Nerves and Muscles diseases

Klinika Neurologii Dziecięcej WUM

Different causes of muscle weakness:

damage of the :

> brain

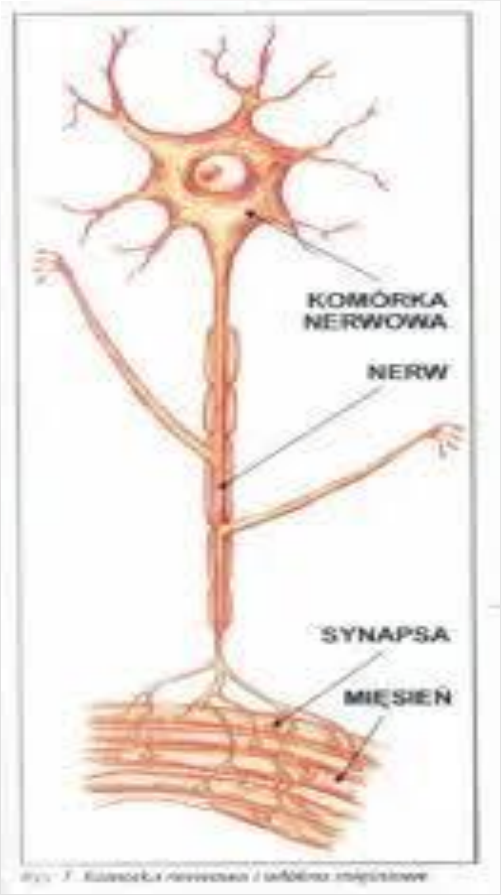
> spinal cord

> nerve roots

> peripheral nerves

> neuromuscular junction

> muscle



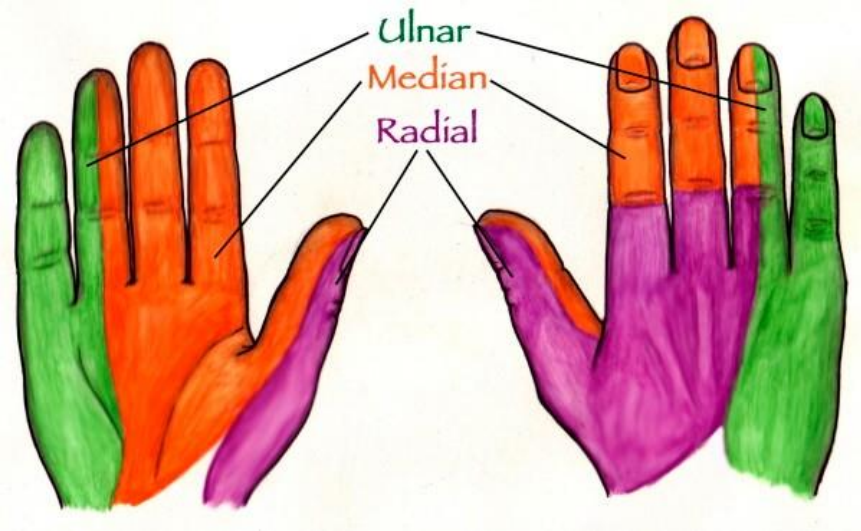
NEUROPATHY

- distal weakness
- concomitant sensory symptoms
- reflexes lost early
- +/- fasciculations
- autonomic dysfunction

