DIFFERENTIAL DIAGNOSIS FROM LIMB-GIRDLE MUSCULAR DYSTROPHIES

Marianne de Visser
Dept. of Neurology
Amsterdam University Medical Centre
Amsterdam, The Netherlands
m.devisser@amsterdamumc.nl

Disclosure

- On site PI Pharnext (CMT)
- Co-investigator FORCE trial (postpolio syndrome)
- Member Adjucation Committee Bristol-Myers Squibb Company (myositis), member Data Safety Monitoring Board Novartis
- Chair International Sata Monitoring Committee Dynacure

Learning objectives

At the end of this lecture

- the learner is able to make a differential diagnosis if a patient presents with limb-girdle syndrome
- the learner is able to diagnose the most frequent causes of limb-girdle syndrome

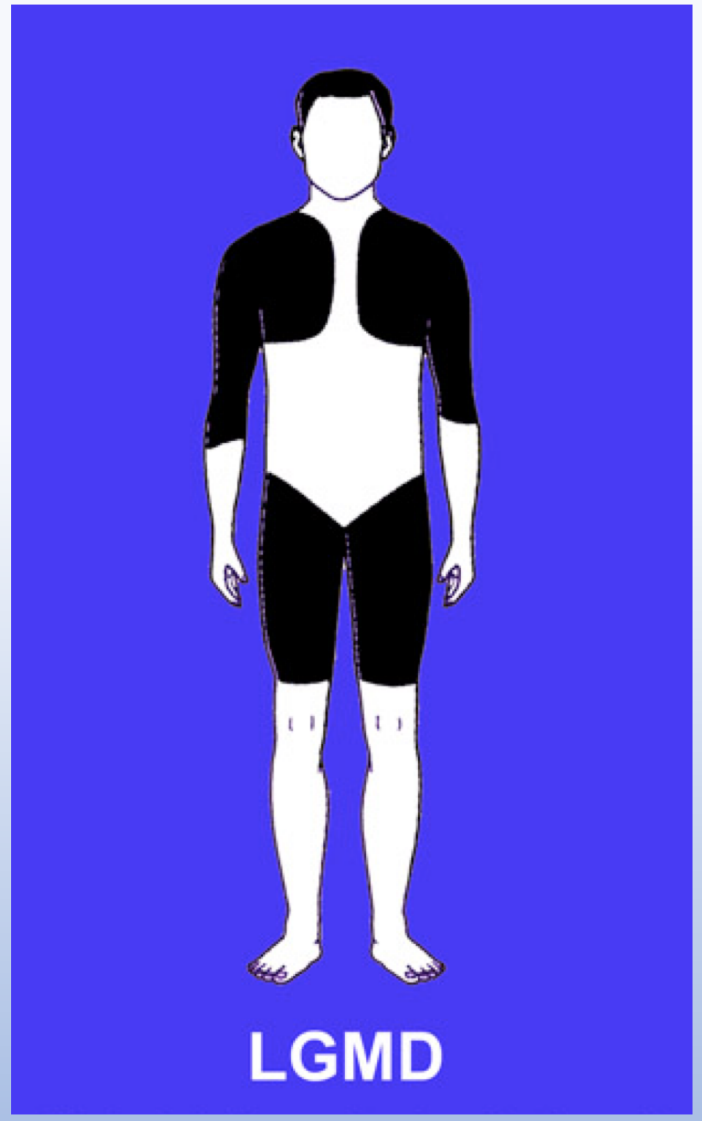
Limb Girdle Muscular Dystrophies – Nomenclature and reformed Classification

Date: 17-19th March 2017

To reassess the nomenclature of the limb girdle muscular dystrophies (LGMD)

EUROPEAN NEURO MUSCULAR CENTRE

Consensus on the term LGMD



The term ‘limb girdle’ is used to describe these disorders because the muscles most severely affected are generally those of the hip and shoulders – the limb girdle muscles

Creatine kinase activity is elevated

Proposed subtype classification:
"LGMD, inheritance (R or D), order of discovery (number), affected protein"

LGMD D

LGMD D1 DNAJB6-related
LGMD D2 TNPO3-related
LGMD D3 HNRNPDL-related
LGMD D4 calpain 3-related
LGMD D5 collagen 6-related

LGMD R

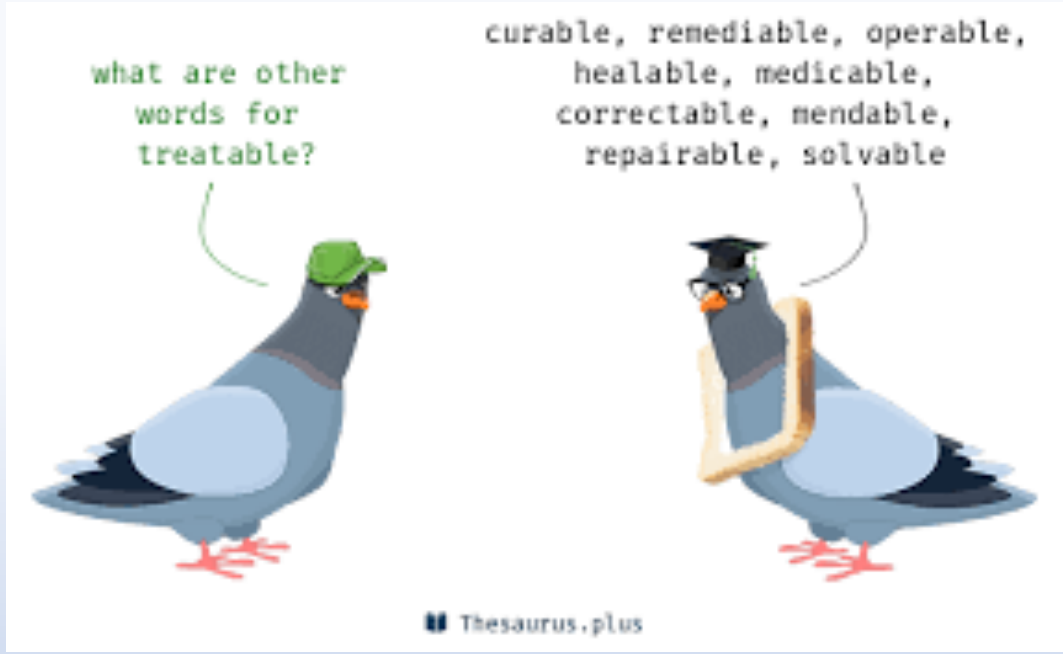
LGMD R1	calpain 3-related
LGMD R2	dysferlin-related
LGMD R3	α-sarcoglycan-related
LGMD R4	β-sarcoglycan-related
LGMD R5	γ-sarcoglycan-related
LGMD R6	δ-sarcoglycan-related
LGMD R7	telethonin-related
LGMD R8	TRIM32-related
LGMD R9	FKRP-related
LGMD R10	titin-related
LGMD R11	POMT1-related
LGMD R12	anoctamin 5-related
LGMD R13	fukutin-related
LGMD R14	POMT2-related
LGMD R15	POMGnT1 -related
LGMD R16	dystroglycan-related
LGMD R17	plectin-related
LGMD R18	TRAPPC11-related
LGMD R19	GMPPB-related
LGMD R20	ISPD-related
LGMD R21	POGLUT1-related
LGMD R22	collagen 6-related
LGMD R23	laminin α2-related
LGMD R24	POMGnT2-related

Mimics of LGMD (proximal muscle weakness + hyperCKemia)

Inherited

Spinal muscular atrophies (types 3 and 4)
Metabolic myopathies
- Pompe disease - TREATABLE
- Mitochondrial myopathies

Myotonic dystrophy type 2
Facioscapulohumeral muscular dystrophy
Emery-Dreifuss muscular dystrophy



Acquired - TREATABLE

Idiopathic inflammatory myopathies (inclusion body myositis only symptomatic treatment)
Drug-induced myopathies
Endocrine myopathies (e.g. hypothyroid myopathy)

SMA is currently a treatable disease

- In December 2016 the U.S. Food and Drug Administration approved nusinersen (Spinraza™) as the first drug approved to treat children and adults with SMA (increases production of the full-length SMN protein). EMA followed in April 2017.
- In August 2020, the FDA approved the orally-administered drug risdiplam (Evrysdi) to treat patients age two months of age and older with SMA, including SMA type 3. Recommended for approval by EMA in February 2021.

