Cardiac Manifestations of Pompe Disease

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Pediatric Cardiology Meeting

05.06.09

תאור מקרה

בן חודשיים

- אושפז במחלקה בשל קוצר נשימה

תאור מקרה – הערכה קרדיאלית

אנמנזה

- הריון ולידה תקינים
- עולה במשקל טוב
- הורים קרובי משפחה
- אחיין של אבא נפטר ממחלת לב

בבדיקה

- נאנח צפצופים
- היפוטוניה בולטת בגפיים וצוואר
- קולות לב סדירים ללא קולות נוספים
- אוושה סיסטולית 2\6 ב LSB ונשמעת בגב

מעבדה

- CPK 813 (0-195)
- AST 168 (13-40)
- LDH 935 (337-888)

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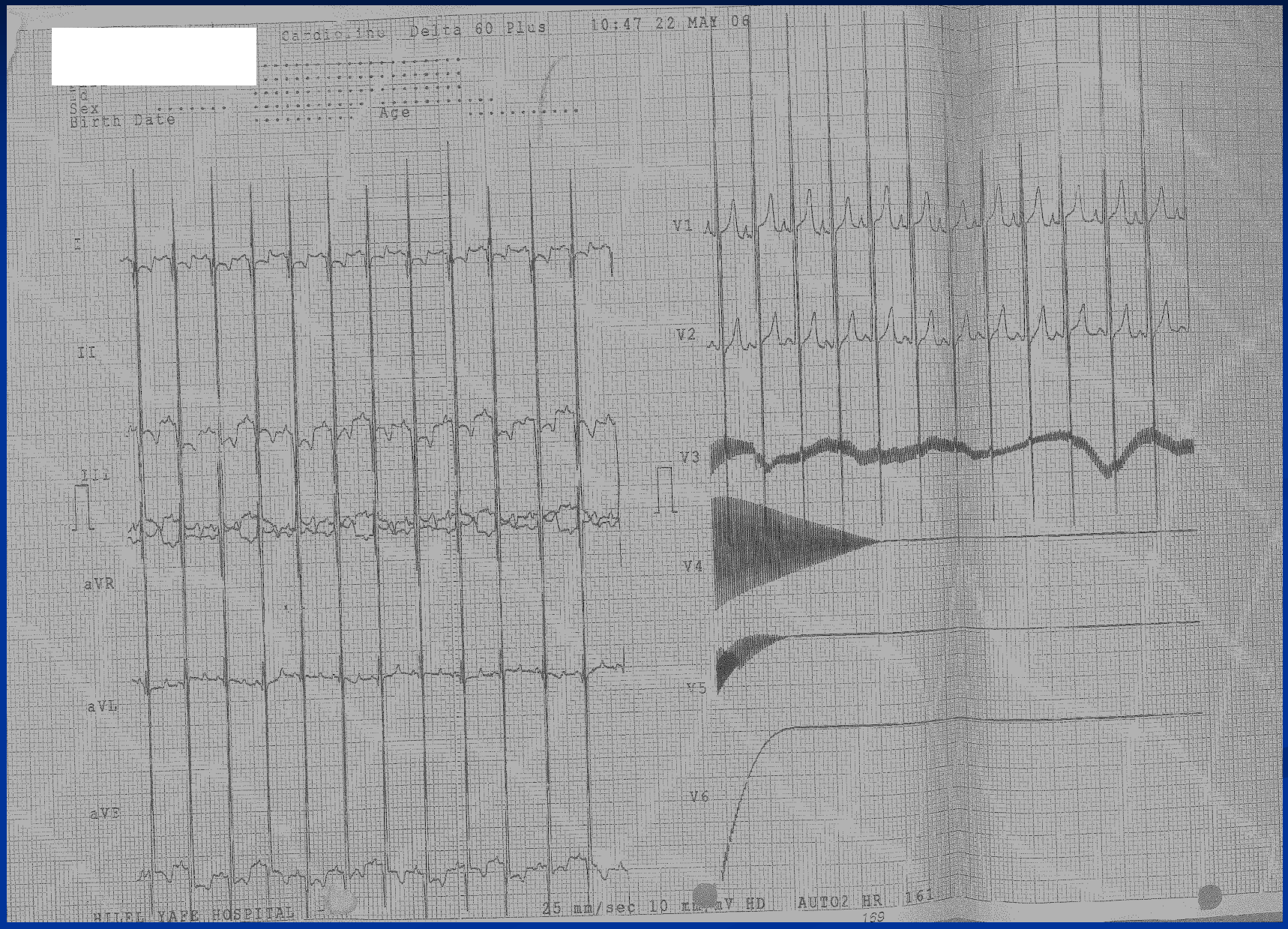
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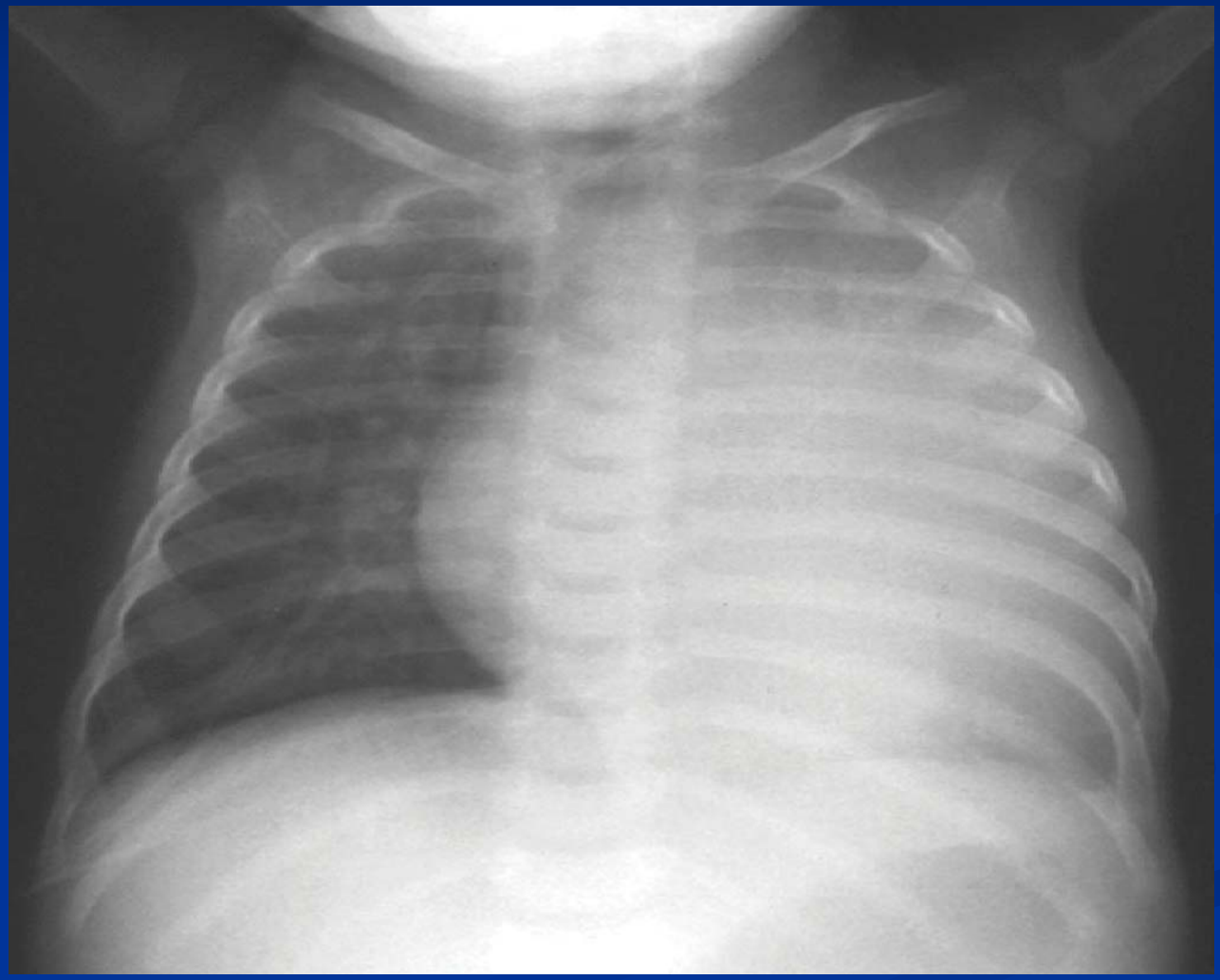
צלום חזה



