Identifying Prognostic Factors

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Disclosures

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• Advisory board: Bayer Healthcare, Genzyme, Medison, Merck, Neopharm, Novartis, Roche Teva and TG-Therapeutics

• Research grants: Bayer Healthcare, Medison, Merck-Serono, Novartis and Teva
Learning objectives

• Recognize risk factors for MS
• Identify prognostic factors for poor prognosis early in the course of MS
• Consider prognostic factors in the treatment decision-making process
Increasing disability/deterioration

Subclinical (RIS)
Mono-symptomatic (CIS)
Relapsing-Remitting
Secondary Progressive

Subclinical
Mono-
symptomatic
Relapsing-
Remitting
Secondary Progressive

Earliest treatment
Earlier escalation

Later treatment

Time

Level of disability

Brain volume

Cognitive dysfunction

Level of disability

Early intervention

Later intervention

Accumulated MRI lesion burden

$T_1$ BH lesion load

Acute (new and Gd+) MRI activity

BH = black hole; Gd = gadolinium; MRI = magnetic resonance imaging.

MS takes a highly variable course
MS takes a highly variable course

Important to consider:

- **Risk factors** that put individuals at increased risk of developing the disease
- **Prognostic factors** that may predict a patient’s disease course (disease progression and disability)

Prediction is very difficult, especially about the future.

--- Niels Bohr, Book of a Thousand Days
MS is a complex disease

Genetic risk factors

• worldwide prevalence of familial MS is 12.6%\textsuperscript{1}
• Strongest genetic susceptibility factors- HLA DR*2 (in Caucasians)\textsuperscript{2} (other HLA loci in Mediterraneans)
• Additional >233 susceptibility alleles, mostly in immune system related loci\textsuperscript{3,4}

IMSGC, Science 2019;365:eaav7188
Environmental risk factors for MS$^{5-7}$

- EBV infection
- CMV infection
- Low vit. D
- Smoking
- Obesity
- Latitude/UV radiation
- Diet (NaCl, alcohol, coffee…)
- Gut microbiome
- Chemicals/pollutants
- Shift work

Most factors seem to have the greatest effect during adolescence

Prognostic factors
Epidemiologic factors

• Age
  – Older age at onset is associated with a more rapid progression\(^8\)
  – Mean time to an EDSS score of 6 decreases as age of onset increases\(^9\)

• Sex/Sex hormones (controversial)
  – Male sex might predict worse outcomes in RRMS and SPMS\(^8\)
  – Multiple pregnancies may be protective\(^10\)
  – Oral contraceptives → a milder course in RMS\(^11\)
  – Total free testosterone/Estradiol ratio\(^12\)
Lifestyle factors

- **Smoking**
  - Heavy smokers have higher chance of developing MS than never smokers\(^{13}\)
  - Smoking RRMS patients progress faster to SPMS (HR=2.5) than non-smokers\(^{14}\)
  - Smoking is associated with increased MRI Gd+ number (\(P=0.002\)) and volume (\(P=0.014\))\(^{14}\)
  - Ex-smokers have slower disease progression than current smokers\(^{15}\)

- **Other habits**
  - Consumption of alcoholic beverages, coffee, and/or fish is associated with a milder disease course in RMS\(^{16}\)
Low vit. D is a risk factor as well as a prognostic factor in MS

Characteristics of initial attacks

- Type (motor, sphincter or cognitive), location (cerebellum, brainstem, SC) and number of systems involved\(^8,9,17-19\)
- Incomplete recovery\(^9,18-21\)
- Shorter interval between the first and second attack\(^8,17,18,20,22\)
- Frequent attacks years 2-5\(^8,17,18,22,23\)
- Poly-symptomatic (multifocal) relapses\(^17,21\)
- Early vs. late attacks\(^24\)
Other clinical predictors

- Early accumulation of disability\textsuperscript{8,17,19}
- PPMS course\textsuperscript{17,18,25}
- Early secondary progression\textsuperscript{26}
- Chronic depression\textsuperscript{26}
- Cognitive impairment\textsuperscript{26}
- NEDA status\textsuperscript{43}
- Vascular risk factors
- Comorbidities
- No previous treatment
Disease course