J Neurol. 2021 Mar;268(3):923-935. doi: 10.1007/s00415-020-10223-9. Epub 2020 Sep 15.

Nusinersen treatment significantly improves hand grip strength, hand motor function and MRC sum scores in adult patients with spinal muscular atrophy types 3 and 4

Bram De Wel [1 2], Veerle Goosens [3], Atka Sobota [4], Elke Van Camp [4], Ellen Geukens [5], Griet Van Kerschaver [5], Marlène Jagut [6], Kathleen Claes [7 8], Kristl G Claeys [9 10]

Affiliations + expand

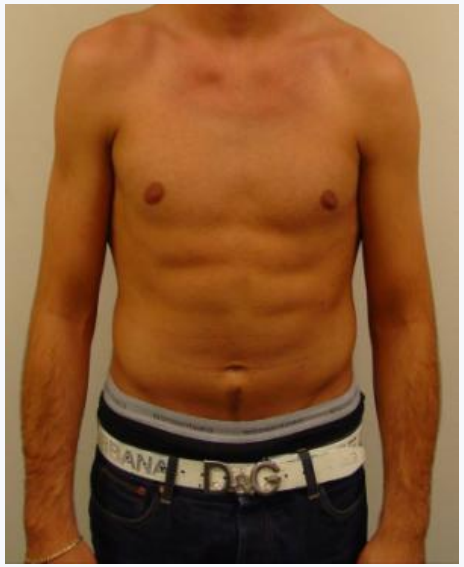
brain sciences

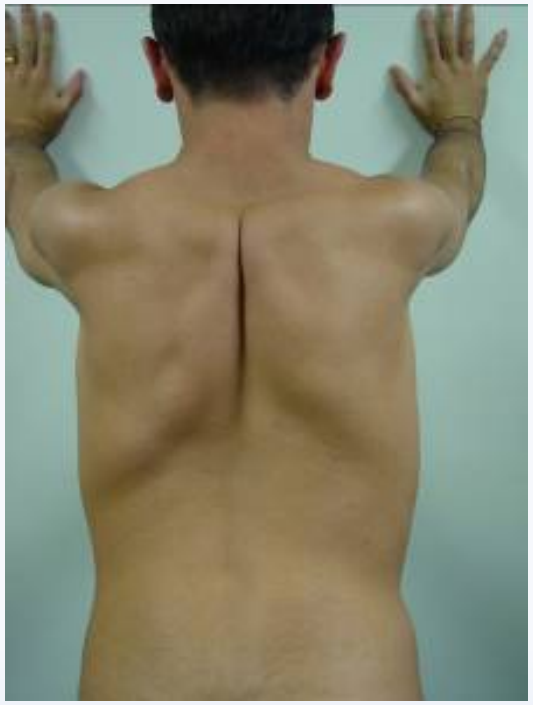
MDPI

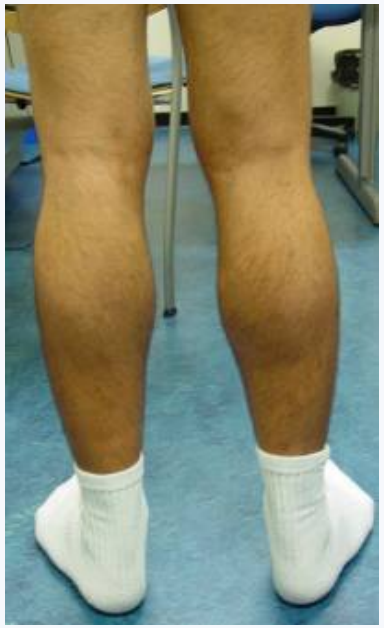
Article

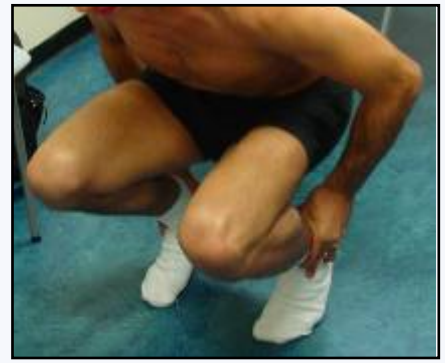
Nusinersen Wearing-Off in Adult 5q-Spinal Muscular Atrophy Patients

Alma Osmanovic *, Olivia Schreiber-Katz and Susanne Petri







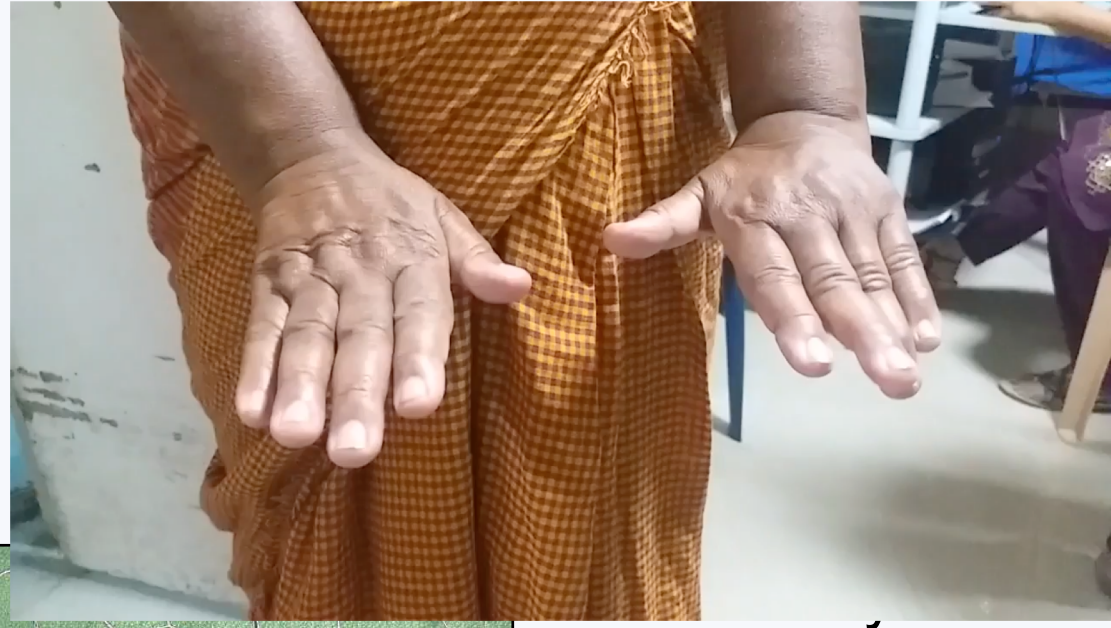


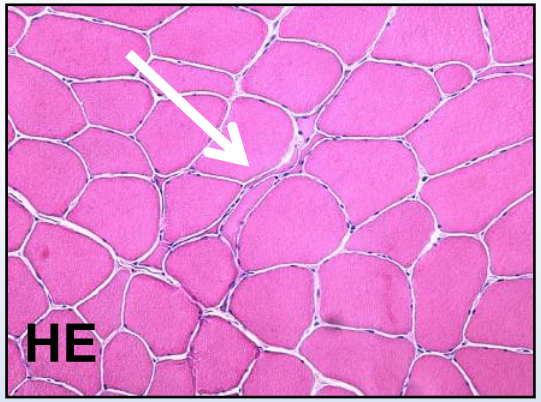
20 y/o male
Hx/ Since 2 years progressive weakness of shoulder girdle and upper leg muscles
Previous hx not relevant
Family history negative

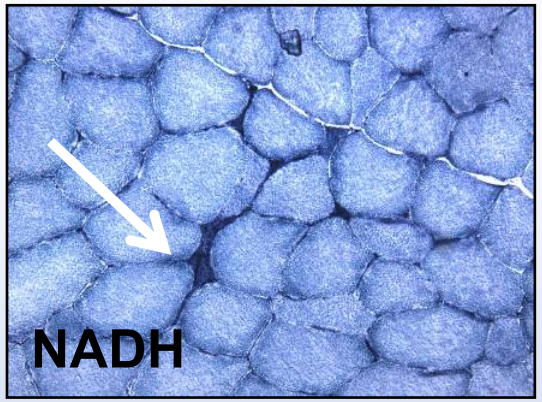
Ex/

- Wasting/weakness of shoulder girdle muscles
- Positive Gowers'sign
- Hypoactive knee jerks
- Tremor hands

Ancillary investigations
sCK 25 x upper limit of normal
Muscle CT: no abnormalities
EMG was not done
Muscle biopsy:







deletion exon 7
SMN gene

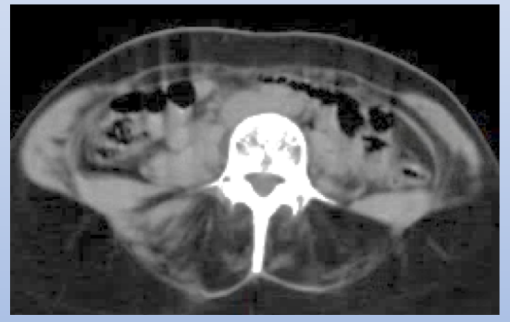
Diagnosis: SMA type 4 (25 x elevated sCK is unusual,
but has been described (Yiu et al. Muscle Nerve 2008;38:930).

