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Multiple sclerosis – clinical presentation

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Learning objectives

- Describe the different clinical courses and their frequency
- List the variety of neurological symptoms seen in MS
- Review the imaging, clinical and laboratory tests that are used to diagnose MS and the key differential diagnosis
- Understand the variability of MS prognosis

Outline of lecture

- MS definition
- Epidemiology and social impact
- Clinical presentation and symptoms
- Clinical criteria for diagnosis
- Differential diagnosis
- Diagnostic procedures
  - CSF
  - MRI
  - Electrophysiological testing
- MS clinical subtypes
- Prognosis
- Complications

Multiple sclerosis: definition

- A chronic inflammatory multifocal demyelinating disease of the central nervous system of unknown cause resulting in loss of myelin and oligodendroglial and axonal pathology
- Typically affecting young adults with exacerbating-remitting pattern or chronic progressive evolution

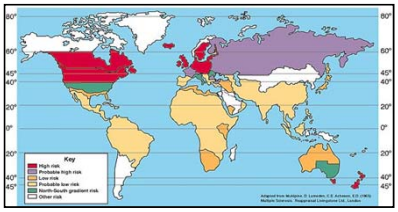
MS: Frequency and distribution

- More common in women than in men (~3:1 to 2:1)
- Onset typically between age 20 - 50
- Uneven geographic distribution
- Prevalence rates range between 80 and 240 in 100,000 in Northern European and –American countries
- Incidence: 3-5 cases/100,000/year

MS: epidemiology

- Latitude gradient
- More common in people of Northern European descent (Viking effect)
- Rare in native Americans, Australian aboriginals and Japanese
- Clusters
- “Epidemics” (British Invasion of Far Oer islands); controversial
- Migration studies

Distribution of MS in the World



Genetic factors

Environmental factors → Pathogenesis ← Viral infections

(latitude gradient - low sunlight exposure?)

Hormones

(Epstein Barr virus?)

MS – genetic factors

- Concordance rates
  - 25-30% in monozygotic twins
  - 2.3% in dizygotic twins
  - 1.9% in non-twin siblings
- Genetic susceptibility from a polygenic trait including mostly immune genes including:
  - HLA-DR2 (a.k.a. DR15 Dw2, or DRB1*1501 /DRB5*0101)
  - IL-7R
  - IL-2R alpha

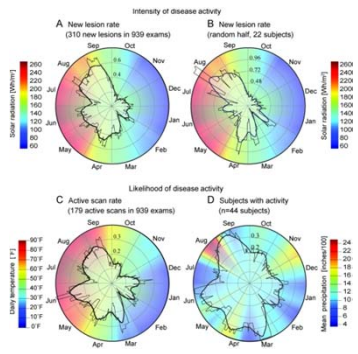
Environmental factors

- MS in migrants
- Infectious agents, particularly viruses (→immunology)
- Vitamin D and sunlight exposure
- Smoking
- Many other hypotheses/claims

Studies of MS in migrants

- Migrants from high-risk to low- risk zones who are under 15 years of age at migration are significantly less likely to develop MS than those who migrate at an older age
  - Migrants aged 15 or older from Northern European high-risk areas to South Africa (low risk) took with them high frequency of origin
  - Migrants aged <15 had the lower frequency of native-born South Africans (Dean and Kurtzke 1971)
  - Same for migration to Australia McLeod et al. 2011 JOURNAL OF NEUROLOGY Volume 258, Number 6, 1140-1149)
- First generation immigrants from low-incidence areas (African, Afro-Caribbean and Indian) to Britain have a much lower incidence of multiple sclerosis than their second generation counterparts (Elian et al JNNP 1990)

Seasonal prevalence of MS disease activity



Neurology. 2010 Aug 31;75(9):799-806.
Meier DS, Balashov KE, Healy B, Weiner HL, Guttmann CR.

MS: social impact

- Usually presenting between the ages of 20 and 40 years
- After stroke, Parkinson's disease and MS are the two commonest disabling diseases of the CNS in the UK
- In young adults, most common non-traumatic cause of disability
- Most frequent demyelinating disease of the central nervous system (CNS)
- In the UK ~85-100 K people have MS
- 2-3 M have MS worldwide

MS: main clinical manifestations and their *tempo*

- Symptoms result from disruption of myelinated tracts in the CNS
  - Visual
  - Motor
  - Sensory
  - Cognitive and psychiatric
  - Bowel, bladder
  - Sexual
- Onset: hours to days
- Recovery: days to months

