Imperial College London

Neuroinflammation of the CNS

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Outline of lecture

- Introduction
- Multiple sclerosis
- Other CNS inflammatory conditions
  - 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

Examples of CNS inflammatory disorders

- **MS, neuromyelitis optica, ADEM,** Sjogren's, neuro-SLE, Behcet's, sarcoidosis, CIDP with CNS demyelination, anti phospholipid antibodies syndrome
- CNS vasculitides

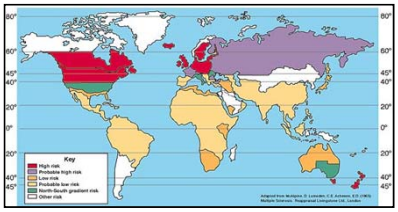
Multiple sclerosis: definition

- 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 (~3:2 to 2:1)
- Onset typically between age 20 - 50
- Incidence: 3-5 cases/100,000/year
- Prevalence rates range between 80 and 240 in 100,000 in Northern European and –American countries
- 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
- In the UK ~85-100K people have MS

Distribution of MS in the World



Genetic factors

Environmental factors → **Pathogenesis** ← **Viral infections**

(latitude gradient - low sunlight exposure?)

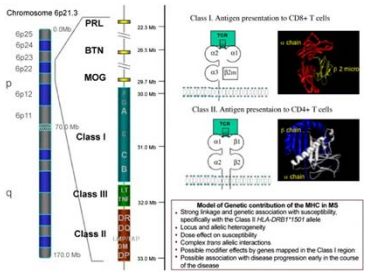
(Epstein Barr virus?)

Hormones

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:
  - HLA-DR 15 Dw2
  - IL-7R
  - IL-2 R alpha
  - CD58

The 6p21-23 Chromosomal Region and MS



Hauser and Oksenberg, Neuron 2006

Environmental factors

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

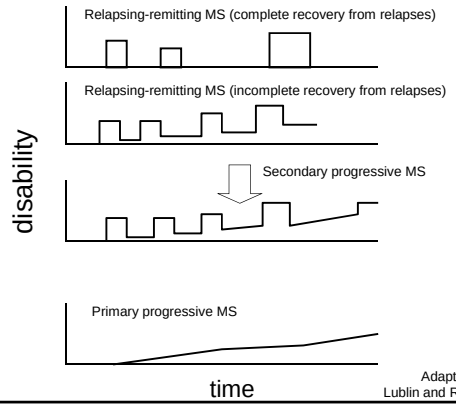
MS: main clinical manifestations and their *tempo*

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

MS clinical subtypes

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

Clinical subtypes of multiple sclerosis



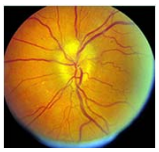
Adapted from Lublin and Reingold, 1996

MS: objective signs

- Weakness, spasticity, increased reflexes
- Objective loss of sensation
- Impaired coordination and action tremor
- Nystagmus, diplopia
- Unilateral vision loss
- Fundoscopy: normal, optic disc pallor or papillitis

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)

Fundoscopy in optic neuritis

retrobulbar optic neuritis (2/3 of cases)

papillitis (1/3 cases)

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**

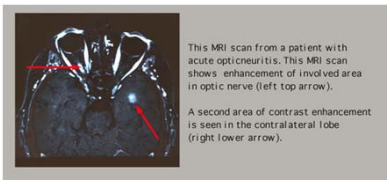
A few of the many other CNS inflammatory disorders

- **Systemic immune diseases affecting the CNS**
  - Neurosarcoidosis
  - Systemic lupus erythematosus
  - Anti-phospholipid syndrome
  - Sjogren's syndrome
- **CNS-specific inflammatory syndromes**
  - Acute disseminated encephalomyelitis
  - Neuromyelitis optica

Tests supporting diagnosis of MS

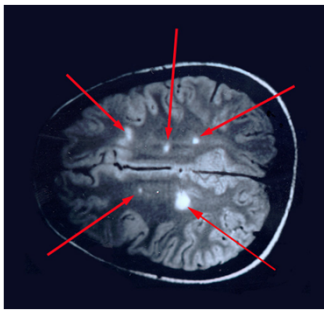
- MRI
- Cerebrospinal fluid (CSF) analysis