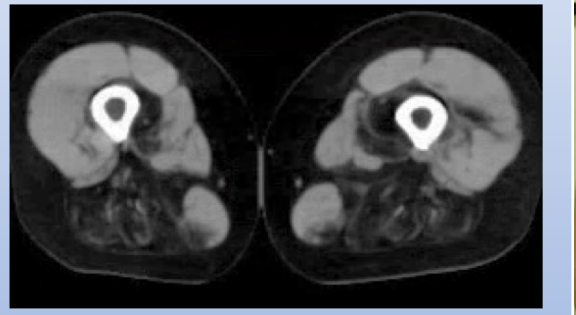
Take-away: Tremor of hands (polyminimyoclonus) is characteristic of SMA

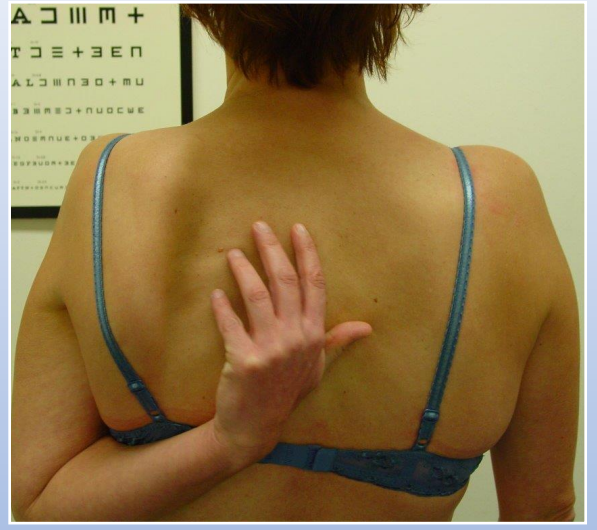
Late onset Pompe disease

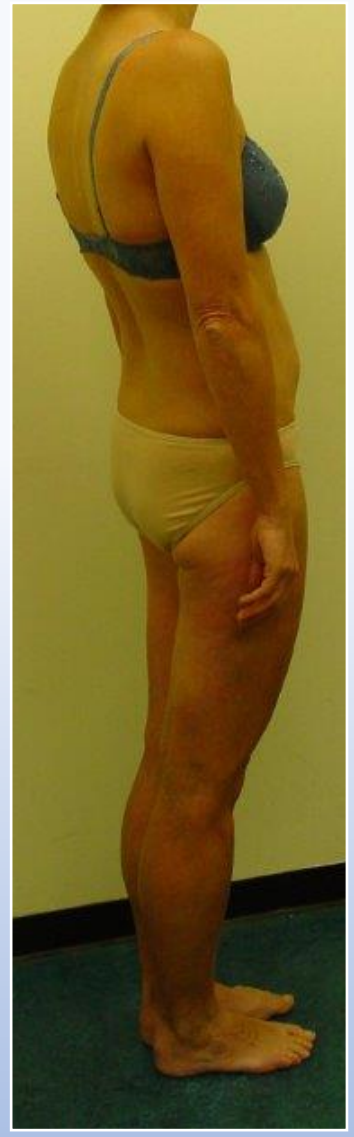
51 y/o female
Hx/ ~ 2 years difficulty getting up the stairs and mounting a horse. In retrospect, symptoms may have been present since age 40 years.
Fam hx: 9 sibs (eldest sister same problems?)

Ex/ Positive Gowers' phenomenon
Weakness pelvic girdle and thigh muscles
Scapulae alatae





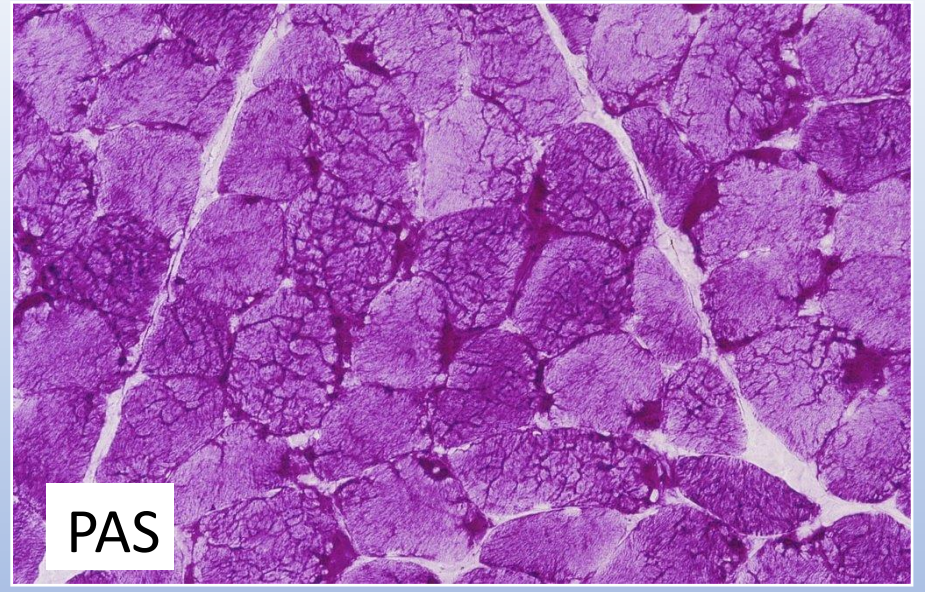




Late onset Pompe disease

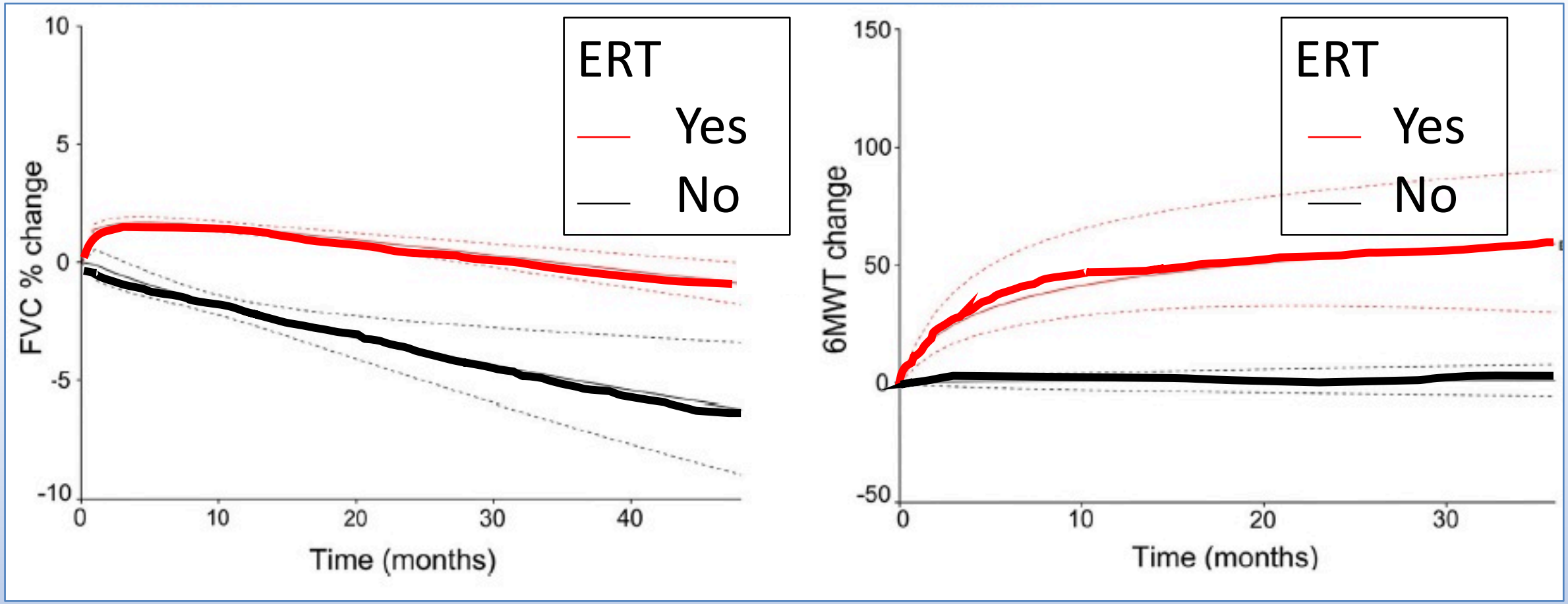
CK: 5 x ULN
Muscle bx: glycogen accumulation in vacuoles
Deficiency of acid maltase in leukocytes: 21 (N 60-250)
DNA analysis: compound heterozygote for c.IVS1-13T>G and C.379-380delTG (p.Cys127fs) mutations in the GAA gene

