MULTIPLE SCLEROSIS

Multiple Sclerosis (MS)
- MS: chronic inflammatory disease of the CNS
- of autoimmune character
- with damage of myeline and axons
- Inflammatory infiltrates /lesions: disseminated in the white and gray matter
- Periventriculary, in corpus callosum, brain stem, cerebellum and spinal cord

Epidemiology
- Occurrence: young adults
- Onset: 20-40 year
- F: M = 2 : 1
- Prevalency, Slovakia: 100 -150 / 100 000 inhabitants

Genetics of MS
- MS etiology is polyfactorial:
  - genetic + external enviromental factors
    (smoking, obesity, vitamin D deficiency)
- „Susceptibility“ to MS - 30 genes

Etiopathogenesis
Trigger factor of MS onset:
- INF-γ, viral infection (EBV, CMV, Herpetic virus)
- A. loss of T-Ly cells tolerance to own antigens
- B. antigen similarity (molecular mimicry)

MS - Etiopathogenesis
- activated T-H1 cells admitt to CNS =>
  cytokines (TNFα, IL-2, INFγ) activate Ma, B-Ly, antibodies production => myeline destruction
- perivascular infiltrate T-Ly, macrofages
  => demyelinating lesion-plaque (Sclerose en plaque)
**Etiopathogenesis**

Myelin loss + variable degree of axon damage → progressive degeneration and nervous pathways atrophy → neurodegeneration, astrogliosis (plaque)

**Disease course, MS forms**

- **Relaps - remitting form / RRMS** 55-85%
  - a half of them go on to SP form after cca 10 years of disease course (1 attack-CIS, Clinically isolated syndrome)
- **Primary progressive form / PPMS** 15%
- **Secondary – progressive form / SPMS**
- **Relapsing – progressive form / RPMS** 5%
- **CIS- Clinically isolated syndrome, the first clinical manifestation of MS**

**Symptoms of MS**

- Neurological symptoms are caused by conductive block, or slowing of neuronal impulses in demyelinating fibers
  - Axonal loss - irreversible symptoms
- Depends on localization of the lesion, the pathway in which the lesion is located
  - Summation of residual symptoms after relapses
- Overall clinical stage is progressive worsening

**EDSS Scale / John F. Kurtzke/**

Disability grading scale in MS:

<table>
<thead>
<tr>
<th>Functional systems:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Vision</td>
</tr>
<tr>
<td>2. Brain stem</td>
</tr>
<tr>
<td>3. Motor/pyramidal system</td>
</tr>
<tr>
<td>4. Sensory</td>
</tr>
<tr>
<td>5. Cerebellum</td>
</tr>
<tr>
<td>6. Sphincters</td>
</tr>
<tr>
<td>7. Mental and mood problems- fatigue, cognitive, depression, anxiety</td>
</tr>
<tr>
<td>8. Ambulation</td>
</tr>
</tbody>
</table>

**EDSS scale (Kurtzke)**

Expanded Disability Status Scale - modified scale of John Kurtzke; 0 (min.) - 10 (max.) - impairment, disability
MS onset, the first episode = Clinically isolated syndrome/CIS – monofocal or multifocal manifestation

Optic neuritis
- Unilateral optic nerve inflammation
- Blurred vision
- Retrobulbar pain
- Good prognosis of partial or completed recovery

Myelitis
- Cervical segments
- Partial transverse lesion
- Sense difficulties
- Motor difficulties
- Lhermitte sign
- Sfincter problems
- Sense of "belt"
- Chest numbness
- Acute dystonia

Brainstem- cerebellar syndrome
- Oculomotor palsy (internuclear ophthalmoplegia)- diplopia
- Nystagmus
- Sensitive syndromes
- Vertigo, ataxia
- Hemiparesis
- Trigeminal neuralgia
- Hemifacial spasm
- Cerebellar ataxia, dysarthria
- Rubral tremor

Clinical symptoms
There is no symptom specific only for MS!

- Vision - blurred vision, scotoma, loss of colors, blindness, pain of eye bulb with movements
- Eye bulb movement disorder - diplegia (IV,VI, nerve), ophthalmoplegia, nystagmus
- V, VII, VIII, IX nn. lesion - neuralgia, paroxysmal vertigo
- Sensitivity disease - tactile, vibratory, paresthesias, dysesthesias, hypesthesia, anesthesia, ...

- Movement disorders - spastic paresis, or plegia, MP, HP, PP, TP, KP
- Cerebellar symptoms - ataxia, dysarthria, intention tremor, titubations
- Sfincter dysfunction - imperative micturition, urine retention, incontinence
- Cognitive dysfunction - deficit of attention, concentration, memory, information processing speed
- Fatigue
- Autonomic dysfunction - arrhythmia, hyperhidrosis, orthostatic hypotension, cold and cyanosis of limbs, ...
**Prognosis of MS**

- Depends on
  - frequency of relapses in the first 2 years
  - period between 1. a 2. relapse

After 10 years - 50% of pts disable to work
After 25 years - 50% of pts disable to walk
- Total surviving is 7 years shorter than common population (immobility, decubitus, infections, ...)