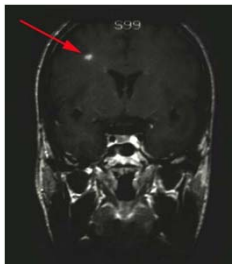
MRI – optic neuritis



Courtesy of Dr J Rose, Univ. of Utah

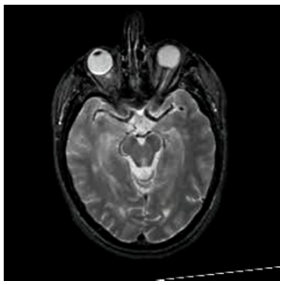
MRI in MS – multiple areas of hyperintense signal

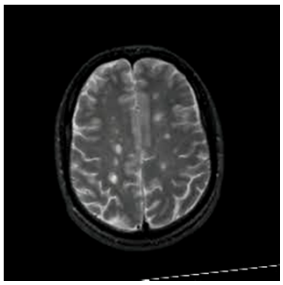




Courtesy of Dr J Rose, Univ. of Utah

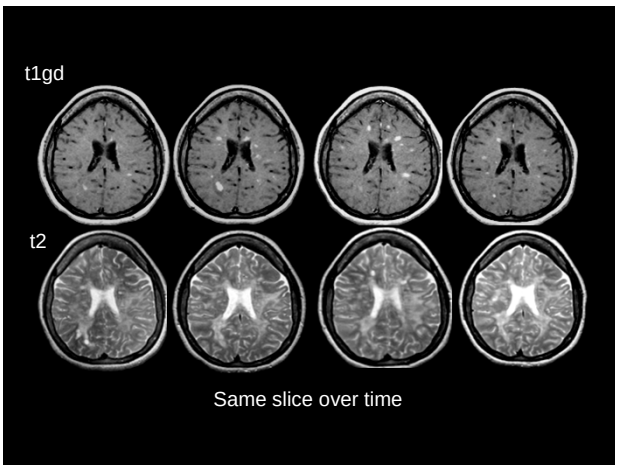
MRI lesions evolving over a period of 1 year in a patient with MS





Kinematic view of 12 monthly images

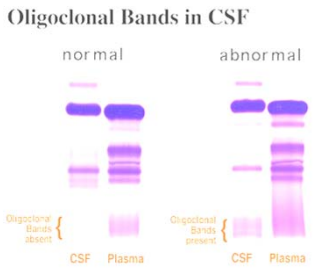
© The whole brain Atlas



CSF abnormalities in MS

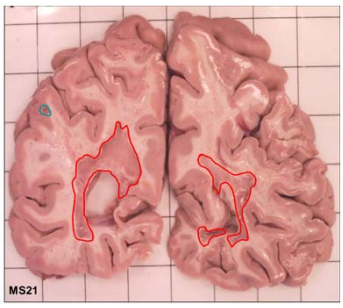
- White cells counts (normal or) mildly increased (leukocytes)
- There can be a minor protein increase
- Increased production of IgG in the CNS
- CSF oligoclonal bands:
  - Sensitive test: positive in 90% of patients
  - Unspecific