Approach after diagnosis:
Lung function was measured
and ERT was provided



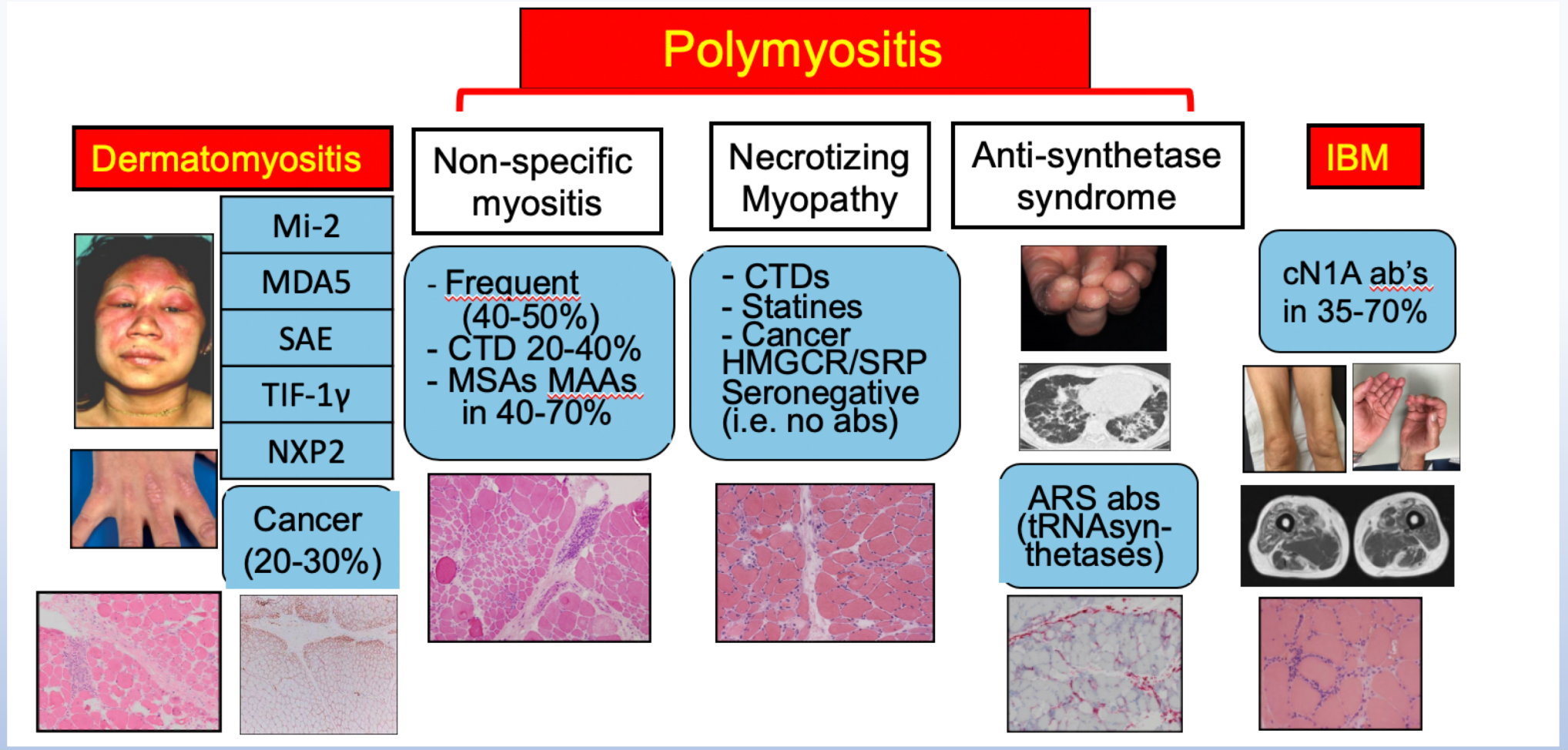
Beneficial effect of Alglucosidase alfa

in Late onset Pompe Disease



Schoser et al. J Neurol 2017

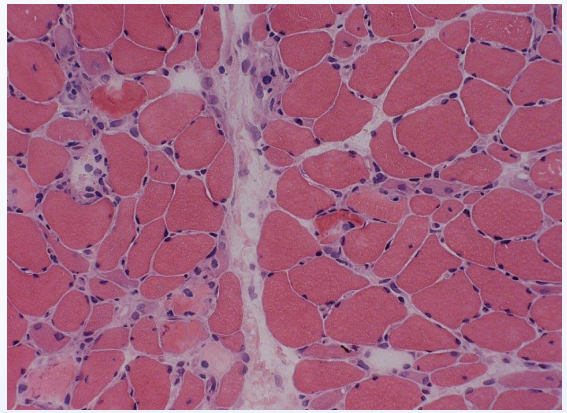
Idiopathic inflammatory myopathies

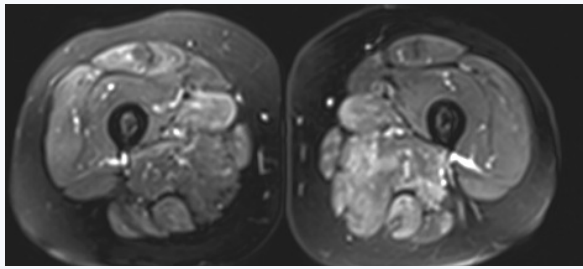


Immune-mediated necrotizing myopathy

61 y/o woman

Hx/ Progressive limb-girdle muscle weakness since ~4 months and difficulty swallowing





Ex/ Weakness limb-girdle muscles

- CK 9982 IU/L
- Positive antibodies against 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR)

Treatment: pulsed high dose dexamethasone (6 months, one cycle/month) and muscle weakness resolved.

Myositis or muscular dystrophy?

