IZOMBETEGSÉGEK

DIAGNOSZTIKÁJA

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MYOPATHIÁK

Örökletes	Szerzett
Izomdystrophiák	Myositisek (PM, DM, IBM)
Congenitalis dystrophiák	Endokrin (pl. hypothyreosis)
Congenitalis myopathiák	Toxikus (pl. steroid, statin)
Metabolikus myopathiák	

Progressziv dystrophiák

- DMD/BMD (Duchenne/Becker: proximalis-generalizált)
- DM1/DM2 (Dystrophia myotonica)
- FSHD1/FSHD2 (Facio-scapulo-humeralis)
- LGMD1/LGMD2 (végtagövi)
- Distalis (Welander, Miyoshi, Nonaka, Udd, Laing, stb.)
- SPMD (Scapuloperonealis)
- OPMD (Oculopharyngealis)
- EDMD (Emery-Dreifuss)

Congenitalis dystrophiák (MDC)

- Normális mentális fejlődéssel
  (MDC1: merosin hiány, Ullrich sy, Bethlem, RSMDC)
- Mentális deficittel
  (Fukuyama, MEB, WWS)

Congenitalis myopathiák

- Nemalin, central core, myotubularis/centronuclearis, CFTD

Metabolicus myopathiák

- Lipid tárolás (carnitin hiány, CPT-hiány,…)
- Glycogen tárolás (Glycogenosis, GSD (Pompe, McArdle, …)
- Mitochondrialis (encephalo-) myopathiák
- Ioncsatorna betegségek

Szerzett myopathiák

- Myositis (PM, DM, IBM, infectios)
- Endocrin (hypo-, hyperthyreosis, stb.)
- Toxicus (alkohol, gyógyszer: statin, steroid)

Leggyakoribb neuromuscularis betegségek

	(prevalencia)
Mitokondriális betegségek	10-20/100.000
Dystrophia myotonica (DM1)	5-10/100.000
FSHD	4/100.000
Duchenne/Becker (DMD)	3/100.000

ALS	5/100.000
CIDP	4/100.000

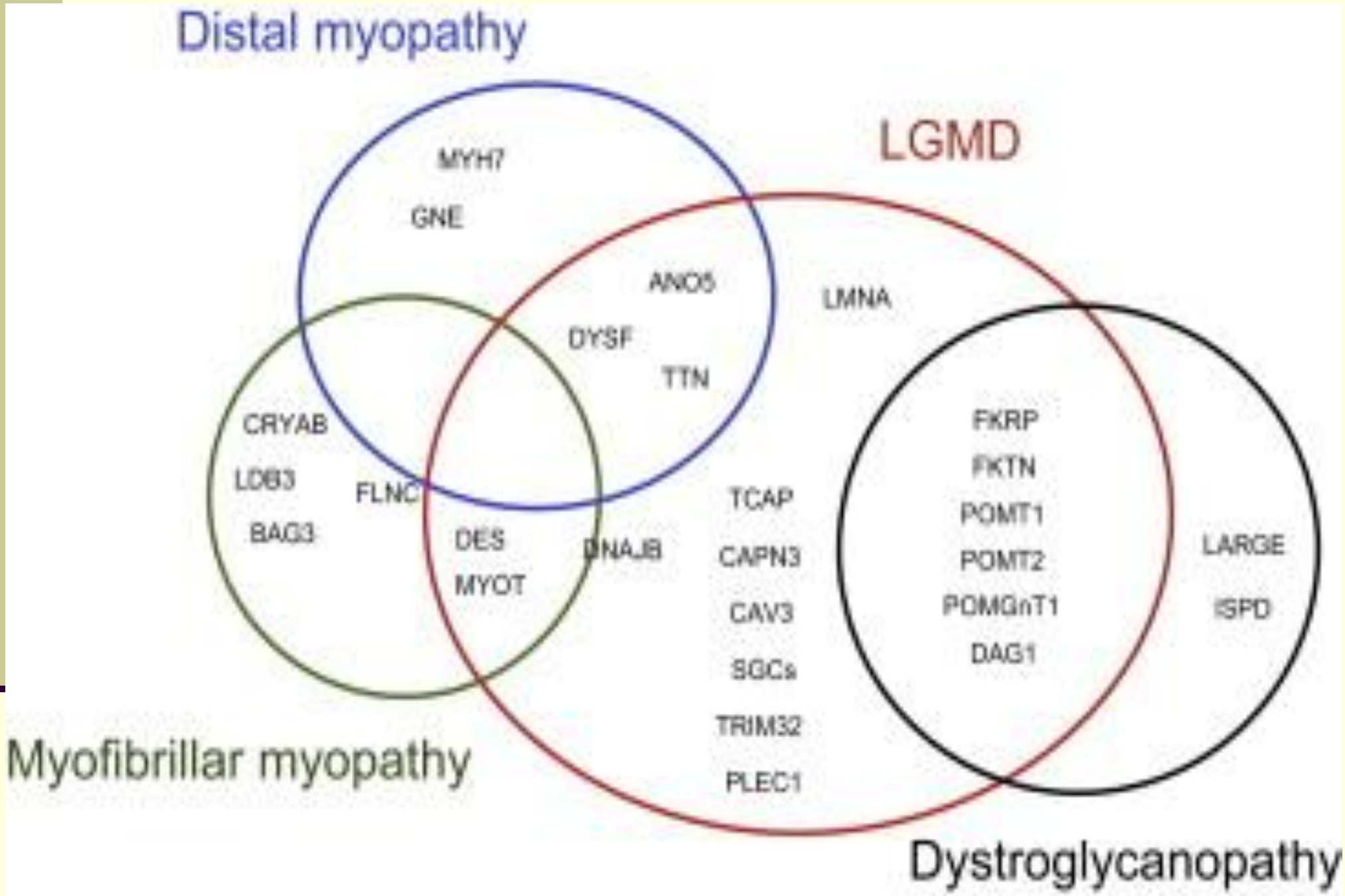
Dermatomyositis	8/100.000
Polymyositis	7/100.000
IBM	2/100.000
MG	10-15/100.000

Epidemiológia

Neurogenetics, Ch. 11. The muscular dystrophies Bushby K, Sheerin UM.

Table 11.1. The relative frequencies of different inherited muscular dystrophies and other muscle disorders in a clinic population of approximately 1000 patients in the northeast of England [117]

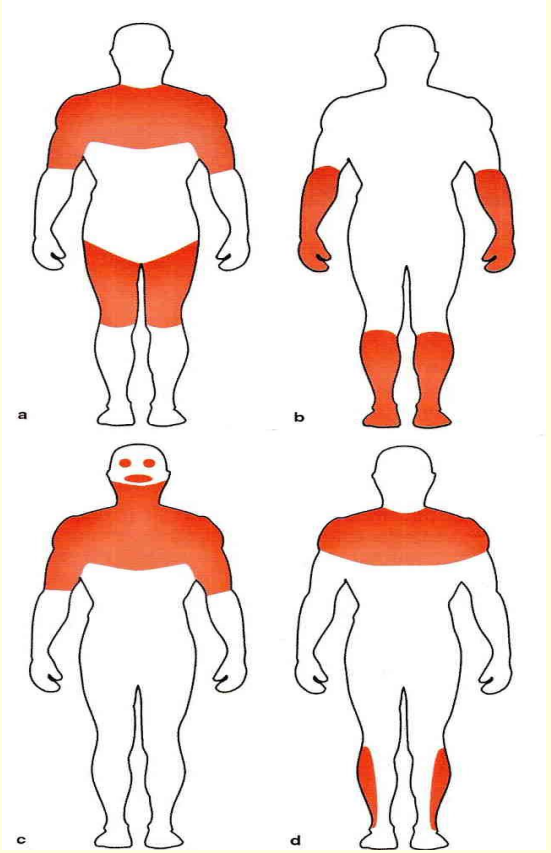
Condition	% of Northern region clinic population	First line diagnostic test
Myotonic dystrophy	28%	DNA test for expansion in DMPK(DM1), ZNF9 (DM2)
Dystrophinopathy	20%	DNA test (MLPA) for deletions/duplications
Facioscapulohumeral muscular dystrophy	10%	DNA test for D4Z4 deletion on chromosome 4q35
Spinal muscular atrophy	4%	DNA test for SMN deletions/gene conversion events
Limb-girdle muscular dystrophy	4.5%	Common C826A mutation for LGMD2I, consider lamin A/C mutation testing otherwise likely to require muscle biopsy to select further genetic testing (see Table 11.3)
Bethlem myopathy	<3%	Collagen VI immunolabeling of cultured fibroblasts
Congenital muscular dystrophies	<3%	Muscle biopsy for laminin alpha 2, alpha dystroglycan, and collagen VI will direct genetic testing (see Table 11.3)
Congenital myopathies	<3%	Muscle biopsy for structural features to direct genetic testing
Myofibrillar myopathies	<2%	Muscle biopsy for structural features to direct genetic testing
Emery–Dreifuss muscular dystrophy	<2%	Emerin and lamin A/C mutation analysis: muscle biopsy for emerin positivity
Distal myopathies	<2%	Muscle biopsy for structural features to direct genetic testing


Distal myopathy
LGMD
MYH7
GNE
ANO5
LMNA
DYSF
TTN
CRYAB
LDB3
FLNC
BAG3
DES
MYOT
DNAJB
TCAP
CAPN3
CAV3
SGCs
TRIM32
PLEC1
FKRP
FKTN
POMT1
POMT2
POMGnT1
DAG1
LARGE
ISPD
Myofibrillar myopathy
Dystroglycanopathy

Myopathia gyanúja esetén

Anamnézis

1. Negativ és pozitiv tünetek, panaszok
2. Időbeli lefolyás, kezdet
3. Családi anamnézis
4. Kiváltó tényezők

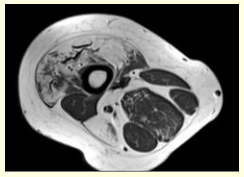


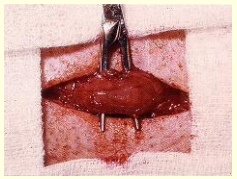
Fizikális vizsgálat

5. Izomérintettség eloszlása
6. Társuló tünetek

Kiegészítő vizsgálatok

7. Laboratórium (CK, elektrolit, endokrin)
8. EMG
9. MRI
10. izombiopszia



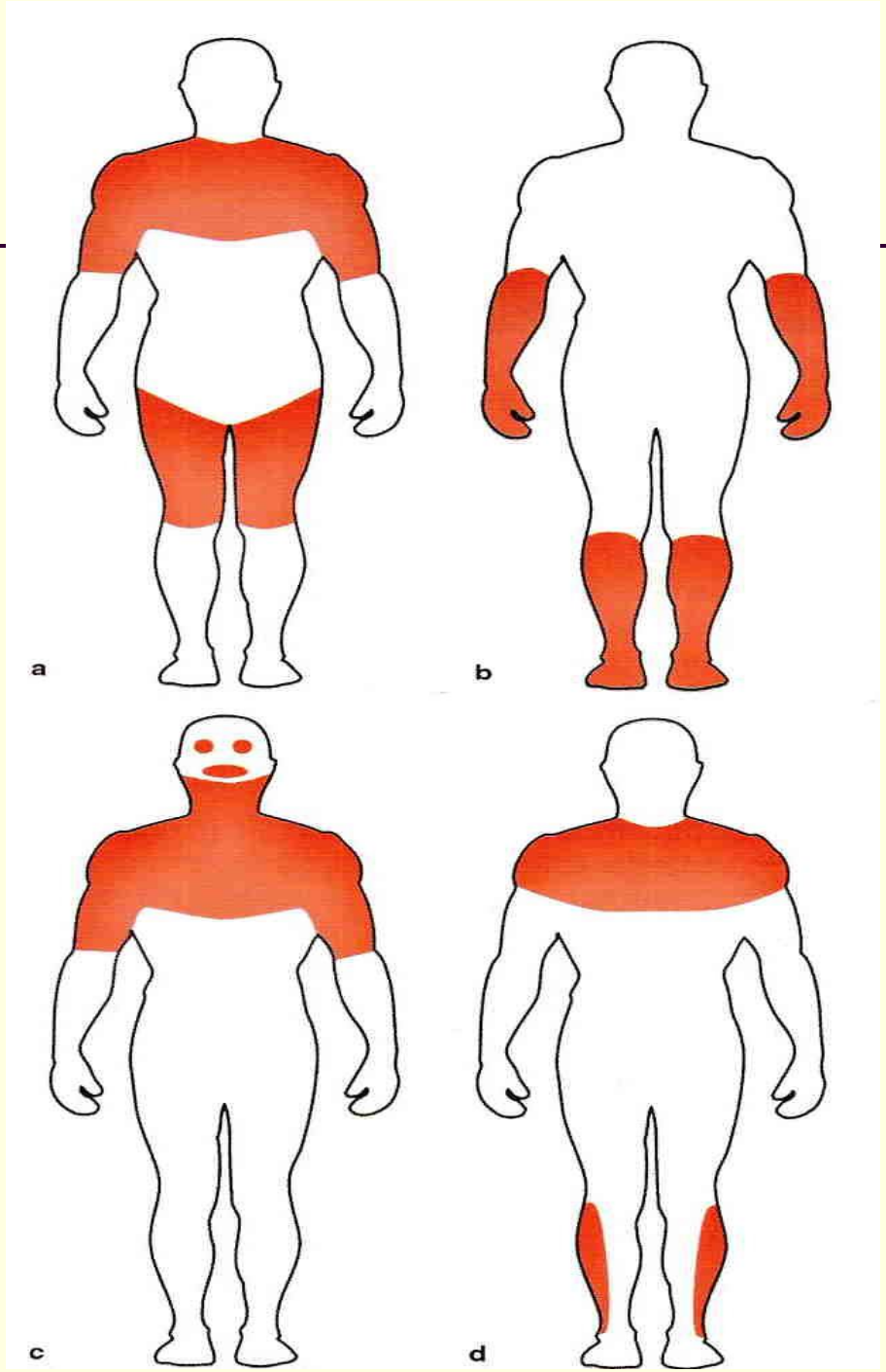


ÖRÖKLŐDÉS

AD	AR	XR
LGMD 1A-H	**LGMD 2A-Q**	**DMD** (Duchenne)
(*MYOT, CAV, LMN*,..)	(*CAPN, DYSF, SGA*,..)	**BMD** (Becker)
DM 1-2	**GSD II (Pompe)** *(GAA)*	**Danon** *(LAMP2)*
FSHD	**Lipid tárolás**	**XMEA** *(VMA21)*
OPMD	(CPT, MCAD, VLCAD,..)	
EDMD *(LMNA)*		**EDMD** *(EMERIN)*
MFM *(DES, MYOT, CRYAB)*	**MFM** (*DES, CRYAB*)	
Distalis *(MYH7, TIA1, TTN)*	**Distalis** *(GNE, DYSF)*	
	MDC1 *(LAMA2)*	
Central core *(RYR1)*	**Nemaline** *(NEB, ACTA1)*	
CNM *(DNM2, MYF6)*	**CNM** *(TTN, BIN1, RYR1)*	**CNM** *(MTM1)*

LGMD

Distalis



FSHD

Scapulo-peronealis

Gyengeség eloszlása

- **1. Proximalis (végtagövi)**
  - Leggyakoribb (DMD, BMD, LGMD, steroid, Dermato/Poly/Necrotisalo myositis, Pompe)
- **2. Proximalis felső végtag/Distalis alsó végtag**
  - FSHD, Pompe, Emery-Dreyfuss
- **3. Distalis felső végtag/proximalis alsó végtag**
  - DM1, IBM (aszimmetrikus)
- **3. Distalis**
  - Ritka ! DM1, FSHD, IBM, Distalis myopathiák
  - Diff dg: polyneuropathia- érzészavar !
- **4. Nyak extensor**
  - MG, ALS, FSHD, DM1, Myositisek (DM/PM), MYH7
- **5. Ptosis**
  - Ophthalmoplegiával: MG/LEMS, PEO, OPMD
  - Ophthalmoplegia nélkül: MG, DM1, congenitalis myopathia

Kórlefolyás

Kezdet:

- **Születéskor**
  - Congenitalis dystrophia, dystrophia myotonica, GSDII (Pompe)
  - Congenitalis myopathiák (central core, etc.)
  - Congenitalis myasthesia syndroma (CMS)
- **Gyermekkorban**
  - Izomdystrophiák (Duchenne (DMD), sarcoglycanopathiák **(SCARMD),** FSHD, DM1, distalis: MYH7)
  - Metabolikus (glycogen, lipid tárolás, mitochondrialis: Leigh)
- **Felnőttkorban**
  - Izomdystrophiák (LGMD (Dysferlin: 2. évtized), BMD, FSHD, MD1-2)
  - Distalis (GNE: 4-5. évtized), OPMD
  - Gyulladások (myositis) (DM, PM, IBM)
  - Toxicus
  - Metabolicus (mitochondrialis, endocrin, lipid, GSD II, V.)

Társuló tünetek

- **Cardialis**
  - Dystrophia myotonica (DM1)
  - Duchenne, Becker
  - Polymyositis
  - LGMD (1B, 2C-F, 2G)
- **Légzési elégtelenség**
  - Korai:
    - Dystrophia myotonica
    - Pompe
  - Késői
    - Duchenne
    - Polymyositis
- **Más:**
  - Cataracta
  - Mentalis retardatio
  - Contractura

Laboratórium

Rutin értékek
CK
TSH
Elektrolitok
Laktát

We, CRP, immunserologia

Pompe szűrővizsgálat (medenceövi tünet, CK)

Laboratórium

Creatine Kinase (CK)

- **A betegség aktuális aktivitását, de nem a súlyosságát jelzi**
- **Jelentősen emelkedett:**
  - Duchenne (100X), Becker
  - LGMD 1C, 2A, 2B
  - Myositis (PM, DM)
- **Mérsékelten emelkedett:** statin myopathia, hypothyreosis
- **Átmeneti:** erős fizikai aktivitás, izom sérülés, epilepsziás roham
- **Normalis CK nem kizáró myopathia irányába**
- **Benignus HyperCKaemia** (<3x, nincs panasz, tünet, fájdalom, normális EMG)

átmeneti izompanaszok, CK tartós

Erős fizikai terhelés (sportolók, spinnig !)

Vírusfertőzés

Gyógyszer

Toxicus (alkohol, cocain, heroin)

Elektrolitzavar
(hyponatraemia, hypokalaemia, hypophosphataemia)

Izom trauma
(sérülés, injekció, EMG, epilepsziás roham)

Sebészeti beavatkozás

Izom ischaemia (thrombosis, embolia)

Izom dystrophiák

Metabolikus myopathiák

Congenitalis myopathiák

Benignus hyperCKaemia

Myositisek (PM, DM, IBM, NM)

Sarcoidosis

Paraneoplasia

Gyógyszer (statin)

Endocrin (hypothyr. /hyperthyr)

Eur J Neurol. 2010 Jun 1;17(6):767-73. doi: 10.1111/j.1468-1331.2010.03012.x. Epub 2010 Apr 5.

EFNS guidelines on the diagnostic approach to pauci- or asymptomatic hyperCKemia.

Kyriakides T, Angelini C, Schaefer J, Sacconi S, Siciliano G, Vilchez JJ, Hilton-Jones D; European Federation of Neurological Societies.

Abstract

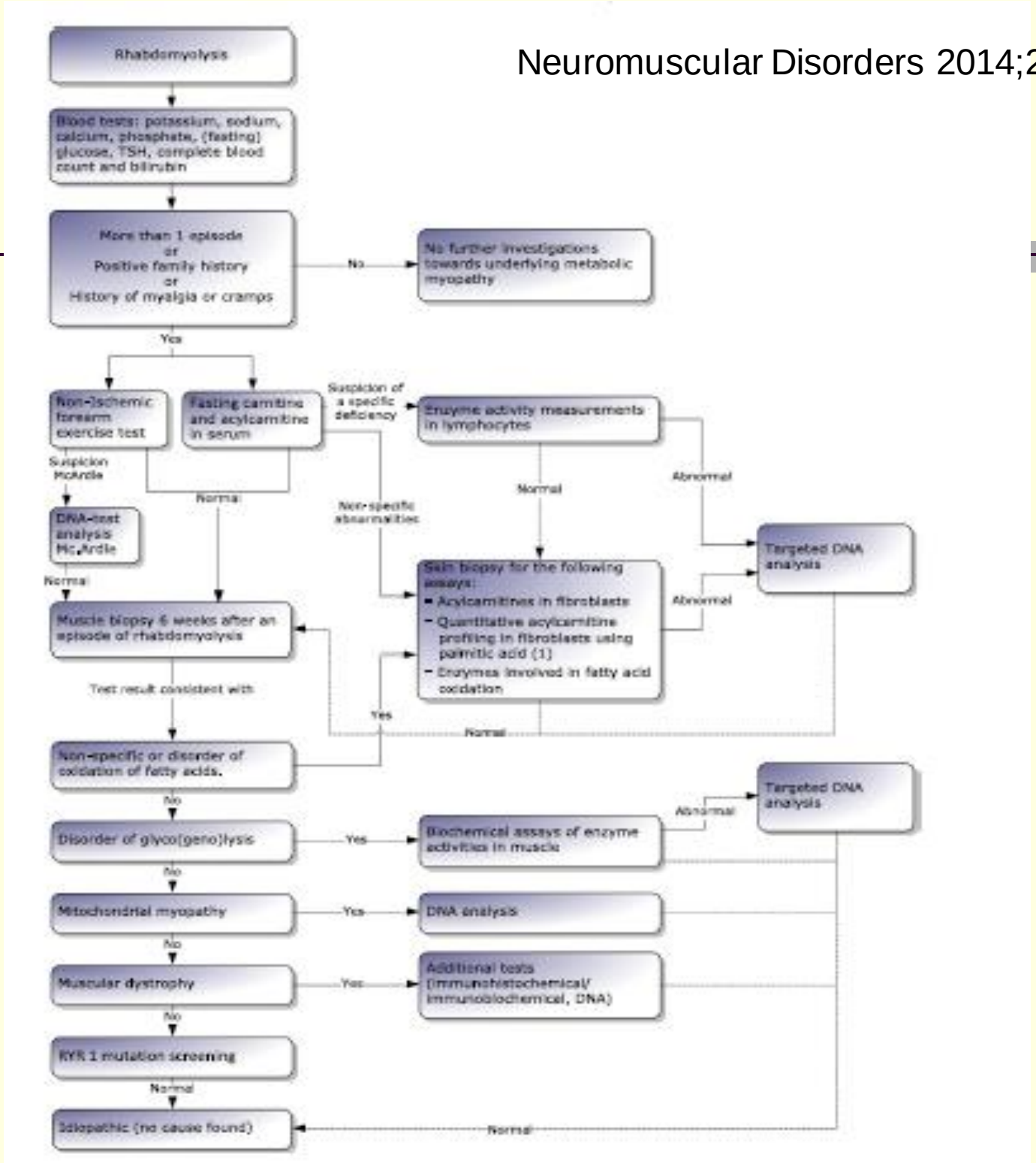
OBJECTIVE: To provide evidence-based guidelines to general neurologists for the assessment of patients with pauci- or asymptomatic hyperCKemia.

BACKGROUND: Recent epidemiologic studies show that up to 20% of 'normal' individuals have an elevated creatine kinase activity in the serum (sCK). The possibility of a subclinical myopathy is often raised, and patients may be unnecessarily denied treatment with statins. Search strategy: Electronic databases including Medline, the Cochrane Library and the American Academy of Neurology were searched for existing guidelines. Articles dealing with series of patients investigated for asymptomatic/pauci-symptomatic hyperCKemia and articles dealing with myopathies that can present with asymptomatic hyperCKemia were identified and reviewed.

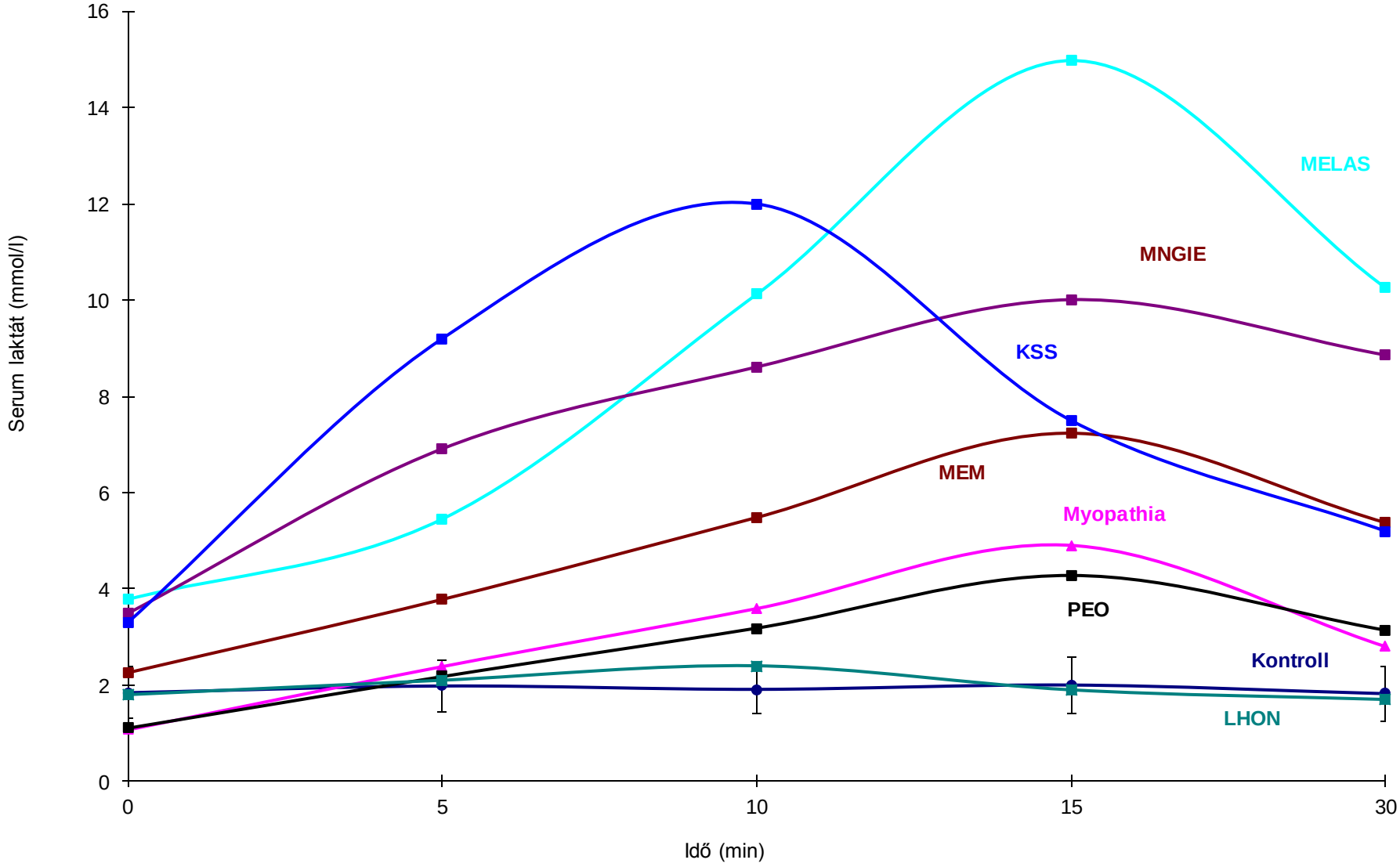
RESULTS: The only guidelines found were those approved by the Italian Association of Myology Committee, and the only relevant articles identified describe class IV studies.

RECOMMENDATIONS: HyperCKemia needs to be redefined as values beyond 1.5 times the upper limit of normal (which itself needs to be appropriately defined). Pauci- or asymptomatic hyperCKemia with no apparent medical explanation may be investigated with a muscle biopsy if one or more of the following are present; the sCK is >or=3x normal, the electromyogram is myopathic or the patient is <25 years of age. In addition, women with sCK<3 times normal may be offered DNA testing because of the possibility of carrying a dystrophin mutation.

