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FAKULTNÍ NEMOCNICE BRNO

NEUROLOGICKÁ KLINIKA LF MU a FN BRNO

MYOPATHIES, MOTOR NEURON DISEASES

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MYOPATHIES - DEFINITION

= **disorders of skeletal muscles**

- encompass **a wide variety of illnesses** that cause **weakness, pain, and fatigue** in any combination.
- !!! **Similar clinical symptoms may result from**:
  - the disorders with primary involvement of the anterior horn cells (e.g., amyotrophic lateral sclerosis and the spinal muscular atrophies)
  - neuromuscular junction disorders (myasthenia gravis, Lambert-Eaton syndrome, and congenital myasthenia)
  - and certain polyneuropathies (e.g., chronic inflammatory demyelinating polyneuropathy)
- **Consider in differential diagnosis!!!**

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BASIC TERMS USED

- **MYOPATHY** simply refers to an abnormality of the muscle and has no other connotation.
- **Muscular dystrophies - inherited** (genetic), **progressive** muscle disorders resulting from defects in one or more genes needed for normal muscle structure and function (mostly leading to the disturbance of a structural proteins of the muscle membrane); dystrophic changes (eg, muscle fiber necrosis and regeneration) are seen on biopsy specimens.
- **Congenital myopathies** are muscle diseases mostly present at birth (**congenital**), but in some patients may not be apparent until later in infancy or childhood. They also result from genetic defects (mostly related to the genes coding contractile proteins or Ca2+ signaling pathway). The conditions are often **stable or slowly progressing.**
- **Metabolic myopathies** are inherited myopathies, that refer mainly to abnormalities of muscle biochemistry that impair the resynthesis of adenosine triphosphate (ATP) (mitochondrial myopathies) or cause an abnormal storage of material in the cell (m. Pompe, McArdle…).

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BASIC TERMS USED II

- **Myotonias** are diseases in which the occurrence of involuntary, persistent muscle activity, accompanied by abnormal repetitive electrical discharges, distorts the normal contractile process. This occurs after percussion or voluntary contraction. Mostly inherited (ion channel disorders, myotonic dystrophies), rarely acquired.
- **Acquired myopathies** are the disorders of skeletal muscles without the genetic background.
- **Myositis** implies an inflammatory disorder and is usually reserved for disorders in which the muscle histology shows an inflammatory response.
- The term **endocrine myopathy** refers to myopathies associated with disorders of the thyroid and parathyroid glands and to myopathies associated with increased corticosteroid levels.
- **Toxic (drug induced) myopathies** are acquired muscle diseases caused by a toxic effect of some external substance including (but not limited to) alcohol or some commonly prescribed medications (cholesterol lowering medications…). Clinical manifestations of toxic myopathies range from muscle pain to more serious muscle damage leading to rhabdomyolysis.

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MYOPATHIES – TYPICAL FEATURES

- The most prominent clinical symptom is the **weakness** (the loss of strength or power, manifesting in the inability to generate normal force).
- **Muscle pain and fatigue** may also be present
- The decrease of the muscle strength in myopathies is usually **proximal and symmetrical**.

  These often result in particular difficulties arising from chair or squat or holding up one's arm against gravity.
  - Some of the muscular dystrophies represent an exception – in these conditions, the weakness may affect mainly certain muscle groups by where in the body symptoms begin and remain most expressed
- **Deep tendon** (muscle stretch) **reflexes typically remain normal.**
- **No sensory disturbance** (no hypoesthesia, no paresthesias).

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MYOPATHIES – TYPICAL FEATURES

- The **weakness is stable, non fluctuating** within the day or during the activity.
  - NOTE the **difference with the neuromuscular junction diseases**, which are characterized by fluctuating strength based on muscle use. For example, myasthenia gravis results in decreasing power with continuous contraction. On the other hand, Lambert-Eaton myaesthetic syndrome (LEMS) results in increased strength with repeated contraction.
- There is usually **minimal atrophy until late in the course** (muscle dystrophies again represent an exception).
  - Note the **difference with motor neuron diseases or sever neuropathies**, where prominent atrophies develop someties even early with the course of the disease

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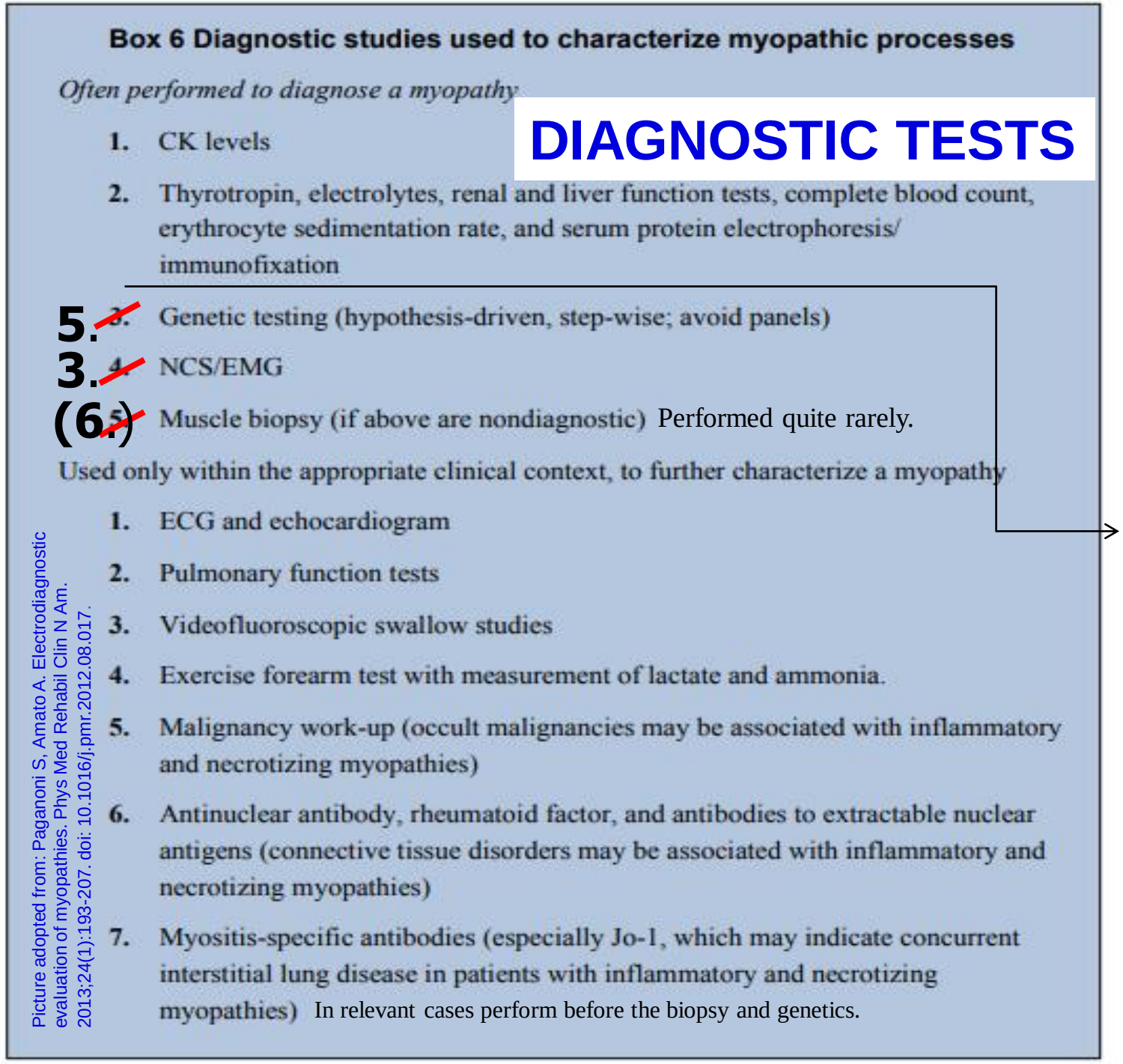

Box 6 Diagnostic studies used to characterize myopathic processes

Often performed to diagnose a myopathy

1. CK levels
2. Thyrotropin, electrolytes, renal and liver function tests, complete blood count, erythrocyte sedimentation rate, and serum protein electrophoresis/ immunofixation
3. Genetic testing (hypothesis-driven, step-wise; avoid panels)
4. NCS/EMG
5. Muscle biopsy (if above are nondiagnostic) Performed quite rarely.

