Late Onset Lysosomal Myopathies

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DISCLOSURES

In the last two years, Prof. A. Toscano has received from Genzyme-Sanofi, some reimbursements for teaching courses and for the participation to the meetings of global Pompe advisory board.

Lysosomal myopathies

“Hereditary muscle disorders due to a primary defect in lysosomal proteins and morphologically characterized by the presence of autophagic vacuoles in myofibers”

Lysosomal myopathies

- **Pompe disease**
- **Danon disease**
- **X-linked myopathy with excessive autophagy (XMEA)**
- **Autophagic vacuolar myopathy (AVM)**

WHAT IS POMPE DISEASE?

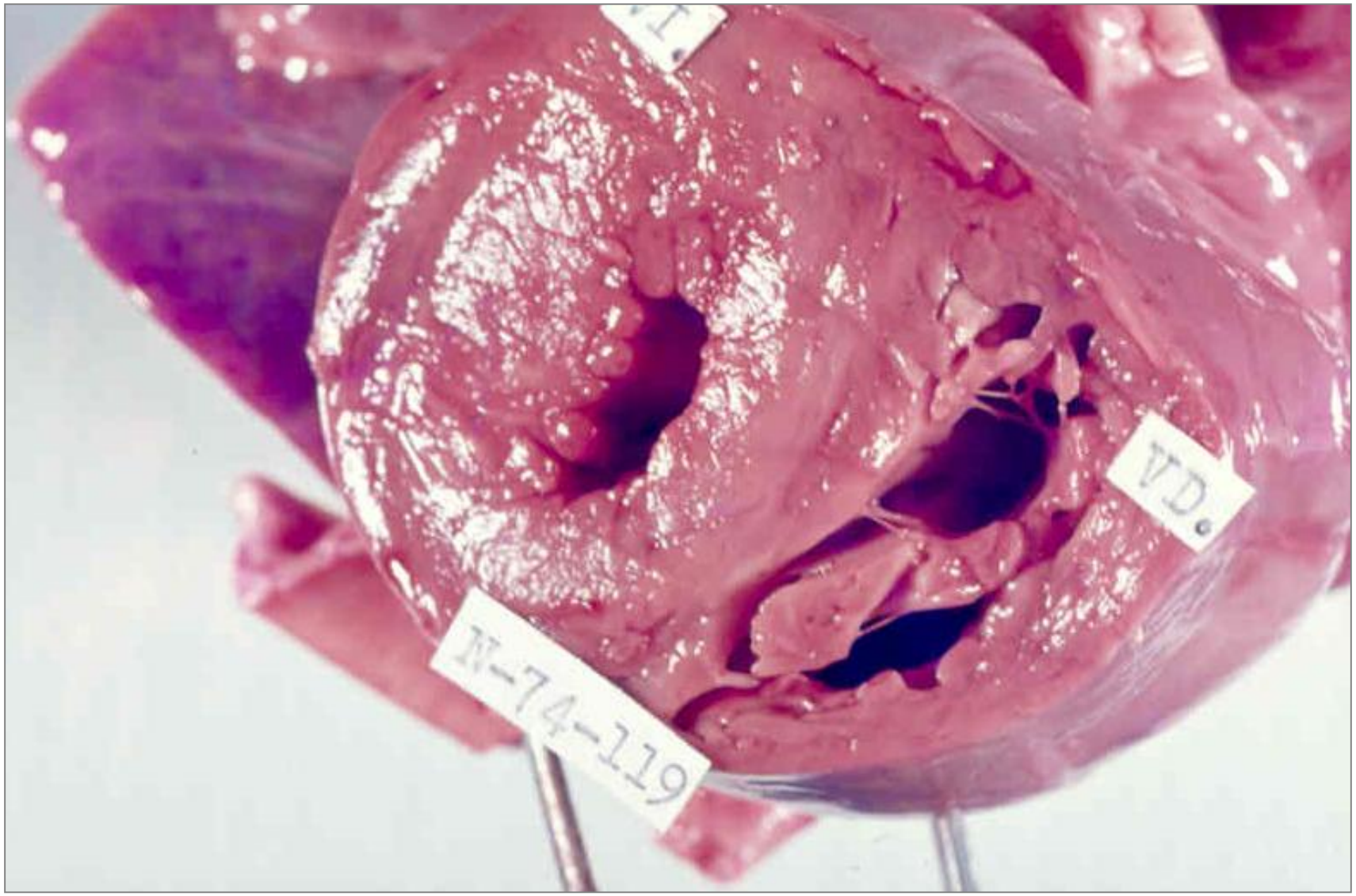
- Synonyms
  - Glycogen storage disease, type II (GSD-II)
  - Glycogenosis type II
  - Acid maltase deficiency (AMD)
- Disease Families
  - Lysosomal storage disease
  - Glycogen storage disease
  - Neuromuscular disease/metabolic muscle disease

JC Pompe
1901-1945

GSD II. Infantile form

Pompe JC. Over Idiopathische hypertrophie van het hart. Nederl Tijdschr Geneesk 1932; 76:304-312.

GSD II - Infantile form



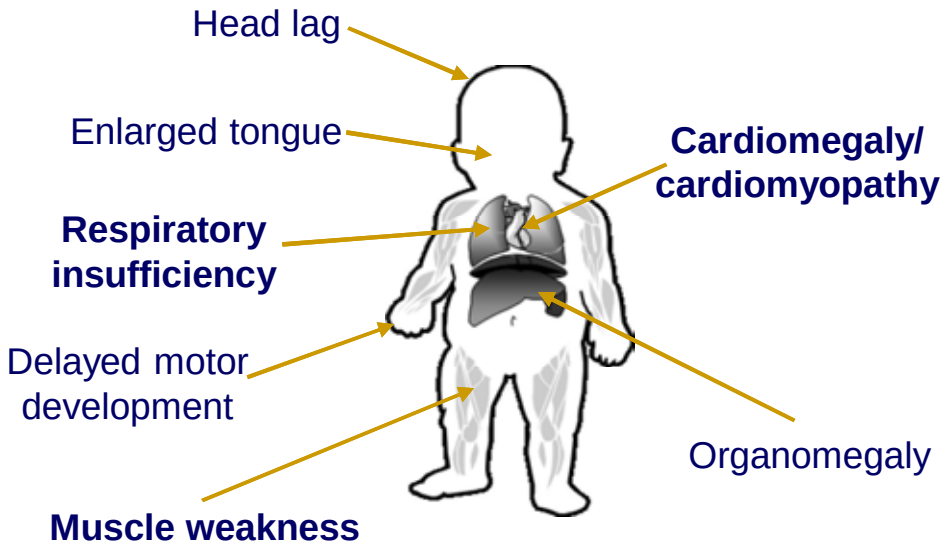
Massive Cardiomegaly

GSD II (Pompe Disease)

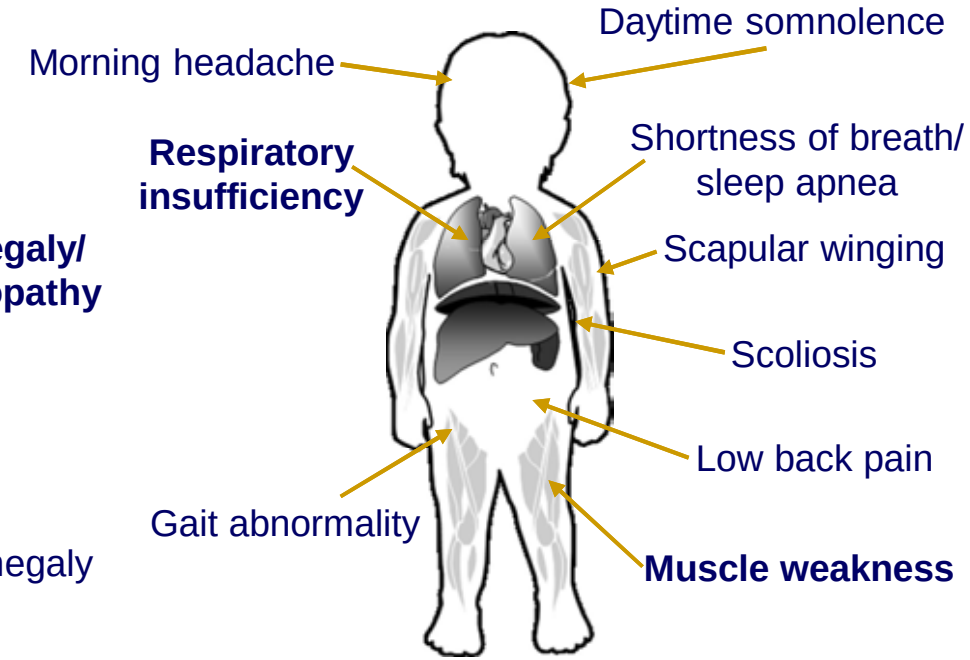
Enzyme Deficiency:	?áglucosidase (GAA)
Pathology:	Accumulation of glycogen in tissues, primarily skeletal muscle
Inheritance:	Autosomal Recessive
Frequency:	Overall: 1:40,000
Onset:	Infantile onset: within 1st year of life Late onset: childhood to adulthood
Clinical Course:	Infantile onset: death in 1st 2 years of life (before ERT) Late onset: variable progression

Pompe Disease: clinical clues

Infantile onset < 12 months



Late onset > 12 months

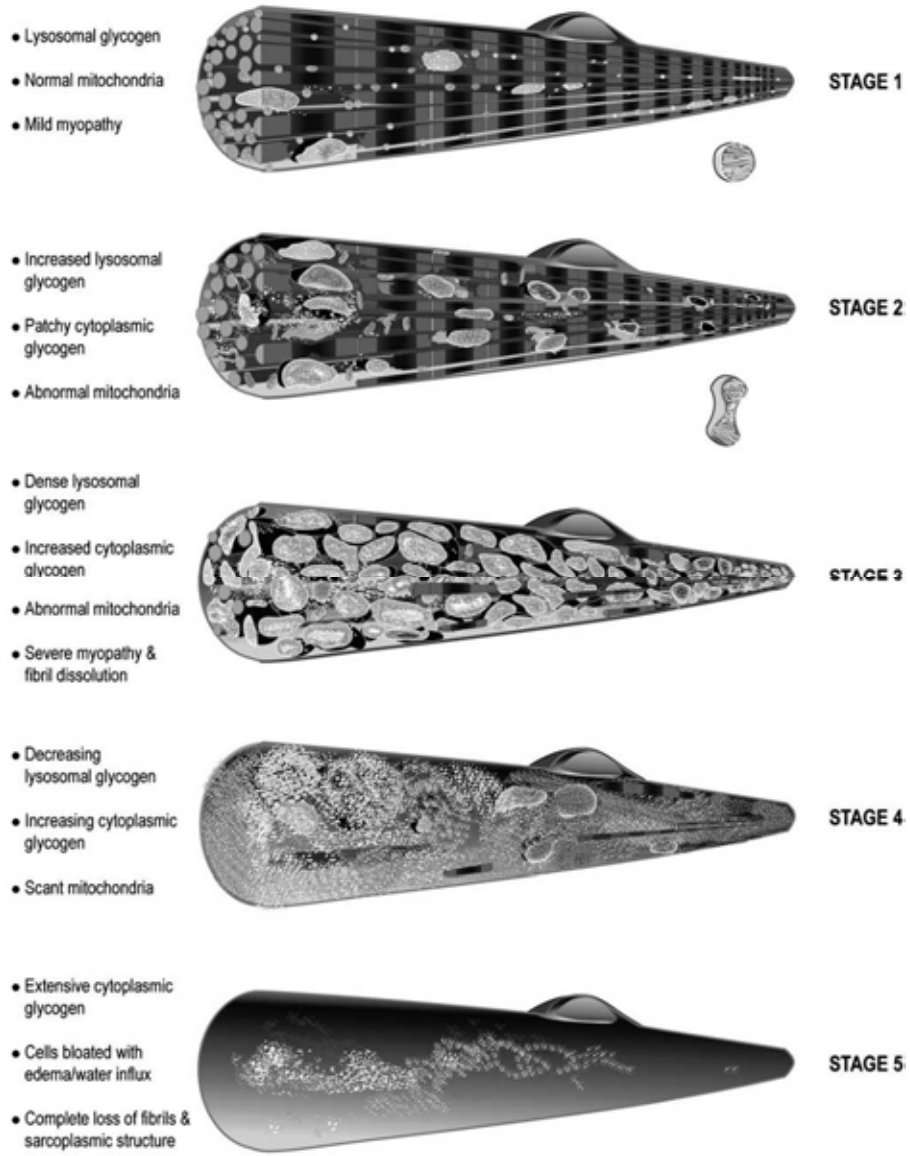


Look also for ***unusual*** symptoms or ***clusters*** of more common symptoms

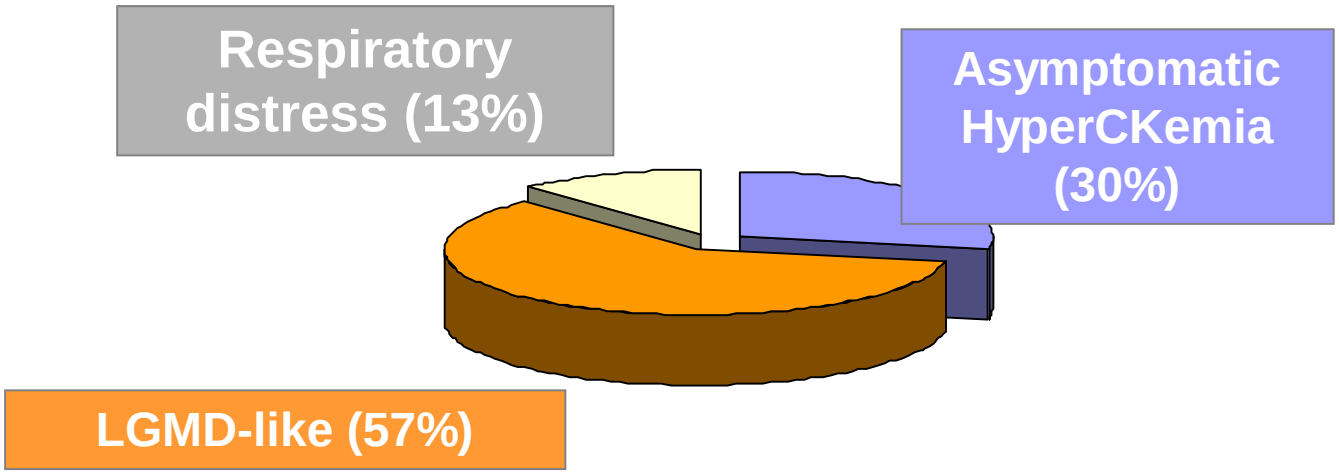
Hirschhorn R, Reuser AJJ. In: *The Metabolic and Molecular Bases of Inherited Disease*. 2001:3389-3420.