Neuromuscular Disorders 2014;24:651-690

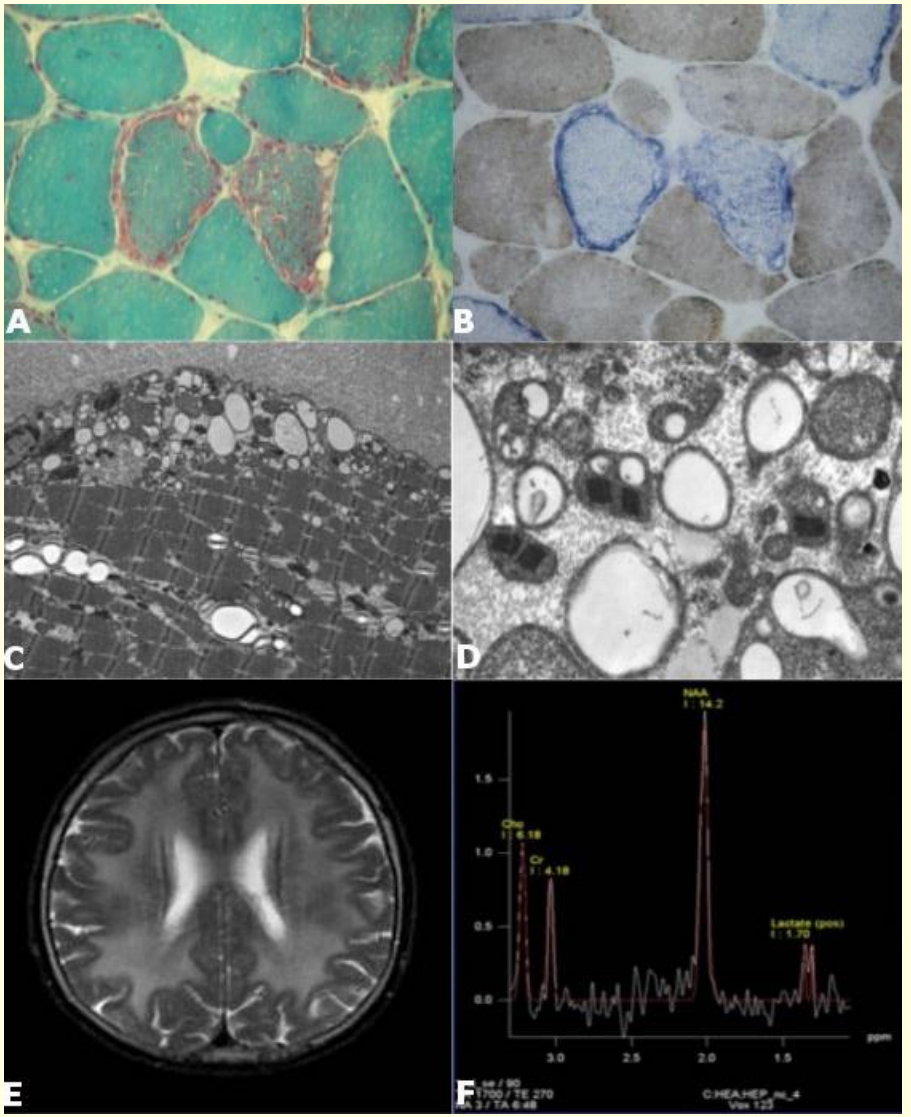


Laktát

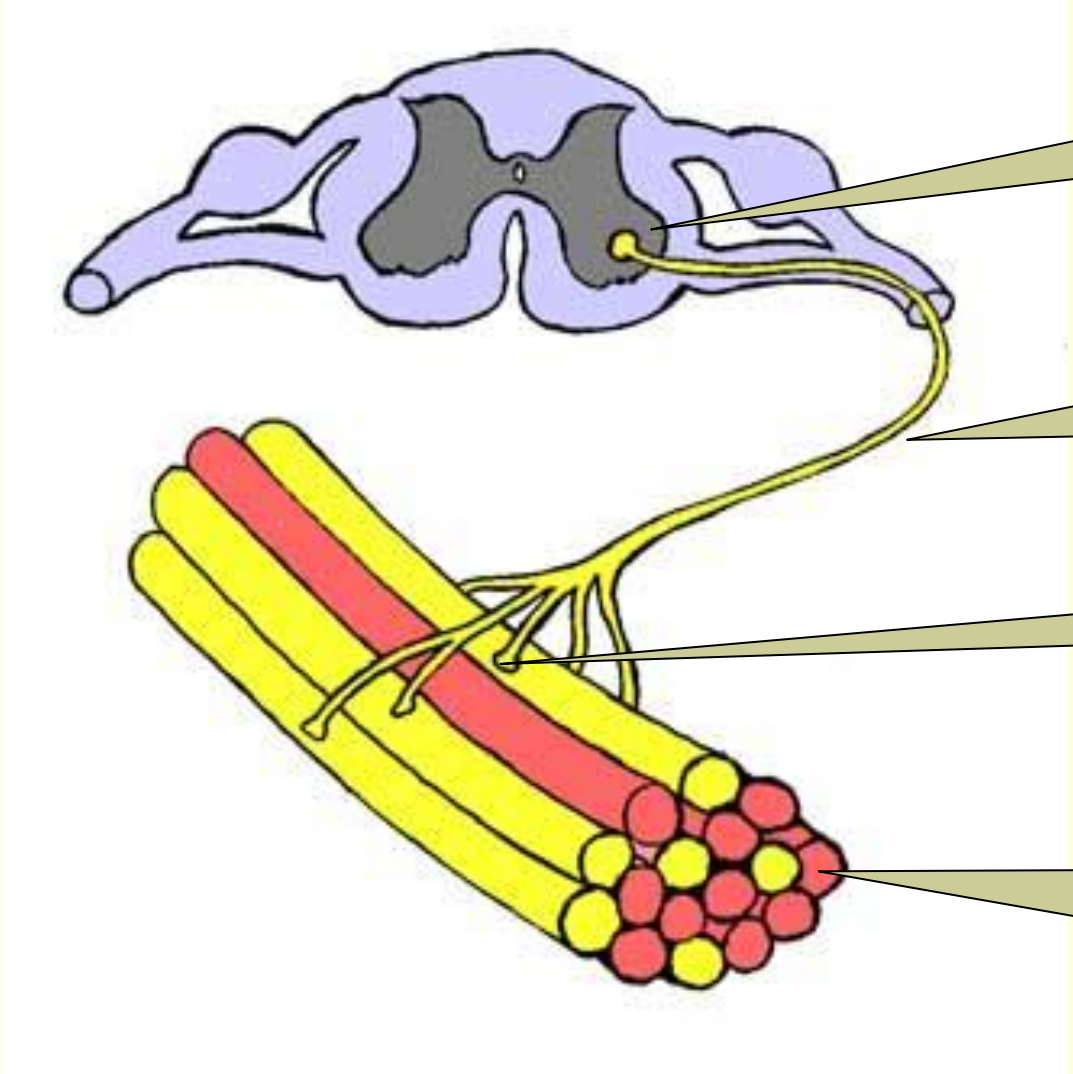

16
14
12
10
8
6
4
2
0
Serum laktát (mmol/l)
0
5
10
15
30
Idő (min)
MELAS
MNGIE
KSS
MEM
Myopathia
PEO
Kontroll
LHON

MR-SPECTROSCOPIA

MNGIE



A PERIFÉRIÁS IDEGRENDSZER VIZSGÁLATA



Motoneuron
- EMG, MEP
- MRI

Perifériás ideg
- ENG
- Idegbiopszia

NMJ
- EMG

Vázizom
- EMG
- MRI
- Izombiopszia

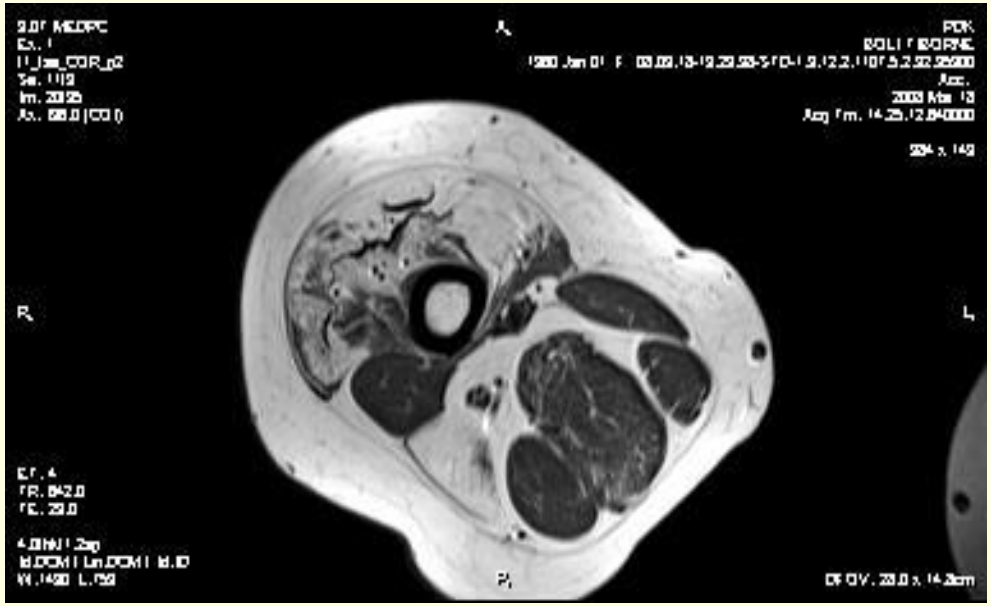
EMG/ENG

- Diff. Dg. Neurogen atrophia (óriás MEP)
  Motoneuron betegség
  NMJ betegség (MG/LEMS)
  Myopathia (rövid MEP)
- Honnan készítsünk biopsziát

- EMG - myopathia:
  - Rövid tartamú, kis amplitúdójú MEP

Izom MRI

- **Biopszia helyének kiválasztása**
- Izomérintettség mintázata
- Súlyosság
- Focalis elváltozások (pl. myositis)



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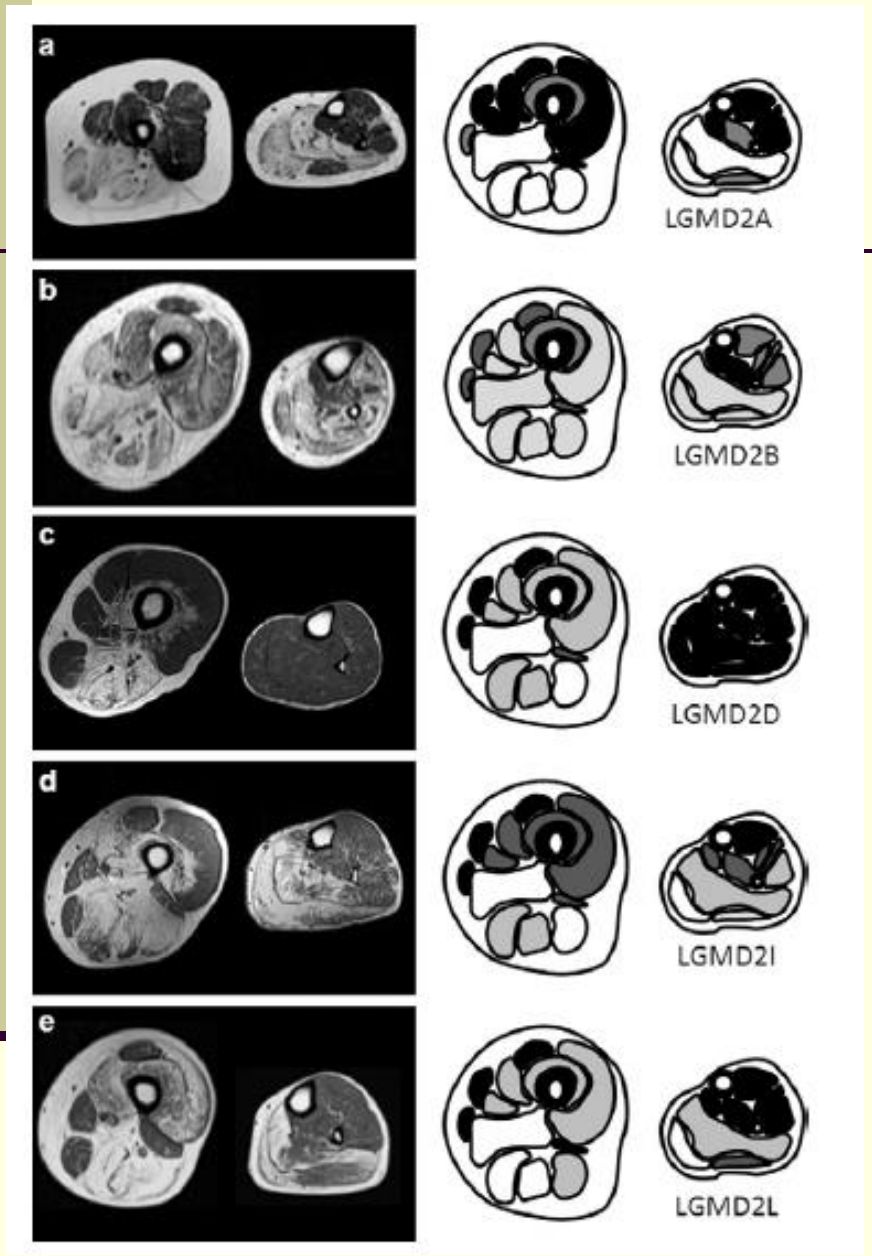

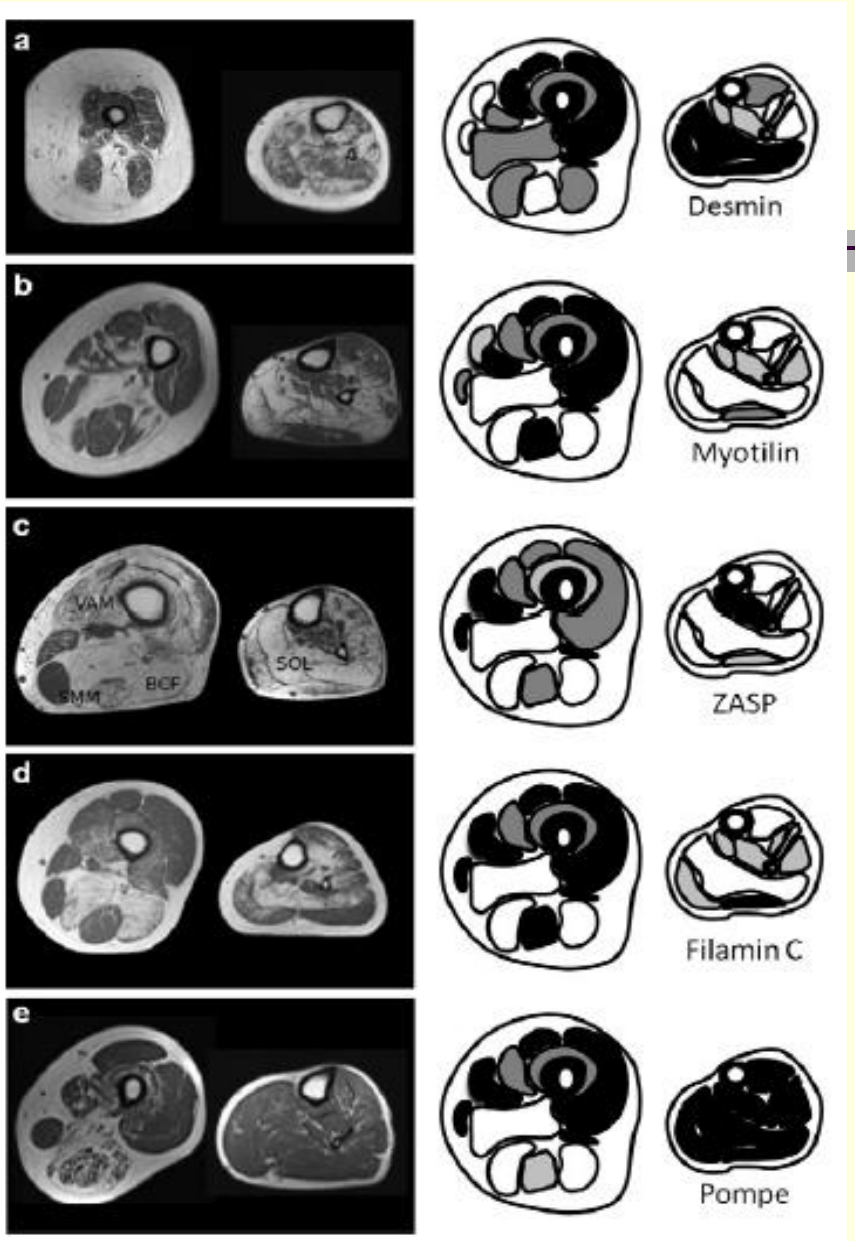

TREAT-NMD workshop: Pattern recognition in genetic muscle diseases using muscle MRI 25–26 February 2011, Rome, Italy

Neuromuscular Disorders 22 (2012) S42–S53

Volker Straub [a,*,1], Pierre G. Carlier [b,1], Eugenio Mercuri [c,1]

Izom MRI

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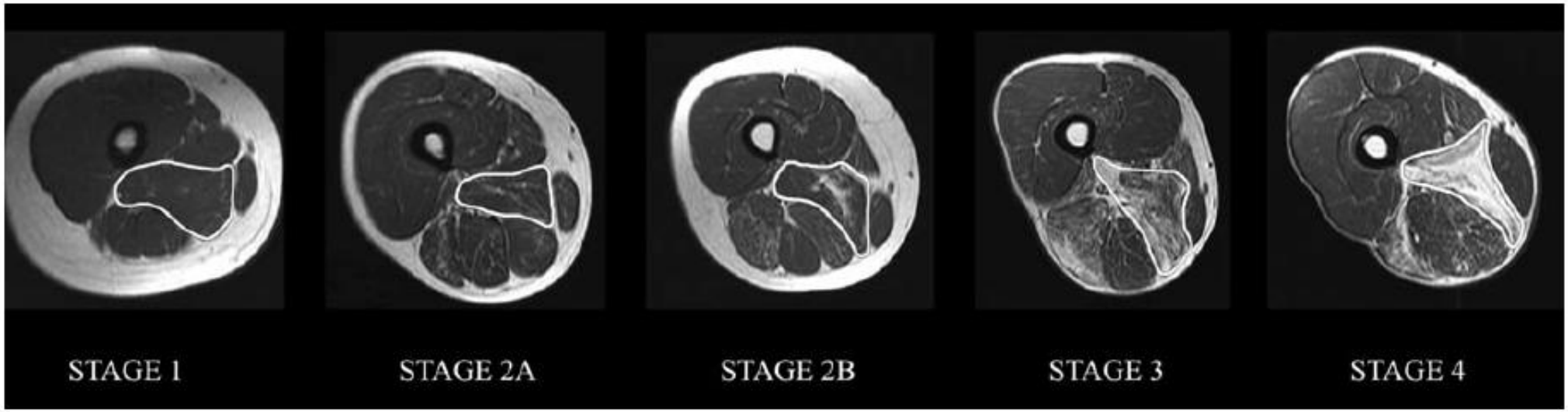


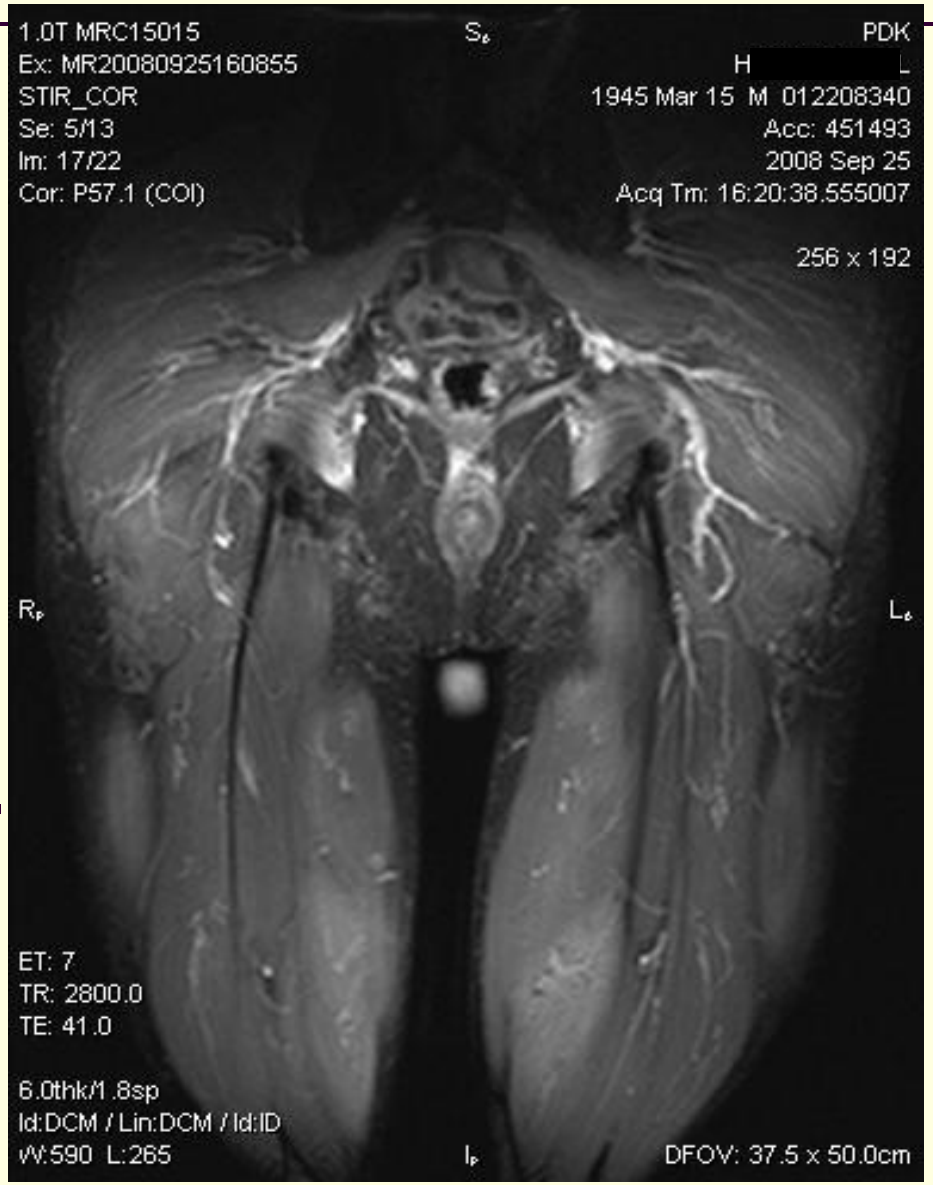
Fig. 1 Axial T1-weighted images of the thigh showing fatty infiltration according to the Mercuri scale.

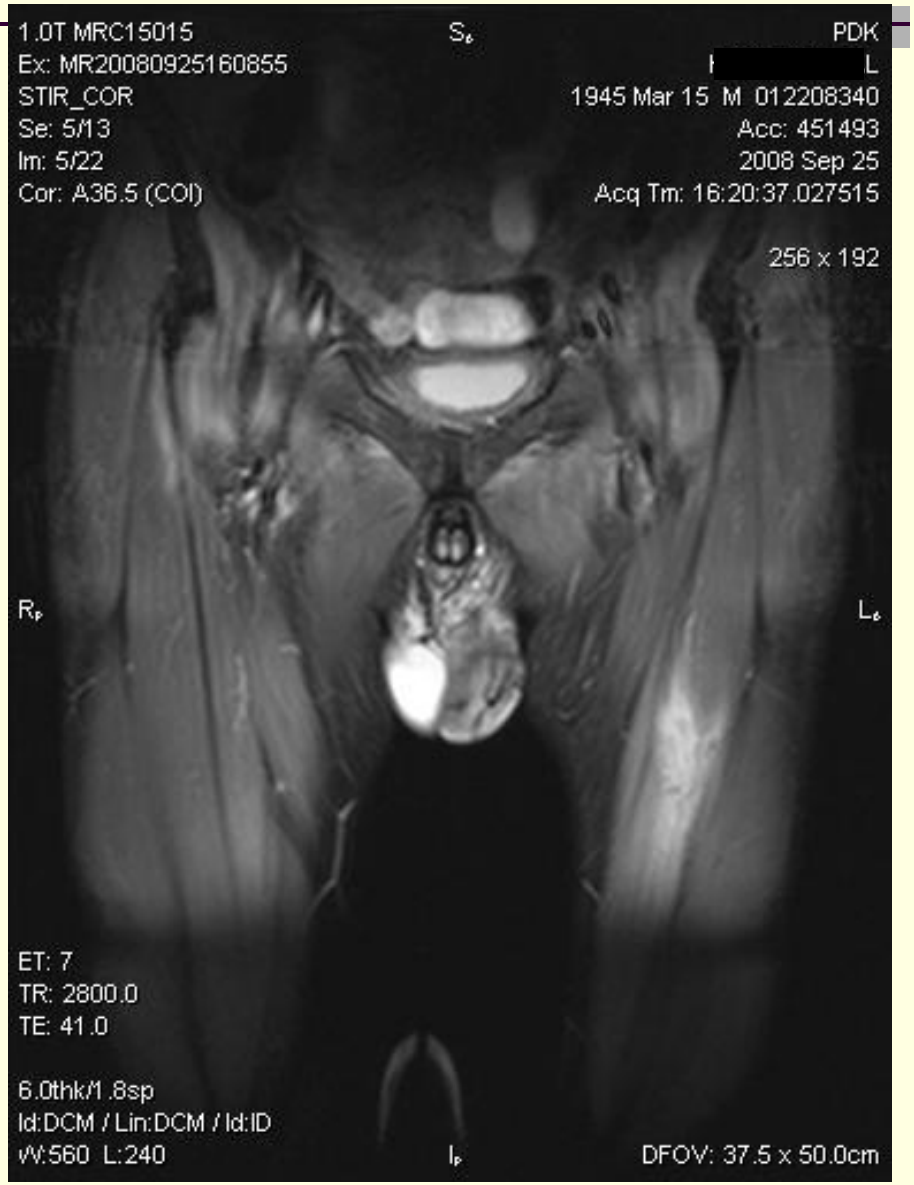
T1: atrophia, zsiros degeneráció, STIR: oedema, aktív gyulladás

Izom MRI

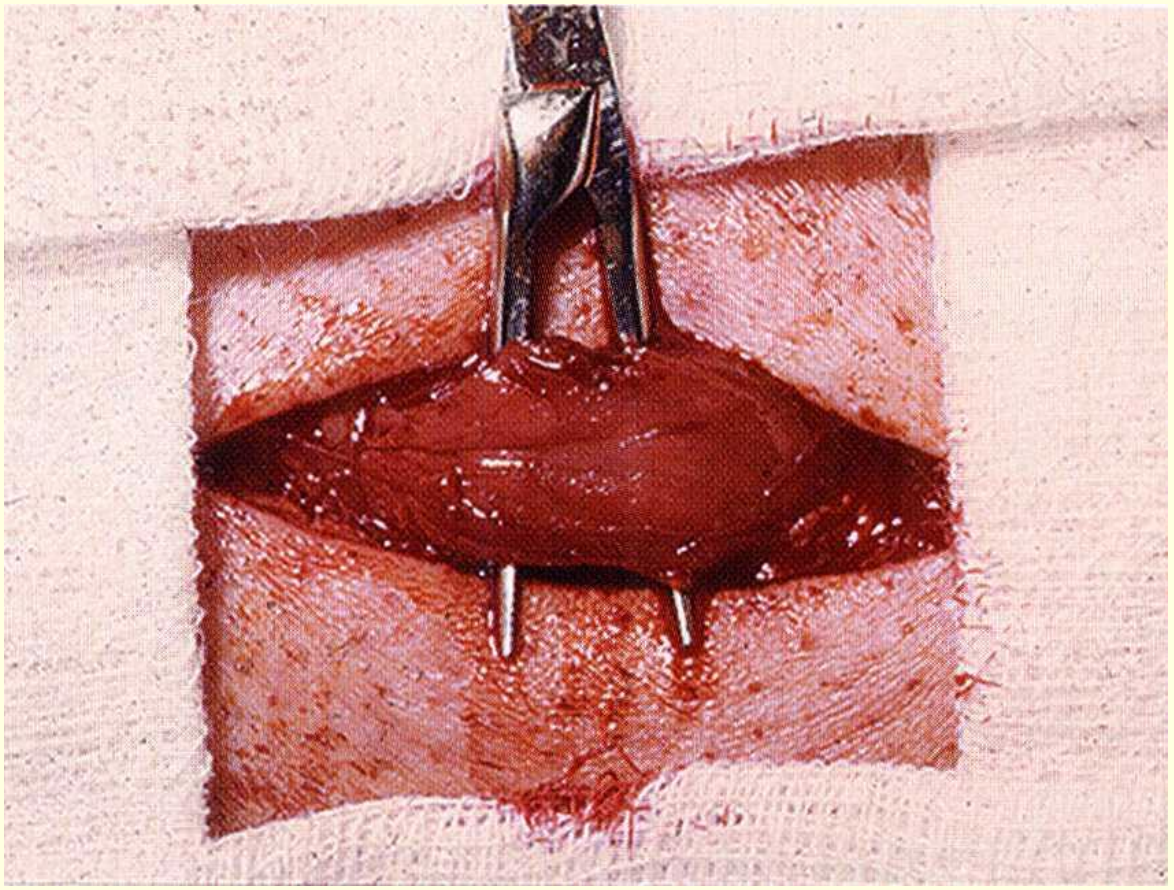
- Biopszia helyének kiválasztása
- Izomérintettség mintázata
- Súlyosság
- **Focalis elváltozások (pl. myositis)**

