Imperial College London

Neuroinflammation of the CNS

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Learning objectives

- Understand the clinical presentation, pathophysiology and diagnosis of:
- Multiple sclerosis
- Other CNS-specific inflammatory syndromes
  - Acute disseminated encephalomyelitis
  - Neuromyelitis optica
-

Definition of CNS inflammatory disorders

- Virtually any type of acute injury to the CNS results in some degree of inflammation (e.g. infections, tumours, stroke)
- We consider ***neuro-inflammatory*** those conditions characterised **primarily** by inflammation
- Aetiologies are unknown or thought to be autoimmune

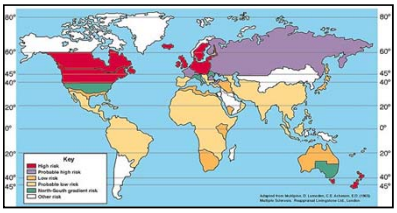
Multiple sclerosis: definition

- 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 social aspects

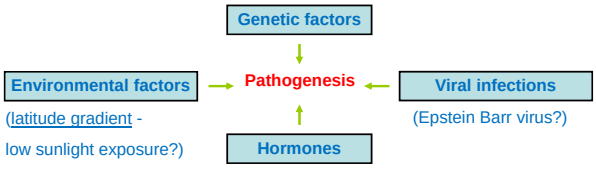
- More common in women than in men (F:M between 3:1 to 2:1)
- Onset typically between age 20 - 50
- Prevalence ranges between 80 and 240 in 100,000 in Northern European and – American countries
- In the UK ~100K people have MS

Distribution of MS in the World



Uneven: note latitude gradient

MS has a complex, multifactorial pathogenesis

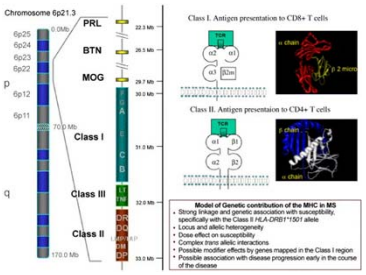


Cause: UNKNOWN

MS – genetic factors

- Increased frequency of MS in affected families
  - In monozygotic twins pairs, both have the disease in 25-30%
  - In dizygotic twins and non-twin siblings, both have the disease in ~2%
- Genetic susceptibility from multiple genes, mostly encoding immune proteins, e.g.
  - HLA-DR 15 (by far top of the list)

The 6p21-23 Chromosomal Region and MS



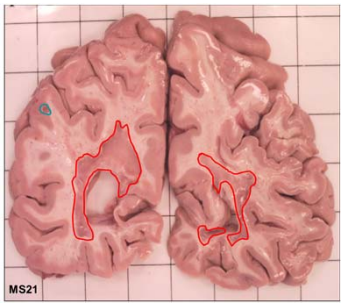
Hauser and Oksenberg, Neuron 2006

Environmental factors

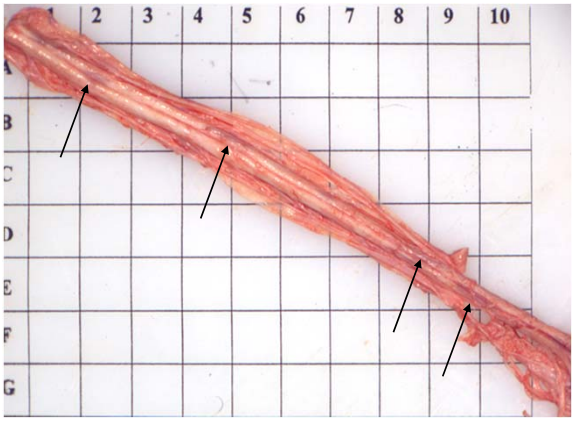
- Infectious agents, most likely viruses (→triggers of inflammation?): EBV?
- Low sunlight exposure and reduced vitamin D levels
- Smoking
- Many other hypotheses/claims

Questions?

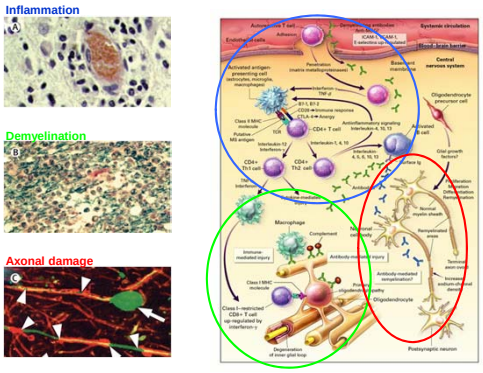
MS - Gross Pathology



The essential CNS lesion in MS is the demyelinated plaque which can be identified at post-mortem as discolored areas in the white and grey matter
Extensive lesions (outlined here in red) often surround the lateral ventricles

