Myasthenia gravis

Myopathy

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Myasthenia gravis and myasthenic syndromes

MG- epidemiology

- Incidence: 14.8 / mil. inhabitants
- Prevalence: 191 /mil. inhab. /Slovakia 2007/
- Disease onset: mostly: 30. year (F), 60.-70. year (M)
- Sex rate F:M= 1,7:1
- No hereditary cases, familial increased susceptibility for autoimmune disease (HLA)

MG- manifestation

- Clinical symptoms: progradient muscle weakness during daily activities, with evening acces, repair after rest time
- Onset: small muscles – eye (diplopia), pharynx (dysphagia), soft palate (rhinolalia), general ...
- Thymus abnormalities - ¾ of MG patients
- 85% - hyperplasia
- 15% - thymoma (benign / malign)

Acquired autoimmune disease

Ab+ Ach-Receptor => functional block and destruction => decrease postsynaptic actional potential => insufficient muscle contraction => muscle weakness

Antibodies against Ach-R (Acetylcholine Receptor), or other antigens of postsynaptic membrane (titin, MUsK-enzyme, ...)

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MG- disease course

- **Subjective**: abnormal muscle fatigue, weakness - paresis, recovery after resting
- **Objective**:
  - repetitive muscle activity provokes weakness - ptosis, diplopia, rhinolalia, dysphagia, dysarthria, dysphonia
  - weak of jawing, mimic paresis
  - neck decrease
  - short breathing
  - tendon reflexes - presented or slight decrease

MGFA (Foundation of America)- Clinical symptoms scaling (Osserman's classification)

1. Ocular form MG
2. Ocular + slight generalised MG (limbs / bulbar)
3. III: Moderate weakness of ocular + extraocular muscles (limbs, respiratory, bulbar muscles)
4. IV: Severe weakness of ocular + extraocular muscles
5. V: Respiratory failure, suported ventilation

MG- diagnosis

1. History and clinical picture
2. EMG
3. Laboratory tests: serum antibodies anti-Ach-R (75% positivity)
4. Clinical tests: Simpson's test - vertical gaze
   Seeman's test - dysarthria
   Gorelick's test
   pharmacol. Tensilon test: iv. amp. inhibit. AchE
5. X-rays chest, mediastinal CT, MRI

Static and dynamic (repetitive) tests

- Demasking of latent MG or enhancing of present muscle weakness
  - **Simpson's test** - slight ptosis - patient is looking upward 1 minute - more severe ptosis
  - **Gorelick's sign** - bilateral asymmetrical ptosis: patient is looking up, finger elevation of eyelid opposite side, on contralateral side wa can see total decrease
  - (pathognomic for MG)

MG- EMG

- EMG - repetitive stimulation, low freq. stimulation - 3Hz
  Abnormality: **gradual decrement of response amplitude**
- min. 15%, max. in the 2.- 4. response, normalization of EMG after Tensilone inj.

MG- therapy

Currently - no deaths, previously - 30% mortality

1. **Pharmacological**: IS + symptomatic th
2. **Surgical** – thymectomy

**Pharmacological therapy**:

- Immunosupression: Prednisone, Azathioprine, Cyclosporine A
- Plasma exchange or IVIG
- inhibit ChE (Pyridostigmine, Mestinon)
**LEMS, Lambert- Eaton myasthenic syndrome**

- A rare autoimmune disorder of the limb
- Antibodies against presynaptic voltage-gated calcium channels, and likely other nerve terminal proteins
- Prevalence: 3.4 cases/million
- Around 60% of LEMS have an underlying malignancy, small cell lung cancer, paraneoplastic syndrome
- KP: fatigue, weakness of proximal mm., inferior extremities, spared eye and bulbar mm.
- Autonomic difficulties: dry mouth, low lacrimation, orthostatic collapses, impotence

**LEMS**

High frequency repetitive EMG (30 Hz) => gradual increase of AP amplitude

**Therapy:**

steroids, Azathioprine, plasma exchange

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**Transient neonatal myasthenia**

- 10-15% of myasthenic patients
- Transplacental Ab penetration
- Transient clinical symptoms - 2-5 weeks
- Spontaneous elimination of Ab from child organism
- Th: CHE inhibitors, steroids

**Myopathy**

- **Classification:**
  1. Progressive muscular dystrophies
  2. Congenital myopathy (structural lesions)
  3. Myotonia / myopathies of ionic channels
  4. Myotonic dystrophy
  5. Myopathies caused by toxic substances
  6. Familial periodic palsy
  7. Endocrine myopathies
  8. Metabolic myopathies (mitochondrial)
  9. Inflammatory myopathy - myositis, dermatomyositis

**Myopathy**

- **Muscular symmetric weakness!**
  - Limb girdle muscles, duck gait, hyperlordosis, body "climbing", pseudohypertrophy, muscle atrophy, cramps, myalgia
- **Laboratory tests:**
  - high CK, LDH, aldolase, myoglobin
- **Muscle biopsy:**
  - Muscular degeneration, necrosis
- **EMG:** pattern of myopathy
Progressive muscular atrophy
- Myopathy
  - Tendon jerks - decreased or absent
  - Progressive muscle atrophy
  - CSF - normal
  - MRI mm.spectroscopy (31P) - shows energetic metabolism abnormalities
  - CT or MRI – abnormal muscle density - early subclinical abnormalities
  - Molecular genetics - gene analysis, abnormal gene identification (PCR)