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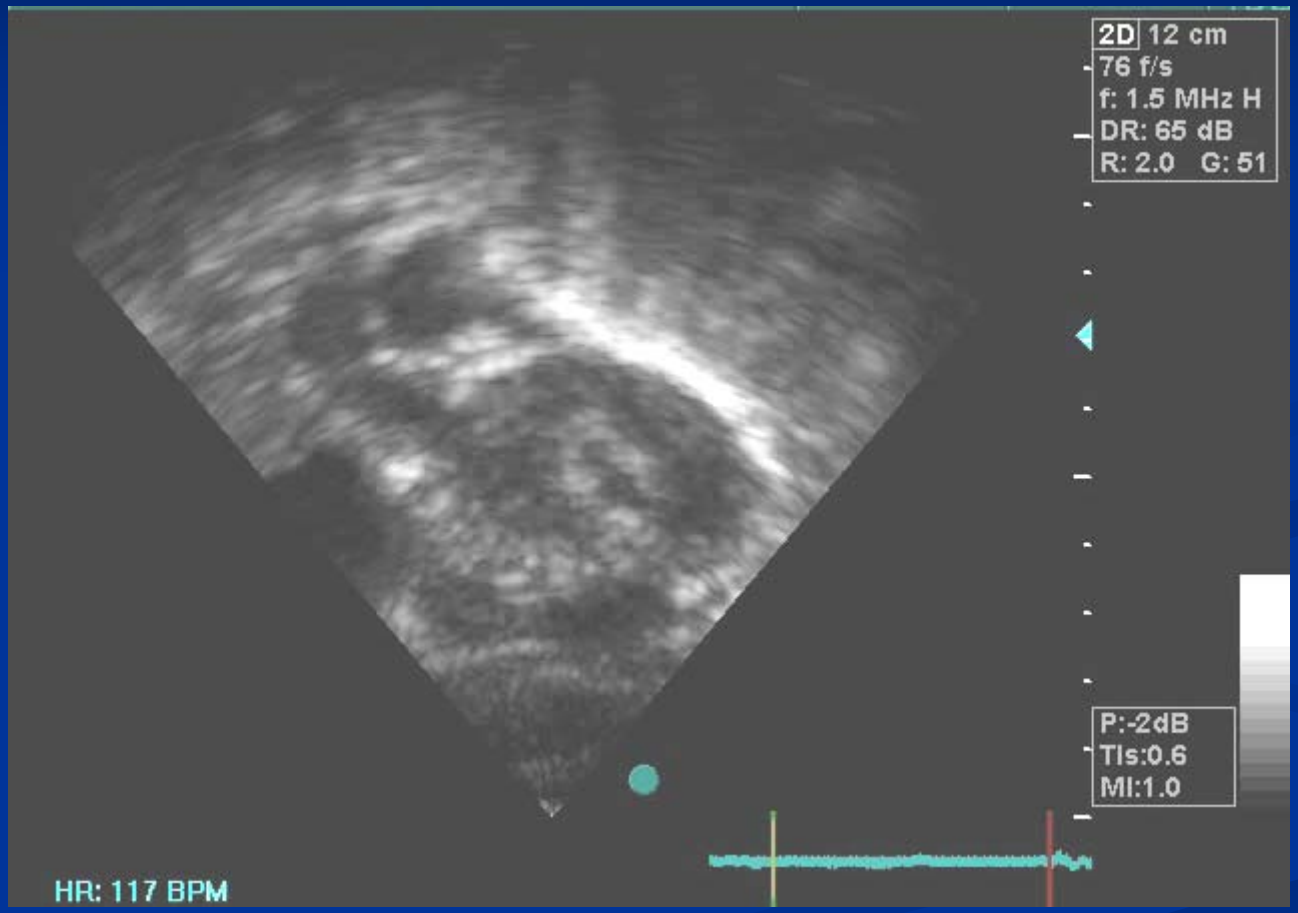
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HYPERTROPHIC CARDIOMYOPATHY

- IDIOPAHIC
- FAMILIAL

} Genetic

- INFANT OF DIABETIC MOTHER
- HYPERTENSION
- LEFT VENTRICLE OUT FLOW OBSTRUCTION
- INBORN ERROR OF METABOLISM
- HYPOTHYROIDISM
- FRIEDREICH'S ATAXIA

HYPERTROPHIC CARDIOMYOPATHY and HYPOTONIA

Diagnosis	Shared signs and symptoms
Spinal muscular atrophy I	Hypotonia, progressive proximal muscle weakness, absent reflexes, feeding difficulties
Danon disease	Hypertrophic cardiomyopathy, skeletal muscle myopathy, vacuolar glycogen storage
Endocardial fibroelastosis	Breathlessness, feeding difficulties, cardiomegaly, heart failure
Carnitine deficiency	Cardiomyopathy, muscle weakness

HYPERTROPHIC CARDIOMYOPATHY

Diagnosis	Shared signs and symptoms
GSD II and III and IV	Hepatomegaly, hypotonia, cardiomegaly, muscle weakness, elevated CK
Idiopathic hypertrophic cardiomyopathy	Biventricular hypertrophy
Myocarditis	Inflammation of myocardium contributing to cardiac enlargement
Mitochondrial disorders	Hepatomegaly, cardiomyopathy, myopathy

DIAGOSIS

- **Deficiency:**

  acid alpha-glucosidase (GAA)

POMPE DISEASE

DIAGNOSIS: POMPE DISEASE

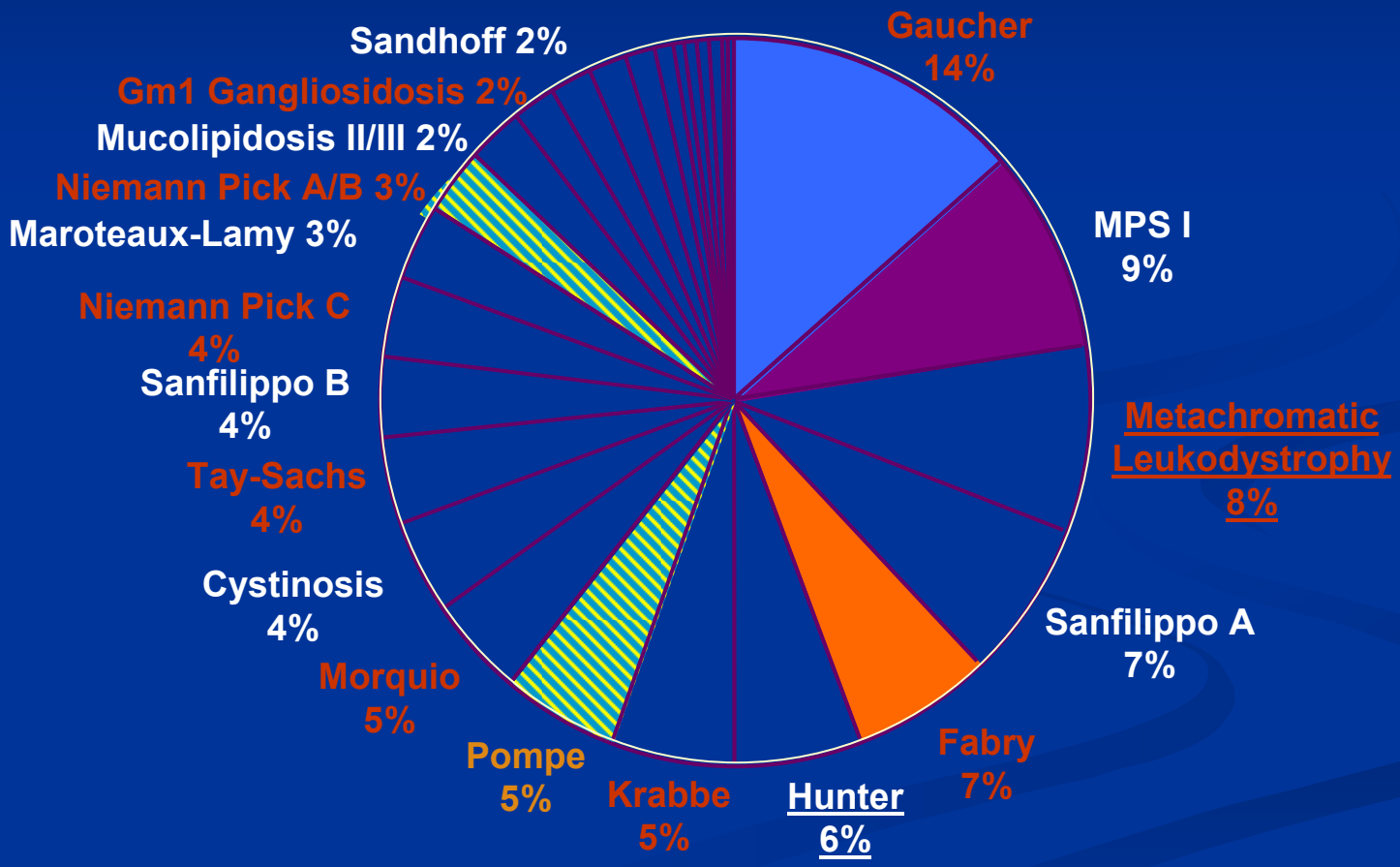
- Synonyms
  - Glycogen storage disease type II (GSD-II)
  - Acid maltase deficiency (AMD)
  - Glycogenosis, type II
- Disease Families
  - Lysosomal storage disease
  - Glycogen storage disease
  - Neuromuscular disease/metabolic muscle disease

