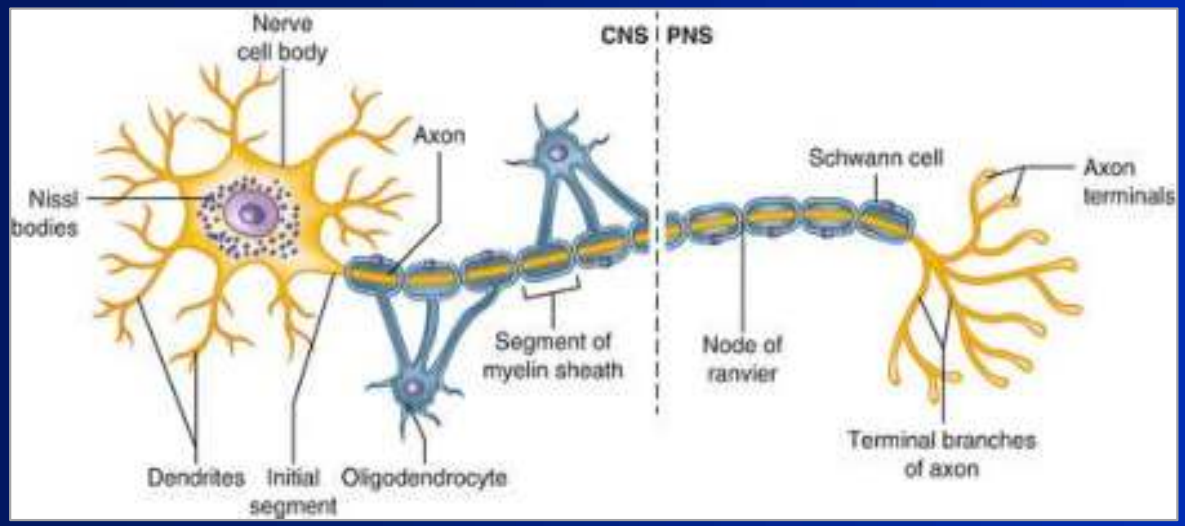
Demyelinating disorders
of the Central Nervous System

MULTIPLE SCLEROSIS
NMOSD
MOGAD
ADEM

Demyelinating disorders of the CNS

- Hereditary
- Acquired



van der Knaap,2005; Franklink, R. J. M. & ffrench-Constant, C. *Nature Reviews Neuroscience,* 2008.

Demyelinating disorders of the CNS

- Classification by etiology:

A - Acquired:

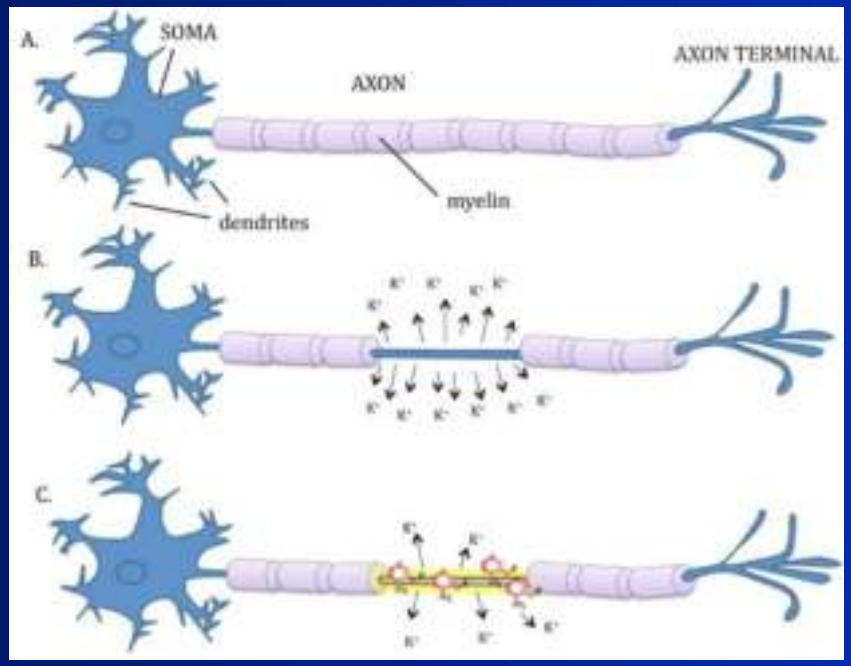
1. **Inflammatory non-infectious – immune- mediated** (MS, ADEM, NMOSD, MOGAD, CLIPPERS)
2. **Inflammatory infectious** (viral - PML, HIV, VZV)
3. **Metabolic, toxo-metabolic** (central pontine and extrapontine myelinolysis with hyponatriemia, alcohol liver disease, cyclosporine)
4. **Hypoxic-ischaemic** (AH, small vessel disease, KPR, MI, CO intoxication, cyanid)
5. **Focal compression** (trigeminal neuralgia)

B - Hereditary: leukodystrophia (AD, AR) childhood onset/adult onset

van der Knaap,2005.

Demyelinating disorders of the CNS - classification

- **Demyelination + axonal lesion**
- **Rupture and loss of axon = loss of neuron = neuro-degeneration**

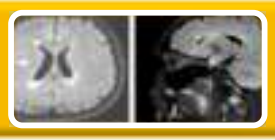


Vural A et al., Can J Neurol Sci. 2016;

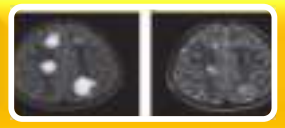
Differential diagnosis of diseases manifested by demyelination in the CNS

Primary, idiopathic, inflammatory demyelinating diseases	MS - Multiple sclerosis NMOSD - Neuromyelitis optica spectrum disorders MOGAD - Myelin- oligodendrocyte glycoprotein (MOG) - associated disease ADEM - Acute disseminated encephalomyelitis CLIPPERS - Chronic lymphocytic inflammation with pontinne perivascular enhancement responsive to steroids
Infectious diseases	Meningitis, encephalitis, PML, borreliosis, brain abscess, ventriculitis, rhombencephalitis
Genetic diseases	Leucodystrophy, Leber´s hereditary optic neuropathy, Fabry d., Alexander d., Cerebrotendinous xantomatosis, Krabbe d.
Metabolic diseases	B12 vitamin deficit, cupper deficit, Wernicke´s encephalopathy, Marchiafava-Bignami syndróm
Vascular diseases	Small- vessel disease, Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Susac syndrome, Primary CNS angiitis, A-V malformation, spinal cord infarction
Systemic immune mediated diseases	Systemic lupus erythematosus, Behçet d., Sarcoidosis, Sjögren syndrom
Neurodegenerative diseases	ALS, multisystemic atrophy
Headache	Migraine

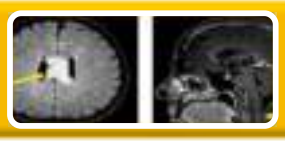
Primary demyelinating CNS disorders



MS (Multiple sclerosis)



ADEM



NMOSD (AQP4-NMOSD)

MOGAD

CLIPPERS

ADEM - Acute disseminated encephalomyelitis
NMOSD - Neuromyelitis optica spectrum disorders
MS - Multiple sclerosis
CLIPPERS - Chronic lymfocytic inflammation with pontine perivascular enhancement responsive to steroids
MOGAD - Myeline oligodendrocyte glykoprotein-associated diseases

Multiple Sclerosis (MS)

- **C**hronic inflammatory demyelinating and secondary neurodegenerative disease of the CNS
- The most common non-traumatic cause of chronic neurological disability in persons of productive age
- Autoimmune character
- Course and prognosis: lifelong disease with varying activity and prognosis

- Inflammatory infiltrates /lesions: disseminated in the white and gray matter - periventricular, corpus callosum, brain stem, cerebellum and spinal cord

Epidemiology

- **Prevalence: 36/100 000**
- **Europe: 108/100 000**
- **Occurance:** young adults
- **Onset:** 20 - 40 year
- **F: M – 3 : 1**
- **Most common onset: 32 yrs**
- **Prevalency, Slovakia: 120 / 100 000 inh.**

Etiology

- The causes of MS are unknown
- Heterogeneous conditional non-hereditary disease
- Etiology: multifactorial + interactions between genetic susceptibility and environmental risk factors
- Triggering factor: viral infections + loss of tolerance of T-Ly to own tissues (antigenic similarity, molecular mimicry)

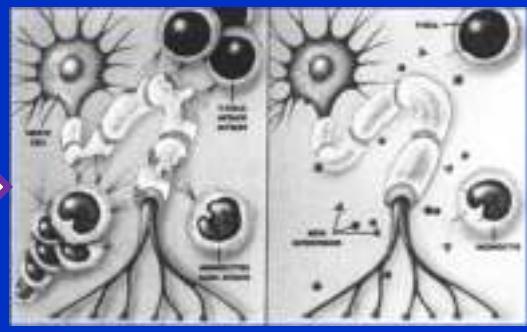
MS - Etiology

Environmental factors and life style

- Deficit vitamin D (pregnancy, childhood)
- Infection Epstein–Barr vírus in adolescence
- Infections v. Rubeola, VZV, Herpes, Morbilli
- Smoking tabacco (active and passive)
- Lack of sun exposition
- Obesity in adolescence
- Night work
- Alcohol, nicotine, caffeine,, organic solvents
- Intestinal dysmicrobia

Genetic factors

- **Susceptibility genes**
- **Genes of HLA system**
- **Sex (females)**
- **Single nucleotide polymorfism**
- **50 genes suspected**
- alels HLA-DR-B1
- Familiar occurrence **10–30 %**
- the child's risk of developing MS if he has a parent with MS is **2-5%**



Olsson, et al. Nat. Rev. Neurol. 2017; Celarain and Tomas-Roig, J. J Neuroinflammation 2020

Pathogenesis

Activated TH1-Ly and B-Ly in the blood enter the CNS

↓

CD4+ and CD8+ T-Ly activation

↓

Macrophages + B-Ly - interferon-gamma, TNF-alpha, cytokines

↓

Inflammation, focal and diffuse, myelin damage = demyelination + exposed axons = axonal loss- brain atrophy, neuroaxonal loss

↓

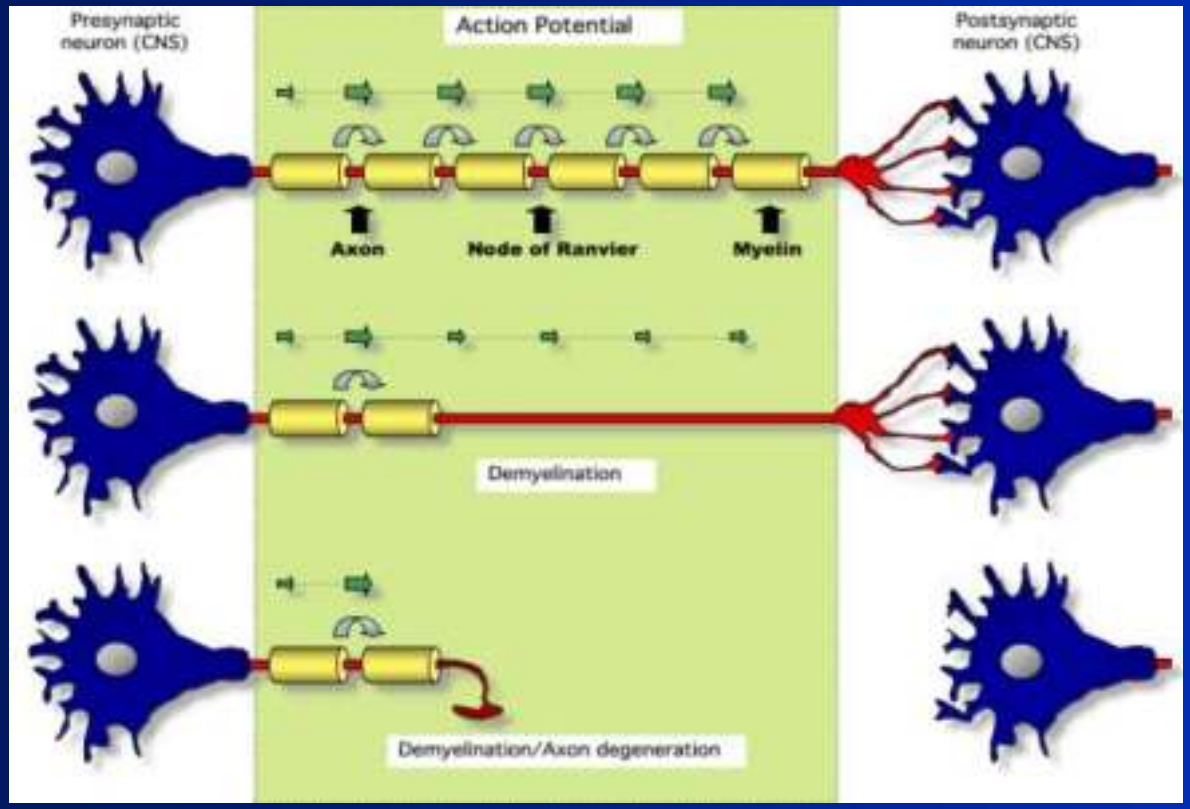
Accumulation of lesions (plaques) in the white and gray matter around post-capillary venules