Late Onset Pompe Disease (LOPD)

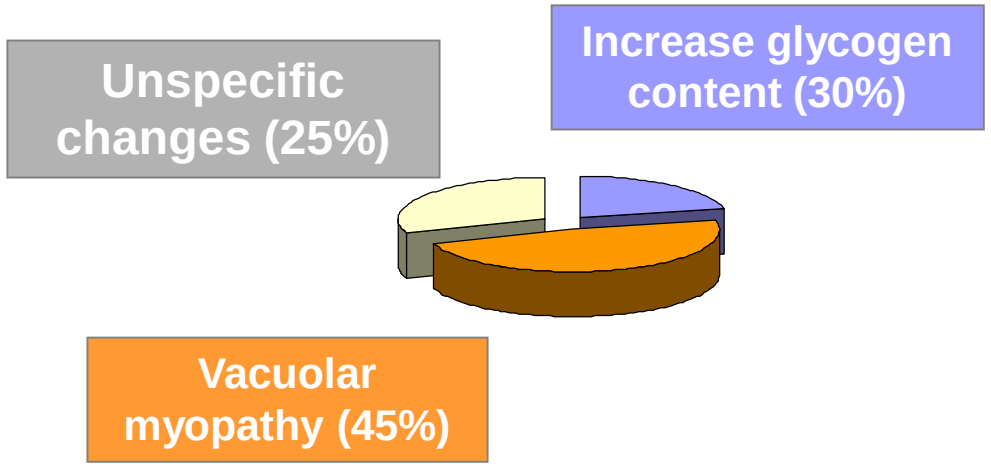
- The late onset forms are clinically heterogeneous and may present with a **limb-girdle muscle weakness with or without respiratory distress**.
- Asymptomatic subjects may be accidentally diagnosed because of **hyperCKemia**
- The pathogenesis of late-onset forms has been attributed to intralysosomal accumulation of glycogen and to the presence of **autophagic vacuoles**, causing disruption of muscle fibers.
- It has also been shown that an **increased muscle protein turnover** may contribute to muscle weakness and wasting.


• Lysosomal glycogen
• Normal mitochondria
• Mild myopathy
STAGE 1
• Increased lysosomal glycogen
• Patchy cytoplasmic glycogen
• Abnormal mitochondria
STAGE 2
• Dense lysosomal glycogen
• Increased cytoplasmic glycogen
• Abnormal mitochondria
• Severe myopathy & fibril dissolution
STAGE 3
• Decreasing lysosomal glycogen
• Increasing cytoplasmic glycogen
• Scant mitochondria
STAGE 4
• Extensive cytoplasmic glycogen
• Cells bloated with edema/water influx
• Complete loss of fibrils & sarcoplasmic structure
STAGE 5

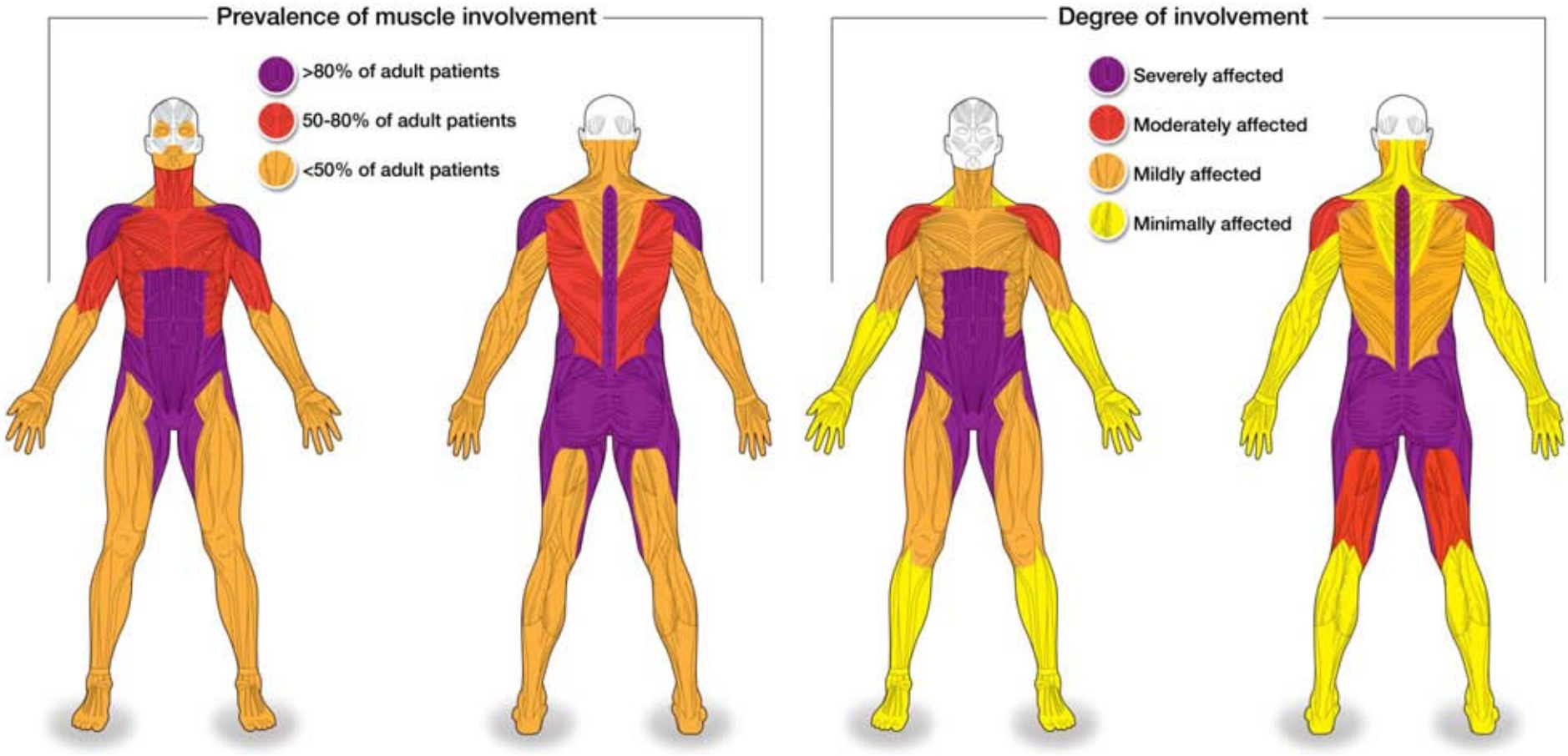
Clinical presentation in 41 cases



Morphological aspects

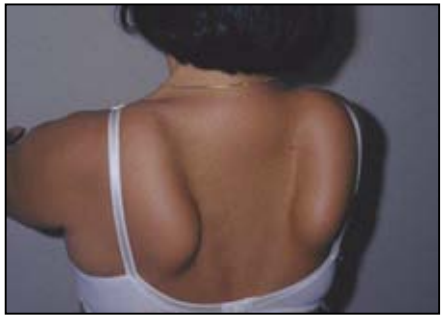


Muscle Involvement Pattern in Late Onset GSDII

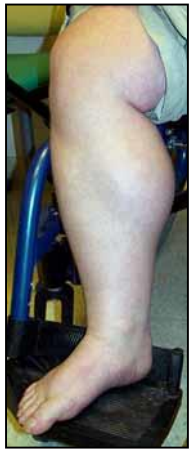


Specific clinical indicators - Red flags-

- **Scapular winging:**
  - LGMD2A
  - LGMD2C
  - LGMD2F
  - FSHD
  - Pompe disease



- **Muscle hypertrophy:**
  - LGMD1C
  - LGMD2C
  - LGMD2F
  - LGMD2I



- **Tongue hypertrophy**
  - LGMD2C
  - LGMD2F
  - LGMD2I
  - Pompe disease

Limb Girdle Muscular Weakness (LGMW): differential diagnosis

- **LGMW can be observed in both genetic and acquired disorders as** :

  – Limb Girdle Muscle Dystrophies

  – Metabolic myopathies (i. e. Mitochondrial myopathies)

  – Inflammatory myopathies (i.e PM, IBM, DM)

  – Toxic (i.e. steroids, statins, etc) and endocrine myopathies (thyroid, etc)

Cardiac and respiratory involvement : Red Flags

Cardiac involvement very common in:

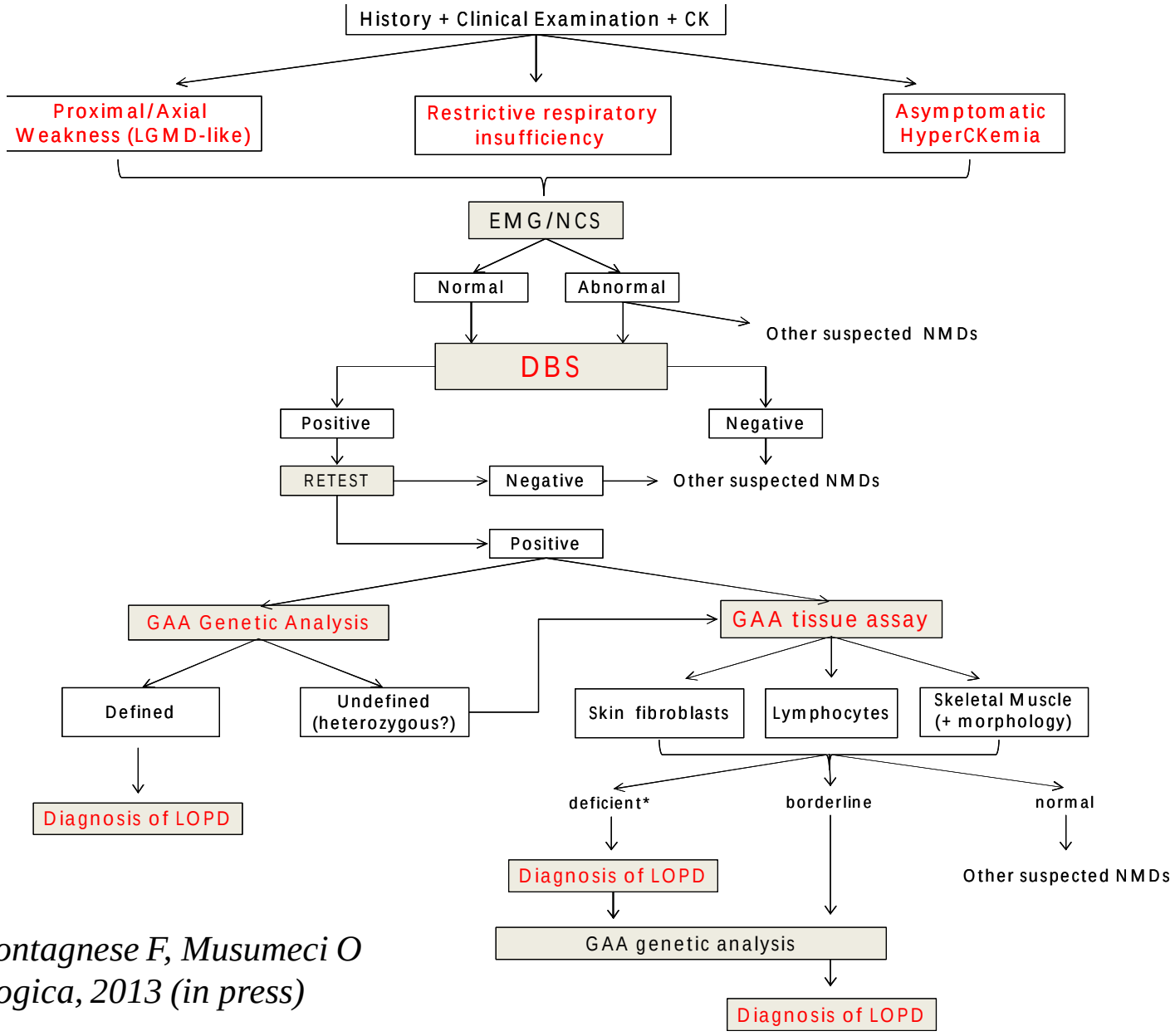
- LGMD1B, 2C, 2F and 2I
- Danon disease
- Myotonic dystrophies
- Pompe disease (infantile form)