Used only within the appropriate clinical context, to further characterize a myopathy

1. ECG and echocardiogram
2. Pulmonary function tests
3. Videofluoroscopic swallow studies
4. Exercise forearm test with measurement of lactate and ammonia.
5. Malignancy work-up (occult malignancies may be associated with inflammatory and necrotizing myopathies)
6. Antinuclear antibody, rheumatoid factor, and antibodies to extractable nuclear antigens (connective tissue disorders may be associated with inflammatory and necrotizing myopathies)
7. Myositis-specific antibodies (especially Jo-1, which may indicate concurrent interstitial lung disease in patients with inflammatory and necrotizing myopathies) In relevant cases perform before the biopsy and genetics.

5.
3.
(6.)

Picture adopted from: Paganoni S, Amato A. Electrodiagnostic evaluation of myopathies. Phys Med Rehabil Clin N Am. 2013;24(1):193-207. doi: 10.1016/j.pmr.2012.08.017.

1. **Creatine kinase (CK) + myoglobin** levels are often elevated (as well as **ALT/AST**, but not GGT levels – note the **difference from hepatopathy** – frequent mistake!)

3. **NCS** are usually **normal** (with the exception of pronaunced atrophies)

Needle EMG may show myopathic features (see next slides)

+ (4) **Muscle MRI** becomes a gold standard– it´s often performed before the biopsy and genetic testing and may help to identify target mucles for the biopsy and to select an appropriate genetic/metabolic test (based on **specific patterns** – some muscles are more severly affected than the others)

+ (5) **Metabolic (enzyme activity) testing** (Pompe, McArdle…)

NEEDLE EMG

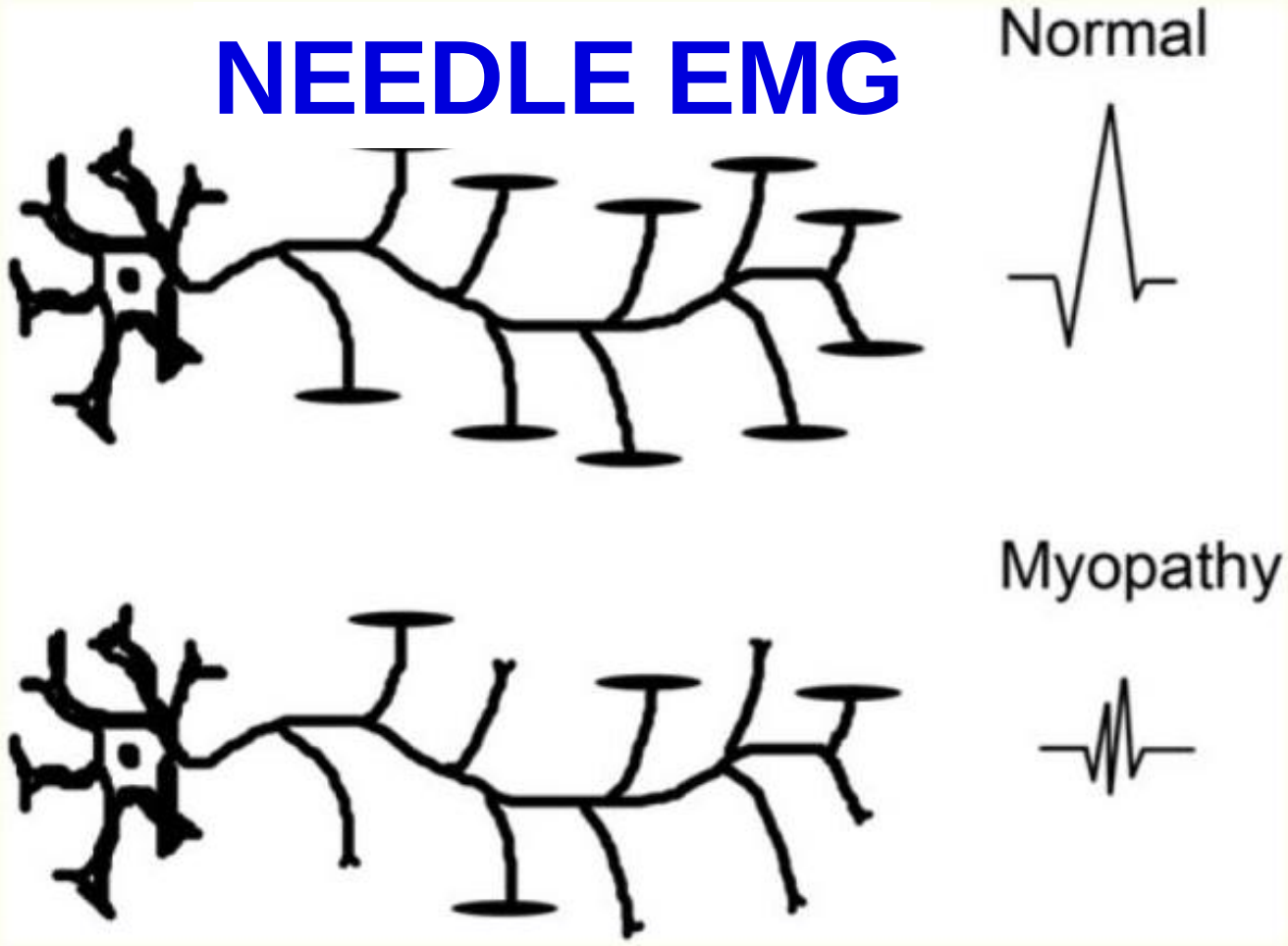

Fig. 1

Physiologic model of motor units in myopathies. The pathologic process in myopathies results in dysfunction and dropout of individual muscle fibers located randomly within the motor unit. Motor neurons and motor axons are not affected. As a result, each MUAP is generated by fewer motor fibers. MUAPs become polyphasic, short in duration, and low in amplitude.

Picture taken from: Paganoni S, Amato A. Electrodiagnostic evaluation of myopathies. Phys Med Rehabil Clin N Am. 2013;24(1):193-207. doi: 10.1016/j.pmr.2012.08.017.

MUPs are **small, short, and polyphasic** and **recruit early**. In long-standing disease, a mixed population of small and long duration MUAPs may be seen.

In rapidly progressing myopathies (i.e. mainly in inflammatory myopathies or muscular dystrophies), there is also the presence of prominent muscle membrane irritability (**fibrilations, PSWs,** and even myotonic discharges), especially in proximal muscles – this aktivity is believed to reflect the ongoing disease activity

In myotonias, **myotonic discharges** are frequent.

