Neuromuscular diseases

Judit Boczán MD, PhD

Neuromuscular diseases

- Motoneuron (motoneuron diseases)
- Spinal roots (pl. disc herniation)
- Plexus (brachial, lumbosacral)
- Peripheral nerves (mono- and polyneuropathies)
- Neuromuscular junction (eg. myasthenia gravis)
- Skeletal muscle (myositis, myopathies, muscular dystrophies)

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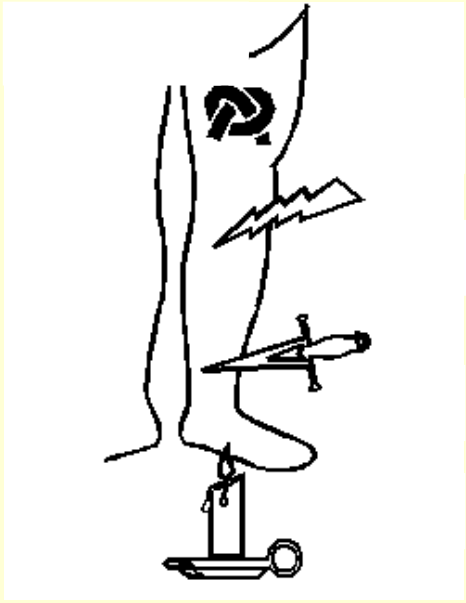
Anamnesis - Complaints

- *Motor system* (YES)
  - weakness
  - fatigue
  - clumsyness
  - Involuntary movements of muscle, cramps

- *Sensory system (NO)*
  - numbness
  - pain
  - hypesthesia
  - dysequilibrium



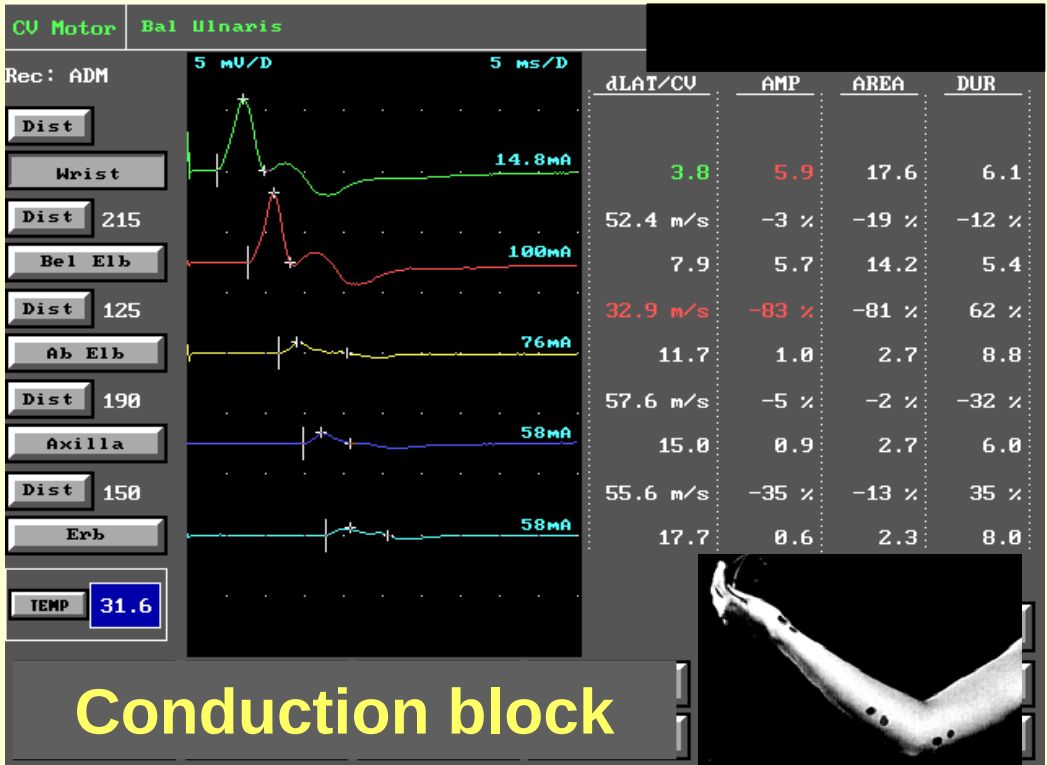
Symptoms

- *Motor system*
  - Trophism: atrophy
  - Tone: hypotonia
  - Strenght: paresis
  - motor “on” sign:
    fasciculation, myokymia

