Multiple sclerosis

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Multiple Sclerosis

- Approximately 350 000 people in the United States are affected by MS
  - Prevalence strongly dependent on latitude (25-224/100 000 Israel-Scotland)
- MS is typically diagnosed in young adults between the ages of 20 and 40
- Two-thirds of people diagnosed with MS are women

PATHOGENESIS: multifactorial causation

- genetic predisposition: association with HL-A A3, B7, B18, and DW2/DRW2
- environmental exposure
- abnormal immune regulatory response
  - may be related to infection with several viruses: antibodies in the serum and CSF in MS
- age of individual at exposure

MS precipitating factors:

- infection
- trauma
- surgery
- pregnancy and puerperium (the exacerbation rate falls during pregnancy and climbs after delivery)

Symptoms of MS

- Weakness
- Numbness
- Fatigue
- Vision problems
- Speech difficulty
- Poor coordination
- Short-term memory loss
- Depression
- Bladder and bowel dysfunction
- In severe cases, partial or complete paralysis

Pathology of MS

- Perivascular inflammation
  - axonal transection
  - microglia mediated removal of myelin
- Persistent demyelination despite some remyelination (oligodendrocyte dystrophy);
- Chronic lesions show further axonal loss and gliosis.
- Pathological heterogeneity!!

- In primary progressive MS there is pronounced axonal degeneration with or without a preceding inflammatory phase.

What is MS?

- A chronic, inflammatory disease of the central nervous system (CNS)
- Results in periodic loss of neurological function and often progressive disability
- Occurs when the myelin (demyelinisation), and protecting neurons (neurodegeneration), is destroyed
- When the myelin is lost in multiple areas, plaques and lesions (inflammation and sclerosis [scar tissue]) occur

White matter plaques are scattered randomly

- cervical posterior columns
- optic nerve and chiasm
- corpus callosum
- periventricular white matter
- brainstem
- floor of the fourth ventricle - pyramidal tract

Motor symptoms

- spastic weakness, „fatique”
- hyperactive deep tendon reflexes
- extensor plantar response
- often absent abdominal reflexes

Cerebellar symptoms

- incoordination: intention tremor
- ataxic gait
- dysarthria: spastic weakness or ataxic speech, "syllabic" or "scanning" speech
- "Charcot triad" of cerebellar signs: nystagmus, scanning speech, intention tremor

Visual symptoms

- retrobulbar neuritis "blindness" in one eye
- central scotoma (larger for red and green than for white)
- papillitis may occur
- residual optic atrophy with temporal pallor of the disc

Sensory symptoms

- tingling, numbness, painless paraesthesia
- posterior column lesion: impaired vibration sensation, joint position sensation

Disturbance of ocular movement

- diplopia
- internuclear ophthalmoplegia
- nystagmus

Vestibular symptoms

- vertigo with vomiting

Mental symptoms, emotional changes

- sense of mental and physical well-being euphoria
- depression
- uncontrolled outbursts of crying and laughing
- dementia

