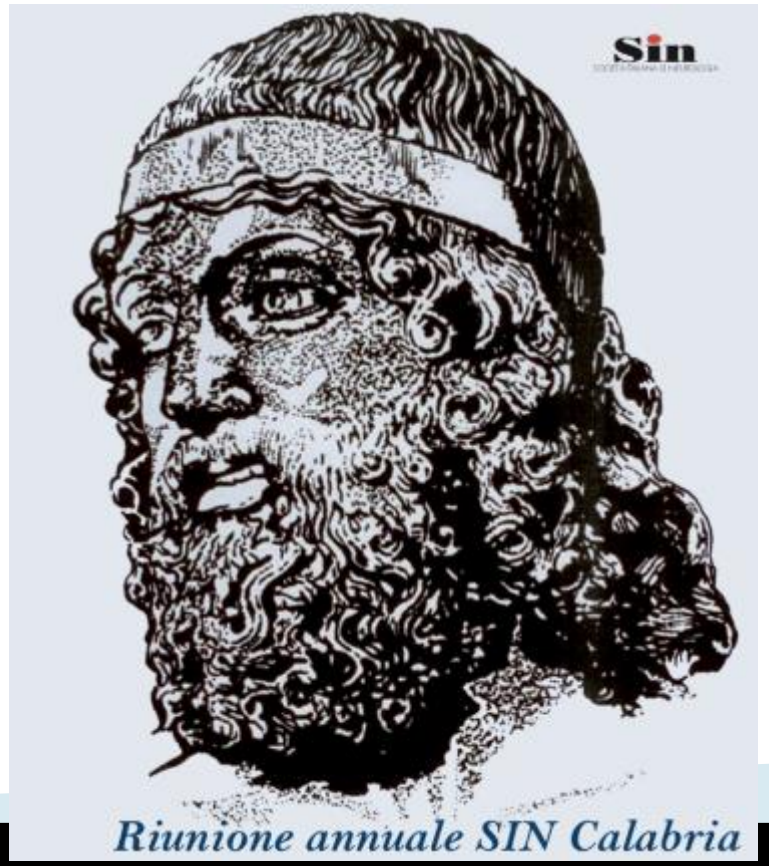
Consiglio Nazionale delle Ricerche
Istituto di Bioimmagini e Fisiologia Molecolare

Diagnosi differenziale della Malattia di Pompe



Rita Nisticò

Università Magna Graecia di Catanzaro
23 novembre 2019

QUALI SONO I SINTOMI DELLA MALATTIA DI POMPE?

SINTOMI NELLA MANIFESTAZIONE TARDIVA DELLA M

POLMONI
- Respirazione difficoltosa
- Insufficienza respiratoria
- Infezioni polmonari
- Apnea notturna
- Sonnolenza
- Mal di testa mattutino

DISTURBI GASTROINTESTINALI
- Difficoltà a masticare e deglutire
- Scarso aumento di peso
- Stitichezza cronica
- Perdita di controllo di vescica o intestino

SCHELETRO E MUSCOLI
- Debolezza muscolare soprattutto agli arti inferiori
- Mal di schiena
- Difficoltà a camminare
- Difficoltà a salire le scale
- Difficoltà nell'attività fisica
- Andatura irregolare
- Irrigidimento delle articolazioni
- Ridotta motilità della colonna
- Scoliosi
- Ritardo nei movimenti
- Scapola alata

Table 1. Neuromuscular disorders with signs and symptoms that mimic Pompe disease.[9,10]

Disorder type	Diagnoses
Dystrophies	Limb-girdle muscular dystrophy
	Dystrophinopathies (Duchenne and Becker muscular dystrophies)
	Myofibrillar myopathy
	Myotonic dystrophy type II
	Scapuloperoneal syndromes
	Danon disease
	X-linked myopathy with excessive autophagy
	Facioscapulohumeral muscular dystrophy
Inflammatory myopathies	Polymyositis myopathies
	Inclusion body myositis
Congenital myopathies	Nemaline rod myopathy
	Central core and multiminicore myopathy
	Centronuclear myopathy
	Hyaline body myopathy
	Other congenital myopathies
Metabolic myopathies	Glycogen storage diseases
	Debranching enzyme deficiency myopathies
	Branching enzyme deficiency
	McArdle disease (late-onset)
	Mitochondrial myopathy
	Lipid disorder myopathies
Motor neuron disorders	Spinal muscular atrophy types II and III
	Kennedy disease
	Amyotrophic lateral sclerosis
Neuromuscular junction Disorders	Myasthenia gravis
	Congenital myasthenic syndromes
	Lambert-Eaton syndrome
Peripheral neuropathy	Hereditary neuropathies
	Chronic inflammatory demyelinating polyneuropathy
	Amyloid neuropathy