↓

Lesions localization: periventricular, corpus callosum, brainstem, cerebellum, spinal cord

Pathogenesis

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

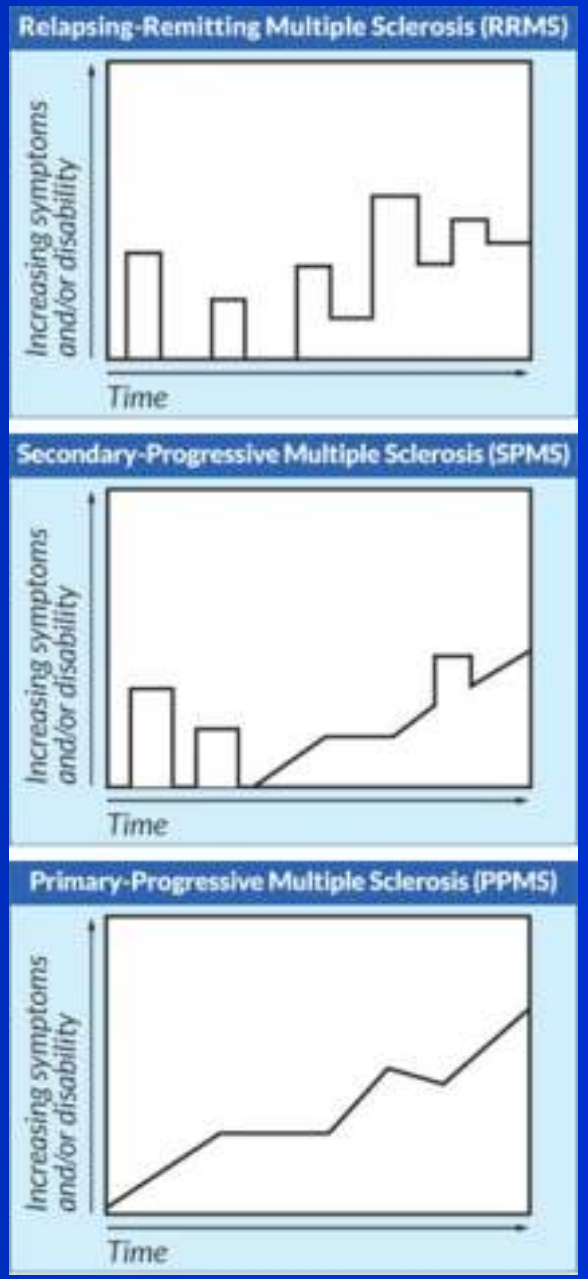


Disease course, MS forms, phenotypes

- **Relapsing-remitting form / RRMS 55-85%**
- CIS - Clinicaly isolated syndrome= the first clinical manifestation of MS - RRMS

- **Secondary – progressive form / SPMS**
- 50-80% of RRMS go on to SP form after approx. 7-15 yrs of disease course

- **Primary progressive form / PPMS 10-15%**



https://mymsaa.org/ms-information/overview/types/

Symptoms of MS

- Caused by conductive block, or slowing of neuronal impulses in demyelinative fibers
- + axonal loss - irreversible deficit

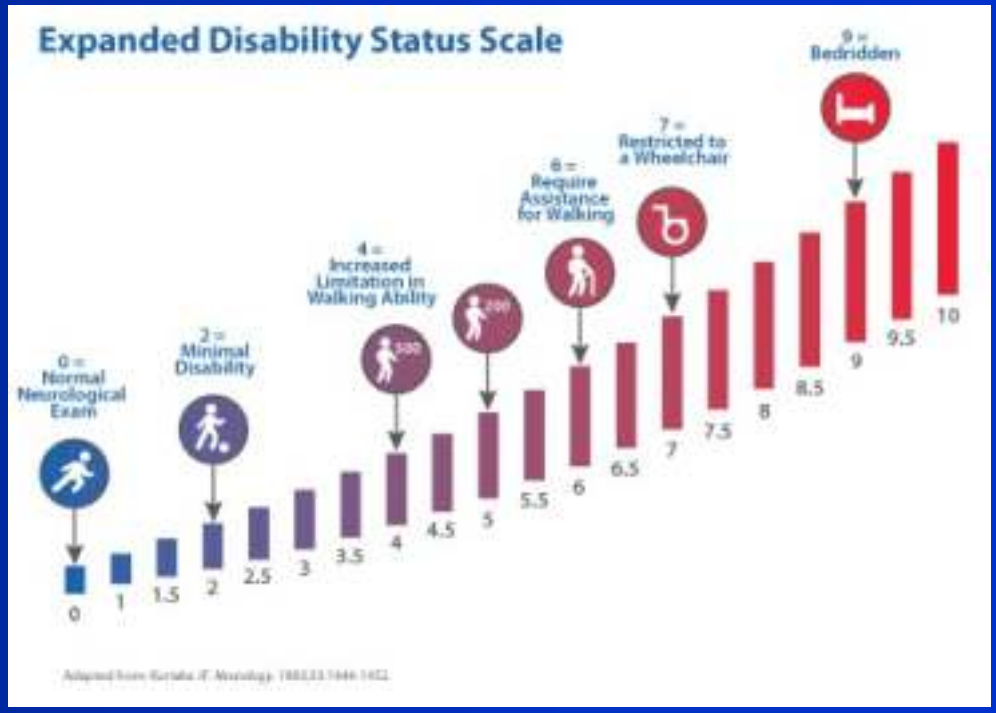
- Depends on lesion localization, the pathway in which the lesion is located

- Summation of residual symptoms after relapses

EDSS (Expanded Disability Status Scale)

0 (min.) - 10 (max.) - impairment, disability

Disability grading scale in MS:

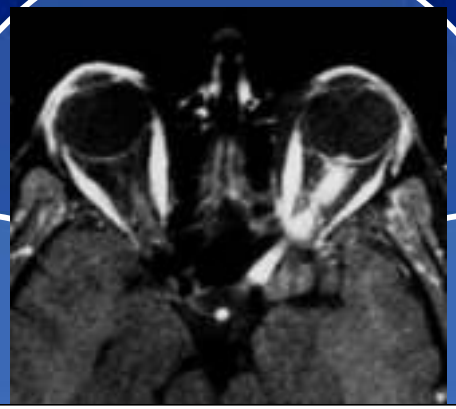


Functional systems:

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

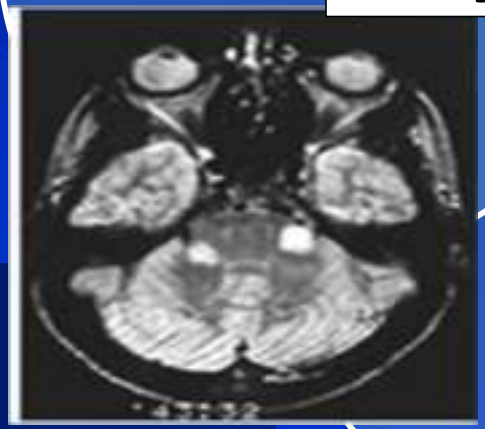
MS onset, the first episode = Clinicaly Isolated Syndrome/CIS – Monofocal or Multifocal manifestation

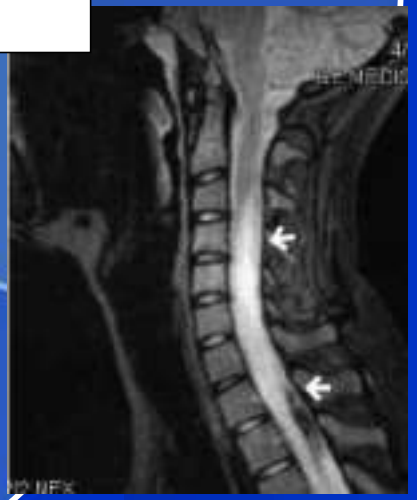
Optic neuritis



Multifocal syndrome

Brainstem/ cerebellar syndrome

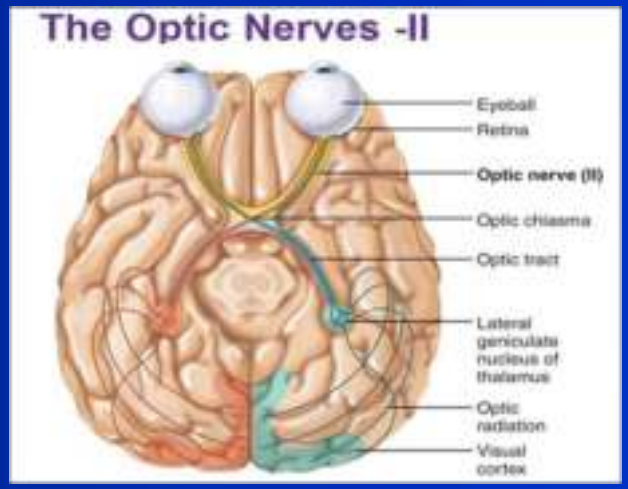


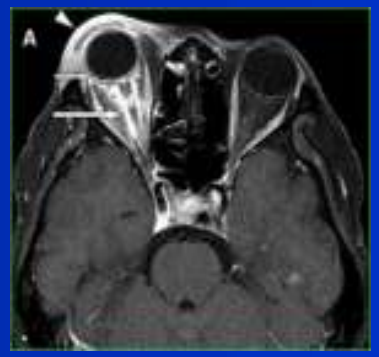


Myelitis - spinal cord inflammation

Optic neuritis

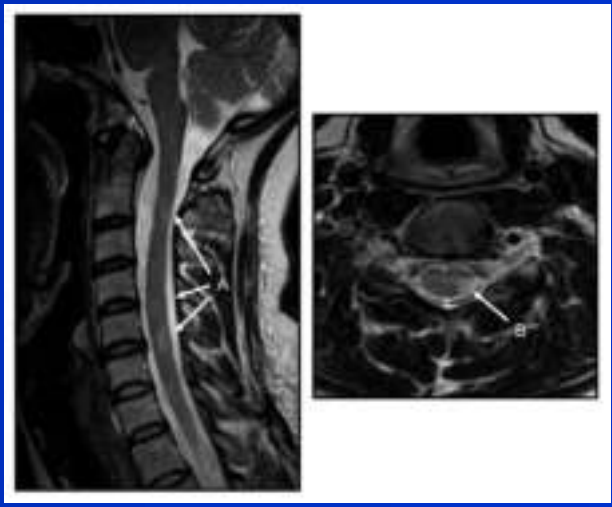
- Unilateral optice nerve (n.II) infammation, usually unilateral
- blurred vision
- pain when moving the bulb
- central scotoma
- loss of color vision, even blindness
- almost always some degree of improvement





Myelitis

- Cervical segments - usually C2-C5
- Partial transverse myelitis
- Sensitivity disorders - paresthesias of hands, feet, trunk
- Disorders of depth sensitivity, lesions in the posterior spinal columns = spinal ataxia
- Trunk - feeling of a hoop on the stomach/chest
- Motor disorders (paresis) below the lesion site
- Positive Lhermitte sign
- Lower urinary tract control dysfunction



Brainstem- cerebellar syndrome

- Oculomotor palsy (anterior internuclear ophthalmoplagia) - diplopia
- Nystagmus , vertigo, ataxia
- Sense disease, hemiparesthesias
- Hemiparesis
- Trigeminal neuralgia
- Hemifacial spasm
- Cerebellar ataxia, tremor, dyzartria
- Rubral tremor

MS symptoms

- **Symptoms of a developed disease accumulate after several attacks**

- **Vision -** blurred vision, scotoma, loss of colors, blindness, pain of eye bulb with movements
- **Eye bulb movement disorder –** diplopia, ophthalmoplegia, nystagmus
- **Cranial nerve n.V, VII, VIII, IX lesion -** neuralgia, paresthesia, vertigo
- **Sense and sensitivity disease -** tactile, vibratory, paresthesias, dysesthesias, hypesthesia, anesthesia, ...

