiff**.

However, 20%-30% of individuals with LOPD may not show these muscle-specific changes

Histochemical evidence of glycogen storage in muscle is supportive of a glycogen storage disorder it is not specific for **Pompe** disease.



ESTABLISHING THE DIAGNOSIS

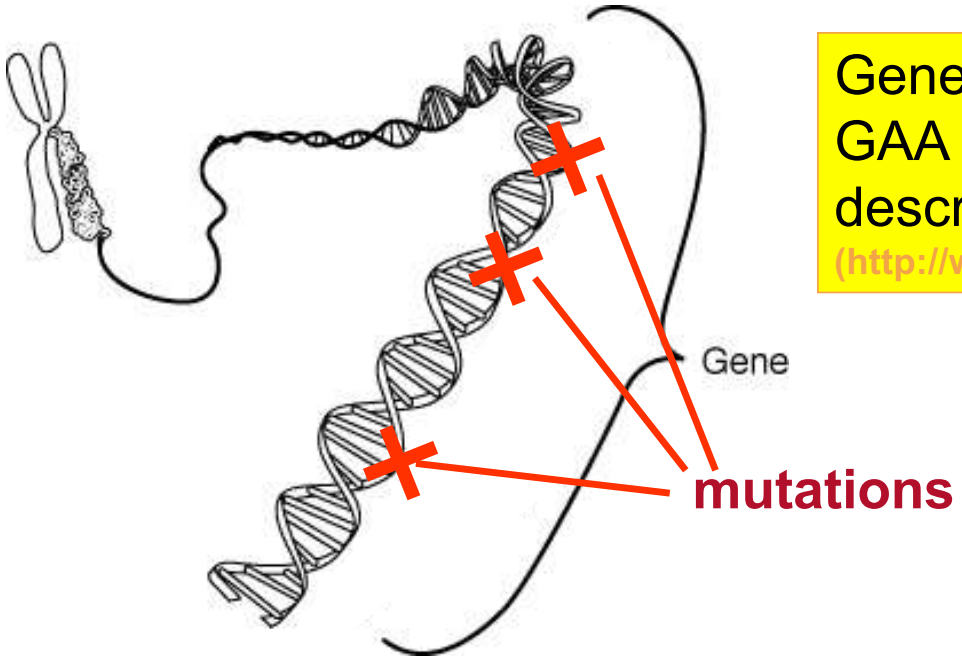
The diagnosis of GSD II **is established** with either:

- deficiency of acid alpha-glucosidase enzyme activity OR
- biallelic pathogenic variants in *GAA* gene on molecular genetic testing

Complete deficiency of GAA enzyme activity (<1% of normal controls) → IOPD

Partial deficiency of GAA enzyme activity (2%-40% of normal controls) → LOPD

MOLECULAR DEFECT: GAA GENE MUTATIONS



Genetic heterogenity: 272 GAA gene mutations so far described
(http://www.pompecenter.nl)

AFTER THE DIAGNOSIS

Establish the extent of the disease:

- ECG/ECHO
- Pulmonary evaluation: clinical evaluation and pulmonary function testing
- Nutrition and Feeding
- Audiology
- Disability inventory: assessment of motor skills and overall functioning

THE TURNING OF THE TIDE

Intravenous Administration of Phosphorylated Acid α-Glucosidase Leads to Uptake of Enzyme in Heart and Skeletal Muscle of Mice

A. T. Van der Ploeg,*‡ M. A. Kroos,* R. Willemsen,* N. H. C. Brons,§ and A. J. J. Reuser*
**Department of Cell Biology and Genetics, Erasmus University, Rotterdam, The Netherlands; ‡Sophia Children's Hospital, Rotterdam; and §Department of Clinical Immunology, University of Groningen, Groningen, The Netherlands*

