SUSPECTED MECHANISMS INVOLVED IN MS AND PUTATIVE INTERACTIONS WITH HEPATITIS B VACCINE IN MS

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EPIDEMIOLOGY OF MS

- Most common chronic CNS inflammatory demyelinating disease
- 300,000 (0.1%) individuals in USA
- 2/3 women
- Highest incidence between 20 - 40 years
- More frequent in Caucasians
- MS prevalence: 50-250 / 100,000 in high-risk areas
Multiple sclerosis in the United States. Case/control ratios (× 100) for white male veterans according to place of residence prior to enlistment.³
COURSES OF MS

- Relapsing Remitting
- Secondary Progressive
- Primary Progressive
- Progressive Relapsing
MS DIAGNOSIS

- Clinical recurrent episodes of CNS dysfunction
  - dissemination in time
  - dissemination in space

- MRI: white matter lesions on T2 and FLAIR sequences. Possible Gd+ lesions.

- CSF: IgG index and oligoclonal bands

- Evoked Potentials
McDonald’s Criteria include MRI

- **dissemination in space**
  - = 3 of 4 of the following criteria:
    - (1) One gadolinium enhancing lesion or 9 T2 bright lesions if there is no enhancement,
    - 2) at least one infratentorial lesion,
    - (3) at least one juxtacortical lesion,
    - (4) at least three periventricular lesions

- **dissemination in time**
  - = a new T2 or a GD+ lesion on repeat MRI
Natural History of MS: Clinical and MRI Measures

- Measures of brain volume
- Relapses and impairment
- MRI burden of disease
- MRI activity

Preclinical  Relapsing-remitting

Secondary progressive

Time
LESION EVOLUTION
ETIOLOGY OF MS

- **Cause of MS = unknown**

But participation of:

- **A genetic susceptibility**
- **And environmental factors**
GENETIC SUSCEPTIBILITY

- 15-20% of patients with MS: family history
- Risk x 10-20 for 1st-degree relatives but small (1-3%)
- Concordance in dizygotic twins/other siblings 2-5%
  in monozygotic twins 30-35%.
- Multiplex studies: HLA-DR2 (DRB*1501, DQB*0602)
- Complex susceptibility: 15-20 loci may contribute
  - Susceptibility to develop MS
  - Modifier of clinical expression of MS
  - Modifier of response to MS modifying treatment
ENVIRONMENTAL FACTORS

- Suggested by:
  - Higher incidence in northern latitudes,
  - Native risk kept if migration after age 15 years
  - Clusters

- But infectious agent not reproducibly found.
MACROSCOPIC MS LESION
MICROSCOPIC MS LESION

Axonal Demyelination in MS Lesions

BRAIN ATROPHY OVER TIME

Co-registered images acquired over the course of 7 years from a single untreated MS patient.
STEP 1  SYSTEMIC ANTIGEN PRESENTATION TO T CELLS

Endothelial cells

BLOODSTREAM

Macrophage

MHC  Ag  TCR

B7  CD28  T cell

ICAM-1

Basement membrane

CNS
THE T CELL RECEPTOR COMPLEX
STEP 2

ADHESION OF T CELLS TO VASCULAR ENDOTHELIUM

Cytokines  
Proteases

VLA-4  
VCAM-1

LFA-1  
ICAM

Astrocyte foot processes
STEP 3
TRANSMIGRATION OF T CELLS THROUGH VASCULAR ENDOTHELIUM

Blood

Endothelial cells

Basement membrane

CNS

Proteases

T cell
STEP 4  REACTIVATION AND CLONAL EXPANSION OF T CELLS WITHIN THE CNS
EAE can be induced:
- Actively by injection of myelin antigens,
- Passively by adoptive transfer of antigen specific T cells

Role of activated CD4+ T cells (Th1 versus Th2)
- But also CD8+ T cells
- And humoral response
PATHOGENESIS OF MS

- Two main concepts discovered from the EAE models:
  - Molecular mimicry
  - Superantigens
MOLECULAR MIMICRY

- Microbial or viral antigenic determinant may cross-react with a self protein determinant.

