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REVIEW ARTICLE

Multiple Sclerosis: New Insights and Trends

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The past few years have witnessed major advancements in our ability to diagnose multiple sclerosis (MS) and begin treatments that can favorably modify the course of the disease. In addition, there is now a much better understanding of the pathogenesis of the disease and an increasing interest in "decoding" the complex genetic factors responsible for, not only the susceptibility to the disease, but also different clinical phenotypes and disease progression.

In this update on MS, the main clinical aspects and the basic features of the diagnosis, including the new McDonald criteria, will be discussed. Next, new insights into the genetics, immunology, and pathology, with emphasis on MS as a disease with early axonal injury, will be reviewed. Finally, a brief description of the available treatments will be presented.

Symptoms and Clinical Course

MS is the most common inflammatory-demyelinating disease of the central nervous system (CNS) and the most frequent cause of nontraumatic neurologic disability in young and middle-age adults.[1] MS is estimated to affect 400,000 persons in the United States and 2 million people worldwide.[2] Women are affected twice as frequently as men, between the ages of 20 and 40, and whites are especially vulnerable, particularly those of northern European extraction. Though clearly not inherited in a simple Mendelian pattern, MS tends to cluster within families, because there is a 1%–5% risk of developing MS if a parent or sibling has the disease and ≥25% concordance among monozygotic twins.[3]

Variability and diversity characterize the symptoms and presentation of MS. There is virtually no neurologic complaint that has not been ascribed to MS. In a significant number of patients who later develop typical MS, the clinical onset is with an acute or subacute episode of neurologic disturbance due to monoregional involvement of the CNS. This form of presentation is known as clinically isolated syndrome (CIS). These may consist of optic neuritis, isolated brain stem, partial spinal cord syndrome, or hemispheric syndromes. In a review of all published work, McAlpine[4] found that the incidence of the initial symptoms was weakness in one or more limbs (40%), optic neuritis (22%), paraesthesiae (21%), diplopia (12%), vertigo (5%), disturbance of micturition (5%), or other (5%).

Likewise at onset, deficits of sensory, motor, cerebellar, brain stem, and autonomic functions are the most common clinical manifestations in the more advanced stage of MS. There does not seem to be any predictable pattern in the timing or location of lesions. Some clinical presentations are distinctive of MS, for example, the presence of bilateral internuclear ophthalmoplegia. Fatigue has been described as the most common complaint in 80% of patients and the worst complaint in 40%[5] Neuropsychologic investigations demonstrated that cognitive dysfunctions are common in MS patients, affecting 40%–65% of them.[6]

Most MS patients (85%) experience a relapsing-remitting (RRMS) course of the disease characterized by the episodic onset of symptoms followed by residual deficits or by a full recovery within a few weeks, especially in the early stage of the disease.[7] Most definitions of a relapse require that new symptoms or signs be present for at least 24 hours and that they not be associated with a fever, because elevated body temperature can unmask subclinical lesions. Approximately 20% of patients with RRMS will remain clinically stable or nearly stable for at least 2 decades (benign MS). Specifically, benign MS is when a patient remains fully functional in all neurologic systems 15 years after disease onset. Within 25 years, however, most untreated RRMS patients will evolve into a secondary progressive phase (SPMS) characterized by a chronic and steady increase of physical symptoms and disability.[7] Approximately 10%–15% of MS patients experience a primary progressive (PPMS) course. PPMS differs from the RRMS subtype in that it affects both men and women at equal rates, occurs in older individuals, exhibits lower levels of inflammatory markers and myelopathic features, and is unresponsive to immunomodulatory agents.[8] Progressive relapsing MS, which is defined as progressive disease from onset, with clear acute relapses, with or without recovery, and with periods between relapses characterized by continuing progression is quite uncommon. Although MS is not a fatal disease, very rarely it may exhibit a malignant course leading to significant disability in multiple neurologic systems or death within a short time after disease onset.[9]

