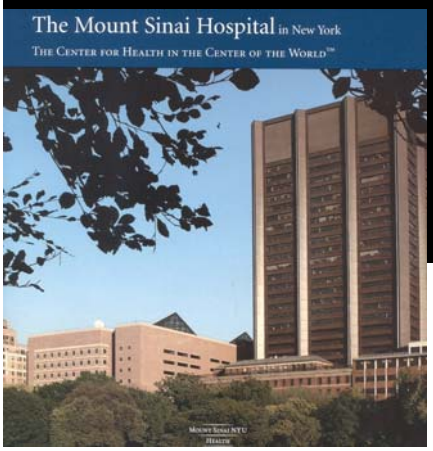
Defining the Course of Multiple Sclerosis
CMSC Symposium, 27 May 2015



Fred D. Lublin, M.D.
Corinne Goldsmith Dickinson
Center for Multiple Sclerosis
Icahn School of Medicine
at Mount Sinai
New York, NY

Mount Sinai

Corinne Goldsmith Dickinson Center for Multiple Sclerosis

Themes

- Revised Clinical Courses
- Revised Definitions
- Consequences of the Changes

MS Clinical Courses -- 1996

Views & Reviews

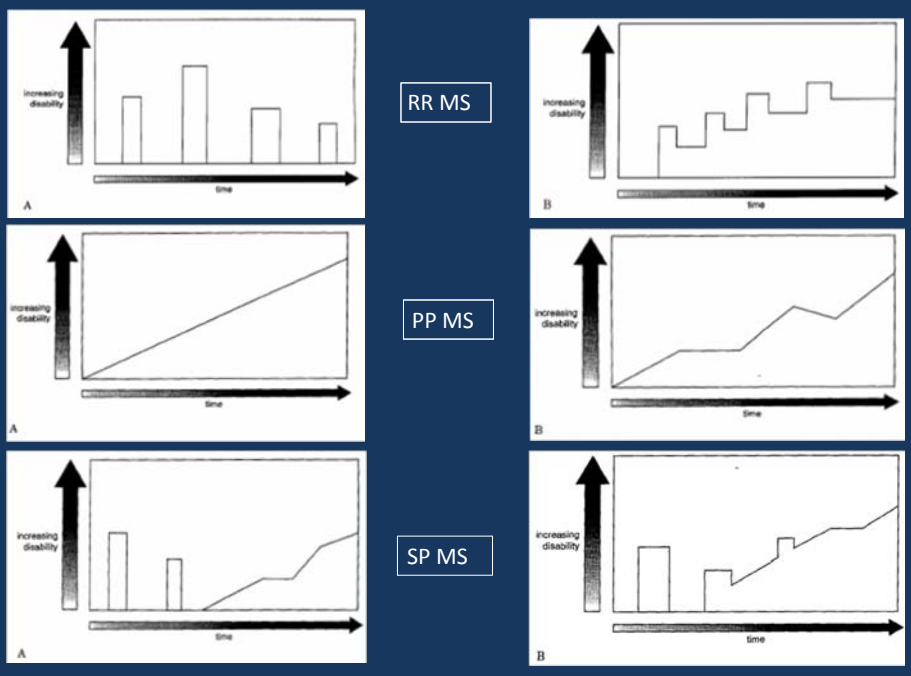
Defining the clinical course of multiple sclerosis:

Results of an international survey

Fred D. Lublin, MD, and Stephen C. Reingold, PhD, for the National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis*

Article abstract—Standardization of terminology used to describe the pattern and course of MS is essential for mutual understanding between clinicians and investigators. It is particularly important in design of, and recruitment for, clinical trials statistically powered for expected outcomes for given patient populations with narrowly defined entry criteria. For agents that prove safe and effective for MS, knowledge of the patient populations in definitive clinical trials assists clinicians in determining who may ultimately benefit from use of the medication. An international survey of clinicians involved with MS revealed areas of consensus about some terms classically used to describe types of the disease and other areas for which there was lack of consensus. In this report, we provide a summary of the survey results and propose standardized definitions for the most common clinical courses of patients with MS.