NOTE that **EMG may be normal in selected myopathies** (certain endocrine, metabolic, congenital, and mitochondrial myopathies)!

Box 1 Role of electrodiagnostic studies in the diagnosis of myopathies

1. Exclude neuromuscular conditions that may mimic a myopathy
    a. Motor neuron disease
    b. Motor neuropathies
    c. Neuromuscular junction disorders
2. Provide EMG evidence of the presence of a myopathy (although EMG may be normal in the presence of selected myopathic processes)
3. Characterize the myopathy
    a. Location (proximal, distal, symmetric, or asymmetric)
    b. Presence/absence of abnormal spontaneous activity
    c. Severity
4. Identify target muscles for biopsy

Picture taken from: Paganoni S, Amato A. Electrodiagnostic evaluation of myopathies. Phys Med Rehabil Clin N Am. 2013;24(1):193-207. doi: 10.1016/j.pmr.2012.08.017.

MYOPATHIES - CLASSIFICATION

1. **INHERITED**
   - **muscular dystrophies**
   - **congenital myopathies**
   - **metabolic myopathies**
     - Mitochondrial myopathies
     - Storage diseases (glycogen, lipid – Pompe, McArdle)

2. **ACQUIRED**
   - myositis (**inflammatory** myopathies, mostly caused by an autoimmune process)
   - **endocrine** myopathies
   - external substance induced myopathy (**toxic**) (alcoholic, glucocorticoid, statin).
   - **rare others** (infectious – infuenza, lyme disease, toxoplasmosis, …)

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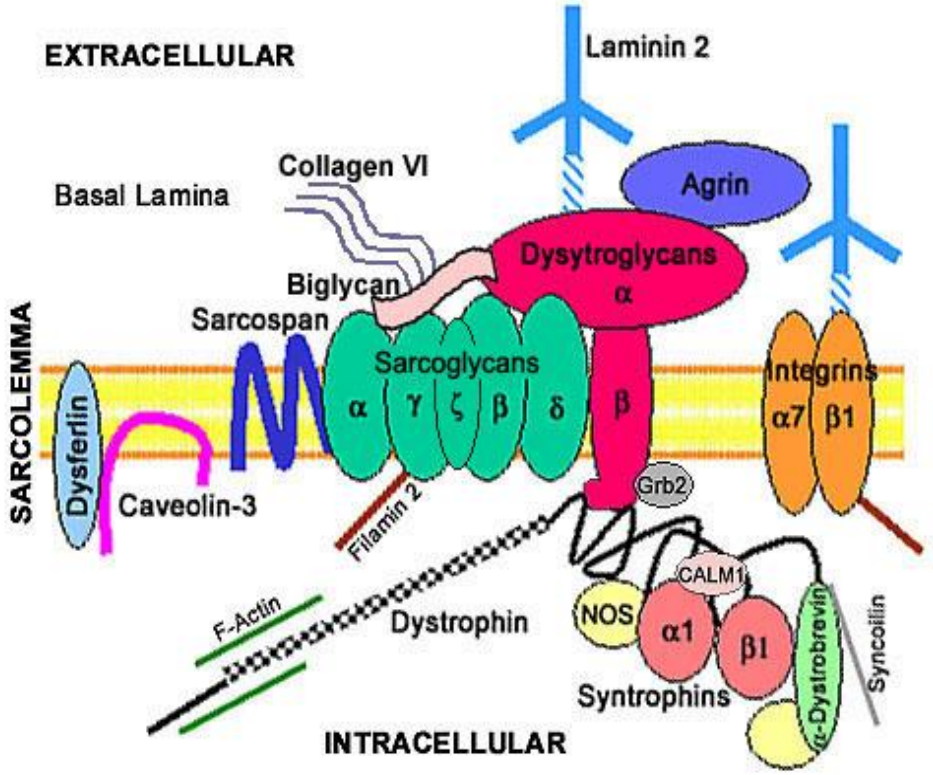
MUSCULAR DYSTROPHIES

- Muscular dystrophy is a group of diseases that cause **progressive weakness and loss of muscle mass**.
- Due to gene mutations interfering with the production of proteins needed to form healthy muscle (mostly the **membrane proteins**).
- There are many kinds of muscular dystrophy.
  - In some of them, the symptoms begin in childhood, mostly in boys (DMD, BMD).
  - Other types don't surface until adulthood (FSHD, LGMD, MD1,2)
- The main sign of muscular dystrophy is **progressive muscle weakness**. Specific signs and symptoms begin at different ages and in different muscle groups, depending on the type of muscular dystrophy.
- The **treatment options are limited**
- Medications and other therapy (physical therapy) can also help manage symptoms and slow the course of the disease.



MEMBRANE-ASSOCIATED PROTEIN COMPLEXES

https://neuromuscular.wustl.edu/musdist/dag2.htm

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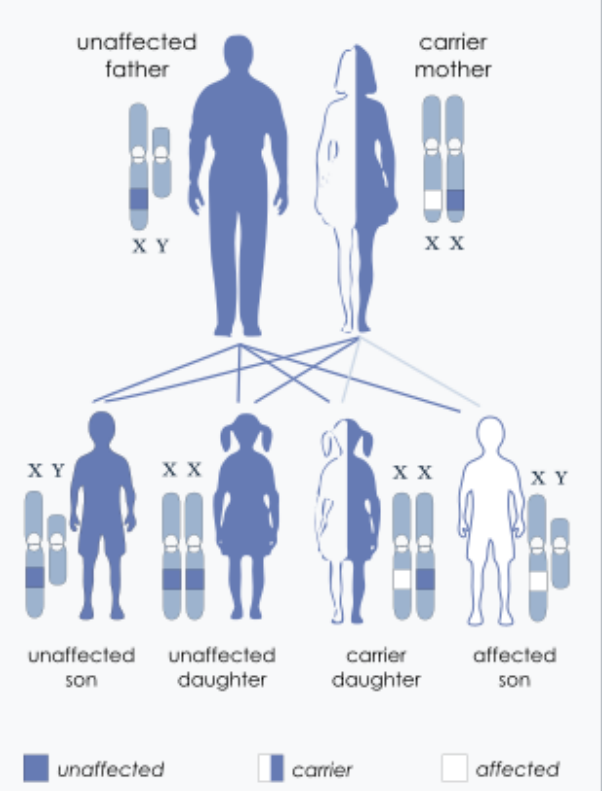
DUCHENNE TYPE MUSCULAR DYSTROPHY (DMD)

- **Dystrophinopathy** (mutations in the **dystrophin gene)**
- the **dystrophin protein** is absent
  - Dystrophin is a large protein located on the cytoplasmic face of the muscle membrane.
  - It represents the first step in the connection of actine/myosine complex to the muscle cell membrane
  - It´s coded by a gene on the short arm of the X chromosome.
- **XR** – **mostly affects boys** (although girls can be carriers and mildly affected)
- the incidence in boys of about 200 per million birth (1 out of 5000)
- DMD = the most common form of muscular dystrophy



Adopted from:
https://neuromuscular.wustl.edu/musdist/dmd.html
https://en.wikipedia.org/wiki/Becker_muscular_dystrophy

DUCHENNE TYPE MUSCULAR DYSTROPHY (DMD)

- Signs/symptoms typically **appear in early childhood (mainly 2-5 yrs**) and might include:
  - Frequent **falls, muscle pain** and stiffness
  - Difficulty rising from a lying or sitting position
    (**Gowers sign** - standing up with the aid of hands pushing on knees, butt- first)
  - Trouble running and jumping, **wadling gait, loss of ambulation**
    - usually at the age of 9 - 13 years, later with steroid treatment
  - Walking on the toes, large calf muscles (**pseudohypertrophy**)
  - Dilated **cardiomyopathy** (especially > 15 years)
  - Scoliosis
  - Mental retardation: Mean IQ ~ 88
  - **Progressive generalized weakness** in later phases, ventilation support mostly needed
- **life expectancy** is estimated to be around 25-26. The most common direct cause of death in people with DMD is respiratory failure or dilated cardiomyopathy. With respiratory assistance, the median survival age can reach up to 40-50.


