Multiple Sclerosis: Continuity of Care from Diagnosis Through Disability

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Section 1

Overview of Multiple Sclerosis

Multiple Sclerosis: Continuity of Care from Diagnosis Through Disability
Section 1: Learning Objectives

By the end of this section, you will be able to:

• Recognise the natural history of MS.
• Recognise the socioeconomic and personal disability associated with MS.
• Recognise how to use the Expanded Disability Status Scale (EDSS) as a method to quantify disability in MS.
The Emotional Responses to a Diagnosis of MS

1. Denial
2. Anger
3. Bargaining
4. Depression
5. Acceptance
6. Anxiety

These emotional responses are based on Elisabeth Kübler-Ross’s model, the five stages of grief. The sixth stage, anxiety, has been added to reflect the uncertainty that comes with a diagnosis of a chronic disease with an uncertain prognosis.


Clinical Subtypes of Multiple Sclerosis

- Primary progressive multiple sclerosis: Steady increase in disability without attacks.
  - 10-15% of patients
- Relapsing-remitting multiple sclerosis: Unpredictable attacks which may or may not leave permanent deficits followed by periods of remission.
  - ~85% of patients
- Secondary progressive multiple sclerosis: Initial relapsing-remitting multiple sclerosis that suddenly begins to have decline without periods of remission.
Natural History of Relapsing Remitting MS

- Clinically Isolated Syndrome to Clinically Definite MS: 80% in 20 years
- Clinically Definite MS to Secondary Progressive MS: >80% in 20 years

1. Median time to EDSS 6 (walking aid) from onset is ~20 years
2. Median time to EDSS 7 (wheelchair) from onset is ~30 years
3. Average life expectancy reduced by 5-14 years

Population-based MS Mortality Studies

<table>
<thead>
<tr>
<th>First Author</th>
<th>Population &amp; time period</th>
<th>Size of cohort</th>
<th>Standardised mortality ratio (SMR)</th>
<th>Additional survival measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grytten Torkildsen N</td>
<td>Western Norway 1953-2003</td>
<td>878</td>
<td>2.68</td>
<td>• Median survival time from onset: 41 years MS vs 49 years general population</td>
</tr>
<tr>
<td>Smestad C</td>
<td>Oslo 1940-1980</td>
<td>368</td>
<td>2.47 (95% CI: 2.09-2.80)</td>
<td>• Reduction of median life expectancy vs. general population</td>
</tr>
<tr>
<td>Brønnum-Hansen H.</td>
<td>Danish MS Registry 1946-1996</td>
<td>9881</td>
<td>2.89</td>
<td>• Median survival time (from disease onset) vs. general population: ~10 years life lost in MS</td>
</tr>
<tr>
<td>Hirst C</td>
<td>South Wales 1985-2006</td>
<td>373</td>
<td>2.79</td>
<td>• Median age of death: ~63.1 years MS vs 70.6 years general population</td>
</tr>
<tr>
<td>Sumelahti ML</td>
<td>Finland 1964-1993</td>
<td>1595</td>
<td>2.8 (95% CI: 2.0-3.1)</td>
<td>• Survival decreases with disease progression: SMR: 2.0-3.1 years after diagnosis: 2.4</td>
</tr>
<tr>
<td>Wallin MT</td>
<td>USA 1956-1996</td>
<td>2489</td>
<td>2.18</td>
<td>• Healthy soldier effect speculated to have a favourable effect on survival</td>
</tr>
<tr>
<td>Leray C</td>
<td>West France 1976-2004</td>
<td>1079</td>
<td>1.3 (95% CI: 1.01-1.5)</td>
<td>• Mean follow-up duration of 12.7 years from clinical onset may be being estimated on relatively immature dataset</td>
</tr>
</tbody>
</table>

The Survival Disadvantage in MS Is Greater Than in Other Chronic Diseases

<table>
<thead>
<tr>
<th>SMRs in chronic diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
</tr>
<tr>
<td>Early breast cancer</td>
</tr>
<tr>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>MS</td>
</tr>
<tr>
<td>MS (2.9.9 years after diagnosis)</td>
</tr>
<tr>
<td>MS (≥10 years after diagnosis)</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
</tr>
</tbody>
</table>


