Diagnosis and Treatment of Multiple Sclerosis and related diseases

Bernhard Hemmer
38 years old women. 20 years ago she developed unilateral vision loss. Vision improved after corticosteroid treatment. Within the next five years she developed 4 additional relapses affecting the spinal cord, cerebellum and the optic nerve. Recovery was incomplete after the last two relapses. 5 years ago she noticed that her walking distance decreased, 2 years ago she became dependent on a crane and now she requires a wheelchair for longer distances. She suffers from fatigue, incontinence and mild cognitive impairment. She has stopped working two years ago.
Overview

- MS prevalence and course
- Clinical symptoms & findings
- Diagnostic criteria
- Pathogenetic concepts
- Treatment strategy
- Related diseases
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Prevalence of MS in Germany

- Onset between the age of 20 and 50 years
- Most common non traumatic cause of disability in young adults
- Currently more than 250,000 people affected in Germany
- Prevalence will increase over the next two decades

Daltrozzo, Front Neurol 2018
ECTRIMS

10 – 12 OCTOBER
2018
BERLIN, GERMANY
# Prevalence of MS in Africa

<table>
<thead>
<tr>
<th>Population group</th>
<th>Number of people &gt;15 years</th>
<th>Crude prevalence per 100 000 (95%, CI)</th>
<th>Age standardized rate per 100 000 to the world Segi population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whites</td>
<td>409 554</td>
<td>25.63 (20.97–31.04)</td>
<td>25.64</td>
</tr>
<tr>
<td>Indians</td>
<td>632 262</td>
<td>7.59 (5.60–10.07)</td>
<td>7.15</td>
</tr>
<tr>
<td>Coloureds</td>
<td>102 663</td>
<td>1.94 (0.24–7.04)</td>
<td>1.72</td>
</tr>
<tr>
<td>Blacks</td>
<td>5 316 060</td>
<td>0.22 (0.12–0.40)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

CI = confidence intervals.
Prevalence of MS in different ethnic groups in London

Albor, MSJ 2017
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Diagnosing Multiple Sclerosis

Neurological symptoms

Imaging of brain and spine

CSF
Symptoms of Multiple Sclerosis

First event during the course:
- Visual impairment: 49%
- Motor impairment: 43%
- Sensory impairment: 41%
- Ataxia: 21%
- Incontinence: 10%
- Neuro-psychiatric symptoms: 4%

During the course:
- Visual impairment: 100%
- Motor impairment: 88%
- Sensory impairment: 87%
- Ataxia: 82%
- Incontinence: 63%
- Neuro-psychiatric symptoms: 39%

Uncommon: Aphasia, Seizures, Hemianopia, Neglect
**Lhermitte Sign**
Electric sensation along the spine with neck movements

**Uthoff Sign**
Impairment gets worse with higher body temperature (e.g. fever, high sun exposure)

**Internuclear Ophtalmoplegia**
Ipsilateral impairment of adduction and contralateral dissociated nystagmus
Course of MS

Onset of disease

Relapsing-remitting 90%  Primary progressive 10%

Primary progressive 10%  Relapsing-remitting 90%
Course of MS

Early  ~20-30 years  Late

Relapsing  Secondary progressive  Primary progressive
• Cerebral lesions in characteristic locations periventricular, juxtacortical und infratentorial
• Corpus callosum: „Dawson-Fingers“
• ± Gadolinium enhancement
Spinal cord lesions
- cervical > thoracic cord
- usually not in central location
- not extending > 3 spinal segments

Optic nerve in the context of optic neuritis
Diagnostic workup

Cerebrospinal fluid

- Supports the diagnosis, Prognostic marker, DDx

Cellular compartment

- 50% milde pleocytosis up to 50/µl
- lympho-mononuclear cells

Proteins

- Protein levels: normal – slightly elevated
- 70% intrathecal IgG-synthesis (Reiber-scheme)
- 95% oligoclonal bands

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Objective evidence for the occurrence of lesions disseminated in space and time typical for MS, which cannot be explained by other diseases or conditions.

MS diagnostic criteria: revision 2017

Thompson et al, Lancet Neurol 2018
Diagnostic criteria

Clinical findings

Clinical findings / MRI / CSF

Dissemination in space

Dissemination in time

MS
MRI criteria for dissemination in space

at least 1 lesion in 2 of 4 regions

infratentorial  periventricular  juxtacortikal cortikal  spinal
MRI/CSF criteria for dissemination in time

Relapse and 1 dissociation criterion

Gadolinium + and - lesions or a new lesion in a follow up scan or OCBs in CSF
Differential diagnosis

- ADEM, Neuromyelitis Optica
- Susac’s Syndrome
- Mb. Behcet, Neurosarkoidosis
- Lupus, Mb. Wegener, mPAN, Sjögren Syndrome, CNS-vasculitis
- CADASIL, MELAS, LHON
- Mb. Fabry, recurrent strokes
- HIV, syphilis, lyme disease, tuberculosis
- Hereditary leukodystrophies
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MS risk factors

Genes

HLA-DR15, 3, 13

> 200 genetic risk factors

Environment

Infections
Epstein-Barr Virus? others?