MUSCLE &NERVE

Letter to the Editor | Full Access

How common is misdiagnosis in late-onset pompe disease?†

	Incorrect diagnosis	Correct diagnosis
N	11 (4 males)	12 (5 males)
Mean age at symptom onset (years)	33.3 ± 16 (95% CI 21–40)	40.4 ± 11 ($P = 0.35$) (95% CI 33–47)
Mean year of symptom onset	1988 (range 1983–2008)	1993 ($P = 0.35$) (range 1975–2008)
Mean time to diagnosis from symptom onset (years)	10.5 ± 10.7 (95% CI 2.6–18.6)	2.5 ± 2.3 ($P = 0.009$) (95% CI 0.24–3.76)
Mean maximum CK level (reference: 30–220 U/L)	540 ± 415 U/L (95% CI 261–818)	403 ± 278 U/L ($P = 0.18$) (95% CI 216–590)
Prior incorrect diagnosis and presenting symptoms	Deconditioning (1)*	Low back pain, leg weakness
	Lumbar radiculopathy (1)*	Dyspnea, leg weakness
	Lupus (1)	Limb weakness
	Muscle strain (1)	Low back pain, leg weakness
	Musculoskeletal disease (1)	Difficulty running
	Obstructive sleep apnea (1)*	Exercise intolerance, headaches
	Polymyalgia rheumatica (1)	Leg weakness, myalgias
	Polymyositis (1)*	Difficulty walking
	Polymyositis + fibromyalgia (1)*	Leg weakness, myalgias
	Postpolio syndrome (1)*	Low back pain, leg weakness
	Psychogenic weakness (1)*	Leg weakness, myalgias

*Diagnosis made by a neurologist.

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Late Onset Glycogen Storage Disease Type II: Pitfalls in the Diagnosis

G.K. Papadimas K. Spengos C. Papadopoulos P. Manta

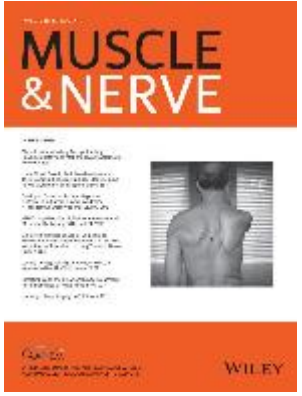
Patient No.	Age at first symptoms decades	Misdiagnosis	Age at GSD-II diagnosis years	Mutation	GAA in fibroblasts nmoles/mg/min (normal: 0.29–6.23)	GAA in muscle, PH:4 nmoles/g/min	
						maltose (normal: 75.7–131.1)	MU&G (normal: 3.1–5.5)
1	2rd	hypothyroid myopathy	45	IVS1–13 T>G (homozygous)	0.21	NP	NP
2	4th	connective tissue disorder	60	IVS1–13 T>G ?	0.20	NP	NP
3	2nd	liver disease	32	IVS1–13 T>G and c.2071_2072insAGCCG	0.20	NP	NP
4	1st	muscular dystrophy	31	NP	NP	33.8	1.21

Case 1

- Donna di 41 anni obesa presentava dall'adolescenza facile faticabilità a salire e scendere le scale. Ipotiroidea, B bloccanti per ipertensione, statine per iperocolesterolemia.
- Esami di laboratori: ipercpkemia, aumento enzimi epatici.
- Biposia di muscolo: segni aspecifci.
- Diagnosi di Miopoatia da ipotiroidismo
- la paziente presentava una marcata ipostenia prossimale prevalentemente agli arti inferiori.
- Con un ritardo di circa 20 anni fu confermata la diagnosi di malattia di Pompe

Case 2

- Donna di 45 anni con ipostenia prossimale,
- Facile faticabilità, ptosi palpebrale dx
- Lieve ipercpkemia, PCR elevata, FR positivo.
- Biopsia di muscolo: aspecifica
- Diagnosi di di connettivite in trattamento con steroidi
- All'età di 59 anni presentava insufficienza respiratoria con ipostenia diaframmatica
- Seconda biopsia di muscolo: segni di miopatia metabolica
- Diagnosi di Malattia di Pompe