Neuropathy

Mononeuropathy

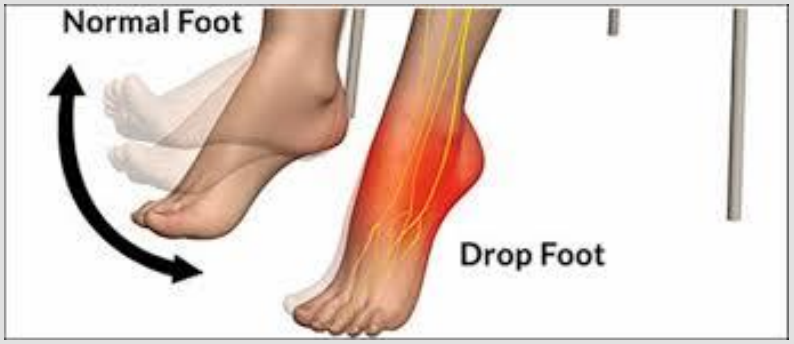
Polyneuropathy



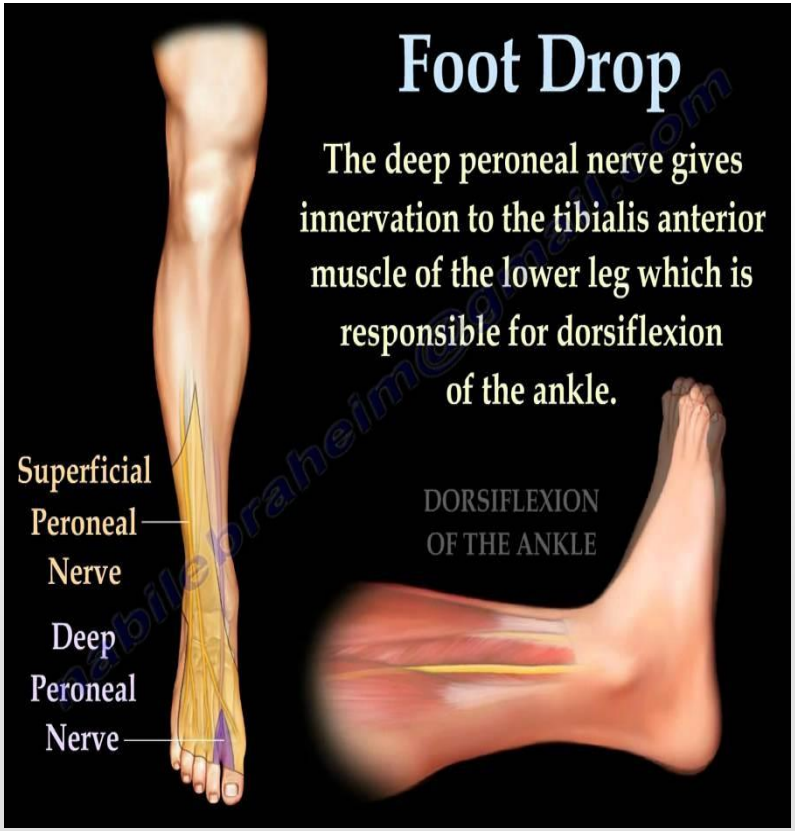
Mononeuropathy

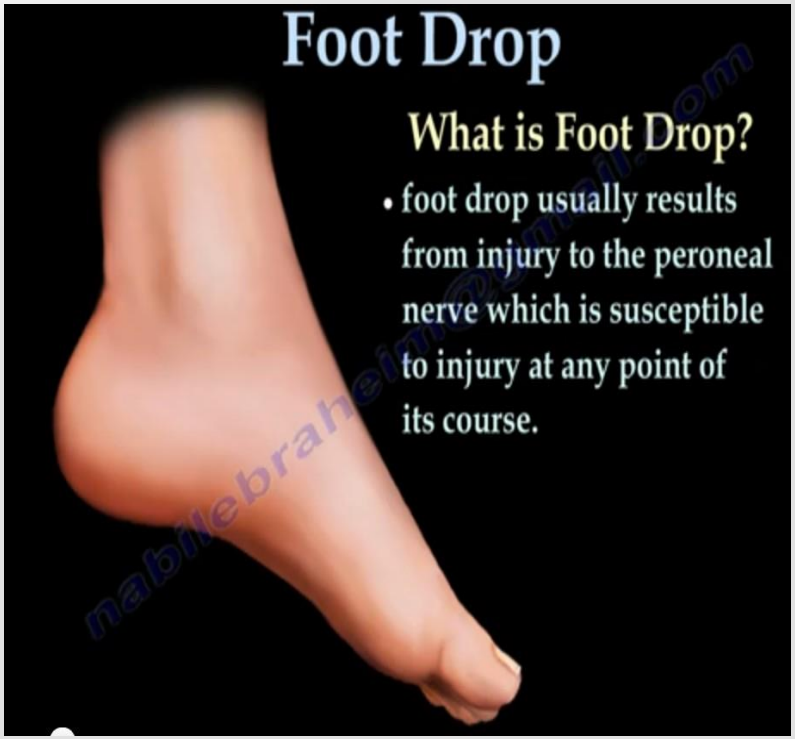
- trauma or compression
- deficits reflect the anatomic distribution of the nerve (for example carpal tunnel syndrome)

Mononeuropathy
- which nerve was damaged?



Foot drop


Foot Drop
The deep peroneal nerve gives innervation to the tibialis anterior muscle of the lower leg which is responsible for dorsiflexion of the ankle.
Superficial Peroneal Nerve
Deep Peroneal Nerve
DORSIFLEXION OF THE ANKLE


Foot Drop
What is Foot Drop?
• foot drop usually results from injury to the peroneal nerve which is susceptible to injury at any point of its course.

Polyneuropathy

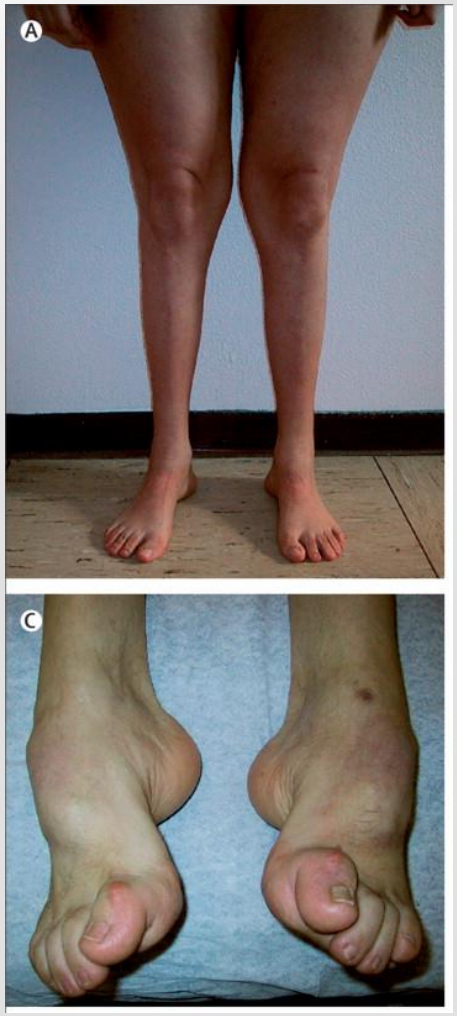
Clinical signs and symptoms :

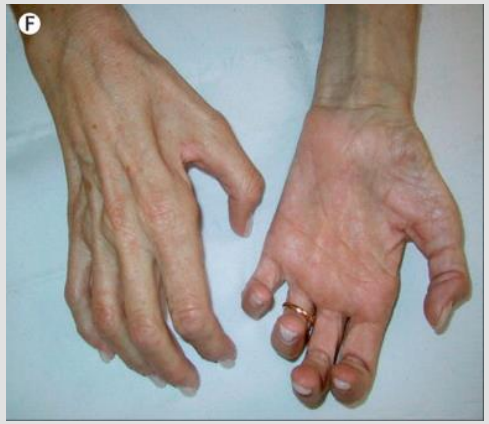
- symmetrical, featuring weakness
- numbness, pins-and – needles, burning pain
- it usually begins in the hands and feet ("stocking and glove" pattern) and may progress to the arms and legs
- loss or decrease of reflexes
- muscle atrophy (secondarily)
- autonomic disturbances (orthostatic hypotension, incontinence, impotence, sweating abnormalities)

Polyneuropathy - causes:

- diabetes mellitus, uraemia, hypothyroidism
- rheumatologic disease
- medications (chemotherapy)
- toxins (alcohol)
- vitamins deficiencies (B vitamin)
- inflammatory polyneuropathy (GBS)
- hereditary polyneuropathy

Charcot – Marie – Tooth disease CMT :
AD, AR or linked to chromosome X, above 90 genes have been described





FACIAL NERVE (N. VII) PARALYSIS:

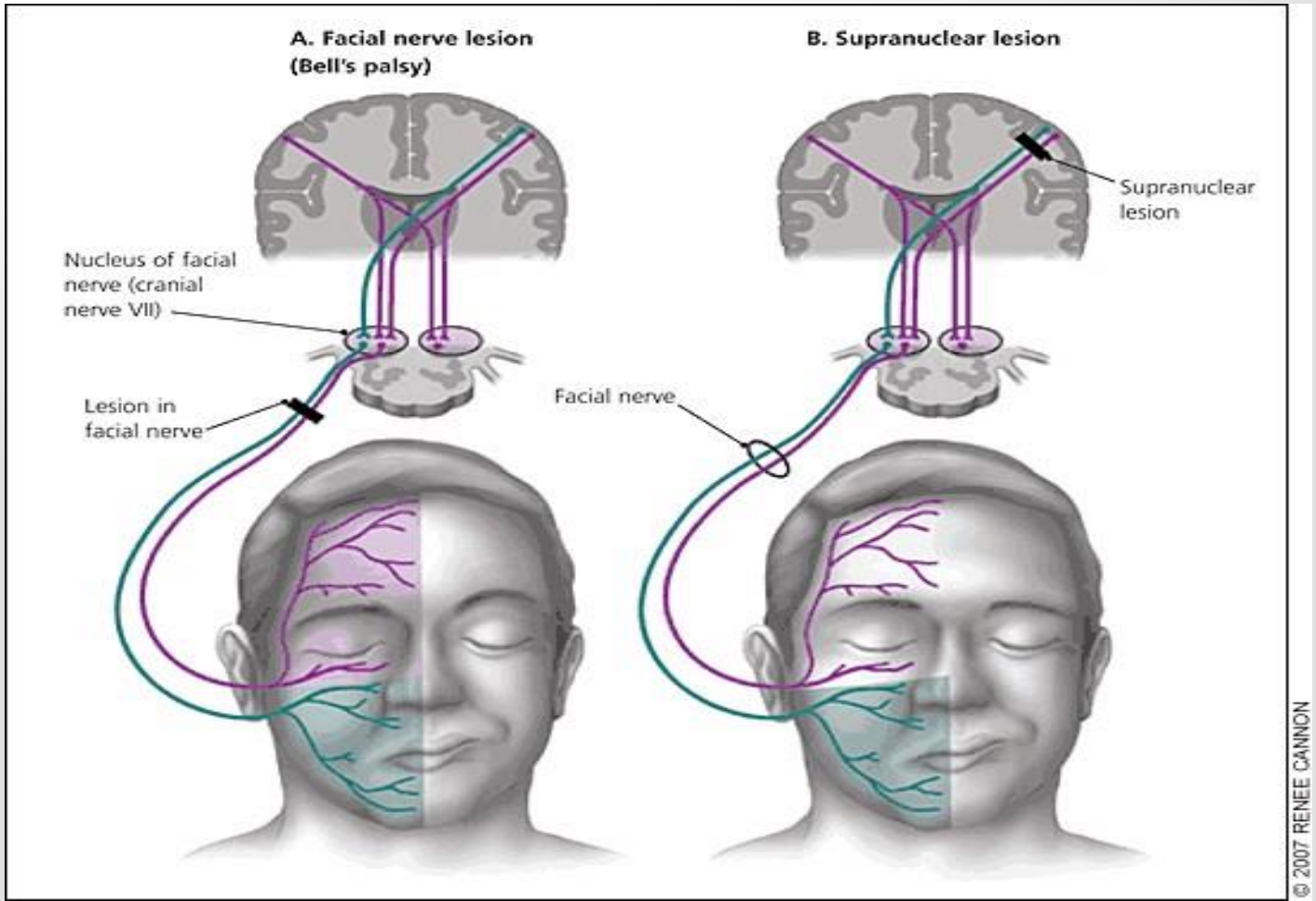
- The pathway of the facial nerve is long and relatively convoluted, and so there are a number of causes that may result in facial nerve paralysis.

- The most common is Bell's palsy,
  an idiopathic disease that may only be diagnosed by exclusion.

- Facial nerve paralysis may be divided into **supranuclear (central) and infranuclear (peripheral)** lesions.

Facial nerve lesion (N. VII)

Peripheral **Central**



Central - SUPRANUCLEAR facial lesion

can be caused by a lacunar infarct (stroke)

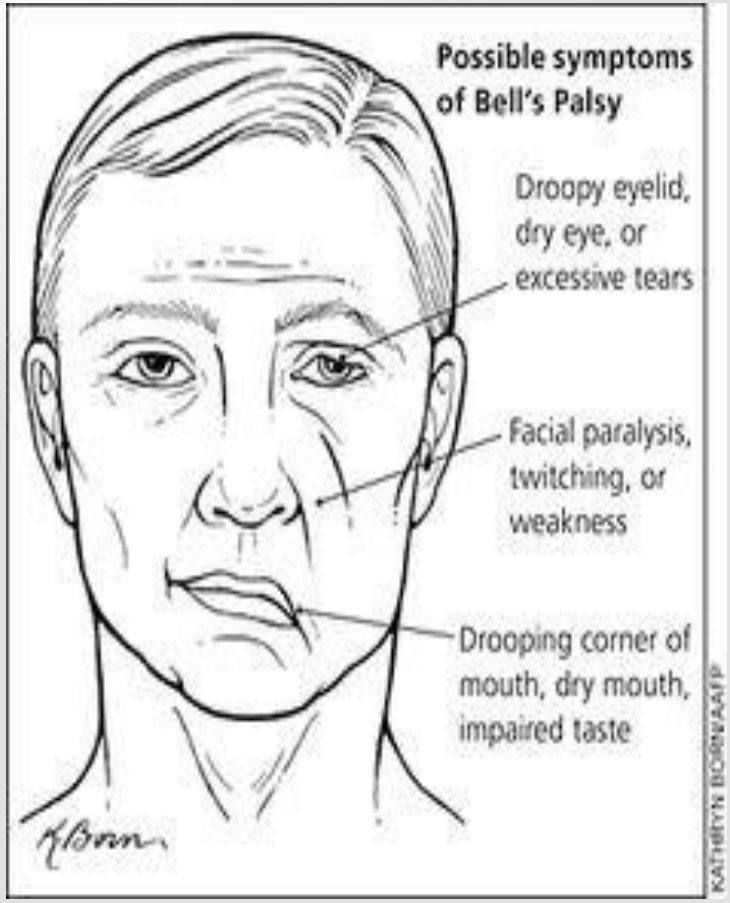
Symptoms:

weakness of the muscle of the lower part of the face opposite to the damage side

Peripheral = INFRANUCLEAR LESION

Symptoms:

- characterised by unilateral weakness of face,
- loss of taste
- hyperacusis
- decreased salivation and tear secretion
- acute facial pain radiating from the ear may precede the onset of other symptoms.