Respiratory muscle weakness is common in

- LGMD2C-F and in 2I
- Pompe disease

LATE ONSET POMPE DISEASE

Diagnostic Algorithm

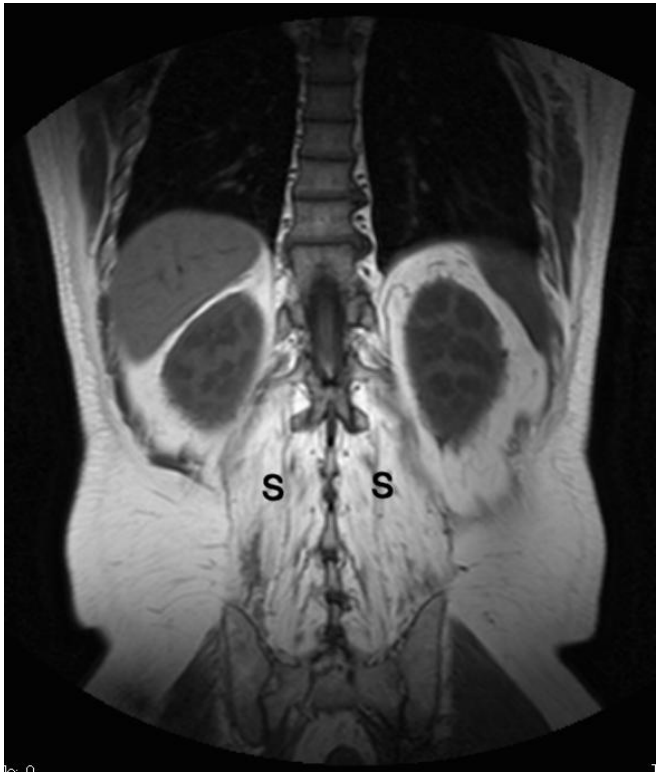


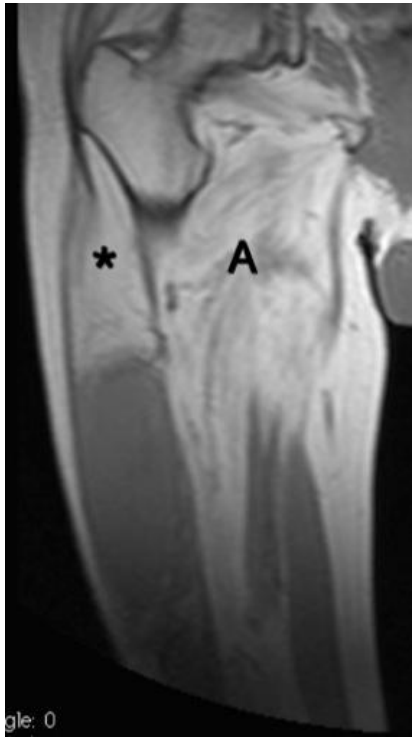
Toscano A., Montagnese F, Musumeci O
Acta Myologica, 2013 (in press)

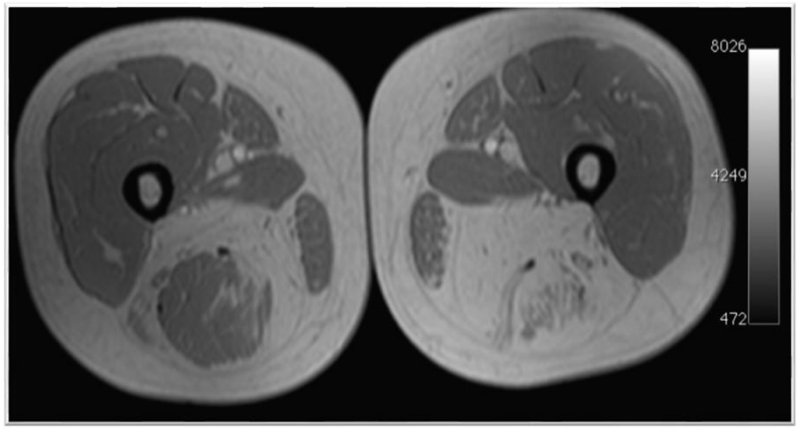
Pompe disease: spontaneous activity

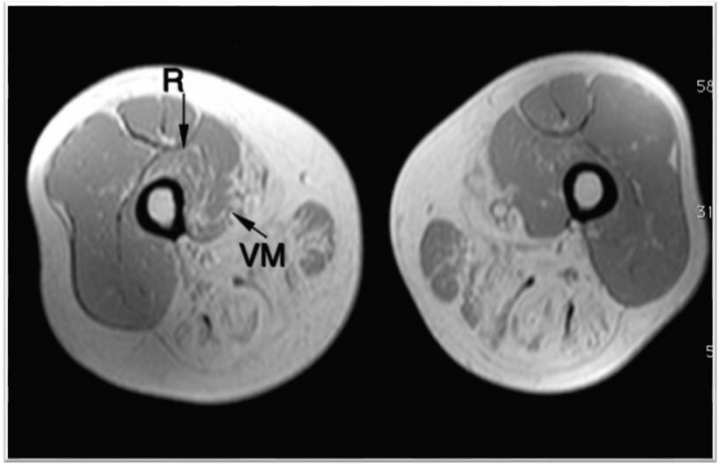
Potenziali di Fibrillazione	Scariche Miotoniche	Scariche Ripetitive Complesse
LESIONI NEUROGENE Poli/dermatomiosite Miopatia a corpi inclusi Distrofia muscolare (Duchenne) Rabdomiolisi Miopatie tossiche (alcool, clorochina) Deficit Maltasi Acida Glicogenosi (Debrancher) Miopatia miotubulare Paralisi periodica ipercaliemica Miopatia nemalinica Deficit carnetina muscolare Miopatie Mitocondriali	Distrofia miotonica Miotonia congenita Paramiotonia congenita Paralisi periodica ipercaliemica Poli/dermatomiosite Deficit Maltasi Acida Glicogenosi (Debrancher) Miopatia ipotiroidea Miopatia miotubulare Miopatie tossiche (clorochina) Sindrome di Schwartz-Jampel XMEA: miopatia x linked con eccessiva autofagia	LESIONI NEUROGENE Poli/dermatomiosite Distrofia muscolare (Duchenne) Miopatia a corpi inclusi Deficit Maltasi Acida Glicogenosi (Debrancher)