CASES OF THE MONTH

POMPE DISEASE, THE MUST-NOT-MISS DIAGNOSIS: A REPORT OF 3 PATIENTS

ALBERTO DUBROVSKY, MD,[1] JOSE CORDERI, PT,[1] THEODORA KARASARIDES, BA,[2] and ANA LIA TARATUTO, MD, PhD[3]

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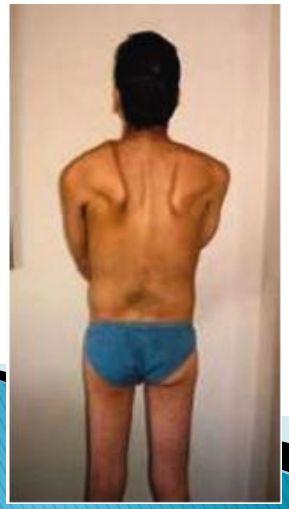
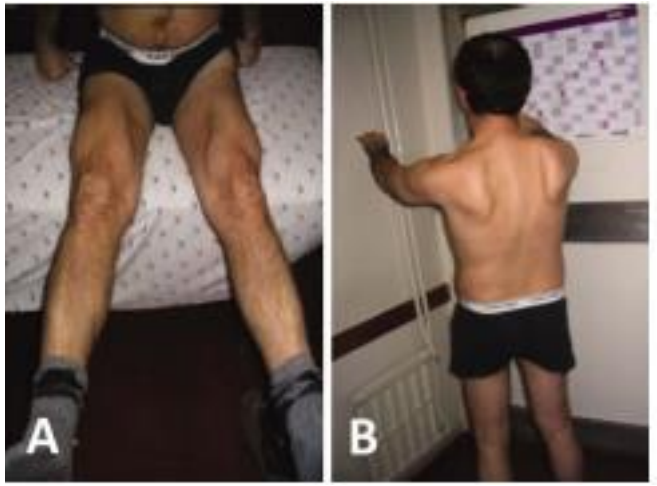
[3]Department of Neurology, Institute of Neurological Research, FLENI, Buenos Aires, Argentina

Accepted 19 August 2012

- 45-year-old male initially diagnosed with unspecified limb girdle muscle dystrophy. Diagnostic delay: 13 years.
- 40-year-old male misdiagnosed with unspecified limb girdle muscle dystrophy with respiratory involvement. Diagnostic delay: 10 years.
- 78-year-old female initially diagnosed with possible mitochondrial myopathy due to eyelid ptosis and muscle weakness. Diagnostic delay: 30 years