Causes of Facial Paralysis

Cause	Description or Examples
Congenital	Möbius syndrome, Vascular anomaly, Hemifacial microsomia, Goldenhar, Poland, Melkersson-Rosenthal, Other syndromes, No associated syndrome
Birth-related	Traumatic or difficult delivery
Bell's	Unknown cause, Viral infection
Traumatic injury	Temporal bone fracture, Blunt force to cheek, Laceration, Swelling involving facial nerve
Infectious	Ear infections, Lyme disease, Viral infections (VZV (Ramsay Hunt), HSV, EBV), Mycoplasma, Mastoiditis
Neoplastic	Central, Parotid, or Acoustic tumors
Iatrogenic	Brain, Middle ear, and Facial surgery
Ischemic	Loss of blood supply to the nerve or muscle
Neurogenic	Guillan-Barré
Hematologic	Leukemia, Hemophilia
Hypertension	High blood pressure

Facial paralysis: investigation and diagnosis:

- medical history,
- neurological examination,
- laryngological examination with audiometry and tympanometry
- blood tests (CRP, Borrelia, thyroid function)
- CT / MR of temporal bone/ brain,
- ophthalmological consultation
- lumbar puncture
- EMG/ENG

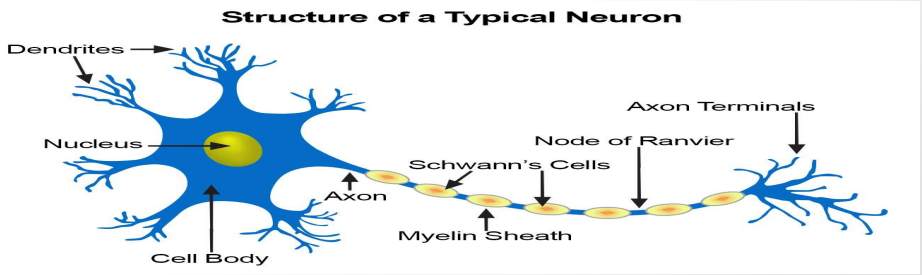
Treatment of the peripheral facial palsy

- steroids (i.v. or oral or locally)
- witamins B
- Eye protection (moisturizing drops, Corneregel, sticking the eye overnight)
- rehabilitation (exercises for mimic muscles, massage, solux, laserotherapy, electrostimulation)

Depending on the medical history and research results:

- Herpes virus type 1 and 2, varicella zoster: Acyclowir (i.v.) or p.o. Heviran
- Borreliosis (ceftriaxon, doxycyklinum)

Guillain – Barre syndrome (GBS)



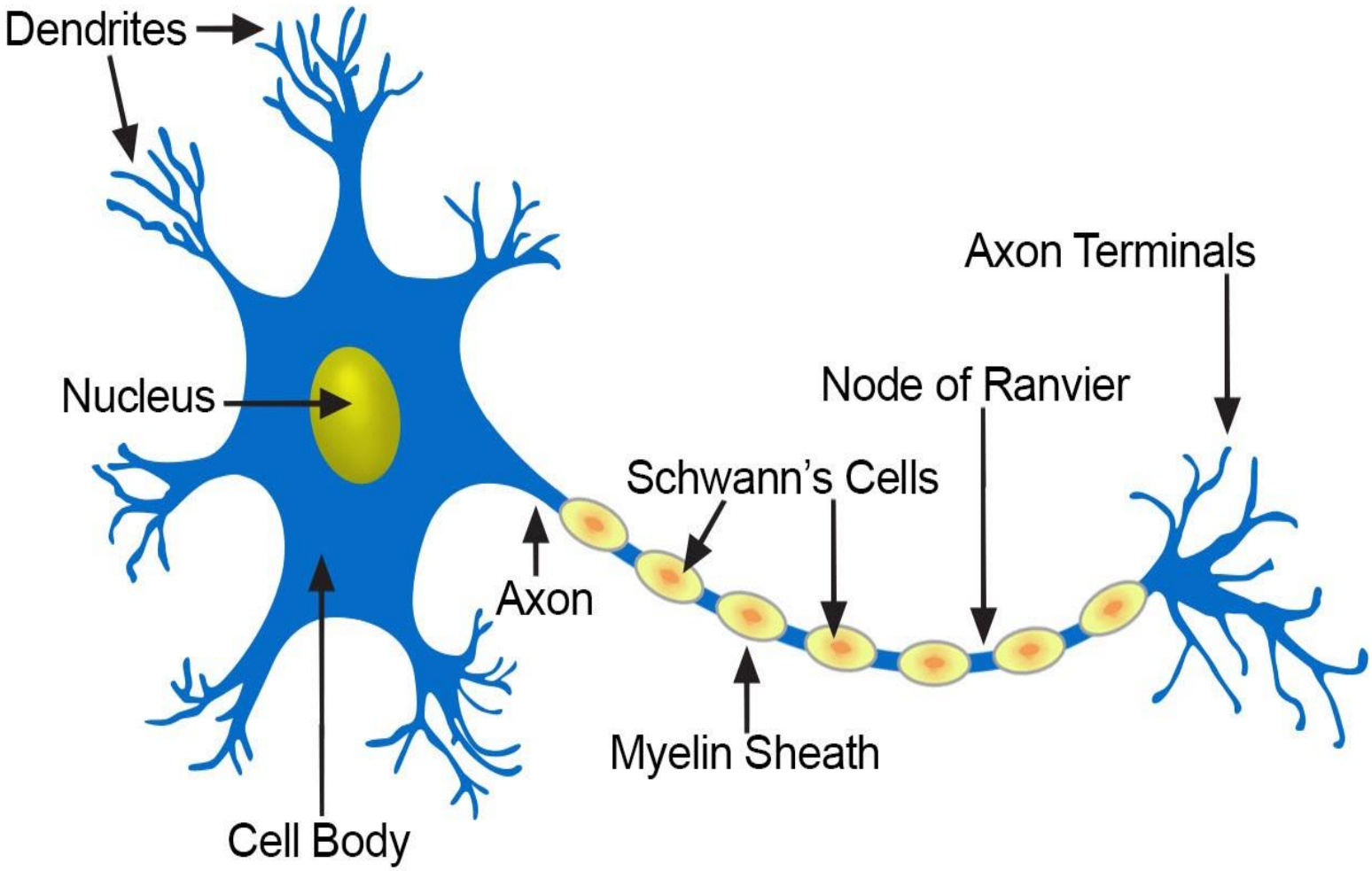
- acute polyneuropathy
- rapid-onset symmetrical muscle weakness , both sides equally, cranial nerve is involved in 50%
- changes in sensation or pain is reported by the patient
- some are affected by changes in the function of the autonomic nervous system, which can lead to dangerous abnormalities in heart rate and blood pressure
- the symptoms develop over half a day to two weeks to reach the maximum, then plateau phase, then improvement
- during the acute phase, the disorder can be life-threatening with about a quarter developing weakness of the breathing muscles and requiring mechanical ventilation (in 25 %)

Guillain – Barre Syndrome (GBS)

- This is autoimmune disease caused by the body's immune system mistakenly attacking the peripheral nerves and damaging their myelin sheath.
- Molecular mimicry - the production of antibodies after an infection - the immune system is reacting to microbial substances but the resultant antibodies also react with substances occurring naturally in the body.