1991 -Arnold Reuser and Ans van der Ploeg

Showed enzyme replacement therapy could work

Mannose-6-phosphate

TIMELINE

1932 - JC Pompe discovers disease

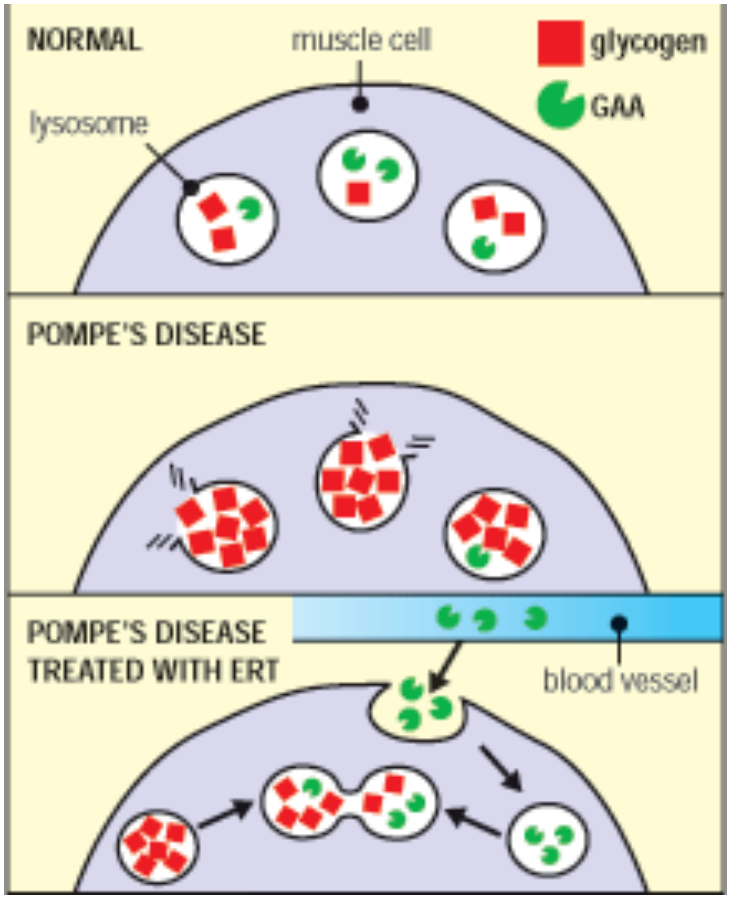
1965 - Hers explains disease

1991 - Reuser and van der Ploeg demonstrate treatment

1999 - first clinical trials

2006 – FDA Approval as a medicine

ENZYME REPLACEMENT THERAPY (ERT)



ENZYME REPLACEMENT THERAPY (ERT)

1. Enzymes are taken up by lysosomes via **receptor-mediated pathways.**
2. Effects are **dose-dependent.**
3. Enzyme replacement therapy (ERT) requires **continuous treatment** to prevent re-accumulation of substrate.
4. ERT is **safe and well-tolerated**; infusion-associated reactions can occur especially if IgG antibodies have developed, but are generally transient.

ENZYME REPLACEMENT THERAPY (ERT)

	Alglucosidase alfa (**Myozyme®**)
PROS	• Improves muscle morphology, improves cardiac function, decreases left ventricular wall thickness and mass • In later-onset: improves walking distance, stabilizes neuromuscular and pulmonary function • Increases survival and improved motor function with early treatment
CONS	• Lower distribution to skeletal muscle • Highly variable clinical response • May develop high IgG antibodies

MDT MANAGEMENT

Management and Prevent Secondary Complications

- Physiotherapy, Occupational therapy and Speech therapy
- Aggressive treatment of infections
- Immunizations including RSV prophylaxis and annual Influenza vaccine
- Cautious use of anesthesia

Surveillance

- Cardiology evaluation
- Assessment of Respiratory status
- Musculoskeletal and overall functional status
- Nutritional and feeding assessment
- Development, growth and use of adaptive equipment
- Hearing


Speech therapy
Physical therapy
Genetic counseling
Care Coordinator
Psychosocial therapy
Respiratory therapy
Nutritional & dietary therapy
Occupational therapy

IS THIS ENOUGH

Successful and life saving but not the complete answer

Next generation treatment – Gene replacement therapy

THE FUTURE: CLOSER THAN YOU THINK

Gene therapy to correct the underlying enzyme defect is under investigation [Raben et al 2002, DeRuisseau et al 2009, Mah et al 2010].

