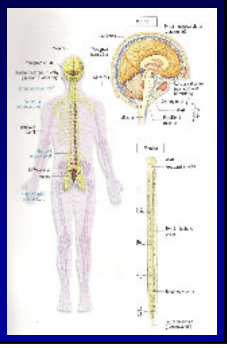
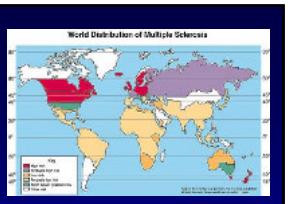
MULTIPLE SCLEROSIS

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



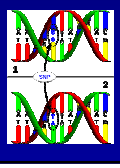
Epidemiology



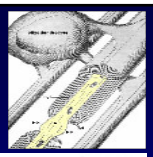
- **Occurance:** young adults
- **Onset:** 20- 40 year
- **F: M – 2 : 1**
- **Prevalency, Slovakia: 100 -150 / 100 000 inhabitants**

Genetics of MS

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



Etiopathogenesis

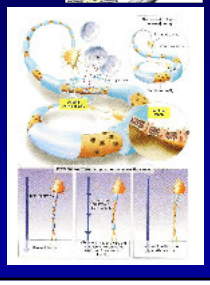


Trigger factor of MS onset:

- **î INF-γ,viral infection (EBV, CMV, Herpetic virus)**

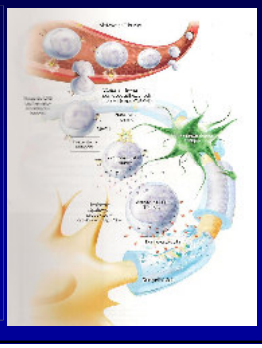
A loss of T-Ly cells tolerance to own antigens

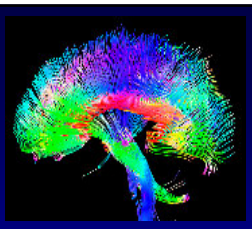
B antigen similarity (molecular mimicry)

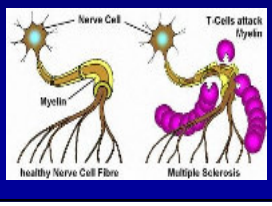


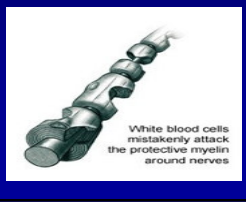
MS - Etiopathogenesis

- **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 => demyelinative lesion-plaque (Sclerose en plaque)**



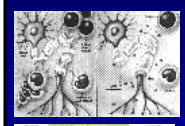


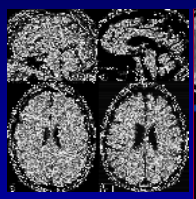


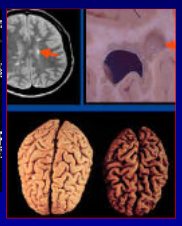


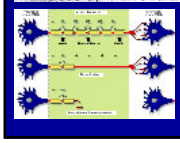
Etiopathogenesis

myelin loss + variable degree of axon damage = > progredient degeneration and nervous pathways atrophy = > neurodegeneration, astrogliosis (plaque)



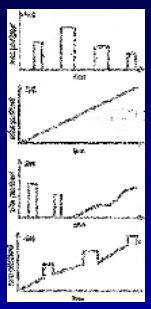






Disease course, MS forms

- 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- Clinicaly isolated syndrome, the first clinical manifestation of MS*



Symptoms of MS

- neurol. symptoms are caused by conductive block, or slowing of neuronal impulses in demyelinative 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
- owerall clinical stage is progressive worsening

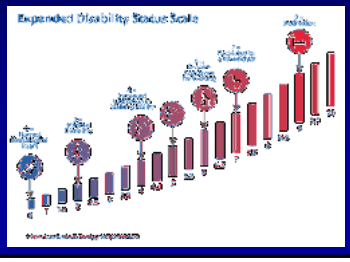
EDSS Scale /John F. Kurtzke/

Disability grading scalein MS:

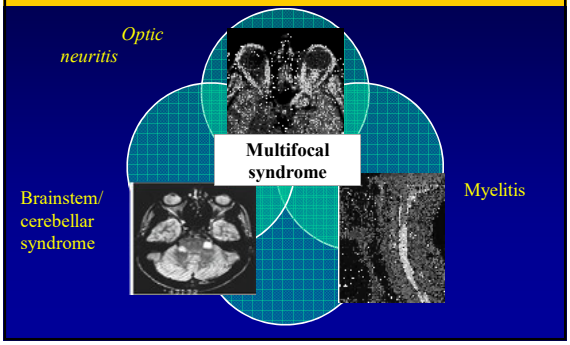
Functional systems:
1.Vision
2.Brain stem
3.Motor/pyramidal system
4.Sense
5.Cerebellum
6.Sfincters
7.Mental and mood problems- fatigue, cognitive f., depression, anxiety
8. Ambulation

EDSS scale (Kurtzke)

- ***Expanded Disability Status Scale*** - modificated scale of John Kurtzke; 0 (min.) - 10 (max.) - impairment, disability

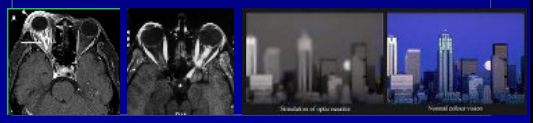


MS onset, the first episode = Clinicaly isolated syndrome/CIS – monofocal or multifocal manifestation



Optic neuritis

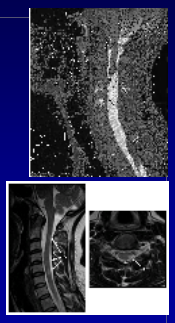
- Unilateral optice nerve infammation
- Blurred vision
- Retrobulbar pain
- Good prognosis of partial or completed recovery



Myelitis

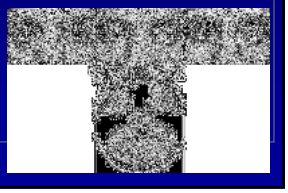
- Cervical segments
- Partial transverse lesion

- Sense difficulties
- Motor difficulties
- Lhermitte sign
- Sfincter problems
- Sense of „belt"
- Chest numbness
- Acute dystonia



Brainstem- cerebellar syndrome

- Oculomotor palsy (Internuclear ophthalmoplagia)- diplopia
- Nystagmus
- Sensitive syndromes
- Vertigo, ataxia
- Hemiparesis
- Trigeminal neuralgia
- Hemifacial spasm
- Cerebellar ataxia, dyzartria
- 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** - diplopia (III,IV,VI nerve), ophthalmoplegia, nystagmus
- **V, VII, VIII, IX nn. lesion** - neuralgia, paresthesia, vertigo
- **Sensitivity disease** - tactile, vibratory, paresthesias, dysesthesias, hypesthesia, anesthesia, ...

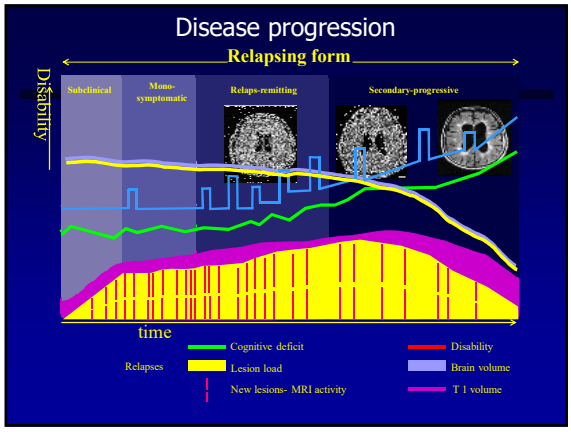
- **Movement disorders** - spastic paresis, or plegia, MP, HP, PP, TP, KP
- **Cerebellar symptoms** - ataxia, dysarthria, intention tremor, titubations
- **Sfincter dysfunction** - imperative micturition, urine retention, incontinence
- **Cognitive dysfunction** - deficit of attention, concentration,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