10
Obrázek č. 2 - „Gowersův“ manévr


BERNSTEIN

DUCHENNE TYPE MUSCULAR DYSTROPHY

- **The diagnosis based on clinical picture**
- **+ very high CK levels!!! (**Up to 100x upper limit of normal, decreasing with increasing age and disability)
- + **myopathic EMG changes** (frequently not necessary, particularly in typical clinical pictures with very high CK level and/or positive family history).
- **+ genetic examination (type of mutation)** + MR + muscle biopsy

- Treatment: **Prednisone weekly** (5-10 mg/kg/week). Treatment effects: walking prolonged by 2 to 5 years, increased strength, improved pulmonary functions.
- for particular types of mutations (so called nonsense mutations – about 13 % of DMD patients) gene therapy is already available (**ataluren – translarna**) (price about $300.000/yr)
- **Physical therapy, cardiology follow-up (pacemaker?), respiration assistance**

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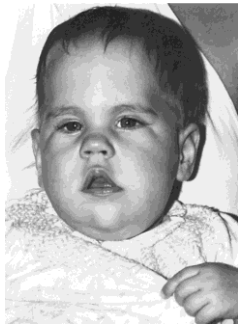
BECKER MUSCULAR DYSTROPHY

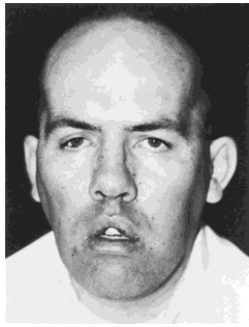
- Signs and symptoms **are similar to those of Duchenne** muscular dystrophy but tend to be **milder** and progress **more slowly**.
- **XR-linked** – only **boys** are affected
- The **same gene** is affected, but the **dystrophine is not completely absent**
- Symptoms generally begin in the teens (**above 7 years of age**) but might not occur until the mid-20s or later.
- **Muscle weakness, mostly proximal**, legs and arms, slowly progressive
- Failure to walk at the age of 16 - 80 years
- The diagnostic and therapeutic options similar to DMD

Adopted from: https://neuromuscular.wustl.edu/musdist/dmd.html

large calf muscles (pseudohypertrophy) + hyperlordosis

MYOTONIC DYSTROPHY (MD)





- the most common muscular dystrophy that begins in adulthood (at least 1 in 8,000 people worldwide)
- characterized by **progressive muscle wasting and weakness** and the inability to relax certain muscles after use (**myotonia**, e.g. a person may have difficulty releasing their grip on a doorknob or handle).
- Other signs and symptoms of MD include **cataracts and cardiac conduction defects**.
- In affected men, hormonal changes may lead to **early balding and infertility**.
- The features of this disorder often develop **during a person's twenties or thirties**, although they can occur at any age. The severity of the condition varies widely among affected people, even among members of the same family.
- There are **two major types** of myotonic dystrophy with similar signs and symptoms: type 1 and type 2 (the latter tends to be milder). They are caused by mutations in different genes.
- Myotonic dystrophy type 1 is caused by mutations in the DMPK gene (DM1 protein kinase), while type 2 results from mutations in the CNBP gene (CCHC-type zinc finger nucleic acid binding protein, also called ZNF9).: tri/ tetranucleotide repeat expansion.
- **No specific treatment available**, Gene therapy is in the early stages of study in humans

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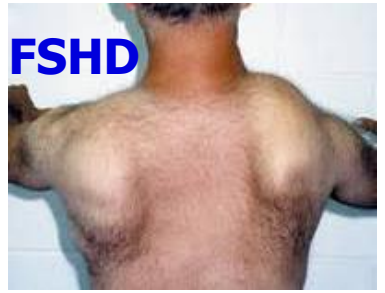
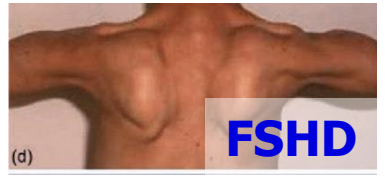
OTHER TYPES OF MUSCULAR DYSTROPHY

- Some types of muscular dystrophy are defined by a specific feature or by **where in the body symptoms begin and remain most expressed** (before genetic testing, the classification of muscular dystrophies was based on the distribution of the symptoms):

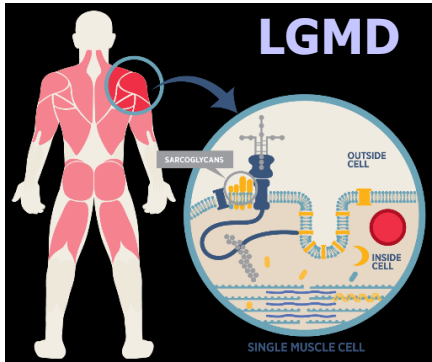
- **FACIOSCAPULOHUMERAL (FSHD).** Muscle weakness typically begins in the face, hip and shoulders. The shoulder blades might stick out like wings when arms are raised. Onset usually occurs in the teenage years but can begin in childhood or as late as age 50.



- **LIMB-GIRDLE (LGMD).** Hip and shoulder muscles are usually affected first. People with this type of muscular dystrophy might also have peroneal paresis and so might trip frequently. Onset usually begins in childhood or the teenage years.



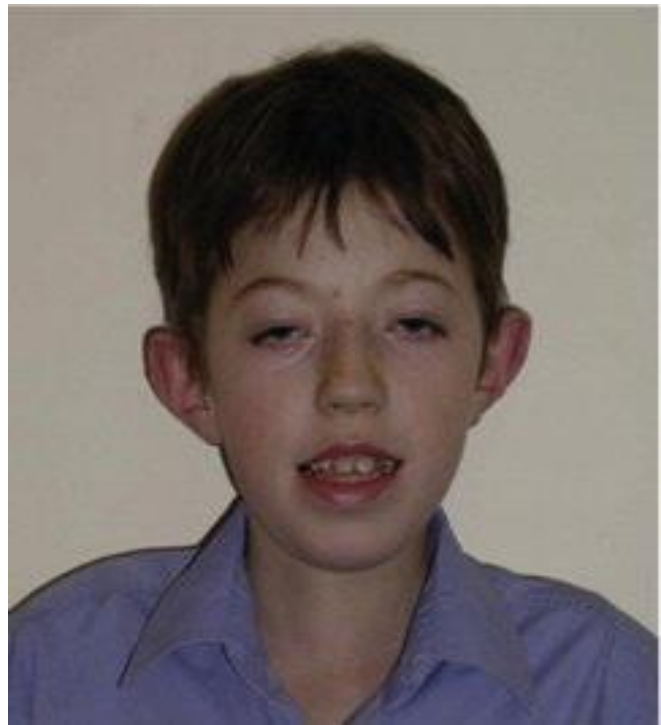
- **OCULOPHARYNGEAL (OPMD).** Dysfagia, tongue weakness, ptosis and external ophthalmoplegia (often incomplete and asymmetric) are prominent features. Mild proximal weakness of the lower (70 %) or upper limbs.



