Active and progressive

A new duality of MS classification

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In this issue of *Neurology*®, Lublin and over 30 multiple sclerosis (MS) specialists from around the world propose a new consensus framework for MS classification.[1] The increasing importance of MRI in clinical management and treatment trials, together with expanding treatment options and improved understanding of the pathophysiology of MS, motivated the present re-examination of MS phenotypic classifications and clinical course descriptions. The new schema supplants the one proposed by Lublin and Reingold[2] in 1996 depicting 4 courses of MS that has been widely embraced in research and in clinical practice. The original 4 clinical subtypes were based on an international survey of MS clinicians, and utilized clinical information alone to describe relapsing-remitting, primary progressive, secondary progressive, and progressive-relapsing phenotypes. However, distinctions among the original 4 subtypes are imprecise and do not reflect current capabilities to target MS treatments based on integrated assessment of clinical and MRI data.

Ten disease-modifying therapies (DMTs) for relapsing MS are approved in the United States, with an 11th, alemtuzumab, approved elsewhere in North America and in Europe. Although effective against the inflammatory pathology of MS, as measured by reduction of clinical relapses and accrual of new MRI lesions, currently approved therapies do not effectively abrogate the neurodegenerative processes that appear to underlie the primary and secondary progressive forms of MS. However, new types of therapies directed at arresting progressive MS or reversing damage via remyelination or neural regeneration, including 2 potential remyelinating agents that lack anti-inflammatory properties, anti-LINGO-1 and rhIgM22, are being evaluated in clinical trials.[3,4] Improved patient classification is essential to ensure that imprecision in enrollment criteria does not lead to misleading findings or confusing differences in the outcomes of similarly conducted controlled trials.[5]

The new classification scheme retains core concepts of relapsing and progressive disease and adds clinically isolated syndrome (CIS) as a distinct MS phenotype (although CIS without an accompanying MRI that reveals gadolinium-enhancing and nonenhancing lesions does not meet current MS diagnostic criteria).[6] The group stops short of including radiologically isolated syndrome, which is the detection of MRI lesions consistent with MS in the absence of clinical symptoms and signs, and recommends that such patients be monitored prospectively.[7]

Two modifiers of the core phenotypes based on activity and worsening are proposed. Within a 1-year time frame, the occurrence of clinical relapses or MRI-detected CNS lesions (gadolinium-enhancing T1 lesions or new or clearly enlarging T2 lesions) are used to distinguish patients who have active MS from those with inactive disease. At least yearly brain MRI is strongly recommended to assess activity in relapsing MS, but no consensus was reached on the frequency of MRI scans for progressive MS. The proposed activity modifier renders the progressive relapsing phenotype from the 1996 schema obsolete; such patients would now be described as having primary progressive MS with disease activity. The group suggests implementing the term worsening to describe patients with MS whose impairment is increasing due to relapses, reserving the term progression for those patients with established progressive MS whose function is deteriorating independent of relapse activity. Therefore, patients may be described as having (1) relapsing MS that is active or inactive, with or without worsening; or (2) primary or secondary progressive disease that is active or inactive, with or without progression. The panel proposes to use the term confirmed worsening over a specified time period, eschewing the often-used term sustained because sustained implies a permanence that often is not borne out. The panel acknowledges the need for further data and offers a research agenda.

Whether benign and malignant MS are useful terms has long been debated.[8,9] The panel recommends retaining these terms with the traditional caveat that these terms be used with caution and only retrospectively. A quantitative definition based on the rate of disability increase over time is favored, with

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the additional caveat that this rate of change is not linear and can "change significantly and unpredictably." As disability may not be evident for a decade or longer in patients with relapsing MS, the rate of disability accumulation is typically greater in progressive forms of MS. However, some patients with very active relapsing disease may worsen more rapidly and in more functional systems than patients with progressive MS. How to apply the benign and malignant modifiers meaningfully across the spectrum of clinical courses of MS is unclear. Whether benign MS is simply the left side of a bell-shaped curve or whether it has unique features that might eventually define it remains to be established. Similarly, a more comprehensive understanding of malignant MS is important; its definition may need to be individualized to phenotype. One commonly malignant form of MS-like illness with a unique pathogenesis, neuromyelitis optica (NMO), has now been separated from MS.[10] Understanding and discriminating "malignant" course by presentation (relapsing vs progressive), or with other phenotypic descriptors (e.g., tumefactive, Marburg), MRI techniques (e.g., magnetization transfer, spectroscopy, diffusion imaging), or biomarkers (e.g., aquaporin 4 IgG for NMO) remains a challenge.

Despite extensive research, discovery of biomarkers that correlate with or predict disease outcome or therapeutic response has proven to be a largely elusive goal. New technology including advanced imaging techniques and optical coherence tomography promises to allow more precise quantitation of noninflammatory neurodegeneration, but at this time no technique adequately reflects the totality of CNS neurodegeneration in MS, and none was endorsed by the panel as being ready for clinical implementation. Lublin and colleagues' contribution recalibrates the interpretation of clinical and conventional MRI data, a necessary step for future biomarker validation. Clinical implications of the new classification schema will be subject to debate and their practicality may differ across the world, particularly with respect to requirements for annual MRI scans for relapsing MS. Evaluation of clinical course, like MS diagnosis, is now more MRI-dependent. Our hope is that the proposed refinements will lead to improvements in communication, research, and appropriate therapeutic choices for patients.

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