MULTIPLE SCLEROSIS - REVIEW AND UPDATE

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- MS is primary demyelinating disease of the central nervous system.
- MS is considered to be immune mediated, although actual development of MS will depend on many other factors, such as genetic, environmental and others, not yet been determined.
The risk of developing MS in the general population is approximately 0.1%.

The risk for a child with one parent who has MS is approximately 2%.

The risk for a child with two parents who have MS is approximately 12.2%.

The risk for a dizygotic twin and other siblings is approximately 5%.

The risk for monozygotic twins is approximately 25%.

The risk for second-degree and third-degree relatives is approximately 1%.
VARIANTS OF MS

- relapsing remitting
- secondary progressive
- primary progressive

COMMON PRESENTATIONS OF RRMS

- Optic neuritis
- Numbness, paresthesia, weakness
- Brainstem syndrome (e.g. INO, cerebellar findings, dysarthria)
# DIAGNOSIS OF MULTIPLE SCLEROSIS

- Clinical diagnosis by McDonald criteria
- History
- Exam
- MRI
- CSF: oligoclonal bands, IgG index
- Screening labs
### HISTORY OF DIAGNOSTIC MS CRITERIA

- Schumacher 1965
- Posner 1983

Dissemination in time and space remains sine qua non!

- Disease activity continues even in the absence of clinical symptoms
- Axons are injured as well as myelin
- Inflammation is more widespread than visualized on standard MRI

Conclusion: Start treatment early
FDA APPROVED TREATMENTS FOR MULTIPLE SCLEROSIS

- Betaseron 1993 (interferon beta-1b)
- Avonex 1996 (interferon beta-1a)
- Copaxone 1997 (glatiramer acetate)
- Novantrone 2000 (mitoxantrone)
- Rebif 2002 (interferon beta-1a)
- Tysabri 2006 (natalizumab)
- Extavia 2009 (interferon beta-1b)
- Gilenya 2010 (fingolimod)
- Aubagio 2012 (teriflunomide)
- Tecfidera 2013 (dimethyl fumarate)
- Plegridy 2014 (peginterferon beta-1a)
- Lemtrada 2014 (alemtuzumab)
- Glatopa 2015 (generic glatiramer acetate)
- Ocrevus 2017 (ocrelizumab)
- Mayzent 2019 (siponimod)
- Mavenclad 2019 (cladribine)

FDA APPROVED DMT-S

**Injections:** interferon, glatiramer, 

**Oral meds:** fingolimod, tecfidera, aubagio

**Infusions:** tysabri, alemtuzumab, ocrelizumab mitoxantrone cladribine siponimod
SEVERE MS

- Rampant or fast progression of disability over a short time period, often referred to as having 'aggressive' disease
- Fast accumulation of new MRI lesions or high number of contrast enhancing lesions
- Patients with aggressive MS are at increased risk of rapid accrual of disability and disease progression, so early detection is critical
- Per most recent AAN Practice Guidelines (2018), clinicians should prescribe high efficacy therapy for people with highly active MS

PREDICTORS

<table>
<thead>
<tr>
<th>Good prognosis</th>
<th>Poor prognosis</th>
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<tbody>
<tr>
<td>• Young</td>
<td>• Older age of onset</td>
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<tr>
<td>• Female sex</td>
<td>• Male sex</td>
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<tr>
<td>• Onset with optic neuritis or an isolated sensory symptom</td>
<td>• “Multifocal” onset</td>
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<td>• Full recovery from attack</td>
<td>• Efferent system affected (motor or cerebellar)</td>
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<td>• Long interval to second relapse</td>
<td>• High relapse rate in the first 2-5 years</td>
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<td>• No disability after 5 years</td>
<td>• Substantial disability after 5 years</td>
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<tr>
<td>• Normal MRI / low lesion load</td>
<td>• Abnormal MRI with large lesion load</td>
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<tr>
<td>• No posterior fossa lesions</td>
<td>• Posterior fossa lesions</td>
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<td>• Possible genomic factors</td>
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Adapted from Miller et al., Lancet Neurology 2009; 4; 281-288
**Preclinical**

**First Clinical Event**

**RRMS**

**SPMS**

**Clinical Threshold**

**Time**

**Treatment of RRMS**

**Treatment after a first event**

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**PML**

- HIV infection, lymphoproliferative disorders, transplant recipients, non biologic and biologic drug use

- AMS, visual symptoms, hemiparesis

- Cortical signs (aphasia, apraxia, new onset seizures) should prompt evaluation for alternative diagnosis

- Ultrasensitive JCV DNA PCR in CSF vs JCV Ab titer monitoring in serum
NATALIZUMAB ASSOCIATED PML DATA

- 3/4 individuals survived vs almost 100% mortality in HIV related PML*

- Predictors for improved survival:
  - Younger age at diagnosis
  - Less functional disability prior
  - Lower JC viral load
  - More localized brain involvement by MRI

- Recent data showed that natalizumab extended interval dosing (5-8 weeks) is associated with a significantly lower risk of PML than standard interval dosing**.

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**Natalizumab Extended Interval Dosing (EID) Is Associated with a Significant Reduction in Progressive Multifocal Leuкоencephalopathy (PML): Risk Compared with Standard Interval Dosing (SID): Analyses of TOUCH Prescribing Program Data, AAN 2018
Severe, immune-mediated demyelination and axonal damage predominantly targeting the optic nerves and spinal cord, but also the brain and brainstem

Disease-specific anti-aquaporin-4 (AQP4) antibody

Women 10 x more affected than men, median age 39

Diagnostic criteria:
- Optic neuritis
- Acute myelitis
- Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
- Acute brainstem syndrome
- Symptomatic narcolepsy or acute diencephalic clinical syndrome
- Symptomatic cerebral syndrome with NMO-like brain lesions
Thank you!