UNIVERSITATEA DE STAT DE MEDICINĂ ȘI FARMACIE
„NICOLAE TESTEMIȚANU” DIN REPUBLICA MOLDOVA

Afecțiunile neurologice cu transmitere (predispoziție) ereditară

Vitalie LISNIC

Prof. univ., d.h.ș.m.,
Catedra Neurologie 1
USMF „Nicolae Testemițanu”

Obiective

- **Distrofiile musculare progresive**
- **Miotoniile**

- **Maladia neuronului motor**
- **Scleroza laterală amiotrofică**
- **Boala Strumpell**
- **Amiotrofiile spinale și neurale (Charcot – Marie – Tooth)**

- **Boala Wilson**

- **Ataxiile ereditare**

Costul tratamentului maladiilor rare neuromusculare

Drug	Disorder	Average US List Price
Edaravone	Amyotrophic lateral sclerosis	$145,524/year[23]
Riluzole	Amyotrophic lateral sclerosis	$1800-$8400/year[24]
Immunoglobulin	Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	$47,854/year[25]
Deflazacort	Duchenne muscular dystrophy	$81,400/year[26]
Eteplirsen	Duchenne muscular dystrophy	$1,002,000/year[26]
Dichlorphenamide	Hypokalemic/hyperkalemic periodic paralyses	$109,500/year[27]
3,4-Diaminopyridine (3,4 DAP)	Lambert-Eaton myasthenic syndrome	$375,000/year[28]
Eculizumab	Myasthenia gravis, acetylcholine receptor antibody positive	$678,000/year[29]
Nusinersen	Spinal muscular atrophy	$750,000 for the first year; $375,000/year thereafter[30]
Onasemnogene abeparvovec-xioi	Spinal muscular atrophy	Onetime infusion $2,125,000[30]
Patisiran	Hereditary transthyretin amyloidosis	$345,000/year[31]
Inotersen	Hereditary transthyretin amyloidosis	$300,000/year[31]

[a] Data from the National Institutes of Health Genetic and Rare Diseases Information Center.[22]

Rising Drug Costs for Neurologic Diseases.
Crowell, Jason; Burns, Ted

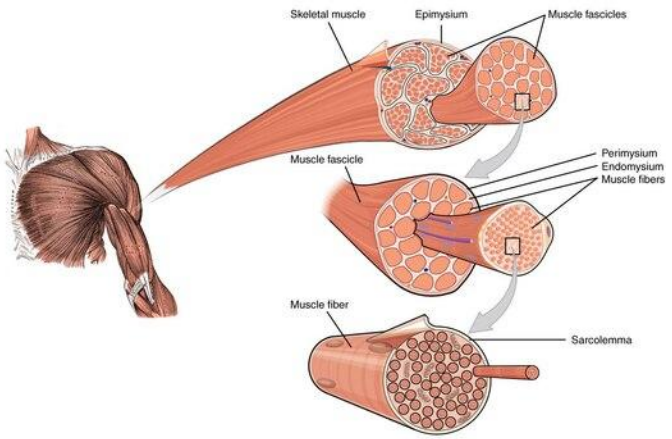
CONTINUUM: Lifelong Learning in Neurology. 26(5):1392-1406, October 2020.

Semnele tipice asociate unei miopatii

Negative	Pozitive
Slăbiciunea musculară	Crampe
Atrofiile	Contracturi
Fatigabilitatea	Mialgii
Intoleranța exercițiilor	Incordări
	Hipertrofie (pseudo) musculară
	Mioglobulinurie

Clasificarea miopatiilor

EREDITARE	DOBÂNDITE
Distofiile musculare - Distrofinopatii (Duchenne, Baker) - În centură (Erb-Rot) - Facioscapulohumerală (Landouzy-Dejerine) - Oculofaringeală - Distală - Miotonică	**Inflamatorii** - Dermatomiozita - Polimiozita - Miozita cu corpi de incluzie - Miozita infecţioasă
Congenitale - Central core - Nemalină - Miofibrilară - Centronucleară - Miotubulară	**Toxice**
Metabolice - Mitocondriale - Glicogenoze - Lipidoze	**Endocrine**



Patternurile de afectare musculară

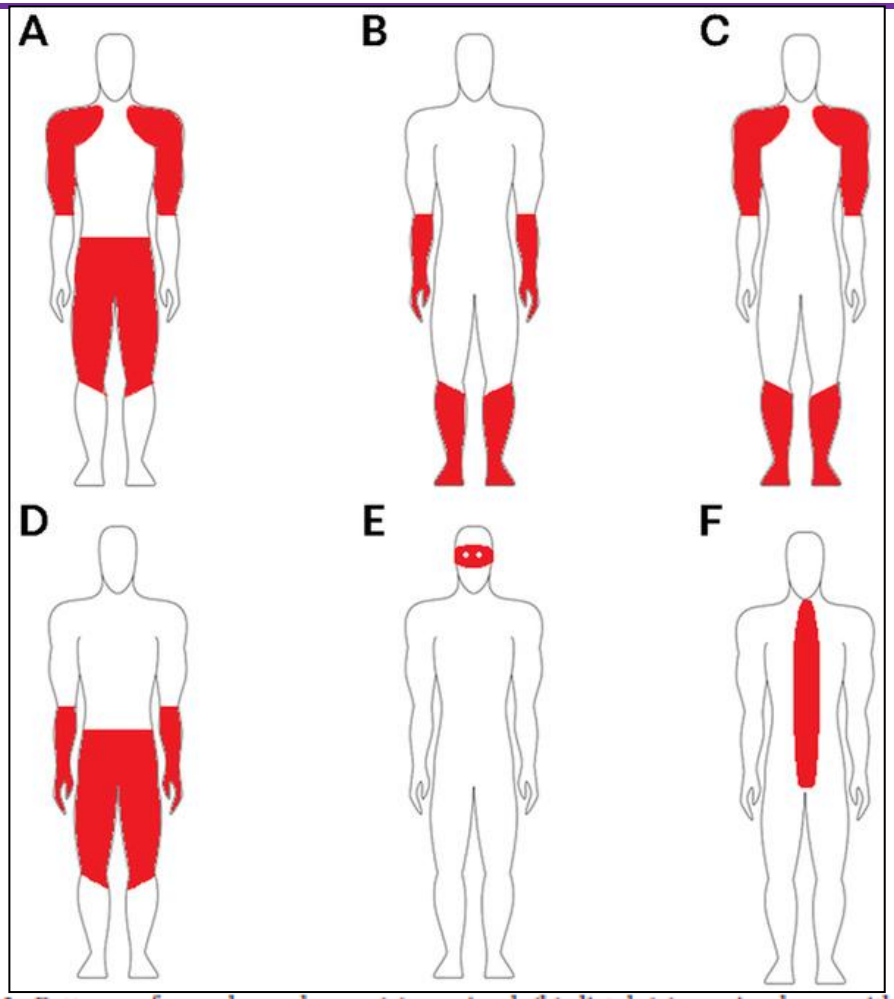
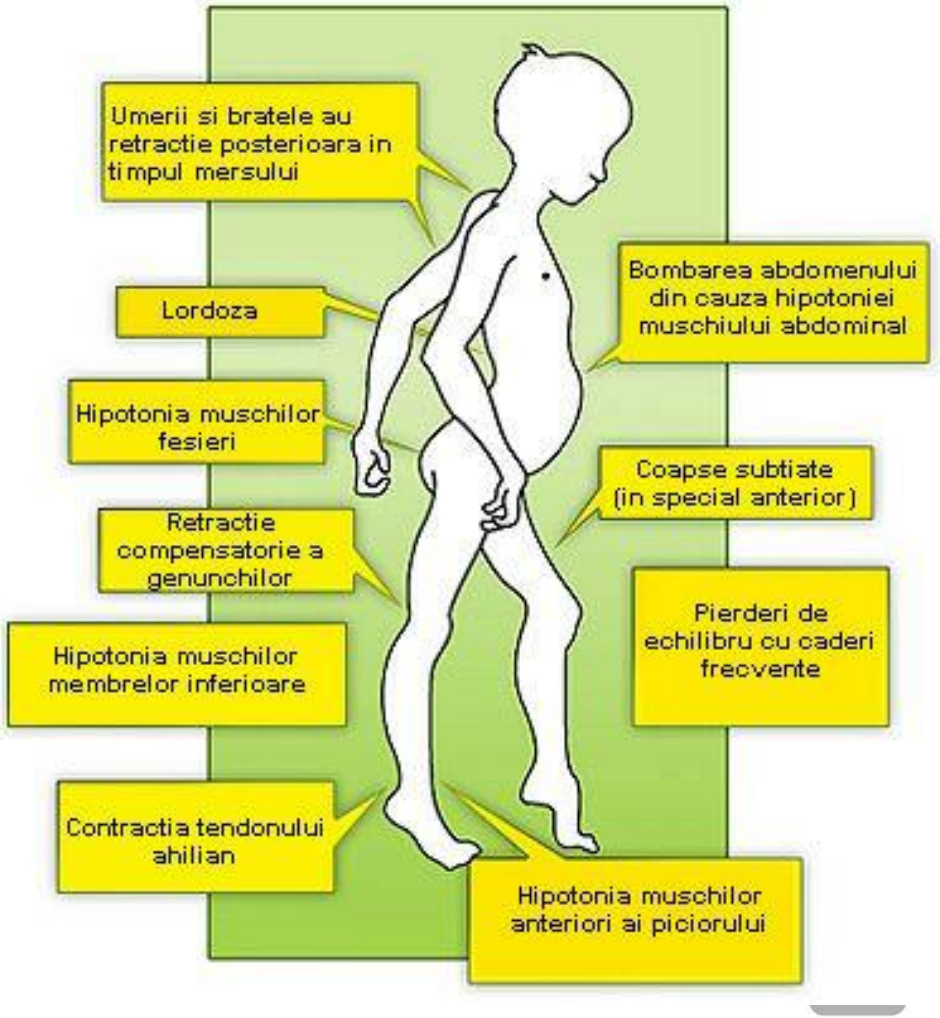


Figure 2.1. Patterns of muscle weakness: (a) proximal; (b) distal; (c) proximal arm with distal leg; (d) proximal leg with distal arm; (e) ptosis; and (f) axial muscles.

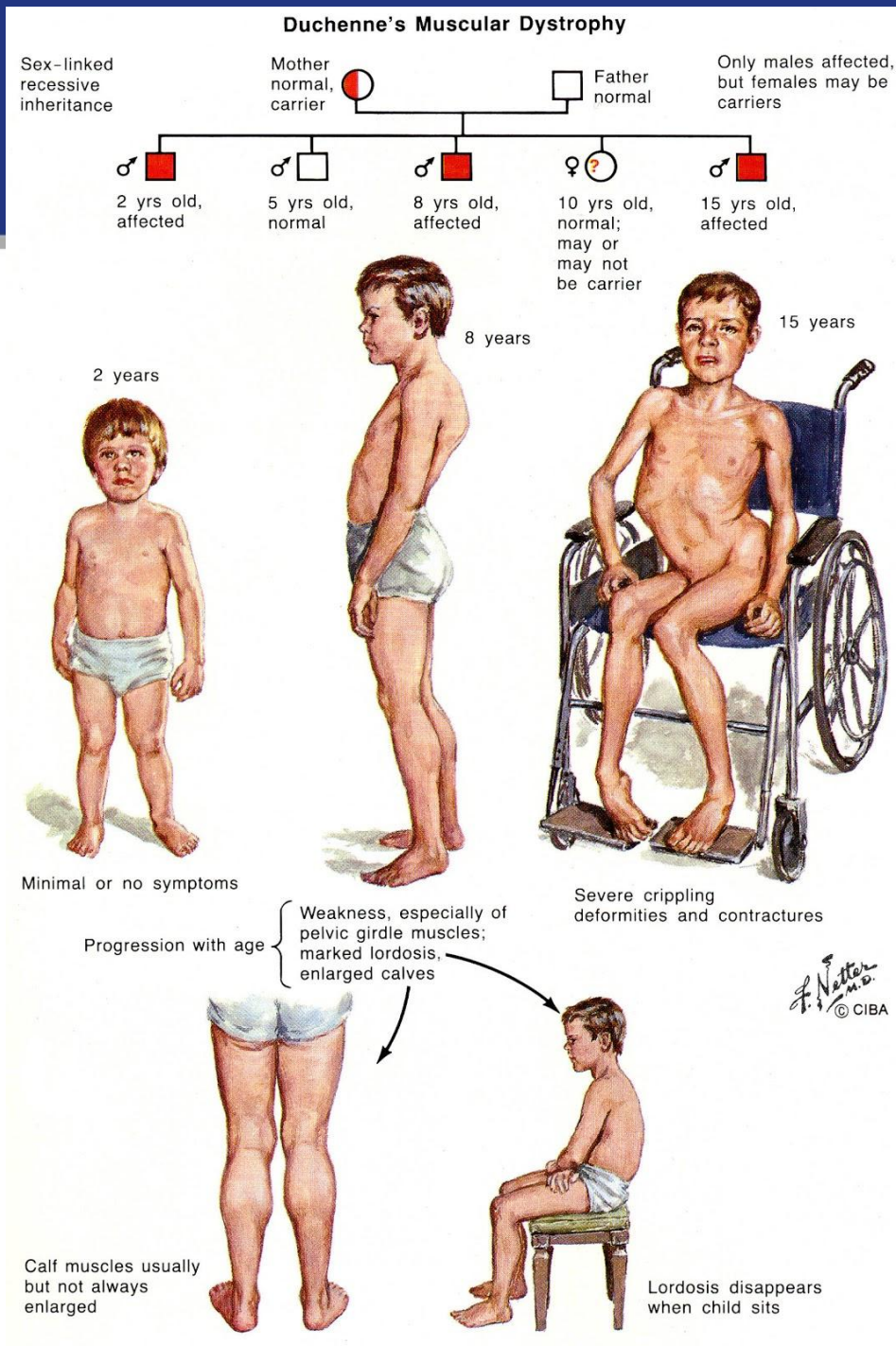
Distrofiile musculare progresive

Un grup de maladii ereditare, caracterizate prin slăbiciune musculară şi atrofia muşchilor

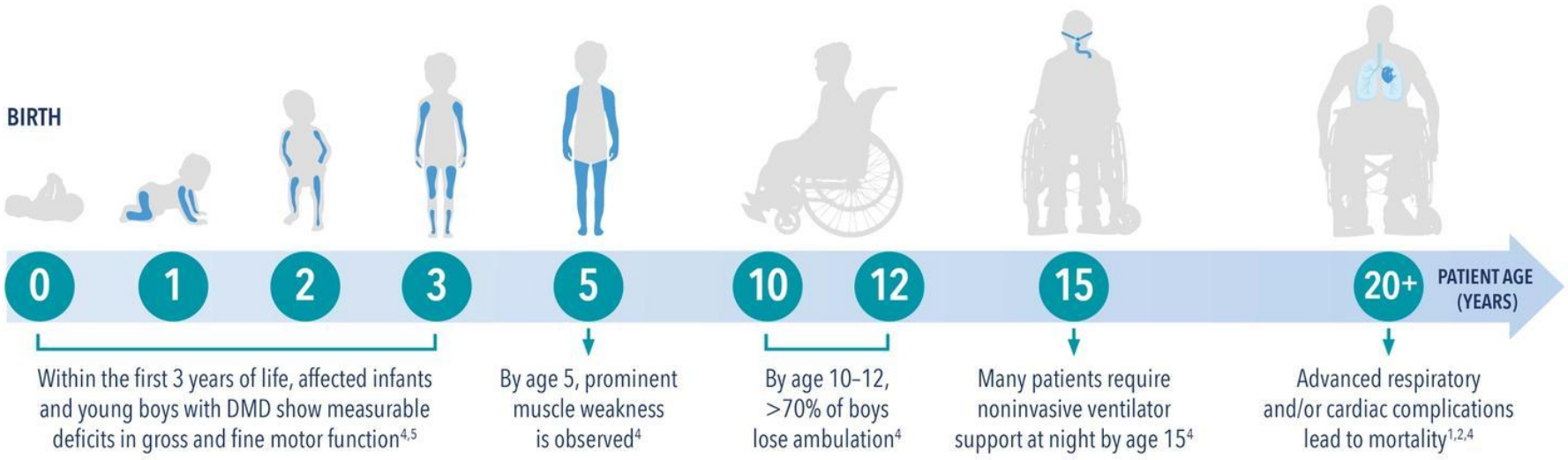


DM Duchenne

- cea mai frecventă formă de distrofie musculară
- Tipul de moștenire – recesiv X- lincat (exclusiv suferă băieții)
- Debut – până la vârsta de 5 ani
- În adolescență – deficiențe motorii majore
- În deceniul 3 al vieții – exitus



DM Duchenne



Simptome precoce:

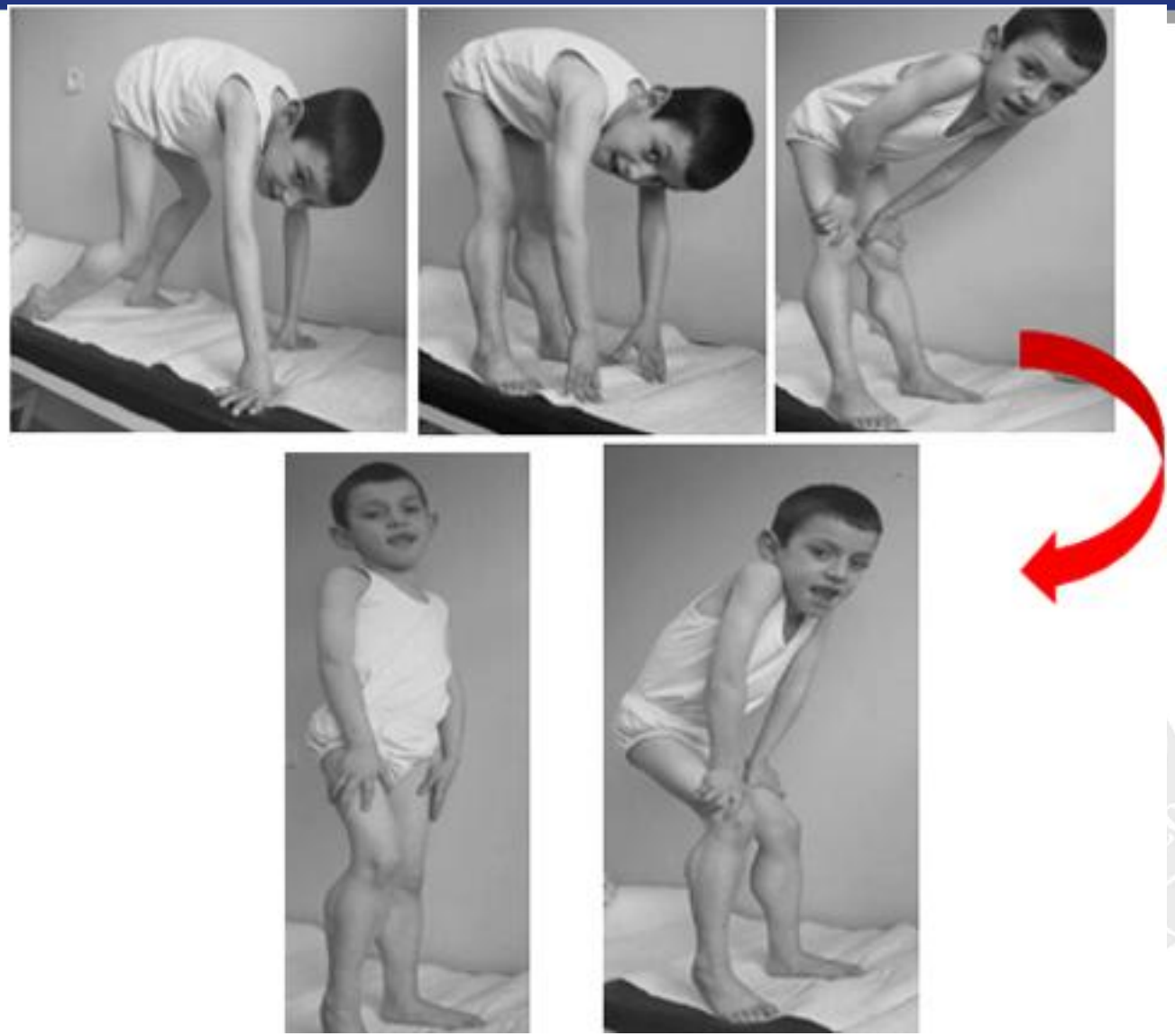
- **Mers pe vârful degetelor**
- **Mers de raţă**
- **Imposibilitatea alergării**

Iniţial se afectează muşchii centurilor pelviene, apoi humero-scapulare, ulterior – muşchii membrelor şi muşchii respiratori

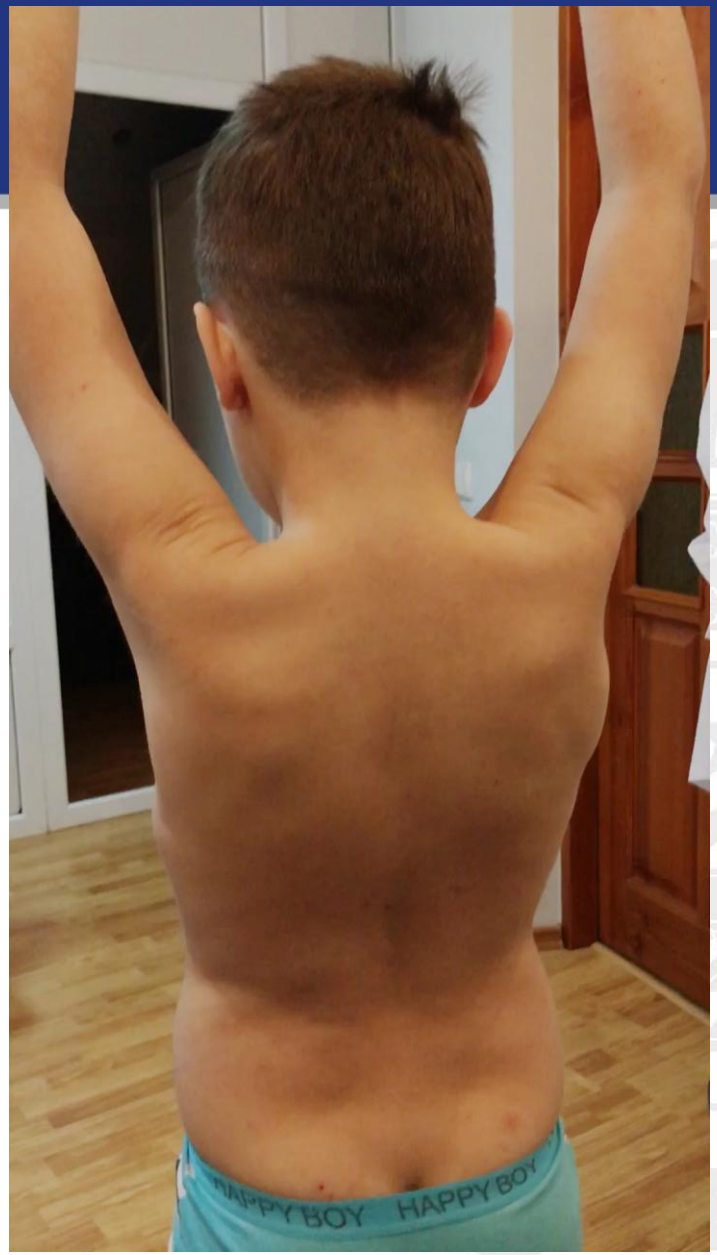
Pseudohipertrofia muşchilor gambelor

Semnul Govers

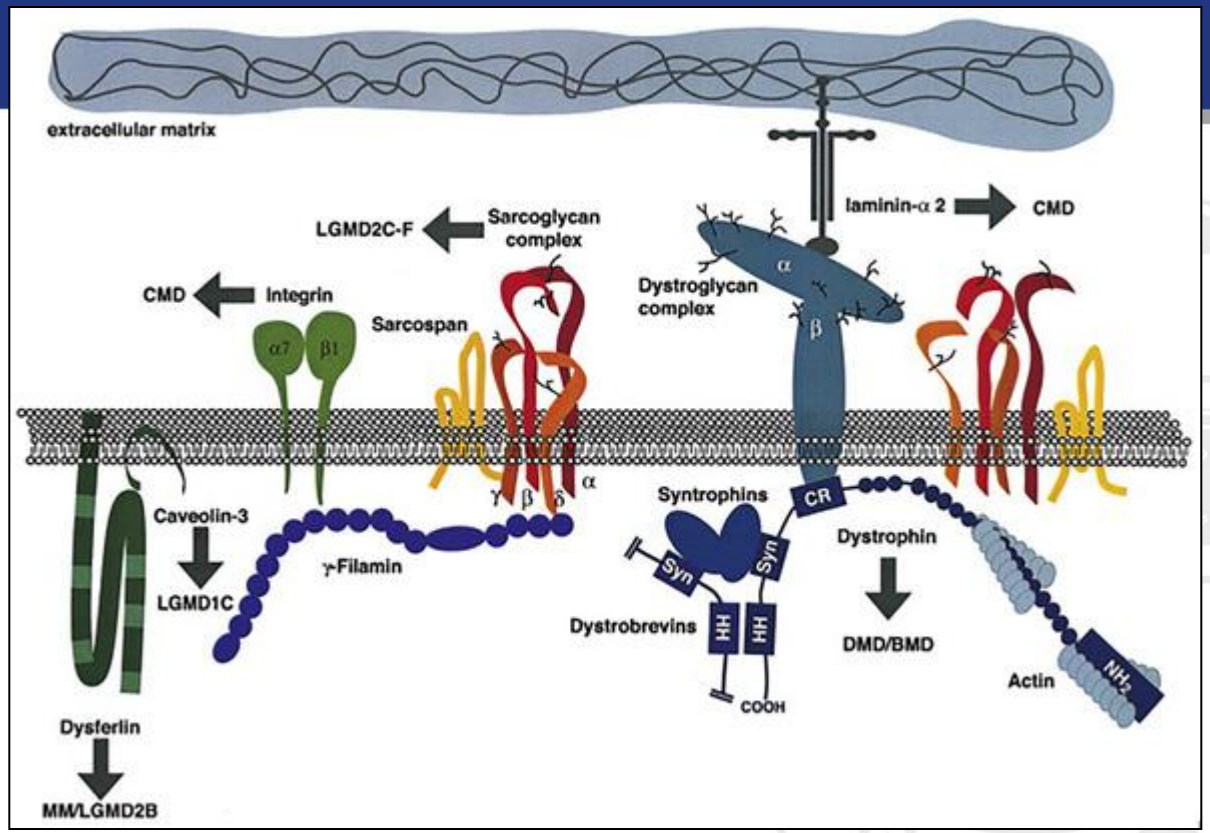
Semnul Govers



Semnul Govers


HAPPY BOY
HAPPY BOY

Distrofina și alte complexe proteice ale membranei celulare

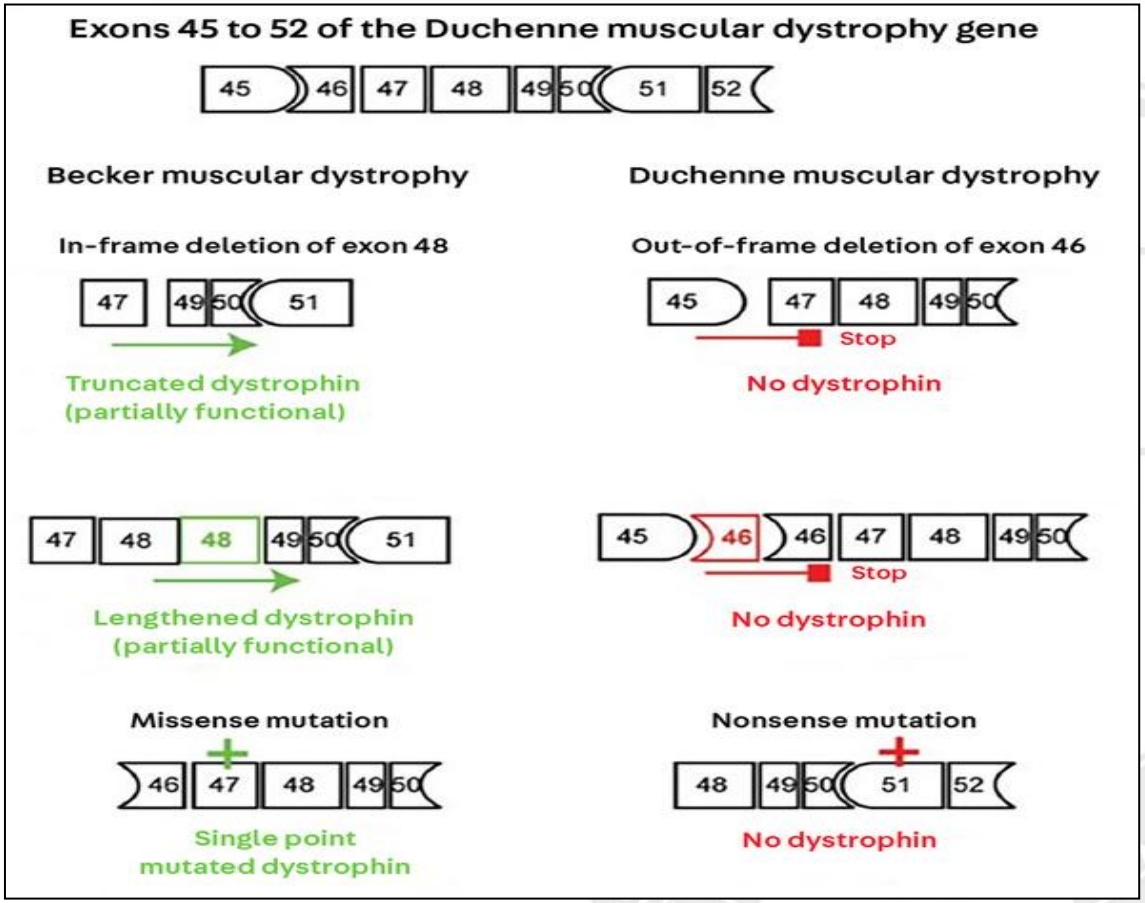


Distrofina este implicată în stabilizarea mecanică a sarcolemei. Mutația sarcoglicanelor, caveolinei – 3, disferilinei induc distrofiile musculare în centură.