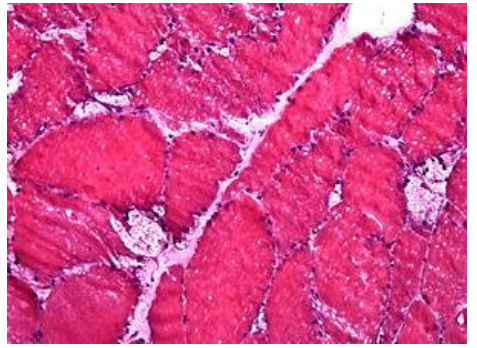
CONGENITAL MYOPATHIES

- Congenital myopathies are rare muscle diseases **mostly present at birth (congenital**, but may not be apparent until later in infancy or childhood)
- result from genetic defects (mostly related to the genes coding contractile proteins or Ca2+ signaling pathway).
- There are **many different types** (e.g. central core disease, nemaline myopathy, centronuclear myopathies) and signs and symptoms and their severity vary depending on the type.
- The conditions are often **stable or slowly progressing**.
- most share common features, including **lack of muscle tone and weakness** (including facial weakness and drooping eyelids) + **delayed motor skills**
- Other signs and symptoms of some congenital myopathies include feeding and breathing difficulties, as well as skeletal conditions, such as curvature of the spine (scoliosis), weak bones (osteopenia) or hip problems.
- The diagnosis is often based on morphological findings on muscle biopsy (no dystrophic changes, no inflammation). **No specific treatment**.

Pictures taken from: https://neuromuscular.wustl.edu/syncm.html
And North KN et al. Approach to the diagnosis of congenital myopathies. Neuromuscul Disord 2014;24(2):97-116.



POMPE DISEASE, GLYCOGEN STORAGE DISEASE TYPE II



- an **inherited AR** disorder caused by the **accumulation of glycogen** in certain organs and tissues (mainly muscles and liver cells), which impairs their function.
- Caused by the mutation of the ***GAA* gene**, which encodes an enzyme called **acid alpha-glucosidase** (also known as acid maltase). This enzyme is active in lysosomes and normaly breaks down glycogen into glucose, which is impaired in Pompe disease.
- **Confirmed by enzyme activity examination**, followed by genetic testing in relevant cases
- Treatment available! – since 2006, enzyme replacement therapy using **biologically active recombinant human alglucosidase alfa** (produced in Chinese Hamster Ovary cells) is available (costs about 300.000 USD per year and must be taken for patients´entire life).
  - Clearly prolongs the survival. Early diagnosis and early treatment leads to much better outcomes

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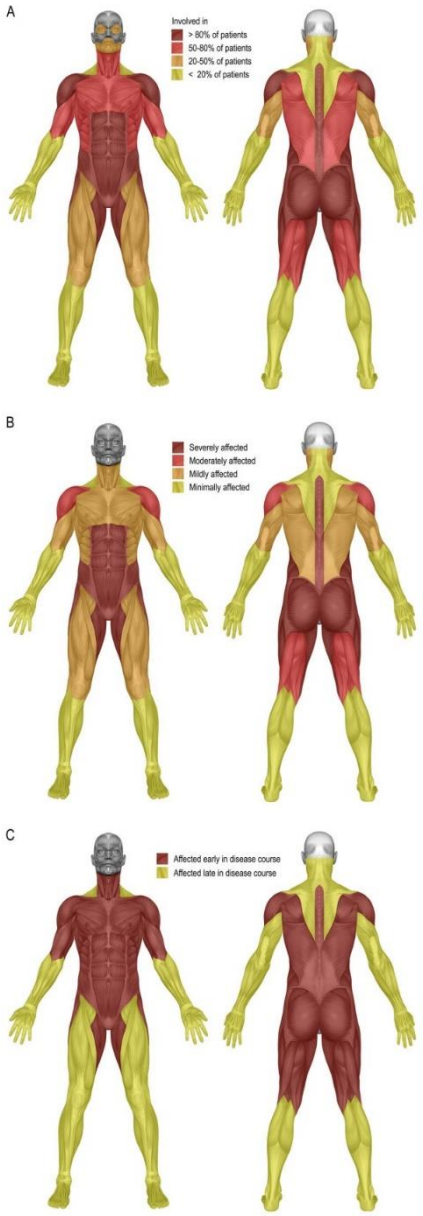
POMPE DISEASE, GLYCOGEN STORAGE DISEASE TYPE II

- **The classic form of infantile-onset Pompe disease** begins within a few months of birth and presents with **muscle weakness, hypotonia and hepatomegaly**, and **heart defects**. Affected infants may also fail to gain weight and grow at the expected rate and have **breathing problems**. If untreated, this form of Pompe disease leads to death from heart failure in the first year of life.

- **The late-onset type of Pompe disease** may not become apparent until later in childhood, adolescence, or adulthood. Late-onset Pompe disease is usually **milder** than the infantile-onset forms of this disorder and is less likely to involve the heart. Most individuals with late-onset Pompe disease experience **progressive muscle weakness**, especially in the legs and the trunk, including the muscles that control breathing (with the progress, it can lead to **respiratory failure)**.



Picture taken from: Van der Beek N et al. Clinical features and predictors for disease natural progression in adults with Pompe disease:a nationwide prospective observational study. Orphanet J Rare Dis. 2012 ;7:88.

SPECIFIC IMMUNE/ INFLAMMATORY MYOPATHIES

- **Immune myopathies**
  - Polymyositis (mostly antisynthetase antibodies –anti Jo)
  - Other syndromes (e.g. anti HMGCR – rare immune-mediated myopathy caused by the statins)
- **Dermatomyositis**
- **Rare others**
  - Infections
  - Lupus, polymyalgia rheumatica
  - Celiac disease
  - Inclusion body myositis – IBM….

Most of the general information applies to the most frequent ones (dermato-, polymyositis) (**proximal symmetrical progressive weakness** as a dominant feature, **pain** in about half of the patients, mostly mild)

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INFLAMMATORY MYOPATHIES

- Dermatomyositis and polymyositis both have **an autoimmune basis,** but the basic mechanism is different. In dermatomyositis, the illness results from humoral attack on the (not only muscle) capillaries, whereas in polymyositis, the muscle fibers are under attack by cytotoxic T cells.
- Typically associated with the **presence of autoantibodies** (various types in each syndrome)
- Both the basic types can be **differenciated by:**
  - clinical picture (**absence/presence of skin** or other systems changes),
  - **autoantibodies present**,
  - **CK levels** (more elevated in polymyositis since the pathological process is directed against muscle fibers)
  - **muscle biopsy findings**.

- Treatment: general agreement exists to treat polymyositis and dermatomyositis with **corticosteroids** or some other form of immunosuppression (**IVIG, azathioprim, methotrexate, cyclosporine, or even Mycophenolate mofetil**), or a combination of these.

