Multiple Sclerosis

Epidemiology
Genetics, Environmental Factors
Treatment

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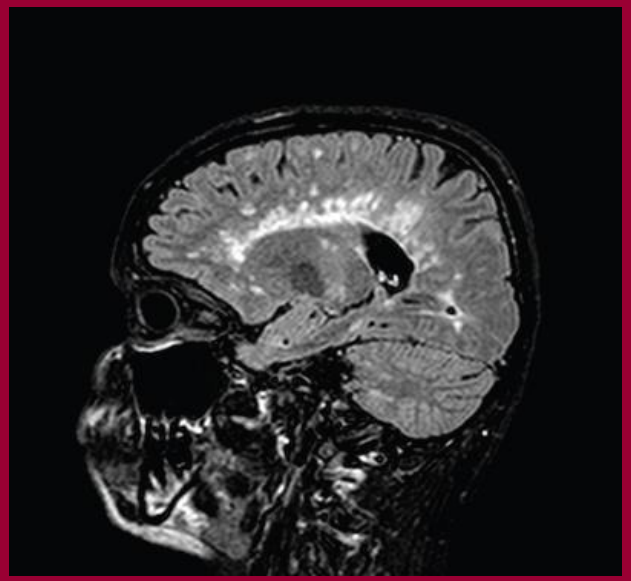
Multiple Sclerosis

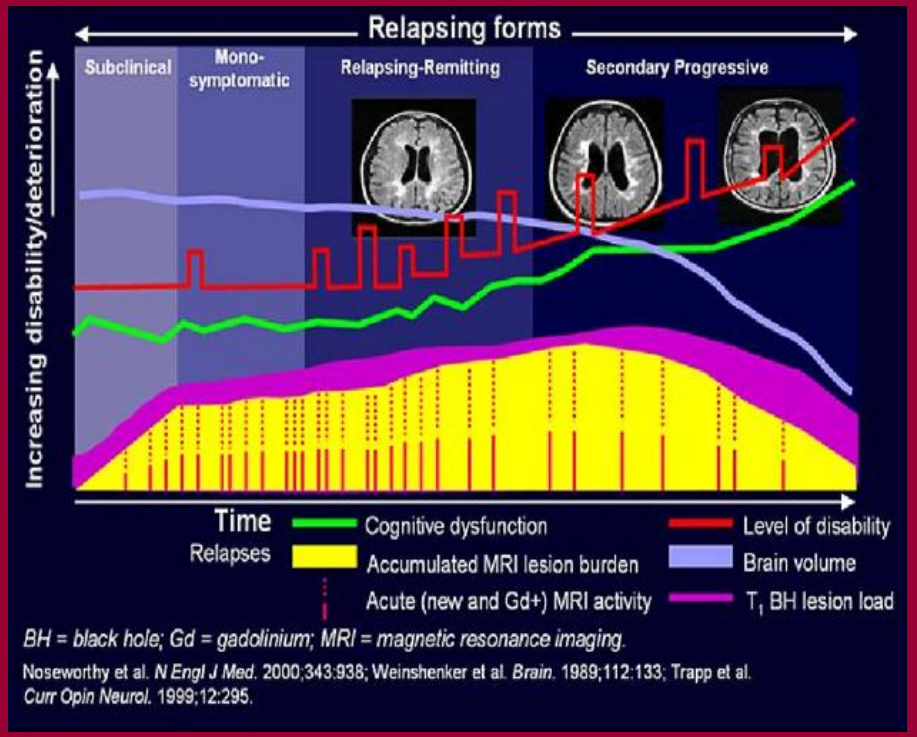
- Multiple sclerosis is a chronic, autoimmune demyelinating, degenerative disorder of the CNS
  - brain, spine, optic nerve
  - Typical sign of MS is repeating demyelinaition, disseminated in spase and time
  - Axonal degeneration
  - gliosis



- Affects around 2.5 millions people
- MS is the main cause of neurological disability in young people

Multiple Sclerosis

- Affects young people 20-40 years rarely children, after 60
- Mostly female – 2.5:1
- Incidence and prevalence in recent years increasing [1]
- Autoimmune disease-
- SLE incidence 90%



- *1Orton SM et al., Lancet Neurol , 2006*

Multiple Sclerosis

- MS is a multifactorial disorder
- No single factor is responsible for conferring susceptibility

- The aetiology is complex
- Involving both environmental and genetic factors

Multiple Sclerosis

- **Environmental factors**
- Evidence from geographical and migration studies has suggested that environmental factors play an important role in either increasing or decreasing the risk of MS in patients with a genetic susceptibility to the disease

- **Genetic factors**
- Population genetics and twin studies have shown how important the genes are in conferring susceptibility to MS
- Involved 200 small genes

Environmental factors

- There is evidence for playing roles
- both infection and the chemico-physical environment

- infection, sunshine, vitamin D, geographical gradient, race, hormonal influence, stress

- Additional data are needed to conclusively prove which factors are the most important in MS

Geographical Distribution of MS

- The prevalence of MS increases with lalitude
- increasing from the equator

- Prevalence in CR 150/100 000 inh

- North USA, Canada and Europe 250-300/100 000

- South USA, Europe, Australia 50-100/100 000

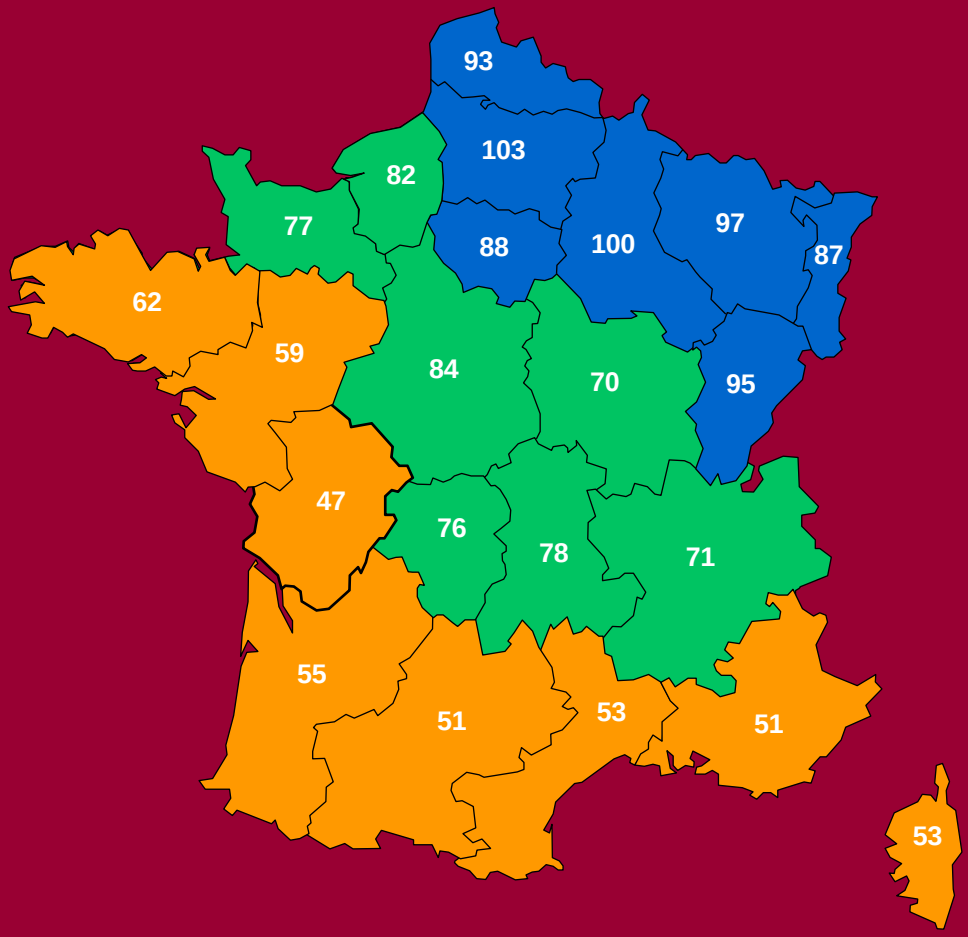
Geographical Distribution of MS

- Lowest risk
  Asia, Africa 5/100 000
- Latin America 29/100 000
  Middle East

- For the geographical distribution of MS, an environmental factors (relation infections, sunshine exposure, vitamin D)
  are a likely candidate