The Dystrophinopathies. Lee, Bo

CONTINUUM: Lifelong Learning in Neurology. 28(6):1678-1697, December 2022.

Reprezentarea schematică a distrofinei pe baza variației genetice și a fenotipului corespunzător (distrofia Becker versus Duchenne)



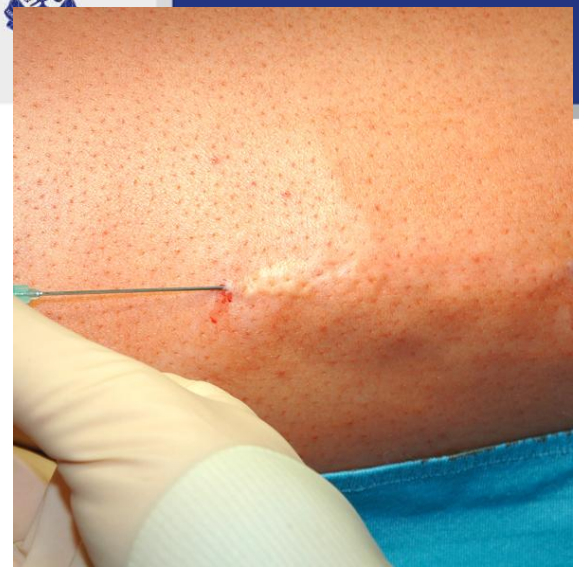
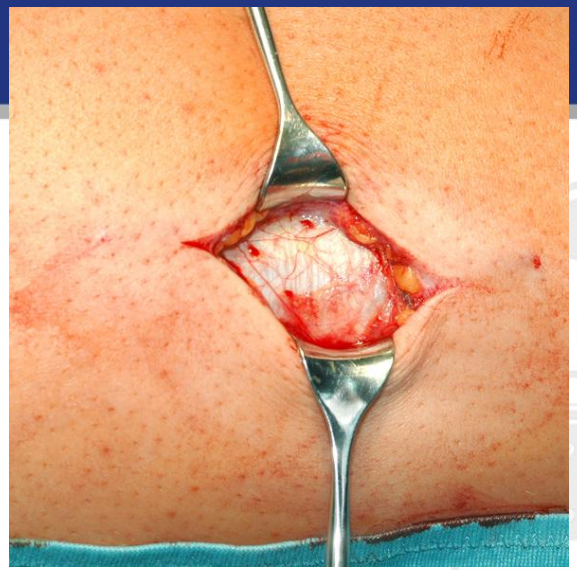
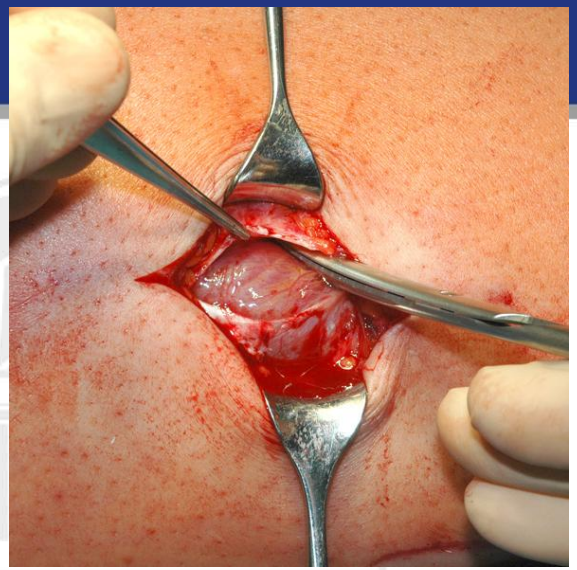
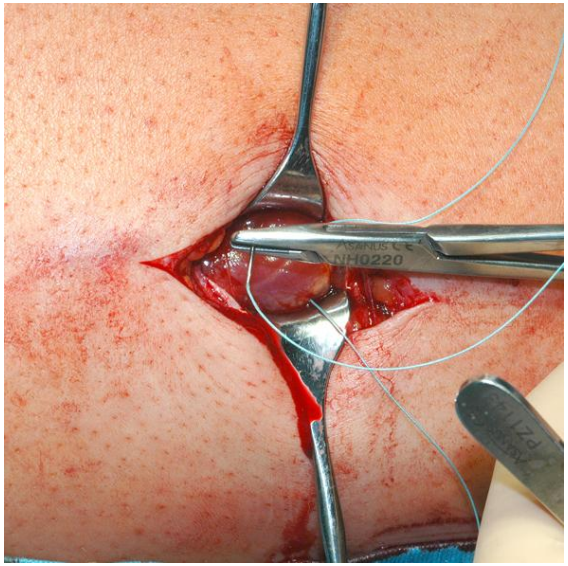
The Dystrophinopathies.
Lee, Bo

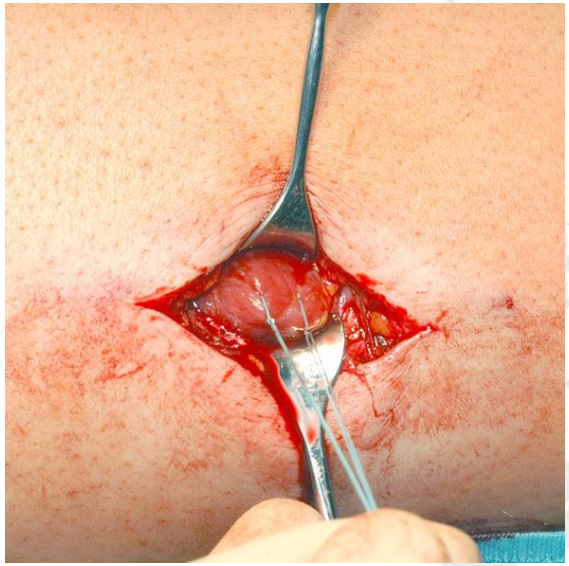
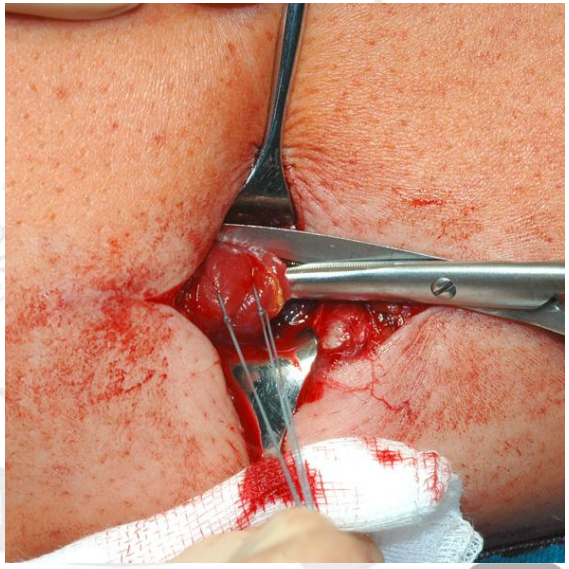
CONTINUUM: Lifelong Learning in Neurology. 28(6):1678-1697, December 2022.

Distrofia musculară Duchenne
Diagnosticul

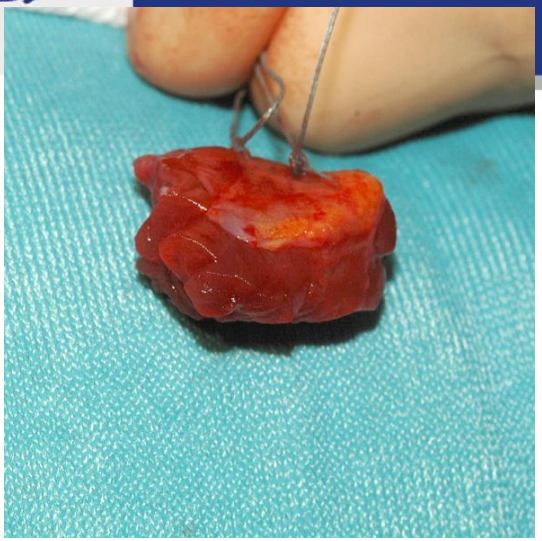
- EMG
- Creatinfosfokinaza – majorare exprimată
- Biopsia musculară
- Examinare genetică-moleculară – gena codifică distrofina

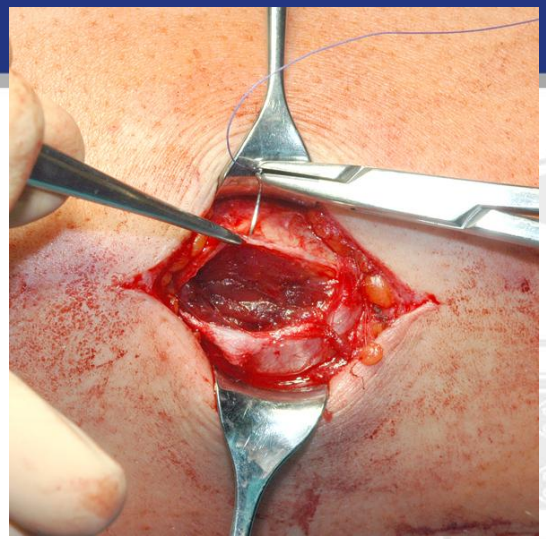
Biopsia musculară

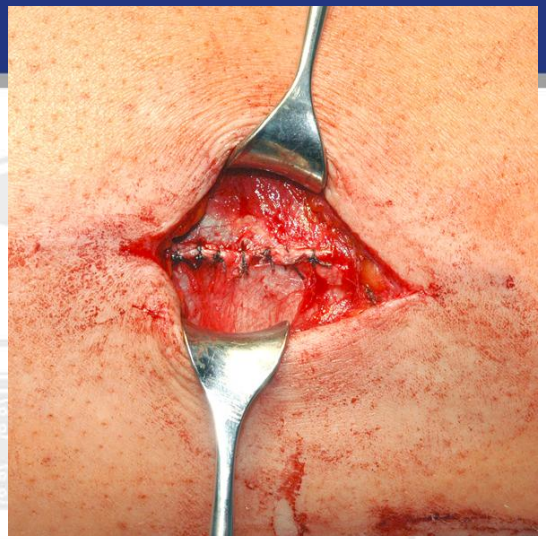





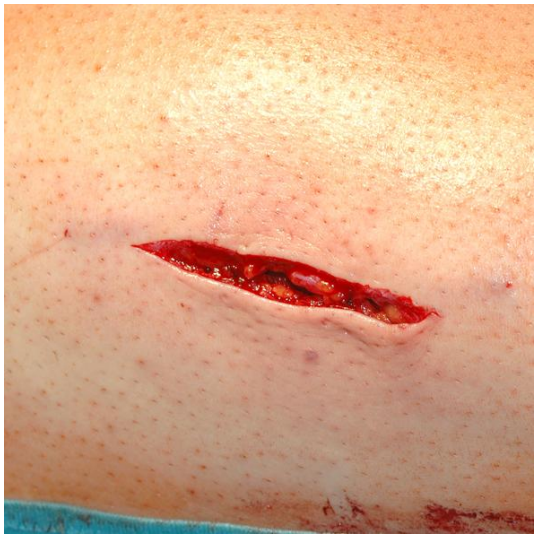



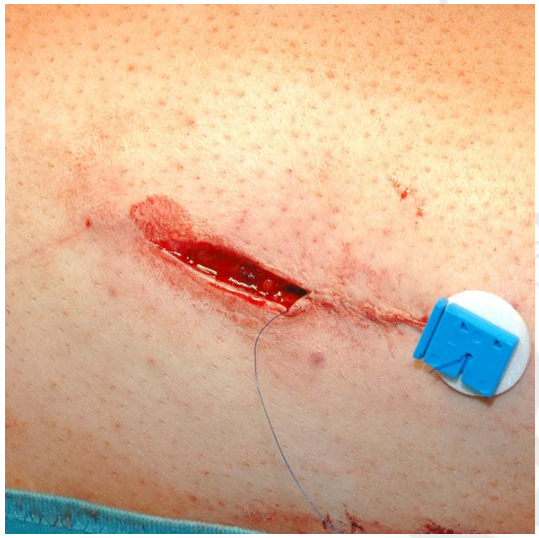
Biopsia musculară

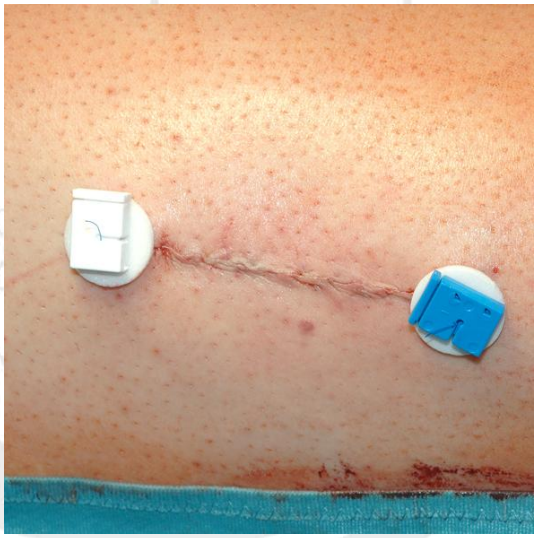


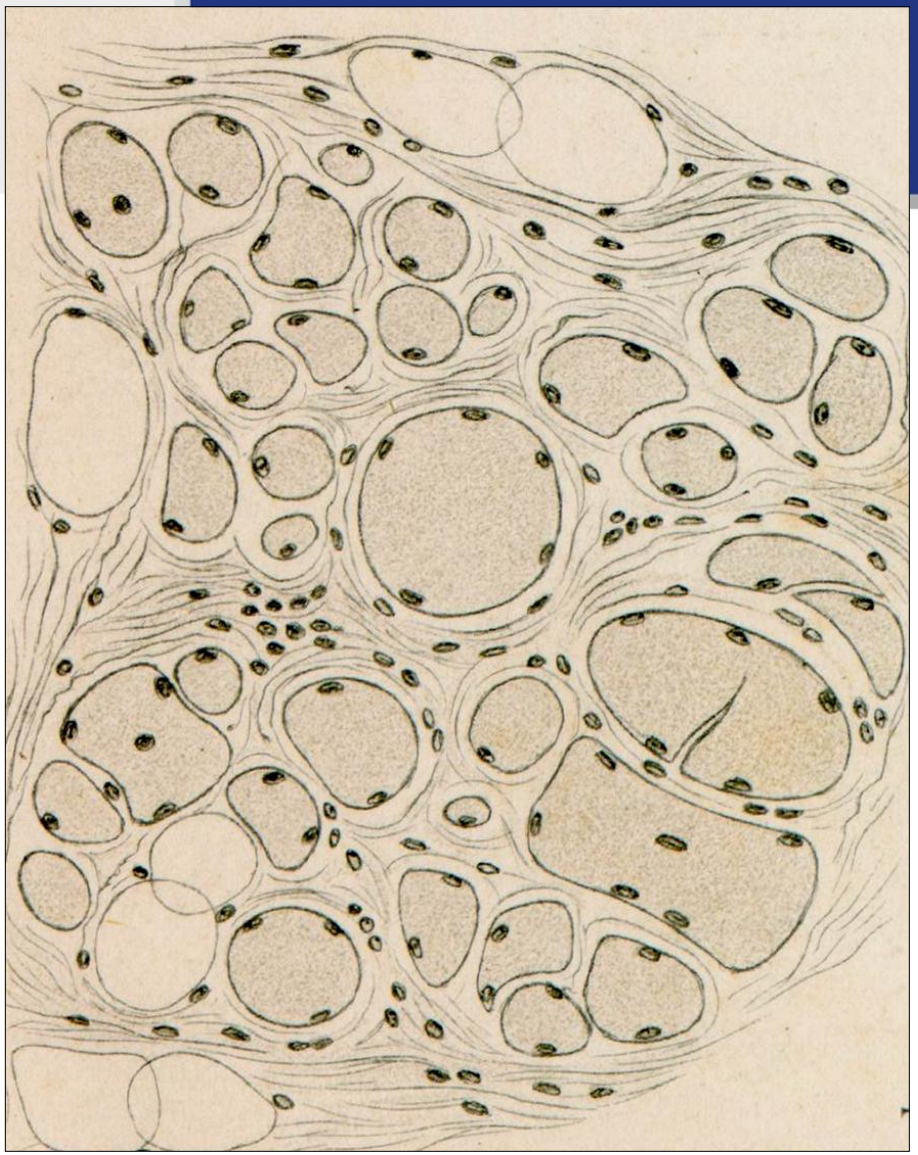




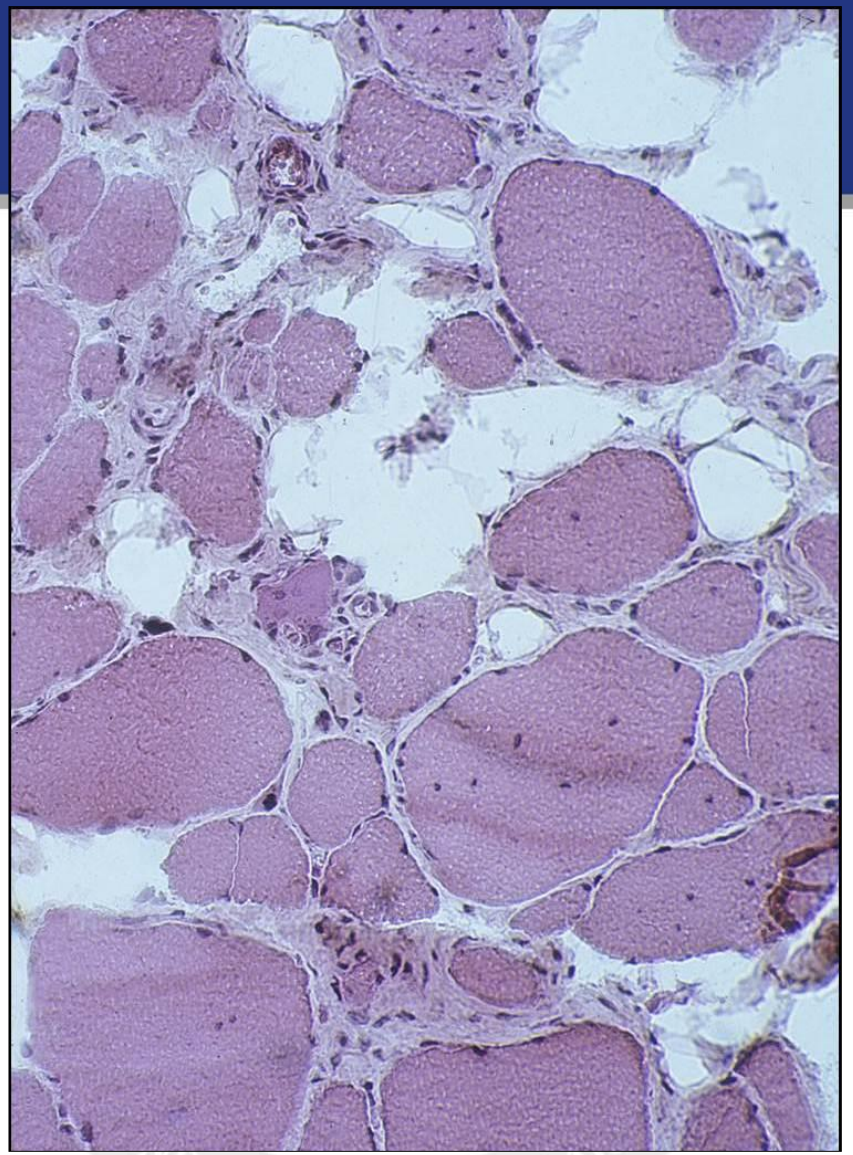








Wilhelm Erb:
Dystrophia muscularis progressiva (1891)



Muskeldystrophie heute

Serum CK as a guide to the diagnosis of muscle disease

Dimitri Renard

Correspondence to
Dr Dimitri Renard, Department of Neurology, CHU Nîmes, Hôpital Caremeau, Place du Pr Debré, Nîmes Cedex 4 30029, France;
dimitrirenard@hotmail.com

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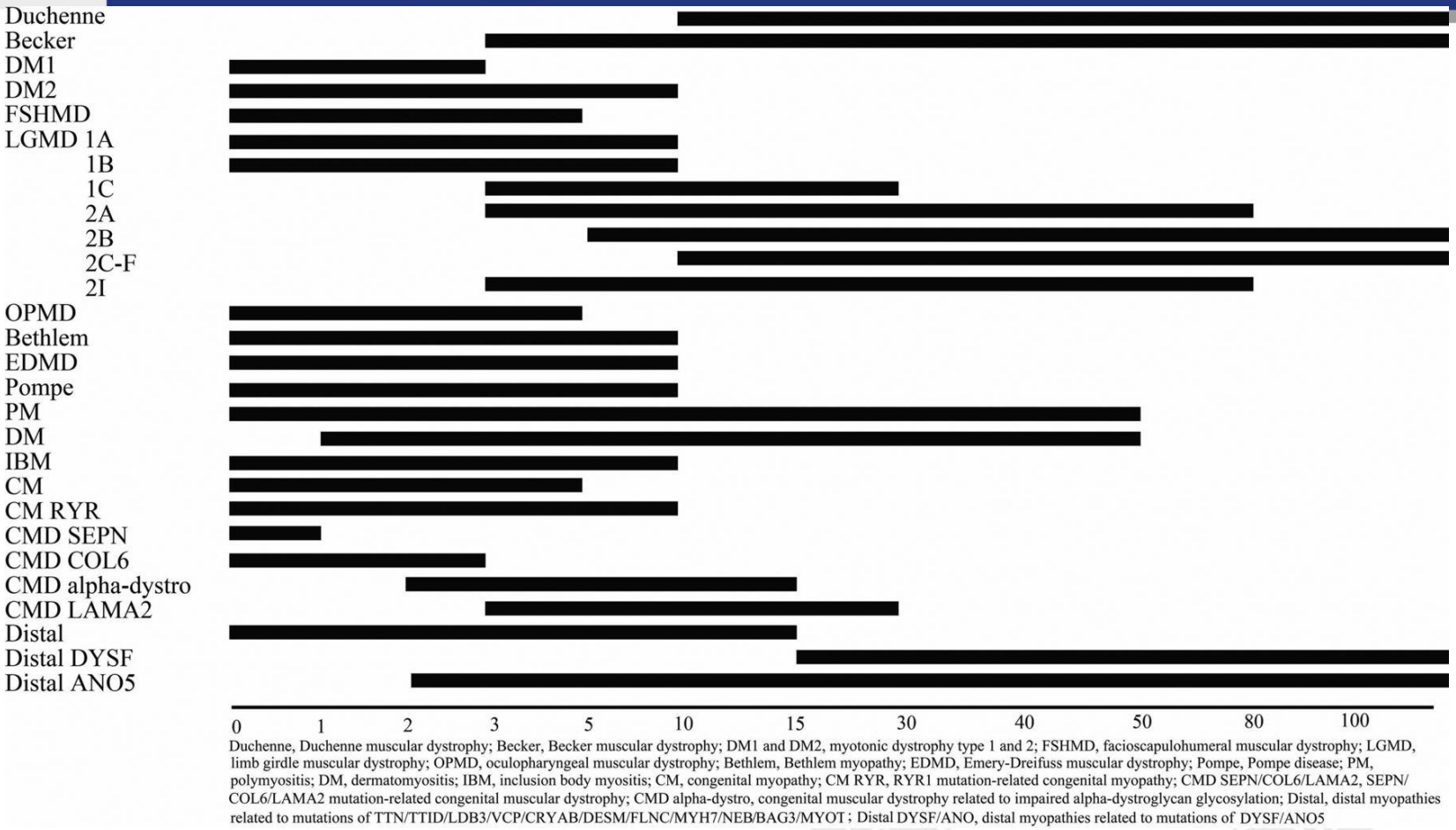
The serum creatine kinase (CK) concentration is often—but not always—elevated in muscle disease. The degree of elevation, together with clinical, electrophysiological, radiological and histological characteristics, can help to characterise individual myopathies.[1] [2]

normal serum CK concentration. To the best of my knowledge (and to my surprise) there have been no previous similar one-image overviews covering the most common myopathies and their serum CK concentrations. This kind of image should help neurologists who are trying

Dimitri Renard Pract Neurol 2015;15:121

Majorarea CK la pacienții cu distofii musculare



Duchenne, Duchenne muscular dystrophy; Becker, Becker muscular dystrophy; DM1 and DM2, myotonic dystrophy type 1 and 2; FSHMD, facioscapulohumeral muscular dystrophy; LGMD, limb girdle muscular dystrophy; OPMD, oculopharyngeal muscular dystrophy; Bethlem, Bethlem myopathy; EDMD, Emery-Dreifuss muscular dystrophy; Pompe, Pompe disease; PM, polymyositis; DM, dermatomyositis; IBM, inclusion body myositis; CM, congenital myopathy; CM RYR, RYR1 mutation-related congenital myopathy; CMD SEPN/COL6/LAMA2, SEPN/COL6/LAMA2 mutation-related congenital muscular dystrophy; CMD alpha-dystro, congenital muscular dystrophy related to impaired alpha-dystroglycan glycosylation; Distal, distal myopathies related to mutations of TTN/TTID/LDB3/VCP/CRYAB/DESM/FLNC/MYH7/NEB/BAG3/MYOT; Distal DYSF/ANO, distal myopathies related to mutations of DYSF/ANO5

Dimitri Renard Pract Neurol 2015;15:121

Distrofia musculară Duchenne

- În stadiile tardive – implicarea mușchilor cardiaci și retard mintal
- Administrarea

Prednisolon 0,75 mg/kg/zi, sau

Deflazacort 1,0 mg/kg/zi

puțin ameliorează progresia maladiei

Therapeutic Landscape of Duchenne Muscular Dystrophy, Including Drugs Recently Approved by the US Food and Drug Administration and Drugs Currently in Development

Treatment modality	Pharmacologic agent
Corticosteroids	Prednisone, deflazacort[a]
Nuclear factor-kappa B inhibitor	Vamorolone
Stop-codon readthrough	Ataluren
Exon skipping	Eteplirsen (exon 51 skip-amenable),[a] golodirsen (exon 53 skip-amenable),[a] viltolarsen (exon 53 skip-amenable),[a] casimersen (exon 45 skip-amenable)[a]
Gene replacement	Mini-dystrophin, microdystrophin
Antifibrotic	Pamrevlumab
Muscle regeneration promoters	Follistatin, allogeneic cell therapy

[a]Drugs with FDA approval for use in Duchenne muscular dystrophy.