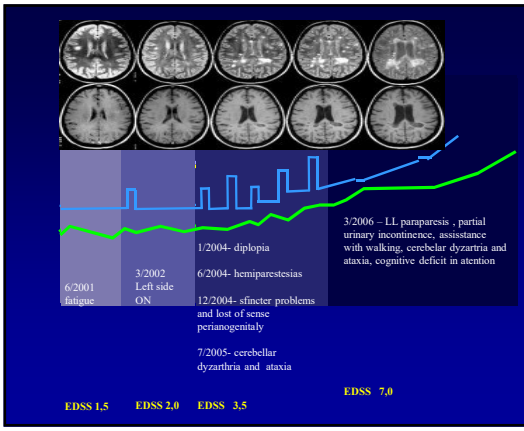
Prognosis of MS

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

After 10 years - 50% of pts disable to work
After 25 years - 50% of pts disable to walk

- Total surviving is 7 years shorten than common population (immobility, decubits, infections, ...)





MS diagnosis

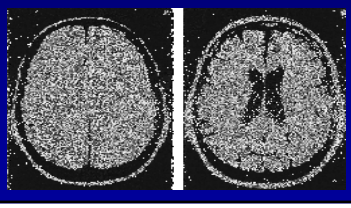
Presence of lesions disseminated in the CNS in time and space !!!

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

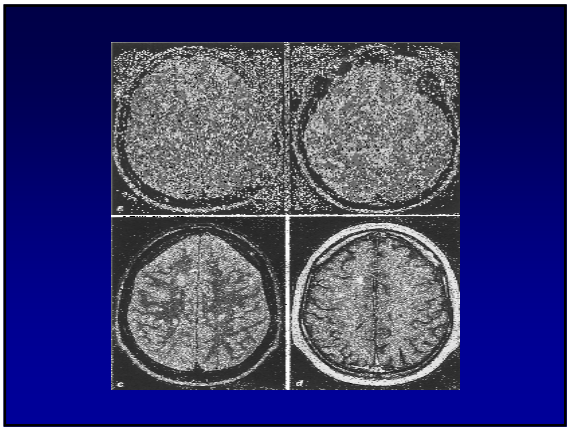
No of paraclinical investigative method is specific for MS !!!

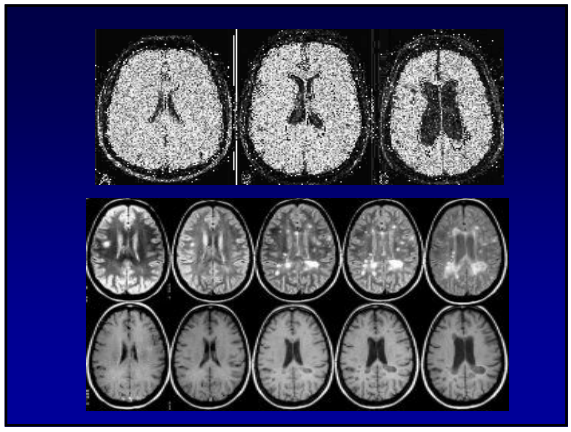
Magnetic resonance (MRI)

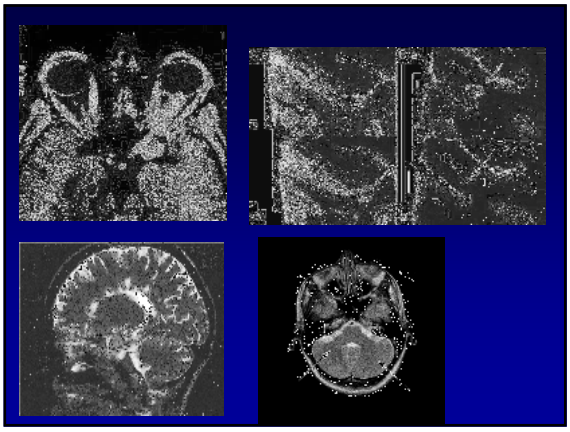
- T2-weighted imaging - hyperintensive lesions in the white matter, periventriculary
- T1-weighted imaging – hypointensive lesions= axonal loss, progressive brain atrophy