Diagnosis

MS is a clinical diagnosis, dependent on a detailed history, careful neurologic examination, and supportive paraclinical investigations, including MR imaging scans, CSF, evoked potentials, and blood tests to exclude confounding diagnoses. The classic MS diagnostic criteria are the evidence of lesions in the CNS disseminated in time and space (ie, more than one clinical episode involving more than one area of the CNS [brain, spinal cord, and optic nerves]). The use of MR imaging, since its introduction by Young et al,[10] has had a major impact on the early and more precise diagnosis of the disease. In patients with clinically definite MS, brain MR imaging reveals multifocal cerebral white matter (WM) lesions in more than 95% of patients and in 75%–85% there are focal spinal cord lesions. About two thirds of patients experiencing a single episode of suspected demyelination or CIS have cerebral WM lesions indistinguishable from those seen in definite MS.[11] Because the presence of such lesions increases the likelihood of developing clinically definite MS, it is not surprising that formal MR imaging features for dissemination in space and time

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have been incorporated within the diagnostic criteria for MS by an international panel in 2001.[12] The previous diagnostic criteria for MS by Poser[13] were established for use in clinical trials of MS and included clinically definite MS, laboratory (CSF)–supported definite MS, probable MS (either clinically or laboratory supported), and possible MS. Because MR imaging scanning was relatively new at the time of these criteria, it was included as a paraclinical element but was not further defined.

According to the new McDonald criteria, the diagnosis of MS requires objective evidence of lesions disseminated in time and space: MR imaging findings may contribute to the determination of dissemination in time or space; other supportive investigations include CSF and visual evoked potentials (VEPs); diagnostic categories are possible MS, MS, or not MS. For dissemination in space, McDonald criteria include the Barkhof-Tintore MR imaging criteria,[11,14] which require 3 of the following 4 elements: (1) at least one gadolinium-enhancing lesion or 9 T2 hyperintense lesions; (2) at least one infratentorial lesion; (3) at least one juxtacortical lesion; (4) at least 3 periventricular lesions. A spinal cord lesion can substitute for any of the above brain lesions. If there are immunoglobulin abnormalities in the CSF, the MR imaging criteria are relaxed to only 2 T2 lesions typical of MS. For dissemination in time, the MR imaging can be equally useful. If an MR imaging scan of the brain performed at ≥3 months after an initial clinical event demonstrates a new gadolinium-enhancing lesion, this would indicate a new CNS inflammatory event, because the duration of gadolinium enhancement in MS is usually less than 6 weeks. If there are no gadolinium-enhancing lesions but a new T2 lesion (presuming an MR imaging at the time of the initial event), a repeat MR imaging scan after another 3 months is needed with demonstration of a new T2 lesion or gadolinium-enhancing lesion.

Subsequent application of these criteria in several natural history or treatment trial cohorts indicated that they were robust in allowing an earlier diagnosis and predicting an increased likelihood of conversion to clinically definite MS when there was MR imaging evidence for dissemination in space and time in patients with a CIS.[15–17] Specificity was high, and in particular this was the case when dissemination in time was present: dissemination in space per se was less specific. The requirement for a gadolinium-enhancing lesion to fulfill dissemination in time after 3 months had poor sensitivity, but it was noted that allowing a new T2 lesion instead overcame this limitation.[18] In the light of subsequent studies, and in view of the criticism—from the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, which recommended 1–3 lesions per se as sufficient evidence for diagnosing MS[19]—the 2001 criteria were revised by a reconvened international panel during 2005.[20] A constant feature in both 2001 and 2005 is the use of the Barkhof-Tintore criteria. They differ in the extent to which a spinal cord lesion can also assist with fulfillment of dissemination in space: in 2001, only one cord lesion could substitute for one brain lesion, whereas in 2005 any number of cord lesions can substitute for brain lesions and a cord lesion is also assigned the same status as an infratentorial lesion. This change may have been based on a study in 107 early but definite MS patients, where cord lesions substantially increased the proportions with dissemination in space from 67% by using brain MR imaging alone to 94% by using all available cord lesions to complement brain lesions.[21] Also cord MR imaging allows the exclusion of alternative pathology in patients with cord syndromes and the higher specificity for MS than brain MR imaging findings when comparison is made with other neurologic disorders and with older healthy controls who frequently have WM lesions due to small vessel disease.[22]