Progressive muscular dystrophy
- Duchenne muscular dystrophy-dystrophinopathy
  - Gene abnormality of dystrophin protein (muscle, brain, heart)
  - Gene mutation Xp21: abnormal muscle metabolism
  - Clinical symptoms: boys, disease onset between 2-5 yr.
  - Hyperlordosis, duck gait
  - Climbing, unable to run
  - Freq. falls, altar scapules, PHT of legs, scoliosis
  - Immobility at least 13 yrs, death about 30 yrs
  - 1/3 mental retardation
  - 1% cardiomyopathy – lethal complications

Duchenne muscular dystrophy-dystrophinopathy
- Diagnosis: onset age, clin. symptoms + labs + EMG + biopsy
  - Blood: extreme high CK, myoglobin
  - Biopsy - dystrophin absence, degenerative changes, atrophy, regenerative changes

Becker muscular dystrophy-dystrophinopathy
- 5x decreased incidence than Duchenne m.d.
- more benign
- inability of gait - about 30 yrs
- surviving about 40 - 50 yrs
- mental retardation, scoliosis, CMP - not present
- biopsy - dystrophin is present (small %)
- individual disease course - different prognosis
**Duchenne MD (DMD)**

![Duchenne MD Image]

**Muscular dystrophy**

- **EDMD- Emery- Dreifus MD-** X-chrom linked, protein emerin, onset 6.-12.y., benign slow progression of musc. weakness, CMP-limit of surviving (AV block)
- **Facio-scapulo-humeral dystrophy:** 20.y., facies myopathica, benign course
- **Limb- girdle muscular dystrophy-** benign forms, 20.-40.y., deficit of sarcoglycan adhaline
- **Distal muscular dystrophy**
- **Ocular muscular dystrophy**
- **Oculo-pharyngeal muscular dystrophy**

**Other progressive muscular dystrophies**

1. DMD (A)
2. BMD (A)
3. Emery- Dreifus MD (B)
4. Limb girdle MD
5. Facioscapulo-humeral MD (D)
6. Distal MD (E)
7. Oculopharyngeal myopathy (F)
8. Ocular myopathy

**Myositis - inflammatory myopathy**

- **A – infectious**
  - viral: Coacktie B, ECHO, influenza
  - bacterial: staph., tbc, borreliosis
  - parasitic: trichinelosis, cysticercosis, toxoplasmosis
  - myotic

- **B - autoimmune**
  - Polymyositis - PM
  - Dermatomyositis - DM
  - Inclusion body myositis - IBM

**Dermatomyositis / DM**

- **Children, young adults**
- **Skin changes:** red, extensor areas, facial „butterfly“ erythema, violet “periortbital edema, “heliotropic rush”, pulmonary and cardial complications
- DM and PM are often associated with collagen diseases (scleroderma, polyarteritis nodosa, RA, Sjogren sy) – „overlap sy“
Dermatomyositis

Fig 1A-C — Features of dermatomyositis(A) are discoloration of the upper eyelids, peri-orbital edema, malar rash, and dry, shiny, erythematous skin on the forehead. Cutaneous papules of the hands/feet show erythematous and slightly scale. Bases on the metacarpophalangeal joints. Dermatomyositis of the chest(C) shows an exanthematous eruption in a macular distribution over light-exposed areas. Reprinted from the Clinical Side Effects of the Rheumatic Disease, copyright 1991, 1995. Used by permission of the American College of Rheumatology.

Polymyositis / PM

- Older persons, paraneoplastic syndrome (10%)
- severe disease course, high lethality
- proximal mm. weakness
- myopathic syndrome (dysphagia, dysphonia)
- myalgia
- atrophy, contractures, immobility, ...

PM, DM, IBM

- Labs: high CK, LDH, myoglobin, CKI, C3, Ig, ANF
- EMG: myopathic pattern
- Biopsy: immune complexes (IgG, IgM, C3) deposits in vessel wall of muscles resulting to muscle infarctions and muscle fibre necrosis, atrophy
- Therapy: steroids, CPA, Cyclosporine, MTX, Azathioprine, PE
- IBM - chronic progressive course, old patients, paraneo sy, slow atrophy, dysphagia, inclusion bodies (Alzheimer of muscle), therapeutic resistance(steroids)

Metabolic myopathies

- Glycogenosis - multisystemic disease (muscles, liver, kidney, myocard)
- Pompe’s disease - hypotonia, CMP, hepatomegaly, infantile and adult forms,
- Mc Ardle’s disease
- Carnitine myopathy — „floppy infant sy”, proximal weakness, CMP
- Th. Carnitine substitution

Mitochondrial myopathy

- Kern- Sayre syndrome
- MELAS - mitoch. encephalomyelopathy lactate acidosis stroke
- MERRF- mitoch. encephalopathy ragged red fibre myopathy
- Alpers’s disease
- NARP
- LHON

Toxic myopathy

- Acute myopathy: vincristine, narcosis
- Chronic myopathy: steroids, lithium, digoxin, Ca-blockers, beta-blockers, D-penicillamine, Zidovudin (anti-HIV)
- Myositis: AE-hydantoinates, procainamide, L-Dopa, PNC
- Rhybdomyolysis, fibrosis: heroin, amfetamine, methadon, isoniazid, barbiturates, ...
- Local muscle atrophy or myopathy: steroid inj., opiates, chlorpromazin, diazepam,...
### Endocrine myopathy

- **Thyroid hyperfunction**: myopathy, myalgia, atrophy, orbitopathy, diplopia
- **Thyroid hypofunction**: myalgia, cramps, myoedema, myopathy, weakness
- **Steroid myopathy**: girdle atrophy, myalgia, PM
- **Hyperparathyreosis**
- **Acromegalia**
- **Diabetes mellitus**