Molecular Genetics and Metabolism xxx (2015) xxx–xxx

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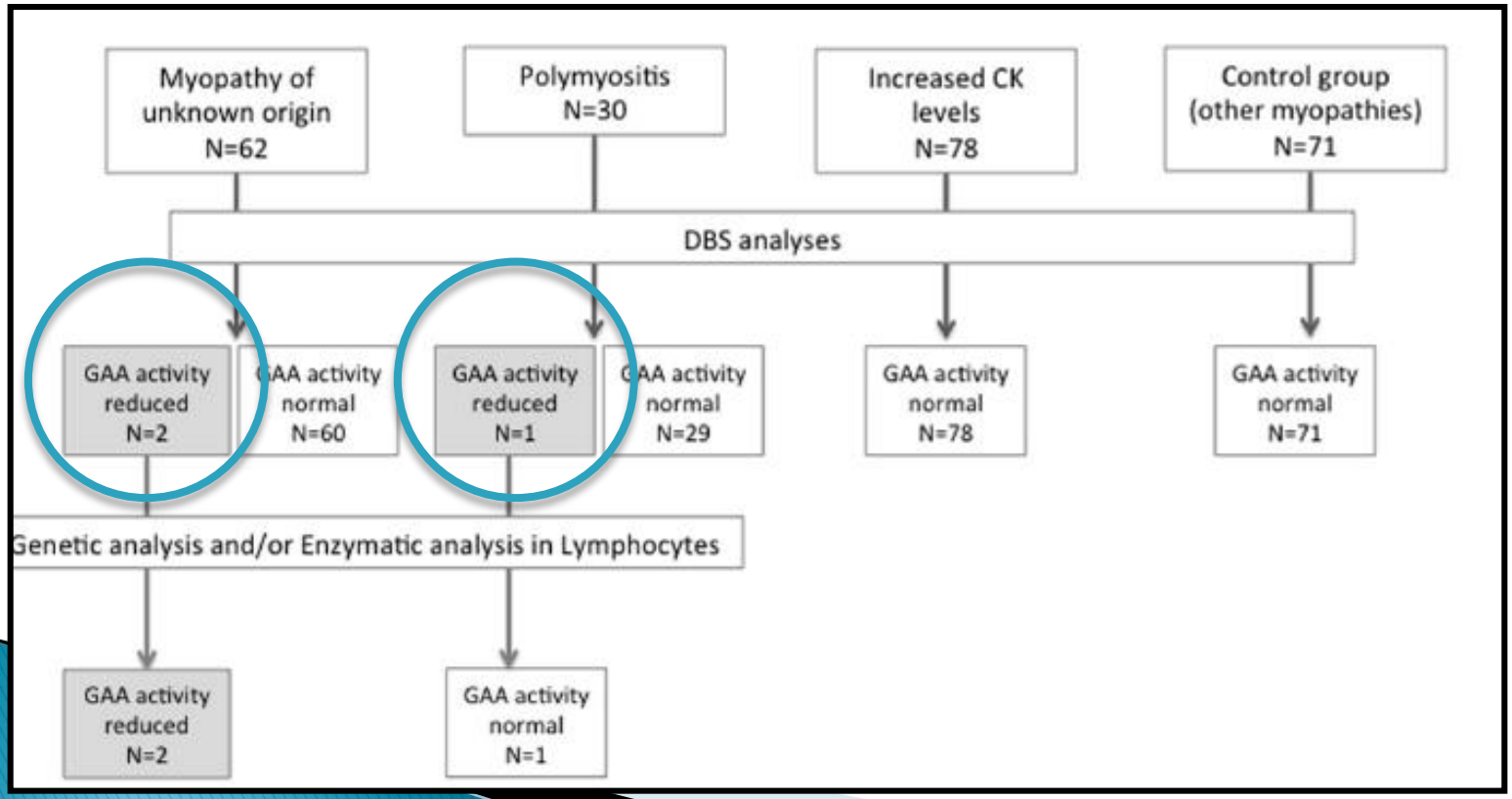
Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Delayed diagnosis of late-onset Pompe disease in patients with myopathies of unknown origin and/or hyperCKemia



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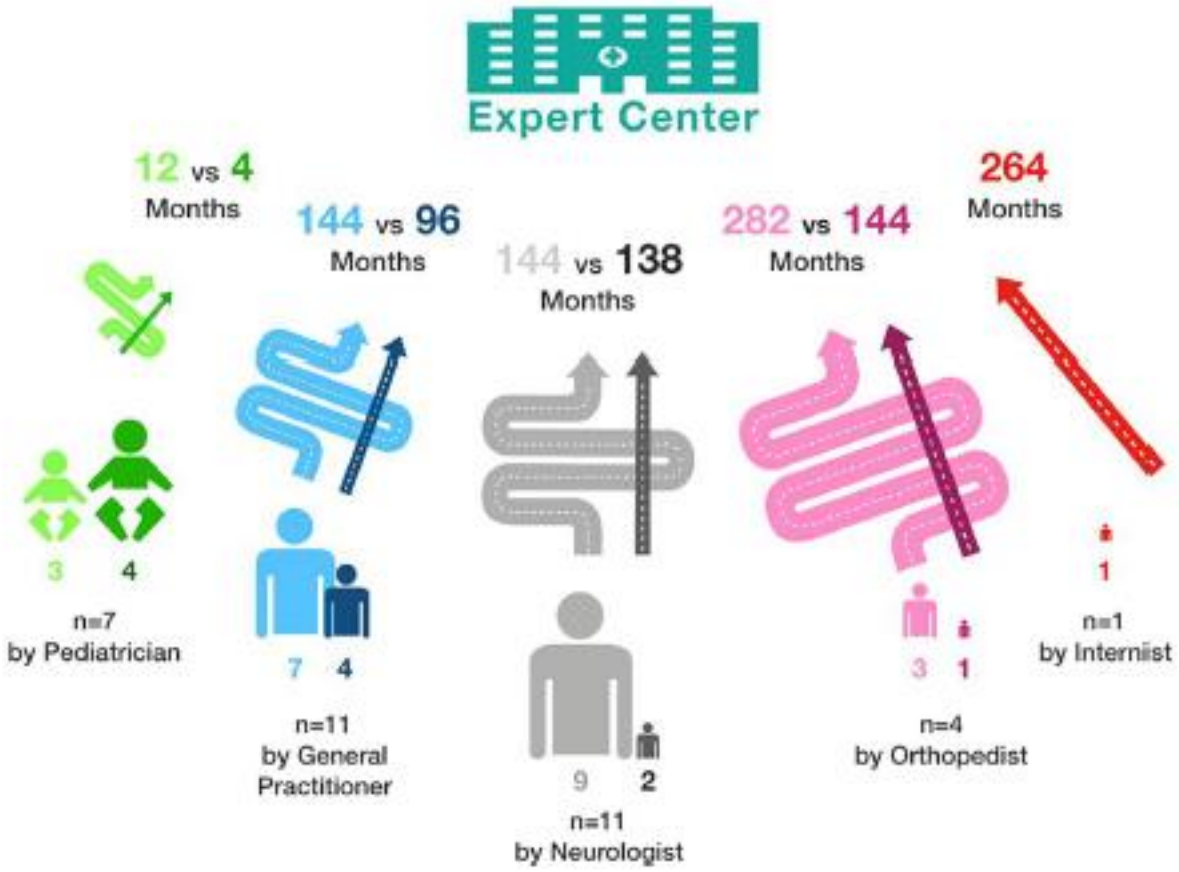
journal homepage: www.elsevier.com/locate/ymgme