Lysosomal Storage Disorders

- A Group of Over 40 Genetic Disorders
- Due to a deficiency of a lysosomal enzyme resulting in the accumulation of substrate in the cells

Prevalence: 1:7700 newborn

Lysosomal Storage Disorders



POMPE DISEASE EPIDEMIOLOGY

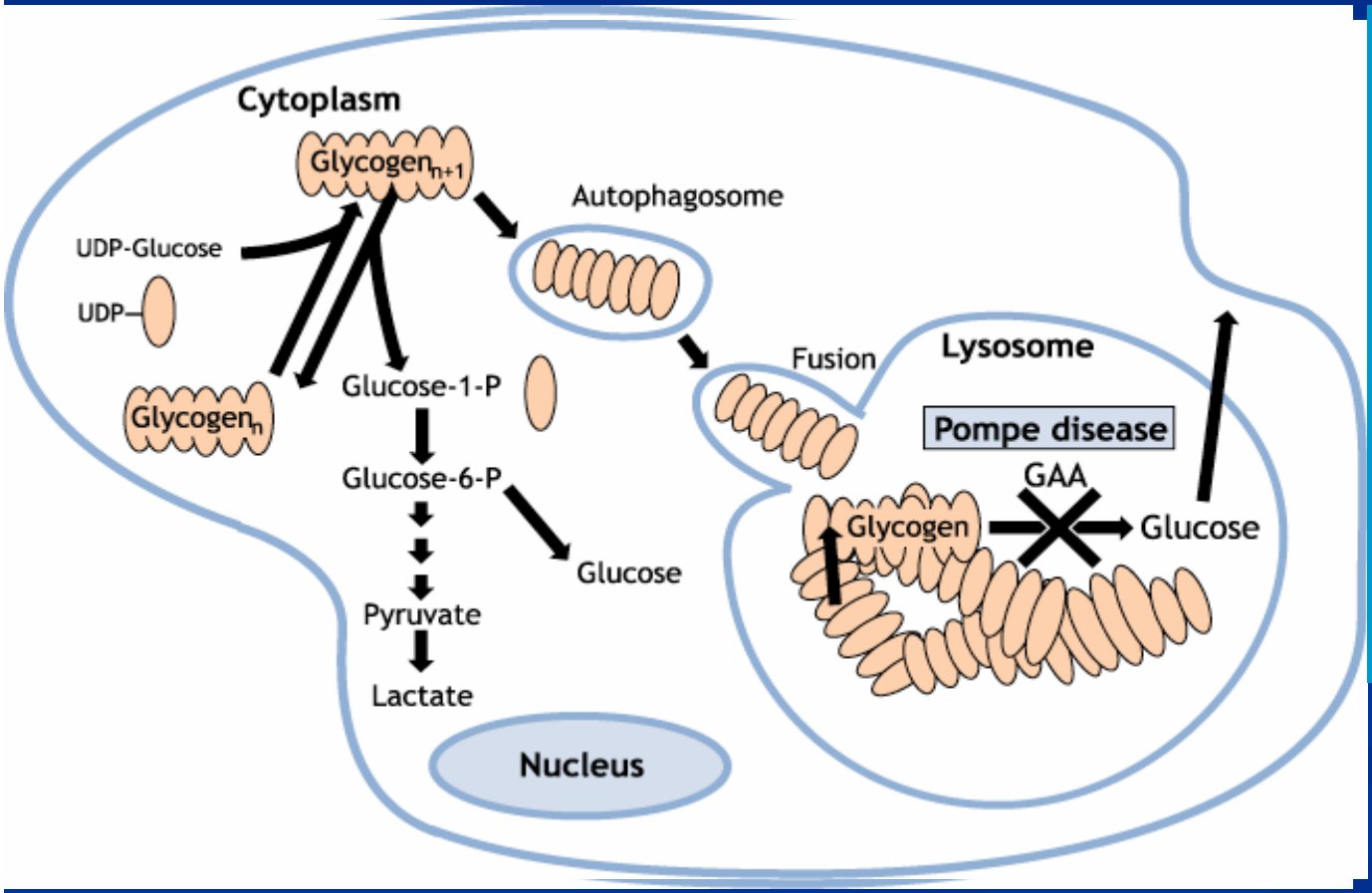
Pompe Disease Subtype	Incidence (95% CI)
Infantile-onset	1/138,000 (1/43,000-1/536,000)
Late-onset	1/57,000 (1/27,000-1/128,000)
Overall incidence	**1/40,000 (1/17,000-1/100,000)**

Ausems MGEM, et al. *Community Genet*. 1999;2:91-96.
Hirschhorn R, et al. In: *The Metabolic and Molecular Bases of Inherited Disease*. 2001:3389-3420.

POMPE DISEASE

Irreversible pathology caused by deficiency of lysosomal acid alpha-glucosidase (GAA)

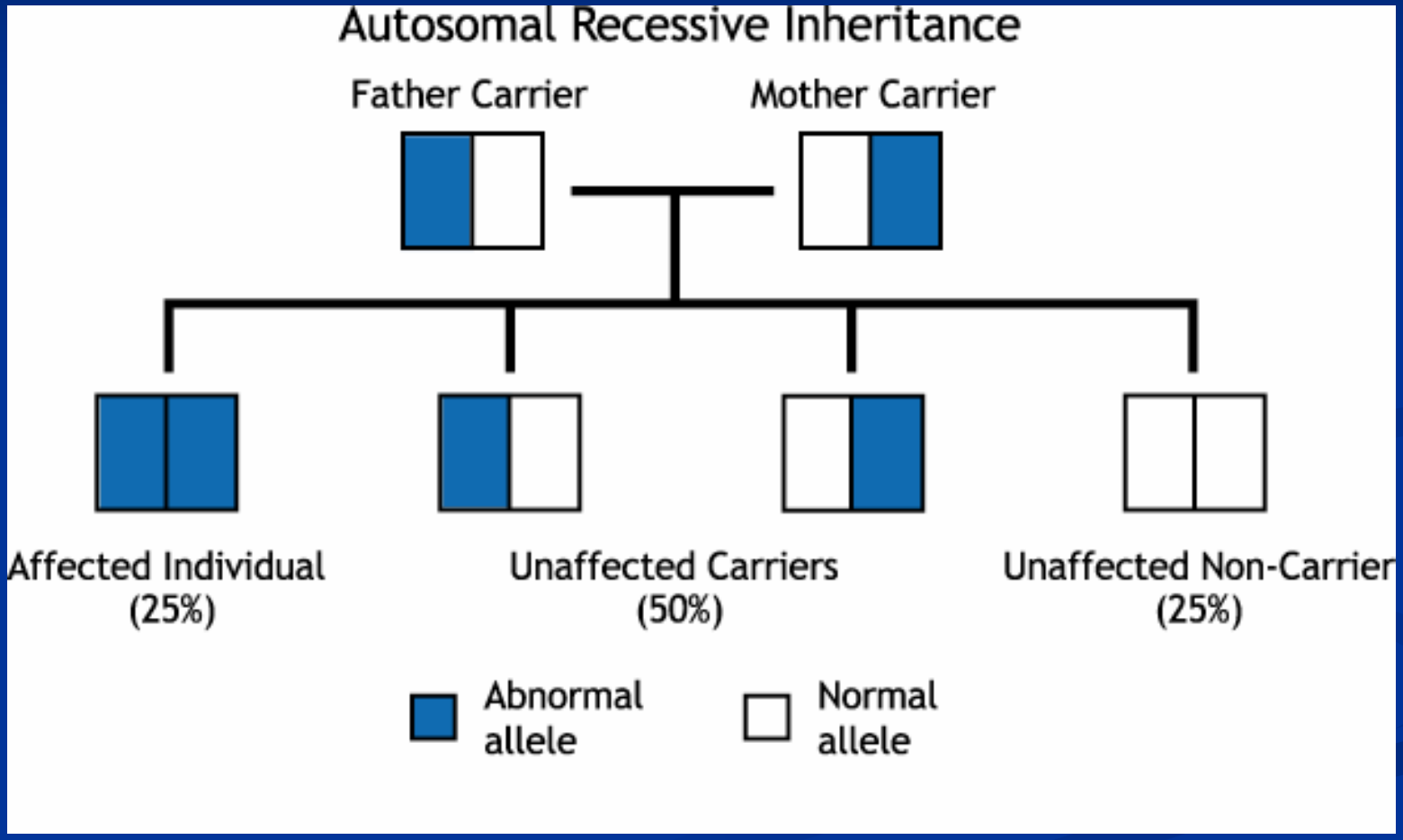
POMPE DISEASE PATHOGENESIS



- GAA essential for degradation of lysosomal glycogen
- Deficit causes accumulation and distention

Raben N, et al. *Curr Mol Med.* 2002;2:145-166.

POMPE DISEASE INHERITANCE PATTERN



Hirschhorn R, et al. In: *The Metabolic and Molecular Bases of Inherited Disease*. 2001:3389-3420.

