Multiple sclerosis, other autoimmune demyelinating diseases and differential diagnoses

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Demyelination – selective loss of myelin with axonal preservation

Multiple sclerosis

Neuromyelitis optica

Adrenoleukodystrophy (ALD)

PML/IRIS*

*Progressive multifocal leukoencephalopathy/
Immune reconstitution inflammatory syndrome

All images: LFB/PAS
Mediators of demyelination

- T-cells
- Antibodies/complement
- ROS/NO-radicals
- Death ligands/death receptors (Fas/FasL, TRAIL)
- Cytokines (e.g., TNFα)
- Microbes/toxins
- Cytotoxic T-cells
Outline

• **Antibody-mediated** demyelination
  – Target: myelin/oligodendrocytes (ADEM)
  – Target: astrocytes (NMO)
• **Oligodendrocyte damage** (viral (PML), toxic, metabolic)
• **Unknown** mechanism of demyelination (MS)
Acute disseminated perivenous encephalomyelitis (ADEM)

- 6 days to 6 weeks after antigenic challenge (vaccination, infection)
- Sudden onset of multifocal neurological symptoms
- Maximum of symptoms reached within several days
- Often similarly rapid remission
- Monophasic disease, favourable long-term prognosis
Acute disseminated encephalomyelitis (ADEM)
ADEM

- Perivascular inflammatory infiltrates (T-cells, macrophages, granulocytes)
- Perivenous, but may coalesce
- May be accompanied by Ig and complement deposition

Young et al., Brain 2010
Anti-MOG antibody titres in ADEM

Abs against conformational epitopes of myelin oligodendrocyte glycoprotein (MOG) are detected in a proportion of ADEM patients.

O’Connor, Nature med 2007
Localization of MOG in the myelin sheath

(Mayer et al., 2012) J Neurol Sci
Neuromyelitis optica (M. Devic)

- Severe transverse myelitis and uni- or bilateral optic neuritis
- Monophasic or relapsing
- Female : male = 9 : 1
- Inflammation: macrophages, lymphocytes and granulocytes (eosinophilics)
- In early lesions, Ig deposition and complement activation
Anti-AQP4 antibodies are a sensitive and specific biomarker for NMO

Lennon et al., J Exp Med 2004
Recombinant anti-AQP4 antibodies from NMO patients deplete astrocytes in vivo

Bennett et al., Ann Neurol 2009
Loss of AQP-4 in early NMO lesions

Roemer et al., Brain 2007
Typical features of NMO lesions

Astrocyte loss

Complement deposition

Apoptotic oligodendrocytes

Astrocyte repopulation

GFAP

C9neo mk

NogoA

CM1

AQP4
37 y/o female

At age 27: tetraparesis
9 months later: ON left eye
T2-hyperintense lesion C2 to C7, no brain lesions
No OCB
Suspected MS

Two relapses per year, despite IFNβ, Mitoxantrone, Natalizumab

Now, 10ys later:
Spastic tetraparesis, cortical blindness, impaired consciousness
FLAIR: large occipital lesion
Anti-AQP4 Ab +
Occipital NMO lesion, biopsy, 37y old female patient
Occipital NMO lesion, biopsy, 37 y old female patient

LFB/PAS
Occipital NMO lesion, biopsy, 37y old female patient
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Principle mechanisms of demyelination:

Direct damage to the myelin sheath

Damage to the oligodendrocyte
Multiple sclerosis (MS)

- Prevalence ~ 1:1000
- f:m = 3:1
- Age of onset: 25-35
- Inflammatory-demyelinated lesions throughout the CNS
- Autoimmune disease
Diagnosis of multiple sclerosis

- „Typical“ clinical presentation
- MRI
  - dissemination of lesions in space and time
  - Lesion location (juxtacortical, periventricular, infratentorial)
- Oligoclonal bands (intrathecal immunoglobulin synthesis)
- No other disease (dg. of exclusion)
- No biomarker available so far
Late stage, chronic MS lesion

- Demyelination
- T cells
- Microglia
- Axonal loss
- Fibrillary gliosis
Early, actively demyelinating MS lesion

- Demyelination
- Axonal damage
- Inflammation
- Gliosis
Inflammatory and demyelinating lesions – differential diagnosis

- Tissue necrosis
- Steroid-treated lymphoma
- Progressive multifocal leukoencephalopathy (PML)
- Vasculitis
- Encephalitis
- Astrocytoma
- Neuromyelitis optica
- ADEM
The evolution of a multiple sclerosis lesion

<table>
<thead>
<tr>
<th>initial</th>
<th>early active</th>
<th>late active</th>
<th>demyelinated/remyelinated</th>
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Myelin degradation products in macrophages
- MOG, MAG
- MBP, PLP
- LFB
- PAS, sudanophilic lipids

Macrophage antigen expression in MS lesions
- MRP14
- 27E10
- 25F9
- MRP8
- MHC II

mRNA expression of inflammatory mediators
- TNFα
- iNOS
Diagnostic approach to inflammatory demyelinating lesions

- HE, LFB/PAS, Bielschowsky
- **Inflammation:** CD3, CD4, CD8, CD20, CD138, KiM1P, MRP14, IgG
- **Complement:** C9 neo (MAC)
- **Myelin proteins:** MBP, PLP, MAG, MOG, CNP
- **Oligodendrocytes:** NogoA, p25 (TPPP), Olig2
- **Axons:** NF200, SMI31, SMI32, APP
- **Astrocytes:** GFAP, AQP4
- **Others:** JC-Virus
- **If necessary:** Ki67, Gomori, EvG, Actin
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Pattern of demyelination in steroid-treated lymphoma and MS
More intense T lymphocyte infiltration in steroid-treated lymphoma than MS
Criteria helping to distinguish inflammatory demyelination from ST-PCNSL

• **ST-PCNSL:**
  – More intense (diffuse) T cell infiltration (~5x)
  – Less complete myelin loss (LFB, MBP)

• **MS:**
  – Sharp and expanding lesion edge
  – Efficient myelin phagocytosis
Progressive multifocal leukoencephalopathy (PML)

Demyelination

Pleomorphic astrocytes
Loss of oligodendrocytes
Ki67 ↑
p53 +
JC-Virus +
X-Adrenoleukodystrophy

Loss of oligodendrocytes
Inclusions in macrophages

LFB/PAS
Vasculitis

Tissue necrosis
Vessel wall alterations (infiltration/necrosis)
Capillary proliferation

HE

Gomori
Summary

• The pathomechanisms of autoimmune demyelination are beginning to be elucidated
• Distinct pathological features characterize different demyelinating diseases
• Stringent lesion staging required
• Include clinical and neuroradiological data for adequate assessment of surgical biopsies with inflammatory and demyelinating features
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