The Dystrophinopathies.
Lee, Bo

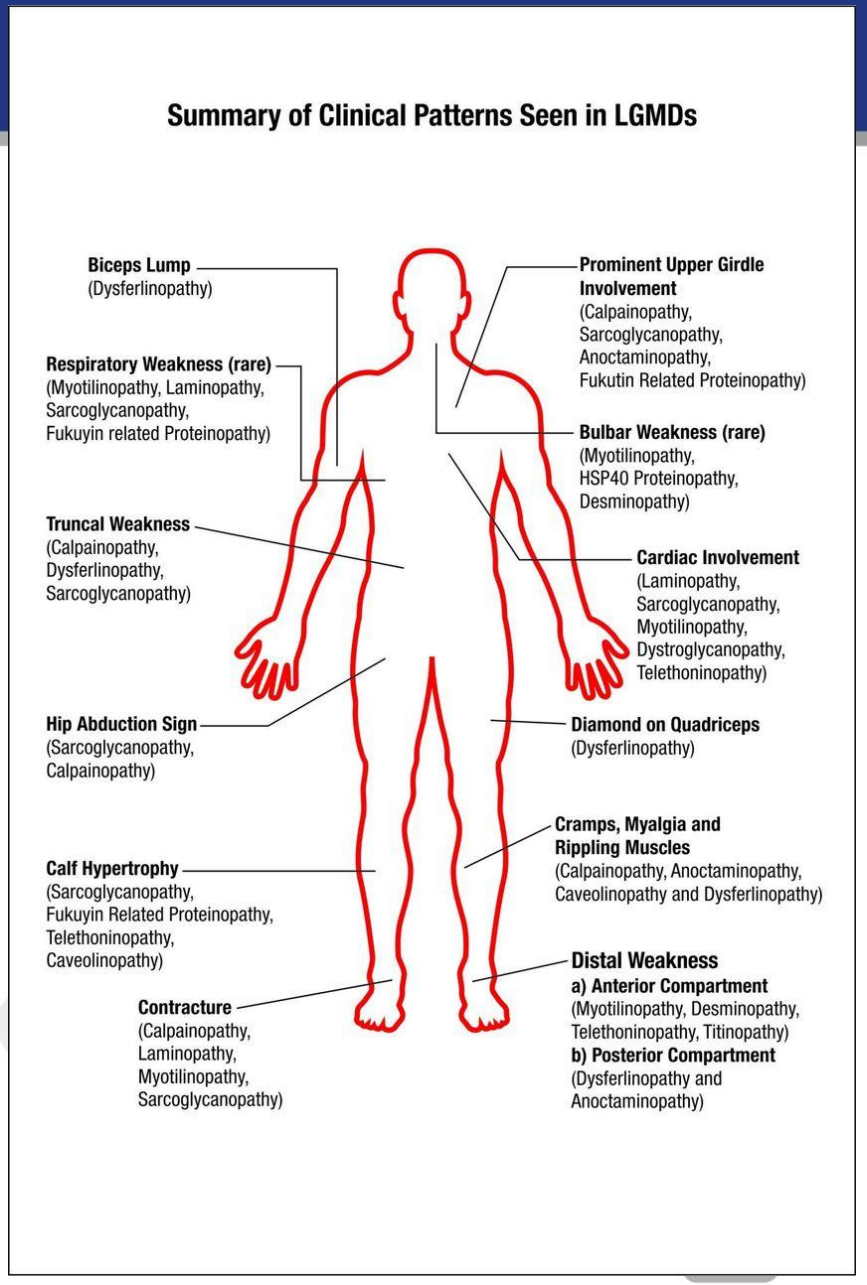
CONTINUUM: Lifelong Learning in Neurology. 28(6):1678-1697, December 2022.

Distrofia musculară Becker

- Se aseamănă cu distrofia Duchenne
- Nivelul distrofinei în muşchi nu este modificat, dar este calitativ diferit
- Debut mai tardiv – 10-11 ani
- Exitus mai târziu – 42 ani

Miopatiile distrofice în centură (Erb-Rot)

Wilhelm Erb (1840-1921)



Miopatiile distrofice în centură (Erb-Rot)

Table 1 Genetic classification of LGMDs

Disease	Gene	Protein	Inheritance
LGMD 1A (myotilinopathy)	*MYOT*	Myotilin	Autosomal dominant
LGMD 1B (laminopathy)	*LMNA*	Lamin	
LGMD 1C (caveolinopathy)	*CAV3*	Caveolin	
LGMD 1D (HSP40 proteinopathy)	*DNAJB6*	HSP40	
LGMD 1E (desminopathy)	*DES*	Desmin	
LGMD 1F (transportinopathy)	*TNPO3*	Transportin 3	
LGMD 1G (HNRPDL proteinopathy)	*HNRPDL*	Heterogeneous nuclear ribonucleoprotein D-like protein	
LGMD 1H	Gene locus 3p23	To be identified	
LGMD 2A (calpainopathy)	*CAPN3*	Calpain	Autosomal recessive
LGMD 2B (dysferlinopathy)	*DYSF*	Dysferlin	
LGMD 2C, 2D, 2E and 2F (sarcoglycanopathy)	*SGCG, SGCA, SGCB* and *SGCD* respectively	Gamma-sarcoglycan, alpha-sarcoglycan, beta-sarcoglycan and delta-sarcoglycan	
LGMD 2G (telethoninopathy)	*TCAP*	Telethonin	
LGMD 2 hour (TRIM32 proteinopathy/ Sarcotubular myopathy	*TRIM32*	E3 ubiquitin ligase	
LGMD 2I (fukutin-related proteinopathy)	*FKRP*	Fukutin-related protein	
LGMD 2J (titinopathy/Finnish distal myopathy)	*TTN*	Titin	
LGMD 2K, 2N, 2O and 2P (alpha-dystroglycanopathies)	*POMT1, POMT2, POMGNT1, DAG1*	POMT1, POMT2, POMGNT1, DAG1	
LGMD 2L (anoctaminopathy)	*ANO5*	Anoctamin 5	
LGMD 2M (fukutinopathy)	*FKTN*	Fukutin	
LGMD 2Q (plectinopathy)	*PLEC1*	Plectin	
LGMD 2R (desminopathy)	*DES*	Desmin	
LGMD 2S (TRAPPC11 proteinopathy)	*TRAPPC11*	Trafficking protein particle complex 11	
LGMD 2T (GMPPB proteinopathy)	*GMPPB*	GDP-mannose pyrophosphorylase B	
LGMD 2U (ISPD proteinopathy)	*ISPD*	Isoprenoid synthase domain containing	
LGMD 2V	*GAA*	Acid alpha-glucosidase	
LGMD 2W	*LMS2*	Lim senescent cell antigen-like domain-2	
LGMD 2X	*BVES*	Blood vessel epicardial substance	
LGMD 2Y	*TOR1AIP1*	Torsin-1A interacting protein-1	
LGMD 2Z	*POGLUT1*	Protein-O-glucosyltransferase-1	

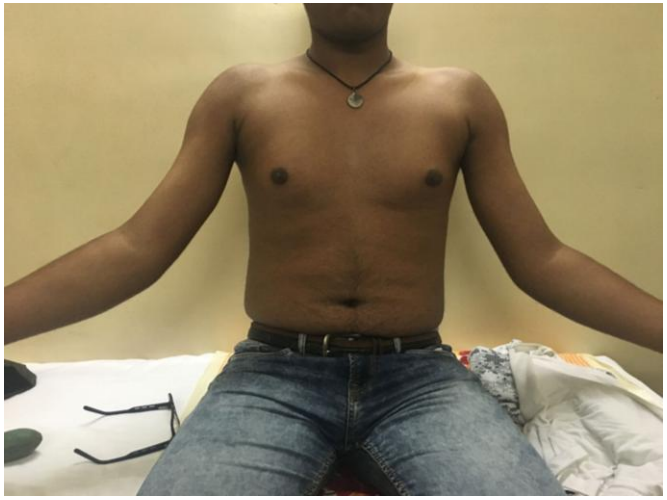
DAG1, dystroglycan 1; LGMDs, limb girdle muscular dystrophies; POMGNT1, protein O-linked mannose 1,2-N-acetylglucosaminyltransferase; POMT1, protein O-mannosyltransferase 1; POMT2, protein O-mannosyltransferase 2.

LGMD 1 (AD – lamin, caveolin)

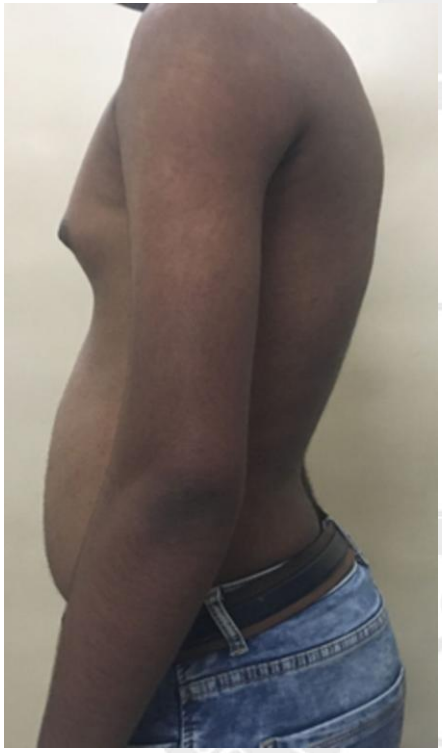
LGMD 2 (AR –sarcoglican, disferilin, calpain)

Calpainopatie LGMD2A

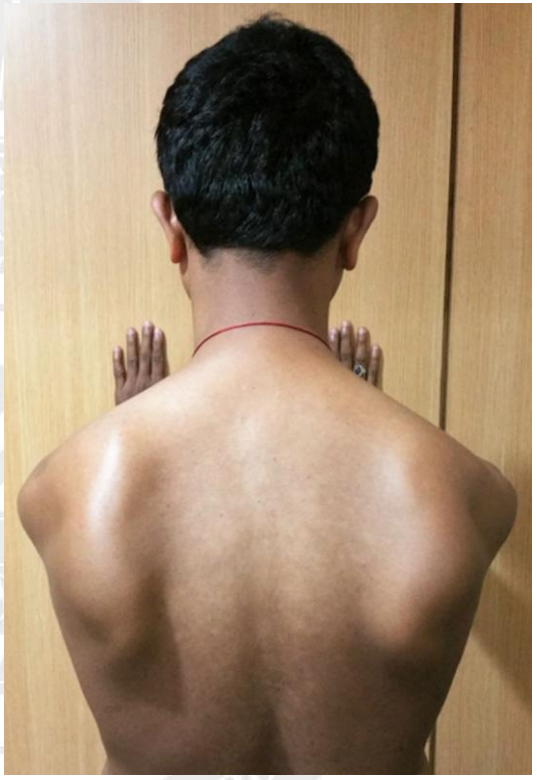
Contractura cotului



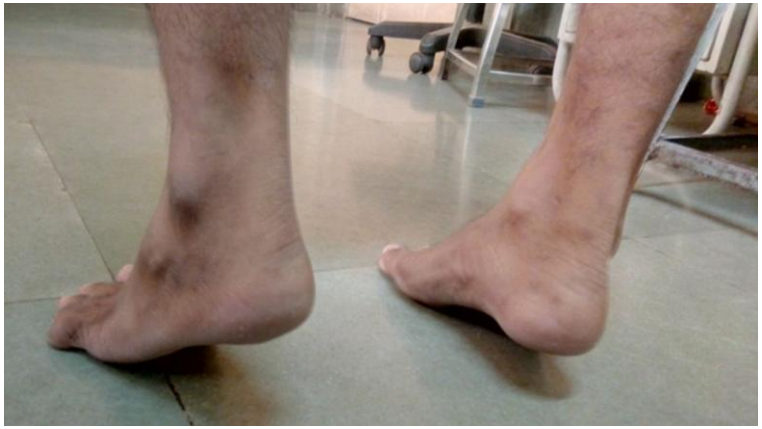
Hiperlordpză lombară



Aripi scapulare

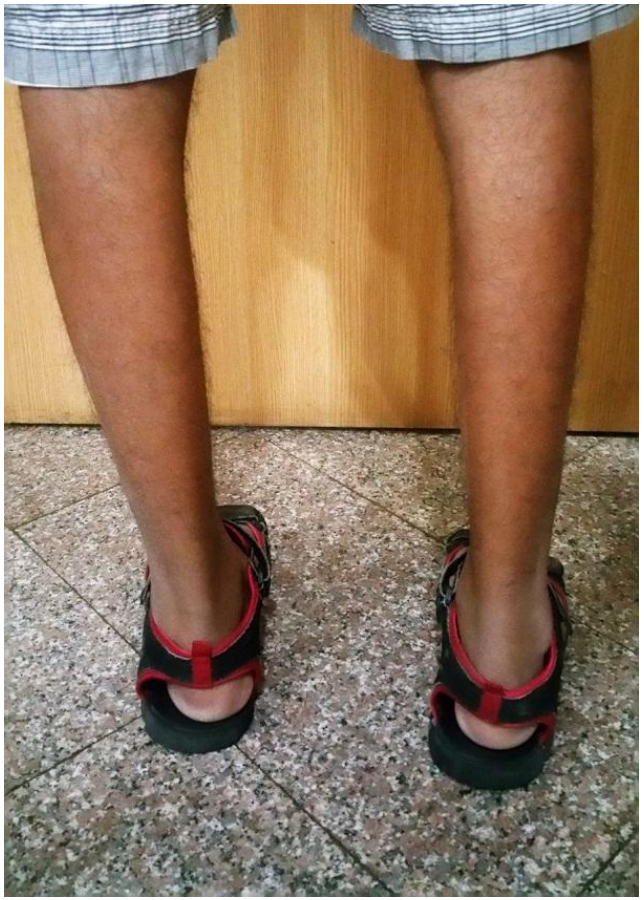


Contractura achiliană



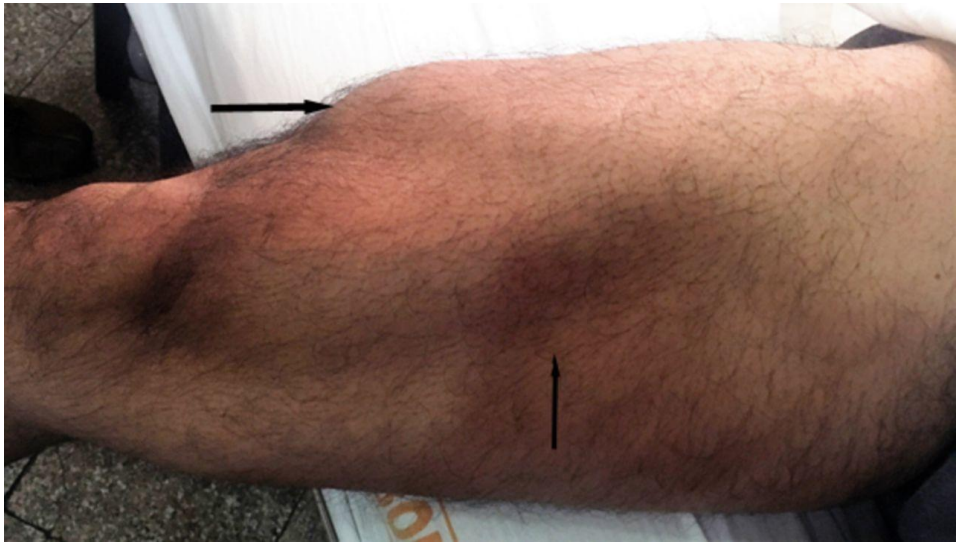
Satish V Khadilkar et al. Pract Neurol 2018;18:201-210

Disferilinopatie LGMD 2 B

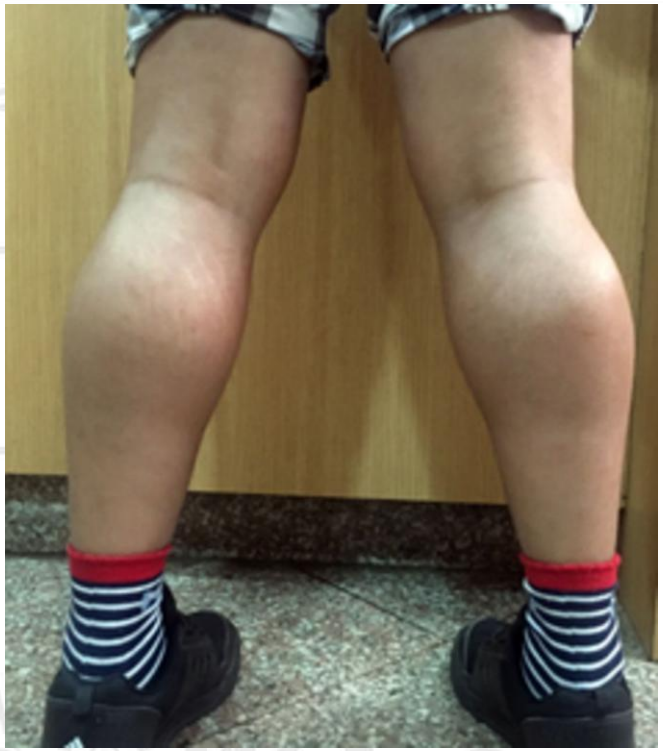


Atrofia gambelor

Sarcoglicanopatie LGMD2C



Hipertrofii și atrofii ai mușchilor coapsei



Pseudohipertrofia gambelor – mimează DMD

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RESEARCH PAPER

MRI in sarcoglycanopathies: a large international cohort study

Giorgio Tasca,[1] Mauro Monforte,[1] Jordi Díaz-Manera,[2,3] Giacomo Brisca,[4] Claudio Semplicini,[5] Adele D'Amico,[6] Fabiana Fattori,[6] Anna Pichiecchio,[7] Angela Berardinelli,[8] Lorenzo Maggi,[9] Elio Maccagnano,[10,11] Nicoline Løkken,[12] Chiara Marini-Bettolo,[13] Francina Munell,[14] Angel Sanchez,[15] Nahla Alshaikh,[16] Nicol C Voermans,[17] Jahannaz Dastgir,[18] Dmitry Vlodavets,[19] Jana Haberlová,[20] Gianmichele Magnano,[21] Maggie C Walter,[22] Susana Quijano-Roy,[23] Robert-Yves Carlier,[24] Baziel G M van Engelen,[17] John Vissing,[12] Volker Straub,[13] Carsten G Bönnemann,[18] Eugenio Mercuri,[25] Francesco Muntoni,[16] Elena Pegoraro,[5] Enrico Bertini,[6] Bjarne Udd,[26,27,28] Enzo Ricci,[1] Claudio Bruno[4]

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For numbered affiliations see end of article.

Correspondence to
Dr Giorgio Tasca, Istituto di

ABSTRACT

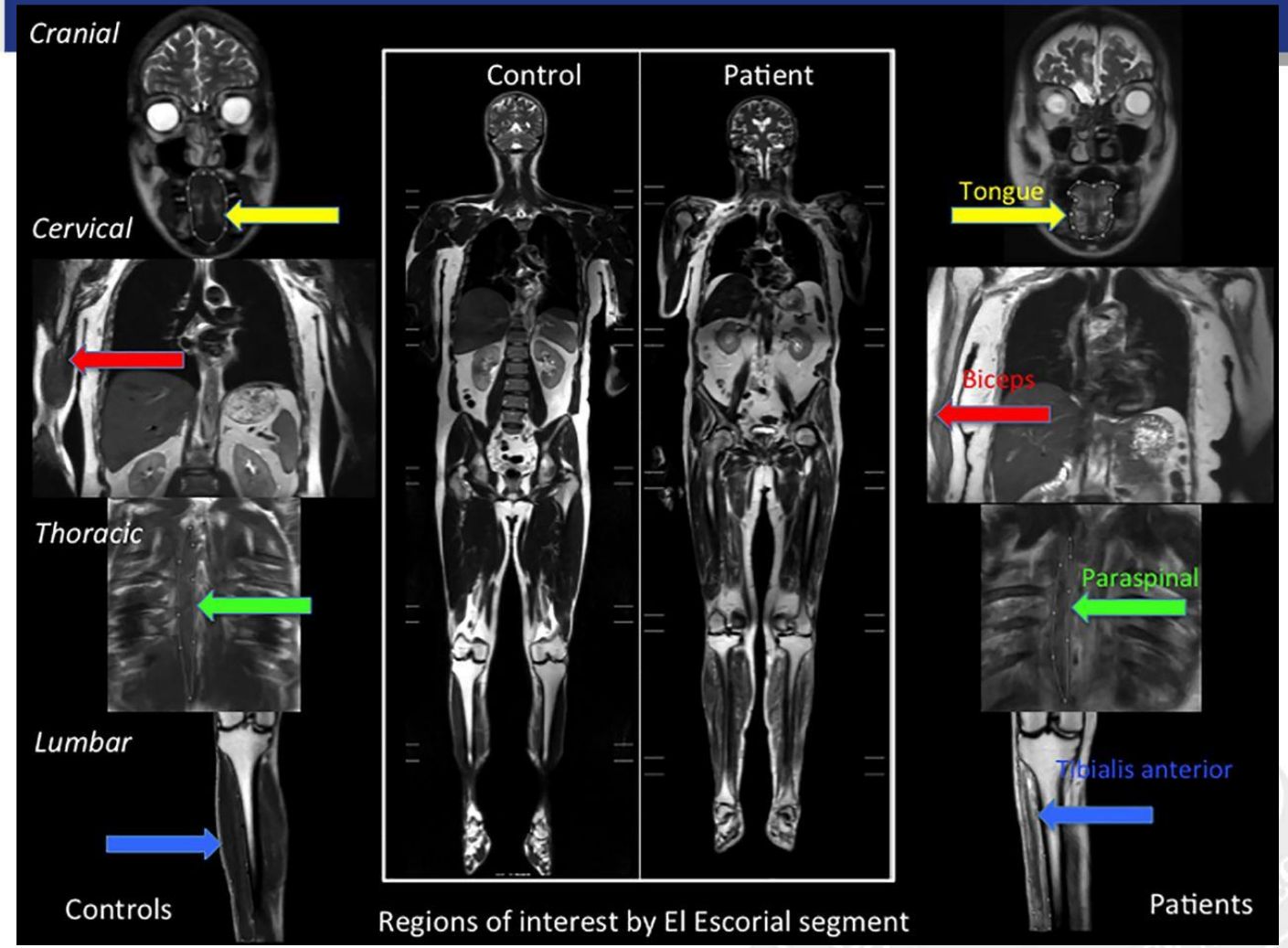
Objectives To characterise the pattern and spectrum of involvement on muscle MRI in a large cohort of patients with sarcoglycanopathies, which are limb-girdle muscular dystrophies (LGMD2C–2F) caused by mutations in one of the four genes coding for muscle sarcoglycans.

Methods Lower limb MRI scans of patients with LGMD2C–2F, ranging from severe childhood variants to milder adult-onset forms, were collected in 17

proteins at the level of the sarcolemma, to form the so-called dystrophin-associated glycoprotein complex (DAGC).[1]

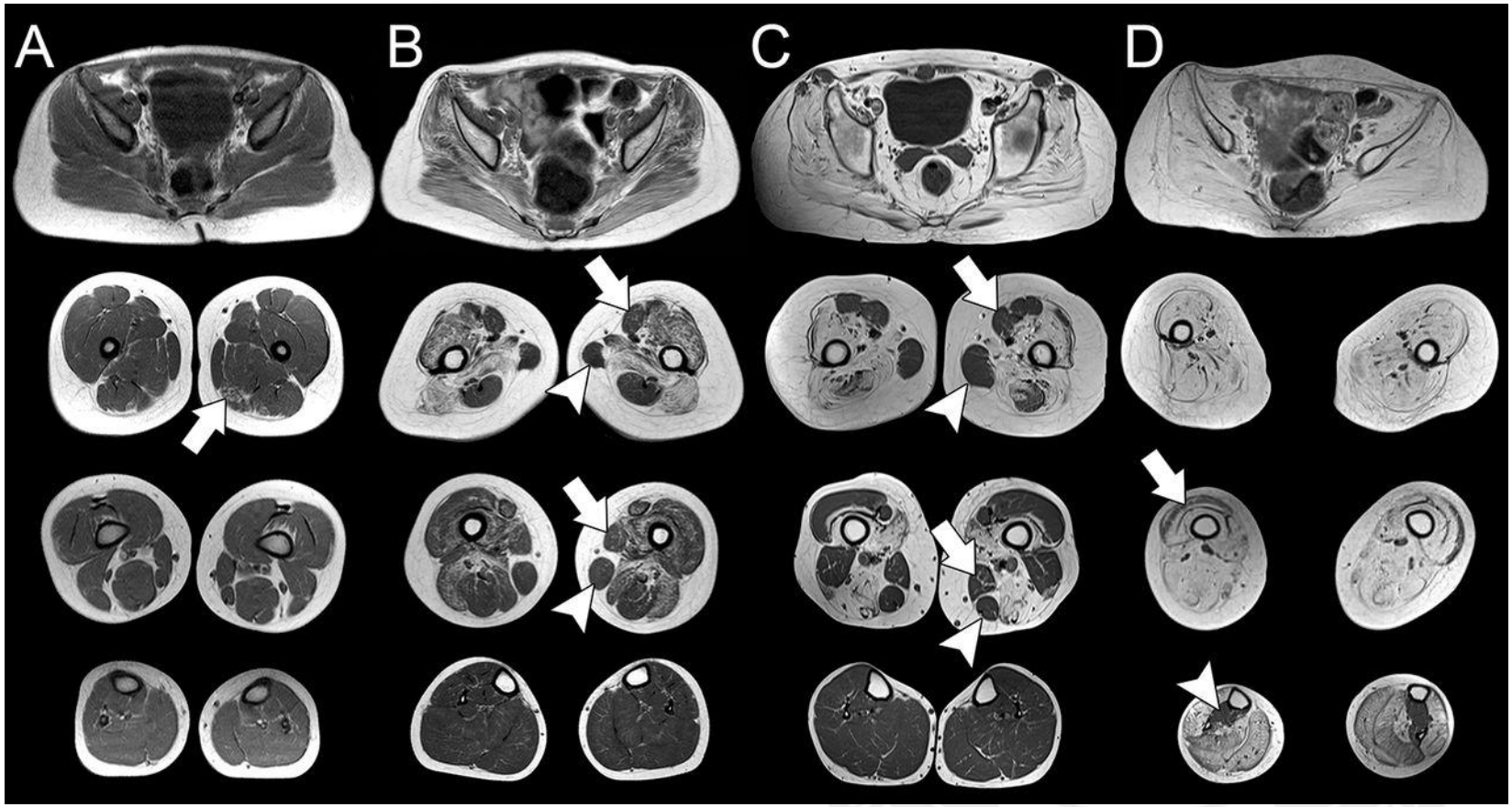
As for all the LGMDs, the correct molecular diagnosis is of great importance for adequate care management, planning the genetic counselling, scheduling the correct follow-up and allowing enrolment in ongoing and future gene therapy trials.[2] Sarcoglycanopathies can have a paediatric or

IRM muscular



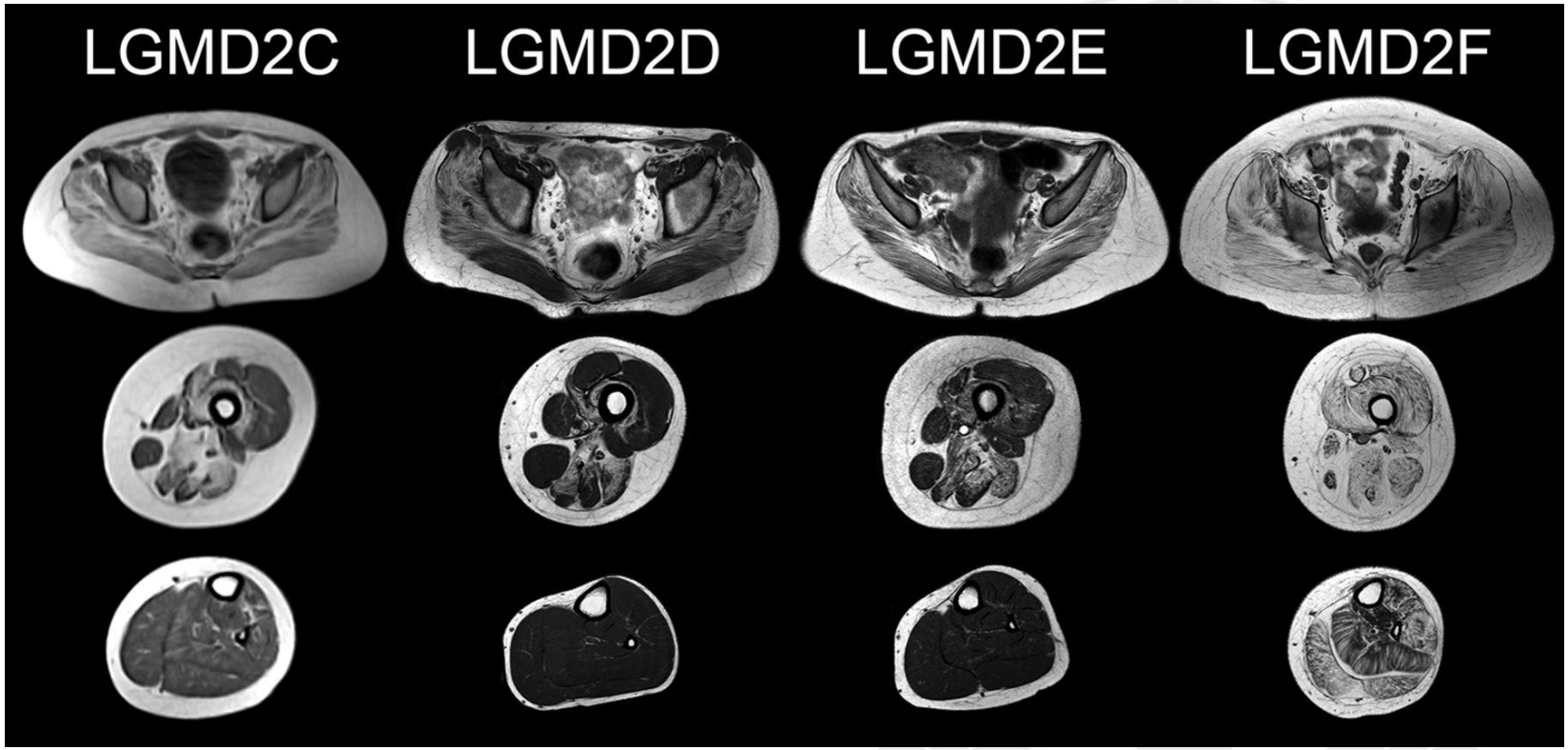
Thomas M Jenkins et al. J Neurol Neurosurg Psychiatry 2018;89:248-255