A Phase I/II trial to investigate the ability of AAV-alpha glucosidase to improve ventilation reported outcomes of children with IOPD treated with ERT.

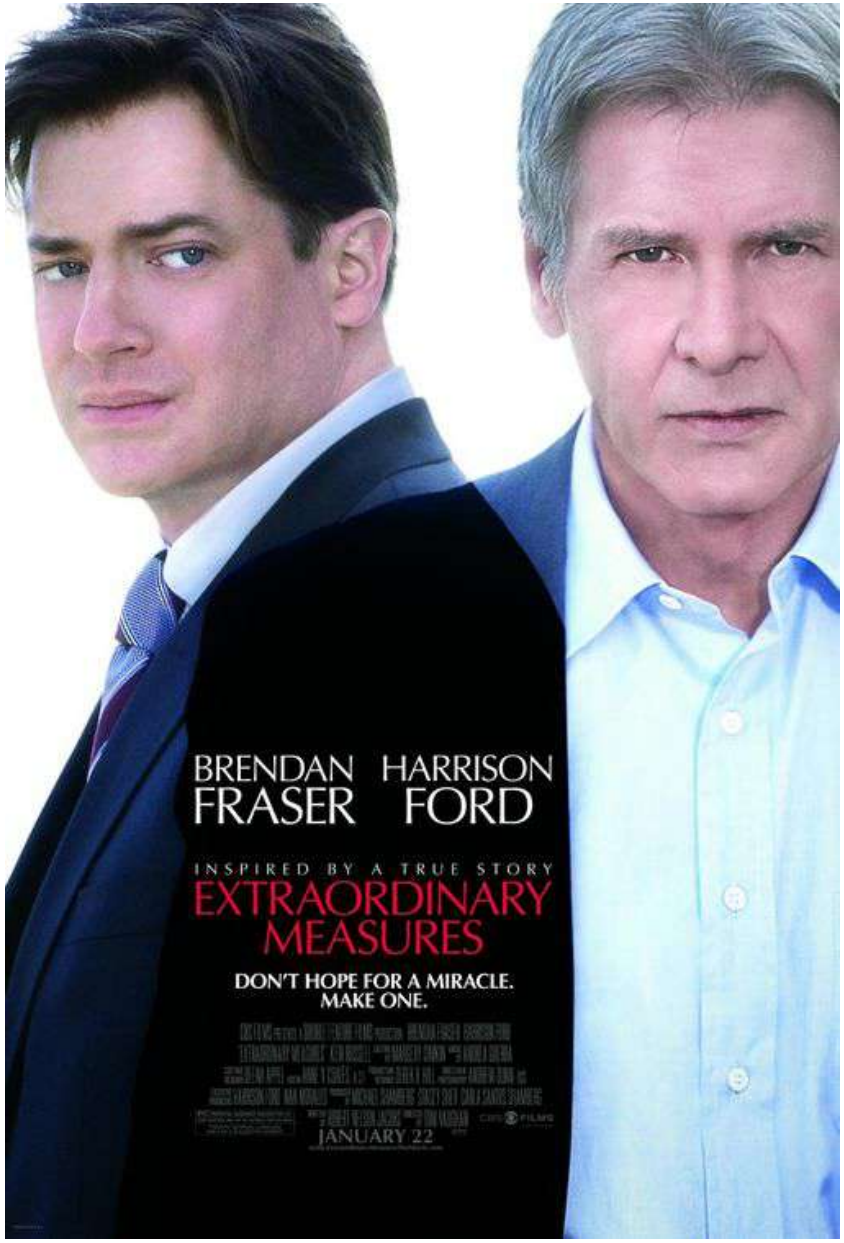
In this trial of phrenic nerve injected AAV-alpha glucosidase and ventilatory training, the rate of ventilatory decline was attenuated in a subset of children, particularly those who were not already dependent on ventilatory assistance full time at the time of intervention