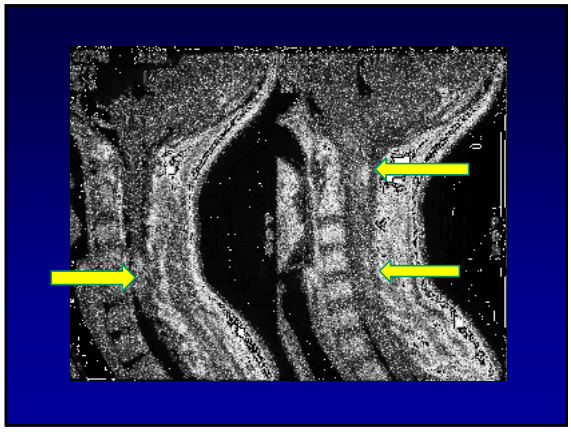


Magnetic resonance



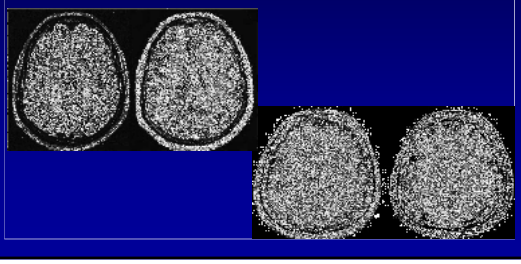






MS diagnostic McDonald criteria 2010 - DIT and DIS

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



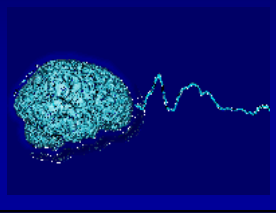
Evoked potentials, EP

- Evidence of clinical asymptomatic, silent lesions
-
- Pathol. results:

- conduction slowing
- complete block of impulse spreading
- abnormal wave shape

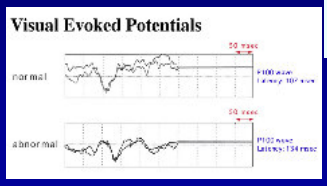
Evoked potentials, EP

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



VEP, visual EP

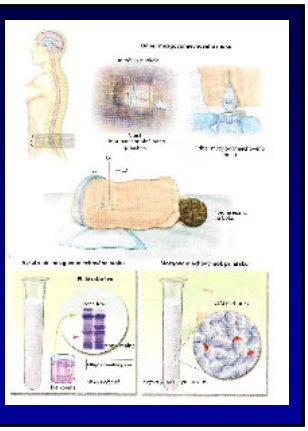
- **prolonged l atency of P100 wave – positivity in 90% persons after ON, 50 % patients without ON history**



CSF evaluation

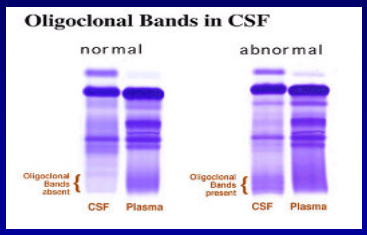
Useful in establishing MS and differential diagnosis

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



CSF evaluation

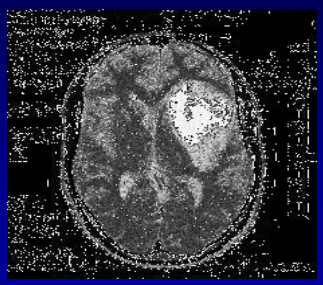
✓ Intrathecal synthesis of IgG - IgG index
✓ Oligoclonal bands -IgG antibodies- 95% of MS



Differential diagnosis

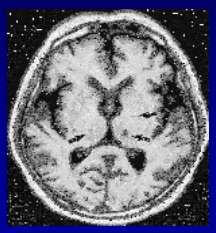
- Tumors of CNS – glioma, dif dg:PET, CSF, biopsy
- Intervertebral disc lesion- spinal cord compression
- AV vascular malformation - AG, DSA
- Neuroborreliosis - Lyme disease, CSF Ab detection
- CNS vasculitis , SLE
- Hereditary spinal / spinocerebellar ataxia
- Leucodystrophy – adult onset
- Mitochondrial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