- *Reflexes*
  - Decreased deep tendon reflexes
  - No pyramidal signs

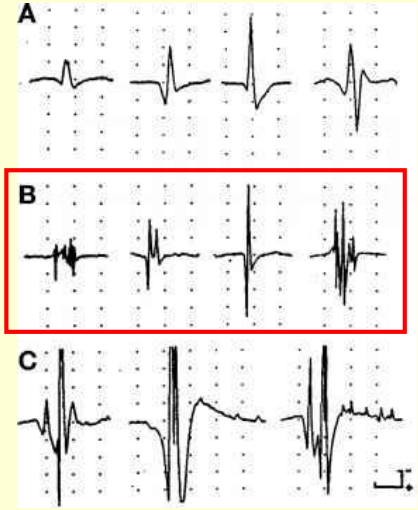
Examinations
Electroneurography (ENG)

- Functional examination method of peripheral nerves
- Motor, sensory
- Axonal? Demyelinisation?
- Diagnosis, follow up..



Examination
Electromyography (EMG)

- Differentiation between myogen and neurogen processes
- Concentric needle electrode
- Activity in relaxed muscle? (no, fibrillation, positive sharp wave, fasciculation)
- Voluntary contraction: motor unit potentials (amplitude, duration)



normal

myopathy

neuropathy

Neuromuscular diseases

- Motoneuron diseases

- Diseases of the neuromuscular junction

- Skeletal muscle diseases

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Motoneuron diseases (MND)

- Upper motoneuron

- Upper + Lower motoneuron (ALS)

- Lower motoneuron (SMA, SBMA)

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Upper motoneuron diseases

- Hereditary spastic paraparesis (HSP)
- Lesion of the pyramidal tract
- Spasticity (mainly lower extremities)
- No or minimal atrophy
- Increased tendon reflexes, pyramidal signs
- Spastic gait
- AD, AR
- Diff. DG: other myelopathies (inflammatory, compression, hypovitaminosis B12..)

Motoneuron diseases (MND)

- Upper motoneuron

- Upper + Lower motoneuron (ALS)

- Lower motoneuron (SMA, SBMA)

Amyotrophic lateralsclerosis (ALS)

- 1874: Jean-Martin Charcot
- Progressive loss of UMN and LMN
- Lethal within 3-10 years
- Incidence: 1-3/100 000, Prevalence: 4-10/100 000
- Male:Female ratio: 1,5:1
- Onset: majority of cases: 55-65 years of age
- Hereditary: 10% (SOD1 – 15%, c9orf72 ….)

ALS (Lou Gehrig's disease)

Lou Gehrig (1903-1941)

- New York Yankees
- Onset: 1939
- Died: 1941 (37 year old)

Stephen W. Hawking (1948 – 2018)

Big Bang, black holes

Lucas-professor of Cambridge University

(like Isaac Newton in the 17th century)

ALS - symptoms

- *Upper motoneuron* (pyramidal tract):

  spasticity, increased tendon reflexes,

  pyramidal signs

- *Lower motoneuron*: hypotonic muscles,

  pronounced muscle atrophy, fasciculation,

  paresis, bulbar signs (tongue atrophy,

  fasciculation, dysarthria, dysphagia)

Hirano - 4 negative criteria

NO:

- Sensory signs
- Eye movement problems
- Vegetative signs (bladder and bowel)
- Taint for decubitus