GENE THERAPY

Dwight Koeberl - Duke University

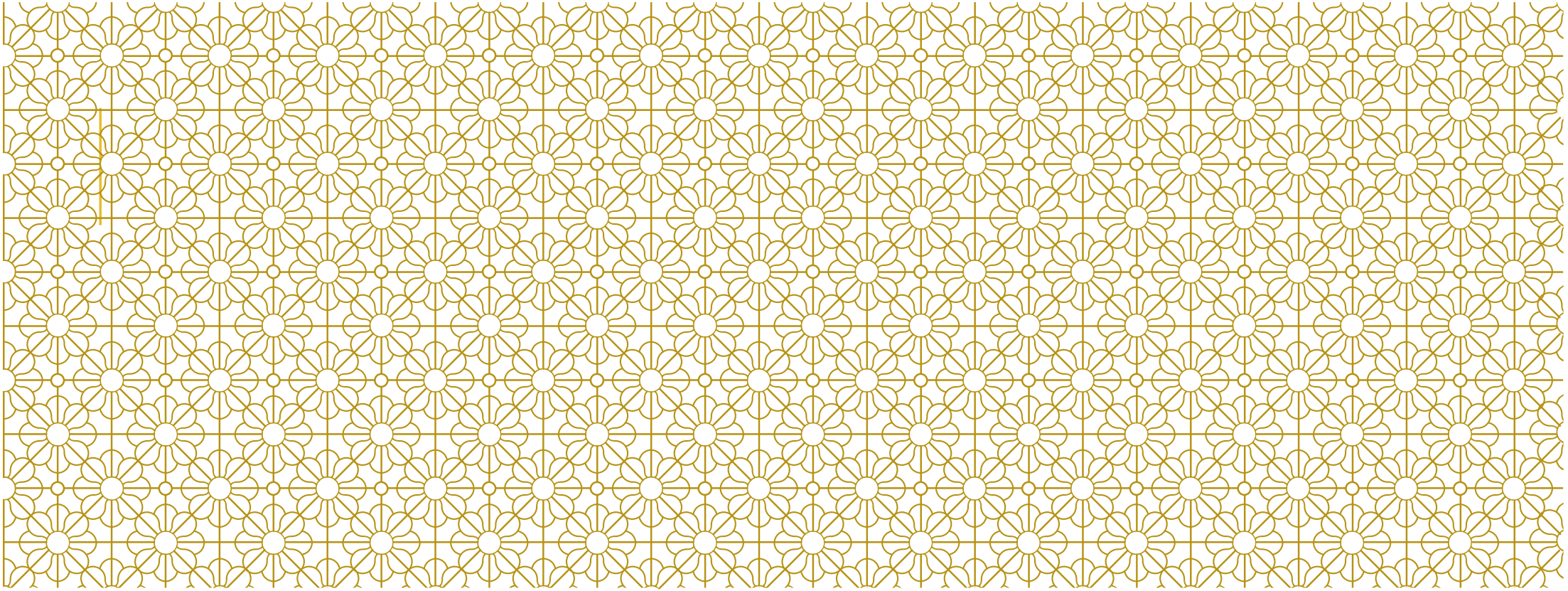
studies being done to give gene therapy for Pompe disease

https://www.youtube.com/watch?v=JV7eaBUG0Jk



THE HOLLYWOOD VERSION

"*Don't hope for a miracle. Make one up*."



THANK YOU