NEUROLOGY 1996;46:907–911



Lublin & Reingold 1996

The MS Phenotype Group – 2012/2013

Fred D. Lublin, New York City NY
Stephen C. Reingold, Salisbury CT
Jeffrey A. Cohen, Cleveland OH
Gary R. Cutter, Birmingham AL
Per Soelberg Sørensen, Copenhagen DK
Alan J. Thompson, London UK
Jerry S. Wolinsky, Houston TX
Laura J. Balcer, New York City, NY
Brenda Banwell, Philadelphia PA
Frederik Barkhof, Amsterdam NL
Bruce Bebo Jr., Portland OR
Peter A. Calabresi, Baltimore MD
Michel Clanet, Toulouse FR
Giancarlo Comi, Milan IT
Robert J. Fox, Cleveland OH
Mark S. Freedman, Ottawa CA
Andrew D. Goodman, Rochester NY
Matilde Inglese, New York City NY
Ludwig Kappos, Basel CH
Bernd C. Kieseier, Düsseldorf DE
John A. Lincoln, Houston TX
Catherine Lubetzki, Paris FR
Aaron E. Miller, New York City NY
Xavier Montalban, Barcelona ES
Paul W. O'Connor, Toronto CA
John Petkau, Vancouver CA
Carlo Pozzilli, Rome IT
Richard A. Rudick, Cleveland OH
Maria Pia Sormani, Genoa IT
Olaf Stüve, Dallas TX
Emmanuelle Waubant, San Francisco CA
Chris H. Polman, Amsterdam NL

Goals and Aims

- Re-examine 1996 phenotype descriptions
  - Improve clinical descriptive terminology?
  - Assess value of MRI and other imaging techniques?
  - Assess value of fluid biomarkers?
  - Evaluate other assays, including electrophysiology
- Summarize our deliberations
  - What we know
  - What we recommend
  - What we still need to discover
- Recommend research strategies to move phenotype evaluation forward where data or consensus are lacking

Conclusions: The 2013 Revisions (1)

Core Phenotypes and Modifiers

- The core MS phenotypes (relapsing and progressive disease) should be retained with some modification
- Assessment of disease activity, measured by clinical relapses or CNS lesion activity is an important modifier of the core phenotypes
- Assessment of ongoing progression of disability is an important modifier of the core phenotypes

Lublin, et al; Neurology, 2015

Conclusions: The 2013 Revisions (2)

PR MS, PP MS, CIS and RIS

- The Progressive-Relapsing MS (PR MS) phenotype is eliminated; such patients would be categorized as Primary Progressive MS (PP MS) with activity
- Primary Progressive MS (PP MS) is part of the spectrum of progressive disease; differences from other forms are relative rather than absolute.
- Clinically Isolated Syndrome (CIS) is part of the spectrum of MS phenotypes and should be followed to determine subsequent disease course
- Radiologically Isolated Syndrome (RIS) should not be considered an MS phenotype, as patients lack clinical signs and symptoms

Conclusions: The 2013 Revisions (3)

Terminology and Biological Markers

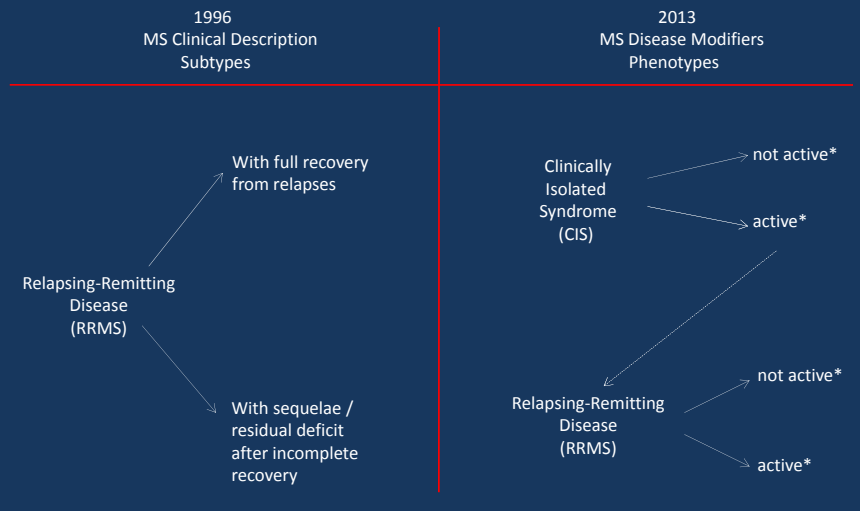
- The term “worsening” is preferable to “progressing” to describe patients with relapsing disease whose disease is advancing due to frequent relapses or incomplete relapse recovery, reserving the term “disease progression” for those in a progressive phase with evidence of gradual worsening over time.