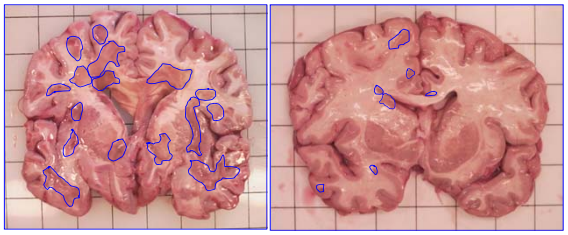
Common disturbances in MS

- Optic neuritis
  - Monocular vision loss
- Spinal cord lesion
  - Weakness of limbs with spasticity and hyperreflexia
  - Paraesthesiae, pain or sensory loss in limbs or trunk
  - Lhermitte's sign (electric shock radiating down back and triggered by neck flexion)
  - Urinary urgency and incontinence
- Brainstem lesion
  - Diplopia
  - Paraesthesiae, pain (incl.trigeminal neuralgia) or numbness of face or tongue
  - Vertigo and nystagmus
  - Dysarthria
- Cerebellar lesion
  - Incoordination of limbs
  - Ataxic gait
- Cerebral lesions
  - Impairment of concentration or memory
  - Hemiparesis
  - Hemisensory loss
  - Visual field defect
- Severe fatigue

Adapted from Pender, MJA 2000

Why are symptoms so varied

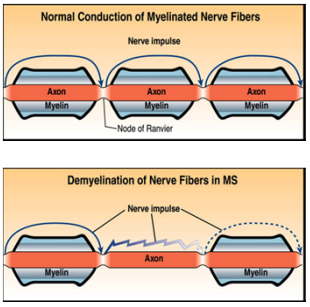
Because the amount and location of damage to the nervous system is different in each person with MS



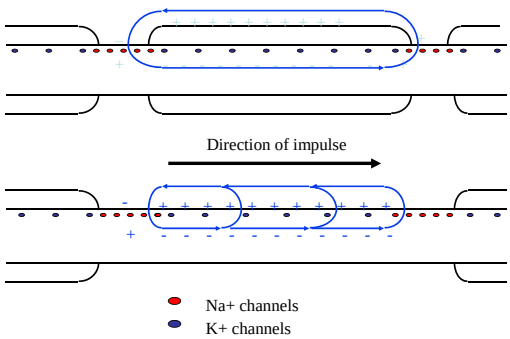
Disease duration <20 years, age 44

Disease duration 35 years, age 71

Effects of demyelination on nerve impulse conduction



Courtesy of Dr J Rose, Univ. of Utah

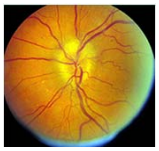


MS: objective signs

- Weakness, spasticity, pyramidal signs
- Sensory loss
- Impaired coordination, action and intention tremor
- Unilateral visual loss
- Conjugate eye movement disorders: diplopia, nystagmus

Examples of abnormal findings at neurological examination

Retrobulbar optic neuritis (2/3 of cases)



Optic neuritis with papillitis (1/3 of cases)

Intention tremor and dysmetria (cerebellar dysfunction)

Short break

Diagnosis of MS

- Primarily a clinical diagnosis. Requires:

1. **Exclusion of other likely causes**
2. Evidence of **dissemination in space and time** of CNS lesions

Differential diagnosis
(main possibilities out of many CNS inflammatory disorders)

- **Systemic immune diseases affecting the CNS**
  - Neurosarcoidosis
  - Systemic lupus erythematosus
  - Anti-phospholipid syndrome
  - Sjogren's syndrome
  - Vasculitides (but also primary CNS vasculitis exists)
- **CNS-specific inflammatory syndromes**
  - **Acute disseminated encephalomyelitis (ADEM)**
  - **Neuromyelitis optica (NMO)**

McDonald's diagnostic criteria

2005 Revised McDonald MS Diagnostic Criteria[1]

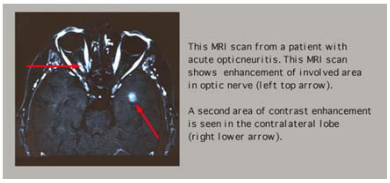
CLINICAL (ATTACKS)	OBJECTIVE LESIONS	ADDITIONAL REQUIREMENTS TO MAKE DX
2 or more	2 or more	None. Clinical evidence alone will suffice; additional evidence desirable but must be consistent with MS
2 or more	1	Dissemination in space by MRI ***or*** 2 or more MRI lesions consistent w/ MS plus positive CSF ***or*** await further clinical attack implicating other site
1	2 or more	Dissemination in time by MRI ***or*** second clinical attack
1	1	Dissemination in space by MRI ***or*** 2 or more MRI lesions consistent with MS plus positive CSF **AND** dissemination in time by MRI ***or*** second clinical attack
0 (progression from onset)	1 or more	Disease progression for 1 year (retrospective or prospective) **AND** 2 out of 3 of the following: • Positive brain MRI (9 T2 lesions ***or*** 4 or more T2 lesions with positive VEP) • Positive spinal cord MRI (2 or more focal T2 lesions) • Positive CSF