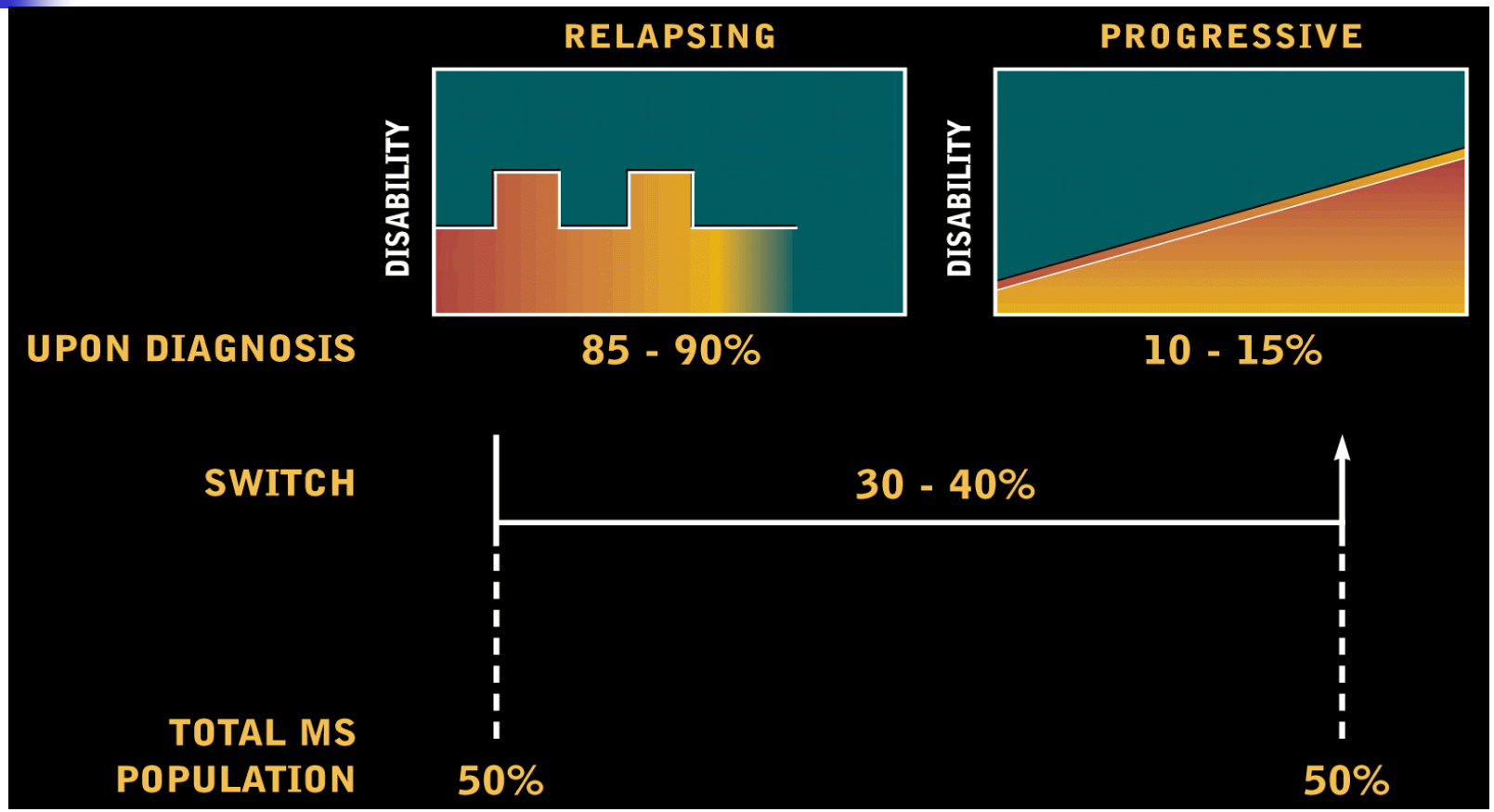
Sphincter disturbance

- urgency and precipitancy of micturition
- incontinence
- urinary retention
- impotence

What is the Range of MS Severity?

- People with MS usually fit into one of two general categories according to the predominant course of the disease:
  - Relapsing
  - Progressive

Types of multiple sclerosis



How is MS Diagnosed?

- MS is difficult to diagnose:
  - symptoms come and go
  - similar warning signs as other diseases of the central nervous system

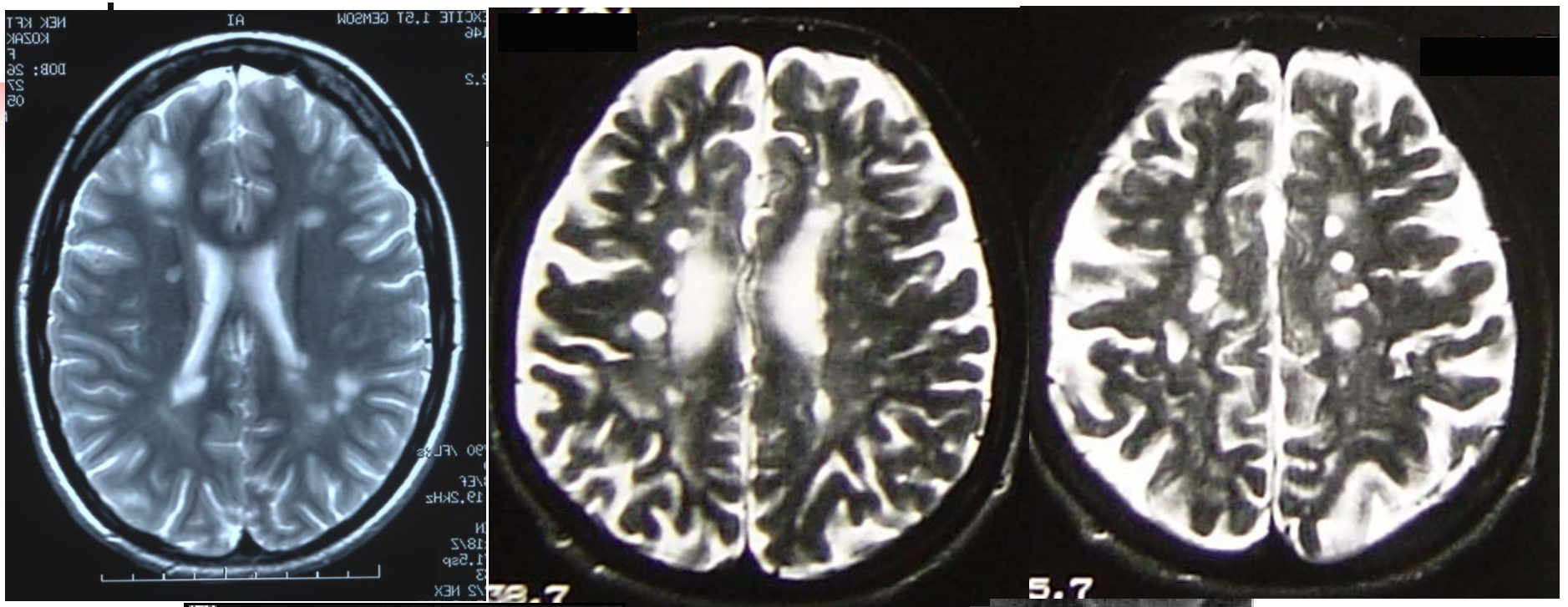
How is MS Diagnosed?