PPMS Course

Early conversion to SPMS

Time from the Onset of MS to EDSS=4


Depression

Cognitive impairment


Pitteri M et al. Cognitive impairment predicts disability progression and cortical thinning in MS. *MSJ* 2017;23:848-54
NEDA Status

Multifactorial predictors of NDOs 16 years after randomization to the pivotal IFN beta-1b clinical trial in RRMS

BOD: burden of disease; EDSS: Expanded Disability Status Scale; NDO: negative disability outcome; NEDA: no evidence of disease activity


RESULTS A total of 99 of 215 patients (46.0%) had NEDA for clinical and MRI measures at 1 year, but only 17 of 216 (7.9%) maintained NEDA status after 7 years. No differences were found in NEDA status between patients with early vs established MS. A dissociation was found between clinical and MRI disease activity. Each year, 30.6% (64 of 209) to 42.9% (93 of 217) of the cohort had evidence of either clinical or MRI disease activity but not both. NEDA at 2 years had a positive predictive value of 78.3% for no progression (Expanded Disability Status Scale score change ≤ 0.5) at 7 years. Only minor improvement was found in the positive predictive values with additional follow-up of 1 to 3 years.
fatigue

Conversion to EDSS=3

Table 2. Multivariate logistic regression analysis of the association between fatigue and conversion to sustained EDSS ≥3 (converters = 1, non-converters = 0).

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Standardized regression coefficient</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MFIS</td>
<td>4.34</td>
<td>1.42–16.93</td>
<td>0.009</td>
</tr>
<tr>
<td>EDSS</td>
<td>3.58</td>
<td>1.67–9.40</td>
<td>0.001</td>
</tr>
<tr>
<td>CES-D</td>
<td>1.43</td>
<td>0.40–5.39</td>
<td>0.568</td>
</tr>
</tbody>
</table>

CI: confidence interval; MFIS: Modified Fatigue Impact Scale; EDSS: Expanded Disability Status Scale; CES-D: Center for Epidemiological Studies Depression scale; SD: standard deviation.

In order to compare the effect of predictors measured by different scales on the conversion to sustained EDSS ≥3, the coefficient referring to MFIS, EDSS, and CES-D is expressed as standardized regression coefficient, that is, odds ratio per SD increase in the predictor (SD of total MFIS, EDSS, and CES-D scores across all subjects: 17.3, 0.8, and 6.9, respectively).
### Comorbidities

#### Physical

**Factors**

<table>
<thead>
<tr>
<th>No. of comorbidities</th>
<th>Coefficients and 95% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted findings</td>
<td></td>
</tr>
<tr>
<td>British Columbia</td>
<td>0.54 (0.41, 0.66)</td>
</tr>
<tr>
<td>Nova Scotia</td>
<td>0.69 (0.56, 0.81)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.61 (0.46, 0.76)</td>
</tr>
</tbody>
</table>

*Test for heterogeneity: $\chi^2=2.76$, df=1, $p=0.10$*

| Adjusted findings     |                             |
| British Columbia      | 0.15 (0.01, 0.29)           |
| Nova Scotia           | 0.21 (0.08, 0.35)           |
| Overall               | 0.18 (0.09, 0.28)           |

*Test for heterogeneity: $\chi^2=0.40$, df=1, $p=0.53$*

- Likely to be associated with a lower EDSS score
- Likely to be associated with a higher EDSS score

#### Psychiatric

**Factors**

**Table 3**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1*</th>
<th>Model 2*</th>
<th>Model 3*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$</td>
<td>SE</td>
<td>$p$ Value</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>1.94</td>
<td>0.12</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>No depression (ref)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>0.22</td>
<td>0.08</td>
<td>0.0039</td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>1.92</td>
<td>0.04</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>No anxiety disorder (ref)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>0.06</td>
<td>0.08</td>
<td>0.4740</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>1.92</td>
<td>0.05</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>No bipolar disorder (ref)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>0.32</td>
<td>0.17</td>
<td>0.0592</td>
</tr>
</tbody>
</table>

* Adjusted for disease duration.  
** Adjusted for disease duration, age at onset, sex, socioeconomic status, and disease course.  
*** Adjusted for disease duration, age at onset, sex, socioeconomic status, disease course, disease-modifying therapy use, and physical comorbidity count.