- GBS very often is triggered by an infection of upper respiratory system or diarrhoea 3-6 weeks before or some vaccination.
- Causes: Campylobacter jejuni, Mycoplasma pneumoniae, viruses (EBV, CMV, Varicella zoster, influenza, RSV, Zika, SARS- CoV 2)

Structure of a Typical Neuron



Different types of Guillain–Barré syndrome feature different types of immune attack:

- 1/ the demyelinating variant (AIDP) features damage to the myelin sheath by white blood cells (T lymphocytes and macrophages) this process is preceded by activation of a group of blood proteins known as complement
- 2/ the axonal variant is mediated by IgG antibodies and complement against the cell membrane covering the axon without direct lymphocyte involvement

Guillain – Barre syndrome (GBS)- diagnosis:

- The signs and symptoms: rapid development of muscle paralysis, absent reflexes, neurological examination : reduced power and reduced or absent tendon reflexes (hypo or areflexia)

Medical history (disease/ vaccination in the past 2-3 weeks

- Examination of cerebrospinal fluid (CSF): "albuminocytological dissociation" - increased of spinal fluid protein concentration but a normal cell count

Despite this, the CSF is unremarkable in 50% of people with Guillain–Barré syndrome in the first few days of symptoms, and 80% after the first week; therefore, normal results of CSF do not exclude the condition

Guillain – Barre syndrome (GBS)- diagnosis:

- nerve conduction studies (ENG) and electromyography (EMG) – demyelinization or/and axonal abnormalities.

But in the first two weeks, these investigations may not show any abnormalities so neurophysiology studies are not required for the diagnosis

- MRI of the spinal cord - enhancement of the nerve roots
- antigangliosyde antibodies, onconeuronal antibodies
- Mycoplasma pneumoniae, EBV, borreliosis, chest X-ray, abdominal ultrasonography

Type	Symptoms	Population affected	Nerve conduction studies	Antiganglioside antibodies
Acute inflammatory demyelinating polyneuropathy (AIDP)	Sensory symptoms and muscle weakness, o^en with cranial nerve weakness and autonomic involvement	Most common in Europe and North America	Demyelinating polyneuropathy (↓CV)	No clear association
Acute motor axonal neuropathy (AMAN)	Isolated muscle weakness without sensory symptoms in less than 10%; cranial nerve involvement uncommon	Rare in Europe and North America, substantial proportion (30–65%) in Asia and Central and South America; sometimes called "Chinese paralytic syndrome"	Axonal polyneuropathy (↓ amplitude) , normal sensory action potential	GM1a/b, GD1a & GalNac–GD1a
Acute motor and sensory axonal neuropathy (AMSAN)	Severe muscle weakness similar to AMAN but with sensory loss			
Miller Fisher syndrome	Ataxia, eye muscle weakness (ophtalmoplegia), areflexia but usually no limb weakness	This variant occurs more commonly in men than in women (2:1 ratio). Cases typically occur in the spring and the average age of occurrence is 43 years old	Generally normal, sometimes discrete changes in sensory conduction or H-reflex detected	GQ1b, GT1a

GBS Treatment:

- Immunotherapy: intravenous immunoglobulins (IVIG) or plasmapheresis

both are equally effective, but IVIG is usually used first in practice

IVIG total therapy 2g/kg usually 0,4 g/kg/ day

x 5 doses

- Pain medication
- Rehabilitation

- Mechanical ventilation /Intensive care - in case of Respiratory failure

MYOPATHY

- usually proximal weakness
- usually no sensory deficit
- reflexes preserved until late
- fasciculation absent
- contractures usually present
- muscle tenderness

- may be associated with myocardial dysfunction : rhythm and/or conduction disturbances, dilated cardiomyopathy

Inherited forms of myopathy:

- Muscular dystrophies
- Myotonia
- Congenital myopathies with microscopic changes (nemaline myopathy- with nemaline rods, minicore myopathy, centronuclear myopathy)
- Mitochondrial myopathy - defects in mitochondria, which provide a critical source of energy for muscle
- Metabolic myopathies: glycogenosis: Pompe disease : treatment is available - Myozyme (alglukozydaza alfa), lipidoses

Duchenne's muscular dystrophy (DMD)
Becker's muscular dystrophy (BMD)