IMPLICAREA MUȘCHILOR ÎN sarcoglicanopatii (examenul IRM)



Giorgio Tasca et al. J Neurol Neurosurg Psychiatry 2018;89:72-77

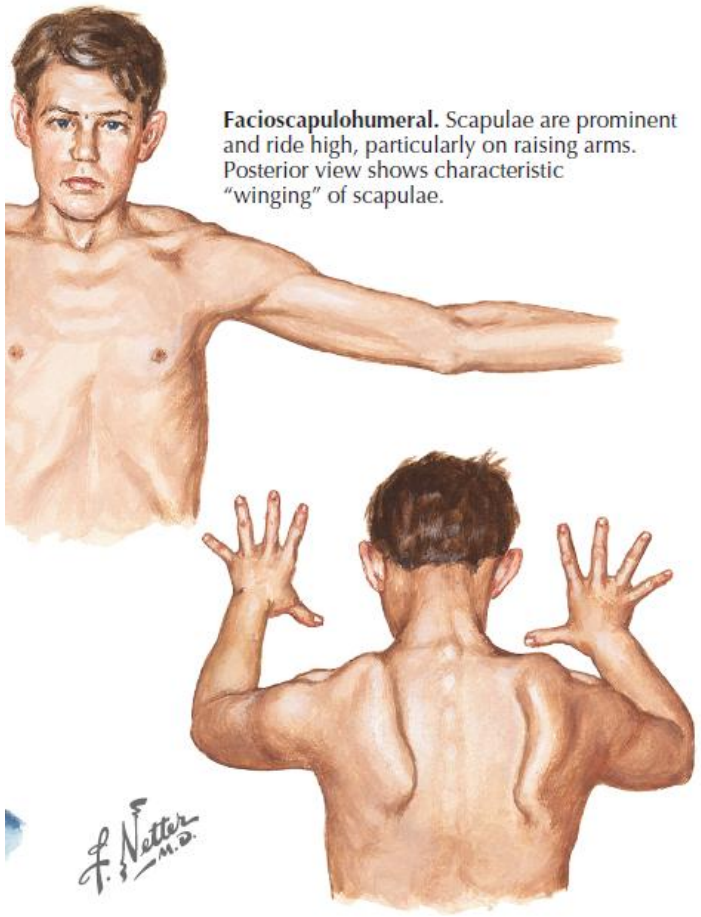
IMPLICAREA MUȘCHILOR ÎN sarcoglicanopatii (examenul IRM)



Giorgio Tasca et al. J Neurol Neurosurg Psychiatry 2018;89:72-77

Forma facioscapulohumerală (Landouzi-Dejerine)

- **AD**
- **Contractarea D_4Z_4 pe cromozomul 4q35**



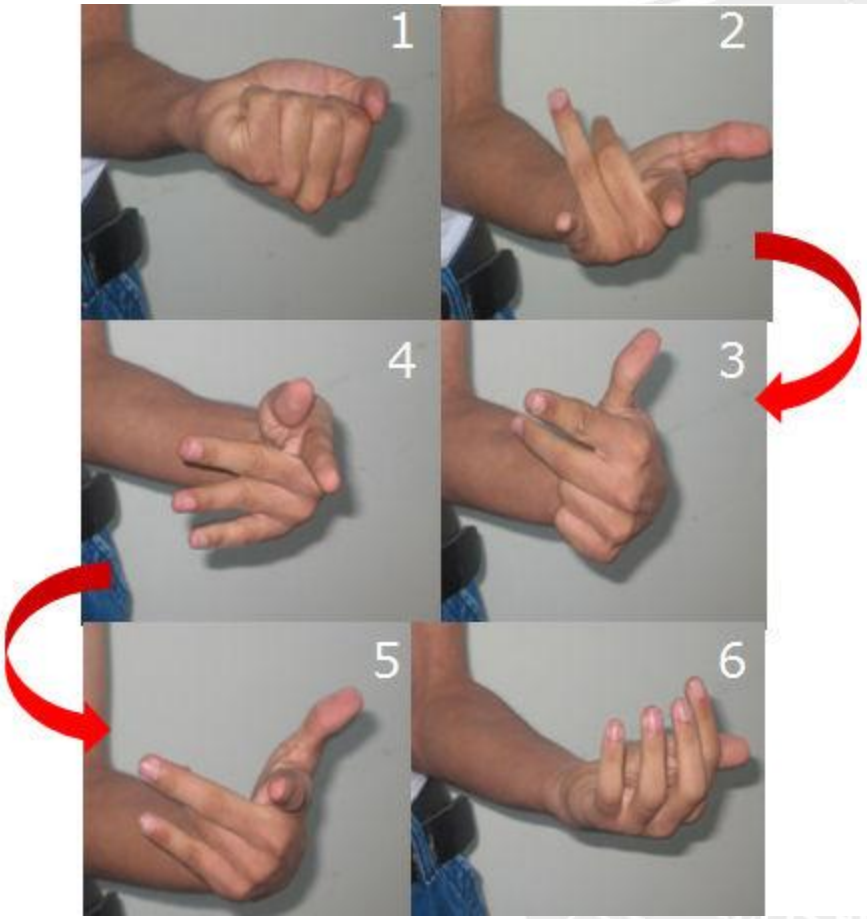
Miotonia

- **Se caracterizează prin relaxare întârziată a mușchilor după contractarea lor datorată modificărilor patologice ale membranei fibrelor musculare**

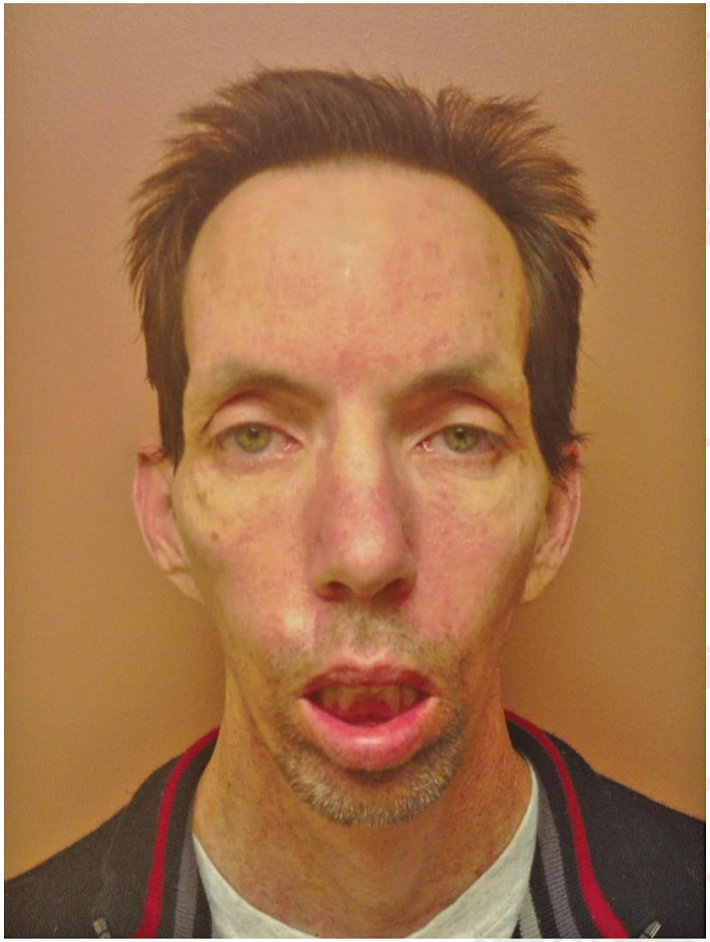
Distrofia miotonică tip I

- **Distrofia miotonică tip I (DMI) – cea mai frecventă distrofie musculară la adulți**
- **Prevalența 10-100.000**

Miotonie



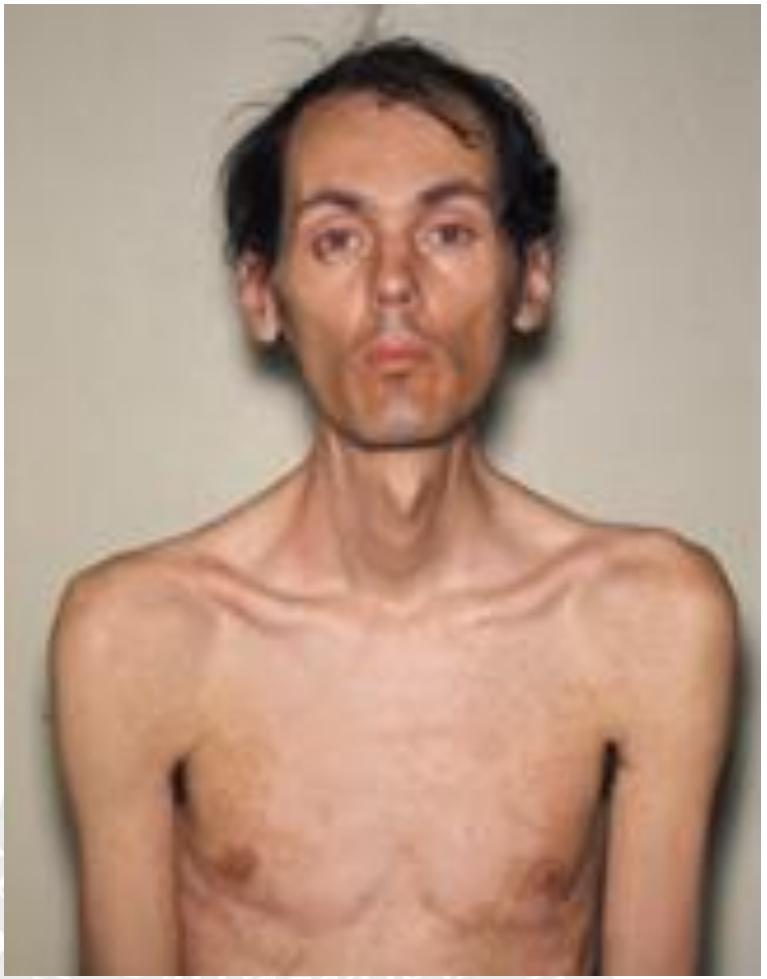
Distrofie miotonică: chelie frontală, ptoză, atrofie temporală și gură deschisă.



First Encounters in Instant Neurological Diagnosis (3 edn), https://doi.org/10.1093/med/9780197699461.003.0001

Distrofia miotonică I

- **AD**
- **Se manifestă în deceniile 3-4 ale vieții**
- **Majorarea numărului repetărilor trinucleotidelor (CTG) (>37) în gena DMPK pe cromozomul 19 (19q13.2 - 19q13.3), codifică miotonin-proteinkinaza**

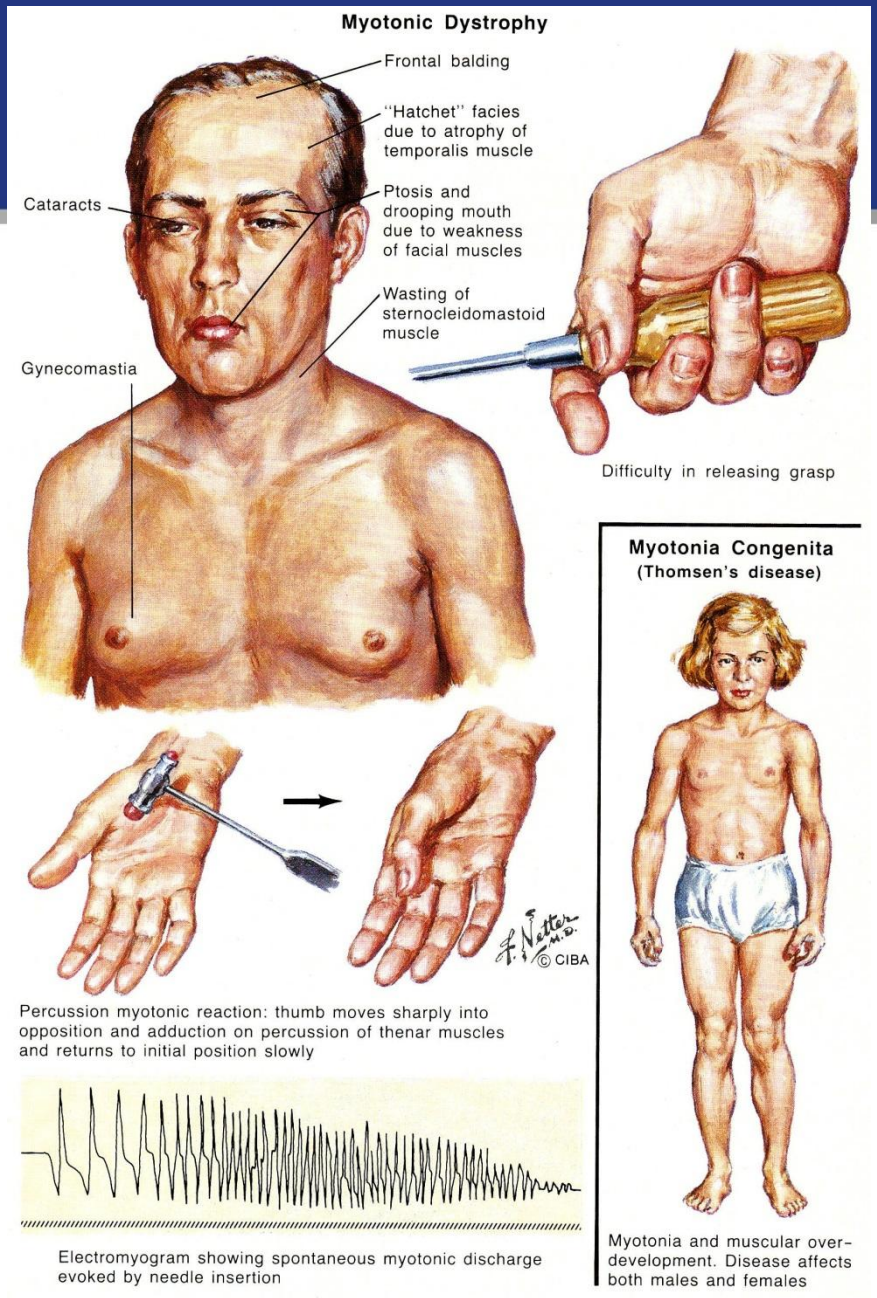


Distrofia miotonică I

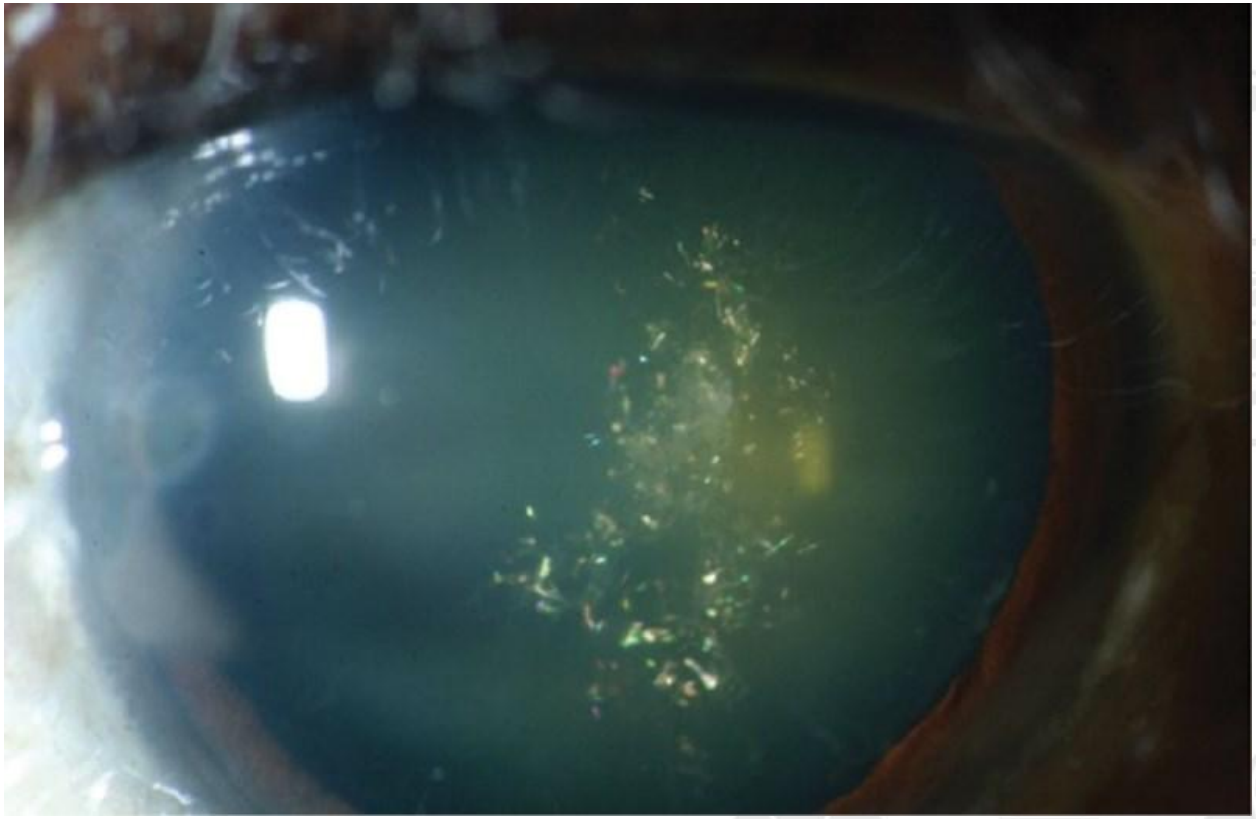
- **Slăbiciunea şi atrofia**

mm mimici, sternocleidomastoideus, temporalis, flexori ai antrebraţelor, flexorii dorsali ai gambelor

- **Cataractă (până la 50 de ani)**
- **Pleş frontal**
- **Diabet zaharat**
- **Tulburări de conducere cardiacă**
- **Modificări de intelect**



Cataractă de tip Pomul de Crăciun



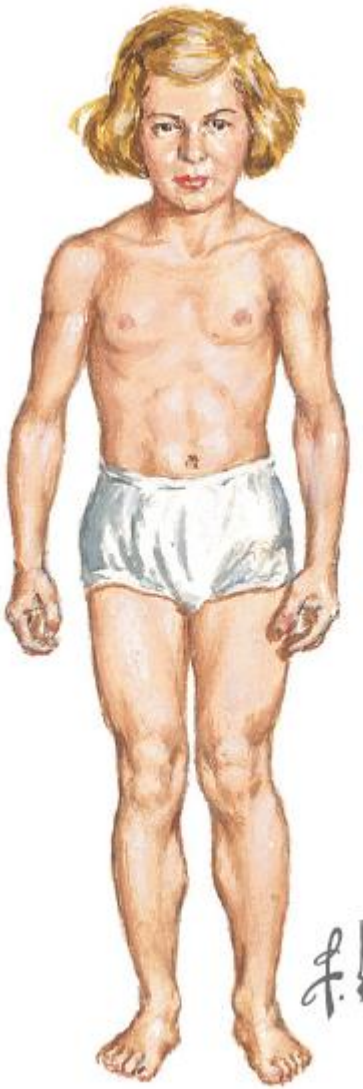
Myopathy and Motor Neuron Disorders in Instant Neurological Diagnosis (3 edn),
https://doi.org/10.1093/med/9780197699461.003.0007

Miotonia congenitală (boala Thomsen)

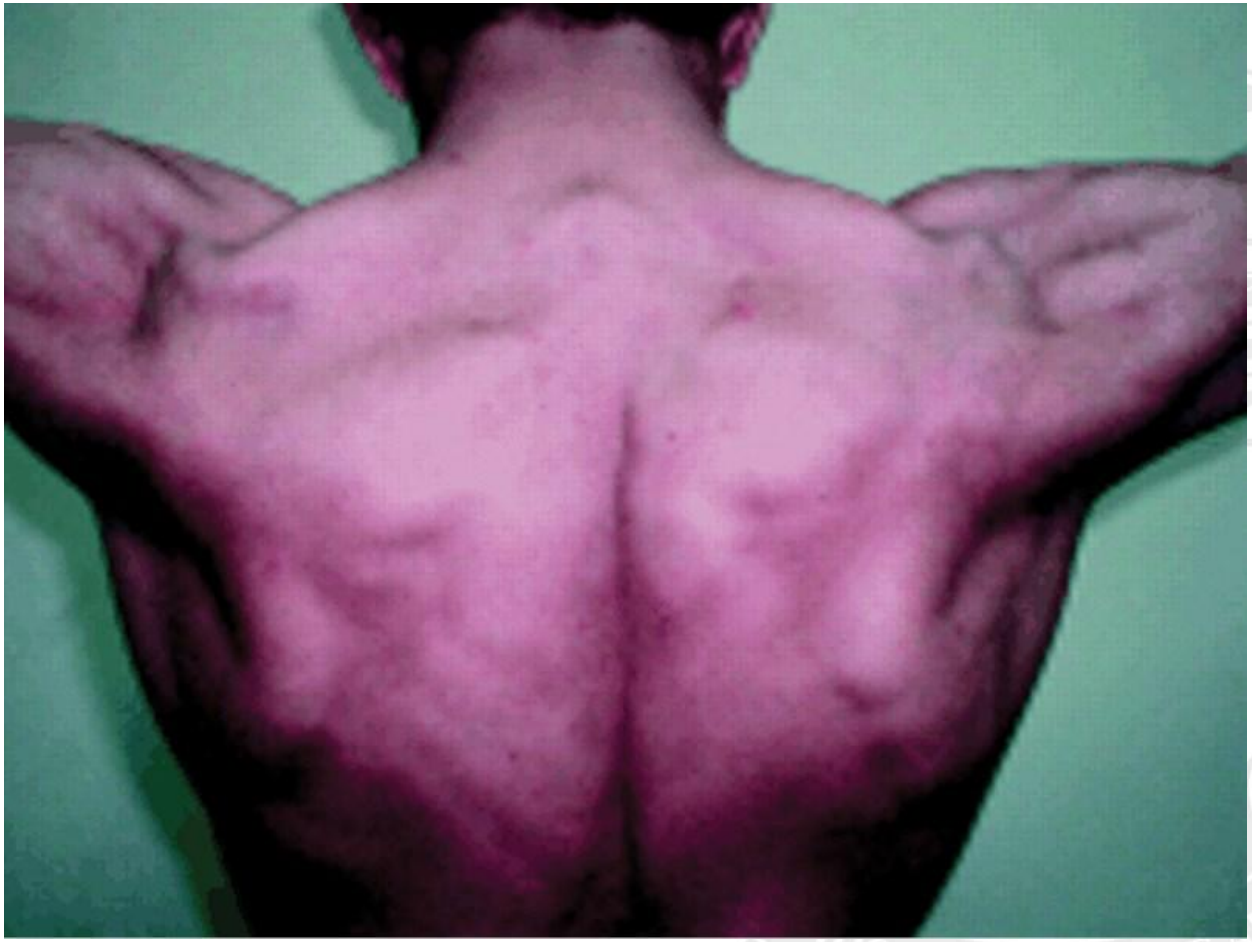
- AD
- Mutație pe cromozomul 7 (CLC – 1 7q)

(canale cloride)

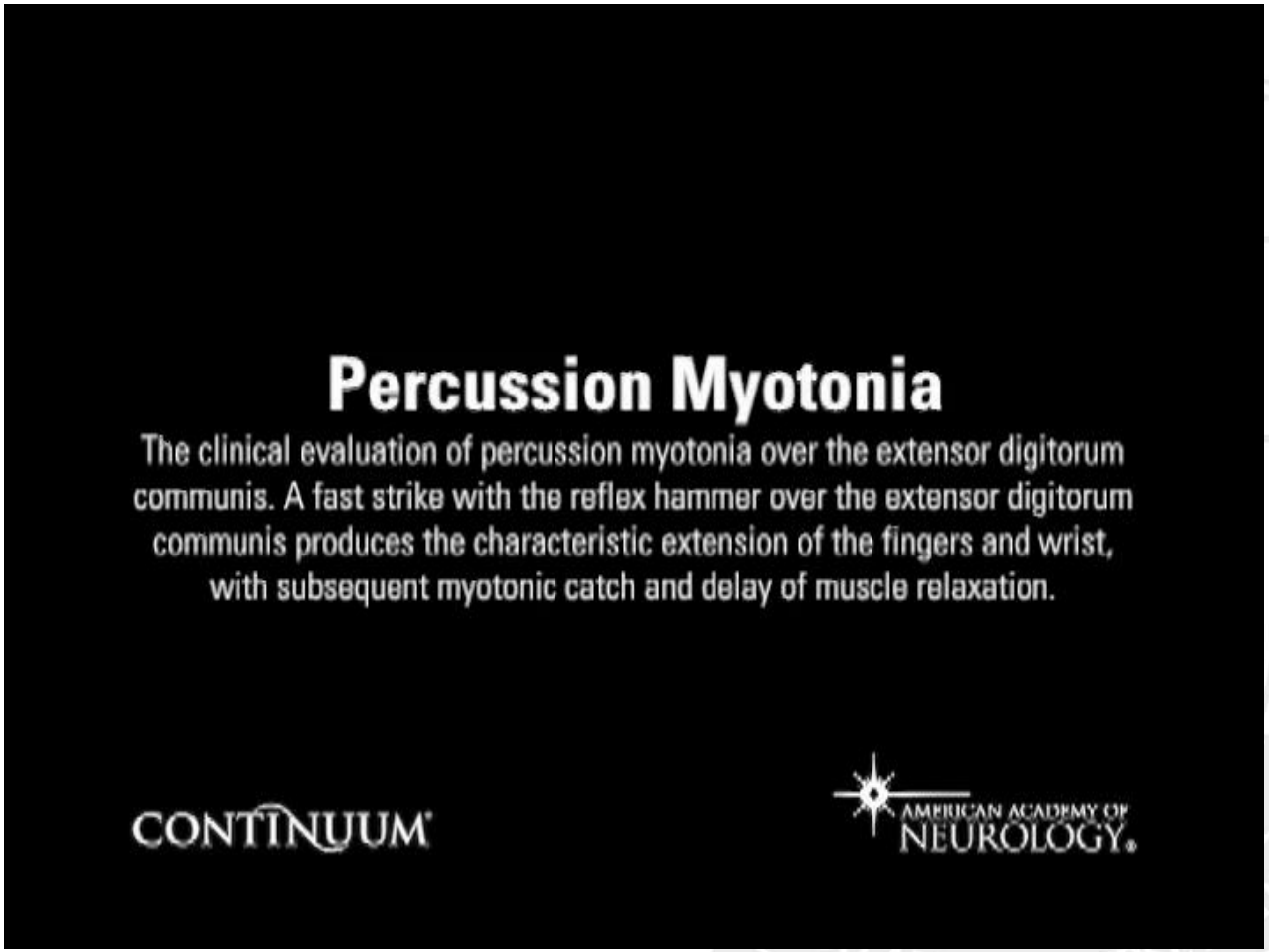
- Miotonie generalizată fără de slăbiciune musculară și atrofii
- Se manifestă îndată după naștere