Differential diagnosis

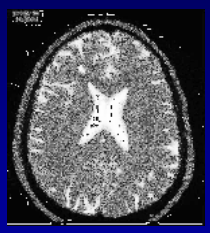


Differential diagnosis

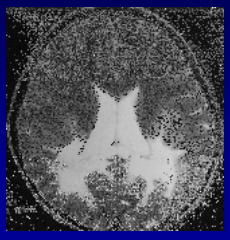
Stroke, lacunar infarcts



S lupus E



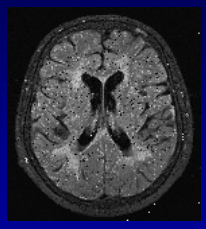
Differential diagnosis



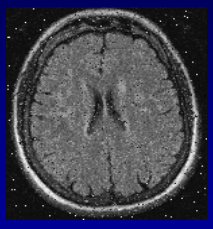
Adrenoleucodystrophy

Borreliosis

Differential diagnosis



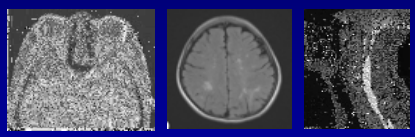
Arterial hypertension



Hashimoto thyroiditis

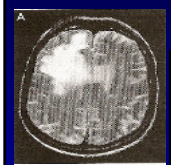
Neuromyelitis optica (NMO, Devic disease)

- 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

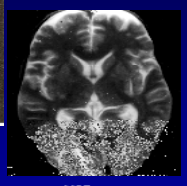


Wingerchuk DM, et al. Neurology. 2006

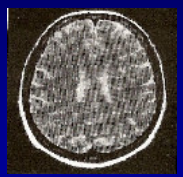
Infectious inflammatory diseases



PML

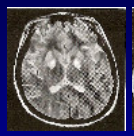


SSPE

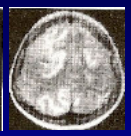


Neuroboreliosis

Toxo-metabolic diseases

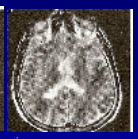


Intoxiication CO demyelinizäiation



Drug-induced

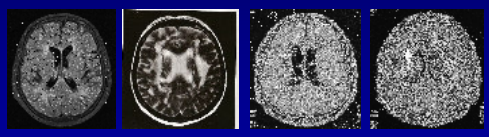
(metotrexát, cyklosporin)



Central pontinne and extrapontine myelinolysis

Hypoxic-ischemic diseases

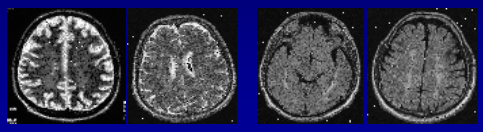
- Arterial hypertension, diabetes mellitus, dyslipidemia



Arterial hypertension Diabetes mellitus

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 neurodegeneratice disease course*
- *we cannot stop the disease at all, only to slow and subdue severity of neurological symptoms*

MS treatment

1. Immunosupressives - corticosteroids, cytostatics
2. Immunomodulation - INF-beta, glatirameracetate, natalizumab, fingolimod , teriflunomide, dimetylfumarate
3. Symptomatic treatment
4. Fyziotherapy

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

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Long-term treatment

High disease activity – DMT=disease modifying treatments

IMMUNOMODULANTS / IMMUNOSUPRESSANTS:

- INF-beta:RRMS, ↓relapses, Effic:35-45%,↓ARR and relaps severity
- Glatirameracetate : RR MS
- Teriflunomide
- Dimethylfumarate
- Natalizumab – monoclonal Ab anti VLA4 adhesive mol
- 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: intermitent autocathetrisation
- Incontinence: anticholinergics, ADH / night
3. **TREMOR:** clonazepam, beta-blockers, talamic electrostimulation / VLnc.

Symptomatic treatment

4. Tonic spasms and trigeminal neuralgia: carbamazepine, pregabalin, gabapentin

4. Fatigue: amantadine

5. Rehabilitation, fyziotherapy, psychotherapy, vitamins: D, B, E vit.