POLYMYOSITIS





IZOMBIOPSZIA



IZOMBIOPSZIA

Indikáció

- **Izombetegség fennállásának gyanúja:**
  izomatrophia, gyengeség, izomgörcs, fáradékonyság
  myopathiás EMG, emelkedett CK*
  myositis
- **Neurogén izomatrophia tipizálása: NEM !**
  SMA (genetika !), ALS (klinikai kép, elektrofiziológia)
- **Szisztémás betegség, mely izomtünetekkel járhat:**
  vasculitis, sarcoidosis

Nem indikált:

Myasthenia gravis, myotonia, rhabdomyolysis

IZOMBIOPSZIA

Hely kiválasztása

Krónikus betegség

Kevésbé érintett izmok

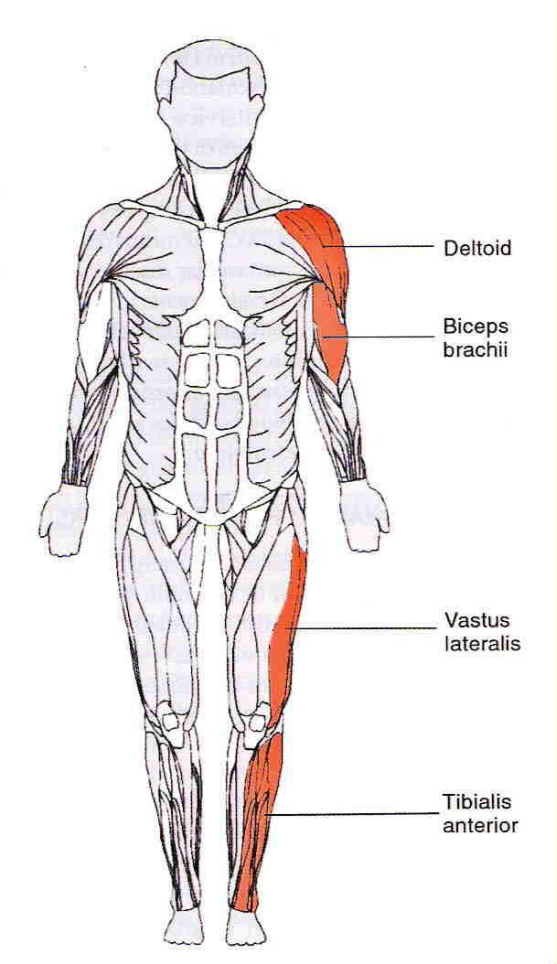
Akut betegség

Súlyosan érintett izmok

Legspecifikusabb izmok

m. deltoideus, biceps brachii,
m. quadriceps, tibialis anterior

MRI



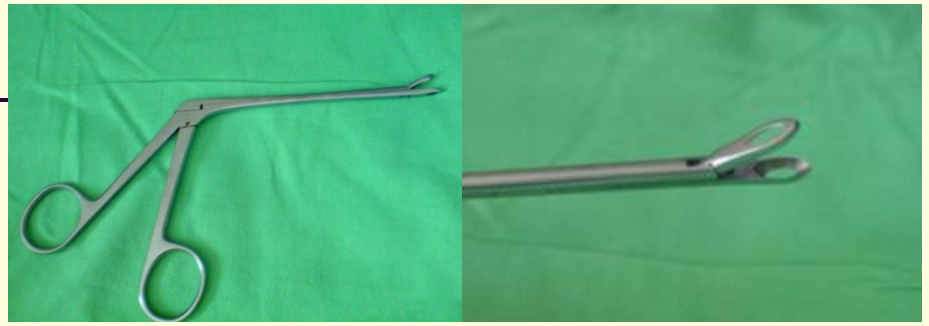
Izombiopszia

- **Myopathia vagy Neurogen atrophia**
- **Gyulladás**
- **Izomdystrophia: necrosis, regeneráció**

- Mitokondriális betegségek (**RRF**-ragged red fibers)
- Tárolásos betegségek (Glycogen: **Pompe**)

- **Immunhisztokémia: protein hiány (dystrophia)**
- **Immunhisztokémia: gyulladás, MHC (myositis)**
- Elektronmikroszkópia (mitokondrialis, congen.myop., zárvány)
- Biokémiai vizsgálat (Western blot, enzimek)
- Genetika (mitokondriális)

BIOPSZIA TECHNIKÁJA



Nyilt biopszia

Helyi érzéstelenítés, Steril körülmények

Több minta eltávolítása: nativ minta !

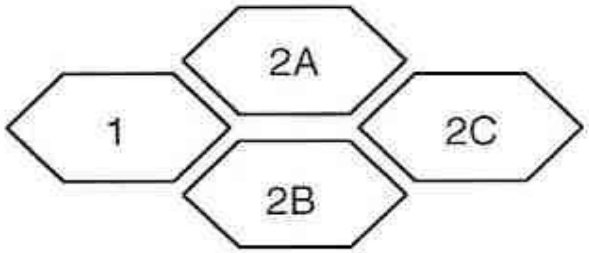
Fénymikroszkópia (fagyasztás: izopentán+ folyékony nitrogén)

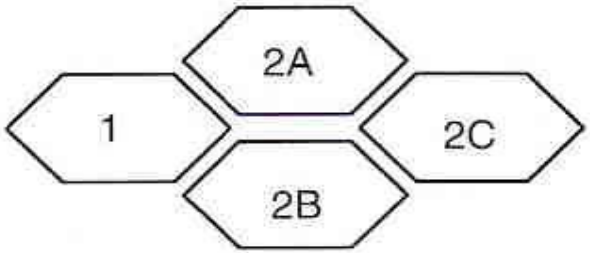
Elektronmikroszkópia (fixálás, műgyantába ágyazás)

congenitalis myopathiák, mitokondriális myopathia

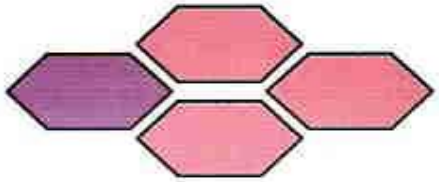
Tárolás folyékony nitrogénben, vagy -80°C

biokémia / molekuláris biológia / genetika (mitokondriális betegségek)

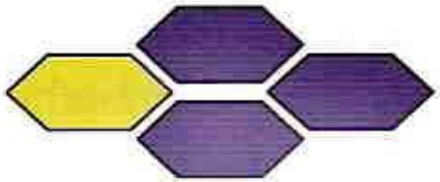




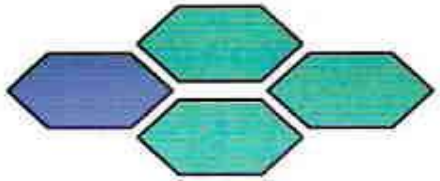
Haematoxylin and eosin



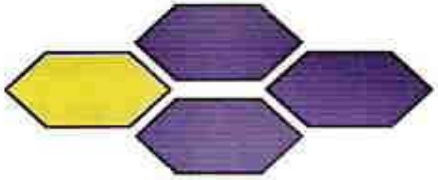
Myophosphorylase



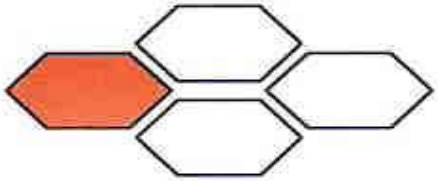
Gomori



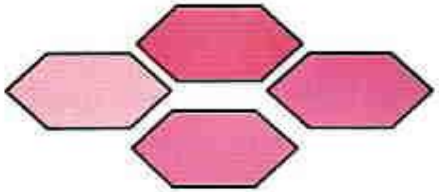
Phosphofructokinase



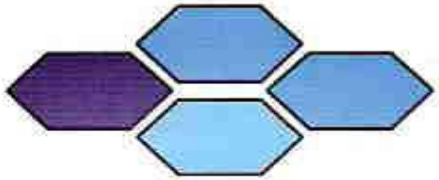
Oil-Red-O



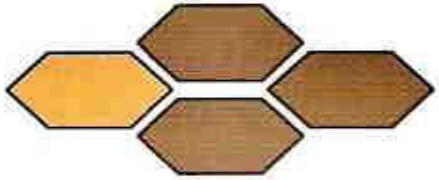
Periodic acid–Schiff (PAS)



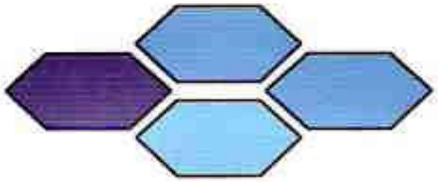
NADH-TR



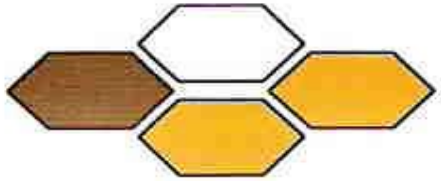
ATPase pH 9.4–10.2



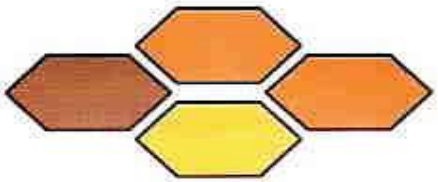
Succinic dehydrogenase



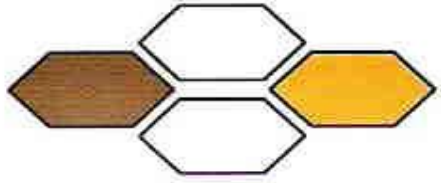
ATPase pH 4.5



Cytochrome oxidase

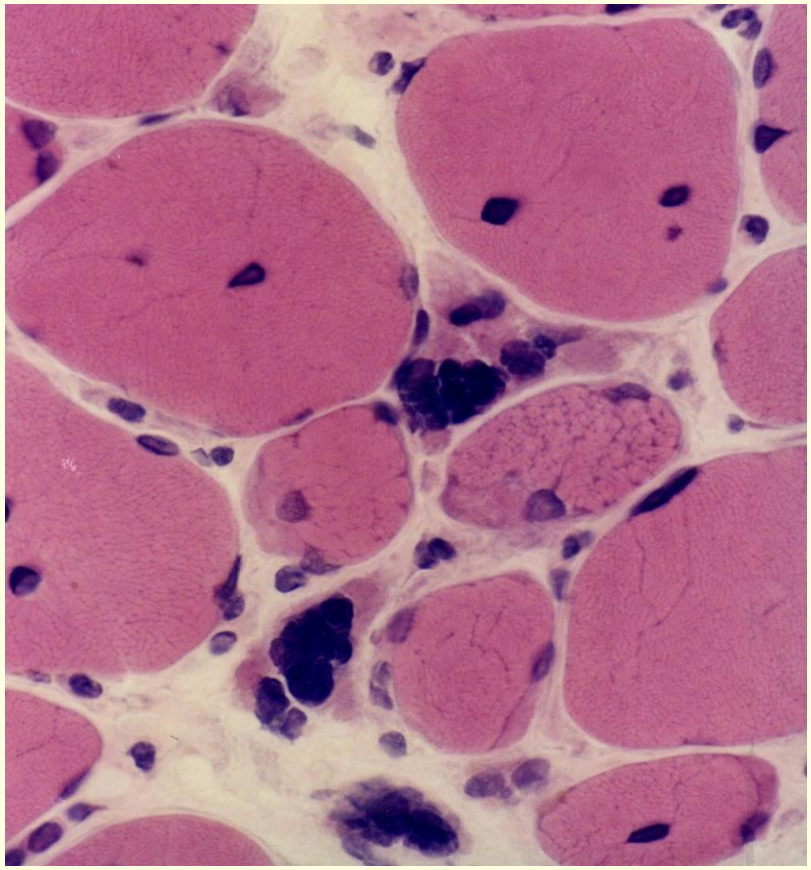


ATPase pH 4.2

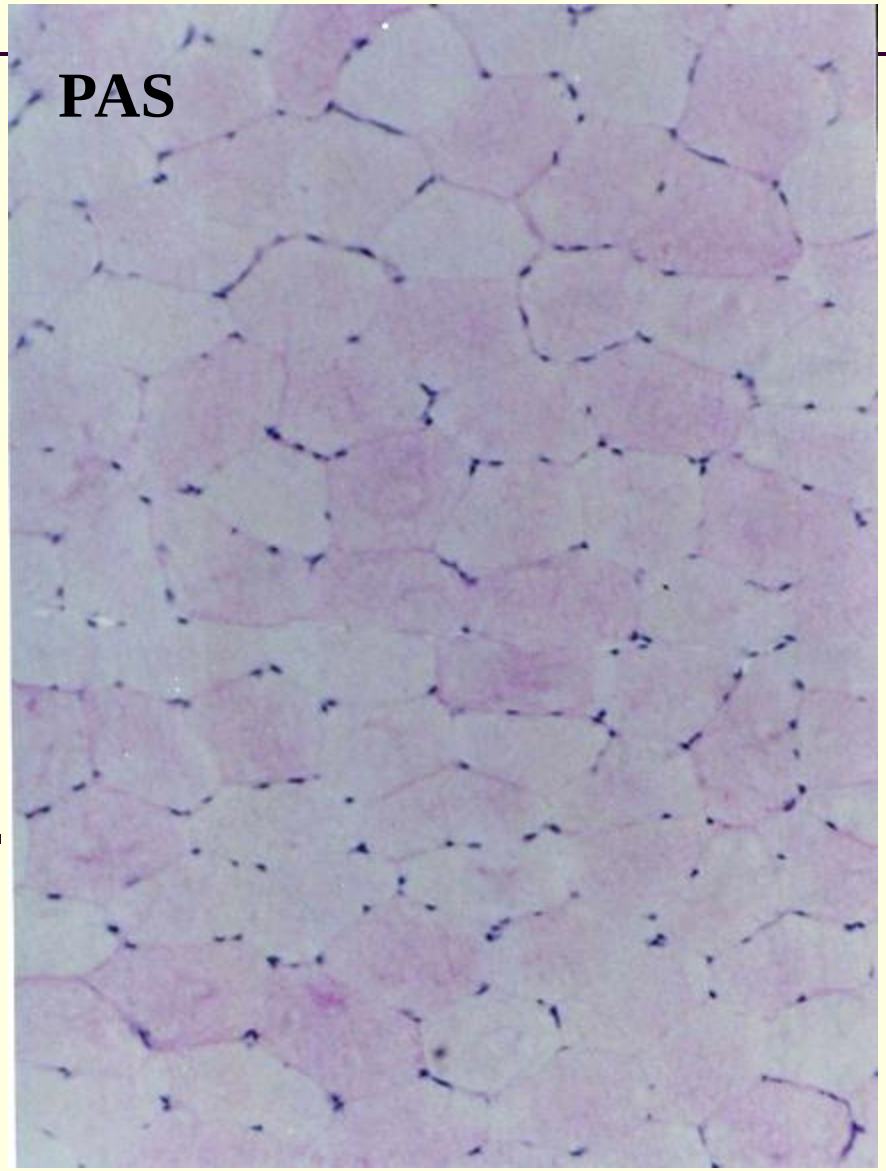


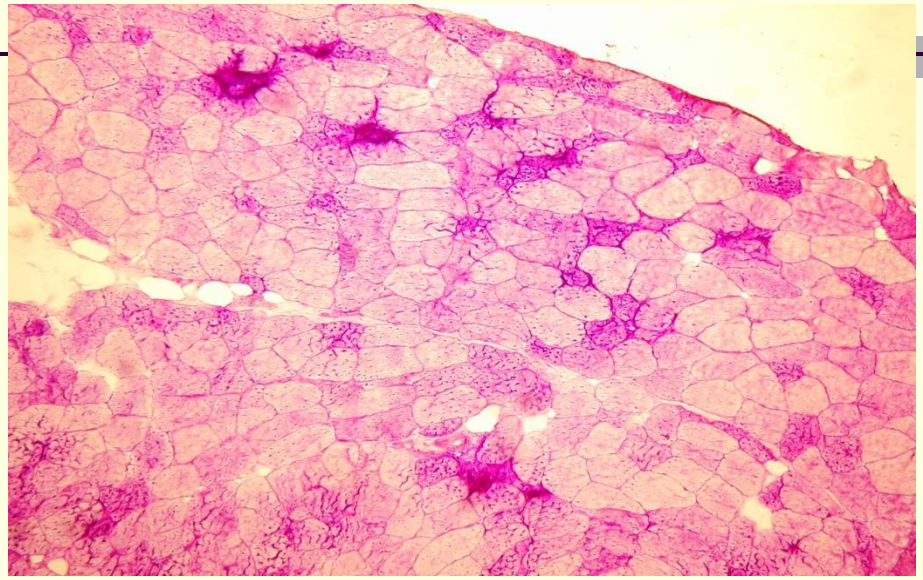
PATHOLÓGIA

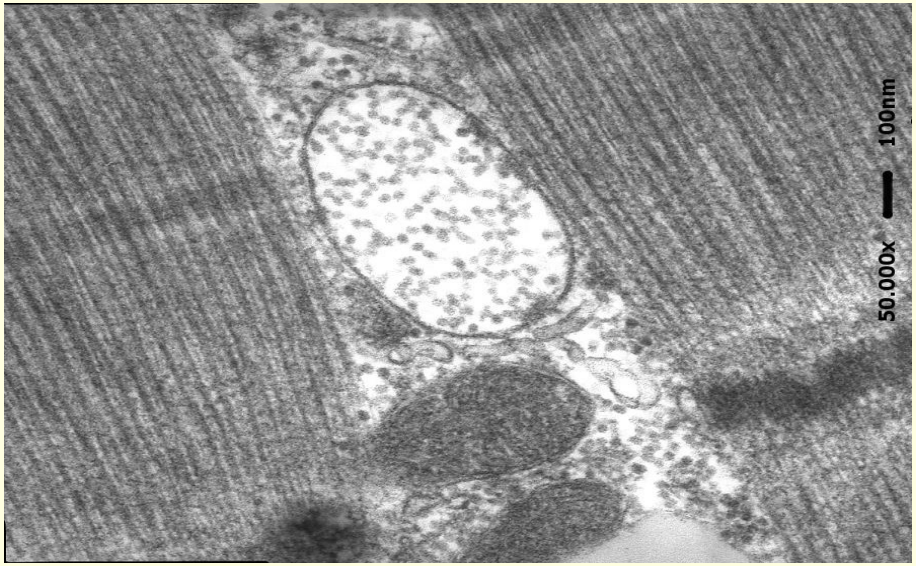
- **Myopathia**
  - Elszórt atrophia
  - Kerek atrophiás rostok
  - Belső magok
  - Necrosis
  - Degeneráció
  - Regeneráció
  - Kötőszövet-szaporulat

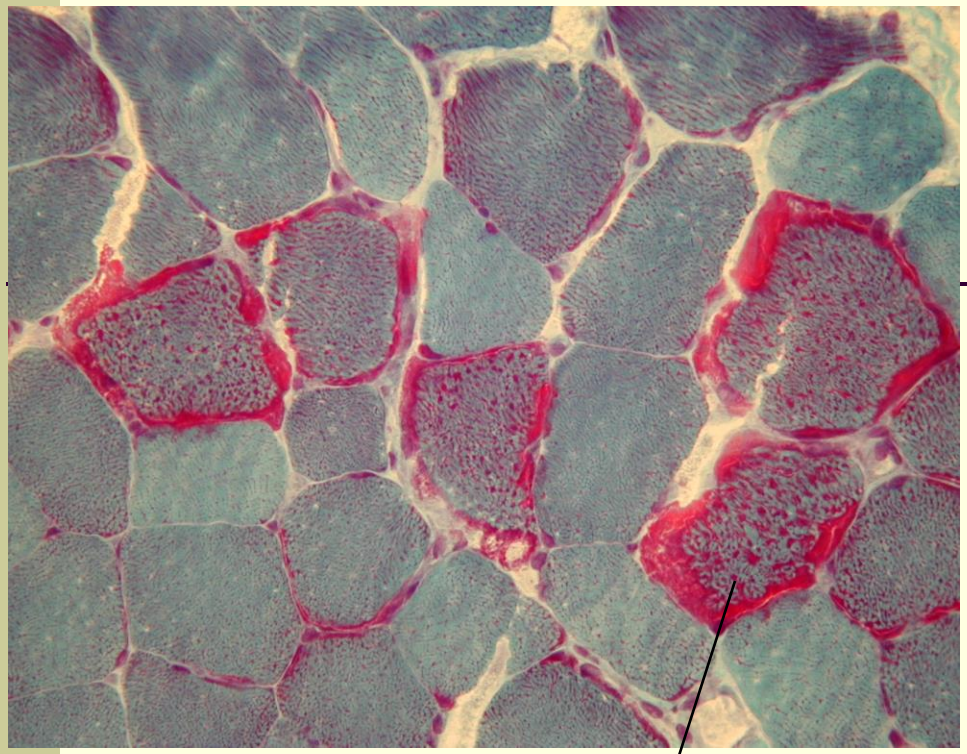


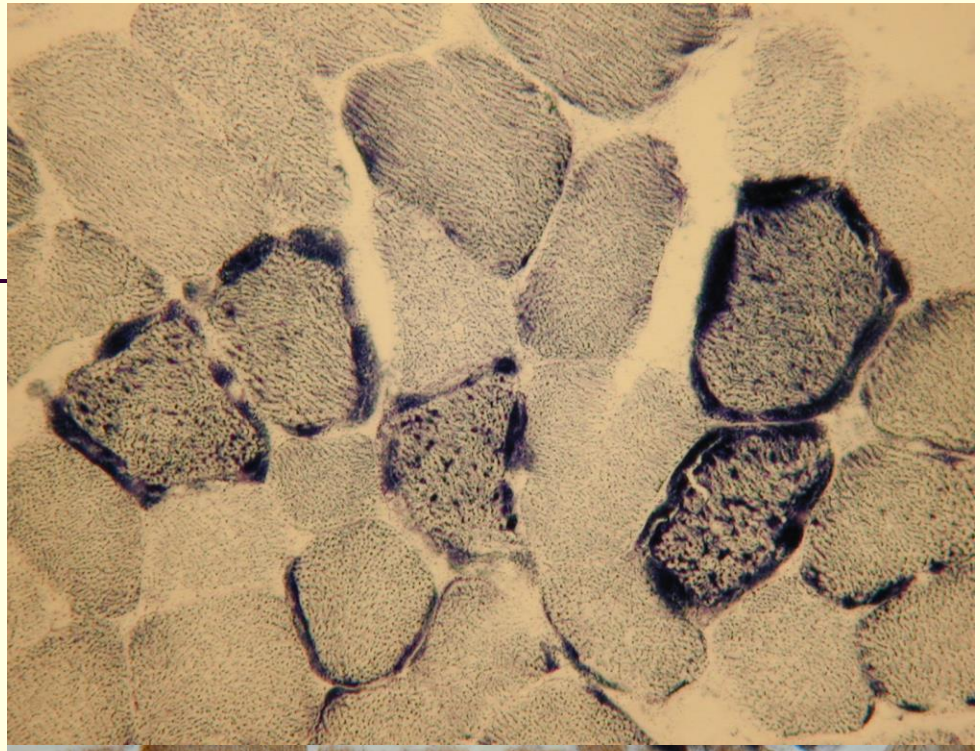
Szövettani technika I.