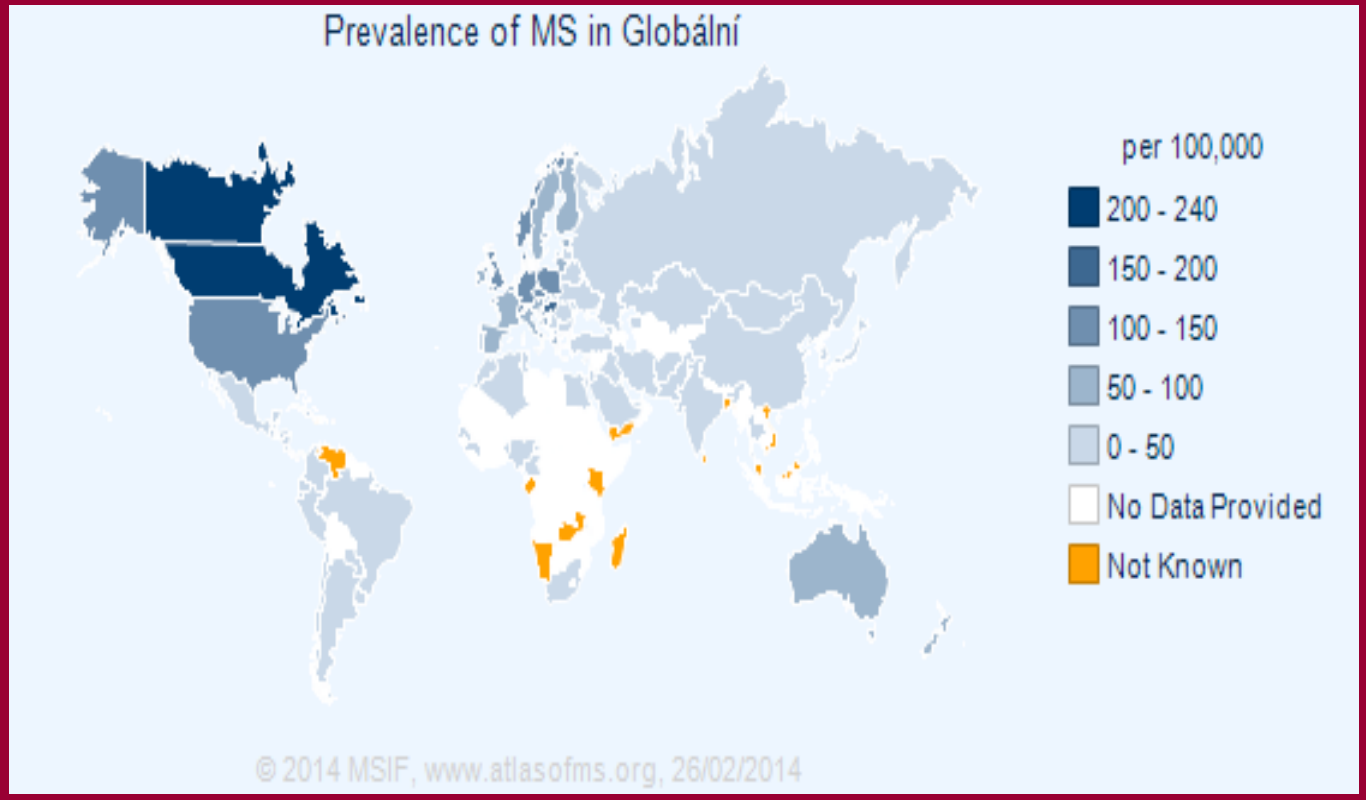
Geographical Distribution of MS
Prevalence Increases away from the Equator

- Study in France confirms that MS prevalence shows a gradient increasing from the equator
- in homogenous populations
- 4 mil. farmers
- S-N
- 69% F



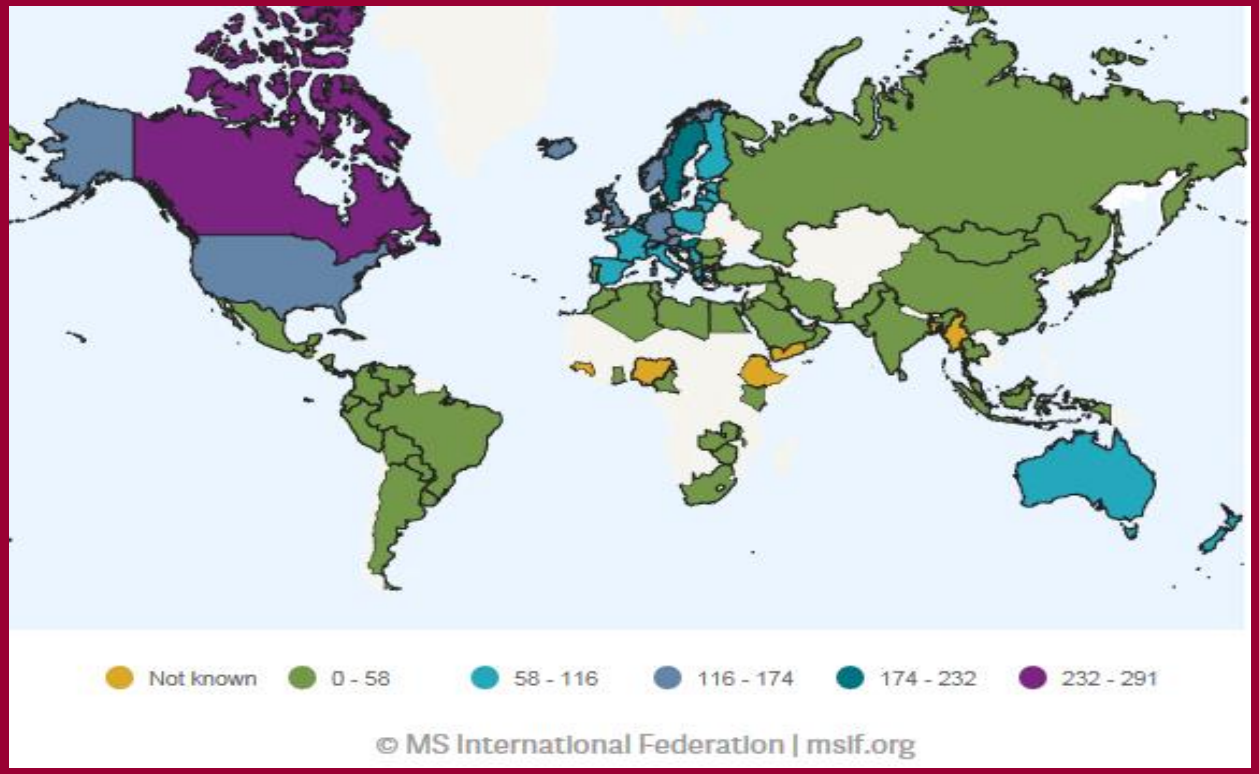
Vukusic S *et al. J Neurol Neurosurg Psychiat* 2007;**78:**707–709.

World Health Organisation
Atlas MS resources in the world 2008



World Health Organisation. Multiple sclerosis International Federation [on-line]. Atlas Multiple sclerosis resources in the world 2013. Dostupné z WWW: <http://www.atlasofms.org/>.

World Health Organisation
Atlas MS resources in the world 2013



World Health Organisation. Multiple sclerosis International Federation [on-line]. Atlas Multiple sclerosis resources in the world 2013. Dostupné z WWW: <http://www.atlasofms.org/>.

The Effect of Migration on MS Prevalence

- Individuals migrating after age of 15 have the risk of the country of origin

- An environmental factor (an infectious agent acquired during infancy/puberty is plausible for the age-related migration effects, sunshine exposure, vitamin D)

Population genetics

- MS prevalence varies with ethnic ancestry: white populations are at greatest risk 1 (areas in which Nordic invasions took place)
- Black population 0.5 risk
- Oriental 0.1 risk

- **Racial differences**
  may explain some of the geographic distribution differences
  Britain 200/100.000
  Japan 1.4/100.000- Devic
  although both countries lie at the same latitude

Genetics

- Genetic factors contribute
  to the aetiology of MS
  It is not classic Mendelian type of heridity

- Multiple small genes and their combination confer susceptibility for development of autoimmune process [1] 200

- The first genetic investigations arised from higher occurence of MS in families

- Ebers, G., 1995. Genetic factors in multiple sclerosis. MS Forum, Modern Management Workshop, Boston.