POMPE DISEASE
GENETICS

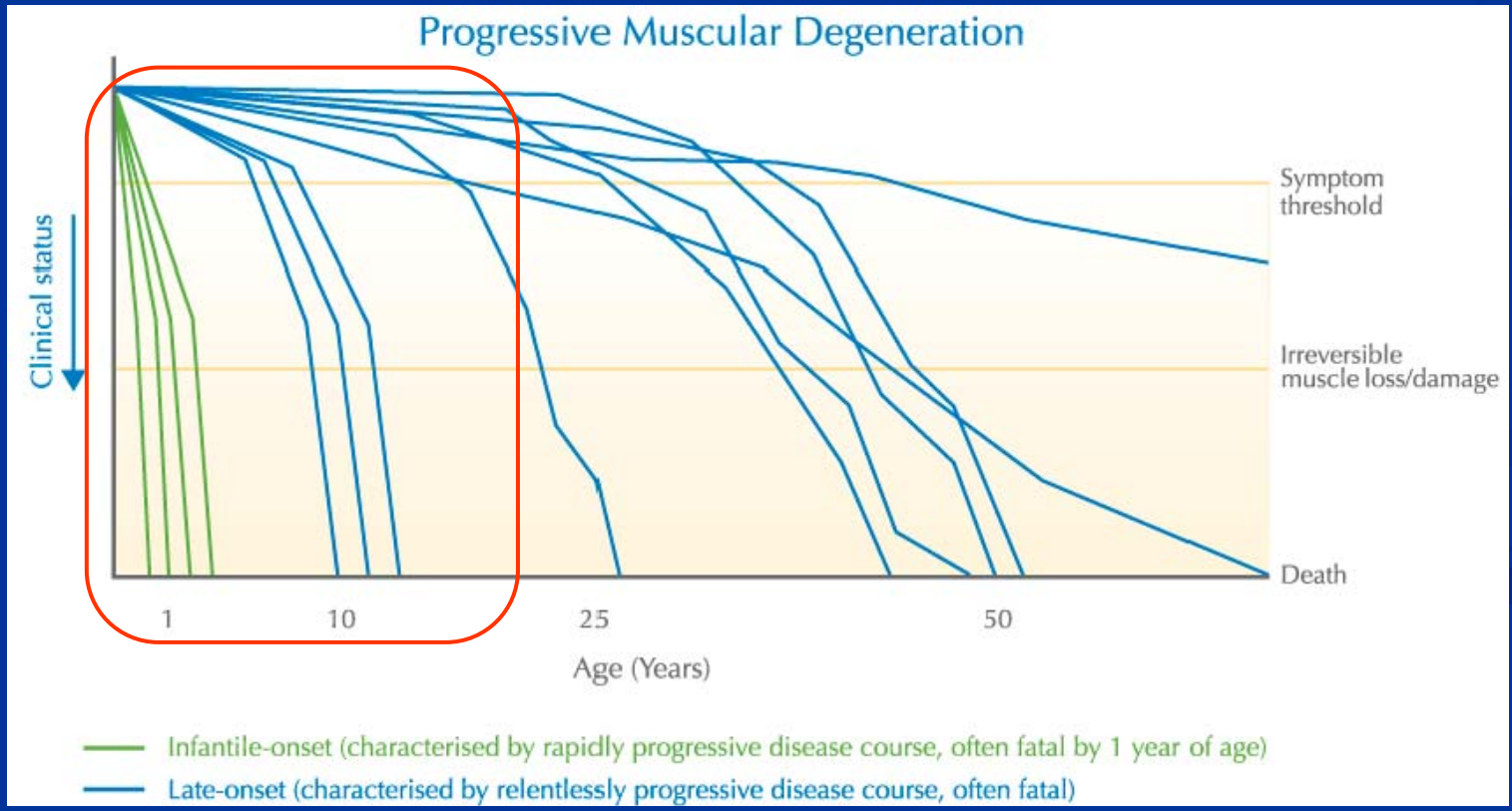
- GAA gene located on chromosome 17

- Around 150 mutations in GAA gene identified to date
  - Some mutations are common in general populations or certain ethnic groups, but most are private mutations identified in individual patients

Cardiac Manifestations of Pompe Disease and treatment results with Myozyme

Introduction

- Pompe disease variability: from a rapidly progressive course (fatal by 1 year of age) to relentlessly progressive course with significant morbidity and/or premature mortality



Cardiac Manifestations of Pompe Disease and treatment results with Myozyme

Clinical Signs & Symptoms - Infants

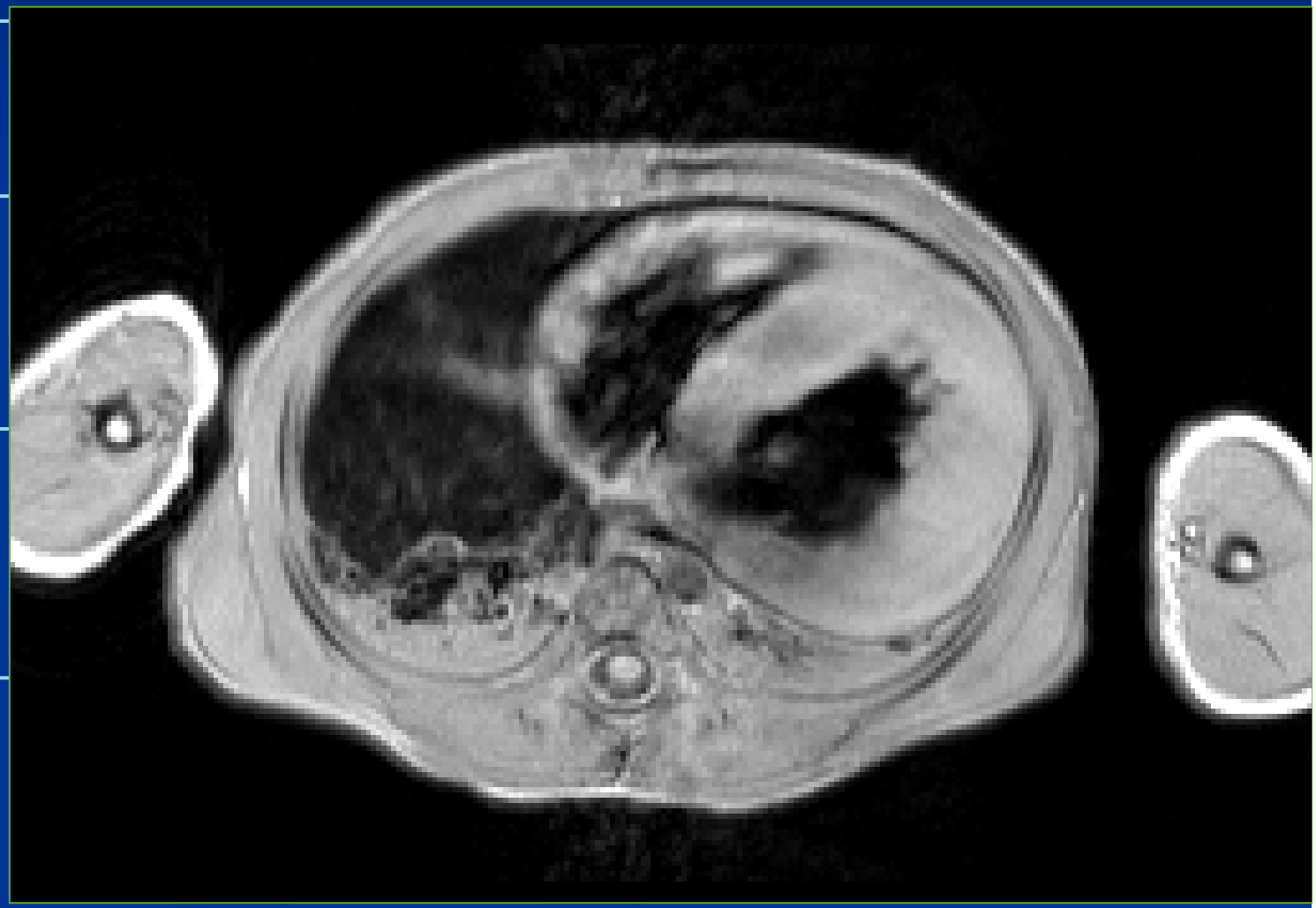
Symptom Frequency and Onset

Clinical Manifestations	Frequency n (%)	Age at onset, months Mean (± SD)
Cardiomegaly	154 (92)	4.1 (3.1)
Hypotonia	148 (88)	3.9 (2.7)
Cardiomyopathy	147 (88)	4.2 (4.7)
Respiratory distress	131 (78)	4.3 (4.4)
Muscle weakness	105 (63)	4.5 (3.1)
Feeding difficulties	96 (57)	3.4 (2.7)
Failure to thrive	89 (53)	4.2 (2.6)
Congestive heart failure	84 (50)	5.1 (2.4)
Gastroesophageal reflux	16 (10)	5.3 (5.6)
Sleep apnea	6 (4)	4.0 (2.4)