Cerebrospinal fluid analysis

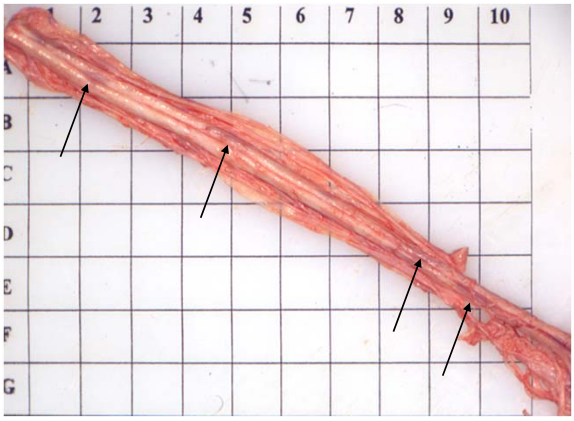


Courtesy of Dr J Rose, Univ. of Utah

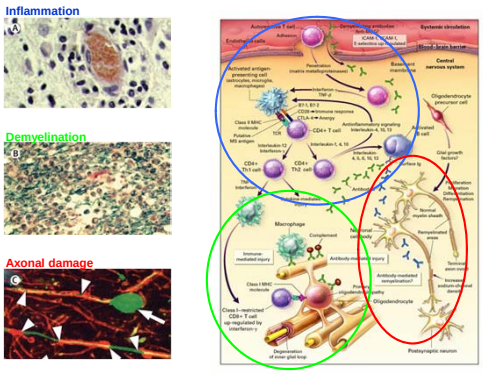
MS - Gross Pathology



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

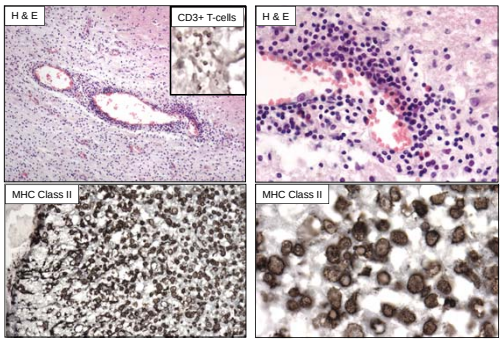


Histopathology of MS – 3 main components



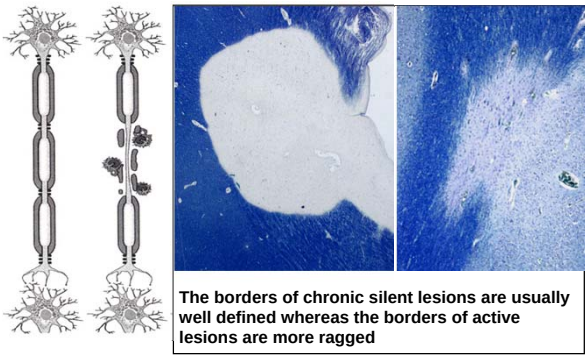
Adapted from Compston and Coles, Lancet 2008 and Noseworthy et al. NEJM 2000

Inflammation and MS - the earliest events



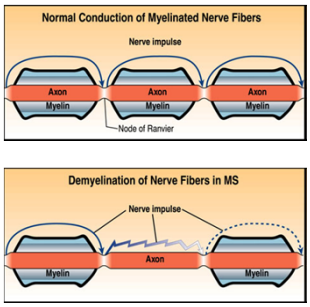
T-lymphocyte infiltration is only seen during the very early stages of lesion formation and even during active demyelination (above) only few T-cells are found in the brain parenchyma. B-lymphocytes may also be found in small numbers. The majority of inflammatory cells in the MS lesion are monocytes/macrophages.

Demyelination in MS



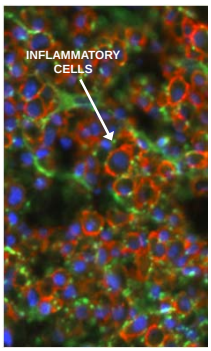
The borders of chronic silent lesions are usually well defined whereas the borders of active lesions are more ragged

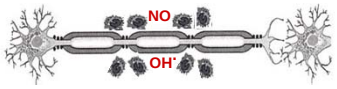
Effects of demyelination on nerve impulse conduction



Courtesy of Dr J Rose, Univ. of Utah

Inflammation produces transient symptoms



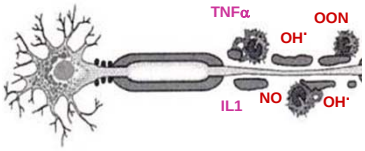


Inflammatory cells release free radicals and cytotoxic mediators

reversible block of electrical signals

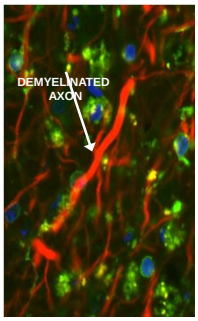
+

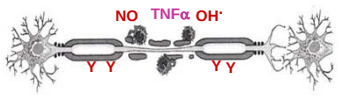
demyelination



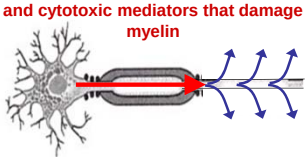
Immunomodulatory treatments aim to stop these effects