Diagnosis

- ENG: motor axonal neuropathy (sensory - spared)
- EMG: denervation signs at rest (fibrillation, fasciculation), neuropathic potentials, signs of reinnervation
- Magnetic evoked potentials (MEP): dysfunction of the pyramidal tract
- Brain and cervical MR: negative, BUT precentral gyrus atrophy is possible
- Muscle biopsy

Subgroups, incidence, prognosis

- *Primary Lateral Sclerosis (PLS):*

  5%, UMN + later LMN signs, mean survival: 20 years

- *Amyotrophic Lateral Sclerosis (ALS):*

  65-70%, UMN+LMN signs, mean survival : 3-4 years

- *Progressive Muscular Atrophy (PMA):*

  10%, LMN, later UMN signs, mean survival: 5 years

- *Primary Bulbar Paresis (PBP):*

  12-20%, bulbar signs, signs, mean survival: 2 years

Therapy

- Incurable
- Riluzole: slowing progression, increases survival with 3-6 months
- Goal: improve the quality of life of the patient and his family
- PhysicoTH, exercises, medical aids (eg. handrail, wheelchair..)
- Muscle relaxants for decreasing spasticity
- Improve communication (eg. “camera mouse”)
- Dysphagia: pulping, condensation of fluids, … percutaneous gastrostomy
- Dyspnea: noninvasive ventilation, home ventilation
- Psychotherapy (patients, family, alternative Th-s..)

Motoneuron diseases (MND)

- Upper motoneuron

- Upper + Lower motoneuron (ALS)

- Lower motoneuron (SMA, SBMA)

Spinal muscular atrophies (SMA)

Incidence: 1:6000-10 000 / birth

2nd most frequent AR disease in childhood

Survival motor neuron 1 - SMN1 gene 7-8. exon del (5q) – carrier fr: 2-3%

- SMA0: congenital, reduced movements, respiratory insufficiency, death: 1st month
- SMA I (Werdnig-Hoffmann) onset < 6 m, hypotonia, prox. dominant. paresis, swallowing and respiratory insuff. Death: 1-2 years.
- SMA II.: onset: 6 months – 2 years
- SMA III (Kugelberg-Welander): onset: 12-15 years, lower extremity dominant, proximal, symmetric weakness and atrophy,

  cramps, death: adult
- SMA IV: onset: adult, norm. lifespan

Dg.: EMG, muscle biopsy, genetic test

Spinal muscular atrophies (SMA)

Therapy: Spinraza (nusinersen)

- Antisense oligonucleotide
- Intrathecal injection
- FDA approval: 2016
- SMA is caused by loss-of-function mutations in the *SMN1* gene which codes for survival motor neuron (SMN) protein.
- Patients survive owing to low amounts of the SMN protein produced from the *SMN2* gene.
- Nusinersen modulates alternate splicing of the *SMN2* gene, functionally converting it into *SMN1* gene, thus increasing the level of SMN protein in the CNS

Kennedy's disease (SBMA)

SBMA: spino-bulbar muscular atrophy

Prevalence: 1: 40 000

Androgen receptor (X chromosome) CAG repeat expansion

- Onset: 27-43 years, progression: decades
- cramps, atrophy (face, tongue, extremities), paresis, fasciculation
- Bulbar muscles (dysarthria, dysphagia)
- Gynecomastia, testes atrophy, infertility
- CK increased
- ENG: sensory-motor PP
- EMG: denervation, neurogen
- Lifespan is close to normal

Neuromuscular diseases

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- Diseases of the neuromuscular junction