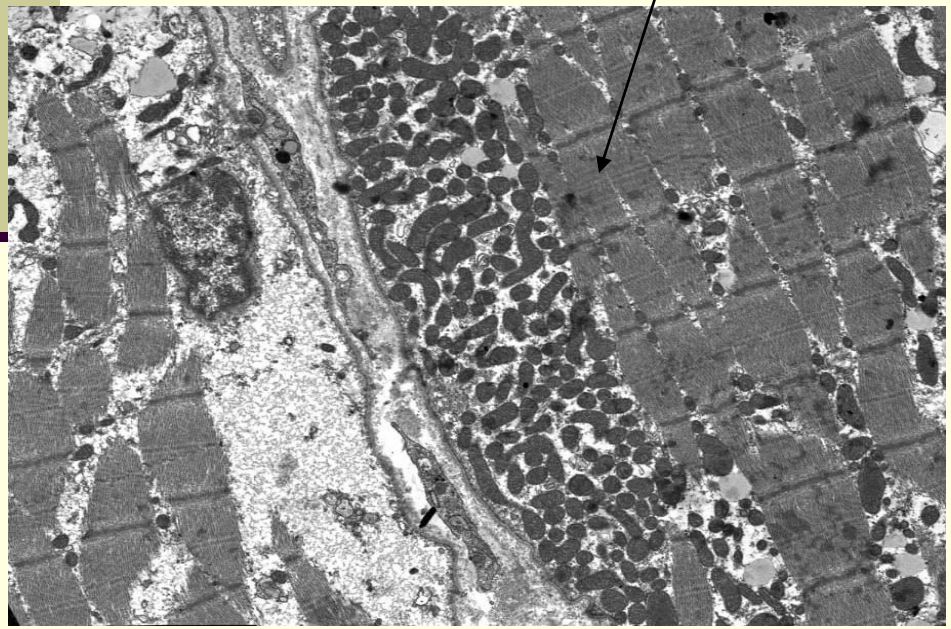


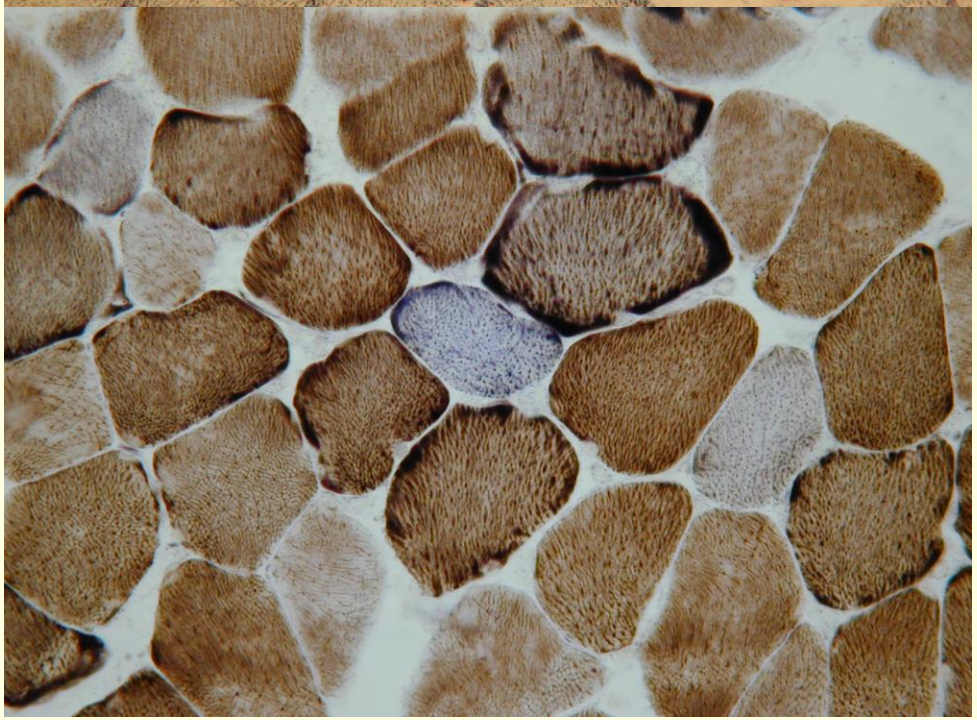






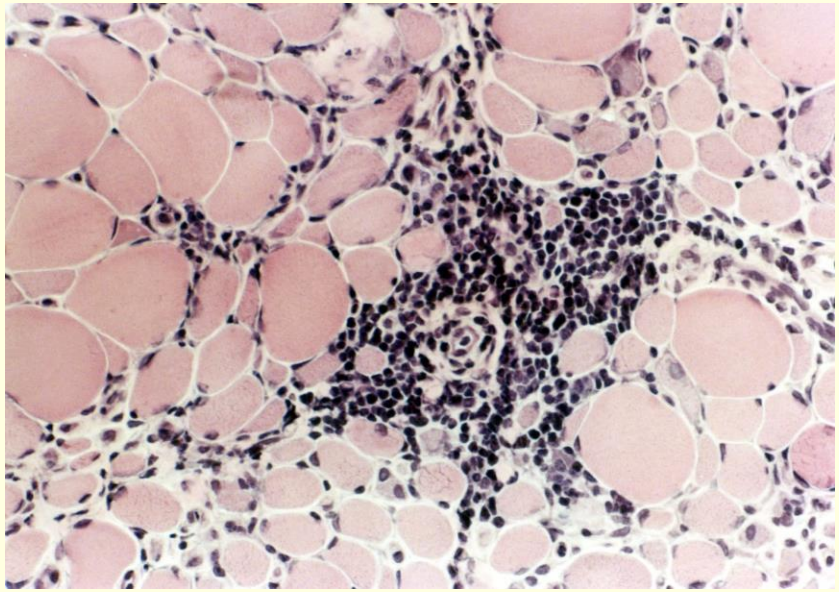
RRF

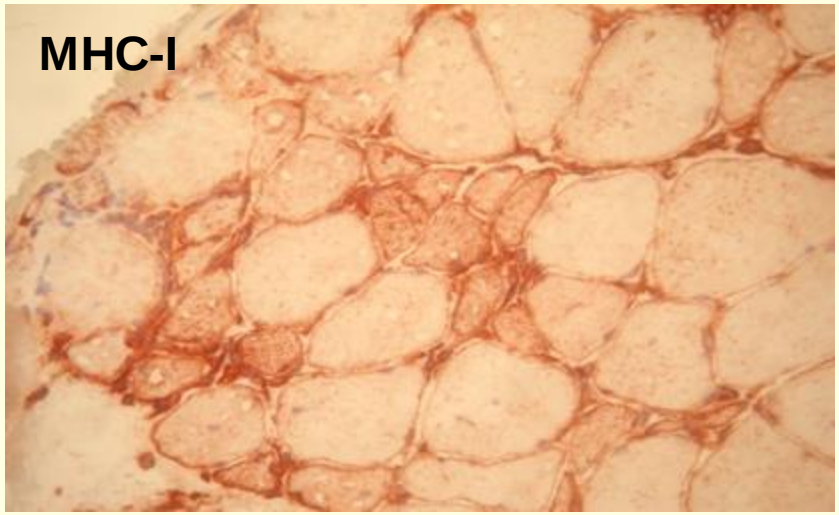


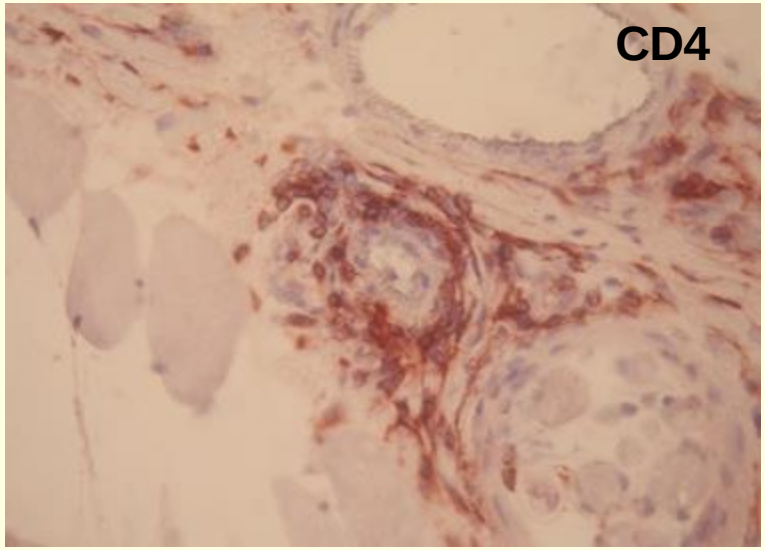


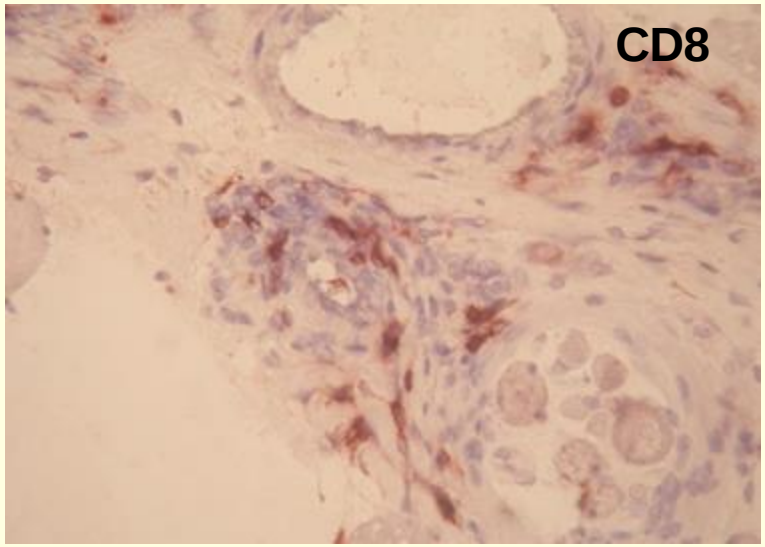
IMMUNHISZTOKÉMIA

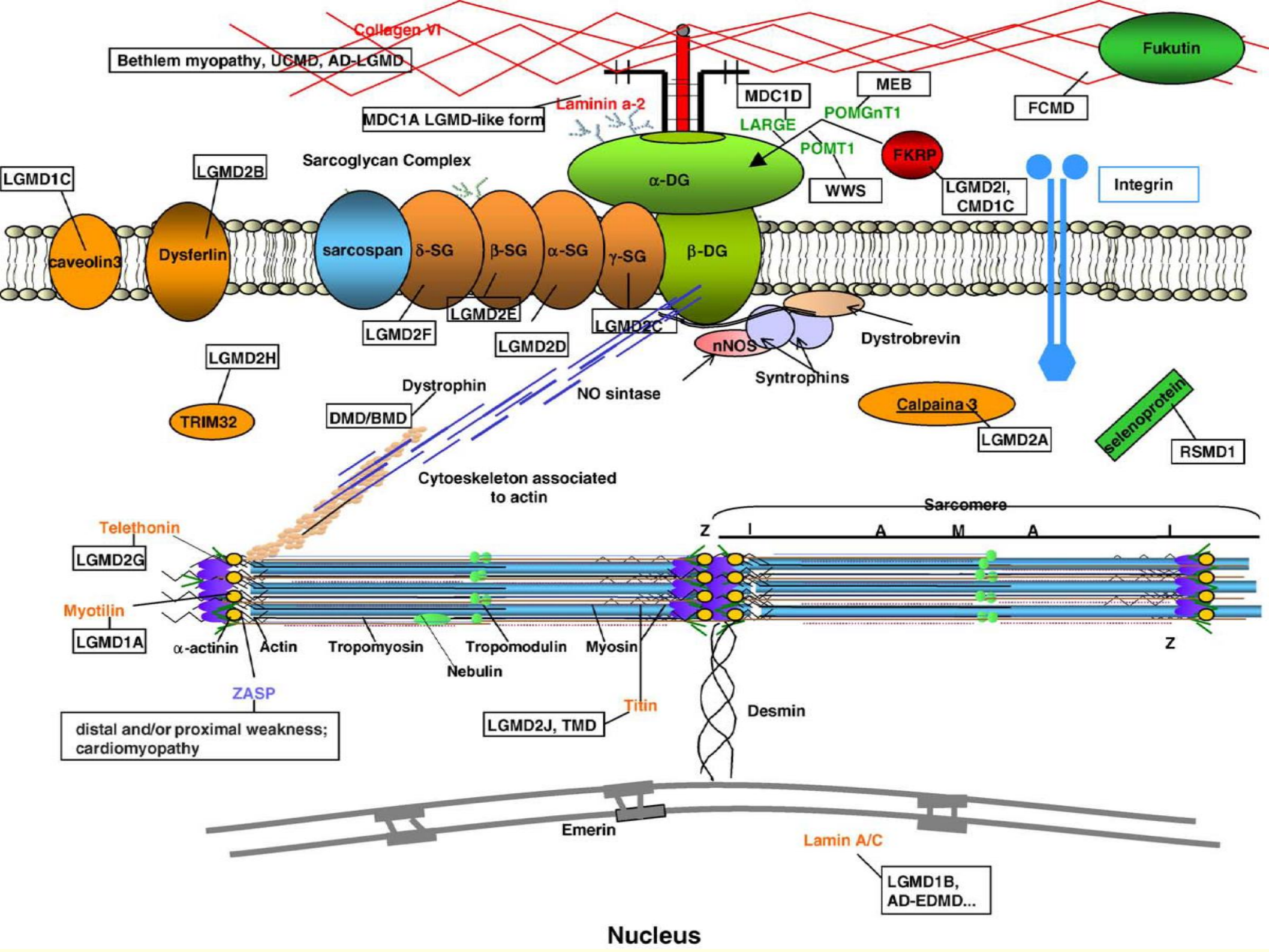
Myositisek: MHC-I, CD3, CD4, CD8, CD68, c5b9, ubiquitin

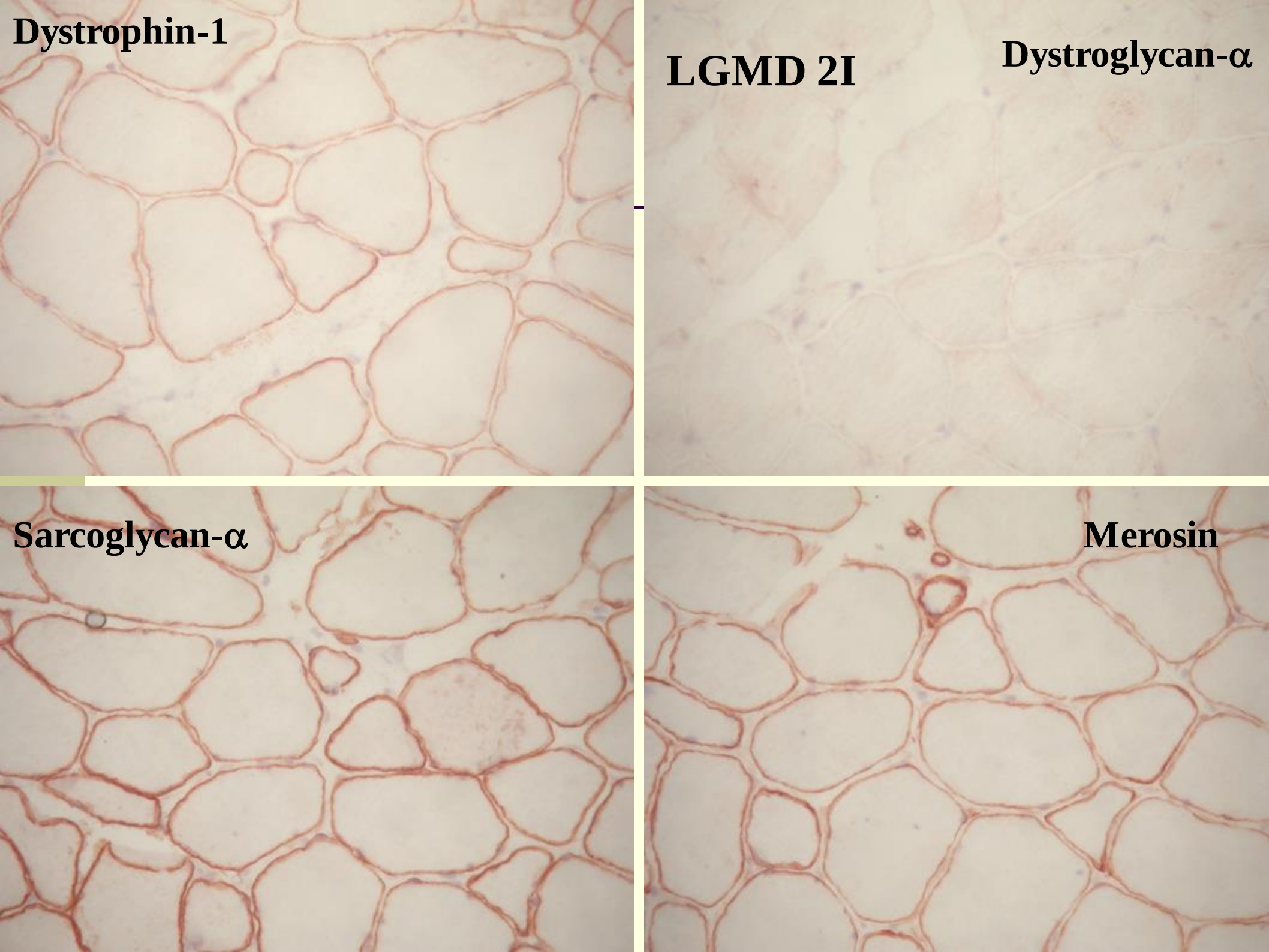


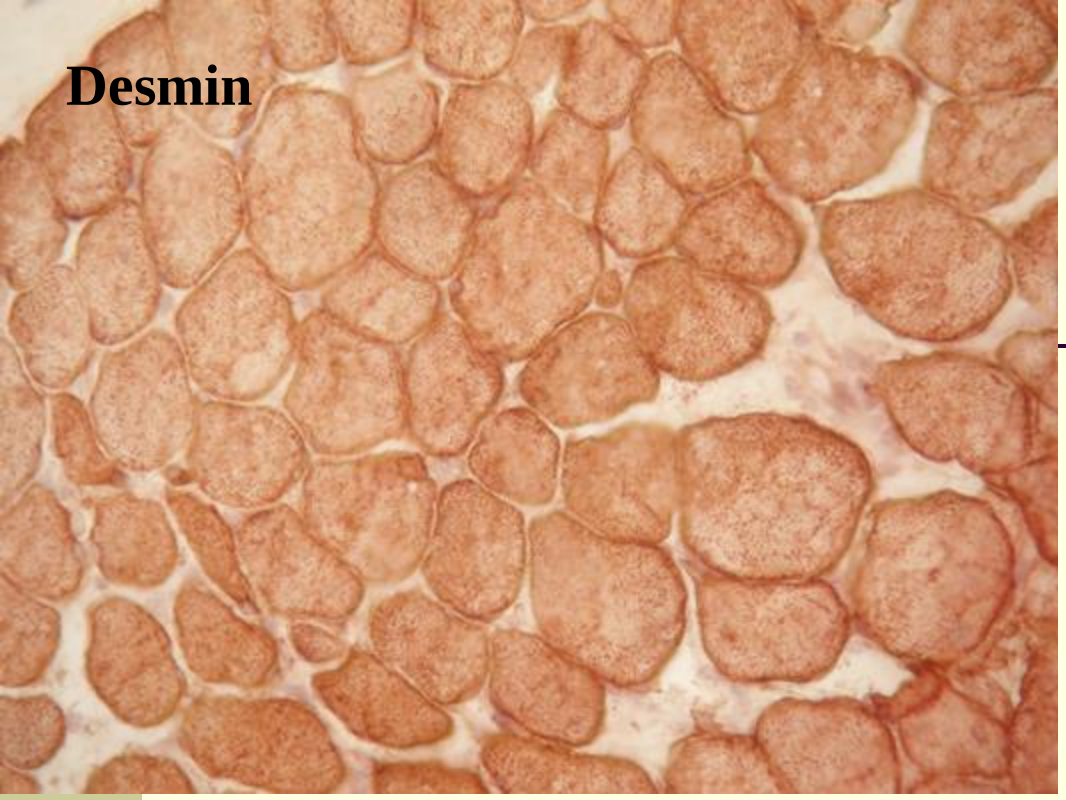


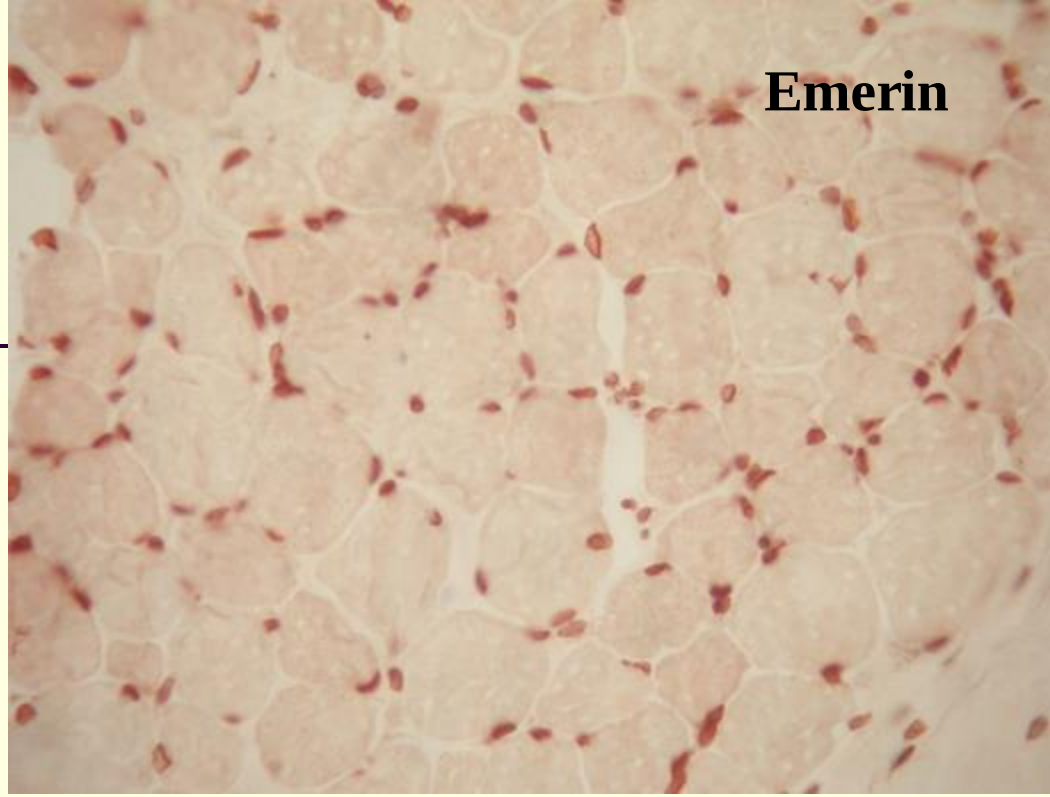


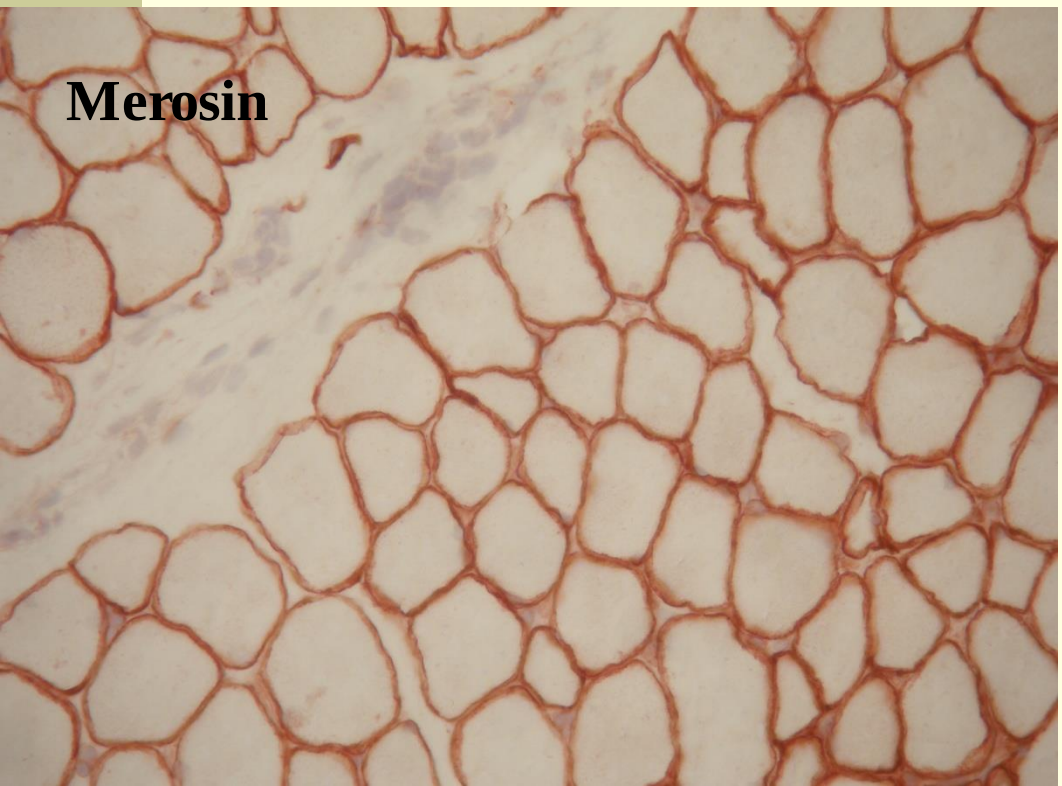


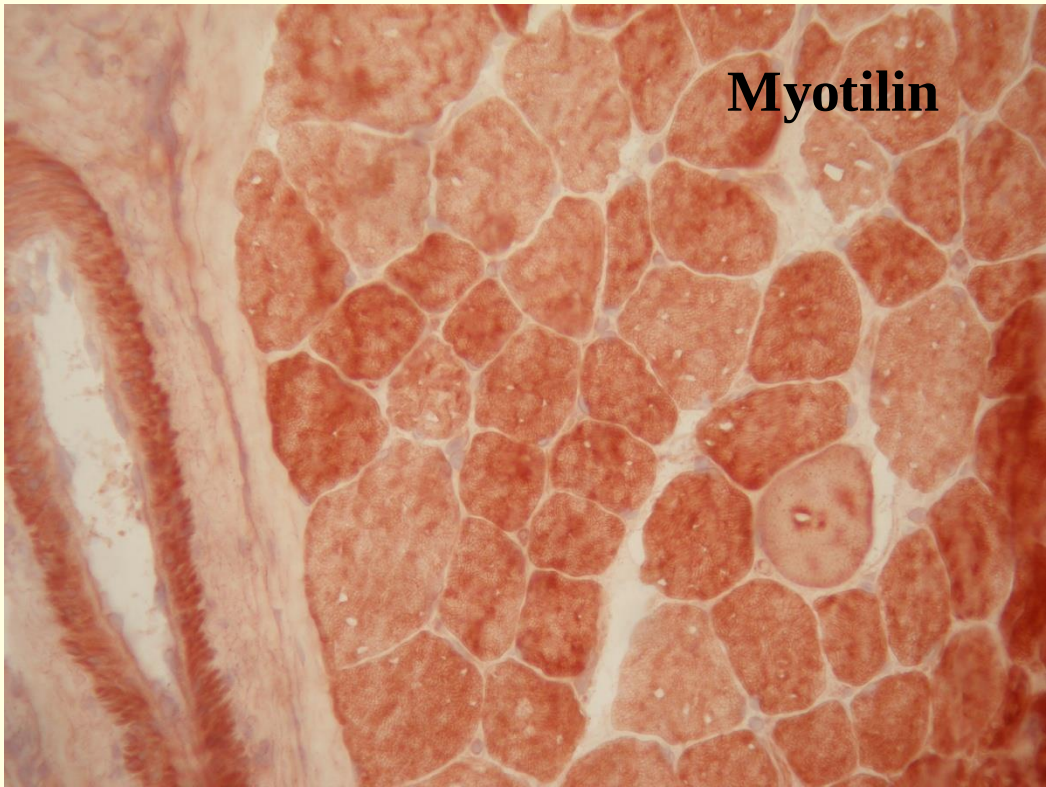

Collagen VI
Bethlem myopathy, UCMD, AD-LGMD
Laminin a-2
MDC1A LGMD-like form
MDC1D
MEB
POMGnT1
LARGE
POMT1
WWS
FKRP
LGMD2I, CMD1C
Fukutin
FCMD
Integrin
Sarcoglycan Complex
α-DG
β-DG
LGMD1C
caveolin3
LGMD2B
Dysferlin
sarcospan
δ-SG
β-SG
α-SG
γ-SG
LGMD2F
LGMD2E
LGMD2D
LGMD2C
nNOS
Syntrophins
Dystrobrevin
LGMD2H
TRIM32
Dystrophin
DMD/BMD
NO sintase
Calpaina 3
LGMD2A
Selenoprotein
RSMD1
Cytoeskeleton associated to actin
Sarcomere
Z
I
A
M
A
I
Z
Telethonin
LGMD2G
Myotilin
LGMD1A
α-actinin
Actin
Tropomyosin
Nebulin
Tropomodulin
Myosin
Titin
LGMD2J, TMD
Desmin
ZASP
distal and/or proximal weakness; cardiomyopathy
Emerin
Lamin A/C
LGMD1B, AD-EDMD...
Nucleus


Dystrophin-1
LGMD 2I
Dystroglycan-α
Sarcoglycan-α
Merosin


Desmin


Emerin


Merosin


Myotilin

V. KIEGÉSZÍTŐ VIZSGÁLATOK

Biokémia

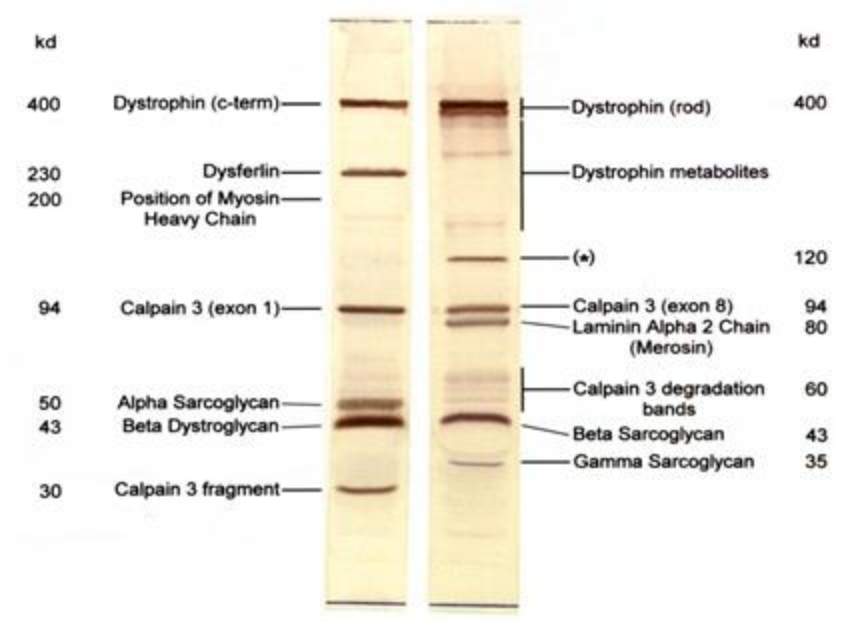
Enzimaktivitás
Mitokondriális (citrát szintáz, komplex I-IV)
Glikolizis, foszforiláz, acid-maltáz, stb.