Genetic susceptibility

- Studies of families and twins provide suport
  - the life-time risk of developing MS is about 1/1000 in the general population
  - about 15% of patients with MS have an affected relative
  - children are at risk of about 5%
  - about 30% risk in monozygotic twins
  - 3-5% risk for same-sex dizygotic twins

Twin Studies

- High MZ versus DZ concordance rates reflect genetic factors
- Concordance rates vary with background prevalence:
  - Canada, Denmark, Finland, UK, USA[1] — **MZ = 25–30% DZ = 3–5%**
  - France[1] — MZ = 5.9% DZ = 3%
  - Italy[2] — MZ = 14.5% DZ = 4%

[1]Willer CJ *et al. PNAS* 2003;**100:**12877–12882; [2]Ristori G *et al. Ann Neurol* 2006;**59:**27–34.

Cumulative Effect of Adding Shared Genes

- Baseline population rate of 1/1000 – add in the risk of increasing gene sharing:
  - Cousin has MS 7/1000
  - Paternal half-sibling 13/1000
  - Maternal half-sibling 24/1000
  - Full sibling 35/1000
  - MZ twin (all genes are common) 270/1000

- DZ twins have a higher MS risk than full siblings
- both share 50% of their genome
- suggesting the role of gestational and environmental factors

Ebers GC. Unpublished data.

Genetics

- Regions of interest in MS identified on all chromosomes, but only one confirmed[1]
- The major histocompatibility complex (HLA) on chromosome 6 has been identified as one genetic determinant for MS
- Positive results for HLA Class I/II, T-cell receptor α, IL7-R, IL2-R, and cytotoxic T-lymphocyte-associated protein 4

[1]Colhoun HM *et al*. *Lancet* 2003;**361:**865–872; [2]Gregory SG, *et al. Nat Genet* 2007: published online: 29 July 2007. doi:10.1038/ng2103; [3]Dyment DA *et al*. *Lancet Neurol* 2004;**3:**104–110.

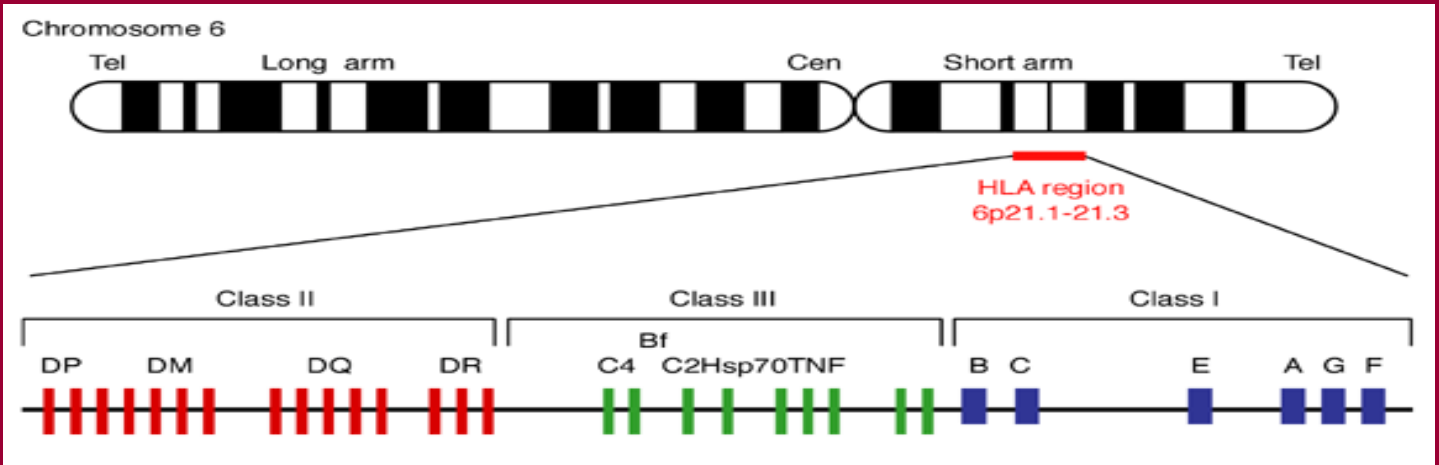
Genetics

- I. and II. class HLA genes
- play a key role in the autoimmune response and antigen presentation for CD4+ and CD8+ lymphycytes

- I class genes (HLA-A, HLA-B, HLA-C) Presentation for CD8+ lymphycytes

- II class genes (HLA-DP, HLA-DQ, HLA-DR) expression on B-, T-lymphocytes, macrophages

HLA genes - I and II class

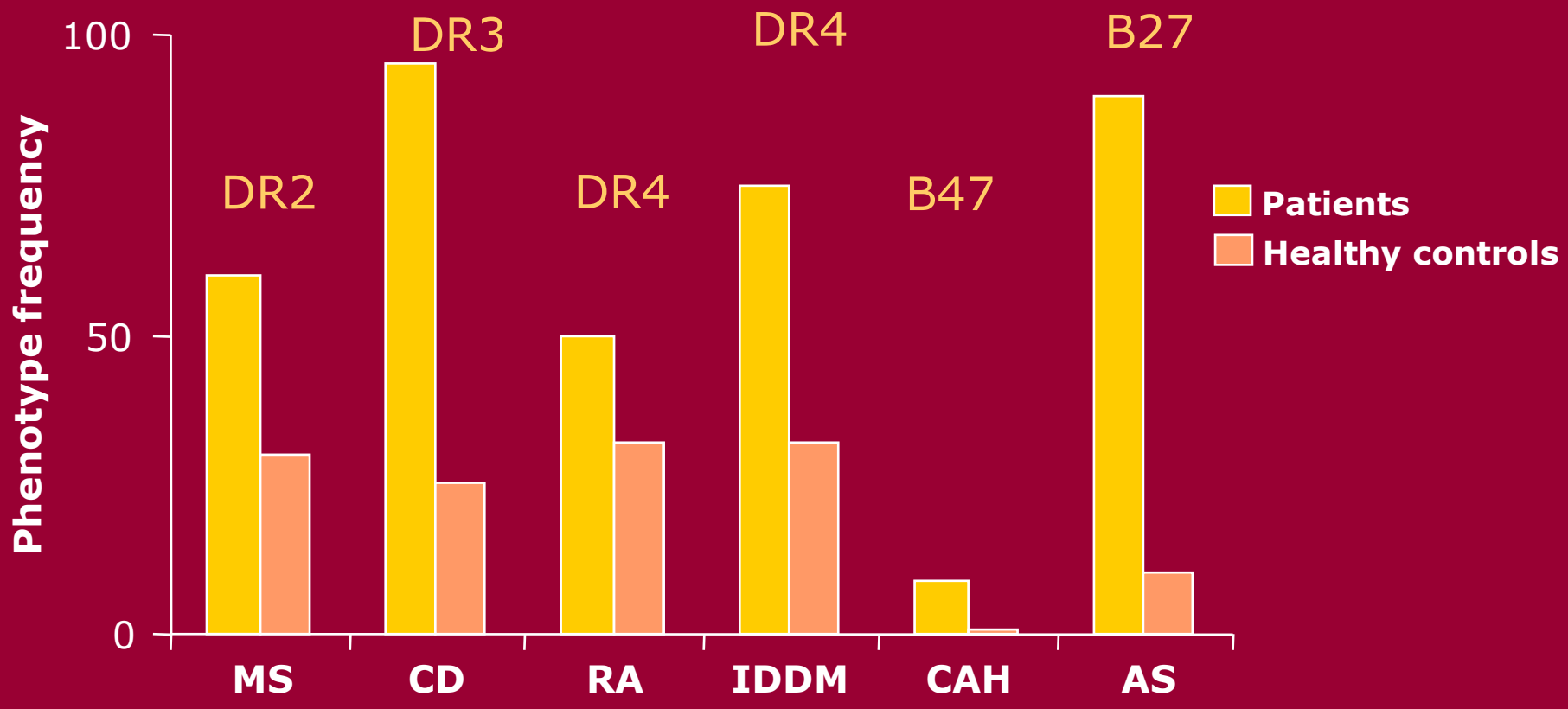


- Short arm of the 6. chromosome-most polymorphic
- Endode cell surface proteins
- Play essential role in initiating an immune response
- Presentation of antigens for CD8+, CD4+ ly