Untreated MS Is a Devastating Disease

Cognitive dysfunction
- Prevalence: 43% to 65%\(^1,2\)
- Affects employment, activities of daily living, and social functioning\(^2\)

Life shortening
- 5- to 14-year decrease in life expectancy\(^3-7\)
- 2- to 7-fold increase in suicide risk\(^5,8\)
- ~50% of patients with MS die of disease-related causes\(^5,6,8\)

QOL
- EDSS and utility* have shown a significant inverse relationship

Mortality
- Mortality ratio of patients with MS exceeds CV disease,\(^3,10\) stroke,\(^3,10\) and early breast cancer\(^10\)

Employment
- 40% of patients with MS are unemployed as of EDSS 3.0 and/or after 10 years from diagnosis\(^13\)

Healthcare costs
- Bulk of cost attributed to services (28.5%) and long-term sick leave and early retirement (30%)\(^9,14\)

Relationships
- Compared with the general population, patients with MS have a higher probability of separating/divorcing and doing so sooner\(^12\)

*In this study, utility measures were derived from EQ-5D using the EuroQol instrument;
**In patients with type 2 diabetes;
†In patients with valvular heart disease in Olmsted County, Minnesota.
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**Expanded Disability Status Scale (EDSS)**


**Consequences of Increasing EDSS* Scores: Loss of Employment in the European Union**

The proportion of patients employed or on long-term sick leave is calculated as a percentage of patients aged 65 or younger. Kobelt G, Berg J, Lindgren P, Fredriksson S, Johnson B. Costs and quality of life of patients with multiple sclerosis in Europe. J Neurol Neurosurg Psychiatry. 2006;77:918-926.


*EDSS; Expanded Disability Status Scale
The Effect of MS on Quality-of-Life (QoL)

EDSS and utility\(^a\) show a significant inverse relationship\(^b\)

- MS is one of the most common causes of neurological disability in young adults
- Natural history studies indicate that it takes a median time of 8, 20, and 30 years to reach the irreversible disability levels of EDSS 4, 6, and 7, respectively

Utility measures are derived from EQ-5D using the EuroQol instrument.

Error bars depict 95% confidence intervals. Half points on EDSS are not shown on graph axis, except at EDSS 6.5.


Divorce and Separation

Figure 1. Crude probability of remaining in a relationship after onset of MS (life table method).

Baseline Prognostic Factors in MS and their Impact on Disease Progression and Disability

**Good prognosis**
- Young
- Female sex
- Optic neuritis
- Isolated sensory symptom
- Full recovery from attack
- Long interval to second relapse
- No disability after five years
- Normal MRI/low lesion load

**Poor prognosis**
- Older age of onset
- Male sex
- “Multifocal” onset
- Efferent system affected (motor or cerebellar)
- High relapse rate in the first two to five years
- Substantial disability after five years
- Abnormal MRI with large lesion load


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Section 1: Summary

Here is a quick recap of what we covered so far:

- The most inclusive way to view MS, and its impact on patients and families affected, is to view it holistically.
- The SMR is a quotient derived from the observed to the expected number of deaths and is used to compare mortality rates for patients with MS and the general population.
- The EDSS is a method of quantifying disability in MS and monitoring changes in the level of disability over time.
- Employment is adversely affected for half of MS patients within 10 years of their diagnosis, and interpersonal relationships are frequently destroyed. As MS-associated disability progresses, quality-of-life dramatically worsens.
Section 2

Getting the Diagnosis Correct and Predictors of Long-term Outcome

Section 2: Learning Objectives

By the end of this section, you will be able to:

• Recognise the evolving definition of MS.
• Recognise the MS timeline from asymptomatic disease to death.
• Relate the link between various MS disease parameters and prognosis.
Definition of Multiple Sclerosis

- **Pathological Definition**: Inflammatory disease of the CNS characterised by demyelination and variable degrees of axonal loss and gliosis

- **Clinical Definition**: Objective CNS dysfunction (involvement of two or more white matter structures separated by time) with no other etiology

The Evolving Clinical Definition of MS


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**Will Rogers Phenomenon in MS**

![Graph showing probability to reach EDSS ≥3 over time for Poser and McDonald criteria]


**Baseline Number of Brain Lesions Predicts Progression to EDSS Score ≥3.0**

![Graph showing progression of disability based on baseline number of brain lesions]

The data presented for years 5, 10, 14, and 20 were obtained from different publications based on the same longitudinal study. The exact relationship between MRI findings and the clinical status of the patient is unknown.