Low Vitamin D level?

Obesity?

Smoking?
MS pathology

Disability progression

Underlying progression

SPMS

R-SPMS

RRMS

Inflammation

Demyelination

Scar formation

Axonal damage

Pathogenesis of MS

Genes - environment

altered immunity

peripheral activation

migration across the blood-brain barrier

infiltration of immune cells

immune mediated damage

Oligodendrocyte
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MS treatment strategies

- Revert clinical symptoms from relapse
- Prevent relapses and disease progression
- Treatment of symptoms
Relapse treatment

Duration of disease

Corticosteroids (1. line)
Plasma exchange (2. line)
Relapse treatment

Methylprednisolon 500-1000mg/day, oral or i.v. for 3-5 days, taper possible

Plasma exchange or immunabsorption, 5 (-8) times
Preventing new relapses and progression

Genes - environment

altered immunity

peripheral activation

migration across the blood-brain barrier

infiltration of immune cells

immune mediated damage

Push

access denied

Preventing new relapses and progression
### Immunotherapies for relapsing MS

**Class I**  
Moderate efficacy  
- Beta-interferons  
- Dimethylfumarate  
- Glatiramer  
- Teriflunomide (Azathioprine)

**Class II**  
Moderate-high efficacy  
- Fingolimod  
- Cladribine

**Class III**  
High efficacy  
- Alemtuzumab  
- CD20 antibodies*  
- Natalizumab  
  (Mitoxantrone)

* Ocrelizumab or Rituximab (off label!)
Immunotherapies

Duration of disease

Early

Late

Efficacy
Immunotherapies for relapsing MS

- Fewer new brain and spinal cord lesions (▼ 60-98%)
- Fewer relapses (▼ 30-80% ?)
- Less disability progression (▼ 10-50% ?)

- Some drugs have rare but severe side effects
- Some drugs impact on quality of life
- Some drugs require intense monitoring
- The efficacy of the drugs decreases with disease duration and age
- All approved drugs are very expensive
Costs of immunotherapy

Therapiekosten / Jahr [€]

1994 2018

Betaferon
Avonex
Copaxone
Rebif 22
Rebiff 44
Extavia
Gilenya
Aubagio
Lemtrada
Tecfidera
Plegridy
Zinbryta
Clift
Mavenclad
Ocrevus
Rituximab (2x500)
Rituximab (2x1000)
Rituximab (2x2000)

off label
CD20 antibodies in MS

Immunotherapy of MS in countries with limited resources

Rituximab (e.g. Rituxan but also several others): every 6 months 500mg i.v.

Good safety profile (so far at least in Europe), convenient and well tolerated by patients

Low treatment cost in Germany 3000€/year, in India 300€/year

Not licensed for MS but works very well in daily practice (e.g. most used drug in MS in Sweden)

But should only be given to patients with established diagnosis and proven disease activity

Should not be given to patients with chronic infections (e.g. HIV, Hepatitis)
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41 years old women. 5 years ago she developed unilateral vision loss. Vision did not improved after corticosteroid treatment. Over the next five years she developed 5 additional relapses affecting 3 times the optic nerves and twice the spinal cord. The relapses affecting the spinal cord led to sever motor and sensory impairment of both legs and were accompanied by severe pain. After the last relapses the patient remained impaired by moderate paraparesis and unilateral vision loss.
NMO: optic nerve
Optic neuritis und acute myelitis

+ two of the three following criteria

1. cMRI does not fulfill the criteria for Multiple Sclerosis
2. Spinal MRI with a lesion that extends over 3 or more spinal segments
3. NMO-IgG antibodies in serum

Wingerchuk et al., Neurology 2006
NMO: brain lesions

typical: periependymal lesions
## Diagnostic criteria of Neuromyelitis optica (2015)