[1]Polman et al. Diagnostic Criteria for Multiple Sclerosis: 2005 Revisions to the "McDonald" Criteria. *Annals of Neurology* (2005) 58: 840-846

Diagnosis of MS

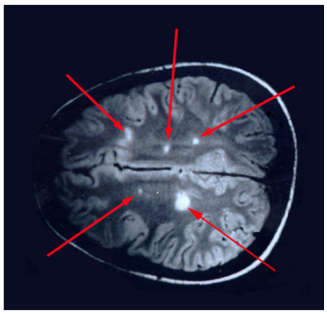
- MRI
- Cerebrospinal fluid (CSF) analysis
  - Increased production of Immunoglobulin in CSF
  - Oligoclonal bands
- Electrophysiology
  - Visual evoked potentials (VEP)

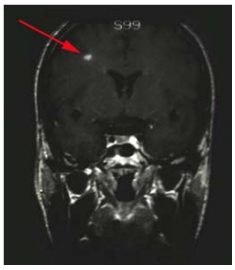
MRI – optic neuritis



Courtesy of Dr J Rose, Univ. of Utah

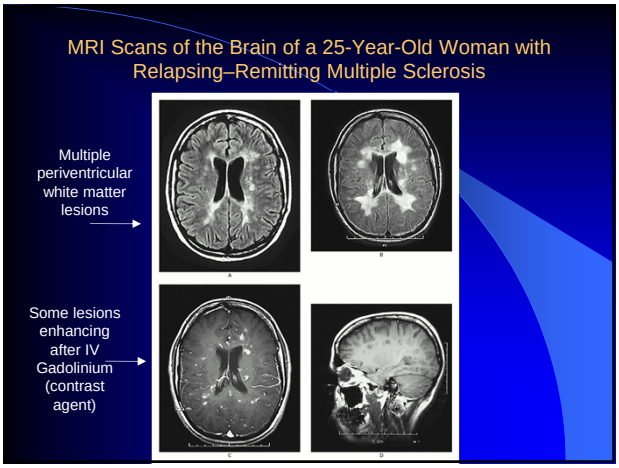
MRI in MS – multiple areas of hyperintense signal



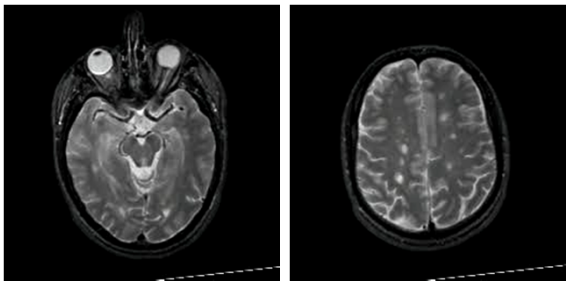


Courtesy of Dr J Rose, Univ. of Utah

MRI Scans of the Brain of a 25-Year-Old Woman with Relapsing–Remitting Multiple Sclerosis