POMPE DISEASE
OVERVIEW OF CLINICAL FEATURES

Infantile-onset

- Cardiac
- Musculoskeletal
- Pulmonary
- Gastrointestinal



ERT – (POMPE DISEASE)
10 mg\kg recombinant human acid alpha-glucosidase (rhGAA)

- Best results when started early (Acta Neurol Belg 2006:82-6)
- Improvement in brain myelination (Pediatr Res 2006:349-52)
- ECG response (Genrt Med 2006:297-301)
- Histologic response (Lab Invest 2006)

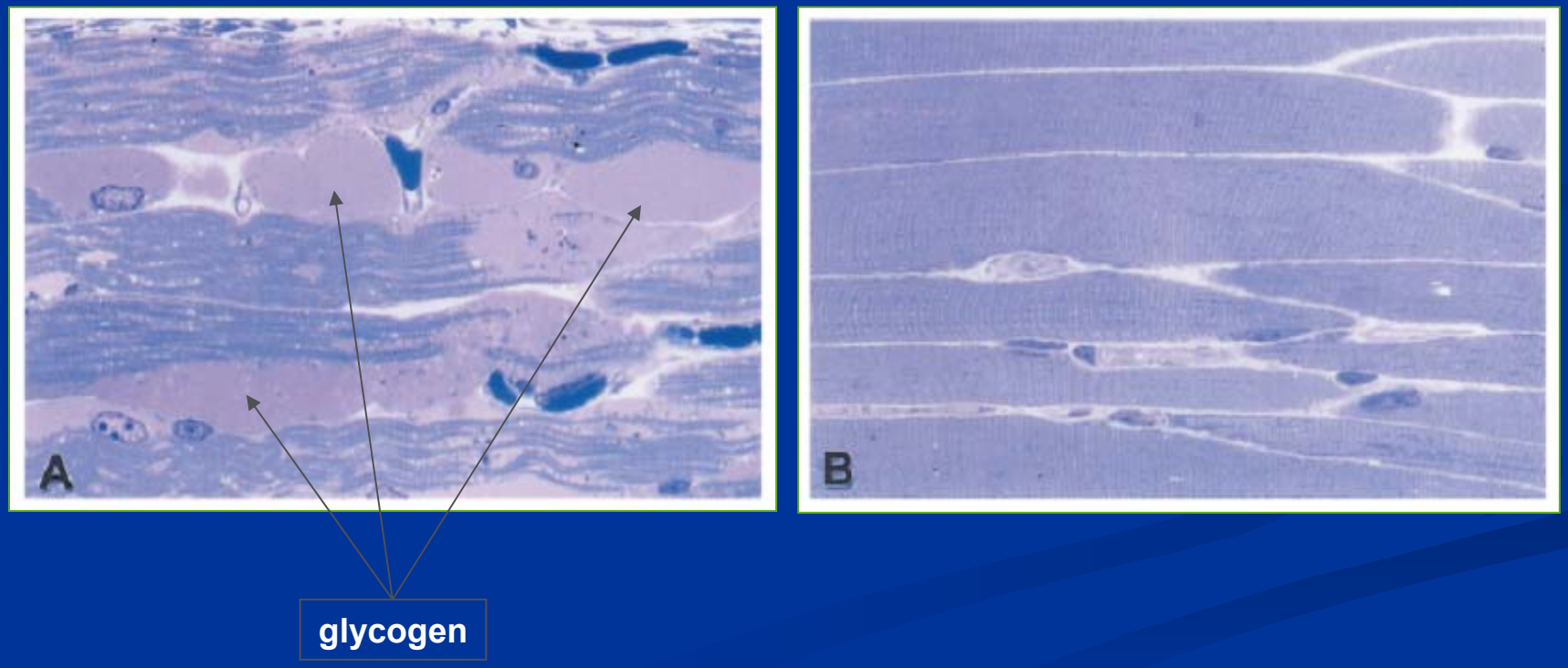
Cardiac Manifestations of Pompe Disease and treatment results with Myozyme

Treatment – Myozyme

Myozyme Phase I / II – Glycogen Clearance

Pre-treatment

4 months Post-treatment



Amalfitano et al. Genetics in Medicine 2001 V3 N2 P132

Cardiac Manifestations of Pompe Disease and treatment results with Myozyme

Treatment – Myozyme

Myozyme Phase I / II – Reduction of Cardiomegaly

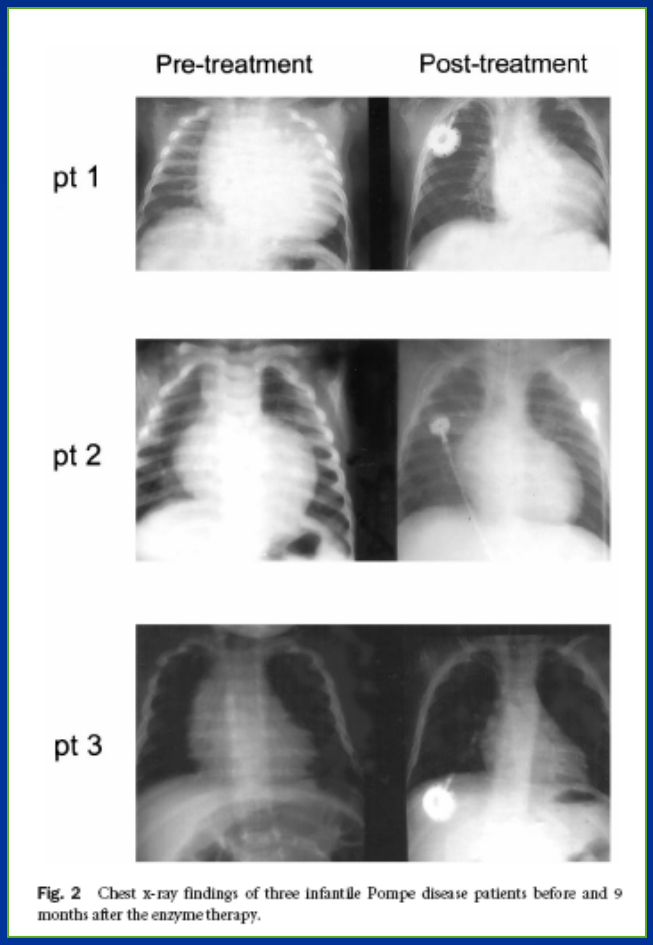
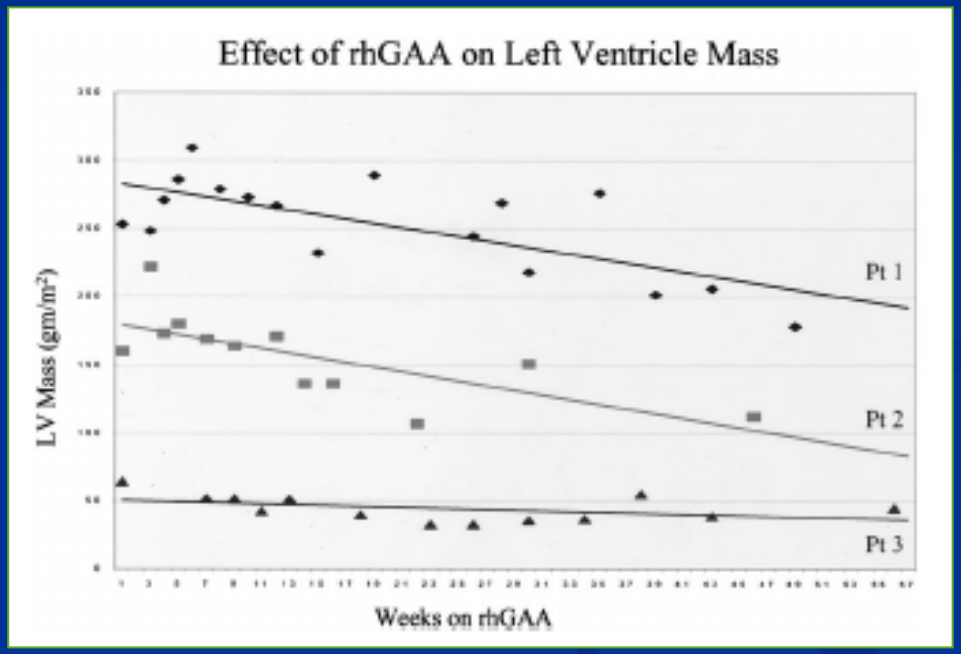


Fig. 2 Chest x-ray findings of three infantile Pompe disease patients before and 9 months after the enzyme therapy.