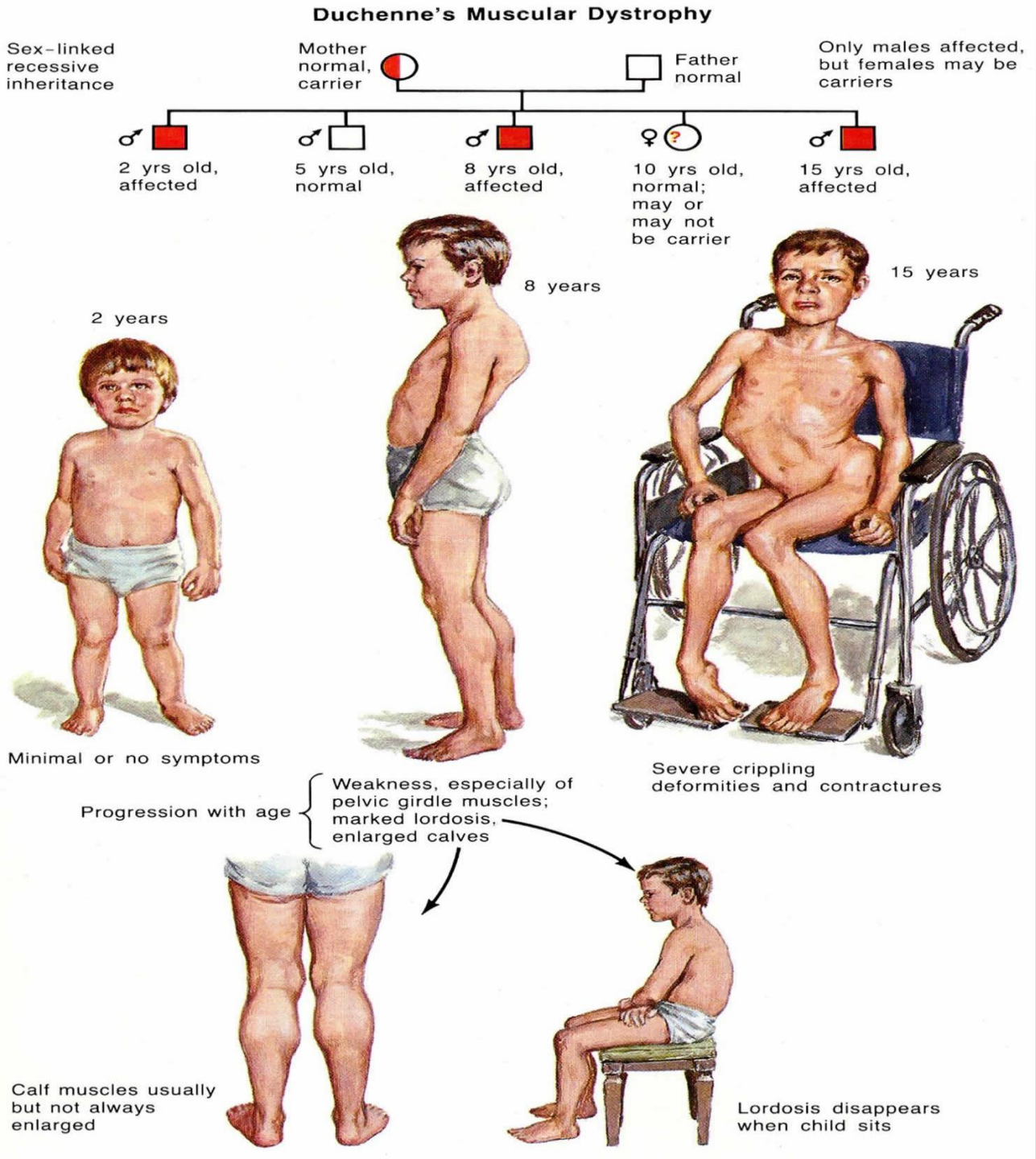
- The pattern of BMD symptom development resembles that of DMD but with a later, and much slower rate of progression.
- an X-linked recessive inherited disorder (carrier females, affected boys)
- a mutation of the dystrophin gene at locus Xp21, located on the short arm of the X chromosome which codes for the protein dystrophin
- Dystrophin is an important component within muscle tissue that provides structural stability to the dystroglycan complex of the cell membrane.

Muscular dystrophy

Dystrophin is important component of the muscles which provides structural stability of muscles

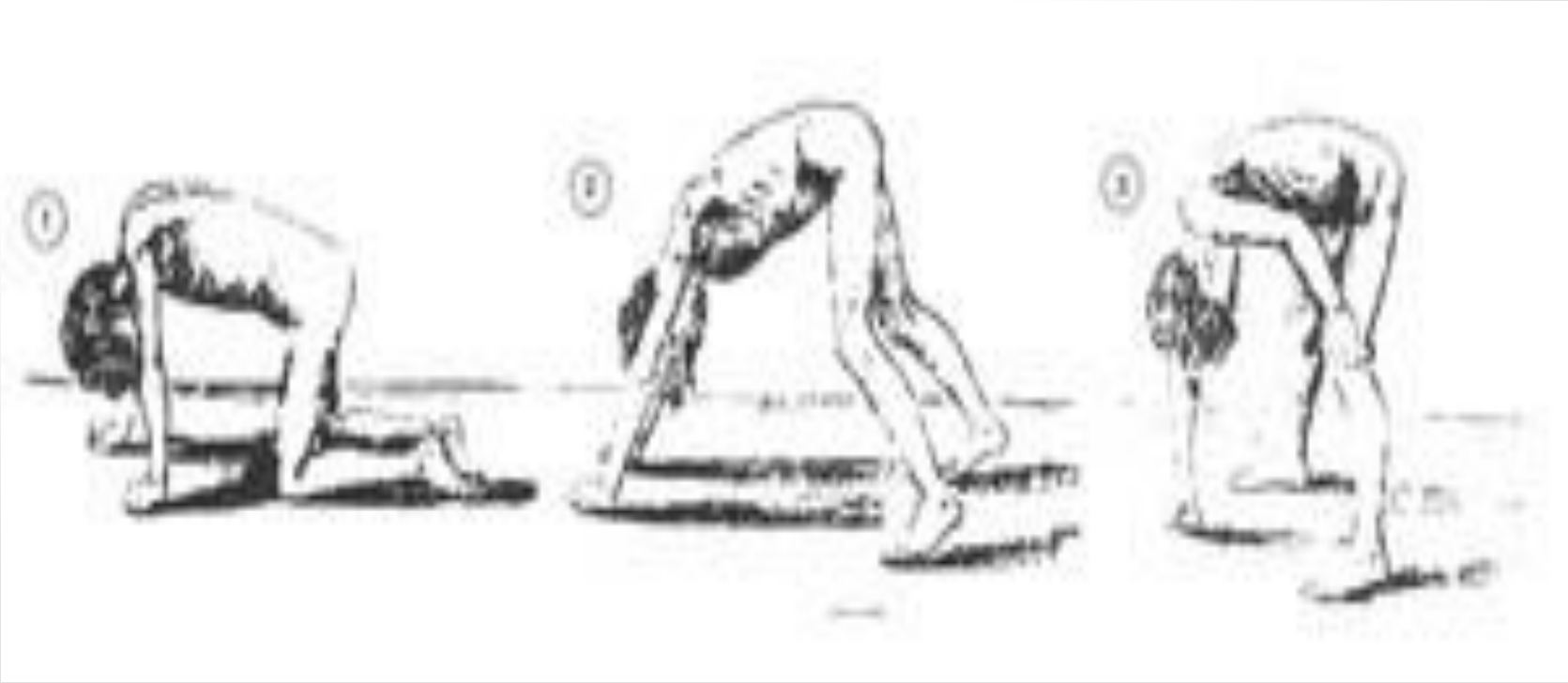
In affected muscle the tissue becomes disorganized and the concentration of dystrophin (green) is greatly reduced, compared to normal muscle.

