MS DIAGNOSIS AND CLASSIFICATION

Myla Goldman

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system[1]. The prevalence of MS in the United States is estimated at 250,000 to 350,000 individuals, although there are recent indications that the prevalence may be somewhat higher. The mean age of disease onset is 30 years, with 70% of individuals presenting between the ages of 20 to 40. Woman account for approximately 70% of the cases. MS is the most common non-traumatic cause of neurologic disability in young adults. The protean manifestations, clinical heterogeneity, and chronic course after onset in early adulthood make management of MS challenging.

The underlying cause of MS remains unknown. The prevailing hypothesis is that MS results from a cell-mediated autoimmune attack directed against myelin antigens. Evidence shows the pathogenesis of the disease to be complex with a number of abnormalities in immune regulation. Not only is the immunopathogenesis of MS complex, but it appears that there may be four-or five pathogenic subtypes and the predominant immune mechanisms may differ from patient to patient[2, 3]. How this heterogeneity relates to disease course and severity, genetics, imaging characteristics and response to treatment is the focus of intense study.

Historically, demyelination has been emphasized as the main pathophysiologic mechanism producing neurologic manifestations in MS. While inflammatory demyelination and resultant block of nerve conduction in central pathways probably accounts for the reversible manifestations of acute relapses, accumulating evidence suggests that permanent disability results from axonal damage. Axonal damage occurs acutely as a consequence of inflammatory demyelination. Subsequent gradual degeneration occurs in chronically demyelinated fibers and can proceed at least in part in the absence of concomitant inflammation[4, 5].

The lesions of MS are multifocal and can occur in any anatomic location within the central nervous system. Therefore, the possible clinical manifestations are protean. These manifestations vary from patient to patient and in individual patients over time, both in terms of the symptoms present, their anatomic distribution, and their severity. Previously, MS was classically characterized by 4 phenotypes: Relapsing Remitting, Secondary Progressive, Primary Progressive, Progressive Relapsing MS[6] Recently, these 4-phenotypes were reviewed and new guidelines “Defining the Clinical Course of MS: the 2013 revisions” were published[7]

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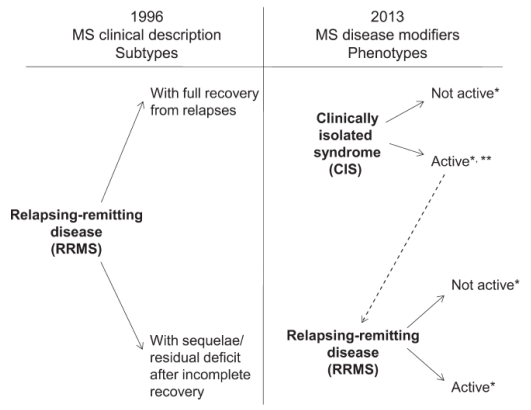
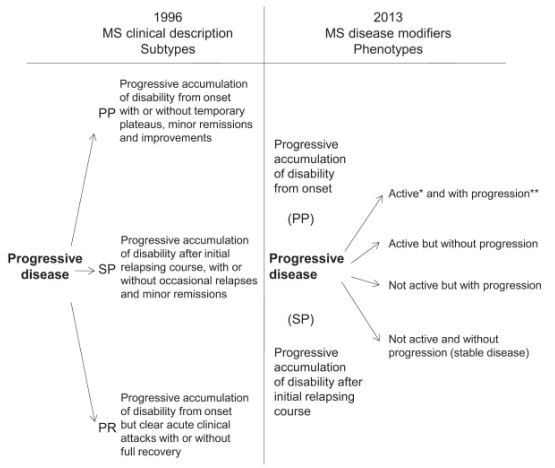
Figure 1 The 1996 vs 2013 multiple sclerosis phenotype descriptions for relapsing disease



*Activity determined by clinical relapses and/or MRI activity (contrast-enhancing lesions; new or unequivocally enlarging T2 lesions assessed at least annually); if assessments are not available, activity is "indeterminate." **CIS, if subsequently clinically active and fulfilling current multiple sclerosis (MS) diagnostic criteria, becomes relapsing-remitting MS (RRMS).

Figure 2 The 1996 vs 2013 multiple sclerosis phenotype descriptions for progressive disease



*Activity determined by clinical relapses assessed at least annually and/or MRI activity (contrast-enhancing lesions; new and unequivocally enlarging T2 lesions). **Progression measured by clinical evaluation, assessed at least annually. If assessments are not available, activity and progression are "indeterminate." MS = multiple sclerosis; PP = primary progressive; PR = progressive relapsing; SP = secondary progressive.