• 63-year-old female initially diagnosed with limb girdle muscle dystrophy at 37 years/old due to proximal muscle weakness, myopathic gait, dysphagia.

• 61-year-old female initially presented proximal muscle weakness in arms and lower limbs.
Diagnostic delay was 9 years.

JIMD REPORTS SSIEM WILEY

Extent, impact, and predictors of diagnostic delay in Pompe disease: A combined survey approach to unveil the diagnostic odyssey



RESEARCH PAPER

LOPED study: looking for an early diagnosis in a late-onset Pompe disease high-risk population

Multicenter observational study by the "Italian Group for the Study of Glycogen storage disease type II“ (Italian Association of Myology, AIM) designed to evaluate the prevalence of GSD II in a large population of patients at high risk for the disease, by means of different biochemical DBS methods:
-Fluorimetric technique
-Tandem mass spectrometry

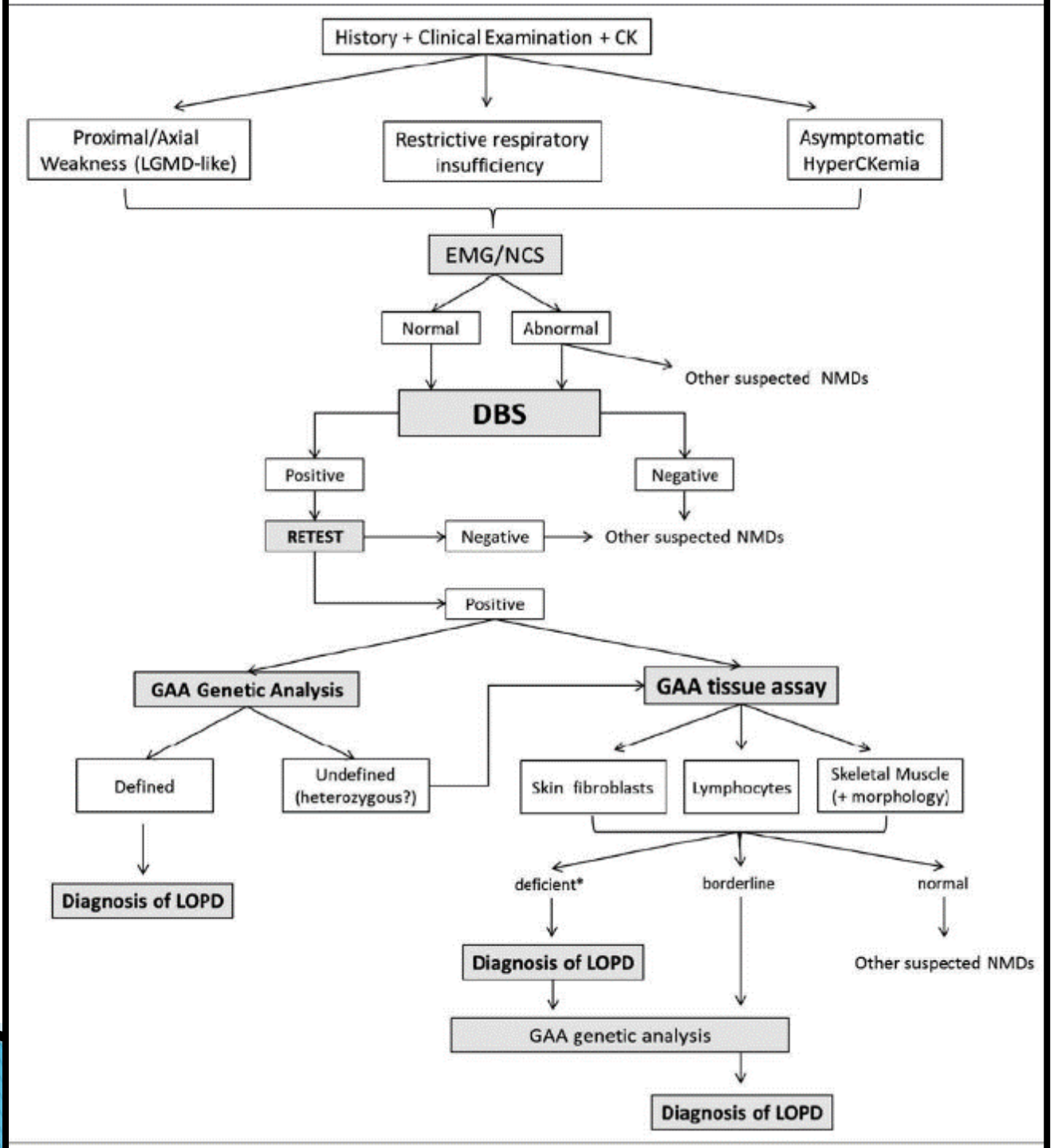
17 pazienti positivi con deficit biochimico confermato