- Can trigger T and B cells to be activated.
MOLECULAR MIMICRY

TCR

T cell

APC

Foreign Ag

Self Ag

APC
SUPERANTIGENS

- May directly activate T cells through the TCR independent of antigen specificity
- May activate humeral response:
  - Crosslink TCR and MHC class II molecule → Ig production
  - Activation of B cells through their Ig receptor
- May activate macrophages to release inflammatory mediators
SUPERANTIGENS
Following immunization with a major determinant of a CNS antigen:

- Disease relapses due to recruitment of CD4+ T cells recognizing secondary determinants:
  - of the same auto-antigen (intramolecular spreading)
  - or of another encephalitogenic auto-antigen (intermolecular determinant spreading)
Regulation of inflammation

CD40

gp39

MHC II

CD28

B7-1
/
2

TH1

TH0

TH2

CD4+

TH1

TH0

TH2

CD4+

CD28

B7-1
/
2

IFN-γ

IL-2

MHC II

APC

Systemic Circulation

Blood Brain Barrier

IL-12

CD40

gp39

IL-2

IFN-γ

Processed antigen

Superantigen

Myelin antigen

CNS-APC

Central Nervous System

CNS-
APC

Superantigen

APC

TNF-α

IFN-γ

Inflammation

Oligodendrocyte-
Myelin-
Complex

Regulation of inflammation

IL-5

IL-10

TGF-β

CD28

B7-2/1

IL-4

Activated

Activated
TRIGGER OF MS RELAPSES

- Immediate post-partum
- Upper respiratory viral infections
- Interferon gamma
- Experimental drugs:
  - Recombinant TNF receptor p55 Ig fusion protein
  - Altered peptide ligand
- Stress?
MS IN CHILDREN

- Less frequent than in adults
- Pediatric cases = 0.3 to 2% of all MS cases
- Isolated ADEM, optic neuritis more frequent in children than adults and also more frequently preceded by infections
CNS IN CHILDREN

- Structural and functional maturation of CNS throughout childhood and adolescence
- Different isoforms of some myelin proteins?
- Quantitative and qualitative differences between immature and mature CNS \(\rightarrow\) different MS prevalence?
Neonates can develop a protective immune response to vaccines within hours of birth.

Approximately 90% of infants develop active protective immune response to primary series of vaccines between 2-6 months.
MS DIFFERENTIAL DIAGNOSIS

- Acute disseminated encephalomyelitis
- Others such as lupus, Behcet, neurosarcoidosis, Lyme disease, neurosyphilis, HTLV-1 myelopathy, vitamin B12 deficiency, spinocerebellar degenerative disorders
Acute disseminated encephalomyelitis (ADEM)

- Monophasic illness usually 1 - 20 days after:
  - Infection or Immunization
- Symptoms:
  - Decreased consciousness, headaches, seizures
  - Sensory loss, meningism, weakness, spasticity
  - Mortality: ~ 5%
- Micro: Demyelination + CNS inflammatory infiltrates
- MRI: Subcortical CNS white matter abnormalities
Post infection ADEM

- 1/1000 measles infection
- <1/10,000 varicella infections
- <1/20,000 rubella infections
- Other viruses: influenza, mumps, coxsackie B, EBV, HSV, HIV, HHV-6, hepatitis B
- Bacteria: mycoplasma and legionella
1885: Pasteur develops vaccine against rabies

“Paralytic accidents” are being reported in 0.1% of recipients

Cause: myelin components in the vaccine
Postimmunization ADEM

- **Incidence:** 1 - 2 / million (live measles vaccine)

- **Associated with:**
  - Measles
  - Mumps
  - Rubella
  - Influenza
  - Hepatitis B
ADEM VERSUS MS

- ADEM = monophasic, rarely with early relapse
- MS = multiphasic

- Clinical and MRI differences?
- Preliminary infection more frequent in ADEM
- ADEM = retrospective diagnosis

- ADEM = infectious mechanisms? Secondary autoimmune response?
Do immunizations trigger MS or MS relapses?
Evidence for the role of hepatitis B vaccine in CNS disease