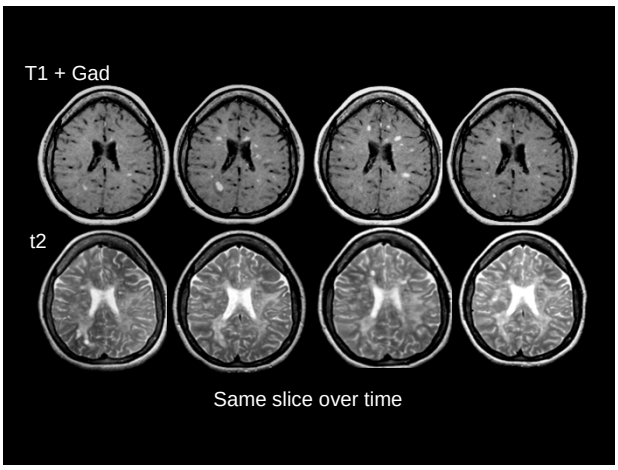


MRI lesions evolving over a period of 1 year in a patient with MS



Cinematic view of 12 monthly images

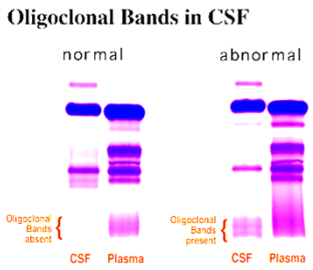
© The whole brain Atlas



CSF abnormalities in MS

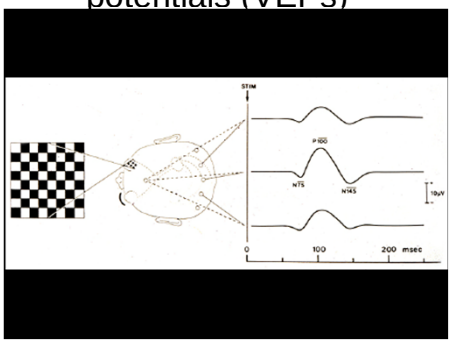
- White cells counts (normal or) mildly (10-20 cells/mm3) increased, >50 WBC suspect alternative diagnosis
- 90% lymphocytes, 5% PMN
- Protein normal in 2/3 of cases, minor (0.5-0.7 g/L) protein increase in about 1/3
- Increased IgG, elevated IgG index
- **Oligoclonal bands** of IgG selectively in CSF
  - Sensitive test: positive in >95% of clinically definite MS (Andersson et al 1994) when IEF is used
  - Unspecific

CSF oligoclonal studies

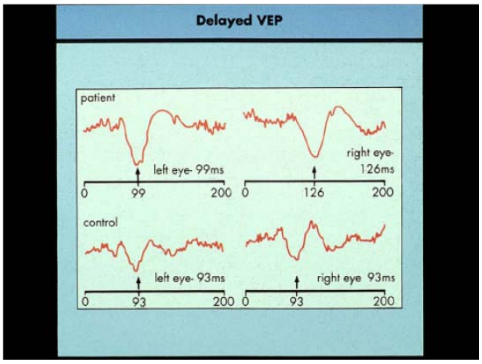


Courtesy of Dr J Rose, Univ. of Utah

Electrophysiology: Visual evoked potentials (VEPs)



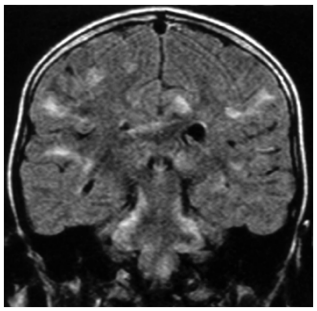
VEPs



Acute disseminated encephalomyelitis (ADEM)

- Childhood age of onset
- Usually antecedent infection or immunization
- Molecular targets unknown
- Monophasic
- Fever, headache, meningism
- Seizures, coma
- Multifocal neurological deficits
- Bilateral optic neuritis
- CSF pleocytosis, elevated protein
- OCB+ in 30% and may disappear
- MRI may resemble MS but usually shows larger lesions, mass effect, uniform enhancement, more grey matter and subcortical lesions
- Marked resolution of lesions at follow up

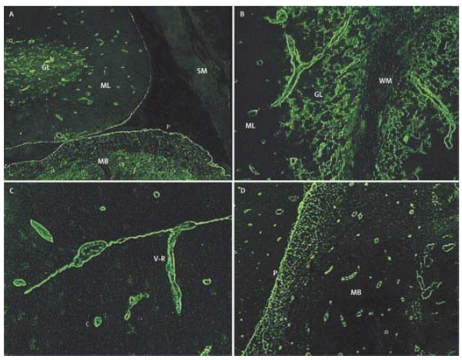
Coronal FLAIR sequence of a boy aged 8 showing multiple areas of high signal within the white matter, typical of ADEM



Neuromyelitis optica (NMO) – a newly recognized CNS channelopathy

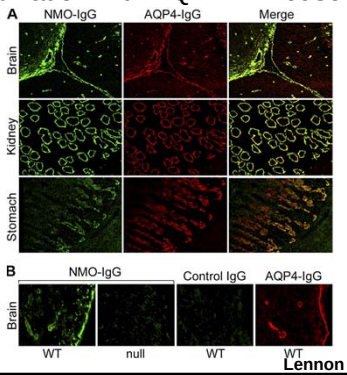
- NMO (Devic's disease) is a clinically defined severe CNS demyelinating syndrome characterized by optic neuritis and acute myelitis
- Characteristic immunopathology: IgG, IgM and complement deposited in a vasculogenic pattern suggest role for autoantibody
- IgG specific for NMO in serum of 73% of patients; binds to the **aquaporin-4** water channel
- MRI brain can be normal
- OCB usually negative