Amalfitano et al. Genetics in Medicine 2001 V3 N2 P132

Cardiac Manifestations of Pompe Disease and treatment results with Myozyme

Treatment – Myozyme

Study 1*

- Design and Patients Characteristics
  - Open label, international, multi-center trial
  - 18 infantile-onset patients aged 6 months or less at the onset of treatment
  - Cardiomyopathy (LVMI ≥ 65 g/m^2)
  - no ventilator use at study entry

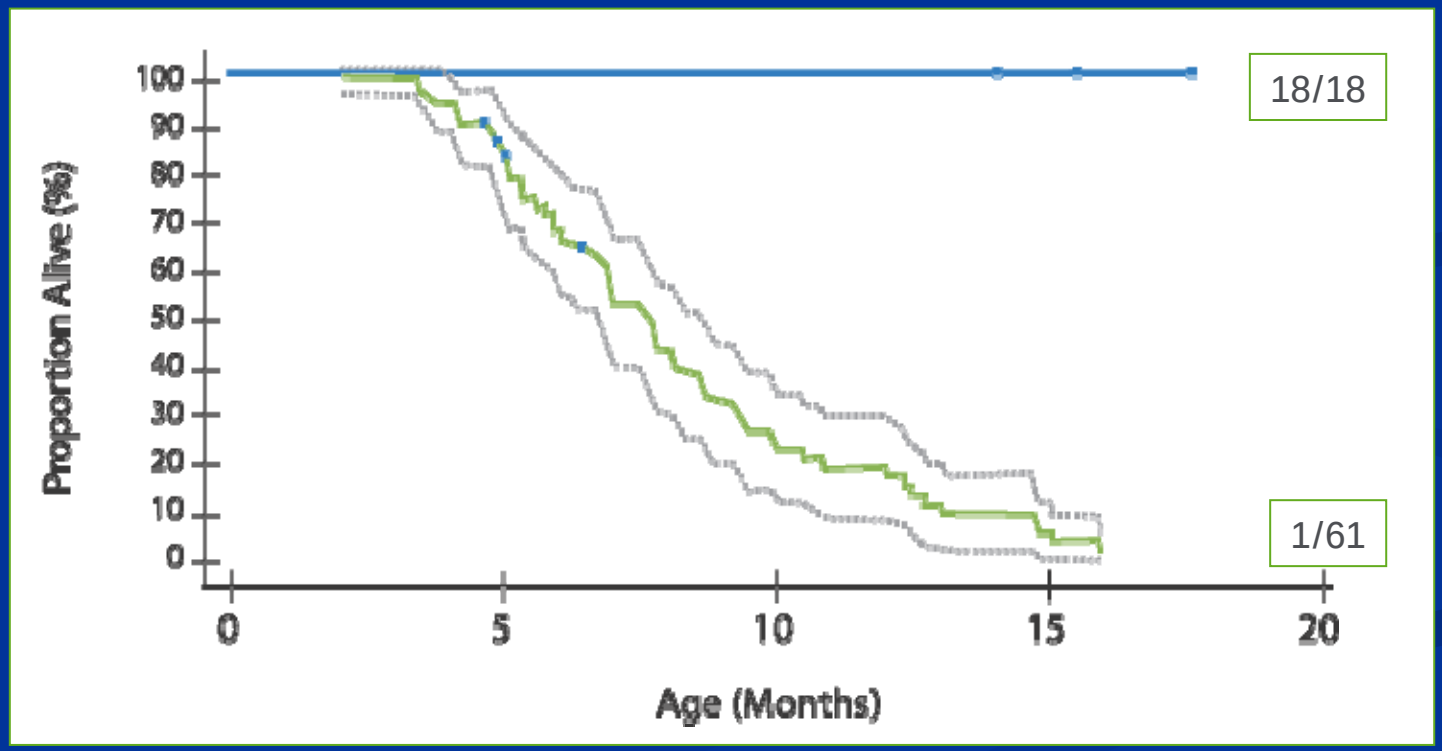
- Control Group – Matched Historical Cohort
  - 61 untreated patients born between 1982 and 2002
  - unethical to have a placebo

*Kishnani et al. Recombinant human acid–glucosidase :Major clinical benefits in infantile-onset Pompe disease; NEUROLOGY 68 January 9, 2007

Cardiac Manifestations of Pompe Disease and treatment results with Myozyme

Treatment – Myozyme

Study 1 Results:
Kaplan Meier Curve for Myozyme Study in 18 Infants Under 6 Months Old at Treatment Initiation: Proportion Alive



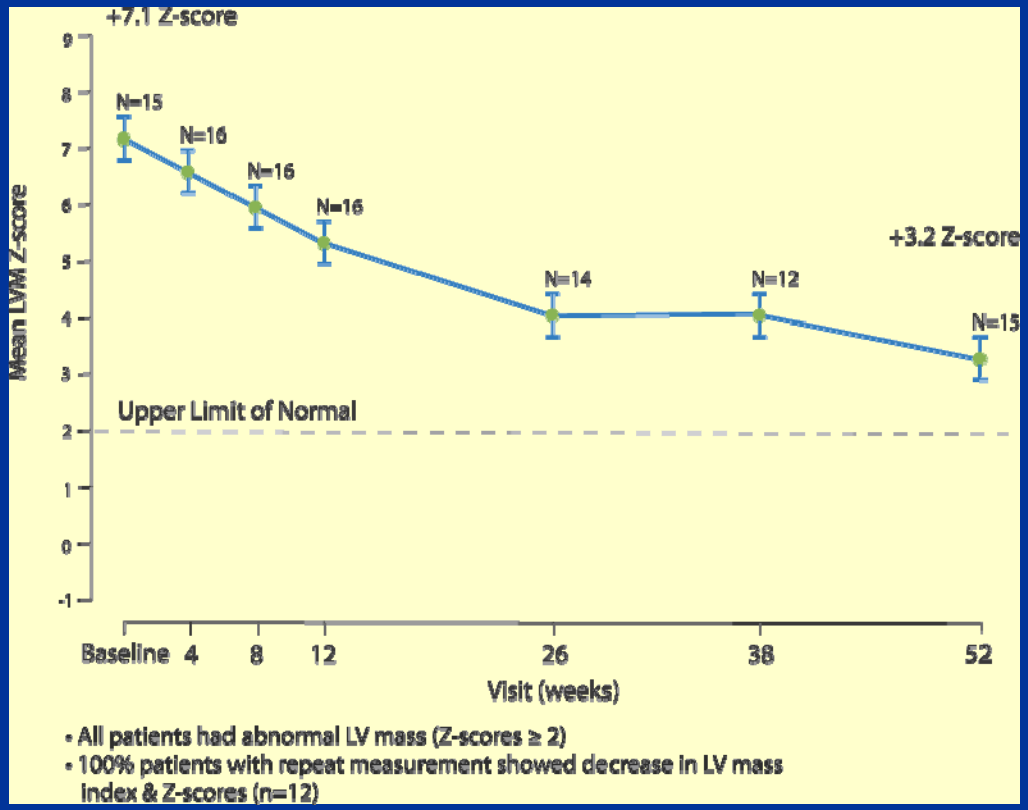
*Kishnani et al. Recombinant human acid–glucosidase :Major clinical benefits in infantile-onset Pompe disease; NEUROLOGY 68 January 9, 2007

Cardiac Manifestations of Pompe Disease and treatment results with Myozyme

Treatment – Myozyme

Study 1 Results:

Improvement of Cardiomyopathy as Measured by Decrease in Left Ventricular Mass



- 58% mean decrease in left ventricular mass (LVM) as compared to baseline
- Improvement observed in all 12 patients measured

Cardiac Manifestations of Pompe Disease and treatment results with Myozyme

Treatment – Myozyme

Study 2*

- Design and Patients Characteristics
  - Open label, international, multi-center trial
  - 21 Pompe patients aged 6 months to 3.5 years with more advanced stage of the disease
  - All had cardiomyopathy
  - 5 had ventilator support at baseline
  - Dose: 20 mg/kg every two weeks