Fehérje-expresszió

Immunoblot (DMD/BMD, LGMD)

Genetika

Vér + izom (mitDNS)



Molekuláris genetika

- Egyes betegségeknél nincs szükség biopsziára:
  - Spinalis izomatrophia (SMA)
  - Spinalis-bulbaris izomatrophyia (SBMA)
- Hordozó/Prenatalis diagnózis
- Magyarországon:
  - Duchenne/Becker dystrophia, LGMD 2A, 2B, 2I, **2L** (***ANO5***)
  - FSHD (facio-scapulo-humeralis dystrophia)
  - DM1 (Dystrophia myotonica)
  - Mitokondriális betegségek (PEO, MERRF, MELAS, stb.)
  - ***MYH7*** (Laing korai kezdetű distalis myopathia)

Diagnosztikus algorimus: gyermek

- **Születéskor**
  - Congenitalis dystrophia, dystrophia myotonica, GSDII (Pompe)
  - Congenitalis myopathiák (central core, etc.)
  - Congenitalis myasthesia syndroma (CMS)
- **Gyermekkorban**
  - Izomdystrophiák (Duchenne (DMD), sarcoglycanopathiák **(SCARMD),** FSHD, DM1, distalis: MYH7)
  - Metabolikus (glycogen, lipid tárolás, mitochondrialis: Leigh)

Diagnosztikus algorimus: gyermek

1. Fenotípus meghatározása („floppy baby” heterogén etiológiájú)

2. Elektrofiziológia: myogén és neurogén betegség elkülönítése
CMS (congenitalis mysthenia szindróma)

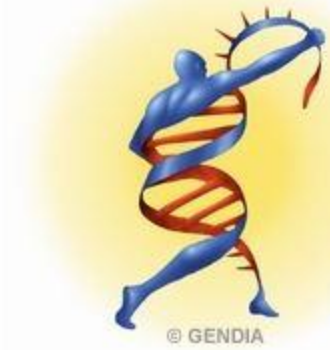
3a. Neurogén betegség, SMA: genetika

3b. Myopathia: legtöbb esetben izombiopszia szükséges

Biopszia orientálja a genetika vizsgálatot:

Duchenne esetén: genetika (MPLA)
LGMD 2C-F, I: célzott genetika
LGMD specifikus pathológia nélkül: gentika - NGS (külföld)
Congenitalis dystrophia (DGA, MER, collagén VI): célzott genetika v. NGS
Congenitalis myopathia
Specifikus eltérések: Genetika (célzott gén vizsgálat: MYH7, ACTA1)
Nem specifikus eltérések: Genetika – NGS

Nem specifikus eltérések/tipusos klinikum: CMS: *CHRNE*, vagy NGS



MUSCULAR DYSTROPHY (CONGENITAL) (PANEL 5)	• B3GALNT2 • B3GNT1 • CHKB • COL12A1 • COL6A1 • COL6A3 • DAG1 • DPM1 • DPM3 • FKRP • FKTN • GMPPB • GOSR2 • ISPD • ITGA7 • LAMA2 • LARGE • LMNA • POMGNT1 • POMGNT2 • POMK • POMT1	25 genes (Sequencing)	2200

gendia.net

	• POMT2 • ST3GAL4 • TMEM5		
MUSCULAR DYSTROPHY			

MYASTHENIA (PANEL 3)	• AGRN • BLK • C5 • CCL21 • CCR6 • CD2 • CD28 • CD40 • CD58 • CHAT • CHRNA1 • CHRNB1 • CHRND • CHRNE • CHRNG • COLQ • DOK7 • GFPT1 • IL2 • IL21 • IL2RA • IL2RB • IL6ST • IRF5 • MUSK • PRDM1 • PRKCQ • PTPRC • RAG1 • RAPSN • RBPJ • SCN4A • STAT4 • TAGAP • TNFAIP3 • TNFRSF14 • TRAF1 • TRAF3IP2 • TRAF6 • VAMP2	40 genes (Sequencing)	2100

Diagnosztikus algorimus: felnőtt

1. Fenotípus meghatározása (LGMD/FSHD/Distalis)

2. Kórtörténet (örökletes/szerzett)

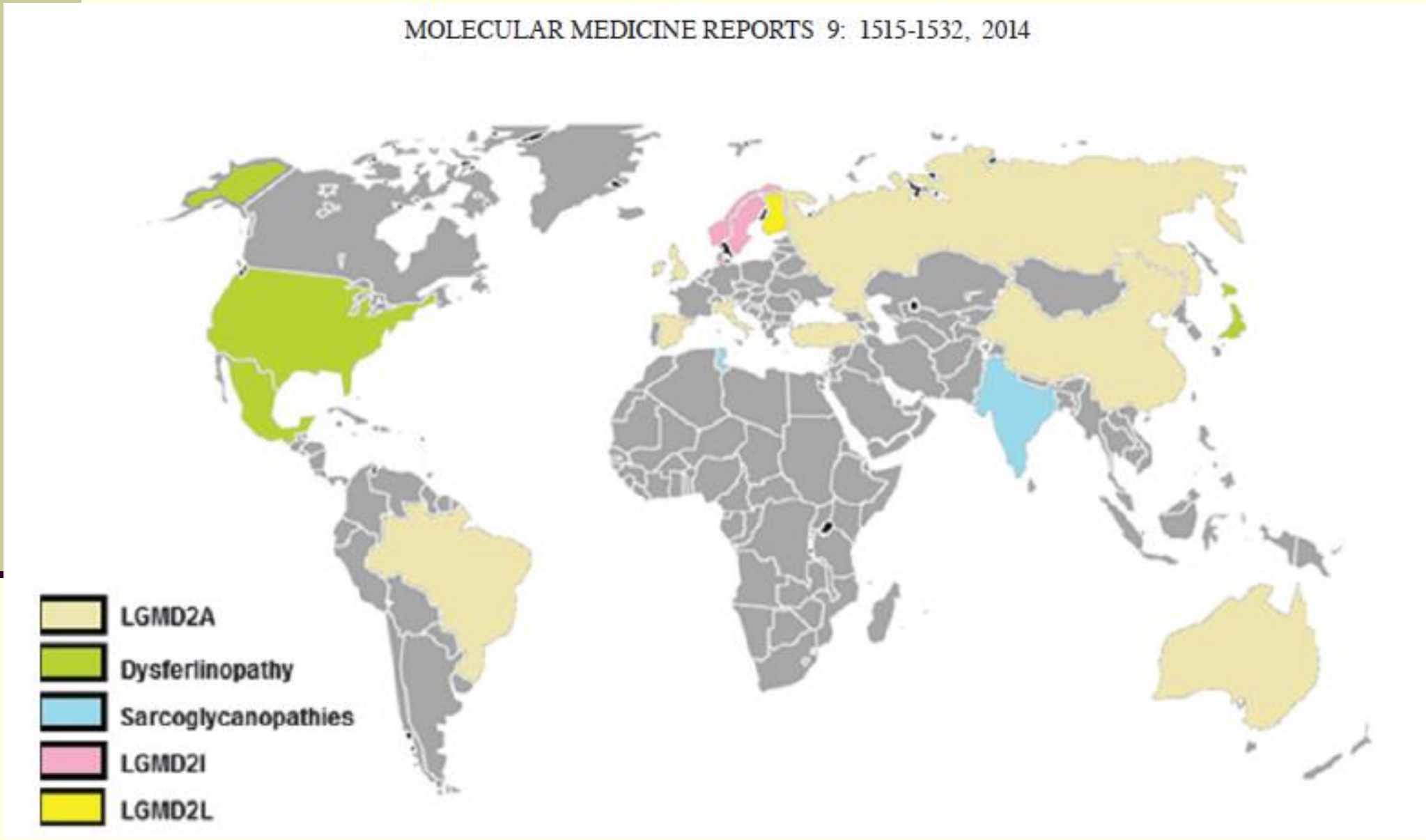
3. Elektrofiziológia: **myopathia v. neurogén betegség**
NMJ betegség (MG/LEMS)

4a. Neurogén betegség: ALS, SBMA, SMA, Polyneuropathia

4b. Myopathia:

DM1 gyanúja: genetika
FSHD gyanúja: genetika
LGMD: (MRI), izombiopszia, célzott gén v. NGS
Distalis myopathia: MRI, izombiopszia
OPMD: izombiopszia
Myositis: izombiopszia

Végtagövi izomdystrophiák (LGMD)



	Fehérje	Kezdet	CK	CMP	Hot spot	Spektrum, jellemző
LGMD 1A	Myotilin	18-35 év	n. ↑	-	-	Biopszia: RV (zárvány)
LGMD 1C	Caveolin3	4-35 év	10x	-	-	Asympt.CK -
LGMD 2A	Calpain3	8-15 év	10x	-	c550delA	Szimm. scapula alata
LGMD 2B	Dysferlin	2. évtized	50x	-	-	Miyoshi (distalis) myopathia (MMD1)
LGMD 2C	Sarcoglycan γ	Gyermekkor	10x	-	C283Y del525T	SCARMD, Roma/Mediterrán régió
LGMD 2D	Sarcoglycan α	3-15 év	20x	-	-	SCARMD
LGMD 2E	Sarcoglycan β	5-15 év	20x	-	-	SCARMD
LGMD 2I	FKRP (DGα)	11-50 (Gyk)	10x	+	c826C>A	MDC
LGMD 2L	ANO5	35 év	50x	-	c.191dupA c.2272C>T	Asympt.CK - MMD3 (aszimmetrikus)

MUSCULAR DYSTROPHY (PANEL 1)	• ANO5 • CAPN3 • CAV3 • DAG1 • DMD • DYSF • EMD • FHL1 • FKRP • FKTN • LMNA • MYOT • PLEC • POMGNT1 • POMT1 • POMT2 • SGCA • SGCB • SGCD • SGCG • SYNE1 • SYNE2 • TCAP • TRIM32 • TTN	25 genes (Sequencing)	2100

MYOFIBRILLARIS MYOPATHIÁK

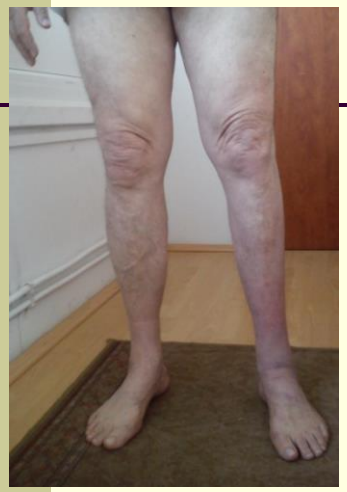
MYOFIBRILLARIS MYOPATHIÁK

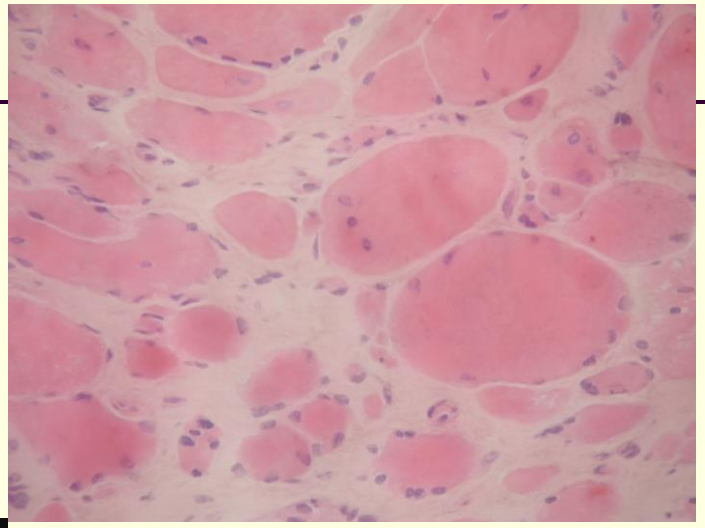
-	**Desminopathia**	***DES***	***IM filamentum***
–	**αB-crystallinopathia**	***CRYAB***	***Z-lemez***
-	**Myotilinopathia**	***MYOT***	***Z-lemez***
-	**ZASPopathia**	***LDB3***	***Z-lemez***
-	**Filaminopathia**	***FLNC***	***Actin-binding***
-	**Bag3opathia**	***BAG3***	***Prot. degradatio***
-	**FHL1opathia**	***FHL1***	***Sarcomer fenntartás***

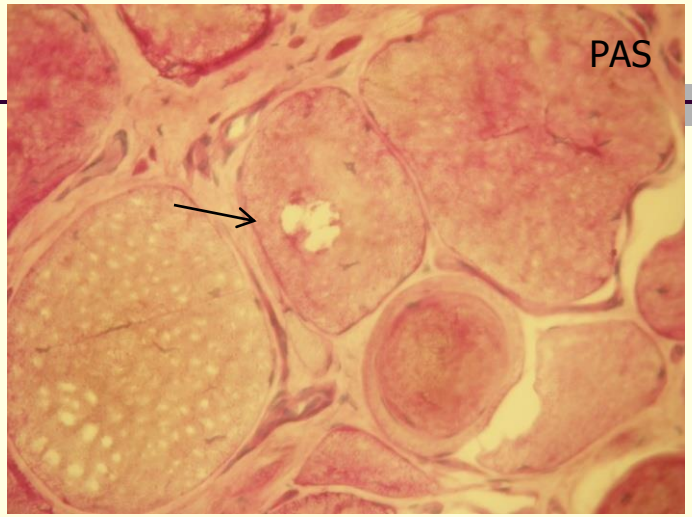
MYOFIBRILLARIS MYOPATHIÁK: klinikai jellemzők

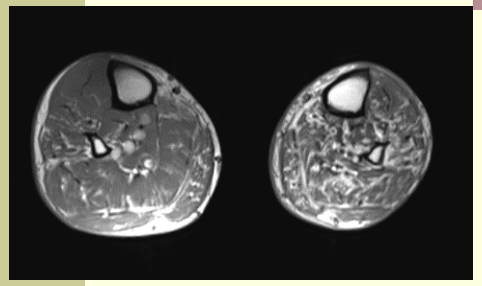
Spheroid body myopathy
Sarcoplasmic body myopathy
Cytoplasmic body myopathy
Protein aggregate myopathy
Hereditary inclusion body myopathy

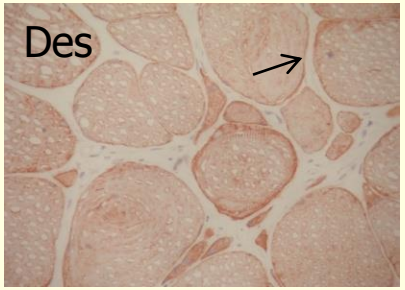
Z lemez-asszociált fehérjék: <u>vázizomban és szívizomban</u>
<u>Hasonló klinikai kép:</u>
- felnőttkori kezdet, distalis izmok, lasssú progresszió
- kivétel: BAG3 és FHL1: gyermekkori, progresszív
EMG: myopathia, ENG: neuropathia
CK: normális, vagy kissé emelkedett
Kardialis érintettség gyakori (arritmia, CMP)
Cataracta: αB-crystallin
Hasonló ultrastruktúrális eltérések






PAS

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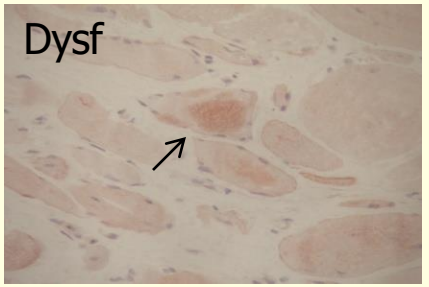
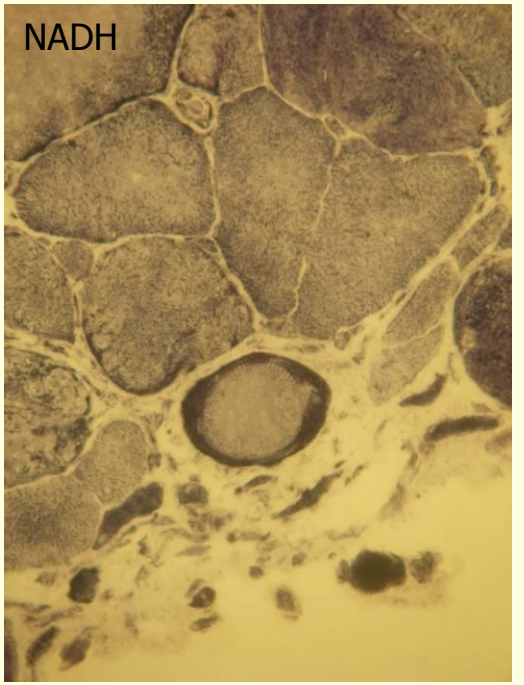
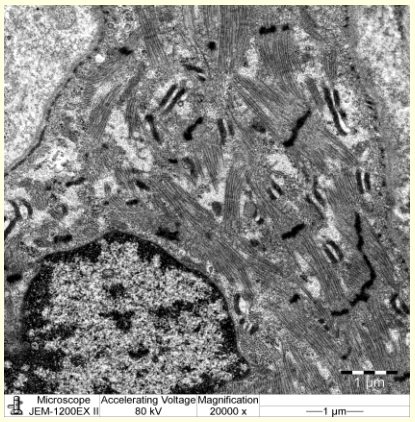
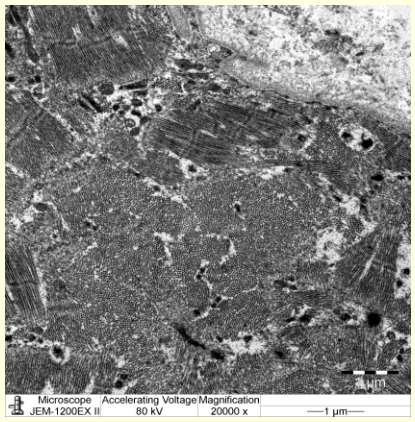

Dysf


NADH


Microscope Accelerating Voltage Magnification
JEM-1200EX II 80 kV 15000 x
2 µm

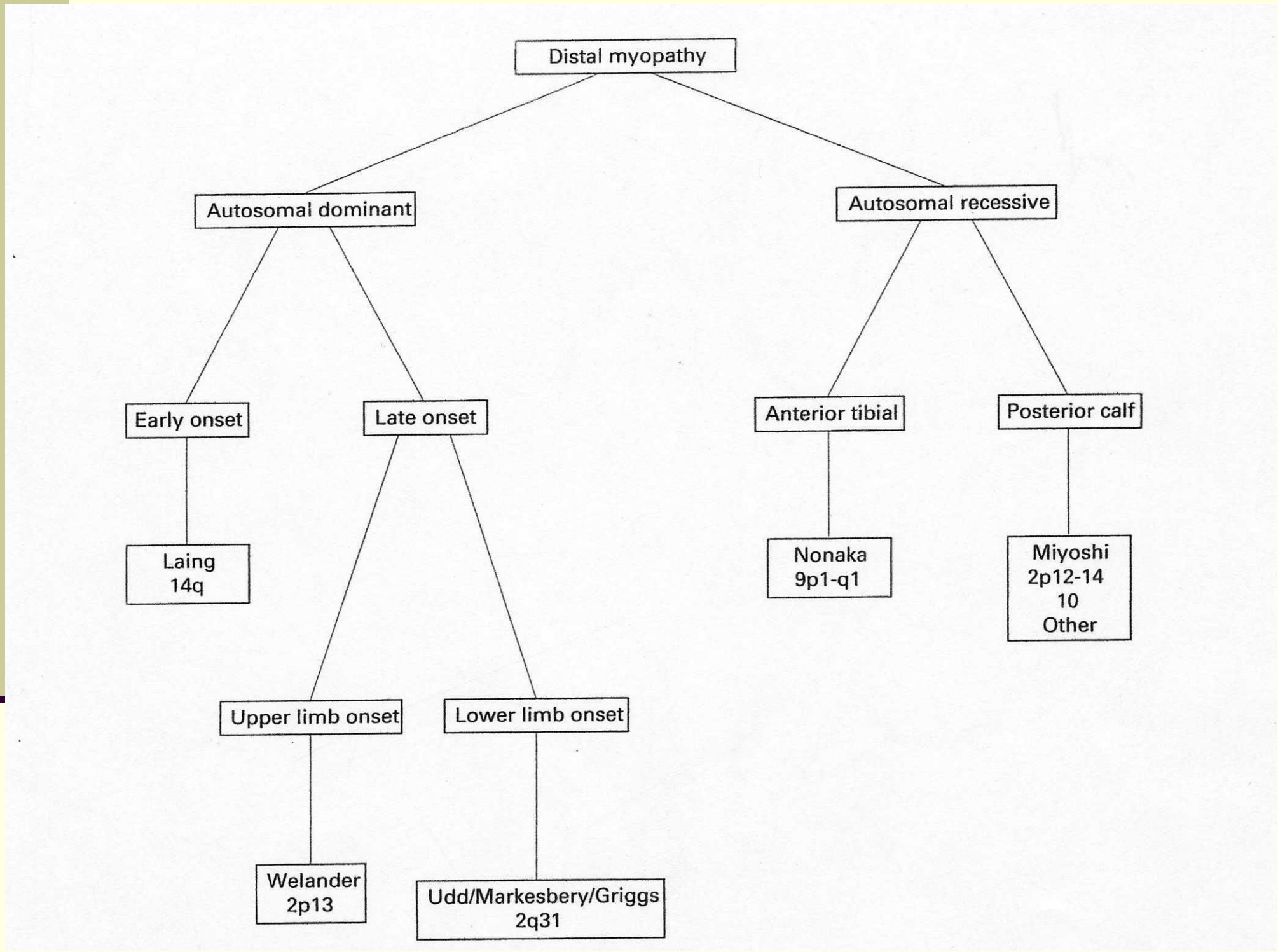

Microscope Accelerating Voltage Magnification
JEM-1200EX II 80 kV 20000 x
1 µm

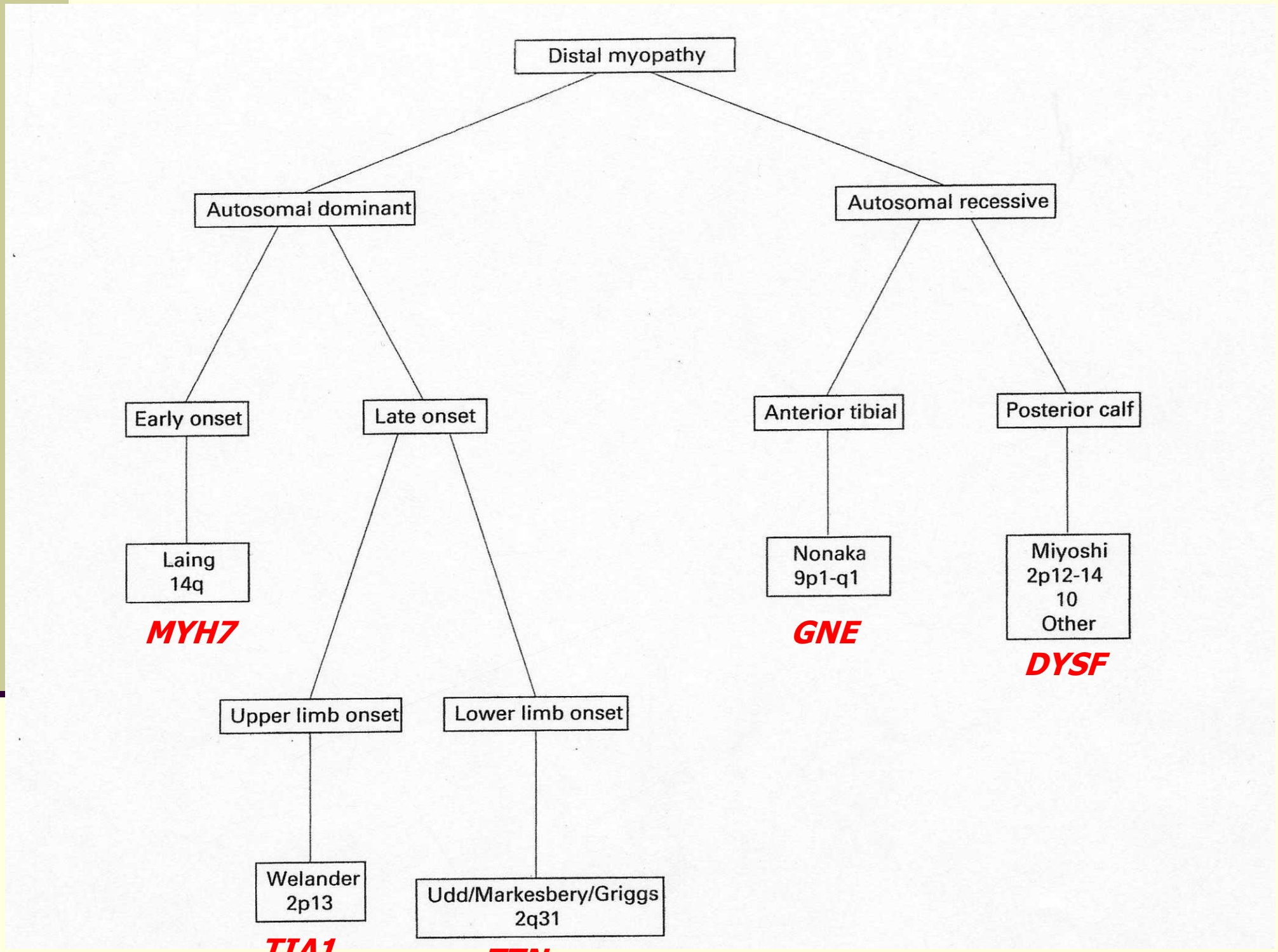

Microscope Accelerating Voltage Magnification
JEM-1200EX II 80 kV 20000 x
1 µm

Myofibrillaris myopathiák

- Distalis myopathia
- Myopathia + neuropathia együtt
- Jellemző izombiopsziás kép (zárványok)

Distalis myopathiák


Distal myopathy
Autosomal dominant
Autosomal recessive
Early onset
Late onset
Anterior tibial
Posterior calf
Laing
14q
Nonaka
9p1-q1
Miyoshi
2p12-14
10
Other
Upper limb onset
Lower limb onset
Welander
2p13
Udd/Markesbery/Griggs
2q31