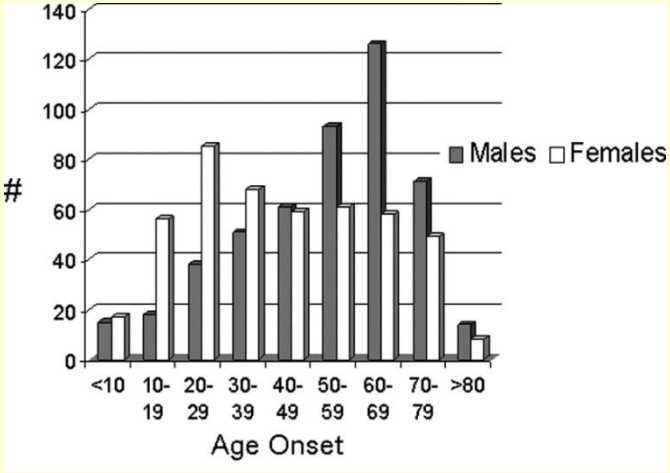
- Skeletal muscle diseases

Myasthenia gravis

- **Autoimmun appr. 99%, congenital app. 1%**

- **Prevalence: 2-10/100 000 → Rare disease**

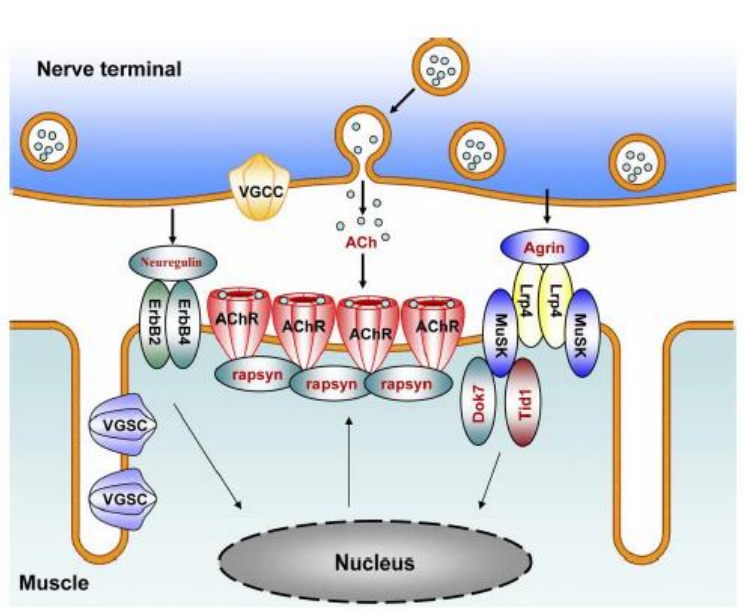
- **Increasing incidence in elderly (lifespan ↑, better DG workup)**



Sanders, Massey: Handbook of Clinical Neurology, Vol. 91

Autoantigens in MG

No.	Antigén	Prevalencia MG-ban
1	nAChR	Kb. 85%
2	MUSK	4-70%
3	Lrp4	? 1-7%
4	Titin	30-75%
5	Ryr	50-90%
6	DHPR	37%
7	TRPC3	36%
8	Tropomyosin	32%



Gomez et al., *Autoimmunity*, 2010; 43(5–6): 353–370

NMJ: 3x safety factor (EPP generates AP)

Others: pl. agrin, cortactin, actomyosin, rapsyn, AChE

Pathophysiológy

anti-AChR antibody (IgG1 és 3, C’ fixing)

↓

No of AChR ↓

↓

Ampl. of EPP ↓

↓

AP is late or missing

- Desorganisation of the postsynaptic membrane

- Granulocyta infiltration in the NMJ

- Synaptic boutons detach from the sarcolemma

- The postsynaptic membrane will be simpler (disappearance of the T-tubule system)

Complaints, symptoms

Fatigue, skeletal muscle weakness increases with physical exercise, and during the day

According to the muscles affected:

- Ocular - ptosis, diplopia
- Bulbar – masticatory muscles, muscles of facial expression (facies myasthenica), dysarthria, dysphonia, dysphagia
- Generalized – Proximal muscles, neck, respiratory muscles!!!

Frequent co-morbidities

- Thyroid gland diseases
- Persistent thymus, thymoma (chest CT!)