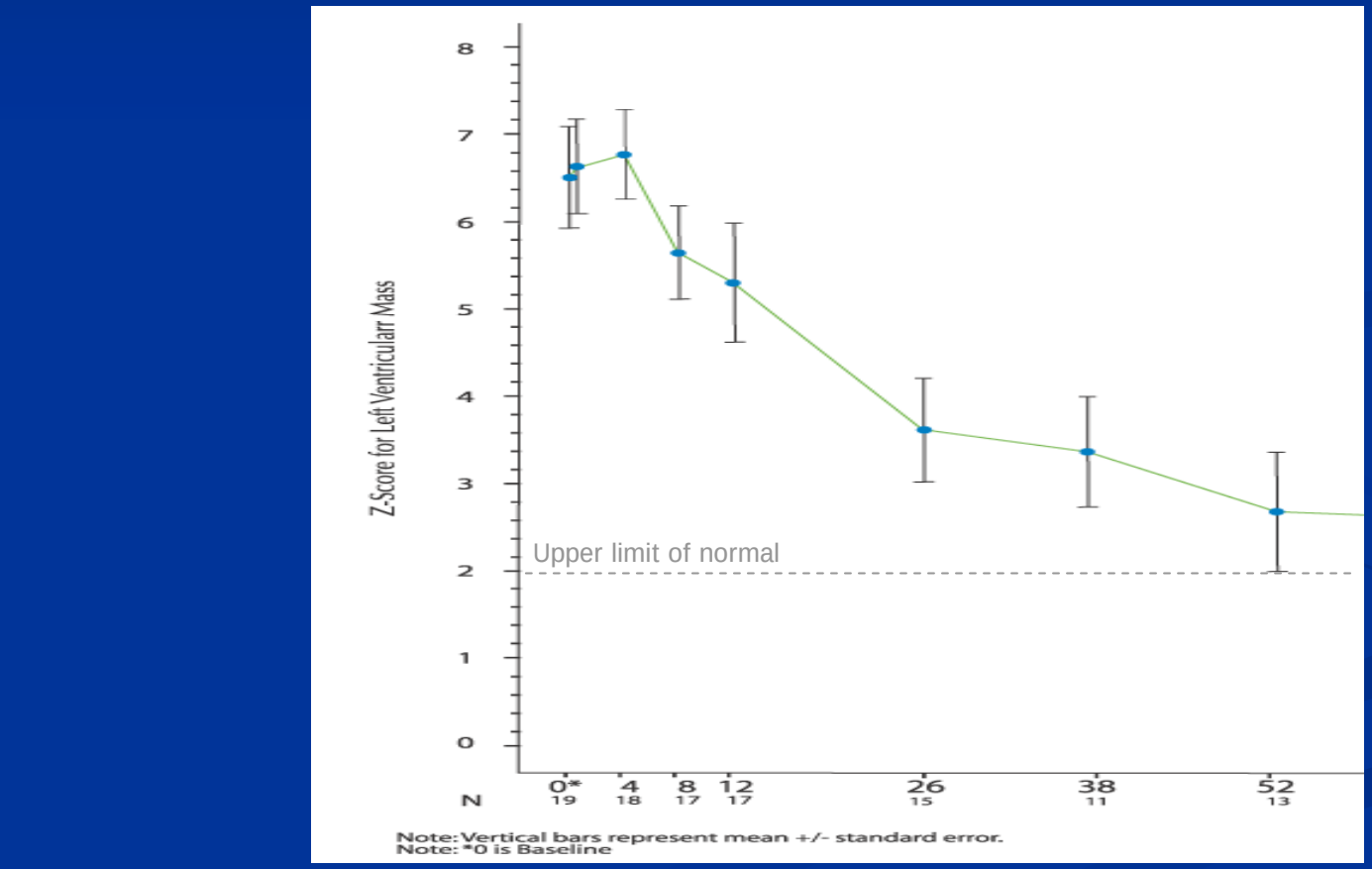
- Control Group – Historical Cohort (unethical to have a placebo)
  - Control derived from a retrospective Pompe natural history study
  - n=48

*Genzyme Data on File

Cardiac Manifestations of Pompe Disease and treatment results with Myozyme

Treatment – Myozyme

Study 2 Results: Decrease in Left Ventricular Mass

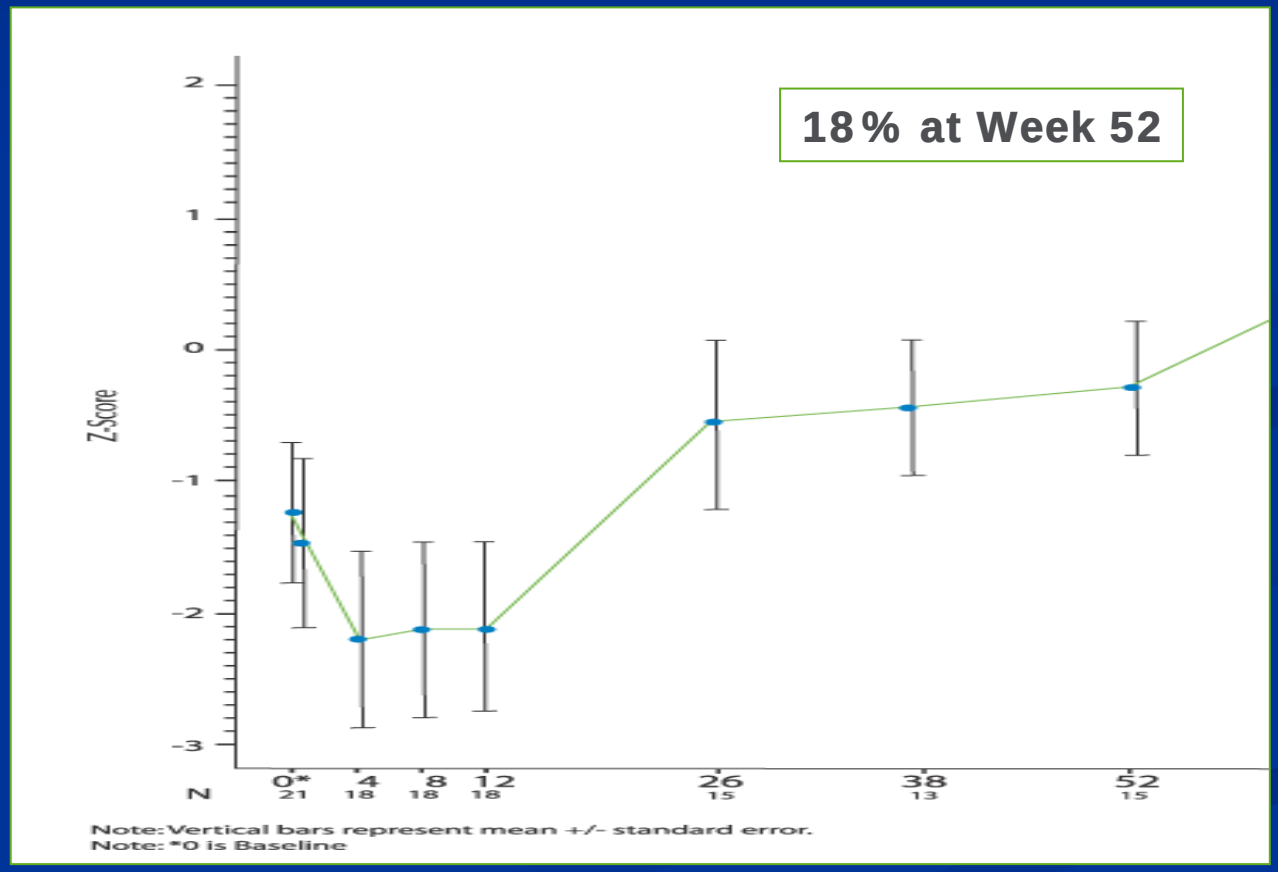


*Genzyme Data on File

Cardiac Manifestations of Pompe Disease and treatment results with Myozyme

Treatment – Myozyme

Study 2 Results: Increase in Ejection Fraction



*Genzyme Data on File

Cardiac Manifestations of Pompe Disease and treatment results with Myozyme

Treatment – Myozyme

Myozyme Study Results: Importance of Early Treatment

Parameter	Study 1 (n=18) (< 6 months at ERT)	Study 2 (n=21) (6-36 months at ERT)
Alive	**100%** at 18 months age (n=18)	**73%** after 1 year of ERT (n=15)
Decrease in LVM	**100%** (12/12 pts with data)	**87%** (n=15)

Cardiac Manifestations of Pompe Disease and treatment

Treatment – Myozyme

Case Presentation

- **Treated by ERT – short period of improvement**
- **Intolerance to rh-GAA (ERT) – ANTI rhGAA antibodies**
- **Negative cross reactive immunological material (CRIM)**

  Pediatrics , 113, e448-e457,2004
- **Tolerance to CRIM negative mice by induction to ERT after hematopoieic stem cell gene transfer GAA**

  The Journal of Gene Medicine vol 11,2009

POMPE DISEASE INVESTIGATIONAL TREATMENT: GENE THERAPY

- Goal to supply functional gene for enzyme needed
  - Usually delivered via modified virus
- Currently no approved gene therapies