- **Motor,movement disorders** - spastic paresis, or plegia, MonoParesis, HemiP, ParaP, TriP, KvadruParesis
- **Cerebellar symptoms** - ataxia, dysarthria, intention tremor, titubations
- **Sphincter dysfunction** - imperative micturition, urine retention, stool and urinary incontinence
- **Cognitive dysfunction** - deficit of attention, concentration, memory, information processing speed
- **Fatigue**
- **Autonomic dysfunction** - arrythmia, hyperhidrosis, orthostatic hypotension, cold and cyanosis of limbs,...

MS prognosis

- **Disease course - unpredictable**
- Prognosis 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 predictors of higher risk of progression and transition of RRMS to SPMS form

- Demographics: male gender, older age at onset (over 35 years), longer disease duration
- Clinical: multifocal syndrome at onset, EDSS ≥ 3.0, more attacks in the first 2 years, short time between the 1st and 2nd attack
- Radiological (MRI): Gd+ lesion, spinal cord lesions, infratentorial lesions, microglia activity, leptomeningeal inflammation, Fe-RIM in active lesions
- Laboratory: high levels of NfL(neurofilament light chain), GFAP (astrocyte activity)
- Survival is generally 7 years shorter in MS than in the general population (immobility, pressure ulcers, infections, renal failure)

Gd- gadolínium, RNFL- retinal nerve fiber layer, GFAP- Glial fibrillary acidic protein, GCC- ganglion cells lcomplex

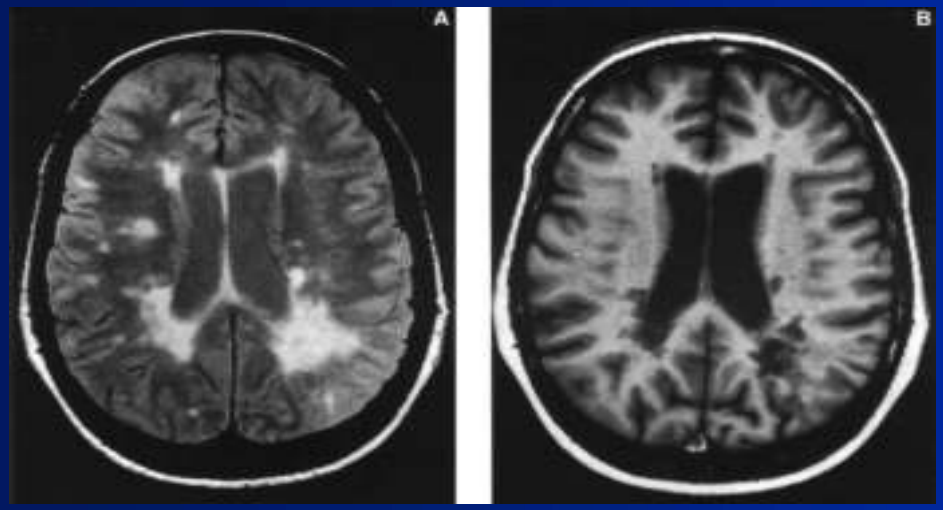
MS diagnosis

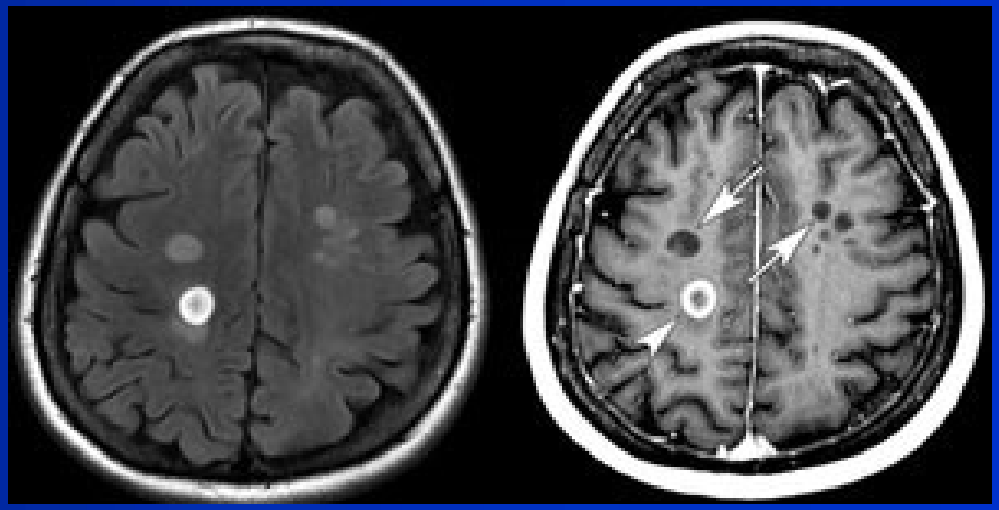
McDonald (2017) diagnostic criteria: presence of lesions disseminated in the CNS in the time (DIT) and disseminated in the space (DIS)

1. History, clinical course, symptoms
2. MRI (brain, spinal cord)
3. CSF - diff. diagnosis
4. Evoked potentials - VEP
5. Exclusion of other diseases with similar clinical or MRI findings (laboratory results, e.g. AQP4 antibodies, MOG antibodies)

! None of these tests are specific for MS; No paraclinical or laboratory test can 100% confirm MS

Magnetic resonance (MRI)





T2-weighted imaging – **hyperintensive lesions in the white matter, periventricular, corpus callosum, brain stem, spinal cord**

T1-weighted imaging – **hypointensive lesions (black holes) = axonal loss**

Gd+ enhancing lesion (Gd - gadolinium) - new, "active", inflammatory lesion (6 - 12 weeks)

T2 T1 Gd+T2 GD+T1

MS diagnostic criteria: McDonald 2017

- **Evidence of dissemination of demyelinating lesions in space** (DIS - Dissemination in space) **and evidence of dissemination in time** (DIT- Dissemination in time) **based on clinical examination or paraclinical methods when alternative similar diseases are excluded**

- **≥ 1 T2 lesions in ≥ 2 CNS locations typical for MS**
  1. periventricular
  2. juxtacortical /cortical
  3. in the posterior fossa
  4. in the spinal cord

Patient with MS should meet the criteria:

- **DIS** - 2 or more T2-lesions in typical location (1-4)
- **DIT** - new T2- lesion or Gd+ enhancing lesion, or positive OCB in CFS

OCB - Oligoclonal bands
CSF - Cerebrospinal fluid

Evoked potentials, EP

- **Evidence of clinical asymptomatic, silent lesions**

- **Pathol. results:**

- conduction slowing

- complete block

  of impulse spreading

- abnormal wave shape

VEP-prolonged P100 latency

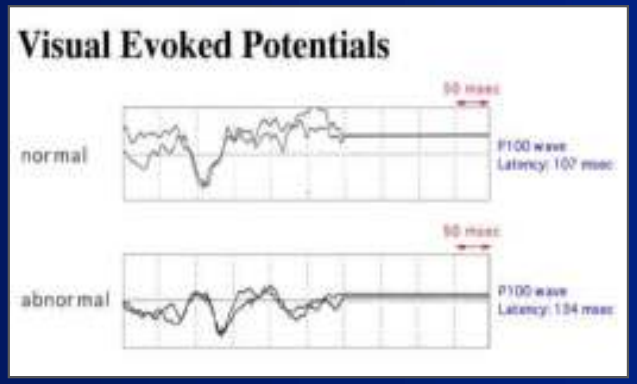
- in 90% patients with MS
- optic neuritis(ON) residuum
- abnormal in 50% patients without ON history

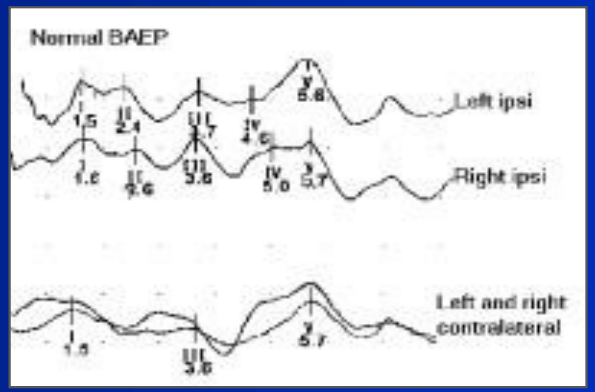
BAEP, brainstem auditory EP

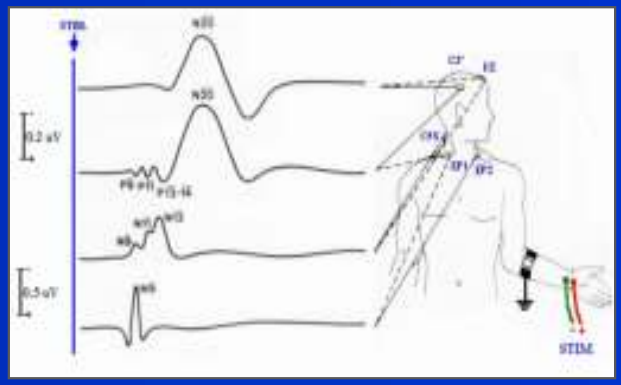
- Prolonged brainstem responses latencies waves II.-V. + amplitude decline

SEP, somato-sensoric EP

-Conduction slowing at the level of the spinal cord or brain







CSF evaluation in MS

Examination of the cerebrospinal fluid is useful for excluding other diagnoses within the differential diagnosis:

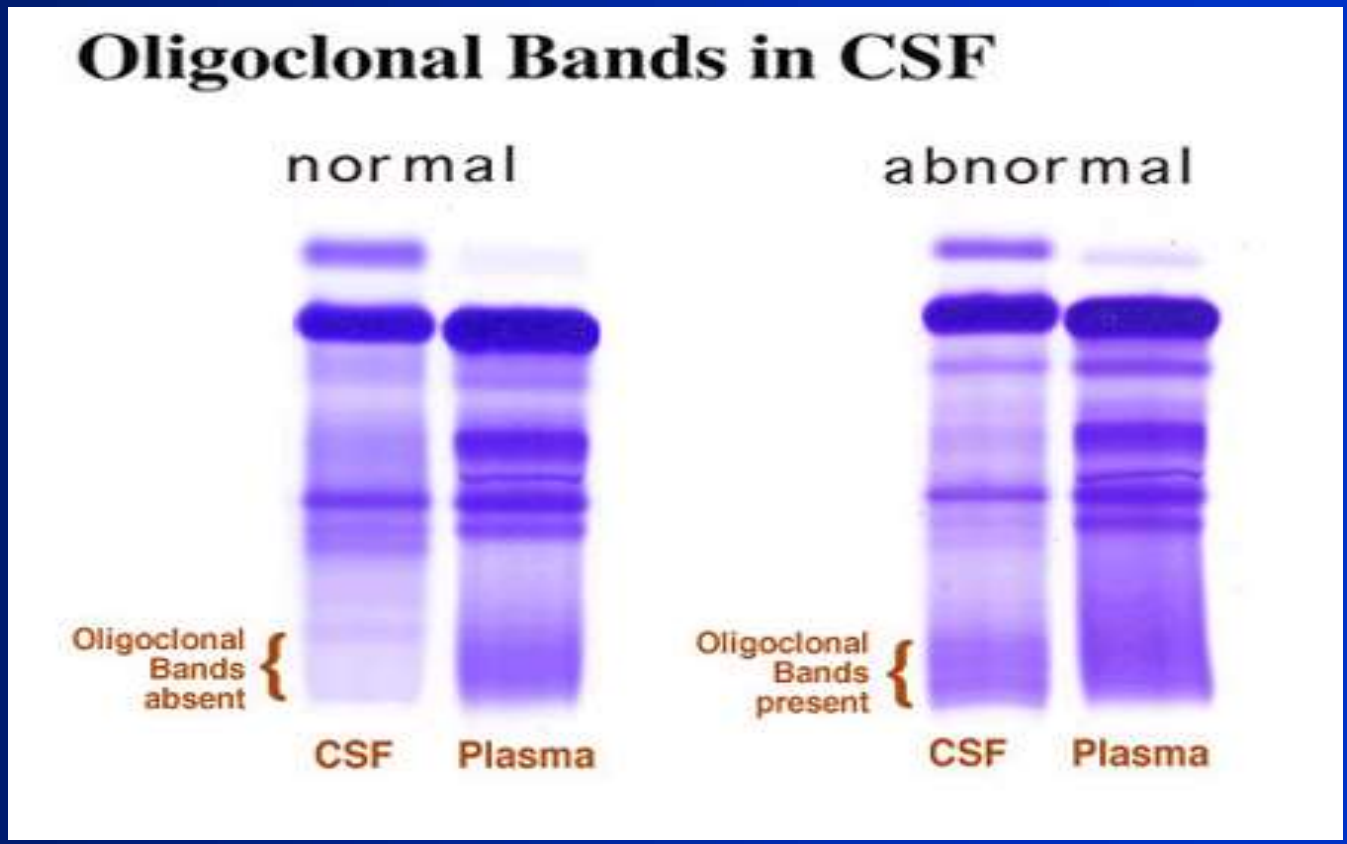
Findings in the cerebrospinal fluid in MS:

- **Total proteins -** in the norm (up to 400 mg/l)
- **Cellular elements -** normal, except for plasma cells (B-Ly plasmocyt)
- **Intrathecal synthesis of IgG -** present, higher IgG index
- **Oligoclonal bands (OCB) IgG** (or IgM, IgA) - present in 85-92%

- *OCB - expanded B-Lymphocyte clones*

CSF evaluation

- ✓ **Intrathecal synthesis of IgG – higher IgG index**
- ✓ **Oligoclonal bands > 2 – IgG antibodies - 95% of MS**

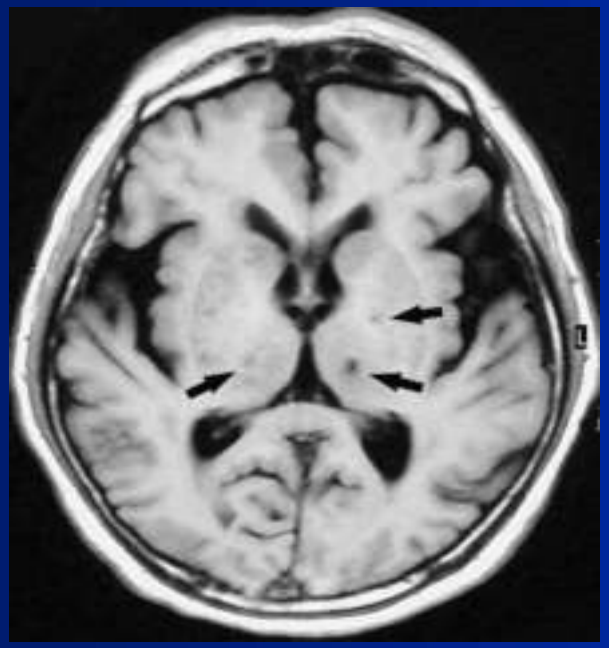


MS - differential diagnosis

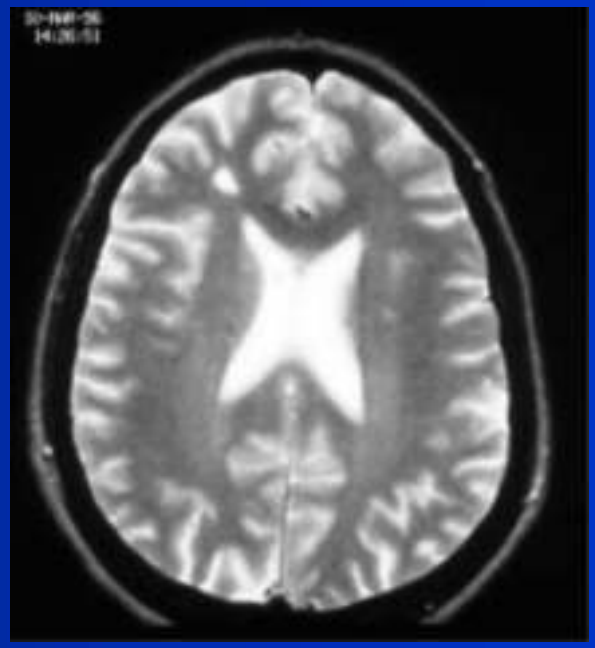
- **NMOSD, MOGAD, CLIPPERS, ADEM**
- Stroke – small vessel disease, lacunar stroke, cardioembolic stroke, arterial hypertension
- Migraine
- Tumor – glioma, lymfoma (dif dg: PET, CSF, biopsy)
- Intervertebral disc lesion - spinal cord compression
- AV vascular malformation - AG, DSA
- Neuroborreliosis
- CNS vasculitis, SLE
- Leucodystrophy – adult onset
- Mitochondrial diseases
- Celiakia
- Thyreopathy