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POLYMYOSITIS

- **acute or subacute** illness that occurs in adults
- more frequent in **women** than in men, as are other autoimmune diseases
- the course commonly **relapses and remits**, especially when treated with immunosuppression or corticosteroids.
- Systemic symptoms are common at onset, such as malaise, fever, and anorexia
- **Frequent cardiac involvement** (myocarditis, pericarditis) – up to 70%
- **Autoimmune disease**, the cause of polymyositis is unknown and may involve viruses (Coxsackie) and autoimmune factors.
- Associated with the presence of autoantibodies of which the **Jo-1 antibodies** (directed against histidyl tRNA-synthetase) are the most common.
- **Serum CK** concentration should always be elevated (more than in dermatomyositis or IBM).
- **Certain risk of cancer** (1.4x to 2x increased) (not that high as in dermatomyositis)

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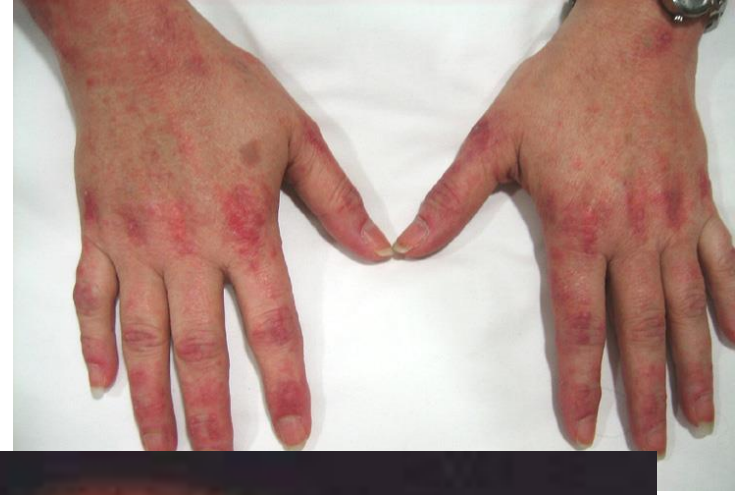
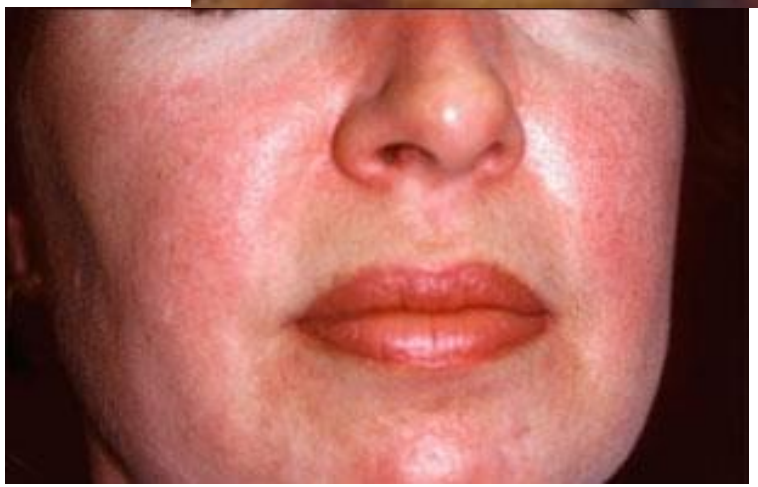
DERMATOMYOSITIS

- **Muscle is not the only tissue involved** in dermatomyositis. Muscle weakness is associated with:
  - a characteristic **skin rash**. It is characteristically a purplish discoloration of the skin over the cheeks and eyelids (Heliotrope rash). It often has a butterfly distribution and blanches on pressure. The rash may spread widely over the body. The skin over the elbows, knees, and knuckles is particularly prone to develop a reddened, keratotic, indurated appearance (Gottron's sign and papules). Nailford lesions (petechia and erythema).





DERMATOMYOSITIS

- Vascular abnormalities, such as **Raynaud's phenomenon**.
- **Cardiac involvement** ranges from conduction defects to congestive cardiac failure secondary to cardiomyopathy.
- **Interstitial pneumonitis** and fibrosis may cause a nonproductive cough and respiratory distress.
- **Delayed gastric and esophageal emptying** occurs in the illness, indicating an abnormality in the smooth muscle of the upper gastrointestinal tract.

- The illness often follows a **relapsing-remitting course**, although occasionally the illness is clearly monophasic even to the point of recovering spontaneously without treatment.
- **Juvenile or adult form**. The latter is associated with an **increased risk for cancer** (3x to 6x increased). Up to 32 % of adults will develop a cancer, mostly within 2 to 3 years of presentation of the myositis.
- The serum CK concentrations are usually elevated but can be normal earlier in the course or in patients with a very indolent course.

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OTHER ACQUIRED MYOPATHIES

- **Endocrine myopathies** - associated with disorders of the thyroid and parathyroid glands and to myopathies associated with increased corticosteroid levels.
- **External substance induced myopathy** (alcoholic, glucocorticoid, statin).
- **Rare others** (**infectious** – infuenza, lyme disease, toxoplasmosis, …)
- Mostly quite **typical clinical pattern** (proximal weakness + myalgia)
- **CK and myoglobine usually only mildly elevated**
- **Minimal or even no EMG changes**
- Treatment: **no specific**, treat the causing disease (if possible) (infectious or endocrine diseases, cessation of toxic substances)

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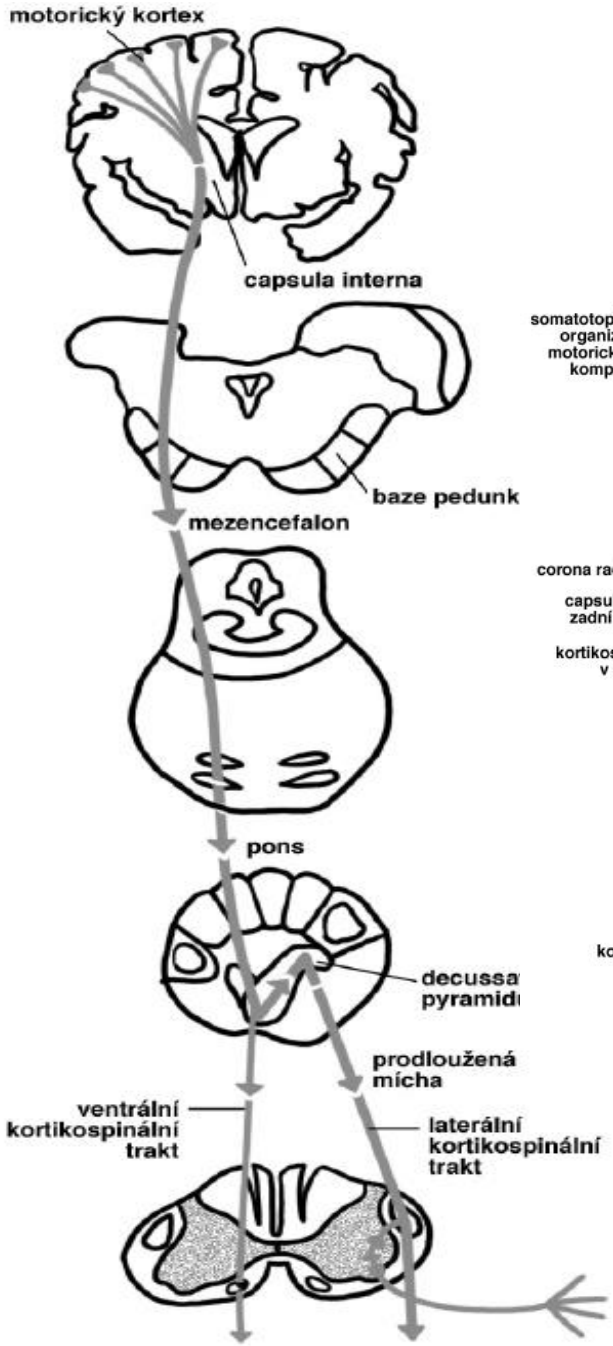
MOTOR NEURON DISEASES