- Gene map of the HLA region. Expert Reviews in Molecular Medicine 2003 Cambridge University Press, 2003, Cambridge University Press, 2003

HLA-associated Diseases

Considerable data on HLA haplotype frequencies and autoimmune diseases



coeliac disease; type 1 diabetes; congenital adrenal hyperplasia; ankylosing spondylitis

Genetics

- Genome-wide association studies (GWAS)
- International MS Genetic Consortium (IMSGC)
- MS Genetics Group studies

- **It was proved association with DR2 haplotype in European population with MS**
  - HLA-DRB1*1501-DQA1*0102-DQB1*0602 [1-5]

- Carriers of this haplotype have a 3-fold increased risk of developing disease, in homozygotes even 6-fold

Genetics

- Metaanalysis ass studies (GWAS) in group of 9.772 patients from Europe, 17.376 2013
- Data were made by 23 research groups 15 countries, 465 434 polymorfisms
- Proved with HLA-DRB1*1501 risk allele
- (p=1x10–320, OR=3.1)
- Other populations Sweden- 61 % in MS compared to 31 % in control group
- Other ethnic groups – Japan, Middle East
- Protective effect HLA-A*02 class HLA I
- It was proved next 101 suspect gene polymorphisms

- 1 International Multiple Sclerosis Genetic Consortium: Sawcer S et al. Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. Nature 2011; 10:214-9

Genetics

- Non-HLA genes take part in the development and progression of the disease Several international studies
- Proved significant association with gene polymorphisms for CD25 and CD 127
- encoding cytokines IL-7 and IL-2
- The whole genome of 931 families was examined International MS genetic consorcium [1]
- Hafler et al., 2007

Genetics

- It was proved association with MS
  HLA A 02 and DRB1 15 have
  23 times increase risk for development of MS

- Mutations in the genes encoding inflammatory proteins may influence the expression level as well as the stability of mRNA,
  which could influence the aetiopathogenesis of the MS process

- Brynedal-2007

Genetics

- **Genes coding**

- **Cytokines** CXCR5, IL2RA, iL7R, IL7, IL12RB1, L22RA2, IL12A,
- L12B, IRF8, TNFR

- **Costimulation molecules** CD37, CD40, CD58, CD80, CD86,
- CLECL1

- **Signal molecules** CBLB, GPR65,MALT1,TYK2

- **Lack of genes** take part in neurodegenerative process

Environmental Factors

- Infections
- Sunshine and Vitamin D_3
- Stress
- Social and cultural factors

Multiple Sclerosis

Environmental Factors

Infections

Possible Candidate Microorganisms

- Chlamydia
- **Herpesviruses**
  - HHV-6
  - HSV
  - CMV
  - EBV
  - Varicella zoster
- Canine distemper virus
- Measles virus
- Rubella
- HTLV-1
- HERV
- Corona virus
- *Bordetella pertussis*
- Mumps virus

Soldan SS *et al*. *Nat Med* 1997;**3:**1394–1397.

Infectious Aetiology of MS

Viruses all have been reported to be present in patients with MS

Probable no single virus is the trigger for demyelination in all patients with MS

Instead, several different viruses may be involved

EBV and MS Risk – Epidemiological Evidence

- EBV has a potential role in MS aetiology in many sero-epidemiology studies [1–8]
- MS risk very low in people never infected with EBV[2]
  - >99% of MS patients infected with EBV (~90% of controls)[3]
- Higher risk of developing MS following symptomatic EBV infection- mononucl. than if no prior history persists for 3 decades[1]

[1]Nielsen TR *et al*. *Arch Neurol* 2007;**64:**72–75; [2]Thacker EL *et al*. *Ann Neurol* 2006;**59:**499–503; [3]Ascherio A *et al*. *Epidemiol* 2000;**11:**220–224; [4]Ascherio A *et al*. *JAMA* 2001;**286:**3083–3088; [5]Levin LI *et al*. *JAMA* 2003;**289:**1533–1536; [6]Levin LI *et al*. *JAMA* 2005;**293:**2496–2500; [7]Sundstrom P *et al*. *Neurology* 2004;**62:**2277–2282; [8]DeLorenze BN *et al*. *Arch Neurol* 2006;**63:**839–844; [9]Munch K *et al*. *Acta Neurol Scand* 1998;**98:**395–399.

Potential Mechanisms of EBV Involvement in MS

- As-yet unknown mechanisms
- Autoimmune
  - Molecular mimicry[1,2]
  - Cross reactivation between antigens EBV and PLP
- Oligodendrocyte infection
  - New symptomatic MS lesions contain evidence of extensive oligodendrocyte apoptosis [4]
- Bystander activation
  B-lymfocytes infected by EBV express new antigen alfa B crysatllin, and lead secondary to T-lymphocyte activation

[1]Lang HLE *et al*. *Nat Immunol* 2002;**3:**940–943; [2]van Sechel AC *et al*. *J Immunol* 1999;**162:**129–135; [3] Pender MP. *Trends Immunol* 2003;**24:**548–588;

HHV-6

- Evidence to support HHV-6:
  - Increased titres of HHV-6 in MS – association controversial[1–4]
  - HHV-6 showed a positive association in 29/37 MS studies[5]
  - Positive association in 78% of studies (*n*=38) if active and latent virus differentiated[6]

[1]Sanders VJ *et al*. *J Neurvirol* 1996;**2:**249–258; [2]Soldan SS *et al*. *Nat Med* 1997;**3:**1394–1397; [3]Ablashi DV *et al*. *Mult Scler* 1998;**4:**490–496;[4]Ablashi DV *et al*. *J Clin Virol* 2000;**16:**179–191; [5]Ablashi DV. http://www.hhv-6foundation.org/febpressrelease.pdf; [6]HHV Foundation. www.hhv-6foundation.org;[7] Munger KL *et al*. *Epidemiology* 2003;**14:**141–147; [8]Munger KL *et al*. *Neurology* 2004;**62:**1799–1803; [9]Bagos PG *et al. Mult Scler* 2006;**12:**379–411.

Multiple Sclerosis

Environmental Factors

Sunshine and Vitamin D_3

Multiple Sclerosis
Sunshine and Vitamin D_3

- Vitamin D3
  is very important environmental factor
  and a potent immunomodulator

- Hypothesis of relationship between chronic vitamin D_3 deficiency and increased risk for developing MS in definite geographic distribution is in relation with prevalence of this illness in temperate zone

The Main Biological Effects of Vitamin D_3

- Calcium homeostasis
  - Regulates Ca and phosphorus
  - Promotes bone formation and mineralisation

- Vitamin D_3 is a potent immune modulator
  - Enhances macrophage phagocytosis
  - Induces expression of cytokine IL-10 (anti inflammatory)
  - Inhibits production and function of Th1-inducing pro-inflammatory cytokines (IL-1)
  - Inhibits transcription of IFNγ target genes
  - Induces expression of antimicrobial peptides

The Main Biological Effects of Vitamin D_3

- Neuroprotection
  - Induces expression of nerve growth factor
  - Protects against reactive oxygen species-induced oxidative damage
- Immune system regulation
  - Promotes immunosuppression, phagocytosis by macrophages, anti-tumour activity
  - vitamin D_3 supplementation correlated with reduced risk of some cancers