17 y/o girl

- Slowly progressive muscle weakness ~ 1 year
- No swallowing difficulty
- Family history not contributory

Ex:

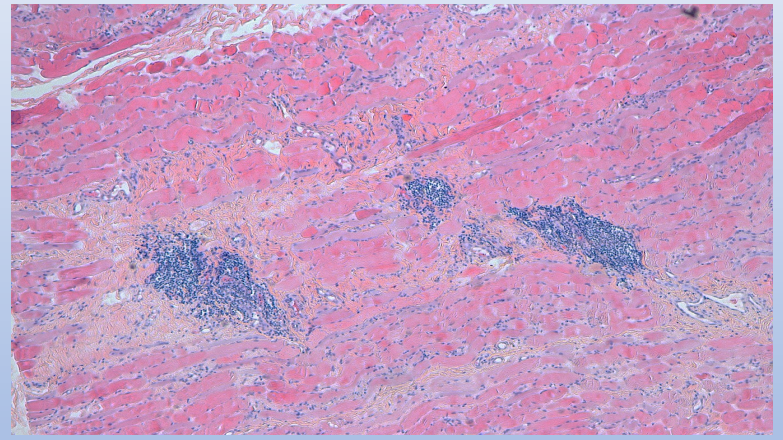
- Weakness neck flexors and proximal muscles MRC grade 3
- Positive Gowers' phenomenon (not able to get up from a squat), waddling gait, scapular winging
- Slight contractures elbows, wrists
- No skin changes

Ancillary investigations

- CK : 14.467 IU/L
- Muscle CT: no abnormalities
- EMG: myopathic

DD
- Limb girde muscular dystrophy
- Myositis

- Muscle biopsy:



Myositis may mimic muscular dystrophy

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Neuromuscular Disorders 24 (2014) 335–341

NMD

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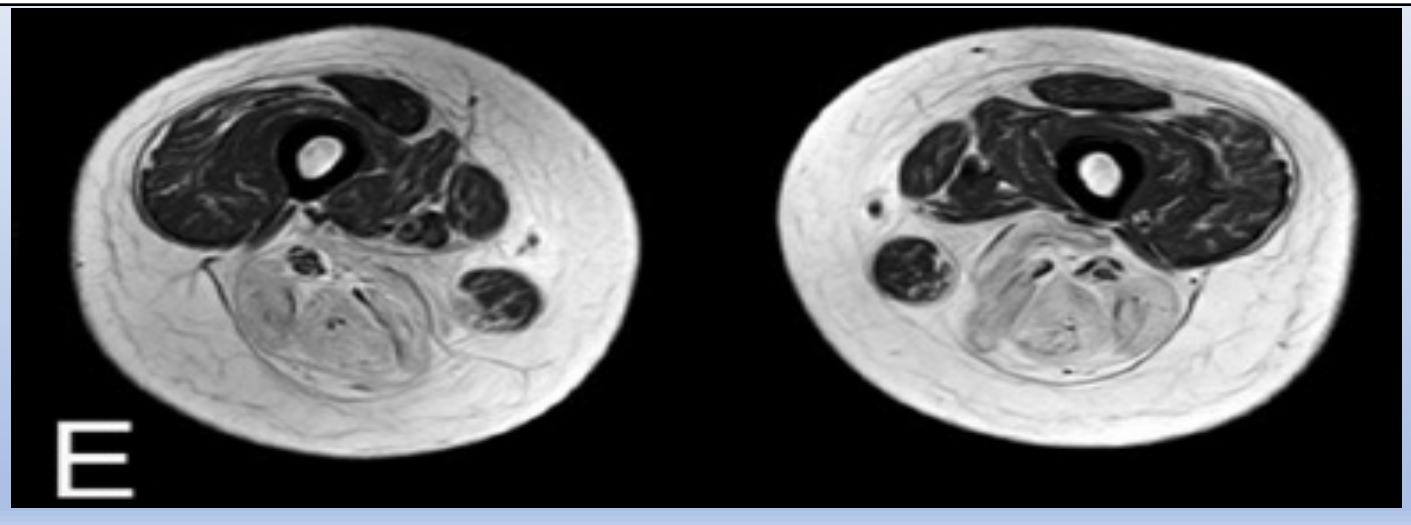
Myopathy with anti-signal recognition particle antibodies: Clinical and histopathological features in Chinese patients ☆

Lu Wang, Linlin Liu, Hongjun Hao, Feng Gao, Xiao Liu, Zhaoxia Wang, Wei Zhang, He Lv, Yun Yuan *



A puzzling case

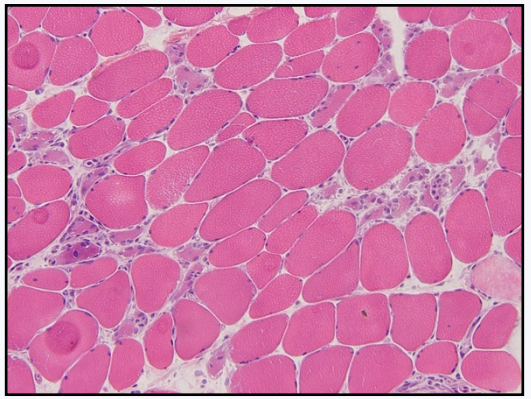
Hx/

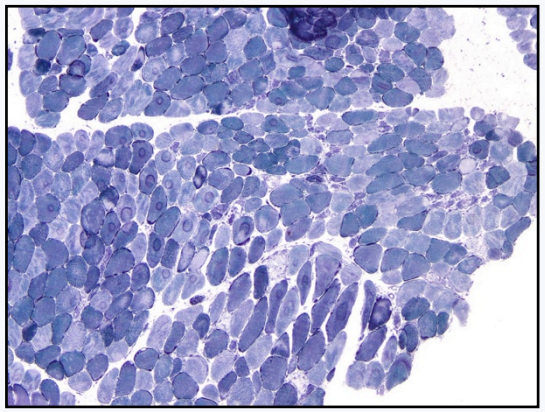
- 41-year-old male with a 6-month history of exercise-related muscle pains, cramps, and muscle weakness
- Past medical history unremarkable
- Family history negative for neuromuscular disorders

Ex/

- Slight wasting and weakness of shoulder girdle muscles
- Increased lumbar lordosis, positive Gowers' phenomenon
- Firm calves
- Normal sensation. Normal reflexes

Ancillary investigations





- Serum CK activity 3530 IU/L
  (N < 130)
- Biopsy from quadriceps muscle
- Acid maltase activity in leucocytes: normal
- DNA analysis for various genes: no pathogenic variants

Course of the disease

- Increase in muscle weakness; nasal dysarthria; sleep-apnea syndrome
- Markedly increased TSH (185 mE/L, normal 0.4-4) and free T4 < 2mE/L (N 10-23)
- Anti-thyroid peroxidase antibodies present

Dx/ Auto-immune thyroiditis manifesting with hypothyroidism and myopathy

Myopathy and hypothyroidism

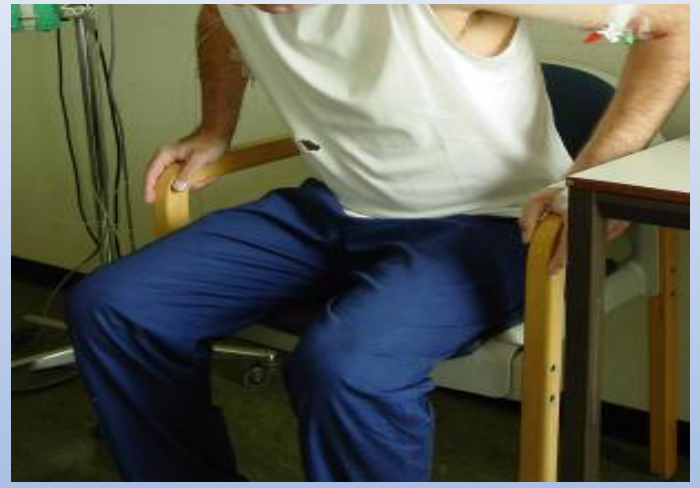
- 79%, including
  - weakness (54%)
  - fatiguability, muscle pain, stiffness or cramps (42%)

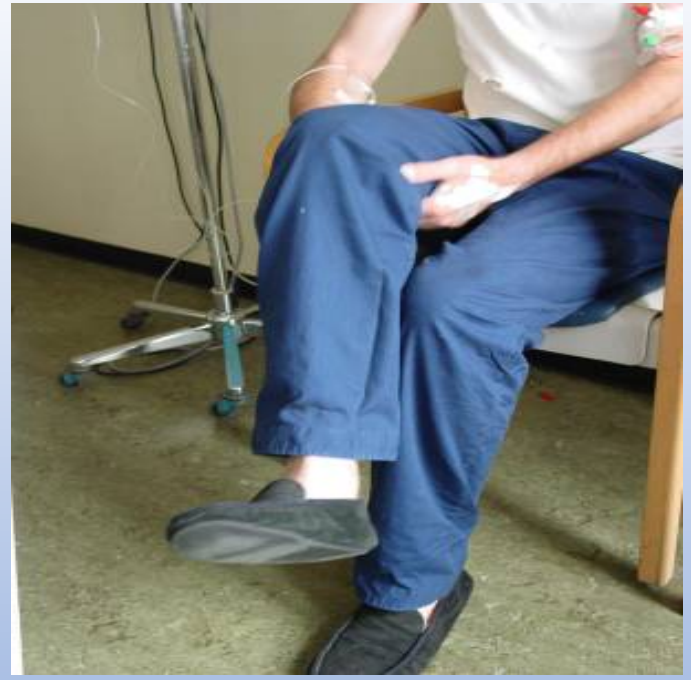
- Detectable proximal muscle weakness (37%)
- Few cases of myxoedema or rhabdomyolysis