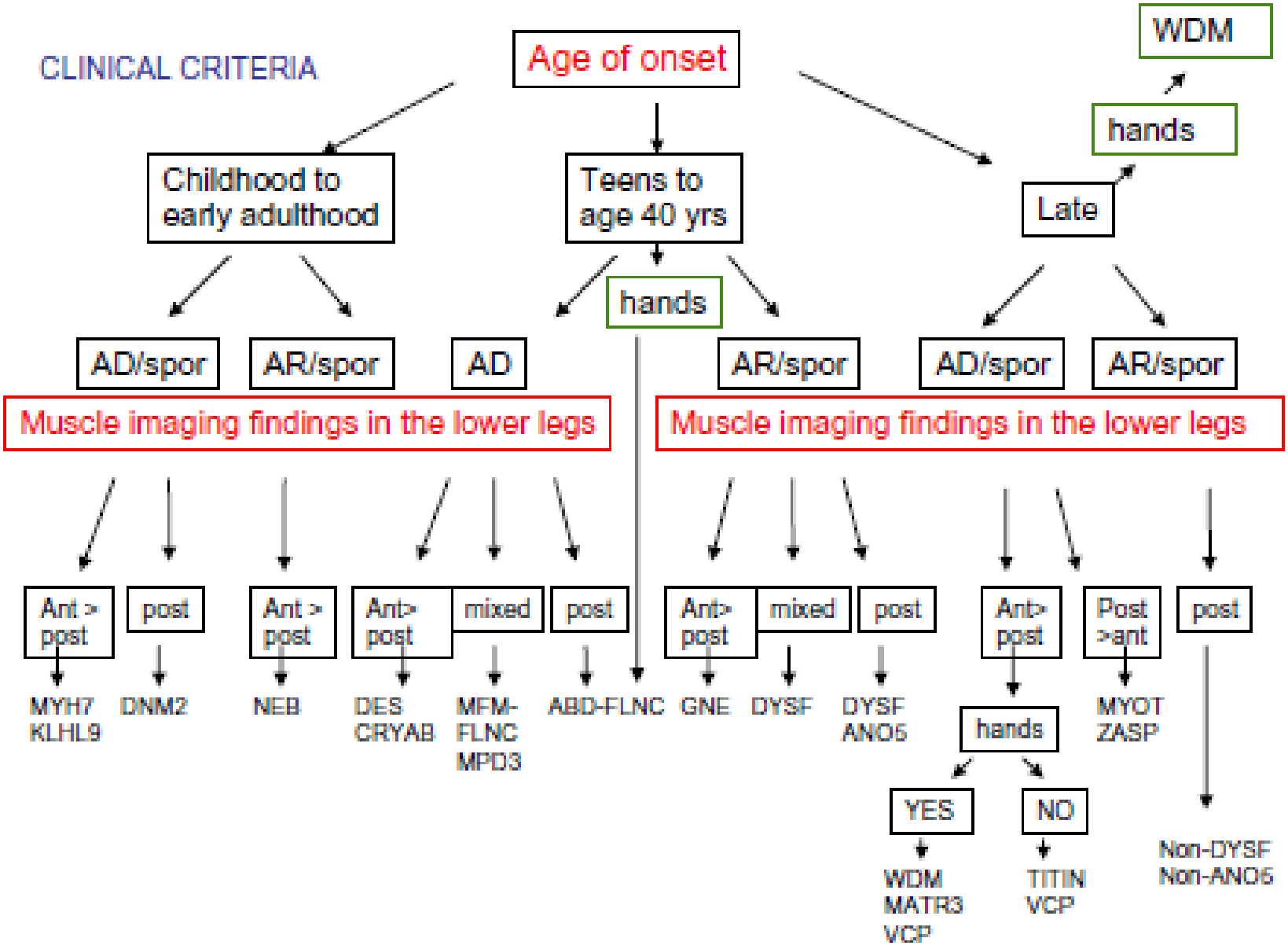

Distal myopathy
Autosomal dominant
Autosomal recessive
Early onset
Late onset
Anterior tibial
Posterior calf
Laing
14q
MYH7
Nonaka
9p1-q1
GNE
Miyoshi
2p12-14
10
Other
DYSF
Upper limb onset
Lower limb onset
Welander
2p13
TIA1
Udd/Markesbery/Griggs
2q31
TTN

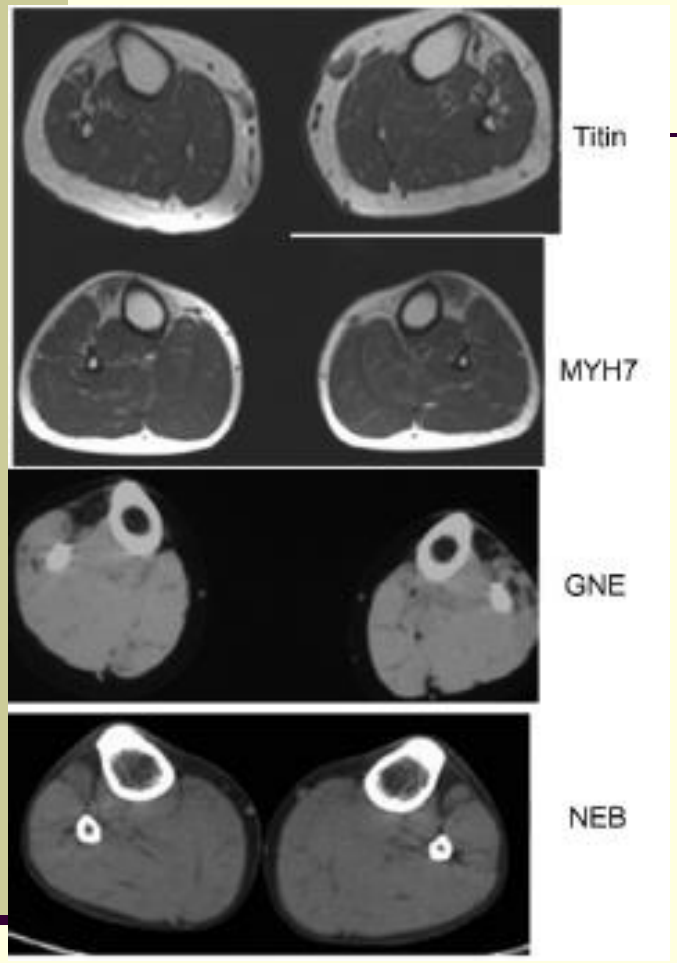
Genetically determined distal myopathies.

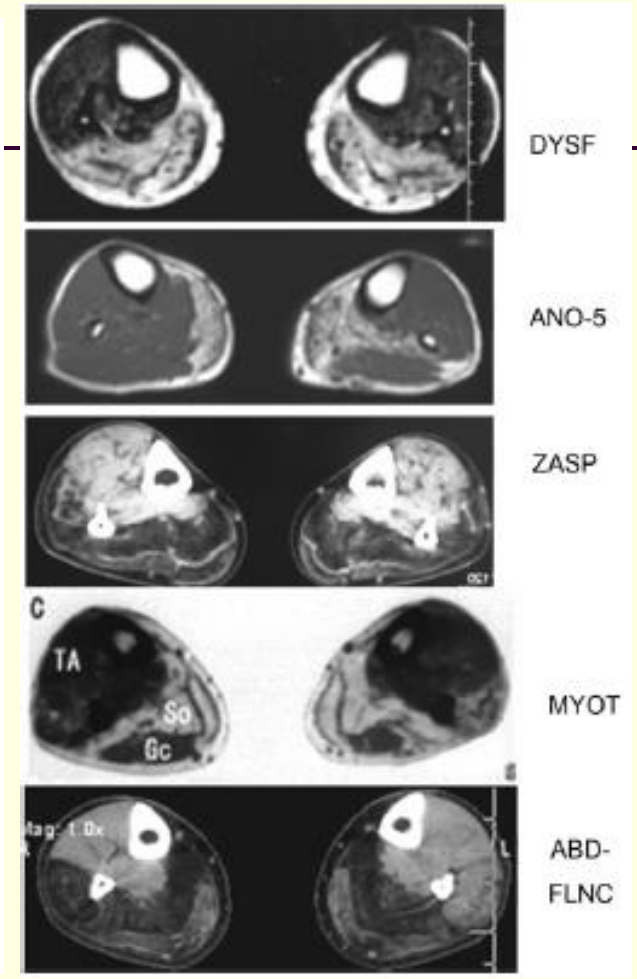
	Gene	Protein	Ref.
1. Late adult onset autosomal dominant forms			
a. Welander distal myopathy	*TIA1*	*TIA1*	Welander [1]
b. Tibial muscular dystrophy (TMD, Udd myopathy)	*TTN*	Titin	Udd et al. [5]
c. Distal myotilinopathy	*TTID*	Myotilin	Penisson-Besnier et al. [30]
d. ZASPopathy (Markesbery–Griggs)	*LDB3*	ZASP	Griggs et al. [18]
e. Matrin3 distal myopathy (VCPDM, MPD2)	*MATR3*	Matrin3	Senderek et al. [35]
f. VCP-mutated distal myopathy	*VCP*	VCP	Palmio et al. [36]
g. Alpha-B crystallin mutated distal myopathy	*CRYAB*	αB-crystallin	Reichlich et al. [38]
2. Adult onset autosomal dominant forms			
a. Desminopathy	*DES*	Desmin	Sjöberg et al. [14]
b. Distal ABD-filaminopathy	*FLNC*	Filamin-C	Duff et al. [42]
c. Finnish-MPD3	nd	nd	Mahjneh et al. [57]
d. Italian 19p13-linked distal myopathy	nd	nd	Servidei et al. [55]
e. US-Polish family	nd	nd	Felice et al. [56]
f. Oculopharyngeal distal myopathy, OPDM	nd	nd	Durmus et al. [54]
3. Early onset autosomal dominant forms			
a. Laing distal myopathy (MPD1)	*MYH7*	Beta-MyHHC	Laing et al. [8]
b. KLHL9 mutated distal myopathy	*KLHL9*	KLHL9	Cirak et al. [46]
4. Early onset autosomal recessive forms			
a. Distal nebulin myopathy	*NEB*	Nebulin	Wallgren-Pettersson al. [47]
5. Early adult onset autosomal recessive forms			
a. Miyoshi myopathy (MM)	*DYSF*	Dysferlin	Miyoshi et al. [2]
b. Distal Anoctaminopathy	*ANO5*	Anoctamin-5	Bolduc et al. [52]
c. Distal myopathy with rimmed vacuoles (DMRV)	*GNE*	GNE	Nonaka et al. [4]
d. Oculopharyngeal distal myopathy, OPDM	nd	nd	Durmus et al. [54]
6. Adult onset autosomal recessive form			
a. Calf myopathy non-DYSF/ANO5	nd	nd	Linssen et al. [59]

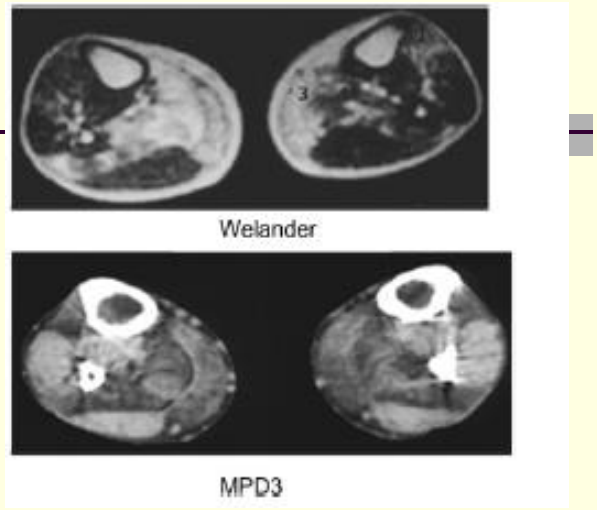
Udd, B. Neuromusc. Disord. 2012;22:5-12.

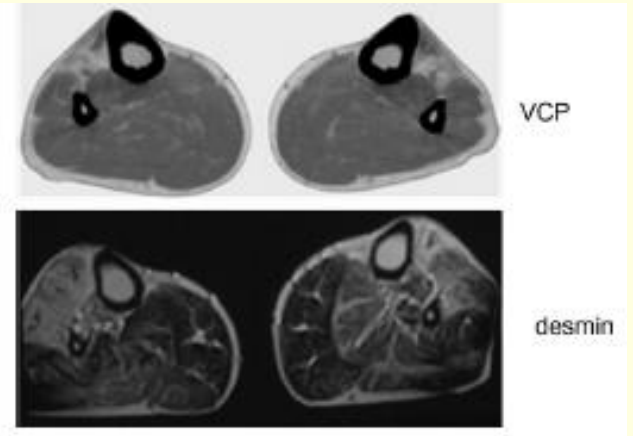
Distalis myopathiák





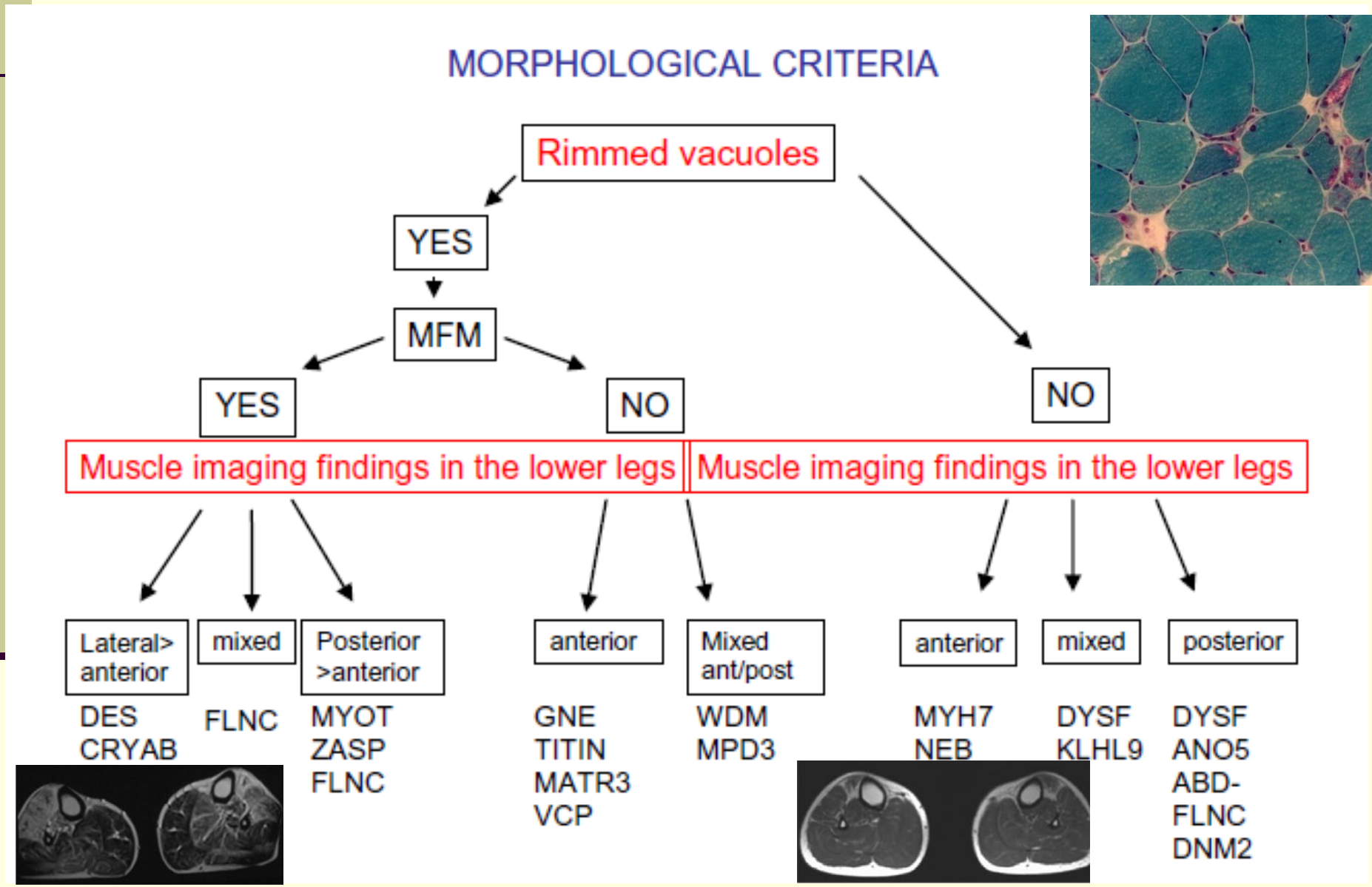






Udd, B. Neuromusc. Disord. 2012;22:5-12.

Bjarne Udd, Neuromuscular Disorders 22 (2012) 5–12



DISTALIS MYOPATHIÁK: összefoglalás

Heterogén betegség csoport: számos genetikai forma ismert

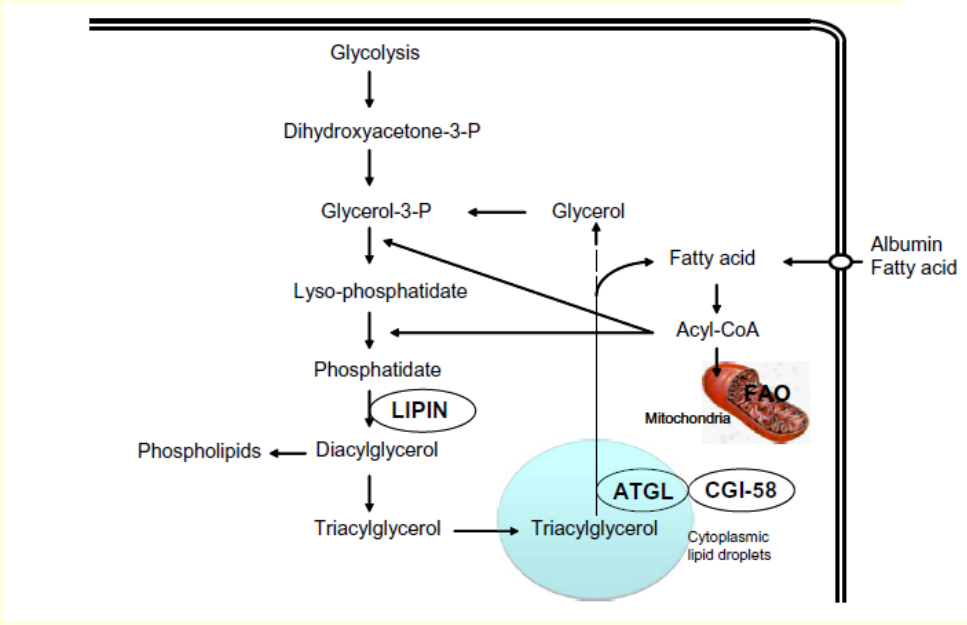
Differenciál diagnosztika alapja:

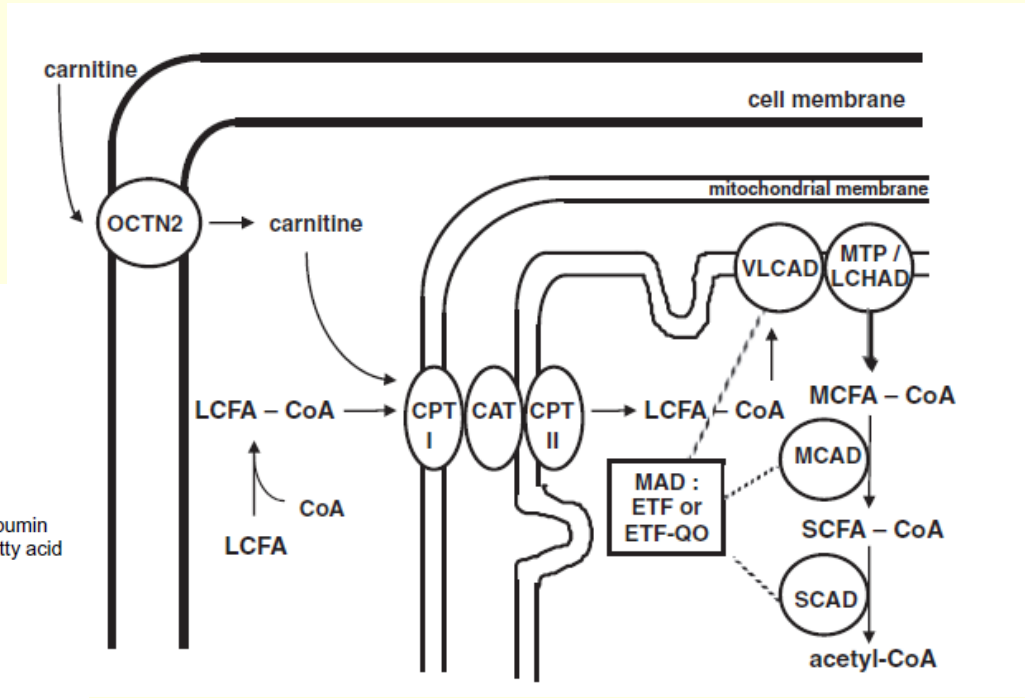
1. **Izomérintettség eloszlása (felső/alsó végtag, elülső/hátsó lábszárizmok): MRI**
2. **Életkori kezdet (gyermek v. felnőtt)**
3. **Izombiopszia (myofibrillaris eltérések, RV (rimmed vacuola) jelenléte v. hiánya**

GNE* myopathia:** ***ERT aceneuramic acid (sialic acid) extended release (ER) kezelés

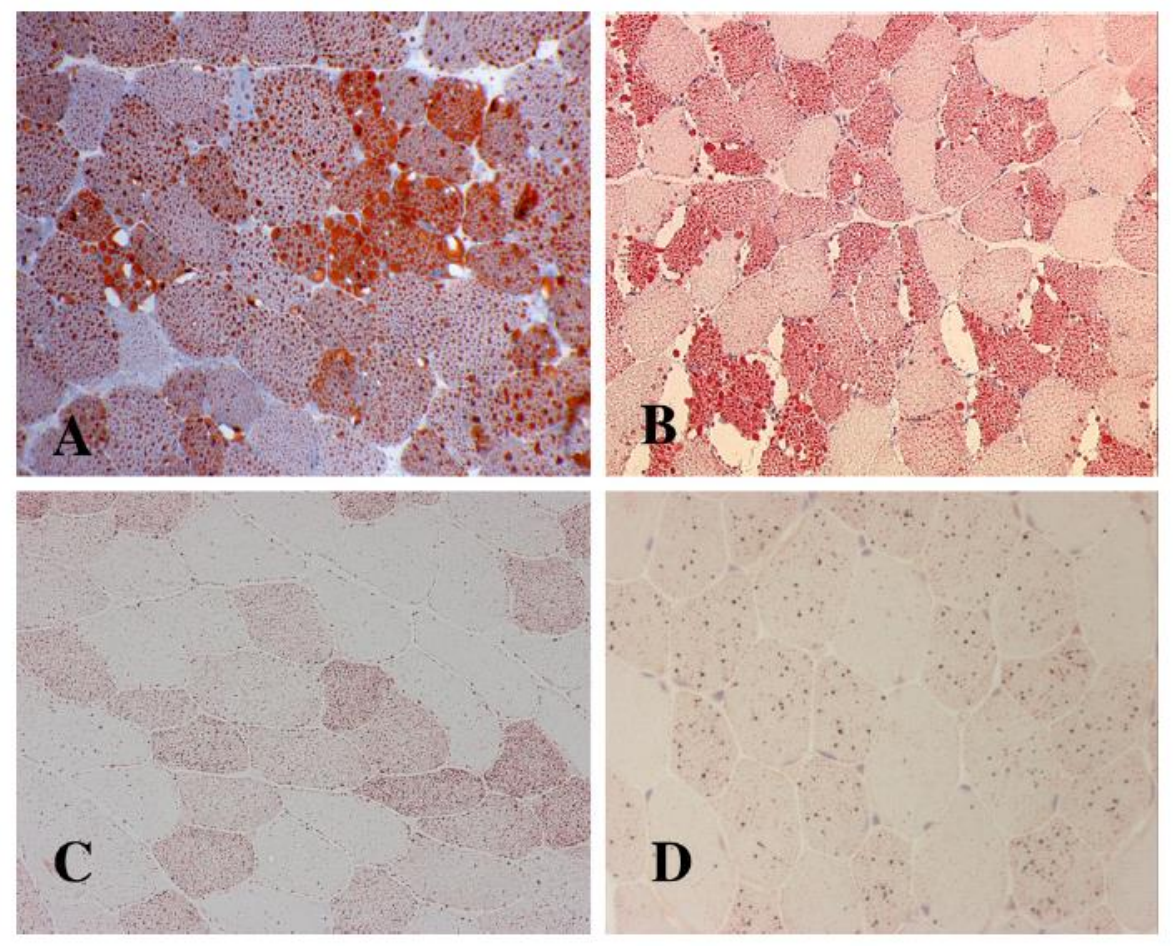
TÁROLÁSOS BETEGSÉGEK

Lipid tárolásos betegségek





Lipid tárolásos betegségek



Lipid tárolásos betegségek

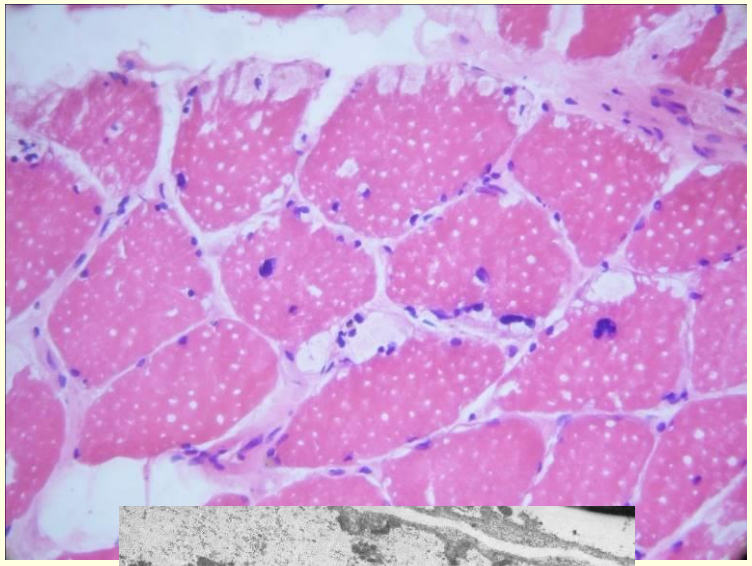
Main clinical neuromuscular and biological features of metabolic disorders with muscle lipidosis.