Typical muscle MRI features in LOPD

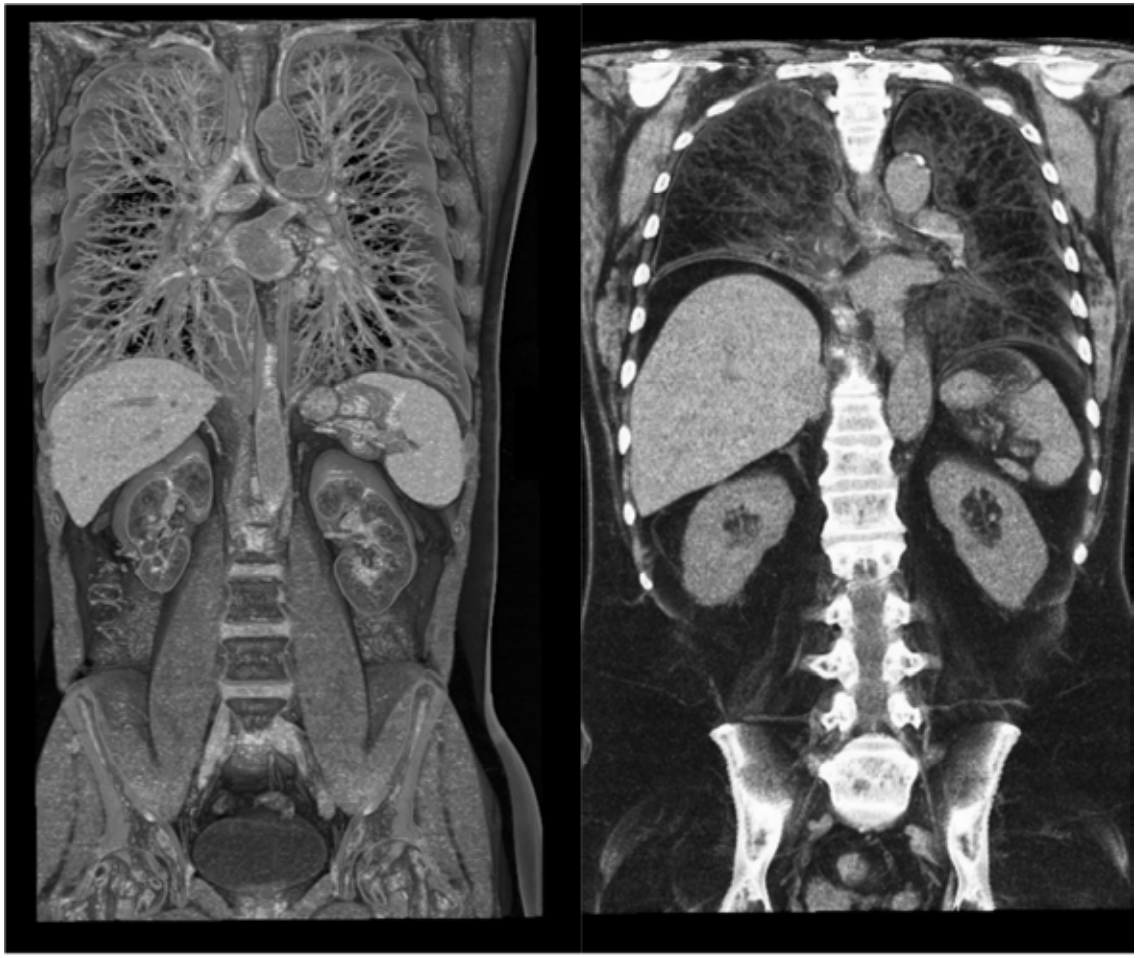


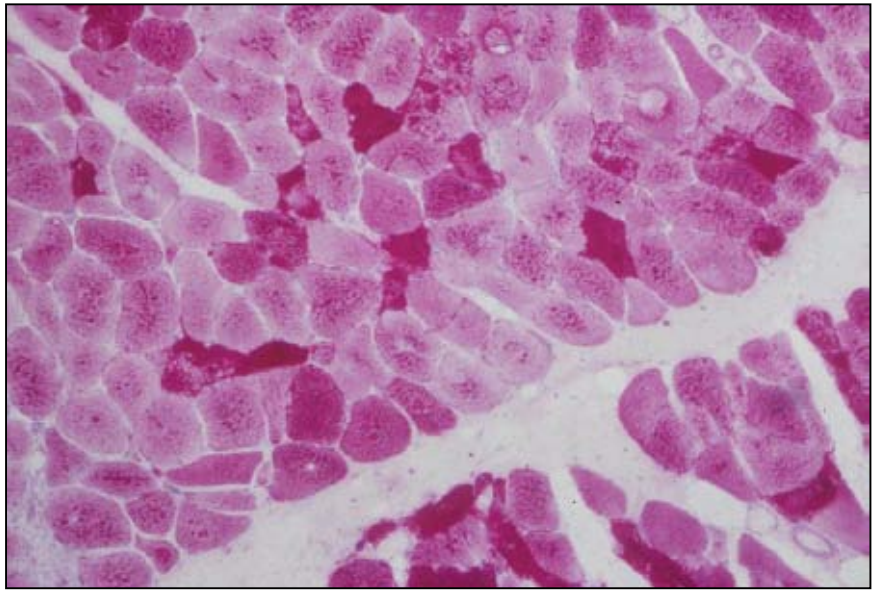


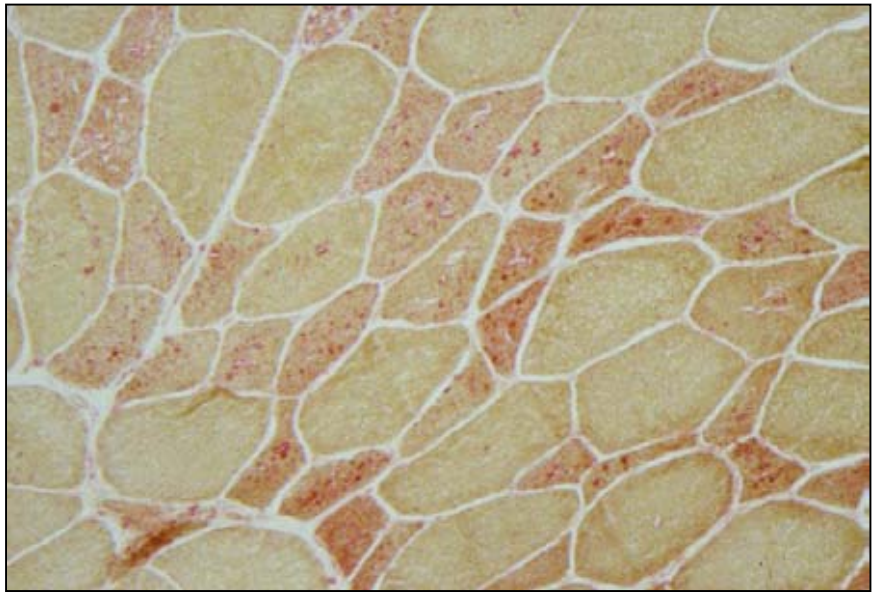


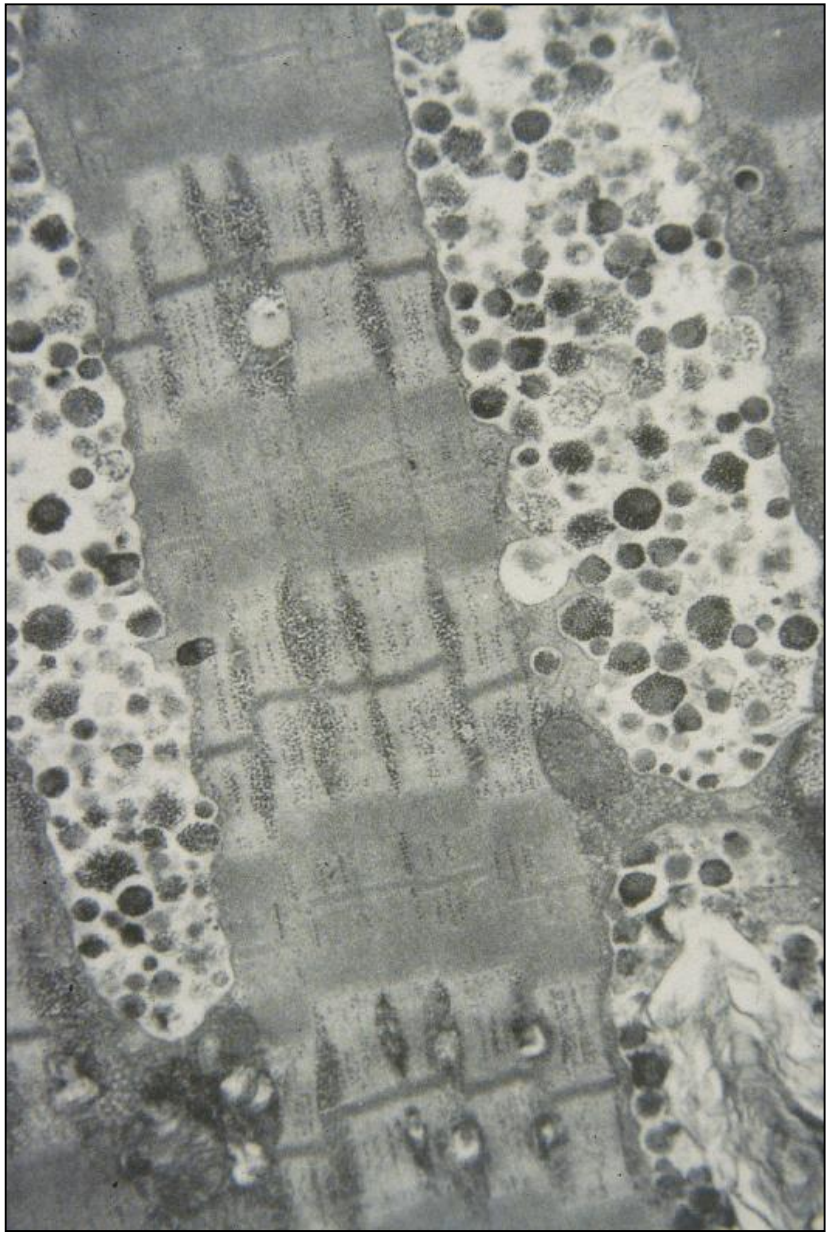


Respiratory muscles involvement in LOPD









GSD II

Biochemical Analysis

GAA activity

Preliminary assay — **Dried blood spot (DBS)**

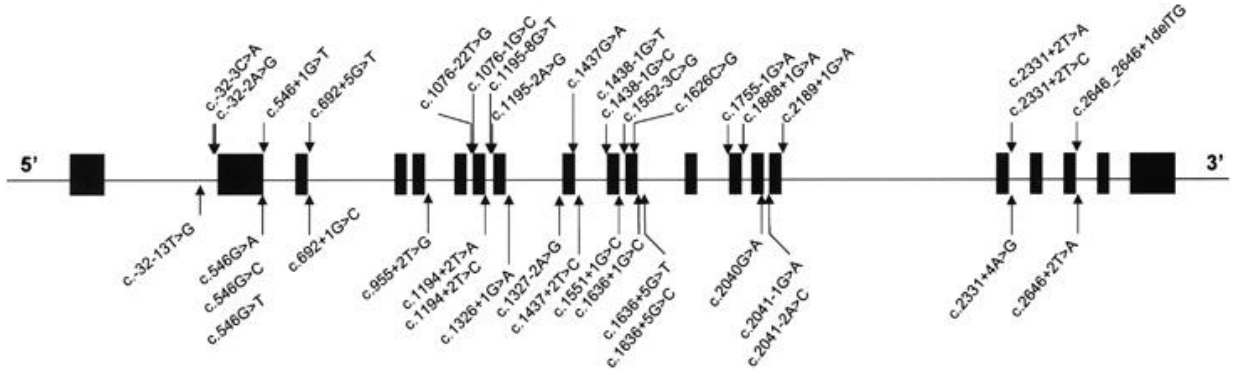
Confimatory assay
(In one of those tissues)

- **Fibroblasts**
- **Muscle**
- **Lymphocytes**

Genetic analysis

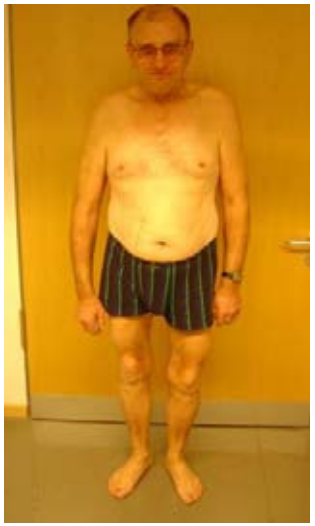
Autosomal recessive disorder due to mutations in *GAA* gene

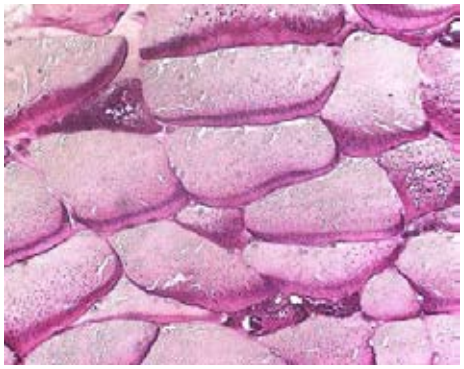
More than 300 mutations have been described



More common mutations

- **IVS 1-13 t>g splice** common in adult Caucasian patients
- **Asp645Glu** common in infants Pompe disease from Taiwan
- **Arg854X** common in African or African-American infants
- **del525T** and **del exon 18** common in Dutch infants





- Since first approval in 2006 for Pompe Disease treatment, increasing data are becoming available on the safety and efficacy of Myozyme

- Longer-term data (> 3 years) are also starting to become available although, due to the later approval in many countries, the sample size remains small

CONSENSUS TREATMENT RECOMMENDATIONS FOR LATE-ONSET POMPE DISEASE

EDWARD J. CUPLER, MD,[1] KENNETH I. BERGER, MD,[2] ROBERT T. LESHNER, MD,[3] GIL I. WOLFE, MD,[4] JAY J. HAN, MD,[5] RICHARD J. BAROHN, MD,[6] and JOHN T. KISSEL, MD,[7] of the AANEM CONSENSUS COMMITTEE ON LATE-ONSET POMPE DISEASE

Muscle Nerve **45:** 319–333, 2012

Table 5. Treatment recommendations based on the stage and severity of Pompe disease.

Condition	Recommendations
Presymptomatic patients without objective signs	• Patients should be examined every 6 months for proximal muscle weakness and pulmonary function • Enzyme replacement therapy (ERT) should be started at: – Onset of symptoms – Onset of detectable proximal muscle weakness or reduced forced vital capacity in either upright or supine position
Presymptomatic patients with objective signs	• ERT should be started if: – Presymptomatic patients have proximal muscle weakness detectable on the Medical Research Council scale or reduced forced vital capacity in either upright or supine position
Symptomatic patients	• ERT should be started if: – There is either reduction in forced vital capacity in either upright or supine position or increased limb weakness – Patient has difficulty completing activities of daily living – Is or is not using noninvasive ventilation
Severe symptoms	• If the patient is confined to a wheelchair and is using invasive ventilation during the day and at night: – ERT is recommended for 1 year, followed by evaluation of the effectiveness of therapy – After one year, ERT is recommended on a case-by-case basis for patients who require continuous invasive ventilation, using the collective information acquired by the multispecialty team – Continue ERT if severe signs and symptoms are stabilized or improved
Length of ERT	• One year followed by reassessment to consider whether to continue the treatment
Monitoring	• Patients receiving enzyme replacement therapy should be monitored for IgG antibodies every 3 months for 2 years, then annually thereafter

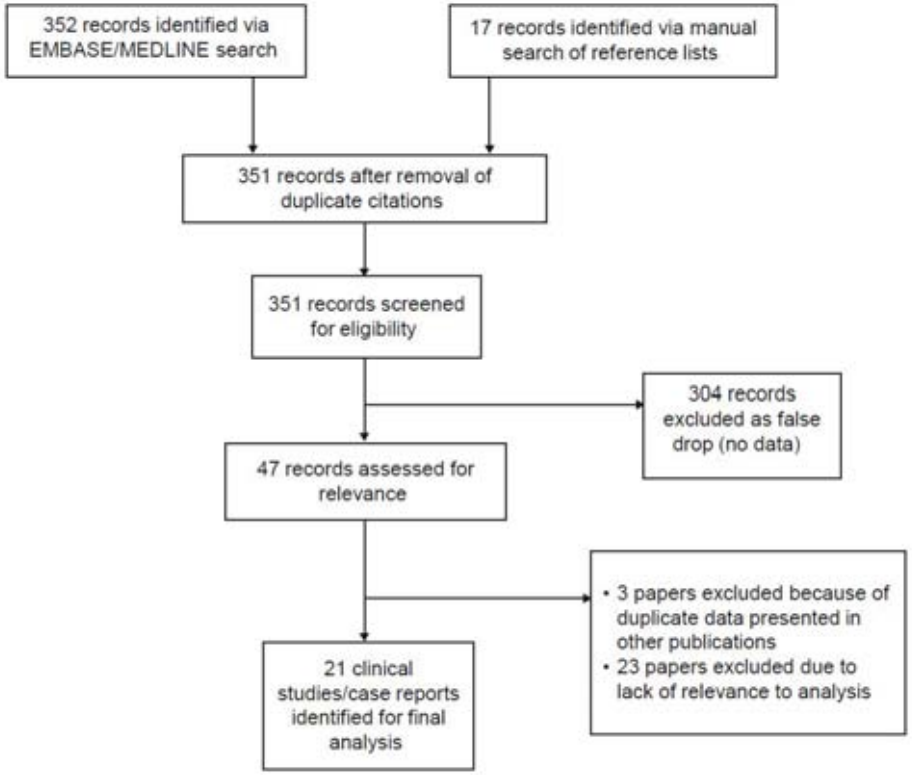
J Neurol
DOI 10.1007/s00415-012-6636-x

REVIEW

Enzyme replacement therapy in late-onset Pompe disease: a systematic literature review

Antonio Toscano · Benedikt Schoser

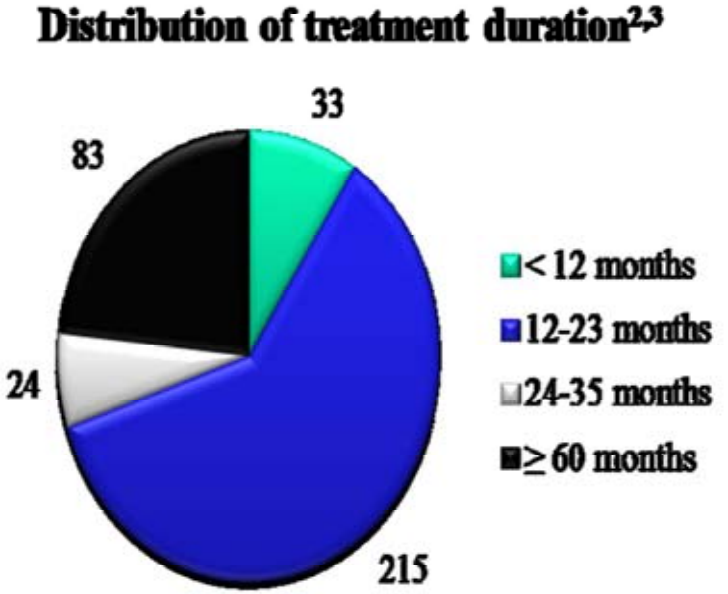
20 July 2012

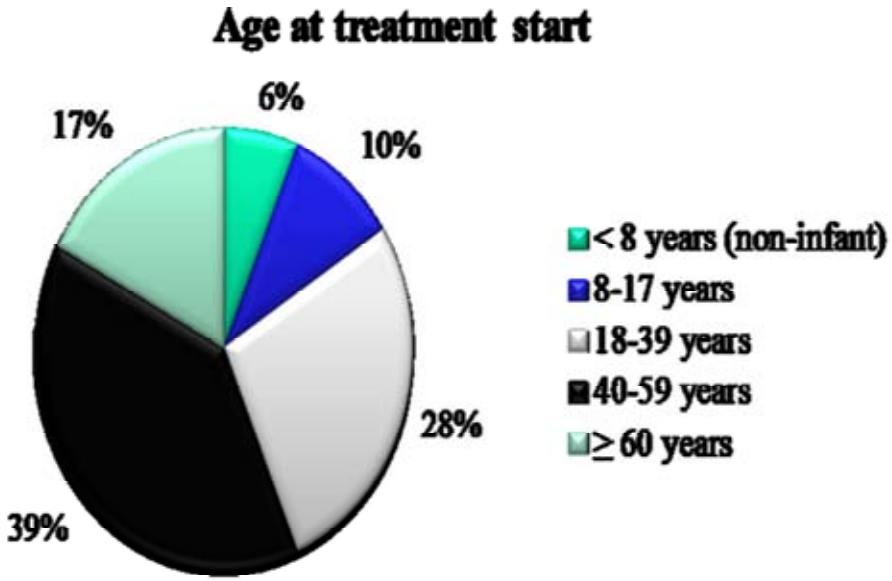


Data source: EMBASE and MEDLINE

Patient characteristics

- Total of 385 patients over the age of 2 were included
  - 190 male - 195 female
  - 44 juvenile 281 adult