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Other clinical predictors

- Early accumulation of disability\textsuperscript{8,17,19}
- PPMS course\textsuperscript{17,18,25}
- Early secondary progression\textsuperscript{26}
- Chronic depression\textsuperscript{26}
- Cognitive impairment\textsuperscript{26}
- NEDA status\textsuperscript{43}
- Comorbidities
- Vascular risk factors

\textbf{MS} = Brain loss

\textbf{Time} = Brain

\* \* \* MS = Time-dependent brain loss
Imaging factors

• T2 lesion count and volume in the first 5 years\textsuperscript{27-29}
• Location: Cortical, posterior fossa or spinal cord\textsuperscript{30-32}
• Gray matter involvement and atrophy\textsuperscript{33,34}
• Atrophy: Thalamus, spinal cord, CC, brain\textsuperscript{31,35-41}
• Gd enhancement\textsuperscript{42}
• Chronic black holes\textsuperscript{44}
• OCT\textsuperscript{45,46}
T2 lesion count and volume in the first 5 years

Probability of developing EDSS

<table>
<thead>
<tr>
<th>Baseline T2 lesions (n)</th>
<th>Patients reaching EDSS &gt; 6 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1-3</td>
<td>20</td>
</tr>
<tr>
<td>4-10</td>
<td>40</td>
</tr>
<tr>
<td>&gt;10</td>
<td>60</td>
</tr>
</tbody>
</table>

Brex, NEJM 2002

T2 lesion volume: 5Y FU of 84 pts with CIS

<table>
<thead>
<tr>
<th>MRI at presentation</th>
<th>Conversion to CDMS</th>
<th>EDSS &gt; 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>2/32 (6%)</td>
<td>0/32</td>
</tr>
<tr>
<td>Abn &lt;1.23 cc</td>
<td>17/31 (55%)</td>
<td>7/31 (32%)</td>
</tr>
<tr>
<td>Abn &gt;1.23 cc</td>
<td>19/21 (90%)</td>
<td>11/21 (52%)</td>
</tr>
</tbody>
</table>


Filippi M et al. Neurology 1994
Lesion location

Infratentorial

Cortical lesions

Spinal Cord

Calabrese M et al. Arch Neurol. 2007
Cortical lesion volume

\[ r = 0.59; \ P < 0.001 \]

T2 lesion volume

\[ r = 0.41; \ P < 0.001 \]

Normalized neocortical gray matter volume

\[ r = -0.47; \ P < 0.001 \]
Cortical atrophy and cognition in early RRMS

2.5 years of follow-up

$\text{NCV Changes}$

$\text{Stable/Improving}$

$\text{Worsening}$

$p = 0.007$

Amato MP et al. Arch neurolo 2007
Gray matter damage

Table 2. Demographic, clinical and adjusted\(^a\) BL MRI volumes (as percentage of whole-brain volume) of 241 RRMS patients, and of the four subgroups: RR→RR, RR→SP, EDSS < 4 and EDSS > 4.

