Defining the clinical course of multiple sclerosis:

Results of an international survey

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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.

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The clinical course of MS may follow a variable pattern over time but usually can be characterized by either episodic acute periods of worsening (relapses, exacerbations, bouts, attacks), gradual progressive deterioration of neurologic function, or combinations of both. Although the terms used to describe these clinical forms have been used for many years,[1-7] there is no clear common meaning among clinicians for the terms used to describe forms or clinical stages of the disease. There is often lack of clarity about exactly which patient group is described. This creates real and potential problems in communication among investigators and in the design of, and recruitment for, multicenter clinical trials for new therapeutic agents that are based on expected clinical outcomes for defined patient groups and require narrow entrance criteria. The success of such trials may depend on the homogeneity of the population of MS patients entered into the study.

MS recently joined the growing ranks of treatable neurologic diseases, with reports of data on new therapies demonstrating clinical efficacy in pivotal clinical trials, such as interferon beta-1b (Betaseron, manufactured by Berlex Laboratories, Richmond, CA),[8] interferon beta-1a (Avonex, manufactured by Biogen, Cambridge, MA),[9] and copolymer I (Copaxone, manufactured by Teva Pharmaceutical Industries, Petah Tiqwa, Israel).[10] Many new trials begin each year. Although each of these studies uses a narrowly defined population of patients, clinicians look for guidance as to exactly which broader patient groups will likely benefit from treatment. The terms used to describe patient populations are crucial for this guidance.[11]

Informal discussions among clinicians and clinical researchers and consensus developed among investigators attending a 1994 MS clinical trials design workshop[12] revealed that there was no unanimous agreement on definitions for the various clinical subtypes of MS. This lack of unanimity resulted from the lack of clear biological markers to distinguish the various forms of MS. This required use of descriptive terms for these clinical subtypes, for which there was no consensus. These facts and perceptions underscored the need for a reassessment of the terminology used to describe MS and for more uniform definitions of MS clinical subtypes.

Methods. In the absence of agreed on biological markers, the Advisory Committee on Clinical Trials of New Agents in MS of the National Multiple Sclerosis Society (NMSS) (USA) undertook a survey to develop a perspective and consensus on definitions and terminology used to describe clinical outcomes and course patterns in patients with MS, to standardize terminology, and to facilitate a broader understanding of patient recruitment parameters in MS therapeutic trials. Those surveyed included 215 members of the international MS clinical research community, including members of the NMSS Medical Advisory

* See page 910 for Committee members.

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Board (current and past), members of the NMSS Advisory Committee on Clinical Trials of New Agents in MS, attendees at the 1994 International Workshop on Outcomes Assessment in MS Clinical Trials held in Charleston, South Carolina,[12] and other individuals known to be principally involved in MS clinical research and care. Survey forms developed by the authors in consultation with others with known interest in this issue were mailed in early January 1995, with respondents asked to reply by early February 1995. Of the 215 surveys, 125 (58%) were completed and returned.

The survey form asked respondents to choose among several possible clinical patterns commonly used to define the following MS disease courses and types: relapsing-remitting (RR), relapsing-progressive (RP), primary progressive (PP), secondary progressive (SP), benign, and malignant. The survey allowed respondents to provide their own definitions if they were not satisfied with those provided in the survey. Because respondents were asked to indicate all definitions that, in their view, applied to the disease type, more than 125 total responses were collected for some questions.

The results of the survey were collated and distributed to members of the NMSS Advisory Committee on Clinical Trials. After meeting, revising, and approving revised clinical definitions based on the survey responses, the definitions were presented to the executive committee of the NMSS Medical Advisory Board and the full NMSS Medical Advisory Board where additional clarifications and revisions were made. The final definitions, presented here, did not differ substantively from those in the initial survey document.