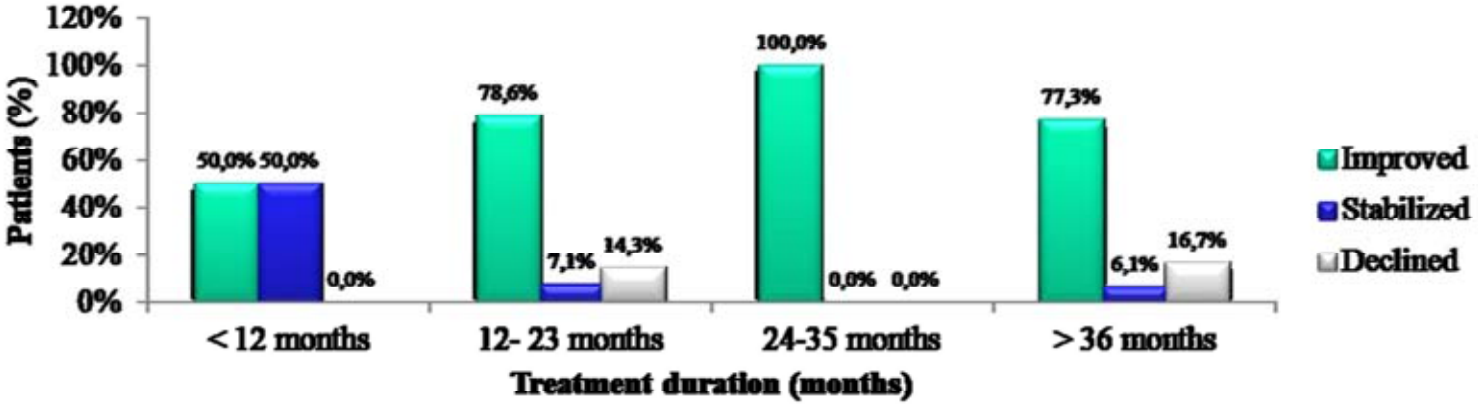




[1]Data not available for 60 patients; [2]Data not available for 39 patients; [3]11 patients reported at time points in both groups

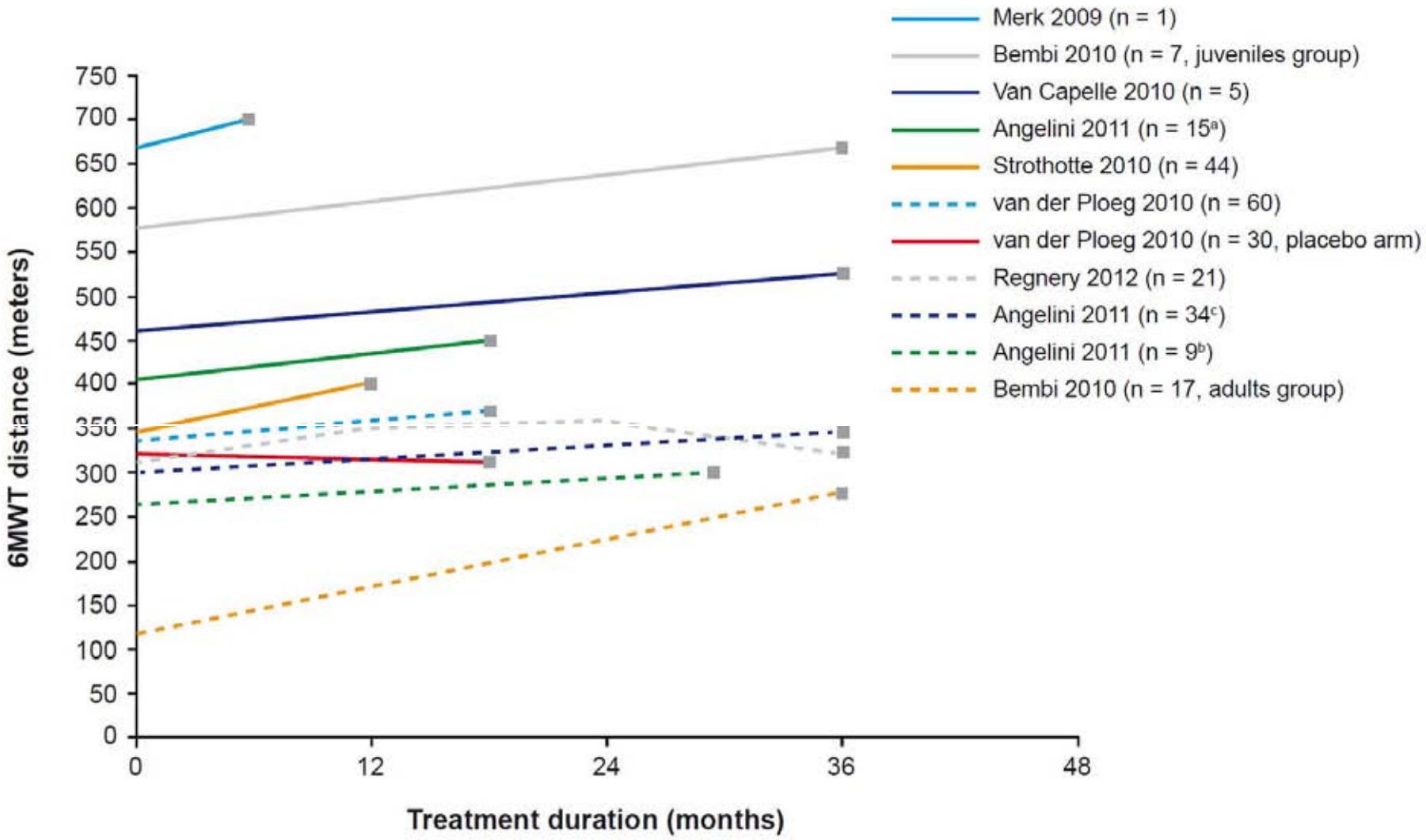
Motor performance – 6MWT

- The mean 6MWT distance declined by 3m in Pompe Disease patients in the placebo arm of a randomized controlled trial[1]
- 6MWT data were available for 122 treated patients
  - 77.9% improved
  - 8.2% stabilized
  - 13.9% declined
  - Range of mean improvement reported was 10-149m
- The majority of benefit in 6MWT was achieved at 12 months
  - There is no clear correlation between longer treatment and further improvement[1]



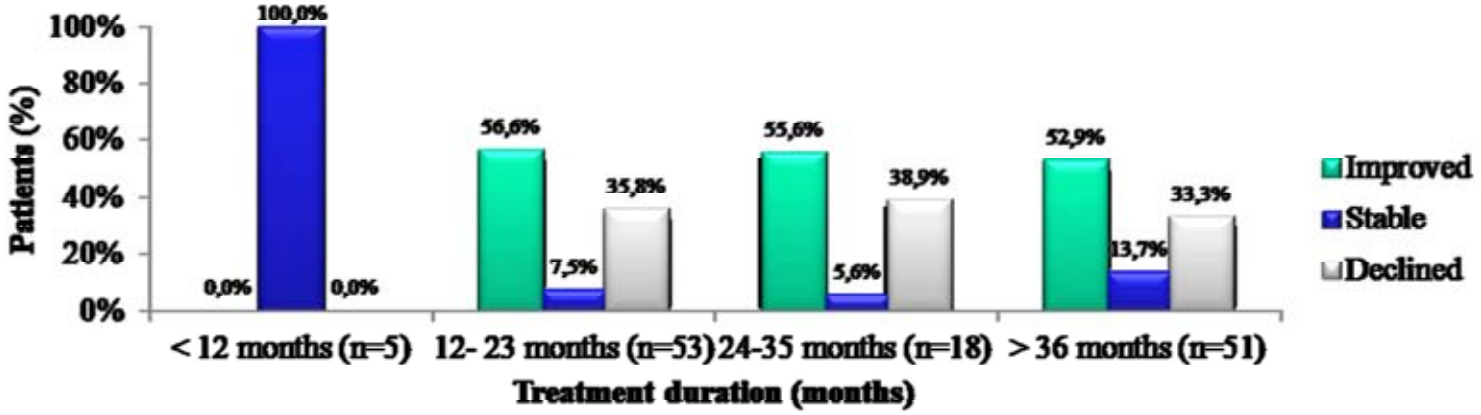
[1]van der Ploeg et al. N Engl J Med. 2010;362:1396-406; [2]Angelini et al, J Neurol (in press 2011)

6 MWT


6MWT distance (meters)
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
0
12
24
36
48
Treatment duration (months)
Merk 2009 (n = 1)
Bembi 2010 (n = 7, juveniles group)
Van Capelle 2010 (n = 5)
Angelini 2011 (n = 15[a])
Strothotte 2010 (n = 44)
van der Ploeg 2010 (n = 60)
van der Ploeg 2010 (n = 30, placebo arm)
Regnery 2012 (n = 21)
Angelini 2011 (n = 34[c])
Angelini 2011 (n = 9[b])
Bembi 2010 (n = 17, adults group)

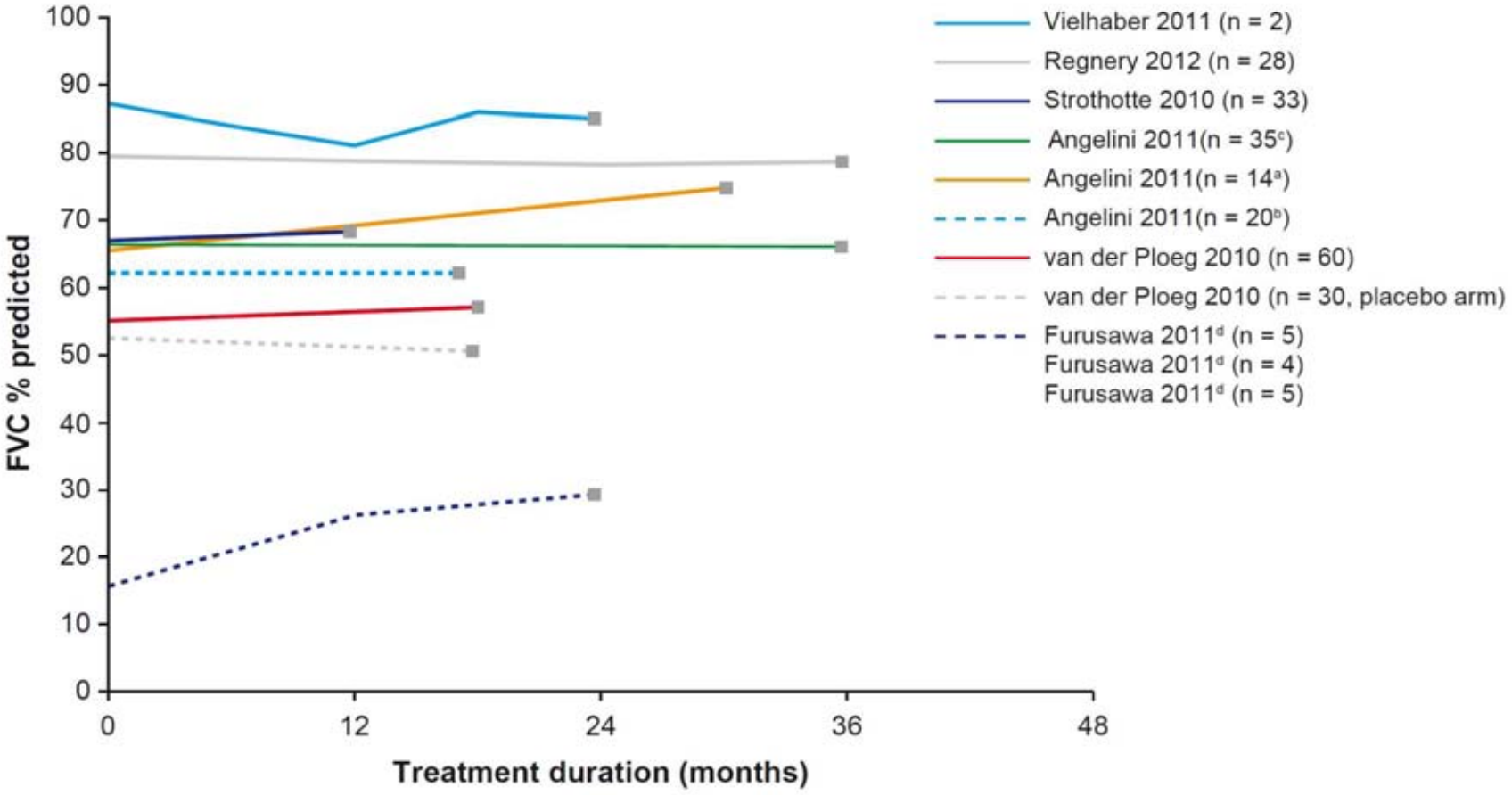
Respiratory status - FVC

- FVC declines in over 70% of untreated Pompe disease patients[1], with studies suggesting a mean drop of ~1.5% per year following diagnosis[2]
- FVC data was available for 127 treated patients
  - 52.8% had improved FVC status following treatment
  - 13.4% had stable FVC status following treatment
  - 33.8% had declining FVC status following treatment
- No clear trend was observed between treatment duration and FVC response



[1]van der Beek et al. Mol Gen Metab. 2011 (in press); [2]van der Beek et al. Neuromuscul Disord. 2009;19:113-117.