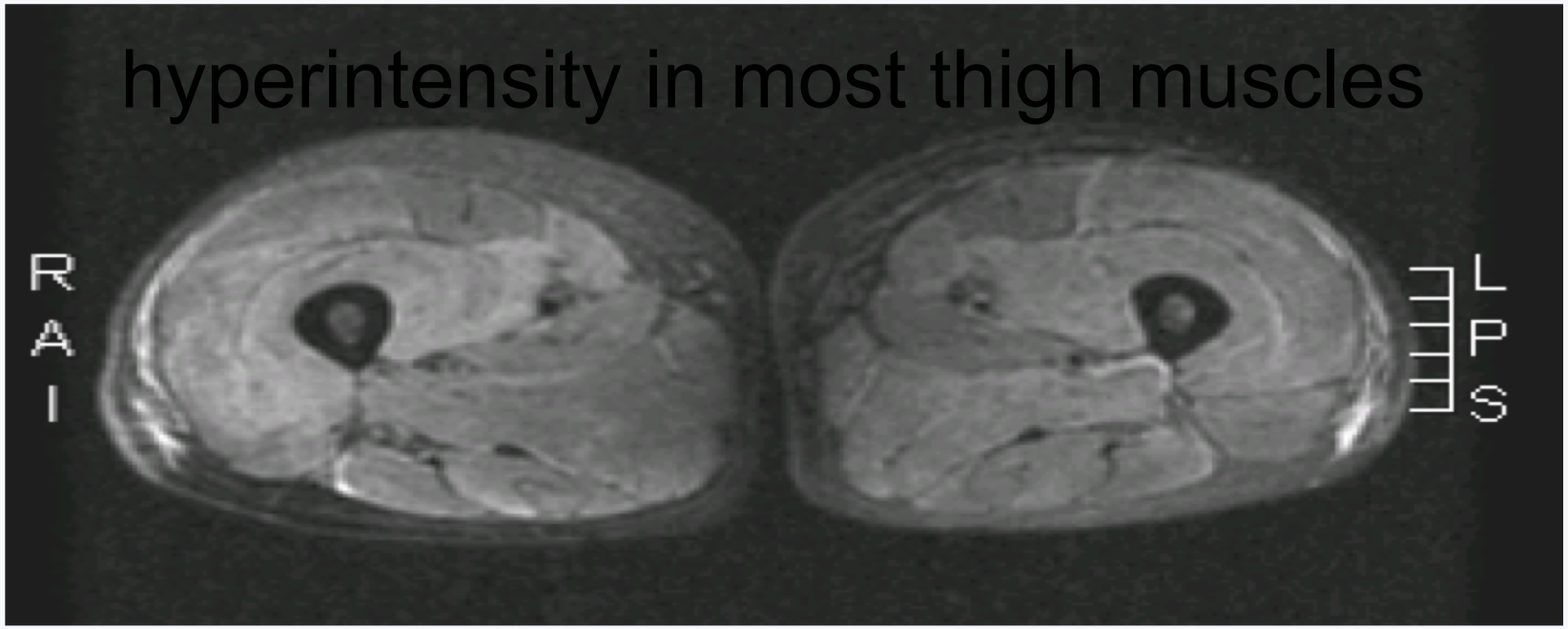
  (Scott et al. Muscle Nerve 2002)

Drug-induced myopathy

47 y/o man developed proximal weakness and myalgia over a period of two weeks.
Ex/ proximal muscle weakness, legs > arms.
sCK > 30.000 IU/L
Medication: Simvastatin and Gemfibrozil







Dx: rhabdomyolysis

Withdrawal of this medication led to normalisation of sCK and improvement of muscle strength.

Statin myopathy

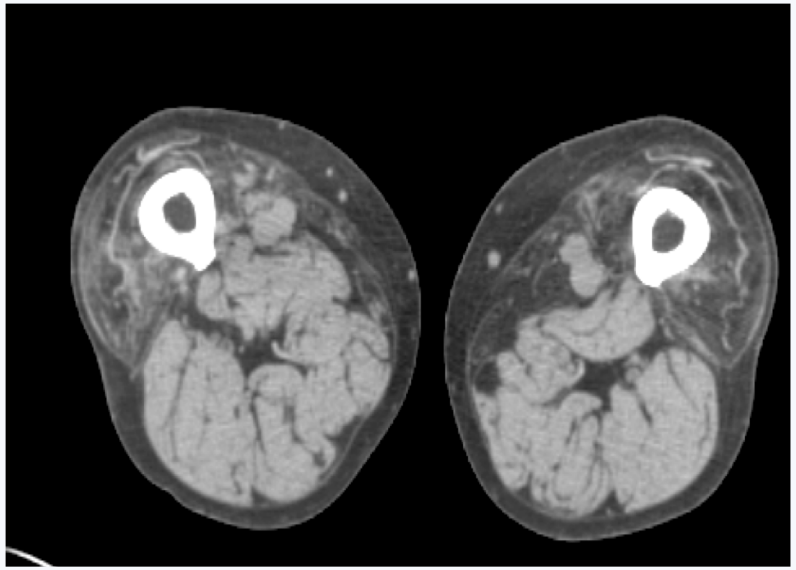
- Asymptomatic hyperCKemia
- Myalgia (usually ↑ CK)
- Self-limited statin myopathy
- Rhabdomyolysis – rare, but occurs more frequently when a statin is used with gemfibrozil, a medication that likely has a direct toxic effect on muscles.
- Immune-mediated necrotising myopathy (rare)

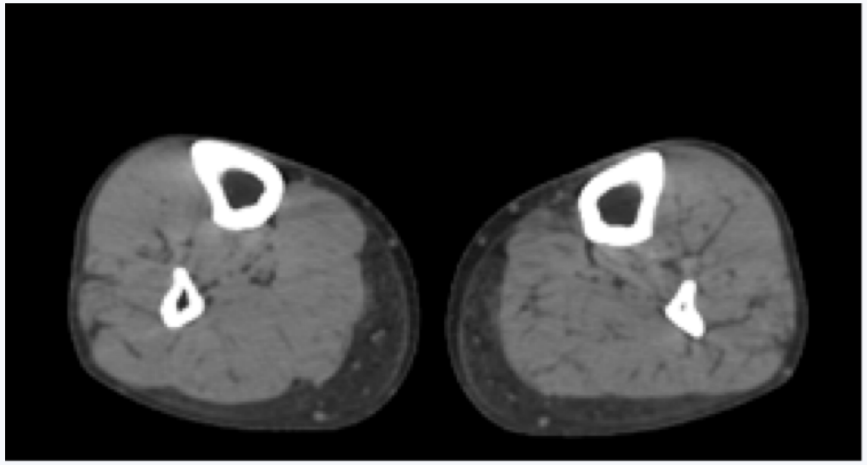
Inclusion body myositis – presentation with proximal muscle weakness

Male, 57 y/o
Hx: Since ~ 5-6 years progressive muscle weakness of thighs.
No dysphagia. Previous and family history: not relevant.

Ex/ severe wasting and weakness quadriceps muscles.
Weakness of the iliopsoas
Slight weakness of the facial muscles.
Positive Gowers phenomenon. muscles.