Differential diagnosis

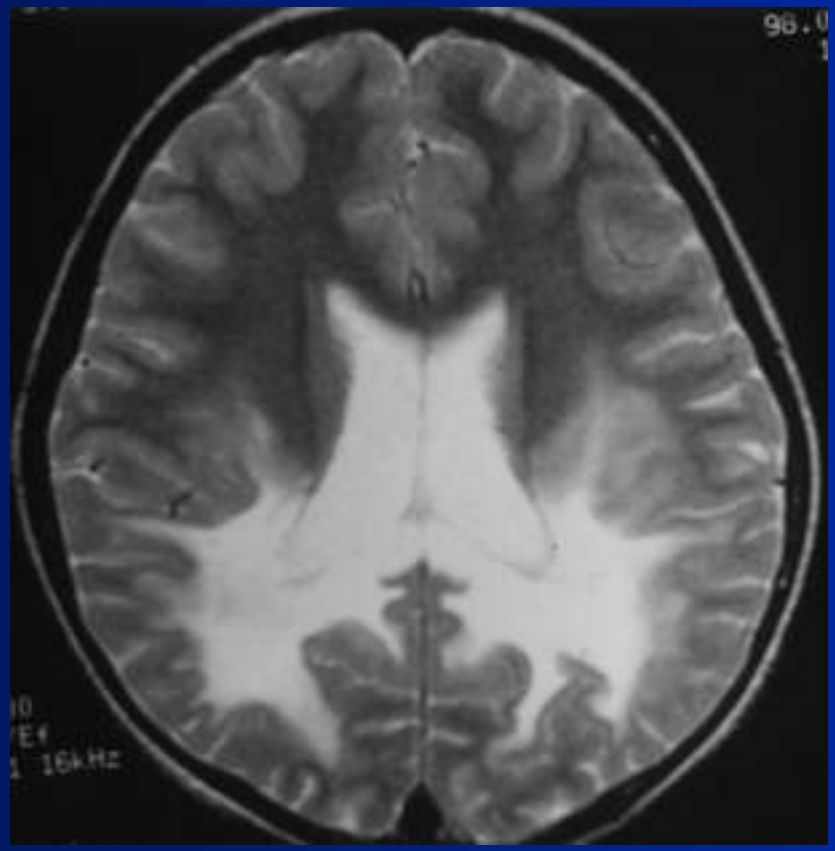
Stroke, lacunar infarcts



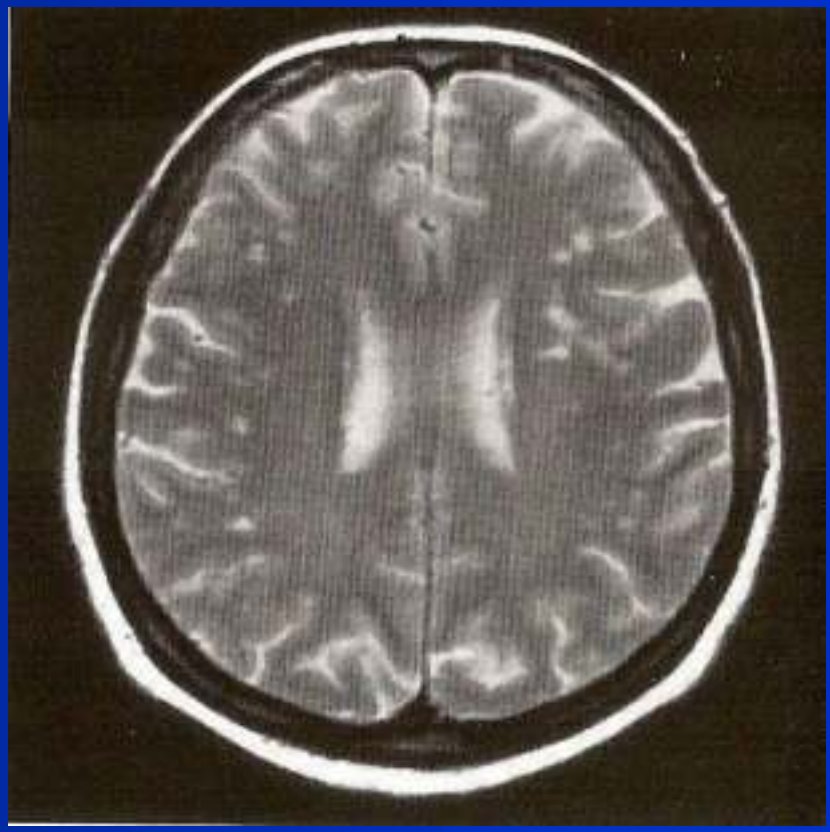
SLE- Systemic lupus erythematosus



Differential diagnosis

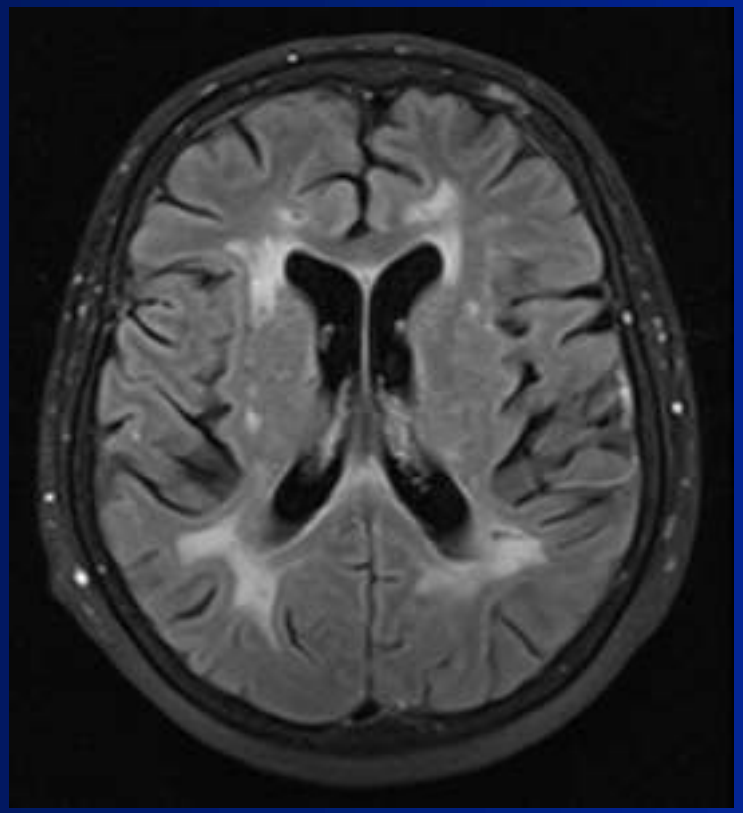


Adrenoleucodystrophy

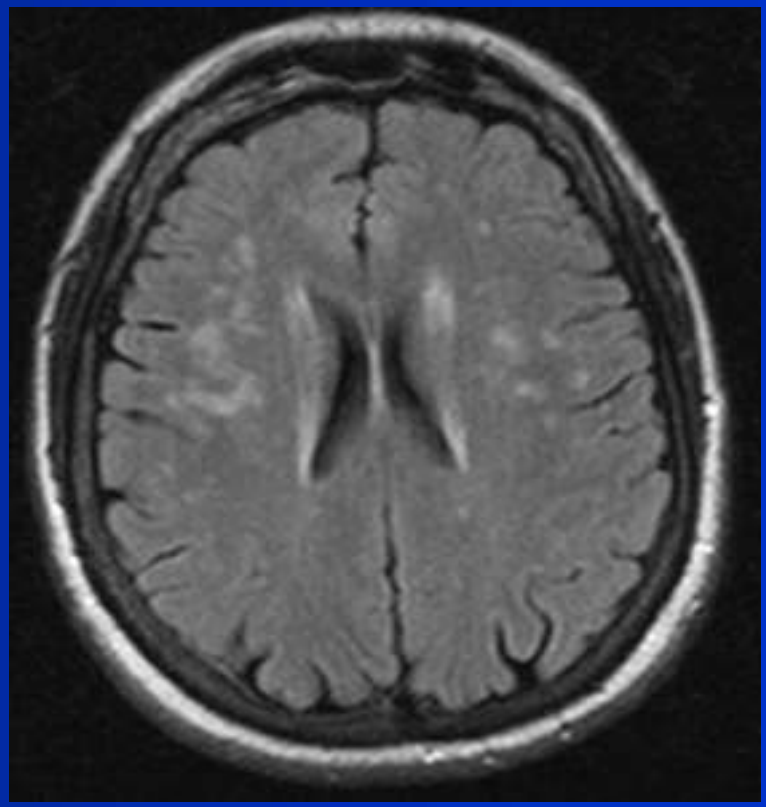


Borreliosis

Differential diagnosis



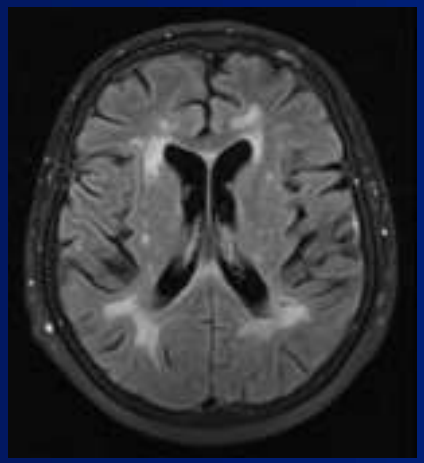
Arterial hypertension

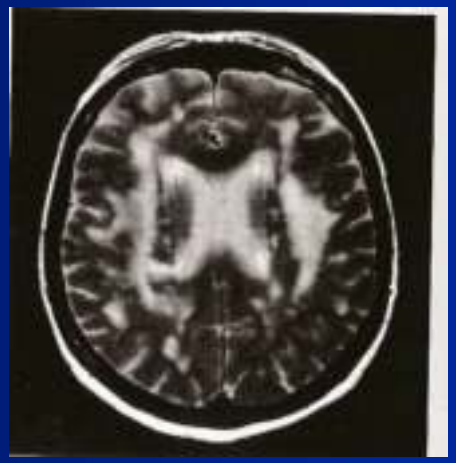


Hashimoto thyroiditis

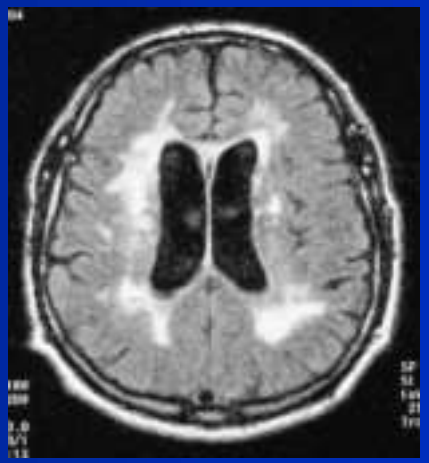
Hypoxic-ischemic diseases

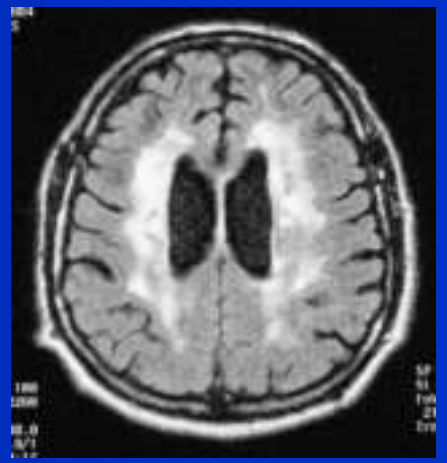
- Arterial hypertension, diabetes mellitus, dyslipidemia





Arterial hypertension

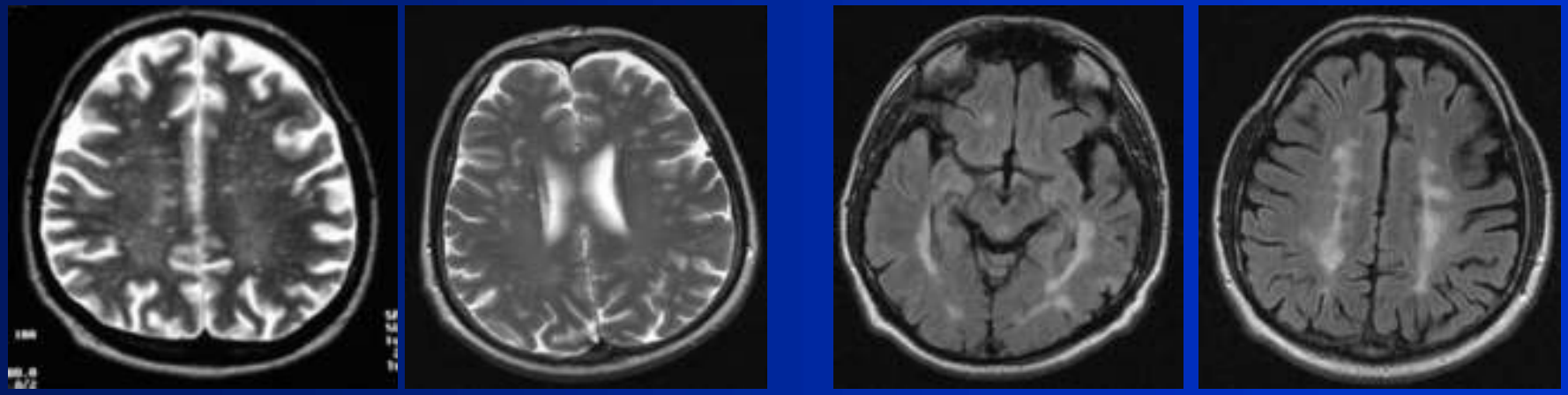




Diabetes mellitus

Hereditary thrombophilia

- FV Leiden
- MTHFR mutation
- Hyperhomocysteinemia
- protein C and protein S deficit



Differential diagnosis of MS: laboratory and paraclinical investigations

- **Serum antibodies**: AQP4-IgG, MOG- IgG, NMDAR, anti-thyroidal Ab (TPO, ATG), antineuronal Ab (anti-Hu, anti-Ri, anti-Yo), antigliadin, antiphospholipid Ab, ANA, ENA, ANCA, AcLA, LA,SS-Ro, SS-LA, rheumatoid factor

- Vitamin B12 level, vitamín D
- Folic acid, homocystein, lactate, Ig , lipid status, fatty acids

- Hemocoagulation: protein C a S, APC-rezistency, factor V Leiden, MTHFR gene

- Doppler US (cardial or venous embolisation)

- X ray- lung, cardiologic, ophthalmic, endokrinologic, dermatologic, infektologic, rheumatologic, imunologic and psychiatric investigation

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 tratment

DMT - Disease modifying therapy - cessation of clinical and radiological (MRI) activity) and disease progression

NEDA - No Evidence of Disease Activity

Concept NEDA-3 :

1. Clinical relaps
2. Worsening in disability degree (scale EDSS)
3. MRI activity, brain (Gd+T1/2 T2-lesions)

Disease activity and disability progression = need DMT change

ACTIVITY - clinical - new relaps

- MRI- new or enlarged T2-lesions, Gd+ enhancing lesions, new T1-lesions CNS

PROGRESSION - disability worsening (EDSS score increase more than 1 point)

Gd - gadolínium, cobtrast material, EDSS - Expanded Disability Status Scale

Giovannoni et al, Mult Scler. 2016; De Stefano N, et al. CNS Drugs. 2014

Treatment of attack / relapse

CORTICOSTEROIDS- Antiinflammatory effect

- Methylprednisolone i.v.
- Total dose 3 – 5 g
- then Prednison p.o. – 30 - 80 mg tbl /day, with slow dose decrease

Non-responders: Plasma exchange

Long-term treatment

DMT= Disease modifying treatments

IMMUNO-MODULANTS / IMMUNO-SUPRESSANTS:

1) DMT for moderate disease activity:

- **INF-beta, Glatirameracetate**
- **Teriflunomide, Dimethylfumarate**

2) DMT for high disease activity (high effective treatments, HET):

- **Natalizumab -** monoclonal Ab anti VLA4 adhesive molecule
- **Fingolimod, Siponimod, Ponesimod -** selective immunosupressant SP1 rec. inhibitors
- **Alemtuzumab -** monoclonal Ab anti-CD52 Ly
- **Ocrelizumab, Ofatumumab -** monoclonal Ab anti-CD20 Ly
- **Cladribine**

Symptomatic treatment

SPASTICITY: Central myorelaxances - Baclofen, Tizanidine, Botulotoxin, Cannabinoids

SFINCTER DYSFUNCTION:

Retention: intermitent autocathetrisation

Incontinence: anticholinergics, ADH / night

TREMOR: clonazepam, beta-blockers

Trigeminal neuralgia, neuropathic pain: pregabalin, gabapentin

Rehabilitation, psychotherapy

Vitamins: Vitamin D supplementation, Omega 3 and Omega 6 fatty acids + borage oil + vitamin E + beta carotene, vitamin C

Diet - intestinal microbiota

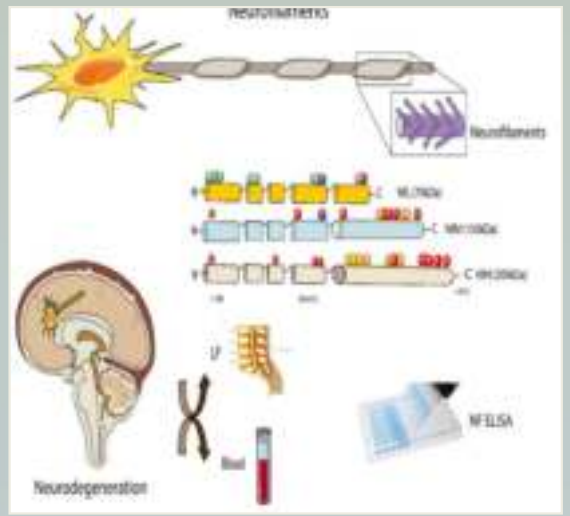
Vaccination - unsuitable live vaccines (TB, measles, mumps, rubella, yellow fever, poliomyelitis, typhoid)

Pregnancy - planned, during the period of at least 6 months of disease stability

New biomarkers of MS disease activity and treatment response

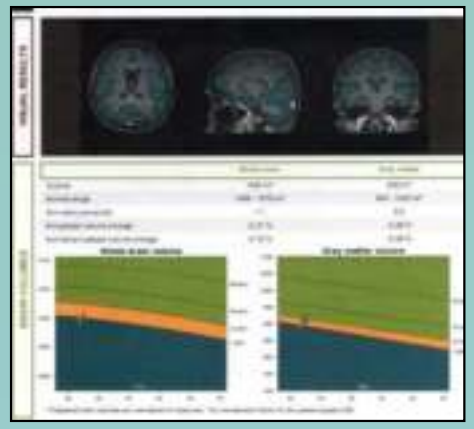
Neurofilaments

- **pNfL**- plasmatic neurofilament light chain



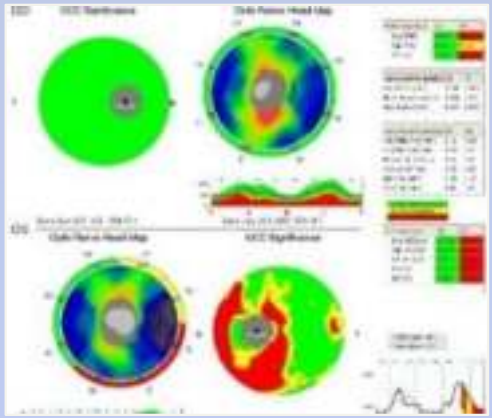
MRI-brain volumetry, atrophy

- Whole brain atrophy
- Gray matter atrophy
- White matter atrophy
- Annual brain volume loss (BVL)



Optic coherent tomography - OCT

- **pRNFL** (peripapillaryl retinal nerve fibre layer)
- **GCC**- ganglion cell complex



Disease activity

NMOSD

- NEUROMYELITIS OPTICA SPECTRUM DISORDERS

Neuromyelitis optica, NMO (Devic disease)

- Inflammatory process of the CNS - astrocytopathy
- Formation of auto-antibodies against the AQP4 channel
- Inflammation preferentially at sites with AQP4 channels on astrocytes in the brain and spinal cord

- Optic nerve and spinal cord = neuro-myelitis optica

- Prevalence: low, rare disease (Slovakia: 1.4/100,000)
- Worldwide: 0.5-4/100,000 population
- Occurrence: worldwide, more affected women, F : M = 9 : 1

Wingerchuk DM. et al. *Neurology,* 2006

Neuromyelitis optica spectrum disorders, NMOSD

- **Core clinical symptoms/syndromes:**
- 1. Optic neuritis
- 2. Myelitis
- 3. Acute brainstem syndrome
- 4. Area postrema syndrome
- 5. Narcolepsy syndrome, diancephalic syndrome
- 6. Cerebral lesions/syndrome

Wingerchuk DM. et al. *Neurology,* 2006; Wingerchuk DM. et al. 2015

NMOSD (Neuromyelitis optica spectrum disorders)

Clinical picture:

- severe visual deficit (blindness)
- lower limb spastic paraparesis/paraplagia
- sfincter problems (urgent, incontinence)
- spinal ataxia
- walking problems