<table>
<thead>
<tr>
<th></th>
<th>Mean (range)</th>
<th>SD</th>
<th>Median</th>
<th>IQ ranges</th>
<th>RR→RR n = 199</th>
<th>RR→SP n = 42</th>
<th>EDSS &lt; 4 n = 135</th>
<th>EDSS &gt; 4 n = 73</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at FU</td>
<td>44.4 (22–77)</td>
<td>9.1</td>
<td>34</td>
<td>28–40</td>
<td>38</td>
<td>30–47</td>
<td>33</td>
<td>27–39</td>
</tr>
<tr>
<td>Age at onset</td>
<td>27.3 (13–54)</td>
<td>8.0</td>
<td>26</td>
<td>21–33</td>
<td>26</td>
<td>21–35</td>
<td>25</td>
<td>21–31</td>
</tr>
<tr>
<td>AWM-f</td>
<td>1.2 (0–9.61)</td>
<td>0.6</td>
<td>0.6</td>
<td>0.2–1.4</td>
<td>1.4</td>
<td>0.3–2.6</td>
<td>0.6</td>
<td>0.1–1.2</td>
</tr>
<tr>
<td>CSF-f</td>
<td>14.9 (5.8–33.4)</td>
<td>4.7</td>
<td>13.9</td>
<td>11.2–16.4</td>
<td>17.1</td>
<td>13.3–20.9</td>
<td>13.7</td>
<td>10.9–16.2</td>
</tr>
<tr>
<td>GM-f</td>
<td>51.4 (39–58.2)</td>
<td>3.1</td>
<td>52.1</td>
<td>49.9–53.7</td>
<td>49.8</td>
<td>47.7–51.9</td>
<td>52.4</td>
<td>50.5–54.5</td>
</tr>
<tr>
<td>BL EDSS</td>
<td>2.3 (0–4.5)</td>
<td>1.2</td>
<td>2</td>
<td>1.5–2.5</td>
<td>3.3</td>
<td>2.5–3.5</td>
<td>2</td>
<td>1.5–2</td>
</tr>
<tr>
<td>DD at BL</td>
<td>8.5 (1–35)</td>
<td>6.5</td>
<td>7</td>
<td>3–11</td>
<td>7</td>
<td>5–15</td>
<td>6</td>
<td>3–10</td>
</tr>
<tr>
<td>DD at FU (years)</td>
<td>17.4 (10–44)</td>
<td>6.4</td>
<td>15</td>
<td>12–20</td>
<td>16</td>
<td>14–24</td>
<td>15</td>
<td>12–19</td>
</tr>
</tbody>
</table>

BL: baseline; MRI: magnetic resonance imaging; RR: relapsing–remitting multiple sclerosis; SP: secondary progressive; SD: standard deviation; FU: follow-up; AWM-f: abnormal white matter fraction; CSF-f: cerebrospinal fluid fraction; GM-f: gray matter fraction; EDSS: Expanded Disability Status Scale; DD: disease duration; IQ: interquartile. \(^a\)Adjusted for age, gender and education.

“Conversion from RR to SP (OR 0.79; CI 0.7–0.9), progression of EDSS (OR 0.85; CI 0.77–0.93), achievement of EDSS 4 (OR 0.8; CI 0.7–0.9), and time to reach EDSS 4 (HR 0.88; CI 0.82–0.94) were all predicted by baseline gray matter volume”

Gray matter atrophy

Correlations of brain volume measurements with clinical features

<table>
<thead>
<tr>
<th></th>
<th>EDSS (n = 73)a (44b)</th>
<th>MSFC (n = 67)a (41b)</th>
<th>Z-PEG (n = 70)a (42b)</th>
<th>Z-WALK (n = 68)a (40b)</th>
<th>Z-PASAT (n = 68)a (42b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMF a</td>
<td>-0.48 (&lt;0.001)</td>
<td>0.56 (&lt;0.001)</td>
<td>0.59 (&lt;0.001)</td>
<td>-0.40 (0.001)</td>
<td>0.27 (0.026)</td>
</tr>
<tr>
<td>GMF b</td>
<td>-0.41 (0.005)</td>
<td>0.55 (&lt;0.001)</td>
<td>0.44 (0.003)</td>
<td>-0.49 (0.001)</td>
<td>0.32 (0.038)</td>
</tr>
<tr>
<td>WMF a</td>
<td>-0.20 (0.086)</td>
<td>0.03 (0.784)</td>
<td>0.16 (0.176)</td>
<td>-0.11 (0.337)</td>
<td>-0.07 (0.537)</td>
</tr>
<tr>
<td>WMF b</td>
<td>-0.11 (0.443)</td>
<td>0.10 (0.526)</td>
<td>0.28 (0.071)</td>
<td>-0.09 (0.560)</td>
<td>-0.04 (0.761)</td>
</tr>
</tbody>
</table>