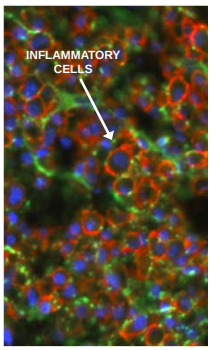


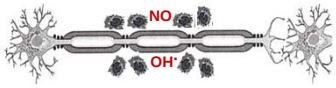
Histopathology of MS – 3 main components



Adapted from Compston and Coles, Lancet 2008 and Noseworthy et al. NEJM 2000

1. Inflammation (produces transient symptoms)

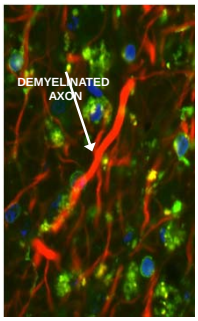


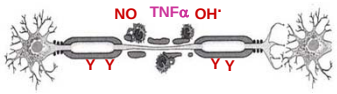


Blood derived immune cells infiltrate CNS and begin an inflammatory reaction

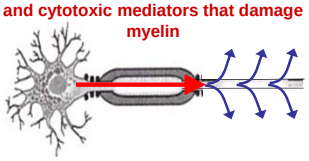
Immunomodulatory treatments aim to prevent this

2. Demyelination (produces both reversible and chronic persistent symptoms)





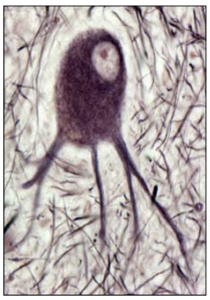
Inflammatory cells release antibodies and cytotoxic mediators that damage myelin

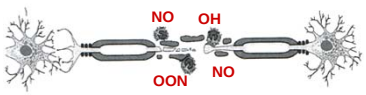


Without myelin electrical signals leak out and fade away and axons become more vulnerable to damage

Spontaneous repair (remyelination) is abundant in early MS

3. Neurodegeneration (leads to chronic progression)





Inflammatory cells release free radicals and cytotoxic mediators

A build up of damage kills the neuron

This is irreversible but there is spare capacity

Questions?

Diagnosis of MS

- Primarily a clinical diagnosis. Requires:

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

Differential diagnosis (simplified)

- **Systemic immune diseases affecting the CNS**
  - Neurosarcoidosis
  - Systemic lupus erythematosus
  - Anti-phospholipid syndrome
  - Sjogren's syndrome
- **CNS-specific inflammatory syndromes**
  - Acute disseminated encephalomyelitis
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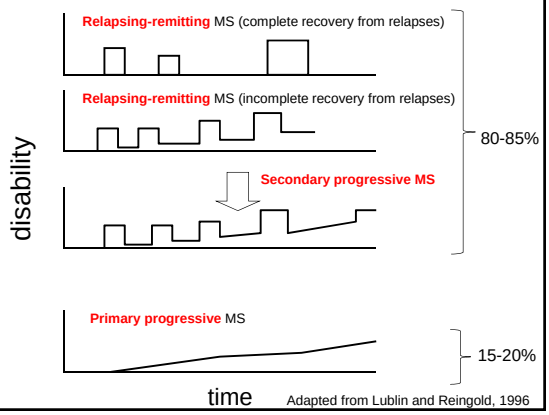
MS: main clinical manifestations and their *tempo*

- Symptoms:
  - Visual
  - Motor
  - Sensory
  - Cognitive and psychiatric
  - Bowel, bladder, sexual dysfunction
- Relapsing MS
  - **Onset**: hours to days
  - **Recovery**: days to months
- Progressive MS
  - **Onset**: months to a year
  - **Recovery**: none

Clinical course of multiple sclerosis



Adapted from Lublin and Reingold, 1996

MS: objective signs

- Weakness, spasticity, increased reflexes
- Objective loss of sensation
- Impaired coordination and tremor
- Nystagmus, diplopia
- Unilateral vision loss

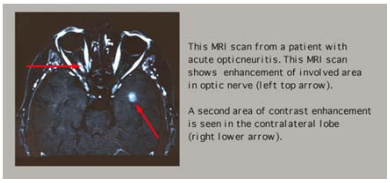
Examples of abnormal findings at neurological examination

Intention tremor and dysmetria
(cerebellar dysfunction)

Tests supporting diagnosis of MS

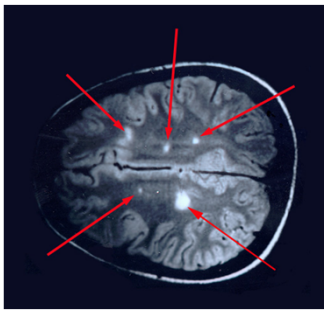
- MRI
- Cerebrospinal fluid (CSF) analysis