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Because MS has no absolutely pathognomonic clinical, laboratory, or imaging features, making the diagnosis ultimately remains a clinical decision based on weighing the factors supporting the diagnosis versus those that fail to support the diagnosis or suggest an alternative one. The potential differential diagnosis of MS is extensive[8]. The clinical picture determines how aggressively alternative diagnoses need to be addressed in a particular patient.

Principal differential diagnosis of MS

Infection	Lyme disease, syphilis, progressive multifocal leukoencephalopathy, HIV, HTLV-1, Herpes zoster, HHV-6
Inflammatory	Systemic lupus, Sjogren's syndrome, vasculitis, sarcoidosis, Behcets, Susac's syndrome, celiac disease
Genetic and metabolic	Vitamin B12 deficiency, lysosomal disorders, adrenoleukodystrophy, mitochondrial disorders, other genetic disorders, CADASIL
Neoplastic	Primary central nervous system lymphoma
Spine disease	Vascular malformations, degenerative spine disease

Establishing the diagnosis of MS is straightforward when patients exhibit the classic clinical features with onset at the appropriate age and developing with a RR or SP course. In this situation, the likelihood of finding another cause is very small, and extensive testing is unnecessary other than cranial MRI and selected blood tests. However, the clinician must remain vigilant for certain "red flags" that suggest an alternative diagnosis needs to be considered[9]. In these cases, more extensive testing, guided by the clinical picture, is warranted to provide additional support for the diagnosis of MS and to eliminate other diseases.

Red Flags for the potential mistaken diagnosis of MS

- Onset of symptoms before age 20 and after age 40
- Very prominent family history
- Atypical course
  - Gradually progressive from onset, particularly in a young patient or with manifestations other than a myelopathy
  - Abrupt onset of symptoms
- Unifocal manifestations (even if relapsing or progressive)
- Presence of neurologic manifestations unusual for MS
- Presence of systemic manifestations

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The underlying concept of MS diagnosis – dissemination in time and space, was first conceptualized in 1965 by Schumacher. Over the ensuing years, these diagnostic criteria were modified and updated to integrate the evolving MRI technology and increased understanding of MS disease course[10-14]. The most recent of iteration of this criteria was published in 2010 and is now considered the diagnostic standard for clinical trials and care in MS[15].

TABLE 4: The 2010 McDonald Criteria for Diagnosis of MS

Clinical Presentation	Additional Data Needed for MS Diagnosis
≥2 attacks[a]; objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack[b]	None[c]
≥2 attacks[a]; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or Await a further clinical attack[a] implicating a different CNS site
1 attack[a]; objective clinical evidence of ≥2 lesions	Dissemination in time, demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack[a]
1 attack[a]; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For DIS: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or Await a second clinical attack[a] implicating a different CNS site; and For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack[a]
Insidious neurological progression suggestive of MS (PPMS)	1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria[d]: 1. Evidence for DIS in the brain based on ≥1 T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions 2. Evidence for DIS in the spinal cord based on ≥2 T2 lesions in the cord 3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

If the Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is "MS"; if suspicious, but the Criteria are not completely met, the diagnosis is "possible MS"; if another diagnosis arises during the evaluation that better explains the clinical presentation, then the diagnosis is "not MS."

[a]An attack (relapse; exacerbation) is defined as patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection. It should be documented by contemporaneous neurological examination, but some historical events with symptoms and evolution characteristic for MS, but for which no objective neurological findings are documented, can provide reasonable evidence of a prior demyelinating event. Reports of paroxysmal symptoms (historical or current) should, however, consist of multiple episodes occurring over not less than 24 hours. Before a definite diagnosis of MS can be made, at least 1 attack must be corroborated by findings on neurological examination, visual evoked potential response in patients reporting prior visual disturbance, or MRI consistent with demyelination in the area of the CNS implicated in the historical report of neurological symptoms.

[b]Clinical diagnosis based on objective clinical findings for 2 attacks is most secure. Reasonable historical evidence for 1 past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristics for a prior inflammatory demyelinating event; at least 1 attack, however, must be supported by objective findings.

[c]No additional tests are required. However, it is desirable that any diagnosis of MS be made with access to imaging based on these Criteria. If imaging or other tests (for instance, CSF) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS, and alternative diagnoses must be considered. There must be no better explanation for the clinical presentation, and objective evidence must be present to support a diagnosis of MS.

[d]Gadolinium-enhancing lesions are not required; symptomatic lesions are excluded from consideration in subjects with brainstem or spinal cord syndromes.

MS = multiple sclerosis; CNS = central nervous system; MRI = magnetic resonance imaging; DIS = dissemination in space; DIT = dissemination in time; PPMS = primary progressive multiple sclerosis; CSF = cerebrospinal fluid; IgG = immunoglobulin G.

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