DIAGNOSIS: Edrophonium-chlorid test

- **Acetylcholine-esterase inhibitor**
- **max. 10 mg iv**

Positive:

- **Ocular MG: 60-95%**
- **Generalized MG: 72-95%**
- **BUT: aspecific positive reaction might occur in eg. motoneuron disease, brainstem lesion, other myopathies**
- **Mild symptoms: negative**

- **Side effect: salivation, nausea, fasciculation, sweating, (hypotension, bradycardia)**

DIAGNOSIS: Ice cube test

- 2 minutes chilling with and ice cube

→ ptosis decreases

- might be positive in edrophonium negative cases
- meta analysis of 6 studies:

  Sensitivity: 89%

  Specificity: 100%

DIAGNOSIS: Antibody test

- **Ab titer does NOT correlate with severity**

BUT:

- **AB positivity = Myasthenia**
- **Diagnostic kits on the market (AChR, MUSK)**
- **Cell based assays for Lrp4**

DIAGNOSIS: Repetitive stimulation (3 Hz)

More sensitive at proximal muscles!

- **Axillary nerve – deltoid**
- **Accessory nerve – trapezius**
- **Ulnar – hypothenar**

Positive:

- Ocular MG: 50%

- Generalized MG: 75%

- anti-MUSK MG: 57%

DIAGNOSIS: single-fiber EMG (SF-EMG)

- **Most senstivive electrophysiologic test**
- **Often + in a non-paretic muscle**
- **Generalized and ocular MG > 95% sensitivity**

BUT: ALS, polymyositis: false +

CHEST CT

- **Persistent thymus, thymoma, thymic carcinoma**

Therapy – Inhibition of Ach esterase

- **quick effect, short T1/2**
- **pyridostigmine (Mestinon, 0-6x60 mg), ambenonium chlorid (Mytelase 10mg)**
- **Fit the dose to the patient's actual need**
- **Side effects:**

  muscarinergic: salivation, diarrhoea, vomitus, increased bronchial secretion

  nicotinergic: muscle twitches, cramps

- **If symptoms worsen with AChE inhibition:**

  immunosuppression

Thymectomy

- **Persistent thymus, generatlized MG, AChR AT +:**
  up to 40-45-50 years of age

- Thymoma – should be removed due to an oncologic indication

- **Operation techniques:**
  transsternal
  transcervical and infraaxillar VAT
  “Robot-assisted” operation

- **In the first year of myasthenia**

Steroid

- **Progression despite of high dose of AChE inhibitor**
- **start: 16 mg metilprednizolon per os**
- **increase with 4 mgs every second day**
- **max. 1 mg/kg (! DM, side effects), hold for 1-3 months**
- **taper down with 4 mgs every second week, then stop**

- **Check: RR, glucose, GI complaints, edema!!!!**

Chronic immunosuppression

- azathioprin (Imuran): effective steroid lowering drug in MG
- 2,5 mg/kg, pregnancy is NOT a contraindication!
- Blood cell count, liver function control!
- Increases the incidence of non-melanoma skin cancers
- Skin protection against UV light is recommended

Myasthenic crisis

- **Respiratory failure requiring intubation, ventilation**

- **Occurence in 15-20% of cases**

- **Provoked by: infection, changes in medication (eg. steroid withdrawal or initiation with high dose; other drugs)**

- **Mortality 4-6%**

- **Treatment:** **plasma exchange (PLEX)**
  IVIG

Neonatal myasthenia

- **Antibody penetrates the placenta**
- **Respiratory failure and severe dysphagia in newborns**
- **Delivery only at wards with PIC facility!**
- **Temporal mechanical ventilation, nasogastric feeding if necessary**
- **Spontaneous remission**