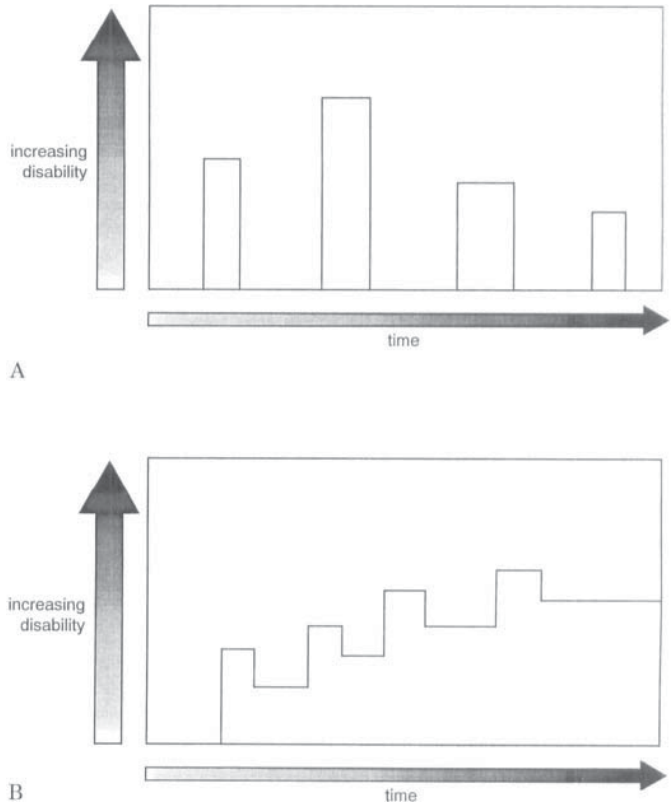

Figure 1. Relapsing-remitting (RR) MS is characterized by clearly defined acute attacks with full recovery (A) or with sequelae and residual deficit upon recovery (B). Periods between disease relapses are characterized by lack of disease progression.

Results. *Clinical course definitions.*

Relapsing-remitting (RR) MS. The consensus definition is as follows: clearly defined disease relapses with full recovery or with sequelae and residual deficit upon recovery; periods between disease relapses characterized by a lack of disease progression (figure 1, a and b).

The defining elements of RR-MS are episodes of acute worsening of neurologic function followed by a variable degree of recovery, with a stable course between attacks. Although a clear majority (105/134) of responses included this definition, some (16/134) favored using the term relapsing-remitting only for those patients who fully recover between relapses. However, the lack of evidence for a biological difference between those who recover fully (figure 1a) and those who recover partially (figure 1b) and potential differences in the vigor with which one might seek to determine the extent of recovery (clinical examination, evoked potentials, and so on) favored the more inclusive definition.

Primary-progressive (PP) MS. The consensus definition is as follows: disease progression from onset with occasional plateaus and temporary minor improvements allowed (figure 2, a and b).

The essential element in PP-MS is a gradual nearly continuously worsening baseline with minor fluctuations but no distinct relapses. Eighty-one of 131 responses included this definition. Although nearly continuous progression is required, it was recognized that progression at a constant rate throughout disease (figure 2a) was unlikely and that accommodation must be made for variations in the rate of progression over time (figure 2b). A small number of respondents suggested that the definition of PP-MS should include evidence from MRI to distinguish this from other forms of disease (see Discussion).

Secondary-progressive (SP) MS. The consensus definition is as follows: initial RR disease course followed by progression with or without occasional relapses, minor remissions, and plateaus (figure 3, a and b).

SP-MS may be seen as a long-term outcome of RR-MS in that most SP patients initially begin with RR disease as defined here. However, once the baseline between relapses begins to progressively worsen, the patient has switched from RR-MS to SP-MS. Eighty-four of 124 respondents chose the above definition.

Relapsing-progressive (RP) MS. There is no consensus definition.

Although this has been one of the most commonly used terms to describe an important clinical form of MS characterized by a combination of relapse and progression, there was no consensus for a definition of RP-MS. Some respondents used this term to describe RR patients who do not fully recover (39/138 responses), which was clearly favored for inclusion in the RR definition (above). Others used this term for those patients who are also defined above as SP (41/138). A smaller group (26/138) indicated that the best definition of this group included patients with disease progression from onset with acute episodes of worsening. Because of the lack of consensus and the overlap of definitions with other categories, we conclude that the term