<table>
<thead>
<tr>
<th>NMOSD With AQP4-IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. At least 1 core clinical characteristic (at right)</td>
</tr>
<tr>
<td>2. Positive test for AQP4-IgG*</td>
</tr>
<tr>
<td>3. Exclusion of alternative diagnoses**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NMOSD Without AQP4-IgG or Unknown AQP4-IgG Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. At least 2 core clinical characteristics (at right) resulting from 1 or more clinical attacks and satisfying all of the following requirements:</td>
</tr>
<tr>
<td>a) At least 1 of: ON, acute myelitis with LETM, or APS</td>
</tr>
<tr>
<td>b) Dissemination in space (≥2 different core characteristics)</td>
</tr>
<tr>
<td>c) MRI requirements, if applicable (at right)</td>
</tr>
<tr>
<td>2. Negative test(s) for AQP4-IgG* or testing unavailable</td>
</tr>
<tr>
<td>3. Exclusion of alternative diagnoses**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Core Clinical Characteristics of NMOSD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Most common:</strong></td>
</tr>
<tr>
<td>1. Optic neuritis (ON)</td>
</tr>
<tr>
<td>2. Acute myelitis</td>
</tr>
<tr>
<td>3. Area postrema syndrome (APS): episode of otherwise unexplained hiccups or nausea and vomiting</td>
</tr>
<tr>
<td><strong>Less common:</strong></td>
</tr>
<tr>
<td>4. Acute brain stem syndrome</td>
</tr>
<tr>
<td>5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions</td>
</tr>
<tr>
<td>6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Supporting MRI Requirements for NMOSD Without AQP4-IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute optic neuritis</strong>: brain MRI normal or demonstrating only nonspecific white matter lesions; OR optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over &gt;1/2 optic nerve length or involving optic chiasm</td>
</tr>
</tbody>
</table>
# Immunotherapy of NMO

Trials supporting the use of immunosuppressive drugs in the treatment of NMO.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Date</th>
<th>Lead Author</th>
<th>Location</th>
<th>Population size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>1998</td>
<td>Mandler</td>
<td>United States</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>2008</td>
<td>McKeon</td>
<td>United States</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>2010</td>
<td>Bichuetti</td>
<td>Brazil</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>2010</td>
<td>Sarhaian</td>
<td>Iran</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>2011</td>
<td>Constanzi</td>
<td>United States</td>
<td>99</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>2009</td>
<td>Jacob</td>
<td>United States</td>
<td>24</td>
</tr>
<tr>
<td>Rituximab</td>
<td>2005</td>
<td>Cree</td>
<td>United States</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>2008</td>
<td>McKeon</td>
<td>United States</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>2008</td>
<td>Jacob</td>
<td>United States</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>2011</td>
<td>Bedi</td>
<td>United States</td>
<td>23</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>2011</td>
<td>Pellkofer</td>
<td>Germany</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>2011</td>
<td>Kim</td>
<td>Korea</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>Minagar</td>
<td>United States</td>
<td>8</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>2007</td>
<td>Watanabe</td>
<td>Japan</td>
<td>11</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>2006</td>
<td>Weinstock-</td>
<td>United States</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Guitman</td>
<td>Korea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2011</td>
<td>Kim</td>
<td>Korea</td>
<td>20</td>
</tr>
</tbody>
</table>
Rituximab in NMO

Jacob, Arch Neurol 2008

Kim, Jama Neurol 2014
New drugs in NMO

- Complement inhibitor Eculizumab (Solaris ®)
- Interleukin-6 receptor blocker (e.g. Tocilizumab®, Satralizumab® (SA 237)
- CD19 antibody
Multiple sclerosis is the most prevalent autoimmune disease of the nervous system in Europe and will most likely become much more prevalent in Africa in the future.

The criteria of dissemination in space (DIS) and time (DIT) have to be met to diagnose MS.

MS relapses can be treated with high dose corticosteroids or plasma exchange.

Many drugs are approved for immunotherapy of MS. CD20 antibodies are a new treatment option with particular interest for countries with limited financial resources.

Neuromyelitis optica differs from MS with respect to phenotype and pathophysiology. NMO relapses are treated similar to MS relapses. Rituximab and immunosuppressants are the most widely used drugs for treatment of NMO.
Thanks for your attention!
Lesions in regions with strong AQP4-expression (Pittock 2006)
NMO: brain lesions

typical?: periependymal lesions of lateral ventricles

Barnett 2013
NMO: brain lesions

periventricular lesions

Barnett 2013
NMO: brain lesions

callosal lesions

Barnett 2013
Therapie der NMO

- **Combination therapy**
  - Tocilizumab
  - Third-line therapy

- **Second-line therapy**
  - Mycophenolate Mofetil, Mitoxantrone, Methotrexate

- **First-line therapy**
  - Azathioprine ↔ Rituximab (IVlg*)

*Includes:

a) combination of steroids plus cyclosporin A or methotrexate or azathioprine
b) combination of immunosuppression plus intermittent plasma exchange
c) combination of rituximab with methotrexate or intravenous immunoglobulins (IVlg)

Trebst, *J Neurol* 2014