Normal **Dystrophy**


Duchenne's Muscular Dystrophy
Sex-linked recessive inheritance
Mother normal, carrier
Father normal
Only males affected, but females may be carriers
2 yrs old, affected
5 yrs old, normal
8 yrs old, affected
10 yrs old, normal; may or may not be carrier
15 yrs old, affected
2 years
8 years
15 years
Minimal or no symptoms
Severe crippling deformities and contractures
Progression with age
Weakness, especially of pelvic girdle muscles; marked lordosis, enlarged calves
Calf muscles usually but not always enlarged
Lordosis disappears when child sits

DMD signs

- Boys are affected, first signs about 3 - 4 years of old
- Frequent falls
- Fatigue
- Difficulty with motor skills (running, hopping, jumping)
- Trouble getting up from lying or sitting position
- A positive Gower's sign reflects the more severe impairment of the lower extremities muscles. The child helps himself to get up with upper extremities: first by rising to stand on his arms and knees, and then "walking" his hands up his legs to stand upright.



Gowers' sign

DMD signs:

- Lumbar hyperlordosis
- Muscle contractures of Achilles tendon
- Progressive difficulty walking
- Muscle fibre deformities
- Pseudohypertrophy (enlarging) of tongue and calf muscles. The muscle tissue is eventually replaced by fat and connective tissue, hence the term pseudohypertrophy.

- Higher risk of neurobehavioral disorders (e.g., ADHD), learning disorders (dyslexia) and non-progressive weaknesses in specific cognitive skills (in particular short-term verbal memory), which are believed to be the result of absent or dysfunctional dystrophin in the brain.

DMD signs:

- Eventual loss of ability to walk (usually by the age of 12)
- Skeletal deformities (scoliosis)

- Abnormal heart muscle (dilated cardiomyopathy)
- Congestive heart failure or irregular heart rhythm (arrhythmia) – Echocardiography and ECG is required

- Respiratory disorders, including pneumonia and swallowing with food or fluid passing into the lungs (in late stages of the disease)

DMD/BMD - DIAGNOSIS:

- Creatinine kinase (CPK) levels in the bloodstream are extremely high !!!

- DNA test: The muscle-specific isoform of the dystrophin gene is composed of 79 exons, and DNA testing and analysis can usually identify the specific type of mutation of the exon or exons that are affected.

DNA testing confirms the diagnosis in most cases.

- Prenatal test possible

- Muscle biopsy

- EMG – myogenic changes but not specific for DMD/BMD

DMD- Treatment :

Treatment is generally aimed at controlling the onset of symptoms to maximize the quality of life, and include the following:

- corticosteroids - increase energy and strength and defer severity of some symptoms
- Ataluren (Translarna) in walking patient > 2 years of old with nonsense mutation
- Mild physical activity such as swimming is encouraged; inactivity can worsen the muscle disease
- Physical therapy is helpful to maintain muscle strength, flexibility, and function
- Orthopedic appliances (such as braces and wheelchairs) may improve mobility and the ability for self-care. Form-fitting removable leg braces that hold the ankle in place during sleep can defer the onset of contractures
- Appropriate respiratory support (vaccinations !!!) as the disease progresses is important
- Cardiologic care (echo, ECG, Holter ECG)

Acguired forms of myopathy:

- external substance induced myopathy : drug induced (statins, glucocorticoid), alcoholic, other toxic agents
- dermatomyositis
- polymyositis

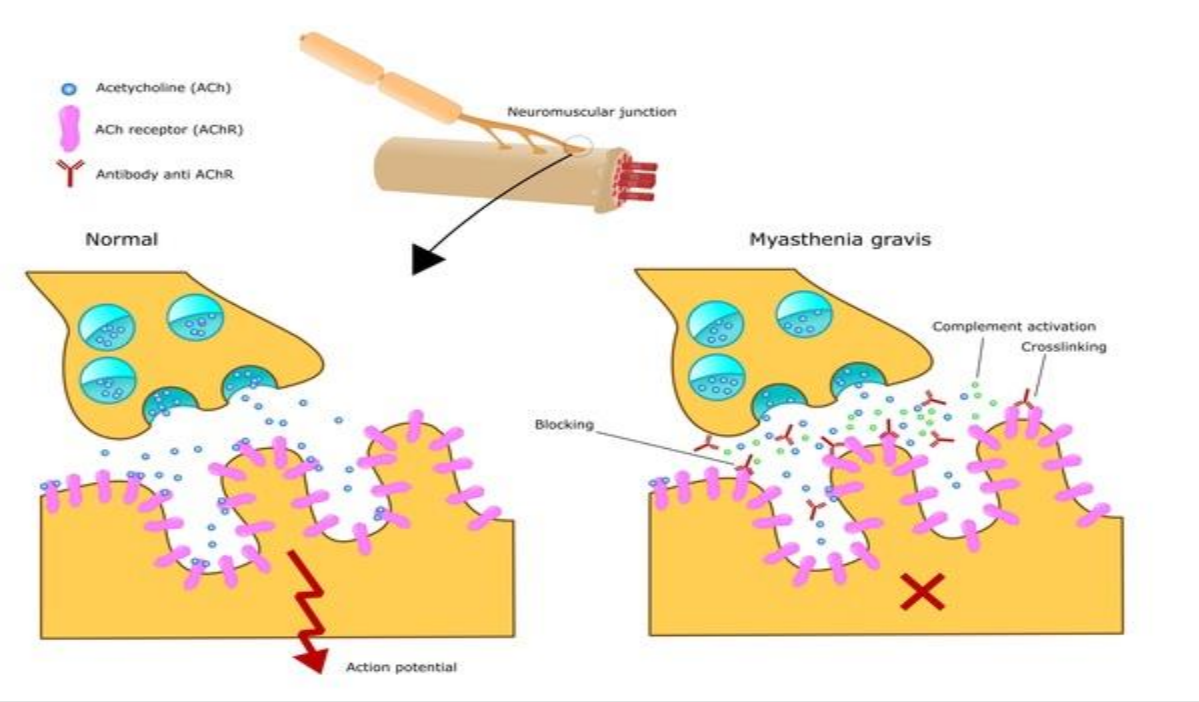
- BACM (Benign Acute Childhood Myositis): mainly boys 6-9 years old, few days flu-like symptoms then severe pain in the calves, inability to walk, very high CK !!!!