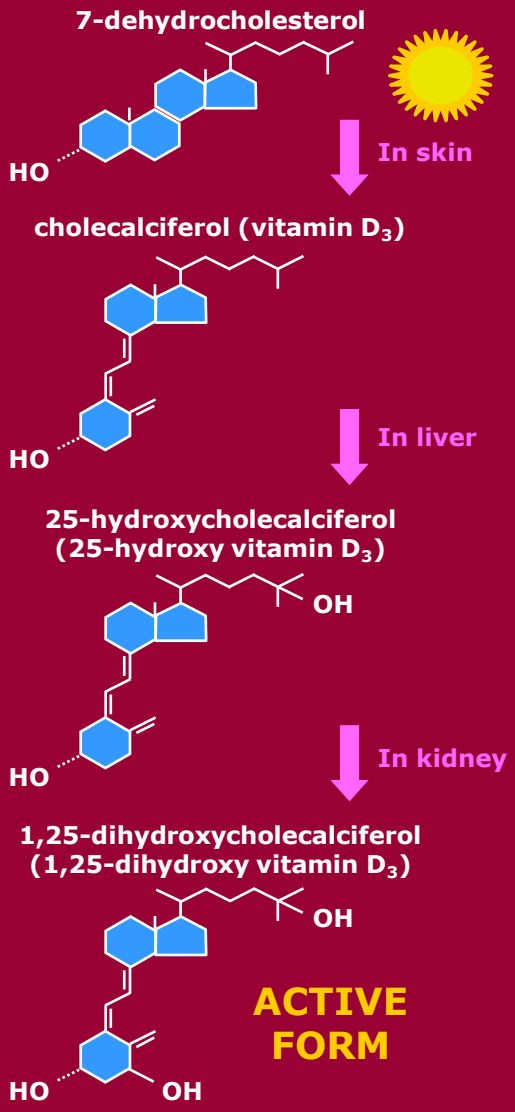
Sunshine and Vitamin D_3

- Hypothesis of relation between chronic vitamin D_3 deficiency and increased risk for developing MS in definite geografical distribution is in link with prevalence of this illness in temperate zone- geographical gradient

- Insuficient production of vitamin D3 due to low sunlight exposure
- Calcitrol - active metabolit of vit D3
  strong EAE inhibitor suplementation to severe disabled mouse improvement of disability

Biological Effects of Ultraviolet Radiation on Vitamin D_3

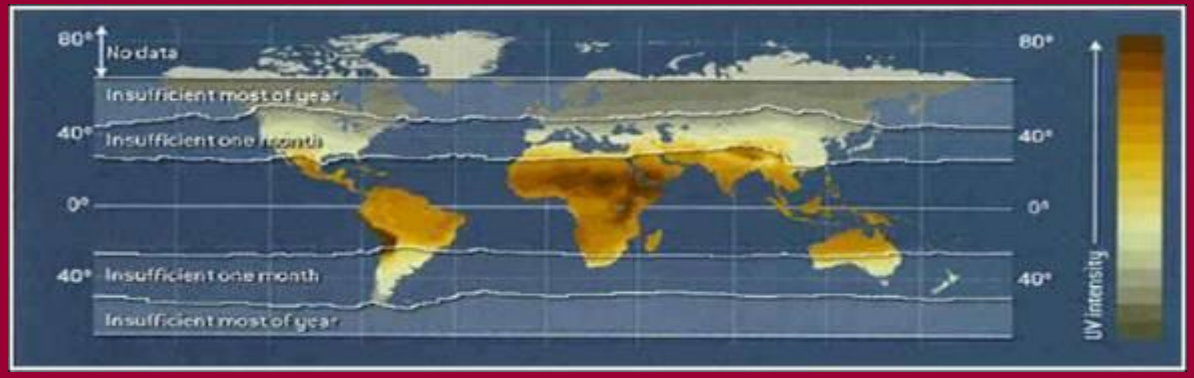
- Vitamin D_3
- Generated in skin when light energy is absorbed by a precursor molecule (7-dehydrocholesterol)
- Inactive until converted to the hormonally-active form **($1,25(OH)_2D_3$) calcitrol**



Sunshine and Vitamin D_3

Months/year when sunshine cannot produce sufficient vitamin D_3 in the skin[1–3]

No vit D for >6 m/y
No vit D for 1–6 m/y
Vit D all year
No vit D for 1–6 m/y
No vit D for >6 m/y



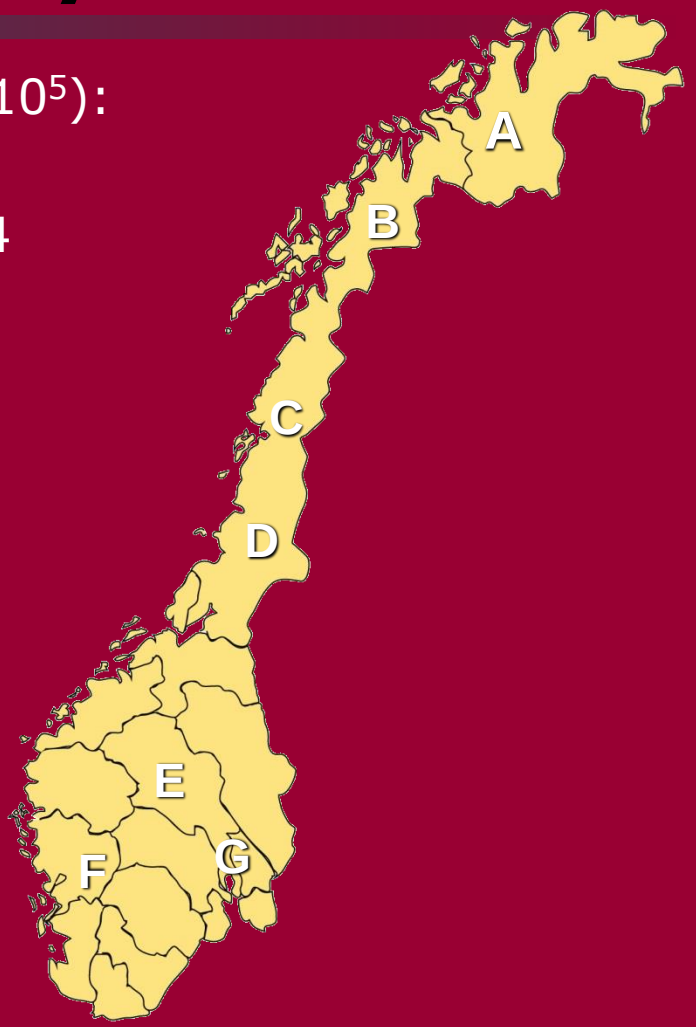
Courtesy of Sarah Chen

Theoretical skin colour based on environmental variables[1–3]

[1]Jablonski NG, Chaplin G. *J Hum Evol* 2000;**39:**57–106; [2]Jablonski NG, Chaplin G. *Scientific American* 2002;**287:**74–81; [3]Chaplin G. Am J Phys Anthropol 2004;**125:**292–302.

Prevalence of MS in Norway

- Prevalence data for counties in Norway (/10^5):
  - A Finnmark[1] (2003) >83
  - B Troms[1] (2003) >104
  - C Nordland (1999) 106
  - D Nord Trøndelag (1999) 164
  - E Oppland[2] (2002) 190
  - F Hordaland (2003) 151
  - G Oslo[2] (2005) 154
- In Norway, MS prevalence does not rise with increasing latitude, unlike other northern European countries and the USA
- Lower incidences of MS in coastal fishing areas than inland farming areas[1] due to higher nutrition intake of vitamin D3 - fishing



[1]Kampman MT *et al*. *J Neurol* 2007;**254**:471-477. [2]Personal communication.

Sunshine Implicated in Several Diseases

Reduced sunlight exposure has been linked to rickets and possibly to:

- Autoimmune diseases
  - MS
  - Rheumatoid arthritis
  - Type 1 diabetes
- Cancer (other than skin cancers)
- Seasonal Affective Disorder

Holick MF. *Am J Clin Nutr* 2004;**80:**1678S–1688S.

Vitamin D_3 in Humans: Supplementation

- Oral vitamin D_3 supplementation should be given strong consideration
- US Nutrition Guidelines: LOAEL for vitamin D_3 in humans is 2000 IU/D
  - Probably too low 200 IU/D
- The tolerable upper intake level for vitamin D_3 should probably be raised from 2000 IU/D to 10 000 IU/D[3]

- Vieth R *et al*. *Am J Clin Nutr* 2007;85:649–650; [3]Hathcock JN *et al*. *Am J Clin Nutr* 2007;85:6–18.