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CIS Patients
n = 40

Healthy Controls
n = 30

P < .0001

Deficits were found mainly in memory, speed of information processing, attention, and executive functioning

What Constitutes a Useful Diagnostic Test or Set of Criteria?

<table>
<thead>
<tr>
<th>DIAGNOSTIC TEST RESULT</th>
<th>PRESENT</th>
<th>ABSENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>-</td>
<td>c</td>
<td>d</td>
</tr>
<tr>
<td></td>
<td>a + c</td>
<td>b + d</td>
</tr>
</tbody>
</table>

From these we determine the sensitivity and specificity as follows:

SENSITIVITY = a/(a+c) >80%
SPECIFICITY = d/(b+d) >80%

A Clinico-Pathoanatomical Study of the MS Diagnosis

SENSITIVITY AND SPECIFICITY

- Neuropathological examination of 518 consecutive patients with clinically definite MS revealed a correct diagnosis in 485 cases (94%)...appropriate sensitivity
  - Clinical diagnosis had been established by a neurologist in all cases
  - Erroneous diagnosis included a variety of other neurological disorders
- In this example, 33 patients had a false-positive diagnosis
- Similar deficiency with false negatives or specificity


What Is Benign MS?

Benign multiple sclerosis
Cognitive, psychological and social aspects in a clinical cohort

163 patients with benign MS
(disease duration >15 years and EDSS <3.5):

- 45% cognitive impairment
- 49% fatigue
- 54% depression

No Evident Disease Activity (NEDA)

Treat-2-target

No evidence of disease activity defined as:
× No relapses
× No sustained disability progression
× No MRI activity
  × No new or enlarging T2 lesions
  × No gadolinium (Gd)-enhancing lesions


The Natural History of Multiple Sclerosis: A Geographically Based Study

2. Predictive Value of the Early Clinical Course


(From the Department of Clinical Neurological Sciences, University of Western Ontario, London, Ontario, Canada)

0-1 attacks in first 2 years

>4 attacks in first 7 years

>= 5 attacks in first 2 years

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Predictors of Long-Term Outcome in Patients With MS Treated With Interferon Beta-1a

*BSCRG, Multiple Sclerosis Collaborative Research Group


Predictors of Long-Term Outcome in Patients With MS Treated With Interferon Beta-1a (con’t.)


Multiple Sclerosis: Continuity of Care from Diagnosis Through Disability
Relapse on Interferon β Therapy Increases Risk of Sustained Disability Progression

HR of EDSS Increase in Patients During the First Two Years of Interferon Treatment

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>SE</th>
<th>P Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No relapses (reference = 1)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One relapse</td>
<td>3.41</td>
<td>1.47</td>
<td>.005</td>
<td>1.46-7.98</td>
</tr>
<tr>
<td>Two or more relapses</td>
<td>4.37</td>
<td>1.74</td>
<td>.000</td>
<td>1.90-9.57</td>
</tr>
</tbody>
</table>


Relapses and Residual Deficits


Multiple Sclerosis: Continuity of Care from Diagnosis Through Disability
Predictors of Long-Term Outcome in MS Patients Treated with Interferon Beta-1a


MRI to Monitor Treatment Response to Interferon β: a Meta-analysis

Multiple sclerosis is defined as a disease based on a clinicopathological correlate. However, this definition is evolving as new innovations are emerging and getting incorporated into the diagnostic criteria. Early in the disease neuronal reserve allows patients with MS to adapt to the damage; once the reserve capacity is exhausted, they enter the progressive phase of the disease. Cognitive function is affected in CIS. A larger number of lesions present at the first demyelinating event is associated with a greater risk of progressing to an EDSS score ≥3. NEDA is defined by the absence of clinical attacks and disease progression and being free of pathologic MRI activity.
Section 3: Learning Objectives

By the end of this section, you will be able to:

• Recognise the relationships between disease activity and disability progression in therapy.
• Identify brain atrophy as a major cause of disability.
• Identify the paradigm shift in managing MS related to reducing end organ damage.
**100 Patients With MS**

Who Are the Responders?