“Gray matter fraction correlated with EDSS and cognitive function, whereas white matter fraction did not”

Gray matter atrophy correlated with disability and was more marked with disease progression: atrophy rate was 3.4-fold faster than normal in patients converting from CIS to RRMS and 14-fold faster in patients converting to SPMS

Fisniku LK et al. Gray matter atrophy is related to long term disability in MS. Ann Neurol. 2008;64:247-54
Brain atrophy

Spinal cord atrophy

Corpus callosum atrophy

Corpus callosum damage predicts disability progression and cognitive dysfunction in primary-progressive MS after five year

Deep GM atrophy (thalamus, putamen, hippocampus)

“Short-term accrual of thalamic damage predicts the long-term accumulation of disability in PPMS”


“Deep GM volume loss drives disability accumulation in MS, and temporal cortical GM shows accelerated atrophy in SPMS than RRMS”

Smoldering chronic active lesions with darkened rims

<table>
<thead>
<tr>
<th></th>
<th>Spearman Correlation Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EDSS</td>
</tr>
<tr>
<td></td>
<td>p</td>
</tr>
<tr>
<td>Log lesion volume</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Log rim-lesion volume</td>
<td>0.0003</td>
</tr>
<tr>
<td>Log number of rim lesions</td>
<td>0.0005</td>
</tr>
<tr>
<td>Normalized brain volume</td>
<td>0.59</td>
</tr>
<tr>
<td>Normalized cortex volume</td>
<td>0.12</td>
</tr>
<tr>
<td>Normalized WM volume</td>
<td>0.0007</td>
</tr>
<tr>
<td>Normalized thalamus volume</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Normalized caudate volume</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Normalized putamen volume</td>
<td>0.09</td>
</tr>
<tr>
<td>Normalized ventricular CSF volume</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Normalized sulcal CSF volume</td>
<td>0.0003</td>
</tr>
</tbody>
</table>
“Cross-sectional and longitudinal monitoring of pRNFL is useful as a biomarker for prediction of physical and cognitive disability progression in patients with RRMS in everyday clinical practice”

Bsteh G et al. NSJ 2019;25:196-203
Imaging factors

- T2 lesion count and volume in the first 5 years\textsuperscript{27-29}
- Location: Cortical, posterior fossa or spinal cord\textsuperscript{30-32}
- Gray matter involvement and atrophy\textsuperscript{33,34}
- Atrophy: Thalamus, spinal cord, CC, brain\textsuperscript{31,35-41}
- Gd enhancement\textsuperscript{42}
- Chronic black holes\textsuperscript{44}
- OCT\textsuperscript{45,46}
CSF/Serum biomarkers

- OCB (IgM>IgG)\textsuperscript{29,47}
- Neurofilament light chain (NFL)\textsuperscript{48} (also in serum)\textsuperscript{49}
- Chitinase-3-like 1 (CHI3L1)\textsuperscript{50}
  inflammatory markers (cytokines, chemokines, MMPs…) of T cells, B cells, monocytes\textsuperscript{47,51}
- Other: NO, GFAP, BDNF, anti-viral Ab’s…\textsuperscript{47}

The clinical utility of CSF biomarkers in everyday practice is not well established
Neurofilament light chain (NfL)

CSF

Prediction for EDSS development

4 Quartiles of NfL

“CSF levels of NfL at the time of diagnosis seems to be an early predictive biomarker of longterm clinical outcome and conversion from RRMS to SPMS”

Bhan A et al. MSJ 2018;24:1301-7

Blood

Elevated sNfL was associated with poorer neurologic function and diabetes”

Fitzgerald K et al. ECTRIMS 2019

“NfL and OCBs are prognostic biomarkers in RIS and predict conversion to CIS and MS”

Matute-Blanch C et al. Brain 2018;141:1085-93

“OR for severe vs. mild disability:
2.50 (1.71, 3.67)
p<0.0001”