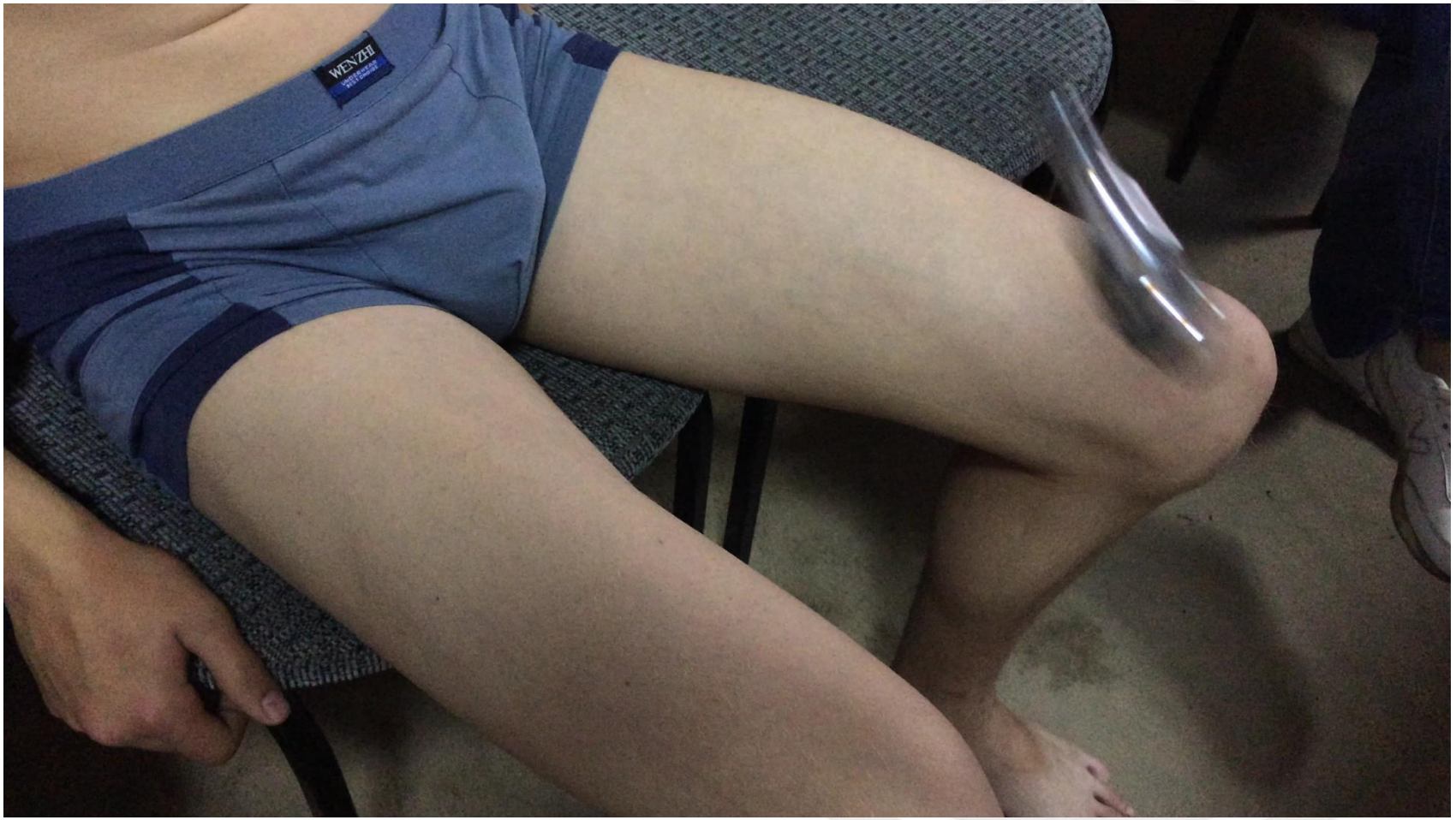


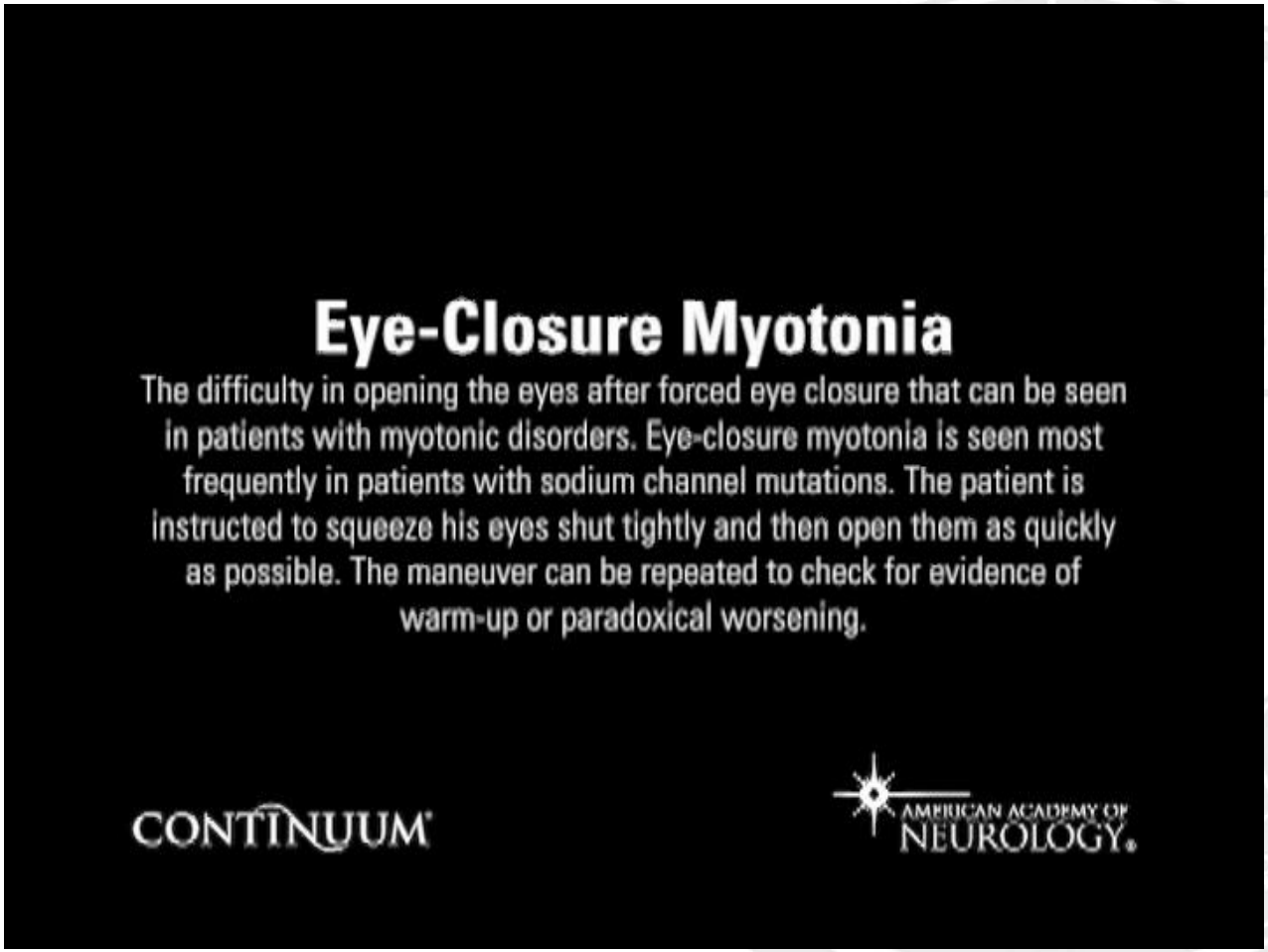
Miotonie congenitală.
Hipertrofie musculară pronunțată.



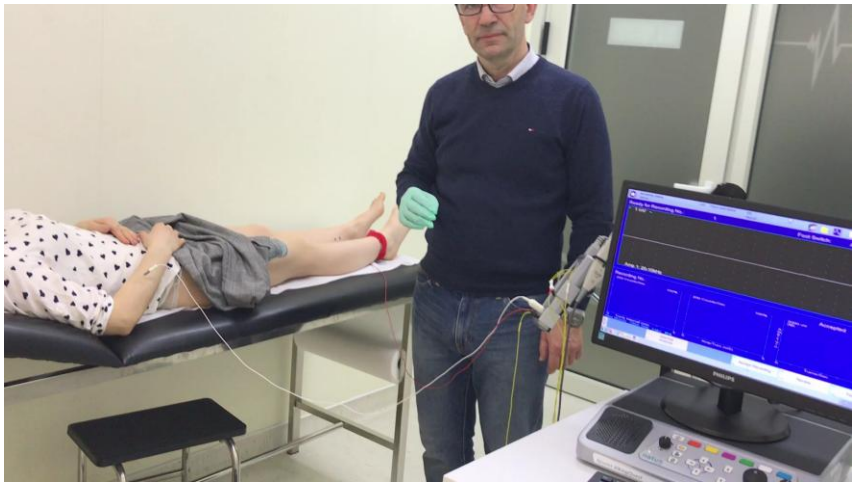
Myopathy and Motor Neuron Disorders in Instant Neurological Diagnosis (3 edn),
https://doi.org/10.1093/med/9780197699461.003.0007


Percussion Myotonia
The clinical evaluation of percussion myotonia over the extensor digitorum communis. A fast strike with the reflex hammer over the extensor digitorum communis produces the characteristic extension of the fingers and wrist, with subsequent myotonic catch and delay of muscle relaxation.
CONTINUUM
AMERICAN ACADEMY OF NEUROLOGY


WENZHI


Eye-Closure Myotonia
The difficulty in opening the eyes after forced eye closure that can be seen in patients with myotonic disorders. Eye-closure myotonia is seen most frequently in patients with sodium channel mutations. The patient is instructed to squeeze his eyes shut tightly and then open them as quickly as possible. The maneuver can be repeated to check for evidence of warm-up or paradoxical worsening.
CONTINUUM
AMERICAN ACADEMY OF NEUROLOGY

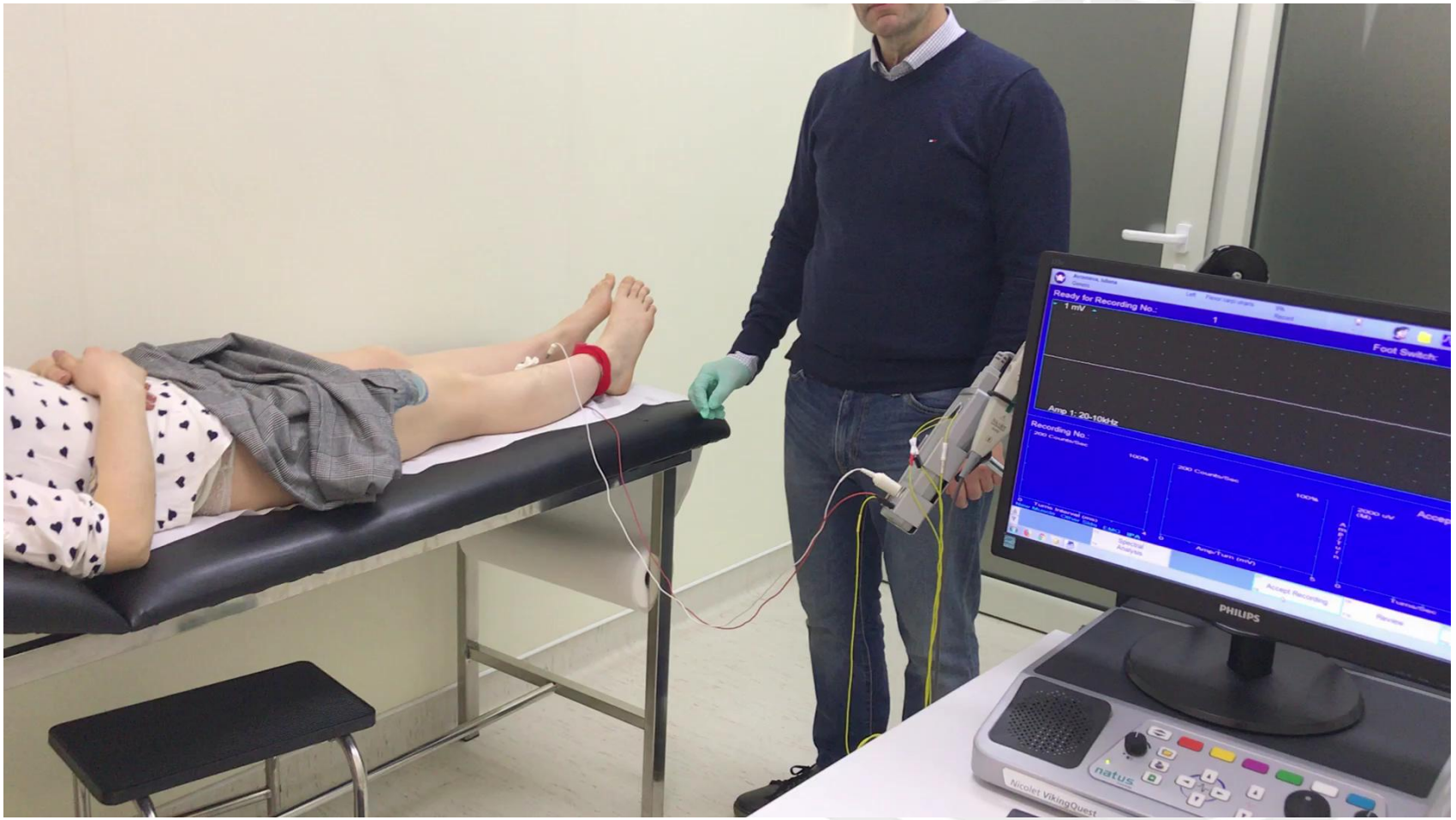
Distrofia miotonică



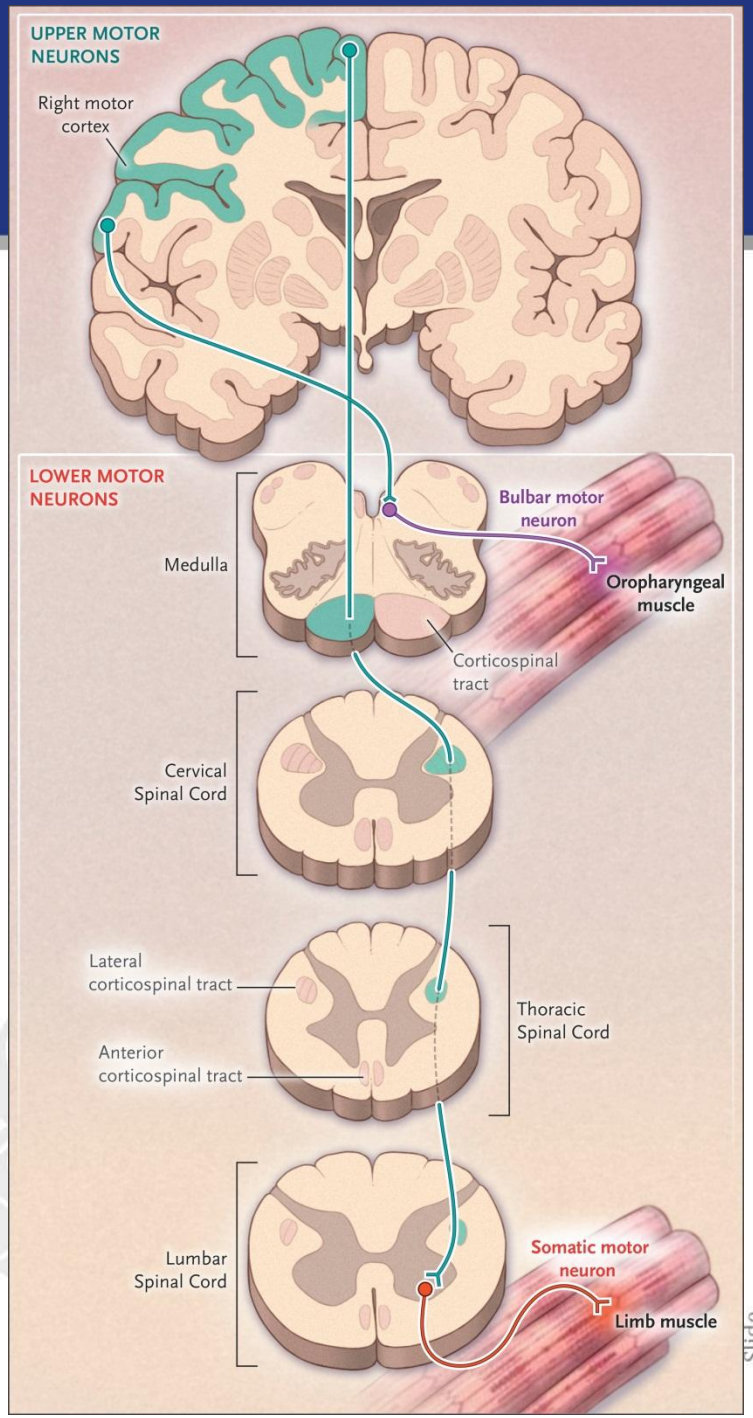
- **EMG – descărcări de frecvență înaltă, amplitudinea cărora undulat crește și se micșorează– sunet pentru "bombardier în cădere"**
- **Pentru diminuarea miotoniei:**

- **sulfat de chinină (300 – 400 mg 3 ori/zi)**
- **procainamid (0,5-1 g 4 ori/zi)**
- **fenitoină (100 mg 3 ori/zi)**

EMG în miotonie



Maladia neuronului motor



MALADIILE NEURONULUI MOTOR
Clasificicarea

NMCentral

SL Primară

PSE

Paraplegie spastică Ereditară

NMPeriferic

AMS
Amiotrofie spinală

Neuropatie motorie multiplă

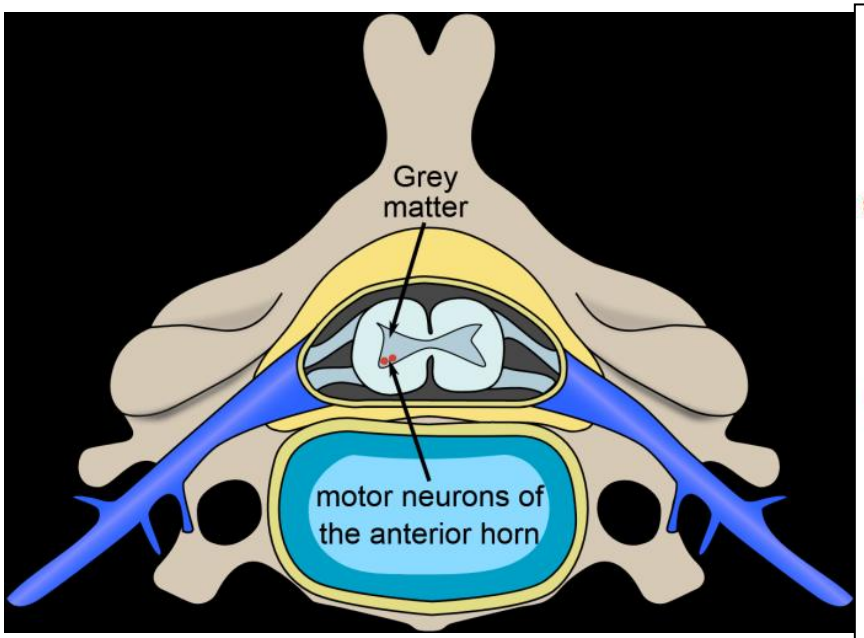
Sindrom post-polio

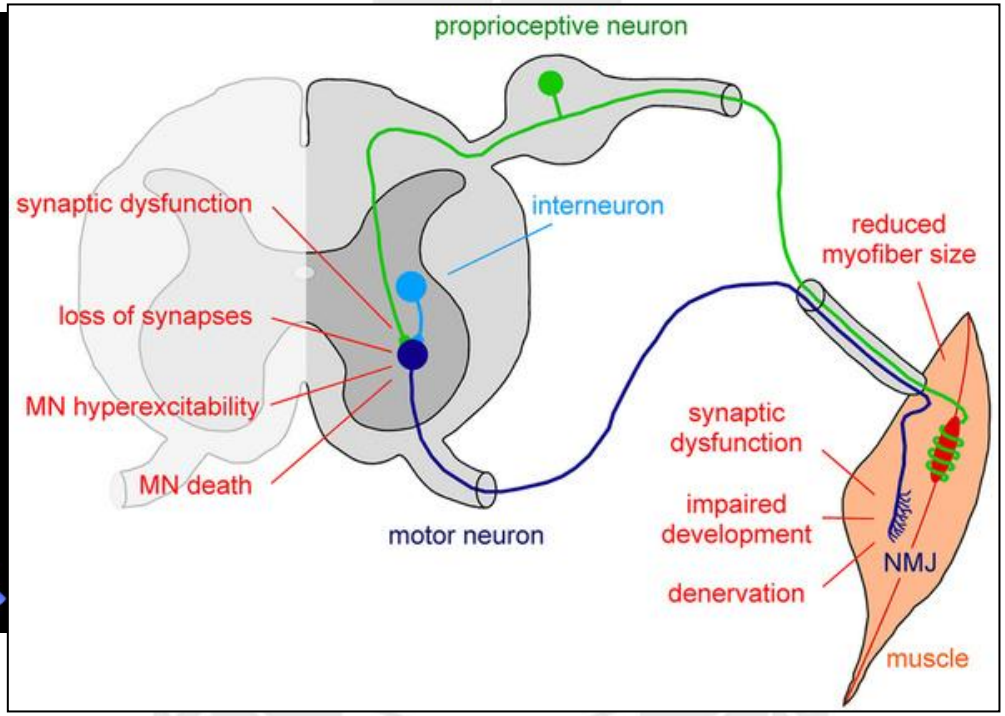
Sindrom post-iradiere

NMC + NMP

SLA

Atrofia musculară spinală

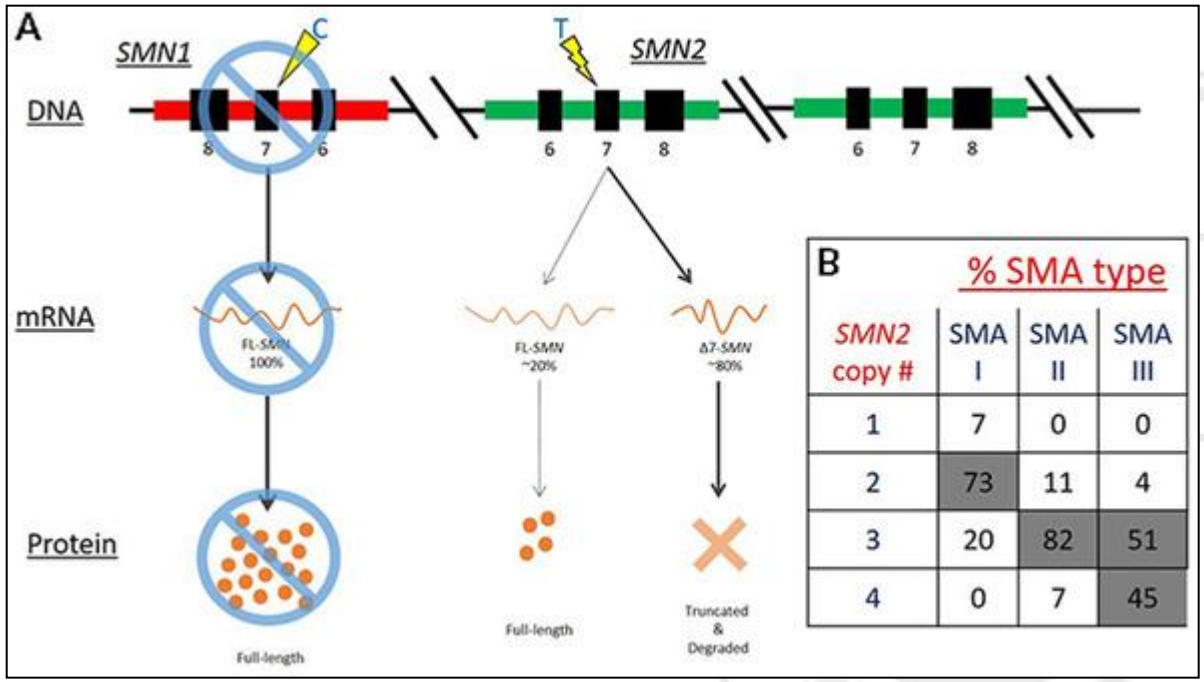




Spinal Muscular Atrophy.
Nance, Jessica

CONTINUUM: Lifelong Learning in Neurology. 26(5):1348-1368, October 2020.

Mecanismul genetic al atrofiei musculare spinale (SMA)



B

SMN2 copy #	% SMA type SMA I	SMA II	SMA III
1	7	0	0
2	73	11	4
3	20	82	51
4	0	7	45

A, Region of interest in the SMN gene on chromosome 5q13 showing the deleted SMN1 gene and variable copy number of SMN2 gene. In the absence of the SMN1 gene, motor neuron survival depends upon a diminished amount of SMN protein that can be produced from the mutated SMN2 gene. **The majority of SMN2 mRNA lacks exon 7 ([DELTA]7-SMN**) and produces a protein product that is degraded. Exon 7 is included in a minority of transcripts (FL-SMN) that produce functional SMN protein.

B, The severity of the SMA phenotype can generally be predicted by the SMN2 copy number and is inversely related to the patient's number of copies..

Spinal Muscular Atrophy.
Nance, Jessica

CONTINUUM: Lifelong Learning in Neurology. 26(5):1348-1368, October 2020.

Atrofia musculară spinală

SMA 5q este a doua cea mai frecventă tulburare autosomală recesivă în copilărie, după fibroza chistică, cu o incidență la naștere de **1 la 10.000.**

Frecvența purtătorilor pentru SMN1 este de **1:50.**

SMA 5q este cauzată de o deleție în neuronul motor de supraviețuire 1 (SMN1) situat pe cromozomul 5q, ceea ce duce la niveluri scăzute de expresie a **proteinei neuronului motor de supraviețuire (SMN).**

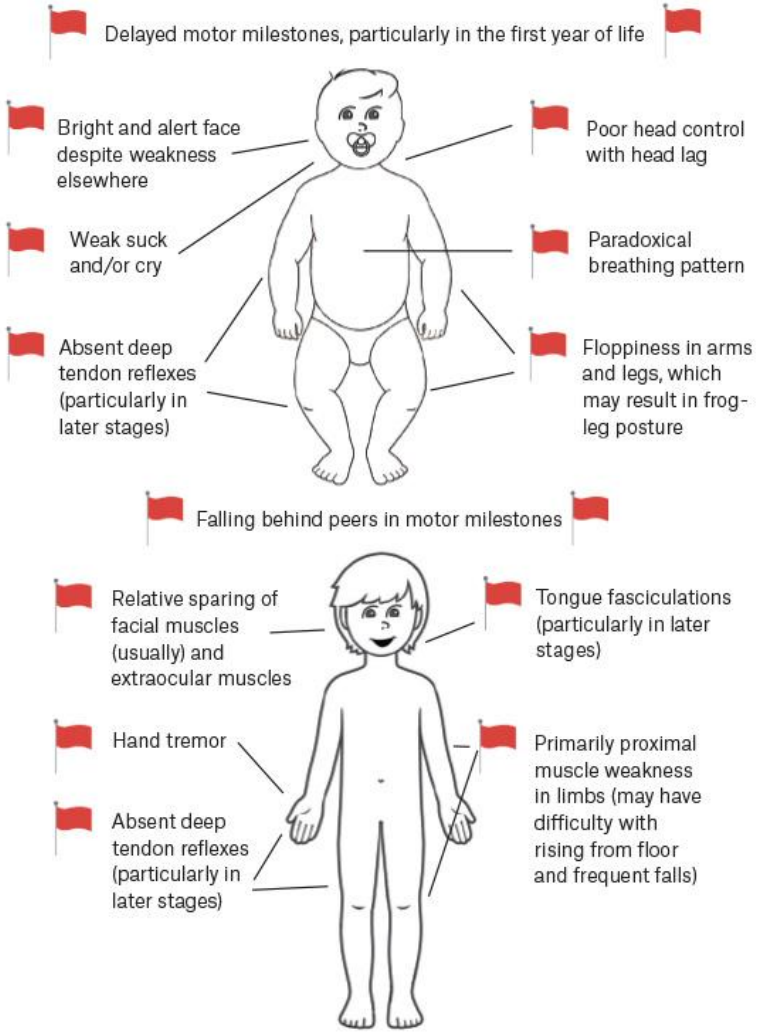
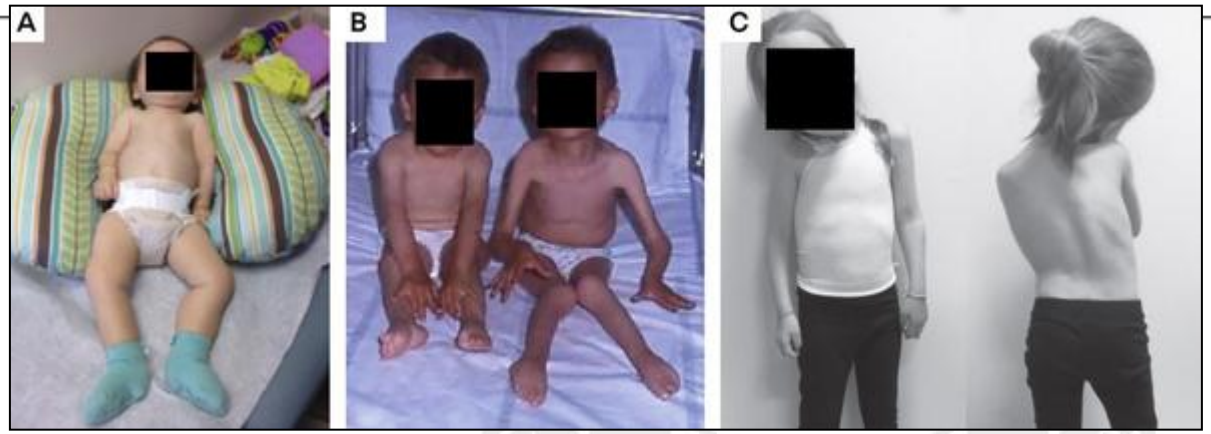


Table 1. A summary of spinal muscular atrophy (SMA) subtype classification and presentation[2,4,7,23–25]

SMA type	Incidence	Age of onset	Best motor milestone	Untreated life span	Typical *SMN2* copy number	Presenting features
1	~60% of cases	0–6 months	Never sits	<2 years (without respiratory support)	80% of patients have 1–2 copies	Poor head control, hypotonia, absent tendon reflexes, 'frog leg' posture, tongue fasciculations, poor swallow, paradoxical breathing
2	~27% of cases	6–18 months	Sits independently	Most (~70%) alive at 25 years	>80% of patients have three copies	Absent tendon reflexes, scoliosis, low muscle tone, proximal weakness, motor delay with difficulty standing/ walking, hand tremor
3a	~12% of cases	>18 months	Stands and walks	Almost normal	96% of patients have 3–4 copies	Proximal weakness greater in legs than arms, waddling gait, trouble with stairs and rising from floor, hand tremor
3b		>3 years				
4	~1% of cases	>21 years	Normal	Normal	75% have four or more copies	Adult-onset mild proximal weakness

SMN, survival motor neuron



A, Baby with SMA type 1 showing diffuse weakness, prominent frog-leg posturing, and bell-shaped chest.