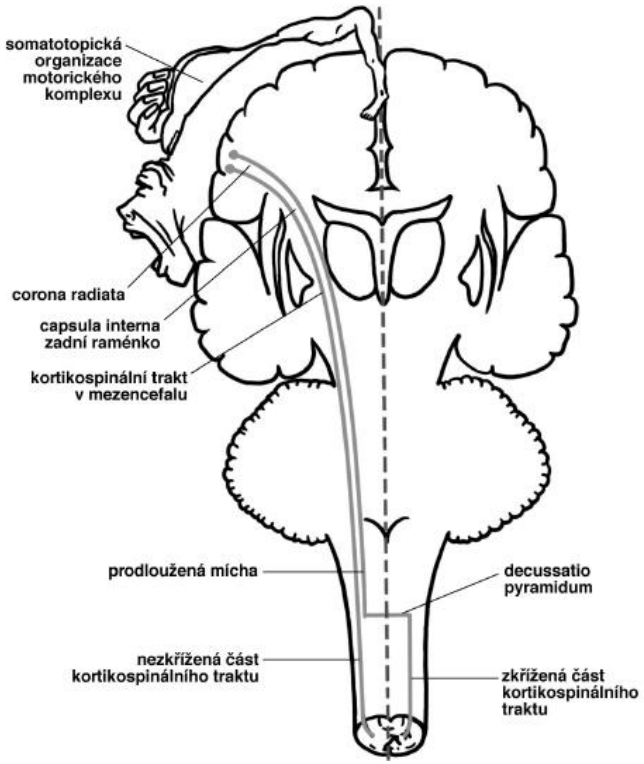
- term refers to the broader family of disorders that may **affect the upper and/or lower motor neuron system** as well as nonmotor systems
- Some of the units affect only the function or upper or lower motor neuron, while others typically combine the impairment of both types of motor neurons.
- The **most important diagnostic units** in this group are the following:
  - Amyotrophic lateral sclerosis (motor neuron disease) (ALS) and it´s variants
  - Spinal muscular atrophy (SMA)
  - Spinobulbar muscular atrophy (SBMA, Kennedy's Disease)

  - **Mostly inherited or degenerative conditions**, rarely affected by infection (acute poliomyelitis) or other causes

MOTOR NEURONS

- **The upper motor neuron** (UMN) is a motor neuron, the cell body of which lies within the motor cortex of the brain, and the axon of which forms the corticobulbar and corticospinal tracts.
- **Lower motor neurons** (LMNs) lye in the brainstem motor nuclei and the anterior horns of the spinal cord and directly innervate skeletal muscles.
- The UMNs are rostral to the LMNs and exert direct or indirect supranuclear control over the LMNs





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SIGNS AND SYMPTOMS OF UPPER MOTOR NEURON INVOLVEMENT

- **Weakness** (decreased muscle strength – mostly mild) + the loss of dexterity
- Increased muscle tone (**spasticity**)
- Increased deep tendon reflexes (**hyperreflexia**) (even in atrophic limb = probable UMN sign)
- Decrease of exteroceptive reflexes + the presence of **pathological reflexes** (Babinsky….)
- **Pseudobulbar palsy** (or spastic bulbar palsy) develops when there is disease involvement of the corticobulbar tracts that exert supranuclear control over those motor nuclei that control speech, mastication, and deglutition.
  - The prefix “pseudo-” is used to distinguish this condition from “true” bulbar palsy that results from pure LMN involvement in brainstem motor nuclei.
  - Clinically, articulation, mastication, and deglutition are impaired, and combined with spontaneous or unmotivated crying and laughter (This is also termed *emotional lability*, *hyperemotionality, labile affect*, or *emotional incontinence)*
  - often very stressfull for the the patient.

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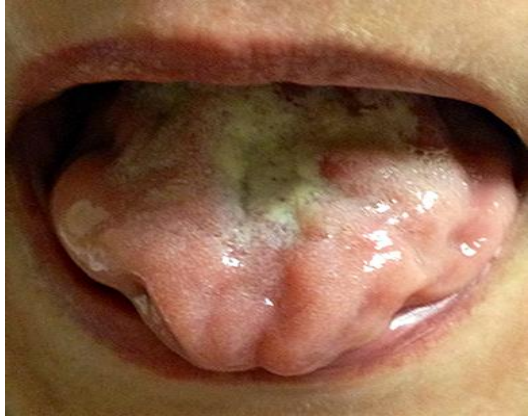
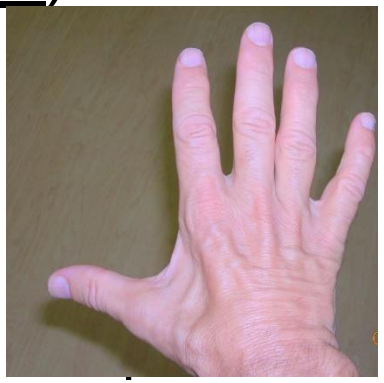
SIGNS AND SYMPTOMS OF LOWER MOTOR NEURON INVOLVEMENT



- Loss of muscle strength (moderate to severe **weakness**)
- Muscle **atrophy** (decrease of the muscle mass)
- Decreased deep tendon reflexes (and exteroceptive reflexes) (**hyporeflexia**)
- Decreased muscle tone (**flacidity**)
- **Fasciculations**
- **Muscle cramps**
- **Pure motor dysfunction** (no positive/negative sensory symptom unless there is a combination with some other disease – polyneuropathy, CTS…)



- In some diseases (typically ALS) both UMN a LMN signs **are combined**

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METHODS USED TO CONFIRM UMN/LMN LESIONS

- ***LMN***: NCS/EMG – **nerve condution studies are typically normal** (the decrease of CMAP amplitudes is possible) – performed mostly to exclude other explanatory diagnosis
- **Needle EMG** shows the **reinnervation potenials** (polyphasic MUPs, broad, and high in amplitude, reduced number of MUPs that have an increased firing rate), frequently combined with **denervation** potentials (fibrilations and PSW) and/or **fasciculations**

- ***UMN:*** besides clinical examination, **motor evoked potentials (MEP)** using the transcranial magnetic stimulation can be used.

- Genetic testing is relevant in inherited diseases (SMA, SBMA, familial ALS)

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SPINAL MUSCULAR ATROPHY

- a group of disorders caused by degeneration of anterior horn cells **– LMN only**!!!
- Almost all cases are **genetically determined**, with most being AR due to homozygous deletions of the survival motor neuron gene in chromosome 5.
- The incidence of infantile to juvenile AR SMA is estimated to be 1 in 6000 newborns
- Clinical picture in type I: **hypotonia**, severe generalized muscle **weakness,** deep tendon **reflexes are absent**, weak cry - floppy" baby.
- Intercostal muscles are severely weakened (causing **respiratory distress**)
- In type II or III, delayed motor milestones are first hints to diagnosis, otherwise similar

SMA TYPE	AGE AT ONSET	SURVIVAL/PROGNOSIS	INHERITANCE	DEFECTIVE GENE
Infantile SMA (Werdnig-Hoffmann) – type 1	Birth to 6 mo	Death by 2 yr old, never able to sit without support, unable to lift their heads when placed prone	AR	SMN gene
Intermediate SMA – type 2	Before 18 mo	No walking, adulthood	AR	SMN gene
Juvenile (Kugelberg-Welander) – type 3	After 18 mo	Adulthood	AR	SMN gene
Adult-onset SMA (pseudomyopathic SMA)	After 20 yr (Most > 30 yr)	Slow progression of mucle weakness, proximal or distal	AR, AD "Sporadic"	SMN gene, distal overlap with HMN-5

No need to know it in detail – just that this disease exist and may start in various age ☺

SPINAL MUSCULAR ATROPHY

- Patients with SMA have **normal or above-average intelligence**.
- They attend school, and when they reach adulthood often live and work outside the home (Stewen Hawking?).