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### Strongest Predictor of Disability Progression on Interferon β Therapy Is Progression Itself

Disease activity during two years of treatment and prediction of disability progression* at six years

<table>
<thead>
<tr>
<th>Group</th>
<th>Sensitivity (%) (CI)</th>
<th>Specificity (%) (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. An increase of at least one EDSS step confirmed at six months</td>
<td>85 (64-95)</td>
<td>93 (86-97)</td>
</tr>
<tr>
<td>B. Occurrence of any relapse</td>
<td>80 (58-92)</td>
<td>51 (41-61)</td>
</tr>
<tr>
<td>C. Occurrence of two or more relapses</td>
<td>45 (26-66)</td>
<td>81 (72-82)</td>
</tr>
<tr>
<td>D. A decrease in relapse rate less than 30% compared to two years before therapy</td>
<td>40 (22-61)</td>
<td>86 (77-91)</td>
</tr>
<tr>
<td>E. A decrease in relapse rate less than 50% compared to two years before therapy</td>
<td>40 (-61)</td>
<td>81 (72-88)</td>
</tr>
<tr>
<td>F. No decrease or identical relapse rate compared to two years before therapy</td>
<td>35 (18-57)</td>
<td>88 (79-93)</td>
</tr>
<tr>
<td>G. Definition A or B</td>
<td>90 (70-97)</td>
<td>48 (38-58)</td>
</tr>
<tr>
<td>H. Definition A or E</td>
<td>85 (64-95)</td>
<td>76 (66-83)</td>
</tr>
<tr>
<td>I. Definition A and B</td>
<td>75 (53-89)</td>
<td>97 (91-99)</td>
</tr>
<tr>
<td>J. Definition A and E</td>
<td>40 (22-61)</td>
<td>99 (94-99)</td>
</tr>
</tbody>
</table>

*EDSS score ≥6.0 or increase in at least three EDSS steps

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Pros and Cons of Maintenance vs. Induction Therapies

**Maintenance therapies**

- Continuous treatment
- Low to very high efficacy
- Reversible
- Perceived to be lower risk

**Examples**

- Daclizumab, GA, IFN-beta, teriflunomide, BG12, fingolimod, natalizumab, daclizumab

**Breakthrough disease**

- Suboptimal or failure to respond
- NEDA reliable metric for efficacy

**Rebound activity**

- Highly likely
- Can be life threatening

**Pregnancy**

- Contra-indicated

- No potential for a cure
- Rebound
- SPMS & progressive brain atrophy

**Induction therapies**

- Short-courses or pulsed therapy
- Very high efficacy
- Irreversible
- Perceived to be higher risk

**Examples**

- Cladribine, alemtuzumab, anti-CD20*, BMT

**Breakthrough disease**

- Marker for retreatment
- NEDA unreliable to assess efficacy

**Rebound activity**

- Less likely
- Unlikely to be life-threatening

**Pregnancy**

- Strategy of choice

**Potentially curative**

- 15-20 year experiment
- BMT, alemtuzumab, cladribine

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*Anti-CD20, a B-cell depleting therapy, is included as a possible induction therapy. It is currently in phase 3 development.