In time, the 2005 criteria for dissemination were more substantially revised to include a new T2 lesion occurring more than 1 month after clinical onset. This should increase the sensitivity while retaining specificity in making an earlier diagnosis of MS in CIS patients. In PPMS, the presence of CSF oligoclonal bands is no longer required, though in their absence it is necessary to have at least 2 spinal cord lesions and either 9 brain lesions or 4–8 brain lesions plus abnormal VEPs.

Although MR imaging is the most sensitive investigational technique for MS, it is important to keep in mind that the appearance of multiple lesions on MR imaging is not specific for MS. In the clinical setting, however, this appearance provides an important ancillary diagnostic tool that may establish the multifocality of CNS involvement. MR imaging is also used to assess MS disease activity, disease burden, and the temporal, dynamic evolution in these parameters. Finally, MR imaging is 4–10 times more sensitive than the clinical evaluation in capturing CNS lesions, and serial studies have demonstrated that clinically apparent changes reflect only a minor component of disease activity. Lesions in the cerebrum are much more likely to be clinically silent compared with lesions in the brain stem or spinal cord.

Pathogenesis

The etiology of MS is still unknown, but according to current data the disease develops in genetically susceptible individuals and may require additional environmental triggers. According to the pathogenesis, derived from the experimental autoimmune encephalomyelitis, autoreactive peripherally activated $CD4^+$ T cells recognize autoantigens within the CNS parenchyma in the context of class II molecules of the major histocompatibility complex (MHC) expressed by both local glial antigen-presenting cells and dendritic cells,[23] which commit T cells toward a T_H1 phenotype.[24] Activated T_H1 cells cause myelin disruption and the release of new potential CNS autoantigens. Secreted proinflammatory cytokines, such as interferon-γ and tumor necrosis factor (TNF)-α,[25] and chemokines recruit additional unspecific inflammatory cells and specific antimyelin antibody-forming B cells that amplify tissue injury. Finally, the apoptotic death of T cells and their conversion toward a T_H2 phenotype positively modulate the outcome of the lesion.[25] Additional cells are necessary for the typical MS lesions to occur such, as the $CD8^+$ cells, which show a more prominent clonal expansion within MS plaques and better than $CD4^+$ correlate with the extent of acute axonal injury.[26,27] The pre-existing autoreactive T cells are activated outside the CNS by foreign microbes, self-proteins, or microbial superantigens. The activated T cells cross the blood-brain barrier through a multistep process. First, activated T cells that express integrins can bind to adhesion molecules on the surface of the endothelium. Then the T cells must pass through a

barrier of extracellular matrix (ECM) in a step that involves matrix metalloproteases, enzymes that play a role in both the degradation of ECM and the proteolysis of myelin components in MS. Antimyelin antibodies—activated macrophages or microglial cells—complement and TNF-α are believed to cooperate in producing demyelination. In the neurodegenerative phase of the disease, excessive amounts of glutamate are released by lymphocytes, microglia, and macrophages.[27] The glutamate activates various glutamate receptors (AMPA and kainate receptors), and the influx of calcium through ion channels associated with different glutamate receptors may cause necrotic damage to oligodendrocytes and axons.

It is clear that genetic factors play a prominent role in susceptibility to MS.[3] Both genetic and nongenetic environmental factors may be involved in susceptibility as well as outcome. Any environmental factor is likely to be ubiquitous and act on a population-basis rather than within the family microenvironment. It is likely that there are several independent or interacting polymorphic genes, each exerting a small, or at most moderate, effect to the overall risk. It is also likely that genetic heterogeneity exists, meaning that specific genes influence susceptibility and pathogenesis in some individuals but not in others. Concordance in families for early and late clinical features has been observed as well, which indicates that, in addition to susceptibility, genes influence disease severity or other aspects of the clinical phenotype. Therefore, some genes may be involved in the initial pathogenic events, whereas others could influence the development and progression of the disease. The strongest and most consistently replicated evidence for an MS susceptibility gene has been localized to the MHC. The proportion of the total genetic susceptibility explained by the MHC locus is estimated to range between 20% and 50%.[3]