B, Siblings with SMA type 2 are able to sit. Note diffusely decreased muscle bulk and prominent joint contractures.

C, Patient with SMA type 3 is able to stand and walk. Note decreased muscle bulk, joint contractures, and scoliosis.

Table 2. A summary of disease-modifying therapies for spinal muscular atrophy[10,13–16]

Therapy	TGA indication and PBS reimbursement in Australia	Mechanism of action	Administration	Safety information
Nusinersen	Patients with SMA types 1–3 initiating treatment before 18 years of age. Presymptomatic SMA with two *SMN2* copies.	Antisense oligonucleotide that targets an intronic splicing silencer and thus promotes exon 7 inclusion in *SMN2* pre-mRNA to encode full-length SMN protein.	Intrathecal with four loading injections in first two months then ongoing maintenance every four months.	Reported side effects largely relate to mode of administration and may include significant treatment anxiety, localised pain and post–lumbar puncture headache.
Onasemnogene abeparvovec (previously known as AVXS-101)	Presymptomatic and symptomatic SMA with 1–3 copies of *SMN2* aged less than nine months. PBAC recommendation of Section 100 (Highly Specialised Drugs Program) listing at September 2021 meeting. An outcomes-based Risk Sharing Arrangement is required before possible PBS reimbursement.	*SMN1* gene replacement therapy, using an adeno-associated virus capsid to supply a functional *SMN1* gene to motor neuron cells.	Single dose of virus vector given intravenously.	Liver enzymes may become elevated and cause acute serious liver injury. Decreased platelet counts could occur following infusion and can result in thrombotic microangiopathy. Patients will receive an oral corticosteroid before and after infusion and will undergo regular blood tests to monitor liver function.
Risdiplam (originally known as RO703406)	PBS listed for patients with SMA types 1–3 initiating treatment between the ages of two months and 18 years.	Small molecule that promotes exon 7 inclusion in *SMN2* pre-mRNA and full-length SMN protein production.	Oral medication with good bioavailability in the CNS and peripheral tissues.	No serious adverse events related to the medication have been reported in studies to date.

CNS, central nervous system; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; SMA, spinal muscular atrophy; SMN, survival motor neuron; TGA, Therapeutic Goods Administration

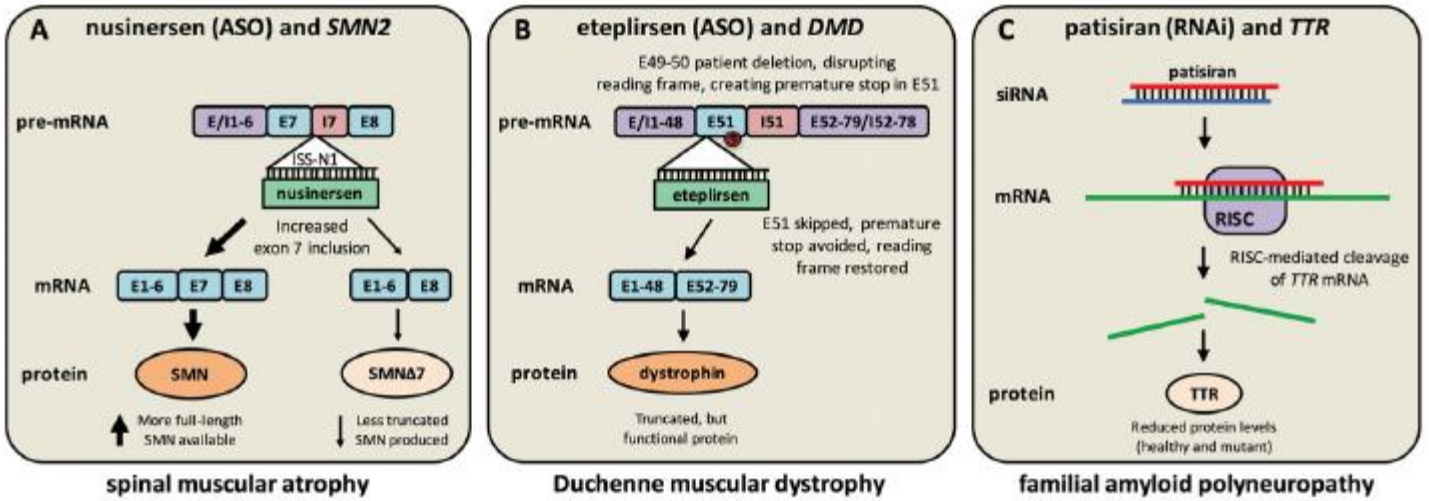
Antisense oligonucleotides and other genetic therapies made simple

Alexander M Rossor,[1,2] Mary M Reilly,[1] James N Sleigh[2]

[1]MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology and the National Hospital for Neurology and Neurosurgery, London, UK

ABSTRACT

Many genetic neurological diseases result from the dysfunction of single proteins. Genetic therapies aim to modify these disease-associated proteins nucleotides that bind target RNAs through Watson-Crick base pairing, but they differ in their composition and modes of action.



SPINAL MUSCULAR ATROPHY - OVERVIEW

Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disease.It is caused by mutations in the survival motor neuron 1 (SMN1) gene. The disease is classified on the basis of age of onset and clinical course.

SMA type 0 (prenatal SMA)
The most severe form. Children usually succumb to the disease before the age of 6 months.

SMA type 2 (chronic infantile SMA)
Serious muscle weakness (assisted sitting and walking). Symptoms usually appear between 7-18 months of age.

SMA type 1 (Werdnig-Hoffman disease)
Symptoms appear within the first few months of life. Children rarely survive passed their 2nd birthday.

SMA type 4 (adult onset SMA)
Not a life-threatening condition. Symptoms appear in adulthood.

SMA type 3 (Kugelberg Welander disease)
Children are able to stand and walk, but worsen with time. Symptoms usually appear after 18 months of age.

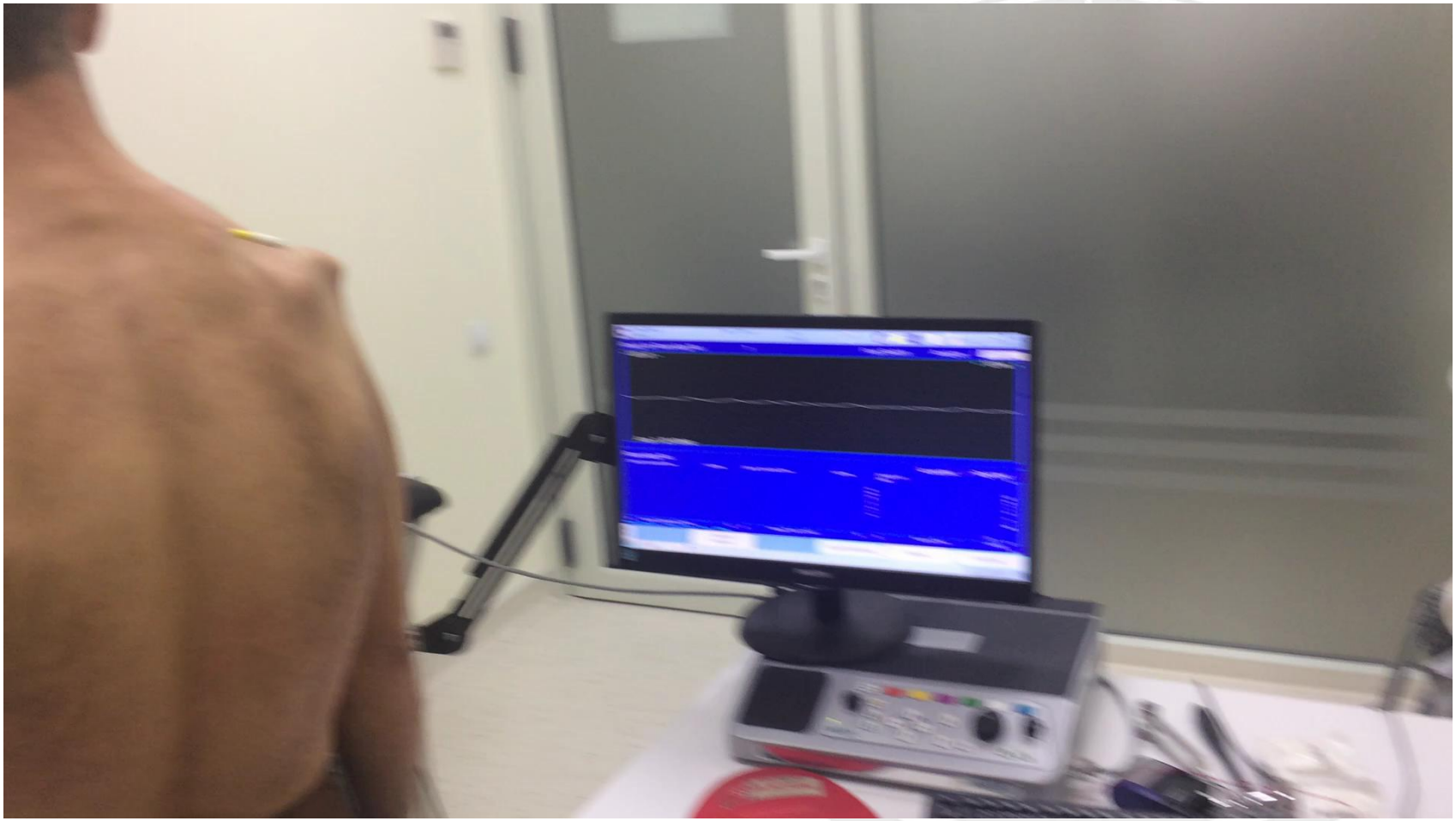
Finkel type SMA
Also an adult onset disease, it is caused by mutations in another gene called VAPB.

SMARD1 (Distal SMA)
Clinically and genetically distinct and uncommon form of SMA.

SMA NEWS TODAY

www.smanewstoday.com

EMG în amiotrofie spinală



Nusinersen (Spinraza)

- Dozare: 12 mg intratecal
- Primele 4 doze – la fiecare 2 saptamani, apoi doza de menținere 12 mg la 4 luni
- Cost: 125.000 USD o doză

RESEARCH PAPER

Nusinersen for SMA: expanded access programme

Michelle A Farrar,[1,2] Hooi Ling Teoh,[1,2] Kate A Carey,[1,2] Anita Cairns,[3] Robin Forbes,[4,5] Karen Herbert,[6] Sandra Holland,[1] Kristi J Jones,[1,7] Manoj P Menezes,[1,7] Margot Morrison,[1] Kate Munro,[3] Daniella Villano,[4] Richard Webster,[1,7] Ian R Woodcock,[4,5] Eppie M Yiu,[4,5] Hugo Sampaio,[1,2] Monique M Ryan[4,5,8]

Department of Neurology, Sydney Children's Hospitals Network, Sydney, Australia
School of Women's and Children's Health, UNSW Medicine, The University of New South Wales, Sydney, Australia
Department of Neurology, Lady Cilento Children's Hospital,

ABSTRACT

Background Spinal muscular atrophy (SMA) is a devastating motor neuron disorder causing progressive muscle weakness and respiratory insufficiency. We present the initial Australian experiences implementing the expanded access programme (EAP) to enable preapproval access to nusinersen, the first disease-modifying therapy for SMA type 1

SMA focused on managing the complications caused by weakness, feeding and breathing difficulties.[3]

Recent clinical trials of nusinersen, an antisense oligonucleotide developed to alter the splicing of SMN2 pre-mRNA and thus increase concentrations of functional SMN protein, have shown acceptable safety and tolerability and promising clinical efficacy.[4–6] Nusinersen is administered intrathecally

Paraplegia spastică familială (boala Strumpell - Lorrain)

Moștenirea AD, AR și X – lincată

Paraplegia spastică familială AD

Lincare cu locusuri pe cromozoamele 2, 8, 10, 12, 14, 15.

Mutația genelor spastin sau paraplegin pe cromosomul 2.

Penetranță semnificativă.

Debut insidios

Vârstă diferită de debut până la și după 35 de ani

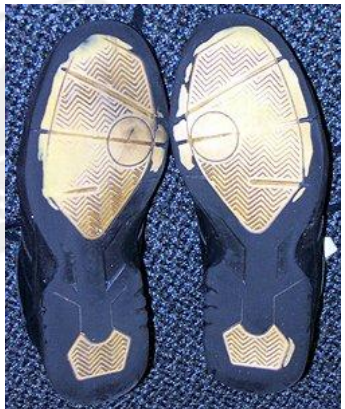
Autosomal recesivă

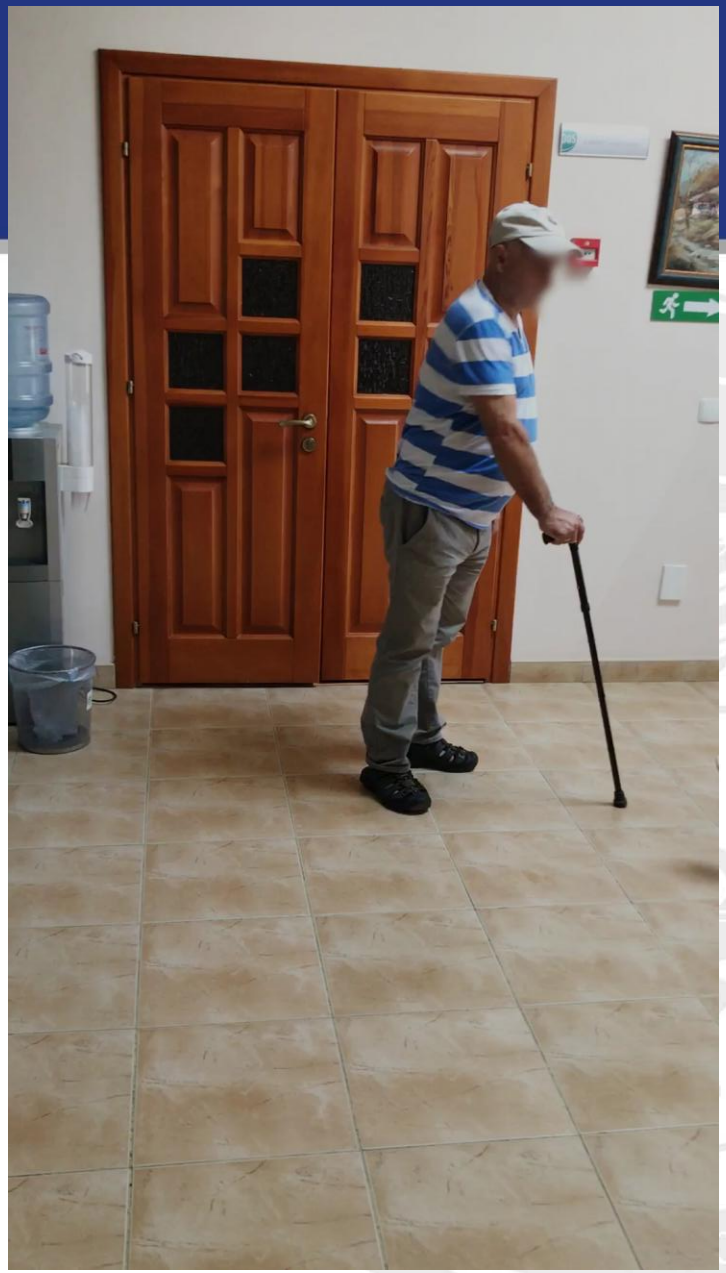
Foarte rară

Locusuri pe cromozoamele 8, 15, 16.

Paraplegia spastică familială (boala Strumpell)

- **Paraparezǎ spastică inferioară profundă (până la paraplegie)**
- **Limitate mişcările în membrele inferioare, preponderent din cauza spasticităţii şi nu slăbiciunii**
- **Tulburări de sensibilitate li sfincteriene nu se depistează, reflexele abdominale s păstrate**

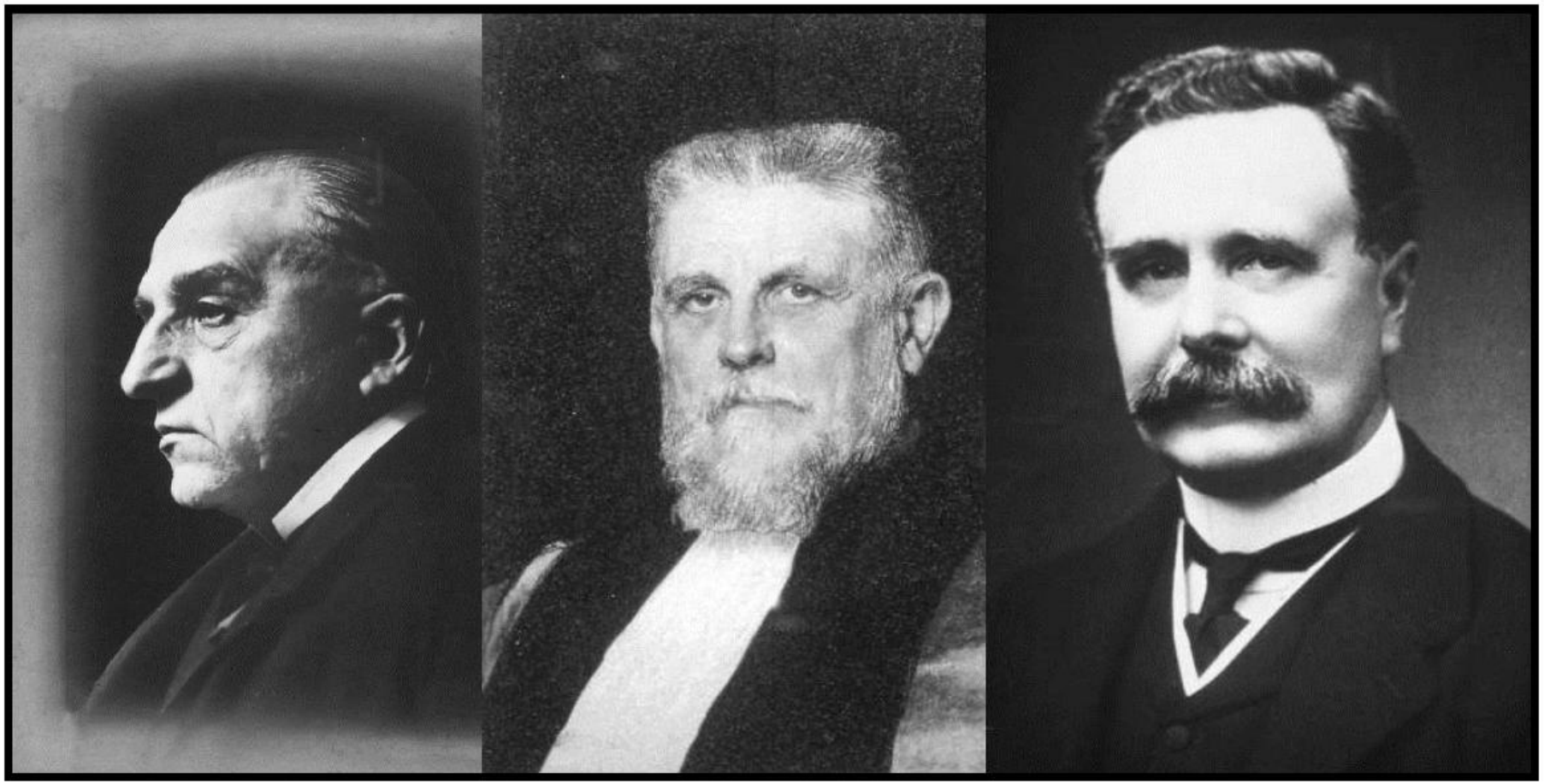




Paraplegia spastică familială (boala Strumpell)

- Pacientul merge cu dificultăți, dar poate sta în picioare timp îndelungat
- Progresează lent, pacienţii mult timp pot fi apţi de lucru
- Baclofen, tizanidin, toxina botulinică – pentru micşorarea tonusului muscular.
- Tratament ortopedic

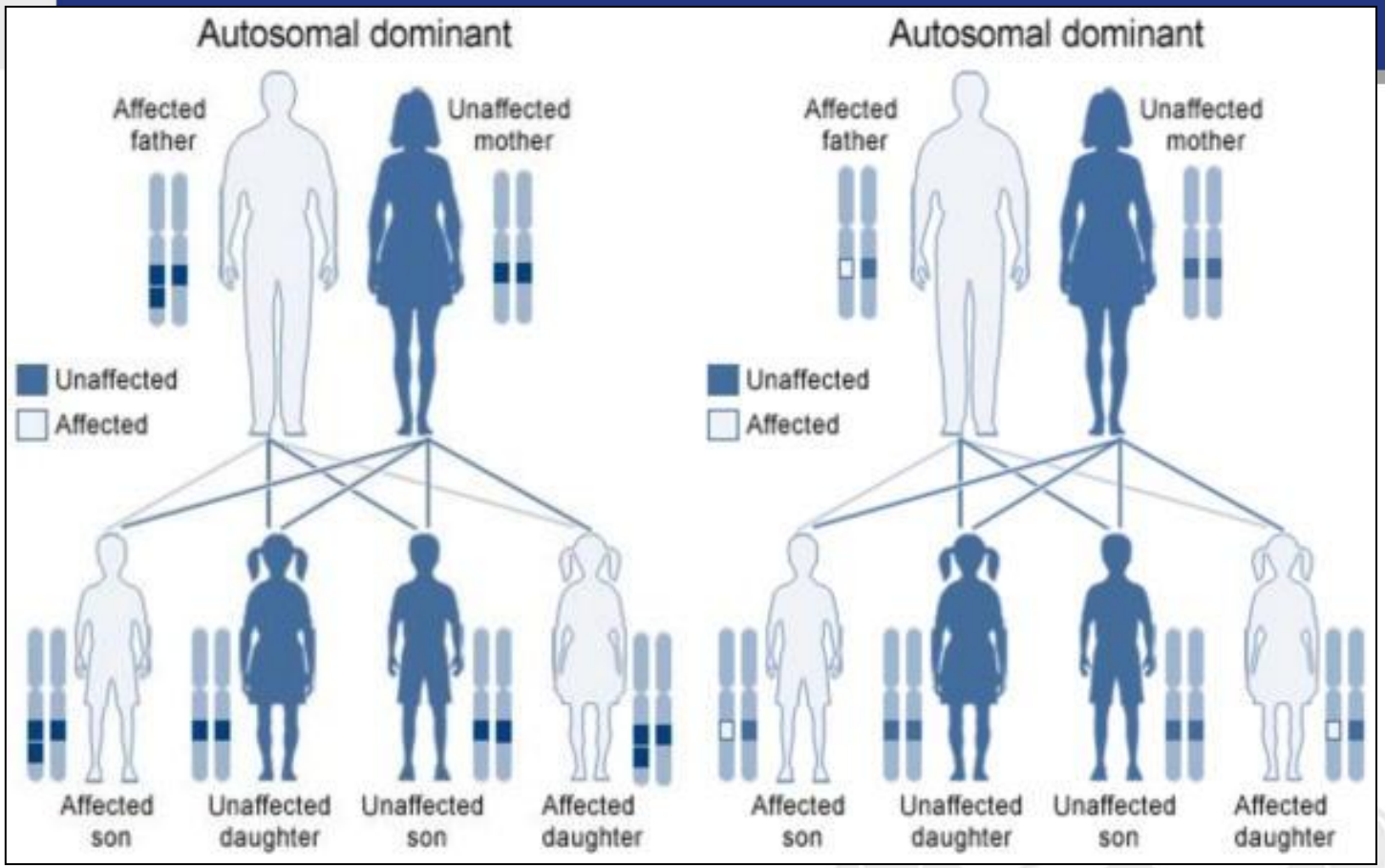
CHARCOT-MARIE-TOOTH DISEASE



CMT

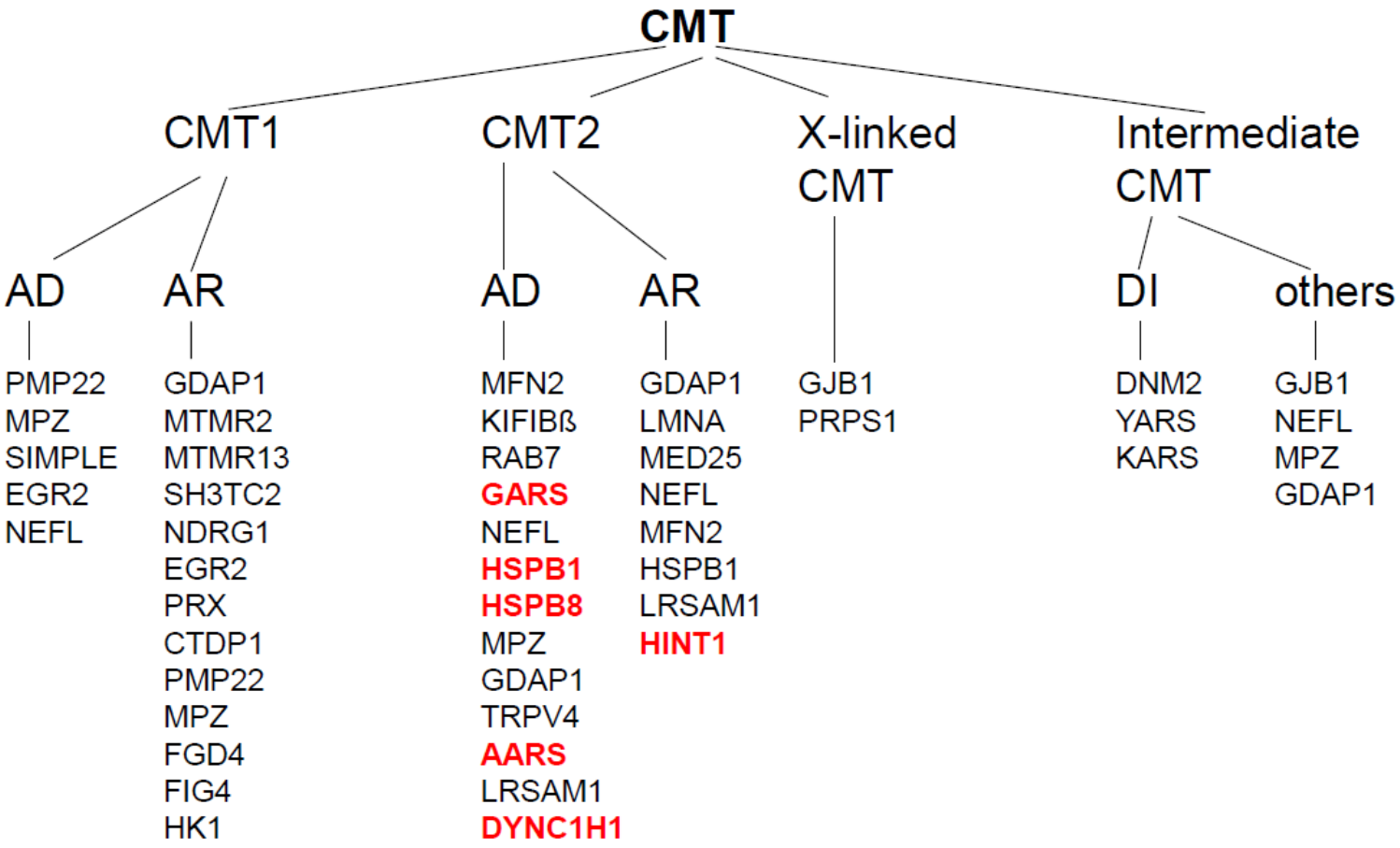
- **Preponderent se transmite pe cale autosomal-dominantă**
- **Slăbiciunea şi atrofia porţiunii distale ale membrelor**
- **Picior scobit**
- **Abolirea ROT**
- **Îngroșarea trunchiurilor nervoase la palpație**
- **Cu sau fără de tulburări de sensibilitate**

Transmiterea autosomal – dominantă în cadrul CMT



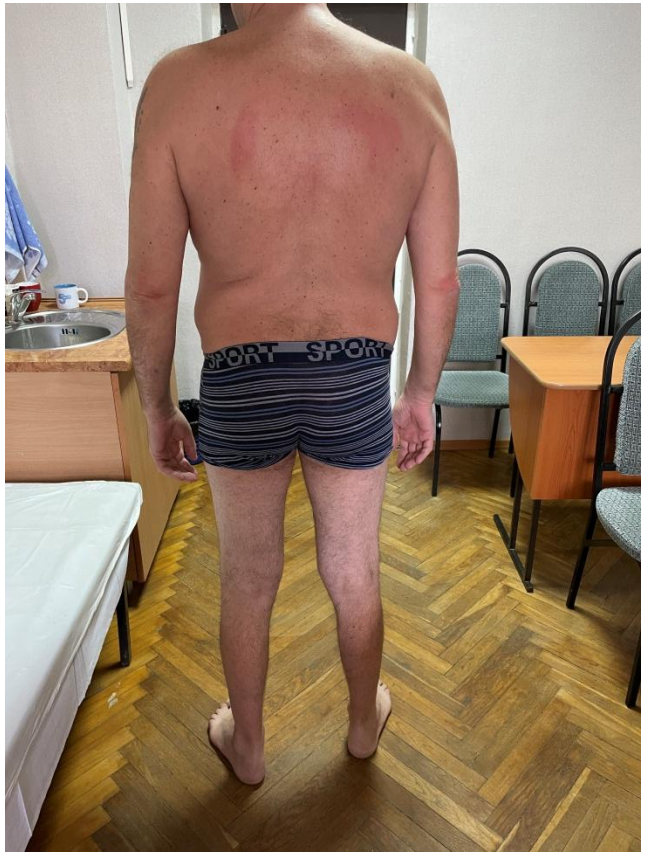
CONTINUUM: Lifelong Learning in Neurology. 18(1, Peripheral Neuropathy):39-59, February 2012.