Immunofluorescence pattern of bound NMO-IgG in mouse CNS



Lennon et al., Lancet 2004

Immunofluorescence reveals NMO-IgG colocalization with AQP4 in mouse tissues

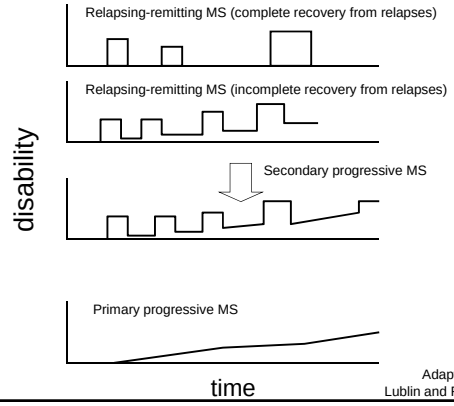


Lennon et al., JEM 2005

MS clinical subtypes

- "Pre-MS"
  - Clinically isolated syndrome
    - Often optic neuritis
- Main clinical subtypes of definite MS
  - **Relapsing Remitting (RR)** 80-85% of cases at onset
    - Becomes **Secondary Progressive (SP)** in ~80% of cases
    - Remains "benign" MS in ~10-15%
  - **Primary progressive (PP)** 15-20%

Clinical subtypes of multiple sclerosis



Adapted from Lublin and Reingold, 1996

Spectrum of severity of disease phenotype

Clinical evolution extremely variable

Benign MS (little or no disability after 15 years of disease)
Lublin and Reingold 1996

Disease severity

Malignant MS (death in 5 years from diagnosis)

??? Long term prognosis

Patients expectations

Clinical management

Prognosis in MS

About prognostic accuracy in MS – an analogy

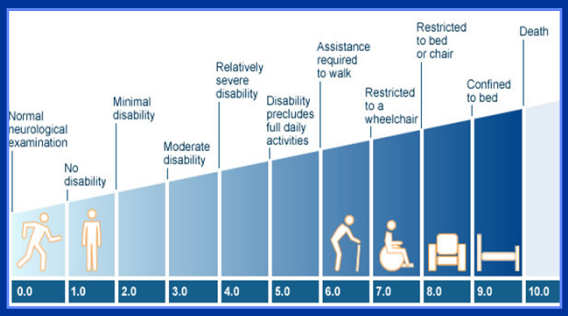
MS prognosis

No single feature or test has good predictivity

Good prognostic features
- Young onset
- Female
- Optic neuritis or only sensory symptoms at onset
- Low frequency of attacks
- Complete symptom remission
- Long first interattack interval

Bad prognostic features
- >40 years at onset
- Male
- Insidious pyramidal tract involvement
- Prominent cerebellar involvement
- Frequent attacks
- Rapid development of fixed disability

Disability Status Scale (Kurtzke 1955)



Measuring disability – the EDSS

- Expanded Disability Status Scale (Kurtzke)
- From 0 (healthy) to 10 (death due to MS) in 0.5 intervals
- Landmark EDSS scores
  - EDSS 1.0 = no disability, minimal sign
  - EDSS 2.0 to 6.0 = minimal to moderately severe disability
  - EDSS 6.0 = need cane to walk about 100 m
  - EDSS 7.0 = wheelchair
  - EDSS 8.0 = bed-bound

Secondary complications of MS

- Depression
- Urinary tract infection
- Limb contractures due to spasticity
- Gastroparesis and intestinal pseudo-obstruction
- Accelerated lumbar spondylosis due to abnormal posture
- Aspiration pneumonia and bronchopneumonia
- Pulmonary thromboembolism
- Pressure sores

Adapted from Pender, MJA 2000

Recommended reading

Reference book:
- McAlpine's Multiple Sclerosis, Fourth Edition, Churchill Livingston, 2005 (in CX library)

Review articles:
- Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *N Engl J Med* 2000;**343**(13): 938-52.
- Compston & Coles (2008) Multiple Sclerosis. *Lancet*. 372(9648):1502-17.

Take-home points

- MS: inflammatory + demyelinating + degenerative disease of the CNS
- Diagnosis is clinical, but supported by MRI and CSF analysis (+/- VEP)
- Diverse clinical forms and poorly predictable long term outcome
- Differential diagnosis includes
  - ADEM
  - NMO

Questions?