CK 2 x ULN
EMG: spontaneous muscle activity quadriceps and gastrocnemius

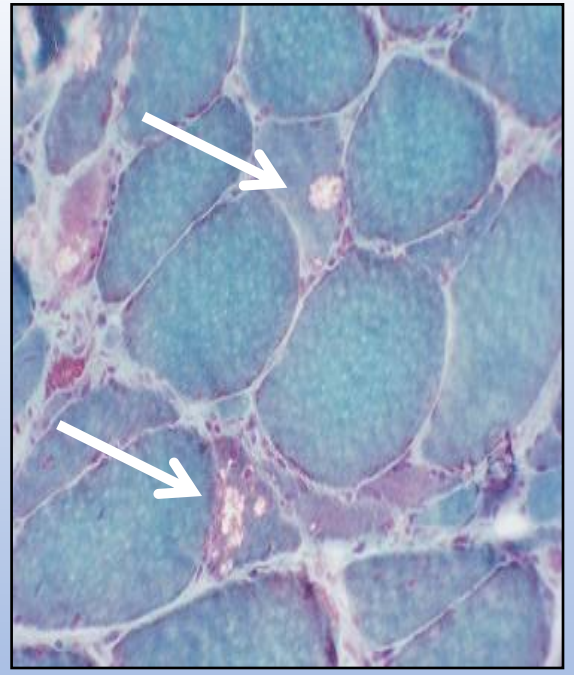




Muscle bx: consistent with IBM
Serology: positive anti-cN1A auto-antibodies

Dx: Inclusion body myositis

Follow-up: Progressive dysphagia



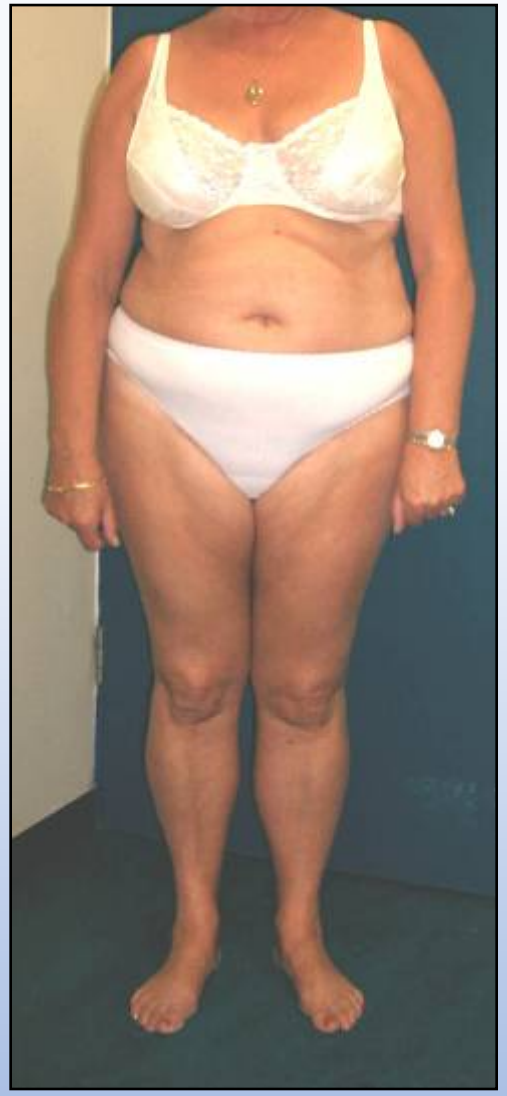
Myotonic dystrophy type 2:
Family history is crucial for diagnosis

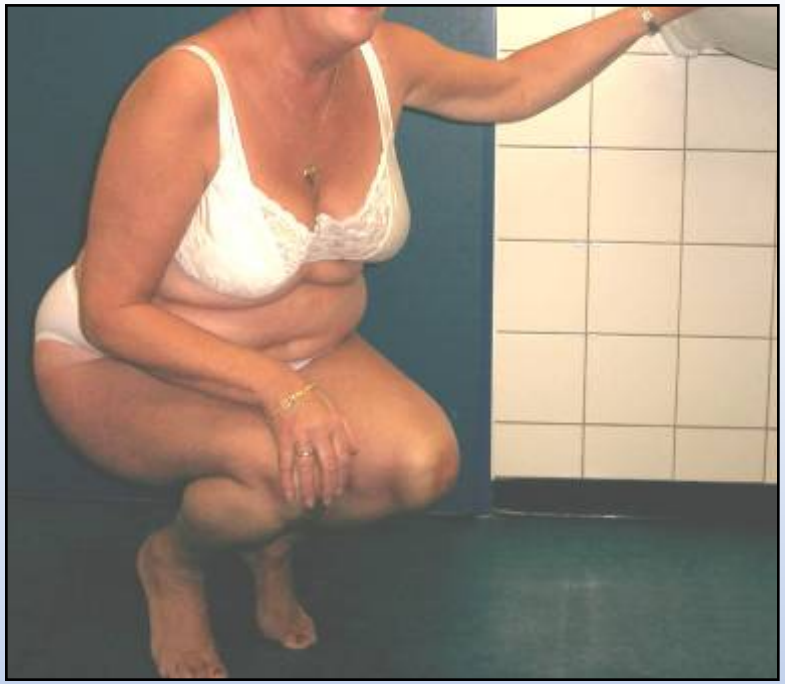
60 y/o female

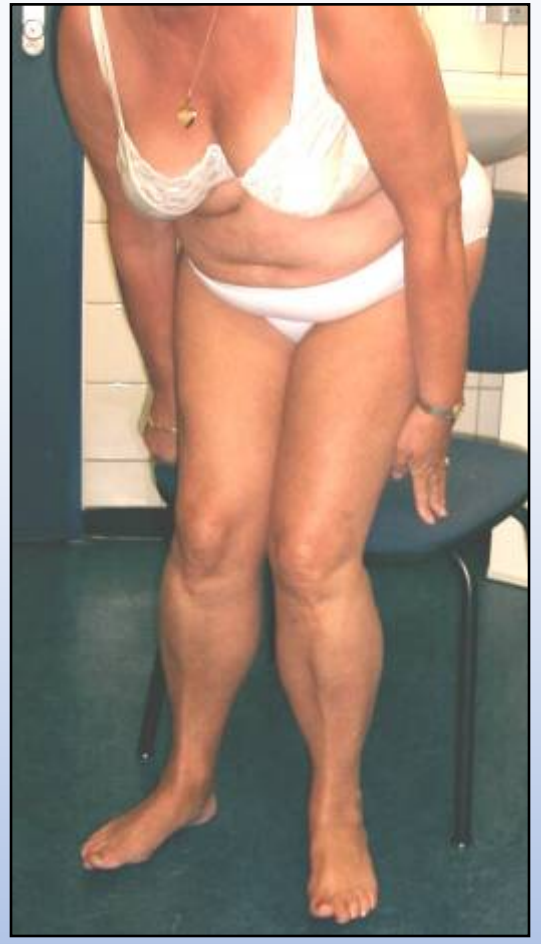
- Muscle weakness from age 50 years onwards
- In particular difficulty with climbing stairs
- Exercise-induced myalgia
- Cataract surgery at age 58 years