OR for moderate vs. mild disability:
1.26 (0.96, 1.66)
p=0.09

PDDS

CSF levels of NfL at the time of diagnosis seems to be an early predictive biomarker of longterm clinical outcome and conversion from RRMS to SPMS”

Matute-Blanch C et al. Brain 2018;141:1085-93

“NfL and OCBs are prognostic biomarkers in RIS and predict conversion to CIS and MS”

Fitzgerald K et al. ECTRIMS 2019

“Elevated sNfL was associated with poorer neurologic function and diabetes”
Evoked potentials can predict future disability in people with clinically isolated syndrome. J Neurol 2019

Crnošija L et al. Evoked potentials can predict future disability in people with clinically isolated syndrome. J Neurol 2019

Genomic factors

• HLA genotypes
  – HLA-DRB1, DRB*07, DRB*44, -DQB1*0301, -DQB1*0302, -DQB1*0602, and -DQB1*0603

• NLRP3 and NLRC4 (inflammasome components) variants

• Other MS susceptibility polymorphisms

Risk of MS and disability accumulation after CIS

CDMS Multivariate analysis

- Low: Males, Females
- Medium: 40-49 years, 30-39 years, 20-29 years, 0-19 years, Other, Optic neuritis
- High: OR absent, OR present, 0 lesions, 1-3 lesions, 4-9 lesions, ≥10 lesions, DMT after 2nd attack, DMT before 2nd attack

EDSS3 Multivariate analysis

- Low: Men, Women
- Medium: 40-49 years, 30-39 years, 20-29 years, 0-19 years, Other, Optic neuritis
- High: OR absent, OR present, 0 lesions, 1-3 lesions, 4-9 lesions, ≥10 lesions, DMT after 2nd attack, DMT before 2nd attack

Conversion to CDMS is associated with baseline no. of MRI lesions

No. of MRI lesions

- ≥10
- 4-9
- 1-3

Time since first attack

Cumulative probability of developing CDMS

Making treatment decisions
I. Define your treatment goals

T2T: Treat to Target

- **Clinical disease activity**
  - Delay disability progression
  - Reduce relapse frequency

- **MRI disease activity**
  - Prevent new/enlarging $T_2$ lesion and new Gd$^+$ $T_1$ lesions

Traditional Goals$^{1,2}$

- Stabilize function and/or improve pre-existing disability
- Reduction in relapse severity; no relapses
- Freedom from clinical disease activity

Evolving Treatment Goals$^{3-6}$

- Reduction in brain atrophy
- Freedom from MRI disease activity

MS disease activity free

Patient considerations

Gd=gadolinium; MRI=magnetic resonance imaging

## II. Determine the risk of your patient

### Factors at disease onset associated with poor prognosis

<table>
<thead>
<tr>
<th>Epidemiologic / Life Style</th>
<th>Environmental / Life Style</th>
<th>Clinical</th>
<th>Paraclinical / Biologic</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset &gt; 40</td>
<td>EBV infection</td>
<td>Type (motor, cerebellar, sphincter or cognitive) and no. of systems involved</td>
<td>IgG or IgM OCB (CSF)</td>
<td>Location: Intracortical, posterior fossa or spinal cord lesions</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>Low Vit. D</td>
<td>Topography: cerebellum, brainstem, spinal cord</td>
<td>Biomarkers (CSF, blood CHI3L1, neurofilament)</td>
<td>High lesion load</td>
</tr>
<tr>
<td>Ethnic origin (Asian or African)</td>
<td>Smoking</td>
<td>Polyregional (multifocal) symptoms</td>
<td>Abnormal evoked potentials</td>
<td>Contrast enhancement</td>
</tr>
<tr>
<td>Latitude (?)</td>
<td>Obesity</td>
<td>Partial or no recovery from initial attacks</td>
<td>Genomic factors (e.g. ApoE4, HLA-DRB1*15)</td>
<td>Brain, thalamic or spinal cord atrophy</td>
</tr>
<tr>
<td>Ageing</td>
<td>Diet (e.g. high salt, sweetened drinks, mediterranean)</td>
<td>Frequent attacks during the first years</td>
<td>Inflammatory markers in CSF</td>
<td>Smoldering chronic active lesions with darkened rims</td>
</tr>
<tr>
<td></td>
<td>Organic solvents</td>
<td>Short interval between the first two attacks</td>
<td>High plasma ceramides</td>
<td>Chronic T1 black holes</td>
</tr>
<tr>
<td></td>
<td>CMV infection (↑ in the ME, ↓ in Europe)</td>
<td>Rapid disability progression during the first years</td>
<td></td>
<td>Cortical pathology</td>
</tr>
<tr>
<td></td>
<td>Exercise (protective)</td>
<td>Progressive dis. from onset</td>
<td>NEDA status</td>
<td>Gray matter damage</td>
</tr>
<tr>
<td></td>
<td>Sun exposure</td>
<td></td>
<td>OCT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alcohol, coffee, fish, oral tobacco (protect.)</td>
<td>Cognitive impairment, Depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Microbiome</td>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Night work</td>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vascular risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Risk Calculator?