Musumeci O, *et al. J Neurol Neurosurg Psychiatry* 2016;87:5–11. doi:10.1136/jnnp-2014-310164

Table 3 Summary of demographic and clinical features of the 17 patients with LOPD

	Patients (n=17)
Age, years, mean (SD)	40±14.36
Gender, n (%)	
Female	9 (52)
Male	8 (47)
Clinical presentation, n (%)	
Isolated hyperCKaemia	5 (29.4)
HyperCKaemia+LGMW	11 (64.7)
LGMW	1 (5.9)
Timing of diagnosis, years, median (IQR)	5 (2.5–10)
BMI, mean (SD)	25.2±5.8
Serum CK, mean (SD)	600±302
Muscle biopsy, n (%)	
Vacuolar myopathy	11 (64.7)
Unspecific changes	6 (35.2)
Muscle GAA %, mean (SD)	9.4±3.8
EMG, n (%)	
Myogenic pattern	10 (58.8)
Normal	7 (41.1)
MRI findings, n (%)	
Abnormal	14 (82.3)
Normal	3 (17.6)
%Predicted FVC, mean (SD)	73±11
6MWT, mean (SD)	452±9
ERT, n (%)	
Yes	14 (82.3)
No	3 (17.6)

6MWT, 6 min walk test; BMI, body mass index; CK, creatine kinase; EMG, electromyography; ERT, enzyme replacement therapy; FVC, forced vital capacity; GAA, acid α-glucosidase; LGMW, limb-girdle muscle weakness; LOPD, late-onset Pompe disease.


History + Clinical Examination + CK
Proximal/Axial Weakness (LGMD-like)
Restrictive respiratory insufficiency
Asymptomatic HyperCKemia
EMG/NCS
Normal
Abnormal
Other suspected NMDs
DBS
Positive
Negative
RETEST
Negative
Other suspected NMDs
Positive
GAA Genetic Analysis
GAA tissue assay
Defined
Undefined (heterozygous?)
Skin fibroblasts
Lymphocytes
Skeletal Muscle (+ morphology)
Diagnosis of LOPD
deficient*
borderline
normal
Diagnosis of LOPD
Other suspected NMDs
GAA genetic analysis
Diagnosis of LOPD

Quando inviare il paziente?

Proximal/axial weakness

(LGMD-like)

The combination of paravertebral and abdominal muscle involvement

Asymptomatic HyperCKemia

Restrictive Respiratory insufficiency