Pathology

The pathologic hallmarks of MS are demyelinated plaques within the WM combined with inflammatory infiltrates consisting of lymphocytes (T cells and B cells) and activated macrophages/microglia.[26] Demyelination, followed by a variable degree of remyelination, is associated with oligodendrocyte loss during the chronic stage of the disease. Axonal loss and gliosis with astrocyte proliferation and glial fiber production are important pathologic features of MS. Recent histopathologic studies of MS lesions, however, have revealed a great variability within lesions of different subjects with respect to the extent of inflammation, oligodendrocyte pathology, and neuroaxonal injury.[28] Four different patterns of pathology with resulting demyelination have been observed in MS lesions: Type 1 are T cell-mediated and account for 19% of lesions where demyelination is macrophage-mediated, either directly or by macrophage toxins. Type II lesions are both T cell and antibody mediated and, at 53%, are the most common pathology observed in MS lesions. This pattern results in demyelination via specific antibodies and complement. Type III represent the 26% of lesions and are related to distal oligodendropathy; degenerative changes in distal processes occur that are followed by apoptosis. Type IV is responsible for only 2% of lesions and results from primary oligodendrocyte damage followed by secondary demyelination. This latter pattern was observed only in a small subset of PPMS patients.[29] Of note, the pattern of demyelination found in type III lesions mimics that found in the early stages of WM ischemia and may therefore reflect hypoxic WM damage. A pathologic process similar to ischemia could be induced in inflammatory conditions by 2 mechanisms: vascular impairment leading to defective microcirculation or local production of toxins that alter the mithocondrial energy metabolism.[30]

There is increasing evidence that neuroaxonal damage is a key feature in MS lesions and that it has a major impact on permanent neurologic deficits.[31] Axonal damage occurs within both acute and chronic plaques, as well as in normal-appearing WM, and it is already present in the early stage of the disease.[32] It may occur either in parallel with myelin destruction or during a second phase, when the axon is demyelinated and more susceptible to damage. The immunologic attack, triggered by myelin-reactive T cells, leads to the release of free oxygen radicals and nitric oxide (NO) by microglial cells, causing myelin breakdown. The increased concentration of NO in MS lesions can mediate axonal injury possibly by mitochondrial injury and subsequent energy depletion, which can be prevented by sodium channel blockers.[33] The increase of glutamate in MS lesions is another potential mechanism of cell-mediated cytotoxicity.[34] In the later phase, microglia and T cell activation are less important, whereas the up-regulation of sodium and calcium channels along degenerating axons may play an important role in the disease process.[35]

In addition to axonal injury, the presence of cortical plaques has long been described in MS.[36] A systematic description of these lesions identified 7 plaque types depending on the topography within the cortex.[37] Cortical plaques are characterized by less lymphocyte infiltration and predominant microglial activation.[38] The involvement of neuroaxonal structures in the disease process is characterized by neuronal apoptosis, loss of dendritic arborization, and transected and demyelinated axons.[39]

Therapy

The most important goal of MS therapy is to prevent permanent neurologic disability. Acute relapses of MS are usually treated with corticosteroids that shorten symptoms, reduce inflammation, seal the blood-brain barrier, enhance nerve conduction, and alter the immune system, all of which are potentially beneficial in treating MS. Five drugs are currently approved by the Food and Drug Administration as disease-modifying agents that alter the natural history of RRMS. The 4 self-administered drugs are intramuscular beta-interferon-la (Avonex), subcutaneous beta-interferon-1a (Rebif), subcutaneous beta-interferon-1b (Betaseron), and glatiramer acetate (Copaxone). These medications reduce the number of attacks in RRMS. These therapies, however, appear to be ineffective against the purely progressive form of the disease. Furthermore, longitudinal brain MR imaging data indicate that the accumulation of focal lesions early in the course of MS is associated with late progressive disability. Because available disease-modifying drugs can reduce the formation of such focal lesions, these data support the early institution of disease modifying therapy, especially in patients who are at high risk for future attacks and significant disability. Nevertheless, these treatments seem to have little effect once the disease has entered a secondary progressive phase. For SPMS, the most convincing data favors mitoxantrone (Novantrone) as most likely

to retard progression and delay disability.[40] Several symptomatic treatments are also available to alleviate spasticity, bladder disturbances, neuropathic pain, and fatigue.