Demyelination produces both reversible and chronic persistent symptoms





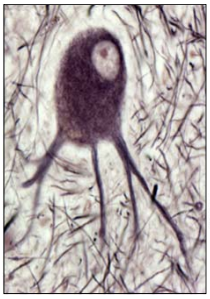
Inflammatory cells release antibodies and cytotoxic mediators that damage myelin

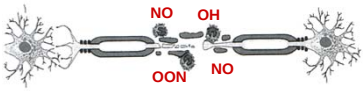


Without myelin electrical signals leak out and fade away and axons become more vulnerable to damage

Spontaneous repair (remyelination) is abundant in early MS

Neurodegeneration leads to chronic progression



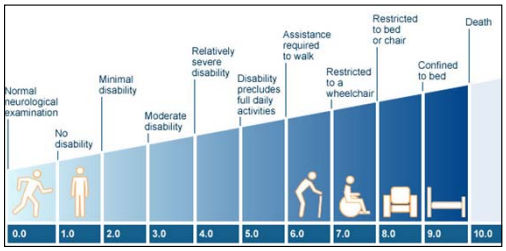


Inflammatory cells release free radicals and cytotoxic mediators

A build up of damage kills the neuron

This is irreversible but there is spare capacity

Axonal damage is the main cause of chronic progression leading to advanced disability



Expanded disability status scale (EDSS)

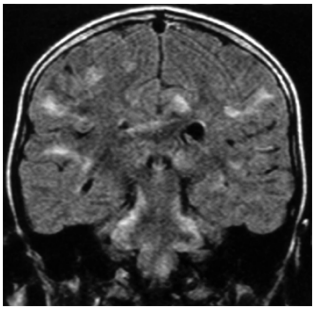
Some of the many other CNS inflammatory disorders

- **CNS-specific inflammatory syndromes**
  - Acute disseminated encephalomyelitis
  - Neuromyelitis optica
- **Systemic immune diseases affecting the CNS**
  - Neurosarcoidosis
  - Systemic lupus erythematosus
  - Anti-phospholipid syndrome
  - Sjogren's syndrome

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

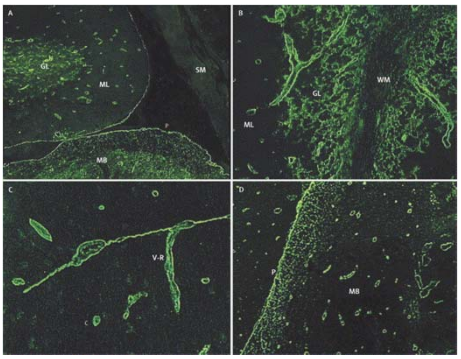
Coronal FLAIR sequence of a boy aged 8 showing multiple areas of high signal within the white matter, typical of ADEM



Neuromyelitis optica (NMO) – a newly recognized CNS channelopathy

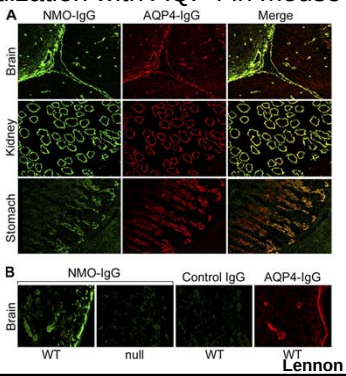
- NMO (Devic's disease) is a clinically defined severe CNS demyelinating syndrome characterized by optic neuritis and acute myelitis
- Characteristic immunopathology: IgG, IgM and complement deposited in a vasculogenic pattern suggest role for autoantibody
- IgG specific for NMO in serum of 73% of patients; 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

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

Review article:

- Compston & Coles. Multiple Sclerosis. *Lancet* 2008.

Reference Book:

- McAlpine's Multiple Sclerosis, Fourth Edition, Churchill Livingston, 2005 (relevant sections)