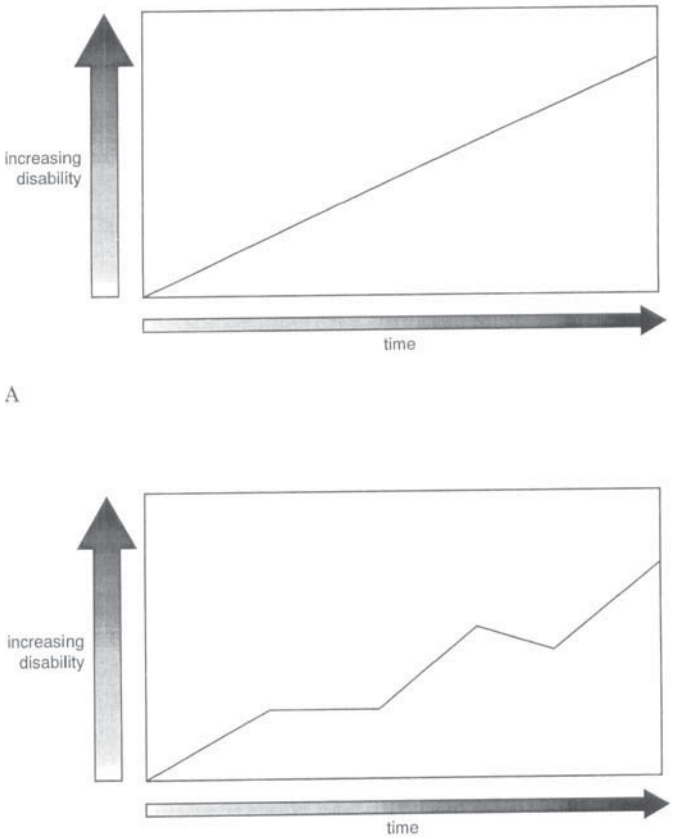

Figure 2. Primary progressive (PP) MS is characterized by disease showing progression of disability from onset, without plateaus or remissions (A) or with occasional plateaus and temporary minor improvements (B).

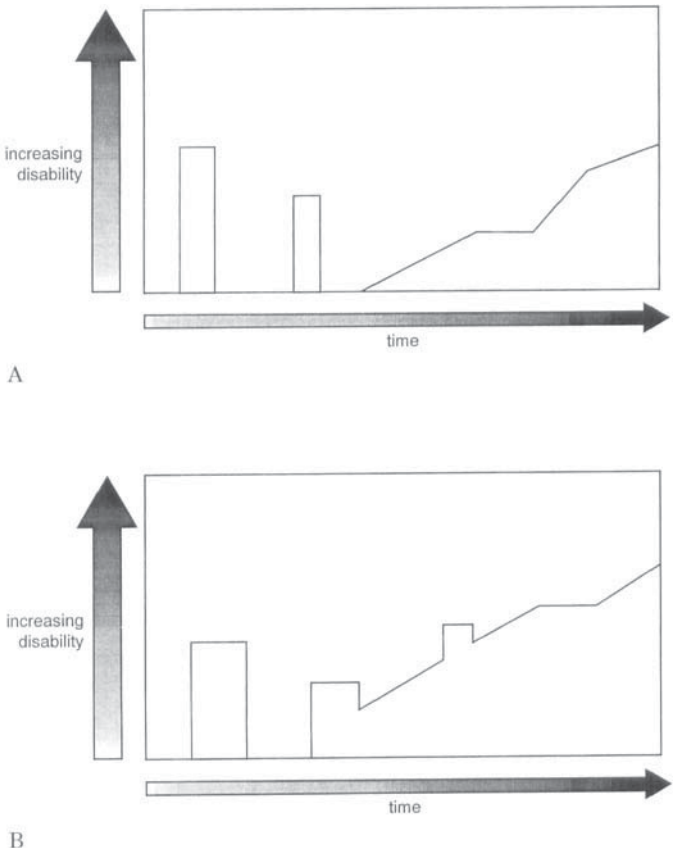

Figure 3. Secondary progressive (SP) MS begins with an initial RR course, followed by progression of variable rate (A) that may also include occasional relapses and minor remissions (B).

RP-MS does not correspond to a clearly defined and distinguishable clinical population and should be abandoned.

Progressive-relapsing (PR) MS. The consensus definition is as follows: progressive disease from onset, with clear acute relapses, with or without full recovery; periods between relapses characterized by continuing progression (figure 4, a and b).

Based on the survey and additional discussion, we determined that PR-MS was an additional, albeit rare, clinical course that deserved a separate definition, as it was not included in the other definitions. We propose that this form of MS be termed PR to reflect its progressive onset and to distinguish it from the term RP, for which there was no consensus.

Clinical severity definitions. The above definitions pertain to clinical courses that patients with MS may follow. The survey also queried respondents on two severity outcome definitions, for benign and malignant disease. There was no overwhelming consensus on definitions for these terms and less so for benign disease than malignant disease. Further, many respondents believed that precise definitions were not needed or useful as these terms were not likely to be used as enrollment criteria or end point measures in clinical trials. Although classic definitions have often indicated a set or minimal score on the Kurtzke Expanded Disability Status Scale (EDSS) clinical rating scale,[2,13,14] there was consensus that these should not be used, as they might narrow the clinical picture being described. Further, as these terms do not necessarily reflect future course, it was agreed that they should not be the sole determinant of the appropriateness of any available therapeutic measures. It was additionally emphasized that these terms were most useful in the context of research studies and should be used with care in communication with affected individuals, family members, and third-party payers.

Benign MS. The consensus definition is as follows: disease in which the patient remains fully functional in all neurologic systems 15 years after disease onset.

Malignant MS. The consensus definition is as follows: disease with a rapid progressive course, leading to significant disability in multiple neurologic systems or death in a relatively short time after disease onset.