Other factors

- There is no evidence that MS is worsened by pregnancy
- Should be advised against routine influenza vaccination
- Surgery, anaesthesia, and lumbar punctures also have been implicated in MS, but controlled studies failed to show any relation

Multiple sclerosis
Stress

- Stress is important factor for development and progression of MS
- Play important role in activation of immune system
- Nervous, immune a endocrine systems are influenced

Multiple Sclerosis
Genetics and Environmental Factors

How could the various factors interact to cause MS

Genetically susceptible individuals
(HLA haplotype)

↓

Lack of sunlight or vitamin D_3 during gestation
and/or early life (latitude- or skin tone-related)

↓

Developmental alterations may result from deficiency in
sunlight interfering with the maturation of the nervous
and/or immune systems and the establishment of tolerance

↓

Tolerance breakdown precipitated by viral infections and
non-specific immune stimulation (EBV?)

Course of Multiple Sclerosis

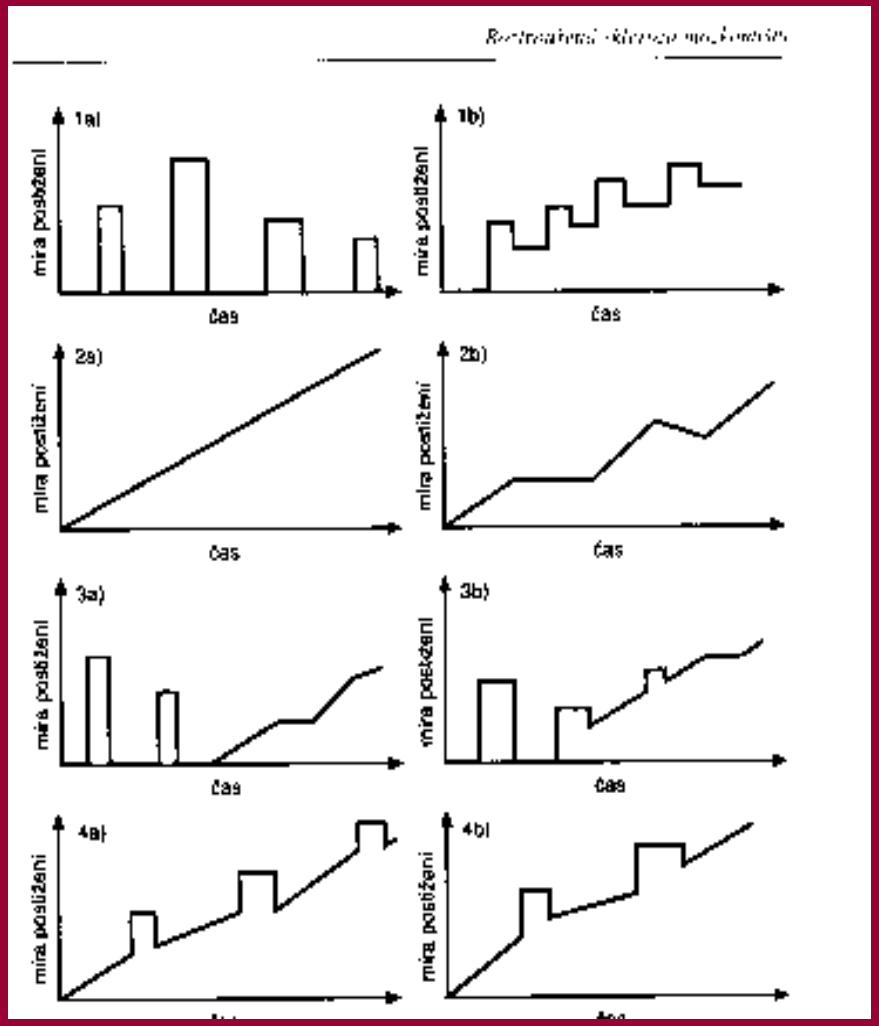
- **Relapsing-remitting MS**

- 85% of patients – the MS begins with new clinical neurological signs
- Activation of inflamation- **attack, relaps** 24 hours

Complete remission of the first symptoms occurs frequently, but during next attacks remissions do not occur or are incomplete then neurologic disability increase gradually

Follow clinical remision- months, years (1-2)

Course of the disease



- Relapsing -remitting (80-85%)
- Primary progressive (10-15%)
- Sec. chronic-progressive (30-40%) 15 years
- Relapsing-progressive 3%

Syptoms and signs

- MS varies from benign, largely symptom-free disease to a rapidly progressive and disabling disorder

- Clinical course extends for many decades in most cases
- Rare are fatal within a few months of onset

- The optic nerve, chiasm, brain stem, cerebellum, pyramidal tract and spinal cord, especially the lateral and posterior columns - are involved

Syptoms and signs

Retrobulbar neuritis, a common manifestation of MS**-25%**, is characterized by gradual decrease of visual acuity (1-2 weeks), resolve 4-6 weeks, residual impairment of color vision, dim …
Atrophy of the optic nerve
may not be associated with any fundoscopic abnormality
35 to 50% of patients with optic neuritis develop MS

Visual field defects ranging from a unilateral scotoma or field contraction to homonymous hemianopia, a central scotoma is the most characteristic field loss

Syptoms and signs

Diplopia **15 %**, VII, VIII

Limb weakness is the most common sign, monoparesis, hemiparesis, 50 %
qvadriparesis may be present, an asymmetric paraparesis

Spasticity and ataxia increase the gait disturbance
Slowly progressive spastic paraparesis
is particularly in patients with late onset

Dysarthria, gait ataxia, tremor, incoordination of the trunk or limbs

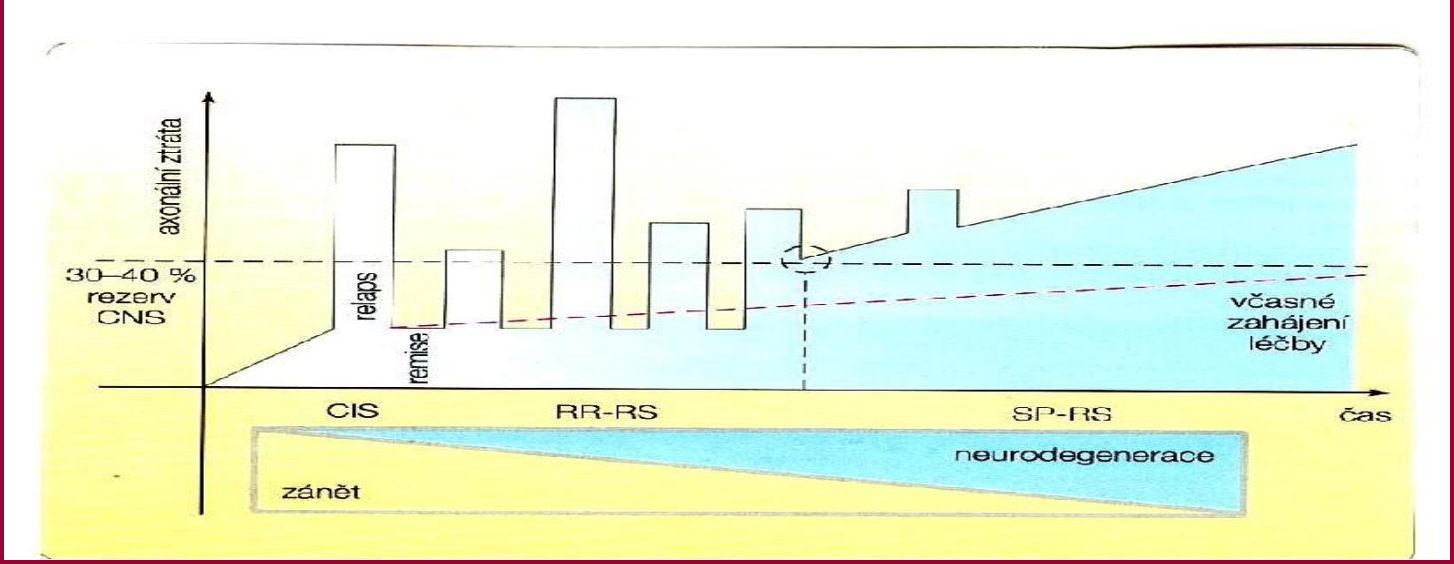
Symptoms and sign

- tremor of the head
- urinary symptoms-urgent miction, incotinency
- paresthesias and sensory impairment
- Mental symptoms
- Depression is more common than the euphoria
- Fatigue- chronic 85%
- Cognitive impairment