Disease course: 90 % - **relapsing-remitting**

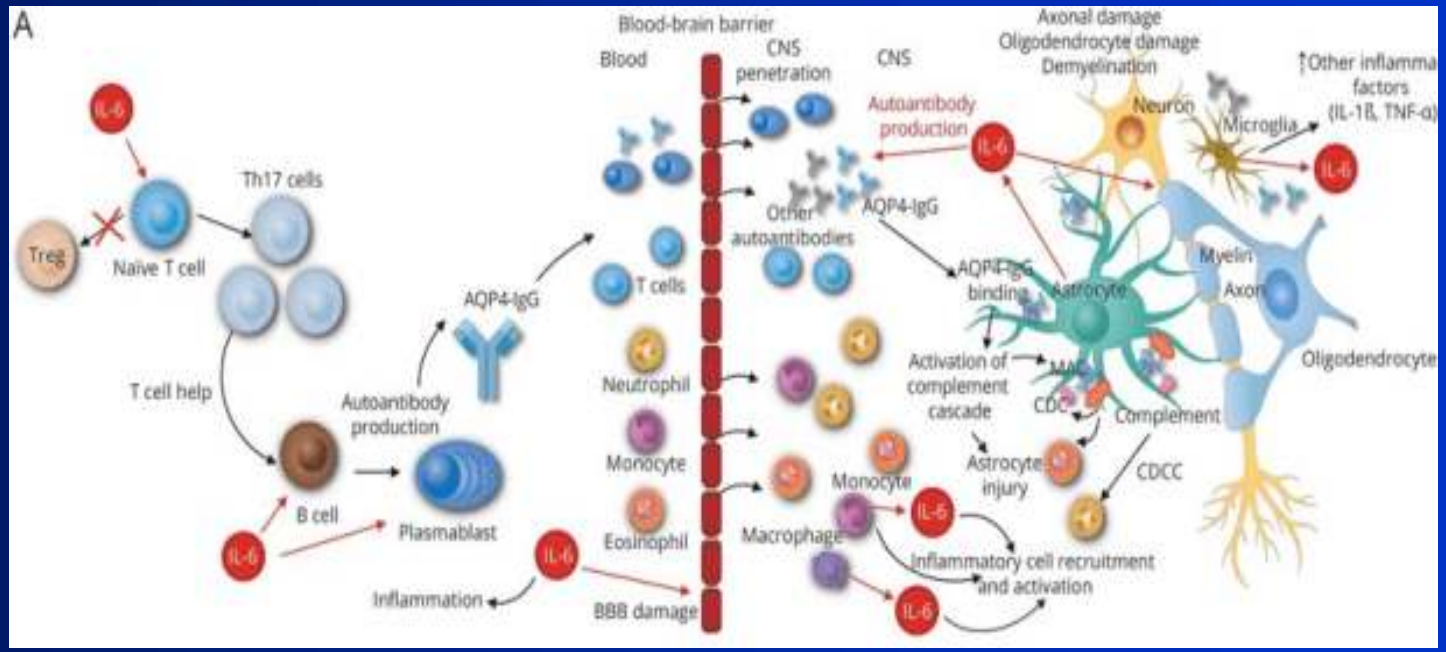
10 % - **monophasic**

Wingerchuk DM. et al. *Neurology,* 2006

NMOSD

Antibodies AQP4-IgG

- high sensitivity (75 – 91%) and specificity (91 – 100%)
- binding to the target antigen (AQP4 channel on astrocyte cell)
- pathological immune process with complement activation + lymphocytes and granulocytes - **infiltrate brain tissue** (optic nerve and spinal cord)
- the result is an **inflammatory lesion + demyelination + axonal loss**



Fujihara et al, Neurol Neurimmunology and Neuroinlamm2020; Wingerchuk DM. et al. *Neurology*, 2006

NMOSD 2015 IPND – Revised diagnostic criteria

2015 IPND Neuromyelitis Optica Spectrum Disorder (NMOSD) Diagnostic Criteria

NMOSD With AQP4-IgG

1. At least 1 core clinical characteristic (at right)
2. Positive test for AQP4-IgG*
3. Exclusion of alternative diagnoses**

NMOSD Without AQP4-IgG or Unknown AQP4-IgG Status

1. At least 2 core clinical characteristics (at right) resulting from 1 or more clinical attacks and satisfying all of the following requirements:
   a) At least 1 of: ON, acute myelitis with LETM, or APS
   b) Dissemination in space (≥2 different core characteristics)
   c) MRI requirements, if applicable (at right)
2. Negative test(s) for AQP4-IgG* or testing unavailable
3. Exclusion of alternative diagnoses**

* Using best available detection method (cell-based assay strongly recommended).
** Evaluation for alternative diagnoses guided by "red flags."

SOURCE: International Panel for Neuromyelitis Optica Diagnosis in affiliation with The Guthy-Jackson Charitable Foundation International Clinical Consortium. www.guthyjacksonfoundation.org/special-projects-and-programs/ipnd-diagnostic-criteria/. Accessed Aug. 24, 2015.

Core Clinical Characteristics of NMOSD

Most common:

1. Optic neuritis (ON)
2. Acute myelitis
3. Area postrema syndrome (APS): episode of otherwise unexplained hiccups or nausea and vomiting

Less common:

4. Acute brain stem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions

Supporting MRI Requirements for NMOSD Without AQP4-IgG

1. **Acute optic neuritis:** brain MRI normal or demonstrating only nonspecific white matter lesions; OR optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm
2. **Acute myelitis:** spinal cord MRI showing attack-associated lesion extending ≥3 contiguous segments (LETM); OR ≥3 contiguous segments of focal cord atrophy in patients with prior history of acute myelitis
3. **Area postrema syndrome:** dorsal medulla/area postrema MRI lesion
4. **Acute brain stem syndrome:** peri-ependymal brain stem lesions

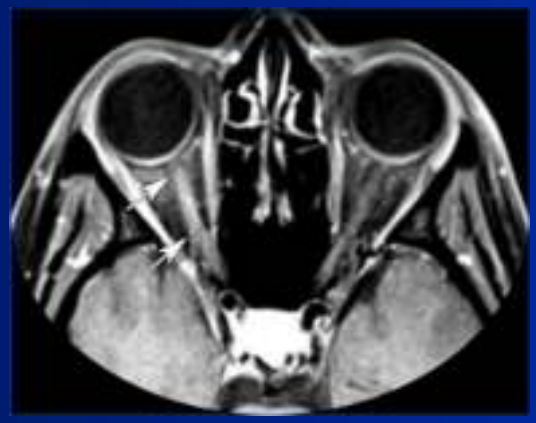
Wingerchuk DM. et al. *Neurology,* 2006; Wingerchuk DM. et al.

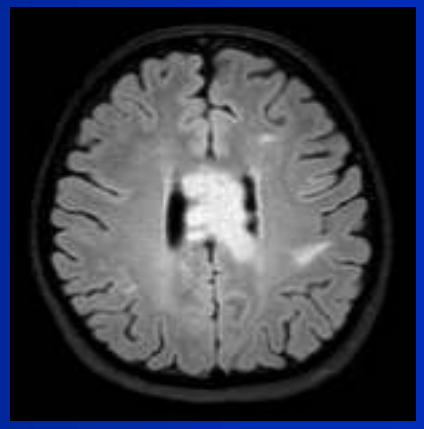
NMOSD diagnosis

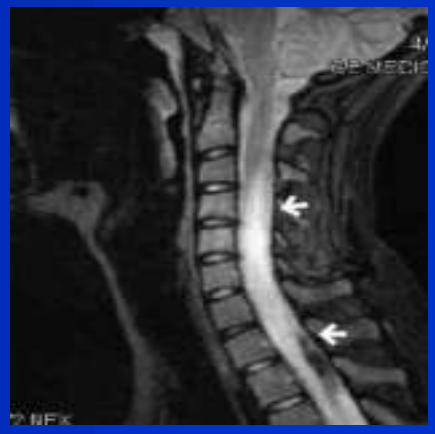
- **Laboratory tests**: serum Ab AQP4-IgG (positive in **80%)**
- **MRI:** brain, optic nerve + optic chiasma, spinal cord lesions
  - T2-lesions peri-ependymal areas (corpus callosum, around the III. and IV. vertricle), MO - area postrema

    - brain MRI may be normal or lesions atypical for MS

    - spinal lesions - longitudinal extensive transversal myelitis/LETM over 3 segments
- **CSF** (positive in 15-20% OCB)
- **VEP**
- **OCT**







- https://www.frontiersin.org/articles/10.3389/fneur.2018.00888/full; Borisow N et al, Front. Neurol. 2018

NMOSD: treatment

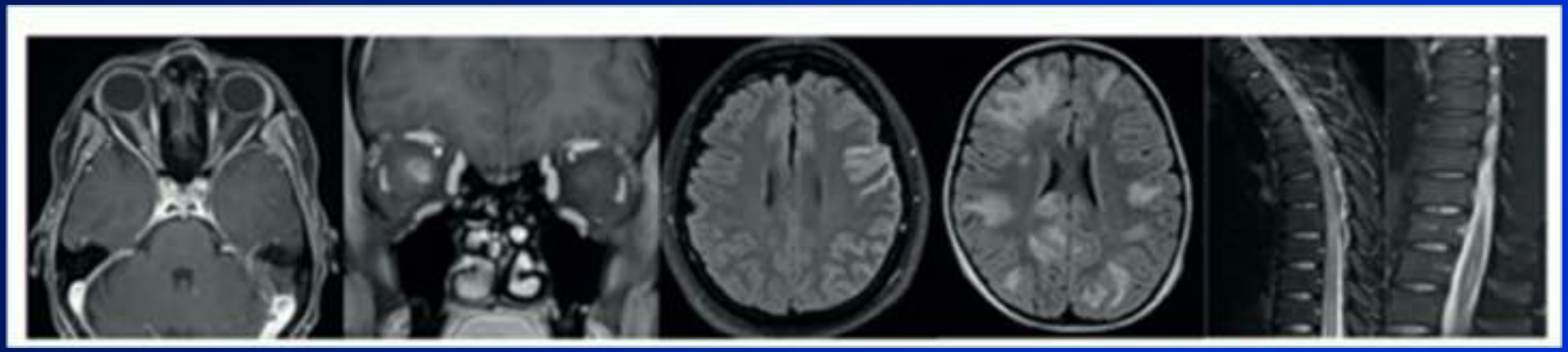
- **Acute relaps:**
- immunosupressive drugs - **Corticosteroids (Methylprednisolone** 3 - 5 g/cure) or
  - **Plasma-exchange**
- **Long-term therapy:** Azathioprin + Prednison
  Rituximab (anti-CD19 B-Ly MoAb), off-label
  Satralizumab (anti-IL6 MoAb)
  Tocilizumab
  Inebilizumab
- **NMOSD prognosis:**
- Worse than MS
- Permanent serious neurological deficit (visual deficit, paraparesis)

MOGAD

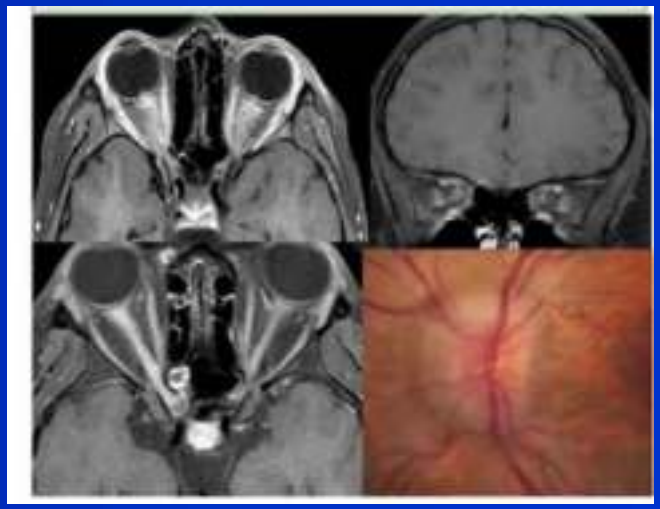
MOG antibody - associated disease

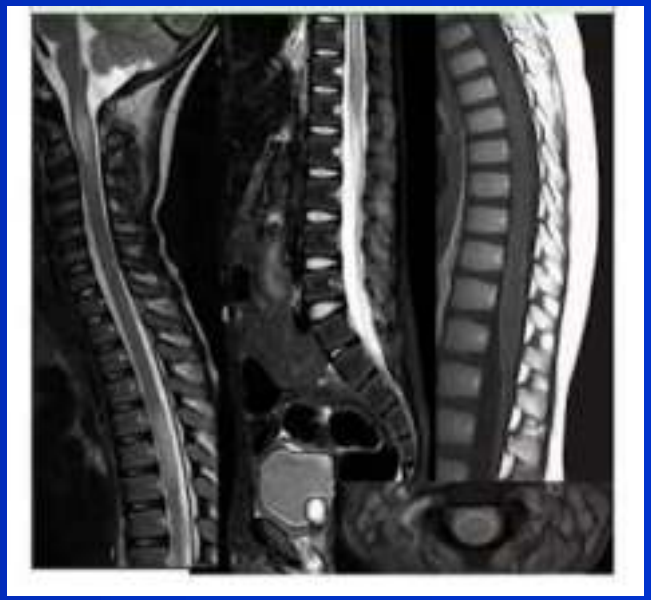
MOGAD

- Inflammatory CNS disease associated with myelin oligodendrocyte glycoprotein antibodies (MOG)
- characterized by attacks of immune-related demyelination predominantly affecting the optic nerves, brain and spinal cord