FVC % predicted



Güngör et al. Orphanet Journal of Rare Diseases 2013, 8:49
http://www.ojrd.com/content/8/1/49

ORPHANET JOURNAL OF RARE DISEASES

RESEARCH Open Access

Impact of enzyme replacement therapy on survival in adults with Pompe disease: results from a prospective international observational study

Deniz Güngör[1,2], Michelle E Kruijshaar[1,2], Iris Plug[1,2], Ralph B D'Agostino Sr[3], Marloes LC Hagemans[1,2], Pieter A van Doorn[1,4], Arnold JJ Reuser[1,5] and Ans T van der Ploeg[1,2,6*]

Methods: Data were collected as part of an international observational study conducted between 2002 and 2011, in which patients were followed on an annual basis. Time-dependent Cox's proportional hazards models were used for univariable and multivariable analyses.

Results: Overall, 283 adult patients with a median age of 48 years (range, 19 to 81 years) were included in the study. Seventy-two percent of patients started ERT at some time during follow-up, and 28% never received ERT. During follow-up (median, 6 years; range, 0.04 to 9 years), 46 patients died, 28 (61%) of whom had never received ERT. After adjustment for age, sex, country of residence, and disease severity (based on wheelchair and ventilator use), ERT was positively associated with survival (hazard ratio, 0.41; 95% CI, 0.19 to 0.87).

Conclusion: This prospective study was the first to demonstrate the positive effect of ERT on survival in adults with Pompe disease. Given the relatively recent registration of ERT for Pompe disease, these findings further support its beneficial impact in adult patients.

Considerations on ERT

- Studies of the natural history of Pompe disease indicates that patients are likely to deteriorate without treatment
- **At least two-thirds of juvenile and adult Pompe disease patients stabilize or improve when treated with ERT**
- However, direct comparison between studies remains difficult due to the variety in outcomes reported
  - The development of internationally accepted “Guidelines” would aid studies comparison
- There is a paucity of long-term data in Pompe disease patients
  - Important to collect data on a larger cohort of patients
  - It should allow identification of phenotypic predictors of response
  - **Recently (2012), it has been recommended that all patients has to start ERT at diagnosis if there is evidence of clinical symptoms and have to be assessed at 1 year.**
  - Presymptomatic individuals have to be regularly monitored (i.e., every 6 months) in order to start ERT when they become objectively affected

[Autophagy 2:4, 318-320; October/November/December 2006]; ©2006 Landes Bioscience

Addenda

Autophagy and Lysosomes in Pompe Disease

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Evelyn Ralston[2]
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ABSTRACT

In Pompe disease, a deficiency of lysosomal acid alpha-glucosidase, intralysosomal glycogen accumulates in multiple tissues, with skeletal and cardiac muscle most severely affected.[1] Complete enzyme deficiency results in rapidly progressive infantile cardiomyopathy and skeletal muscle myopathy that is fatal within the first two years of life. Patients with partial enzyme deficiency suffer from skeletal muscle myopathy and experience shortened lifespan due to respiratory failure. The major advance has been the development of enzyme replacement therapy, which recently became available for Pompe patients. However, the effective clearance of skeletal muscle glycogen, as shown by both clinical and preclinical studies, has proven more difficult than anticipated.[2-4] Our recent work published in Annals of Neurology[5] was designed to cast light on the problem, and was an attempt to look beyond the lysosomes by analyzing the downstream events affected by the accumulation of undigested substrate in lysosomes. We have found that the cellular pathology in Pompe disease spreads to affect both endocytic (the route of the therapeutic enzyme) and autophagic (the route of glycogen) pathways, leading to excessive autophagic buildup in therapy-resistant skeletal muscle fibers of the knockout mice.

Human Molecular Genetics, 2008, Vol. 17, No. 24 **3897–3908**
doi:10.1093/hmg/ddn292
Advance Access published on September 9, 2008

Suppression of autophagy in skeletal muscle uncovers the accumulation of ubiquitinated proteins and their potential role in muscle damage in Pompe disease

Nina Raben[1,*], Victoria Hill[1], Lauren Shea[1], Shoichi Takikita[1], Rebecca Baum[1], Noboru Mizushima[3], Evelyn Ralston[2] and Paul Plotz[1]

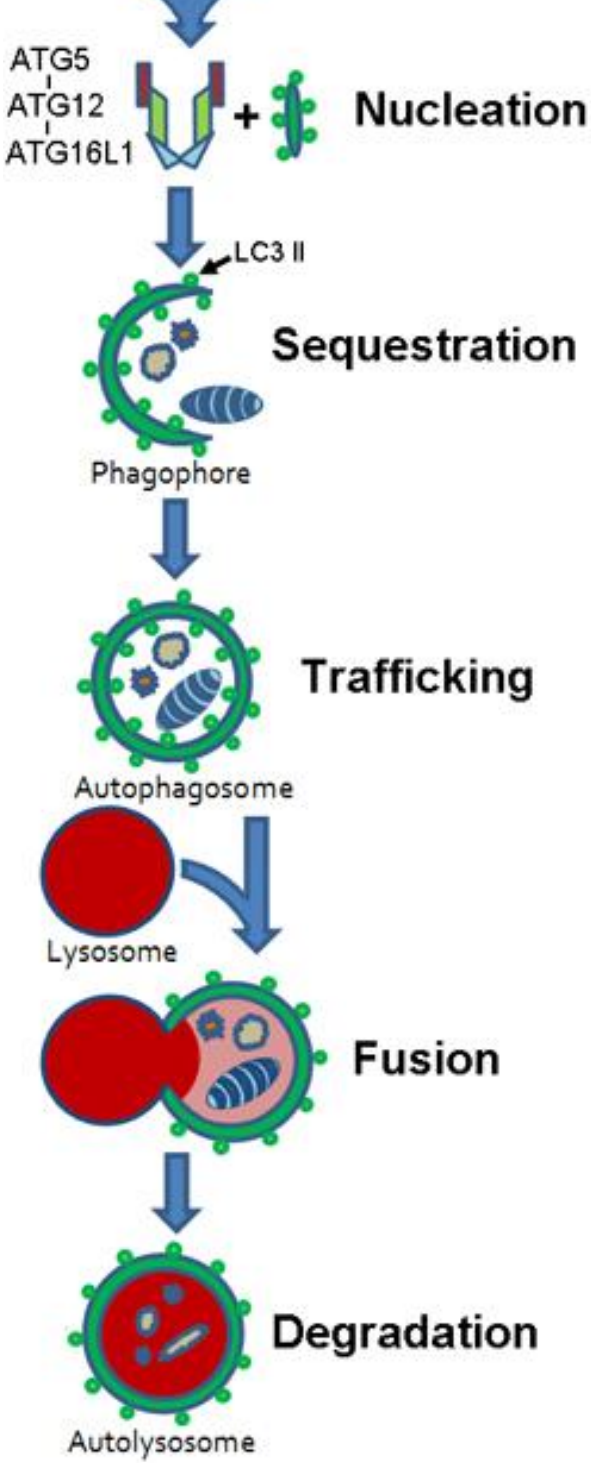
[Autophagy 5:1, 111-113; 1 January 2009]; ©2009 Landes Bioscience

Article Addendum

When more is less

Excess and deficiency of autophagy coexist in skeletal muscle in Pompe disease

Nina Raben,[1,*] Rebecca Baum,[1] Cynthia Schreiner,[1] Shoichi Takikita,[1] Noboru Mizushima,[2] Evelyn Ralston[3] and Paul Plotz[1]


ATG5
ATG12
ATG16L1
+
Nucleation
LC3 II
Sequestration
Phagophore
Trafficking
Autophagosome
Lysosome
Fusion
Degradation
Autolysosome

Danon disease
Synonyms

- Glycogen Storage Disease type IIb (GSD IIb)
- Lysosomal glycogen storage disease with normal acid maltase
- PseudoPompe
- Glycogen Storage Disease due to LAMP-2 deficiency
- Pseudoglycogenosis
- X-linked vacuolar myopathy and cardiomyopathy

Danon Disease

- Danon disease is an X-linked dominant lysosomal disease, initially described by Danon et al. in 1981, in two unrelated 16-year-old boys manifesting with cardiomyopathy, skeletal myopathy, and intellectual disability

Neurology. 1981 Jan;31(1):51-7.

Lysosomal glycogen storage disease with normal acid maltase.

Danon MJ, Oh SJ, DiMauro S, Manaligod JR, Eastwood A, Naidu S, Schliselfeld LH.

Abstract

Two unrelated 16-year-old boys had mental retardation, cardiomegaly, and proximal myopathy. One also had hepatomegaly. Histochemistry and electronmicroscopy of muscle biopsies showed lysosomal glycogen storage resembling acid maltase deficiency. Biochemical studies of skeletal muscle showed increased content of glycogen of normal structure; acid alpha-glucosidase activity in both urine and muscle was normal. Other enzymes of glycogen metabolism were also normal. The cause of this apparently generalized glycogenosis with no demonstrable enzyme defect is unknown.

PMID: 6450334 [PubMed - indexed for MEDLINE]

Nature 2000

Primary LAMP-2 deficiency causes X-linked vacuolar cardiomyopathy and myopathy (Danon disease)

Ichizo Nishino*†, Jin Fu‡, Kurenai Tanji*, Takeshi Yamada§, Sadatomo Shimojo‖, Tateo Koori¶, Marina Mora#, Jack E. Riggs☆, Shin J. Oh**, Yasutoshi Koga††, Carolyn M. Sue*, Ayaka Yamamoto†, Nobuyuki Murakami†, Sara Shanske*, Edward Byrne‡‡, Eduardo Bonilla*, Ikuya Nonaka†, Salvatore DiMauro* & Michio Hirano*

Infantile autophagic vacuolar myopathy is distinct from Danon disease

Article abstract—Lysosomal glycogen storage disease with normal acid maltase (Danon) is caused by primary lysosome-associated membrane protein-2 (LAMP-2) deficiency. Typically, the disease begins after the first decade; however, two infantile patients had similar histologic features. The infantile disorder is distinct from Danon disease, because, in both infants, LAMP-2 protein is present in skeletal muscle. Deposition of C5b-9 and multilayered basal lamina in one patient suggest that the infantile disease is pathogenically similar to X-linked myopathy with excessive autophagy.

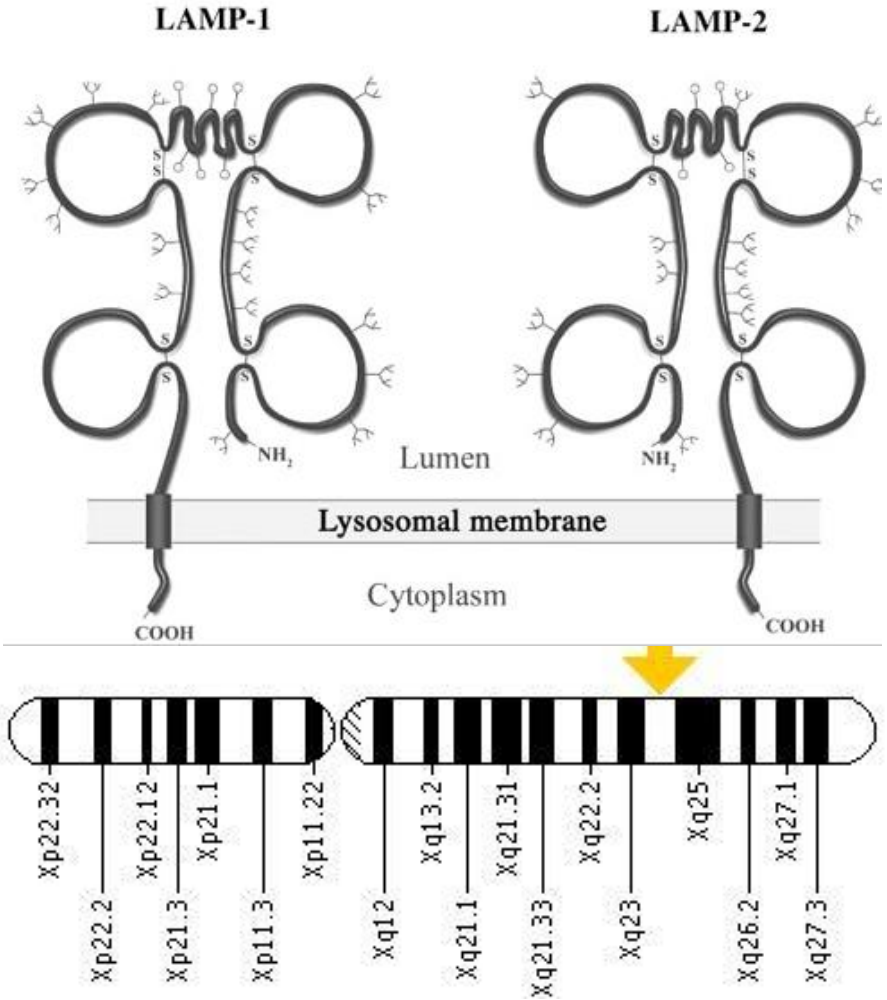
NEUROLOGY 2001;57:903–905

A. Yamamoto, MD; Y. Morisawa, MD; A. Verloes, MD; N. Murakami, MD, PhD; M. Hirano, MD; I. Nonaka, MD, PhD; and I. Nishino, MD, PhD