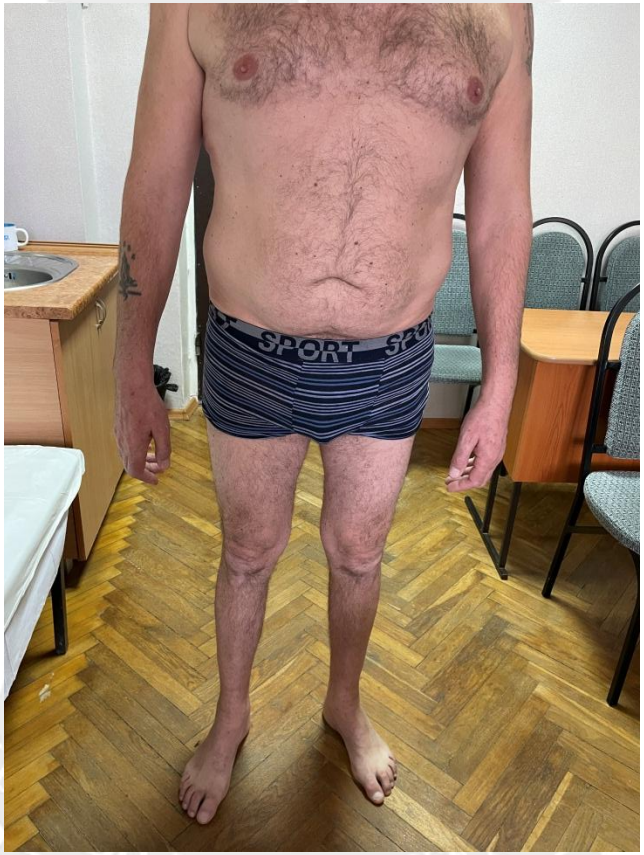
Genele care determină CMT



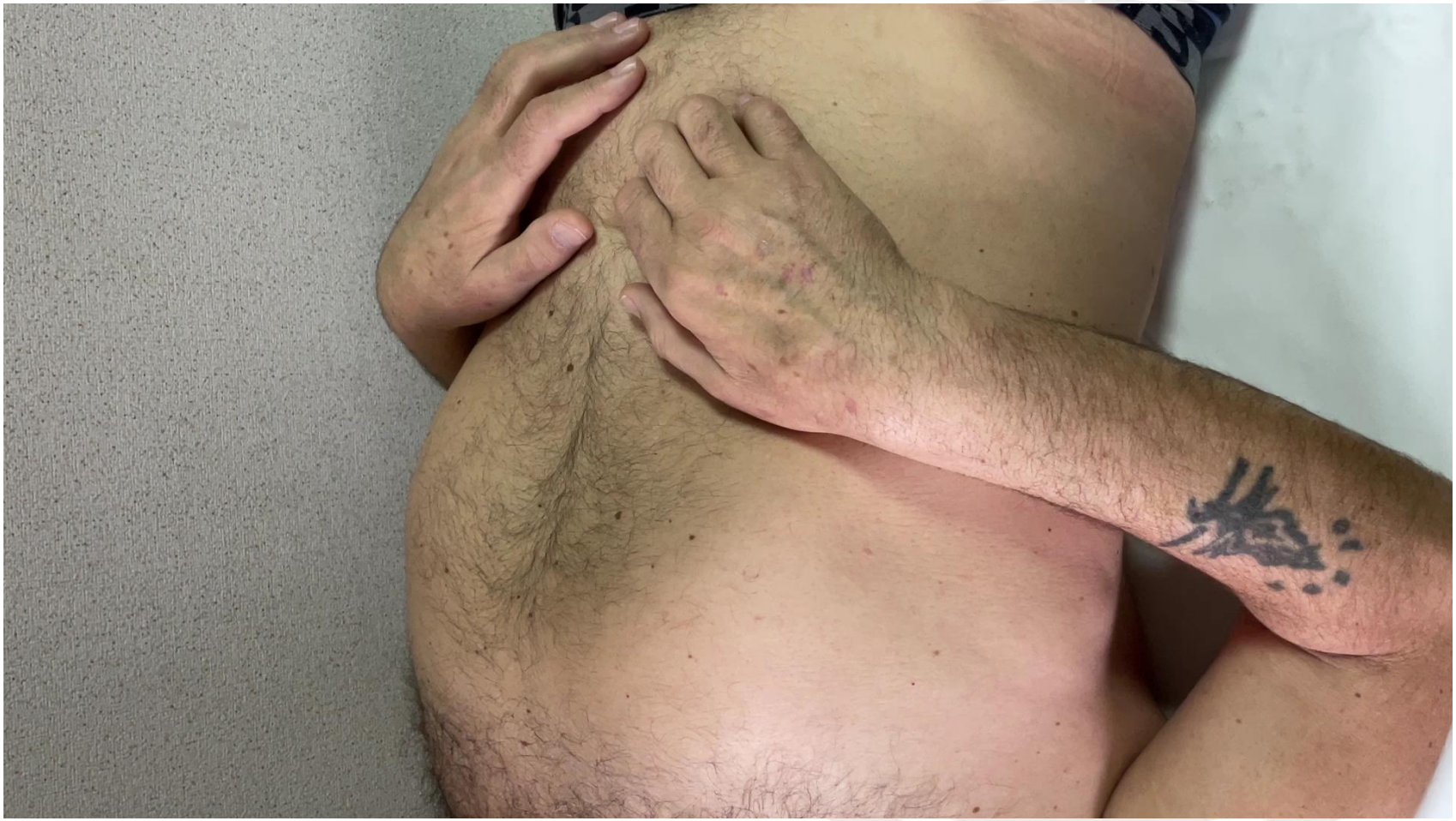
Reilly M, 2013

Aparenţa membrelor inferioare în cadrul CMT1A (atrofii distale, picior scobit, degete în ciocan)

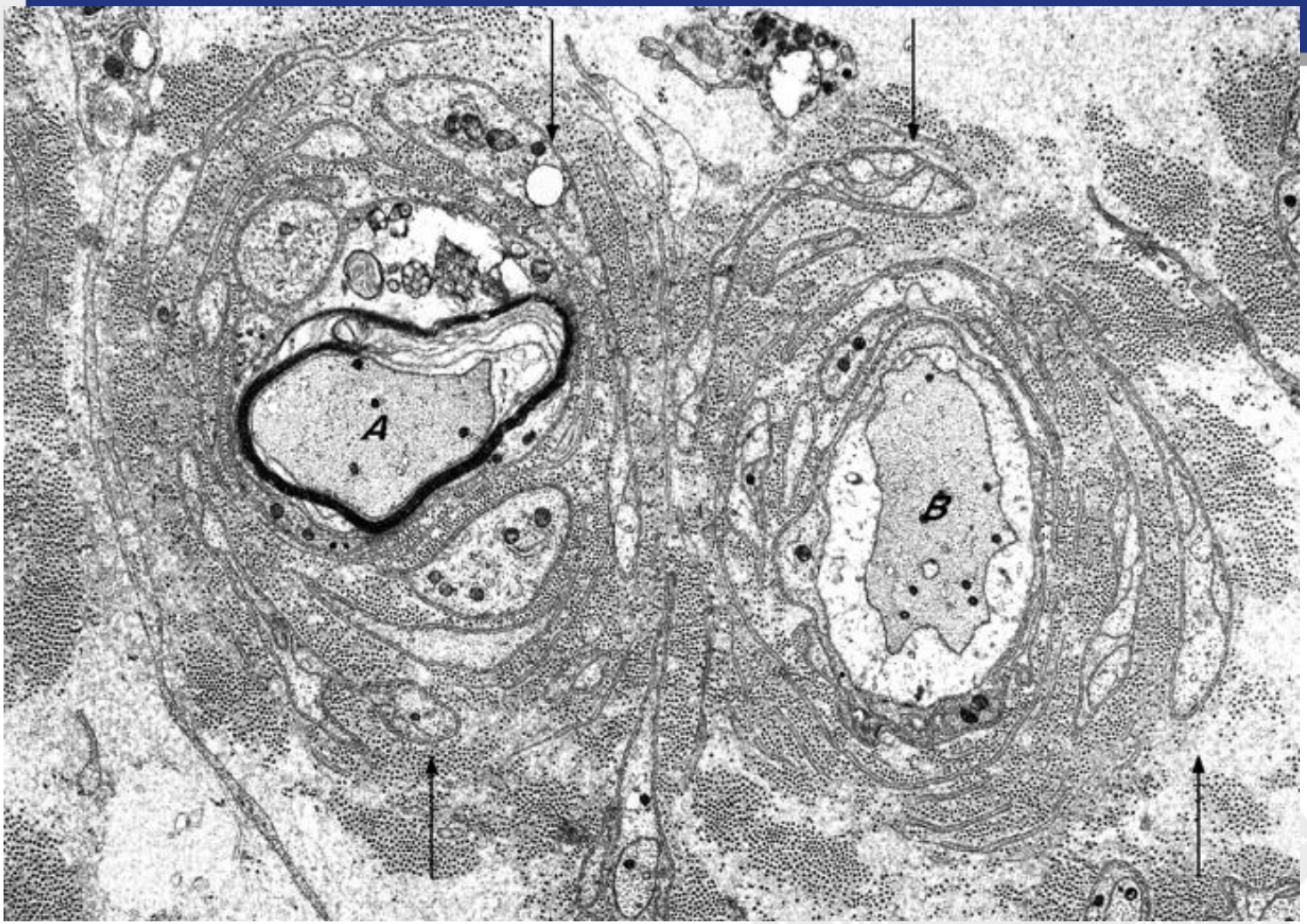




CMT



2 formaţiuni „bulbi de ciapă” la biopsia n. sural nerve în cadrul CMT1.



Reilly M M Pract Neurol 2007;7:93-105

Boala Wilson
Ataxiile ereditare

Boala Wilson

- **Boala Wilson – evoluția poate fi modificată prin tratament**

- **S. A. Kinnear Wilson – prima descriere (Brain, 1912)**

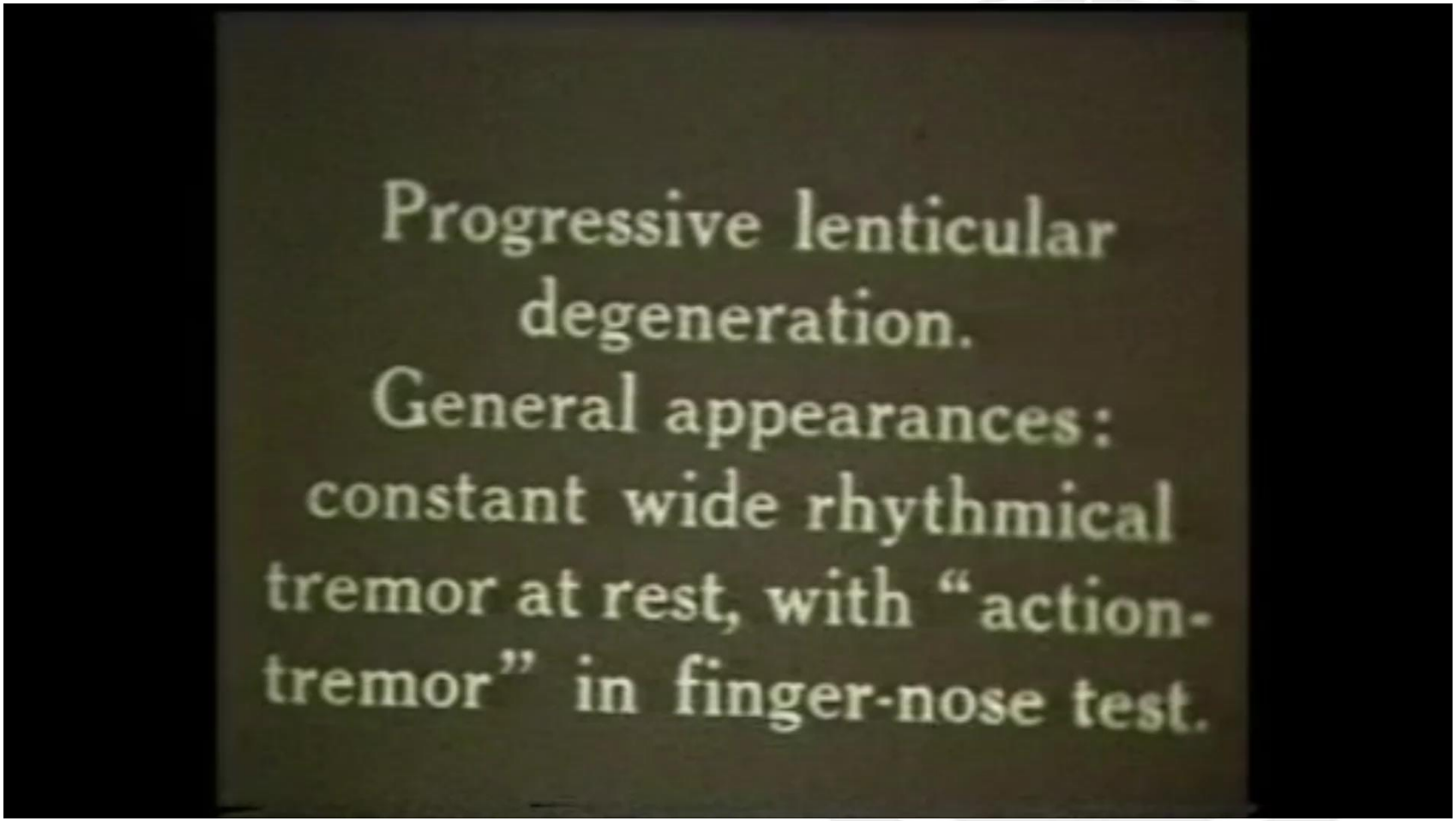
"Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver".

- **Fondatorul**

Journal of Neurology and Psychopathology

actualmente **Journal of Neurology, Neurosurgery and Psychiatry**

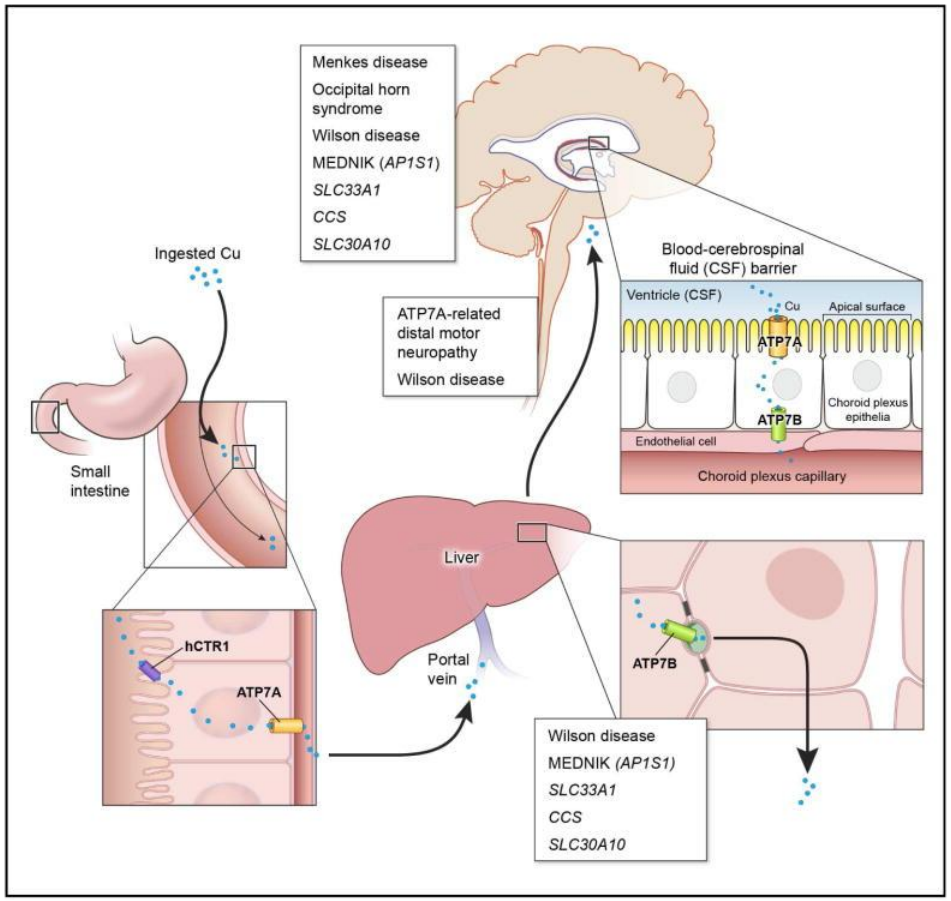
Kinnier Wilson
1878 - 1937



A Film of Patients with Movement Disorders Made in Queen Square, London in the Mid-1920s by Samuel Alexander Kinnier Wilson

Movement Disorders, Vol. 26, No. 14, 2011

Aspecte de bază ale metabolismului normal al cuprului și mecanismele moleculare ale diferitelor boli ale transportului cuprului



- **Perturbarea excreției biliare a Cuprului**
- **Acumularea Cu , afectarea tisulară (inițial în ficat, apoi alte organe țintă, inclusiv în creier)**
- **Majorarea concentrației tisulare a Cuprului induce stresul oxidativ, formarea radicalilor liberi, disfuncția mitocondriilor**
- **Lancet Neurol. 2015 January ; 14(1): 103–113**

Introducere

- **Maladie monogenică, autosomal recisivă, majoritatea pacienților – heterozigoți**

- **1993 – ATP7B, cr. 13**

800 mutații , frecvente H1069Q (40-50%) și R778L
(http://www.wilsondisease.med.ualberta.ca/database.asp)

- **Proteina (ATP7B) plasată în rețeaua Golgi în hepatocite**

- **Transportează Cu în membranele organelelor**

- **Incorporează Cu în apoceruloplasmină pentru a forma ceruloplasmina**

- **În boala Wilson – concentrații reduse ale ceruloplasminei**

- **La 17% pacienți BW (citeriile Leipzig) nu se atestă mutația genei *ATP7B***
(Durand F, 2007)

Epidemiologia

- **Prevalența 1/7000 (RU,** Coffey AJ et al., Brain, 2013**)**
- **Prevalența este mai mare decât se considera înainte** (Brandmann O. et al., 2015)
- **Incidența 1/55,000 (SUA,** Olivares L. et al, 2001**)**
- **Vârsta de debut 10-20 de ani (5-70)**
- **Întârzierea în diagnostic – 2 ani** (Litwin T et al., J Neurol Sci, 2012)
- **Nici un pacient nu se aseamănă cu altul** (Walshe JM et al., JNNP, 1992)
- **Diagnosticul precoce este crucial pentru inițierea tratamentului adecvat**

Manifestările clinice
Afectare multisistemică

Hepatice
Neurologice
Psihiatrice
Oftalmice
Hematologice
Musculoscheletale
Cardiace
Renale
Dermatologice

Wilson Disease.
Pfeiffer, Ronald; MD, FAAN

CONTINUUM: Lifelong Learning in Neurology. 22(4):1246-1261, August 2016.

Manifestările hepatice

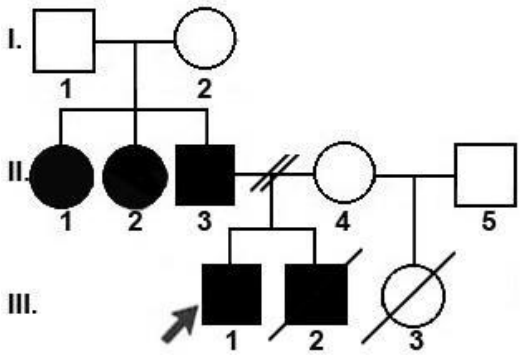
Insuficiență hepatică lent progresivă cu ciroză
Mimează hepatita virală acută
Mimează hepatita cronică activă autoimună
Insuficiență hepatică fulminantă

Wilson Disease.
Pfeiffer, Ronald; MD, FAAN

CONTINUUM: Lifelong Learning in Neurology. 22(4):1246-1261, August 2016.

Caz clinic

- Pacient 18 ani
- August 2021 – probleme digestive
- August 2022 Hepato-splenomegalie, Ciroza hepatică
- Tatăl pacientului și surorile lui au **ciroză hepatică** de la 35-40 ani
- Fratele mai mic a fost diagnosticat cu **ciroza hepatică** și a decedat la 12 ani



- August 2022 – tulburări de vorbire

Manifestările hepatice

- **Prima prezentare clinică la 40-50% pacienți**
- **Insuficiență hepatică progresivă cu ciroză, ascită, varice ale esofagului, splenomegalie**
- **Apar mai devreme comparativ cu manifestările neuropsihiatrice – 11 – 15 ani**
- **Diagnosticul – mai rapid – cu 30 de luni, comparativ cu debut neuropsihiatric**

Manifestări neurologice la debut

Manifestări neurologice (în 4 serii de cazuri independente)	Pacienți (%)
Disartrie	46-97
Dereglări de mers	28-75
Distonie	38-69
Tremor postural	55
Disfagie	50
Choree/atetoză	6-30
Convulsii	6-28
Tremor în repaos	4

Wilson Disease. An overview and approach to management
C. Muliggan; J.M. Bronstein

Neuro Clin 38 (2020): 417-432

Mișcări involuntare esențiale, simptome bulbare și manifestări adiționale la pacienții cu boala Wilson (pot exista în combinări diferite)

Mișcări involuntare core	Simptome bulbare	Manifestări neurologice adiționale
Tremor	Disartrie	Disfuncție cerebelară
Distonie	Hipersalivare	Coree
Parkinsonism	Disfagie	Hiperreflexie
		Convulsii
		Tulburări cognitive

Shribman et al. Ann Trans Med 2019

Tremorul – cea mai frecventă manifestare neurologică

53 pacienți cu BW:

Tremor- 62%

Distonie – 15%

Parkinsonism – 11%

Czlonkowska A.et al. , BMC Neurol, 2018

Distonia

- **Distonia – până la 69%**
- **Focală**
- **Segmentară**
- **Generalizată**
- **Contracturi severe**
- **Risus sardonicus**

ATP 7B
mutaţia p. H1069Q în stare heterozigotă în exonul 14

Manifestările neurologice

- **Parkinsonism – 40%**
- **Mai rar corea, atetoza, miocloniile**
- **Disfuncția cerebelară – 30%**
- **Tulburările de mers – 45-75% - parkinsonian - cerebelar**
- **Disartria (poate fi cerebelară sau hipokinetică), poate progresa până la anartrie totală**
- **Disfagia – până la 50%**

ATP 7B - neg

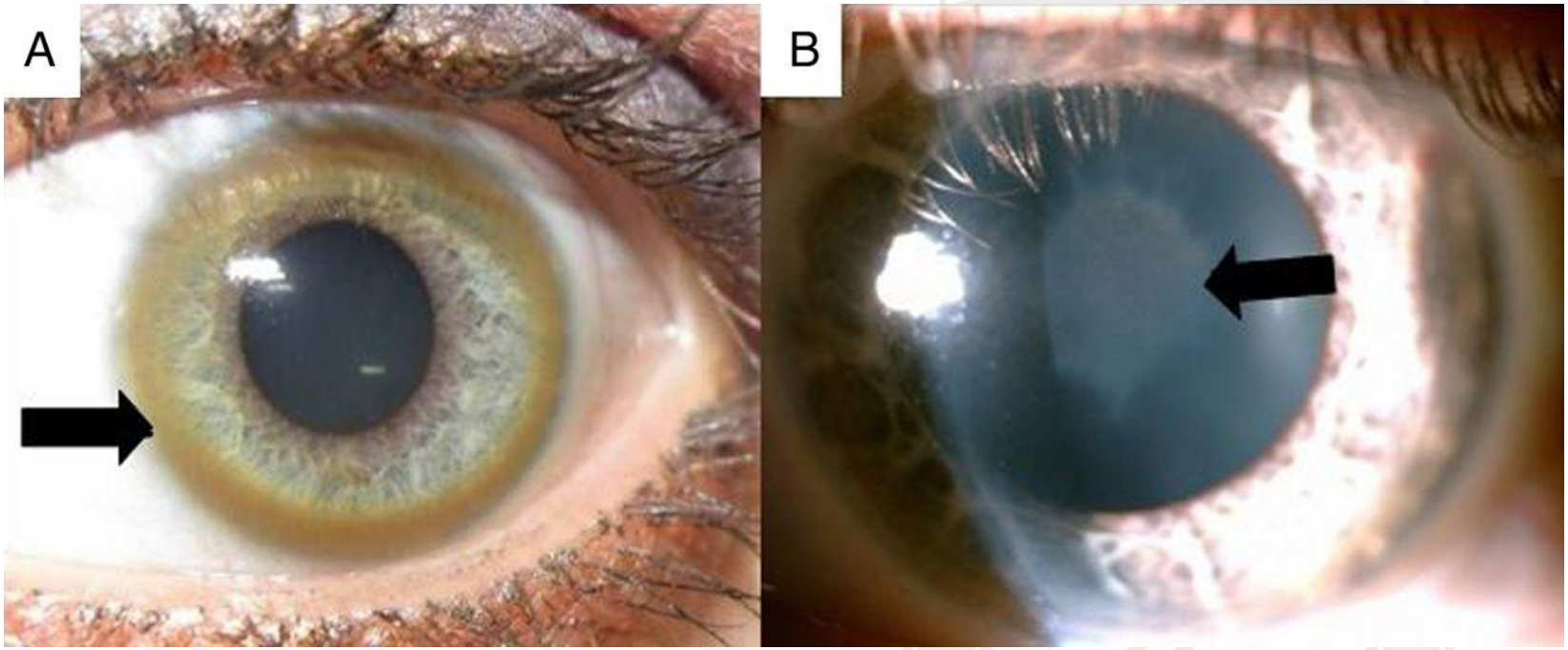
Manifestări psihiatrice

Modificări de personalitate
Depresie
Psihoză acută
Tulburări cognitive

- Sunt evidente la 30-40% pacienți de la modificări subtile până la psihoză
- Psihoza poate fi prima prezentare cu halucinații sau chiar catatonie
- Depresia cu comportament suicidal
- Deficit cognitiv ușor exprimat