Recognition, Diagnosis, and Treatment of Fabry disease

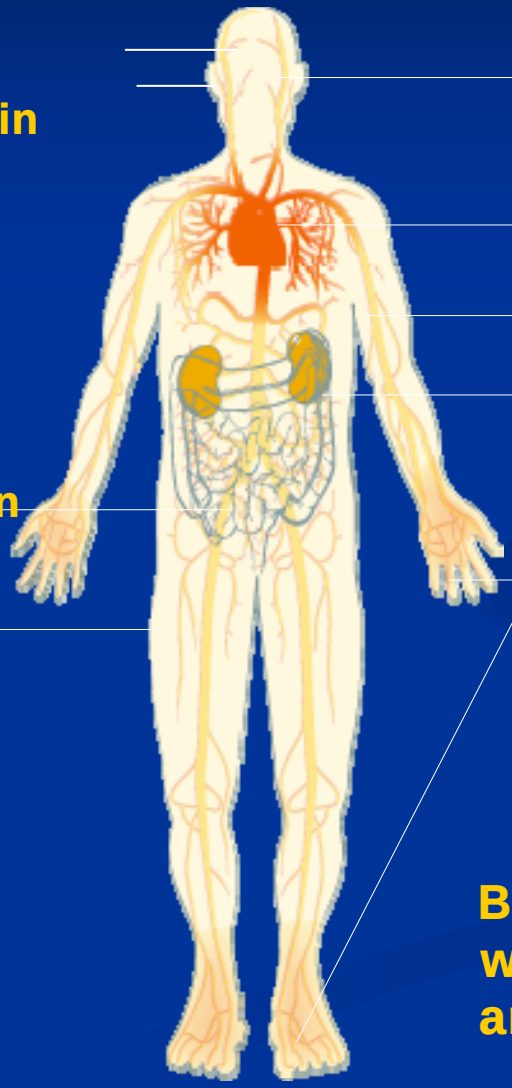
Fabry Disease Background

- Under-recognized, genetic (X-linked) lysosomal storage disorder
- Progressive, often life-threatening
- Characterized by deficiency of the lysosomal enzyme alpha-galactosidase A (α-GAL)
- Enzyme deficiency leads to progressive cellular accumulation of glycosphingolipids (fatty substances), particularly globotriaosylceramide (GL-3), in many body tissues
- Progressive, pathologic changes result in end-organ damage in most classic Fabry cases

Fabry Signs & Symptoms

Starburst pattern on cornea

Hearing loss, ringing in ears



Stroke

Irregular heartbeat, enlarged heart

Lack of ability to sweat

Chronic kidney disease, kidney failure

Diarrhea, abdominal pain

Pain in the hands and feet

Reddish purple skin rash

Because GL-3 accumulation is widespread, Fabry symptoms are widespread as well.

Clinical Presentation to a Range of Specialists

- Nephrologists
- Cardiologists
- Neurologists
- Pediatricians
- Primary Care Physicians
- Ophthalmologists
- Dermatologists

Clinical Presentation to Cardiologist

Patients may present with:

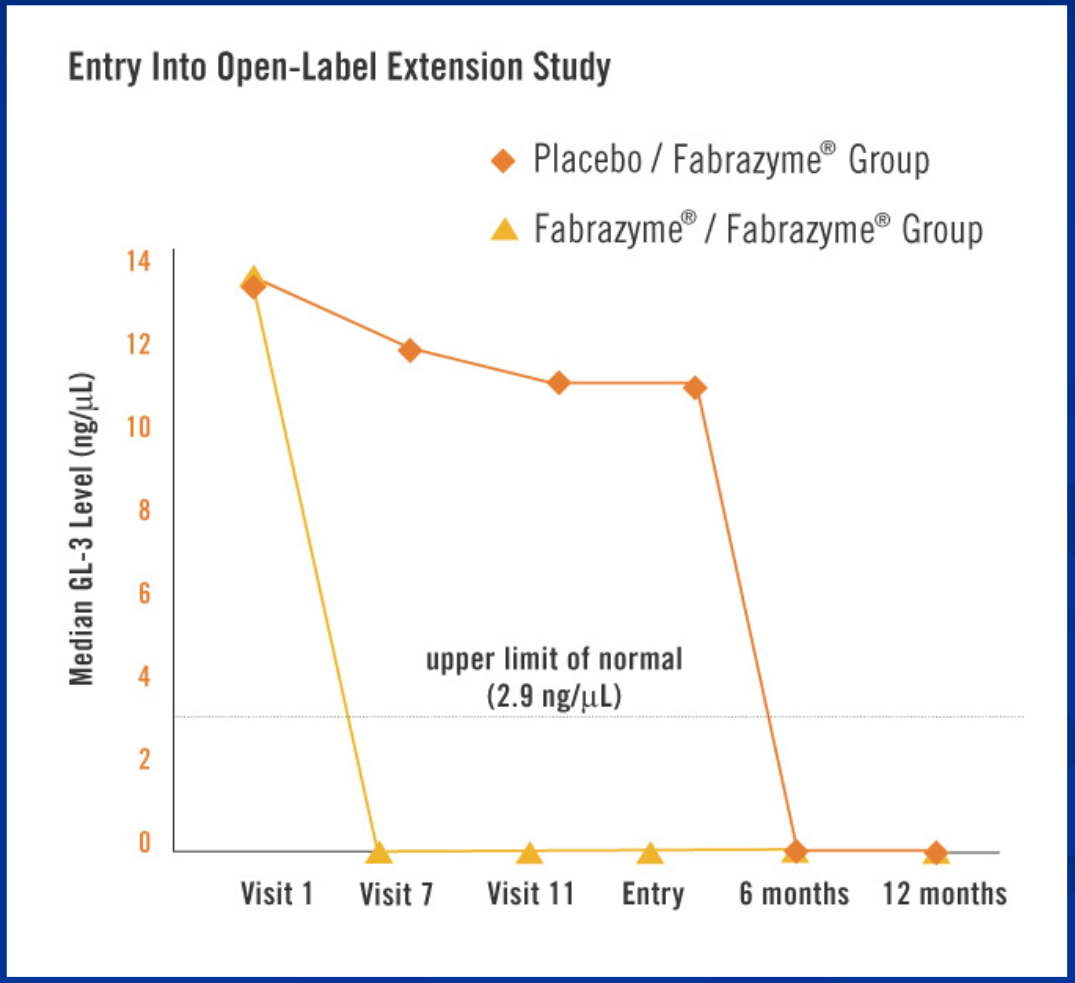
- Left ventricular hypertrophy
- Mitral valve prolapse and/or regurgitation
- Premature coronary artery disease
- Angina
- Myocardial infarction
- Arrhythmia

Diagnosis

- Disease usually presents in childhood, yet disease often goes unrecognized until adulthood[1,2]
  - Underlying pathology is advanced
- Median age of diagnosis is 28.6 years[3]
- Delayed diagnosis may be due to under-recognition of early signs and symptoms
- Symptoms of Fabry disease similar to those of other more common disorders
- Early diagnosis is important
  - Disease is progressive

1. Shelley ED, Shelley WB, Kurczynski TW. Painful fingers, heat intolerance, and telangiectases of the ear: easily ignored childhood signs of Fabry disease. Pediatr Dermatol 1995; 12:215-9.
2. Menkes DL, O'Neil TJ, Saenz KK. Fabry's disease presenting as syncope, angiokeratomas, and spoke-like cataracts in a young man: discussion of the differential diagnosis. Mil Med 1997; 162:773-6.
3. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA 1999; 281:249-54.

Phase 3 Extension Study Results: Median Plasma GL-3 Level

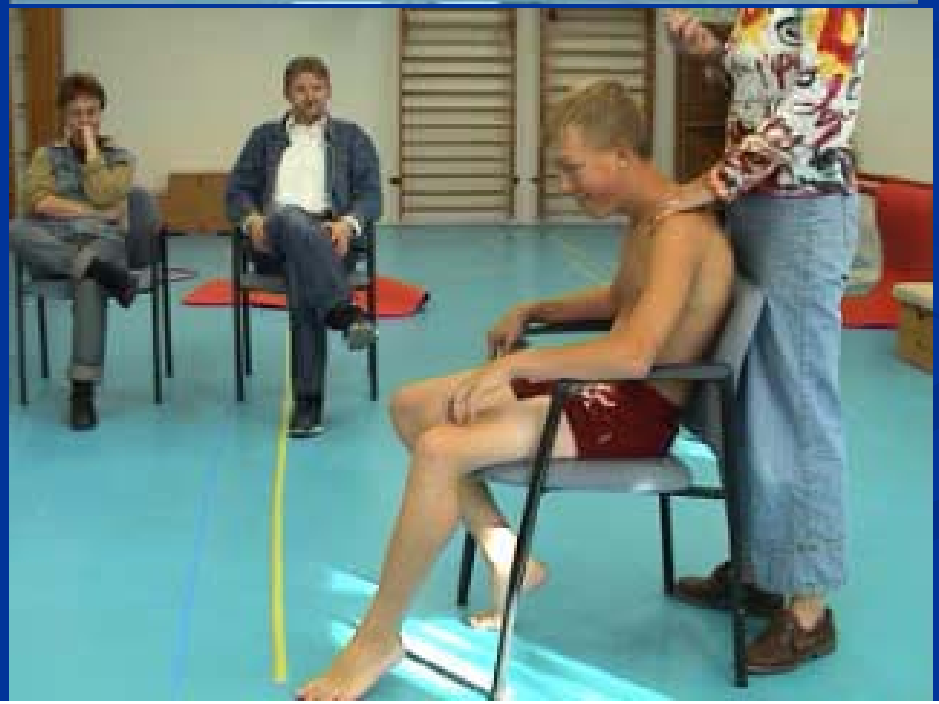


ERT – ENZYME REPLACEMENT THERAPY

- Gaucher disease – Cerezyme
- Mucopolysaccharidosis type I and VI
- Pompe disease
- Fabry disease

Future ?


SCRENING FOR POMPE !!
Pediatrics 120,e1327-e1334,2007
SCREENING FOR FABRY !!



תודה על הקשבה

ד"ר איאס קאסם