Neurology 2001

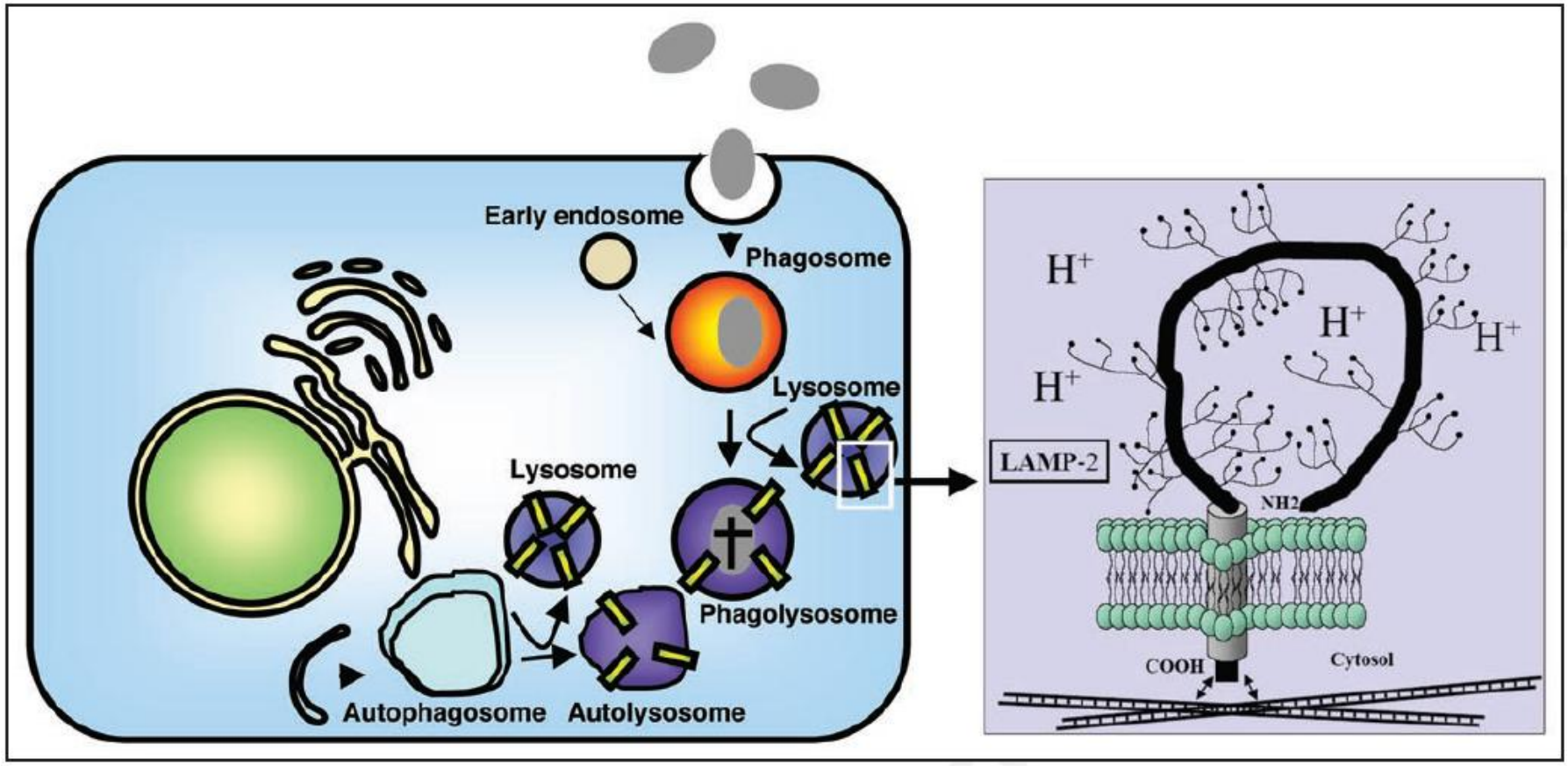
Etiopathogenesis

- The disease is due to the primary deficiency of Lysosome-Associated Membrane Protein - 2 (LAMP-2) gene
- LAMP-2 is a major constituent of the lysosomal membrane proteins
- The gene encoding LAMP-2 is located in Xq24.
- Lamp-2 open reading frame consists of 1,233 nucleotides containing 9 exons.
- To date, less than 100 cases have been reported with about 60 mutations

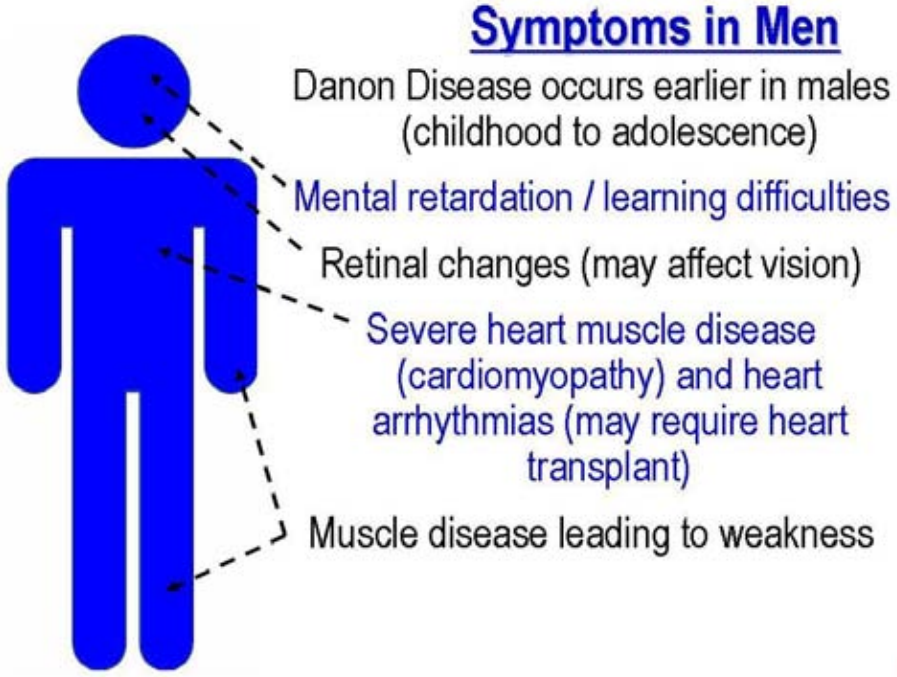


Etiopathogenesis

- Deficiency of LAMP-2 leads to a failure in the normal progression of autophagic maturation with accumulation of Autophagic Vacuoles with Sarcolemmal Features (AVSF)



Clinical presentations



Symptoms in Men

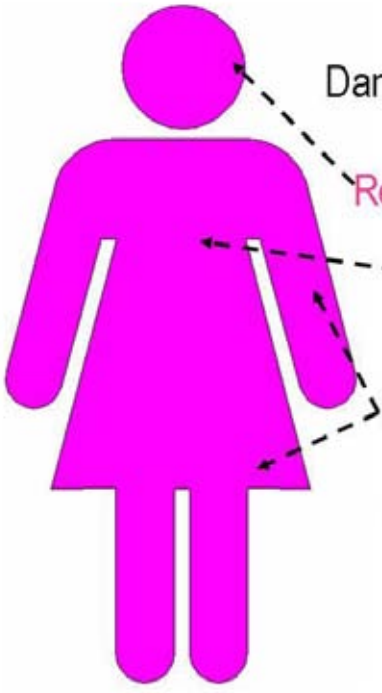
Danon Disease occurs earlier in males (childhood to adolescence)

Mental retardation / learning difficulties

Retinal changes (may affect vision)

Severe heart muscle disease (cardiomyopathy) and heart arrhythmias (may require heart transplant)

Muscle disease leading to weakness



Symptoms in Women

Danon Disease occurs later in females (adolescence to adulthood)

Retinal changes (may affect vision)

Heart muscle disease (cardiomyopathy) and heart arrhythmias

Mild muscle disease leading to weakness

Some women will have severe progressive symptoms and may need a heart transplant

ARTICLE

Natural history of Danon disease

Dana Boucek, BA, Jean Jirikowic, MS, and Matthew Taylor, MD, PhD

Genetics IN Medicine • Volume 13, Number 6, June 2011

- Clinical data on 82 pts with Danon disease from 36 families

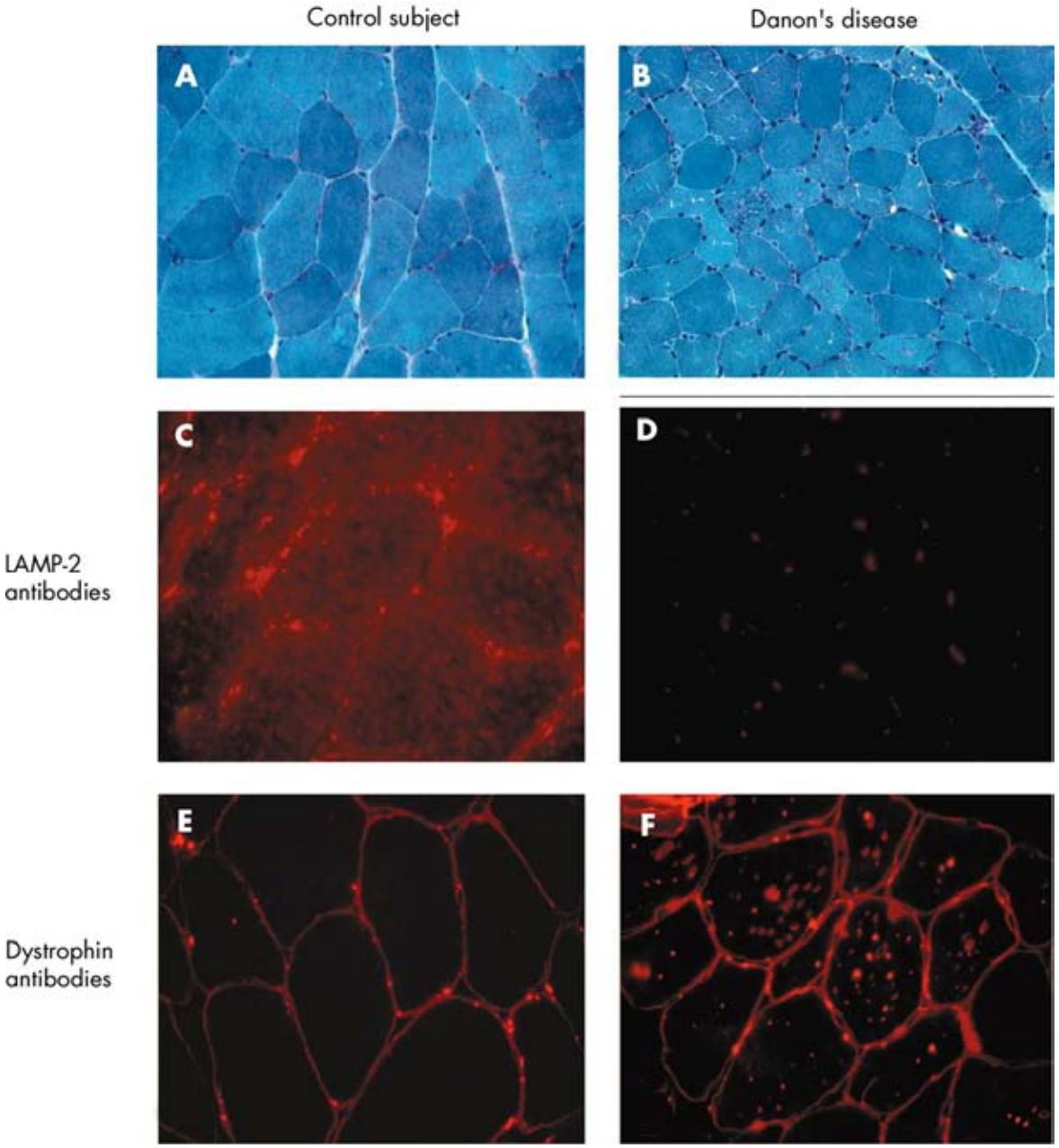
Table 1 Danon disease population

	Men (n = 43)[a]	Women (n = 39)
Symptomatic clinical disease	37 (94.9)	31 (91.2)
Clinical diagnosis[b]	39 (100)	32 (94.1)
Cardiac transplant	13 (33.3)	6 (17.6)
Living	23 (59.0)	23 (67.6)
Mean age (yr)		
First symptom	11.7 (±6.4)	26.8 (±14.2)
Diagnosis[b]	13.1 (±7.0)	30.9 (±15.2)
Cardiac transplant	20.8 (±6.7)	32.3 (±14.5)
Death	20.1 (±5.2)	40.2 (±12.6)

Table 3 Reported clinical characteristics

	Men (n = 26)	Women (n = 18)
Cardiac		
Symptomatic heart disease	88.5	77.7
Chest pain	41.6	37.5
Palpitations	76.5	68.8
Hypertrophic cardiomyopathy	88	33.3
Dilated cardiomyopathy	12	27.7
Conduction abnormality	86.4	80
Wolf-Parkinson-White	68.2	26.7
Cardiac ablation	53.3	30.8
Defibrillator implantation	41.2	31.3
Neurologic		
Learning and cognitive problems	100	46.6
Visual and retinal abnormalities	69.2	64.2
Symptomatic muscle disease	80	50
Muscle cramping	9.1	15.3
Neuropathy	9.1	38.5
Respiratory		
Symptomatic respiratory disease	50	16.7
Gastrointestinal		
Symptomatic GI disease	76.5	50

Pathological findings (basofilic inclusions and AVSF)



PERGAMON

Neuromuscular Disorders 15 (2005) 409–411

www.elsevier.com/locate/nmd

Case report

Asymptomatic hyperCKemia in a case of Danon disease due to a missense mutation in *Lamp-2* gene

Olimpia Musumeci[a,*], Carmelo Rodolico[a], Ichizo Nishino[b], Giuseppe Di Guardo[c], Alba Migliorato[a], Mohammed Aguennouz[a], Anna Mazzeo[a], Corrado Messina[a], Giuseppe Vita[a], Antonio Toscano[a]

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Received 23 August 2004; received in revised form 20 December 2004; accepted 3 February 2005

Case report 1

Clinical history

23 year-old-man.
At age 20, diagnosis of Wolf-Parkinson-White syndrome.
One year later, non-obstructive hypertrophic cardiomyopathy .