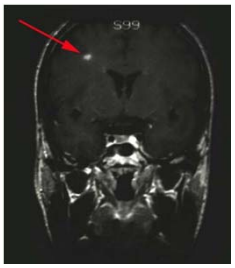
MRI – optic neuritis



Courtesy of Dr J Rose, Univ. of Utah

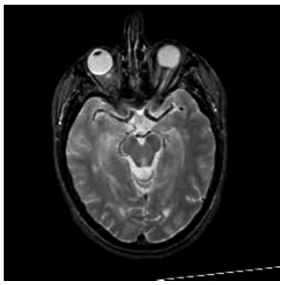
MRI in MS – multiple areas of hyperintense signal

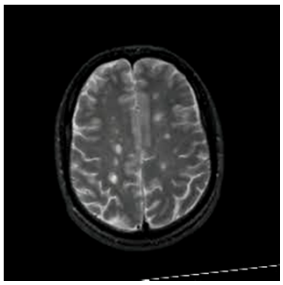




Courtesy of Dr J Rose, Univ. of Utah

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





Kinematic view of 12 monthly images © The whole brain Atlas

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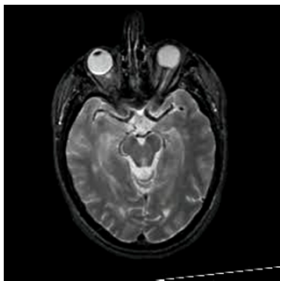

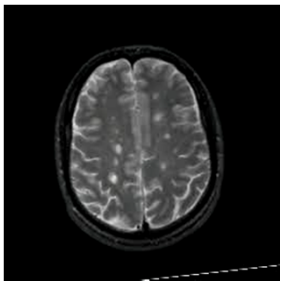

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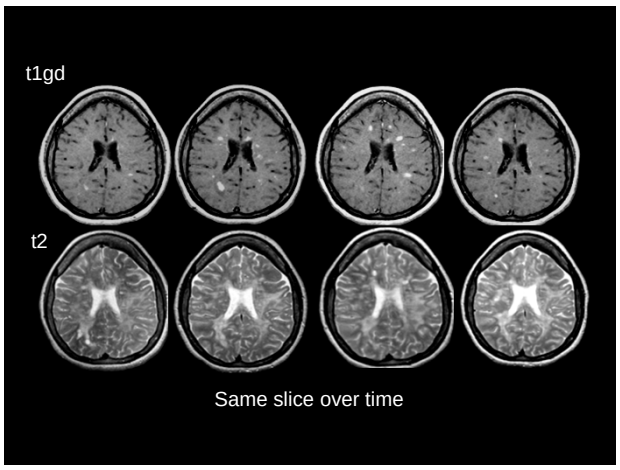
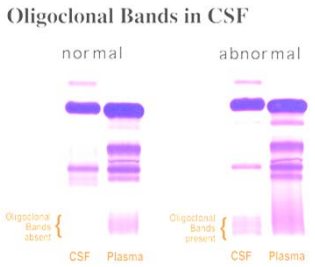


CSF abnormalities in MS

- White cells (leukocyte) numbers (normal or) mildly increased
- Increased production of Ig in the CSF
- Oligoclonal bands:
  - Sensitive test: positive in 90% of patients
  - Unspecific



Questions?

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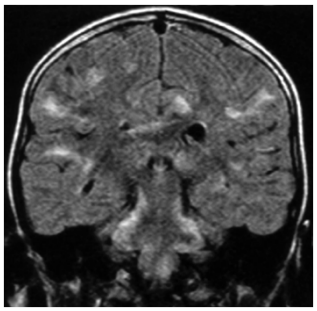
Acute disseminated encephalomyelitis (ADEM)

- Childhood age of onset
- Usually preceded by infection or immunization
- Monophasic – one off
- Fever, headache, seizures, coma, multiple neurological deficits
- CSF cell increase, elevated protein
- OCB+ in 30% and may disappear
- MRI may resemble MS but usually shows larger lesions
- Usually good prognosis

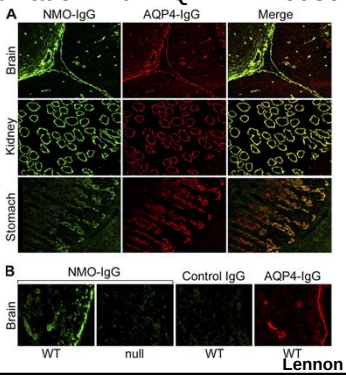
Coronal FLAIR sequence of a boy aged 8 showing multiple areas of high signal within the white matter, typical of ADEM



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: Ig and complement deposited in around blood vessels
- IgG specific for NMO in serum of 73% of patients; binds to the **aquaporin-4** water channel
- MRI brain can be even normal (but abnormal optic nerves and spinal cord)
- OCB usually negative

Immunofluorescence reveals NMO-IgG colocalization with AQP4 in mouse tissues



Lennon et al., JEM 2005

Take-home points

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

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.
- Leake et a.. Acute Disseminated Encephalomyelitis in Childhood: Epidemiologic, Clinical and Laboratory Features. Pediatr Infect Dis J 2004; 23: 756-764.

Questions?