- monosymptomatic onset is most common

Disease course

- Two processes- inflammation, neurodegeneration
- In the beginning – predominate inflammation
- Attack-relaps- activation of inflammation
- Later – predominate neurodegneration
- Cause of neurological disability



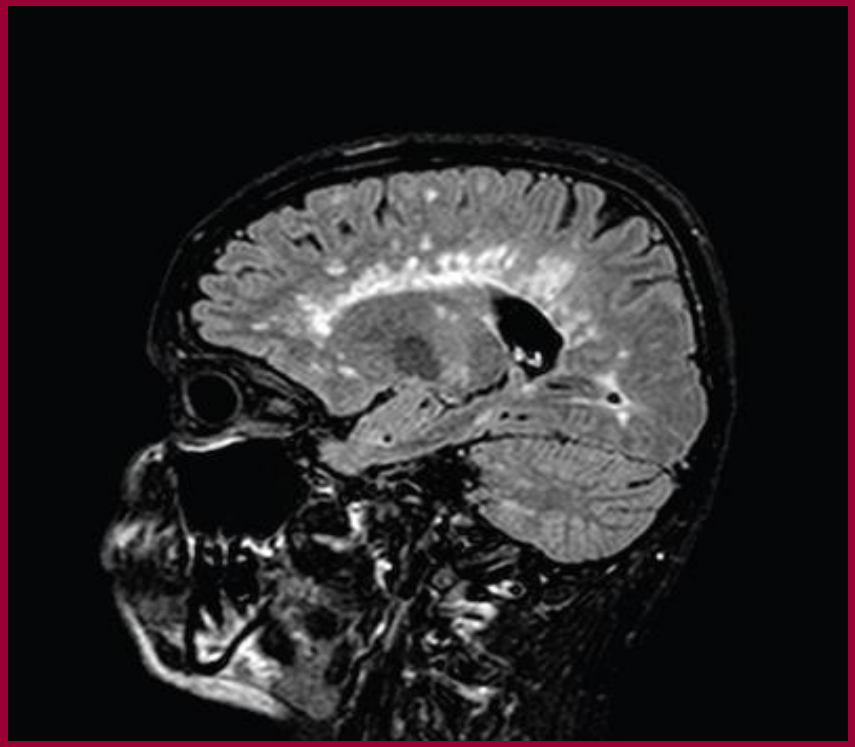
Multiple sclerosis

- Chronic inflammatory disorder of the CNS
- Demyelination and axonal degeneration
- White matter plaques in the brain
  periventricular regions
  brainstem, spinal cord, optic nerve
- brain and spinal cord atrophy
- various neurological symptoms

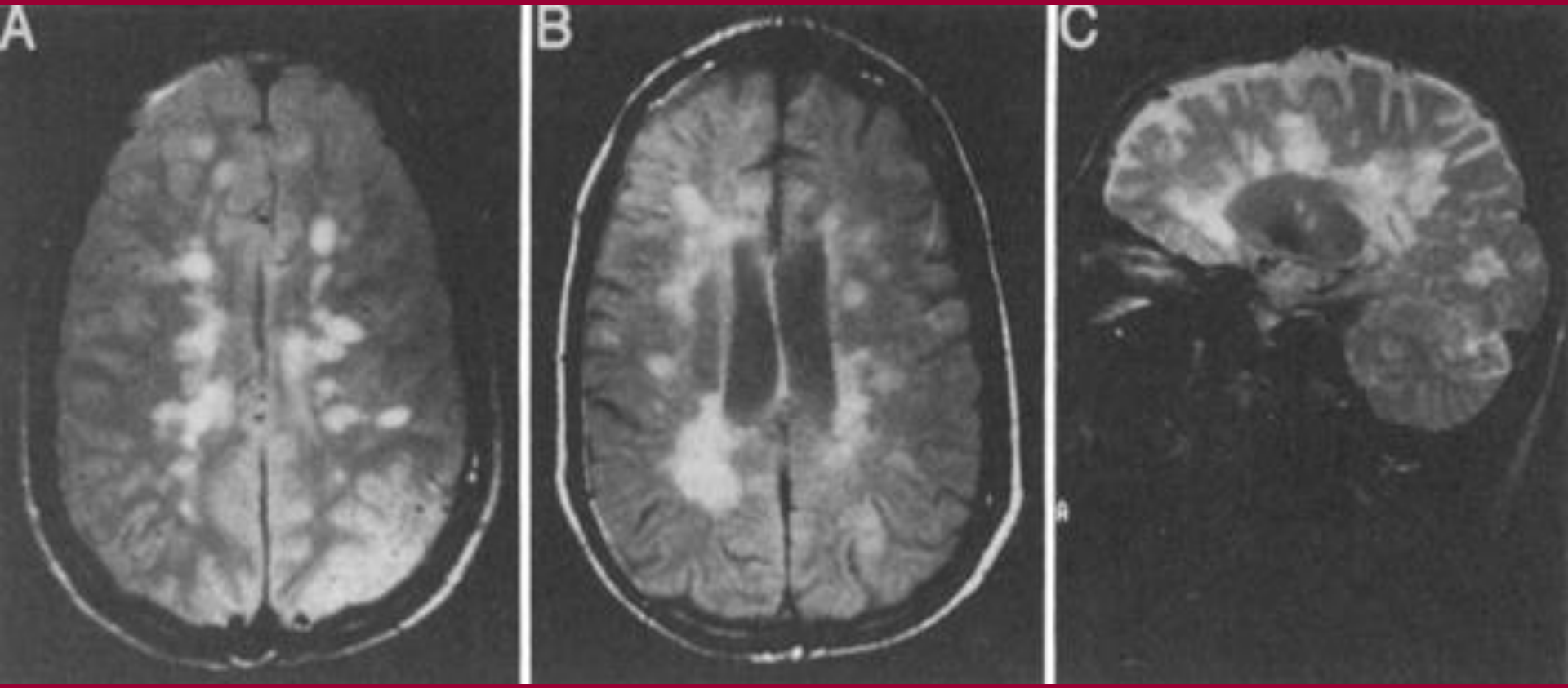
- reversibile x irreversibilile neurological deficit

Multiple sclerosis

- White matter plaques
- in the brain
- Periventricular regions brainstem, spinal cord, optic nerve, juxtacortical
- Brain and spinal cord atrophy
- Various neurological symptoms



Source: MRI scans provided by Department of Radiology University Hospital Brno.
Patient with advanced demyelinating disease- Flair Dawson fingers.



Patient with advanced demyelinating disease with typical periventricular lesions.
Source: MRI scans provided by Department of Radiology University Hospital Brno.