- The term “confirmed worsening” in EDSS, over a defined period of time, is preferable to “sustained worsening”

- “Benign” and “malignant” disease are often misused and should be used with caution

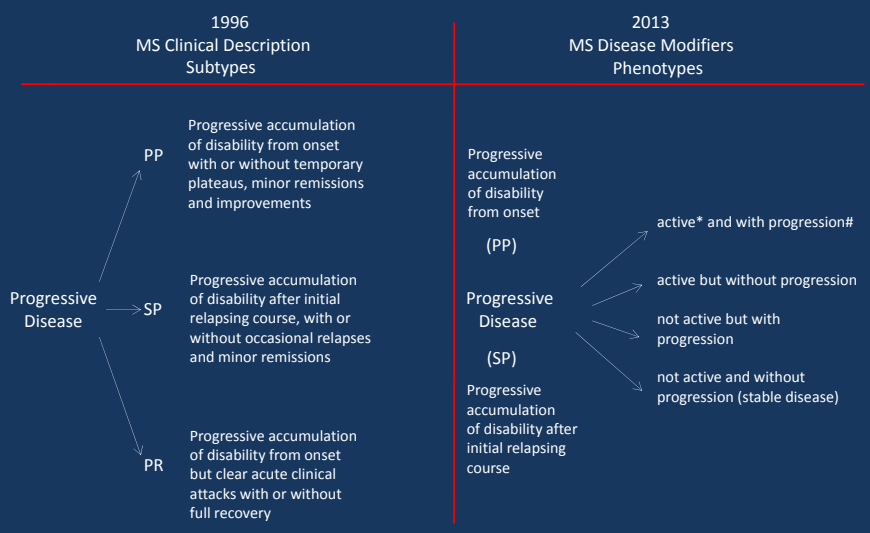
- Further research is needed to better define phenotype-relevant imaging and biological markers, as none reliably describe or predict disease course at this time

1996 vs 2013 MS Phenotype Descriptions
Relapsing-Remitting Disease



*activity = clinical relapses and/or MRI (Gd-enhancing MRI lesions; new/enlarging T2 lesions

1996 vs 2013 MS Phenotype Descriptions
Progressive Disease



*activity = clinical relapses and/or MRI (Gd-enhancing MRI lesions; new/enlarging T2 lesions)
#progression measured by clinical evaluation at least annually

Definitions (1)

Active Disease
(over n time- e.g., 1 year)

Clinical: relapses, acute or sub-acute episodes of new or increasing neurological dysfunction followed by full or partial recovery

in the absence of fever or infection

Imaging (MRI): occurrence of contrast enhancing T1 hyperintense or new or unequivocally enlarging T2 hyperintense lesions

Definitions (2)

Progressive Disease

(over n time- e.g., 1 year)

Clinical: steadily increasing objectively documented neurological dysfunction/disability without unequivocal recovery (fluctuations and phases of stability may occur)

Imaging (MRI): no standardized imaging measures of disease progression are established

increasing number and volume of T1 hypo-intense lesions, brain volume loss and changes in MTI and DTI are being explored

Definitions (3)

Worsening, Progression and Confirmed Worsening

Worsening disease: documented increase in neurological dysfunction/disability as a result of relapses or progressive disease

Disease Progression: reserved for solely those patients in a progressive phase of the illness

Confirmed Progression or Worsening: increase in neurological dysfunction confirmed throughout a defined time interval (e.g., 3, 6 or 12 months)

since neurological dysfunction may improve (especially in relapsing disease) even if initially confirmed, we recommend abandoning the term "sustained"

Specify if confirmed in the same functional system (more rigorous) or only by EDSS

Consequences

- What is a relapsing form of MS?
- How often should MRI be done?
- How to weight MRI
- How to measure disease course

What is a Relapsing Form of MS?

RR

CIS

SP

PP with relapse (old PR)

PP with gad or new T2 (PP active)???

Consequences

- What is a relapsing form of MS?
- How often should MRI be done?
- How to weight MRI
- How to measure disease course

Consequences

Perform MRI at least annually to assess activity in relapsing MS

No consensus for progressive disease

Consequences

- What is a relapsing form of MS?
- How often should MRI be done?
- How to weight MRI
- How to measure disease course

Consequences

Clinical relapse and MRI activity (Gad or new T2) are equally weighted for this determination.

Consequences

- What is a relapsing form of MS?
- How often should MRI be done?
- How to weight MRI
- How to measure disease course

Disease Free State Proposal

DAFS; NEDA: should only refer to 'activity' as defined here (relapses or new MRI lesions), which would exclude confirmed EDSS change.

But:

Progression ≠ Activity

Need a better acronym

NMDAW: **No measurable disease activity or worsening**
NEDAP: No evidence of disease activity or progression
MS NAP: No Activity or Progression

Consequences

- Choosing therapies
- Switching therapies
- Prognostication
- Outcome measures
- Disease free state

Potential Uses

- Course characterization
  - Predicting onset of progressive disease
- Study inclusion criteria
- Study outcome measure
  - Time to activity
  - AAR (annualized activity rate)
  - Time to progression
- Adequacy of therapy
- New study designs
- Biomarker studies
  - Genetics of course, severity

Mount Sinai

The Corinne Goldsmith Dickinson Center for MS

Thank You