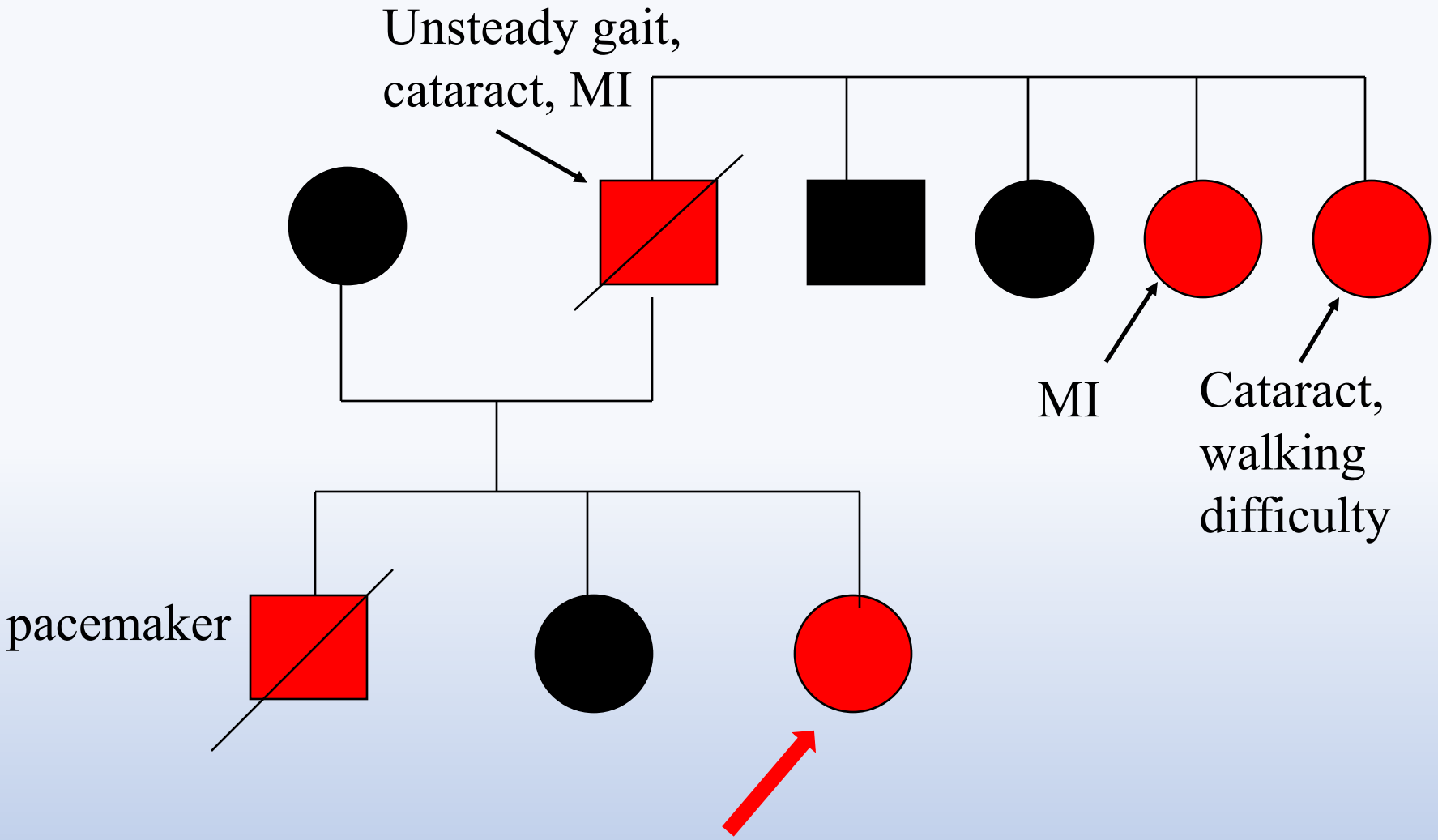
Ex/

- Limb-girdle muscle weakness
- Firm calves
- No myotonia








Unsteady gait,
cataract, MI
MI
Cataract,
walking
difficulty
pacemaker

Ancillary investigations

- sCK slightly elevated
- EMG: myopathy, no myotonia

- DNA: repeat expansion intron 1 of the ZNF9 gene

Dx: Myotonic dystrophy type 2

Cardiac monitor implanted because of two syncopes

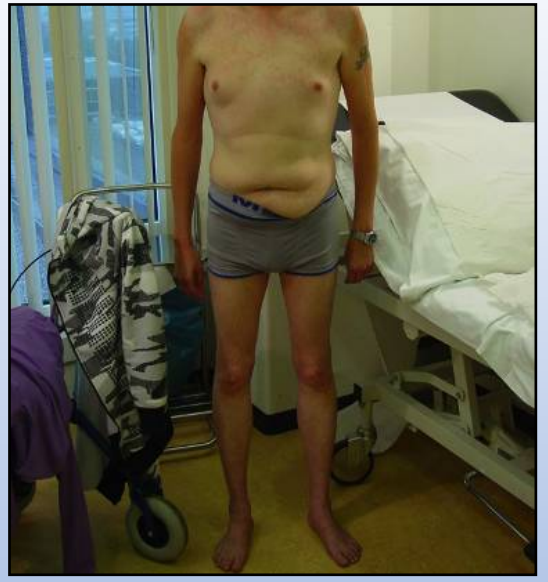
Mitochondrial myopathies

32 y/o male
Hx/

- Generalized muscle weakness since age 30
- Surgery to remove several lipoma’s

Ex/

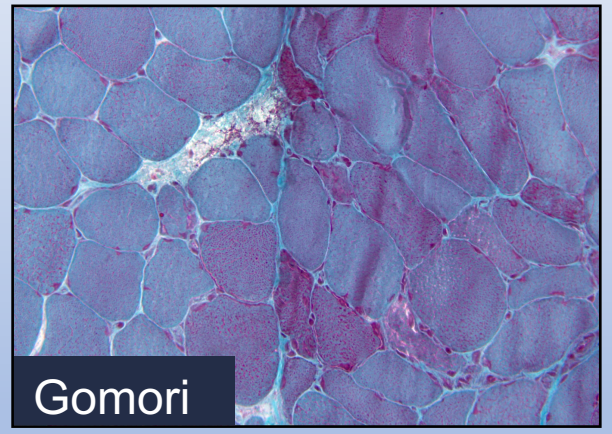
- Lipoma’s
- Limb-girdle pattern of muscle weakness
- VC 72%

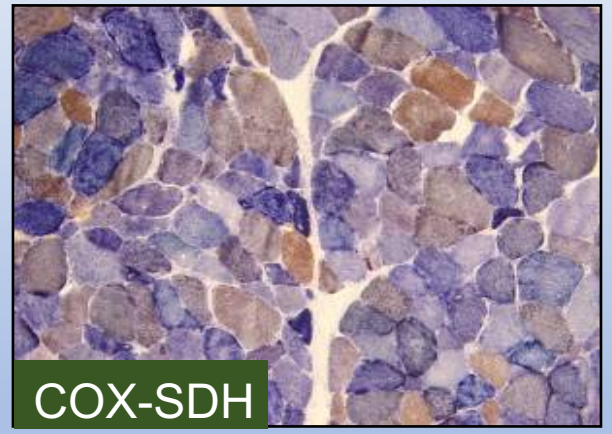


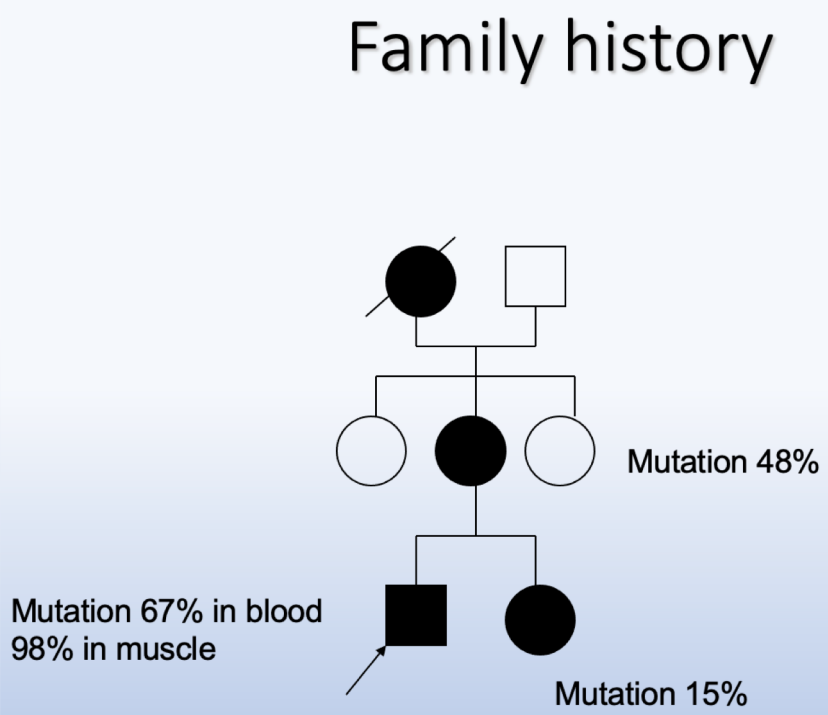
Ancillary investigations

- Serum lactate 12.5 mmol/L
- CK slightly (~2x) elevated
- High-density lipoproteins (HDL): elevated
- Muscle biopsy showed numerous RRF
- DNA analysis: m.8363G>A point mutation in tRNA-lys gene of mt DNA

>> **Madelung disease**







Differential diagnosis - Limb girdle syndrome

- Don’t miss the potentially treatable disease, i.e. spinal muscular atrophies type 3 and 4 and Pompe disease
- And in particular hypothyroid myopathy – measure the TSH level is CK is raised!
- Drug-induced myopathies - medication history!
- IBM may mimic treatable idiopathic inflammatory myopathies – anti-cN1A autoantibodies and imaging may be helpful
- Diagnosis of mitochondrial myopathies and myotonic dystrophy type 2 important because of cardiological complications and counseling of family members