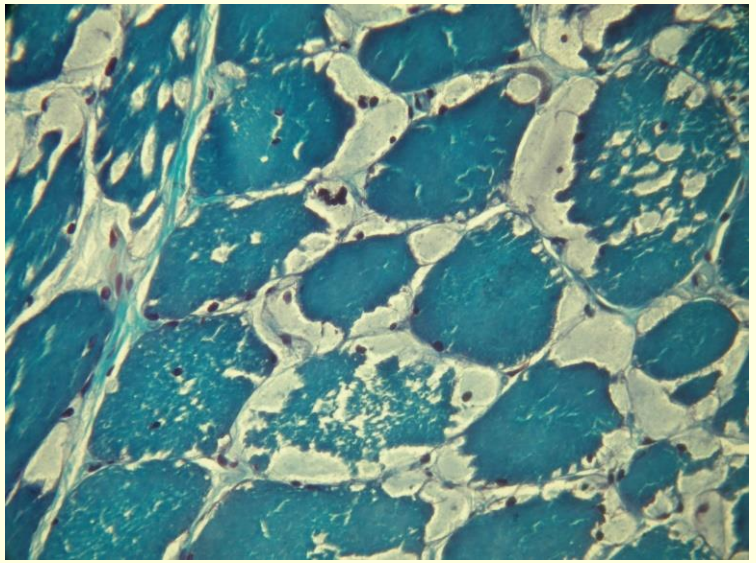
Disorder	Main neuromuscular symptoms [a]	Increase in muscle lipid droplets	Laboratory features[b]	Gene
Primary carnitine deficiency	Proximal muscle weakness, cardiomyopathy	+++	**Very low plasma and muscle carnitine** No acylcarnitines	*SLC22A5*
Neutral lipid storage disease (NLSD)	Proximal or distal muscle weakness, cardiomyopathy	+++	Normal plasma carnitine Normal acylcarnitine profile **Lipid vacuoles in leukocytes**	*ABHD5* *PNPLA2*
Multiple acyl-CoA dehydrogenase (MAD) deficiency	Proximal and axial weakness Rhabdomyolysis (rarely)	++ to +++	Low plasma carnitine **Increased acylcarnitines of all chain lengths** **2-Hydroxyglutaric aciduria ± acylglycines**	*ETFDH*
Carnitine palmitoyl transferase II (CPT II) deficiency	Rhabdomyolysis episodes	0 to +	Normal or moderately reduced plasma carnitine **Increased long-chain acylcarnitines (C_{16}, $C_{18:1}$, C_{18})**	*CPT2* (p.Ser113Leu prevalent mutation)
Very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency	Rhabdomyolysis episodes Cardiomyopathy	0 to +	Normal or moderately reduced plasma carnitine **Increased long-chain acylcarnitines ($C_{14:1}$ as main species)** Dicarboxylic aciduria	*ACADVL*
Mitochondrial trifunctional protein (MTP) deficiency	Rhabdomyolysis episodes Cardiomyopathy Axonal peripheral neuropathy	0 to +	**Increased long-chain 3-hydroxyacylcarnitines** Dicarboxylic and 3-hydroxydicarboxylic aciduria	*HADHA* *HADHB*
Phosphatidic acid phosphatase deficiency	Rhabdomyolysis episodes	0 to +	Normal plasma carnitine Normal acylcarnitine profile Normal urinary organic acids	*LPIN1*
Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency	*Muscle weakness* *Rhabdomyolysis episodes*	0 to +	Low plasma carnitine **Increased medium-chain acylcarnitines (C_6, C_8, C_{10}, $C_{10:1}$)** Dicarboxylic aciduria + **acylglycines**	*ACADM* (p.Lys304Glu prevalent mutation)
Short-chain acyl-CoA dehydrogenase (SCAD) deficiency	*Muscle weakness*	0 to +	**Increased butyrylcarnitine (C_4)** **Ethylmalonic aciduria**	*ACADS* (p.Gly209Ser or p.Arg171Trp prevalent variations)

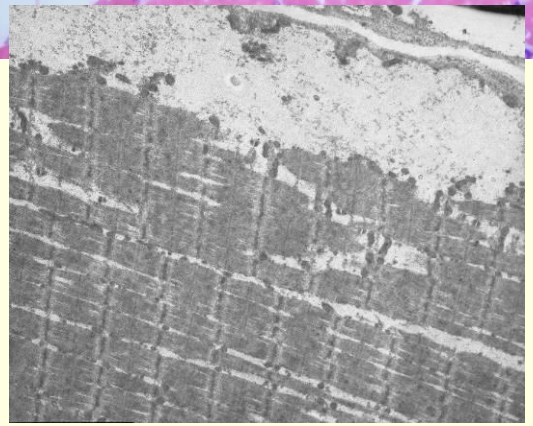
Glycogén tárolásos betegségek (GSD)

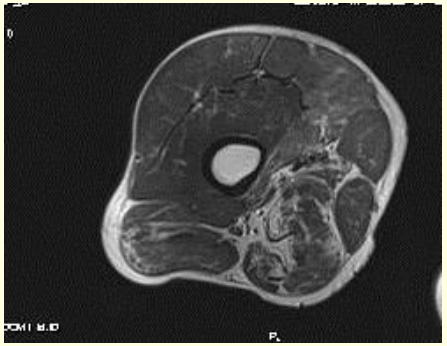
Glycogen storage						
Type	Enzyme	Gene	Chromosome	Muscle signs/symptoms	Other main symptoms	Muscle pathological features
II	Acid α-glucosidase	*GAA*	17	Infancy: progressive weakness, hypotonia Childhood: progressive weakness Adulthood: progressive weakness	Cardiomegaly Hepatomegaly	PAS-positive diastase digestible material
III	Debranching enzyme	*AGL*	1	Infancy: hypotonia and weakness Adulthood: distal and proximal weakness	Hepatomegaly, cardiopathy, hypoglycemia	PAS-positive diastase digestible material
IV	Branching enzyme	*GBE1*	3	Congenital: hypotonia Childhood and adulthood: proximal weakness APBD	Hepatic failure, cardiopathy	PAS-positive partially diastase digestible material PG accumulation
V	Myophoshorylase	*PYGM*	11	Exercise intolerance; myalgia and cramps Myoglobinuria, fixed weakness (late onset)	"Second wind"	Subsarcolemmal and intermyofibrillar deposits of glycogen
VII	Phosphofructokinase	*PFKM*	12	Exercise intolerance; myalgia and cramps Myoglobinuria, fixed weakness (late onset)	Hemolytic anemia No "second wind"	Subsarcolemmal deposits of glycogen PG accumulation
VII	Phosphorylase kinase	*PHKA1*	X	Exercise intolerance; myalgia and cramps Myoglobinuria, weakness	Hepatopathy, cardiopathy	Normal or subsarcolemmale PAS-positive diastase deposits of glycogen
IX	Phosphoglycerate kinase	*PGK1*	X	Exercise intolerance; myalgia and cramps Myoglobinuria	Hemolytic anemia Seizure, mental retardation	Mild, diffuse deposits of glycogen
X	Phosphoglycerate mutase	*PGAM2*	7	Exercise intolerance; myalgia and cramps Myoglobinuria	None	Normal or diffuse deposits of glycogen
XI	Lactate	*LDH-A*	11	Exercise intolerance; myalgia and cramps Myoglobinuria	Acroerythema	Nonspecific myopathic changes
XII	Aldolase	*ALDO-A*	16	Exercise intolerance; weakness (fever)	Hemolytic anemia	Fiber size variability
XIII	β-Enolase	*ENO*	17	Exercise intolerance; weakness	None	Subsarcolemmal deposits of glycogen
XIV	Phosphoglucomutase	*PGM-1*	1	Exercise Intolerance, myoglobinuria	None	Subsarcolemmal deposits of glycogen
Glycogen depletion						
Type	Enzyme	Gene	Chromosome	Muscle signs/symptoms	Other main symptoms	Muscle pathological features
XV	Glycogenin	*GYG1*	3	Weakness	Hypertrophic cardiomyopathy	Absence of glycogen; mitochondrial proliferation
0	Glycogen synthase	*GYS1*	19	Exercise intolerance	Cardiac arrhythmias	Absence of glycogen; mitochondrial proliferation

Glycogén tárolásos betegségek (GSD)

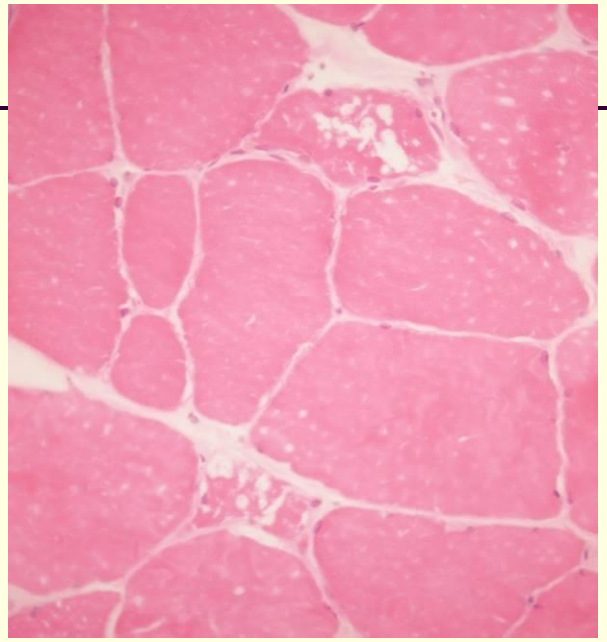


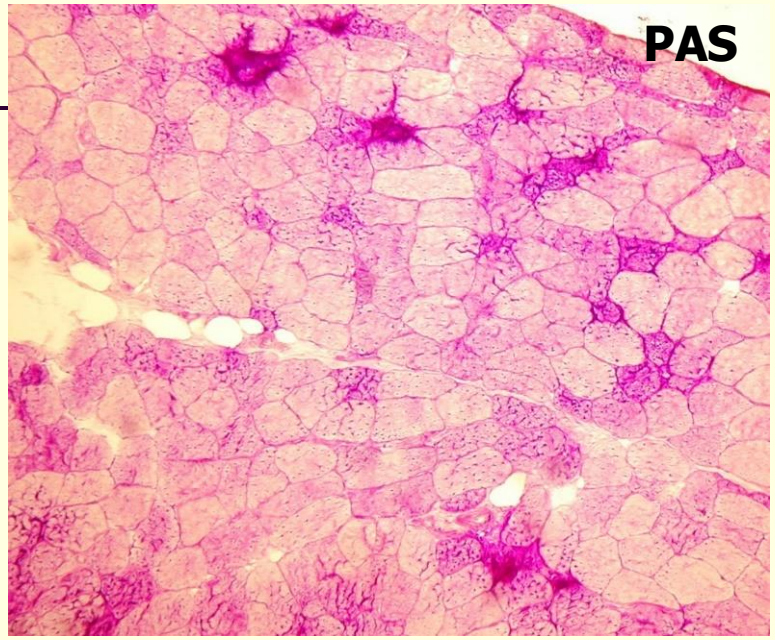


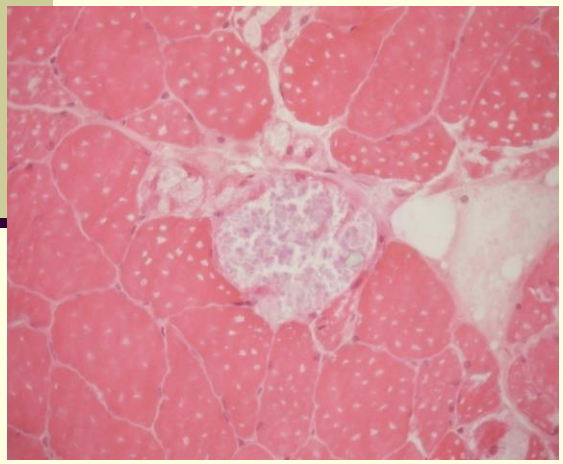


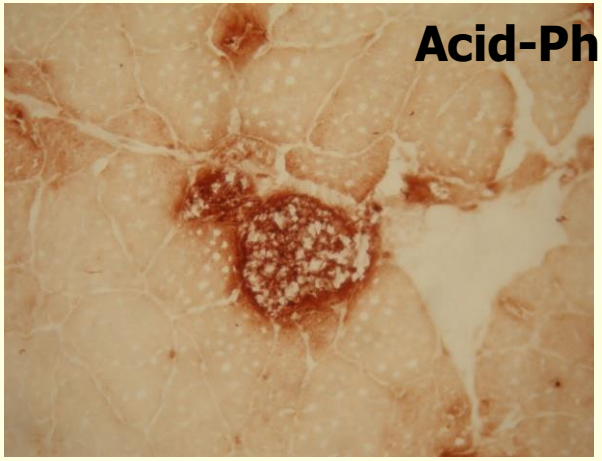


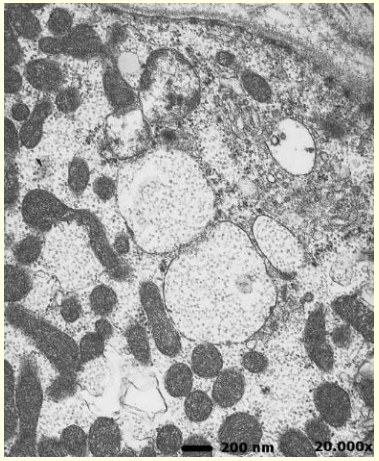
Pompe betegség

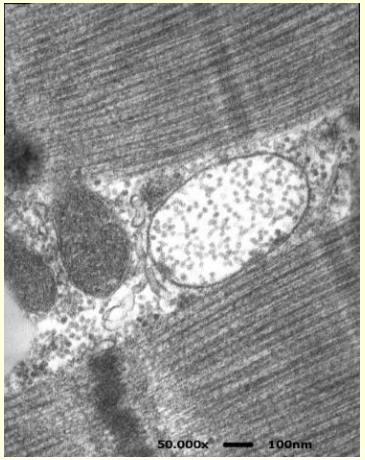












Pompe diagnózis (1-2/100.000)

1. Klinikai tünetek
   - Medenceövi izomgyengeség, atrophia (93%)
   - Paraspinalis izomgyengeség: scoliosis (50%)
   - Légző (rekesz)izom gyengeség: légzészavar (67%)
2. Labor (nem specifikus, mérsékelt CK emelkedés)
3. EMG (myogén károsodás, myotonia)
4. Légzésfunkció (ülve és fekve: >10% csökkenés !)
5. Enzimaktivitás mérés (DBS)
6. Izombiopszia (vacuolaris myopathia, glikogén)
7. MRI: combizmok szelektiv degenerációja
8. Genetika

TH: ERT

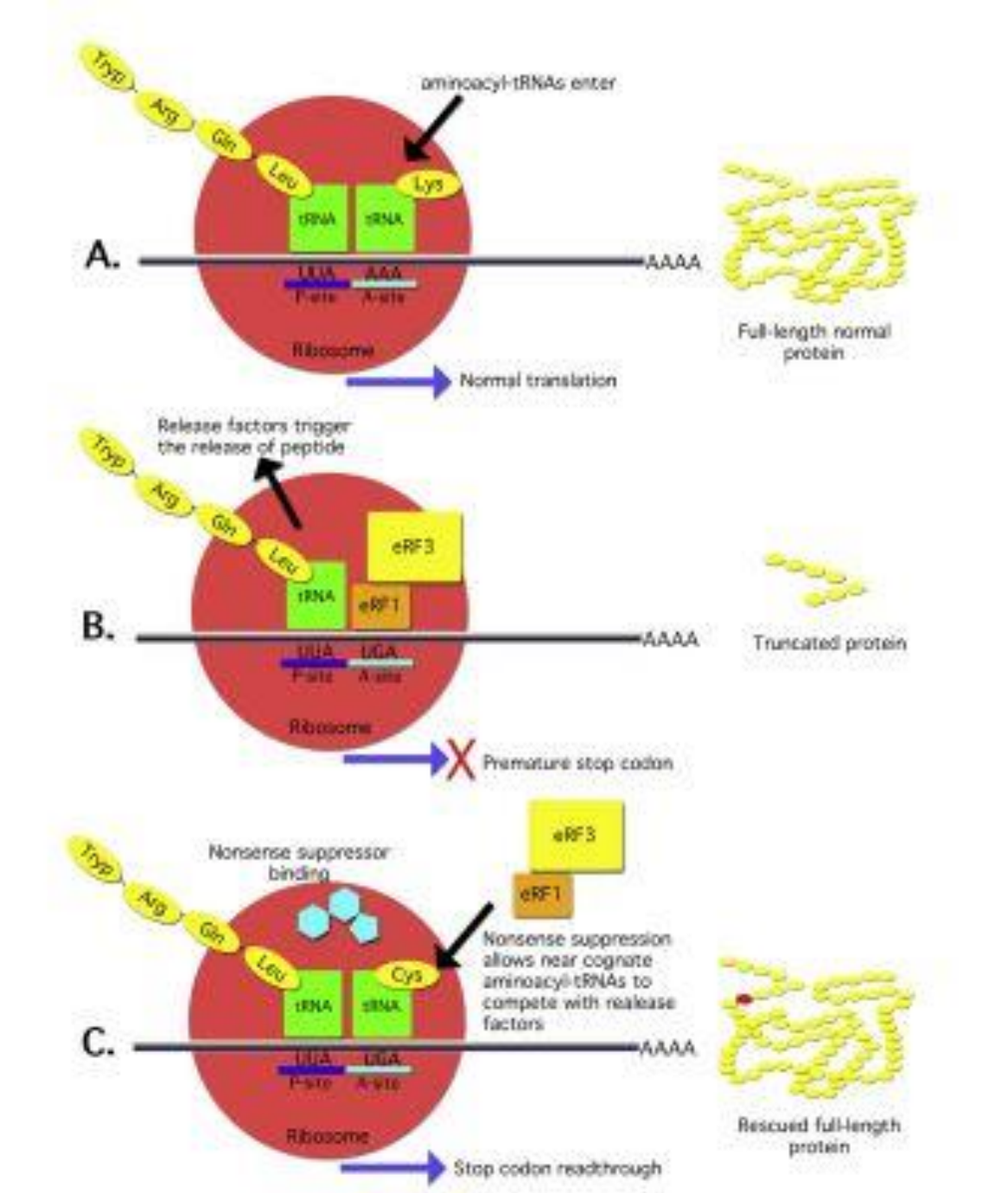
THERÁPIA

Table 1. Experimental Therapies for DMD.

Agent	Mechanism	References	Stage
Ataluren (PTC124)	Premature stop codon readthrough	86, 87	Phase III, conditionally approved in Europe
Derisapersen	Exon-skipping oligonucleotide	95, 96	Phase III completed, open-label extension ongoing
Eteplirsen	Exon-skipping oligonucleotide	97	Phase III ongoing
AAV-Minidystrophin	Gene therapy	102	Phase I completed
SMTC1100	Utrophin upregulation	106	Phase I completed
S48168/ARM210	RyR stabilizer	109	Entering Phase I
Idebenone	Antioxidant	112, 113	Phase III completed
CAT-1004	Anti-inflammatory		Phase I completed
VBP15	Anti-inflammatory	115	Preclinical
Naproxcinod	Anti-inflammatory	117	Tested clinically in a few indications ; preclinical in DMD
HT-100 (Halofuginone)	Antifibrotic	128, 129	Phase II
Sildenafil	PDE5 inhibitor	133, 135, 136	Phase II/III trials completed
Tadalafil	PDE5 inhibitor	134, 135	Phase III trials ongoing
PF-06252616	Myostatin-neutralizing antibody		Phase II
IGF-1	Muscle growth	39	Phase II
Givinostat	HDAC inhibitor	139	Phase II

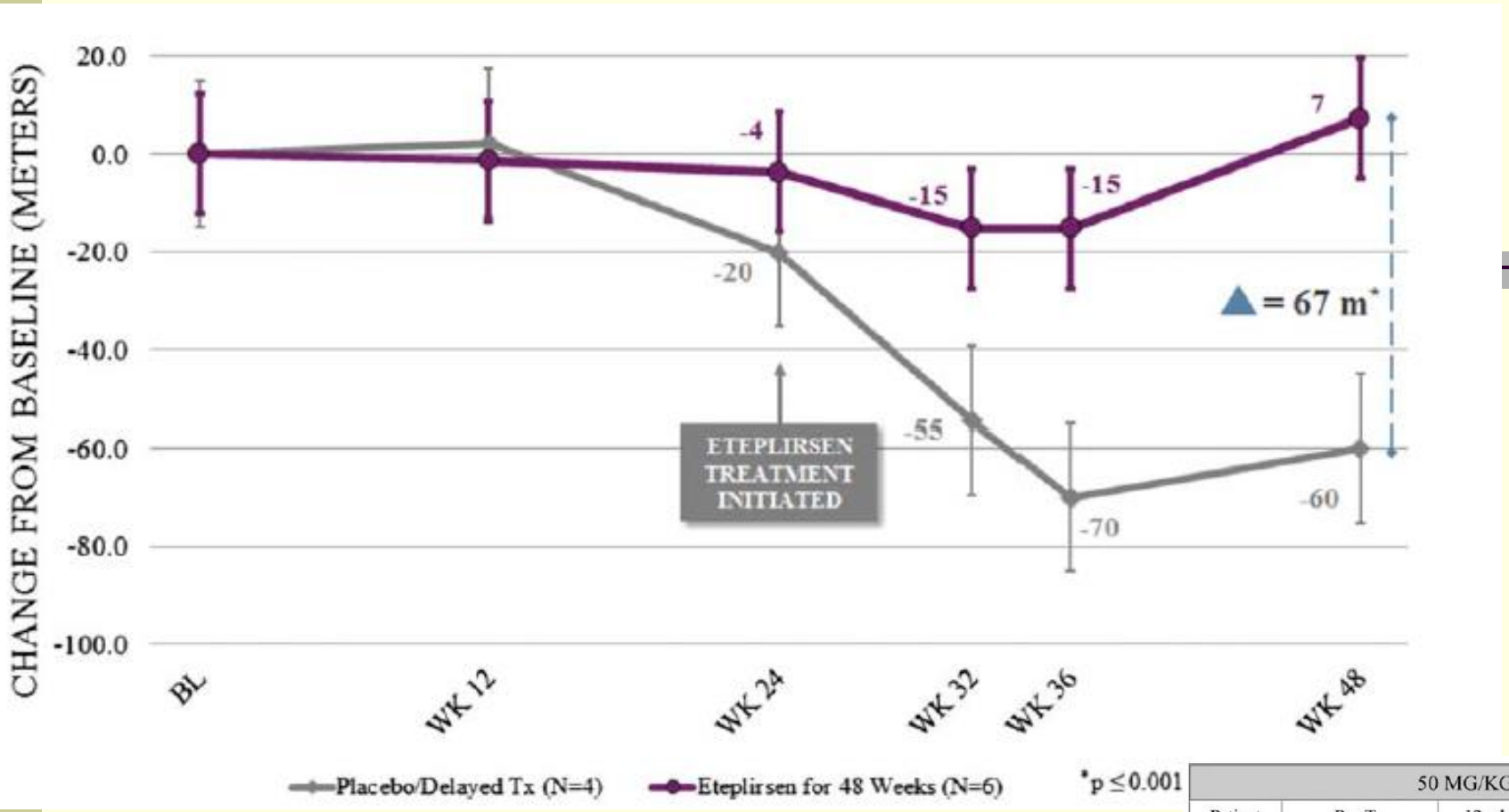
References refer to both clinical and preclinical studies. Information regarding the current clinical status of the different agents was obtained from https://clinicaltrials.gov.
AAV, adeno-associated virus; DMD, Duchenne muscular dystrophy; HDAC, histone deacetylase; RyR, ryanodine receptor.

Journal of Biomolecular Screening
2015, Vol. 20(10) 1189–1203



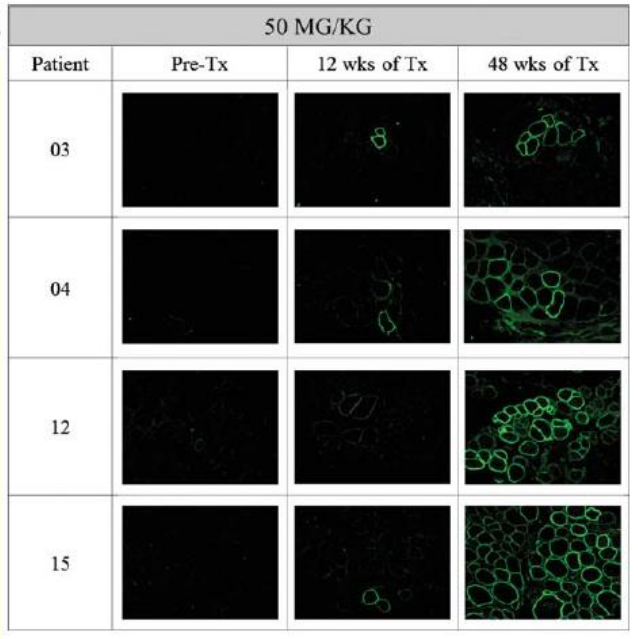
Ataluren

Experimental Eye Research 155 (2017) 24e37



Eteplirsen for the Treatment of Duchenne Muscular Dystrophy

ANN NEUROL 2013;74:637–647



Mitokondriális betegségek I.

Etiológia: mitokondriális légzési lánc komplexek defektusa, a mitokondrialis, vagy a nuklearis DNS mutációja következtében.

Tünetek:

Idegrendszer	myoclonus, epilepszia, ataxia
Vázizom	myopathia, ophthalmoplegia (PEO)
Fül	süketség
Szem	retinitis pigmentosa, látásvesztés
Csontvelő	anaemia
Gastrointestinalis	csökkent motilitás, diabetes mellitus
Szív	cardiomyopathia, vezetési zavar
Vese	tubularis acidosis
Más	lactát acidosis

Szindrómák:

PEO (progresszív externalis ophthalmoplegia)

MELAS (mit. encephalopathia, lactat acidosis, stroke epizódok)

MERRF (myoclonus epilepszia +ragged red fibers)

LHON (Leber herediter opticus neuropathia)

Kearns-Sayre syndroma (alacsony termet, PEO, süketség, retinitis pigmentosa, ataxia, atrioventicularis blokk)

Leigh syndrome (csecsemőkori encephalopathia: hypotoniás izomzat, légzési elégtelenség, lactat acidosis, metalis zavar)

Mitokondriális betegségek II.

Dg: EMG: myogén károsodás

Serum: laktát szint magas (elsősorban fizikai terhelésre)

MRI: Koponyában törzsdúcok meszesedése, fehérállományi károsodás (MRS: lactat)

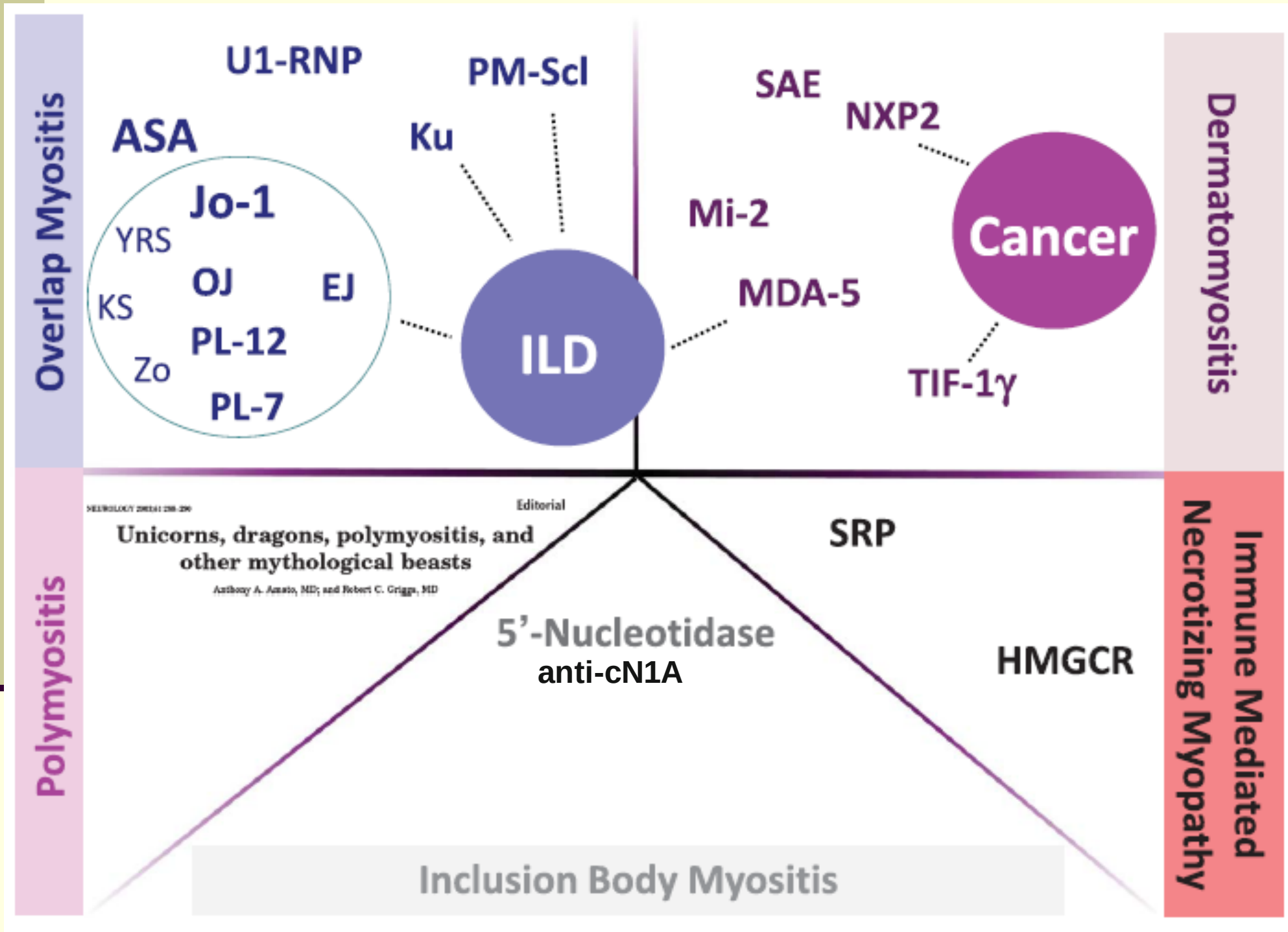
Izombiopszia: az izomrostokban kóros mitokondriumok szaporodnak fel

Biokémia: mitokondriális enzimek aktivitása csökken

Genetikai: mitokondriális (izomból) v. nuclearis (vérből) DNS mutációk

Th: Antioxidánsok (B vitamin, C-vitamin, E vitamin, Koenzim Q10, karnitin)
Aktív torna (izomrostok regenerációjának serkentése)