	Drugs worsening myasthenia	**Replacement**
Antibiotics	**Aminoglycosids, tetracyclin** Polymyxin, penicillin (high dose)	Cephalosporins, ampicillin Erythromycin, co-trimoxazol Nitrofurantoin
Anticonvulsants	**Phenytoin, barbiturate**	Carbamazepin
Cardio- vascular drugs	beta blockers, antiarrhythmic drugs, ganglion-inhibitors	digitalis, reserpin
Antirheumatics	**penicillamin**	Acetylsalicylic acid, phenylbutazon Indomethacin
Antiparkinson drugs	amantadin	L-DOPA
Psychiátric drugs	**Tranquillants, neuroleptics, Lithium**	atosil Benzodiazepines (low dose, with care)
Narcotics and muscle-relaxants	Ketamin, aether, Pancuronium, d-tubocurarin	Halothan, fentanyl N_2O, suxamethonium
Others	corticosteroids, ACTH oral contraceptives thyroid hormones laxans (Mg!)	

Lambert-Eaton myasthenic syndrome

- frequently associates with SCLC
- AB against the praesynaptic Ca^{2+} channel
- Repetitive stimulation: differentiates from MG!!

    3 Hz: decrement

    post-activation: amplitude increment

    30 Hz stimulation (ulnar nerve): minimum 100% increment

Neuromuscular diseases

- Motoneuron diseases

- Diseases of the neuromuscular junction

- Skeletal muscle diseases

Skeletal muscle diseases

- Myositis
- Myopathies
- Muscular dystrophies
- Ion channel diseases

Complaints - Symptoms:

- **Muscle weakness**
- **Muscle pain**
- **Muscle atrophy**
- **Skin-, joint .. symptoms**

Subgroups:

- **Polymyositis (prox.)**
- **Dermatomyositis (prox.)**
- **IBM (distal, BUT: can be hereditary, too)**
- **Associated with other connective tissue disease**
- **Infective**

Diagnosis:

- **laboratory: CK, LDH, GOT, GPT, ANA, myositis spec. AB-s**
- **EMG (myogenic potentials, fibrillation - acute)**
- **muscle MRI**
- **biopsy (histochem, IH), myogenic, lymphocytes, MHC expression..**

Therapy: **steroid, chr. Immunosuppression, IVIG, PLEX**

Skeletal muscle diseases

- Myositis
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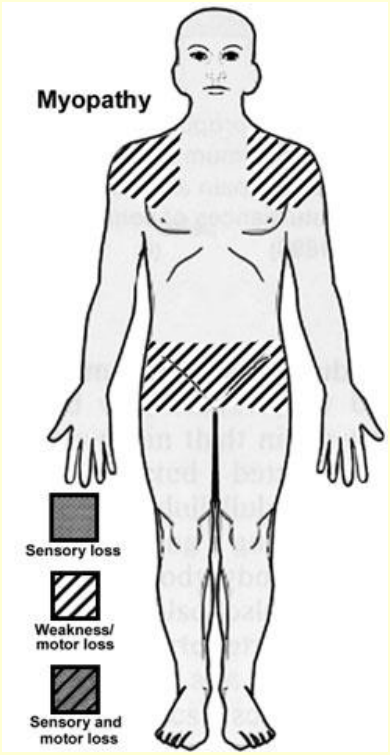

Weakness of proximal muscles (no sensory!)

Causes:

- **Metabolic (mitochondrial, fat- or carbohydrate) – inherited**
- **Endocrine (thyroid gland, parathyroid gland..)**
- **Toxic**
- **Drug induced (statins!)**
- **Critical illness myopathy**

Diagnosis:

- laboratory: t és iCa, Mg, phosphate, CK, LDH, GOT, GPT, thyroid function, calcitonin, parathormon..,

- EMG (myogen potentials)

- biopsy (histochem, IH), myogenic/neurogenic?, deposits?