Influenza virus type B, adenoviruses, enteroviruses

Feature	Neuropathic	Myopathic
Distribution of weakness	Distal	Proximal
Reflexes	Absent	Usually Present
Sensory loss	Usually present	Absent
Atrophy	Present	Absent until late
CPK	Normal	Elevated
Nerve conduction Velocity	Usually decreased	Normal
EMG	Fibrillations and fasciculations	Small motor units
Muscle biopsy	Group atrophy	Irregular, necrotic fibers

MYASTENIA GRAVIS:

- Fluctuating muscle weakness and fatigue
- In the most common cases, muscle weakness is caused by circulating antibodies that block acetylcholine receptors at the postsynaptic neuromuscular junction, inhibiting the excitatory effects of the neurotransmitter acetylcholine on nicotinic receptors at neuromuscular junctions.



Myasthenia gravis (MG) signs:

- Apokamnosis - The muscle weakness becomes progressively worse during periods of physical activity, and improves after periods of rest.

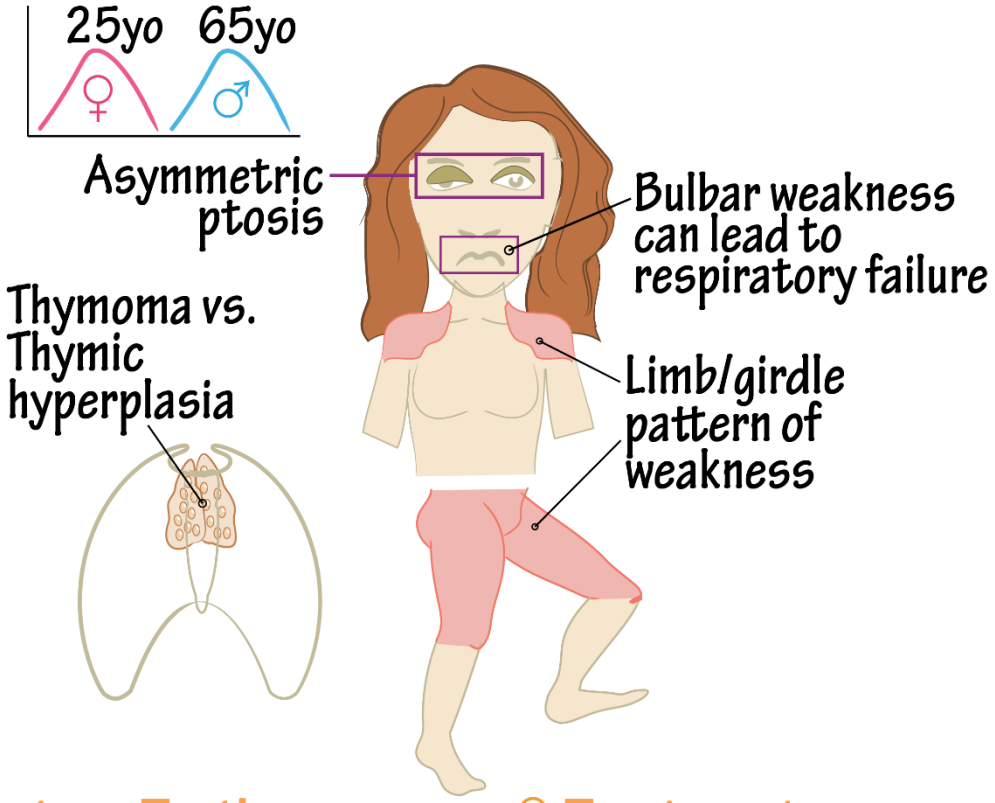
- In about two-thirds of individuals, the initial symptom of MG is related to the muscles around the eye. There may be eyelid drooping (ptosis- weakness of levator palperbae superioris) and double vision (diplopia due to weakness of the extraocular muscles)
- Dysphagia, dysarthria, hypophonia
- Facial weakness - manifesting as inability to hold the mouth closed (the "hanging jaw sign")

- In a myasthenic crisis - a paralysis of the respiratory muscles

Myasthenia gravis diagnosis:

- Serology - test for antibodies against the acetylcholine receptor (anti-AChR) and/or antibodies against the Muscle - Specific Kinase (anti-MuSK)
- CT/MR of mediastinum - myasthenia very often associated with thymoma
- Positive test with Tensilon
- EMG: repetitive nerve stimulation (RNS) and single fibre test (SF- EMG)

Myasthenia Gravis



Laboratory Testing

- AchR Ab ~ 85% Generalized MG
- MuSK Ab ~ 40% of Non-AchR Ab

EMG/NCS

Repetitive stim. at slow frequency (2-3 Hz)

Treatment

- *Symptomatic*: Pyridostigmine
- *Immune suppression*: Steroids, azathioprine, etc...
- *Rescue*: Plasmapharesis and IVIG

Myasthenia gravis management:

- acetylcholinesterase inhibitors - to directly improve muscle function (Mestinon, Mytelase)
- immunosuppressant drugs to reduce the autoimmune process.
- Thymectomy is a surgical method to treat MG.
- Myasthenia crisis – plasmapheresis/IVIG

SMA - spinal muscular atrophy

- Autosomal recessive disease caused by a genetic defect in the SMN1 gene, which encodes SMN
- SMN is apparently selectively necessary for survival of motor neurons, as diminished abundance of the protein results in loss of function of neuronal cells in the anterior horn of the spinal cord and subsequent system-wide muscle wasting
- SMA types: I , II, III, IV
- Areflexia
- Muscle weakness, poor muscle tone - "Floppy baby syndrome"
- Difficulty achieving developmental milestones, difficulty sitting/standing/walking
- Loss of strength of the respiratory muscles: weak cough, weak cry (infants)
- Fasciculation
- Serum creatine kinase (CK) may be normal or increased
- Genetic testing: deletion of exon 7 of the SMN1 gene, number of gene SMN2 copies

➢ Treatment is available for all types of SMA : Nusinersen (since 1 Jan 2019 refunded for all types of SMA)

➢ Gene therapy (Zolgensma)


TREAT-NMD
Neuromuscular Network


SMA Europe


fundacja
SMA


EUROPEAN
CMT
FEDERATION
Together we are stronger


EURORDIS
RARE DISEASES EUROPE


Orphan
Krajowe Forum na rzecz terapii chorób rzadkich

Thank You