Myositisek

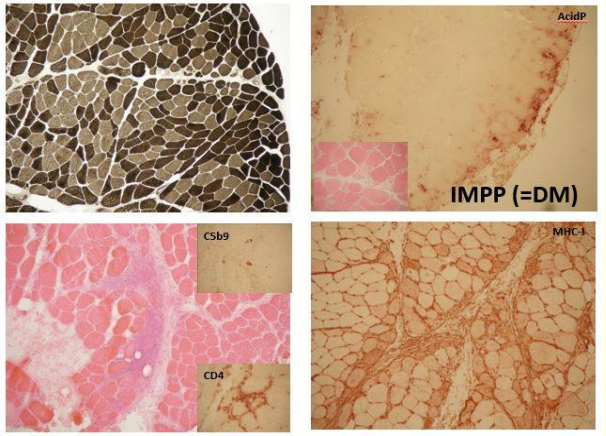


Allenbach Y. and Benveniste O. J **Neuromusc. Dis. 2 (2015) 13–25**

PATHOLOGIC CLASSIFICATION

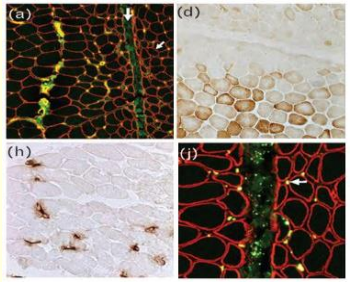
1/a IM+Perimysial pathology (IMPP)

Feature: Connective tissue pathology



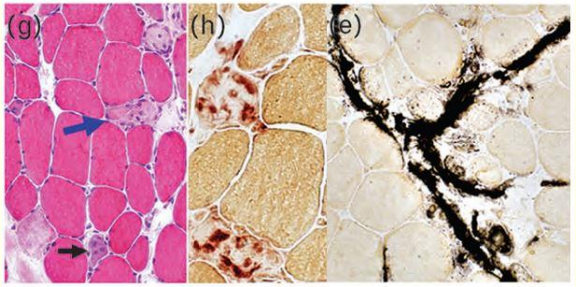
1/b Myovasculopathies

Feature: Damage to large or small vessels



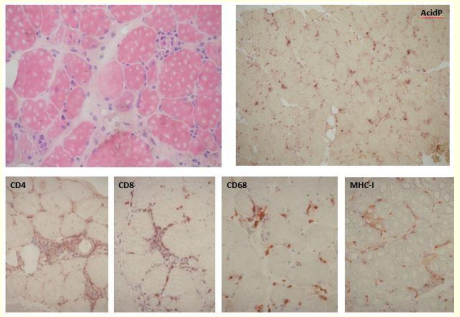
2. Immune Polymyopathies

Features: Little inflammation; Necrosis



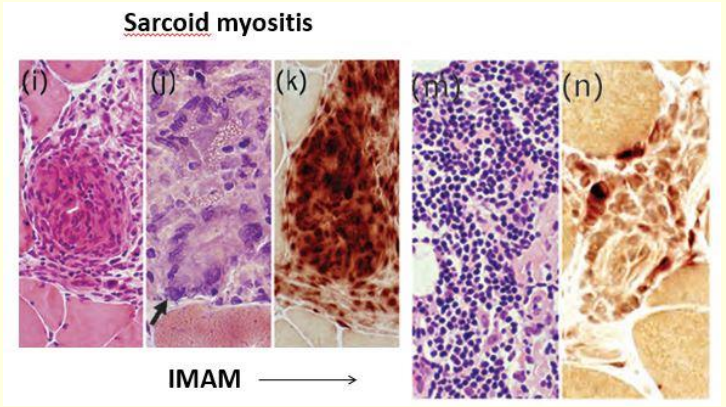
3. IM + Endomysial Pathology (IM-EP)

Features: C_{5b9} deposits; Glycoprotein Δ



4. Histiocytic Myopathies

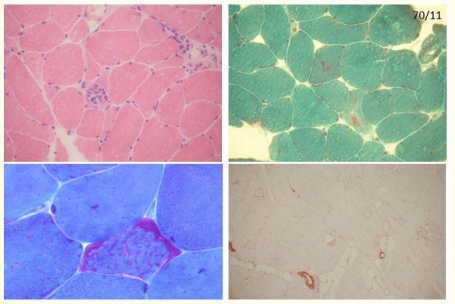
Feature: Foci of histiocytic cells



5. IM-VAMP syndromes

Features: Foci of T-cells but not B-cells

Vacuoles, **A**ggregates or **M**ito **P**ath

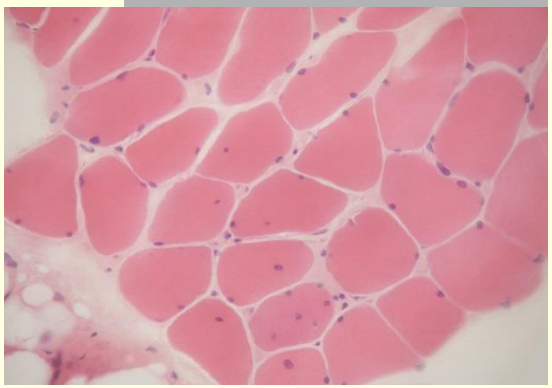


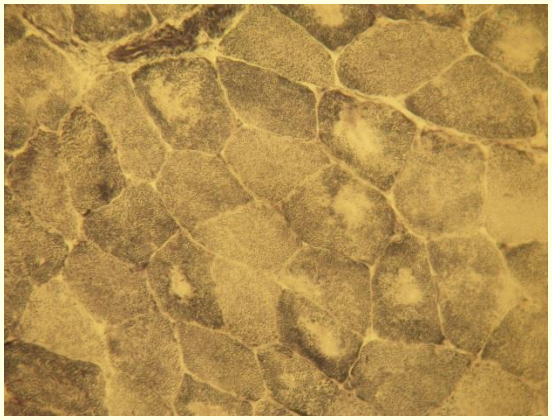
Pestronk A., Current Opinion in Rheumatology 2011, 23:595–604

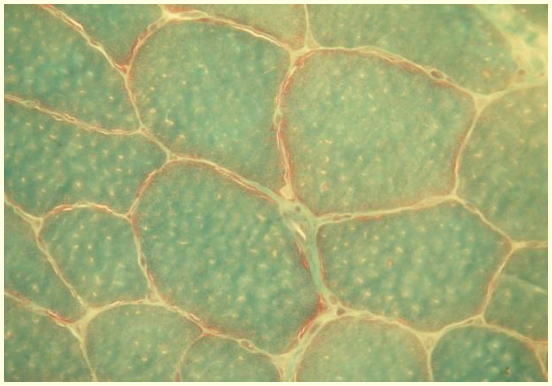
Hypothyreosis

Chronicus gyengeség
- Proximalis hangsúlyú gyengeség
- Lassan progrediál
- Myalgia, izomgörcsök
- Hypothyreosis tünetei
- CK emelkedett (<1500)
- Kezelésre kevéssé reagál

Pathológia:
- Atrophia
- Mitochondrialis dysfunctio
- Lipid/glikogén szaporulat







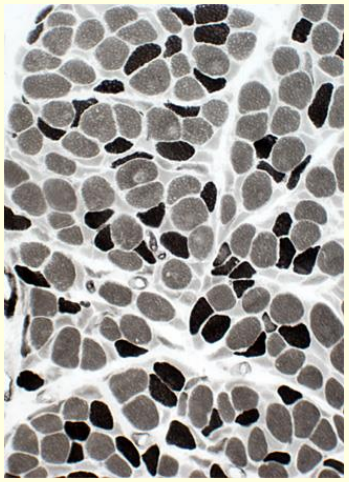
Critical illness myopathy

Incidencia:

Gépi lélegeztetés 4-6 napig	30-85%
ARDS	34-60%
Intenziv osztály > 7nap	56-80%
Septicus shock	100%

Pathologia:

- Acut necrosis és regeneratio
- II-es rost atrophia
- Vastag filamentumok (myosin) selectiv hiánya



Pathomechanizmus:

- Immobilisatio (GDF-15)
- Mitochondrialis dysfunctio
- Septis okozta cytokinek (IL1, IL6, TNFa) gátolják a PI3-K/AKT/mTOR útvonalat, ami csökkent protein szintézishez vezet

Toxicus myopathiák (gyógyszer)

Lipid csökkentők
- **Statinok**
- Fibrátok

Antiviralis szerek
- Zidovudin

Antineoplasiás szerek
- Vincristin
- Methotrexat
- Azathioprim

Rheumatológiai gyógyszerek
- **Glucocorticoidok**
- Colchicin
- Chloroquin

Neurolepticumok
- Haloperidol, clozapine, olanzapine, risperidon, quetiapine

Antidepressivumok
- Citalopram, fluoxetine, paroxetine
- Sertraline

Egyéb
- Cyclosporin
- Mycophenolate mofetil
- Cimetidine
- Amiodaron, Soltalol
- D-penicillamin
- Antibioticumok (penicillin)
- Propylthiouracil
- Interferon-alpha

Steroid myopathia

- Gyakoriság: Chr. Steroid kezelés során 60%

- Jellemzői
  - Chr. myopathia
    - Fájdalmatlan, proximalis izomatrophia (**m. quadriceps fem**.)
    - Proximalis gyengeség (csipőizmok)
    - EMG: myopathia v. negativ
    - CK: normális

  - Ritkán előfordulhat acutan nagy dózisú steroid kezelés során
    - ICU, COPD, depol.izomrelaxans mellett

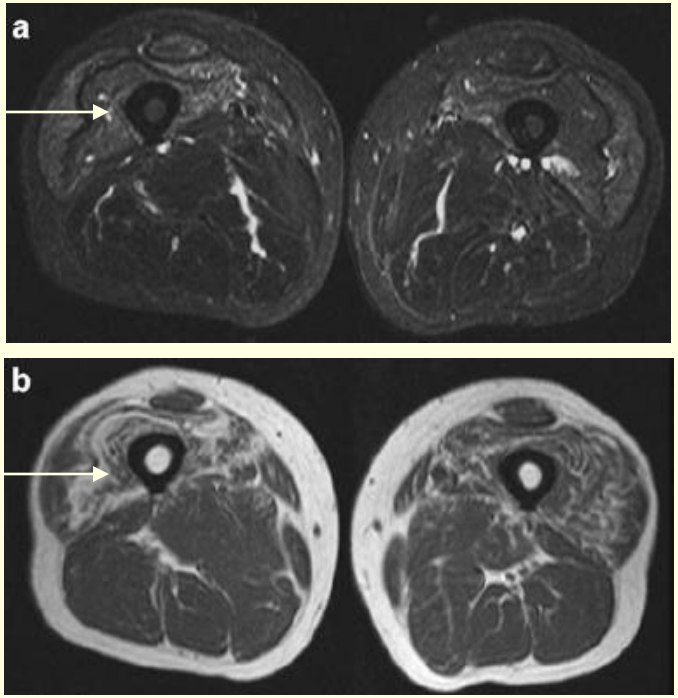
- Hajlamosító tényezők:
  - Steroid típusa (dexa-, beta-, triamcinolon> hydrocort., prednisolon)
  - Dózisfüggő (>10 mg/die, ált. 20-30 mg/die, chr. oralis kezelés)
  - Nő/férfi 2:1
  - Idős kor

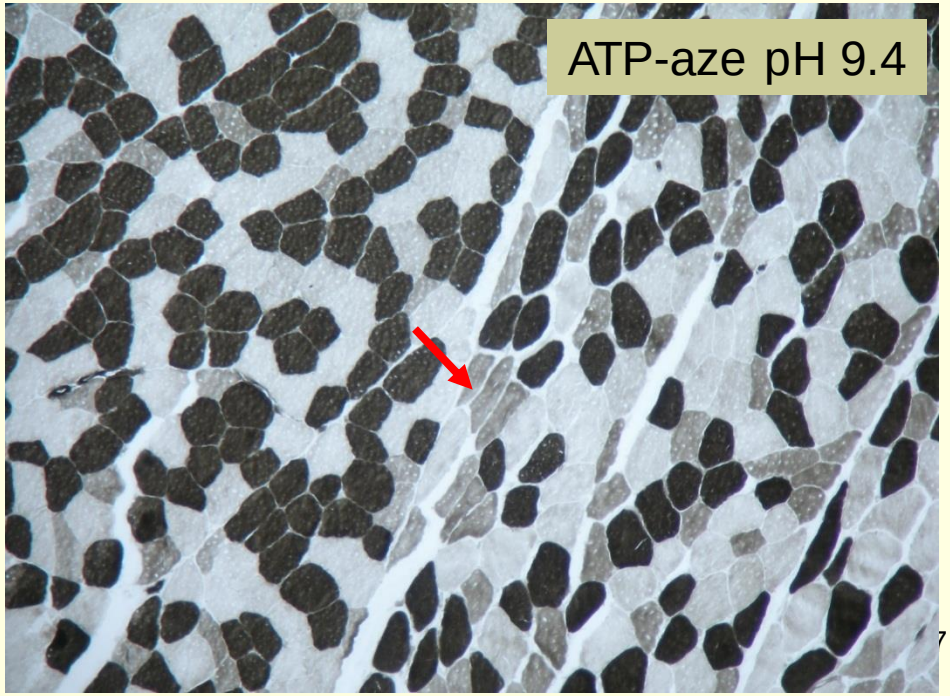
Steroid myopathia

- Mechanizmus:
  - Protein katabolizmus, IGF-I, atrogin-1, myostatin
- Pathológia: Izomrost (II/b) atrophia
- TH: steroid dóziscsökkentés, fiziotherápia

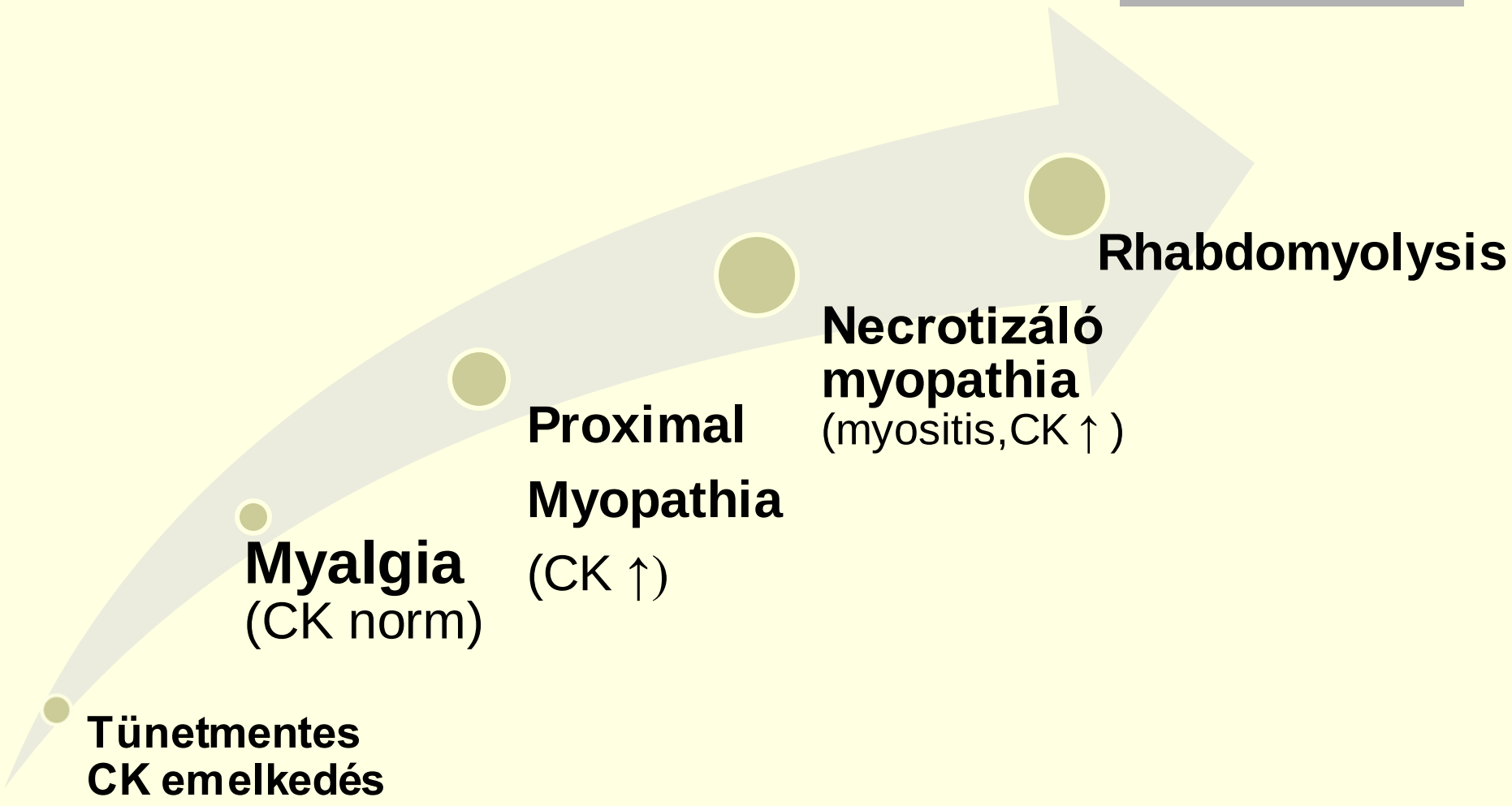
STIR

T1





Statin myopathia



Incidencia: **10-20%** **2-7%** **0.03-0.1%**

Kialakulás: 1 hónap (1 hét-4 év) **Javulás, CK normalizálódás: 2-3 hónap**

Statin myopathia

Rizikófaktorok

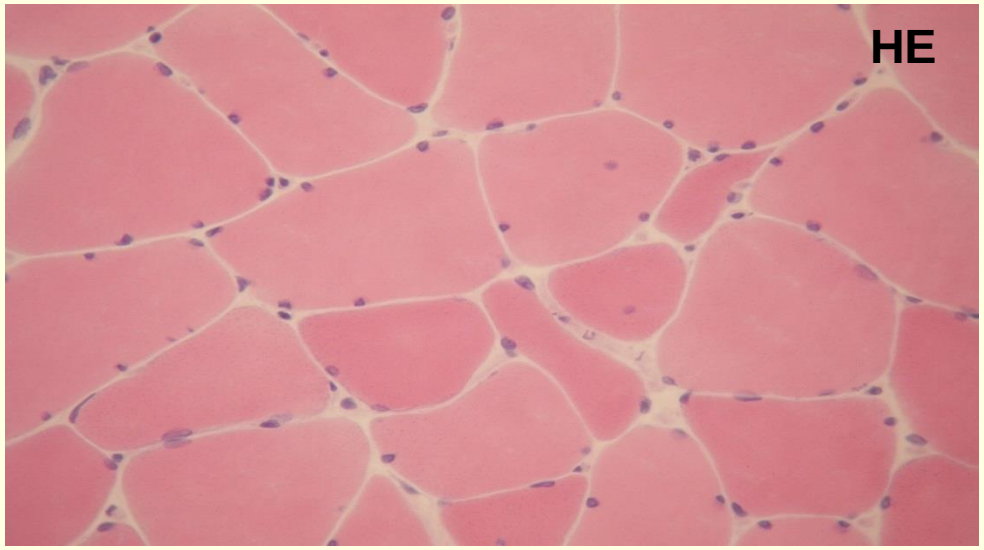
- Kor (kifejezett rizikó 80 év felett)
- Női nem · alcsony BMI
- Co-morbiditás hypothyreosis
  Alacsony D3 vitamin szint
  Vesefunkciós zavar (különösen diabetes mellitus)
- Fizikai aktivitás
- Sebészi beavatkozás
- Statin myopathia az anamnézisben, a családi anamnézisben

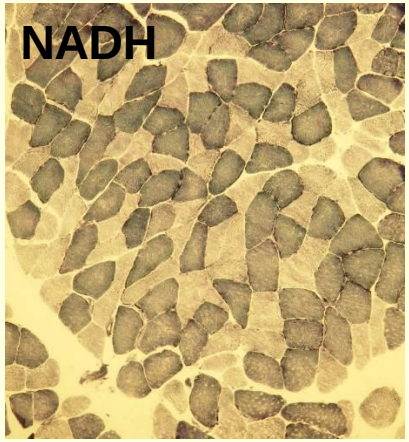
- Magasabb statin dózis
- Statin típusa: atorvastatin, lovastatin, simvastatin > pravastatin, rosuvastatin, fluvastatin
- Gyógyszer interakciók:
  CYP2C9 inhibitorok (warfarin)
  CYP3A4 inhibitorok (diltiazem, erythromycin, fluconazol, cyclosporin, proteáz inhibitorok, amiodaron, grapefruit (>200 ml/die))
  Gemfibrozil /fibrátok/ 10x
  Alkohol abúzus

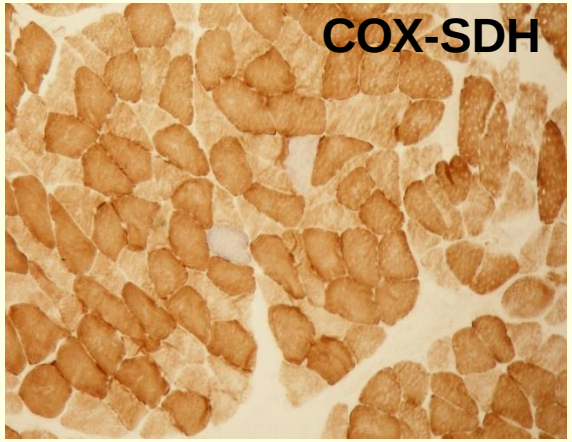
- Genetikai polimorfizmus: ***SLCO1B1, COQ2, CYP3A4*** / **HLA DR 11 (B1*11:01)**

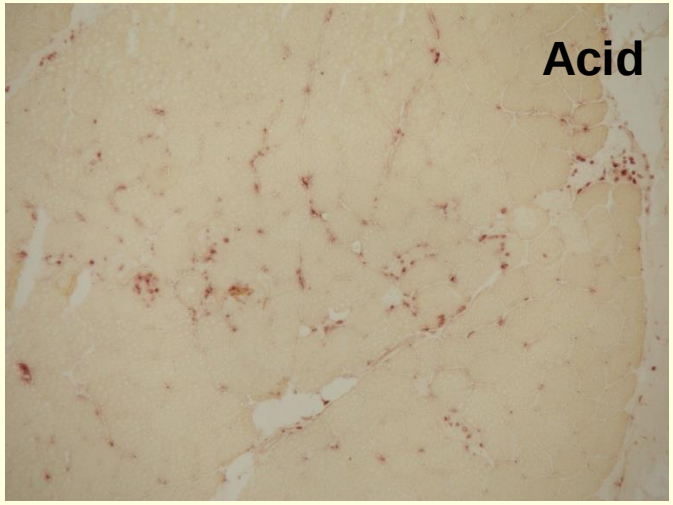
Statin myopathia

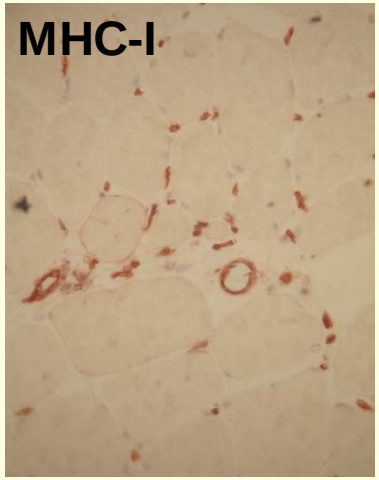
Pathológia: **myopathia** **myositis**

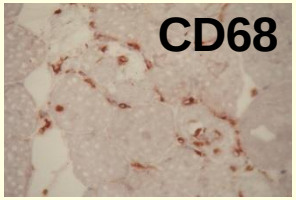


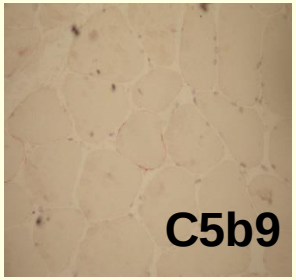




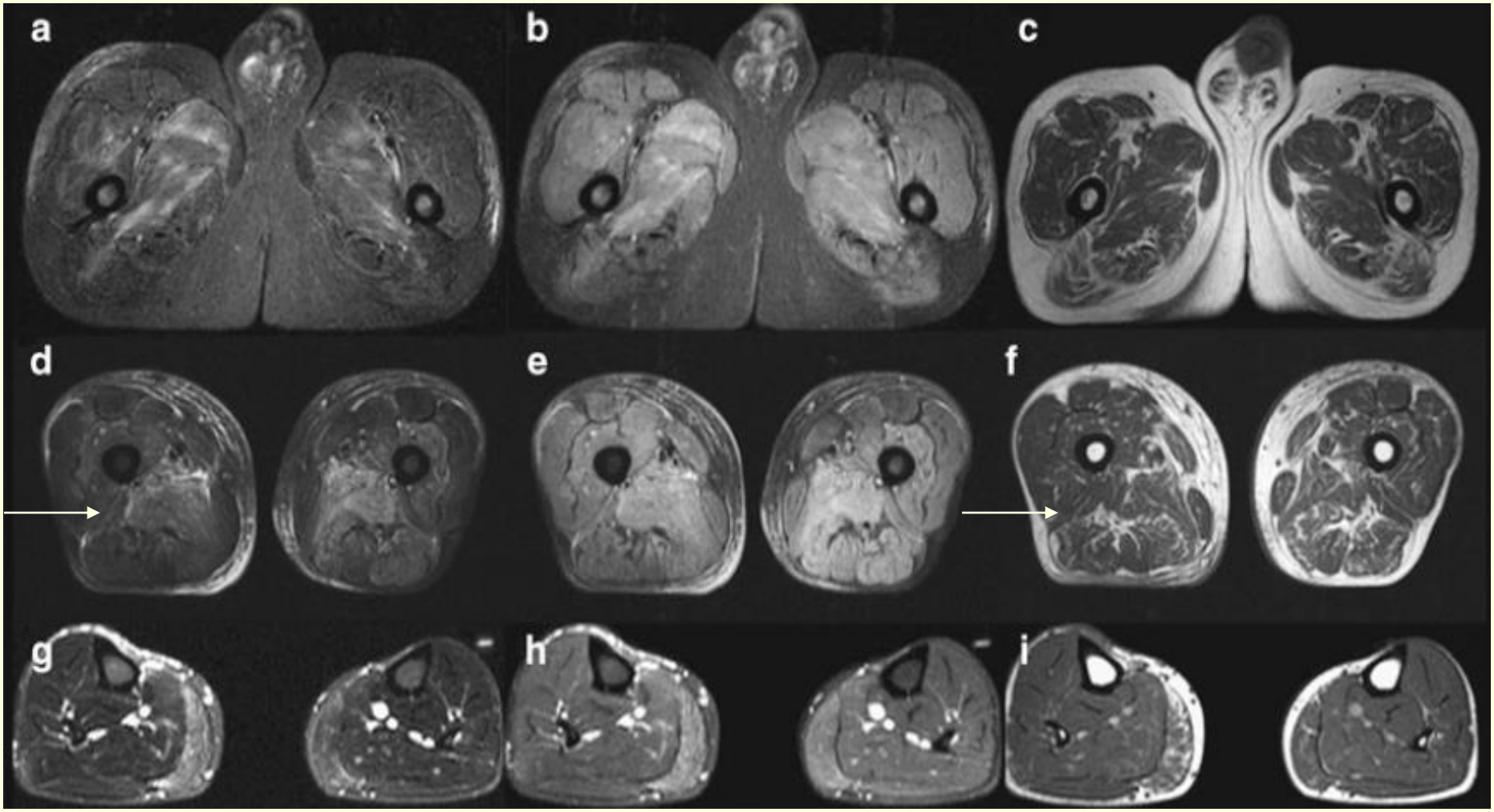








Statin myopathia



M.P. Wattjes and D. Fischer (eds.), *Neuromuscular Imaging*, DOI 10.1007/978-1-4614-6552-2_27

Statin myopathia

Therápia:

- **Gyógyszer interakciók kerülése**
- **Mütéteknél, nagy fizikai aktivitás előtt statin elhagyása**
- **Ha panaszokat okoz:**
  - **Dóziscsökkentés**
  - **Váltás más statinra (fluvastatin, rosuvastatin)**
  - **statin elhagyása**
- **Más koleszt. csökkentő adása (pl. ezetimib, halolaj)**

- **Vitamin D3**
- **Koenzim Q10**

- **Immunmoduláció (necrotizáló myopathia esetén)**

Ha a klinikai kép progresszív, vagy nem reverzibilis: izombiopszia !