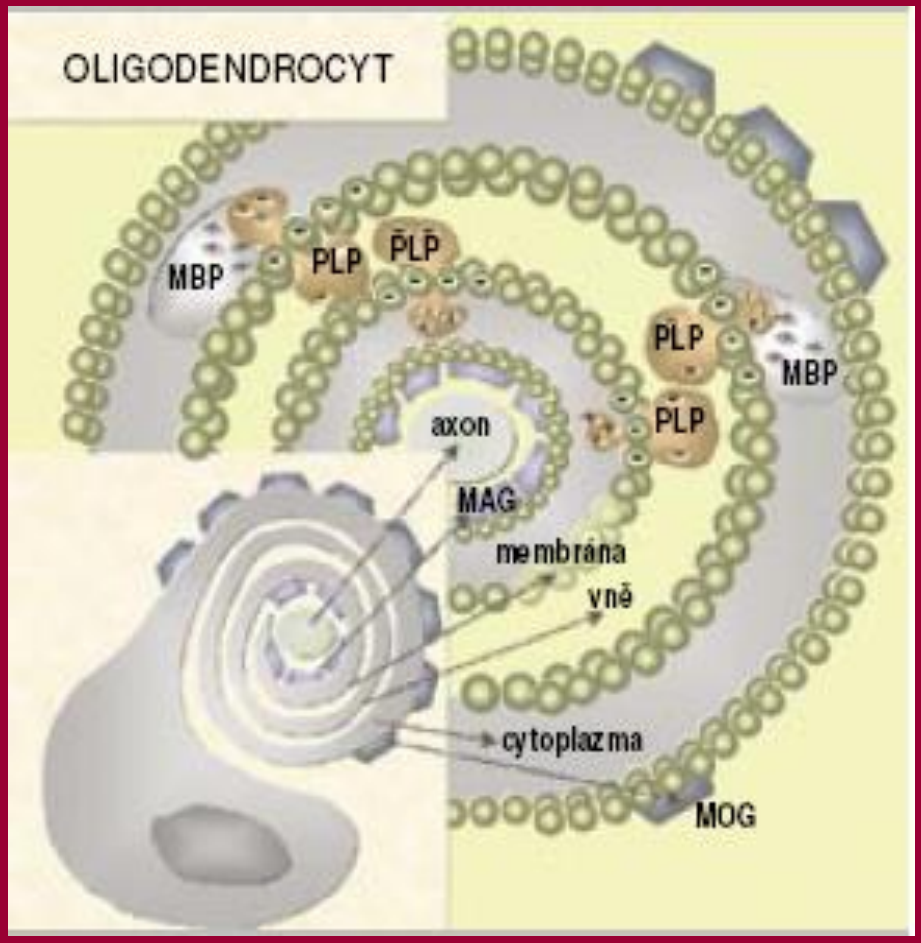
Multiple sclerosis- pathogenesis

- Autoimmune response direct against CNS antigens (MBP, MOG, MAG) and secondary autoantigens
- Activation and clonal expansion of T-cells CD-4+ and cytotoxic CD-8+
- Secrete immune mediators- cytokines,chemokines TNF, IFN, IL
- Activation B-cells, synthethise antibodies
- Activated T-cells, B-cells,microglia, macrophages migrate across BB barrier

Multiple sclerosis- pathogenesis

- Autoimmune response direct against CNS antigens (MBP, MOG,MAG) and secondary autoantigens

- Recognition of ‘non-self’ antigen generally results in an immune response.
- Similar aminoacid sequence as in viruses-herpetic, EBV ..



Multiple sclerosis- pathogenesis

- Inflammation is a major contributor to the formation of acute lesions
  destruction of myelin sheats
  axonal degeneration
  demage of oligodendrocytes
- Degree of inflammation is in correlation with the extent of axonal loss
- primarily axonal degeneration

- **Four patterns of active MS lesions**

Management

- Course can be modified
- No treatment completly stops the disease

Approved therapies

- Interferon β-1a -Rebif® Avonex®, Plegridy® (30ug i.m./weekly)
- Interferon β-1b Betaferon® 0,25 mg every other day s.c.

- Glatiramer acetate- Copaxone® 40 mg/D s.c.
- Teriflunomide – Aubagio p.o.

- Slow accumulation of neurologic disablity by 30-40%, reduction of number and the severity of clinical attacks, and increasing MRI lesions

The first line therapy

Drug	Admin	Dose	Frequency	Name
INF beta- 1b	s.c.	250	EOD	Betaferon
INF beta- 1a	s.c.	22, 44	3 x weekly	Rebif 22 Rebif 44
INF beta- 1a	i.m.	30	1x weekly Every two weeks	Avonex Plegridy
Glatiramer acetát	s.c.	40	3 x weekly	Copaxone

Indication criteria for the initiation of DMD therapy

- CIS
- RR-MS
  2 attacks in the past year
  3 attacks in the past 2 years

- Attack treatment
- methylprednisolon-
  Solu-Medrol 3-5 grams
- It reduces inflammation activity
  It will not affect the progression of the disease even with repeated administration

- Interferon beta is an antiproliferative multifunctional cytokine

- Complex immunomodulatory effect -
  reduction of activation and penetration of autoaggressive T ly into the CNS
  reduction of proinflammatory cytokine production, interferon gamma
  increased production of anti-inflammatory cytokines
  It reduces the permeability of the blood-brain barrier

Glatiramer acetate- Copaxone

- Copolymer of four amino acids (glutamate, lysine, alanine, tyrosine) contained in the same ratio as MBP
  Autoaggressive ly bind to GA
  produce anti-inflammatory cytokines
  and produce neuroprotective BDNF

- S.c. at a dose of 40 mg 3x week
  Total reaction - histamine, redness, shortness of breath, lasting a few minutes, local reactions

Second line treatment

- Patient treated with interferons or glatiramer acetate

  The persistent high activity of the disease

- Tysabri-Natalizumab
- Fingolimod- Gilenya
- Tecfidera-Dimethyl fumarate
- Ocrevus- Ocrelizumab
- Mavenclad- cladribinum
- Lemtrada-Alemtuzumab

Natalizumab - Tysabri

- Monoclonal antibody

  It binds to the adhesion molecule VLA-4 on the surface of white blood cells and blocks its binding to vascular endothelial cells
  Prevents white blood cells from penetrating into the CNS

  Reduces RR - up to 60%
  It slows the progression of disability
  Significantly reduces brain MR activity by up to 90%

Natalizumab - Tysabri

- It is given as monotherapy
  This highly effective treatment is unfortunately associated with the risk of developing Progressive Multifocal Leukoencephalopathy – PML

- Unfortunately, at present, there are no screening tests that would allow a reliable measure of risk

- Significant risk factors include duration of therapy
  Previous treatment with immunosuppressants
  The presence of ELISA antibodies detected in serum JC virus

Natalizumab - Tysabri

- Risk of developing PML

Treatmen duration	**Anti-JCV Antibody Negative**	**Anti-JCV Antibody Positive**
	Immunosupressive therapy **-**	Immunosupressive therapy +
1-24 months	<1/1.000	2/1.000
25-48 months	4/1.000	11/1.000

FINGOLIMOD- GILENYA

- It is a synthetic analog of myriocin, derived from Isaria Sinclair's mushroom

  It binds to four of the five subgroups of sfigosine-phosphate receptors in the human body

  The S1P1 receptor is responsible for the immunomodulatory effect of Fingolimod

  Binding of this receptor on the surface of white blood cells leads to their reduced travel from the lymphatic tissue

FINGOLIMOD- GILENYA

- There is a significant reduction of MRI lesions
  lower annual RR
  up to 77% of patients are without an attack

Second line treatment

- **Ocrelizumab- Ocrevus** directed against CD 20 antigen on mature B cells, but not plasma cells
- for non-Hodkin´s lymphoma and RA
- fairly safe medication (market 2019)
- i.v. infusions, 2 weeks apart, every 6 months

- **Alemtuzumab-Lemtrada**
  AB against CD 52,
  antigen on most B and T ly (leukemia)

- **Cladribine- Mavenclad**

Generalized immunosupression

- Corticosteroids
- Methylprednisolon 1 g per day for 3-5 days
- Medrol 4mg/day
- Prednison 5 mg/day

Generalized immunosupression

- Azathioprine-modest effect
- Mitoxantrone- immunosupressant (side effect cardiomyopathy, promyelocytic leukemia)- in rapidly progressive MS
- Cyclophosphamide??
- Methotrexate-slight effect
- Cyclosporine A (renal side effects)

Symptomatic treatment

- Fatigue: Amantadine 2x100 mg (Viregyt)
- Spasticity: Baclofen, Sirdalud
- Spastic blader: Spasmex, Ditropan
- Amitriptyllin 25 mg
- Antineuralgic treatment: Lyrica, Gabapentin

Current treatment of RR-RS

- Long-term treatment slow the progression of the disease
- Treatment of acute attack of the disease

- Disease modifying drugs - DMD
  Slow progression
  immunomodulatory and immunosuppressive effect
- Anti-inflammatory effect

Current treatment

- At present, we have a range of therapeutic options in MS treatment.
- These drugs have in particular an anti-inflammatory effect.

  Therefore, our primary goal remains the early diagnosis of MS, the earliest initiation of treatment and thus the prevention of the development of the neurodegenerative process.
- To prevent the disability of the patients