<table>
<thead>
<tr>
<th>Total Risk Score</th>
<th>Risk Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 5</td>
<td>Low</td>
</tr>
<tr>
<td>6 - 10</td>
<td>Moderate</td>
</tr>
<tr>
<td>11 - 15</td>
<td>High</td>
</tr>
<tr>
<td>16 - 20</td>
<td>Very High</td>
</tr>
<tr>
<td>≥ 21</td>
<td>Extreme</td>
</tr>
</tbody>
</table>
Tailoring initial treatment

- Prognostic factors can help determine likely outcomes and guide treatment decisions

**Multiple poor prognostic factors:**
More likely to do poorly, likely greater benefit from high efficacy therapy

**All other patients:**
Patient and clinician choice after weighing potential risks and benefits

**Few poor prognostic factors and/or positive prognostic factors:**
More likely to do well, potentially less accepting of ‘risk’ with high-efficacy therapy

- In clinical practice, it can be difficult to identify patients not at the extremes
III. Consider additional factors

- Efficacy
- Safety
- Tolerability
- Clinical or MRI disease activity
- Cognitive dysfunction
- Response to previous DMTs
- Drug properties, metabolism, MoA
- Comorbidities
- Concomitant medications
- Current immunity or immunization status
- Previous immunosuppressive therapy
- Monitoring
- Adherence to treatment and monitoring
- Physician experience
- Patient's preferences (convenience, route and frequency of administration, side effects, individual tolerability)
- Patient’s expectations
- Patient's life style
- Childbearing potential, pregnancy and family planning
- Cost
- Treatment access and logistics
- Regulatory status
- Social and family support systems
IV. Select a treatment strategy

• **Escalation therapy**
  – Standard but “failure-based” approach
  – Appropriate for patients with inactive disease, good prognostic factors
  – High-quality supportive evidence is limited
  – Questions: definition of treatment failure, sequence of escalation, washout, additive risks of immunosuppression

• **Induction therapy**
  – Appropriate for highly active patients or those with poor prognostic factors at disease onset
  – Short course may improve risk-benefit ratio
  – Long-term benefit still unclear

• **Combination therapy**
  – Limited evidence
  – Future strategy?
V. Assess Benefit/Risk ratio
VI. Share decisions, Monitor and assess for disease activity/treatment failure

“If it weren’t for the great variability of individuals, medicine might as well be a science and not an art”
Sir William Osler, M.D. 1892
Conclusions

• MS is highly variable and unpredictable, however, several factors have emerged as predictive of the course and prognosis of the disease

• Some genetic and environmental risk factors that affect the likelihood of developing MS may also predict its course

• There are multiple epidemiological, environmental, clinical, imaging and biological prognostic factors to be considered

• Prognostic factors are important for decision making and selecting the most appropriate treatment for the individual patient with MS
Thank You Ashkelon
References


51. Calabrese M, et al. Intrathecal inflammatory profile predicts disease course in Multiple Sclerosis. ECTRIMS 2019