MOGAD





- **Core clinical symptoms/syndromes:**
- 1. Optic neuritis
- 2. Myelitis
- 3. ADEM
- 4. Brainstem or cerebellar deficit
- 5. Cortical encephalitis often with seizures
- 6. Cerebral monofocal or multid focal lesions/deficit

Wingerchuk DM. et al. *Neurology,* 2006; Wingerchuk DM. et al. 2015

MOGAD

Epidemiology:

- Incidence: 1,6 – 3,4 / million/ year
- Prevalence: 4/100 000 or 20/ million

Demography:

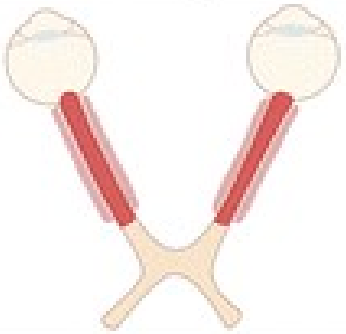
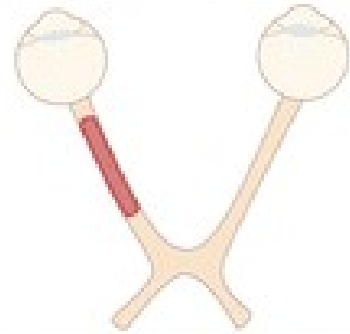
- ✓ All ages, all races
- ✓ Equal gender ratio (women 49-57%)
- ✓ Average age of onset : between 20.-30. y, average 33 years (min.6 –max. 70.y)

B. Banwell, JL Bennett, R. Marignier, et al. Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: International MOGAD Panel proposed criteria. Lancet Neurol. 2023; 22: 268-82.

MOGAD

- Compared to AQP4+NMOSD, MOGAD has a different immunopathogenesis, prognosis and treatment
- Clinical deficit is linked to attack/relapse
- There is no progressive neurological deterioration, regardless of relapses
- In the long term, the main deficit is the decrease in vision (VA) after ON (optic neuritis)
- MR activity only during attacks, rarely outside relapses

Optic neuritis: NMOSD-AQP4 vs MOGAD vs MS

	NMOSD-AQP4-IgG+	MOG-IgG+	Multiple Sclerosis
A) Optic nerve			

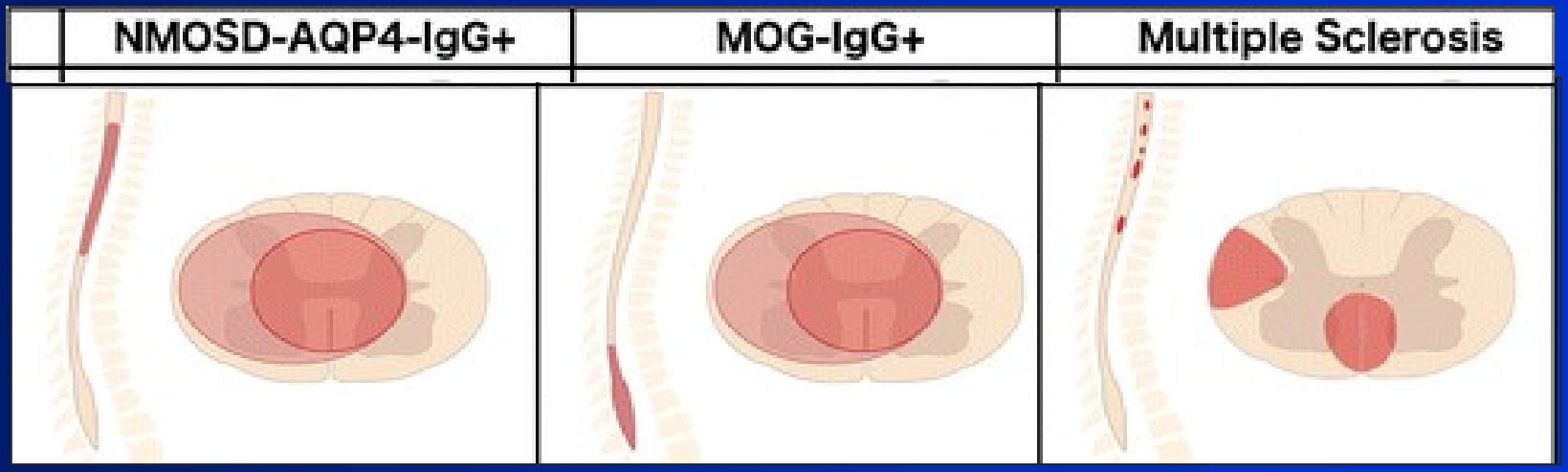
AQP4-NMOSD
- long lesions
- bilateral
- posterior part and chiasma
- severe deficit

MOGAD
- long lesions
- bilateral
- anterior part
- papilitis frequent
- Gd+lesions

MS
- short lesions
- unilateraly

Dutra BG et al. Neuromyelitis optica Spectrum disorders: spectrum of MR imaging findings abd rheir doifferential diagnosis , 2018; radioGraphics 38:169-193.

Myelitis: NMOSD-AQP4 vs MOGAD vs MS



AQP4-NMOSD

- C and Th segments
- central and lateral parts
- LETM
- severe residual deficit
- Gd+lesions
- more than 50% spinal cord area

MOGAD

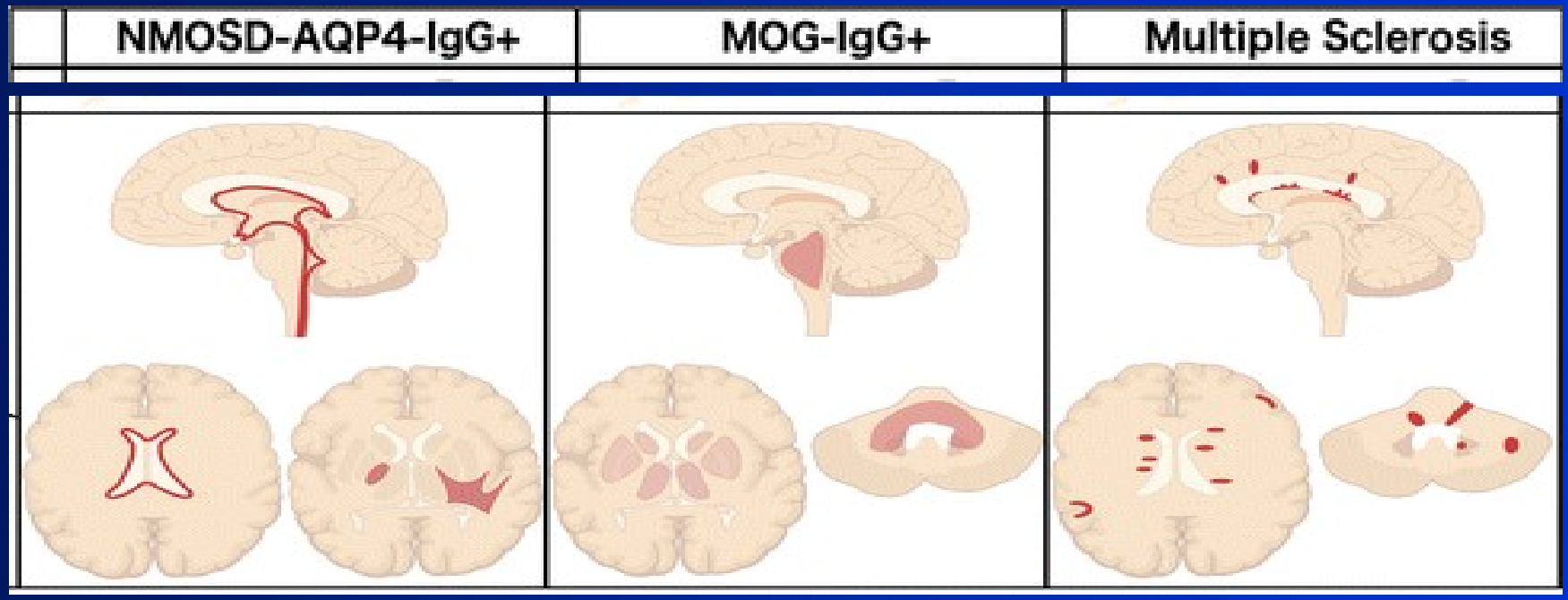
- Th-L segments and conus medullaris
- moderate degree
- better impromevent
- central and peripheral parts
- LETM
- H- sign

MS

- C segments
- longitudinal short lesions
- peripheral and dorsal areas

Dutra BG et al. Neuromyelitis optica Spectrum disorders: spectrum of MR imaging findings abd rheir doifferential diagnosis , 2018; radioGraphics 38:169-193.

Brain/cerebral lesions: NMOSD-AQP4 vs MOGAD vs MS



AQP4-NMOSD
- periventricular lesions
- pyramidal tract
- area postrema
- brainstem
- IV. ventricle

MOGAD
- brainstem
- thalamus
- midbrain
- cerebellar peduncles

MS
- periventricular
- periventrikulárne, corpus callosum
- cortico-juxtacortical
- Infratentorial (intrapontine)

Dutra BG et al. Neuromyelitis optica Spectrum disorders: spectrum of MR imaging findings abd rheir doifferential diagnosis , 2018; radioGraphics 38:169-193.

CSF:NMOSD-AQP4, MOGAD and MS

AQP4-NMOSD

- **Pleiocytosis > 50/3**
- Lym, Neu, Eoz
- OCB positive in **10-30%**

MOGAD

- **Pleiocytosis**
- Lym, Neu
- OCB positive in **10%**

MS

- **Oligocytosis**
- Lym, Plaz
- OCB positive in **> 95 %**

Jarius S et al, J Neuroinflammation. 2016; Jarius S et al, J Neuro Sci. 2011

ADEM

Acute Disseminated Encephalomyelitis

Acute disseminated encephalomyelitis – ADEM

- **Immune-mediated inflammatory demyelinating disease of CNS**
- **Pathogenesis:** abnormal autoimmune reaction against myeline antigens within CNS
- **Monophasic course, no relapses**
- **In 75% - post-infection and post-vaccination complication**
- **Occurrence:** children, young adults
- **Incidence:** 0.8/100,000 inhabitants/year

Acute disseminated encephalomyelitis – ADEM

- **ADEM onset 7 - 14 days after**
  - **Infection :**
  - Borrelia burgdorferi, Chlamydia, Legionella, Mycoplasma pneumoniae, Rikettsia rickettsia, Coronavirus, Coxackie B, Epstein-Barr v., Hepatitis virus (A and C), Herpes simplex virus, HIV
  - Streptococcus
  - **Vaccinations:** Hepatitis B, Japanese encephalitis B, Measles, Mumps, Pertussis, Polio, Rabies, Rubella, Tetanus
  - **some medicines**
  - **toxins**
  - **febrile illness**

Acute disseminated encephalomyelitis – ADEM

Disease course: development of neurological manifestations – subacute 1 - 2 weeks after previous infection or vaccination