- The diagnosis mainly based on a typical **clinical picture**
- Most important test is a **molecular genetic analysis** to identify homozygous deletions in the *SMN* gene on chromosome 5q
- In unclear cases, **EMG** can confirm suspition and support the indication of molecular genetic analysis
- Serum CK may be elevated up to 10 times normal levels in SMA type 3 but is typically normal in the infantile and intermediate types.

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SPINAL MUSCULAR ATROPHY

- Treatment: **multidisciplinary approach**: **Physical therapy** (to maintain active mobility and independence and prevent the development of contractures and kyphoscoliosis), occupational therapy, **orthopedic evaluation** (frequent scoliosis), and emotional support
- To assist in breathing, **non-invasive ventilation** (BiPAP) is frequently used (tracheostomy in more severe cases). Nutrition via a **feeding tube or gastrostomy**.
- ***Nusinersen*** is used to treat spinal muscular atrophy. It is an antisense nucleotide that modifies the alternative splicing of the SMN2 gene. It is given directly to the central nervous system using an intrathecal injection (initially 6x /year, later 3x/ year – price $750,000 in the first year, than $375,000 each year). It was approved in the US in 2016 and in the EU in 2017.
- **Onasemnogene abeparvovec** (Zongelsma) is a gene therapy treatment which uses self-complementary adeno-associated virus type 9 (scAAV-9) as a vector to deliver the SMN1 transgene. As an intravenous formulation, it was approved in 2019 in the US to treat those below 24 months of age (price: $2.125 million, only one administration is needed).

AMYOTROPHIC LATERAL SCLEROSIS

- Charcot's disease, motor neuron disease, and, in the US, Lou Gehrig's disease
- **neurodegenerative** disorder of undetermined etiology that primarily affects the motor neuron cell populations in the **motor cortex, brainstem, and spinal cord**.
- Genetic predispositon (in familial and to lesser extent in sporadic), association with FTD in some mutations.
- Presents with a **progressive pure motor weakness** (leading in therminal phase to respiratory failure), typically **spreading** from one part of the body (one extremity) with slow generalization.
- In most typical cases presents with the **combination of UMN and LMN** (increased deep tendon reflexes and Babinsky sign in atrophic limb represent very typical sign), frequent bulbar involvement.
- **Fasciculations** are a typical phenomenon (but not exclusive for ALS!!!)

- Some patients may have:
  - UMN onset (Primary lateral sclerosis)
  - LMN onset (Progressive muscular atrophy
  - Bulbar onset (Progressive bulbar palsy)
  - dyspnea at onset

+ later usually develop signs of involvement of the other parts of the motor system

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AMYOTROPHIC LATERAL SCLEROSIS

- **Median survival 2-4 years from the diagnosis**
- The diagnosis is based on a **typical clinical picture** (slow spreading of the pure motor symptoms/signs, not explained by spondylogennic disease or any other diagnosis) – revised ElEscorial criteria
- **NCS/EMG can confirm the diagnosis** (pure motor axonal lesion, reinnervation + denervation changes and fasciculations present in upper and lower extremities, trunk and also in cranial nerve distribution) and/or exclude other possible causes
- Treatment multidisciplinary:
- **Physical therapy** (to maintain active mobility and independence and prevent the development of contractures and kyphoscoliosis), emotional support
- To assist in breathing, **non-invasive ventilation** (BiPAP) is frequently used (tracheostomy in more severe cases). Nutrition via a **feeding tube or gastrostomy**.
- **Riluzole** prolongs survival by 2-5 months, **edaravon** partly efficient

MAIN SOURCE OF INFORMATION

- https://www.mayoclinic.org/diseases-conditions/
- https://neuromuscular.wustl.edu/ (some pictures are also taken from this page)
- https://ghr.nlm.nih.gov
- Paganoni S, Amato A. Electrodiagnostic evaluation of myopathies. Phys Med Rehabil Clin N Am. 2013;24(1):193-207. doi: 10.1016/j.pmr.2012.08.017
- Murray B, Mitsumoto H. CHAPTER 78 – Disorders of Upper and Lower Motor Neurons. In Bradley WG, Daroff RB, Fenichel GM, Jankovic J. Neurology in Clinical Practice, 5th ed. London: Elsevier 2008.
- Amato AA, Brooke MH. CHAPTER 83 – Disorders of Skeletal Muscle. In Bradley WG, Daroff RB, Fenichel GM, Jankovic J. Neurology in Clinical Practice, 5th ed. London: Elsevier 2008.

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CONGENITAL MYOPATHIES

- There are different types of congenital myopathies (just to get some idea, no need to know in detail), some of which include:
- **Central core disease.** This condition causes muscle weakness and developmental problems. Some people may develop a significant reaction to general anesthesia (malignant hyperthermia).
- **Centronuclear myopathies.** These rare conditions cause muscle weakness in the face, arms, legs and eye muscles, and breathing problems.
- **Congenital fiber type disproportion myopathy.** Small fibers are found on muscle tissue during a biopsy. This condition causes muscle weakness in the face, neck, arms, legs and trunk.
- **Nemaline myopathy.** Nemaline myopathy is one of the more common and causes muscle weakness in the face, neck, arms and legs, and sometimes scoliosis. It may also cause breathing and feeding problems.
- **Multiminicore disease.** This condition has several subtypes and often causes severe muscle weakness in the arms and legs, and scoliosis.
- **Myotubular myopathy.** This rare condition, which occurs only in males, causes muscle weakness, floppiness and breathing problems.
- **Other myopathies.** Other rare myopathies include autophagic vacuolar myopathy, cap disease, congenital myopathy with arrest of myogenesis, myosin storage myopathy and zebra body myopathy

MYOTONIC DYSTROPHY (MD)

- The muscle weakness associated with **type 1** particularly affects the lower legs, hands, neck, and face. Muscle weakness **in type 2** primarily involves the muscles of the neck, shoulders, elbows, and hips.
- The two types of myotonic dystrophy are **caused by mutations in different genes.**
- Myotonic dystrophy type 1 is caused by mutations in the **DMPK gene (DM1 protein kinase**), while type 2 results from mutations in the **CNBP gene (CCHC-type zinc finger nucleic acid binding protein, also called ZNF9).** The specific functions of these genes are unclear. The protein produced from the DMPK gene may play a role in **communication within cells**. It appears to be important for the correct functioning of cells in the heart, brain, and skeletal muscles. The protein produced from the CNBP gene is found primarily in the heart and in skeletal muscles, where it probably helps **regulate the function of other genes.**
- Type 1 myotonic dystrophy results from a mutation in the *DMPK* gene known as a **trinucleotide repeat expansion** (50-5000 repeats, while it´s only 5 to 34 in healthy individuals)
- Type 2 myotonic dystrophy results from a mutation in the *CNBP* gene known as a **tetranucleotide repeat expansion (**75-11000, in most healthy people no more than 26)

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