Conclusion

The past few years have seen increasing improvement in the development of laboratory and imaging approaches to study MS, leading to a better understanding of the immunopathogenesis, pathology, and genetics of the disease. In addition, MR imaging criteria have been incorporated, for the first time, into formal clinical diagnostic criteria for MS and a few disease-modifying therapies are currently available. These treatments, however, are less effective in the progressive stage of the disease. There is hope that ongoing research will identify appropriate molecular targets of intervention and novel diagnostics and, more importantly, will enable the development of new and more effective therapies.

References

1. Rodriguez M, Siva A, Ward J, et al. **Impairment, disability, and handicap in multiple sclerosis: a population-based study in Olmsted County, Minnesota.** *Neurology* 1994;44:28–33
2. Hauser S. **Multiple sclerosis and other demyelinating diseases.** In: Isselbacher KJ, Martin JB, Fauci AS, et al, eds. *Harrison's principles of internal medicine.* New York: McGraw-Hill;1994:2287–95
3. Oksenberg JR, Hauser SL. **Genetics of multiple sclerosis.** *Neurol Clin* 2005;23:61–75
4. McAlpine D. *Multiple sclerosis: a reappraisal.* Edinburgh: Churchill Livingstone; 1972
5. Reingold SC. **Fatigue and multiple sclerosis.** *MS News Br Mult Scler Soc* 1990;142:30–31
6. Bagert B, Camplair P, Bourdette D. **Cognitive dysfunction in multiple sclerosis: natural history, pathophysiology and management.** *CNS Drugs* 2002;16:445–55
7. Weinshenker BG, Bass B, Rice GP, et al. **The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability.** *Brain* 1989;112:133–46
8. Montalban X. **Primary progressive multiple sclerosis.** *Curr Opin Neurol* 2005;18:261–66
9. Lublin FD, Reingold SC. **Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis.** *Neurology* 1996;46:907–11
10. Young IR, Hall AS, Pallis CA, et al. **Nuclear magnetic resonance imaging of the brain in multiple sclerosis.** *Lancet* 1981;2(8255):1063–66
11. Barkhof F, Filippi M, Miller DH, et al. **Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis.** *Brain* 1997;120:2059–69
12. McDonald WI, Compston A, Edan G, et al. **Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the Diagnosis of Multiple Sclerosis.** *Ann Neurol* 2001;50:121–27
13. Poser CM. **Diagnostic criteria for multiple sclerosis: an addendum.** *Ann Neurol* 1987;22:773
14. Tintore M, Rovira A, Martinez MJ, et al. **Isolated demyelinating syndromes: comparison of different MR imaging criteria to predict conversion to clinically definite multiple sclerosis.** *AJNR Am J Neuroradiol* 2000;21:702–06
15. Dalton CM, Brex PA, Miszkiel KA, et al. **Application of the new McDonald criteria to patients with clinically isolated syndromes suggestive of multiple sclerosis.** *Ann Neurol* 2002;52:47–53
16. Tintore M, Rovira A, Rio J, et al. **New diagnostic criteria for multiple sclerosis: application in first demyelinating episode.** *Neurology* 2003;60:27–30
17. Barkhof F, Rocca M, Francis G, et al. **Validation of diagnostic magnetic resonance imaging criteria for multiple sclerosis and response to interferon beta1a.** *Ann Neurol* 2003;53:718–24
18. Dalton CM, Brex PA, Miszkiel KA, et al. **New T2 lesions enable an earlier diagnosis of multiple sclerosis in clinically isolated syndromes.** *Ann Neurol* 2003;53:673–76