- For a conclusive diagnosis, the following must be shown:
  - At least two neurological attacks occurring at separate times
  - Evidence on neurologic exam of two separate lesions or evidence on exam of one lesion with Magnetic Resonance Imaging (MRI) evidence of a separate lesion

Diagnosis of MS

- No specific diagnostical test!
- McDonald criteria (2001):
- Clinical
- MRI – dissemination of lesions in both time and space
- CSF
- Evoked potential

T2-weighted MRI showing classic periventricular location of plaques



CSF

- mild pleocytosis (T and B lymphocytes)
- total protein is often normal or moderately raised
- the proportion of gamma globulin is raised by electrophoresis
- oligoclonal bands by gel electrophoresis are found in up to 95% after the first attack of symptom

VEP

- The large positive wave:
- the latency delayed beyond 110 msec or absent
- or the amplitude of the waves may be reduced

Differential diagnosis

- Microangiopathies
- Vasculitis
- NMO
- ADEM
- Leukodystrophies
- Lymphoma
- B12 deficienty
- Borreliosis
- PML

Therapy of MS

- Treat the relapse
  - Methylprednisolon 1 g/day i.v. for 3-5 days
- Decrease the number of relapses (underlying disease: altering the immune response against the myelin sheath)
- Symptomatic treatment (disease-related complications)
- Improve the quality of life

Long term immunomodulatory treatment – first line

- Chance to stabilize the course of disorder
- Decrease the number of relapses

- Indication: ambulatory relapsing-remitting (RR) course
- having at least two medically documented acut exacerbations during 2 years before enrollment

Long term immunomodulatory treatment – platform therapy – long term safety

- Reduction in the relapse rate by about 32 %,
  - Interferon beta 1b*:* **Betaseron , Extavia** (10 000 dollar/a year) – 250 µg every other day s.c.
- Slowing in disability (EDSS score)
  - Interferon beta 1a:
  - **Avonex** 30 µg/week i.m.
  - **Rebif** 44 µg weekly 3x s.c.
- Reduction in the relapse rate by about 28 %,
- Copolymer 1, glatiramer acetate:
  - **Copaxone** weekly 3x s.c.

Immunomodulatory treatment – first options

- reduction in the relapse rate by about 30 %
  - *Teriflunomide: Aubagio* – 1x14 mg/day p.o.

- reduction in the relapse rate by about 44-50 %
- *Dimethylfumarate: Tecfidera* 2x240 mg/day p.o.

- First line in Europe/ second line in USA:
- reduction in the relapse rate by about 49-55 % to INFB
  - *Alemtuzumab: Lemtrada* 12 mg/day x 5 i.v. in 1st year, 3x in 2nd year cycle

  (monoclonal antibody targeting CD52)

Second line treatment in RRMS

- Immunosuppressive MS therapy:
- Fingolimod (Gilenya®): oral drug
  - non-responders for DMT – Europe
  - First line – USA
  - or highly active disease onset

- Ocrelizumab (Ocrevus®): non-responders, relapsing progressive
- and PRIMARY PROGRESSIVE MS
- (CD20+ B cell depleting Ab) - 6 monthly i.v.

Second or third line treatment

- Immunosuppressive MS therapy:
- Cladribine (Mavenclad®): short course of oral drug – inhibit DNA synthesis
  - treating highly active relapsing MS –
  - 2017 in Europe

- Mitoxantrone (Oncotrone ®): non-responders and relapsing progressive (1453 $/month)

  3 monthly i.v. 12.5 mg/m^2 – to 2 years, cardiotoxic (AML)

Symptomatic treatment

- spasticity: Baclofen (Lioresal®), Dantrolene, Tizanidin (Zanaflex®), Botulinum toxin, oromucosal spray nabiximol (Sativex)
- fatigue: dalfampridine (AMPYRA®), Amantadine (Symmetrel®)
- paroxysmal pain: amitriptyline for neurogenic pain and emotional lability, carbamazepine
- bladder dysfunction: cholinergic-anticholinergic drugs: oxybutynine chlorid (Ditropan)
- depression: SSRI

Summary

- Multiple sclerosis (MS) is a chronic disorder, that affects the central nervous system and a leading cause of disability in young adults.
- The clinical course is variable.
- Diagnosis should be based on objective evidence of two or more neurologic signs that are localized to the brain or spinal cord and are disseminated in time and space (detailed medical history, physical and neurological examination, MRI scan – spinal tap).
- There is no cure for MS, but medicines may slow it down (immunomodulations) and help control symptoms.

WEB pages

- http://www.nationalmssociety.org/
- http://www.mscare.org/
- http://www.ms-gateway.com/
- http://www.aan.com/go/practice/guidelines