(A) Inelul Kayser – Fleischer în corneea dreaptă
(inelul pigmentat maro al marginii externe a corneei)

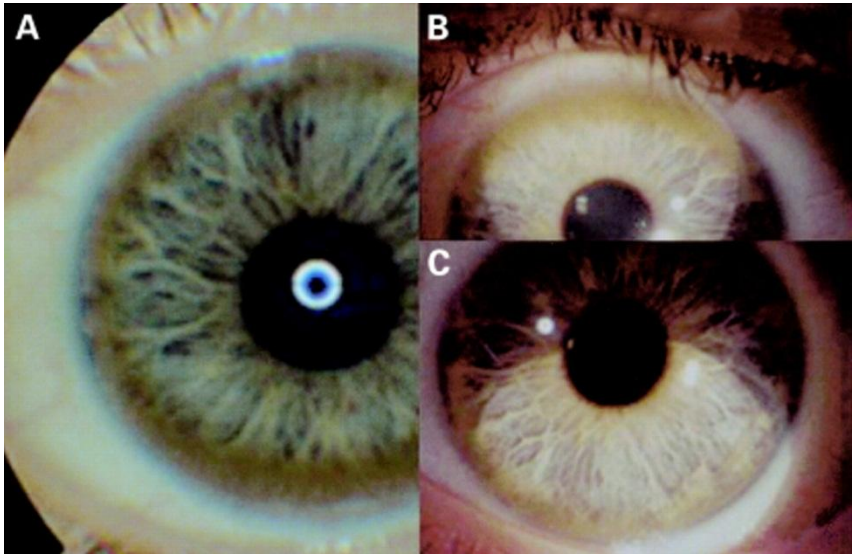
(B) Cataractă de floarea-soarelui în ochiul drept
(disc central cu spițe radiante asemănătoare petalelor situate sub capsula lentilei anterioare)



Litwin T., Langwińska-Wośko E, Dzieżyc K, Członkowska A.
Pract Neurol 2015;15:385-386

Manifestări oftalmice

Inelul Kayser - Fleischer

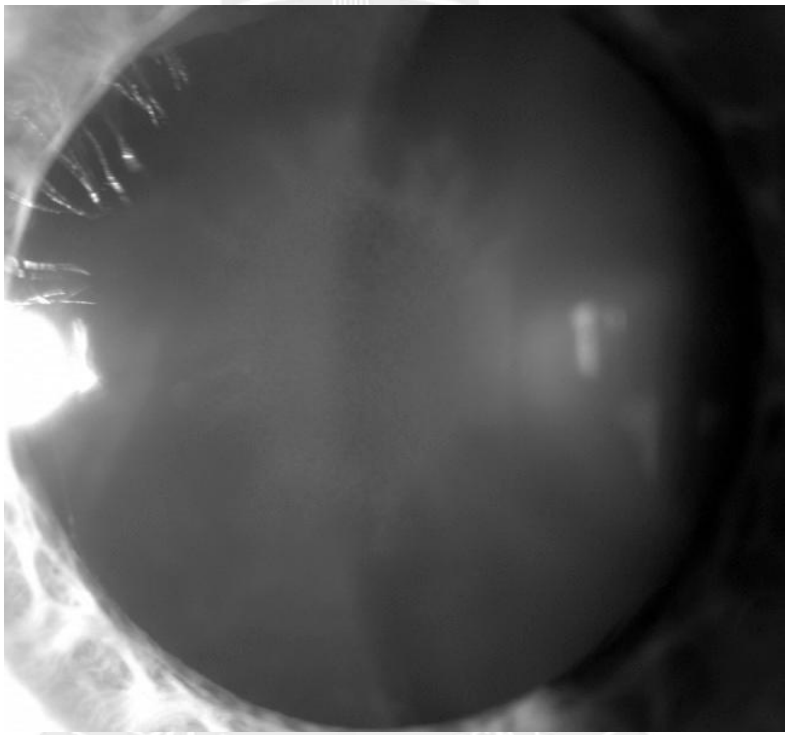


- Descris în 1922
- Depozitarea cuprului pe membrana lui Descmet
- La 100% pacienți cu manifestări neuropsihiatrice
- 50% pacienți cu prezentare doar hepatică
- 20-30% pacienții presimptomatici

Nicholl D J et al. J Neurol Neurosurg Psychiatry 2001;70:514-516

Manifestări oftalmice
Cataracta Floarea soarelui

- În 2-17% cazuri
- 1922 descrisă de Oloff și Siemerling
- Depozite de cupru după cristalin, nu afectează acuitatea vizuală
- Mimează floarea soarelui, vizibilă cu ochiul liber



Langvinska-Wosko E. et al, Acta Neurol Belg 2016; 116: 325–328

Diagnosticul

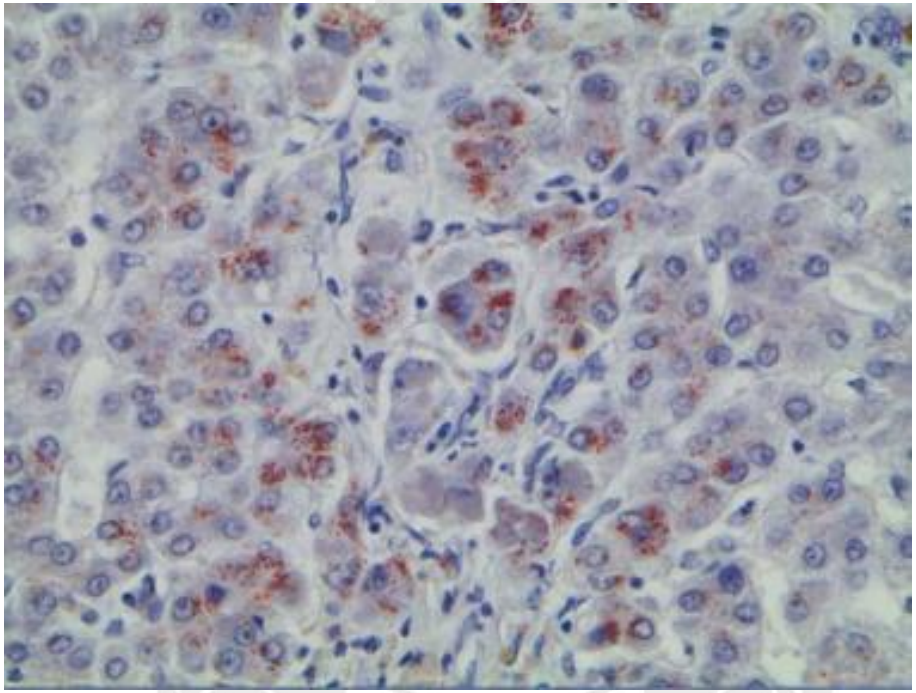
Prezentare hepatică	Modificări patognomonice
Examinarea cu lampa în fantă	Inelul Kayser-Fleischer poate fi prezent
Ceruloplasmina	Redusă
Curpul urinei în 24 de ore	Majorat > 100 mcg/d
Biopsia ficatului	Majorarea cuprului
Testare genetică	Mutaţia ATP7B
Prezentare neuropsihiatrică	**Modificări patognomonice**
Examinarea cu lampa în fantă	Inelul Kayser-Fleischer prezent
Ceruloplasmina	Redusă
Curpul urinei în 24 de ore	Majorat
Biopsia ficatului	Majorarea cuprului
Testare genetică	Mutaţia ATP7B

Biospia ficatului

- **Cel mai precis test**
- **Majorarea concentrației Cu**

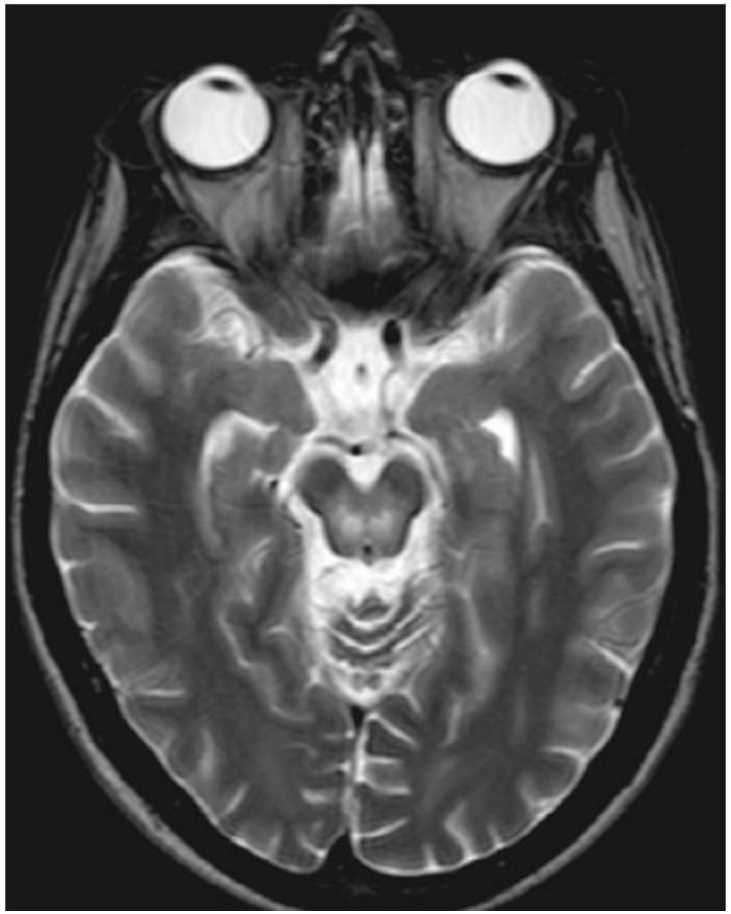
> 250 mcg/g țesut uscat (Nr 15-55 mcg/g).

Coloraţie cu rhodanine (specifică pentru depozitele de Cu)

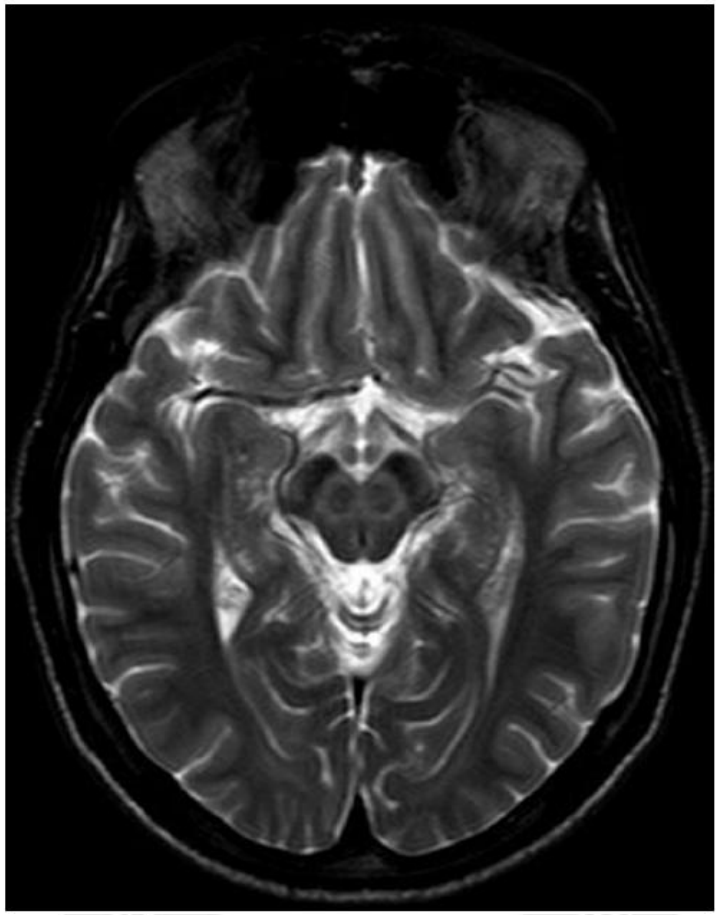


https://emedicine.medscape.com/article/183456-overview

Modificări IRM tipice



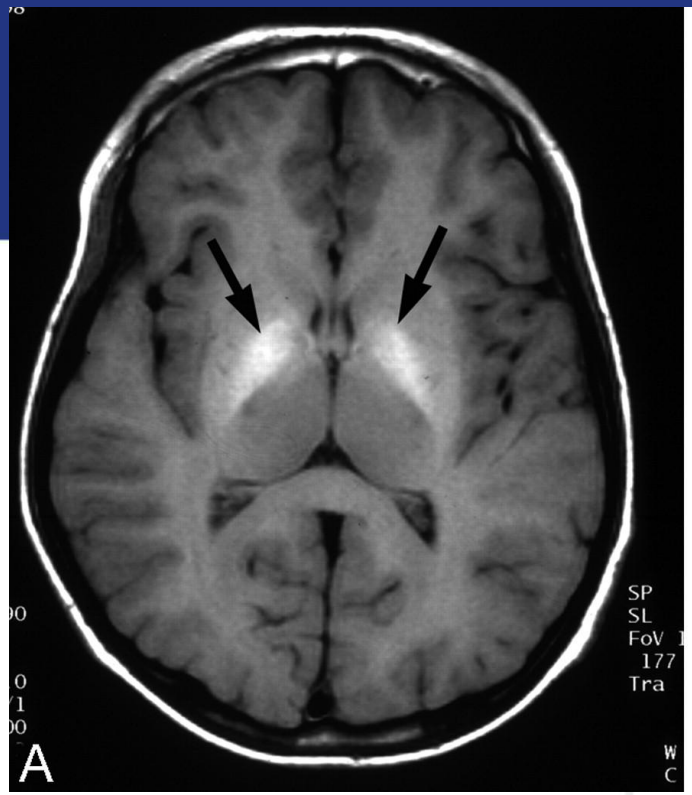
Hipersemnal T 2 la nivelul mezencefalului și punții

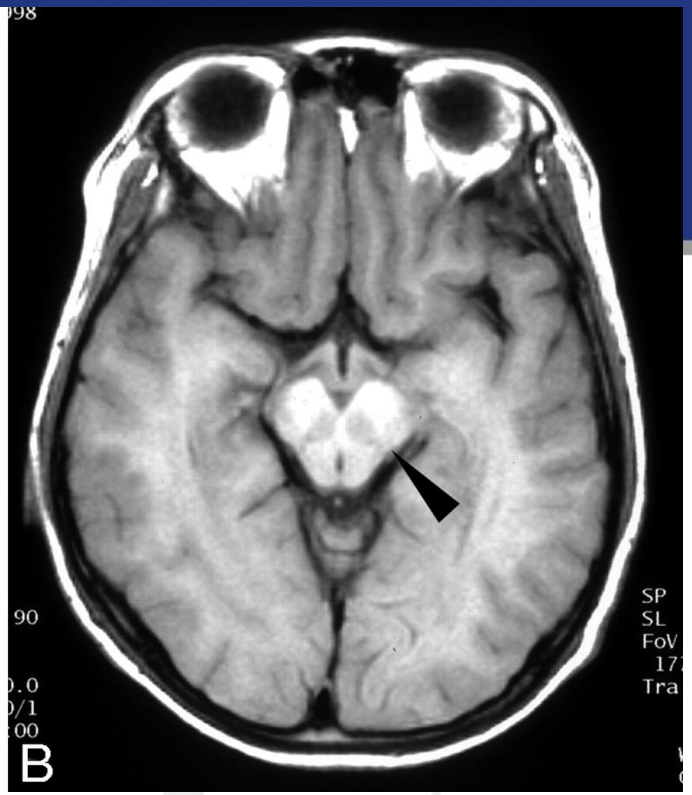


Semnul "Giant panda"

Czlonkowska A. et al, Handbook Clin Neurol, 2017

IRM





“Semnul pandei gigantice” depistat doar la 14.3%.

Hiperintensitatea laminei tectale (75%)

Modificări similare mielinolizei pontine centrale (62.5%)

Modificări concomitente ale semnalului în ganglionii bazali, talamus şi trunchiul cerebral (55.3%)

Rareori – leucoencefalopatie difuză

Prashanth LK, Sinha S, Taly AB, Vasudev MK. Do MRI features distinguish Wilson’s disease from other early onset extrapyramidal disorders? An analysis of 100 cases. Mov Disord. 2010; 25(6):672–8.

Tratamentul

Tratamentul dietetic

Limitarea (excluderea) produselor ce contin Cu

- **Produse de mare**
- **Ficat**
- **Nuci**
- **Ciocolată**
- **Ciuperci**

Inhibarea absorbției Cu intestinal

- **Zinc acetate, gluconate sau sulfate pe stomac gol**
- **50 mg x 3 ori pe zi**

Chelatori de Cu

- **Penicilamina 250 mg – 500 mg x 4 ori pe zi pe stomac gol**
- **Doza medie zilnică – 750-1500 mg**
- **Inițierea cu o doză mică – 125 mg, majorare la fiecare 3-4 zile.**
- **Ameliorarea peste câteva luni**
  - **90% funcțiile hepatice**
  - **55% manifestările neurologice**
- **Poate produce agravarea paradoxală a funcțiilor neurologice după inițiere a tratamentului (11-50%)**
- **O mulțime de efecte secundare (erupții cutanate, febră, proteinurie, căderea părului, nevrita optică, deficiență de piridoxină etc.)**
- **Trientine, mecanism similar de acțiune cu penicilamina, dar este mai puțin viguros.**

Transplantul de ficat

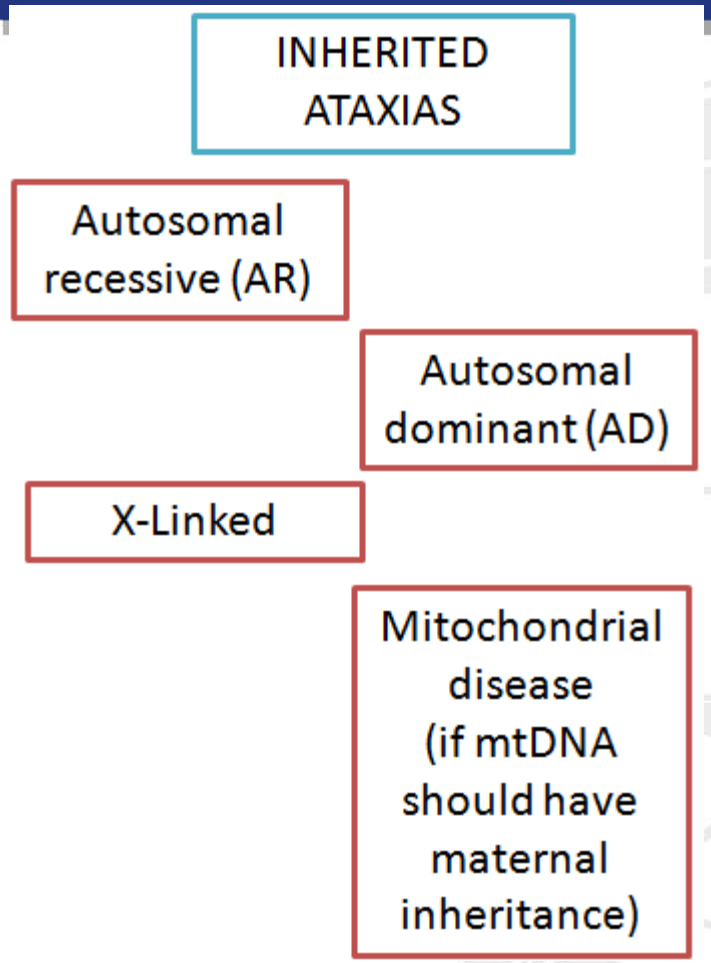
- **Tratamentul pentru insuficiența hepatică acută**
- **Supraveţuirea > 5 ani – 80 – 90%**
- **Ficatul transplantat nu conține defectul genetic, proteina ATP7B funcționează normal**
- **Se normalizează metabolismul Cu**

Prognosticul este bun în cazul tratamentului precoce

NETRATAT	TRATAT PRECOCE	EVOLUȚIE PROGRESIVĂ ÎN POFIDA TRATAMENTULUI
Fatal Cauza decesului – patologia ficatului Longevitatea vieții – 5 ani după instalarea manifestărilor neurologice	Prognostic excelent Longevitatea vieții nu-i modificată	10-30% - agravare inițială din cauza mobilizării cuprului din depozite în ficat

Litwin T, et al. J Neurol Sci. 2015;355(1-2):162-167.

Ataxiile ereditare



Ataxiile ereditare autosomal recesive

- **Debutul până la 20 ani**
- **Ataxia Friedreich – cea mai frecventă formă (40%)**

Ataxia Friedreich

Se transmite pe cale autosomal - recesivă

Majorarea numărului repetării trinucleotidelor GAA

Gena Frataxin 9q13-q21.1

Ataxia Friedreich

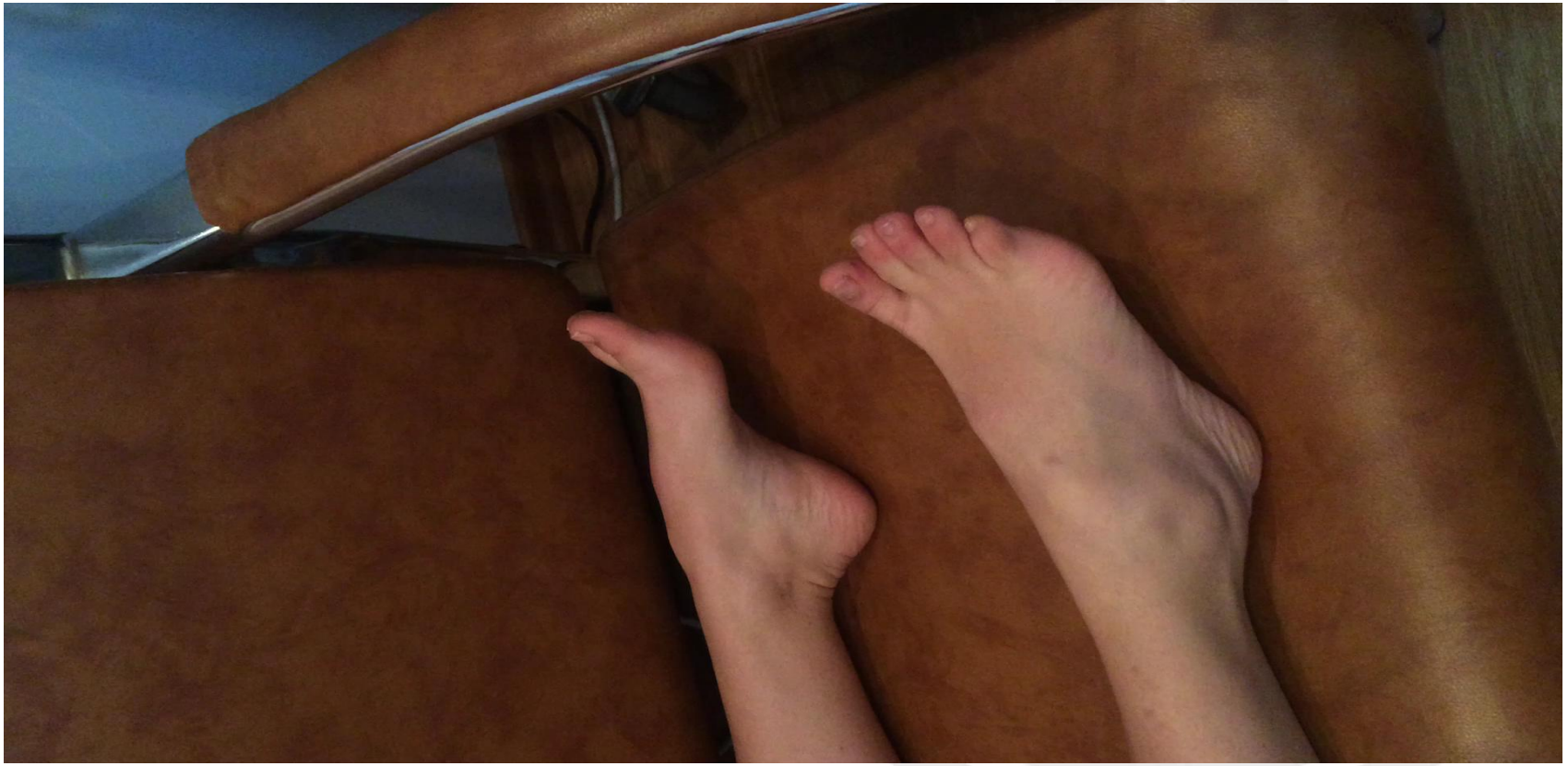
- Prevalența 2/100,000.
- Ataxie la mers și a membrelor progresivă
- Particularități adiționale:
- **Neuropatie axonală sensorie - motorie**
- **Implicarea tractului piramidal**
- Cardiomiopatie hipertrofică
- Modificări scheletale
- Atrofie optică
- Surditate
- Diabet zaharat

Nicolas Fridreich 1863

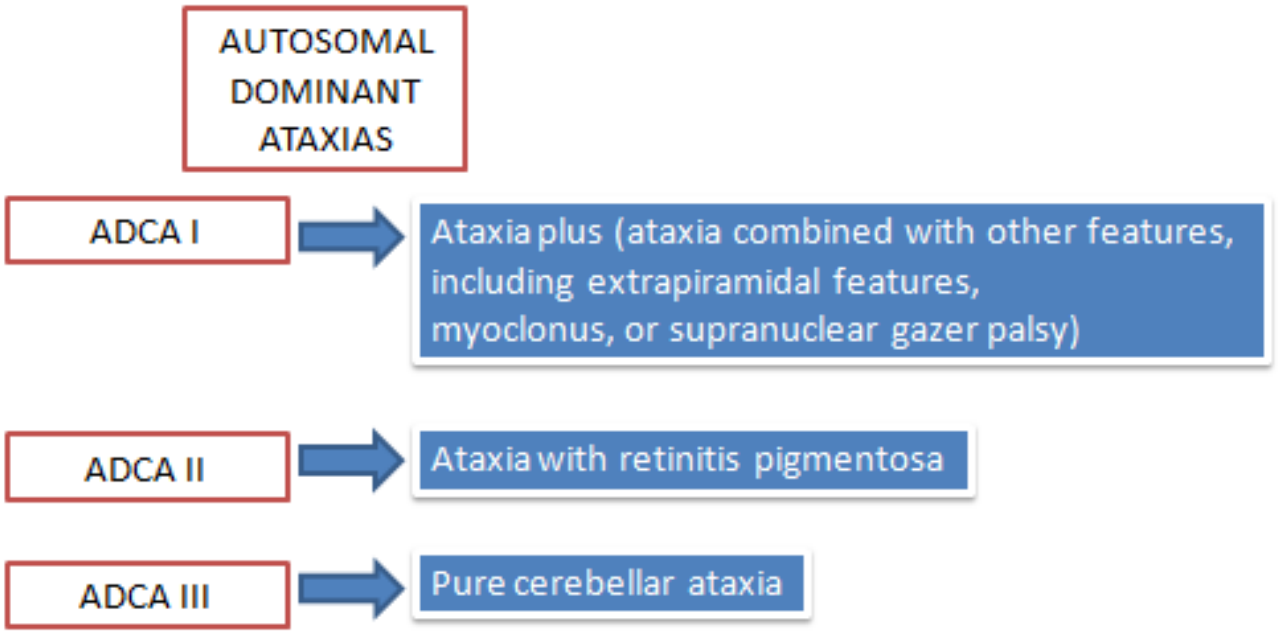
Ataxia Friedreich

- Campuzano (1996) – identificarea genei **frataxin** – repetarea trinucliotidelor (GAA) în intronul 1. Expansiunea ambelor alele – 96%.
- 100-2000 repetări (Normal 7-22)
- **Frataxin** implicat în metabolismul ferului în mitocondrii

Semnul Babinsky



Ataxii Spinocerebelare Autosomal Dominante



Ataxii Spinocerebelare Autosomal Dominante

- **Ataxie cerebeloasă progresivă.**
- **Se transmite pe cale autosomal-dominantă**
- **Gena patologică - grad mare de expresie. Nu se observă omiterea generaţiilor.**

Ataxii Spinocerebelare Autosomal Dominante

- **Hipoplazia cerebelului, uneori – atrofia olivelor, punții Varoli**
- **Degenerescență combinată a sistemelor spinale, asemănătoare cu ataxia spino-cerebelară Friedreich**
- **Vârsta medie de debut - 34 de ani**