- Biological plausibility
- Clinical plausibility
Biological plausibility

- HB virus polymerase shares six consecutive aa (75%) with an encephalitogenic site of rabbit MBP
- Animal injected with peptides from HBVP develop antibody response against HBVP and native MBP
- CNS infiltrates but no clinical EAE (hepatitis B vaccine does not include HBVP)
Clinical plausibility

- Hepatitis B vaccination and MS onset
- Hepatitis B vaccination and MS relapses
- (no MRI information)
Hepatitis B vaccination and MS

- 1982: HB vaccine
- 1992: France: School based vaccination program
- Case reports/series suggest an increased risk of:
  - Developing MS
  - Exacerbating existing MS
- July 1998: Lawsuit on behalf of 15,000 French citizens is filed against the French government for allegedly understating the risks of HB vaccine, and exaggerating its benefits
- October 1998: French health authorities suspend HB vaccination of adolescent schoolchildren
Retrospective cohort study on 134,698 individuals enrolled in US healthcare database from 1988 to 1995

Risk of developing MS not significantly different between vaccinated and non-vaccinated individuals at any time point

Post-immunization risk of demyelinating diseases in children

- Incidence of demyelinating diseases not increased after hepatitis B immunization in children under age 14 years (Zipp et al)

- Hepatitis B vaccination in children 11-12 year old did not increase the risk to develop MS in adolescence or ADEM (Sadovnick et al)
HB vaccination and MS (cont.)

- Case control study

- Two large cohorts:
  - Nurses’ Health study (121,700 women since 1976)
  - Nurses’ Health study II (116,671 women since 1989)

- Vaccinated with recombinant HB vaccine:
  - 192 MS and 645 Controls

- RR of developing MS after HB vaccination given any time before onset: 0.9 (95% CI, 0.5 - 1.6)

- RR within 2 years before onset: 0.7

Ascherio et al. NEJM 2001;344:327-32.
Short-term risk of MS relapse after vaccination

- Multicenter case-crossover study of 643 patients (EDMUS)
  - 40% of patients at least one vaccination
  - 15% of patients received 135 vaccinations within 12 months of a preceding relapse (HB:28.9%, Influenza:17%)
  - 2.3% of patients vaccinated during 2 months preceding a relapse - "risk period"

- RR of relapse associated with vaccination during the previous 2 months = 0.71 (95% CI, 0.4-1.26)

- No short-term risk of relapse

Selection of patients

- These studies included definite MS cases using strict diagnosis criteria
  → non-MS cases were eliminated,

- BUT
  - initial bouts of MS not included
  - MRI was not used to monitor MS activity
Macrophagic myofasciitis and MS-like cases

- MMF related to aluminium-containing vaccines? (Gherardi 1998)
- Few cases associated to neurological symptoms (Authier 2001)
- Some do not meet criteria for definite MS:
  - no MRI findings or a single T2 bright signal,
  - no oligoclonal bands (5/7).
- Delay between immunization and neurological symptoms:
  - unknown in 1 patient,
  - In 6 patients: 3 to 78 months.
- Too preliminary to draw conclusions from a single report
PERIPHERAL DEMYELINATING DISEASES

- Acute inflammatory demyelinating polyneuropathy (Guillain Barre syndrome)
  - Days or weeks after infection with campylobacter, HIV, EBV, CMV or immunization
  - Usually monophasic
  - Molecular mimicry between some of these antigens and PNS myelin antigens
  - More frequently after infection or immunization than MS
STRUCTURE OF CENTRAL MYELIN
PERIPHERAL AND CENTRAL MYELIN

- Different myelin antigens ($P_0$ in PNS, MOG in CNS)
- One Schwann cell myelinates a single PNS axon
- One oligodendrocyte myelinates multiple CNS axons
- Different regulation of myelination:
  - PNS = contact axon-Schwann cell
  - CNS = presence of astrocytes
- Remyelination in PNS > CNS
CONCLUSIONS

- MS = very heterogeneous disorder with multifactorial pathogenesis,
- No screen for MS risk
- Positive association between HB vaccine and MS = theoretical consideration
- The best currently available biological and clinical evidence argue strongly against it.