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**Table 3**

Multiple regression model for outcome at long term follow-up derived with stepwise model selection procedure: fitted regression model including predictors with p=0.5 to enter; p=0.1 to stay in the model.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>SE</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-0.81</td>
<td>0.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EDSS at baseline</td>
<td>0.02</td>
<td>0.02</td>
<td>0.06</td>
</tr>
<tr>
<td>NEDA at 12 months</td>
<td>0.03</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>NEDA at 36 months</td>
<td>0.03</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>SFMT at 12 months</td>
<td>0.02</td>
<td>0.01</td>
<td>0.05</td>
</tr>
<tr>
<td>SFMT at 36 months</td>
<td>0.02</td>
<td>0.01</td>
<td>0.05</td>
</tr>
</tbody>
</table>

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References:

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Different Treatment Philosophies: Maintenance-Escalation vs. Induction

Survival analysis

"Start safe and smooth"

"Hard and early"

MS is a neurodegenerative disease hypothesis

MS is an autoimmune disease hypothesis

MS Iceberg

- Relapses
- Unreported relapses
- Clinical disease worsening
- Subclinical relapses: focal MRI activity
- Focal grey and white matter lesions not detected by MRI
- Brain atrophy
- Spinal fluid neurofilament levels

No evident disease activity

END ORGAN DAMAGE

Biomarkers

Clinical activity

Focal MRI activity

Hidden focal and diffuse MRI activity

Microscopic or biochemical pathology
End-Organ Damage

Brain Atrophy Occurs Across All Stages of the Disease

n= 963 patients with MS


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Treatment-Effect on Atrophy Correlates With Treatment-Effect on Disability


Treatment Effect on Disability Predicted by Effect on T2-Lesion Load and Brain Atrophy

Meta-analysis of treatment effect on EDSS worsening (y) vs. effects on MRI lesions and brain atrophy, individually or combined, in 13 placebo-controlled RRMS trials (13,500 patients)

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**AFFIRM Study: Natalizumab and Brain Atrophy**

![Graph showing Mean (SE) percentage change in BPF over Years 0-2, Year 0-1*, and Year 1-2 for Placebo (N=315) and Natalizumab (N=627).](image)

- Difference between treatments; †Change from baseline


**Fingolimod Has an Early and Sustained Effect on the Rate of Brain Atrophy Compared With Placebo and Interferon beta-1a Intramuscular Injection**

![Graph showing Change in mean BV from baseline (%)](image)

- 0.40% vs. IFNb-1a IM P < .001
- 0.24% vs. placebo P < .001

Reduction in Brain Atrophy on Alemtuzumab

No Evident Disease Activity (NEDA)

_Treat-2-target_

No evidence of disease activity defined as:
- No relapses
- No sustained disability progression
- No MRI activity
  - No new or enlarging T2 lesions
  - No Gd-enhancing lesions

Normalisation of brain volume loss needs to be included in future definitions of NEDA

Gd, gadolinium.


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Treating-2-Target

Define the Individual’s MS
- MS prognosis
- Lifestyle and goals
- Shared goals for therapy

Choosing therapy
- Patient’s preferences?
- Your choice?

Rebaseline:
- IFNβ, natalizumab, fingolimod, teriflunomide,
- DMF = 3-6 months
- Glatiramer acetate = 9 months
- Alemtuzumab = 24 months

Individual measures:
- Evidence of disease activity?
- Tolerability/safety?
- Adherence?
- Drug or inhibitory markers?

Monitoring

Treatment failure?

DMF = dimethyl fumarate

Treatment Objectives in Relapsing MS

Treat early

NEDA

T2T - NEDA

Reduced ongoing damage

Zero tolerance

Global Multiple Sclerosis Academy
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Treatment Objectives in Relapsing MS (con't.)

- Treat early
- NEDA
- Functional improvement
- Reduced ongoing damage
- Maintain reserve capacity
- CNS repair
- Healthy ageing
Treatment Objectives in Relapsing MS (con’t.)

- Improved quality of life/brain health
- Treat early
  - NEDA
  - Functional improvement
  - CNS repair
- Reduced ongoing damage
- Maintain reserve capacity
- Healthy ageing

Section 3: Summary

Here is a quick recap of what we covered so far:

- MS disease-modifying treatments can be classified as either maintenance therapies or induction therapies.
- Patients with MS are at a higher risk of brain atrophy. The new findings suggest that a treatment focus on brain atrophy might markedly change the meaning of continuity in care.
- The emerging treatment objective in multiple sclerosis is to treat early with the target being no evident disease activity.
- Suppressing all evidence of disease activity should improve the quality of life of patients with MS.
References


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References

References