In several occasions, blood tests revealed persistently increased serum CK levels (max 783 IU/L, n.v. <200).

Neurological examination : normal

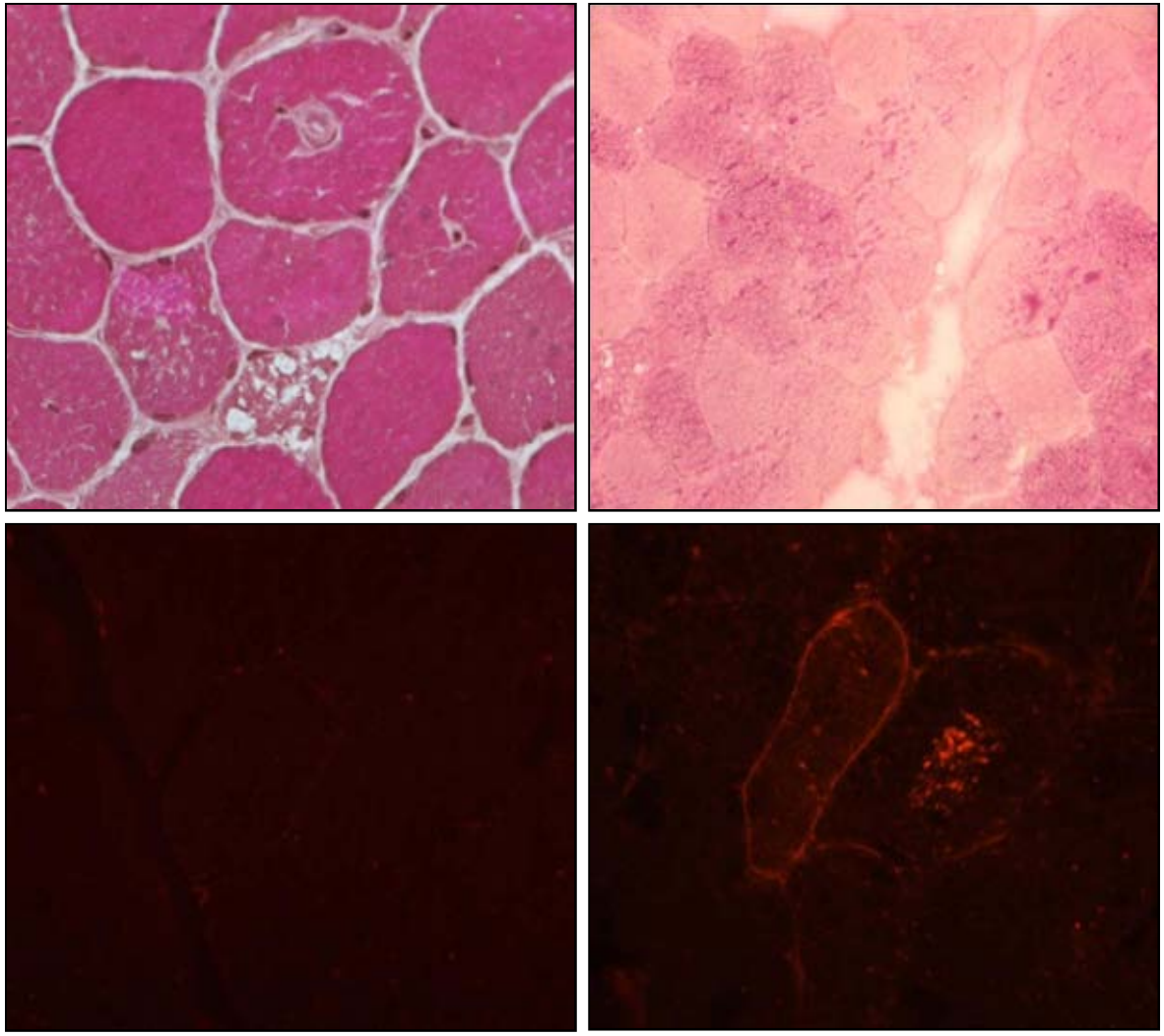
Laboratory studies: serum CK 680 IU/L n.v. <200

EMG: increased polyphasic potentials

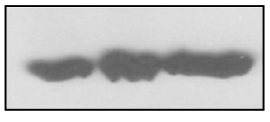
Echocardiogram: left ventricular hypertrophy especially of the lateral and posterior walls, with diffuse hypokinesia and decreased contractility.

Neuropsycological battery tests: normal cognitive status.

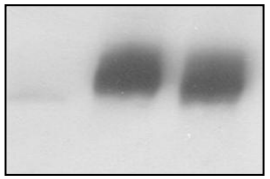
Case report 1



Biochemical and molecular genetic investigations

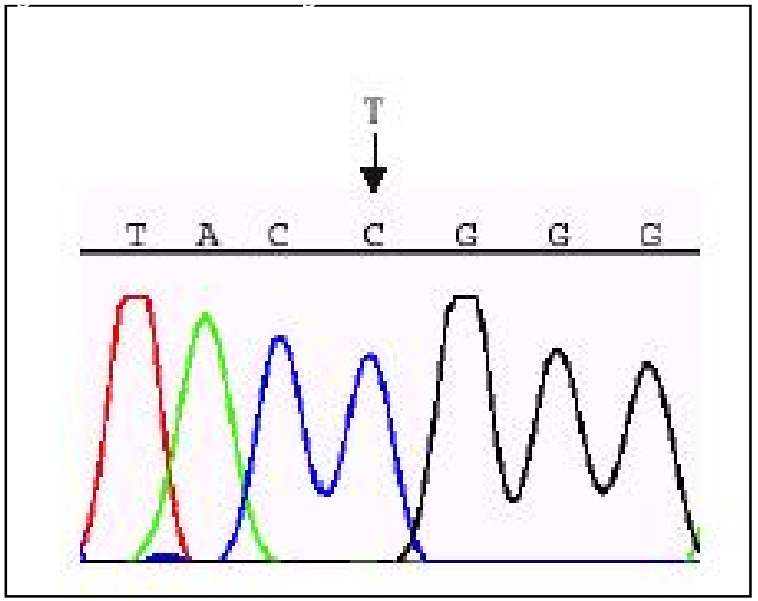


b-actin



LAMP-2
(126kd)

P C1 C2



W321R

Patient	SIANNNLSYRDAPLGSSYMC
Homo sapiens	SIANNNLSYWDAPLGSSYMC
Mus musculus	NISNKNLSFWDAPLGSSYMC
Cricetul gris	SVANNNLSFWDAPLGSSYMC
Gallus gallus	SADNNNLSKWDASLGNSYMC

Case report 2

Clinical history
6-yr-old male with no family history of cardiac disease, muscle disorder or metabolic disorders

Since the first months of life, the patient presented asthmatic bronchitis

At the age of 7 months, episode of pneumonia, increased transaminases and CK levels

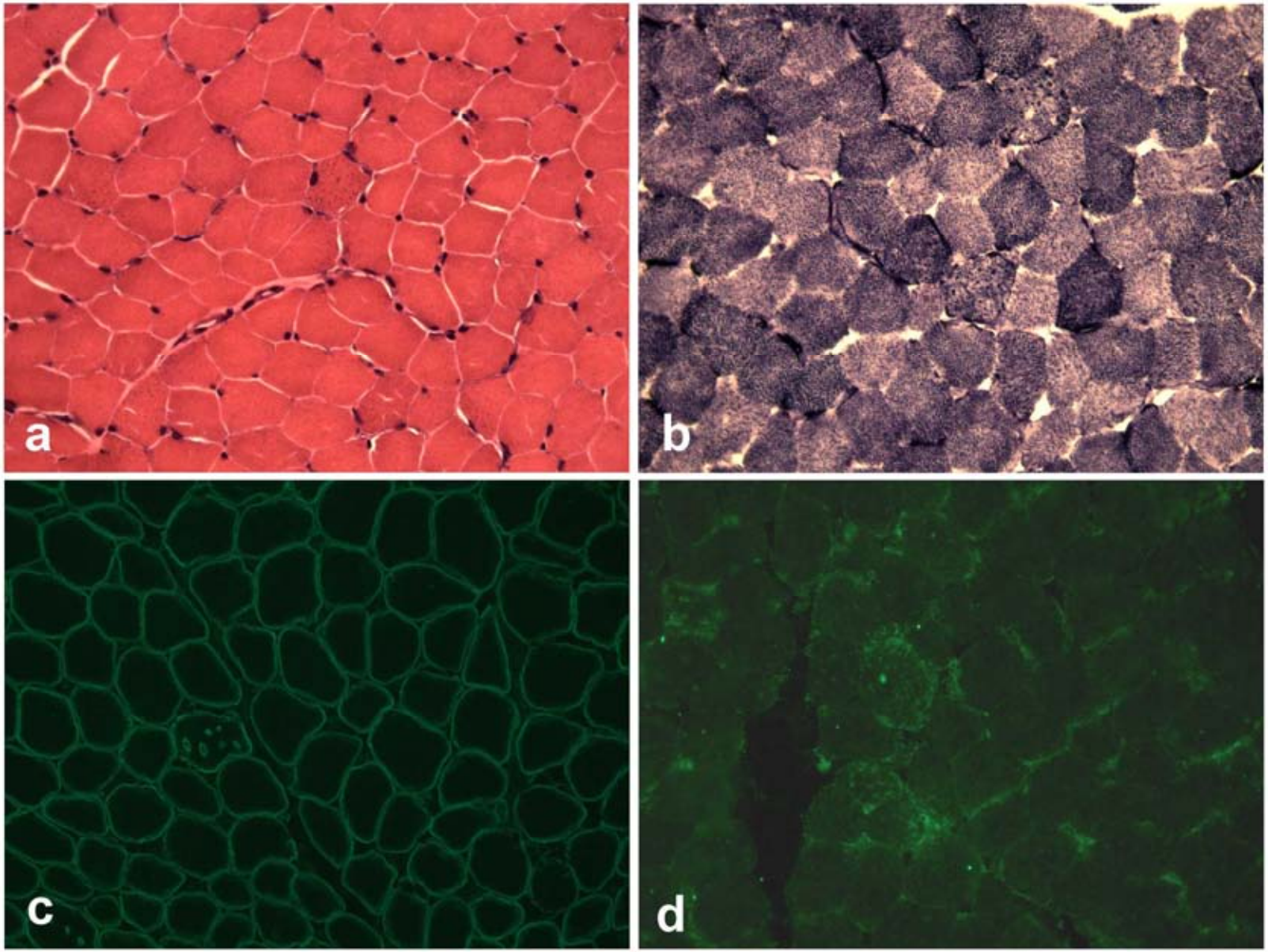
At the age of 5 the patient had been referred to our evaluation

Laboratory studies: serum CK 512 IU/L n.v. <200

ECG short PQ interval with stiffness of ST-segment and high voltages of R in left precordial leads

Echocardiogram: heart hypertrophy most significant at the inter-ventricular septum level.

Neuropsycological battery tests: normal QI, mild form of dyslexia and dysorthography



Lamp-2 gene analysis : c.222 T>A exon 3 (p. Y74X)

X-linked myopathy with excessive autophagy (XMEA)

- XMEA is a rare X-linked recessive AVM originally identified in a Finnish family
- It is characterized by a slowly progressive weakness and atrophy of the proximal muscles
- No Cardiac or CNS involvement
- Female carriers are normal or mildly affected
- Electromyography shows myotonic discharges without clinical myotonia

XMEA etiopathogenesis

- Muscle pathology is similar to Danon disease
- Mutations in VMA21 are responsible of XMEA
- VAM21 is an essential assembly chaperone of the vacuolar ATPase. Its deficiency raises lysosomal pH, reduces lysosomal degradative ability and blocks autophagy *(Ramachandran et al Acta Neuropathol 2013)*

Take home messages

- Late onset lisosomal myopathies are rare diseases but less rare than thought
- Clinical knowledge about similar but different presentations as well as a correct and specific algorythm are necessary to achieve the final diagnosis
- Early diagnosis = early therapeutic intervention
- Nowadays, pathogenetic clues are relevant to design future “tailored” therapies

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