Discussion. We report here the results of a survey of the international MS clinical research community on terminology commonly used to describe clinical course and outcomes for the disease. We were gratified to find clear preferences and striking agreement on the meaning of the terms RR, PP, and SP forms of MS. Based on survey results and resultant consensus, we added a new term, PR, to represent those patients whose course differs, as diagrammed in figures 1 to 4, from the other definitions. We expect that this represents a small fraction of MS patients.

We found no clear consensus on the definition of

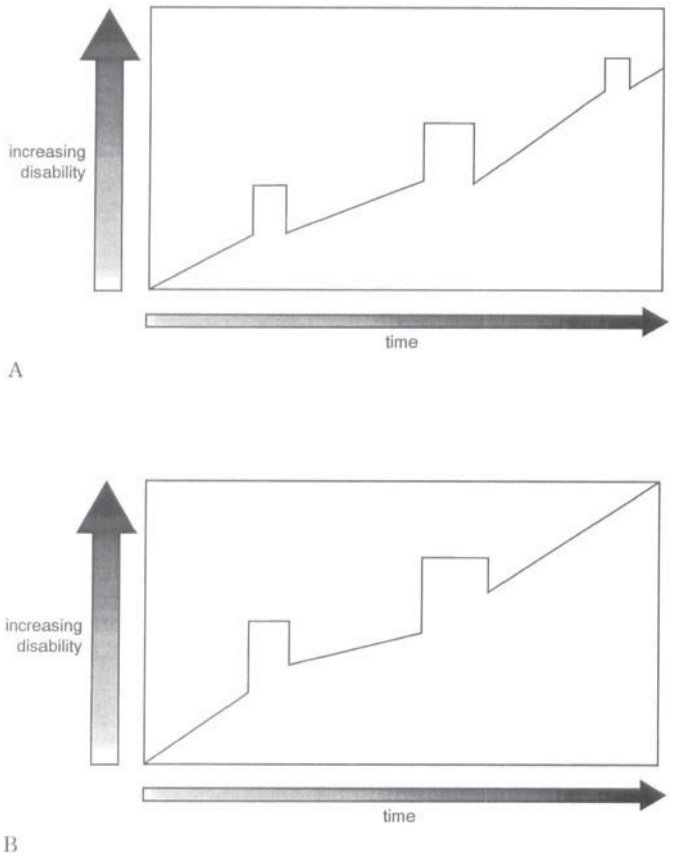

Figure 4. Progressive-relapsing (PR) MS shows progression from onset but with clear acute relapses with (A) or without (B) full recovery.

RP-MS, and because the survey results made it clear that its common usage overlaps with either RR or SP as defined here, we recommend that the term RP-MS be abandoned. Similarly, as the classically used term chronic progressive (CP) MS includes the more recently distinguished groups of PP, SP, and PR patients as newly defined here, we recommend that this term also be abandoned, as being too vague and including forms of MS that differ considerably in clinical course and MRI correlates.[15]

We have not included MRI parameters in these definitions, despite reported differences in MRI lesion load in certain forms of MS (e.g., PP versus SP-MS)[15] because our respondents and committee members with special MRI expertise believed that the current level of knowledge did not allow sufficiently confident association of MS clinical course and MRI findings. This situation could change in the future, as it could for developments relating to any potential biological or surrogate marker of disease activity. If so, we expect the definitions proposed here to be modified accordingly.

We also have not defined a relapse. A relapse implies an acute episode of new disease activity, either a new lesion or fresh activity in an old area of involvement. Both MRI data and neuropathologic studies detail a discordance between the occurrence of MS lesions in the CNS and the development of symptoms or signs.[16-19] A clinical relapse is dependent on involvement of an "eloquent" area of the CNS. Various authors provide definitions. McAlpine defined a relapse as a new symptom or the reappearance of a previous symptom at a time after an initial attack.[1] Schumacher et al.[20] added a requirement for a duration of symptoms of at least 24 hours when evaluating a treatment. For the purposes of a clinical trial, the nature of a relapse will need to be defined by consensus among investigators for each protocol to ensure standardization of the study design. Similarly, for trials of agents being tested for their ability to slow or stop disease progression, duration and rate of progression need to be defined by consensus for inclusion and treatment failure criteria for each trial.

Because at present there are no known clear biological markers that define the various clinical courses of MS, definitions must be made in clinical terms and by consensus among workers in the field. We therefore conclude that the definitions we propose are tenable because they derive from an international survey and input from a large group of MS clinical investigators. Use of these definitions in a standardized fashion will allow more uniformity in clinical descriptions, both in reports in the literature and in designation of patient populations for clinical trials of new agents in MS.

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