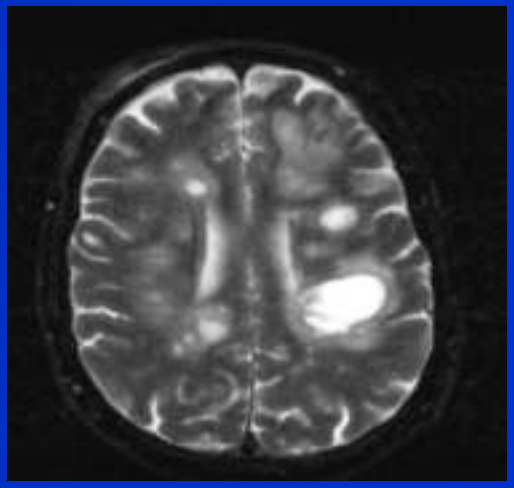
- Symptoms are more severe than MS

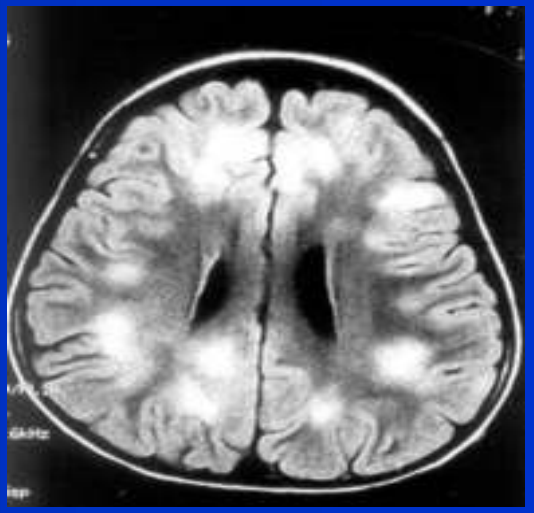
- **Disease manifestation:**
  - **Encephalopathy** = headache, subfebrility, meningeal syndrome, drowsiness, lethargy and behavioral disorders, altered consciousness
  - **Focal to multifocal manifestations** - hemiparesis/quadriparesis, ataxia, epileptic paroxysms, cranial nerve lesions, cognitive disorders, involuntary movements - chorea, myoclonus etc.,.
- 2-18% of ADEM will progress to MS!
- Very heterogenous course

- *Prognosis/outcome*: complete recovery or persistent residual symptoms

Diagnosis:

- **History**
- **Neurological examination**
- **Laboratory tests** (JCV)
- **MRI brain**:
  - large T2-hyperintensive lesions in white and gray matter
  - Gd+
  - no new lesions in follow-up
  - often regression of lesions in control MRI
- **CSF:**
  - Ly pleiocytosis (50%)
  - moderate hyperproteinorhachia
  - negative OCB or OCB in 12-20%





ADEM

Treatment: - corticosteroids high dose iv. (Methylprednisolone)

- i.v. Immunoglobulins, or
- plasma exchange (plasmapheresis)

Prognosis: relatively good

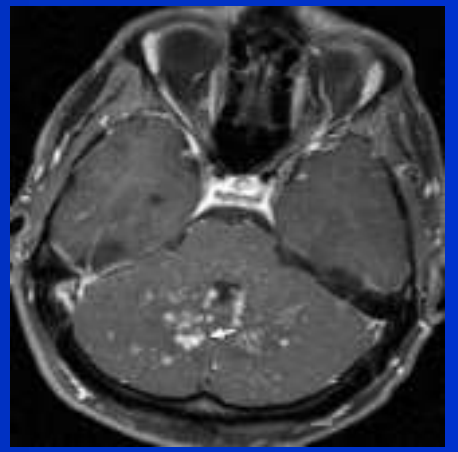
- with complete improvement in 50- 75 % patients (3 - 6 months)
- moderate residual symptoms in 10 % (hemiparesis, epilepsy)
- mortality – around 5 %

- 2 - 18% children with ADEM develop MS

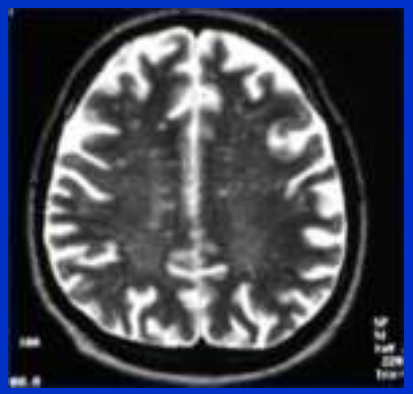
CLIPPERS

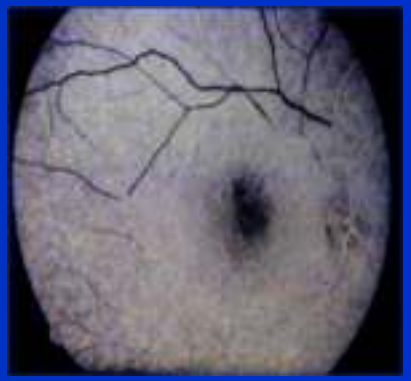
Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids

- **Subacute ponto-cerebellar syndrome: triad**
- **Vertigo + ataxia + dysarthria with/without CNS symptoms** (cognitive changes, myelopathy)
- CNS manifestations, PNS involvement is absent
- **MRI:** Gd+ punctate homogeneous bilateral symmetrical small <3 mm demyelination in pons, medulla oblongata, cerebellum, peduncles
- **Histology:** perivascular infiltrate with small lymphocytes
- **CSF**: normal, OCB not present
- **Treatment:** responsive to corticoids



Susac syndrom
Retino-cochleo-cerebral angiopathy





- Triad: encephalopathy with/without focal neurological symptoms + retinal artery occlusions + balance/hearing impairment

- **Dg criteria:**
  - Definitive SS - 3/3 criteria
  - Probable SS - 2/3 criteria

1. **Retinal artery occlusions - BRAO** (Branch retinal artery occlusions) FLAG, visual deficit (even blindness)
2. **Vestibulo-cochlear** - vertigo, ataxia, cochlear disease/deafness
3. **Cerebral** – cognitive and behavioral problems, headache, memory problems, corpus callosum syndrom

CSF: normal
Treatment: cortisteroids

Progressive multifocal leukoencephalopathy (PML)

- PML: a disease of the white matter of the brain, caused by a virus infection (polyomavirus JCV - John Cunningham virus) that targets oligodendrocytes
- JC virus remains latent in most immunocompetent hosts, in immunosuppressed hosts virus reactivats to recombination of genes

- **PML risk conditions**: immunocompromised states - AIDS, post solid organ and bone marrow transplant recipients, malignancies, and chronic inflammatory conditions, treatment with some monoclonal antibodies

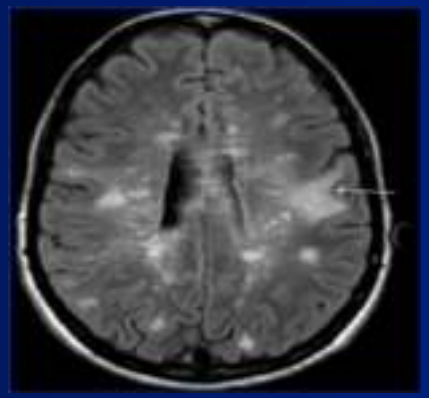
- **Pathogenesis:** oligodendrocyte infection with JC virus, JCV virus activation and mutation

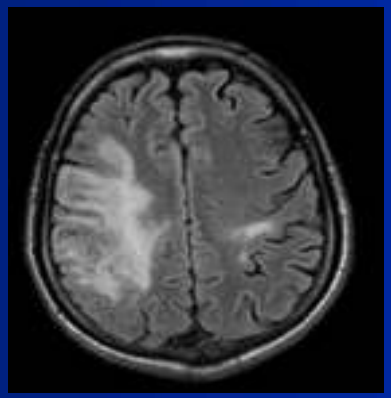
- **Disease course:** demyelinations and axonal loss, severe, progressive, fatal demyelinating disease

Chowdary et al., 2008

Progressive multifocal leukoencephalopathy (PML)

- **Symptoms:** subacute development od personality, behavior change, cognition (memory) problems, hemianopsia, ataxia, paresis/plegia, extrapyramidal manifestations
- **MRI** brain: large progredient lesions initially solitary/multifocal, gradually later merging with rapid progression
- **CSF:** presence of JC virus in the CSF (PCR, number of copies)
- **Mortality:** 20%!
- Treatment: currently effective treatment for the complete cure for PML has not been found
- Cidofovir, cytarabine, mefloquine - have been investigated, they have not shown to be clinically benef



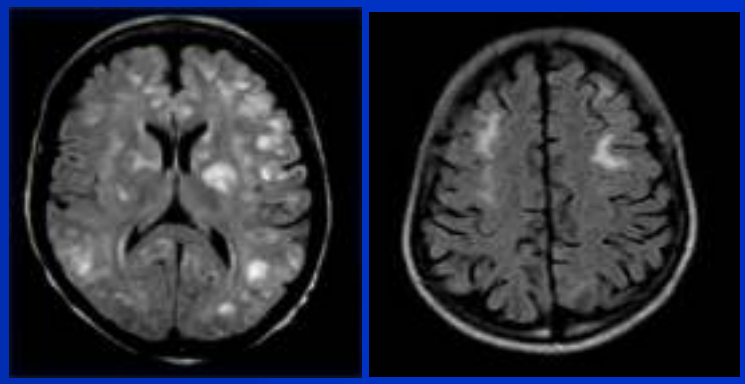


Chowdary et al., 2008

Brain small vessels vasculitis

- **Isolated primary CNS vasculitis**

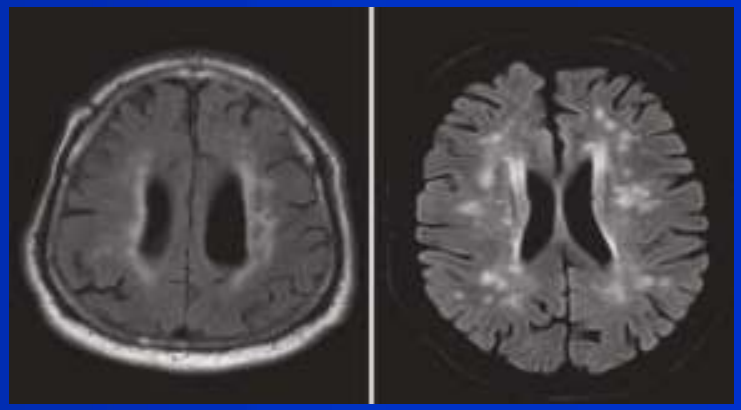
- **Systemic vasculitis**
  - **1) Primary vasculitis**
  - **2) Secondary vasculitis**
    - caused by infection
    - in systemic connective tissue diseases
    - paraneoplastic
    - drug induced



Watts et al., 1997

Small vessel disease

- elderly people with small vessel diseases
- vessels of small caliber < 50 µm
  - arteriosclerosis
  - arterial hypertension
  - diabetes mellitus
  - smoking
  - dyslipidemia
  - atherosclerosis

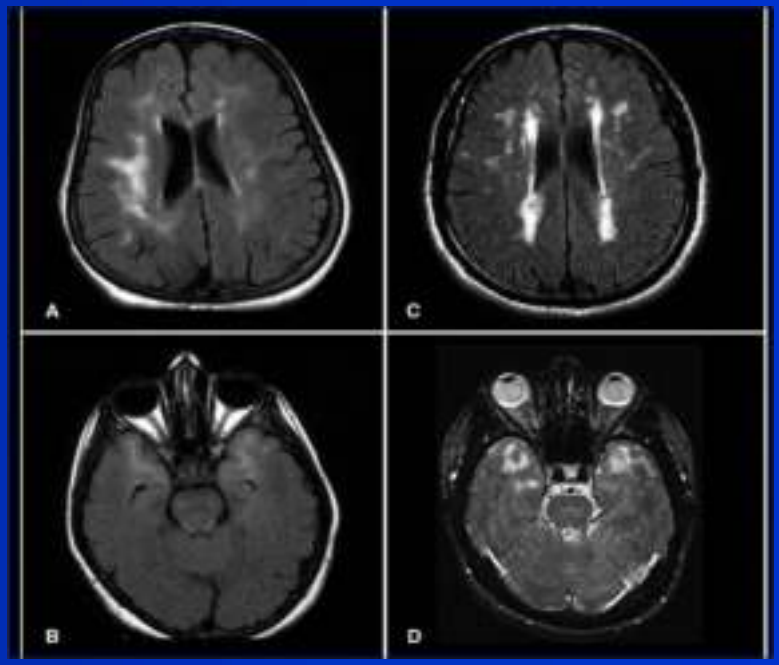


- MRI brain lesions:
  - subcortical / centrum semiovale
  - periventricular so-called caps and halo effect
  - Ischaemic- no enhancement after Gd-gadolinium administration
- CSF: negative OCB

Fillipi et al., 2005.

Leukodystrophy

- **Leukodystrophies** - a group of rare, genetic disorders that affect the white matter of the brain
- Brain- imperfect abnormal white matter growth -



- **Adult-onset leukodystrophy with neuroaxonal spheroids and pigmented glia** (HDLS and POLD) gene CSF1R
  - **CADASIL** - Cerebral arteriopathy with subcortical infarcts and leukoencephalopathy, gene: NOTCH3
  - **CARASIL** - Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; gene: HTRA1

- **Dif dg:** Wilson´s disease, Spastic paraplegia, Fabry disease