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Muscular dystrophies

- **Duchenne/Becker (DMD-BMD, dystrophin)**
- **Limb-girdle (LGMD)**
- **Facio-scapulo-humeral (FSH)**
- **Myotonic dystrophy**

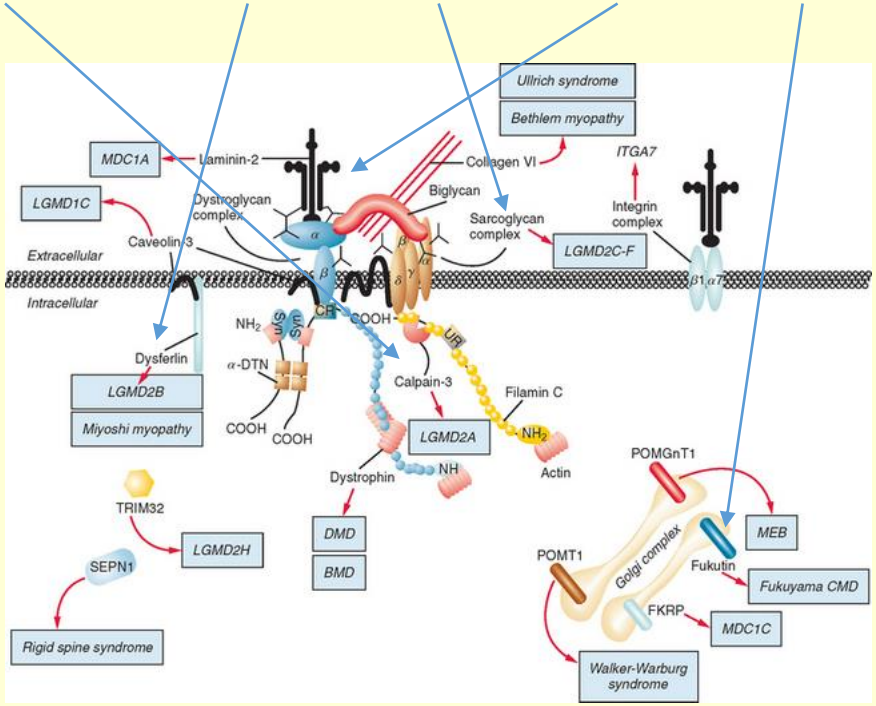
Duchenne dystrophy

- XR, dystrophin gene
- Prevalencie: kb. 1 : 7250, 5-24 year old boys
- Onset: 2-5 years
- Progressive weakness of proximal muscles, Gowers sign
- Lumbar hyperodosis, wingigng of the scapula, pseudohypertrophy of the calf, belly sticks out, Achilles contract., scoliosis, CK extremely elevated
- Loss of ambulation: 9-13 year
- Cardiomyopathy
- Respiratory failure
- Death: 15 - 25 year

Therapy: steroid, symptomatic

New: CRISPR/Cas9 – genetherapy in certain cases

Limb girdle muscular dystrophy



Facio-scapulo-humeral muscular dystrophy (FSHD)

- AD: in 70-90% of cases, migt be sporadic, 4q35.2 del
- Prevalence: 1 : 16 000
- Onset: 3rd decade
- Facial, periscapular muscles, biceps, leg dorsiflexion, later thigh,

  linear progression up to 20-50 year (DG FROM THE DOOR)
- Mental retardation, cardiomyopathy might occure
- CK: 70-1400 U/l (normal in 25%)
- Wheelchair: only in 20 %
- Frequently normal lifespan (spared bulbar and respiratory muscles)
- 20% of pts have no symptoms!!

Therapy: symptomatic

Myotonc dystrophy

- AD, myotonin protein kinase (DMPK, CTG triplet expansion)
- Prevalence: 13.5 / 100 000 birth
- Frontal baldness
- Cataracta
- Difficulty in muscle relaxation, paresis
- Myopathic face
- Cardiomyopathy
- Therapy: mexiletin

THM

- *Rare diseases:* *- many rarities - a lot in total*
  - it's 100% for that patient
- *Phenotype: from mild to severe*
- *Push the diagnostic workup as much as possible*
- *Gene therapy is around the corner*
- *Prenatal diagnosis in severe cases*
- *Focus on quality of life*