19. Frohman EM, Goodin DS, Calabresi PA, et al. **The utility of MRI in suspected MS: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.** *Neurology* 2003;61:602–611
20. Polman CH, Reingold SC, Edan G, et al. **Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria."** *Ann Neurol* 2005;58:840–46
21. Bot JC, Barkhof F, Polman CH, et al. **Spinal cord abnormalities in recently diagnosed MS patients: added value of spinal MRI examination.** *Neurology* 2004;62:226–33
22. Bot JC, Barkhof F, Lycklama a Nijeholt G, et al. **Differentiation of multiple sclerosis from other inflammatory disorders and cerebrovascular disease: value of spinal MR imaging.** *Radiology* 2002;223:46–56
23. Pashenkov M, Teleshova N, Link H. **Inflammation in the central nervous system: the role for dendritic cells.** *Brain Pathol* 2003;13:23–33
24. Hafler DA, Slavik JM, Anderson DE, et al. **Multiple sclerosis.** *Immunol Rev* 2005;204:208–231
25. Link H. **The cytokine storm in multiple sclerosis.** *Mult Scler* 1998;4:12–15
26. Lassmann H. **Pathology of multiple sclerosis.** In: Compston A, Ebers G, Lassmann H, et al, eds. *McAlpine's multiple sclerosis.* London: Churchill Livingstone; 1998:323–57
27. Steinman L. **Multiple sclerosis: a two-stage disease.** *Nat Immunol* 2001;2:762–64
28. Lassmann H, Bruck W, Lucchinetti C. **Heterogeneity of multiple sclerosis pathogenesis: implications for diagnosis and therapy.** *Trends Mol Med* 2001;7:115–21
29. Lucchinetti C, Bruck W, Parisi J, et al. **Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination.** *Ann Neurol* 2000;47:707–17
30. Lassmann H. **Hypoxia-like tissue injury as a component of multiple sclerosis lesions.** *J Neurol Sci* 2003;206:187–91
31. Trapp BD, Ransohoff R, Rudick R. **Axonal pathology in multiple sclerosis: relationship to neurologic disability.** *Curr Opin Neurol* 1999;12:295–302
32. Trapp BD, Peterson J, Ransohoff RM, et al. **Axonal transection in the lesions of multiple sclerosis.** *N Engl J Med* 1998;338:278–85
33. Kapoor R, Davies M, Blaker PA, et al. **Blockers of sodium and calcium entry protect axons from nitric oxide-mediated degeneration.** *Ann Neurol* 2003;53:174–80
34. Werner P, Pitt D, Raine CS. **Multiple sclerosis: altered glutamate homeostasis in lesions correlates with oligodendrocyte and axonal damage.** *Ann Neurol* 2001;50:169–80
35. Craner MJ, Newcombe J, Black JA, et al. **Molecular changes in neurons in multiple sclerosis: altered axonal expression of Nav1.2 and Nav1.6 sodium channels and Na+/Ca2+ exchanger.** *Proc Natl Acad Sci USA* 2004;101:8168–73
36. Brownell B, Hughes JT. **The distribution of plaques in the cerebrum in multiple sclerosis.** *J Neurol Neurosurg Psychiatry* 1962;25:315–20
37. Kidd D, Barkhof F, McConnell R, et al. **Cortical lesions in multiple sclerosis.** *Brain* 1999;122:17–26
38. Bo L, Vedeler CA, Nyland H, et al. **Intracortical multiple sclerosis lesions are not associated with increased lymphocyte infiltration.** *Mult Scler* 2003;9:323–31
39. Peterson JW, Bo L, Mork S, et al. **Transected neurites, apoptotic neurons, and reduced inflammation in cortical multiple sclerosis lesions.** *Ann Neurol* 2001;50:389–400
40. Calabresi PA. **Considerations in the treatment of relapsing-remitting multiple sclerosis.** *Neurology* 2002;58(8 suppl 4):S10–22