**Disease progression**

- Relapsing form
- Secondary-progressive
- Relaps-remitting
- Subclinical Mono-symptomatic

**MS diagnosis**

Presence of lesions disseminated in the CNS in time and space !!!

1. History, clinical course
2. Neuroimaging CNS
3. CSF
4. Evoked potentials

No of paraclinical investigative method is specific for MS !!!

**Magnetic resonance (MRI)**

- T2-weighted imaging - hyperintensive lesions in the white matter, periventricularly
- T1-weighted imaging – hypointensive lesions= axonal loss, progressive brain atrophy
MS diagnostic McDonald criteria 2010 - DIT and DIS

- DIS-2 or more T2 lesions in typ.location
- DIT - new T2 lesion on Gd+ enhancing lesion

Pathol. results:
- conduction slowing
- complete block of impulse spreading
- abnormal wave shape

Evoked potentials, EP
- Evidence of clinical asymptomatic, silent lesions
- Pathol. results:
  - conduction slowing
  - complete block of impulse spreading
  - abnormal wave shape
Evoked potentials, EP

- **VEP**: visual EP
- **SEP**: somatosensory EP
- **BAEP**: auditory brainstem EP
- **MEP**: motor EP

**CSF evaluation**

Useful in establishing MS and differential diagnosis

- ✓ Total proteins: normal (up to 400 mg/l)
- ✓ Presence of plasmatic cells (plasmocytes - B-Lymphocytes)

**VEP, visual EP**

- Prolonged latency of P100 wave – positivity in 90% persons after ON, 50% patients without ON history

**CSF evaluation**

- ✓ Intrathecal synthesis of IgG - IgG index
- ✓ Oligoclonal bands - IgG antibodies - 95% of MS

**Differential diagnosis**

- Tumors of CNS – glioma, dif dp: PET, CSF, biopsy
- Intervertebral disc lesion - spinal cord compression
- AV vascular malformation - AG, DSA
- Neuroborreliosis - Lyme disease, CSF Ab detection
- CNS vasculitis, SLE
- Hereditary spinal / spinocerebellar ataxia
- Leucodystrophy – adult onset
- Mitochondrial diseases
- Stroke - lacunar, cardioembolic, arterial hypertension
- Celiakia
**Differential diagnosis**

- Stroke, lacunar infarcts
- SLE

**Differential diagnosis**

- Adrenoleucodystrophy
- Borrelia

**Differential diagnosis**

- Arterial hypertension
- Hashimoto thyroiditis

**Neuromyelitis optica (NMO, Devic disease)**

- Optic nerve and spinal cord demyelination
- Antibodies against aquaporin-4 receptor (NMO-IgG)
- MRI lesions over 3 spinal segments, brain MRI is normal or with non-MS lesions

**Infectious inflammatory diseases**

- Neurorickettsiosis
- PML
- SSPE

**Toxo-metabolic diseases**

- Central pontine and extrapontine myelinolysis
- Drug-induced (methotrexate, cyclosporine) demyelination
Hypoxic-ischemic diseases
- Arterial hypertension, diabetes mellitus, dyslipidemia
- Hereditary thrombophilias
  - FV Leiden
  - MTHFR mutation
  - Hyperhomocysteinemia
  - protein C and protein S deficit

MS treatment
- we are able to influence only active, inflammatory phase of disease- not later neurodegenerative disease course
- we cannot stop the disease at all, only to slow and subdue severity of neurological symptoms

MS treatment
1. **Immunosuppressives** - corticosteroids, cytostatics
2. **Immunomodulation** - INF-beta, glatirameracetate, natalizumab, fingolimod, teriflunomide, dimethylfumarate
3. Symptomatic treatment
4. Fyzioterapia

Treatment of attack / relapse
**CORTICOSTEROIDS**
- Methylprednisolone i.v. – infusion,
- 2,5-5g, then Prednison p.o. 30-80mg tbl/day, with slow dose decrease

**CYTOSTATICS** – steroid nonresponders

Long-term treatment
High disease activity – DMT=disease modifying treatments
**IMMUNOMODULANTS / IMMUNOSUPPRESSANTS:**
- INF-beta:RRMS, ↓relapses, Effic:35-45%, ↓ARR and relaps severity
- Glatirameracetate : RR MS
- Teriflunomide
- Dimethylfumarate
- Natalizumab – monoclonal Ab anti VLA4 adhesive molecule, eff. 75%
- Fingolimod - selective immunosupressant, efficacy 55%
- Alemtuzumab- monoclonal Ab anti-CD52 Ly
- Ocrelizumab (2016-2017)
Symptomatic treatment

1. **SPASTICITY**: stiffness, spasms  
   Central myorelaxances - Baclofen, Tizanidine  
   Analgetics, Botulotoxin, Cannabinoids
2. **SFINCTER DYSFUNCTION**:  
   • Retention: intermittent autocathetrisation  
   • Incontinence: anticholinergics, ADH / night
3. **TREMOR**: clonazepam, beta-blockers, talamic electrostimulation / VLnc.

4. **Tonic spasms and trigeminal neuralgia**: carbamazepine, pregabalin, gabapentin
5. **Fatigue**: amantadine